Green Chemistry and Sustainable Technology

Justyna Płotka-Wasylka
Jacek Namieśnik *Editors*

Green Analytical Chemistry

Past, Present and Perspectives

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ISSN 2196-6982 ISSN 2196-6990 (electronic)
Green Chemistry and Sustainable Technology
ISBN 978-981-13-9104-0 ISBN 978-981-13-9105-7 (eBook)
https://doi.org/10.1007/978-981-13-9105-7

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

This book is dedicated in honour and memory of Prof. Jacek Namieśnik (10 December 1949–14 April 2019), a visionary analytical chemistry leader and a mentor to so many. You will be missed.

Preface

Care about global climate change, pollution of environment and hazards to human health have increased significantly. These fears have led to a call for changes in the field of chemistry science and chemists' action including those that are connected with chemical analysis. Analytical chemistry is a central science that provides the evolution in other chemical fields. There is no doubt analytical laboratories have an essential role to play in environmental protection through monitoring of pollutants in air, water or soil. On the other hand, analytical activities involve the use of many reagents and solvents, thus generating toxic residues. For these reasons, Green Analytical Chemistry (GAC) was introduced in 2000 to reduce or remove the side effects of analytical practices on operators and the environment.

This idea has attracted a great deal of interest among chemists, particularly those concerned with making laboratory practices in analytical chemistry environmentally friendly. As it is a great challenge to reach an acceptable compromise between increasing the quality of results and improving environmental friendliness of analytical methods, it is important to follow the guidelines and principles of Green Analytical Chemistry which have been introduced, and provide a framework for GAC.

All this makes the appearing field of Green Analytical Chemistry a "hot topic" not only in academia but also in industrial and governmental laboratories. This book starts by introducing the history of Green Analytical Chemistry as well as laws and principles that are based on the GAC ideology. Another important issue that will determine the future of Green Analytical Chemistry is education of this concept in the society; thus, the subject connecting with teaching of GAC based on several examples is also discussed. It then goes on to present the trends and future perspectives of the analytical laboratories. Developments and new achievements in such fields as direct techniques of detection and determination of trace analytes, extraction of trace constituents, and nature of the derivatization process and green chromatographic techniques are widely discussed. Flow injection analysis towards Green Analytical Chemistry as well as remote monitoring of environmental pollutants is presented. The book also contains chapters which are focused on the smart

sorption materials and new types of solvents used in the field of analytical chemistry.

As the greenness of analytical procedure is multivariable aspect, many greenness criteria should be taken into consideration. From the other side, modern analytical chemistry offers dozens of analytical methodologies, based on different methods and techniques, which are used for determination of analytes in a given matrix. Due to such complex decision-making processes, multi-criteria decision analysis tools are applied as systematic approach to deal with complex decisions. In this book, the reader will find the description of step-by-step approach to application of three multi-criteria decision analysis tools as Green Analytical Chemistry systems. In addition, several tools that can be applied to evaluate the developed analytical procedures are presented.

The book concludes with a discussion of how GAC is both possible and necessary. The final chapter summarizes contemporary problems and gives future perspectives of Green Analytical Chemistry. Green Analytical Chemistry is aimed at managers of analytical laboratories but will also interest teachers of analytical chemistry and green public policy-makers.

This book aims to celebrate the advancements in Green Analytical Chemistry, which encompasses all measurement techniques for all types of applications that minimize or eliminate the generation of chemical waste. We believe that this book will allow the reader to identify that GAC can operate in all contexts, not only in environmental application but also in the industrial and the sanitary. We hope that this book contributes to move from the theory to the practice; therefore, editors and authors are convinced of the necessity of this book.

We would like to express our thanks to the personnel of Springer who have offered all the time their support, especially June Tang and Sunny Guo for their help to make this book possible. The generosity, patience and good work of all the authors are acknowledged. We are convinced that this book is the starting point for future cooperation in a new analytical chemistry.

Gdańsk, Poland Justyna Płotka-Wasylka

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Chapter 1
History and Milestones of Green Analytical Chemistry

Justyna Płotka-Wasylka, Magdalena Fabjanowicz, Kaja Kalinowska and Jacek Namieśnik

Abstract Due to the increased environmental consciousness, Green Analytical Chemistry (GAC) is an important concept steadily gaining popularity, as its implementation facilitates the decrease the detrimental effect analytical chemistry methodologies may have on the environment. In this chapter, a brief overview of the history of Green Analytical Chemistry (GAC) and its milestone was given. Emphasis has been put on the beginnings of green chemistry awareness and on the possibilities of increasing and evaluating the greenness of both currently used and designed analytical chemistry methodologies. In addition, the prospects of implementation of 12 principles of Green Analytical Chemistry have been briefly described.

1.1 Introduction

Concern and interest for the state of the environment are constantly increasing; therefore, it becomes significant to examine those chemists and chemical engineers' activities which may impact on the environment state, on both the laboratory and the industrial scales [1]. Introduction of the green chemistry idea is associated with the dissemination of the principles of sustainable development and the highly visible tendency to the implementation of these principles in laboratories and chemical plant. In fact, principles of green chemistry have been adopted in the specific fields of chemistry. However, in the literature, it can be observed that before the popularization of the green chemistry concept, there was a consciousness among analytical chemists of the need to develop sustainable methodologies, in order to save solvents and reagents, as well as to replace the most toxic solvents by other innocuous or less toxic ones [2]. The adverse effects of the application of analytical procedures may commit damage to the environment and serious risks for operators; therefore, for these reasons, it is essential to think about the effects as well as consequences

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J. Płotka-Wasylka and J. Namieśnik (eds.), *Green Analytical Chemistry*,
Green Chemistry and Sustainable Technology,
https://doi.org/10.1007/978-981-13-9105-7_1

of action as researchers/users of analytical methods. Hence, from the viewpoint of people who take care of the environment and themselves as well as part of economic aspects of analytical methodologies, the special attention should be paid on the inherent risk of some samples type, aliquot of reagents and solvents used, the consumption of energy related to more and more modern instrumentation and, without a doubt, produced laboratory wasted and emissions coming from the numerous steps of analytical methodologies [3].

In this chapter, we will shortly describe the history and milestones of Green Analytical Chemistry (GAC). In addition, the facts which made possible the tremendous interest in Green Analytical Chemistry exist today, and the origin of many of terms is currently used.

1.2 The Birth of the Concept of Green Analytical Chemistry

Nowadays, GAC is the concept which every chemist analyst should know. Therefore, it is not surprising that analytical chemistry studies in the frame of chemistry degrees around the world have evolved in different ways. However, a responsibility among the analytical chemists' society appeared long before the introduction of the GAC term. Many innovative advances in the area of sample preparation, measurement as well as data handling associated with microwave-assisted flow injection analysis (FIA), sample digestion and extraction (MAE), and chemometrics were represented in the middle of the 1970s. It needs to be noted that the methodological milestones (Fig. 1.1) which were invented to increase the green character of the analytical protocols were mainly reached before the formulation of GAC idea [2]. An essential step on the way to introduce the GAC idea was concept developed in 1993 regarding the possibility offered by the combination of the processes of photo-assisted degradation linked to FIA manifolds carried out in the spectrometric determination of phenolic compounds [2]. Another important idea was the application of the term "clean waste" instead of word "waste", suggesting an alternative method which includes an additional chemical effort to reduce the environmental impact of FIA determinations. That was the beginning of the clean analytical chemistry concept. In 1995, the potentiality proposed by the degradation processes' contribution and FIA to enhance analytical methods was confirmed.

In the same year, the article entitled "Towards environmentally conscientious Analytical Chemistry through miniaturization containment and reagent replacement" was published, and it is obvious that this was the first declaration of the principles of what is today called Green Analytical Chemistry [4]. In another manuscript [5], a term "waste minimization" was proposed and recommended to analytical practice. Although the term Green Analytical Chemistry was not applied in this manuscript,

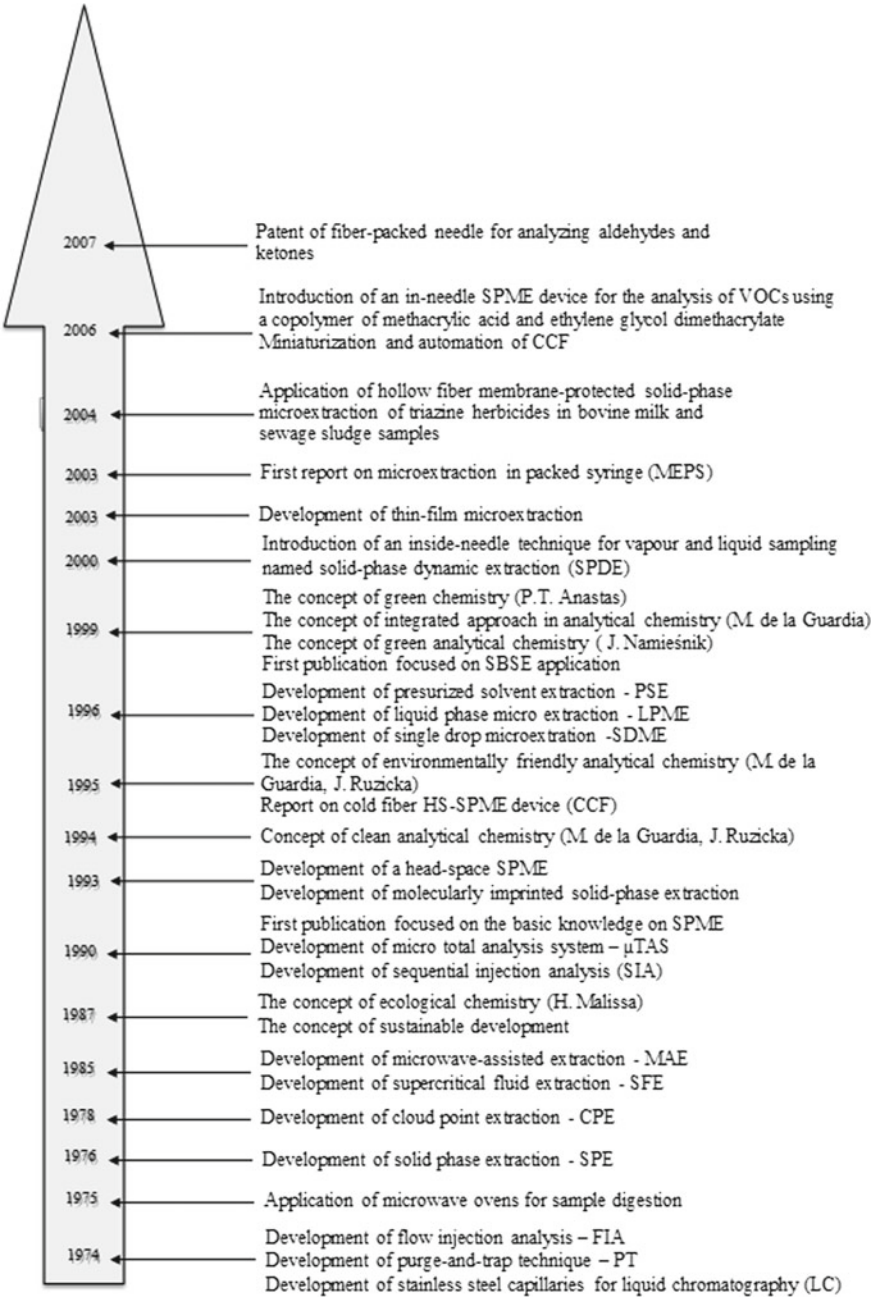


Fig. 1.1 Milestones of Green Analytical Chemistry

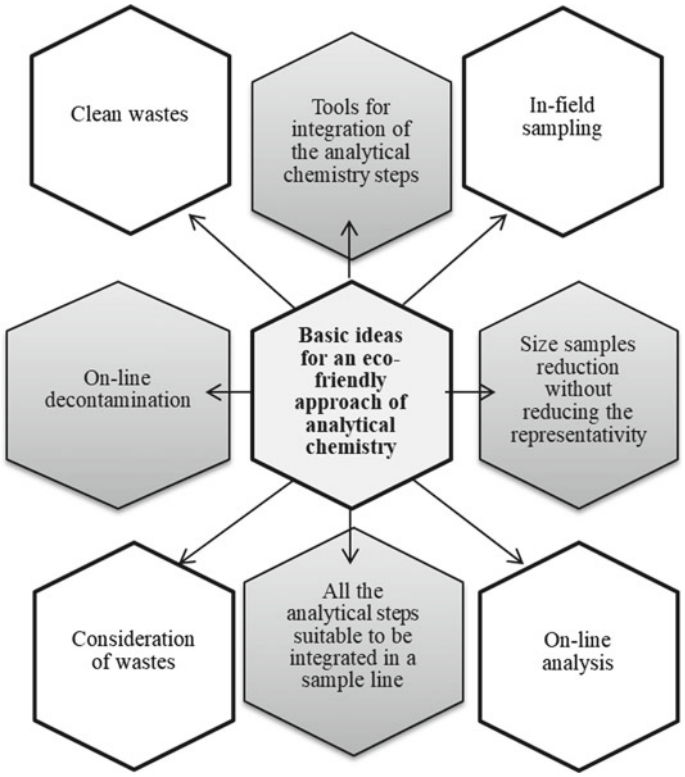


Fig. 1.2 Basic ideas for an integrated eco-friendly approach of Analytical Chemistry

it is allotted as the precursor works of GAC because the green idea was inherently present. Since this time, green idea development in analytical practice was going very quickly. Thus, more and more improvements, in both procedures and instrumentations, were developed and introduced what can be seen in Fig. 1.1. Moreover, the basic ideas for an integrated environmentally friendly approach of analytical chemistry were pointed out (Fig. 1.2).

In 1973, an important work entitled "Trends in the Teaching of Analytical Chemistry in American Universities" was published. In this work, a well-known sentence "the usual approach to predict the future is to project past trends" has been cited [6], showing that scientific activities must be adapted to societal needs in order to surmount any crises by a correct projection of the past to the future, making adequate behavioural changes to avoid errors made in the past and to incorporate new ideas into old practices [2]. This idea was extended in 1987 at the Euroanalysis VI Conference, under the title "Changes of paradigms in Analytical Chemistry". In this presentation,

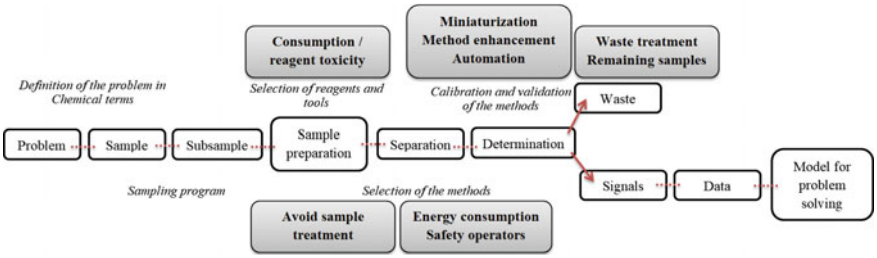


Fig. 1.3 Steps of the analytical process to be considered in the frame of the Ecological Paradigm

the term paradigm was used not only as a pattern and a syntax-like scheme but also as a guide for new friends in our academic society to give them novel tools for solving problems and a new platform for discussion and communication [2, 7]. In addition, six successive paradigms in the evolution of Analytical Chemistry—from archeochemistry to alchemy, iatrochemistry, chemiology, chemiurgy and finally ecological chemistry—were identified. In this presentation, it has been presented that Analytical Chemistry today must be closely associated with environmental protection. In addition, all analytical activities must consider the different aspects connected to the preservation of our ecosystem. Therefore, we must be conscious that in our professional activity, it is required to take care of the operator's safety and the environment preservation. Although there is no clear transition between the archaeological period and the different paradigms, nowadays the ecological mentality must inform the work of the analyst and relationship with society. Thus, taking into account the analytical process, the attention should be paid not only to the problems, samples and data to be obtained, but also to the nature and amounts of the reagents to be applied, the emissions and wastes generated during the whole process, the energy requirements and the risks to operators and the environment [2, 7]. Steps of the analytical process to be considered in the frame of the Ecological Paradigm are presented in Fig. 1.3.

Without a doubt, the analytical activity increase on the environmental samples and on the undesirable environmental constituents had the knock-on effect of increasing the number of analytical wastes and provided notable changes in the laboratories' mentality about the impact of their residues. Evolution of the ecological mentality within analytical laboratories is very visible (Fig. 1.4), and it is a consequence of the bad conscience about the side effects of the increase of reagent consumption and waste generation. This is hard evidence that the new opportunities proposed by chemistry at the end of the last century were closely associated with the ecological mentality, and here, the idea of GAC offered excellent opportunities from the academic as well as business points of view.

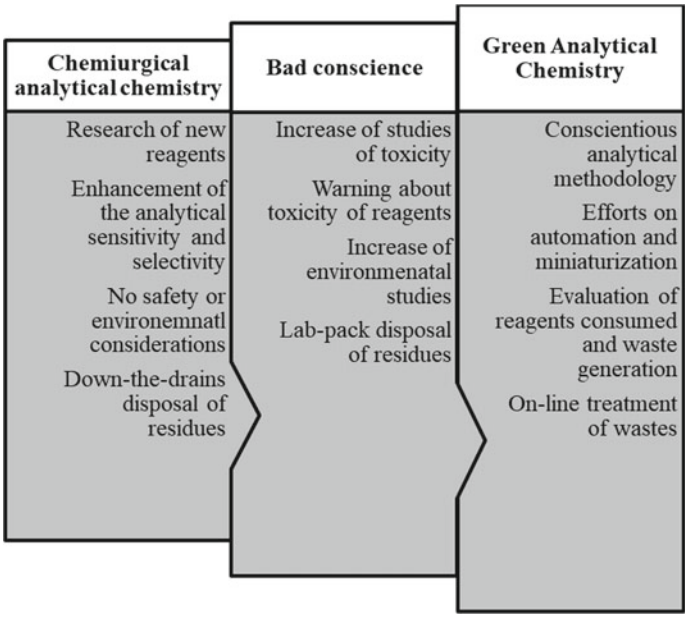


Fig. 1.4 Steps of the evolution of the ecological mentality within analytical laboratories

1.3 The Evaluation of Methodologies from Traditional Analytical Chemistry to Green Analytical Chemistry

In the 1990s, Paul Anastas edited a series of texts concerning the need for the movement towards environmentally benign chemistry, about Green Analytical Chemistry and its importance in the frame of green chemistry [2]. In particular, Anastas emphasized its twofold role in the environmental protection, caused by the fact that various analytical chemistry methodologies could not only contribute themselves to detection of potentially undesirable environmental constituents but possibly also take part in the increase of pollution's amount and further ecological problems. Because of that it is important to work on greening the analytical methods, while taking their accuracy, sensitivity and precision under consideration.

1.3.1 Principles of Green Analytical Chemistry

In 1998, Anastas and Warner created the 12 principles of green chemistry [8]. However, since they were coined in order to be applied in the field of synthetic chemistry, only some of them could be employed to the analytical chemistry. Because of that there was a need to adapt the rules in a way that would make their implementation

Fig. 1.5 Goals of the Green Analytical Chemistry

in the field of analytical chemistry possible. Thus, 12 undermentioned principles of Green Analytical Chemistry have been designed [9]:

1. If possible, sample treatment should be avoided by the use of direct methods.
2. The number and size of the samples should be as small as possible.
3. Measurement should be performed in situ.
4. Processes and operations should be integrated.
5. If possible, automation and miniaturization of analytical methods should be selected.
6. Derivatization should be avoided.
7. The number of wastes generated should be as little as possible, and it should be managed accordingly.
8. Multi-analyte and multi-parameter methods should be applied wherever it is possible.
9. Use of the energy should be minimal.
10. Reagents from renewable sources should be preferred.
11. Toxic reagents and solvents should be eliminated or replaced.
12. Safety of the operators should be improved.

Based on the principles of both green chemistry and Green Analytical Chemistry, four points have been designated as top priorities (Fig. 1.5), since their implementation would be a significant step in greening analytical methods [1].

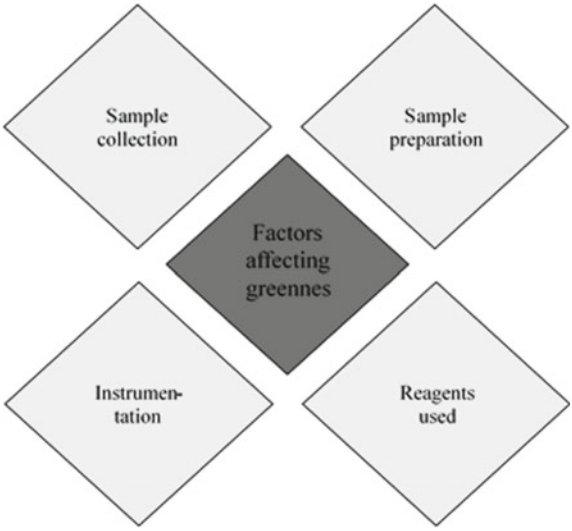


Fig. 1.6 Types of factors evaluated during greenness assessment

1.3.2 Clean Analytical Methods

The first descriptions of clean analytical method appeared in 1995 [10]. This term has been coined in order to speak about methods in which additional effort was made in order to decrease the negative impact the analysis has on the environment, such as detoxification of wastes or recovery of the catalysts [2]. Based on the all aforementioned priorities and principles of GAC, an ideally clean analytical method would be direct, nondestructive, reagentless procedure that requires only a minimal energy, while at the same time is also fast and capable multiple parameters and analytes in a single run.

However, in case of many analytical problems, it is not possible to use a so-called ideal method that would be in accordance with all principles of Green Analytical Chemistry, since not many analytes and parameters can be determined simultaneously or from an untreated sample. Because of that, it is important to evaluate all aspects of analytical methods that affect their sustainability and that may be improved without affecting their basic analytical characteristics.

In order to minimize the negative environmental impact of already existing methods, each step of analytical procedure (i.e. sampling collection, sampling preparation, analysis and the evaluation of the results) should be evaluated based on their influence on the environment and the possibility of increasing their greenness [11]. Four main categories of factors taken under consideration are depicted in Fig. 1.6 [12].

Characteristics of reagents and solvents used in the analytical process are one of the key factors affecting its greenness, since they may be detrimental to the environment, as well as human health and safety. On many occasions, these compounds are flammable, toxic or otherwise potentially harmful to the biota. Moreover, the use of the nongreen reagents at each step of analytical methodology may result in the neces-

sity of the implementation of expensive and time-consuming waste treatment [13]. Due to the aforementioned reasons, one of the aims of Green Analytical Chemistry is to identify reagents to be replaced and substitute them with nontoxic, harmless alternatives [14].

Out of all steps of the analytical procedure, samples' preparation is usually the most polluting part, since techniques such as extraction or mineralization are often energy-consuming and require the use of various nongreen solvents. Because of that the greenest approach would be to use direct analytical methods, in which the whole step of sample preparation is negligible. However, in many cases, isolation and preconcentration of analytes are unavoidable and direct analysis cannot be performed. Thus, the emphasis should be put on the automation and miniaturization of the process, as well as the use of the least harmful compounds and novel techniques that require much smaller amounts of organic solvent. Reduction and, if possible, elimination of the use of a nongreen solvent in samples preparation should be a priority not only due to being detrimental to the environment but also because it could potentially reduce the cost of the analysis [11].

Samples' collection is usually not associated with being harmful to the ecosystem; nevertheless, transportation, storage and the collection itself involve money, material and energy. Moreover, in the case of environmental or biological samples whose physical or chemical composition changes during storage. Notwithstanding, in the case of the measurements that can be performed directly in the flow system, it is recommended to avoid the sample collection step by using greener in-line system instead of off-line mode [15].

When neither in-line analysis nor direct methods can be used, the emphasis should be put on choosing the greenest approach. The factors such as the amount of waste generated and energy used, as well as the occupational hazard of using the instrument in question, should be taken under consideration.

1.3.3 Green Analytical Evaluation Tools

Since analytical procedures are usually complex and consist of several steps, it might be difficult to assess the overall impact it has on the environment. Moreover, comparison of different methodologies based on their accordance with GAC principles necessitates some form of greenness evaluation [16]. As a consequence, several evaluation tools have been proposed in order to facilitate the evaluation of analytical procedures.

National Environmental Methods Index (NEMI) is a tool in which the procedures are assessed based on their greenness profiles. In order to evaluate a particular method, four main criteria are taken under consideration: toxicity and corrosivity of used chemicals, hazard and waste amount. The procedure in question is seen as green when:

- the chemical used is not hazardous or listed as persistent, bioaccumulative or toxic,
- pH during the analysis is in the 2–12 range,

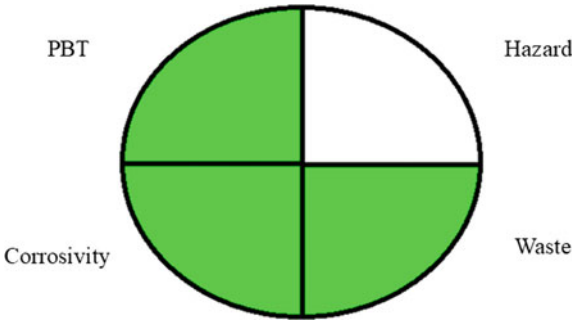


Fig. 1.7 Exemplary pictogram of NEMI

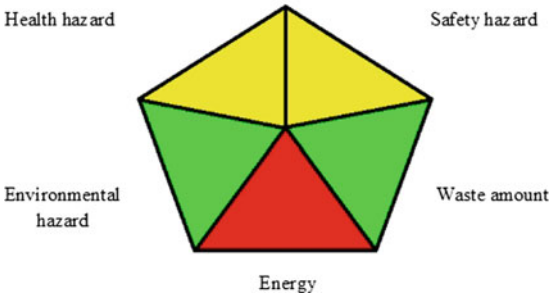
- the amount of waste generated is less than 50 g [17].

The results of the evaluation are presented in the form of the profile's symbol divided into four parts (Fig. 1.7), each one of them provides information about the greenness of the method in relation to a different criterion. NEMI pictograms are easy to read by potential users; however, its use is time-consuming since it requires searching each of the used chemicals on various lists of harmful substances. Moreover, application of NEMI in comparison of different procedures may be difficult, since it provides neither quantitative nor semi-quantitative information. Therefore, in order to increase NEMI applicability in collating multiple analytical methodologies, Guardia et al. proposed the use of a three-coloured scale in order to evaluate the greenness of each aspect of the procedure [10].

Another tool has been proposed by Raynie and Driver [18]. In this case, analytical procedures are evaluated based on five criteria: potential environmental, health and safety risk, amount of generated waste and energy consumption. As can be seen in Fig. 1.8, results are presented in a form of pictogram divided into five parts, each of them marked green, yellow or red based on category's environmental impact. With the use of the visual representation of this tool, it is possible to compare two or more different procedures based on their greenness.

An alternative approach is to use the Analytical Eco-Scale proposed by Namieśnik et al. [19]. In this tool, various parameters of the procedure, such as the number of reagents used or waste generated, are assessed. For each parameter that differs from the principles of GAC, penalty points are assigned and then subtracted from 100. Based on the obtained result, it is possible to evaluate greenness of the method in question: the higher the final score is, the greener the suggested method is. Analytical Eco-Scale can be used in order to evaluate new analytical methods, as well as to compare them with already existing techniques since it enables quick assessment and appraises many aspects of environmental impact in an efficient manner.

The newest tool is the Green Analytical Procedure Index (GAPI). In this approach, greenness evaluation of each step of the analytical procedure is presented in a form of pictogram comprised of five pentagrams that provide information on the greenness of different steps of the analytical procedure (Fig. 1.9). Sample collection and



Category	Green	Yellow	Red
Health Hazard	Slightly toxic, slight irritant; NFPA health hazard score is 0 or 1.	Moderately toxic; could cause temporary incapacitation; NFPA = 2 or 3.	A serious injury on short-term exposure; known or suspected small animal carcinogen; NFPA = 4.
Safety Hazard	Highest NFPA flammability, instability score of 0 or 1. No special hazards.	Highest NFPA flammability or instability score is 2 or 3, or a special hazard is used.	Highest NFPA flammability or instability score is 4.
Environmental Hazard	If less than 50 g of environmental hazards used.	If more than 50 g but less than 250 g used.	If more than 250 g used.
Energy	Wet chemistry method such as titration. Very little solvent evaporation.	An instrumental method such as GC, HPLC; moderate solvent evaporation.	An instrumental method such as GC-MS; high volume of solvent evaporated.
Waste amount	Total waste for processing one sample ≤ 50 g.	Total waste ≤ 250 g.	Total waste > 250 g.

Fig. 1.8 Greenness evaluation tool by Rayne et al.

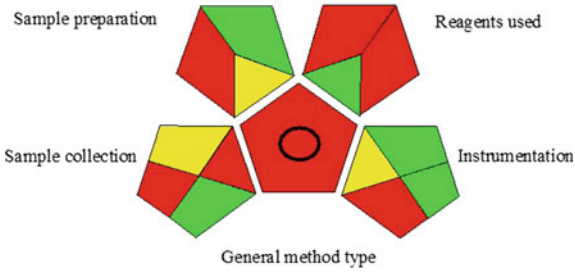


Fig. 1.9 Greenness evaluation tool by Płotka-Wasylka

preparation, reagents used, instrumentation as well as a general method are assessed based on their environmental impact using three-coloured scale [20]. Due to well-defined criteria of assessment and simplicity of its application, GAPI is a good tool for semi-quantitative for greenness comparison and appraisal.

1.4 Basic Ideas for an Integrated Environmentally Friendly Approach of Analytical Chemistry

An integrated environmentally friendly approach of analytical chemistry strongly refers to the review paper published in 1999 by M. de la Guardia in Journal of Brazilian Chemical Society. In the publication, ten keywords were pointed out, which stand for the main problems and challenges of analytical chemistry at the end of the twentieth century, including:

I. traceability
II. chemometrics
III. flow analysis and robotics
IV. in-field sampling
V. microwave-assisted treatments
VI. hyphenation
VII. speciation
VIII. sensors
IX. screening methodologies
X. decontamination of wastes [21].

Most of them are closely related to the green chemistry statements. However, the most important issue, that the author paid attention for, was to develop an integrated approach, which would consider the holistic state of analytical chemistry. One should take into account not only the improvement of new methodologies but also all the steps necessary for the chemical analysis, starting from the sampling and ending at waste decontamination, as presented in Fig. 1.10.

The most preliminary step, at the beginning of each analysis, is obtaining the material for a given research. Common practice is to collect the samples, transport them to the appropriate laboratory/research institute and store until the moment of analysis. Given process is adjusted to many problems like difficulties of the representative sample collection, loss of analytes, sample contamination and time consumption. The goal of the concept of an integrated approach of analytical chemistry is to reduce the size of the laboratory samples and implement enhanced technology for in-field sampling with the use of chemometric models and screening techniques. Moreover, to carry on direct analysis with the on-line preconcentration in order to avoid sample transport and storage and to reduce the time of sample pretreatment process by the implementation of developed sonochemistry, which suggests the use of the microwave—assisted digestion and extraction or ultrasounds. Both techniques significantly reduce the time needed for sample preparation [21].

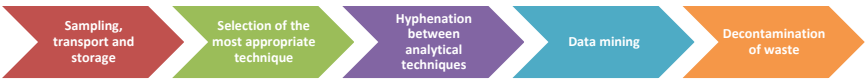


Fig. 1.10 Steps of the analytical process [2]

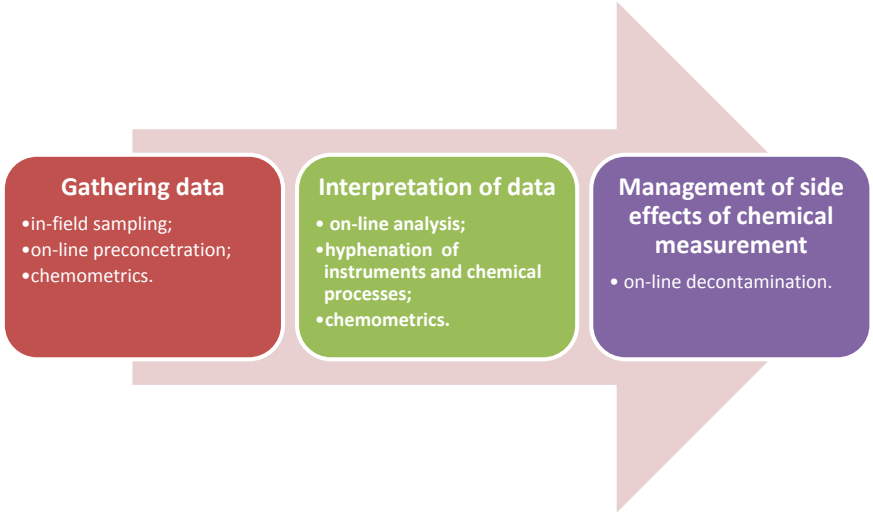


Fig. 1.11 Graphical representation of the integrated approach of Green Analytical Chemistry [2, 21]

Therefore, choosing the appropriate methodology in the context of the whole analytical process, one should think about the main analytical characteristics such as accuracy, precision, sensitivity and selectivity without skipping the practical characteristic described by time consumption, cost, safety and side effects. At the same time, taking care of one single step of analytical procedure, one should think about the consequences it has for the following ones [21].

Finally, it is important to increase awareness not only about the inputs (such as reagents and energy sources) but also about the outputs together with waste treatment. From year to year, the treatment of waste generated during the chemical analysis is of higher and higher importance. Nowadays, the law regulates the carefulness regarding the side effect of each chemical process, and it is said to choose methods generating less amount of waste as well as decontaminate waste generated by the entity engaged in the study [21].

The graphical representation of the integrated approach of green analytical chemistry is presented in Fig. 1.11, which clearly shows the main idea of coupling all the necessary analytical steps and creation of the flow analysis process, which enables reduction of impurities as well as waste generation and time consumption [2, 21].

At the same time, when the need of the integration physical, chemical and additional data, important for sample description, has appeared, researchers started to look for the advanced statistical and computational tool able to treat a large amount of data. Chemometrics, a new discipline, turned out to be a promising tool for the improvement of experimental design and the process of optimization. Chemometrics help among the others to determine the size of analytical data population, to find function of variables that could affect data, to optimize of analytical parameters, to

combine data from different sources, etc. Currently, given tool places a significant role to explore data provided by the analytical instruments [21].

1.5 Compatibility of Green Chemistry Principles and the Main Analytical Figures of Merit

The key point of the green chemistry assumptions is to increase the safety of both the environment and the operator. All of the green chemistry principles are designed in order to protect the environment and what is more the health and safety of working people. The difficulties in the case of greening the analytical chemistry rely on finding the balance between the compatibility of the green chemistry principles and the main analytical figures of merit. Principles of green chemistry, among the other, strongly influence the type of reagent used in the analytical process in order to replace toxic and hazardous reagents to reduce the risk. Moreover, it pays attention to reduce energy and reagent consumption and to decrease the amount of generated waste. However, analytical chemistry is looking for the best accuracy, traceability, representativeness, precision, selectivity and sensitivity. As it is presented in Fig. 1.12, one should find the way how to satisfy the assessment of green chemistry and characteristic of analytical chemistry with the available tools [13].

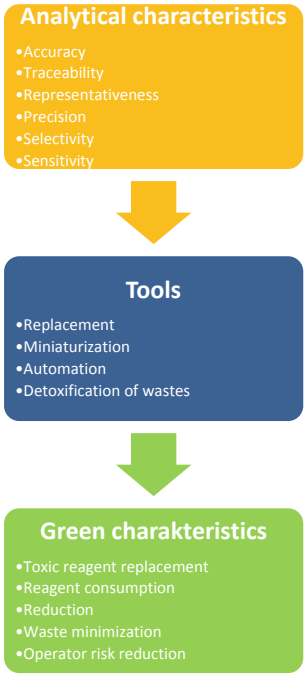


Fig. 1.12 Characteristic of the compatibility of green chemistry principles and the main analytical figures of merit [13]

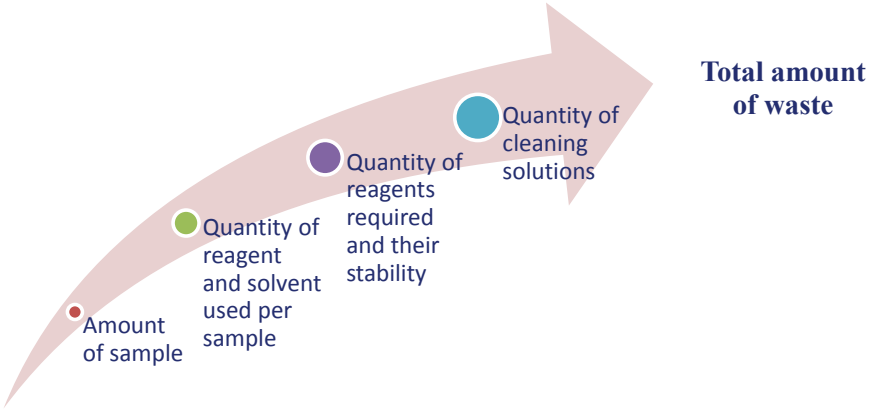


Fig. 1.13 Factors affecting the amount of generated waste [13]

While greening the method of analytical chemistry, one should pay special attention how implemented changes of one factor may influence following ones. Actually, using different reagent than originally dedicated for the analytical analysis may affect the accuracy and selectivity. At the same time, treatment of sample in a different manner should be done such a way to keep similar extraction recovery. Additionally, representativeness of samples can be affected by the sample miniaturization even if it entails a number of advantages. Once the volume of the sample is smaller, the analysis consumes less energy and less amount of reagent and generates less amount of waste. Amount of the sample used for analysis contributes to the following factors presented in Fig. 1.13 [13].

The amount of waste can be calculated as a waste generation per hour regarding the flow system or per 100 analysis. Automation and in-field methods as a way to make the analysis greener have several advantages. However, there are no opportunities for building in the checks. It creates the need for the improvement in order to increase the reliability, which may be achieved by designing the procedure in which it will be possible to run standards between analysed samples or implement any other calibration methods. Obviously, automation strongly helps in greening the method and at the same time lowers the cost. Since the handling is reduced, the traceability and precision are enhanced as well. The only thing one should be aware of is losing the sensitivity [13].

Principles of green chemistry help significantly to preserve the environment and increase the safety of employees, which is very important. The only thing is to find the optimal way to satisfy both the analytical characteristics quality and the evaluation of green chemistry. Each analysis should be focused to maximize the information at minimal cost and risk. Analytical chemists during the design stage of green analytical procedure should be careful to not to lose the main analytical figures of merit [13].

1.6 The State of the Art of Green Analytical Chemistry

The use of GAC methods is increasing since it was proven to be a smart strategy that can be both environmentally friendly and economically beneficial. The development of new greener sample preparation methods, the replacement of potentially harmful reagents with less toxic alternatives, the miniaturization or automatization are only a few out of many ways of improving the analytical process to be cost-effective and in accordance with principles of Green Analytical Chemistry. There are many articles pertaining to the general aspects of GAC, as well as different new methodologies described as sustainable, green or clean. However, it is somewhat difficult to determinate the exact number of studies concerning GAC, since there is no commonly used term that would group a wide variety of actions taken to make analytical methodologies greener.

In order to increase the popularity of Green Analytical Chemistry and to assist in its further implementation, there is a need for emphasis to be put on the importance of so-called green mentality both in the scientific publications concerning new methodologies and in the teaching of Analytical Chemistry [10, 22]. This approach will contribute to the changing of social perception of analytical chemistry and chemistry in general, but also to the integration of efforts made in the field of green chemistry.

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Chapter 2
Teaching Green Analytical Chemistry on the Example of Bioindication and Biomonitoring (B & B) Technologies

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This book chapter is dedicated to our colleagues **Dr. Rebecca R. Sharitz** and **Dr. Jean-Paul Schwitzguébel** who passed away in 2018. Rebecca Sharitz worked at the University of Georgia in Aiken, SC, USA, where she mainly researched highest successful on ecological processes in wetlands. For many years, Becky has been working very effectively in our International Association for Ecology (INTECOL). She was the very first woman to work with INTECOL over such a long period of time to put her scientific interests into practice together with her friends and colleagues, but fought fairly and serenely for equal rights for women in the environmental and natural sciences. Jean-Paul Schwitzguébel worked successfully at the Swiss Federal Institute of Technology in Lausanne, Switzerland, especially in the context of his phytotechnological studies. Particularly, noteworthy is his extraordinary ability in the framework of different European Cooperations in Science and Technology (EU-COST) over many years to bring together scientifically and practically different European and global schools of thought. Jean-Paul had as a francophile Swiss a heart and a feeling for all kinds of "everyday" problems, which we as scientists, whether young or old, private or professional have to deal with. Many young scientists owe it personally to him that they have found their successful way into the future.

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J. Płotka-Wasylka and J. Namieśnik (eds.), *Green Analytical Chemistry*,
Green Chemistry and Sustainable Technology,
https://doi.org/10.1007/978-981-13-9105-7_2

Abstract Teaching of Green Analytical Chemistry (GAC) requires a not inconsiderable willingness on the part of the lecturer to familiarize himself with a relatively new field in analytical chemistry. Although there is much that can be derived from Green and Sustainable Chemistry, the GAC's forward-looking perspectives in particular are independent approaches that must not be neglected. In the first chapter of this article, approaches are pursued "how (teachers) learn to learn," ultimately based on a consensus on ethics, which allows dealing with people, society and the environment to become an interdisciplinary unit. The end of all this is a smart method of conflict management which provides solutions of problems. Available tools include

– Regions concerned with education (learn how to learn)
– Think tanks (to define integrative solutions for problems) and
– Turbodemogracy (to get faster results)

In the second part of the chapter, GAC and nature merge completely, in which mechanical sample collectors are replaced by mosses within the framework of bioindication and biomonitoring (B & B) technologies during atmospheric deposition measurement of chemical elements. Definitions of bioindicators and biomonitors, active and passive B & B technologies and interdisciplinary connections between bioindicative sampling and scientific interpretations of natural systems are given.

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Mosses are distinguished by a rather large resistance toward enhanced levels of various anthropogenic air pollutions permitting their use also in polluted areas.

Keywords Green analytical chemistry · Education · Bioindication/biomonitoring · Atmospheric pollution

2.1 Introduction

Analytical Chemistry moved—at least in parts—to Green Analytical Chemistry as shown in chapter one of the book by Justyna Plotka-Warsylka et al. on "History and milestones of green analytical chemistry."

In order to introduce Green Analytical Chemistry (GAC) in universities, technical colleges and other higher educational institutions on the teaching side, a high degree of high quality and quantitative prerequisites are required, which are particularly placed on teaching staff, i.e., professors and other persons actively involved in the training of students.

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Thus, it is first of all the task of the respective professor and trainer to familiarize themselves with the overall topic of the GAC. Learning how to learn in the sense of a consensus on ethics will be the subject of the first part of this article.

In addition, excellent textbooks have been published on this subject, which describes essential findings from previous years. At the same time, reference is made to some publications which are far from complete and the selection of which represents a subjective character of the authors of this article [1–14].

Analytical Chemistry will no longer do in the future use of technocratic pieces of knowledge to obtain these integrative approaches to overcome the present problems, since:

- Increasing dynamics and complexities of problems need a better, more reflected arguing on the pros and cons of some strategy;
- Crucial (or better: all future) decisions can (ought to) be done exclusively based on provable, objectively stable pieces of information, data and knowledge, while;
- Sufficient transparency must be provided to all the stakeholders.

With "performance being the personal ability of an individual to change and adapt," it takes "education providing the ability to be open and ready, able to learn on all levels."

2.2 Learn How to Learn

Dealing with conflicts smartly and searching for integrative problem solutions are more closely linked to each other than hitherto used to be assumed. Hence, lifelong learning, achievement of quality and competences will get an ever larger relevance both to secure our common future in the society and for personal lives in the spheres of work and profession, family, leisure time, culture and politics likewise.

The individual has to develop his ability to learn for this purpose and keep on learning as the way to obtain personal competence with regards to social, occupational

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and methodical acting [15–18]. Concerning economy and society, these competences become crucial factors for innovation and capability of social self-structuring in order to compete successfully on an international level, rather than losing contact with recent social and cultural developments.

We now need a broad movement to promote lifelong learning, both to develop and maintain individual living chances and to keep socially oriented democracy[1] fit for the future with regards to its economic, ecological, cultural and social perspectives of further development. The system of education must provide the basis to achieve this, given its ends, contents, structures and ways of acting and teaching [15].

Lifelong learning does not just mean to involve as many citizens as possible all over their life phases (at least until retirement) but has qualitative drawbacks on education policy also. Lifelong learning requires to change the attitude toward learning, making learning a process that individual must pursue and shape all along lifetime responsible for himself or herself. With economic innovations and changes in society occurring ever faster, there is responsibility to autonomously adapt one's kinds of qualification. A new cultural sense is required which integrates learning into the processes of everyday life, acknowledging this and fairly estimates outcomes against the difficulties of this process [15–17]. Classical forms of learning and education offered by schools, professional training, university or secondary occupational education will not lose their significance, but must be corroborated by a new key feature of informal learning, which takes place in the "school of life," in social networks, everyday life, at workbench, in family and leisure time. This is really a new principle of learning which must be developed, focused on one's own responsibility and capability to shape this process individually and autonomously [19–21].

With a high degree of individual responsibility and autonomy being required, motivation and support of hitherto less advantaged groups must not be disregarded; these guys otherwise would not be capable of fulfilling such a task of self-motivation and structuring, as a rule. Education politics and practical education rather must be concerned and aware that nobody is taken off his educational and career chances. Groups who are now almost beyond the reach of education[2] must be integrated to avoid producing new obstacles in obtaining education and training. The present

[1] In the German original: "*soziale Demokratie*". This term does refer/allude to "soziale Marktwirtschaft," the concept put forward by later Federal chancellor Ludwig Erhard (1897–1977), sometimes also dubbed "the Rhineland way of doing capitalism" rather than, for example, "Archiv der sozialen Demokratie" which is the central part of the party archives of the German Social Democratic Party (SPD). Anyway, in Germany the link between democracy/federal structuring of state and social norms is part of the constitution and even officially protected against any change (*Grundgesetz* articles 20, 79, 116).

[2] In Germany, this really became a popular term: "bildungsferne Schichten" (people who live in utmost avoidance of education). The Programme for International Student Assessment (PISA) studies revealed Germany to be the one country in the developed world where educational and thereafter occupational chances depend mostly on the educational status (and income levels) of the parents, more so than even in many developing countries. So a vicious circle can be established (parental poverty precludes education of the children to a level now required even to obtain a reasonable apprenticeship position) which is avoided only by more active measures pointing to the corresponding milieus and urban neighbourhoods.

serious level and extent of exclusion of people and groups can be reduced in the near future only if the array of educational contents and kinds becomes more closely related to ongoing economic, cultural changes and those in society, while the offers must become more focused to the demands of any individual [15].

With lifelong learning becoming the paradigm of education, tasks and structures of classical agents of education must also adapt. A culture of learning which conforms to recent demands takes more and novel kinds of coaching and services, but also needs an enhanced degree of flexibility, self-responsibility and communication.

These in turn require novel kinds of partnership with "consumers" and users of this broadened array of education. Institutions of education and culture, those concerned with social and youth welfare, clubs and enterprises, single persons and the activities of all of these must be pushed and motivated to investigate novel ways of learning by new kinds of cooperation [15, 22].

2.2.1 Transborder and International Regions of Education

Border transgressing regions of education which provide the chances of lifelong learning working, and education to all children and youngsters but also parents, teachers and other adults, must be promoted better than before and get (placed) into the focus of public interest. Of course, diverging interests of political powers and parties, regional and national particular notions and interests will persist on either side of the border, but there are also local commons which are a topic of (transcultural) education as such and itself can and must reshape the present topic—focussed into ability—focused curricula of education. A higher level of education becomes more attractive when people notice in remote border regions also: *tua res agitur*; it is your (local) matters that matter, rather than (just) the views and issues of some far away metropolitan region, far away in both topographical and mental terms. Besides better ways of overcoming local problems, this will enhance the wish and positive feelings on lifelong learning, producing competences, self-confidence and thus finally increases occupational chances in border regions also. By the way, a kind of education defined and constructed like this is going to both catalyze and pay itself in the long term mainly.

There are plenty and more of historical burdens and present deviating interests; hence, the first step must be constructing an integrative mode of conflict management on the very site which there gains support by some democratic majority.

Rely on trust rather than treaty—this will work only if the above attitude is given. Diversities of opinions and religious faiths will only become a bonus and a chance to achieve more stability if we become aware of some ethical consensus which can be learnt and which is going to link us, including Muslim or agnostic fellow citizens. This ethical consensus (Fig. 2.1) will include the tolerance of other positions and beliefs and likewise solidaristic acts toward the weaker.

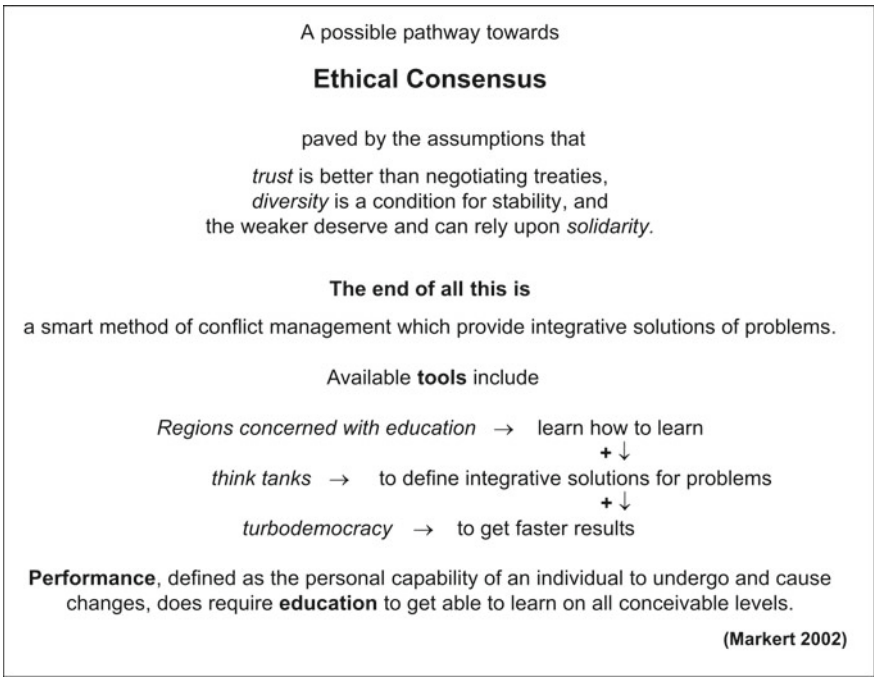

Fig. 2.1 Trust, variety and solidarity provide an indispensable blueprint for solving problems in the regions of education, think tanks and the approaches of "turbodemocracy" [72]

2.2.2 Think Tanks Can Be Sites and Means of Smart Conflict Handling and Identify Integrative Solutions for Problems of Society

Problems and questions which recently arise in society are distinguished by multidisciplinary and international ranges; hence, highly specific expert knowledge and corresponding skills will not solve or even characterize and define such problems, but it takes the readiness of everyone who is involved to mitigate among the often most diverse individual interests and wishes. Hence, the crucial feature of an integrative problem solution rests not so much with technology or funding but with the actual "ability of everybody to honestly and convincingly achieve a solution which is acceptable to all stakeholders."

There are many features of conflicting double binds in modern societies: politicians and the parties which "made" and support them, officials including university professors in public service domains and authorities, physicians and their medical responsibility and ethos, TV producers and TV watching quotas, mothers and fathers who want both to perform and progress in occupation and responsibly, sincerely rise their children, they all are faced with conflicts which cannot be resolved and block

potentials for overcoming these and yet other conflicts even though all are convinced that it takes genuine professional ethics, genuine convictions and their active realization in everyday life to ensure a sustainable and justly motivated structure of society!

In many different societies, psychological obstacles to adhere to these rules are posed by many citizens who already became solidly mistrusted and alienated by actions and premises put forward by politics itself. This alienation is just a symptom but it can block a real, honest dialog in society which is devoted to solving problems by innovative modes of thinking up to the point that it becomes impossible. Hence, Miegel [23, 24] is quite correct in demanding citizens to be fully and honestly informed about the situation before even starting a public discussion on how to deal with it, including the side effects which would arise if the actual situation is neglected any longer. This will be the first rate of a "pound (weight) of honesty": politicians and others in charge of decisions pertinent to society must be courageous enough to be (recklessly and fully) honest. Viable data on the situation and complete transparency toward all ones who are or could become involved are self-evident conditions to get any reasonable acting which can make a meaningful future.

2.2.3 How Much Time Is Left for Solutions Taking Care of and Integrating the Present Problems?

Realistic estimates of the time left to mankind to tackle problems in an integrative manner on global scales, implement and complete them, range from 500 to 1000 years from now. Table 2.1 gives the necessary or possibly optional conditions and steps for this kind of global change. Maybe by 3000, there will be some merger between human and nature shaped like a symbiosis [25]. This would be a harmonized balancing of all the inputs and outputs among all the existing biocoenoses for common and mutual benefit which to plan and realize must be the priority and aim of all human activities then. To achieve this end, it will take 1000 years of global education, which must of course be developed, discussed and effectively implemented for gaining acceptance among all mankind. The practical result which is inevitable is to agree on a globally common criterion of completely just distribution of material and non-material goods and items among all people living on Earth. Before this can be reached, constant global peace must be achieved, which will be about 500 years in the future. In addition, this will be the period of time until the downfall of the last dictatorship on Earth. This is another precondition for the era of stable global peace predicted by a number of colleagues, which in turn is indispensable for justice in the above sense, namely, the just and balanced distribution of all the essential goods.

Table 2.1 gives an idea of the timescale it might take to implement the necessary changes in a "turbodemocracy" once there is common acceptance of education being most urgent: until 2030. This is the period of time it will take to harmonize and equalize in rank intercultural and intracultural activities regarding the many diverse

Table 2.1 Global trends of development predicted for this millennium

By 3000: Man joins a symbiotic relationship with society and the ecosystems in order to survive. He is going to become a symbiotic cell of a huge planetary organism starting to live based on itself: a macroorganism on which our future depends (Joel de Rosnay, director of the museum of future technologies at Paris; Rosnay [25]
By 2500: A just world can only be created of the last dictatorship has been abolished providing the key condition for global justice which is peace. This is going to happen 500 years from now [21]
By 2100: Assuming a further exponential development/increase of our mental capacities for a conflict management which becomes most urgent in the future, the recognition that a more just future world cannot be achieved without global peace will set foot all around the world
By 2030: Creation of the precondition (by 2022–2028) to abolish the present state of "hunger terrorism" which hits large parts of Africa and to put an end to it by the end of this century ("turbodemocracy")

spheres of interest—national and international, mono and multidisciplinary, regional and transregional. There is a desire to give, to share, to understand and to accept other people and cultures which is corroborated by enlightened self-interest, acknowledging that this is the only feasible way to possibly and satisfactorily ensure one's own existence, and this promotion by enlightened self-interest will make us "donate" education and professional training to entire parts of continents such as Black Africa within one generation's time, about 30 years from now. To realize and implement, this will become a common task giving the chance to live in about the decent and self-determined way of decisions after all which we are completely accustomed to. The latter global process may be completed by 2100.

2.2.4 Conclusion

Questions and demands of future will not depend so much on the way to decide whether a new street is planned for purely economic reasons or canceled to protect the environment, but on how fast and efficiently a decision can be done which satisfies all stakeholders involved by some consensus. The "mental blockers" mentioned above are often going to block rational and reasonable solutions, removing the chances of gremia and councils to decide and act successful and efficiently; thus, think tanks which are focused on jointly finding problem solutions are most urgent to establish. Think tanks are established in the US political counseling for as long as the project teams last and they cooperate for several months. These teams are completely independent of political parties, industrial and other lobby groups and are distinguished by utmost competence on their issues; thus, they can develop and offer stakeholders some recommendation on how (on which way) to solve their specific problem.

Think tanks can be associated with schools, universities or other sites of (occupational) education where people meet, live, develop, negotiate and face arguments. Likewise, think tanks can be private institutions (other than private universities) where specialists trained in interdisciplinary thinking create both fast and realistic solution approaches. This can shorten that almost infinitely long, bureaucratic and unbearable route from identifying the original problem to the supreme decision maker and serve to relocate the solution next to its topic. Creative potentials of those taking part are considerably enhanced, increasing readiness to find solutions by personal considerations, experiences and understanding. Think tanks are not primarily challenged with time shortages, while honestly telling that a problem cannot be solved by now because of lacking capacities and pieces of information would suffice to avoid decisions which are premature or outgrowths of political bias. Regional think tanks can thus be a valuable and important tool to develop new strategies, ideas and finally innovations.

This means of education and professional education will decide about life chances in the foreseeable future (Fig. 2.1).

Everybody needs education! Once this is generally acknowledged (hopefully soon), there also will be substantial funding for all respects of education. Parents, children, pupils, students, teachers, people in occupation and retired ones will see and be able to attend informal colleges,[3] kindergartens, integrating centers where youngsters, elderly and other people meet, elementary, occupational and high schools where both teaching and learning are fun again, aiming to be a little better than your neighbor while sharing joy with learnt matters can also go without saying once again. "Knowledge must turn into love [26]." Smart management of conflicts and integrative ways of dealing with problems thus are very honest approaches. We shall describe an example of Green Analytical Chemistry in the forthcoming chapter. Yet honesty takes its price, a price which cannot yet be figured in £, € or $ exactly. But would you like to get some more of it?

By now, we can still freely decide which way to go. We consider that one outlined above to be a peaceful one which cares for human dignity of individuals next to you allowing it to be taken and accepted and succeed. We must be aware there are lots of "scrub" along this—and every other path—which must not be trampled down or destroyed without a chance to retrieve or recover it. Nature, on its part, most often, perhaps all too often, shows that it is going to accept and nourish us. In a partnership, we ought to offer a fair compensation.

Of course, there are alternatives at hand which appear less arduous at first glance. Other, "easy" ways are seductive, displaying, loud, colorful multimedia coverages. It is fun to make use of this while not caring for tomorrow. However, the outcome of this way has been war among peoples, at least 11,000 times just in the 2000 years since Christ was born.

[3] In original German: *Volkshochschule*. These are public institutions which have their part in advanced (not apprentice) professional education, besides universities and universities of applied sciences. There are also courses in computer skills or various modern languages. Some certification of courses at Volkshochschule can actually be used in a profession, unlike a university; an Abitur (school-leaving examination) is not required to attend.

2.3 An Example of Green Analytical Chemistry by Bioindication and Biomonitoring (B & B) Technologies to Observe the Atmospheric Deposition by Use of Mosses

Concentrations of pollutants into the atmosphere are usually monitored by means of chemico-physical devices; whereas, in aquatic monitoring a sampling—not continuous but intermittent—of water samples is assayed.

There are elegant though indirect methods to obtain data on the existence, distribution and above all the effects of pollutants in the environment, namely, bioindication and biomonitoring.

The GAC gains special importance if it goes into the field of environmental chemistry and has to investigate particularly large areas of investigation, for example, with regard to their degree of chemical pollution. Sampling plays an extremely important role here.

In order to determine, for example, the atmospheric deposition of chemical substances on an area of the Federal Republic of Germany, a large number of precipitation collectors must be installed, maintained and protected from mostly human destruction.

In recent decades, so-called biomonitoring with the aid of mosses has established itself here, which is described in detail in the second part of this book chapter.

Accumulative organisms, which are often used in bioindication, offered a solution: They enriched the substance to be determined by several orders of magnitude compared with their environment so that the analytical accessibility is improved and the measuring error reduced.

In addition to improving the analytical prerequisites, bioindicators also offered other advantages which have proven to be useful for environment monitoring (Table 2.2). Thus, it was possible to use bioindicators to cover completely entire areas provided they were widely spread and sufficient in number. The pioneer work conducted by Rühling and Tyler in the late 1960s and early 1970s, as well as heavy metal monitoring using mosses to cover large areas completely, a method developed by these two research workers [27], offered the potential to trace the release and to track the movement of individual heavy metals, even over large areas. Using this method, point source emitters could be detected and long-distance transport of individual metals proven. This procedure appeared to be cost-effective because it did not require the installation of a sampler or measuring instrument at each measuring point and, consequently, neither maintenance nor protection from vandalism was required (Table 2.2).

GAC has thus not only been realized in the actual sense of reducing mechanical rainwater collectors, but has also been sustainably substituted by the replacement of green lower plants, in this case mosses.

These methods make use of the capacity of organisms to signify the presence of pollutants in the environment over either short or long periods of time.

Because bioindicators or biomonitors integrate the environmental burdens (by chemicals) over the time of experiment at their sites, short-term variations are can-

Table 2.2 Comparison of benefits and disadvantages of bioindicators/biomonitors with measuring instruments or sampling devices

Use of bioindicators/biomonitors	Use of measuring instrument/sampler
Advantage	Disadvantage
1. Cost-effective, especially in the case of comprehensive investigations	1. More expensive because of – Purchase – Maintenance/service – Vandalism
2. Allows analytical work at higher concentrations, consequently high sensitive, correctness, and reproducibility of measurement	2. Analytical work requires lower concentration ranges. The total analytical result is more likely to be erroneous
3. The total analytical result can be integrated into a total biological system	3. Integration mostly impossible
4. Retrospective analyses are possible ('Trip into the past', e.g. by peat profile analyses, annual ring analyses on trees)	4. Retrospective analyses mostly impossible
Disadvantage	Advantage
1. The procedure is difficult to standardize, above all with regard to site and time axes	1. Measuring unit can be easily calibrated

celed out. As compared to "conventional" means of measuring pollutants, using bioindication or biomonitoring techniques involves much less expenditure in both personnel and apparatus than, for example, running a deposition sampler. Hence, bioindicators can be employed throughout large areas provided the organisms are sufficiently far spread and abundant, enabling investigations to cover entire countries or even continents which could be done otherwise only if accepting very high demands of work and money [27–39].

Using one or several (different) organisms for the purposes of estimating environmental burdens (Fig. 2.2) brings about yet another advantage: beyond statements on the organism which is embedded in some ecological niche within an ecosystem, the analytical data obtained on it can be integrated into a more comprehensive biological system. Thus, beyond the bioindicator, ecologically relevant statements are possible on larger parts of the biocenosis due to the biotic interactions which interconnect them, unlike when using direct physico-chemical methods.

2.3.1 Definitions

Markert et al. [32] and Markert [40] gave an exact and meanwhile generally valid definition to discern among bioindication and biomonitoring:

- *Bioindicators* are organisms or communities of organisms whose content of certain elements or compounds and/or whose morphological, physiological, histological or cellular structure, metabolic-biochemical processes, behavior or population

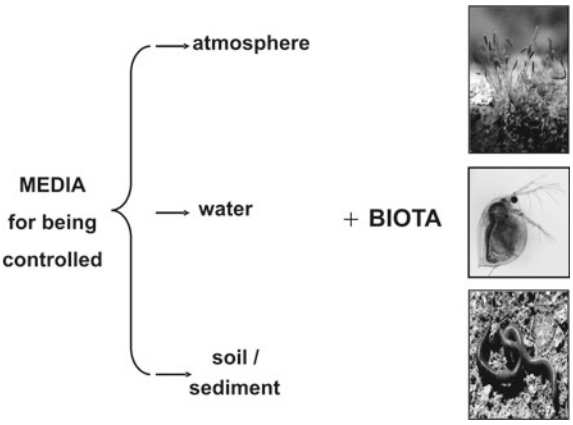

Fig. 2.2 Environmental media and their bioindication using various living organisms, for example, mosses, daphnia, earthworms

structure(s), including changes in these parameters, supply information on the *quality* of the environment or the nature of environment changes. Bioindication compares *relative data* of information (e.g., on contamination) to each other.

- *Biomonitors* are organisms or communities of organisms whose content of certain elements or compounds and/or whose morphological, physiological, histological or cellular structure, metabolic-biochemical processes, behavior or population structure(s), including changes in these parameters, supply information on the *quantitative aspects* of the quality of the environment or the nature of environment changes. Biomonitoring compares *absolute data* (e.g., on contamination) to each other.

We speak of *active* bioindication (biomonitoring) when bioindicators (biomonitors) bred in laboratories or transplanted from unpolluted areas are exposed in a standardized form in the field for a defined period of time. At the end of this exposure time, the reactions provoked are recorded and/or the chemicals taken up by the organism are analyzed. In the case of *passive* biomonitoring, in situ organisms already occurring naturally in the ecosystem are examined for their reactions. This classification of organisms (or communities of these) is hence according to their "origin".

2.3.2 Using Plants as Bioindicators/Biomonitors

Because of an unfavorable location, many plants have developed the ability to enrich high concentrations of individual elements, often regardless of whether these elements are physiologically useful or not. These plants are called accumulators [41–55].

With respect to biomonitoring, there should be a correlation between the environmental concentration of a pollutant to be observed and the content in the organism proper. A linear, indicative interrelation of both measure values has not been found

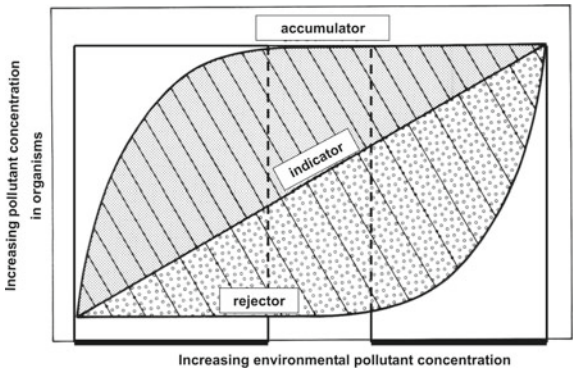

Fig. 2.3 Differing uptake activities in living organisms as a function of the substrate concentration (Markert et al. [32], according to Baker [42])

so far for any organism. The concentration ranges which might be interesting for bioindication and biomonitoring showed very small "measuring ranges" (black bars) in accumulator and excluder organisms (Fig. 2.3).

For example, regardless of the amount of element in the soil, some *Ericaceae* have a high concentration of manganese, and beech has a high level of zinc. The accumulative behavior, which may have genetically predetermined origins rather than ones determined by locations, makes it possible to chemically fingerprint a very wide variety of types of plant. In the future, this might lead to the chemical characterization, and therefore the systematization, of individual plant types which could provide information about evolutionary connections on a phytosociological level. A rejection, or reduced uptake of individual elements, occurs less frequently than does an accumulation of elements, but rejection behavior has been demonstrated for numerous plant species. The reduction in the concentration of an element in an organism can be the result of a complete or a partial exclusion. For example, bacteria, algae and higher plants contain populations which are tolerant to trace metals and which can reduce considerably the uptake of trace metals by excreting mucilaginous substances or by changing their cell walls.

In the context of activity studies, and especially in toxicity monitoring, generally one must differentiate between acute and chronic working models. As is shown in Fig. 2.4, the acute delivery of a substance is usually followed by a direct, short-term effect on the organism or the population. These types of toxic effects are relatively easily generated experimentally in the laboratory by adding different substances to the test organisms. However, it is more difficult to investigate the chronic effects of a substance, meaning the subthreshold, long-term application of a substance which only shows an effect (usually a toxic one) after lengthy constant uptake. These mechanisms of chronic activities are considerably more difficult to study because all other values and parameters which could influence the test organism have to be kept constant over a considerable period of time. Often, the chronic effect of a substance differs from an acute effect only by its chronologically displaced occurrence. Thus, the chronic effect usually only creeps along, and so in reality it is often recognized too late.

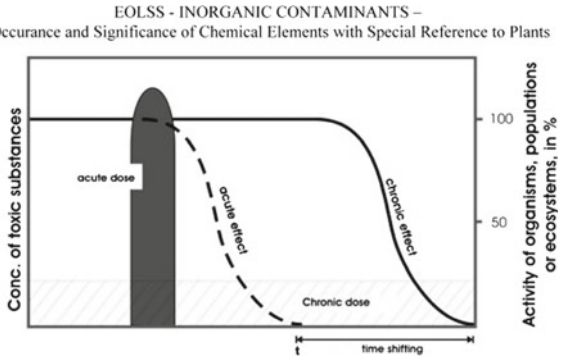

Fig. 2.4 Comparison of effect of acute and chronic doses of toxic substances on living systems [62]

In addition to microorganisms, fungi, algae, mosses, lichens, ferns and higher plants and animals can be used as bioindicators and biomonitors. In comparison with plants, animals have generally developed a greater arsenal of stress-coping mechanisms; in addition, non-sessile animals can avoid a certain number of threatening environmental or anthropogenic stressors by virtue of their mobility or motility [56]. Owing to the generally higher sensitivity of aquatic animals to xenobiotics in comparison with that of terrestrial organisms, they play a major role in acute, subchronic and chronic tests. Under field conditions inquiries into distribution patterns and the difference for the organotropic accumulation of persistent pollutants are the major fields of interest in various bioindicative/biomonitoring approaches [56]. The possible integrative relation of atmospheric element pollution, soil samples, stomach content and tissue and organs of rats in a specific study area is given by Wünschmann et al. [57, 58]. A more general investigation of bioindicative moss monitoring results to human health is given in Fig. 2.10. The results of bioindicative studies of humans are manifold.

For example, Wünschmann et al. [59, 60] gave impressive results on the relation of chemical elements to nutritional intake, human milk and transfer of the milk to babies. In these investigations, it could be clearly demonstrated that human milk cannot be used as bioindicator/biomonitor for the trace metal pollution status of the environment [60].

In addition, some requirements of an "acceptable" bioindicator/biomonitor are given in Fig. 2.5.

In Fig. 2.5, the requirements for a bioindicator are called "simple." But each location in the world is characterized by specific conditions of climate and living conditions. Therefore, it is extremely difficult to find species or group of species which are working in the common sense of a bioindicator or biomonitor as given in the requirements of Fig. 2.5 on a global level. Today, they still do not seem available.

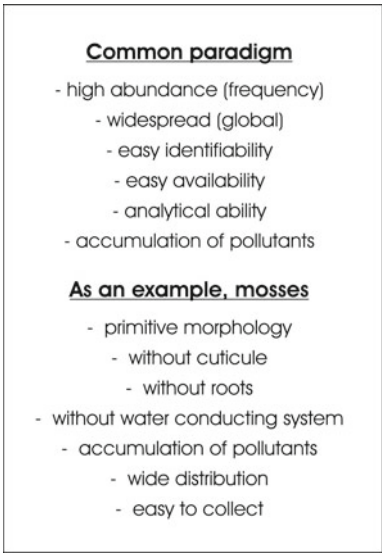

Fig. 2.5 "Simple" requirements for bioindicators/biomonitors

Therefore for each region, each selected indicator has to be handled with care and the experience of the scientists.

2.3.3 Comparison of Instrumental Measurements and the Use of Bioindicators with Respect to Harmonization and Quality Control

In Fig. 2.6, a rough comparison is made between instrumental methods used in the laboratory and biotechniques involving the application of bioindicators or biomonitors. Common problems are related to a representative sampling procedure which can introduce an error up to 1000% if general rules of representative collection of the measuring samples are not taken under strong consideration [61, 62]. It must be clearly stated that instrumental measuring techniques are often an integrated part of bioindication, especially when considering the parameter under investigation, for example, the concentration of a trace metal. In both techniques (instrumental and biological), the sampling procedure is the essential part of the overall procedure. The sampling procedure has to be evaluated in between all (international) participants—at least those involved in the actual investigation—to obtain comparability.

In the same way as the sampling procedure for instrumental measurements and biotechniques has to be under control, terms of precision (reproducibility) and accuracy (the "true" value) have to be checked with strict standards during the overall monitoring procedure. We will not go in detail in this article, but methods to observe precision and accuracy can be obtained in all textbooks of analytical sciences (see,

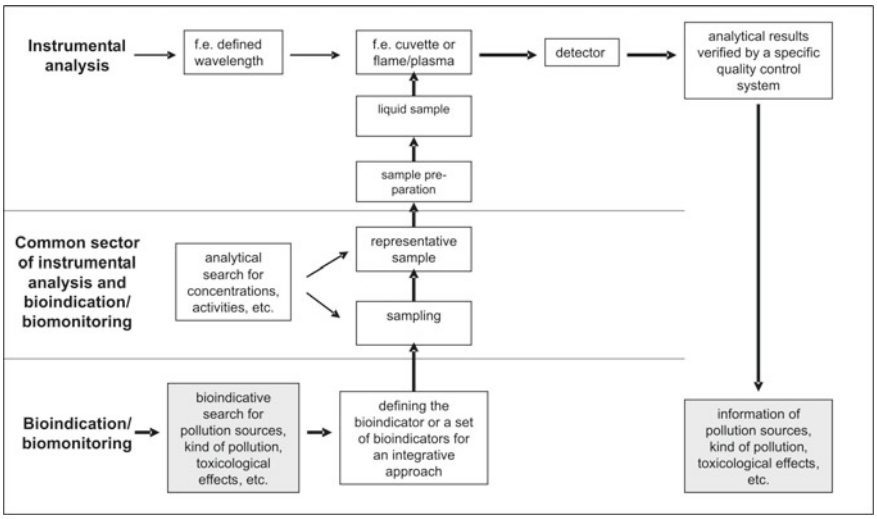

Fig. 2.6 Comparison of measurements performed by spectrometers and bioindicators/biomonitors. In practice, instrumental measurements are often an integral part of bioindication and biomonitoring methods. A full instrumental flow chart for instrumental chemical analysis of environmental samples can be found in Markert [62]

e.g., [62–66]). Basically, two methods are now used to check the accuracy of analytical results:

(1) The use of certified standard reference materials (commercially available samples with a certified content of the compound (e.g., a trace metal) to be assayed in a matrix similar to the original samples to be measured).
(2) The use of independent analytical procedures.

2.3.4 Mosses as Bioindicators/Biomonitors for Controlling the Atmospheric Deposition of Chemical Elements

Mosses are suited for this corresponding work as they lack a cuticular interface. In higher plants, the cuticle limits evaporation, providing protecting against drought. Further, the cuticle is an obstacle to the uptake of water and salts dissolved in it via the surface of a plant. Because there is no cuticle, mosses can directly take up water and minerals required for growth via their leaf surfaces and thus do need neither "genuine" (i.e., mineral-absorbing) roots nor a water conduction organ system. Thus, the "primitive" structure of mosses, as compared to more differentiated vascular terrestrial plants, is a distinct advantage in pollutant level observations, with the pollutants likewise taken up directly through the surface unprotected by a cuticle.

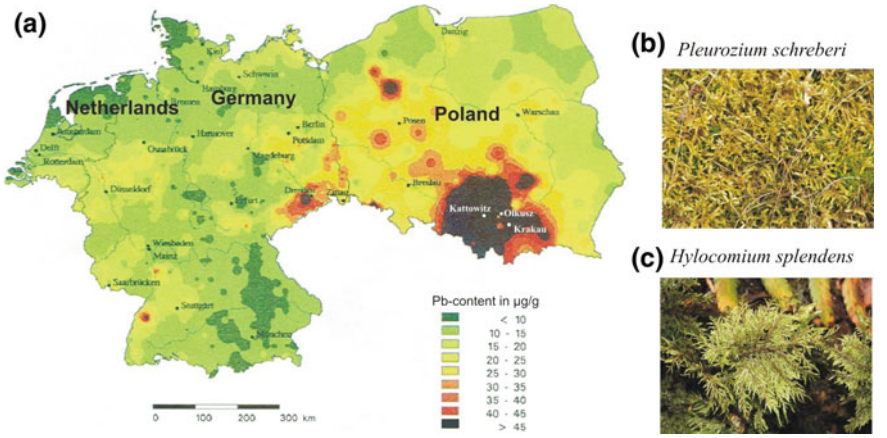

Fig. 2.7 **a** This map gives Pb contents in moss species from different countries (the Netherlands, Germany, Poland), using moss samples taken during 1990–1992 [73]. **b**, **c** Mosses [only two moss species of a total of four of the overall European program are shown as examples: *Pleurozium schreberi* (**b**) and *Hylocomium splendens* (**c**)] are bioindicators/biomonitors for controlling the atmospheric deposition of different chemical elements. (**b**, **c**) Courtesy of: wikipedia

In addition to lacking a cuticle, mosses are distinguished by a rather large resistance toward enhanced levels of various anthropogenic air pollutants, permitting their use also in polluted areas. With many species being far spread (living in quite different regions), larger regions can be monitored using a given species. Owing to their large surface: volume ratio; mosses may readily accumulate chemical elements, mostly as trapped particles onto their surface or as ions bound extracellularly to cell walls sites. Thus, mosses accumulate substances throughout their entire period of vegetation growth, providing information on an averaged pollution situation integrated along the period of growth. As a consequence, mosses are perfectly suited for monitoring atmospheric deposition.

The results from the chemical analysis may be presented as multi-color maps of pollution using appropriate interpolation software and geographic information systems (GIS), providing maps such as that for lead in moss samples from 1990 to 1992 (Fig. 2.7).

As a final output of the above investigations, bioindication results compare in space the relative (analytical) data of (element) concentrations in bioindicator species (moss). In this example, the mosses are represented by different locations around Middle Europe. The same can be done by using bioindicators to obtain temporal trends behavior of chemicals. An example is given for Pb in mosses (*Polytrichum formosum*) collected across some years.

The characterization of typical summer/winter oscillations of Pb (and other elements given in [49, 67]) may be explained by a dilution effect due to biomass production during the spring and summer months, which clearly explains the maximum concentrations of lead found in the winter months and lowest concentrations found

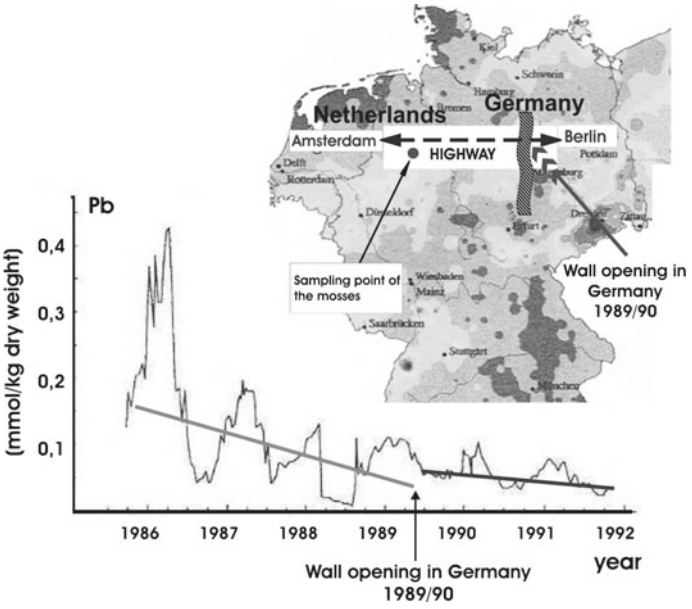

Fig. 2.8 Decrease in Pb concentration in the moss *Polytrichum formosum* near Osnabrück (Germany) after regular sampling (two-week intervals) close to the highway between Berlin and Amsterdam. The seasonal variations can be explained by a dilution effect during biomass production o *Polytrichum formosum* at the beginning of the vegetation period [49, 67]

in the summer months (graph in Fig. 2.8). As a result of lower emission rates, the concentrations for lead decreased during the period from 1985 to 1992. This ranged from 0.2 to 0.005 mmol/kg, that is, a fourfold decrease of the original value. In addition, a reduction of the yearly amplitude can be manifested. The minimum values of lead in Fig. 2.8 should be noted.

The lowest value was 0.01 mmol/kg; a figure which then (summer 1988) had not yet been reached. The reason for this was probably the opening of the Berlin Wall in 1989 (Germany), as the biomonitor study site was no more than 200 m away from a highway. Consequently, it may be assumed that these increased lead concentrations were a result of automobile emissions. After the fall of the wall in 1989/1990 the ex-East Germans bought (cheap) cars which required leaded petrol.

Thus, the amount of leaded petrol used increased and hence also the emissions of lead. These emissions are directly correlated with the much frequented (by "eastern" cars) traffic routes as represented by the highways 2 and 30 between Berlin and Amsterdam [49]. From a statistical point of view (Fig. 2.8), the slopes of lead concentrations before and after November 1989 increased from 0.042 to 0.017, which can be explained by the higher lead input during this period.

Pleurozium schreberi

ICD 401-405: Hypertony and blood high pressure

- by higher Tl concentrations?

age	55-60	60-65	65-70	70-75	75-80	80-85	>85
Be	-0,18	-0,12	-0,03	-0,12	-0,05	-0,10	-0,05
Bi	0,20	0,59	0,76	0,69	**0,81**	**0,82**	**0,86**
Cs	0,42	**0,76**	**0,85**	**0,84**	**0,90**	**0,94**	**0,92**
Mn	-0,09	-0,36	-0,57	-0,48	-0,60	-0,63	-0,71
Na	0,36	0,06	-0,25	-0,12	-0,31	-0,36	-0,49
Tl	0,44	**0,81**	**0,96**	**0,92**	**0,98**	**0,99**	**0,99**

Fig. 2.9 Coefficients of correlation between the incidence of essential and secondary hypertension [International Statistical Classification of Diseases (ICD) 401–405] and element concentrations in *Pleurozium schreberi* in the years 1993–1997, broken down according to age groups. Significant correlation coefficients are printed in bold [70]

For transforming bioindicative (qualitative) into biomonitoring (quantitative) data, the biological values of chemical elements found in mosses can be converted into estimates of atmospheric deposition rates by the formula:

$$D = c \cdot \frac{A}{E_x}$$

where D = estimated deposition, c = measured concentration in moss, A = biomass increase/year and E = efficiency factor of uptake by Berg et al. [68]. The unit of D is given in $\mu g/m^2$ per year. [69] for example, examined the deposition of different elements via mosses in the Euroregion Neisse (ERN, East Germany, a crossbordering region in between Czech Republic, Germany and Poland) in the years 1995 and 1996 as well as in Austria.

The obtained element data from the moss monitoring data may also provide the basis of epidemiological investigations [70]. As can be seen in Fig. 2.9, indications were found that a correlation exists between the thallium content in mosses and the occurrence of cardiovascular disease. Similar results were found between Ce, Fe, Ga and Ge levels in moss and the incidence of respiratory system diseases.

However, comparing moss (element) data with possible effects on human health should be done with caution as depicted in Fig. 2.10.

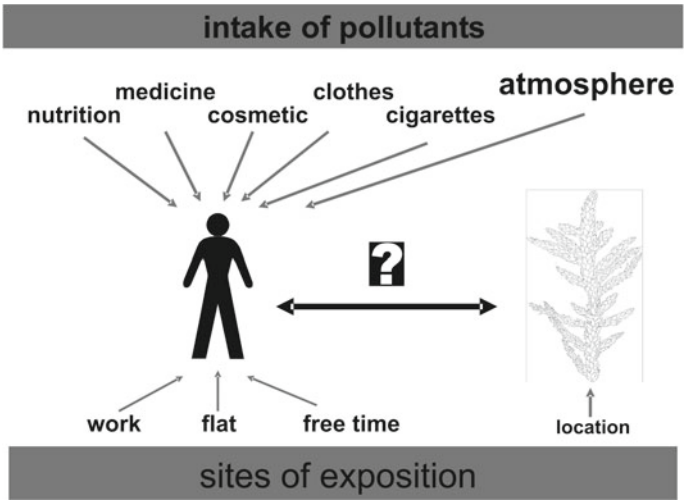

Fig. 2.10 Paths by which pollutants are taken in by human beings and moss. Unlike mosses, human beings are exposed to pollutants in numerous places and take up substances in several routes [70]

Nevertheless, bioindication and biomonitoring may nicely shed light into possible effects of atmospheric pollution on human health over wide regions, clearly indicating high-risk areas. An excellent example of this has been provided of Cislaghi and Nimis [71] in a study comparing the biodiversity of epiphytic (tree inhabiting) lichens with the mortality from lung cancer in N. Italy with.

Acknowledgements A lot of international colleagues have supported us during decades of years through the field of information transfer by communication, scientific support and promotion of ideas. We would like to mention only some as Martin Broadley (Nottingham, UK), Alan Covich (Athens, USA), John Grace (Edinburgh, UK), Gene Turner (Louisiana, USA), Charlotte Poschenrieder (Barcelona, Spain), Stefan Trapp (Kongens Lyngby, Denmark) for supporting this manuscript.

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Chapter 3
Teaching Green Analytical and Synthesis Chemistry: Performing Laboratory Experiments in a Greener Way

Arabinda Kumar Das, Ruma Chakraborty and Miguel de la Guardia

Abstract Our future challenges in resource, environmental and societal sustainability demand efficient and benign-by-design scientific technologies for working with chemical processes and products. In this chapter, we have considered the major aspects of green analytical and synthetic chemistry as a new paradigm and its integration with higher education course curriculum. Teaching green analytical chemistry must be focused on analytical parameters and practices more than on the incorporation of the so-called green parameters to the basic analytical properties. Thus accuracy, representativeness, traceability, sensitivity and selectivity in the renewed paradigmatic chemistry have been complemented and not excluded by additional considerations on the safety of operators and environment. Reduction of risks, reagents, energy and solvent required the search for new innocuous compounds, the highest level of potential information about the samples and measurements and the responsibility of the laboratories about the elimination and/or reduction and decontamination of the analytical wastes. With this end in view, this chapter complies 16 green laboratory experiments which will be useful to the students and the teachers of chemistry alike. The economical consideration of the greening efforts in method development is another very important aspect of green chemistry, and it will be the major reason for extensive practice in the near future.

Keywords Benign-by-design experiments · Clean analytical processes · Green synthesis · Eco-friendly chemistry · Green methodologies · Sustainable education

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J. Płotka-Wasylka and J. Namieśnik (eds.), *Green Analytical Chemistry*,
Green Chemistry and Sustainable Technology,
https://doi.org/10.1007/978-981-13-9105-7_3

3.1 Toward Environmentally Friendly Chemical Processes

It is now well known that the sustainability is the ultimate common goal for the research and development. So, the chemical processes should be environmentally clean, cost-effective, fast and energy saving [1].

In keeping with the modern trend to avoid hazardous chemicals and to use environmentally clean methods, chemists all over the world are engaged in designing and developing green schemes for carrying out experiments in laboratories for both routine analysis and research. Unfortunately, published green experiments designed for use in analytical chemistry teaching laboratory are scarce [2].

Analytical chemistry is an area where efforts have been made for longtime to enhance the main analytical features regarding sensitivity and selectivity of the newly designed methods. However, the other important aspects such as sustainability, safety and environmentally friendly aspects were not so important in the past. Although for a longtime, analytical chemists have been environmentally conscious about the potential risks of the methods for operators and the environment; they have rarely used the word 'green' to describe the efforts on method sustainability; thus, the green developments are little difficult to discern in the literature. The simple aspect which has been greatly modified in the analytical chemistry paradigm has been the incorporation of the so-called green aspects to the basic analytical parameters [3].

Nowadays attention has been concentrated on developing alternative analytical methodologies without using solvents or reagents, reducing the amount of solvents required in sample pretreatment and also reducing the amount as well as the toxicity of solvents and reagents employed in the measurement step, especially through automation and miniaturization of available methodologies. Naturally, green analytical techniques are being practiced which encompass screening methodologies, replacement of toxic reagents, minimization of wastes, recovery of reagents, online decontamination of wastes and solvent-free methodologies. On the basis of the literature report and observations of current trends in chemical analysis and environmental monitoring, it is evident that rapid progress is being made in the development of analytical methodologies that are in accordance with the principles of green chemistry [4]. On the other hand, as the development of green methods is cheaper than the cleaning of polluted environment, green analytical methodologies should become very attractive from both esthetic and economical points of view.

Higher education has a critical role to play in producing sustainable learners by helping them to understand the complex connections and interdependencies between the environment, energy sources and economy. Universities, in particular, have an important responsibility in creating space for alternative thinking and the emergence of new ideas, as well as in critically exploring old ones [5]. Unfortunately, updates to classical teaching experiments have not been widely implemented despite the use of hazardous solvents, highly reactive reagents and unnecessary waste generation. Greening a laboratory requires intuitive considerations additionally than chemical knowledge. Even microscale techniques, which are intended to be more environmentally friendly than classical macro approaches by reducing the amounts of chemicals

used, pose an inherent risk of exposure due to the nature of the chemicals used, even if they are used only in small amounts [6]. With this end in view, the present chapter has been aimed at imparting green chemistry education with special reference to performing laboratory experiments in a cleaner way. So, we have tried to link the fundamentals of green analytical and synthetic methods with the practice of environmentally friendly experiments which could evidence the advantages of the new paradigm.

3.2 Integration of Strategies for Education in Green Chemistry

According to the United Nations Environment Program (UNEP 2006), in order to favor a green curriculum must promote initiatives, from education and scientific organizations all over the world, review programs and curricula in order to address the challenges of sustainable development, strengthen the role of teachers as persons involved in sustainability and attract young people to the profession. In this sense, it is required to develop mechanisms to keep teachers informed and promote knowledge transfers in innovative ways in order to bridge the gaps and inequalities of present knowledge being the aforementioned some of the areas where the universities have a role to play [7].

Now, it is the time to move from the research and development of new green alternatives of the methods of analysis to a thorough evaluation of their advantages in order to improve the incorporation of green methods to solve real problems [3]. Contextualized insertion of the green chemistry principles [8] into the curricula of higher education institutions can contribute to an improved professional education, modulating and engaging students to learn conceptual contents associated to procedural and attitudinal subjects. Figure 3.1 depicts the integration of tonic strategies for education in green chemistry. The strategies illustrate the application of different principles of green chemistry and allow ascertaining that green chemistry is an active ongoing process with the goal of making chemistry as environmentally benign as possible.

Waste minimization: The first principle of green chemistry, often referred to as the prevention principle, is the most obvious and envelopes the other principles [9]. Waste minimization involves efforts to minimize resource and energy use during manufacture and has proven benefits to industry and the chemical laboratories. The focus has now been shifted to less cumbersome methods, wherein the neat reactants undergo easy reactions to provide high yields of pure products and eliminating or minimizing side products and wastes. The practice of green chemistry has become increasingly important in both industrial and academic settings. Thus, few materials are available for teaching students the strategies and techniques of green chemistry. In fact, miniaturization is a valuable analytical tool that, per se, efficiently contributes to greening the analytical process by reducing the amount of solvents and reagents

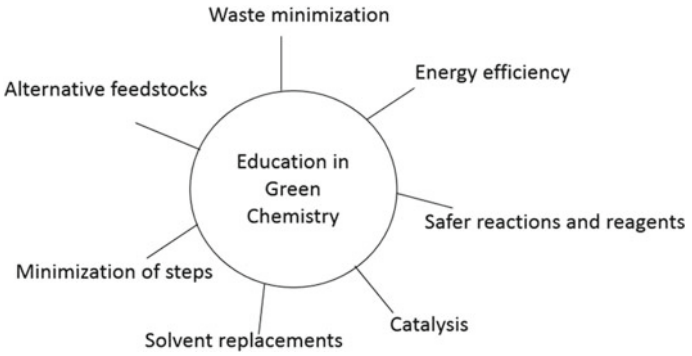


Fig. 3.1 Integration of the strategies for education in green chemistry

involved in the analysis. It also seems evident that miniaturization should be the strategy to follow when dealing with the analysis of size-limited samples. From the education perspective, minimization involves to scale down the size of risks and troubles, also reducing costs.

Energy efficiency: Energy is a key issue for the present society and its major part because in many cases, it is dependent on fossil fuels and other non-renewable sources and most of the energy that is delivered to the point of use is lost in conversion and transmission lines. Moreover, the largest portion of fossil fuel energy is used for transportation services followed by use in space heating and cooling. Traditional methods for generating energy have been found to contribute to global environmental problems and the energy used can be significantly expensive. Principle 6 focuses on creating products and materials in an extremely efficient way and reducing the consumption of energy for obtaining the products and hence reducing the environmental pollution and cost of production [10]. Instead of convection, the use of irradiation energy sources such as microwave irradiation may outperform conventional reaction conditions in various aspects, such as fast and easy work-up, reduction of the usual thermal degradation products, reduction of toxic and expensive quantities of solvents, reduction of secondary products and so on. The method is simple, fast and makes green chemistry accessible to students. Additionally, other systems such as ultrasound-assisted ones can work at reduced power levels and offer energy balance advantages over classical methods for energy supply to samples and reaction mixtures. So, the popularization of the aforementioned tools in university laboratories could be employed for reducing energy consumes.

Safer reactions and reagents: Although the conventional reagents for many organic syntheses and analysis are highly effective, they could cause unwanted health and/or environmental risks. Sometimes, less reactive, less toxic chemicals also work. In fact, the fourth principle focuses on the 'product' that is made. In other words, it is aimed at designing products that are safe, non-toxic and efficacious. Achieving this goal requires an understanding of chemistry, toxicology and environmental sciences. Thus, a comprehensive and cooperative effort between toxicologists and chemists is

required to focus on training the next generation of scientists to design safe chemicals in a truly holistic and interdisciplinary manner [11]. Because of that, it is mandatory to use of data sheets of all the chemicals to be employed in the laboratory to guarantee the safety of students and their deep understanding of the opportunities and threats of chemicals.

Catalysis: Principle 9 focuses on chemical processes using catalysts in front of stoichiometric reactions in order to favor atom minimization, reduce energy requirements, made reactions efficiently and many times faster. Another benefit of using catalyst is that generally small quantities are required to have an effect. Moreover, catalytic reactions minimize separations due to increased selectivity and also permit the use of renewable feedstocks and reduce the amounts of reagents required. For the aforementioned reasons, transition metal catalysis has become one of the most important tools in organic synthesis. It has allowed entirely new transformations which were not possible earlier by classical organic reactions and thus significantly increased the efficiency of synthesis [12]. If the catalyst is truly 'green,' it will have little or no toxicity and it can be used repeatedly in the process. This idea of reusability is very important to be transmitted in the high school, college and university laboratories.

Solvent replacement: Solvents and mass separation agents are extremely significant in chemical processes and the overall greenness of reactions. In many cases, reactions will not proceed without solvents and auxiliary substances because they drive most of the energy consumption in a process. But, traditionally organic solvents are hazardous and highly toxic. They are flammable and volatile which add to pollution and can be extremely hazardous to humans. In fact, Principle 5 focuses on creating products in such a way that they use less hazardous solvents [13]. Some good alternatives for organic solvents include supercritical fluids, ionic liquids, low-melting point polymers, so-called agro-solvents and water. In fact, many of the aforementioned alternative solvents are safer solvents for human health and the environment than traditionally used ones and work as effectively as traditional solvents to recycle.

Minimization of steps: The methods that chemists use to make products and analytical determinations are sometimes highly sophisticated and in many cases involve the manipulation of starting compounds in order to shape the target molecules into what we want them to look like. Principle 8 of green chemistry is to reduce the use of derivatives and protecting groups in the synthesis of target molecules [14]. This means in the analytical field that it is very convenient to reduce the steps of classical analysis and avoids the need of using analyte derivatives instead of making a direct determination of targets. A novel way of doing this in the organic field is the use of one-pot synthesis which is very specific with quantitative yield and in the analytical perspective, to favor remote sensing and the direct analysis of unreacted samples. In fact, the one-pot synthesis of a target molecule in the same reaction vessel is widely considered to be an efficient approach in synthetic organic chemistry, and nowadays there is an increasing interest in the development of portable instrumentation and point-of-care methodologies.

Alternative feedstocks: 90–95% of our daily use products are from petroleum which is used not only for transportation and energy, but also for making

commodities. Principle 7 seeks to shift our dependence on petroleum and to make products from renewable materials that can be gathered and harvested locally. Nature produces about 170 billion tons of plant biomass annually, of which 3.5% are currently used for human needs. It has been estimated that about 40 billion tons of biomass, or about 25% of the annual production would be necessary to completely generate a bio-based economy. The technical challenge toward using such renewable feedstocks is to develop low-energy, non-toxic pathways to convert the biomass to useful chemicals in such a way that does not produce more carbon dioxide than is being removed from the air. In fact, biomass-derived products are not only renewable but also provide a great variety of selective compounds, e.g., biodiesel from plant oils and algae, bio-ethanol and butanol from sugars and lignocelluloses, plastics, foams and thermosets from lignin and plant oils [15]. In the case of methods of analysis, the use of renewable origin reagents and solvents is also a guarantee for the future.

3.3 Greening the Laboratories

A university should be the model of sustainable practices. So, it is important that academics and institutions keep experimenting with, and sharing their efforts to embody sustainability, especially in making it a focus of their disciplines and professions in the process of curriculum design, development and research [16].

Sustainable processes are being sought to explore alternatives to conventional chemical syntheses' transformations, industrial processes and analytical methods. Among several thrust areas for achieving this target includes: the utility of alternative feedstocks, preferably from renewable materials or waste from agricultural or industrial practices; unconventional efficient reaction conditions and eco-friendly reaction media to accomplish the desired chemical transformations with minimized by-products or waste generation and ideally avoiding the use of conventional volatile organic solvents or reduce as much as possible the use of toxic reagents in analytical practices wherever possible. Other avenues for achieving this objective are to explore the generation of efficient catalytic processes and direct methods of analysis. In addition to greener synthesis and analytical methods, the recyclability and reuse aspects for catalytic systems and analytical procedures are extremely significant particularly when it takes into the use of imperiled elements and precious catalysts [17].

Recent efforts to greening the laboratories in every field of chemistry have started to receive attention from academic perspective. Thus, the goal of greening the chemistry is to use procedures that generate less hazardous waste and that are safer to use and more benign to the environment. This goal may be achieved by developing new methodologies or more often simply modifying old methods to incorporate procedures that use either less hazardous chemicals or lesser amounts of hazardous chemicals if safer substitution is not available. There are numerous studies that provide direct methodologies for reduction of reagent consumption or waste minimization based on scaling down the methods, the automation of processes, the recycling of used solvents or replacement of toxic chemicals by non-toxic or less toxic ones.

The development of analytical chemistry continues at a steady rate and every new discovery in chemistry, physics, material science, etc. generates or finds an application in analytical chemistry as well [18]. The green analytical experiments are concerned with the design, development and implementation of products and chemical processes that include the elimination of toxic organic solvents/reagents, solvent-less synthesis, waste minimization, facile methods of preparation with non-toxic chemicals, lower temperature, less reaction time, increased yield, etc. In fact, green experiments are introduced not to abruptly replace the conventional ones; rather they are considered complementary to the existing protocols. This not only gives an opportunity to widen the view of various techniques but also generates innovative minds for future growth and development of the subject with due emphasis to green chemistry. The essence of green analytical chemistry could well be achieving the aim through its practice in laboratories. Incorporation of green experiments into a laboratory course will provide a basis for a discussion of organic synthesis, solvent extraction, trace analysis, waste management, etc. and the benefits of green chemistry including environmental issues in the classroom. This is the challenge and it is the time to take appropriate measures to avoid pollution problems and to increase the safety of the analytical laboratories. Making the laboratory methodologies greener is something of interest not only for the future but also for the present [19]. With the growing awareness of green chemistry, it is increasingly important for students to understand this concept in the context of laboratory experiments.

3.4 Green Laboratory Experiments

In this chapter, 16 laboratory experiments which have been developed by researchers in recent years will be discussed in depth. They are based on different aspects of the guiding principles of green and sustainable chemistry with critical comments; they will be presented as proof of concept of the benefits that could be obtained through greening our teaching practices. The first aspect focuses on the use of catalytic methods and provides instructive procedures that involve the use of recyclable solid phase catalyst and environmentally benign reagents. The second aspect involves the use of green solvents and solventless processes. The third type of experiments considered provides examples of energy saving processes such as the use of microwave-assisted processes. Atom-economic one-pot syntheses could be exemplified under the fourth type of experiments reviewed. Issues related to the limitation of waste generation are included as the fifth type. The experiments have been chosen so that the students can understand that sustainability involves not only avoiding environmental pollution and decontaminating wastes but also reducing the consumption of reagents and energy. The structure of this section will include the presentation of experiments, details about the green methodologies suggested and critical comments on the laboratory practices in order to put the spotlight on the real possibilities to greener the formation of our students in chemistry and related disciplines.

3.4.1 Experiments with Green Catalysts

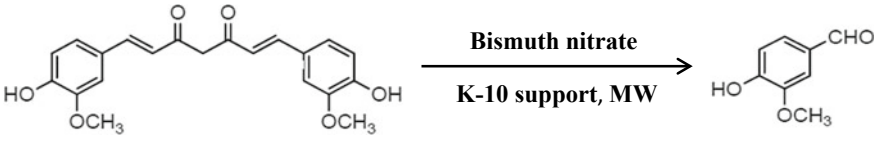
Utilization of catalysis to achieve goals of green chemistry has been carried out with great success. There has been a continuous search for newer green catalysts. For example, the catalytic activity of trivalent bismuth nitrate pentahydrate which acts as a Lewis acid has been evidenced. Novel uses of ionic liquids as catalysts as well as reaction media for organic transformations avoiding hazardous organic solvents and toxic catalysts open up a newer avenue in catalytic processes.

3.4.1.1 Synthesis of Vanillin from Natural Product (Turmeric) Induced by Bismuth Nitrate

Curcumin, a polyphenol derived from *Curcuma longa* (commonly known as turmeric), is an ancient spice therapeutically used in India for centuries, which is commonly employed to induce color in food and in some cases to treat a wide array of diseases. Because of the exceptionally widespread utilization of vanillin in the food, cosmetic, pharmaceutical, nutraceutical and fine chemical industries, considerable attention has been devoted to the improvement of the production processes of vanillin [20]. Starting from curcumin, $Bi(NO_3)_3$ induced synthesis of vanillin has successfully been carried out and the formation of a single product has been observed in good yield in the presence of KSF clay support.

Green methodology [21]: Curcumin (1 mM), $Bi(NO_3)_3{\cdot}5H_2O$ (0.75 equivalent) and KSF clay solid support (500 mg) were mixed in dichloromethane (4 mL) and the solvent was evaporated in a rota-evaporator. The mixture was irradiated inside a kitchen microwave oven, and the reaction was monitored by thin layer chromatography (TLC). After completion, the reaction mixture was extracted with dichloromethane and made alkaline with a saturated aqueous sodium bicarbonate solution. The organic layer was then washed with brine and water and finally dried with anhydrous sodium sulfate. The pure product (77%) was isolated by flash chromatography over silica gel. The one-step method for the preparation of vanillin from naturally occurring curcumin in the presence of bismuth nitrate under microwave irradiation has been shown in Scheme 3.1.

Comments: Bismuth nitrate is the reagent of choice for the oxidative cleavage of curcumin to vanillin in the absence of solvent under microwave irradiation and with no aromatic nitration and rearrangement of curcumin or vanillin. A selective



Scheme 3.1 Synthesis of vanillin from curcumin

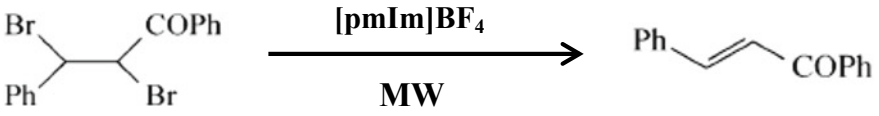
oxidation of the alkene bond of curcumin to vanillin has been taken place. Major advantages of the present method include the uses of alternative renewable feedstock (curcumin), eco-friendly $Bi(NO_3)_3$ and K-10 clay support and shortening of one-step reaction time further by using microwave irradiation. In fact, this experiment fulfills all the important criteria for a successful green synthesis laboratory experiment. However, it must be noticed that the use of dichloromethane to prepare the reaction mixture and to do the extraction of vanillin, together with the rotary evaporation stated to eliminate dichloromethane before to start the reaction inside the microwave oven. These dark points must be also critically discussed with the students in order to look for additionally greening the work opportunities.

3.4.1.2 Debromination of *Erythro*-1-Benzoyl-2-Phenyl-1,2-Dibromoethane Induced by Ionic Liquid

Since the introduction of ionic liquids (ILs) in organic synthesis, they have attracted increasing interest in the context of green chemistry because of their great potential as environmentally benign media for both synthesis and sample pretreatment purposes. Recently, ILs have entered very successfully into the area of catalysis [22]. An easily accessible ionic liquid, 1-methyl-3-pentylimidazolium fluoroborate, $[pmIm]BF_4$, has been evaluated as an efficient catalyst as well as a reaction medium for the stereoselective debromination of a variety of structurally diverse *vicinal* dibromides to the corresponding (*E*)-alkenes in high yields under microwave irradiation. The green protocol does not require any organic solvent and any metal nor conventional reducing agent, and the ionic liquid is recycled without any appreciable loss of its catalytic efficiency.

Green methodology [23]: A mixture of *erythro*-1-benzoyl-2-phenyl-1,2-dibromoethane (368 mg, 1 mM) and $[pmIm]BF_4$ (400 mg, 1.6 mM) was placed in a domestic microwave oven for 2 min using 20% power (240 W) to attain the temperature in the range 130–135 °C. The reaction mixture was allowed to cool and extracted with ether (3 × 5 mL), and the extract was washed with brine and dried by anhydrous Na_2SO_4. Evaporation of the solvent left the crude product, which was purified by column chromatography to provide the pure *trans*-1-benzoyl-2-phenylethene with 92% yield. The reaction scheme is shown in Scheme 3.2.

Comments: The procedure, using an ionic liquid playing its dual role, as catalyst and reaction medium provides a novel and efficient protocol for debromination of



Scheme 3.2 Debromination of *erythro*-1-benzoyl-2-phenyl-1,2-dibromoethane

vicinal dibromides to (*E*)-alkenes and alkynes. The significant advantages offered by this method concern operational simplicity, very fast reaction, high reaction yields, excellent stereoselectivity, general applicability to a wide variety of substrates and no over reduction of carbon–carbon multiple bonds. So, the greenness of procedure is made by avoiding toxic catalysts and hazardous organic solvent during the reaction. Additionally, recyclability of the catalyst is a great advantage which avoids the treatment of the IL as a waste. Thus, it provides an environmentally friendly method with great promise toward further useful applications. On the other hand, the use of domestic microwave ovens to heat the reaction mixtures in the aforementioned two synthesis experiments make easy to do these laboratory practices in not well-financed institutions and offers the possibility to discuss the strengths and weaknesses of the convection heating systems as compared with irradiation ones.

3.4.2 Experiments with Green Solvents

The search for alternative solvents is an important step on the process of using greener methods, where the main target should not be just the replacement, but the introduction of an additional advantage from different properties of these solvents to improve the selectivity, sensitivity and reliability of analysis, as well as to reduce analysis time. During the past decades, there have been proposed many good alternative solvents to commonly employed organic ones; as for example, glycerol or polyethylene glycol is illustrated below to be used in greening synthesis and separation procedures. On the other hand, water-based separation processes as sequential extraction of heavy metals in aqueous biphasic system and the clean separation of molybdenum by pyrohydrolysis from inorganic matrix were proposed as green alternative processes to be used in the nuclear chemistry field.

3.4.2.1 Synthesis of Benzoxazole, Benzimidazole and Quinoxaline Using Glycerol Solvent

Due to environmental concerns, safety considerations, reduction of costs and the simplicity of the process, synthesis reactions using green solvents have drawn great attention in recent years. Quinoxaline, benzoxazole and benzimidazole can be found in a variety of natural products as well as a number of biologically active compounds especially anti-viral, anti-bacterial, anti-inflammatory, anti-protozoal, anti-cancer, anti-depressant, anti-HIV, anti-ulcer, anti-hypertensive and as kinase inhibitors [24]. The earlier reported methods for the synthesis of these compounds suffer from drawbacks such as long reaction time, usage of expensive and corrosive reagent, high temperature with low reaction yield. The use of glycerol as a green solvent could be applied for the preparation of benzoxazole, benzimidazole and quinoxoline via condensation reaction. The advantage of this protocol is that after the work-up proce-

dure, glycerol can be successfully recovered and reused for further reaction without affecting the reaction yields.

Green methodology [25]:

(a) For the synthesis of benzoxazole, glycerol (5 mL) was added to a stirred solution of 2-aminophenol (0.1 g, 0.92 mM) in methanol (1 mL), and the reaction mixture was heated to 90 °C, followed by addition of benzaldehyde (0.1 g, 0.92 mM). The reaction mixture was stirred vigorously at 90 °C. The progress of the reaction was monitored by TLC. When all the starting material was consumed, the reaction was stopped with water (10 mL) and the product extracted with ethyl acetate (2 × 10 mL). The organic phase was separated and dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give the crude product. The pure product was isolated by silica gel column chromatography using the solvent mixture, ethyl acetate/hexane, 1:9.

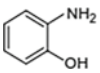
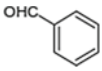
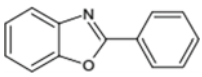
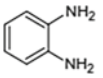
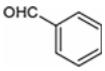
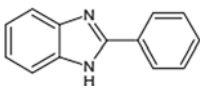
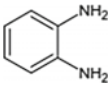
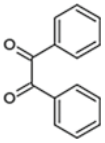
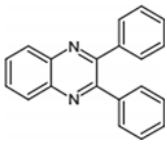
(b) For the synthesis of benzimidazole, glycerol (5 mL) was added to a stirred solution of *o*-phenylenediamine (0.1 g, 0.93 mM) in H_2O (2 mL), and the reaction mixture was heated to 90 °C, followed by addition of benzaldehyde (0.1 g, 0.93 mM). The reaction mixture was stirred vigorously at 90 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the product was isolated as above-mentioned in the (a) case.

(c) For the synthesis of quinoxaline, glycerol (5 mL) was added to a stirred solution of *o*-phenylenediamine (0.1 g, 0.92 mM) in H_2O (2 mL), and the reaction mixture was heated to 90 °C followed by addition of benzil (0.2 g, 0.92 mM). The reaction mixture was stirred vigorously at 90 °C. The progress of reaction was monitored by TLC. After completion of the reaction, the product was isolated as in the above-mentioned cases.

Table 3.1 summarizes the reactants, synthesis time and reaction yield obtained in each case. The structures of the isolated compounds, after column chromatography purification were confirmed by nuclear magnetic resonance (NMR), infrared spectroscopy (IR) and comparison of melting point with reported data.

Comments: The physical characteristics and chemical properties of glycerol, e.g., polarity, low toxicity, biodegradability, high boiling point and ready availability from renewable feedstocks encourage the researchers to extend its use as a green solvent in organic synthesis. The use of glycerol as a green solvent for the preparation of benzoxazole, benzimidazole and quinoxaline via condensation reaction has been evidenced as an efficient protocol correlated with the heterocyclic chemistry. The advantages of the present method include using economically and environmentally benign solvent, no use of catalyst, mild reaction conditions and good reaction yields. However, additional aspects to be greener concern include the reduction of energy consume regarding the heating step and the look for the use of green solvents for compound extraction.

Table 3.1 Reactants and results obtained for the syntheses of benzoxazole, benzimidazole and quinoxaline in glycerol

Reactant 1	Reactant 2	Product	Time (h)	Yield (%)
 I	 II	 III	4	90
 IV	 II	 V	2	75
 IV	 VI	 VII	4	90

I—2-aminophenol, II—benzaldehyde, III—benzoxazole, IV—*o*-phenylenediamine, V—benzimidazole, VI—benzil, VII—quinoxaline

3.4.2.2 Sequential Extraction of Heavy Metals in Aqueous Biphasic System

Partitioning of elements in an aqueous biphasic system (ABS) represents a viable and green alternative to aqueous/organic liquid–liquid extractions. ABS with polyethylene glycol (PEG) as the polymer-rich phase together with an inorganic salt-rich phase has great potential to separate metallic ions from aqueous solutions [26]. An aqueous biphasic extraction system has been designed using different molecular weights of PEG and concentrated salt solutions of Na_2SO_4 to separate heavy metals like Hg, Tl and Pb from Li irradiated Au matrix.

Green methodology [27]: The aqueous biphasic system was prepared by mixing 3 mL of either 50% (*w/w*) PEG 4000 solution or PEG 400/600 (available in liquid form) and 3 mL of a concentrated solution of Na_2SO_4. 100 μL of the active solution was added to the system and the mixture was shaken mechanically for 10 min. The system was centrifuged for 5 min, and 1 mL aliquot from each of the two phases was taken out for γ- spectrometric studies. Counts were measured for a fixed time for both phases at a fixed source to detector geometry. The count of the salt-rich phase was compared with that of the PEG-rich phase. The pH of the Na_2SO_4-rich phase was adjusted using a diluted HCl solution, and the effect of variation of pH on the partition of the heavy metals was studied. To have an idea on the effect of the

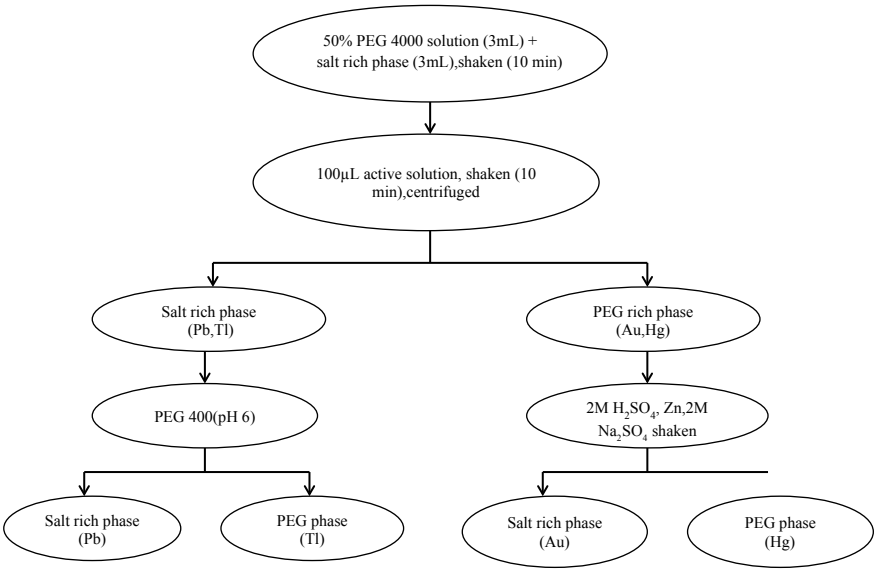


Fig. 3.2 Flow diagram for the sequential separation by ABS of Au, Hg, Pb, Tl. Reprinted from Ref. [27], copyright 2009, with permission from Springer Nature, J Radional Nucl Chem

molecular weight of PEG on the extraction of target metal ions, similar ABS were constructed with PEG 400 and 600 with Na_2SO_4-rich phase (see Fig. 3.2).

Comments: Among the many applications of the aqueous biphasic system, an easy sequential separation of several heavy metals could be possible. ABS offers an environment-friendly method to separate some heavy metals from others by simple adjustments of pH, molecular weight of PEG and the type of salt in the salt-rich phase. In the field of nuclear chemistry, the present work has been described as a cost-effective and environmentally benign method to separate heavy metals viz., Pb, Tl and Hg in their no carrier added state from ^{7}Li irradiated Au matrix.

3.4.2.3 Separation of Molybdenum by Pyrohydrolysis

Presence of molybdenum even at trace levels is undesirable in oxide or mixed oxide fuels of uranium and plutonium because Mo has significant affinity for the oxygen of UO_2 or (U, Pu)O_2. The methods being followed for separating Mo from nuclear fuel matrices (U or U/Pu) involve dissolution of the material in appropriate acid media followed by solvent extraction or ion exchange separations [28]. Unfortunately, these methods are laborious and generate significant amounts of radioactive liquid wastes. Pyrohydrolysis (PH) is an eco-friendly method of separation as it generally uses diluted absorbing solutions for analyte retention. PH is a digestion method allowing the analyte volatilization in a heated system in the presence of water vapor flow.

Mishra et al. [29] carried out a comprehensive investigation of the oxidation and vaporization chemistry of Mo in the presence of steam water at ~1000 °C. Based on the data on the pyrohydrolytic separation, studies were carried out for extracting Mo quantitatively from uranium matrices.

Green methodology [29]: The optimum PH conditions for the quantitative extraction of molybdenum were as follows: (i) sample mass, 50–1000 mg (depending on Mo content); (ii) temperature, 1000 ± 20 °C; (iii) time, 2 h 30 min; (iv) carrier gas flow rate, 2 L min^{-1}; (v) distillate collection rate, 0.3–0.5 mL min^{-1}; (vi) trapping agent, 5 mL of 25 mM NaOH. Since the PH distillate was collected in NaOH medium, Mo remained in the form of MoO_4^{2-} and because of that an ion chromatography method based on the anion exchange separation of MoO_4^{2-} ion was employed for quantification. A mobile phase of 15 mM NaOH at a flow rate of 1 mL min^{-1} was used to separate MoO_4^{2-} from other common anions. Typical results for the determination of Mo in real ammonium diuranate samples by the ion chromatography method after pyrohydrolysis varied from 37 to 52 ppm and for a certified material ILCE-CRM (U_3O_8), containing 47.1 ± 8.7, it was obtained a value of 42 ± 20 ppm of Mo.

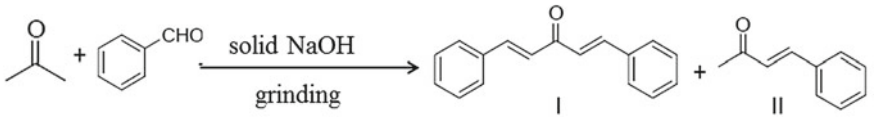
Comments: A green method for pyrohydrolytic separation of Mo directly from the solid matrices without the use of acids and other organic reagents was developed and based on that, an analytical method for the determination of Mo in uranium-based materials using its PH separation followed by ion chromatography determination was applied to samples having enriched uranium.

3.4.3 Organic Synthesis Using Solventless Processes

The use of solvent-free reaction condition has been widely reported as an efficient methodology for the reduction of waste and minimization of energy use, in-line with the principles of green chemistry. Many researchers have considered the utility of solvent-free conditions with regard to high degree of conversion and simplicity of the method. Two solventless organic syntheses are presented below.

3.4.3.1 Solvent-Free Claisen–Schmidt Reaction

The Claisen–Schmidt reaction (crossed-aldol reaction) is a condensation reaction of aldehydes and carbonyl compounds leading to β-hydroxycarbonyl compounds, and it has played an important role in synthetic organic chemistry [30]. These reactions have been classically catalyzed by strong acids and more likely by base. Later on different metal complexes were used as catalysts to replace acids or bases but satisfactory yields were not obtained. Due to the importance of the relevant reaction in synthetic organic chemistry and of α,′α-*bis*-(substituted-benzylidene)-cycloalkanones as precursor for various natural products, an easy solvent-free Claisen–Schmidt reaction using a grinding technique in presence of solid NaOH catalyst has been reported for



Scheme 3.3 Claisen–Schmid reactions in presence of solid NaOH

the synthesis of α,′α-*bis*-(substituted-benzylidene)cycloalkanones, di- and/or monobenzylidene acetone and benzylidene camphor.

Green methodology [31]: The Claisen–Schmidt reaction for acetone and benzaldehyde could be conducted using a reaction time of 2 min giving a mixture of (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one (**I**) and (*E*)-4-phenylbut-3-en-2-one (**II**) in 53 and 42% yields, respectively. **I** and **II** were obtained following the procedure adopted from the mixture of acetone (5.0 mM) and benzaldehyde (10.0 mM). The oily material was collected and purified by flash chromatography on silica gel. **I** was obtained as yellow solid with melting point (mp) 109–111 °C, and **II** was a low-melting solid with mp of 39–42 °C. The reaction was catalyzed by solid NaOH (20 mol%) by applying a grinding technique using a mortar and pestle for 5 min (Scheme 3.3). The regioselectivity of the reaction was examined, and the results indicated that use of excess amount of acetone (>5 equiv) resulted in mainly **II** (96%) with a trace amount of **I**, while on the other hand, when an excess of benzaldehyde (>3 equiv) was used *bis*-benzylideneacetone was obtained in a 98% yield as a single product.

Comments: A solvent-free Claisen–Schmidt reaction between acetone and benzaldehyde was performed with excellent yields. The regioselectivity of the reaction gave the corresponding *bis*-benzylideneacetone also in excellent yield using the same method. The use of solvent-free conditions and solid catalyst, prepared simply grinding NaOH, provided a green and fast alternative to the classical synthesis procedures and is really useful to insist on the interest of the use of catalyzed reactions and the reduction of reagents and solvents.

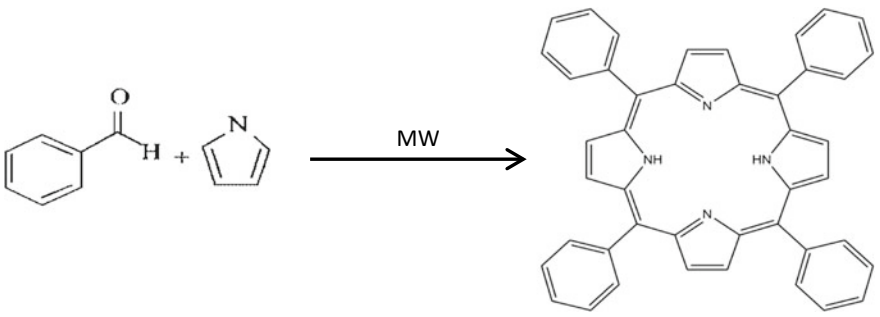
3.4.3.2 Solventless Synthesis of Mesotetraphenylporphyrin

The traditional porphyrin synthesis uses corrosive reagents and solvents [32]. The method presented here avoids the use of corrosive acids and halogenated solvents in this synthesis by performing the reaction in the gas phase or on a solid phase support medium, essentially eliminating all waste produced during the process. Additionally, the chromatography and spectroscopy uses of a solvent mixture of hexane/ethyl acetate (7:1) provide enhanced safety and reduced hazardous waste disposal issues as compared with the traditionally use of halogenated solvents.

Green methodology [33]: 0.43 mL of benzaldehyde and 0.3 mL of pyrrole were mixed in a 25 mL Erlenmeyer flask. Once the reactants were thoroughly mixed, 0.63 g of silica gel was added, the flask stoppered, and the reagents mixed well

until the silica gel was evenly and completely covered with the reactant mixture. The flask containing the reaction mixture was then placed in a 1000 W microwave oven, covered with a Pyrex watch glass and heated for 10 min in five 2-min intervals. Once the reaction was completed, it was allowed to cool to room temperature and *ca.* 15 mL of ethyl acetate added. The solution was filtered to remove the silica gel and then the ethyl acetate was removed using a rota-evaporator. Prior to chromatography separation, the crude reaction mixture was extracted into 1 mL of dichloromethane. This fraction was used for subsequent purification (Scheme 3.4). Next, the metalation was performed in a cleaned, dried glass UV cell. Three drops of the representative fraction from the column chromatography experiment were evaporated to dryness then diluted to 4 mL using *N*-methylpyrrolidinone. The conditions reported here were optimized so that the synthesis and chromatographic purification work reliably in the teaching lab, and these experiments were easily extendable to introduce topics such as NMR spectroscopy. An initial spectrum was then collected. After addition of five drops of the $Zn(OAc)_2$ solution (2.2 mM in DMSO), spectra were collected every 25 min to monitor the progress of the metalation reaction and the process was completed in about 4 h at room temperature.

Comments: The absorption spectrum of mesotetraphenylporphyrin is very characteristic and provides a strong absorbance at 420 nm and four comparatively weak intensity bands at 510, 550, 590 and 645 nm. The experiment presented here effectively demonstrates the opportunity to explore the green chemistry strategies including solventless reaction conditions and the use of benign reagents during synthesis. In addition, the halogenated and aromatic solvents often used to purify the obtained compounds could be minimized. The spectroscopy characterization process was also greened. However, it must be discussed with the students about the additional possibilities, or not, to greener the extraction and metalation steps. Once again the aforementioned laboratory experiment is useful to insist on the advantages to make synthesis in solventless media and to evaluate the energy saving based on the replacement of convective heating processes by microwave-assisted ones.



Scheme 3.4 Synthesis of mesotetraphenylporphyrin accomplished by microwave-assisted irradiation

3.4.4 Greening Through Energy Saving Microwave Processes

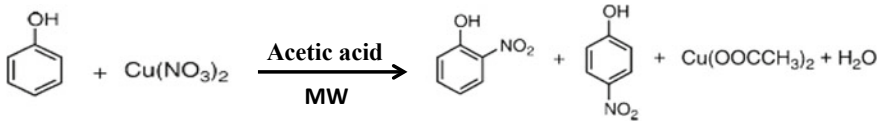
The use of microwave radiation is now common in laboratories throughout the world. It has become a very important tool in both analytical chemistry and synthesis processes in order to save energy and time. In addition to some of the previously described laboratory work, the following two common organic reactions have been carried out by applying microwave energy as a greener tool.

3.4.4.1 Microwave-Assisted Nitration of Phenols Using Cupric Nitrate

Most of the methods reported for nitration of aromatic compounds require the use of corrosive nitric and sulfuric acids [34]. Use of such reagents (especially in excess) creates serious operator risks and environmental issues and the treatment and disposal of the used mixed acid is expensive. These methods also suffer from disadvantages such as overnitration, strongly acidic medium use, tedious work-up and safety issues. $Cu(NO_3)_2$ is used as a nitrating agent and it reacts with glacial acetic acid to give HNO_3. The use of cupric nitrate presents a regioselective as well as high-yielding nitration method of phenol.

Green methodology [35]: Phenol (1.000 g, 0.6 mM) and 5 mL of acetic acid were mixed in a 50 mL glass round-bottomed flask and placed inside the microwave oven. $Cu(NO_3)_2$ (2.385 g, 12.7 mM) was added to the mixture slowly when the resulting color changed to reddish brown and brown fumes were generated. The reaction mixture was stirred with a magnetic stir bar. The reaction was performed with the microwave oven at a power of 320 W, heated to 120 °C and held at this temperature for 1 min. Upon completion of the reaction, the mixture was allowed to cool to room temperature. 10 mL of ethyl acetate was added, stirred and finally filtered. The residue was cupric acetate and the filtrate contained the nitration product. 10 mL water was added to the filtrate and ethyl acetate layer was separated. The organic layer was checked by TLC to evaluate the presence of any impurity or by-products using hexane/ethyl acetate (8:2) solvent mixture. Finally, *o*-nitrophenol and *p*-nitrophenol (major) were isolated by either steam distillation or column chromatography (see Scheme 3.5).

Comments: The present experiment makes nitration of phenol using an environmentally friendly nitrating mixture with a high regioselectivity. Acetic acid, an



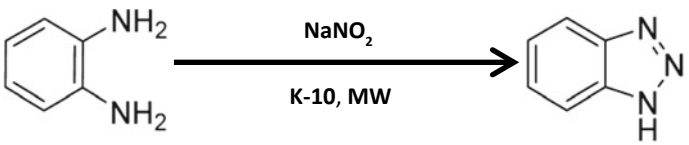
Scheme 3.5 Microwave-assisted nitration of phenol using copper nitrate

excellent absorber of microwave energy, acts as a solvent as well as a reactant and thus it is able to shorten the reaction time to 1 min with overall yields in the range 70–80% with more than 80% *p*-isomer. Copper acetate, the by-product in this nitration reaction, can be used in the preparation of fungicide agrochemicals as a green pigment and also as a reagent for the synthesis of various inorganic and organic compounds. Nevertheless, through this experiment, the students can use a clean and energy efficient nitrating methodology.

3.4.4.2 Microwave-Assisted Solid Phase Diazotization

The conventional method of diazotization uses sodium nitrite and requires a strong acid such as hydrochloric acid, sulfuric acid or *p*-toluenesulfonic acid to in situ generation of nitrous acid. One commonly applied approach to diminish the negative impact of liquid mineral acid catalysis is the application of solid acid-catalyzed heterogeneous methods [36]. A layered aluminosilicate clay mineral, montmorillonite K-10 has been employed as an efficient acid catalyst for various organic transformations. The method presents a microwave-assisted solid acid-catalyzed method for the synthesis of substituted benzotriazoles via in situ solid phase diazotization and subsequent intramolecular cyclization of *o*-phenylenediamines. The approach offers a simple experimental setup, short reaction times, high yield and exclusive selectivities, the use of a recyclable solid acid catalyst and then a filtration and solvent evaporation as a simple purification way. The process can be considered as an environmentally benign alternative to available processes for the preparation of substituted benzotriazoles and in general could serve as a broadly applicable green diazotization method.

Green methodology [37]: K-10 montmorillonite (500 mg), *o*-phenylenediamine (0.5 mM) and $NaNO_2$ (0.5 mM) were suspended in 1.5 mL of water and stirred for 5 min. Water was then evaporated in vacuum until the reaction mixture was completely dry. The dry mixture was transferred inside a microwave reaction vessel and was heated to 110 °C by microwave irradiation (1 h). After completion of the reaction, two portions of 2 mL of ethyl acetate were used to extract the product. Centrifugation was applied to separate the catalyst and the ethyl acetate solution of the product. Finally, ethyl acetate was removed in vacuum to obtain pure solid benzotriazoles (Scheme 3.6).



Scheme 3.6 Solid phase diazotization of *o*-phenylenediamine

Comments: The whole methodology provides an excellent example of green laboratory experiment with many noteworthy features. The reaction itself occurs on the surface of the catalyst which also serves as a medium, thus requiring a minimal amount of water. There is no need for the separate preparation of the diazonium salt as the reaction occurs in a domino way. The yield of the product is highly quantitative (99%), selectivity is exclusive and the product does not require further purification. No harmful by-products are generated and the product isolation entails a simple filtration/evaporation. The combination of microwave irradiation with a strong microwave absorber catalyst/medium ensures short reaction times and high energy efficiency. The approach uses commercially available inexpensive materials, including the substrates, reagent and recyclable catalyst.

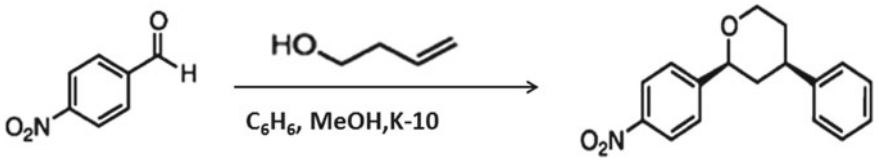
3.4.5 Experiments on One-Pot Synthesis

One-pot synthesis has been described as a strategy to improve the efficiency of a chemical reaction whereby a reactant is subjected to successive chemical reactions in just one reactor. This avoids lengthy separation processes and also purification of the intermediate chemical compounds. It would save time and resources, at the same time chemical yield could be improved. Such a strategy can be described as eco-friendly which is evidenced by the following three examples.

3.4.5.1 Multicomponent Prins–Friedel–Crafts-Type Reaction

The acid-catalyzed condensation of olefins with carbonyl compounds, known as Prins reaction, is an important carbon–carbon bond forming reaction. Again Friedel–Crafts reaction of aromatic and heteroaromatic compounds is one of the fundamental reactions for forming carbon–carbon bond. Multicomponent reactions result in the formation and breaking of multiple bonds in a single step or in one reaction flask, and these reactions are carried out in the presence of a catalyst and with an excellent atom economy they constitute an important component of green chemistry [38]. Prins–Friedel–Crafts-type reaction is an example involving a Montmorillonite K-10 clay-catalyzed multicomponent reaction in an effort to synthesize different tetrahydropyran products. Variation of the starting carbonyl substrates and arenes allows for the potential generation of numerous products by using the same protocol.

Green methodology [39]: In a 25 mL round-bottomed flask, equipped with a magnetic stir bar, the K-10 clay (200 mg) and *p*-nitrobenzaldehyde (recrystallized, 151 mg, 1.00 mM) were mixed with benzene (10 mL), methanol (202 μL, 5.00 mM) followed by the 3-buten-1-ol (purified by vacuum distillation, 94 μL, 1.10 mM). The reaction mixture was refluxed with stirring until complete and evaluated by TLC analysis, using a solution of the starting aldehyde dissolved in dichloromethane as a reference and developing the plate in 1:1 hexane/ethyl acetate. When the reaction was completed, the reaction mixture was allowed to cool to room temperature, and



Scheme 3.7 Synthesis of *cis*-2,4-tetrahydro-2-(4-nitrophenyl)-4-phenyl-2H-pyran

then vacuum filtered through a bed of silica gel (~1 g). The filtrate was transferred to a vial and rota-evaporated to remove benzene and methanol to get the product in 70–90% yields (see Scheme 3.7). Finally, the compound was analyzed by gas chromatography with mass spectrometry detection (GC–MS), IR, ^{1}H and ^{13}C NMR spectroscopy.

Comments: Multicomponent reactions are well known in green chemistry. The tetrahydropyran ring is a part of the backbone of various important carbohydrates and natural products. Montmorillonite K-10 catalyzes the synthesis of tetrahydropyrans using Prins-type cyclization. Environmentally benign clays are ideally suited for greening the method of synthesis. No doubt, the method evidences the tremendous advantages of using one-pot synthesis with minimization of steps and providing good reaction yield.

3.4.5.2 Preparation of Gold Nanoparticles Using Tea Extract

The greener preparation of nanoparticles has been exemplified by using tea extract which functions both as reducing and capping agents avoiding the need to deploy any toxic reducing agent, such as borohydrides [40]. A single-step green method using no surfactant, capping agent, or template, allows to prepare gold nanoparticles using tea leaves and to study the effect of the tea concentration on the size of nanoparticles, which produces color changes that can be monitored by UV–visible spectroscopy. Production of nanoparticles by phytochemically mediated process could be completed at room temperature within 30 min.

Green methodology [41]: The synthetic methodology involves mixing an aqueous solution of tetrachloroauric (III) acid with a solution of tea leaves. The tea stock solution was prepared by vigorous stirring of Darjeeling (India) tea leaves in water with a $HAuCl_4$ solution over a magnetic stir plate for 15 min and filtering with Whatman filter paper. A small volume of a pale yellow gold solution was added to the tea solution with stirring and the solution turned purple–red within 5 min indicating the formation of nanoparticles. Finally, the reaction mixture was stirred for additional 15 min. The applications of gold nanoparticles are dependent on their size, shape and morphology. So, the effect of different concentrations of tea (10, 5, and 1% of stock solution) on the size and dispersion of gold nanoparticles was examined. The particles were characterized by UV–vis absorption spectroscopy. The techniques of

transmission electron microscopy (TEM) and dynamic light scattering (DLS) could also be used to characterize the obtained nanoparticles.

Comments: In the present protocol, water is used as an environmentally benign solvent throughout the preparation, polyphenols and other phytochemicals present in tea solution are used as reducing agents as well as stabilizers of synthesized gold nanoparticles, without the need of use of any reagent or solvent, and it provides robust shielding from agglomeration. Use of tea leaves extract in the synthesis of gold nanoparticles is so simple that no surfactant or heat is required. This is because phytochemicals present in tea serve a dual role, e.g., as effective reducing agents to reduce gold and also as stabilizers to provide a robust coating on the gold nanoparticles in a single step. Therefore, using different concentrations of tea extract in the reaction media enables variation of the size of gold nanoparticles and shows different colors of their dispersion. With no doubts, the method can be considered as an example of environmentally friendly methodology using gold solution and a single reactant easy to be obtained from natural plant product.

3.4.5.3 Synthesis of Silver Nanoparticles

Silver nanoparticles among various metal nanoparticles have received significant consideration because they are effective antimicrobial agent/s that exhibit low toxicity and have diverse in vitro and in vivo applications [42]. Drawbacks associated with physico-chemical methods of silver nanoparticles synthesis include the use of toxic chemicals, high temperature, pressure and production of hazardous by-products. Bio-inspired synthesis using microorganisms and plant extracts for preparation of silver nanoparticles have been suggested as valuable alternatives to chemical methods as it avoids the use of toxic chemicals and high temperature. An aqueous extract of *Terminalia arjuna* leaves has been used for reduction of Ag(I) and in the formation of stable silver nanoparticles, being tested their effects as antimicrobial agents. Arjuna tree is 20–30 m tall evergreen with spreading crown and drooping branches belonging to Combretaceae family distributed in India, Sri Lanka, Myanmar and its leaf extract contains leucoanthocyanidins and hydrolysable tannins. The method used is simple, one-pot, clean and requires no hazardous reactants and is advantageous in large-scale production of silver nanoparticles.

Green methodology [43]: About 20 g of fresh clean leaves was treated in 100 mL double distilled water at 60 °C for 1 h and filtered through Whatman filter paper. The filtered extract was stored in refrigerator at 4 °C for further use. 1.0, 2.0, 3.0, 4.0 and 5.0 mL of leaf extract were added separately to 10 mL aqueous silver nitrate solution (1 mM) taken in separate beakers at room temperature. The solution was kept in a dark chamber until the color of the solution changes to yellow to dark yellow. After 15 min, the solution turns yellow to yellow–red or dark brown indicating the formation of silver nanoparticles. The bioreduction of silver ions was monitored by UV spectroscopy after periodic sampling. The silver nanoparticles were also characterized by various other techniques viz., FTIR spectroscopy, DLS and TEM. It was confirmed that silver nanoparticles functionalized with biomolecules are present

in the natural aqueous extract and are themselves acting as capping agents, thus stabilizing the nanoparticles.

Comments: Silver nanoparticles have been successfully synthesized by a simple, fast, cost-effective, eco-friendly method. As the silver ions are reduced, silver atoms begin to aggregate, forming well-defined nanoparticles in the presence of leaf extract. Therefore, using different concentrations of extract in the reaction media enables the control of the size of silver nanoparticles and, as a result, the colors of their dispersion. The synthesized silver nanoparticles showed efficient antimicrobial activities and the method claims a potential use in medical applications. Once again, this experiment shows the tremendous capabilities of the use of natural and simple products to obtain sophisticated high technology nanoparticles with well-defined characteristics.

3.4.6 Waste Minimization Through Miniaturization

Miniaturization is a valuable analytical tool that efficiently contributes to greening the analytical process by reducing the amount of solvents and reagents involved in the analysis and reducing also the amount of analytical synthetic wastes. Additionally, miniaturization is an excellent alternative for dealing with size-limited samples, when the relevant processes take place in times less than those involved by traditional methodologies and when using separation techniques with limited sensitivity due to their reduced loading capacity. In this section, three analytical approaches will be depicted on the basis of strategies to miniaturize the procedures by reducing the dimensions of the systems used earlier.

3.4.6.1 Determination of Trace Mercury in Milk

Determination of low concentrations of mercury in milk requires the use of highly sensitive analytical procedures such as atomic fluorescence spectrometry (AFS). Atomic fluorescence is the optical emission from gas phase atoms that have been excited to high energy levels by absorption of specific electromagnetic radiation. The AFS is a simpler process than the molecular fluorescence because of the absence of molecular transitions and the resonance between the excitation and emission wavelength, 254 nm for Hg. Mercury in milk can be present as Hg(II) or H_3CHg^+ species. So, it is necessary to treat the samples to obtain an acidic solution of mercury ions. Sonication of milk at room temperature with aqua regia (HCl:HNO_3 in 3:1, *v/v*) for 10 min is enough to extract Hg from the milk. The addition of various reagents before dilution provides an acid slurry of partially deproteinated milk suitable to feed into the AFS system [44].

Green methodology [45]: 2 mL milk sample and 2 mL aqua regia were taken in a vessel. After shaking in an ultrasound water bath for 10 min, 0.5 mL of antifoam A, 2.5 mL of 10% (*m/v*) hydroxylamine solution and 6.25 mL of concentrated HCl were added to the mixture. Then 2 mL of 0.1 M KBr and 2 mL of 0.02 M $KBrO_3$ were

also added and the mixture was diluted to 25 mL. Finally, 2.5% (*m*/*v*) $SnCl_2{\cdot}2H_2O$ in concentrated HCl was added for Hg^o generation. The resulting slurry obtained was directly introduced in the AFS system (see Fig. 3.3). Mercury concentrations in milk samples were calculated by interpolation of the sample signals in a calibration line obtained by the measurement of Hg solutions from 0.02 to 1 μg L^{-1} Hg(II) in the same experimental and instrumental conditions as the samples. The liquid effluent obtained from the CV-AFS system is very acidic. So, the merging of this waste with a solution of Fe (III) and NaOH provides the online co-precipitation of the heavy metals remaining in solution and a neutralization of the waste acidity, moving from an acid waste to a clean waste.

Comments: The method has been designed to feature different key aspects of a green analytical method viz., use of less toxic reagents, room temperature treatment of samples, minimization and detoxification of analytical wastes. The developed experiment can be employed to introduce green analytical chemistry principles to students based on the determination of traces of mercury in milk by AFS and the online management of analytical wastes. Although uses of reagents like $SnCl_2$, $NH_2OH{\cdot}HCl$ are corrosive, cause burns to any area of contact and harmful, if swallowed, this laboratory experiment gives the students hands-on experience in the operation of an AFS in an experiment that uses an alternative environmentally friendly protocol with the fast and sensitive method of determination and deactivation of toxic wastes.

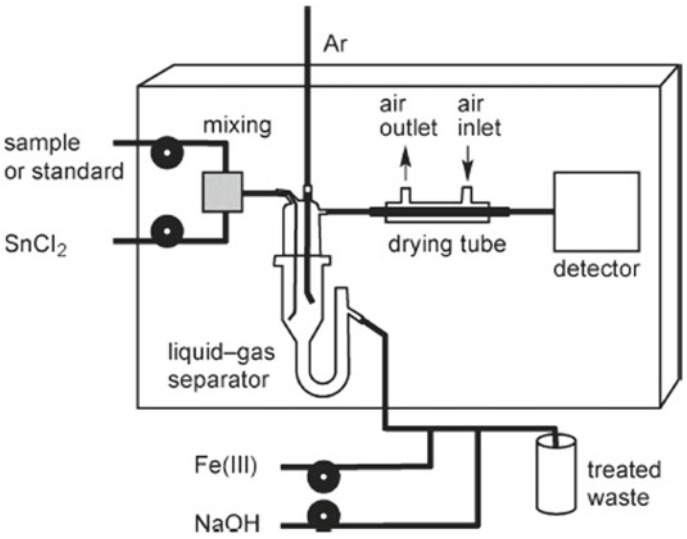


Fig. 3.3 Schematic diagram of CV-AFS system for determination of Hg in milk. Reprinted from Ref. [45], copyright 2011, with permission ACS from J Chem Ed

3.4.6.2 FI Spectrophotometric Determination of L-Ascorbic Acid

The versatility and simplicity of the flow injection analysis (FIA) technique with spectrophotometric detection allow its adaptation with better flexibility for carrying out enormous chemical processes at relatively low cost to the different requirements of a variety of analytical problems. For example, L-ascorbic acid (vitamin C) is necessary in redox processes taking place in biological cell [46]. A green spectrophotometric method for the determination of L-ascorbic acid in biological tissues by flow injection analysis has been reported. The procedure is based on the reaction of the analyte with Fe (III) and 2,2′-dipyridyl. The use of FIA permits to scale down the amounts of reagents and solvents and to reduce the direct contact of operators with the chemicals, thus reducing risks. On the other hand, automation of analytical processes permits to merge the reagents just before their use, thus providing additional reductions of reagents consume and solutions disposal, because stock solutions, non-merged with samples, can be stored and used in several working sessions.

Green methodology [47]: By using a two lines flow injection (FIA) manifold, 100 μL sample solution containing 1–20 mg dm^{-3} of L-ascorbic acid was injected into deionized water carrier and subsequently merged with a stream of Fe (III)-2,2′-dipyridyl reagent. Product of reaction was transferred to the spectrophotometer flow cell and the absorbance read at 510 nm. The flow injection assembly included a multichannel peristaltic pump, a laboratory-made rotary injection valve with exchangeable sample loops. The polyvinyl chloride (PVC) tubing used (0.7 mm i.d.) was connected with perspex connectors. 3.6×10^{-3} M Fe^{3+} and 0.25% 2,2′-dipyridyl solutions, injection rate of 40 samples h^{-1} was chosen as the best condition for measurements in the concentration range of 0.5–20 ppm ascorbic acid with a detection limit of 0.2 mg dm^{-3} and relative standard deviation (RSD) values of 1.2% for $n = 15$ independent determinations.

Comments: The development of FIA commonly applied in analytical chemistry offers immense possibilities for automation of trace analysis. The described method for the determination of L-ascorbic acid in natural samples is green, fast and convenient in comparison with the conventional method. Additionally, reagent consumption is minimum, precision and reproducibility of the adopted spectrophotometric systems are very good. The method demonstrates the development of greener concepts in FIA methodology which minimizes both reagents consume waste production. So, it is an easy-to-make experiment to discuss with students the advantages of reducing the contact of operators with reagents and samples in order to reduce mistakes, based on contaminations or analyte losses, and to avoid operator risks, being also a good way to provide fast and precise measurements.

3.4.6.3 Solid Phase Microextraction of Copper in Biological Fluid

Solid phase microextraction (SPμE) finds increasing applications in sample preparation step before chromatography determination of analytes in complex samples with reduced concentration levels. This technique allows for integrating operations,

such as sample collection, analyte extraction, matrix removal and clean-up and analyte enrichment above the detection limit of a given measuring instrument. SPμE has been applied [48] to reduce the limitations inherent in solid phase extraction and liquid–liquid extraction classical methodologies. A miniaturized SPμE in a micropipette tip filled with activated carbon cloth (ACC) attached with a syringe as the sorbent tool has been used for extraction and preconcentration through adsorption–desorption experiments. The variables influencing the separation/enrichment efficiencies of the desired SPμE procedure were investigated and optimized. Finally, under the best experimental conditions, a green method was applied for the preconcentration/separation of Cu^{2+} in serum samples prior to its determination by flame atomic absorption spectrometry (FAAS).

Green methodology [49]: A polypropylene micropipette tip (with a volume of 100 μL) was washed with distilled, ultrapure water and ethanol sequentially, and then dried at room temperature. The dry micropipette tips were packed with ACC (0.03 g) and connected with a syringe. Prior to extraction, the ACC in the micropipette tip was conditioned by drawing and dispensing repeatedly with acidic ethanol (0.2 mL HNO_3 in ethanol in 1: 10, *v*/*v*) followed by distilled water to remove the co-adsorbed matrix materials from the extraction system. 5 mL of acid digested serum sample portions were taken in a 25-mL-PTFE flask, 1 mL of 4×10^{-3} mol L^{-1} of oxine was added and the pH was adjusted to 6, using 0.1 mol L^{-1} of NaOH solution. The solution was then drawn into the conditioned micropipette tip syringe and dispensed back into the same sample flasks by pulling the plungers back and forth. These two steps were referred to as one drawing/dispensing cycle. Adsorption of Cu^{2+} on the ACC in the syringe tip was performed in the range of 2–8 drawing/dispensing cycles. Finally, analyte retained on ACC was eluted from the tip with 100–200 μL of 2.0 mol L^{-1} of HNO_3 in ethanol into a vial using 2–5 drawing/dispensing cycles. A 100 μL aliquot of eluent was aspirated by using a microsample injection system to FAAS. To reuse the syringe for subsequent analysis, the solid phase was regenerated by passing 5 mL of 2.5 M HNO_3 and then distilled deionized water. The analytical characteristics of the method are presented in Table 3.2.

Comments: The SPμE reduces the consumption of acids and solvents, which makes it more environmentally friendly than classical SPE. The method of deter-

Table 3.2 Analytical characteristics for the determination of copper in serum samples by FAAS after SPμE with activated carbon cloth

Parameter	Value
Concentration range (μg L^{-1})	5–75
LOD (μg L^{-1})	0.36
Correlation coefficient	0.997
RSD (%)	3.7
Enrichment factor	56
Recovery (%)	99.1 ± 0.8

mination of Cu^{2+} in serum samples exhibits the advantages of simplicity, economy, easy to control and could be potentially applied as an alternative tool for preconcentration and analyzing trace levels of Cu^{2+} in biological matrices coupled with FAAS. The green method is more useful than conventional column and batch techniques, reduces the risk of contamination or sample loss and is much cheaper than the use of online methods. So, the aforementioned experiment will take advantage on the simultaneous introduction of microscale assays together with the use and reuse of solid phases in sample preparation.

3.4.6.4 Determination of COD in Waste Water

Chemical oxygen demand (COD) is a common parameter in evaluating the degree of water pollution. The COD or oxidizability of organic matter contained in waters is usually determined as the number of oxygen equivalents consumed in the oxidation of organic substances by strong oxidizing agents such as potassium dichromate or permanganate which requires a time-consuming process of refluxing waste water samples in sulfuric acid medium. Presence of highly poisonous mercuric chloride and expensive silver sulfate catalyst is also essential mandatory in conventional methods [50]. A green method for the determination of COD has been proposed using a nano-Cu modified glassy carbon electrode (GCE) as an electro-catalytic sensor, where measuring principle is based on oxidation current of organic compounds in waste water.

Green methodology [51]: ***Step I/Preparation of nano-CuGCE***—Prior to electrodeposition, a GCE with 3 mm diameter was polished with 0.05 mm alumina slurry on a polishing micro-cloth and rinsed thoroughly with ethanol and doubly distilled water to give a clean surface. Then the copper-sensing film was electrodeposited on the surface of the GCE under potentiostatic conditions at a constant potential (deposition potential) of 0.6 V for a certain time (deposition time) such as 60 s in 50 mM $CuSO_4 \cdot 5H_2O$ containing 0.1 M $NaClO_4$. The resulting nano-Cu modified GCE was rinsed with doubly distilled water to remove any adsorbed species before use. A bulk copper film was electrodeposited by fixed potential electrolysis in an unstirred solution. The solution consisted of 0.05 M $CuSO_4$ and 0.1 M Na_2SO_4. The electrolysis was conducted by fixing the potential at 1.0 V for 20 min. Electrodeposition of copper under this procedure has been well-documented to lead to formation of macro-structured copper film.

Step II/Determination of COD in real water samples using nano-Cu/GCE—Prior to measurements, real water samples were filtrated using Sartorius filtration system (Goettingen, Germany), equipped with cellulose nitrate filter paper (pore size ~0.2 mm). The anodic (LSV) linear sweep voltammetry peak current was determined by using the standard addition method. Standard COD solutions of different concentrations in the range of 20–40 ppm were added to a series of 100 mL flasks, each one containing 5 mL of filtered water sample. Then, the volume of each flask was made up to 100 mL using 0.075 M NaOH. The testing solution was placed in an electrochemical cell for the determination of COD.

Nano-Cu particles in alkaline media can electro-catalytically oxidize a wide range of organic compounds mainly responsible for the COD measurement of water samples. This behavior is typical to that expected for electro-catalytic oxidation in the following two steps:

$$\text{(electronic step): } Cu^{II}(s) + OH^- \longrightarrow Cu^{III}OOH(s) + e$$

$$\text{(chemical step): } Cu^{III}OOH(s) + \text{organic(red)} \longrightarrow Cu^{II}O(s) + \text{organic(ox)} + H_2O$$

The analysis of real samples was carried out by using both, green electrochemical and conventional titrimetric methods. Results obtained are in good agreement as it can be deduced from the equation $y = 0.99\ x + 2.14$ with a coefficient of determination $R^2 = 0.993$, obtained for a series of six water samples with COD values between 40 and 120 mg L^{-1}. Additionally, the relative errors between samples of the COD determination were in the range of 4.2–6.0%, thus evidencing that the two methodologies provided comparable results.

Comments: The main advantage of the nano-Cu/GCE for COD determination is the simplicity of sample preparation and low cost of the device. Owing to the high catalytic activity, the nano-Cu film greatly increased the sensitivity of COD detection. Because of the high electro-catalytic activity, excellent reproducibility and stability, this method can be used for routine analysis of COD in real water samples. Under optimized conditions, the developed nano-Cu-based COD sensor exhibits a linear range of 15–629.3 mg L^{-1} and a detection limit as low as 1.7 mg L^{-1}. No doubt, the safe electro-catalytic sensor method is satisfactory for the COD determination in real water samples and is more environmentally friendly than the conventional method. So, this kind of experiments could be of a great importance to introduce the students in the world of electrochemical sensors and the advantages of working with reduced size samples and using portable instrumentation.

3.5 Future Trends in Green Analytical Chemistry

The debate of incorporation of sustainability issues into curricula of university students has found an important position in recent years. At the center of this debate are university teachers and scholars who, depending on academic freedom to select the contents of courses in different countries, can decide what and how to teach, albeit with varying degrees of guidance from professional bodies, public and student opinion and the government. To shift from the education about sustainability (with a focus on knowledge) to the education for sustainability (with a focus on enhancing students' knowledge, skills, values and necessary capabilities to achieve it) and susceptive learning, of values and attitudes, is highly problematic for higher education, yet is at the heart of 'education for sustainability [52].' Because of that, we are absolutely convinced that an approach based on the use of green laboratory experiments could be really useful to advance in green analytical and synthetic chemistry.

Nevertheless, green chemistry represents the pillars that hold up our sustainable future. It is imperative to teach the value of green chemistry to tomorrow's chemists. So, it is very important that the green chemistry education material must be prepared for different levels of education in different countries which is expected to develop an environmentally friendly culture at an early stage of learning. Thus, the success of green chemistry depends on the training and dedication of a new generation of today's students who at all levels have to be exposed to the philosophy and practice of green chemistry. It is true that the greatest challenge of green chemistry is to implement its principles into practice. The present chapter highlights various laboratory strategies that can be adopted in the green chemistry curriculum to address the pollution preventive measures promoting the use of energy efficient reactions that utilize benign and bio-renewable raw materials in a relatively safer reaction media, thus encompassing the principles of green chemistry [17]. The implementation of such experiments as part of green laboratory exercises will help to raise a generation of chemists who are familiar with the concept of sustainable chemistry from early stages which in turn should be of immense benefit for the society. It may be remembered that green chemistry is a tool, along with many others, used to build a sustainable society. If we are convinced that green analytical chemistry is a challenge for the future of chemistry, it is of great importance to make an extra effort to transmit these ideas to the students in order that they could incorporate the principles and strategies of green analytical chemistry to their future activities [3]. In fact, an improved education through green analytical and synthetic chemistry for the future professionals in the field of chemistry is the key for achieving sustainable development of the world.

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Chapter 4
Mass Spectrometry-Based Direct Analytical Techniques

Renata Marcinkowska, Klaudia Pytel and Bożena Zabiegała

Abstract Direct analysis of samples is considered as one of the most environmentally sustainable solutions in analytical chemistry. In the ideal case, such solutions do not require sample preparation and analytes separation steps, therefore do not consumpt harmful substances (or consumpt only minimum amounts of them) and do not generate hazardous waste. Technical solutions for direct analysis also offer miniaturized and field-portable analyzers or allow for remote measurements, posing no risk for human health. Among available direct analytical techniques, mass spectrometry-based solutions evolved tremendously in recent years and therefore gained a huge popularity, which fostered their implementation in a wide range of areas of interest. In this chapter, MS-based direct analytical techniques providing environmentally friendly analysis of samples of even complex matrix composition were discussed. They were characterized in the context of principles of measurement, advantages, and limitations as well as fields of their applications. Also, important aspects of their applicability were highlighted. Finally, some future trends in direct analysis field were indicated.

Keywords Direct analysis · Mass spectrometry · Real-time analysis · Ambient mass spectrometry · DART-MS · DESI-MS · PTR-MS · SIFT-MS · LA-ICP-MS · SIMS

4.1 Introduction

The concept of Green Chemistry has been introduced to the wider audience at the beginning of the 1990s. Its principles are considered as a guide for chemists to design the process in a way of reducing or totally eliminating the use and generation of hazardous substances [1]. Later on, several research teams have formulated the main

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J. Płotka-Wasylka and J. Namieśnik (eds.), *Green Analytical Chemistry*,
Green Chemistry and Sustainable Technology,
https://doi.org/10.1007/978-981-13-9105-7_4

strategies of implementation of green chemistry principles into analytical chemistry practices [2–4]. One of the most important strategies in this context is the direct measurement of untreated samples, often considered as the greenest approach. This is related to the fact that by excluding sample preparation step, an analytical procedure involves no or minimum organic solvents and/or other toxic reagents and generates no or little amount of waste. Direct techniques of analysis often serve for in situ or *online* measurements which are also advised as green analytical chemistry (GAC) strategies [5].

Tobiszewski and Namieśnik [6] discussed in 2012 direct techniques of analysis, indicating potentiometry, graphite furnace atomic absorption spectroscopy, inductively coupled plasma techniques, neutron activation analysis, X-ray fluorescence, immunoanalysis, and direct sample injection into chromatographic system as environmentally sustainable in the context of GAC.

One of the major tools applied to direct analysis of gas, liquid, and solid samples are mass spectrometry (MS)-based techniques. Mass spectrometry provides highly selective and sensitive identification of a wide range of analytes. For analytical chemistry purposes, it is most widely applied when coupled to a defined chromatographic technique. Samples may be injected to such systems either after multi-step, simple (e.g., dilute and shoot approach) or without any pre-treatment. The second and third types are recognized as direct injection chromatography. Such approach is considered as simple, fast, and environmentally friendly; however, it is limited by several shortcomings: relatively slow and expensive measurements, instrument contamination, and severe difficulties if the sample is characterized by complex matrix composition [7]. Also, in case of direct injection liquid chromatography, organic solvents are used as a mobile phase component; thus, it is to some extent harmful to the environment. For these reasons, evolution in the field of analytical chemistry has been targeted as techniques enabling rapid, accurate, and reliable analysis of different types of samples in their native forms posing reduced or no risk to the human health and the environment.

A great development in the field of MS, which has been observed in recent years, has significantly contributed to the progress in direct techniques of analysis of samples characterized by complex matrix composition with no need of not only sample preparation but also analytes separation. Such solution may be considered as a greenest possible way to obtain the information on the sample components, contaminants, etc.

In this chapter, techniques of direct analysis of samples will be discussed, with a particular focus on MS-based techniques requiring no or very little sample pretreatment and no separation process. Technical background, recent developments, fields of applications as well as advantages and shortcomings of ambient mass spectrometry, techniques dedicated to real-time analysis of gaseous samples and techniques used for elemental analysis of solid samples were described and discussed. Finally, the chapter has been concluded with some remarks on present state of the art and future perspectives of MS-based direct analysis techniques.

4.2 Classification of Direct Analytical Techniques

It is a difficult task to strictly classify analytical techniques dedicated to direct analysis. Considering GAC principles, in brief, these techniques allow for obtaining information on sample composition with minimized or without solvents/reagents consumption and reduced or completely no generation of hazardous wastes. As it was already mentioned, these requirements are met in the case of (i) direct chromatographic/electrophoretic analysis with no sample pre-treatment and no analyte extraction from the matrix, (ii) direct techniques of analysis with no sample pre-treatment, no analyte extraction from the matrix, and no separation process.

Direct techniques of analysis are also considered as techniques dedicated to: (i) in situ/*online* measurements, without the need of sample collection; or (ii) *at-line* measurements, for analyzing samples just collected from technological line. These direct techniques, next to providing fast and environmentally sustainable analysis, are also recognized as relatively low-cost solutions in environmental analytics because they are now available as miniaturized and field-portable analyzers. Field analysis has been significantly improved in recent years by the introduction into practice techniques of real-time measurements, which enabled the monitoring of constant changes and reaction, for example, in atmospheric and indoor air. Direct techniques of analysis are also recognized as those offering remote measurements of a target sample by a device without physical contact. An important feature of some direct techniques is that they provide non-destructive or quasi-non-destructive measurements. This is especially important in case of archeological samples, like, for example, objects of cultural heritage and medicinal analysis, where non-invasive measurements are highly desirable.

Some direct techniques allow for so-called rapid screening providing semi-quantitative data required when decision needs to be made fast. These techniques are currently widely applied in clinical (e.g., ELISA test) and environmental chemistry (e.g., colorimetric tests) [3]. Other direct techniques are aimed at obtaining as much as possible information on chemical composition of the sample keeping the analytical procedure fast, simplified, and environmentally sustainable at the same time. Because such approach often results in obtaining a huge set of analytical data, especially if the analyzed sample is characterized by complex matrix composition; there is a need of applying proper tools in order to evaluate them. For this reason, chemometrics is considered in some cases as a complementary discipline to direct analysis. Similarly, bioinformatics is essential in case of direct metabolomics.

A brief classification of direct techniques of analysis with relevant examples has been schematically presented in Fig. 4.1. It can be seen that some techniques meet several requirements and may be applied for different purposes. Moreover, it is also visible that MS-based techniques play an important role in the direct analysis of untreated samples.

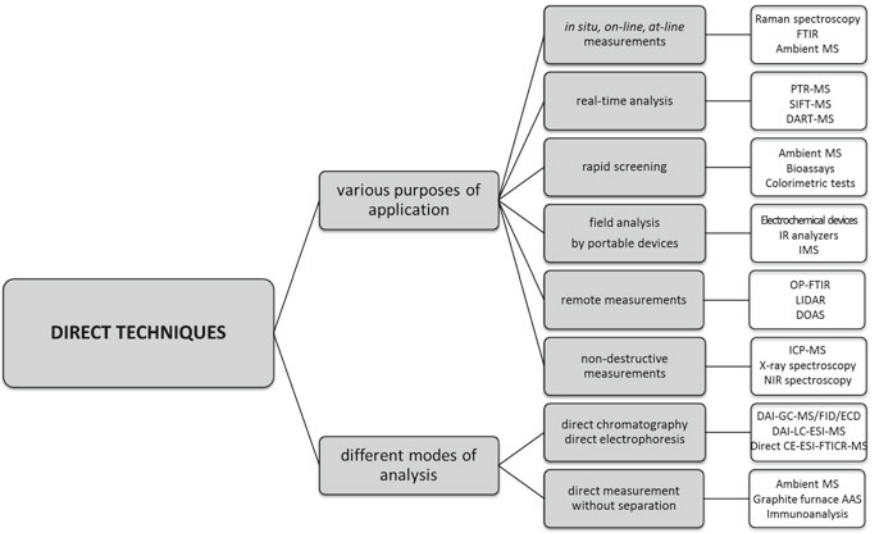

Fig. 4.1 Classification of direct techniques of analysis with selected literature examples

4.3 Mass Spectrometry-Based Direct Techniques of Analysis—The Evolution in Technical Solutions and Applications

The progress in the field of direct analysis was significantly supported by the development and evolution of MS techniques (see Fig. 4.2).

From the first laboratory applications of MS at the beginning of twentieth century, this technique gained extreme popularity among scientists from different field of studies. Since then, the progress which has been made in MS-based techniques was tremendous and, nowadays, they contribute invaluably to numerous scientific achievements. By the 1980s, the ionization process relied on gas-phase collisions between the analyte and a charged particle [8]. Understandably so, the analysis of solid and liquid samples with the use of MS was significantly limited because of the need for transition analytes from condensed to gaseous phase. The development in ionization techniques and introduction into analytical practice of electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI) was a milestone in the progress toward new and advanced MS-based analytical techniques, as it solved the problem of getting the liquidus sample into the vacuum of the spectrometer in the form of ions suitable for mass analysis [9]. These techniques, however, still required a sample preparation process in case of solid and complex liquid samples. This issue strictly hindered the application of MS-based techniques to direct analysis.

The methods of desorption/ionization of molecules under vacuum by energetic charged particles or laser beams appeared to be a partial solution to this problem. Their development is recognized as a critical progress in analysis of liquid and

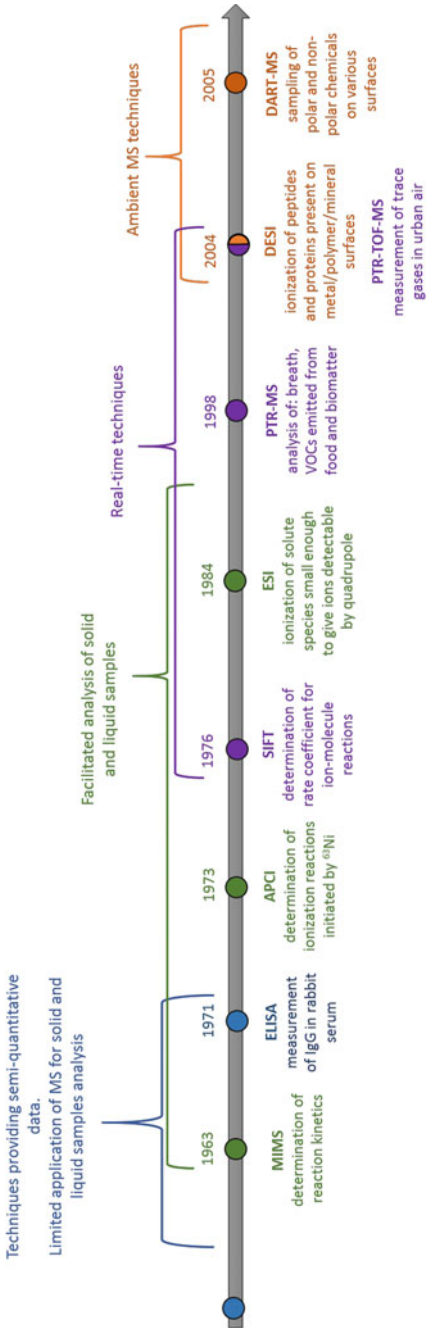

Fig. 4.2 Timeline of the evolution of techniques dedicated to direct analysis. From the very beginning of direct measurements to sophisticated analytical techniques

solid samples by MS [10]. Relatively recently, a new solution of creating ions under ambient conditions (outside the instrument), called ambient mass spectrometry, revolutionized the way of analysis of real, solid, and liquid samples in their native form. Therefore, as it was accurately summarized by Alberici et al. [11], this development brought MS-based techniques into the "real world," which means that it allowed for the in situ analysis outside the laboratory.

An important aspect of direct MS-based analysis is a real-time measurement of volatile organic compounds (VOCs) in gaseous samples. The variety, high reactivity (short lifetime), and multiplicity of atmospheric VOCs as well as understanding their behavior and tracking their environmental fate demand highly advanced analytical instrumentation allowing for real-time direct analysis.

In case of direct elemental measurements of solid samples, an essential role is played by plasma source-based MS, which enable the vaporization of analytes directly from solids.

4.3.1 Ambient Mass Spectrometry Techniques

Ambient MS allows for the direct analysis of samples in their native form and in natural environment without any sample pre-treatment steps, thus simplifying both the workflow and use of MS instruments. An object to be analyzed is placed at the entrance of MS and analyte molecules released from the sample surface are ionized and transferred into the mass analyzer [10]. Because ESI and APCI techniques provided the foundations for ambient MS techniques, they may be categorized as [12]:

(i) ESI-related techniques: e.g., desorption electrospray ionization (DESI), electrospray laser desorption/ionization (ELDI), MALDI-assisted electrospray ionization (MALDESI);
(ii) APCI-related techniques: e.g., direct analysis in real time (DART), desorption atmospheric pressure chemical ionization (DAPCI), plasma-assisted desorption/ionization (PADI).

Two main representatives of these subgroups of ambient MS techniques, namely DESI and DART, were introduced to the wider audience in 2004 [13] and 2005 [14], correspondingly. DESI principle is "no sample preparation" version of ESI. In this technique, the surface of the sample is hit by a spray of charged droplets (usually composed of water and methanol) which desorbs organic (bio)molecules and ionizes them. The ions are further delivered into mass spectrometer by pressure differential around the interface capillary [13]. The process has been schematically presented in Fig. 4.3.

Desorption process efficiency depends on how strongly analytes are bound to the sample surface. It may be, however, enhanced by modifying the composition of the spray. MS signal intensity is strongly dependent on the geometry of the technical solution, i.e., the angle and the distances electrospray emitter-surface and surface-MS

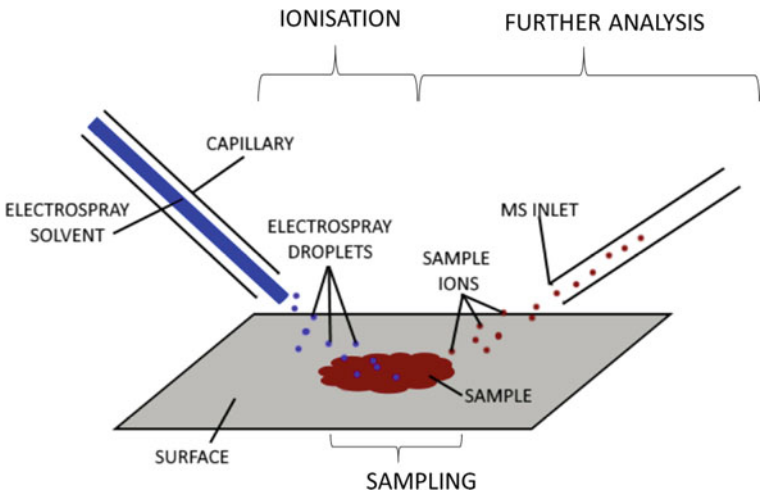

Fig. 4.3 Schematic representation of DESI technique [13]

inlet. Therefore, these technical features are often re-designed in order to improve the sensitivity of the measurements [12]. Applied in DESI desorption/ionization process is soft, thus in the mass spectra mainly molecular ions and very little fragmentation are observed [15]. In order to prevent liquid samples to be blown away from the surface by the high-velocity nebulizing gas employed during ionization process (which may result in poor signal), liquids/solvents are evaporated in the air before ionization. Another solution for avoiding sample losses is to cover a cotton swab or a filter paper with a liquid sample and further ionize the analytes [16, 17]. Mass analyzers most often coupled to DESI are high-resolution ones, e.g., quadrupole/time-of-flight [18], Orbitrap [19], or FT ion cyclotron resonance [20].

DESI-MS allows for carrying out measurements without any sample preparation, rapid and high-throughput analysis and in situ measurements with favorable analytical performance parameters—femtomole limit of detection and reproducibility in quantitative analysis (5% RSD) [12, 21]. DESI is the most often used version of ambient MS. It has been already successfully applied in such fields as biomedicine, pharmaceutics, security/forensics, and environmental chemistry. Literature examples of DESI-MS applications in direct analysis have been listed in Table 4.1.

DART-MS is another widely applied ambient MS-based direct technique. The paper with the first description of this technique was published a few months after DESI-MS was introduced into the public [13, 14]. Schematic representation of DART technique is presented in Fig. 4.4. Its principle is similarly based on picking up the analytes from the surface of the sample by ionization gas/aerosol. Additionally, it also enables the analysis of untreated samples in the open environment, maintaining sample integrity in the same time [22]. DART principle is related to APCI technique. The analytes are thermally desorbed from the condensed phase by a stream of a hot gas (e.g., helium, nitrogen, and argon) with active species formed via a glow discharge

Table 4.1 Selected literature examples of discussed in the chapter MS-based direct techniques of analysis

Category	Technique	Applications	Category	Technique	Applications
Ambient MS	DESI-MS	Biomedicine: • Determination of metabolites in urine [75] • Rat brain tissue imaging [76] • Lipids analysis [77] • Determination of xenobiotics in blood [78] Pharmacology: • Detection of anti-tumor drugs in plants [79] • Imaging drugs and metabolites in tissues [80] • Monitoring of brain lipidomic changes after morphine and cocaine administration [81] Forensics: • Analysis of gunshot residues on skin [82] • Determination of chemical profiles of banknots [83] • Detection of explosives and chemical warfare agents [84] Environmental chemistry: • Imaging of molecular signatures of plants [85] • Determination of organic acids in aerosols [86] • Analysis of immobilized organophosphates [87]	Elemental analysis of solid samples	GD-MS	Environmental chemistry: • Detection of trace radioisotopes in soils and sediments [88] • Elemental and organometallic analysis of soil samples [89] Materials science: • Determination of trace elements in high-purity metals [90] • Polymer fingerprinting [91]
				SIMS	Materials science: • Biomaterial surfaces characterization [92] • Conservation studies on museum objects [93] Biomedicine: • Tissue imaging [94] • Studies on lipid classes distribution in tissues [95]
				LA-ICP-MS	Archeology • Analysis of human dental enamel [96] • Arsenic determination in mummies' hair [97] Biomedicine • Bioimaging of metals in brain tissue [98] • Single cell analysis [99]

(continued)

Table 4.1 (continued)

Category	Technique	Applications	Category	Technique	Applications
	DART-MS	Food analysis: • Determination of mycotoxins in milk [100] • Chicken meat metabolomics [101] • Screening pesticides on fruits and vegetables surfaces [102] Environmental chemistry: • Chemical characterization of submicron organic aerosols [103] • Ozone-PAHs reaction monitoring [104] • Trace analysis of pharmaceuticals and personal care products in environmental samples [105] Forensics: • Detection of explosives in latent fingermarks [106] • Forensic drug screening [107] Biomedicine: • Identification of endogenous skin surface compounds [108] • Analysis of skin metabolome changes [109]	Real-time gas analysis	SIFT-MS	Medicine: • Exhaled breath analysis [110] • Headspace analysis of urine [111] • Antibiotic susceptibility studies [112] Environmental chemistry: • Methane [113] and hydrogen cyanide [114] analysis in air • Hydrocarbon seeps assessment [115] • Exhaust gases analysis [116]
				MIMS	Environmental chemistry: • VOCs determination in atmospheric air [117] and water [118] • Non-invasive online detection of nitric oxide from plants [119] Process monitoring: • Monitoring of biological reactions [120] • Monitoring of water solubilization of ethanol and BTEX from gasoline [121]
	PS-MS	Biomedicine: • Analysis of biofluids [122] • Analysis of tissues [123] Food analysis: • Analysis of contaminants in foods [124] • Determination of NSAIDs in edible oils [125] • Chemical fingerprinting of foods [126]		PTR-MS	Environmental chemistry: • VOCs monitoring in atmospheric air [45] • Measurement of biomass burning emissions [127] Food analysis: • Determination of odor-active compounds in cheese [128] • Analysis of volatile flavor compounds [129] • Wine characterization [130]

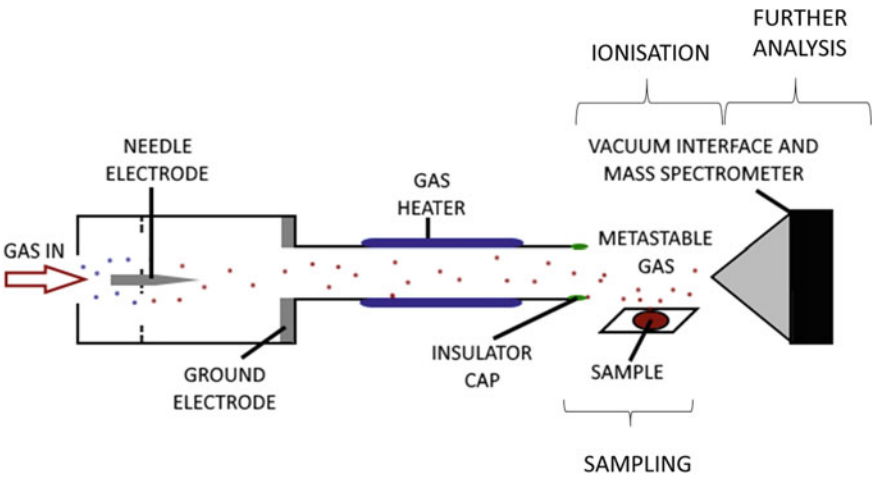

Fig. 4.4 Schematic representation of DART technique [23]

occurring in a compartment separated from the desorption/ionization region. In the sampling region, metastable species carried with the gas react with some ambient atmospheric components to form reactive species, ionizing the analytes. A membrane vacuum pump connected to the interface is responsible for the transfer of the ions through the ceramic tube from the ionization area into MS [23].

Although this ionization mechanism has not yet been fully characterized, there are already several papers which cover comprehensively the processes occurring in DART systems [24–26].

DART produces relatively simple mass spectra, dominated mainly by protonated molecules in: (i) positive ion mode, or (ii) deprotonated molecules in negative-ion mode [23]. The advantage of DART over DESI is the ability to ionize non-polar neutral species. Since the ionization in DART is by heated gas stream, there is no or very little risk of splashing of liquid samples. On the other hand, in case of DART, some volatility of the analytes is required [27], which, depending on the case, may be a limitation (e.g., in the analysis of nucleotides [28]) or an advantage (e.g., in the analysis of small molecules in high mass sample matrix [29]). DART-MS provides rapid analysis of samples in their native forms at low detection levels, however, its performance may be limited by several issues. First of all, intensity of signal is highly dependent on DART source temperature. Too low temperature results in no mass spectrum obtained; however, too high temperature may lead to the evaporation and loss of more volatile analytes [30]. Moreover, the analysis largely depends on the sample matrix, e.g., whether the analyte is on a sample surface or in the whole volume of a sample [31]. It has been also emphasized in the literature that DART may be provided exclusively by Jeol or IonSense companies which in perspective may limit the development of DART technique if there will be no competition [27].

DART-MS found numerous applications in different areas, such as clinical and pharmaceutical analysis, natural products studies, security/forensics, food quality and safety, and environmental analysis. Literature examples of the technique applications in direct analysis have been listed in Table 4.1.

Paper spray ionization (PSI) technique is other interesting solution in ambient mass spectrometry, also suitable for direct analysis. In PSI technique, a sample is loaded onto a piece of paper and then ionized via high voltage, applied to the wetted paper [32]. In brief, this technique may be described as paper ESI, however, a distinct advantage of PSI over this traditional ionization technique is a disposable character of paper-based sample cartridges, as well as their commercial availability, low cost, ease of chemical modification and multiple functionalities [33]. PSI has been successfully applied in the direct analysis of biological fluids and tissues, drug monitoring, and food analysis (see Table 4.1 where detailed applications are listed). Although it cannot be used in in situ analysis of, e.g., tissue samples, which may be considered as a limitation in comparison with DESI and DART, PSI has a serious potential in implementing MS analysis for point-of-care diagnosis. Some literature examples of its application in direct analysis have been listed in Table 4.1.

4.3.2 Real-Time Gaseous Phase Analysis

Trace gas analysis has been dominated over recent decades by gas chromatography techniques. Although intensive development which has occurred in case of this analytical technique enabled fully automated measurements at pptv detection limits, it does not allow for *online* monitoring of complex gaseous mixtures undergoing constant reactions and changes. To overcome this limitation, MS-based techniques have been successfully implemented as *online* gas analyzers in the field studies. Applied for these purpose techniques may be based on:

(i) variants of chemical ionization and tandem mass spectrometry, e.g., APCI-MS^2 or LPCI-MS^2;
(ii) modified and specific sample introduction and ionization systems, e.g., selected ion flow tube mass spectrometry (SIFT-MS), membrane introduction mass spectrometry (MIMS), and proton transfer reaction mass spectrometry (PTR-MS).

In this chapter, real-time gas-phase analyzers listed in the second group will be discussed, whereas analyzers based on tandem mass spectrometry (first group) have been briefly reviewed elsewhere [34].

Membrane introduction mass spectrometry (MIMS) technique was applied for the first time in 1963 by G. Hoch and B. Kok. The innovation in this solution concerns new inlet system for gas spectrometers that allows to analyze gases dissolved in liquid without introducing a liquid phase into mass spectrometer [35]. MIMS technique uses a semi-permeable membrane as a direct interface between sample and mass spectrometer. The membrane interface acts to separate the bulk sample matrix from the low-pressure environment of a mass spectrometer. Depending on the permeability

of the membrane, a range of potential analytes is continuously transferred as a mixture to the ion source (see Fig. 4.5). This arrangement is widely applied in the analysis of gaseous samples [36, 37] and allows for real-time monitoring of volatile compounds with high selectivity [38].

Technical design of this instrument enables to introduce gas sample in its initial state (without pre-concentration or derivatization) and prevents returning of the sample, which minimizes the probability of sample contamination.

Since now, there are a lot of types of applied membranes, which allow to analyze a wide range of analytes. Membranes most commonly used in MIMS are made of hydrophobic polymers such as polydimethylosiloxane, but scientists are constantly working on new solutions and implementing new membrane materials as, for example, Nafion [39] or affinity membranes made of polyphenyl-ethers [40]. Solution proposed by Hoch and Kok overcomes the issue that is very common in other mass spectrum try-based techniques, namely it eliminates the possibility that vacuum in mass spectrometer can be breached. However, MIMS is relatively expensive [41] and all compounds are detected almost at the same time, which complicates the analysis of complex mixtures (where all compounds easily permeate through the membrane) [42]. MIMS technique is widely applied in the analysis of environmental samples (gaseous, liquid, and solid), in medicine and industry. Literature examples of its applications in direct analysis have been listed in Table 4.1.

Proton transfer reaction mass spectrometry (PTR-MS) technique was developed in 1998 by Lindinger and his team in order to carry out online monitoring of trace gases with high sensitivity [43, 44]. This instrument is able to monitor changes in concentration of trace organic components in gas sample over very small periods of time (1–10 s), which enables to obtain very precise picture of analytes concentration, even if it is rapidly changing, for example, very close to the emission source [45]. PTR-MS is composed of an ion source, which is a hallow cathode that produces H_3O^+

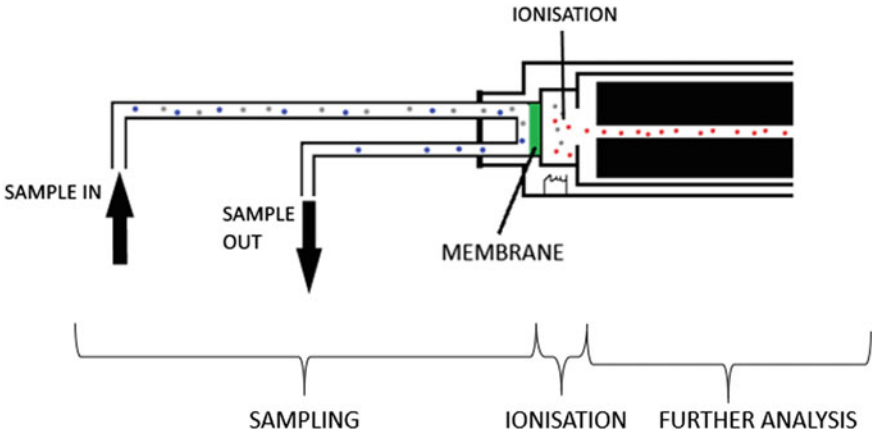

Fig. 4.5 Schematic representation of MIMS system with membrane placed near the ion source [38]

reagent ions from water. Reagent ions and sample molecules are transported through the drift tube in which a controlled proton transfer reaction occurs. All compounds that are characterized by proton affinity higher than water (7.2 eV) will undergo this reaction and will be ionized and detected. Ionized sample molecules are then transported into the mass analyzer where they are divided according to their m/z [43, 46]. Schematic representation of PTR-MS instrument is given in Fig. 4.6.

Simplicity of PTR-MS operation relies on the fact that chemical compounds are determined only on the basis of their nominal m/z. On one hand, it facilitates analysis to a high extend, but on the other hand, it decreases specificity of this device [47] which means that quadrupole mass analyzer is not able to differentiate of isobaric compounds [48]. In order to overcome this limitation, in 2004, Blake and his team [49] developed for the first time a PTR-MS system equipped with time-of-flight (TOF) mass analyzer.

PTR-MS technique serves as a superior solution for gas sample analysis in comparison with traditional chromatographic techniques. First of all, it enables to obtain results showing concentration changes over a time, which is not possible in case of off-line techniques application. Another advantage is that this instrument is designed to be relatively easy in transportation, so analysis can take place in any desired place, even, for example, in aircraft cabins [50]. PTR-based devices are also characterized by high mass resolution, very low detection limit and high sensitivity, especially PTR-TOF-MS, which enables to carry out analysis of ultra-trace components (at the

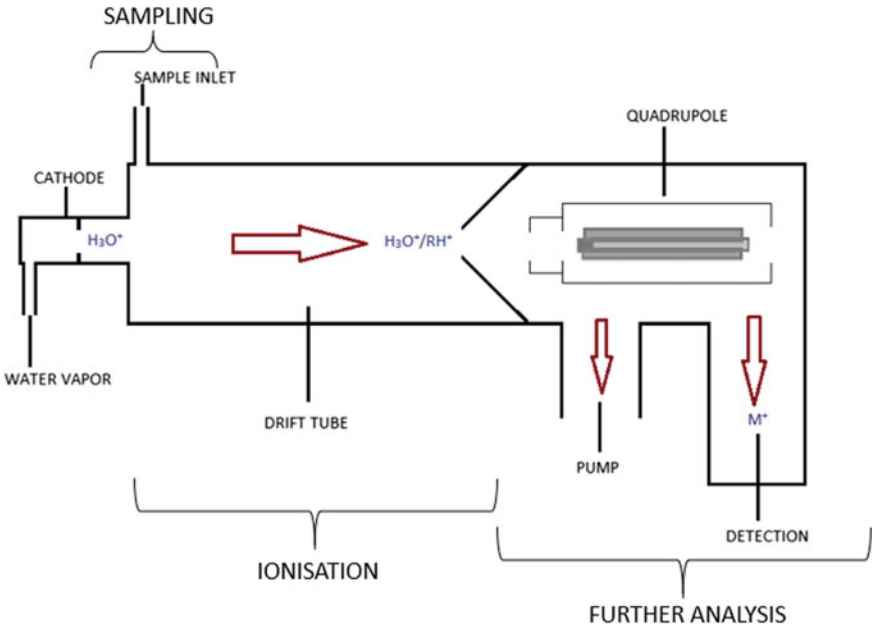

Fig. 4.6 Schematic representation of PTR-MS system [43]

levels of pptv) in a gas sample [44]. However, PTR-TOF-MS is unable to differentiate isomers. Moreover, it was found that during analysis by PTR-MS, some compounds, especially those highly reactive, undergo fragmentation despite the fact that proton transfer reaction is considered as "soft type" of ionization, which in general makes the interpretation of results difficult. Another drawback of PTR-MS technique is that in case of analytes of proton affinities close to water (e.g., formaldehyde); there is a risk of back reactions occurring between protonated analyte and water in the sample. These reactions are temperature-dependent and take place at a high rate during PTR-MS analysis, which severely hinders the measurement of some compounds [51]. PTR-MS has been applied so far in fields such as environmental, medical, and food analysis. Literature examples of its applications in direct analysis have been listed in Table 4.1.

Several issues mentioned in case of PTR-MS may be avoided by the application of another real-time analysis technique—selected ion flow tube mass spectrometry (SIFT). This developed over 40 years ago technique takes the advantage of chemical ionization with selected precursor ions which react with trace components of a gas sample introduced into the system [52]. The schematic representation of SIFT-MS system is presented in Fig. 4.7. Ion source produces different ion species, which are filtered by a quadrupole analyzer in order to obtain a current of ions of defined m/z. This ion beam is further introduced into a fast-flowing carrier gas (most commonly helium) and runs through the flow tube of given length. At the beginning of the tube, there is a sample inlet where a gas sample is introduced into a system. Once sample and reaction ions are in the flow tube, a highly controlled reaction takes place which results in the formation of predictable analyte ions. These ions are further transferred to mass spectrometer, where they are detected and counted [53].

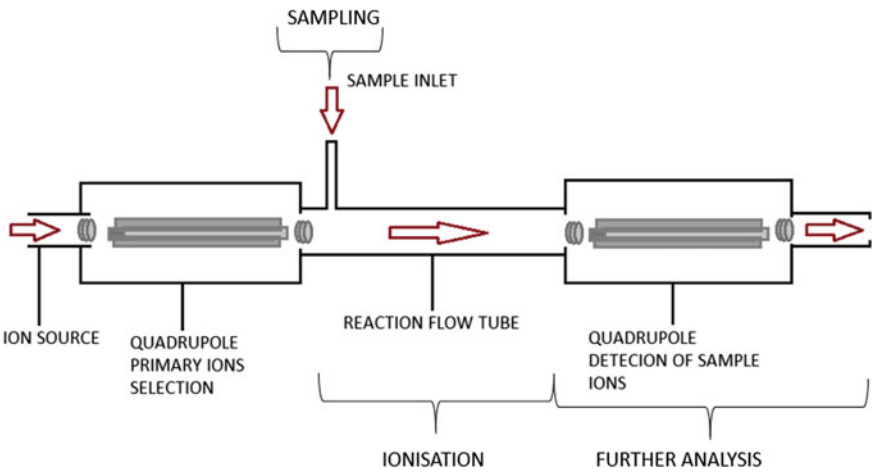

Fig. 4.7 Schematic representation of SIFT-MS instrument [57]

SIFT-MS allows for accurate, real-time, and sensitive simultaneous quantitation of trace constituents present in atmospheric air and exhaled breath [54]. SIFT is included in the group of soft ionization techniques, thus obtained spectra are characterized by reduced fragmentation. Observed degree of fragmentation in case of SIFT-MS was lower than in case of PTR-MS for the same compounds. Another advantage of SIFT-MS over PTR-MS is the wider selection of reagent ions for chemical ionization. While in PTR only H_3O^+ is utilized, SIFT offers the selection of reagent ions from H_3O^+, NO^+, and O_2^+. In this way, not only the ionization of analytes which do not react with H_3O^+ is possible but also the identification of the analyte is facilitated in case when the differentiation only on the basis of H_3O^+ reaction is impossible [55]. In most advanced technical solutions of this technique, eight positively and negatively charged ions are applied to the ionization process, which allows to produce different ions from isomeric compounds (e.g., ethylbenzene and xylene) [56]. The main drawback of SIFT-MS concerns overlapping of analyte ions in complex mixtures and limit of quantification at the level of ppbv, which may be not enough for the detection of analytes at ultra-trace levels (pptv) [57]. By now, SIFT-MS has been successfully applied in a wide range of different areas such as environmental measurements, biomedical analysis, and food science [58]. Literature examples of SIFT-MS applications in direct analysis have been listed in Table 4.1.

4.3.3 Direct Analysis of Elemental Composition of Solid Samples

The initial efforts to develop a "solid-state" ion source for MS were taken relatively lately (1960) [59] taking into consideration that first papers on MS appeared at the beginning of twentieth century. With the introduction of spark source mass spectrometry (SS-MS), it was possible to atomize and ionize solid samples by an electrical discharge or energetic spark. Although several advantages like trace multi-element simultaneous analysis, small sample amount needed, high sensitivity, precision, and accuracy, this technique still required several improvements because of the source instability. As a consequence of technical evolution in the area of direct determination of solid samples elemental composition, glow discharge mass spectrometry (GD-MS), secondary ion mass spectrometry (SIMS), and laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS) have been introduced to the analytical practice.

GD-MS is one of the well-known plasma-source-based analytical techniques dedicated to direct analysis of solid samples. GD-MS system consists of glow discharge atomization/ionization source and mass spectrometer. When the voltage applied between two electrodes in a glass tube exceeds the necessary energy to cause breakdown of the low-pressure gas, a glow discharge with various plasma regions is initiated. In GD-MS system, the sample is usually the cathode and the wall of the chamber is the anode. The atomization occurs at the surface of the cathode, whereas the ion-

ization occurs in the negative glow region of the plasma. Schematic representation of GD-MS instrument has been presented in Fig. 4.8.

Detailed information on processes occurring in the GD source was described elsewhere [60, 61]. GD spectrometers may be equipped with direct current (DC) and radiofrequency (RF) sources. DC sources are dedicated to conductive materials, so if the non-conductive material is to be analyzed, it should be mixed with a conductive one and formed into a pellet. Radiofrequency sources, however, cover the applications to both conductive and non-conductive samples [62].

Atomization and ionization processes in GD-MS systems are separated in time and space. For this reason, observed variations in sensitivity are usually minor. Moreover, there is a little matrix effect observed, thus quantification may be done without matrix-matched standards [64]. GD-MS instruments are also characterized by ease of use and straightforward data interpretation [63]. When coupled to high-resolution mass spectrometers, such instruments provide detection limits at low ppb level, or even beyond if pulsed GD is applied.

GD-MS is, for many years, the basic industrial instrument dedicated to trace elemental analysis of metals and semiconductors [64, 65]. It may be applied to bulk analysis, depth profiling (measurement of element content of a sample as a function of depth), and determination of trace elements and environmental analysis. Literature examples of GG-MS applications in direct analysis have been given in Table 4.1.

SIMS is another widely utilized example of solid mass spectrometric techniques. In this technique, ionized particles are emitted from a solid surface bombarded by energetic beam of primary ions.

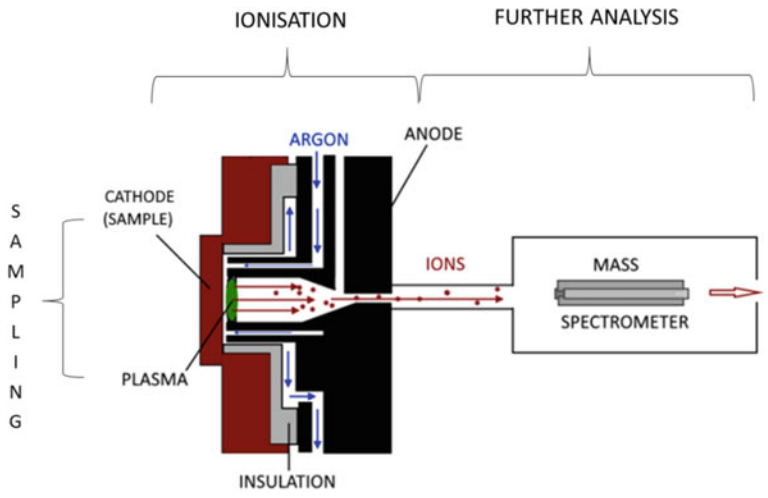

Fig. 4.8 Schematic representation of GD-MS system [65]

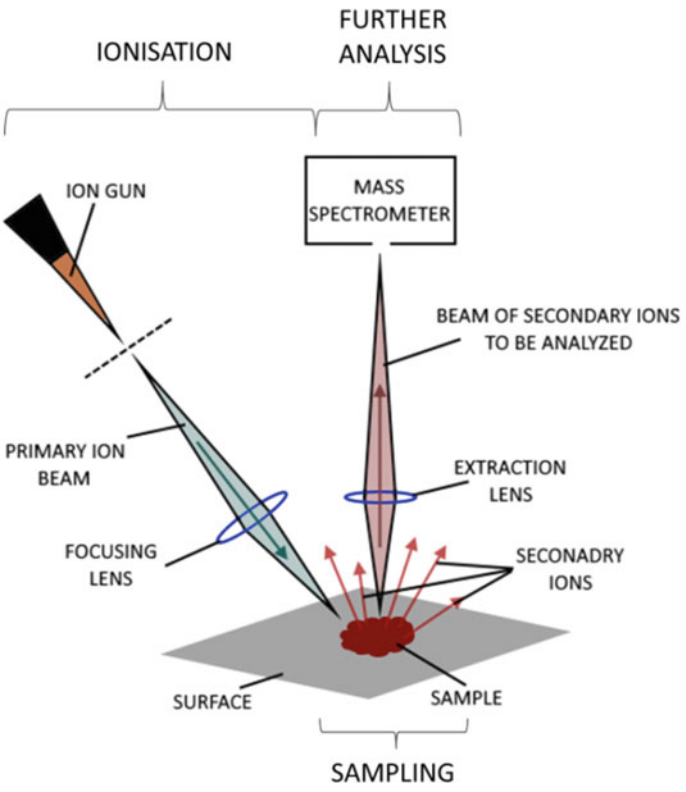

Fig. 4.9 Schematic representation of SIMS [131]

The emitted species are in majority neutral, but there is a small portion of secondary ions positively and negatively charged, which are detected and analyzed by MS (see Fig. 4.9) [66].

Depending on the primary ion dose, two SIMS modes may be distinguished: static and dynamic. In static SIMS, low primary ion flux (10 pA–5 nA) is directed at the solid surface, sputtering up to around 0.1% of top monolayer. This allows for obtaining elemental and molecular information. In dynamic SIMS, high ion flux (μA) causes rapid erosion providing elemental distribution and depth profiling [67]. SIMS technique is in principle destructive, but it has been proved that while a very low primary ion flux density (<1 nA cm^{-2}) is used, data could be obtained in a time scale shorter than the lifetime of the surface monolayer [65].

SIMS technique is highly sensitive (up to ppb) and provides excellent spatial resolution. Carrying out the depth profiling by low-energy, SIMS allows for obtaining resolutions of less than one-nanometer depth. This gives the possibility to monitor ultraslow changes of the material surface (e.g., oxidation and corrosion) without accelerated aging. It can measure trace amounts of all elements and isotopes from the periodic table. The main disadvantage of this technique is related to quantitative

analysis, which is highly affected by several aspects, e.g., matrix effects, surface coverage of reactive elements, or geometry of emission process. It has been observed that in spectra obtained by SIMS, the relative intensities of secondary ion signals do not reflect the relative contents of the species in the sample. However, relative intensities of isotopes signals reflect accurately the relative concentration of these isotopes in the sample [68]. Difficulties in spectra interpretation may be reduced by the utilization of high-resolution mass analyzers. SIMS technique is widely applied in semiconductor industry, materials science, geochemistry, biology, and forensic analysis. Literature examples of its applications in direct analysis have been listed in Table 4.1.

LA-ICP-MS is another well-known MS-based technique of direct analysis of solid samples elemental composition. In this technique, evaporation, atomization, and ionization are obtained by the use of short-pulsed high-power laser beam which interacts with the sample surface. As a result, small particles, atoms, and ions removed from the surface form an aerosol which is further transported by an inert gas stream to ICP system [69]. LA-ICP-MS system has been schematically presented in Fig. 4.10.

LA-ICP-MS does not require defined sample size and its pre-treatment. This technique provides high sample throughput, isotopic information, and the analysis of conductive, non-conductive, opaque, and transparent materials of different states and compositions (e.g., powders, soft, and hard tissues) [70]. Most often mentioned drawback of LA-ICP-MS is so-called elemental fractionation (the abundances of the ions do not represent entire composition of the sample). It is caused by preferred

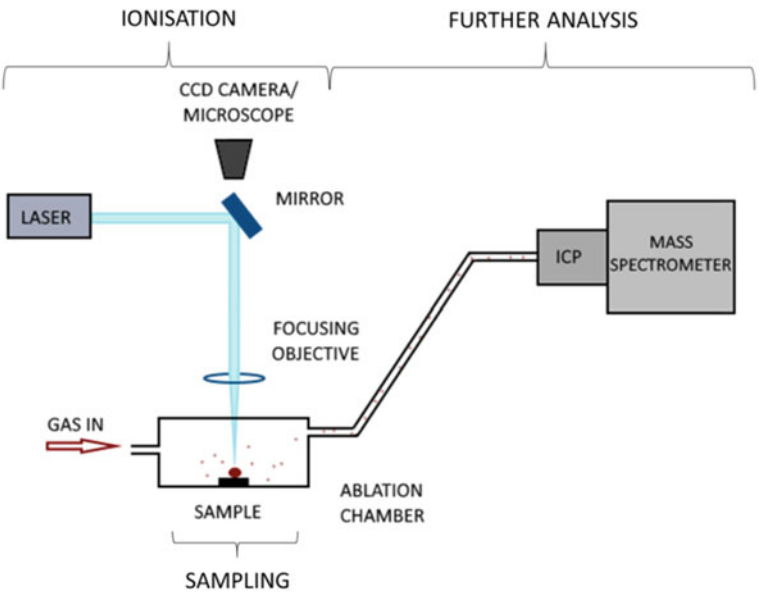

Fig. 4.10 Schematic representation of LA-ICP-MS system [132]

ablation of more volatile compounds, different gravitational settings between smaller and larger particles and less efficient vaporization, atomization, and ionization for larger particles [69, 71, 72]. Another problem of LA-ICP-MS analysis is related to different interactions between sample surface and laser beam depending on the type of the matrix, which results in various sizes and geometries of aerosol particle formation during ablation of different matrices [73]. Both elemental fractionation and matrix effects result in poor representativeness of analytical signals, therefore, hinder complete quantification. For this reason, certified reference materials and matrix-matched analytical standards are of high importance in this case [74].

LA-ICP-MS is used for major, minor, and trace multi-element determination, microanalysis, depth profiling, and elemental mapping. It found numerous applications in the analysis of environmental, biological, biomedical, geological, archeological, and forensic samples. Literature examples of the technique applications in direct analysis have been given in Table 4.1.

4.4 Summary

Eliminating sample preparation and chromatographic/electrophoretic separation from analytical procedure is a milestone in the evolution of analytical chemistry in a broad sense. It brings not only the rules of green analytical chemistry into practice and minimizes the risk of a lot of different human errors, but it also reduces significantly the time and the cost of a single analytical cycle.

The development of direct analytical techniques took advantage of established knowledge and most recent scientific achievements in the field of technical solutions and different areas of potential applications. Therefore, these techniques are now successfully adopted as tools allowing for obtaining wide and diverse analytical information. This information is the basis for further actions/decision making in many areas of human activity (medicine, environmental science, biology, biochemistry, materials science, etc.) in academic research, clinical studies, industrial product development, environmental monitoring, and homeland security.

Mass spectrometry-based techniques of direct analysis should be considered as an inevitable trend in innovative and modern analytical chemistry, likely to dominate common analytical practice in the future, which is already visible while having a look on fields, where they are currently applied and number of applications in the past years presented in Fig. 4.11.

High selectivity and sensitivity, relative simplicity of analysis, and short time needed to obtain complete information of sample composition make MS-based direct analytical techniques a superior solution in comparison with classic ones and is the driving force to further improvements in this new direction of analytical instrumentation development. Nevertheless, it should be taken into consideration that the simplicity of analysis is not equal to simplicity of data evaluation and interpretation. On the contrary, expanded datasets obtained by MS-based direct analytical techniques require the implementation of appropriate and sometimes demanding evalua-

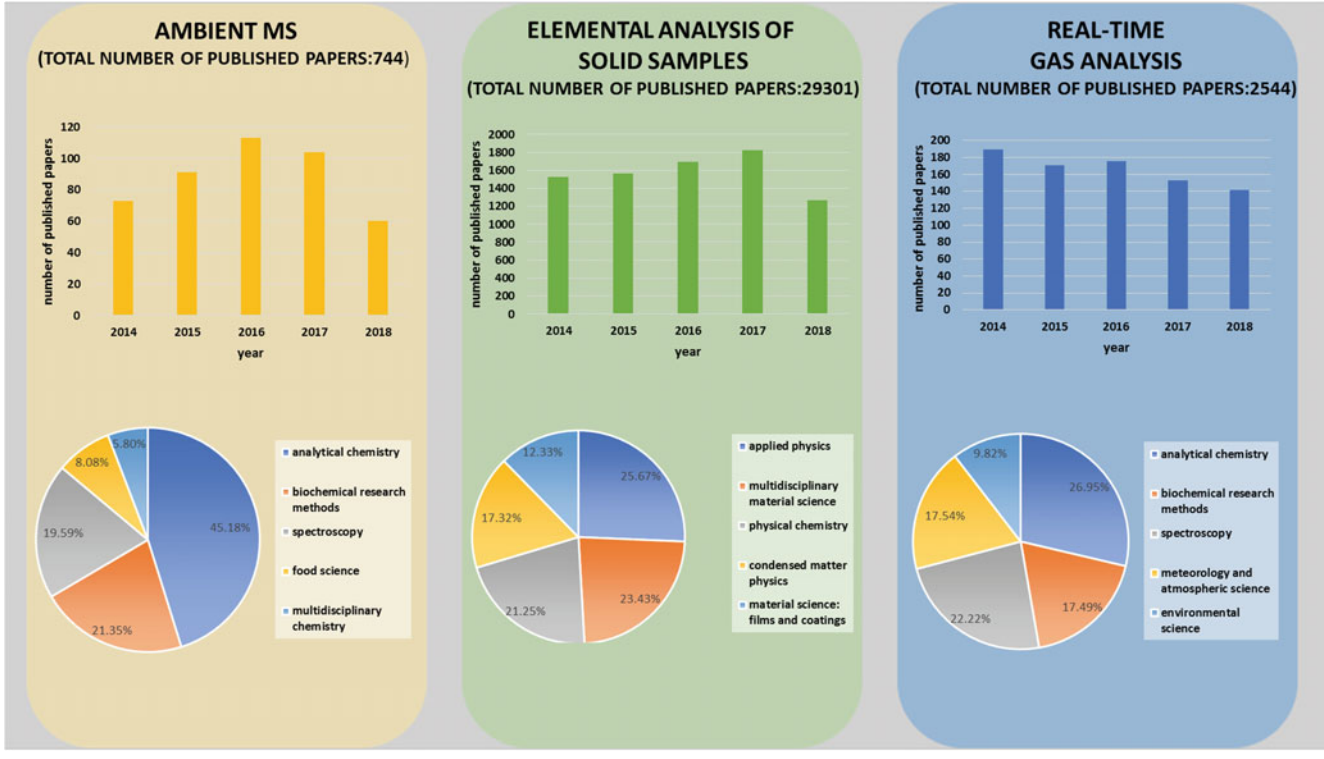

Fig. 4.11 Summary of most popular applications discussed in the chapter MS-based direct analytical techniques (source data were obtained from *Web of Science* database; abbreviated names of techniques, e.g. DART-MS, DESI-MS, PTR-MS were used for searching)

tion tools. Their incorrect application may lead to serious mistakes in interpretation and badly affect the decision-making process.

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Chapter 5
New Achievements in the Field of Extraction of Trace Analytes from Samples Characterized by Complex Composition of the Matrix

Katarzyna Owczarek, Natalia Szczepańska, Justyna Płotka-Wasylka and Jacek Namieśnik

Abstract Without any doubt, the monitoring of compounds present in samples at trace or ultra-trace level usually requires a preliminary step of isolation and/or enrichment of analytes due to the fact that majority of analytical techniques are not sensitive enough for direct determination of trace compounds. On the other hand, sample preparation is considered as crucial part of whole analytical procedures, in particular in samples characterized by complex composition of the matrices. Several new miniaturized extraction techniques have been introduced and extensively applied to different types of samples. Here, you can highlight both solid-phase microextraction (SPME) and liquid-phase microextraction (LPME). Based on the recently published literature data, this review provides an update of the most important features and the application of LPME and SPME techniques. Comparisons of these techniques have been made. Discussions on the present limitations as well as expected future trends of the green techniques of sample preparation for the improvement of the analytical determinations were made. Moreover, special attention was paid on the application of different types of microextraction procedures, used in the different fields of analytical chemistry.

Keywords Sample preparation · Green analytical chemistry · Solid-phase microextraction · Non-fibre SPME techniques

5.1 Introduction

Nowadays, analytical instrumentation is very well developed and advanced; however, sample preparation step, referring to the way in which a sample is treated prior to its analysis by the analytical instrument, is still considered as a bottleneck in analytical

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J. Płotka-Wasylka and J. Namieśnik (eds.), *Green Analytical Chemistry*,
Green Chemistry and Sustainable Technology,
https://doi.org/10.1007/978-981-13-9105-7_5

determination of trace levels of contaminants in the samples of different matrix compositions [1]. Sample preparation is achieved by several processes, which include separation and preconcentration of analytes, removal of interferences and analytes conversion into more suitable form by derivatization (if required). Due to the fact that sample preparation is a combination of different steps and process, as a whole it is the most time-consuming part in analytical method development, as well as is considered a major source of errors in analysis [2]. Hence, it is very important to perform sample preparation in a perfect way.

Due to the fact that there is a continuous demand for precise and accurate measurements of analytes, occurring at trace levels in samples of different matrix compositions, the area of a sample preparation prior to the instrumental detection is rapidly growing and many developments and new microextraction techniques are continuously introduced into laboratory practice. And although modern analytical chemistry offers many techniques and instruments for determination of target analytes in different kinds of samples, they are still some goals to achieve, which arise from assumptions of green analytical chemistry (GAC) [3]. Therefore, different ways to make an extraction process "green" are introduced to analytical practice [3, 4]. One of the ways to make extraction greener is elimination or reduction of the solvents and reagents amounts used in the analysis. If not such solution is applied, solvent recovery and reuse are recommended. Moreover, green media including superheated water, ionic liquids or supercritical fluids are preferable, rather than petrol-based solvents. In addition, the scale of analytical operations has a big impact and should be reduced, while the instruments should be miniaturized. In need to be also mentioned that such aspects as a combination of operations and automation/robotization of sample preparation are also important. Without a doubt, parameters that can enhance the effectiveness of a sample preparation such as high temperature and/or pressure, microwave and UV radiation, and ultrasound energy should be applied, because they also affect the "green" character of the whole procedure.

Taking into account the above information, recently, the sample preparation area is progressing towards several issues, mainly automation, miniaturized extraction procedures, and application of factors that enhanced extraction process. In this sense, the past decades have a rapid growth in the sample preparation area with special emphasis on simplification, miniaturization and automation of extraction procedures. Both traditional extraction and microextraction techniques have been widely adopted as sample preparation methods, and they have certain merits and drawbacks [5]. In general, traditional procedures ensure better efficiency of extraction and clean-ups as they are exhaustive in nature. In contrary, equilibrium-based techniques of microextraction are directed towards the reduced application of solvents and extracting phases, miniaturizing the extracting devices dimensions, and automated coupling with analytical instruments. These objectives are in accordance with the green analytical chemistry principles of [5]. In addition, microextraction is efficient in terms of extraction time, selectivity, sensitivity, enrichment factors and extraction performance what is presented in Fig. 5.1.

This chapter aims to give an overview of the solid- and liquid-phase microextraction techniques. This includes a discussion of the different commercial equipments and extraction formats available, method transfer from traditional sample prepara-

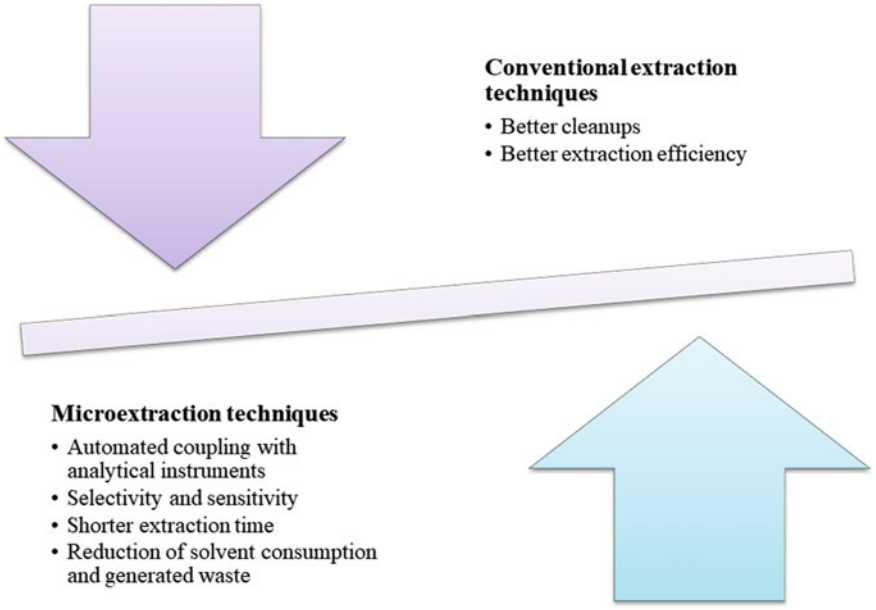

Fig. 5.1 Advantages of conventional extraction and microextraction techniques

tion methods to microextraction and performance as well as robustness for the latter type of systems. In this chapter, a role of the discussed techniques, for improving the overall efficiency of the analytical process from extraction to determination, is presented. Moreover, it can provide guidance on the selection of the technique when dealing with a particular type of extraction challenges or complex matrices.

5.2 Solid-Phase Microextraction

Solid-phase microextraction (SPME) is currently one of the most popular sample preparation techniques to be analysed. SPME was introduced into the analytical practice by Pawliszyn and Arthur in the 1990s in an attempt to redress limitations inherent in SPE and LLE. Its unquestionable advantage consists in reducing to the minimum the amount of organic solvents used; therefore, this method is considered as a green extraction technology. Additionally, the most important advantages of SPME also include high sensitivity, small sample size; simplicity, possibility of automation and possibility of integrating sampling, extraction, preconcentration and injection into a single step, which significantly reduced time and the cost of analysis [6].

The development of analytical procedures and a significant progress in the scope of material engineering have caused that the original construction solution submitted in 1990 have been materially modified over the years. These activities were focused

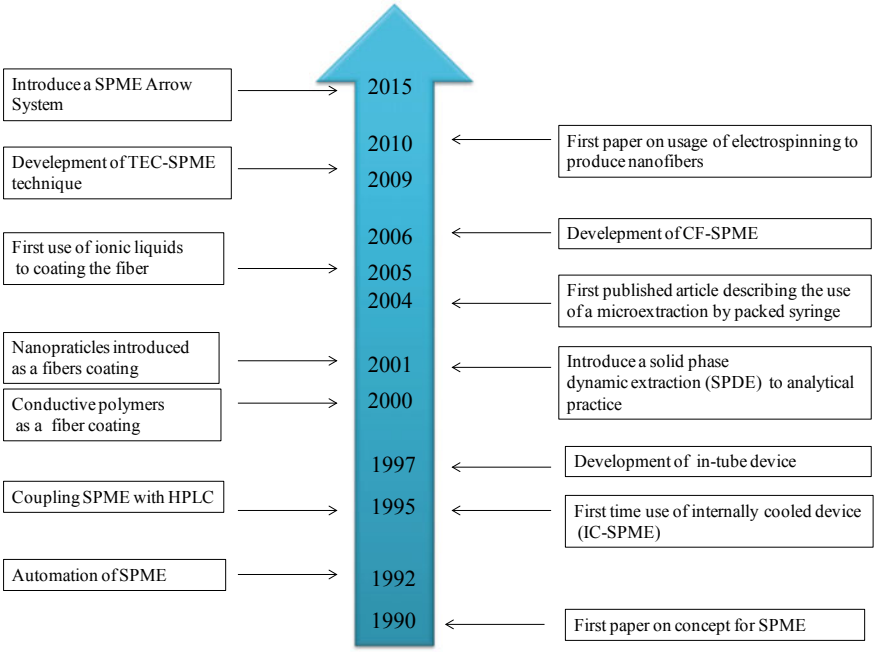

Fig. 5.2 Milestones in the development of the solid-phase extraction technique

mainly on an improvement of the extraction process efficiency and on extending the possibility of using this technology. Apart from the use of newer sorptive materials specified in the published references, there is also a series of information about new construction solutions, based on the use of various methods of sorbent location and the use of factors supporting the extraction process [7, 8]. Figure 5.2 presents the milestones in the scope of microextraction technique to solid phase. Taking into account the potential of SPME technology, it may be assumed that further modifications of a traditional approach shall be developed in forthcoming years.

5.2.1 Fibre Solid-Phase Microextraction

Without any doubts, fibre SPME has become the most popular SPME technique. Quartz fibres or fibres made of other metallic materials with a thin sorbent layer (from 7 to 100 μm thick) are the main element of SPME device. The analyte extraction process is achieved by implementing the fibre to tested gas medium or a liquid medium (direct immersion, DI-SPME) or from the headspace phase over a tested liquid or a solid medium (headspace, HS-SPME) [9]. The compounds present in the sample are divided between all the phases of the composition. The quantity of the

absorbed analyte depends on the partition coefficients between the samples matrix and the sorbent layer coating the fibre, and on the analyte affinity, contact time and other variables [4]. Published references show that the collection of the analytes from the headspace phase is preferred by the analysts than the direct contact of fibre with a sample. It is caused mainly by the fact that the risk of damage and pollution of the sorbent is significantly lower and that the process works with significantly higher selectivity. In addition, it is also possible to modify the sample (e.g. modification of pH value or derivatization). Desorption of analytes from the fibre surface can be effected in two ways, depending on the type of applied technology of the final measurement. If SPME is coupled with GC, analytes are thermally desorbed into the injection port of chromatograph, but if SPME is coupled with LC, desorption is carried out using an organic solvent or a mobile phase [10, 11].

The efficiency of the analyte preconcentration by SPME technique depends on many different parameters, such as fibre type, thickness of the stationary phase, fibre length, mode of extraction, time and temperature of extraction process, sample volume, pH value and salting out [4]. Each of the aforementioned agents has a significant impact on the effectiveness of the isolation process and analyte enrichment; however, the analysis of published data implies that the selection of the most appropriate stationary phases, out of these that are available in the market, has been of the utmost interest for years, as well as preparation of new sorbents. These activities are driven mainly by the fact that commercially available fibres have some defects, such as fragility, limited sorption capacity and significant batch-to-batch variation [12]. Thus, efforts of numerous world research teams are focused on the preparation of a fibre coating that would eliminate all these limitations, moreover would be characterized by a close relationship with collected analytes, would be stable in the whole pH range, and would have high mechanical and thermal resistance [4, 8]. Figure 5.3 presents a classification of sorbents most often described in the literature as sorbents used in SPME technique [4]. Properties of individual modern sorbents have been specified in detail by Płotka-Wasylka et al. [13]. In view of a dynamic development in the area of material engineering, new extraction materials are expected to be developed within forthcoming years, of even better properties that ensure higher selectivity and effectiveness of extraction. Universality of the method and high sensitivity have caused that the technique is used in almost every area of analytical chemistry, starting from environmental to bioanalytical analyses. In Table 5.1, detailed information is presented concerning the use of the method in extraction of analytes from various samples.

5.2.2 In-Tube Solid-Phase Extraction

The internally coated capillary or a needle, which is the base of so-called in-tube techniques, is an alternative to the use of coated fibres. In-tube SPME (also called capillary microextraction) typically uses GC capillary column for analyte retention. This technique was developed in 1997 by Pawliszyn and Eisert, to overcome common

Table 5.1 Application of SPME-based methods in the different fields of analytical chemistry

Matrix	Analyte	Sorbent type	Extraction mode	Extraction time (min)	Desorption	LOD/LOQ	Recovery (%)	Final determination	References
Fibre SPME									
Sludge	Pharmaceuticals and personal care products	DVB/CAR/PDMS	HS	168	Thermal (3 min 250 °C)	10/– (ng/g)	90	GC-MS	[46]
Urine	Amphetamine-type stimulants	Acid-oxidized MWCNTs	HS	20	Thermal (5 min 250 °C)	0.2–1.3/0.7–4.3 (μg/L)	88–107	GC-MS	[47]
Water	Polychlorinated biphenyls	Metal–organic framework	DI	40	Thermal (15 min 230 °C)	0.0013–0.053/0.0042–0.18 (ng/L)	85.9–105.8	GC-MS	[48]
Tap water	UV filters	Double-confined polymeric ionic liquid sorbent	DI	75	Solvent (10 min)	1–5/– (μg/L)	93.2–106.4	HPLC-ESI-TOF	[49]
Water	Fungicides	PDMS/DVB	HS	20	Thermal (5 min 270 °C)	<1/– (μg/L)	92–104	GC-MS/MS	[50]
In-tube SPME									
Hair	Nicotine, cotinine	PDMS	DI	–	Solvent	0.13–0.45/4.4–7.5 (pg/mL)	87–96	LC-MS/MS	[51]
Milk	Sulphonamides	Poly(BMA-EDMA-RGO)	DI	–	Solvent	0.25–0.47/0.78–1.54 (μg/L)	91.1–94.6	CE-LIF	[52]
Water	Triazoles	Poly(4-vinyl pyridine-co-ethylene dimethacrylate)	DI	31	Solvent	0.014–0.031/0.046–0.11 (μg/L)	78.9–106	HPLC-DAD	[53]
Milk	Polyaromatic hydrocarbons	Poly(9-vinylanthracene-co-ethylene dimethacrylate)	DI	–	Solvent	0.10–2.36/0.33–7.78 (μg/L)	75.5–119	HPLC-FLD	[54]
Honey	Chlorophenols	Polypyrrole@copper-chromium-iron ternary layered double hydroxide nanocomposite	DI	15	Solvent	0.14–0.22/0.4–0.6 (μg/kg)	93–107	HPLC-UV	[55]

(continued)

Table 5.1 (continued)

Matrix	Analyte	Sorbent type	Extraction mode	Extraction time (min)	Desorption	LOD/LOQ	Recovery (%)	Final determination	References
Cooled coated fibre device									
Seawater	Polycyclic aromatic hydrocarbons	PEDOT/GO	HS	60	Thermal	0.05–0.13/0.17–0.43 (μg/L)	85–107	GC-FID	[56]
Sand	Polycyclic aromatic hydrocarbons	PDMS	HS	40	Thermal (2 min 300 °C)	0.3–3/0.9–9 (pg/g)	–	GC-FID	[23]
Shampoo	Perfume compounds	PDMS	HS	45	Thermal	0.2–1/– (μg/g)	83–90	GC-FID	[57]
Cork	Chloroanisoles	DVB/PDMS	HS	10	Thermal (3 min 260 °C)	0.25–0.49/0.83–16.2 (ng/g)	–	GC-MS	[25]
Urine	BTEX	CAR/PDMS	HS	15	Thermal (2 min 300 °C)	0.02–0.07/0.07–0.2 (ng/L)	92–102	GC-FID	[58]
In-needle SPME									
Food containers	Phthalates	MWCNTs–polyaniline	HS	30	Thermal (3 min 230 °C)	2–21/8–70 (μg)	64.2–160.81	GC-MS	[59]
Standard solution	Citrus essential oils	PDMS	HS	20	Thermal (2 min 240 °C)	6.78–104.46/22.59–348.21 (μg)	92.11–104.44	GC-MS	[60]
Water	UV filters	Graphene	DI	40	Thermal (5 min 280 °C)	0.5–6.8/– (ng/L)	99–114	GC-MS	[61]
Water	Polybrominated diphenyl ethers	Graphene	HS	20	Thermal (5 min 300 °C)	0.2–5.3/– (ng/L)	74.8–81.9	GC-ECD	[62]
Air	Aromatic amines	Amberlite XAD-2/silica	–	–	Thermal (3 min 280 °C)	0.01–0.02/0.05–0.08 (ng/mL)	93–99.3	GC-FID	[63]

(continued)

Table 5.1 (continued)

Matrix	Analyte	Sorbent type	Extraction mode	Extraction time (min)	Desorption	LOD/LOQ	Recovery (%)	Final determination	References
In-tip SPME									
Rice seedlings	Brassinosteroids	C_8–SO_3H with (4-PAMBA)	Immersion	20	Solvent	0.8–5.7/2.7–19 (pg/mL)	85.7 ± 3.1–107.2 ± 3.4	LC-MS/MS	[64]
Plant	Alkaloids and flavonoids	CNT	Immersion	1.2	Solvent	0.16–0.76/1.02–2.98 (μg/L)	90.5–99.85	UHPLC-UV	[38]
Urine	Drugs	Poly(GMAco-EDMA-MWCNTs)	Immersion	–	Solvent	6.8–15.2/– (μg/L)	72–108	HPLC-UV	[65]
Water	Antimony	POIP	Immersion	3	Solvent	6/100 (ng/L)	95 ± 3–98 ± 4	ETAAS	[41]
Water	Vanadium	MWCNTs-TEPA	Immersion	2	Solvent	0.008/– (μg/L)	98.1 ± 2.6–101 ± 2.7	ETAAS	[66]
SPME Arrow system									
Wastewater	Amines	A-ZIF-8	Immersion	20	Thermal (1 min 250 °C)	– /1 (ng/mL)	91.6–92.1	GC-MS	[45]
Atmospheric air	Amines	DVB/CAR/PDMS	Immersion	30	Thermal (40 s 250 °C)	– /0.13 (μg/L)	88	GC-MS	[43]
Water	Polycyclic aromatic hydrocarbons	PDMS	Immersion	70	Thermal (5 min 280 °C)	–	–	GC-MS	[44]
SBSE									
Soil	Triazines	Molecularly imprinted monolith polymers with magnetic nanoparticles	DI	60	Solvent	LOD 3.6–7.5 (ng/g)	2.4–15.4	HPLC-DAD	[73]

(continued)

Table 5.1 (continued)

Matrix	Analyte	Sorbent type	Extraction mode	Extraction time (min)	Desorption	LOD/LOQ	Recovery (%)	Final determination	References
Environmental waters	PCBs	PANI/α-CD	DI	50	Solvent	LOD 0.048–0.22 (ug/L)	72.6–121	HPLC-UV	[76]
Agricultural wastewater	Insecticide (ethion)	ZrO_2-rGO nanocomposite	DI	30	Thermal (220 °C)	LOD 1.5 (μg/L)	93–97	NCD-IMS)	[75]
Coffee, sage, whiskey	Volatile compounds	PDMS	Dual-phase SBSE, headspace	60	Thermal (250 °C, 5 min)	–	–	GC-MS	[78]
Spiked water samples	45 emerging environmental pollutants	PDMS	Dual stir bar	120	Thermal (280, 6.5 min)	0.5–431 (ng/L)/1.7–1502 (ng/L)	2.5–89.2	GC-MS	[80]
TFME									
Human plasma	Carvedilol	PA-EG	DI	60	No desorption	4.5 ng/mL	91–112	Solid-state spectrofluorometry	[88]
Blood	Benzodiazepines	PS-(DVB)-PAN; (PBA)-PAN	DI, 96-blade	–	–	–	–	HPLC-MS	[97]
Environmental samples	Triazines	Electrospun magnetic PBT	DI	20	Solvent	0.02–0.05 ng/mL/0.1 and 0.2 ng/mL	86–103	GC-MS	[98]
Urine	Methadone	PS	DI	–	Solvent	3 (ug/L)/10(ug/L)	106	GC-MS	[99]
Water samples	Chlorobenzenes	PANI-N6 nanofibres	HS	30	Solvent (10 min)	19–33 (ng/L) 50–60 (ng/L)	93–104	GC-MS	[100]

A-ZIF-8—acidified zeolitic imidazolate framework-8; BMA—n-butyl methacrylate; CE-LIF—capillary electrophoresis—laser-induced fluorescence; DAD—diode array detector; divinylbenzene/carboxen/polydimethylsiloxane; EDMA—ethylene glycol dimethacrylate; FLD—fluorescence detector; MWCNTs—multiwalled carbon nanotubes; PAHs—polycyclic aromatic hydrocarbons; PEDOT—poly(3,4-ethylenedioxythiophene); POPI—polystyrene oleic acid imidazole polymer; RGO—reduced graphene oxide; TEPA—tetra ethylene pentamine; UV—ultraviolet; 4-PAMBA—4-phenylaminomethyl-benzeneboric acid

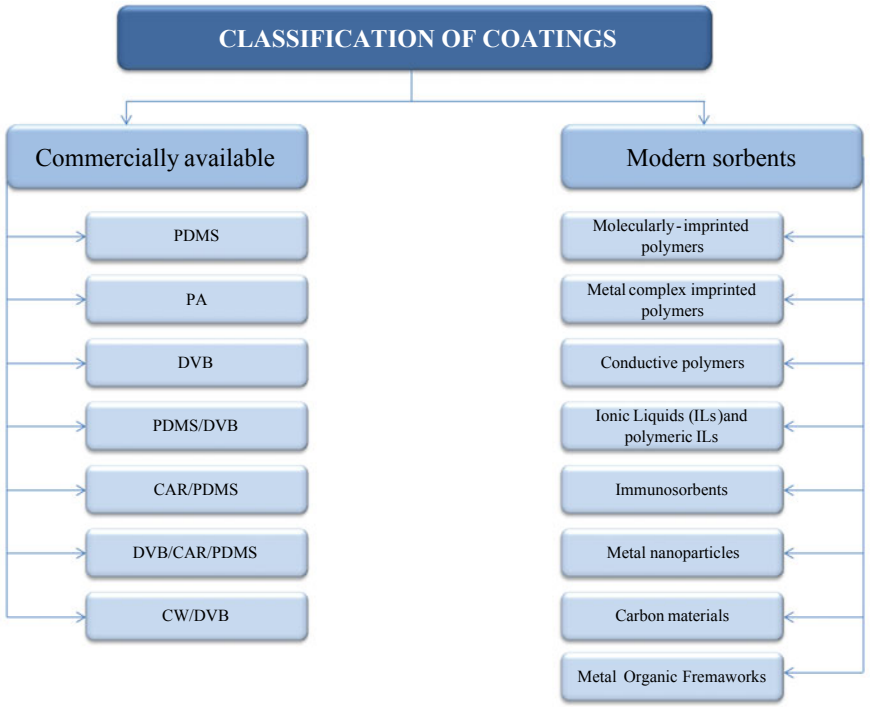

Fig. 5.3 Classification of sorbents used in SPME technique

problems shown during the use of conventional SPME fibre, including its fragility, low sorption capacity and extraction-phase bleeding [14, 15]. The most common capillaries are open tubular. Most of the conventional sorbents are used to coat the inner surface, but the recent literature data indicates more options for the application of modern sorbents, such as MIPs, nanotubes or magnetic nanoparticles. In-tube systems can be used either in a static mode, where the sample passes continuously through the capillary, or in a dynamic mode, where the sample is repeatedly aspirated and dispensed [4]. On the basis of the literature data, it can be concluded that the first mode is applied more often, because it provides good extraction efficiency in a short period of time. There are several different configurations applied to carry out these two extraction modes. One of them bases on the syringe usage and involves between in-tube and in-needle SPME approaches. In this case, the needle is replaced by two concentric capillaries. For the analyte extraction, the syringe is filled with the sample and emptied repeatedly. The desorption process is carried out by passing organic solvent through the capillary. This approach was successfully applied for determination of trace level of polycyclic aromatic hydrocarbons in water samples [16]. Alike extraction, desorption can also be carried out in two ways, i.e. in a static and dynamic way, whereas the latter is more common. Thermal desorption can also be used when in-tube is coupled to GC [17]. Undoubtedly, the advantage of this

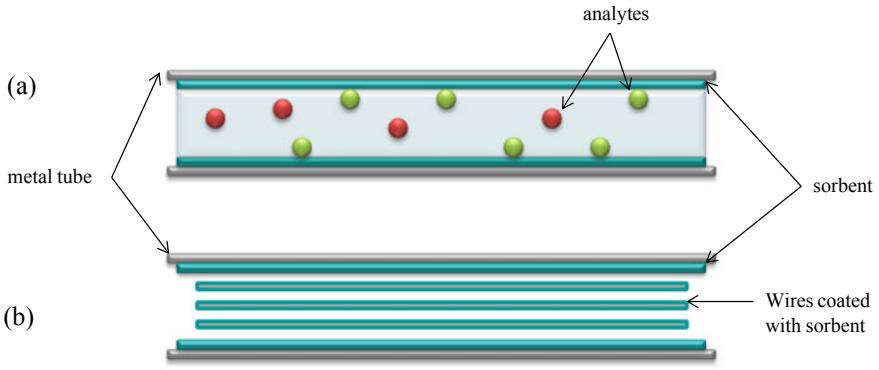

Fig. 5.4 The scheme of the extraction tubes used in **a** in-tube SPME and in **b** wire in-tube

technique consists in combining it to a wide range of separation techniques, e.g. liquid chromatography, gas chromatography, capillary electrophoresis and conventional electrophoresis [14]. It makes in-tube SPME a technique that is widely used in the different fields of analytical chemistry. It is predominantly applied in the environmental analysis, but recently in-tube SPME presence has increased in the biomedical field. Table 5.1 shows several applications of in-tube SPME in the different fields of analytical chemistry. The main drawback of in-tube approach is that it requires more complex instrumentation in comparison to traditional SPME, but with the usage of longer tubes and an increased amount of a sorbent, it can be expected to enhance sensitivity [18]. Another disadvantage of this technique consists in low extraction capacity. To overcome this problem, the fibres were inserted inside the tube. In a classic wire in-tube SPME approach, the fibre is the sorbent and the tube serves only as a support. The scheme of the extraction device is shown in Fig. 5.4.

This combination leads to decrease of dead volume in tube and improves the peak symmetry. Among the fibres used most often in this technique, we can mention carbon fibres, copper fibres, poly(ethylene terephthalate) fibre, commercial Kevlar fibres, carbon nanotube-coated silica fibre, molecularly imprinted silica fibre and poly(*N*-isopropylacrylamide)-coated fibre [19].

5.2.3 Cooled Coated Fibre Device

Undoubtedly, one of the most effective methods to release the analytes from the sample is thermal desorption. Elevated temperature reinforces molecules to escape from their matrix, enhances their mass transfer to pass through the matrix, and increases their concentration in the headspace by increasing vapour pressure [20]. However, due to the fact that the process of the analytes adsorption on a fibre has an exothermic nature, increasing sample temperature can result in reducing the partition coef-

ficients values. That may effect in decreased trapping of the analytes on the coating [21]. Based on the research results, creating a temperature gap between a fibre and the headspace, which increases distribution coefficient of sample headspace and headspace-fibre equilibrium, seems to be the best solution to overcome this problem. This knowledge has become an agent driving to prepare a new methodological approach to enable maintenance of the extracting phase at a relatively low temperature and to heat the sample at the same time to a high temperature. The first internally cooled SPME (IC-SPME) device was introduced by Pawliszyn and Zhang in 1995 [22]. Liquid carbon dioxide was used as a SPME fibre cooling agent, for the extraction of BTEX from clay soil samples. This approach turned out to be very effective; nevertheless, it was characterised by numerous drawbacks connected mainly with blockage of the tubes transferring the cooling agent and troubles with automation. Nevertheless, it should be noted that IC-SPME was a starting point to improve the microextraction methods by the cooling process. Currently, three attitudes for fibre cooling may be distinguished, based on the use of: (i) liquid CO_2 and N_2 gas, (ii) circulation of cooled fluids and (iii) thermoelectric cooler [20, 22].

(i) Liquid CO_2 is used most often as a cooling agent in the so-called Cold-fibre solid-phase microextraction (CF-SPME). This technology was introduced for the first time in laboratory practice in 2006. CF-SPME is an automated and miniaturized version of the previous device, which accommodated the fibre into a stainless steel needle. Figure 5.5a presents CF-SPME device. The use of an external fibre coating has improved its strength, and therefore, its multiple use is possible. High sensitivity and high sample throughput have caused that the technology is used in many areas of analytical chemistry. CF-SPME is successfully used for extraction of polycyclic aromatic hydrocarbons from sediments [23], acrolein from environmental and biological samples [24] and chloroanisoles from cork [25]. In case of extraction volatiles compounds from tropical fruits, higher sensitivity and extraction efficiencies than traditional SPME technique were reported [26]. Table 5.1 presents more possible uses of CF-SPME.

(ii) Ice, alcohol or cold water is alternative to the use of liquid CO_2 as a cooling agent of the extraction phase. This solution involves the use of additional cylinder around the upper part of the extraction vial to which the cooling agent is delivered. Figure 5.5b presents the device with a circulating system as the cooling part. The solution has been used for isolation and enrichment of polychlorinated compounds from contaminated soil samples [27] and methyl *tert*-butyl ether from surface water [28]. Unfortunately, researchers emphasize that the use of this methodological attitude does not allow to cool the fibre to very low temperatures. On average, the temperature of the fibre is 4–5 °C. Thus, the temperature gap between the sample and the coating cannot be significantly high, as in case of other systems. Another defect of this method consists in the risk of losing volatile analytes and of rapid contamination of ion source due to large amounts of water [22].

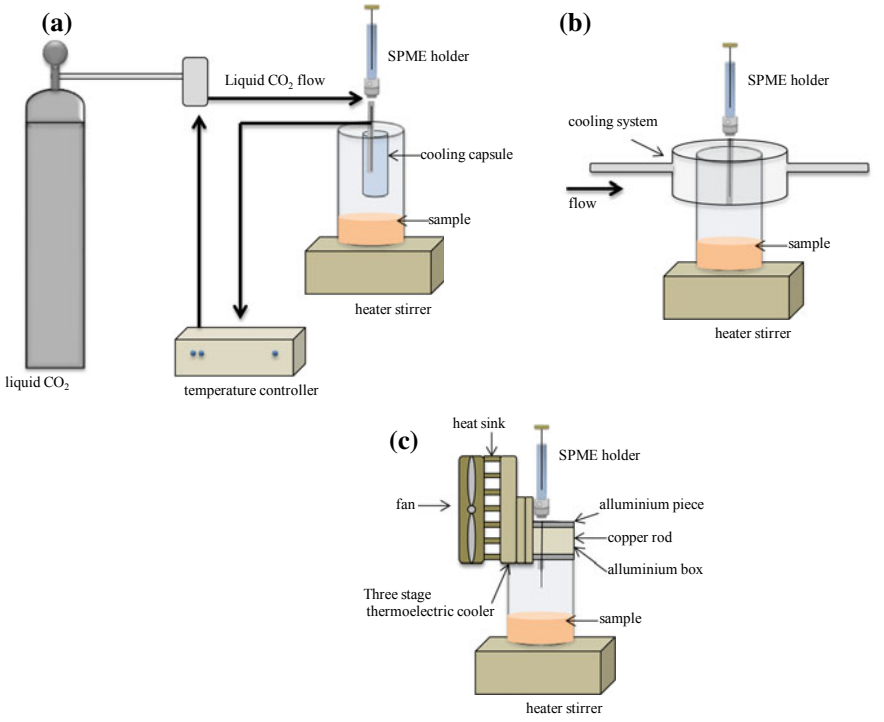

Fig. 5.5 Schematic representation of **a** CF-SPME set-up; **b** HS-SPME device which uses a circulation of cooled fluids; **c** TEC-CF-SPME device

(iii) Thermoelectric cooling system (TEC) was developed in 2009. This methodological solution was introduced to overcome the CF-SPME drawbacks connected with complex construction and fluctuations of the fibre temperature. Haddadi and Pawliszyn used the three-stage thermoelectric cooler for cooling a copper rod coated with PDMS. This approach allowed the decrease of size weight of devices, which resulted in cost decrease, environmental safety and precise temperature control [21, 22]. In Fig. 5.5c, TEC-CF-SPME device is presented. Many types of modifications have been proposed since the first use, in order to reach the best possible values of metrological parameters of the method.

5.2.4 In-Needle SPME Methods

Another modification of the traditional device concerns solutions in which extraction tubes are replaced by a needle. They include: (i) microextraction in packed

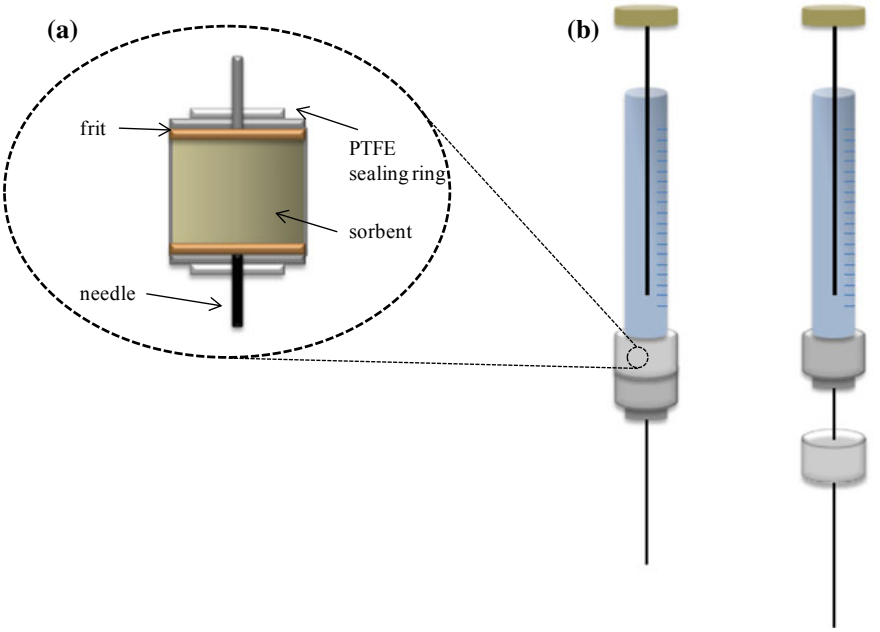

Fig. 5.6 The setting of the sorbent layer used in the MEPS **a** inside a syringe; **b** placed in a small container between the barrel and the needle

syringe (MEPS), (ii) a solid-phase dynamic extraction (SPDE) and fibre-packed needle microextraction (FNME) [29].

(i) Microextraction in packed syringe (MEPS) is a recently developed sample pretreatment technique, based on the miniaturization of conventional SPE. For the first time, MEPS was used in 2004 to determine local anaesthetics in human plasma. Since then, a large number of articles, about the possibilities of its use and analytes enrichment in different types of samples, have been published [30, 31]. In MEPS, approximately 2 mg of the sorbent is packed inside a syringe (100–250 μL) as a plug or placed in a small container between the barrel and the needle [30]. In Fig. 5.6, MEPS device is presented.
When the sample is passed through the solid support, the analytes are adsorbed to the extracting media. In contrast to SPE, the solution flows in two directions (up and down). The analytes are then eluted with an organic solvent [32]. MEPS uses the same sorbents as conventional SPE column. Both commercially available sorbents, such as silica-based sorbents, polystyrene-divinylbenzene and porous graphitic carbon, and modern sorbents are used most often. According to the data published in the specialized literature, molecularly imprinted polymers (MIPs) were successfully applied for isolation and quantitation of fluoroquinolone-related compounds from water samples [33] and for extraction of estrogenic compounds from water samples [34]. It may be supposed

that researchers' interest in this techniques will be constantly growing, as in comparison to other sample preparation techniques the microextraction in a packaged syringe features with significantly shorter extraction time, higher recovery factor values and significantly less sample's capacity and solvent usage. Undoubtedly, full automation is another advantage [30].

(ii) Solid-phase dynamic extraction (SPDE) was introduced to analytical practice in 2001 [35]. In this approach, the internal surface of the steel needle is coated with a suitable extraction phase. In this mode of extraction, the sample is placed in the headspace vial in a heated flushing station. After preincubation, the needle is inserted through the septum in the sample headspace. Extraction is performed by drawing up the sample into the syringe with the use of a syringe plunger. Aspiration and dispensing are performed several times. After several extraction cycles, analytes are thermally desorbed from the stationary phase in the heated injection port of a gas chromatograph [6, 36]. Placing sorbent inside the needle has significantly increased the volume of the extraction phase. Published data shows that the volume can be even six times higher than in the case of using the traditional SPME fibre [6]. In addition, the presence of external protection has significantly increased mechanical resistance of the sorbent. Moreover, there is an additional advantage as SPDE is a dynamic method, so the equilibrium may be achieved significantly faster. The main disadvantage of SPDE is a possibility of carry-over effects and possibility of coating loss [4].

(iii) Fibre-packed needle microextraction (FNME) is another modification of the traditional approach in which short capillary columns were placed inside the needle and used as an extraction medium. Published references say that used capillary are most often made of polyetheretherketone (PEEK), fused-silica or polytetrafluoroethylene (PTFE). FNME was used to isolation and enrichment of PAHs from water samples [37].

5.2.5 In-Tip SPME

One of the newest modifications of the traditional SPME is technique called in-tip SPME. In this type of methodological approach, a sorbent or a fibre is placed in a pipette tip (Fig. 5.7). Analytes are extracted by repeated aspiration and dispension of the sample solution using single channel and multichannel pipettors or syringe [38, 39]. Undoubtedly, the advantage of this mode consists in the possibility of full automation, which contributes to the best control over the sample and solvent manipulation and reduction of the amount of laborious and time-consuming operations. Additionally, undoubted strengths of in-tip SPME refer to the possibility of preparing several samples at the same time. Multi-well plate formats are used especially for isolation and determination of analytes in the biological and pharmaceutical research [40]. In-tip SPME was also successfully applied in numerous research, including environmental or food samples [41, 42]. More detailed information on the application of this technique is provided in Table 5.1.

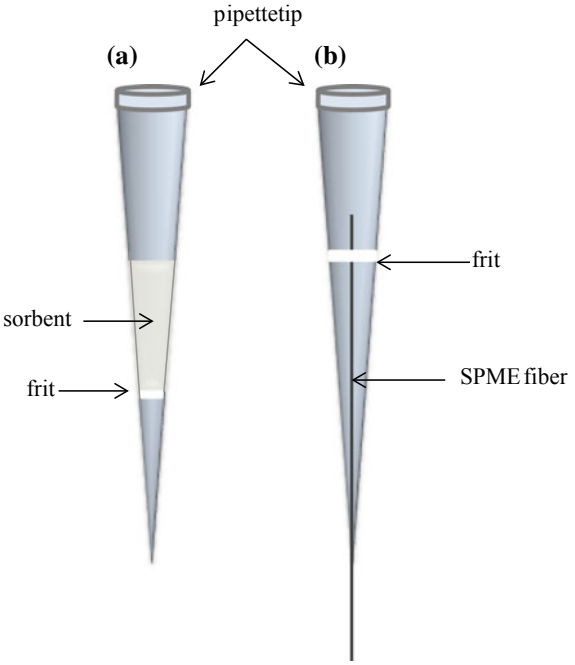

Fig. 5.7 Device for analyte extraction using the in-tip SPME technique: **a** sorbent; **b** fibre placed in a pipette tip

5.2.6 SPME Arrow System

SPME Arrow system is another solution in relation to the SPME, in which the internal surface of the steel rod is coated with a suitable sorbent. Locating the sorbent layer on the internal side of the needle increased the inter-phase contact [43]. In the upper part of this device, a solid tip is placed, which also retains the sorption phase. The use of an external protection of the sorbent has resulted in the elimination of the problem connected with the hazardous impact of external agents on the sorbent. Moreover, it has improved mechanical resistance of the device [44]. Figure 5.8 schematically shows the comparison between classical SPME fibre and the SPME Arrow system.

This technique was used for the first time to determine volatile amines in wastewater and atmospheric samples in 2015 [43]. Since then, interest in its use in many analytical fields has significantly increased. The growing popularity of this method is connected with surpasses limitations of classical SPME fibres, especially in the case when a large volume of sorbents are used [45]. The typical sorbent length in Arrow system is 20–30 mm and sorbent film thickness is 120–250 μm, whereas in SPME technology, it is 10 mm length and the typical thickness of film is 100 μm. Literature data shows that combination of large sorbent volumes of SPME fibre with GC-MS analysis can be problematic without modifications, such as a thermal desorption unit. Due to the dimensions of this system and sharp, closed tip, it is still possible to connect SPME Arrow system with the standard desorption mode in GC

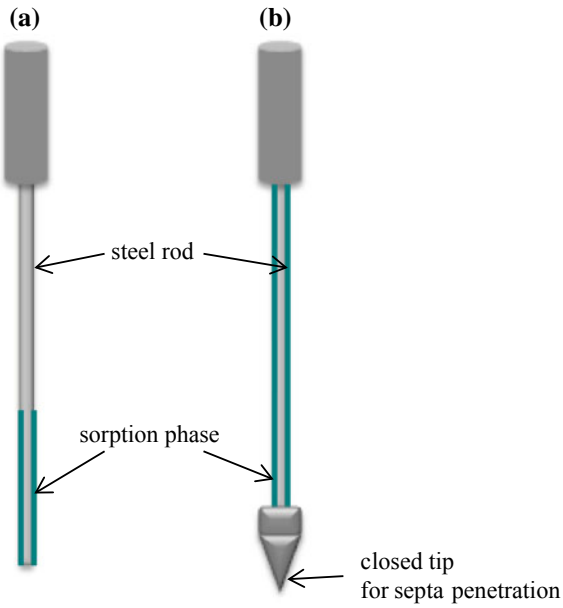

Fig. 5.8 Setting of the sorbent layer used in the **a** SPME and **b** SPME Arrow system

liner. Additionally, SPME Arrow system is characterized by better robustness and sensitivity. Among the extraction phases, conventional sorbents are most often used in the literature, such as PDMS, CAR/PDMS, PDMS/DVB and DVB/CAR/PDMS [43, 44]. However, the use of metal–organic frameworks (MOFs) as a sorptive phase is also known. The use of ZIF-8 modified by hydrochloric acid enabled to obtain higher values of analyte recovery in comparison to the traditional use of the sorbent [45]. Thus, it can be assumed that the use of modern sorbents in this technique will increase in forthcoming years. SPME Arrow system has been successfully applied to determination of PAHs from water samples [44] and for amines from wastewater and food samples [43, 45]. More information on the application of this device can be found in Table 5.1.

5.2.6.1 Stir Bar Sorptive Microextraction (SBSE)

Stir bar sorptive microextraction was first developed in 1999 as a novel geometry of solid-phase extraction, where polydimethylsiloxane (PDMS) is utilized as a sorbent [67]. In this technique, instead of a polymer-coated fibre stir bars, with a layer of sorptive material, are used. Sampling or extraction process is done by straightforward immersing the stir bar in the aqueous sample solution (direct immersion mode—DI) or placing the bar in the liquid, gaseous or solid sample headspace (head space mode—HS). When the bar is stirred in the sample, it absorbs analytes present in the matrix, and then, it is rinsed with deionized water and dried. After that, stir

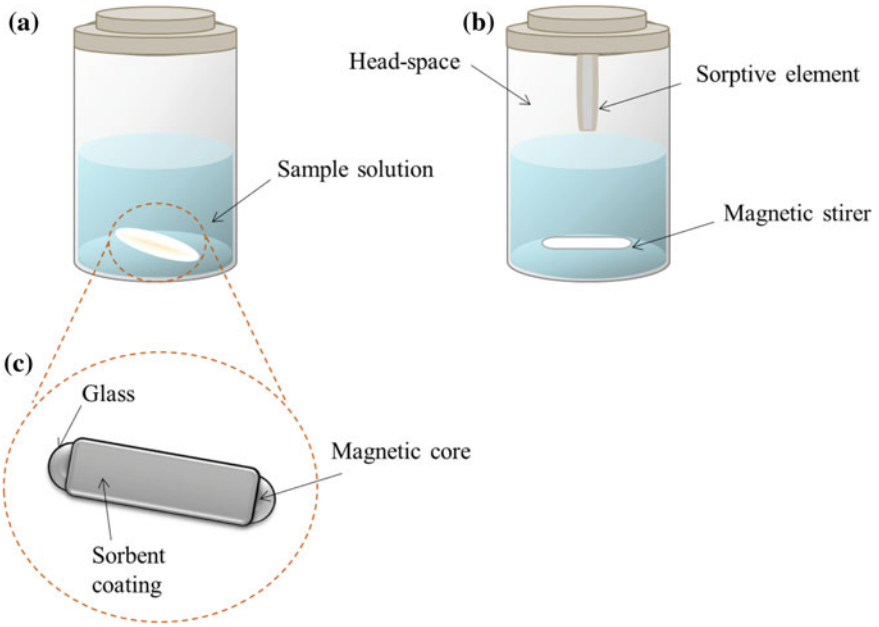

Fig. 5.9 The illustration of SBSE technique set-up **a** DI mode, **b** HS mode, **c** sorptive element

bar undergoes thermal desorption (TD) or liquid desorption (LD) in the case of thermally unstable analytes [67–69]. The schematic representation of a SBSE and stirring sorptive element is given in Fig. 5.9. Stir bar size depends mainly on the sample volume, where 10-mm-long stir bars are suitable for the sample volumes in the range of 10–50 mL, whereas 40-mm-long stir bars are usually used for volumes up to 250 mL [67].

As well as in the case of fibre SPME technique, the extraction process is kinetically governed by the point when the equilibrium state is achieved. SBSE effectiveness is determined mainly by the distribution or partition coefficient of the target compound between both phases (octanol-water partitioning coefficient) and to the phase volume ratio as given on Eqs. 5.1 and 5.2:

$$\frac{m_{\mathrm{SBSE}}}{m_0} = \frac{K_{\mathrm{ow}}/B}{1 + \left(\frac{K_{\mathrm{ow}}}{B}\right)} \tag{5.1}$$

$$B = \frac{\text{Sample volume}}{\text{Stationary phase volume}} \tag{5.2}$$

Along with the other microextraction techniques, such as DLLME or SPME, SBSE is one of the most popular methods for the reduction of chemical waste, which contributes to green character of this solventless technique [70]. Moreover, it is characterized by some other important advantages such as: reduction of sam-

ple preparation time, easy automation, coupling to derivatization techniques or significantly enhanced efficiency, resulting from hundreds to thousands times higher volume of stationary phase (in comparison to SPME method) [71]. On the other hand, it is important to keep in mind certain drawbacks, affecting applicability of SBSE, namely limited number of extractions that can be made before sorptive element degradation, limited precision compared to other techniques or long desorption time [72].

Because the number of commercially available coating types is limited to PDMS, polyacrylate (PA) and ethylene glycol/silicone, in recent years, the development of new coating materials was an important issue in order to make SBSE useful also for the extraction of polar analytes [68]. These coatings include molecularly imprinted polymers (MIPs) to determine triazines in soil samples and cefaclor and cephalexin in environmental waters [73, 74], zirconium dioxide-reduced graphene oxide nanocomposite to determine ethion in river water [75], some composite materials such as polyaniline/cyclodextrin for polychlorinated biphenyls extraction form environmental waters [76] and a broad range of PDMS-based coatings [77]. Besides that, SBSE has been extensively used for extraction of environmental pollutants. In the case of pharmaceutical and clinical fields, this technique is not often applied, due to small sample volume. More applications are given in Table 5.2.

In the case of extracting analytes, belonging to different chemical classes, from one sample, a new approach in SBSE, dual-phase or dual-shot SBSE has been developed. In 2005, dual-phase SBSE was first introduced [78]. The sorptive phase is combined of two or more sampling materials to obtain a synergistic effect, e.g. PDMS tube with different types of activated carbons as packing material.

Dual stir bar extraction, introduced in 2006, is based on two different stirring bars that are placed in the two sample solution aliquots simultaneously [79]. After the extraction process, two stir bars are placed in the same desorption liner and are simultaneously thermally desorbed [80]. The multi-shot version of this extraction is also possible (with more than two stir bars) [81].

5.2.6.2 Thin-Film Microextraction (TFME)

Thin-film microexaction technique was first introduced in 2003 by Brunheim et al. as an alternative to SPME [82]. SPME fibre coating was replaced with a thin sheet of PDMS (polydimethylsiloxane) membrane used as an extraction phase.

Principle of the extraction procedure involves attaching a flag-shaped PDMS membrane to deactivated stainless steel rod and placing it in a sample container. Then, a sample is stirred to induce analytes exchange between the sample matrix and the extraction phase. After that, the membrane is rolled around the steel rod and may be directly placed in GC injector for thermal desorption. TFME may be performed in both direct and headspace modes. The procedure scheme is shown in Fig. 5.10.

TFME shows higher extraction rates in comparison with classic SPME technique, due to increased ratio of surface contact area to extraction-phase volume [82]. In general, the efficiency of the extraction depends on distribution coefficient (K_{es}), volume

Table 5.2 Application of LPME-based methods in the different fields of analytical chemistry

Matrix	Analytes	Extraction solvent type	Solvent consumption (μL)	Extraction time (min)	Extraction mode	LOD/LOQ	Recovery (%)	Enrichment factor	Final determination	References
SDME										
Fruit (mango, banana, papaya, melon, tomato)	Multi-class pesticides	Toluene	10	30	DI	LOD: 0.14–169.20 (μg/kg)	69–119	20–722	GC-MS	[120]
Drinking water	Lead	Chloroform	60	5	DI, automated lab-in-syringe	LOD: 23–75 (nmol/L)	92.2–115.9	–	Spectrophotometry	[121]
Dried food	Heterocyclic amine (2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline	Nanocellulose in imidazolium IL	4	30	DI	LOD: 0.29 (mg/L) LOQ: 2.9 (mg/L)	90.1–95.3	–	CE	[123]
Water	Bromide	EtOH + DMF (98:2 v/v)	2	10	HS	1.4 4.4 (μg/L)	95–110	243	Microvolume fluorospectrometry	[126]
Serum, pharmaceutical tablets	Captopril	GNPs	4.5	20	HS	0.31 nM	95.3–107.4	96	MC-PTLM	[128]
DSDME										
Foodstuffs	Polyphenols (piceatannol, catechin, epicatechin, quercetin, fisetin, resveratrol	Undecanone	10	20	–	0.011–0.13 (ng/mL)/0.037–0.43 (ng/mL)	81–116	413–578	GC-MS	[131]

(continued)

Table 5.2 (continued)

Matrix	Analytes	Extraction solvent type	Solvent consumption (μL)	Extraction time (min)	Extraction mode	LOD/LOQ	Recovery (%)	Enrichment factor	Final determination	References
Cow's milk	Phthalic acid esters	Cyclohexane	100	10		0.001–0.2/0.003–0.7 (μg/L)	70.2–108	–	GC-MS	[178]
Water	Cr(III) and Cr(IV)	1-octanol	154	20		LOD: 1.2, 1.8 (ng/mL)	85–109	60 45	FAAS	[179]
Beverages	Organochlorine pesticides	Isooctane	100	10		LOD: 0.8–5.0 (ng/L)	81–117	–	GC-ECD	[180]
Herb samples	Cadmium	1-undecanol	90	20	SFODME	LOD: 0.0052 (μg/L)	94.5–110.2	–	ETAAS	[181]
CFME										
Environmental samples	Nitroaromatic compounds and chlorobenzenes	Xylene	1–5	10	–	LOD: 0.01–10 (pg/mL)	91.2–104.3	260–1600	GC-ECD	[133]
Water	Pesticides (simazine, fensulfothion, etridiazole, mepronil, bensulide)	CCl_4	3	10		LOD: 0.6–4 (ng/mL)	77.2–106	4.9–296	HPLC-UV	[134]
Water	PAHs	Cyclohexane	5	–		0.0012–0.0101/0.0041–0.0336 μg/L	81.8–105.8	777–978	GC-MS	[137]
Fruit juices	Triazine herbicides	Chlorobenzene	30	–		LOD: 0.5–1.0 (μ/L)	71–90	–	HPLC-UV	[182]

(continued)

Table 5.2 (continued)

Matrix	Analytes	Extraction solvent type	Extraction/ dispersive solvent consumption (μL)	Extraction time (min)	Dispersive solvent	LOD/LOQ	Recovery (%)	Enrichment factor	Final determination	References
DLLME										
Water	Pesticides, personal care products, pharmaceuticals	1-octanol	120/750	–	Acetone	LOQ: 0.0125–1.25 (μg/L)	60–120	–	HPLC-MS/MS	[144]
Environmental samples and foodstuffs	Estrogens, alkylphenols, bisphenols, parabens, triclosan	4-bromoanisole	90/200	1	Acetonitrile	LOD: 0.05–0.40 ng/L	83–116	–	UHPLC-MS/MS	[147]
Water	Pesticides, pharmaceuticals and personal care products	[C6MIM][PF6]	100/500	–	methanol	LOQ: 0.5–2.5 ng/mL	70–120	–	LC-MS/MS	[151]
Aqueous samples	Synthetic musk fragrances	Chloroform	80/880	2	Acetonitrile	LOD: 0.004–54 (ng/L)	71–118	101–115	GC-MS	[183]

(continued)

Table 5.2 (continued)

Matrix	Analytes	Acceptor solution	Solvent consumption (μL)	Extraction time (min)	SLM solvent	LOD/LOQ	Recovery (%)	Enrichment factor	Final determination	References
HF-LPME										
Urine and plasma	Dydrogesterone, cyproterone acetate	(Ph)3PI-EtGly + 20% v/w MeOH	30	30	n-dodecane	LOD: 0.5–2 (μg/L)	85.9–117.5	187–428	HPLC-UV	[164]
Environmental waters	Salicylic acid	Aqueous NaOH solution (pH = 14)	25	180	Octan-1-ol	LOD: 2.6 (μg/L)	88–110	407	CZE-UV	[165]
Urine	Benzodiazepines and metabolites	3.0 mol/L HCl	–	90	Dihexyl ether: 1-nonanol(9:1)	0.1–15/0.5–30 (ng/mL)	20.9–92.7	–	GC-MS	[167]
Wastewater	Chlorophenols	Hexyl acetate	–	20	n-decane	LOD: 0.0004–1.2/0.009–4.1 (μg/L)	92–98	432–785	GC-ECD	[157]
Milk	Aflatoxin M_1 (AFM_1)	50 mg/L of the anti-AFM_1 Antibody in PBS buffer solution	30	50	1-octanol	0.06/0.21 (μg/kg)	61.0–106.7	48	HPLC-MS/MS	[184]

(continued)

Table 5.2 (continued)

Matrix	Analytes	Acceptor solution	Potential (V)	Extraction time (min)	SLM solvent	LOD/LOQ	Recovery (%)	Enrichment factor	Final determination	References
EME										
Wastewater	Salicylic acid, ketorolac, ketoprofen, naproxen, diclofenac, ibuprofen	Basic aqueous solution	10	10	1-octanol	0.0009–9.0/0.003–11.1 (ng/mL)	55–100	28–49	HPLC-DAD-FLD	[169]
Human plasma	Citalopram, loperamide, methadone, paroxetine, pethidine, sertraline	10 mM formic acid	200	10	2-nitrophenyl octylether (NPOE)	LOD: 0.6–3.2 (ng/ml)	97–115	10.8–12.7	LC-MS	[171]
Human plasma	Metaraminol, benzamidine, sotalol, phenyl-propanolamine, ephedrine, trimethoprim	10 mM formic acid	100	20	Bis(2-ethylhexyl) phosphite (DEHPi)	14–71/23–100 (ng/mL)	25–91	2–6.8	HPLC-UV	[172]
Fish, water	Mercury	0.001 mol/L HCl	70	10	Bis(2-ethylhexyl) phosphate in 1-octanol 2% v/v	0.7–12/2.3–40 (ng/g)	89.3–94.7	130–176	UV-Vis spectrophotometry	[177]

CZE—capillary zone electrophoresis; DAD—diode array detector; DI—direct immersion; DMF—*N*,*N*-dimethylformamide; FLD—fluorescence detector; GNPs—gold nanoparticles; IL—ionic liquid; EtOH—ethanol; ETAAS—electrothermal atomic absorption spectrometry; FAAS—flame atomic absorption spectrometry; MC-PTLM—microchip photothermal lens microscopy; PAHs—polycyclic aromatic hydrocarbons

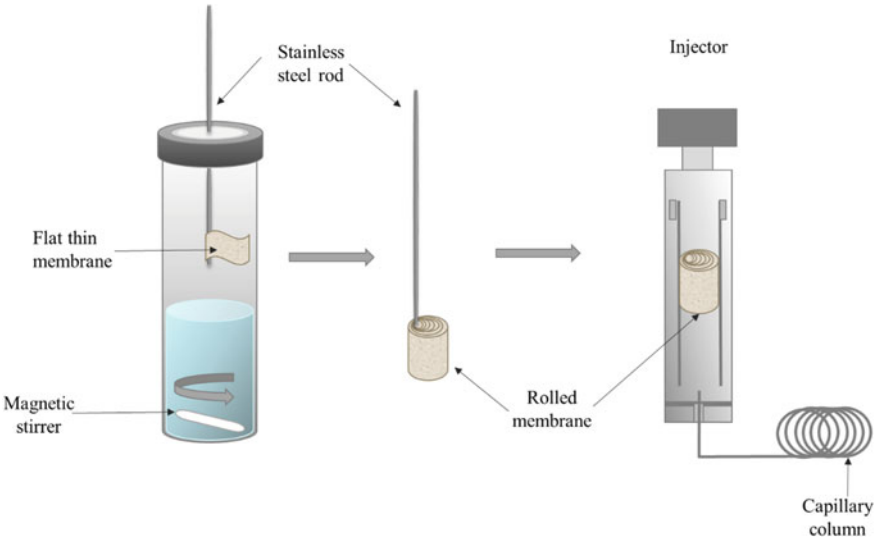

Fig. 5.10 Schematic illustration of TFME system working in the HS mode

of the extraction phase (V_e) and analyte concentration (C_s) (Eq. 5.3). Especially for low analyte concentrations, extraction amount may be increased by larger extraction coating volume [82–84]. Although, increasing that volume results in longer time needed to achieve extraction equilibrium, thus longer extraction time, according to Eq. 5.4, describing kinetic theory of an extraction.

$$n = K_{es} V_e C_s \tag{5.3}$$

$$t_e = t_{95\%} = 3\square K_{es}(b - a)/D_s \tag{5.4}$$

Considering all the above, the best way to gain better efficiency and sensitivity without sacrificing the extraction time is increasing area to volume ratio by using thin film with large surface [82, 83].

Thin film membrane may be used in different formats for microextraction purposes. The simplest way is placing the thin-film extraction phase directly into a sample matrix [85–88]. In other variants, thin film may be supported on a stainless steel rod or cotter pin [82, 89], but in this case, the major drawback is membrane folding during the sample agitation, due to membrane flexibility. To overcome this inconvenience, thin film may be prepared on the external holder, used as a support and to maintain flat shape of the membrane. Examples of this kind of support are stainless steel [90], carbon [91] or glass wool [92] mesh, fibreglass fabric [89] and folded copper mesh [93].

An interesting configuration of this technique is 96-blade TFME which was developed in 2009, where thin-film coating was immobilized on rectangular stainless steel

blades organized in 96-well plate format [94]. That type of configuration shows higher reproducibility and extraction efficiency in comparison to variant, where thin film is supported on rod-shaped substrate, due to more effective sample agitation and larger surface area [93].

A type of thin film is an important factor that induces extraction effectiveness; thus, different types of coating should be considered, depending on the sample matrix and analytes. Most popular thin-film material is PDMS [82, 85, 87, 95, 96] because of its thermal stability, commercial availability and simple manufacture. Although, a broad spectrum of other thin films and PDMS-mixed phases are reported. In 2014, poly(vinylidene fluoride) (PVDF) was utilized as TFME film for the first time for determination of four endocrine disrupting compounds in water samples [86]. PVDF as a membrane material is known with regard to its good thermal stability, mechanical and chemical resistance and high hydrophobicity. For the extraction purpose, square-shaped piece of membrane had been washed with acetone and dried prior to the analysis, in order to remove any possible contaminants, and then placed in the water sample vertically [86]. Authors investigated and compared extraction efficiency for PVDF, polypropylene, nylon and polytetrafluoroethylene. Results achieved with PVDF membrane were proved to be the best towards selected target compounds [86]. In 2016, polyacrylate–ethylene glycol (PA-EG) was introduced as polar THME sorbent for extraction of carvedilol drug from human plasma [88]. Compared to other extraction methods (LLE-GC-MS, SPE-LC-MS, SPE-UPLC-UV), this approach allowed to obtain lower LOD values and eliminate some sample preparation steps such as protein precipitation [88]. Octadecyl (C18) silica particles have also been utilized as thin-film sorbent on 96-blade extraction device [94, 97] for extraction of benzodiazepines. Other examples of different thin-film sorbents are magnetic polybutylene terephthalate nanofibres (PBT) for extraction of triazine herbicides [98], polystyrene membrane (PS) for extraction of methadone in urine [99] and polyaniline-nylon-6 electrospun nanofibres (PANI-N6) for headspace extraction of chlorobenzenes [100]. Different sorbent mixtures like C18/CSX for extraction of carbamazepine and triclosan in wastewater [101] or PDMS mixed with divinylbenzene for determination of pesticides in wastewater [102]. More specific information on TFME applications and main parameters characterizing analytical methods involved is given in Table 5.2.

TFME overcomes the main SPME limitation which is coating volume, but still it should be considered as a different and improved geometry of solid-phase microextraction technique.

5.2.7 Liquid-Phase Microextraction (LPME)

Liquid–liquid extraction (LLE) is one of the most popular and versatile and used as a basis of many standard analytical procedures and sample preparation technique for both organic and inorganic analysis [103]. Despite its broad spectrum of applications, this technique has some main drawbacks like multistep operation and

time-consuming procedures and tedious application. Moreover, usually it consumes large amounts of toxic organic solvents, which influences trace analysis, may pose a health hazards for laboratory personnel, increases analysis cost and produces organic waste affecting environment [104]. Miniaturized mode emerged from LLE, termed liquid-phase microextraction, is more modern and sustainable alternative, since it overcomes most of the above-mentioned disadvantages of LLE. The LPME technique combines extraction, sampling, isolation and analyte preconcentration in one step, preserving at the same time a relatively high enrichment factor (EF) of analyte. In comparison to SPME, LMPE is characterized by faster phase transportation, easier modification, possibility of direct injection, higher extraction capacity, better stability and lower cost [106].

LPME utilizes microlitre volume of a water-immiscible solvent, as an extractant/acceptor, and an aqueous phase (water sample as a donor phase), containing the target compounds [103–105]. Acceptor phase should be compatible with an analytical instrument. Transferring the analytes from relatively large sample volume into few microlitres of acceptor phase usually results in preconcentration, thus final analytical signal may be enhanced, and method selectivity and sensitivity increase [106]. Two-phase and three-phase LPME modes may be distinguished. In case of two-phase variant, the acceptor phase is in the direct contact with a sample matrix. The mass transfer is facilitated so is extraction process, but at the same time, sample clean-up and selectivity decrease. Moreover, two-phase mode is limited only to water-immiscible solvents, which is considered to be the main drawback. In case of three-phase mode, donor and acceptor phases are separated by the third solvent, immiscible with both. This approach allows using aqueous acceptor phase and increases selectivity of the method.

As a versatile method, LPME application is very wide and involves analyte extraction from both simple and complex matrices such as water samples (pesticides [107, 108], polycyclic aromatic hydrocarbons [109, 110], personal care products and pharmaceuticals [111]) or biological samples (trihalomethanes and haloketones in fish and green alga samples [112], illicit drugs in body fluids [113], strobuline and oxazoles fungicides in juices [114]).

In the next section, selected LPME techniques are discussed in detail, based on relevant and recent scientific references, to demonstrate the potential of the liquid-phase microextraction as a versatile sample preparation tool, useful in complex sample analysis.

5.2.7.1 Single-Drop Microextraction (SDME)

Single-drop microextraction (SDME) was introduced for the first time in 1996, mainly for limiting the solvent volume [115]. In this technique, the extraction phase is in the form of a solvent drop, exposed on a tip of a microsyringe needle. The organic droplet is withdrawn back to the syringe after achieving extraction equilibrium, and then microdrop enriched with the analytes may be directly injected to the suitable analytical instrument (Fig. 5.11). Target compounds are partitioned between sample

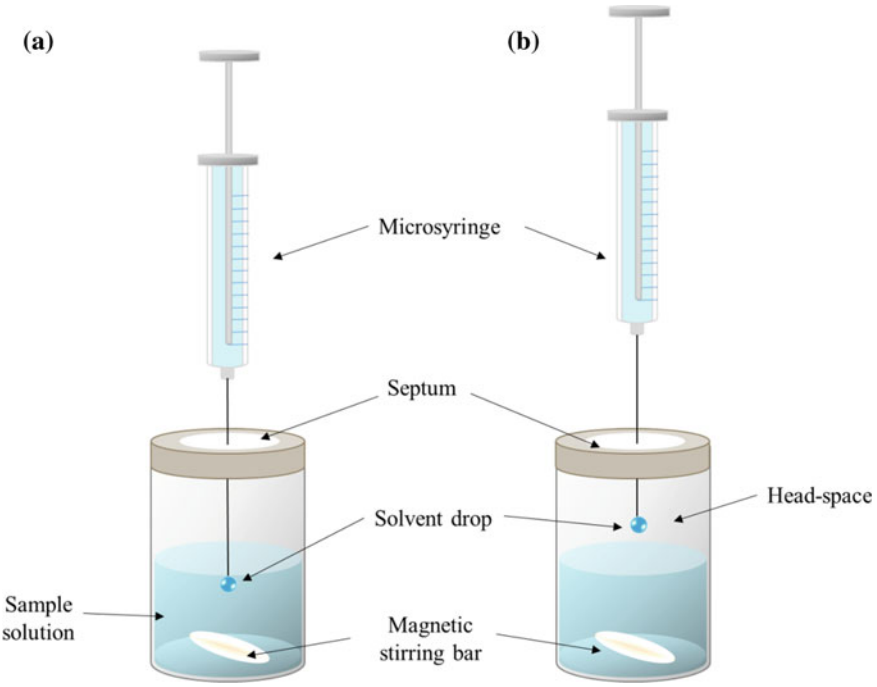

Fig. 5.11 An illustration of SDME technique in **a** DI mode, **b** HS mode

matrix and the extractant phase [116]. High enrichment factor can be achieved due to significantly reduced acceptor phase to sample volume ratio.

One of the key factors in SDME technique is stability of the solvent drop during the extraction process. Another important factor is the droplet volume, which influences extraction capability. The mechanical equilibrium of a microdrop located at the end of a microsyringe needle is given by the balance between forces that impact the drop. When the profile of the drop at the boundary with the capillary is nearly vertical, the maximum drop volume that can be formed can be expressed as:

$$V_{dmax} = (2\pi R_m \delta)/\Delta\rho g \tag{5.5}$$

where R_m is the external capillary radius, δ is the interfacial tension, $\Delta\rho$ is the density difference between the interior droplet phase and the exterior matrix phase, and g is the gravitational acceleration [117]. In the case when drop volumes are larger than V_{dmax} and at the same time is not physically stable, it results in droplet detachment; hence, drop volumes below the V_{dmax} value are recommended for higher reliability.

SDME category may be divided into seven different modes:

- Two-phase modes:
  - Direct immersion SDME (DI-SDME)
  - Continuous flow

  - Drop to drop
  - Directly suspended droplet
  - Bubble in drop [118]
- Three-phase modes:
  - Headspace SDME (HS-SDME)
  - Liquid–liquid–liquid

Direct Immersion and Headspace Modes

Direct immersion mode (DI-SDME) and headspace (HS-SDME) are the most widely used variants of this technique. Their main advantages include simplicity, low cost of the necessary equipment, flexibility in choosing the appropriate solvent for target compounds and green character because of low solvent and sample consumption.

In the case of DI-SDME, the extraction solvent droplet is directly immersed in the stirred sample solution. Average sample consumption and solvent consumption are in the range of 0.3–40 mL and 0.3–3 μL, respectively [103, 119]. It is possible to automate the extraction procedure, using sequential injection manifold systems [120]. DI-SPME is suitable for both non-volatile and volatile compounds, but its utilization is limited by heterogenous samples due to the risk of suspended materials affecting mechanical stability of the solvent drop [106]. The other parameters influencing drop stability like temperature, solvent type, agitation speed and extraction time should be considered as well [119].

Due to the principles of DI-SDME, this mode is best suited for the separation/enrichment of nonpolar or moderately polar, volatile and semi-volatile analytes from relatively clean matrices [119]. Most recent applications of DI-SDME include determination of multi-class pesticides in mango fruit [120], trace analysis of lead in drinking water [121] and determination of acrylamide in potato crisps [122]. Some new extraction solvents were also introduced recently, i.e. ternary composites of nanocellulose, carbon nanotubes and ionic liquids for determination of heterocyclic amines in dried foods [123] or nanofluids of zinc oxide in ionic liquids for determination of fungicides in water samples [124]. More detailed information on DI-SPME applications is referred in Table 5.2.

HS-SDME is the most broadly applied three-phase mode of single drop microextraction. In this case, microdroplet of the extraction solvent is suspended in the headspace of the sample or in the flowing air sample stream to extract volatile and semi-volatile analytes. Mass transfer is higher than that for DI-SDME; thus, extraction time needed to achieve equilibrium state is significantly decreased. It results from the fact that diffusion coefficients in the gas phase are usually greater than the corresponding coefficients in the liquid phase; more rapid stirring and higher temperature may be applied without a risk of droplet destabilization [103, 105, 119]. In comparison to DI-SDME, for headspace mode, wider variety of extracting solvents can be employed, as they may be both miscible and immiscible with sample matrix. The main limitation is necessity to choose extractant phase with low vapour pressure

and high boiling point [125]. Moreover, unlike in DI-SDME, water can be also used as the solvent for extraction of volatile and water-soluble analytes. That results in significantly enhanced range of extractable analytes as well as the range of analytical methods that can be directly coupled to SDME [103].

HS-SDME can be employed for both polar and nonpolar, volatile and semi-volatile compounds. Moreover, because HS-SDME is a three-phase mode, it can be used for sample matrices that are complex, dirty or contain solids, because these do not affect analyte separation and enrichment [120, 125]. Moreover, this mode can be applied not only to liquid samples, but also gaseous and solid matrices. Most recent applications of this technique include trace-level determination of bromide, coupled with microvolume fluorospectrometry [126], extraction of chlorobenzenes with hydrophilic magnetic ionic liquid as an extractant phase [127], extraction of captopril from human serum and pharmaceuticals samples [128] and determination of ammonia in concrete [129]. More detailed information on HS-SDME application is given in Table 5.2.

Directly Suspended Droplet Microextraction (DSDME)

Another mode that undergoes SDME category is directly suspended droplet microextraction, which was first introduced in 2006 [130]. In DSDME, microlitre volume of water-immiscible extraction solvent is added to stirred aqueous sample. The gentle vortex results in the formation of a droplet of extractant phase on the sample surface (Fig. 5.12). The droplet is self-stable and easy to control extraction system. In addition, when the droplet rotates, the mass transfer is enhanced due to internal recycling occurring inside the drop [125, 130, 131]. The key parameters for method optimization are selection of organic solvent type and volume, stirring speed, pH and temperature. The main limitation for organic solvents applicability is their density, which must be lower than sample density [125]. In case of DSDME, the droplet volume may be higher than in DI or HS-SDME modes, without a risk of droplet destabilization. Furthermore, solvent volume should be compatible with the final analytical technique coupled to DSDME. The typical injection volume for HPLC technique is 5–50 μL which falls within acceptable volume range for DSDME. On the other hand, droplets smaller than 2 μL are difficult to collect with microsyringe, which is the main drawback of this technique [125]. To overcome this disadvantage, their mode, named solidified organic drop microextraction (SFODME), was developed in 2007 [132]. In this case, extracting phase must be selected within solvents with a melting point in the range of 10–30 °C. After extraction is completed, vial with sample solution and extraction solvent drop is transferred to an ice bath, where the droplet solidifies and is easy to collect (Fig. 5.12) [132]. Most recent applications of DSDME and SFODME with crucial method parameters are given in Table 5.2.

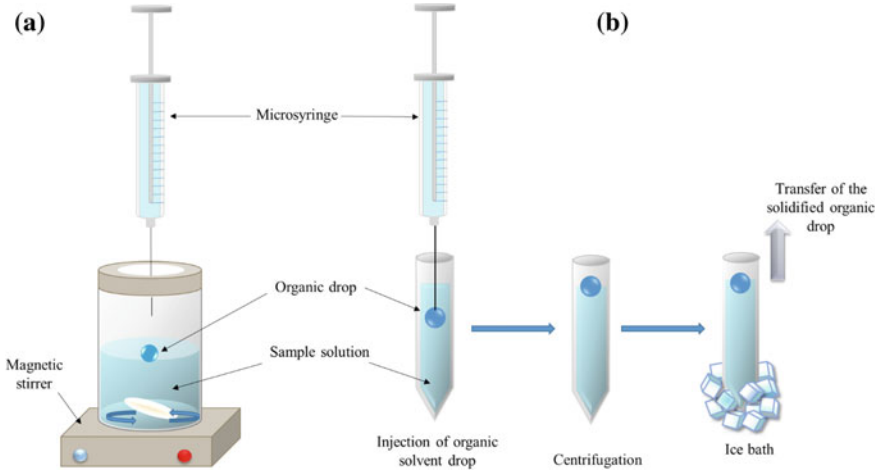

Fig. 5.12 Schematic illustration of **a** SDME and **b** SFODME

Continuous-Flow Microextraction

Continuous-flow microextraction is another SDME two-phase mode, and it was first reported in 2000 [133]. In that technique, 1–5 μL of an organic solvent microdrop is exposed to continuously flowing sample solution. The drop is held at the tip of connecting tubing, placed in a glass chamber and acts as a fluid delivery duct. The sample flows through this tube and the glass chamber to waste, making contact with the solvent drop; thus, the effectiveness of the process results from molecular momentum provided by mechanical forces and from diffusion. HPLC injection valve is used to avoid undesired air bubbles and to achieve the control over the size of the droplet size [133, 134].

This technique provides some advantages like low sample consumption and high preconcentration factor (ranging from 260- to 1600-fold) at the same time. In 2005, CFME modification, where the waste is recycled from glass chamber into the sample vial, was developed. This kind of solution allows reduction of sample size [135]. The schematic representation of CFME procedure is given in Fig. 5.13.

The most important extraction parameters that need to be optimized in order to achieve the best results are the solvent volume, the sample flow rate and extraction time [134]. Most applications of this technique are limited to slightly polar and nonpolar target compounds, because only nonpolar extracting solvents remain stable under flowing system conditions [103]. These applications include determination of pesticides in natural water [134], determination of trace levels of lead in water [136] or determination of polycyclic aromatic hydrocarbons in aqueous samples [137]. More applications and detailed methods parameters are given in Table 5.2.

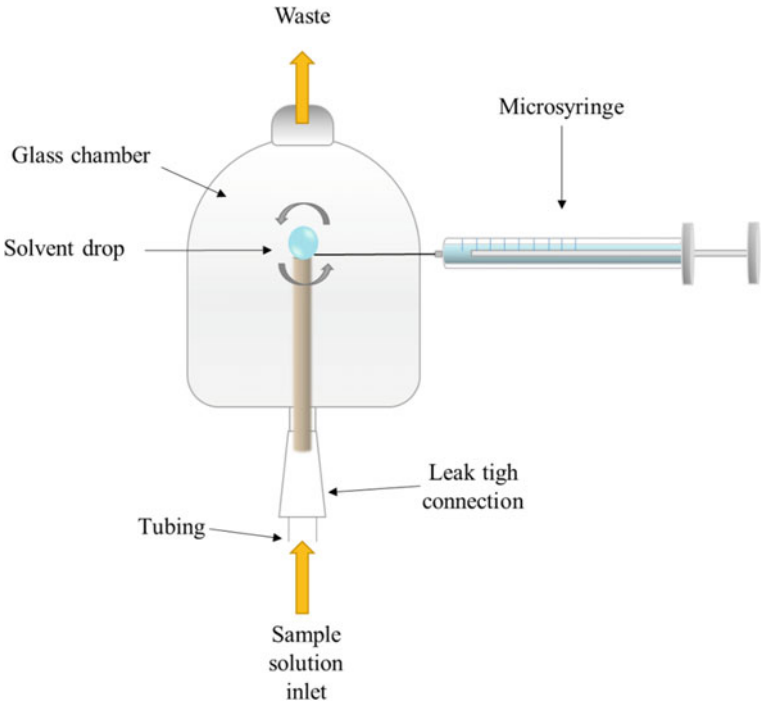

Fig. 5.13 A scheme of CF-LMPE system set-up

5.2.7.2 Dispersive Liquid–Liquid Microextraction (DLLME)

DLLME method was first developed in 2006 as another LLME variant [138]. This technique principle is based on the formation of cloudy solution of water-immiscible extraction solvent and miscible with both extraction solvent and aqueous matrix dispersive solvent, which is rapidly injected to the sample containing target analytes. Chemicals having affinity to organic solvent are enriched in the extractant phase dispersed in the bulk aqueous solution. To separate phases, centrifugation is applied and solvent part, containing target compounds, is collected. Final determination may be performed by conventional analytical techniques. The scheme of DLLME principle is illustrated in Fig. 5.14 [138, 139].

An appropriate selection of extraction and dispersive solvents is one of the crucial steps for DLLME to gain the maximum efficiency. Dispersive solvent helps extractant to form fine droplets that constitute 97–99% total volume of extracting solution. Owing to the large surface contact area between the extracting solvent and the aqueous sample, mass transfer processes speed is increased significantly; thus, equilibrium state is achieved quickly, and the extraction is independent of time. This along with high extraction efficiency is the most important advantage of this method [139–141]. In order to avoid problems connected with inconvenient collection of the

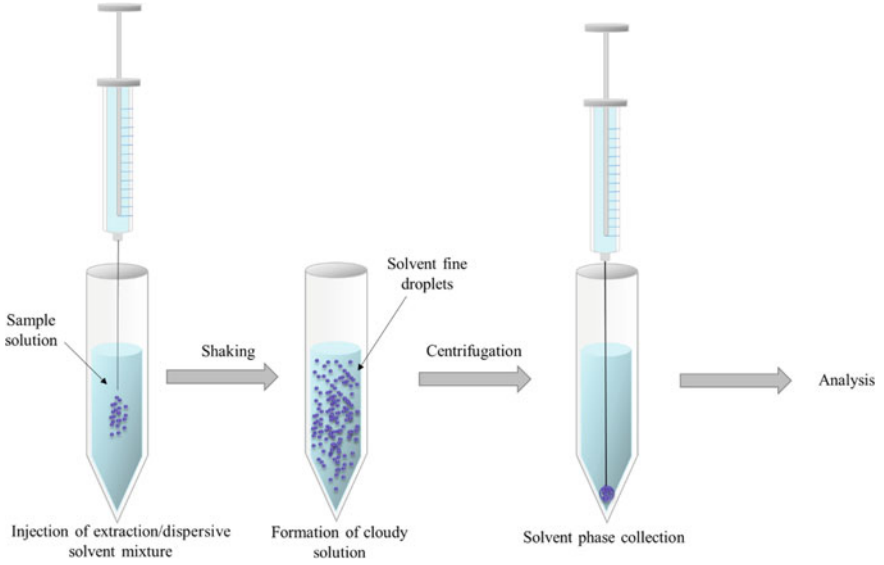

Fig. 5.14 Schematic representation of DLLME procedure

organic phase after centrifugation, solvents characterized by the density higher than water are usually selected. The most common dispersive solvents used are acetone, acetonitrile, methanol and ethanol. To obtain high enrichment factor, the key parameters such as volumes of dispersive and extraction solvent, pH value and salting effect should be optimized. The most common approach is step-by-step optimization. The pH is particularly important in extraction of polar analytes. The value of pH is chosen so as to decrease analyte solubility in the water phase [141, 142]. The main limitations of DLLME technique consist of its lack of suitability to be applied in the case of complex matrices, such as biological samples, or incompatibility of this technique with certain analytical techniques (i.e. ICP-OES) due to utilization of high-density solvents [141]. Moreover, DLLME in some cases needs high volumes of dispersive solvent to obtain cloudy solution. In recent years, an application of different types of auxiliary energy has been shown in order to reduce or eliminate the usage of dispersive solvent [1].

DLLME technique is widely used for determination of both organic and inorganic species in aqueous samples, such as pesticides [143–146], a broad spectrum of endocrine disruptors [147–149] or pharmaceuticals and personal care products [150, 151].

Metals are also a popular group of analytes extracted by DLLME. Procedures used for metals required the use of an appropriate organic compound to transfer these analytes to the extracting solvent. Of the different chelating agents proposed, the most frequently used were ammonium pyrrolidinedithiocarbamate (APDC) [152] and sodium diethyldithiocarbamate (DDTC) [152, 153].

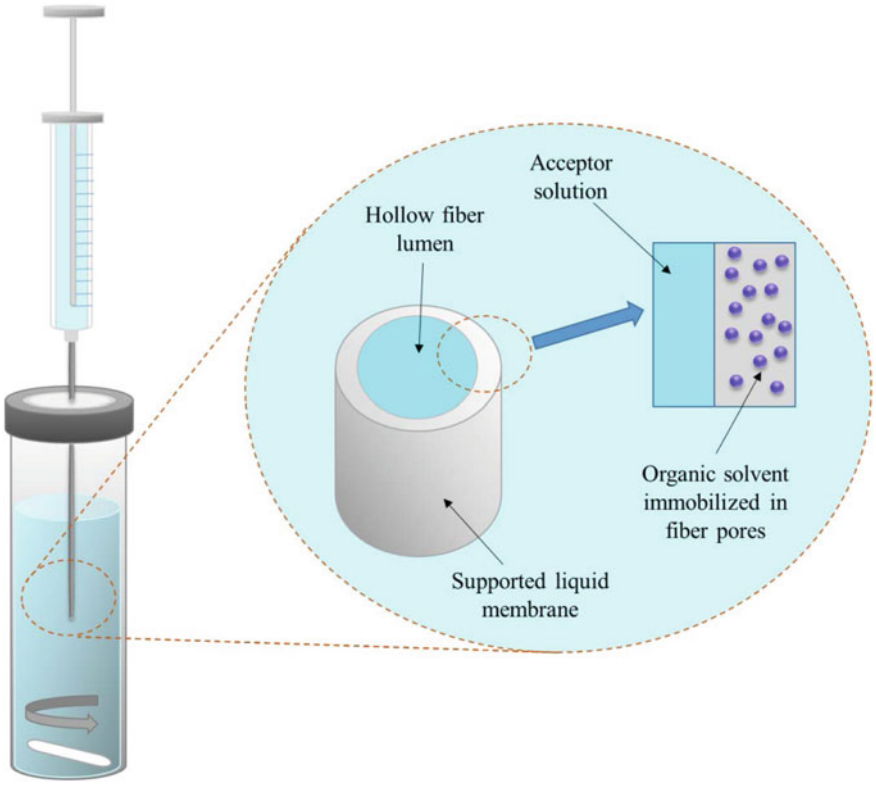

Fig. 5.15 Representation of HF-LPME principle

Table 5.2 contains more detailed information on recent DLLME applications.

5.2.7.3 Hollow-Fibre Liquid-Phase Microextraction (HF-LPME)

A technique that combines SPME with LLME was introduced in 1999 and is named hollow-fibre liquid-phase microextraction (HF-LPME). HF-LPME involves application of porous polypropylene hollow fibre with organic solvent immobilized in its pores [154]. This technique is typically a three-phase microextraction mode, consisting of four main components such as (i) sample solution, which is usually aqueous, as an analyte donor phase, (ii) hollow fibre used as a support for immobilization of organic solvent, (iii) organic solvent in the hollow-fibre pores, (iv) acceptor phase placed in the hollow-fibre lumen (usually an acidic, basic or organic solution) [155, 156] (Fig. 5.15).

The hollow fibre needs to be appropriately prepared prior to analysis, which is done by dipping the fibre into an organic solvent immiscible in water. Due to capillary

forces, the solvent is immobilized in the hollow-fibre pores which results in the formation of a supported liquid membrane. The acceptor solution is introduced into the fibre lumen and afterwards is immersed in sample solution for target compounds extraction. The analytes diffuse from water solution into the acceptor phase. Vigorous agitation and stirring are one of the important factors, having a significant impact on the extraction efficiency. After the time needed to achieve process equilibrium, the acceptor phase is withdrawn and may be injected in a compatible instrument (GC, HPLC or CE) for final analysis [154, 156–159].

Few different types may be distinguished under HF-LPME conception, depending on the prosperities of compounds of interest. In the case of low and medium polarity analytes, which are usually analyzed by GC, two-phase mode is applied. In that case, the organic solvent immobilized in the hollow-fibre pores is the same as the acceptor-phase solvent. The mass transfer is based on the classical partition [160, 161]. For the analytes possessing ionizable functions (acidic or basic compounds), the sample and acceptor pH should be adjusted to the suitable value before extraction. In the case of basic compounds, the sample pH is high, to suppress the ionization when the acceptor solution pH is low. Analytes are first extracted to the supported liquid membrane in their neutral state, and then, they enter the extractant phase, where the protonation occurs. It prevents back-extraction, due to high solubility of the target compound in the acceptor solution. For the acidic chemicals, the process basics are the same, but the pH gradient is reversed [159, 162].

The static and dynamic modes of HF-LPME affect mainly the extraction process speed. In static mode, sample solution is stirred with magnetic stirring bar, while the hollow fibre containing extraction solution is immersed. In case of dynamic mode, small portions of the sample are repeatedly let through the hollow fibre, using syringe plunger, which can reduce the extraction time [160].

The key parameters that influence HF-LPME efficiency are listed below.

- Hollow-fibre materials, slightly hydrophobic materials such as polypropylene, polyethersulfone and polyvinylidene fluoride, are used most commonly due to their ability to immobilize organic solvents as a liquid membrane;
- Acceptor and donor-phase volume influence the enrichment factor;
- Acceptor and donor-phase pH should be adjusted depending on the analytes properties in order to increase the mass transfer;
- Temperature affects the mass transfer rates of analytes and the partition coefficients between the organic and aqueous phases. When the temperature increases, the mass transfer rates of analytes increases, but the partition coefficients decrease;
- Type of the organic solvents, non-volatile, water-immiscible and compatible with the final analytical technique solvents, is preferred.

The major advantage of HF-LPME is the green character of this technique. The organic solvent is applied in microvolumes; i.e., for three-phase mode, the solvent consumption is in the range of 10–20 μL per sample. It should be also highlighted that because of the high sample-to-acceptor-phase volume ratio, excellent enrichment factor may be achieved. Sample clean-up is another major motive to use HF-LPME technique. Due to the fact that most water-soluble components of the matrix are not

able to penetrate the supported liquid membrane and are excluded from the acceptor solution, three-phase HF-LPME gives higher degree of clean-up than two-phase mode. Therefore, polar organic substances, salts and macromolecules (among others) all remain in the sample during HF-LPME [160]. On the other hand, several disadvantages of HF-LPME should not be overlooked. In most cases, a home-built equipment needs to be built for the extraction purposes, because of the lack of commercially available equipment. Hollow fibres need to be appropriately cut and sealed. Moreover, the time required for the equilibrium to be gained is typically from 15 to 45 min. Long extraction time results from the analytes mass transfer through the supported liquid membrane, which is the main speed limitation factor [103, 161–164].

The application of this technique is for extraction and preconcentration of a vast range of chemicals in environmental and water samples. Most recent applications include utilization of novel ionic liquids and deep eutectic solvents for the extraction of steroidal hormones from biological fluid samples [164], determination of salicylic acid in river waters [165], determination of hippuric acid in human plasma using molecularly imprinted sol–gel-based HF-LPME [166] or extraction of trace levels of benzodiazepines in urine [167]. More HF-LPME applications with detailed parameters are given in Table 5.2.

5.2.7.4 Electrokinetic Membrane Extraction (EME)

The electromembrane extraction (EME) technique was proposed in 2006 for the first time, in order to overcome some limitations of HF-LPME, mainly time-consuming extraction process [168]. Similar to HF-LPME, the target compound are extracted from the aqueous sample solution, across a supported liquid membrane containing microvolume of organic solvent, to an acceptor solution placed in the hollow-fibber lumen. The main difference lays in the electrical potential sustained over the SLM that enhances the speed of extraction by electrokinetic migration for ionic chemicals and allows to manipulate the process [168, 169]. The electrical field is achieved by placing two electrodes placed in the sample and inside the lumen [103, 169]. In the case of analysing compounds of interest that have basic nature, the anode needs to be placed in the sample solution and cathode is placed in the acceptor phase. For acidic chemicals, the electrodes placement is reversed. The value of pH is important factor affecting extraction process and needs to be monitored in both sample solution and acceptor phase. After extraction, the acceptor solution is withdrawn and injected to the final analysis instrument, such as HPLC or CE. The schematic illustration of the EME principle is given in Fig. 5.16.

EME combines most of the HF-LPME advantages (excellent sample clean-up, sensitivity, extremely low organic solvent consumption) with significantly reduced extraction time (from 15–45 min to 5 min). Furthermore, the selectivity of the method may be controlled by adjusting the direction and proper magnitude of the electrical potential [170]. The direction controls if cations or anions are to be extracted, whereas the magnitude of the electrical potential controls the type of compounds to be extracted. Furthermore, the extraction selectivity can also be manipulated by the

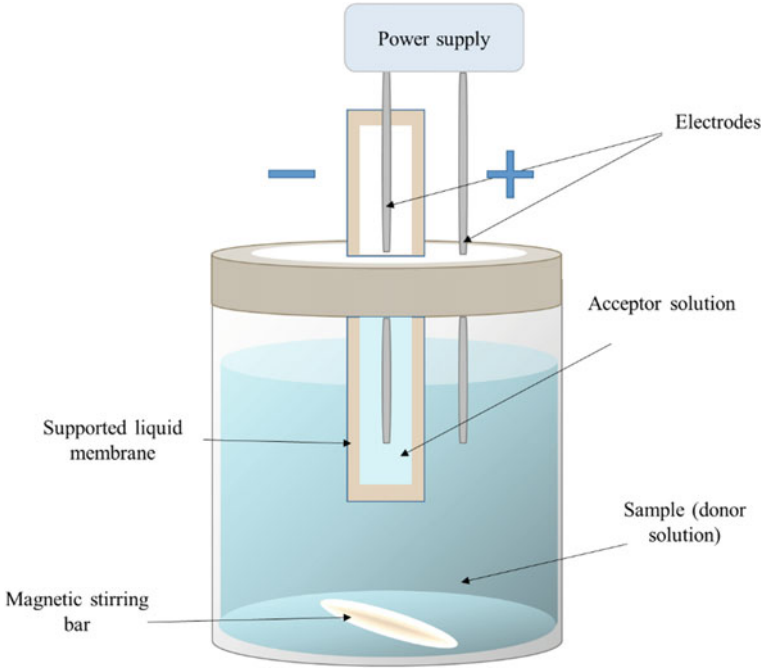

Fig. 5.16 Scheme of the equipment necessary in electromembrane extraction technique

type of organic solvent used as the SLM [103, 170]. Although EME is promising in several aspects, the development of commercially available equipment is mandatory for the future. Currently, home-built equipment used for EME limits the implementation of this technique into more research laboratories.

Because of its advantages, EME has attracted a lot of attention in the recent years. It was successfully applied mainly for the analysis of basic and acidic drugs [169, 171–173] from both environmental and biological samples. It is worth mentioning that simultaneous extraction of both basic and acidic has been a challenge [173]. EME was also applied for extraction of biogenic amines in food samples [174] and a broad range of metal ions [175–177]. More information on EME application has been introduced in Table 5.2.

5.3 Future Trends and Perspectives

Analytical microextraction, which is defined as non-exhaustive preparation of the sample method with a very small extracting-phase volume relative to the sample volume, represents an important development in the field of analytical chemistry. Recently, many microextraction techniques exist, and thus, analytes can be extracted

by the application of a small volume of a solid or semi-solid polymeric material, as in SPME, or alternatively by a small volume of a liquid, as in LPME.

Taking all described here techniques, automated SPME–GC is now a strongly established technique with the original fibre-type SPME device and, to a lesser extent, in-tube approaches. And it seems that future improvements and developments in this area are likely to be focused on the automation of more complicated procedures that apply devices such as the dual-arm sampler or cold-fibre approach [67]. In addition, it could be great if other autosampler modules which could increase the range of tasks that are amenable to automation will be developed. As a more recent example, an automated cold-fibre SPME device that would add significantly to the capabilities of automated SPME can be given. Furthermore, it is expected that several improvements in the robustness of SPME extraction phases will be introduced. This will provide longer analysis periods without user intervention and thus would be particularly beneficial for situations such as automated field analysis.

In contrast, SPME-LC automation is not as much common as SPME-GC, however, has been made possible with the application of in-tube-based extraction devices, but these do have some drawbacks. The challenge is to develop a sampler that can successfully automate the fibre approach or another SPME configuration with LC that will provide a broader applications range [67].

Automated coupling with other analytical equipment including CE and spectroscopic techniques would also be expected to receive attention in the future. Finally, the full automation of other configurations of SPME, such as SBSE, would also be of benefit because of their greater sensitivity.

In contrary to SPME, LPME has recently been accomplished with home-built equipment within a relatively few laboratories around the world. The commercial availability of the equipment is still limited. Thus, the most important issue for the future of LPME is the development of more commercial equipment with a special focus on three-phase extractions. This is in progress based on hollow-fibre technology. The opportunities of three-phase LPME should particularly stimulate more commercial development, and the technique should be of high interest for the analytical chemists [67].

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Chapter 6
Greening the Derivatization Step in Analytical Extractions: Recent Strategies and Future Directions

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Abstract Green analytical chemistry is an emerging subject within the domain of analytical chemistry, and it impacts and dictates about all the procedures and methods involved in the determination of the analytes. The concept of GAC has encouraged shifting the area of the sample preparation toward simplified, miniaturized, and automated methods by declining the multistep, large-scale, and manual methods, respectively. The GAC suggests avoiding the derivatization (chemical conversion) of the analytes. However, due to certain limitations associated with the analytical instrumentation and chemical structures of the analytes, the step of derivatization is unavoidable. To reduce the impact of derivatization on the environment and workers, it may be coupled with micro-extraction procedures that require minimized volumes of solvents and reagents. Indeed, this coupling provides great opportunities to deal with different kinds of analytes and sample matrices. Apart from the amalgamation of micro-extraction and derivatization, the selection of eco-friendly solvents/reagents, the use of greener energy sources such as microwaves or ultrasound and performing online derivatization (in-port, on-column/in-capillary) can significantly contribute toward the "greenness" of the procedure. This book chapter highlights the latest advancements in this direction.

Keywords Green analytical chemistry · Green sample preparation · Micro-extraction · Analytical derivatization · Green reagents

6.1 Introduction

Sample preparation is an unavoidable step during the analysis of some compounds present in different matrices due to many factors such as low concentration of the analytes or the complex nature of the matrix or incompatibility of the chemical

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J. Płotka-Wasylka and J. Namieśnik (eds.), *Green Analytical Chemistry*,
Green Chemistry and Sustainable Technology,
https://doi.org/10.1007/978-981-13-9105-7_6

structure/features of the analytes with the targeted analytical instrument. Sample preparation can be a tedious task comprising several steps if all the above-mentioned factors are combined in the samples of interest. The mismatch of the analyte chemical structure/features with the final instrument requires the conversion of the analytes into suitable derivatives through a process of chemical conversion known as derivatization. The process of derivatization can itself induce a lot of difficulties during the analysis depending on the nature of the matrix. It needs to combine the sample preparation and derivatization to cope with this kind of challenges. Secondly, the use of derivatizing reagents is not encouraged under the emerging ideas of green analytical chemistry (GAC) due to their toxic and hazardous nature. The conventional sample preparation and derivatization will require excessive volumes of extraction and derivatizing reagents putting both the workers and the environment at risk. As derivatization is unavoidable step during the analysis of some classes of analytes, it would be an interesting idea to miniaturize the sample preparation and derivatization steps and if possible to perform them in a single step [1].

The beauty of the derivatization reactions lies in their scope that can be extended to different matrices as well as applications. For example, the same chemical reaction can be used for the derivatization of carbonyl compounds in human breath or air. Similarly, the amino acids present in food or biological matrix will be derivatized same chemical derivatization procedure [2]. Derivatization is performed using pre-, on-, and post-column approaches. Mostly, pre- and on-column modes are performed before GC analysis. The purpose is to improve the volatility, withstanding to high temperatures, separation, and detectability of the analytes. Pre-column extraction is also performed before LC-MS/MS to enhance the retention in the column and then ionization efficiency in MS. Pre-column mode derivatization is generally employed the conversion of polar/ionic analytes to non-polar and volatile derivatives before injecting to GC systems. Post-column derivatization is generally performed with LC. The analytes are derivatized after separation from the LC column to make them detectable by UV or fluorescence detector [3].

Several articles have been dedicated to green analytical derivatizations and methodologies and can be consulted for a comprehensive understanding of the subject [4–6]. This chapter aims to compile the strategies that can be adopted to make the derivatization process “greener” in nature. Emphasis will be given to the importance of coupling derivatization with miniaturized sample preparation technique. A brief account will be provided on instrumental configurations, energy sources, and reagents and solvents that can play a role in achieving the target related to “greener derivatization.”

6.2 Methods for Making Derivatization Process "Greener"

6.2.1 Micro-Extraction Coupled with Derivatization

In past, solid-phase extraction (SPE) and liquid–liquid extraction (LLE) have been widely used for the extraction of derivatized analytes prior to chromatographic separation and determination. The major drawbacks of these classical techniques are huge consumption of toxic solvents, derivatizing reagents, and manipulation of samples. In addition, the automation of these techniques including derivatization step is quite challenging and is scarcely addressed. Micro-extraction techniques have got significant attention in sample preparation during the last few decades. They are developed with the aim of minimizing the volume of the toxic solvents, miniaturizing the scale of extraction, and exploring the opportunities for automation and online coupling with the analytical instrumentation. Thus, various sorbent- and solvent-based micro-extraction techniques have been developed including the famous solid-phase micro-extraction (SPME) and liquid-phase micro-extraction (LPME).

SPME is a green alternative to solid-phase extraction (SPE) in which analytes are extracted onto a small layer of the sorbent coated on silica fiber or metallic support. These extracted analytes can be desorbed by the provision of heat into GC while by solvent desorption into LC. The volume of the required solvent is very small in case of solvent desorption. As the analytes are enriched in a very small amount of the sorbent, SPME leads to very high pre-concentration factors which ultimately extend its applications into ultra-trace-level analysis. The selectivity of SPME can be enhanced by selecting the sorbent phase as per the nature of the analytes. Different analogs of SPME and other sorbent-based micro-extractions have been developed including stir-bar sorptive extraction (SBSE), dispersive micro-solid-phase extraction (D-μ-SPE), and membrane-protected -μ-SPE. LPME is a miniaturized version of liquid–liquid extraction (LLE). LLE is a famous classical extraction technique due to better clean up, simplicity of operation, and selectivity. However, due to the consumption of large volume of solvents, it is not considered as environmental benign technique. Compared to LLE, LPME requires very small volumes of the solvents and it has a performance comparable or even better than LLE. Single-drop micro-extraction (SDME), hollow-fiber liquid-phase micro-extraction (HF-LPME), and dispersive liquid–liquid micro-extraction (DLLME) are among the famous versions of LPME [7].

While coupling derivatization and micro-extraction, the quantity of required derivatizing reagent will reduce significantly in parallel with amounts of sorbent or solvent in micro-extraction. The amount of generated waste will also lessen. Due to the reduction in derivatization scale and miniaturization of extraction, it will be easier to automate the process, which will further reduce the human effort and expected chances of error.

Apart from the GAC and environmental aspects of the combination, the derivatization alone in many cases can introduce complex impurities, side products, and incomplete reactions that may need additional treatment before analysis.

The derivatization step can be performed before, after, or simultaneously with the micro-extraction depending upon the nature of the analytes. The derivatization before micro-extraction can provide higher partition coefficients in micro-extraction and improve the column separation of the analytes during analysis. This mode is preferable when no complications are expected from the derivatization itself. In case, the derivatization can further complicate the sample matrix due to any chemical interactions or extraction of the derivatives is not easy; it is preferable to perform derivatization after micro-extraction. In simultaneous or in situ mode, derivatization and micro-extraction are performed in a single step. This is simpler, easier, and greener in nature compared to other modes, but its application also depends on the nature of the samples.

Above-mentioned derivatizations are performed off-line before the analysis step. However, in specific cases, such derivatizations may result both in loss and contamination of analytes due to procedural steps of heating, evaporation, transferring, re-constitution, and work up. The presence of moisture can also have some major issues as some of the derivatizing reagents and analyte derivatives are highly water-sensitive. Such cases can be handled by micro-extraction followed by online or injection-port derivatization. The extract and the derivatization reagents are injected into hot GC port, where they react in gaseous phase to produce derivatized analytes. The extract and derivatization reagents can be injected together or in separate injections. In case of single injection, an air gap is placed between extract and derivatizing reagent. Online derivatizations not only provide moisture-free environment for reaction and overcome above-listed disadvantages, but they are also effective in terms of time, consumption of sample and reagents, and efficiency of analysis.

6.2.1.1 Sorbent-Based Micro-Extraction and Derivatization

Solid-Phase Micro-Extraction

Solid-phase micro-extraction (SPME) was introduced in 1990 as a solvent-less extraction technique for analytical sample preparation [8]. Since then, a great interest has been developed in micro-extraction approaches. SPME integrates sampling, extraction, and pre-concentration in a single step. Among the different formats of SPME, fiber and in-tube SPME are most common. In fiber-SPME, the analytes are extracted from the samples onto a layer of adsorbent that is coated on a fused silica, metallic, or plastic support using direct immersion or headspace mode. The analytes are then desorbed thermally into GC or by the solvent into LC system for analysis. Due to solvent-less or solvent-minimized nature and less production of waste, SPME is a relatively greener extraction technique and its coupling with derivatization requires little volumes of derivatizing reagents. The first application of SPME and derivatization was reported in 1997 [9]. With SPME derivatization can be performed in sample solution, or on fiber, or in the injection port. In the first case, analytes are derivatized in the samples solution and resulting derivatives are then extracted onto SPME fiber. For on-fiber derivatization, it is first dipped or sprayed

with derivatizing reagent which is then exposed to analytes containing sample solution. For injection-port derivatization, extracted analytes are desorbed into GC port with closed split followed by an injection of derivatizing reagent. SPME-coupled derivatizations are also classified as pre-SPME, post-SPME, in situ with SPME, and injection-port derivatization.

Stir-Bar Sorptive Extraction

Stir-bar sorptive extraction (SBSE) was introduced in 1999 to address some limitations of SPME [10]. In this technique, a sorbent-coated stir-bar is used for the extraction of target compounds from the sample media. PDMS is most commonly employed sorbent, and it is used to extract hydrophobic/non-polar analytes. The analytes are then desorbed thermally or with the aid of the solvent. In case of thermal desorption, non-polar polymer coating might only be applicable to semi-volatile and thermally stable compounds. In case of polar and thermally unstable compounds, derivatization step is required. Derivatization can be performed before, after, in situ, or on-fiber with SBSE depending on the nature of the analytes and matrix. For in situ SBSE derivatization, the derivatizing reagent and SBSE are performed with the sample solution subsequently or simultaneously. SBSE can be performed in DI or HS mode depending on the requirement of analytes and nature of matrix. On-fiber mode works in two ways. In the first way, derivatizing reagent is pre-adsorbed on SBSE coating and derivatization and extraction takes place simultaneously. In the second way, derivatizing reagent is sprayed on SBSE coating after the extraction of analytes. Another approach involves derivatization inside the thermal desorption unit, and this is accomplished by placing derivatizing reagent and analyte containing SBSE device in the unit. This is a good procedure for silylating agents. Few selected examples of SBSE coupled with derivatization are carbonyls in rainwater [11] and chlorophenols in water and body fluids [12].

Micro-Extraction by Packed Sorbent

Micro-extraction by packed sorbent (MEPS) is a miniaturized version of classical SPE with some additional advantages. The sorbent (1–4 mg) is packed inside the cartridge or special container which is then placed within the injection syringe. The cartridge is fitted between barrel and needle (Barrel insert and needle BIN). The sorbent can be used multiple times and the extraction procedure can be automated and coupled online with analytical instruments such as GC, LC, and CE. MEPS can be combined with derivatization using “in situ” and “injection-port” modes. The methods with additional green features such as automation, reduced use of derivatizing reagents, water as reaction medium, and shorter completion times have been reported. Haloacetic acids in water [13], polyamines and related compounds in urine [14], and estrogenic compounds in water [15] are some examples of this combination.

Dispersive/Magnetic Solid-Phase Extraction

Dispersive solid-phase extraction (DSPE) is performed by dispersing/adding few mg of the sorbent directly into the sample solution. This dispersion is assisted by shaking, vortexing, or ultra-sonicating. Due to direct dispersion, the contact area between sorbent and analyte increases and it gives fast extraction. The sorbent is separated after the extraction by centrifugation. The analytes are desorbed into suitable solvent. Most common requirements of SPE such as packing of sorbent in a column or cartridge, blockage of column, large amounts of sorbent, samples, and solvents are avoided in DSPE. Another common mode of DSPE is magnetic solid-phase extraction (MSPE) where magnetic sorbent is employed. After extraction, it provides fast sorbent retrieval due to magnetic separation. DSPE can be combined with derivatization in three ways:

(i) Derivatization is performed in solution before DSPE.
(ii) The sorbent is coated with derivatizing reagent which allows simultaneous derivatization and extraction.
(iii) Derivatization is performed after extraction.

MSPE was combined with in situ derivatization of aldehydes in human urine samples [16].

6.2.1.2 Solvent-based Micro-extraction and Derivatization

LMPE is a solvent- and scale-minimized version of LLE. It overcomes the disadvantages of LLE such as large consumption of solvents, requirement of large volume of samples, longer extraction times, and tedious procedure. LPME combines extraction and pre-concentration into a single step and thus provides very high enrichment factors. The volumes of the extraction solvents are typically in the range of microliters. The famous formats of LPME include SDME, DLLME, and HF-LPME. Integration of LPME with derivatization requires extremely low volumes of derivatizing reagents.

Single-Drop Micro-Extraction

Single-drop micro-extraction (SDME) is carried out by appending a drop of extraction solvent at the tip of the needle of the syringe. SDME can be operated in DI or HS mode. After extraction, this drop can be injected directly into the analytical instrument. It can be easily automated. It provides high enrichment factors due to very low volume of the extraction solvents. The carryover effect and fiber breakage encountered in SPME can be easily avoided by SDME. It is low-cost, highly efficient, and green in nature [3]. It offers fantastic opportunities for coupling with derivatization by employing minimal volumes of derivatizing reagents. Derivatization can be performed after SDME inside the syringe. It can also be used for the

extraction of derivatized analytes from the sample solution. In another mode which allows simultaneous extraction and derivatization relies on suspending a drop that is a mixture of extraction solvent and derivatization reagent. Some selected examples of SDME coupled with derivatization are SDME of phenols from water followed by in-syringe derivatization [17], in-sample derivatization of short-chain fatty acids followed by HS-SDME [18], fully automated simultaneous SDME and derivatization of hydroxylated PAHs from seawater in a single mixture drop [19].

Hollow Fiber Liquid-Phase Micro-Extraction

Hollow fiber LPME (HF-LPME) is performed using porous hollow fiber membranes. The pores of the fibers are impregnated with organic solvent and extraction solvent is filled inside the lumen of the fiber. This fiber is then immersed inside the sample solution. The extraction solvent is taken out with the help of the syringe and injected into an analytical instrument. Every time a fresh piece of fiber is used for extraction, thus the carryover effects can be avoided. This is green approach because of low-solvent consumption and time and energy efficiency. HF-LPME can be coupled with injection-port derivatization for the analysis of polar and semi-volatile compounds such as alkylphenols and bisphenol A. HF-LPME extract and derivatizing reagent are injected into GC-inlet port. The volume of HF-LPME extract (5 μL) is very small and further dilution will decrease enrichment and sensitivity, thus its direct derivation in injection port is preferable [20]. In another mode, derivatization is performed in sample solution extraction. HF-LPME is used to extract derivatized analytes [21]. Derivatization can be performed after HF-LPME in case of complex matrices [22].

Dispersive Liquid–Liquid Micro-Extraction

In dispersive liquid–liquid micro-extraction (DLLME), a mixture of extraction and dispersive solvents are rapidly injected into aqueous solution. It results in the formation of the cloudy solution which is subjected to centrifugation for the separation of organic layer. Dispersive solvent should be miscible both with acceptor (extraction) and donor (aqueous) phase. DLLME is cost-effective, efficient, and rapid extraction technique. It utilizes very low volumes of extraction solvent and thus provides very high enrichment factors. It has been widely coupled with derivatization employing a variety of modes mostly decided by nature of analytes, sample matrix, and final determination instrument. Several DLLME parameters can be manipulated to enhance the green character in DLLME-derivatization combination. Volumes of sample, extraction and dispersion solvent and derivatizing reagents can be substantially decreased. The solvent of derivatizing reagent can also act as dispersive solvent. Dispersion can be avoided using alternatives such as air-, vortex-, shaking-based dispersion. The whole procedure can be automated as well as coupled online with the analytical instrument.

In situ derivatization-DLLME integrates derivatization in a single step. Simultaneous derivatization and DLLME is closely related to in situ with a slight time-scale difference in addition to extraction and derivatizing reagents. These modes are suitable when either the matrix is clean or it is expected not to interfere with the derivatization of analytes. The complex samples like honey, milk, and blood plasma need pre-treatment before simultaneous derivatization and DLLME. As few examples, these modes are used for extraction and derivatization of organotin compounds in water [23], biogenic amines in alcoholic beverages [24] and food samples [25], neurotransmitters and their metabolites in rat urine [26], non-steroidal anti-inflammatory drugs in biological fluids [27], pharmaceutical drugs in urine and plasma samples [28], chlorophenols in water samples [29], sulfonamides in river water and other matrices [30], anilines [31, 32], triclosan and methyltriclosan [33], octylphenol and nonylphenol [34], fatty acids [35] in water, speciation and determination of arsenic (III, V) and antimony (III and V) [36].

Derivatization can also be performed in sample solution prior to DLLME. In such cases, derivatized analytes are extracted by DLLME. This mode is used to get better partition coefficients in extraction and improved separation in chromatographic column. This mode is preferable over in situ or simultaneous mode when the rate of extraction is higher than the rate of derivatization or derivatization reagents extracts better than respective analyte derivative [37]. However, it may need optimization of parameters due to separate steps of derivatization and DLLME. Some examples of this mode include derivatization and extraction of metals from different media [38–43], biogenic amines in food samples [44], melamine in milk and powdered infant formula [45] and steroidal and phenolic EDCs in different kinds of food samples [46].

When the matrix is complex, and derivatization can further complicate it, derivatization is performed after DLLME. This is also a mode of choice, when derivatizing reagent is more reactive toward matrix components than the analytes. It can be lengthy compared to in situ and simultaneous modes due to additional number of steps. It has been used for the extraction and derivatization of estrogens in wastewater [47], hydroxylated benzophenone UV filters in seawater [48], UV filters in environmental waters [49], 13 UV filters and Bisphenol A (BPA) in wastewater [50], etc. In some cases, derivatization is performed between two DLLMEs. In first DLLME, analytes are extracted from complex matrices into a suitable extraction solvent. This solvent is then subjected to derivatization. Second DLLME is performed to remove excess reagents and further pre-concentrate the derivatized compounds. This mode is used for the extraction and derivatization of cholesterol and its metabolic steroid hormones in biological fluids [51]. DLLME can also be followed by online derivatization in the injection port of GC. It helps to avoid the analytes losses due to procedural steps, and the contamination of samples or final extract. Online derivatization is highly suitable for water-sensitive derivatizing reagents or analyte derivatives. Moreover, extremely small volumes of final extract and derivatizing reagents are required. Reaction completes within a closed system in a relatively shorter time. Ion-pair DLLME and GC-MS/MS with injection port derivatization were used for the extraction and determination of PFCAs in water samples [52]. DLLME-injection-port derivatiza-

tion was also employed for the determination of lipophilic compounds in fruit juices [53]. DLLME is not directly coupled with derivatization post-column derivatization. DLLME is performed before chromatographic separation of the analytes, and its main objective is the extraction of analytes from complex samples and their enrichment. After chromatographic separation, analytes are derivatized and detected by UV or fluorescence detector. This mode has been used for the determination of aflatoxins in yogurt samples [54].

6.2.2 Instrumental Configurations

On-column derivatization in LC and in-capillary derivatization in CE are two important instrumental configurations that allow derivatization to take place during analyte separation stage. It consumes low volumes of solvents and derivatizing reagents and whole procedure is automated. In this way, it has several advantages over pre-column or post-column modes of derivatization. Injection-port derivatization in GC also simplifies overall process, and it provides a controlled environment for derivatization utilizing very small volumes of sample and derivatizing agent. The disadvantages related to analyte loss, moisture-sensitive reactions, and waste generation can be circumvented [4].

6.2.3 Energy Efficiency in Derivatization Process

Energy consumption or generation in a chemical reaction is an important factor to consider from environmental and green chemistry perspective. Based on the fourth and ninth principles of GAC, the energy consumption should be minimized for all analytical operations. It is suggested to perform the reactions at room temperature and pressure. Most of the derivatization reactions are assisted by high-temperature conditions, and this is the parameter that consumes energy in the derivatization process. It also affects the cost of the process. Thus, the procedures which are energy-efficient are preferable both in sample preparation as well as analytical measurement. The combination of micro-extraction and derivatization exemplifies some reactions that are energy- and solvent-efficient and thus cost-effective.

The derivatization reactions that are assisted by high-temperature conditions should be performed using alternative energy sources such as ultrasound, microwave, photochemical, vortex, and electrochemical. These sources are comparatively more environmentally friendly as well as effective than conventional sources of heating. Microwave heating accelerates the reaction and reduces total reaction time although it significantly depends on the nature of the reaction. For some reactions, reaction time is reduced from several hours to five minutes with the aid of microwave irradiation [55]. It provides a precise control of temperature and time of microwave irradiation on a smaller volume of reaction mixture thus benefitting in terms of cost

and environmental impact. Microwave can perform simultaneous digestion, extraction of analytes, and derivatization in case of solid samples [56]. Microwave-assisted derivatization is performed in combination with micro-extraction to get synergistic advantages of both.

Ultrasound energy is another important alternative to conventional heating sources. It accelerates derivatization reaction due to underlying cavitation phenomenon that enhances temperature and pressure which ultimately leads to the formation of reactive radicals. Ultrasound is generally applied in the form of baths but other systems like probe or horn can be applied to enhance cavitation. It has a great impact over the shortening of derivatization time. Both microwave and ultrasound help to take place the derivatization reaction under soft conditions.

Another effective parameter in derivatization is vortex and stirring. Due to mechanical mixing, high analyte enrichment might be obtained and analyte degradation due to microwave or ultrasound can be avoided. Vortex and stirring are less costly compared to microwave and ultrasound.

6.2.4 Green Solvents and Reagents

The solvents and reagents that are more often applied in analytical derivatization are toxic, corrosive, and irritant in nature. Thus, their replacement with greener solvents is necessary to have environment-friendly features in the analytical method. The green alternatives to organic solvents should be searched or synthesized. Few potential alternatives for derivatization reactions are

(i) Water
(ii) Bio-derived solvents
(iii) Ionic liquids
(iv) Supercritical fluids
(v) Natural deep eutectic solvents.

Water is the most desirable solvent due to its universal availability, low-cost, and no toxicity. However, its application in derivatization reactions is hindered due to the low solubility of organic reactants and moisture sensitivity of some chemical reactions. Ionic liquids (ILs) have gained a great deal of attention due to their low-volatility, non-combustibility, high thermal stability, and tunable physicochemical properties. They are good alternatives to volatile and flammable organic solvents. They have been widely employed in sample preparation and column preparation in separation science. They have also been used for derivatization reactions, particularly in DLLME. However, they are persistent in environment due to slow degradation and may enter to aquatic environment due to high solubility. Some of them are toxic in nature although that toxicity varies from organism to organism.

Supercritical fluids (SFs) particularly carbon dioxide are employed for derivatization reactions due to their low-toxicity, chemical inertness, and easy disposal.

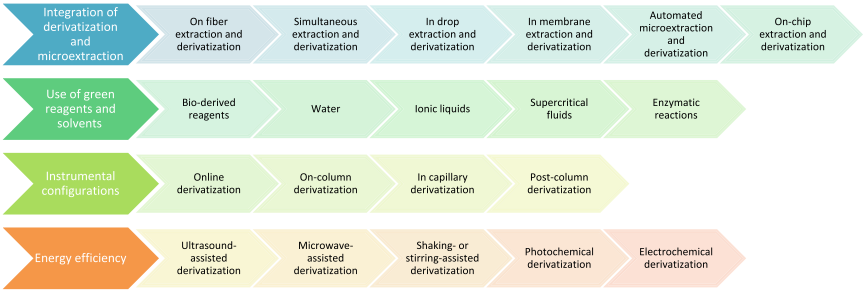

Fig. 6.1 Different strategies to make derivatization process "greener" in nature

However, their low-polarity and high cost of production (energy utilization) make them not very commonly used.

Although the final aim is to search non-toxic and natural compounds for derivatization reactions for sustainable development, the achievements in this field are scarce. Various examples of derivatization by employing unrefined natural reagents derived from plant and animal tissues or microbial cells have been reported [57]. Crude plant extracts may contain chemical compounds that can act as chromogenic or fluorogenic agents. Moreover, the use of natural reagents in combination with a flow injection system can provide many advantages such as the better kinetic control in flow analysis can be helpful in circumventing undesirable side reactions that are expected to take place by use of unrefined reagents [57]. In addition, the quality and lifetime of natural unrefined reagents can be prolonged in a flow analysis system by monitoring their exposure to light and air. Figure 6.1 summarizes different strategies to make the derivatization process "green" in nature.

6.3 Conclusive Remarks

The main objective of the derivatization in analytical chemistry is to enhance the compatibility of the target compounds with the analytical instruments by converting them into suitable derivatives. It improves the sensitivity, selectivity, and detectability of the analysis. Most of the derivatizing reagents are toxic, corrosive, and irritant in nature and thus GAC suggests to avoid the process of derivatization for developing green analytical methods. However, this principle of GAC seems to be less feasible because a large number of analytes cannot be determined by analytical instruments without their derivatization. It is therefore important to find out the ways that can introduce green character in the derivatization process. Among various ways to make the derivatization process "greener," the most effective one is its coupling with microextraction. Basically, it is a way to perform all the procedure at miniaturized scale which results in the reduction of the use of solvents and reagents and resulting waste production. The process of derivatization can be performed online/automated along

with the micro-extraction. In some cases, both extraction and derivatization can be performed simultaneously which saves both energy and time. The other ways to greener derivatization include search and use of environment-friendly derivatizing reagents, solvents, reaction conditions, and energy sources. The use of alternative energy sources such as microwave, ultrasound, shaking, and vortex is encouraged as it not only accelerates the reaction rate but also saves energy and cost. The use of natural reagents can make big difference to encounter the problems of conventional reagents, but a lot has to be done in this area.

Acknowledgements Muhammad Sajid would like to acknowledge Center for Environment and Water, Research Institute, King Fahd University of Petroleum and Minerals, Saudi Arabia.

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Chapter 7
Smart Sorption Materials in Green Analytical Chemistry

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Abstract The use of smart materials as alternative sorption materials for their use in greening sample preparation has been reviewed. It has been taking into consideration recent advances on the use of natural products, without any modification or purification, for making analyte extraction and pre-concentration and the use of specific materials in solid-phase extraction (SPE) and solid-phase microextraction (SPME) approaches. Inorganic materials, such as metal oxides, alumina-based, silica-based, and carbon-based materials together with biomimetic sorbents such as classical immunosorbents, aptamers, and molecularly imprinted polymers, have been reviewed as examples of these materials, stressing the enhancement of analytical features involved in their use and advertising about side effects coming from their production system and use. The main objective has been to put the spotlight on these smart materials, which can offer alternative and simple tools for matrix removal and analyte pre-concentration, improving selectivity and specificity of traditional analytical determinations.

Keywords Aptamers · Carbon-based materials · Immunosorbents · Metal oxides · Molecularly imprinted materials (MIPs) · Nanomaterials · Sample treatment · Solid-phase extraction (SPE) · Solid-phase microextraction (SPME) · Silica-based materials · Sorption materials

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J. Płotka-Wasylka and J. Namieśnik (eds.), *Green Analytical Chemistry*,
Green Chemistry and Sustainable Technology,
https://doi.org/10.1007/978-981-13-9105-7_7

7.1 Sample Preparation: The Bottleneck of Many Methods

The need of sample dissolution or digestion [1] and the required analyte extraction from complex solid samples [2] are the most time-consuming analytical steps. These processes also dramatically affect both classical and green analytical features [3] due to the risks of analyte losses or contamination, as well as the huge amount of caustic or toxic reagents and solvents required. Additionally, it is evident that to move from solid to analyte solutions creates in many cases troubles with the selectivity and sensitivity of the methods to be employed, and thus, a matrix removal and a pre-concentration of target analytes are mandatory [4]. So, it is clear that efforts have been made to avoid sample preparation steps in the green alternative methodologies [5].

However, inherent sensitivity and selectivity of determination methods oblige us, in many cases, to incorporate sample preparation steps before to do the analytical measurement. Fortunately, the automation of the analytical methodologies [6], together with the scaling down of analytical procedures through miniaturization [7] can reduce the consumption of reagents and solvents also reducing the labour and waste generation [8].

The use of flow injection methodologies from classical flow injection analysis (FIA) [9] to sequential injection analysis (SIA) [10], and multicommutation [11] has improved the available methods in three ways by: (i) reducing the contact of operator with reagents and solutions, (ii) scaling down the consumption of chemicals and waste generation, and (iii) providing a fantastic way to integrate in a single manifold the sample preparation steps with the measurement ones [12].

In any case, to move from FIA detection to the laboratory-on-a-chip microfluidic methodologies [13], additionally than the search for the appropriate set-ups, it is mandatory to incorporate high efficient and specific sorption materials to reduce and simplify the sample treatment steps. In this way, the so-called smart materials offer exciting possibilities to obtain enhanced pre-concentration factors with an improved selectivity [14]. These advantages are based on (i) the nature of biomimetic materials similar to classical antibodies, as molecularly imprinted polymers (MIPs) and aptamers, and (ii) the novel practical properties provided by carbon-, silica-, and metal oxide-based materials, including specific interactions and magnetic properties (see Fig. 7.1).

In short, nowadays, the use of smart sorption materials provides an exceptional tool for greening any method that requires the use of a sample preparation step employing solid-phase extraction and, because of that, in this chapter we have focussed the attention on the main properties and benefits that can be obtained from the use of new advanced materials as sorbents in sample preparation for analytical determinations.

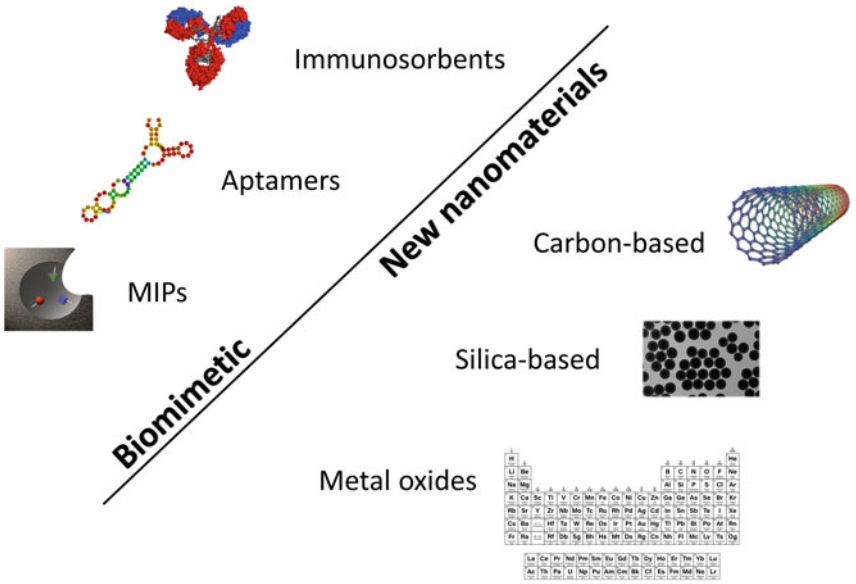

Fig. 7.1 Scheme of smart materials employed for greening sample preparation based on their biomimetic and nanomaterial intrinsic properties

7.2 Natural Sorbents

The term natural sorbents is referred to those sorbents that may be obtained from plants, soils, or animals with a little purification and used immobilized on a solid substrate, or even packed in a column for matrix removal or analyte pre-concentration in sample preparation. Considering the requirements of green analytical chemistry (GAC), natural sorbents can be considered as the most relevant sorption materials. Indeed, the application for sample pre-treatment of unrefined natural reagents with low toxicity, wide sources, and low cost is one of the recent trends in GAC [15].

Several key points should be considered before using natural sorbents in analytical procedures without compromising analytical features of the method. First of all, blank extracts should be analysed to determine the possible interference level due to impurities of natural sorbents. Secondly, it should avoid the use of natural sorbents such as "magic materials/black boxes" and their use should be based on chemical knowledge of their composition.

Pine pollen grains have been used as solid-phase extraction (SPE) sorbent for the enrichment of plant growth regulators from fruits and vegetables [16]. The outer pollen wall, consisting of an extremely stable and complex biopolymer, known as sporopollenin, is chemically and thermally stable [17] with abundant hydroxyl groups. Pollen grain has been applied to the SPE of *trans*-resveratrol from peanut oils [18]. Pollen grains exhibited an excellent adsorption capacity for polyphenolic compounds due to their hydroxyl groups, and saturated and unsaturated aliphatic

chains with aromatic rings. Their stable composition as well as adequate particle size (30–40 μm) also makes them suitable for SPE.

Cotton wool has been used for the purification of glycan and glycopeptide as well as removal of salts, non-glycosylated peptides, and detergents from biological samples [19]. Cotton wool acts as a non-ionic neutral stationary phase, and analyte retention is expected to be caused solely by hydrogen bonding. Cotton wool has been applied in combination with a zwitterionic resin for the SPE retention of glycopeptides from tryptic digests of wheat flour albumin extracts [20]. In this sense, cotton roll dyed by quinalizarin has been used packed inside a minicolumn for the SPE of rare earth elements and uranium at trace levels in environmental samples followed by inductively coupled plasma-optical emission spectrometry (ICP-OES) determination [21].

Pyrolysis of cotton wool in an inert atmosphere provides micrometric carbon fibres with a tuneable polarity, depending on temperature and heating time [22]. These carbon fibres have been employed for the extraction of chlorophenols from urine samples [23].

Another natural sorbent used in solid-phase microextraction (SPME) is bract fibre. The main green advantages of bract fibre are related to its low-cost, renewable, and natural sorbent nature. This sorbent was supported on a nitinol (NiTi) alloy to ensure mechanical stability, high durability, and corrosion resistance [24, 25]. The bract fibre was obtained from *Araucaria angustifolia* (Bertoloni) Otto Kuntze, a coniferous tree present in southern Brazil. This material consists of 45% lignin and 46% holocellulose (cellulose and polyose). Bracts were employed as SPME sorbents in the extraction of polycyclic aromatic hydrocarbons (PAHs) from water samples with a high reproducibility.

Seed powder of *Moringa oleifera*, a natural sorbent, has been used for cadmium extraction from alcohol fuel in an online pre-concentration system coupled to flame atomic absorption spectrometry (FAAS) [26], phthalate ester extraction from milk samples using micro-solid-phase extraction (μ-SPE) [27], and different organic compounds like nitroaromatic compounds and PAHs from aqueous samples [28]. This material can be considered as an efficient and cost-effectively natural material that is naturally enriched with a variety of functional groups and having a network of interconnected fibres.

Other natural sorbents used in SPE for the pre-concentration of metal ions include spider silk [29]; *Agrobacterium tumefaciens* immobilized on Amberlite XAD-4 [30]; unmodified and modified rice husks [31, 32]; clay minerals, zeolites, and meal wood [33, 34]; and carbonized apricot stone [35], among others.

7.3 Inorganic Sorbents

Historically, the development of SPE practices is closely related to the possibilities offered by metal oxides, silica, and modified silica substrates, especially to the use of classical octadecyl silica (C_{18}) cartridges, terribly useful for the separation

of low polar compounds [36]. These inorganic materials provide modified polarity environments and were in the base of the development of many ion exchangers.

In this part, metal oxides such as TiO_2, ZrO_2, and Al_2O_3, together with silica-based and some carbon-based materials, will be discussed in the light of alternative methods for sample clean-up and analyte pre-concentration. Regarding carbon-based materials, the stress will be focussed on the possibilities offered by many of their nanostructures suitable to be employed on SPE and SPME with a high extraction efficacy and specific sorbent–analyte interactions. All the materials considered in this section are basically inorganic in their composition and very flexible to be used in sample preparation for the analysis of different target analytes. However, their main drawback is their lack of specificity and selectivity with target analytes.

7.3.1 Metal Oxides

Metal oxides have been widely used as cation or anion exchangers depending on pH [37]. Moreover, the Lewis acid sites of metal oxide surfaces can provide Lewis acid–base interactions with the target analyte [38]. In addition, metal oxide surface can be functionalized, increasing the potential application of these particles as solid sorbents [39]. In the past decades, metal oxides were applied in sample pre-treatment in virtue of their hydrophilic properties in a variety of areas.

Porous TiO_2 microspheres have been used for the enrichment of glycopeptides and phosphopeptides [40]. Both hydrophilic interaction and ligand-exchange retention mechanisms were involved in the interactions between glycopeptides and TiO_2. Modification of magnetic hollow mesoporous silica spheres by immobilization of TiO_2, by either the sol–gel method or the liquid-phase deposition method, has led to appropriate solid sorbents for the extraction of phosphopeptides from peptide mixtures [41]. These particles were used for the extraction and in situ derivatization of the phytohormones by 3-bromoactonyltrimethylammonium bromide [42] or 4-(*N*,*N*-dimethylamino)phenylboronic acid [43]. The process integrated extraction, purification, and derivatization into one step, offering a highly efficient clean-up. TiO_2 nanotubes have been synthetized to increase surface area of the material and, as a consequence, the extraction efficacy [44].

ZrO_2 particles have been used for peptide enrichment [45]. Recently, ZrO_2 layer-coated mesoporous silica microspheres with mesostructured cellular foams have been prepared for the enrichment of phosphopeptides and glycopeptides demonstrating higher selectivity and enrichment efficiency than bulk ZrO_2 particles and commercial TiO_2 microparticles.

Al_2O_3-based materials have been prepared to selectively enrich glycopeptides [46]. Glycopeptides were retained on Al_2O_3 according to their hydrophilic interaction and ligand-exchange interaction.

Magnetic materials based on Fe_3O_4 generally can simplify the overall analytical procedures. Dispersed sorbents, instead of packed ones, have been extensively used reducing the analysis time due to the improvement of the contact area between the

sorbent and the analytes. Furthermore, the solid sorbent can be separated from the solution by an external magnet, simplifying the Achilles heel of traditional dispersive extraction methods, the centrifugation or filtration step. Moreover, bare Fe_3O_4 nanoparticles can be directly used as sorbent for the extraction of cytokinins from plant extracts [47]. Amine-functionalized Fe_3O_4 or water-coated Fe_3O_4 nanoparticles, prepared with trace amounts of water directly absorbed on bare Fe_3O_4, have been also successfully used for determination of 3-monochloropropane-1,2-diol [48] and organophosphorus pesticides [49] in edible oils.

7.3.2 Silica-Based Materials

Silica-based materials are traditionally the most frequently used sorbents for SPE due to the easy-to-prepare, minimal cost, good mechanical and chemical stability, and uniform properties [50]. It has been estimated that silica-based materials are used in the 90% of manufactured SPE columns, being the rest based on alumina, carbon, Florisil®, and synthetic polymers.

Silica gel is an amorphous, highly porous, and partially hydrated form of silica. It has a rigid backbone with little swelling or shrinking in a broad range of solvents. The silica used for SPE extraction has the general formula $SiO_2 \times H_2O$, being the water present in non-stoichiometric amounts to form the silanol groups. These groups are responsible for the retention of polar organic compounds. Silica particles used in SPE are synthetically manufactured by the polymerization of tetraethoxysilane to form silica gel molecules. They are available in a variety of particle sizes and pore diameters, being typical surface areas between 400 and 600 $m^2\ g^{-1}$. SPE extraction using silica-based materials can be accomplished at pH values between 2 and 9. At low pHs, Si–C bonds of functionalized materials can be cleaved, and at higher pHs than 9, silica is slowly solubilized as silicate.

Using bare silica as sorbent in SPE, without any further modification, cytokinins have been extracted from different plant species [51], and cyclic nucleotides from plasma, tissue, and plant samples [52]. Moreover, bare silica-based SPE approach was also successfully used for phospholipid removal [53].

Additionally, the presence of hydroxyl groups on silica allows modification by addition of different functional groups on the surface of particles for increasing selectivity. These functionalized silica materials show a high versatility, depending on the chemical groups introduced. Applications of functionalized silica materials are deeply discussed next.

Siloxane-bonded sorbents with long alkyl chains maximize retention of small molecules from aqueous solution, while wide-pore materials with short alkyl chains are used to isolate macromolecules. The most widely used SPE materials are based on siloxane-bonded sorbents with alkyl chain lengths ranging between C_1 and C_{18} [50].

Modification of silica with polar functional groups can further improve the extraction performance of silica-based materials in sample pre-treatment. A wide range of polar functional groups, such as aminopropyl, amide, cyano, and polyol groups, have

been chemically bound to the silica surface to prepare sorbent materials [54]. Those materials, which are less retentive than alkylsiloxane-bonded phases for aqueous samples, have been used mainly to isolate macromolecules such as peptides, proteins, antibiotics, and small molecules from organic solvents [50]. Most polar-bonded silica materials contain sulphonic acid ($–SO_3^-$) or quaternary methylammonium ($–N^+(CH_3)_3$) ionic functional groups, which have been used for the extraction of acids and bases from aqueous solutions according to the theories of ion exchange. Recently, diol-modified silica was developed to extract phosphatidylcholine and phosphatidylethanolamine from contaminated salmon samples [55]. The presence of hydroxyl residues of the diol-modified silica allows the interactions via hydrogen bonds, leading to an increase in selectivity. However, the diol-modified silica exhibits lower polarity than silica, limiting the extraction of polar compounds. A highly hydrophilic sorbent can be obtained coating polyvinyl alcohol onto silica gel that has been employed for the extraction of aminoglycoside antibiotics in honey [56].

Amino-bonded silica normally shows higher affinities for acidic compounds, resulting from a combination of partitioning and ion-exchange mechanisms. Using a μ-SPE device packed with a hydrophilic aminopropyl silica, glycans were extracted due to the partitioning between the organic mobile phase and a layer of water adsorbed on the surface of sorbent [57].

Click chemistry has been also widely employed for the easy and simple functionalization of silica materials. A highly hydrophilic material was obtained by linking propiolic acid to the azide–silica material through click chemistry, exhibiting high selectivity for *N*-linked glycopeptides with various glycan structures [58]. Saccharide-modified silica materials, obtained by linking alkynyl–maltose to azide–silica through click chemistry [59], possess abundant hydroxyl groups and exhibit a better extraction performance, in the analysis of glycopeptides from digests, than three different C_{18}-bonded silica materials due to the flexible saccharide chain structure that can enhance the hydrogen bonding interactions. Monosaccharide- and disaccharide-bonded silica materials have been successfully obtained using thiol-ene click chemistry between alkene–saccharides and mercapto–silica, exhibiting a good selectivity towards glycopeptide extraction from the digest of IgG [60]. β-cyclodextrins have been linked to silica gel through an oligo(ethylene glycol) spacer via click chemistry [61] for N-linked glycopeptide enrichment and phosphopeptide enrichment and fractionation [62]. β-cyclodextrin with the oligo(ethylene glycol) spacer and triazole group provide hydrogen bonding and anion-exchange interactions, contributing to the high selectivity for phosphopeptide enrichment.

Furthermore, zwitterionic materials that carry both cationic and anionic moieties have been widely used in SPE. Commercially available sulphobetaine zwitterionic materials (named as ZIC-HILIC) have been widely applied to the SPE of polar analytes, such as glycopeptides [63], polar peptides [64], toxins [65], and drugs [66]. SPE materials have been obtained by modifying silica gel with asparagine or cysteine using "thiol-ene" click chemistry, showing high hydrophilicity and zwitterionic properties [67]. These materials were used as SPE sorbent for selective enrichment of glycopeptides [66] and the purification of bufadienolides from traditional Chinese medicines [68]. Glutathione has been successfully linked to silica surface copper-free

"thiol-ene" click chemistry [69], exhibiting both hydrophilic and cation-exchange characteristics.

Additionally, mesoporous silica materials (MSMs), prepared for the first time in 1992 by the Mobil Oil Company (M41S phase) [70], are powerful materials with an extreme high surface area (>1000 $m^2\ g^{-1}$), large pore volume (>1 $cm^3\ g^{-1}$), uniform vertical mesoporous channels, internal and/or external surface functionalization, easy tailoring of morphology (size, pore, and shape), good water dispersibility, and good chemical and thermal stability, offering green unique properties to be used as sorbent material. The main synthesis procedure is based on the sol–gel technique from molecular precursors (tetraethyl orthosilicate) which condensate in the presence of cationic surfactants (templating or structure-directing agent) under mild chemical conditions. Once the synthesis process has concluded, the surfactant template is removed by calcination or solvent extraction. Although MCM-41 is the most studied and applied MSM, other sorbents with different shape and porous systems have been also described such as SBA-15 [71] and UVM-7 [72]. Moreover, MSMs can be employed as a template core for the synthesis of assorted smart materials by the functionalization of its surface using carbon-based materials [73], MIPs [74], or magnetic nanoparticles [75].

7.3.3 Carbon-Based Materials

Carbonaceous materials, as amorphous activated carbon or graphitized carbon, have been traditionally employed as extraction sorbents, because of π–π interactions with aromatic groups of organic compounds. In the last decade, a novel generation of carbon-based nanomaterials has been synthetized, such as: (i) fullerenes, (ii) graphene, (iii) graphene oxide, (iv) carbon nanotubes, (v) carbon nanodots, (vi) nanohorns, (vii) nanocones/discs, (viii) nanofibres, and (ix) nanodiamonds, with exciting particular physico-chemical properties [76]. Thus, a rise in the development of extraction methodologies based on carbon sorbents has been done due to its non-covalent interactions like π–π, electrostatic, van der Waals, and hydrophobic ones. Moreover, the aforementioned materials show a high surface area, low toxicity, low price, and relatively easy functionalization, which make the use of carbon-based materials a sustainable and very flexible tool for sample preparation.

Fullerenes were the first carbon-based nanomaterials proposed for analyte sorption. These have an ordered structure based on sp^2 carbon atoms arranged of pentagons and hexagons like a soccer ball with a total of 60 (C_{60}) and 70 (C_{70}) carbon atoms that provide characteristic mechanical properties. On the other hand, graphene materials are two-dimensional sheets made by narrow layers of sp^2 carbon atoms with high mechanical and chemical resistance, low reactivity, and an enormous surface area [77]. Synthetic routes of graphene typically provide graphene oxide as intermediate species, which show similar properties than graphene but with an improved reactivity that allow an easy functionalization of its surface [78]. Carbon nanotubes are nanocylinders made by single- or concentric multi-walled graphene sheets with

nanoscale diameters lower than 100 nm [79]. Carbon nanotubes show metallic electronic properties due to the quantum confinement, but their high surface area and specific interactions are more relevant than its electronic properties for the development of extraction procedures. Carbon-based materials with other geometries have been also proposed such as "dahlia-like" clusters made by individual nanohorns [80], conical structures of nanocones/discs [81], or micrometric carbon nanofibres [82]. Carbon nanodots are spherical nanoparticles with diameters lower than 10 nm with a mixed structure where coexist graphene- and diamond-type hybridization regions. This fact provides unusual optical properties of nanodots similar to conventional quantum dots but with lower toxicity than those made with heavy metals [83]. Carbon nanodot applications are frequently focussed on the development of fluorescent sensors, being these applications more interesting than their use in sample treatment [84].

Synthesis of novel carbon-based materials is carried out by specific methodologies depending on the particular material, and in some cases, a clean-up or purification step is required [85, 86]. So, for a deep evaluation of greenness of these materials all the steps regarding their production must be considered. The obtained carbon nanomaterials are mainly inert materials with a low dispersibility in aqueous media. However, their compatibility with water can be improved by the functionalization of its surface by using both, covalent and non-covalent, approaches [87]. Surface functionalized carbon materials considerably increase their versatility by coupling to other smart materials like MIPs, magnetic materials, molecular organic frameworks (MOFs), or biomolecules [14].

Applications developed for the use of carbon-based materials in sample pretreatment are mainly focussed on SPE [88, 89] and SPME [90]. Table 7.1 shows a selection of applications found in the literature for food and environmental and clinical/forensic areas. Most procedures are targeted to organic compound analysis, but these materials have been also employed for the extraction of mineral elements.

The main advantage of carbon nanomaterials concerns the high extraction efficacy provided by the combination of its high surface area and specific π–π interactions. Moreover, these materials provide negligible toxicity and a high versatility for surface functionalization that opens its upcoming possibilities in greening sample preparations, avoiding additional separation steps, and reducing side effects of waste disposal.

7.4 Biomimetic Sorbents

Enzymes are a good example provided by the nature, which shows that specific interactions are possible. Thus, we need to follow the nature on searching for tailored fit sorbents, suitable to interact with target analytes in a highly selective way that could permit, from a green analytical point of view, a considerable decrease of steps concerning analyte retention, matrix removal, and analyte elution.

In this section, selective materials such as immunosorbents, aptamers, and MIPs would be considered, starting from the close similarity to the biological systems,

Table 7.1 Selected applications in SPE and SPME applications using carbon-based materials

Sample	Target analyte	Extraction	Sorbent	Technique	References
Water					
Water	Cd, Pb, Ni	SPE	C_{60}	FAAS	[91]
Water	Cd, Co, Ni, Pb, Fe, Cu, Zn	SPE	CNTs	FAAS	[92]
Water	Cyanazine	SPE	Nanodiamonds	MS	[93]
Water	BTEXs, naphthalenes, PADs	SPME	C_{60}	GC-FID	[94]
Water	Furfural	SPME	Graphene oxide	GC-MS	[95]
Food					
Fruit juice	Carbamate pesticides	SPE	Graphene	LC-MS	[96]
Milk	PBDEs	SPME	CNTs	GC-ECD	[97]
Drinks	Tartrazine	SPE	CNTs	LC-UV	[98]
Honey	Chlorophenols	HS-SPME	CNTs	GC-ECD	[99]
Milk	Diethylstilbestrol	SPME	CNTs	LC-UV	[100]
Environmental					
Soil and water	Chlorotriazine and metabolites	SPE	Nanofibres	LC-DAD	[101]
River water	Nitrophenols	SPE	CNTs	CE-UV	[102]
Tap, river, mineral water	PAHs	SPE	Nanohorns	GC-MS	[103]
Workplace air	Halogenated VOCs	SPME	CNTs	GC-MS	[104]
River water and wastewater	Phenols	SPME	Oxidized CNTs	LC-DAD	[105]
Rainwater	Organochlorinated pesticides	SPME	Graphene	GC-MS	[106]
Clinical/forensic					
Water and tissues	Metal dithiocarbamates	SPE	C_{60}	FAAS	[107]
Urine	Chlorophenols	SPE	Nanocone/discs	GC-MS	[81]
Oral fluids	Amphetamines	SPME	CNTs	LC-FD	[108]

Note BTEX, benzene, toluene, ethylbenzene, and xylene; CE, capillary electrophoresis; CNTs, carbon nanotubes; DAD, diode array detector; ECD, electron capture detector; FID, flame ionization detector; FAAS, flame atomic absorption spectrometry; FD, fluorescence detection; GC, gas chromatography; HS, headspace; LC, liquid chromatography; MS, mass spectrometry; PADs, phthalic acid diesters; PBDEs, polybrominated diphenyl ethers; UV, ultraviolet detector; VOCs, volatile organic compounds

to move to a pure chemistry point of view. The main purpose to incorporate these selective materials as sorbent systems is to increase the effectivity of the extraction process, avoiding potential interferences during the measurement stage, in order to avoid additional clean-up steps in the analytical procedure.

However, in order to provide a complete picture of the use of smart biomimetic materials as a greening sorption way, it must deeply analyse the whole process, from the synthesis and/or preparation of the sorbent materials, to their application. In this sense, there are many doubts about the green character of some of the presented materials due to their complex and plenty of environmental side effects of their production, being the case of monoclonal immunosorbents that require a complex process for the antibody production, or the case of MIPs that involve a high reagent and solvent consumption, which are representative examples of this issue.

7.4.1 Immunosorbents

Immunosorbents are smart materials that contain antibodies or specific biomolecules, such as enzymes or proteins, immobilized on a conventional sorbent. Immunosorbents provide a high selectivity due to the high specificity of the antigen–antibody interaction. Antibodies are immunoglobulins (Ig) synthetized by the immune system of mammals as a response to foreign agents, which can be from different isotypes such as IgA, IgD, and IgG, being the IgG the major isotype produced [109]. The typical structure of an IgG is based on a Y-shape protein with four polypeptide chains, two identical heavy and two identical light chains linked through disulphide bonds. The lower part of the antibody is referred to as constant region (Fc), and it is conserved from antibodies within the same species. The upper part is structured in two identical regions (Fab) that strongly differ between antibodies from different cell lines. The recognition area where the antibody identifies and binds antigen is placed in both Fab regions [110]. Antibodies are typically employed unmodified for immunosorbent approaches, but in some cases it can be fragmented by using enzymes, like papain and pepsin, or by rupture of disulphide bonds using dithiothreitol and diethanolamine, keeping Fab fragments the high specificity of the antigen–antibody interaction [111].

Laboratory-produced antibodies can be mainly monoclonal and polyclonal. Monoclonal antibodies are produced by a single cell line following the Kohler and Milstein method [112] that involves the combination of an antibody-producing lymphocyte from an immunized experimental animal with a myeloma cell, to produce an antibody producer hybrid cell (hybridoma). This hybridoma line can be cultured to large-scale production of identical antibodies with the same specificity and binding strength. However, the development of a suitable cell line for the production of monoclonal antibodies is complex and requires high time, effort, and economical resources [113].

Polyclonal antibodies are obtained from the serum of immunized experimental animals like mice, rabbits, or goats. Polyclonal antibody extracts are purified by assorted techniques, including saturated ammonium sulphate precipitation,

ion-exchange chromatography, and/or immobilized protein G chromatography. The obtained antibodies are very heterogeneous, containing reactive and non-reactive antibodies against the target analyte. Nevertheless, specific antibodies may be obtained after purification of polyclonal antibodies using an antigen-immobilized column [114]. These antibodies are relatively inexpensive and easy to obtain, as compared with monoclonal ones, but their main drawbacks are those related to the moderate specificity provided the limited amount of produced antibody and batch-to-batch homogeneity.

Preparation of immunosorbents is habitually carried out by the immobilization of the selected antibody to a solid support, such as: (i) polysaccharides like agarose, Sepharose, and cellulose; (ii) polymers based on acrylamide, methacrylate, and polyethersulphone, and (iii) derivatized silica and glass beads [115]. Immobilization of antibodies is typically conducted by traditional anchoring chemistries, based on the use of a biomolecule bridge like avidin or protein G, functionalization of antibody carboxylic groups using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and *N*-hydroxysuccinimide, or antibody fragmentation by the reduction of disulphide bonds using dithiothreitol [116].

The use of immunosorbents for sample pre-treatment significantly improves the selectivity of the analytical methods, but also can enhance sensitivity as a consequence of the enrichment factor typically obtained by SPE procedures. Immunosorbent procedures require the use of mild working conditions, close to physiological ones (soft green solutions), such as moderate temperature and pressure, neutral pH, and the use of aqueous solutions. Elution of target analytes from immunosorbents is typically carried out by using chaotropic agents, acidic or basic aqueous buffers, and diluted organic solvent solutions [117].

Applications of immunosorbents are based on the analysis and purification of biomolecules like proteins, but these smart materials can be also used for the determination of small target analytes [110]. Immunosorbents are commercially available for a reduced number of compounds, including mycotoxins, β-agonists, hormones, estrogens, herbicides, or PAHs [118]. Nevertheless, immunosorbents can be also produced by using commercial or laboratory-made antibodies immobilized to the appropriate support to expand the number of applications to an extended type of analytes. Thus, a tuneable selectivity can be obtained by immunosorbents using high specific antibodies against the target analyte or by using medium-specific antibodies able to recognize a series of compounds with similar molecular structures.

Table 7.2 shows the analytical performance of selected immunosorbent-based SPE procedures found in the literature. SPE procedures are the most frequently employed extraction technique for the use of immunosorbents. Other approaches, such as the use of magnetic immunosorbents for its use in dispersive SPE, are focussed on the reduction of antibody consumption and simplicity increase. Online SPE has been also proposed for the automation of the approach, thus enhancing the green character of these methodologies.

The great advantage of immunosorbents is related to their extreme specificity against the target analytes that increases selectivity of the method by the reduction of potential interferences in the analysed extract. Thus, the combination of a sample

Table 7.2 Selected SPE applications based on immunosorbents

Sample	Target analyte	Extraction	Technique	References
Water				
Water	Microcystins	SPE	ELISA and PPI	[119, 120]
Water	Anatoxin-a	MDSPE	IMS	[121]
Food				
Fruit juices	Pyraclostrobin	SPE	LC-UV	[117]
Citrus fruit	Imazalil	SPE	LC-UV	[122]
Fruit juice and wine	Azoxystrobin, picoxystrobin, pyraclostrobin	SPE	IMS	[123]
Pistachio	Aflatoxins B1 and B2	SPE	IMS	[124]
Environmental				
Soil extract	Isoproturon, demethylisoproturon, didemethylisoproturon, chlorbromuron, diuron, fluometuron, chlortoluron, linuron, neburon, monuron	ASE-SPE	LC-DAD	[125]
Soil and dust	Bioallethrin	SPE	ELISA	[126]
Clinical/forensic				
Liver, kidney, muscle	Salbutamol and clenbuterol	SPE	ELISA	[127]
Rat plasma	Fenoterol, methoxyfenoterol, naphthylfenoterol	online SPE	LC-MS	[119]
Urine	Chloramphenicol	DLLME-SPE	IMS	[128]
Urine and plasma	Diethylstilbestrol, dienestrol, hexestrol	SPE	GC-MS	[129]

Note ASE, accelerated solvent extraction; DAD, diode array detector; DLLME, dispersive liquid–liquid microextraction; ELISA, enzyme-linked immunosorbent assay; GC, gas chromatography; IMS, ion mobility spectrometry; LC, liquid chromatography; MDSPE, magnetic dispersive solid-phase extraction; MS, mass spectrometry; PPI, phosphatase inhibition assay; SPE, solid-phase extraction; UV, ultraviolet

treatment with immunosorbents with limited selectivity detection techniques provides reliable methods with excellent analytical performance, avoiding additional sample preparation steps. Furthermore, their main drawbacks are the high cost of antibody production, and the limited availability and variability of antibodies against target analytes. So, another kind of smart materials could be an elective option for greening sample preparation procedures following biomimetic strategies.

7.4.2 Aptamers

Aptamers are a new class of short artificial single-strand DNA or RNA fragments that exhibit molecular recognition with target molecules through stacking, hydrogen bonding, dipole, or van der Waals force interactions [130]. Aptamers, with a molecular weight between 6 and 30 kDa, and including from 20 to 80 bases, exhibit high specificity and binding affinity, good stability, reusability, non-toxicity, low cost, and easy controllable modification. These characteristics make aptamer-functionalized materials very attractive and promising sorbents to be used for sample preparation techniques, such as SPE.

Specific aptamers can be synthetically generated by an in vitro method named systematic evolution of ligands by exponential enrichment (SELEX) [131, 132], in which the aptamer is isolated from a large library containing more than 10^{15} random combinatorial nucleic acid sequences. SELEX strategy includes three steps: (i) incubation of target molecule with random sequence pools; (ii) separation of unbound oligonucleotides and elution of bound ones; and (iii) amplification of selected aptamer by polymerase chain reaction [133]. Different variants of SELEX method have been developed for aptamer selectivity improvement and increment of selection output and to increase capability of aptamer to recognize target proteins, cells, and tissues from complex matrices [134].

Aptamer preparation is easier than other biomaterials and biomimetic materials. As compared with MIPs, which will be discussed in the next section, aptamers only require a small amount of the target analyte as a template; regarding immunosorbents, the aptamer production is cheaper and faster because it does not require the use of laboratory animals and complex selection experiments to produce antibodies. These characteristics make aptamers an attractive alternative to conventional materials to create specific recognition sorbents [135]. Because of that, aptamer-functionalized materials are employed for analysis of target compounds at trace levels, mainly in biological complex samples with an efficient sample preparation including selective extraction, separation, purification, and enrichment steps. Thus, the use of aptamers is also a green strategy to reduce the number of stages of conventional sample treatments. For this purpose, it required the combination of aptamers with an adequate solid support with the desired properties that permit the right aptamer immobilization without blocking its catching properties, also providing chemical and biochemical inertness, adequate mechanical and chemical stability, uniform morphology, and appropriate particle size. Additionally, it is required that selected supports could have

an appropriate surface to facilitate an adequate aptamer attachment but minimizing non-specific interactions. Materials usually employed as a support for aptamer immobilization are silica, Sepharose, synthetic polymers, magnetic particles and beads, gold nanoparticles, organic and inorganic hybrid monolithic materials, carbon nanotubes, and graphene oxide [133].

The most common approach for the immobilization of aptamers involves the covalent bonding of NH_2-modified aptamers with supports that contain reactive carboxyl, epoxide, or aldehyde groups. Detailed procedures for aptamer immobilization processes are described in the literature [135].

Aptamer-functionalized materials have been used for both SPE and SPME approaches, because of the inherent high affinity and selectivity associated with the aptamer. Different types of aptamer-based sorbents have been developed and applied to SPE including packed, open tubular capillary, monolithic, and spin columns [136–139]. Some examples of packed columns include biotinylated aptamer immobilized on modified Sepharose, porous glass beads, or polystyrene porous particles. Different parameters such as type of immobilization and length of the spacer arm, additionally than the nature of the support, affect the efficiency of the selective extraction of target analytes. Open tubular capillary columns, prepared by immobilization of aptamer on the inner surface of a fused-silica capillary, present small loading capacity as a main limitation for their application. On the other hand, monolithic columns including aptamers present advantages of high porosity, high permeability, and fast mass transfer suitable for online coupling with different analytical techniques [140].

Aptamer-functionalized magnetic materials offer many advantages to develop highly selective magnetic SPE-based methods, simplifying the extraction, enrichment, and detection of target analytes from complex matrices with a reduced sample preparation based on the easy separation of the solid phase by using an external magnet [141]. These materials include different formats of magnetic nanoparticles, microspheres, and beads. Their productions require three steps, including: (i) synthesis of magnetic particle, (ii) coating of the magnetic core with an appropriate material (such as silica, styrene/acrylamide copolymer, or gold particles), and (iii) introduction of the aptamer. These materials are an alternative to conventional SPE materials for enrichment of target analytes and removal of interfering compounds of the sample matrix, being easier to improve subsequent separation and detection of analytes.

Aptamer-functionalized surface-affinity SPE supports have been developed to extract, isolate, and enrich selectively trace analytes to permit their detection by different analytical techniques such as: liquid chromatography, gel electrophoresis, mass spectrometry, ion mobility spectrometry, among others. Moreover, aptamer-based materials have been also employed for direct determinations of target analytes based on surface plasmon resonance, surface-enhanced Raman spectroscopy, and atomic force microscopy [142].

Other aptamer-functionalized materials, like nanorods or nanosheets, have been developed and used for the analysis of proteins by pre-concentration/centrifugation methods [143].

Aptamer-functionalized materials also present attractive interest to improve sample throughput, selectivity, biocompatibility, and robustness of SPME compared to traditional sorbents, offering enhanced green methods. In this sense, microfibres including aptamer ligands covalently immobilized have been developed for different applications [144].

On the other hand, aptamer-functionalized materials can be prepared as functionally membrane, as for example by a layer-by-layer self-assembly approach, opening the possibilities for the development of membrane separation techniques using thin films [145] and opening new frontiers for online sample treatments.

Preparation techniques including aptamer-functionalized materials have been incorporated to microfluidic devices and applied to the extraction, enrichment, and purification of analytes at low concentration from reduced sample volume of complex matrices [146]. Poly(dimethylsiloxane) (PDMS) is the most widely used material to fabricate microfluidic devices, and so, aptamers modified with biotin can be easily immobilized on streptavidin-coated PDMS in the surface of a microfluidic channel [147]. Other functionalized materials can be also immobilized, such as: glass, silicon nanowire arrays, microgel particles, microbeads, polymerized microtubules, or gold film, providing microfluidic devices with an elevated binding capacity and high specific recognition capacity for target analytes, thus improving the miniaturization of methods requiring a selective isolation of target analytes.

Table 7.3 summarizes examples of applications of aptamer-based extraction devices for the analysis of target analytes in the field samples, including matrices like water, food, or biological and forensic samples, which indicated the interest of this kind of materials for their use as extraction supports for the development of analytical methods.

In short, it can be concluded that aptamers are a special type of biomimetic smart materials with particular interest in the greening of those methods that require a sample preparation step.

7.4.3 MIPs

MIPs are materials specifically synthetized to have a molecular recognition of a selected analyte. These biomimetic materials are inspired in the selective recognition mechanisms of enzymes and antibodies, based on the creation of *made to measure* sites in the polymer structure suitable to recognize and trap the analytes due to steric reasons and dipole–dipole, ionic, or hydrogen bonding interactions [186].

The synthesis of MIPs starts by the formation of a complex between a template molecule, usually the target analyte or a derivative compound, and a functional monomer that creates a three-dimensional network, which polymerizes using a large excess of a crosslinking agent, a porogen, and a polymerization initiator to create a highly crosslinked organic polymer. In a second step, the template molecule is removed by solvent or buffer washing solutions from the polymer, leaving three-dimensional specific cavities that specifically entrap the target analyte

Table 7.3 Selected applications of aptamer-based extraction devices for the analysis of target analytes in real samples

Sample	Target analyte	Technique	References
Water			
Drinking water	Cocaine	LC-MS/MS	[148]
Drinking water	Dichlofenac	LC-MS/MS	[148]
Food samples			
Chicken egg white	Lysozyme	HPLC–UV detection	[149]
Coffee extract	Ochratoxin A	LC–fluorescence detection	[150]
Ginger powder	Ochratoxin A	UHPLC–fluorescence detection	[151]
Red wine	Ochratoxin A	LC–fluorescence detection	[152]
Wheat extract	Ochratoxin A	Fluorescence detection	[153]
Wheat extract	Ochratoxin A	LC–fluorescence detection	[136]
Wheat extract	Ochratoxin A	LC–fluorescence detection	[154]
Environmental			
River water	17β-Estradiol	LC–UV detection	[155]
Clinical and forensic			
Bacterial lysate	Thyroid transcription factor 1	Gel electrophoresis	[156]
Cell lysate	Histones	SDS-PAGE	[139]
Cell suspension	CCRF-CEM cells	Fluorescence on labelled cells (offline)	[157]
Cell suspension	CCRF-CEM cells	Fluorescence on chip on labelled cells	[158]
Cell suspension	CCRF-CEM cells	Fluorescence on chip on labelled cells	[147, 159]
CHO cell	L-selectin		[143]
Deproteinated cell lysate	ATP	MALDI	[160]
Dialysate from rat cortex	Adenosine	UV detector connected to capillary	[161]
Escherichia coli lysates	His6-tag protein	SDS-PAGE	[162]
Human plasma	Adenosine	LC–MS	[163]
Human plasma	Cocaine	LC–UV detection	[164]
Human plasma	Thrombin	MALDI–TOF-MS	[165]
Human plasma	Thrombin	HPLC-UV detection	[166]
Human serum	CEA (cancer marker protein)	MALDI–TOF	[167]

(continued)

Table 7.3 (continued)

Sample	Target analyte	Technique	References
Human serum	IgE	MALDI	[168]
Plasma	Cocaine/adenosine	MS	[169]
Plasma	Thrombin	Gel electrophoresis	[170]
Plasma (diluted)	Thrombin	UV detector connected to capillary	[140]
Plasma and urine	Tetracycline	ESI–IMS	[171]
Post-mortem blood	Cocaine	LC–MS	[172]
Pure media	AMP (labelled)	Fluorescence on chip	[173, 174]
Pure media	Arginine vasopressin	MALDI–MS	[175]
Pure media	HCV RNA replicase	Fluorescence (labelled proteins)	[176]
Pure media	Thrombin	UV or LIF detector connected to capillary	[177]
Pure media	Thrombin	Electrophoresis/fluorescence (on chip)	[178]
Pure sample	Thrombin	MALDI–TOF	[137]
Serum (diluted)	Cytochrome c	UV detector connected to capillary	[179]
Serum	HCV RNA polymerase	MALDI	[180]
Serum and blood	Thrombin	Digestion–MALDI	[181]
Serum and urine	Anthracyclines	HPLC-UV detection	[182]
Urine	Acetamiprid	PSI-IMS	[183]
Urine	Adenosine	ESI-IMS	[184]
Urine	Codeine	ESI-IMS	[185]
Urine	Codeine	PSI-IMS	[183]

Note AMP, adenosine monophosphate; ATP, adenosine triphosphate; CCRF-CEM, cell lines; CEA, carcinoembryonic antigen; CHO, Chinese hamster ovary; ESI, electrospray ionization; HCV, hepatitis C virus; HPLC, high-performance liquid chromatography, IMS, ion mobility spectrometry; LC, liquid chromatography; LIF, laser-induced fluorescence; MALDI, matrix-assisted laser desorption ionization; MS, mass spectrometry; PSI, paper spray ionization; SPME, solid-phase microextraction; SDS-PAGE, sodium dodecyl sulphate–polyacrylamide gel electrophoresis; TOF, time of flight; UHPLC, ultra-high-performance liquid chromatography

based on the complementarity of their chemical structures [187]. MIP synthesis procedures are diverse, being bulk polymerization strategies the most employed ones that typically involve the use of methacrylic acid, methyl methacrylate, 4-vinylpyridine, acrylamide, or styrene as functional monomers; ethylene glycol dimethacrylate, divinylbenzene, or *N*,*N*′-methylenebisacrylamide as crosslinkers; 1,4-dioxane, tetrahydrofuran or acetonitrile as porogen; and azobisisobutyronitrile or azobis(2,4-dimethylvaleronitrile) as free radical initiator, which are started by using thermal, ultraviolet, or microwave approaches [188].

From the first application to direct drug determination proposed by Sellergren in 1994 [189], MIPs have become extremely popular as an analytical sorbent for SPE processes. MIPs applications usually require the use of small sorbent amounts, from 15 to 500 mg, and elution solvent volumes from 0.5 to 15 mL. Both offline and online strategies have been developed for the matrix removal and pre-concentration processes using MIP-based sorbents [190], involving the traditional steps of SPE but adding an enhanced selectivity. Typically, MIPs show a medium adsorption capacity due to their porous structure, higher than immunosorbents, but lower than unspecific traditional solid sorbents.

MIPs have been also employed as stationary phase in liquid chromatography [191–195], providing exciting possibilities for enantiomer separation [196, 197]. However, the purpose of this chapter is to put the stress on their use as new sorbents for SPE and SPME [198]. Table 7.4 shows some selected SPE applications published about the use of MIPs in different fields from water till food, environmental and clinical and forensic samples. As it can be seen, selectivity of analytical techniques such as liquid chromatography-UV and ion mobility spectrometry has been improved with the use of MIPs in the sample extraction. Typically, the obtained sensitivity was also improved, based on the selectivity of sorbent that provides an extreme clean extract without the presence of matrix constituents or interfering compounds, and in addition, a reduction of the number of analytical steps is achieved.

Especially interesting from the GAC perspective is the use of MIPs in SPME [226], as a way for scaling down the traditional sample preparation techniques, minimizing the solvent consumption and reducing the contact of operators with samples and the time of analysis. Thus, the use of MIPs as coating sorbents for SPME fibres promotes the selective extraction of target analytes. SPME coating is prepared by using different synthesis methods, from the classical sol–gel technology to the electrochemical or physical deposition procedures [227]. In this sense, the development of MIP-based monolithic fibres with an improved thermal stability shows a high potential for its direct desorption to gas chromatography injectors. Table 7.5 shows a detailed picture of SPME applications proposed for the analysis of miscellaneous samples.

7.5 Conclusions and Future Trends

It can be seen from the updated literature survey that the number of applications of smart materials in sample preparation has grown exponentially on both SPE and

Table 7.4 Applications of molecularly imprinting polymers in solid-phase extraction

Sample	Target analyte	Technique	References
Water			
River water and wastewater	Naproxen, ibuprofen, diclofenac	HPLC-UV	[199]
Reservoir and river, water tannery, wastewaters	Phenolic compounds	CE-UV	[200]
Potable and surface waters	Bisphenol A	HPLC-UV	[201]
Food			
Animal foods	Tetracyclines	HPLC-UV	[202]
Barley, peanut oil, beer, beans/corn/formula, feeds	Aflatoxin B1 and M1	HPLC-FLD	[203]
Canned energy drinks	Bisphenols	UHPLC-FLD	[204]
Cucumber	Dimethoate, isocarbophos, methyl parathion	HPLC-UV	[205]
Egg yolk	Sulphadiazine	HPLC-UV	[206]
Egg white	Lysozyme	MALDI-TOF	[207]
Fruit-derived foods	Patulin	HPLC-UV	[208]
Maize, water, soil	Triazine herbicides	HPLC-UV	[209]
Milk	Florfenicol	HPLC-MS	[210]
Olive oil	Fenthion	HPLC-UV	[211]
Pork	Salbutamol and clenbuterol	GC–MS	[212]
Pork and potable water	Clenbuterol	HPLC-UV	[213]
Red wine	Ochratoxin A	HPLC-FLD	[214]
Environmental			
Sediments	Bisphenols	HPLC-UV	[215]
Clinical/forensic			
Animal tissues	OH-PCBs and PBDPEs	GC/HPLC-MS	[216]
Human cerebrospinal fluids	Enkephalins	HPLC-UV	[217]
Human milk	Phospholipids	HPLC-ELSD	[218]
Human serum	HAS	HPLC-UV	[219]
Human serum and water	l-Cysteine	UV–visible	[220]
Milk and blood	Ampicillin	HPLC/UV	[221]
Plasma	Methadone	HPLC-MS	[222]
Plasma and urine	Cannabinoids	HPLC-MS	[223]

(continued)

Table 7.4 (continued)

Sample	Target analyte	Technique	References
Saliva	Cocaine	IMS	[224]
Water and urine	NSAIDs	UHPLC	[225]

Note CE, capillary electrophoresis; ELSD, evaporative light scattering detector; FLD, fluorescence detector; GC, gas chromatography; HPLC, high-performance liquid chromatography; IMS, ion mobility spectrometry; MALDI, matrix-assisted laser desorption ionization; MS, mass spectrometry; OH-PCBs, hydroxylated polychlorinated biphenyls; PBDPEs, polybrominated diphenyl ethers; TOF, time of flight; UHPLC, ultra-high-performance liquid chromatography; UV, ultraviolet

Table 7.5 Applications of molecularly imprinting polymers in solid-phase microextraction

Sample	Target analyte	Technique	References
Water			
Water	Cd(II)	ICP-MS	[228]
Water	Cu(II)	FAAS	[229]
Water	Atrazine	HPLC-UV	[230]
Food			
Apple and pineapple	Organophosphorous pesticides	GC-NPD	[231]
Beverages	Benzoate	UV-Vis	[232]
Beverages	Acesulphame	HPLC-UV	[233]
Chilli tomato sauce and chilli pepper	Sudan I–IV dyes	LC-MS/MS	[234]
Citrus and soil	Thiabendazole	HPLC	[235]
Egg white and human serum	Lysozyme	SDS-PAGE	[236]
Fish and pork	Estrogens	HPLC-UV	[237]
Fishery	Estrogens	HPLC	[238]
Milk	Diethylstilbestrol	HPLC	[239]
Orange juice	Thiabendazole	HPLC-UV	[240]
Pork	Ractopamine	ECL	[241]
Pork, liver, and chicken	Sulfa drugs	HPLC	[242]
Rice, peanut, soil	Imidazolinones	HPLC-UV	[243]
Environmental			
River water, wastewater, and liquid milk	Triazines	HPLC	[244]
Soil and sediment	Parabens	HPLC-UV	[245]
Surface and wastewaters	Abacavir	HPLC-MS	[246]
Surface, ground, tap waters	Triazines	HPLC-UV	[247]
Clinical/forensic			
Human serum	Caffeine	GC/MS	[248]
Human serum	Mn(II)	ICP-MS	[249]

(continued)

Table 7.5 (continued)

Sample	Target analyte	Technique	References
Human serum	Horseradish peroxidase	SDS-PAGE	[250]
Medicinal	Chlorogenic acid	HPLC	[251]
Simulated body fluid and human plasma	Linezolid	HPLC/MS	[252]
Urine	Citalopram	LC-ITMS	[253]
Urine and soil	Fluoroquinolones	HPLC	[254]
Urine and serum	Ephedrine and pseudo-ephedrine	CE	[255]

Note CE, capillary electrophoresis; DPCSV, differential pulse cathodic stripping voltammetry; ECL, electrochemiluminescence; FAAS, flame atomic absorption spectrometry; HRP, horseradish peroxidase; ICP-MS, inductively coupled plasma-mass spectrometry; ITMS, ion trap mass spectrometry; SDS-PAGE, sodium dodecyl sulphate–polyacrylamide gel electrophoresis; TCs, tetracyclines

SPME formats. Thus, the development of novel strategies towards the simplification, minimization, automatization, and reduction of wastes of analytical methods can be facilitated by the introduction of smart materials. The advancements in this field clearly show that on improving the selectivity and capability of the new sorbents, it can reduce drastically the number of steps of the analytical procedure and the reagent and solvent consumption.

Nowadays, the current trend is focussed on the development of novel smart materials, but the use of joint materials allows a substantial increase of its analytical performance, combining their specific properties. In this sense, the combination of smart materials with magnetic ones has significantly simplified the number of steps in analytical procedures, avoiding the use of separation processes and shortening analysis time. In some cases, the improvement in selectivity of sorbents is related to the combined use of different materials as nanoparticles with a high surface area modified with biomimetic materials, thus providing synergistic combinations suitable to solve complex problems of matrix removal. Moreover, the use of restricted access materials, not discussed in this chapter, has shown a high capability to increase the reusability of highly specific SPE sorbents employed in the extraction of biological matrices, avoiding the direct interaction of the employed sorbent with proteins and other macromolecules present in the sample by size-exclusion processes [256].

However, on thinking of new materials and tailored fit sorption systems, it must be taken into account the environmental impact of the production of these materials as sorbents. So, advancements on greening sample preparation provided by smart materials must compensate the raw materials and resource consumption during their synthesis, purification, and functionalization steps, which may involve the use of considerable amounts of reagents, solvents, and energy consumption, and also the generation of wastes. So, efforts in a near future must also be focussed on greening synthesis and modification of new generation of smart materials and their appropriate combination to improve the analytical features of methods. In short, the green

analytical use of new sorbent materials must also integrate the green principles in the preliminary material design, production, and modification, taking into account that other strategies far from green chemistry must be strongly discouraged.

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Chapter 8
Ionic Liquids and Deep Eutectic Solvents in the Field of Environmental Monitoring

Inês S. Cardoso, Augusto Q. Pedro, Armando J. D. Silvestre and Mara G. Freire

Abstract A growing number of compounds resulting from human activities are continuously released into the environment. Many of these compounds may pose serious environmental threats, reinforcing the need of environmental monitoring to understand their impact on the environment and on human health and to create strategies to revert these risks. Although with serious impact, these pollutants are usually present in trace levels in environmental samples, turning their identification and accurate quantification a major challenge. To overcome this drawback, pretreatment techniques are usually employed, both to eliminate interferences and enrich the sample in the target pollutants. Within the significant developments achieved in this field, ionic liquids (ILs) and deep eutectic solvents (DESs) have shown to lead to relevant improvements in the enrichment factor and target pollutants recovery and in the limit of detection of the analytical technique when used as alternative solvents in pretreatment techniques of environmental matrices. These have been applied in the pretreatment of wastewaters, industrial effluents, human fluids, wine, milk, honey, fish, macroalgae, vegetables and soil. A wide number of pollutants, such as polyaromatic hydrocarbons (PAHs), active pharmaceutical ingredients (APIs), endocrine disruptors, pesticides, UV filters and heavy metals, are some of the most analyzed pollutants. In this work, we review and discuss the use of ILs and DESs as alternative solvents in pretreatment strategies in the field of environmental monitoring. We also highlight the most recent works on this area and provide new insights and directions to follow in this field.

Keywords Environmental monitoring · Trace-level pollutants · Environmental matrices · Green analytical chemistry · Pretreatment · Ionic liquid · Deep eutectic solvent

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J. Płotka-Wasylka and J. Namieśnik (eds.), *Green Analytical Chemistry*,
Green Chemistry and Sustainable Technology,
https://doi.org/10.1007/978-981-13-9105-7_8

8.1 Introduction

As the world's population continues to grow and as technology continues to develop, a growing number of compounds possessing serious environmental threats resulting from human activities are released into the environment [1]. Given the negative impact on living beings (and ultimately on humans) resulting from the exposure to these substances, it is crucial to evaluate their persistent, bio-accumulating and toxic character [2, 3]. These substances, which comprise pharmaceuticals, pesticides, endocrine disruptors, heavy metals and several other compounds, and although appearing at trace levels, can severely affect growth, reproduction and development of organisms. They can also compromise the immune system, leading to behavioral changes, cancer, diabetes, thyroid problems, among others [2, 4, 5]. The major exposure route of living beings to these contaminants is by ingestion, which leads to bioaccumulation and biomagnification, particularly toward species at the top level of the food chain [4], as schematized in Fig. 8.1.

A relevant factor contributing to the contamination of soils and water is the global growth of agricultural production, which has been accomplished through the intensive use of pesticides and chemical fertilizers. These compounds can either infiltrate into the soil or directly enter into aquatic systems, causing significant contamination of terrestrial ecosystems [6]. The presence of heavy metals is due to agricultural activities or to their release in pharmaceutical, industrial and domestic effluents [7]. An additional significant source of contamination derives from the extensive use of pharmaceuticals, both by humans and animals. Many drugs are only partially retained, treated, or removed in wastewater treatment plants, therefore being present in relevant levels in the aquatic environment [8]. Based on the exposed, there has been an increasing environmental awareness and interest in creating improved monitoring techniques to all sorts of pollutants, foreseeing to reduce the environmental impact of human activities and ultimately the impact over humans themselves. This trend can be further confirmed by the increasing number of reports dealing with pollutants

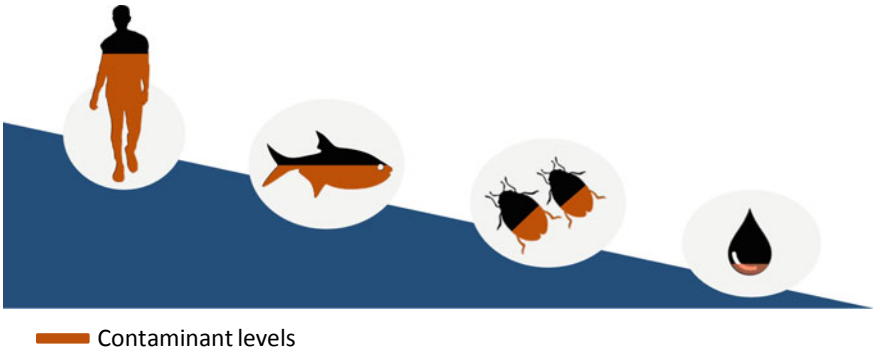


Fig. 8.1 Representation of the biomagnification process

monitoring programs according to a literature survey conducted from 2000 to 2018, as shown in Fig. 8.2 [9].

The increasing awareness of these aspects and also the scientific interest they trigger reinforce the need of establishing new environmental regulations and goals [9], both to preserve environment and human safety. There is thus an expanding need for simple, rapid and cost-effective screening methods to ensure that target pollutants are kept within acceptable levels. Environmental research is entering in a stage where analytical sciences play a vital role, allowing detailed environmental studies and confirming whether environmental goals have been met [9, 10]. Nonetheless, it is important to highlight the fact that neither analytics nor monitoring can solve any problems regarding pollution or environment degradation. They merely represent compelling tools that can provide relevant information required for a supported evaluation of the environment contamination level, ultimately relevant for decision making [3]. The application areas related to environmental monitoring are summarized in Fig. 8.3.

Significant technological progresses have been accomplished to identify and quantify several hazardous chemicals, including herbicides [11–14], pesticides [15–20], insecticides [21], polycyclic aromatic hydrocarbons (PAHs) [22–25], heavy metals [26–29], endocrine disruptors [29–31], active pharmaceutic ingredients (APIs) [32–37] and other organic pollutants [38–41]. Most of these substances display toxicity and endocrine disruptive effects, even at trace levels. However, in samples whose matrices are complex, the presence of interferents plays a significant role [2]. There are therefore several sample preparation techniques intended to reduce potential interferences from the sample matrix, while concentrating the target analytes for a more accurate identification and quantification in environmental samples. Examples of sample preparation techniques or pretreatment methods include organic digestion/dissolution, solid-phase extraction, liquid-phase extraction, aqueous biphasic systems and a wide range of

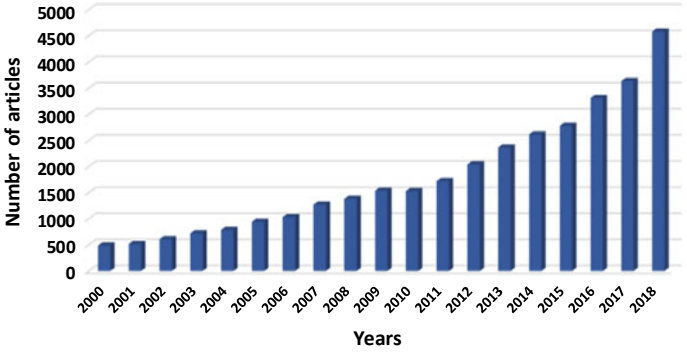


Fig. 8.2 Number of articles *per* year (from 2000 to November 25, 2018) dealing with the monitoring of contaminants of environmental concerns. The search was carried out in the ScienceDirect database using as keywords "water", "environment", "monitoring", "contaminant" and "pollutant"

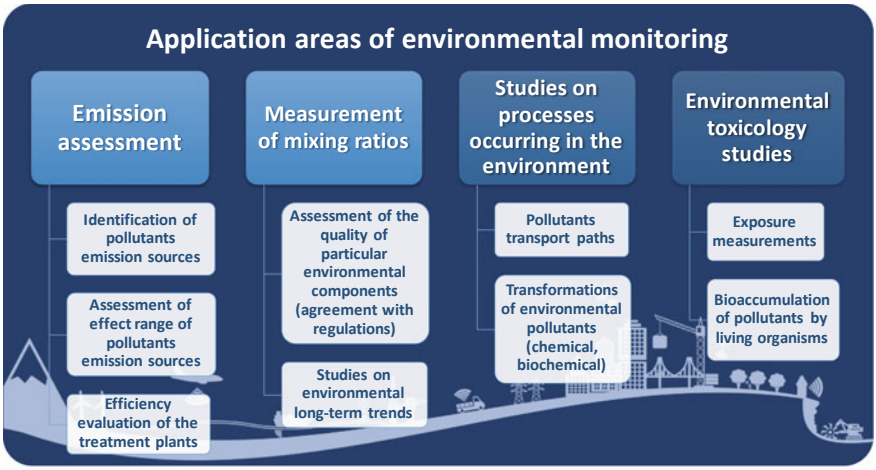


Fig. 8.3 Application areas of environmental monitoring (adapted from [3])

microextraction procedures, which will be further reviewed and discussed. Overall, it is highly desirable to develop reproducible pretreatment methods that can be applied independently of the sample matrix and target pollutant and interferences [4].

Along with the environmental awareness, green chemistry actively seeks for new processes and chemical products aiming at reducing or eliminating the use of hazardous substances and waste [42]. One of the main goals in the green chemistry analytical field consists of the application of sustainable solvents to replace the commonly applied volatile organic compounds, either in the extraction, pretreatment, or quantification steps [43]. In this context, solvents such as ionic liquids (ILs) [44] and deep eutectic solvents (DESs) [45] have been introduced as "greener" alternatives in this field.

The first description of ILs dates to 1914, when Paul Walden reported the physical properties of ethyl ammonium nitrate ($[EtNH_3][NO_3]$) when testing new explosives for the replacement of nitroglycerin [46]. Nowadays, ILs are described as organic salts with melting temperatures below 100 °C, being usually composed of a large organic cation and an organic or inorganic anion. The large dimensions of their ions and the high charge dispersion do not support an organized crystal structure, and as such, ILs are liquid at lower temperatures than conventional inorganic salts. Due to their ionic character, most aprotic ILs present unique characteristics, namely negligible flammability and volatility, high ionic conductivity, high thermal stability and a strong solvation capability for a large variety of compounds [47, 48]. One of the most promising features of ILs is the ability to design their physicochemical properties by a fine customization of the cation and/or anion chemical structure, being often referred to as designer solvents. This way, it is possible to tailor their polarity and selectivity in extraction/separation processes, as well as their biodegradability and toxicologi-

cal impact [46, 49, 50]. Resulting from the described advantageous characteristics, these solvents have been investigated to improve many biological and chemical processes, namely in synthesis, (bio)catalysis, extraction/separation processes, electrochemistry and analytical applications (Fig. 8.4) [51, 52]. The most widely studied ILs are composed of imidazolium, pyridinium, pyrrolidinium, phosphonium and tetraalkylammonium-based cations, combined with anions such as chloride (Cl^-), bromide (Br^-), acetate ($[CH_3CO_2]^-$), bis(trifluoromethylsulfonyl)imide ($[NTf_2]^-$), hexafluorophosphate ($[PF_6]^-$) and tetrafluoroborate ($[BF_4]^-$) [53]. Figure 8.4 depicts the chemical structure of common IL cations and anions and their main applications. However, it should be remarked that the research focused on ILs is moving toward less toxic and more biodegradable formulations, mainly derived from natural sources [54, 55].

In addition to ILs, in more recent years, deep eutectic solvents (DESs) have emerged as promising alternatives over the typically used volatile organic solvents [56]. DESs were first reported in 2001 by Abbott et al. [57], and since then a growing interest in these solvents has been witnessed [58]. DESs consist of a mixture of a hydrogen bond acceptor (HBA) and a hydrogen bond donor (HBD) species, which present a melting point significantly lower than that of the individual components. Beyond eutectic mixtures, DESs do not follow the behavior of an ideal mixture since strong hydrogen-bond interactions are established between both compounds, leading to a significant decrease in the mixture melting temperature. Figure 8.5 shows several examples of HBAs and HBDs and an example of the solid–liquid phase diagram according to the DES composition [56].

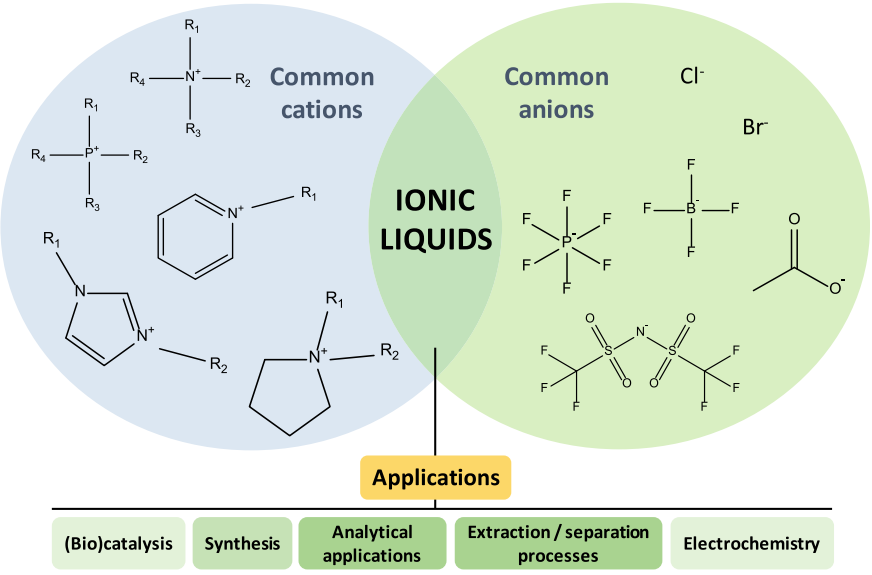


Fig. 8.4 Common cations and anions that form ILs and possible applications of these solvents

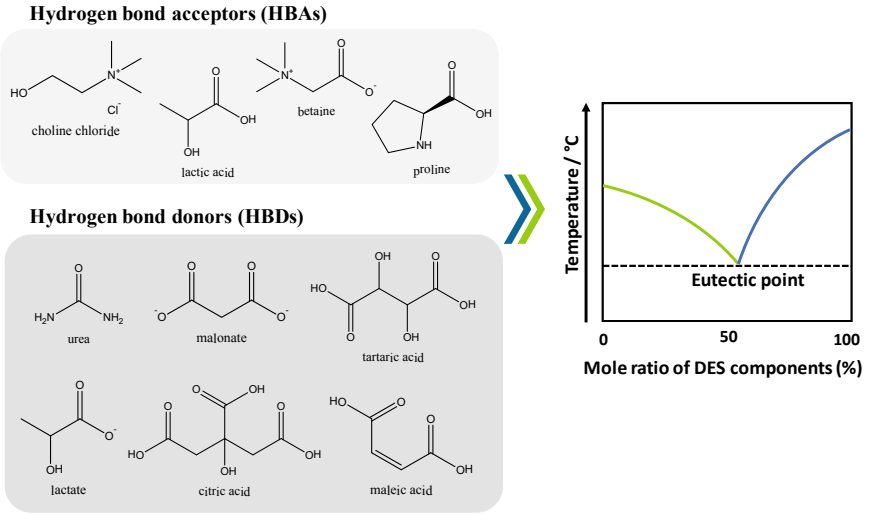


Fig. 8.5 Examples of HBAs and HBDs used in DES preparation and solid–liquid phase diagram representation of a DES

As ILs, DESs are commonly referred to as tunable solvents since a wide range of HBDs and HBAs species can be combined. However, DESs present several advantages over ILs, such as their easy preparation (no chemical reaction required) and easy availability of the individual components, which are usually less expensive and from natural sources, such as amino acids, organic acids, sugars and cholinium derivatives. On the other hand, DESs are often reported as less chemically inert than ILs [59]. Similar to ILs, DESs have found applications in a broad range of domains, spanning from catalysis, organic synthesis, biotechnology-related applications, among others [43, 45, 56, 58].

Based on the potential of ILs and DES as alternative solvents, in this chapter, sample pretreatment strategies proposed in recent years making use of these solvents are reviewed, namely on their use to allow the environmental monitoring of a large variety of pollutants from real matrices. The major drawbacks found and future perspectives are also given. Figure 8.6 summarizes the present work.

8.2 Application of Ionic Liquids in the Pretreatment Step of Real Matrices to Monitor Trace-Level Pollutants

The low concentration of pollutants in environmental samples represents the major challenge associated with their identification and accurate quantification [60]. In this sense, and as previously described, several sample pretreatment techniques have been implemented to extract and preconcentrate these contaminants before subject-

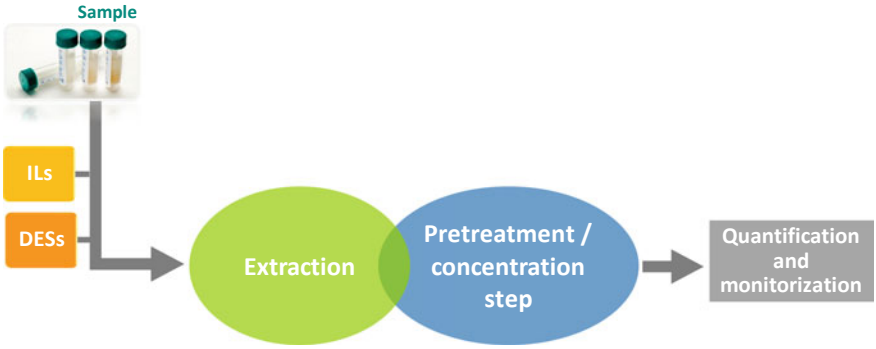


Fig. 8.6 Outline of the information presented in the current chapter focused on the use of ILs and DES in extraction and/or pretreatment/preconcentration steps for trace-level pollutants quantification in real matrices

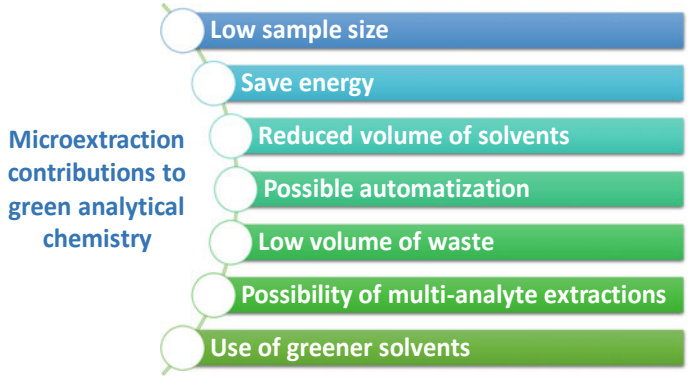


Fig. 8.7 Microextraction contributions to greener pretreatment steps

ing them to analytical quantification [41, 60]. Among those techniques, liquid–liquid extraction (LLE) and solid-phase extraction (SPE) are the most investigated [61–66]. In recent years, several microextraction methods, namely solid-phase microextraction (SPME) and dispersive liquid–liquid microextraction (DLLME), have also been developed to improve the pretreatment procedure, while reducing the amount of solvents used and generating less residues [58]. Figure 8.7 summarizes the microextraction contributions within the green analytical chemistry field.

In this sub-chapter, the most recent trends regarding the use of ILs in the pretreatment of environmentally related samples are reviewed and discussed. In particular, it is described and discussed the application of ILs to improve the identification and quantification of heavy metals, endocrine disruptors, APIs, pesticides, PAHs, aromatic amines, UV filter components and other organic pollutants. Table 8.1 summarizes the information reviewed in this sub-chapter, namely the target pollutant, as well as the yield, type of matrix, IL-based process used, preconcentration/enrichment

factor, analytical method applied and limit of detection (LOD). Table 8.2 lists the ILs considered in this sub-chapter, comprising their names and corresponding chemical structures and acronyms. The next sub-chapters are grouped according to the type of pollutants.

8.2.1 Pharmaceuticals and Endocrine Disruptors

Emerging public health concerns have significantly raised in recent years due to the adverse effects of pharmaceuticals and endocrine disruptors. Some of these pollutants have been detected in wastewater, rivers and even in drinking water [37]. Pharmaceuticals, such as fluoroquinolones (FQs) and other antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs) and endocrine disruptors, have been investigated. Aiming at improving their environmental monitoring, ILs such as [P_{4444}]Cl, [N_{4444}]Cl, [C_4mim][FAP], [C_4mim][NTf_2], [C_4mim][PF_6] and [C_6mim][PF_6] (see Table 8.2 for their chemical structures) have been used in pretreatment strategies. The pretreatment methods applied in this set of works correspond to the use of aqueous biphasic systems (ABS), dispersive liquid–liquid microextraction (DLLME), immersed droplet microextraction (IDME) and magnetic solid phase extraction (MSPE).

Passos et al. [30], Almeida et al. [37] and Dinis et al. [67] proposed the application of one of the most promising liquid–liquid extraction (LLE) methods involving ILs found in the literature—aqueous biphasic systems (ABS)—to successfully extract and concentrate bisphenol A, ciprofloxacin, enrofloxacin, norfloxacin, diclofenac, naproxen, ketoprofen, caffeine and carbamazepine (Fig. 8.8) from urine matrices, wastewater and surface water, aiming at improving their detection and quantification foreseeing an accurate environmental monitoring.

ABS are liquid–liquid systems and allow the extraction of target molecules from one aqueous phase to another. These systems are composed of several pairs of solutes dissolved in water (e.g., polymer–polymer, polymer–salt, polymer-IL, IL-salt), where above specific concentrations there is two-phase formation [48]. Mostly due to their large water content and non-volatile nature of the phase-forming components, these systems have been considered as sustainable liquid–liquid extraction options. The use of ILs as phase-forming components of ABS has been largely investigated in recent years [48]. This trend is due to the designer solvents ability of ILs, which is transposed to IL-based ABS, allowing the design of the phases' polarities and affinities, and thus high selectivity and extraction performance to be achieved [46, 48]. A schematic representation of the ABS separation process and their use as pretreatment strategies is summarized in Fig. 8.9.

Taking advantage of the ability of ABS to design their phases' polarities and affinities, Passos et al. [30] applied ABS composed of [N_{1112OH}]Cl or [C_2mim]Cl and potassium phosphate to extract bisphenol A (Fig. 8.8) from human urine, achieving a preconcentration factor of 100-fold in a single step. Urine contains significant amounts of NaCl and urea, which the authors found as beneficial to improve the

Table 8.1 Summary of the information related to the use of ILs in pretreatment steps of real matrices to monitor environmental pollutants, describing the target analyte, pretreatment process, solvent, yield, type of matrix, enrichment factor, analytical equipment and limit of detection

Target analyte	Pretreatment process	Pretreatment solvent	Yield (%)	Type of matrix	Enrichment factor	Analytical equipment	LOD ($\mu g\ L^{-1}$)	References
Pharmaceuticals and endocrine disruptors								
Ciprofloxacin, enrofloxacin and norfloxacin Diclofenac, naproxen and ketoprofen	ABS[a]	$[N_{4444}]Cl$	≈100	Wastewater	1000	HPLC-DAD	NR[b]	[37]
Paracetamol, ibuprofen, naproxen and diclofenac	MSPE[c]	$[C_4mim][PF_6]$	85–116	Tap, dam and river water	29–34	HPLC-UV-FL	3.2–7.2	[36]
Caffeine, carbamazepine	ABS	$[N_{4444}]Cl$	95–100	Wastewater and surface water	8259–28,595	HPLC-UV	NR	[67]
Amitriptyline	IDME[d]	$[C_6mim][PF_6]$	NR	Hospital wastewater	1100	HPLC-UV	4.0	[68]
Bisphenol A	ABS	$[N_{1112OH}]Cl$ $[C_2mim]Cl$	≈100	Human fluid (urine)	100	HPLC-MS	NR	[30]
Several drugs, hormones, caffeine	DLLME[e]	$[NH_2C_6mpyr][FAP]$ $[C_4mim][NTf_2]$	91–110	Tap and creek water	93	HPLC-UV/Vis	0.1–55.1	[34]
Pesticides								
Triazine	DLLME	$[C_8mim][PF_6]$	85–100	River and underground water; wastewater	NR[f]	HPLC-UV	0.05–0.06	[69]
Sulfonylurea	VA-DLLME[g]	$[C_6mim][PF_6]$	80–104	Wine	NR	HPLC-DAD[h]	3.2–6.6 (given in $\mu g\ kg^{-1}$)	[12]

(continued)

Table 8.1 (continued)

Target analyte	Pretreatment process	Pretreatment solvent	Yield (%)	Type of matrix	Enrichment factor	Analytical equipment	LOD ($\mu g\ L^{-1}$)	References
Clothianidin, imidacloprid, dinotefuran, thiacloprid	CIAME[i]	$[C_4mim][PF_6]$	86–100	Honey	200	HPLC-DAD	0.01	[70]
Disulfoton, famphur, parathion, parathion-methyl, phorate, sulfotep, thionazin and thiethyl thiophosphate	DLLME	$[C_4mim][NTf_2]$	97–113	River, irrigation and marshes water	NR	GC-MS	0.005–0.016	[18]
Phoxim, fenitrothion, chlorpyrifos, phorate and parathion	DLLME	$[C_6H_5mim][NTf_2]$	82.7–118.3	Tap, rain and river water	339	HPLC-UV	0.01–1.00	[71]
PAHs, UV filters and other organic compounds								
Polycyclic aromatic hydrocarbons	DLLME	$[C_8mim][PF_6]$	90.3–103.8	Tap, bottled, fountain, well, river water, rainwater; wastewater	301–346	HPLC-FL	0.0001–0.007	[24]
Polycyclic aromatic hydrocarbons	SBDLME[j]	$[P_{66614}][$ Ni(II)$(hfacac)_3]$	84–115	River, tap and rain water	18–717	GC-MS	0.0005–0.0087	[72]
2,4-dichloroaniline, 1-naphthylamine, 6-chloroanline and *N*,*N*-dimethylaniline	USA-DLLME[k]	$[C_6mim][PF_6]$	92.2–119.3	Melted snow water, river and brook water	NR[l]	HPLC-UV	0.17–0.49	[39]

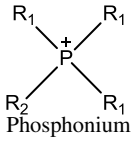
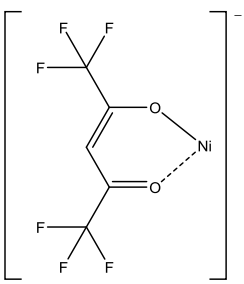
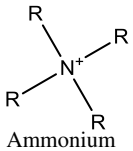
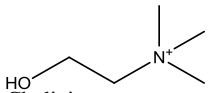
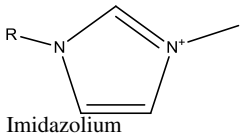
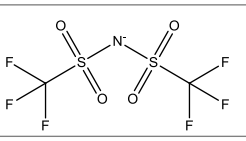
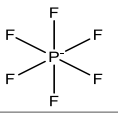
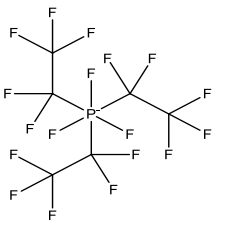
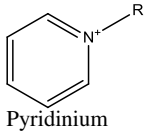
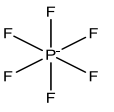
(continued)

Table 8.1 (continued)

Target analyte	Pretreatment process	Pretreatment solvent	Yield (%)	Type of matrix	Enrichment factor	Analytical equipment	LOD ($\mu g\ L^{-1}$)	References
Organophosphate esters	SPME[m]	[C_6mim][FAP]	82.1–123.0	Tap water, sewage treatment plant water	168–2603	GC-MS	0.0005–0.024	[40]
Benzophenone-type UV filters	USA-DLLME	[C_6mim][FAP]	71–118	River, swimming pool and tap water	354–464	HPLC-UV	0.2–5.0	[73]
Benzophenone-type UV filters	HF-LPME[n]	[C_6mim][FAP]	82.6–105.9	River water	216	HPLC-UV	0.3–0.5	[74]
Heavy metals								
Zinc	DLLME	[C_6py][PF_6]	97.1–102.5	Underground tap and spring water; milk	71	FAAS[o]	0.22	[26]

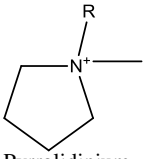
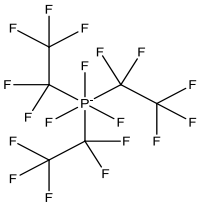
[a]Aqueous biphasic systems
[b]Not reported
[c]Magnetic solid-phase extraction
[d]Immersed droplet microextraction
[e]Dispersive liquid–liquid microextraction
[f]Not reported
[g]Vortex-assisted dispersive liquid–liquid microextraction
[h]Photodiode array detection
[i]Cold-induced aggregation microextraction
[j]Stir bar dispersive liquid microextraction
[k]Ultrasound-assisted dispersive liquid–liquid microextraction
[l]Not reported
[m]Solid-phase microextraction
[n]Hollow-fiber liquid-phase microextraction
[o]Flame atomic absorption spectrometry

Table 8.2 ILs investigated in pretreatment strategies of environmental-related samples, comprising their names, acronyms and chemical structures

Cationic head group	Side chain (*R*)	Anion	Acronym
 Phosphonium	$R_1 = (CH_2)_5CH_3$ $R_2 = (CH_2)_{13}CH_3$		$[P_{66614}][Ni(II)(hfacac)_3]$
 Ammonium	$R = (CH_2)_3CH_3$	Cl^-	$[N_{4444}]Cl$
 Cholinium			$[N_{1112OH}]Cl$
 Imidazolium	$R = CH_2CH_3$		$[C_2mim]Cl$
	$R = (CH_2)_3CH_3$		$[C_4mim][NTf_2]$
	$R = (CH_2)_5CH_3$		$[C_6mim][NTf_2]$
	$R = CH_2C_6H_5$		$[C_6H_5mim][NTf_2]$
	$R = (CH_2)_3CH_3$		$[C_4mim][PF_6]$
	$R = (CH_2)_5CH_3$		$[C_6mim][PF_6]$
	$R = (CH_2)_7CH_3$		$[C_8mim][PF_6]$
	$R = (CH_2)_5CH_3$		$[C_6mim][FAP]$
 Pyridinium	$R = (CH_2)_5CH_3$		$[C_6py][PF_6]$

(continued)

Table 8.2 (continued)

Cationic head group	Side chain (*R*)	Anion	Acronym
 Pyrrolidinium	$R = (CH_2)_6NH_2$		$[NH_2C_6mpyr]$ [FAP]

partitioning of bisphenol A to the IL-rich phase. The authors concluded that these systems require small amounts of IL and allow a reproducible and accurate quantification of bisphenol A in human fluids. Also taking advantage of the ABS tailoring ability, Almeida et al. [37] studied the single-step extraction and preconcentration of FQs and NSAIDs (Fig. 8.8) using ABS composed of $[N_{4444}]Cl$ and a citrate-based salt ($C_6H_5K_3O_7$). This study described the recovery of three FQs (ciprofloxacin, enrofloxacin and norfloxacin) and three NSAIDs (diclofenac, naproxen and ketoprofen) from real effluent samples from wastewater treatment plants. The proposed systems allowed to achieve preconcentration factors of 1000-fold of both FQs and NSAIDs and extraction efficiencies of these APIs close to 100%, without reaching the saturation of the IL-rich phase [35]. This enrichment factor allowed their direct identification and quantification by high-performance liquid chromatography HPLC-UV. Dinis et al. [67] also applied IL-based ABS to extract and concentrate caffeine and carbamazepine from wastewater effluents and surface water samples. Based on the solubility of each pollutant in the IL-rich phase, the authors concluded that the investigated IL-based ABS may allow enrichment factors of 28595-fold and 8259-fold, respectively, and extraction efficiencies of both tracers to the IL-rich phase ranging between 95 and 100%, in a single step [67]. Overall, it is important to stress the ability of these systems to simultaneously extract and concentrate several pollutants without saturating the IL-rich phase at the levels at which they are found in the environment, allowing the analytical quantification without major interferences of the ABS phase-forming components [67].

DLLME is a pretreatment strategy of relevant interest for the preconcentration/enrichment of a wide range of compounds. This technique is a simple, sustainable and low-cost procedure. In DLLME, the cloudy state is created due to the solvent droplets upon injection of the binary solvent mixture, known as extraction and disperser solvents, into an aqueous sample. The large surface area between the fine droplets and the aqueous phase promotes the transfer of analytes from the sample solution into the extraction phase. Usually, a centrifugation step is further applied causing the sedimentation of the droplets at the bottom of the tube (typically of conical shape), being this phase collected using a syringe and further analyzed by the appropriate analytical technique [75]. In this solvent-minimizing technique, only a few microliters of a selected solvent are used to extract analytes in comparison to a large

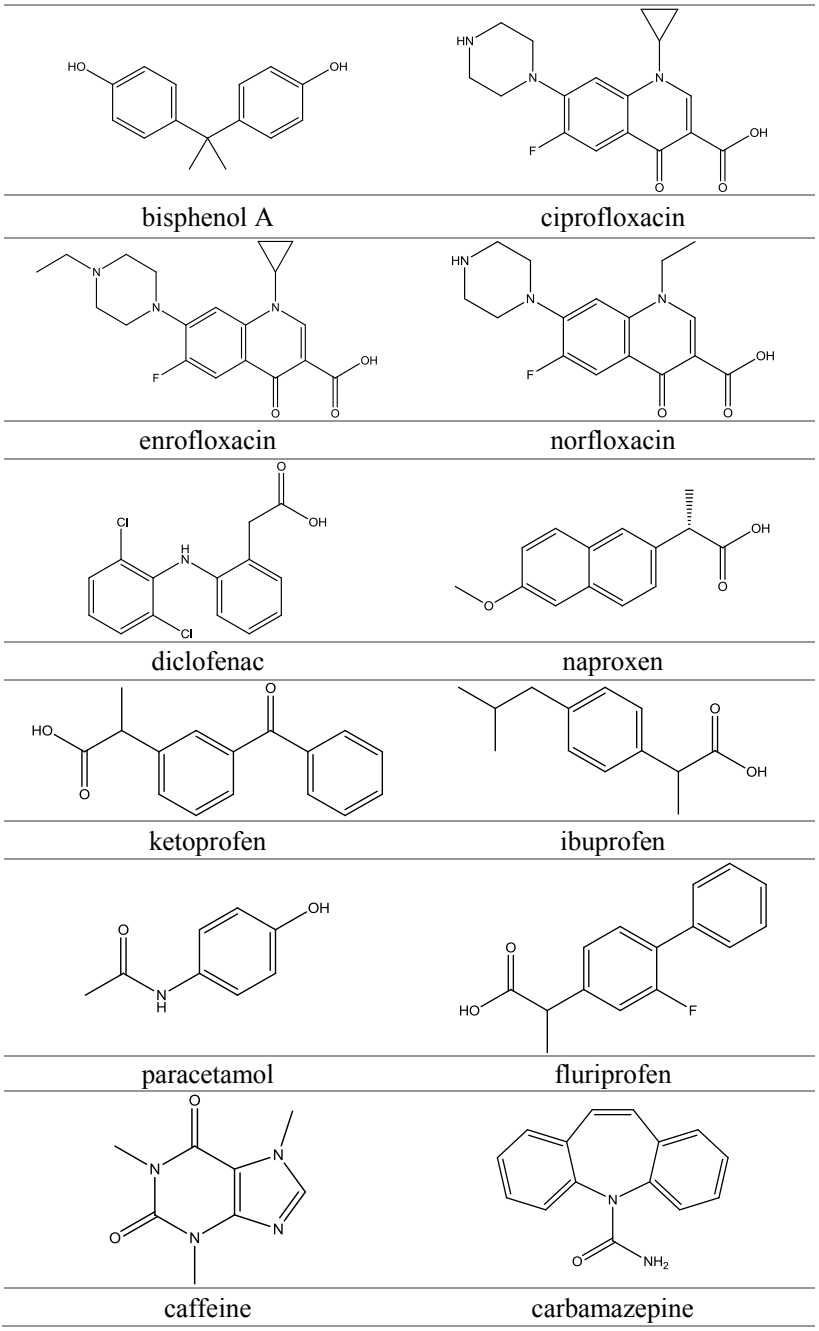


Fig. 8.8 Chemical structures of the investigated endocrine disruptors and pharmaceuticals

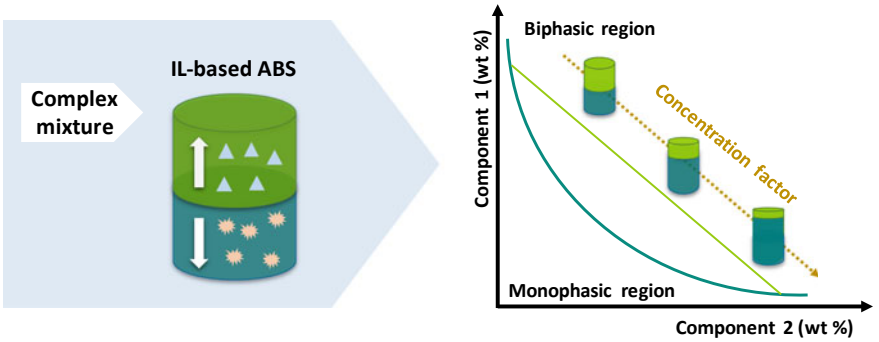


Fig. 8.9 Schematic illustration behind the use of IL-based ABS as pretreatment and concentration platforms

amount of volatile organic solvents often required in traditional LLE. Figure 8.10 summarizes the experimental steps required in DLLME. The type of extraction and disperser solvents, and their volumes, significantly affects the DLLME extraction efficiency and enrichment factors.

Taking advantage of the benefits of DLLME coupled to ILs, Yao et al. [34] proposed the use of functionalized ILs containing the tris(perfluoroalkyl)trifluorophosphate anion ([FAP]) in DLLME for the extraction of 14 emerging contaminants (APIs, hormones, caffeine and endocrine disruptors, whose chemical structures are shown in [32]) from water samples. All ILs investigated are immiscible with water and can thus be directly used in DLLME, contrary to ABS where water-miscible ILs are used requiring the addition of a third component (usually a salt) to create two phases. Compounds containing functionalized tertiary amines are preferentially extracted by $[NH_2C_6mpyr][FAP]$ in comparison to other [FAP]-based ILs. On the other hand, polar or acidic compounds without amine groups display higher enrichment factors using $[C_4mim][NTf_2]$. Real water samples including tap water and creek water were analyzed, yielding recoveries ranging from 91 to 110%. The LOD varied from 0.1 to 55.1 $\mu g\ L^{-1}$ using the $[NH_2C_6mpyr][FAP]$ IL as extraction solvent [34].

Furthermore, since a single operational step is required, in this technique there is less contamination and less loss of analytes compared to conventional solvents extractions. Although both DLLME and conventional extraction methods exhibit similar recoveries, DLLME allows higher enrichment factors [76].

Abujaber et al. [36] and Hamed Mosavian et al. [68] proposed different approaches for the identification and quantification of several pharmaceuticals, such as paracetamol, ibuprofen, naproxen and diclofenac (Fig. 8.8) in natural waters, and amitriptyline (Fig. 8.8) in hospital wastewater, respectively. Abujaber et al. [36] used magnetic cellulose nanoparticles (MCNPs) coated with $[C_4mim][PF_6]$, by electrostatic interactions, as new sorbents for magnetic solid-phase extractions (MSPEs). A schematic representation of the experimental procedure proposed is shown in Fig. 8.11. The

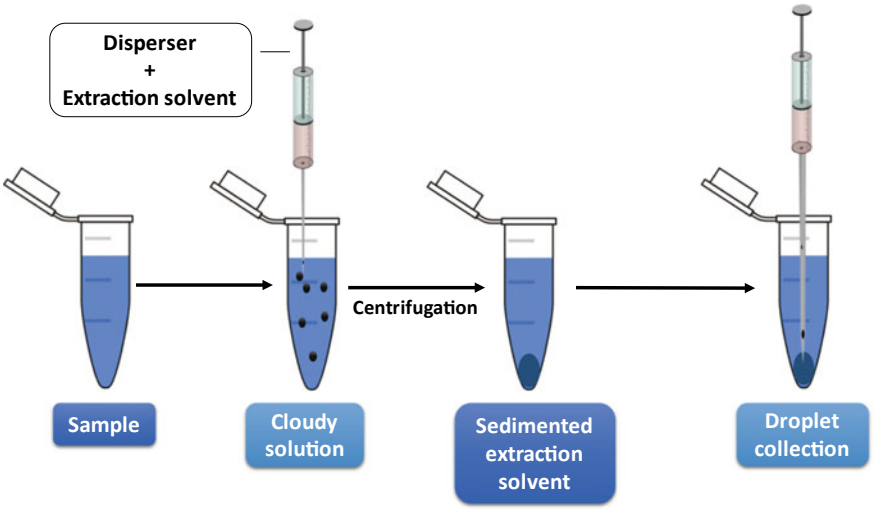


Fig. 8.10 Schematization of the DLLME process

authors studied the influence of several parameters that may affect adsorption (type of dispersive solvent, amount of IL, pH and salt content) and desorption (type of desorption solvent, energy and time) steps to optimize the process. The proposed method provides enrichment factors ranging from 29.0 to 34.2 and extraction recoveries ranging between 85 and 116%. Using HPLC with UV and fluorescence (FL) detectors as the analytical method, LODs of 11–24 $\mu g\ L^{-1}$ were reported. Since the modification of the magnetic nanoparticles occurs by non-covalent interactions, namely by electrostatic interactions, the leaching of the IL should be taken into account. Despite the low water solubility of $[C_4mim][PF_6]$ at room temperature, it is still significant and may contaminate water streams [77]. Hamed Mosavian et al. [68] proposed the use of the same IL for the monitoring of amitriptyline (Fig. 8.8) in wastewater by IL-based immersed droplet microextraction (IDME) prior to HPLC-UV analysis. In IDME, the sample solution is added to a glass vial containing a magnetic bar, and then, a fine IL droplet is immersed into the stirred aqueous solution using a microsyringe and collected from the bottom of the vial. A preconcentration factor of 1100 and a LOD of 0.004 mg mL^{-1} were reported by the authors. The authors also performed a comparative analysis between the proposed method, conventional liquid–liquid extractions and DLLME, concluding that the proposed IL-based IDME allows the highest enrichment factor while avoiding organic solvents use [68].

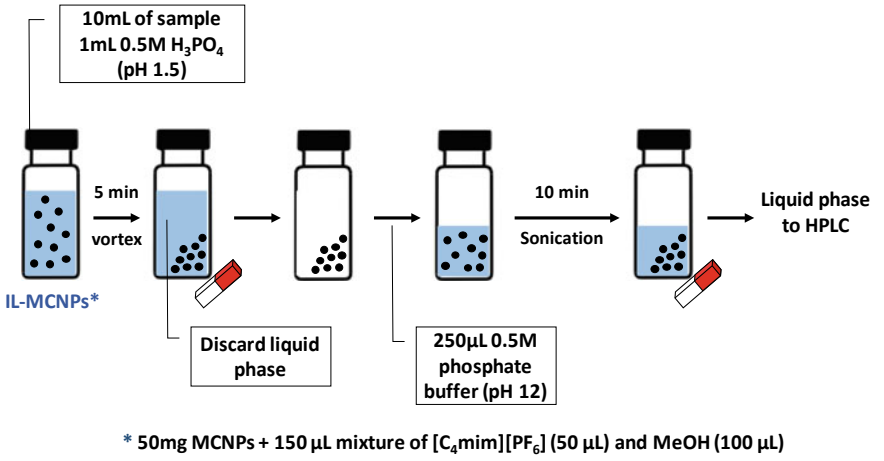


Fig. 8.11 Schematic representation of the analytical method of magnetic solid-phase extraction (MSPEs) using magnetic cellulose nanoparticles (MCNPs) coated with [C_4mim][PF_6]

8.2.2 Pesticides

There are several reports on the use of ILs in microextraction processes, namely DLLME and cold-induced aggregation microextraction (CIAME), to monitor the levels of pesticides [12, 18, 69, 70], whose structures are displayed in Fig. 8.12. This kind of research is mandatory since these pollutants constitute a major anthropogenic source. In this vein, Zhou et al. [69] reported a temperature-controlled DLLME using [C_8mim][PF_6] as the extraction solvent in combination with HPLC-UV, to enrich extracts in triazine herbicides, namely cyanazine, simazine and atrazine (Fig. 8.12) from four real water samples. Under the optimal conditions (pH, centrifugation time, temperature and ionic strength), recoveries between 85.1 and 100% and LOD in the range from 0.05 to 0.06 mg L^{-1} were obtained [69].

Cacho et al. [18] also focused their studies in DLLME, in which the IL extracting phase was placed in a glass micro vial inside the thermal desorption tube. The whole assembly was submitted to a temperature program in the thermal desorption unit. As soon as the IL is heated, the target analytes are vaporized, and a carrier gas impels them to the programmed temperature vaporization injector where they are concentrated before entering the chromatographic column. Since ILs possess negligible vapor pressures, the IL matrix remains in the disposable glass microvial after the heating step [18, 29]. This procedure allows the direct introduction of the IL extracts into the GC apparatus, simplifying the process while increasing sensitivity and accuracy. Moreover, under optimal conditions (temperature, time and gas flow rate) the authors demonstrated the accurate determination of nine organophosphorus pesticides (disulfoton, famphur, parathion, parathion methyl, phorate, sulfotep, thionazin and thiethyl thiophosphate—Fig. 8.12) from environmental waters. In this work, the

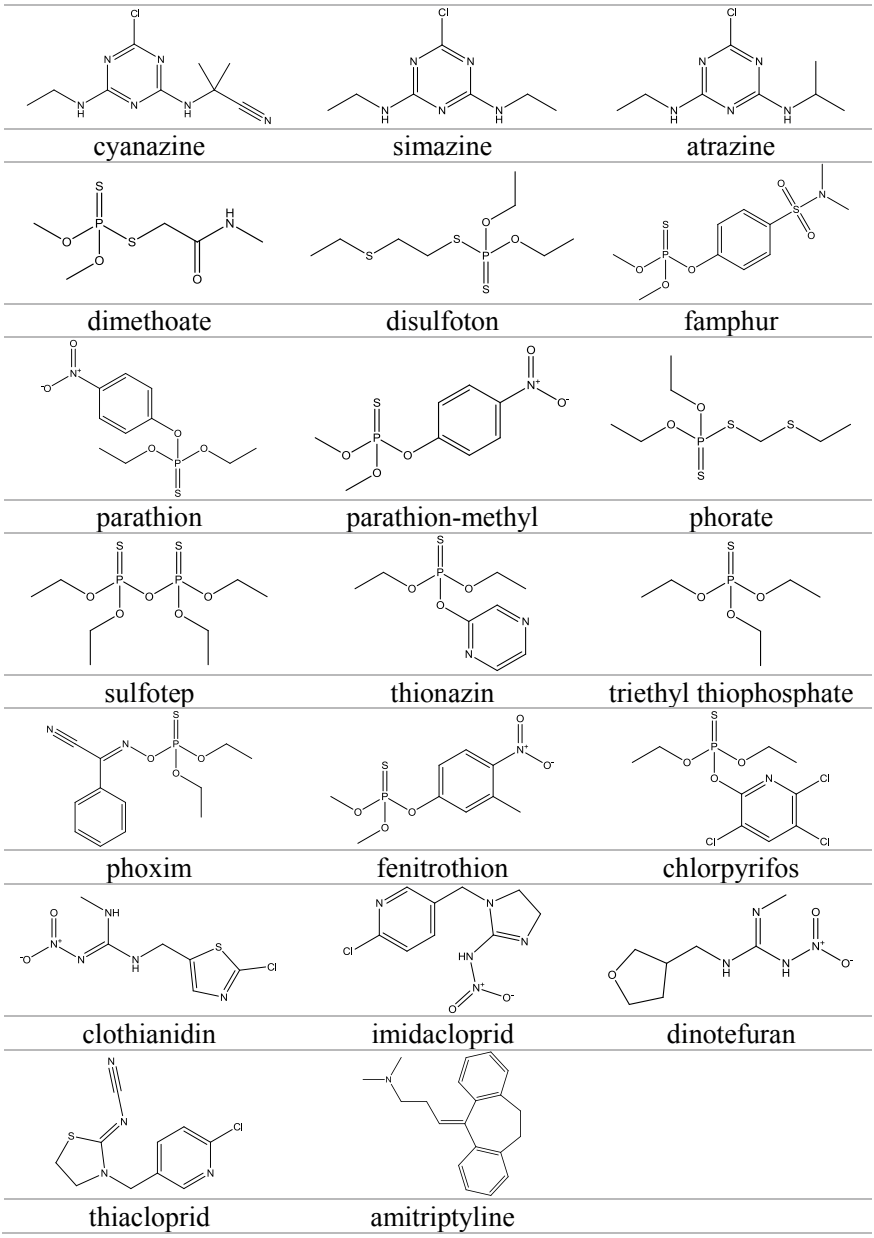


Fig. 8.12 Chemical structures of the pesticides studied by Zhou et al. [69]

use of [C_4mim][NTf_2] led to recoveries in the 85–118% range and to a LOD ranging from 0.005 to 0.016 μg L^{-1} [18]. Taking into account that the proper functionalization of ILs could enhance the extraction efficiency of the target compounds, Wang et al. [71] proposed the use of a benzyl functionalized IL ([C_6H_5mim][NTf_2]) as the extraction solvent in DLLME for the analysis of 5 organophosphorus pesticides (phoxim, fenitrothion, chlorpyrifos, phorate and parathion—Fig. 8.12) in environmental water samples by HPLC-UV. The introduction of the benzyl group into the imidazolium cation significantly increases the extraction efficiency, which may be due to π–π interactions occurring between the IL and the target aromatic compounds. The extraction was performed using 40 μL of [C_6H_5mim][NTf_2] and 1 mL of methanol as dispersive solvent, with a centrifugation time of 5 min. Under the optimal conditions, an enrichment factor of 339, recoveries ranging between 81.4 and 118.3% and LODs ranging from 0.01 to 1.0 μg L^{-1} were reported [71].

In addition to the previous works, some authors focused their studies on strategies that, along with the miniaturization of the process, improve the dispersion of hydrophobic ILs into the aqueous samples. In this context, several DLLME derivative techniques were proposed, such as vortex-assisted dispersive liquid–liquid microextraction (VA-DLLME), air-assisted dispersive liquid–liquid microextraction (AALLME) and ultrasound-assisted dispersive liquid–liquid microextraction (USA-DLLME). Gure et al. [12] suggested the application of VA-DLLME, followed by capillary liquid chromatography for the determination of four sulfonylurea herbicides in wine samples. The IL [C_6mim][PF_6] was used as extraction solvent and was dispersed using methanol into the sample solution, assisted by a vortex mixer. Under the optimum conditions (type and amount of IL, type and volume of disperser solvent, pH, salting-out effect, vortex and centrifugation time), recoveries higher than 80% and LODs ranging between 3.2 and 6.6 μg kg^{-1} were reported [12].

To eliminate the interface between water and the extractant phases, while removing drawbacks from mass transfer effects, cold-induced aggregation microextraction (CIAME) techniques have been developed. The hydrophobic components are preferentially collected by the extraction solvent in fine droplets, and the solution is cooled in an ice bath, forming a cloudy solution. Subsequently, the resulting emulsion can be completely separated by centrifugation. Usually, CIAME is a simple and accurate preconcentration technique applied for the analysis of samples containing high concentration of salts and water-miscible organic solvents. Vichapong et al. [70] proposed a preconcentration approach based on IL-based CIAME before the analysis of the samples by HPLC with a photodiode array detector (HPLC-DAD) to detect neonicotinoid insecticides (clothianidin, imidacloprid, dinotefuran, thiacloprid) in honey samples. The chemical structures of these insecticides are depicted in Fig. 8.12. [C_4mim][PF_6] was used as the extraction solvent and sodium dodecyl sulfate (SDS) as the surfactant. Optimum microextraction conditions were attained, leading to enrichment factors of 200, recoveries above 86%, and LOD of 0.01 μg L^{-1} for all analytes.

8.2.3 Polycyclic Aromatic Hydrocarbons, UV Filters and Other Organic Compounds

Along with the pollutants discussed before, there are other classes of compounds that deserve equal prominence in environmental monitoring, namely PAHs, aromatic amines, organophosphate esters and UV filters (chemical structures given in Fig. 8.13). In this section, several extraction methods, such as DLLME, stir bar dispersive liquid microextraction (SBDLME), USA-DLLME, SPME and hollow-fiber DLLME for the accurate quantification of these types of pollutants, are overviewed and discussed.

PAHs are ubiquitous environmental pollutants primarily generated during the incomplete combustion of organic materials (e.g., coal, oil, petrol and wood), which are associated to toxic and/or carcinogenic properties. Aiming an accurate monitoring of PAHs, Pena et al. [24] explored the application of IL-based DLLME for the analysis of 18 PAHs (Fig. 8.13)—such as naphthalene, acenaphtylene, acenapthene, fluorene, phenanthrene, anthracene, pyrene, benzo[a]anthracene and chrysene—from water samples, namely tap, bottled, fountain, well, river, rainwater, treated and raw wastewater [24]. [C_8mim][PF_6] was used to take advantage of the chemical affinity between this IL and PAHs, allowing the simultaneous extraction and preconcentration from the original samples. Factors affecting the extraction efficiency and enrichment factor (type and volume of IL, type and volume of disperser solvent, extraction time, centrifugation time and ionic strength) were investigated by the authors. High enrichment factors (301–346) and extraction yields, ranging from 90.3 to 103.8%, were obtained. The authors further evaluated the effect of the nature of the water samples, showing that the recovery of PAHs undergoes a progressive reduction with the increasing complexity of the water samples. For instance, with treated wastewater and raw wastewater, a decrease of 40 and 60% in the recovery efficiency, respectively, was found. This trend was attributed to the presence of colloidal organic matter in the samples. The authors also demonstrated that IL-based DLLME provides similar recoveries for all PAHs compared to conventional LLE. However, the proposed procedure is more advantageous since it is faster; simple and smaller volumes of organic solvents are applied [24].

Benedé et al. [72] explored an innovative hybrid approach called stir bar dispersive liquid microextraction (SBDLME) (Fig. 8.14), which combines the advantages of stir bar absorptive extraction (SBSE) and dispersive liquid–liquid microextraction (DLLME) for the determination of 10 PAHs, being the most significant ones described in Fig. 8.13, from tap, rain and river water samples. The extraction was performed using a neodymium stir bar magnetically coated with a magnetic ionic liquid (MIL) as extraction device. In this technique, the [P_{66614}][Ni(II)$(hfacac)_3$] is dispersed into the solution at high stirring rates. Once the stirring is over, the MIL is magnetically retrieved and further subjected to thermal desorption, being directly applied into GC-MS. This method allows enrichment factors between 18 and 717, recovery values ranging from 84 to 115% and LOD ranging from 0.0005 to 0.0087 ng L^{-1}. Furthermore, the authors carried out a comparative analysis of

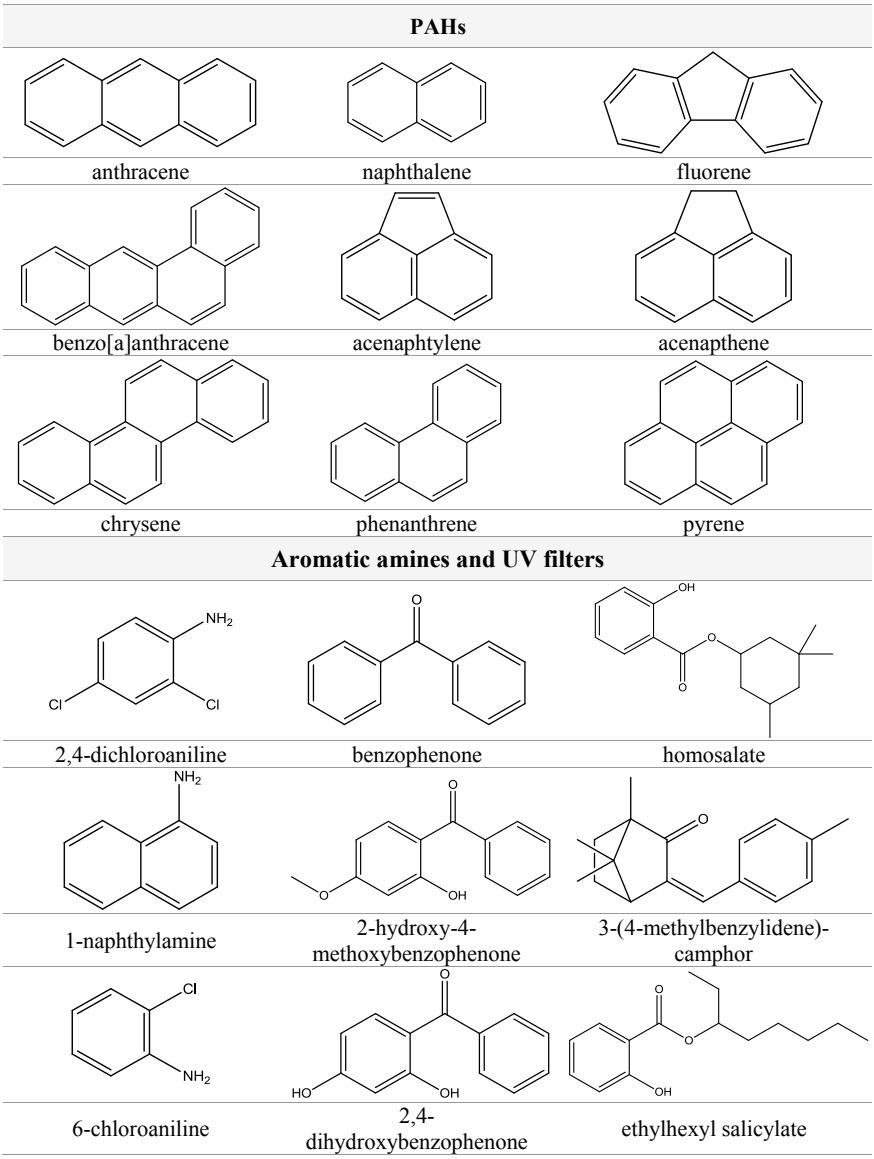


Fig. 8.13 Chemical structures of some of the studied PAHs, aromatic amines and UV filters

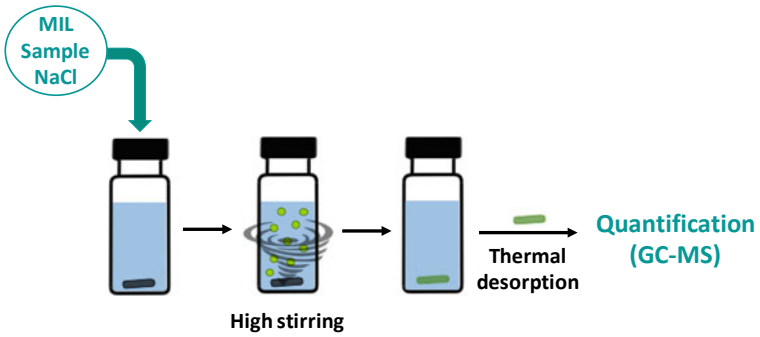


Fig. 8.14 Schematic representation of the SBDLME technique

the proposed SBDLME method with other approaches coupled to GC-MS for the same purpose, verifying a similar analytical performance. Moreover, it is important to point out that the combination of both SBSE and DLLME into the new approach offers an improvement in the versatility and selectivity of the method, mostly due to the low availability of commercial sorbents and the ability to design extraction phases depending on the target analytes. Although the MIL reuse is limited compared to other sorbent-based phases, the MIL could be recovered by soaking in an appropriate solvent. Alternatively, the MIL could be recovered and purified by electrodialysis [72]. Despite the ability to reuse the extraction phase/MIL, it is important to assess the pros and cons of this technique since organic solvents may be required to allow the MIL reusability.

Aromatic amines are emerging environmental pollutants, which are included in the list of priority pollutants by the US Environmental Protection Agency. Their environmental persistence is due to their use as intermediates in the manufacturing of several compounds (pesticides, rubbers, adhesives, pharmaceuticals and engine lubricants). Most aromatic amines are extensively toxic and carcinogenic [39], being mandatory their proper monitoring. With this goal in mind, Zhou et al. [39] reported the application of USA-DLLME using ILs for the determination of aromatic amines from real water samples, namely 2,4-dichloroaniline, 1-naphthylamine and 6-chloroaniline (Fig. 8.13) by HPLC-UV. The IL [C_6mim][PF_6] was used, being dispersed in the aqueous sample solution as fine droplets by ultrasonication, while promoting the easy migration of the analytes into the IL-rich phase. In order to optimize the extraction of these target pollutants into the IL droplets, several variables were investigated, such as the volume of the IL, sample pH, ultrasonication time, extraction time and centrifugation time. The proposed method allows recoveries in the range of 92.2–119.3% and a LOD in the range of 0.17–0.49 $\mu g\ L^{-1}$ [39].

The monitorization of organophosphate esters is particularly relevant since these compounds are widely used as flame retardants, plasticizers, hydraulic fluid, antifoaming agents, lubricants, floor covering and lacquer/paint/glue [40]. Based on this scenario, Shi et al. [40] applied the IL [C_6mim][FAP] as a coating fluid in SPME

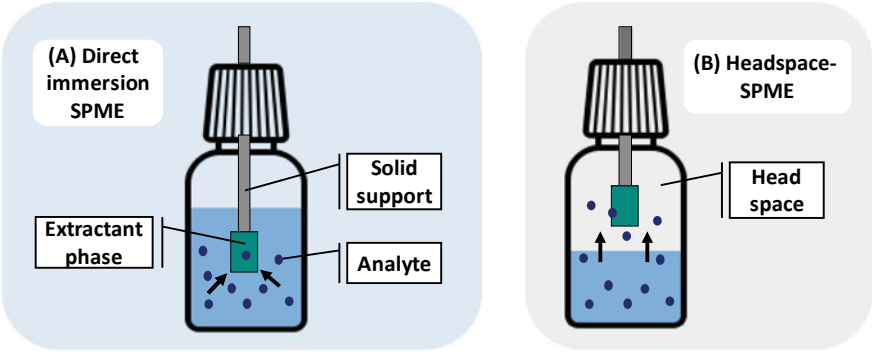


Fig. 8.15 Schematic representation of the SPME technique (A) direct immersion and (B) head space

(Fig. 8.15) aiming at extracting 11 organophosphate esters, which are described in [40], from real environmental water samples. In this work, the fiber was assembled by coating a stainless steel wire with [C_6mim][FAP] using a dip-coating approach. The analysis was carried out by gas chromatography coupled to mass spectrometry (GC–MS). The established SPME (Fig. 8.15) exhibits an excellent selectivity and sensitivity toward the extraction and analysis of organophosphate esters from real aqueous samples, such as tap water, and influent and effluent of sewage treatment plants. The proposed SPME method allows to obtain recoveries between 82.1 and 123%, enrichment factors varying between 168 and 2603, and LODs ranging from 0.50 to 24.0 ng L^{-1}. The reported [C_6mim][FAP]-based SPME coating demonstrated long-term stability, showing no loss of the IL-coatings or reduction of extraction efficiency after at least 65 cycles of use [40].

UV filters are present in a wide range of personal care products and cosmetics. As a consequence, a significant amount of UV filters enters directly into surface water. The nature of these compounds leads to significant bioaccumulation and biomagnification along the food chain [78]. As such, their monitoring is extremely important. Zhang et al. [73] and Ge et al. [74] focused their studies in the detection of UV filter components (Fig. 8.13) in real environmental waters. The two groups of researchers presented two different approaches for the same purpose; however, both used the same IL ([C_6mim][FAP]). This IL was chosen due to its high chemical affinity to the target analytes, thereby allowing the selective isolation of UV filters from the aqueous matrix.

Zhang et al. [73] suggested the application of USA-DLLME to extract and preconcentrate four benzophenone-type UV filters (benzophenone, 2-hydroxy-4-methoxybenzophenone, ethylhexyl salicylate and homosalate—Fig. 8.13). The reported method is based on a ternary solvent system containing small droplets of IL in the aqueous sample solution formed by dissolving an appropriate amount of the IL ([C_6mim][FAP]) in methanol (water-miscible dispersive solvent). Then, an ultrasound-assisted step is performed to enhance the formation of a cloudy solution,

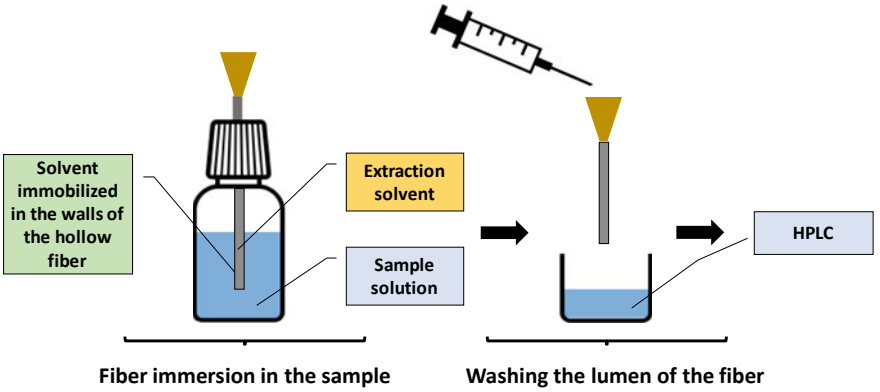


Fig. 8.16 Schematic representation of the HF-DLLME technique

which markedly increases the extraction efficiency, while reducing the equilibrium time. Several parameters that may affect the extraction efficiency were evaluated, namely type and volume of extraction and dispersive solvents, ionic strength, pH and extraction time. Under optimal conditions and depending on the analytes, enrichment factors in the range from 354 to 464 were obtained, with LODs ranging from 0.2–5.0 $\mu g\ L^{-1}$ and recoveries ranging from 71.0 to 118.0% [73]. On the other hand, Ge et al. [74] proposed the application of hollow-fiber liquid-phase microextraction (HF-LPME) to determine UV filters (benzophenone, 3-(4-methylbenzylidene)-camphor, 2-hydroxy-4-methoxybenzophenone and 2,4-dihydroxybenzophenone—Fig. 8.13). In this technique, a hollow fiber containing the extraction solvent is fixed in the tip of a syringe needle for the extraction of analytes from an aqueous sample. Then, the extraction solvent is withdrawn into the syringe and injected into the analytical system (HPLC-UV) (Fig. 8.16). Overall, HF-LPME utilizes a hollow fiber to stabilize the extraction solvent, and the small pore size of the fiber prevents large molecules from entering into the acceptor phase, resulting in the cleanup of the sample during the extraction step. Ge et al. [74] reported that HF-LPME coupled to HPLC-UV provides recoveries ranging from 82.6 to 105.9% and LODs ranging between 0.3 and 0.5 ng mL^{-1}. Despite the environmental burden, this method can be automated, presenting a great advantage over other DLLME techniques that require intensive hand work.

8.2.4 Heavy Metals

Heavy metals are priority compounds of public health concern. Their domestic, agricultural and technological applications have led to their broad distribution in the environment, increasing the awareness over their hazardous effects on both human health and the environment. Regarding the quantification of metals present both in

water and food products, Abdolmohammad-Zadeh et al. [26] explored the application of DLLME using $[C_6py][PF_6]$ as an extractant solvent for the preconcentration of zinc from water and milk samples, quantified by flame atomic absorption spectrometry (FAAS). Zinc was complexed with 8-hydroxyquinoline and extracted into the selected IL, with a LOD of 0.22 $\mu g\ L^{-1}$ and an enrichment factor of 71. The authors stressed that the sensitivity of the method could be further increased by using graphite furnace atomic absorption spectroscopy (GFAAS) as the detection method [26]. Although GFAAS leads to a more time-consuming process, the sample volume is lower, which could be advantageous from a sustainable point of view.

Overall, ILs have been used in several pretreatment methods to improve the detection and quantification of several classes of trace-level pollutants. However, the proposed methods should be tested with several types of environmental matrices and in the analysis of a broader range of compounds, with the goal of finding an IL-based pretreatment strategy that could be broadly applied.

8.3 Application of DESs in the Pretreatment Step of Trace-Level Pollutants from Real Matrices

Green technology is steadily searching for novel solvents able to replace organic solvents which display inherent toxicity. The green character of ILs is often questioned, mainly due to the poor biodegradability and biocompatibility of the most studied ILs. It should be however remarked that "greener" ILs can be indeed used if a proper selection of the cation/anion chemical structures is carried out. DESs have been described as a more sustainable alternative to ILs, mainly because they are prepared from natural-derived compounds and because there is no need of a synthesis/reaction step. Based on their potential, in this sub-chapter the most recent trends regarding the use of DES in environmental monitoring procedures will be discussed. This sub-chapter is particularly focused on the application of several DESs, mostly cholinium-based ones, for the quantification of trace-level pollutants (PAHs, aromatic amines, active pharmaceuticals, pesticides and heavy metals) using several analytical techniques (solvent extraction, DLLME, AALLME, LPME and SPME). Table 8.3 compiles the information reviewed in this sub-chapter, namely the target pollutant, as well as the yield, type of matrix, DES-based process used, preconcentration/enrichment factor, analytical method applied and limit of detection (LOD). Table 8.4 lists the DESs that are considered in this sub-chapter, comprising their names and corresponding chemical structures of their components and acronyms. It should be however remarked that the use of DESs for the pretreatment of environmental samples is still in its infancy, and as such, a significant lower number of works is discussed in this sub-chapter.

Since works dealing with solid samples requiring a digestion step have been found (e.g., vegetables, fish), the following discussion is divided according to the type of samples (liquid versus solid samples), as schematized in Fig. 8.17.

Table 8.3 Summary of the information related to the use of DESs in pretreatment steps of real matrices to monitor environmental pollutants, describing the target analyte, pretreatment process, pretreatment solvent, yield, type of matrix, enrichment factor, analytical equipment and limit of detection

Target analytes	Pretreatment process	Pretreatment solvent	Yield (%)	Type of matrix	Enrichment factor	Analytical equipment	LOD ($\mu g L^{-1}$)	Reference
Active pharmaceutical ingredients (APIs)								
Ketoprofen, flurbiprofen, diclofenac	Solid-phase microextraction	Cholinium chloride: itaconic acid (3:2)	84.5–111.2	Lake water	100	HPLC-UV	0.05–0.5	[35]
PAHs								
Phenanthrene, anthracene, fluoran-thene, pyrene, among others	USA-DLLME[a]	Thymol: camphor (1:1)	73.5–126.2	Effluent from bitumen production	NR[b]	GC-MS	0.0039–0.0098	[22]
Naphthalene, biphenyl, acenaphthylene, fluorene, fluoranthene, anthracene, among others	Organic (diges-tion/dissolution)	Cholinium chloride: oxalic acid (1:2)	71.6–109.6	Fish, macroalgae	NR	HPLC-FL	0.0005–0.00308 ($\mu g/g$)	[23]
Aromatic amines								
Aniline, *p*-toluidine, *p*-chloroaniline, *p*-anisidine, among others	AALLME[c]	Cholinium chloride: *n*–butyric acid	79–94	Tap, surface and river water; wastewater	790–940	GC-MS	0.0018–0.023	[79]

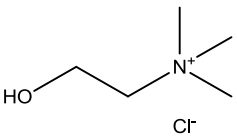
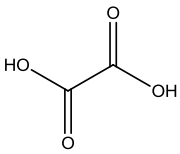
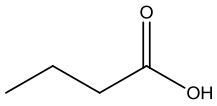
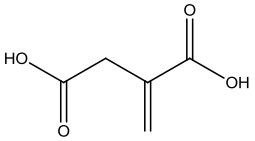
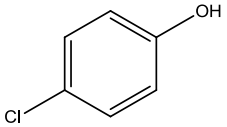
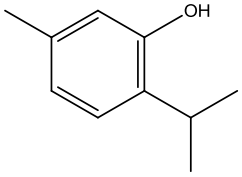
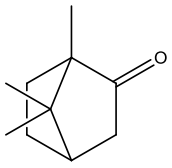
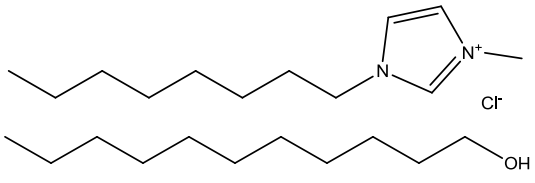
(continued)

Table 8.3 (continued)

Target analytes	Pretreatment process	Pretreatment solvent	Yield (%)	Type of matrix	Enrichment factor	Analytical equipment	LOD ($\mu g L^{-1}$)	Reference
Pesticides								
Diazinon, metalaxyl, bromopropylate, oxadiazon, fenazaquin	Liquid-phase microextraction	Cholinium chloride: *p*–chlorophenol (1:2)	56–93	Juice; vegetables	NR	GC-FID	0.13–0.31	[17]
Heavy metals								
Cu, Zn, Fe	Digestion/dissolution	Cholinium chloride: oxalic acid (1:2)	>95	Fish	NR	FAAS[d]	6–53	[27]
Hg, Pb, Cd	DLLME[e]	1-octyl-3-methylimidazolium chloride: 1-undecanol (1:2)	91–110	Soil and vegetables	114–172	GFAAS[f]	0.01–0.03 (μg/kg)	[29]

[a]Ultrasound-assisted dispersive liquid–liquid microextraction
[b]Not reported
[c]Air-assisted dispersive liquid–liquid microextraction
[d]Flame atomic absorption spectrometry
[e]Dispersive liquid–liquid microextraction
[f]Graphite furnace atomic absorption spectrometry

Table 8.4 DESs investigated in pretreatment strategies of environmental-related samples, comprising their names, acronyms and chemical structures

DES	Chemical structure	
Cholinium chloride: oxalic acid (1:2)		
Cholinium chloride: *n*-butyric acid		
Cholinium chloride: itaconic acid (3:2)		
Cholinium chloride: *p*-chlorophenol (1:2)		
Thymol: camphor (1:1)		
1-octyl-3-methylimidazolium chloride: 1-undecanol (1:2)		

Regarding the monitoring of environmental pollutants in aqueous sample solutions, Wang et al. [35] proposed an innovative in-tube SPME of three NSAIDs—ketoprofen, fluriprofen, diclofenac—(Fig. 8.8) from lake water samples. The DESs composed of cholinium chloride and itaconic acid (3:2) were used as a functional monomer to synthesize a polymeric monolith inside polydopamine-functionalized poly(ether ether ketone) (PEEK) tube. The modification of the inner wall surface of the PEEK tube using dopamine and 3-(triethoxysilyl)propyl methacrylate (γ-MAPS) was firstly carried out, followed by the polymerization

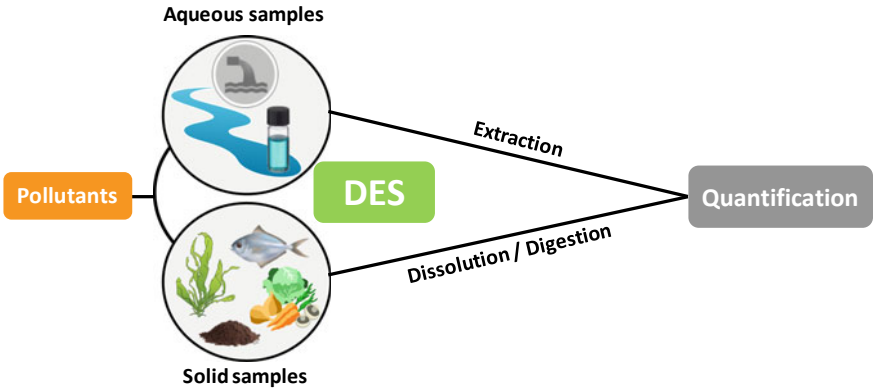
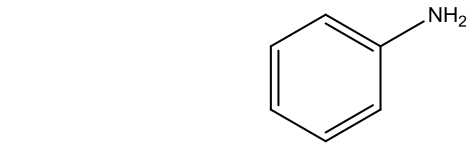


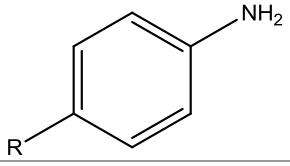
Fig. 8.17 Outline of the studies discussed in the present sub-chapter focused on the use of DESs in the extraction and/or digestion/dissolution processes

reaction including the DES previously prepared. Under the optimized conditions, an online SPME-HPLC method was created by connecting the PEEK tube to the HPLC-UV system. By this approach, it was possible to obtain enrichment factors of ca. 100 and recoveries above 87%. The major advantage of this procedure is that by changing the composition of the DES, different polymer sorbent properties can be explored and applied in the extraction of other compounds. The authors concluded that the developed method gives lower LOD for NSAIDs than other methods with similar UV detector or diode array detector (DAD), while using lower sample volumes and presenting shorter extraction time [35].

The monitoring of PAHs and aromatic amines using DLLME techniques assisted by ultrasounds (USA-DLLME) or air (AALLME) by applying DESs in the pre-treatment step was also proposed [22, 79]. Makoś et al. [22] analyzed 16 PAHs, whose description is shown in [22], in effluents from the production of bitumen using USA-DLLME coupled to GC-MS. The thymol: camphor (1:1) DES was used, leading to higher recoveries under optimized conditions and lower LODs (0.0039–0.0098 $\mu g\ L^{-1}$) [22]. In addition, Torbati et al. [79] reported the simultaneous derivatization and AALLME method based on the solidification of the DES composed of cholinium chloride and *n*-butyric acid coupled with GC-MS to determine aromatic amines (Fig. 8.18) in tap, surface and river water and wastewater. The DES was mixed with ethyl chloroformate, applied as a derivatization agent, and injected into an alkaline aqueous solution containing the target analytes at high temperature. The resulting mixture was drawn into a syringe, allowing the formation of a cloudy solution consisting of fine droplets of the extraction solvent, and which possess the derivatized aromatic amines. Then, the solution was subjected to low temperatures and the solidified extraction solvent (DES) was collected and analyzed [79]. The obtained results revealed LODs varying from 1.8 to 23 $ng\ L^{-1}$, recoveries above 79% and enrichment factors in the interval between 790 and 940. It is important to highlight that the non-toxic nature of the DES individual components, as well



aniline



R=CH_3	p-toluidine
R=Cl	p-chloroaniline
R=OCH_3	p-anisidine
R=$C(CH3)_3$	4-*tert*-butyl aniline

Fig. 8.18 Chemical structures of the studied aromatic amines

as the simple procedures required to prepare DESs in both works, brings major benefits compared to the hazardous solvents commonly used. Furthermore, this method requires a small amount of the extraction solvent, leading to the reduction of the risk to human health and environment [22, 79].

In addition to liquid samples, some researchers applied DESs to digest/solubilize solid samples aiming at monitoring trace-level contaminants, such as pesticides, PAHs (Figs. 8.13 and 8.19) and heavy metals [17, 23, 27, 29].

Helalat-Nezhad et al. [23] and Farajzadeh et al. [17] proposed the use of DESs to improve the detection of pesticides and PAHs in fish and vegetable samples. Helalat-Nezhad et al. [23] developed an innovative sample preparation method based on the complete dissolution of marine biological samples (fish and macroalgae) in the cholinium chloride: oxalic acid (1:2) DES and using minimized volumes of cyclohexane, allowing an efficient extraction of PAHs (anthracene, phenanthrene, fluoranthene, pyrene, benz[a]anthracene, chrysene, benzo[e] and benzo[a]pyrene, with the respective chemical structures depicted in Figs. 8.13 and 8.19). The extracted PAHs were quantified by HPLC-FL with LODs ranging from 0.50 to 3.08 ng g^{-1} [23]. The simplicity of the procedure, high extraction efficiency, short analysis time and use of safe and inexpensive components are very attractive characteristics; however, the use of volatile organic solvents still needs to be avoided.

Farajzadeh et al. [17] presented a LPME approach for the extraction and preconcentration of some pesticides (Fig. 8.19) (diazinon, metalaxyl, bromopropylate, oxadiazon and fenazaquin), from different samples, including apple, grape and sour cherry juices and fresh beet, cucumber, potato and tomato. The solid samples were transformed into juice to be further analyzed, with no application of a digestion step mediated by DESs. DESs were applied in the extraction step only. The DES that displayed better results as extraction solvent is cholinium chloride: *p*–chlorophenol, in a molar ratio of 1:2. The dispersion of the extraction solvent into the aqueous phase was performed by changing the temperature, thereby leading to improvements in the extraction efficiency. Under the optimum extraction conditions, enrichment factors and extraction recoveries were obtained in the ranges of 280–465 and

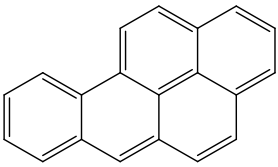
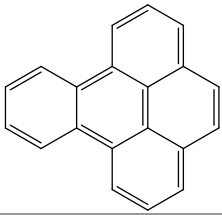
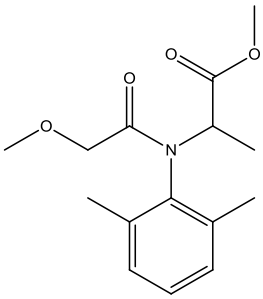
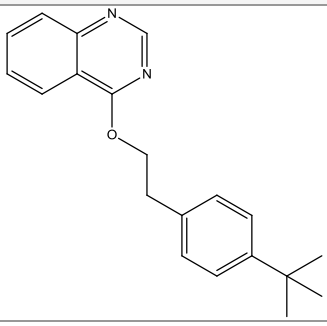
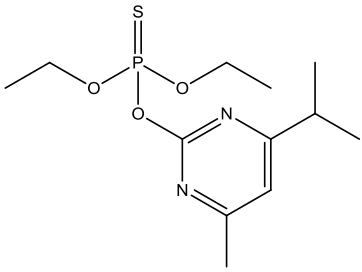
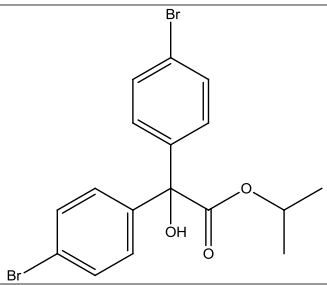
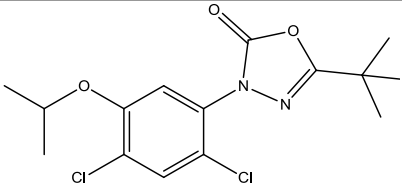
PAHs	
	
benzo[a]pyrene	benzo[e]pyrene
Pesticides	
	
metalaxyl	fenazaquin
	
diazinon	bromopropylate
	
oxadiazon	

Fig. 8.19 Chemical structures of some of the studied PAHs and pesticides

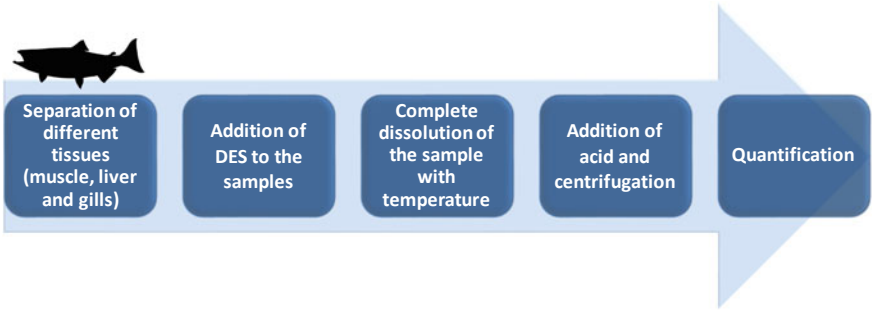


Fig. 8.20 Schematic representation of the digestion of solid samples using DES

56–93%, respectively. Additionally, the LODs obtained ranged between 0.13 and 0.31 ng mL^{-1} [17].

Habibollahi et al. [29] and Habibi et al. [27] quantified heavy metals in fish, soil and vegetable samples. The first group of authors [29] explored the application of DLLME and the subsequent solidification of the DES (DLLME–SDES) prior to the metal (Hg, Pb, Cd) analysis by graphite furnace atomic absorption spectrometry (GFAAS). In this technique, due to differences in the density between the aqueous phase and DES, the fine droplets of DES float at the top of the test tube, which are then transferred into an ice bath leading to the solidification of the DES, which is further melted before the GFAAS analysis. Since solid samples were investigated, these were subjected to a digestion step prior to the extraction step. The authors selected the 1-octyl-3-methylimidazolium chloride (IL) and 1-undecanol to form a DES with a molar ratio of 1:2 as the extraction solvent. Under the optimum conditions, the enrichment factors of the target compounds are in the range of 114–172 and the LODs are in the range of 0.01–0.03 μg kg^{-1} [29]. The DLLME–SDES method does not require an organic solvent as disperser in comparison with other DLLME techniques, which is a major advantage to move to the requirements of green chemistry.

Habibi et al. [27] reported a novel and efficient digestion method of different tissues of fish samples (muscle, liver and gills) based on the cholinium chloride: oxalic acid DES with a molar ratio of 1:2, with the goal of quantifying heavy metals (Cu, Zn and Fe) by flame atomic absorption spectrometry (FAAS) (Fig. 8.20). The sample was dissolved in the DES and HNO_3 was added. After a centrifugation step, the supernatant was filtered and analyzed by FAAS. Under optimized conditions, the extraction recovery of all elements was above 95.3%. The proposed method was successfully applied in the determination of heavy metals in different tissues of fish samples. The authors pointed out the simplicity of the reported experimental method, and the high extraction efficiency, lower analysis time, and use of safe and inexpensive components, further suggesting the incorporation of this procedure in monitoring routines [27].

Overall, the interest in DESs has grown significantly in the past few years since their first description [80]. However, these solvents display two major application

areas: metal processing and as synthesis/dissolution media [59]. In this chapter, it is described the use of DES as efficient solvents for the pretreatment of environmental samples while envisaging environmental monitoring of trace-level pollutants, opening a new path of applications for DESs. Still, a narrow range of DESs has been used, emphasizing the need of expanding the types of hydrogen bond donors and acceptors that can be combined and hence increase the performance of these solvents in a wide variety of applications.

8.4 Conclusions and Future Perspectives

Albeit great advances have been achieved in the monitoring of environmental pollutants, the accurate identification and quantification of trace-level pollutants in complex matrices still require additional improvements. Based on this need, ILs and DESs have been studied as alternative solvents in pretreatment techniques of environmental matrices in the field of environmental monitoring. These have been applied in the pretreatment of wastewater, industrial and municipal effluents, human fluids, wine, milk, honey, fish, macroalgae, vegetables and soil. A broad range of compounds, such as PAHs, APIs, pesticides, heavy metals and UV filters, have been the target pollutants analyzed after pretreatment techniques involving ILs and DESs. As reviewed in this work, these alternative solvents lead to improvements in environmental monitoring, allowing more accurate quantifications by promoting the target pollutants' enrichment factor and recovery, and the LOD. The most relevant property of ILs and DES behind such successful results is their "designer solvent" ability, valuable to tailor the affinities and polarities of these extraction solvents according to the target compound. It should be remarked that ILs and DESs can be also used in the digestion step of solid samples.

Most ILs have been chosen based on their affinity for the target compounds, which may explain the focus on imidazolium-based cations combined with fluorinated anions. However, most of these ILs possess non-negligible toxicity and low biodegradability, reinforcing the need of looking for more sustainable ILs mainly derived from natural sources if the goal is to fulfill the green analytical chemistry guidelines. Although with a different purpose, there are recent studies reporting the synthesis of new and non-toxic bio-based ILs that can also be used in extraction processes and in pretreatment techniques. Furthermore, the ILs recycling is an additional factor that should be considered in future studies in this field.

Although still in its infancy, DESs have been investigated with the aim of environmental monitoring. In most of the reported works, cholinium chloride is the HBA species of choice, combined with HBDs such as oxalic acid, *n*-butyric acid, itaconic acid and *p*-chlorophenol. The recent research on DES reveals a growing interest of the scientific community in the creation of sustainable processes using more environmentally friendly solvents. Still, the use of DESs for the monitoring of pollutant compounds remains largely unexplored, leaving a vast opportunity to expand the knowledge in this field and to explore the dual role of DESs, both as extraction

solvents and digestion agents, ultimately resulting in the creation of integrated and more efficient processes.

The development of sustainable processes is an undeniable current challenge. The research on ILs and DESs as alternative solvents of the commonly applied hazardous organic solvents certainly contributes toward this goal. In this regard, these solvents should be properly designed to display high performance and ideally should be prepared from natural sources or raw materials and should be of low cost, thus contributing to a decrease on both ecological and economic impacts.

Acknowledgements This work was developed within the scope of the project CICECO-Aveiro Institute of Materials, FCT Ref. UID/CTM/50011/2019, financed by national funds through the FCT/MCTES. This work was financially supported by the project POCI-01-0145-FEDER-031106 (IonCytDevice) and DeepBiorefinery (PTDC/AGR-TEC/1191/2014) funded by FEDER, through COMPETE2020—Programa Operacional Competitividade e Internacionalização (POCI), and by national funds (OE), through FCT/MCTES. Inês S. Cardoso acknowledges FCT for her Ph.D. grant (SFRH/BD/139801/2018). M.G. Freire acknowledges the European Research Council under the European Union's Seventh Framework Program (FP7/2007-2013)/ERC grant agreement n° 337753.

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Chapter 9
Green Chromatography and Related Techniques

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Abstract Gas and liquid chromatographic methods are widely used in the analysis of organic compounds in different types of matrices. To protect the environment, it is very important that these methods have a negligible environmental impact. Chromatographic techniques can be greener at all the steps of the analysis, from sample preparation to the final determination of sample components. In this chapter, the different approaches that have been used to achieve the goals of green chromatography are summarized. Regarding sample preparation, it is not always practical to eliminate this step to make the analysis greener; however, solvent-free extraction techniques are considered a good alternative. During all the steps of the analysis, the chief goal is to minimize the organic solvent impact on the environment. There are many approaches used to make chromatographic separation greener, for instance, reducing the solvent consumption, using narrow, shorter analytical columns to shorten the analysis time, and substituting toxic and hazardous solvents with more ecofriendly alternatives. Multidimensional separation techniques such as GC × GC and LC × LC have also the potential to make the analysis of very complex samples greener by reducing the analysis time and waste production.

Keywords Green analytical chemistry · Green chromatography · Green sample preparation techniques · Ecofriendly solvents · Environmental impact

9.1 Introduction

In recent years, awareness about the impacts of harmful chemicals on the environment and health has grown; therefore, numerous efforts have been made to lessen these. "Protection of the environment," "sustainable development," or "ecology"

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J. Płotka-Wasylka and J. Namieśnik (eds.), *Green Analytical Chemistry*,
Green Chemistry and Sustainable Technology,
https://doi.org/10.1007/978-981-13-9105-7_9

have become very popular terms. According to Brundtland Report published in "Our Common Future" book, sustainable development is defined as the development that meets the requirements of the present without compromising the future generation needs [1]. The major goal of sustainable development is improving the quality of human life even if this demands certain limitations to human activities. It pertains to the society, the market, and the environment. Recently, the terms including "green chemistry," "clean chemistry," "ecological chemistry," "ecochemistry," etc., have been used to describe approaches aiming to protect the environment in the area of chemistry.

The concept of green chemistry was first introduced by Anastas and Warner in 1998, who introduced the 12 principles of green chemistry [2]. These principles have become guidelines for many chemists to design new chemical products, reagents, and methodologies that are environmentally benign. Green analytical chemistry (GAC) is a part of the sustainable development concept and is closely related to the trend toward implementation of these principles in analytical laboratories. The main objective of GAC is to reduce or eliminate the harmful impacts of chemical substances on the environment and substituting them with more ecofriendly alternatives without sacrificing method performance. GAC is concerned with different aspects of chemical analysis, including chromatographic techniques which are used to separate and determine the components of complex mixtures in various matrices. Chromatographic procedures are dominant in many research, food, industrial, and environmental fields. The impact of hazardous solvents on the environment and human health cannot be neglected in the process of chromatographic analysis. A conventional liquid chromatographic (LC) method requires a relatively large amount of organic solvent and can generate 1–1.5 L of waste daily; this waste has to be disposed of [3].

Most organic solvents used in LC processes are volatile; therefore, they can easily disperse and harm the environment. A significant number of them may cause acute and chronic toxicity. Consequently, it is the responsibility of analytical chemists to minimize the pollution caused by their activities and prevent, or at least minimize, the negative environmental impacts. GAC aspects should be considered when new analytical methods are being developed. Recently, the concept of green chromatography has gained ever-growing attention among researchers with the aim of reducing or eliminating the use of hazardous organic solvents. This creates great opportunities to reduce the burden on the environment and potentially reduce costs for analytical laboratories, as they no longer have to purchase large quantities of theses reagents.

The objective of this chapter is to present the ways in which liquid and gas chromatographic techniques can become greener according to GAC principles. Sample preparation approaches aimed at minimizing the environmental impact prior to chromatographic analysis are also discussed. The role of miniaturization in sample preparation and chromatographic separations is stressed.

9.2 Green Sample Preparation and Extraction Procedures

9.2.1 Direct Chromatographic Techniques Without Sample Preparation

In general, solid samples require sample treatment prior to actual measurements by analytical procedures, such as drying, grinding, and finally sample dissolution. In addition, to avoid interference from the samples or to increase the concentration of the target components in the analyzed sample in order to fit the sensitivity of the instruments, many other procedures are sometimes required before measurements, such as evaporation, distillation, extraction, recrystallization, and precipitation. As many analytical devices require liquid samples, large volumes of organic solvents are widely used to dissolve solid samples before analysis. Unfortunately, the majority of these solvents have deleterious side effects on the environment as they are disposed into the environment as gas or liquid wastes. Furthermore, most of these solvents create a risk to operators' safety because of their flammability, volatility, and toxicity.

According to GAC principles, using direct chromatographic procedures is considered highly beneficial to avoid the hazardous effect of these chemicals on the analysts' health and the environment. In 2009, Tobiszewski and Namieśnik stated that direct injection of solid and liquid samples can be efficiently performed via GC or LC analysis [4]. It is generally not recommended to directly inject aqueous samples into GC columns due to problems caused by water, such as column bleeding (particularly when using polar stationary phases) and backflush problems caused by water vapor expansion in the injector. However, the installation of a deactivated precolumn in front of the analytical column can prevent the entry of any particles or salts present in water into the system, protecting the column and allowing direct injection of aqueous samples into a GC.

Elimination of the sample preparation step is much more applicable in gas chromatographic techniques compared to liquid chromatographic ones. The early direct gas chromatographic methods proposed by Grob et al. in 1978 focused on the development of on-column injection [5]. In 1984, Grob et al. proposed a combination of on-column injection with electron capture detection to determine halogenated compounds in water samples by direct aqueous injection [6]. Gas chromatographic determination of some volatile organic compounds in water samples was developed using flame ionization detector with direct aqueous injection [7]. Another method was developed to determine polar and non-polar volatile organic compounds in water samples by direct aqueous injection-gas chromatography with mass spectrometric detection [8]. Recently, larger volume direct aqueous injection-gas chromatography was used to determine high-boiling volatile organic compounds in surface water with flame ionization detection, electron capture detection, and flame photometric detection [9].

Although the methodologies that do not require analyte isolation or enrichment are considered very good procedures to avoid environmental problems, these methodologies are only applicable to samples with relatively clean matrices without any

suspended particles, and this is considered the major limitation of such techniques [10]. If the analyzed sample is not clean enough, chromatographic column deterioration might occur rapidly due to deposition of particles or non-volatiles that do not elute from the column. Some clean matrices that can be injected without any pretreatment into chromatographic columns include spirits and petroleum fractions [3]. In liquid chromatographic applications, direct analysis of liquid samples is also limited to clean samples. Pesticide residue was determined directly in water samples by liquid chromatography–mass spectrometry (LC-MS) [11]. Many methodologies can be considered nearly direct as they require only simple sample pretreatment, such as filtration [12], dilution of the sample [13], or centrifugation [14].

Direct chromatographic methodologies meet the objectives of GAC in several ways. The hazardous impact of chemicals and consumables that would have been used during sample preparation (including organic solvents, cartridges, sorbents, etc.) is avoided. The total analysis time (starting from sample collection to getting the final results) is markedly shortened. The chromatographic separation can be performed in an online mode due to the absence of sample preparation step, which can further decrease the analysis time. As a result, direct chromatographic methodologies positively push analytical chemists toward protecting the environment and minimizing the environmental impact of chemical analysis through real-time monitoring [3].

9.2.2 Green Sample Preparation

Sample preparation is considered a critical step of any analytical procedure based on chromatographic separation, particularly for complex samples. There are different ways to make sample preparation step "greener." Herein, sample preparation techniques are only briefly discussed, as more detailed information is provided in another chapter in this book.

9.2.2.1 Gas Extraction Techniques

Gas extraction techniques are solvent-free methods of sample enrichment. In these techniques, an inert gas is used for extraction, so they are considered green. They are used for the isolation and/or preconcentration of volatile pollutants from various matrices. Examples of gas extraction techniques include static headspace (SHS), dynamic headspace (DHS), in-tube extraction (ITEX), purge and trap (PT), and headspace sorptive extraction (HSSE) [11]. The SHS technique is a uniquely green approach to the analysis of complex samples. It is applicable to different types of liquid samples including highly viscous ones, samples forming foam during purging, and samples containing sludge or solid materials. The major limitation of a conventional static HS method is its lower sensitivity compared to dynamic techniques such as PT, and those involving online preconcentration. To enhance the HS sensitivity, the whole headspace injection (WHSI) method has been developed. In this method,

the whole volume of the equilibrated headspace is injected via a microtrap into a GC column. The WHSI method has been applied to the analysis of organic volatiles in spirit drinks [15] and water samples [16].

In dynamic headspace analysis (DHS), a solid or liquid sample is placed in a thermostated closed container and the headspace vapors are eliminated continuously by means of an inert gas flow. The analytes carried by the purge gas are trapped using, e.g., a solid sorbent, then thermally desorbed into a GC injection port. This technique is particularly useful when analytes are present at very low concentrations or have undesirable partition coefficients in static headspace sampling. It can provide more sensitivity than static HS by concentrating the volatiles until their amount is sufficient for thermal desorption and analysis.

There are many advantages of the aforementioned GC-HS as a green analytical technique: (1) applicability to both solid and liquid samples, (2) reduction in the number of analytical steps, (3) use of relatively low temperatures, (4) exclusion of hazardous solvents and reagents, and (5) easy and fast analysis. On the other hand, the following are its limitations: (i) applicability to volatile or semivolatile analytes only and (ii) comparatively low sensitivity [17]. PT is broadly accepted as the method of choice for the routine analysis of volatile organic compounds (VOCs) in water samples [18] and food [19].

9.2.2.2 Solid-Phase Extraction (SPE)

SPE is one of the most popular and routine sample preparation techniques these days. It uses a small amount of organic solvent for sample cleanup and preconcentration. In SPE, the analytes from the original sample are adsorbed on a solid phase. The aqueous sample solution is introduced into the SPE column, and the analytes are trapped on the sorbent. Next, a small volume of a suitable organic solvent is used to elute the analytes, resulting in extraction and enrichment of the analytes [20]. The main advantage of SPE technique over liquid partitioning procedures is its low solvent consumption; hence, it is considered a green sample preparation technique. SPE can be automated using simple and inexpensive equipment, resulting in improvements in accuracy, precision, and laboratory throughput. On the other hand, some drawbacks of SPE must be taken into consideration to avoid poor extraction of target analytes. For instance, the packing material has to be uniform to avoid loss of efficiency; hence, the use of commercial cartridges is preferred. In addition, many conventional sorbents are limited in terms of selectivity and insufficient retention of very polar compounds. The competition of sample matrix with the analytes for retention can further affect the ability of the sorbent to extract the required analytes. Quantitative retention and elution processes must be considered to guarantee efficient extraction of the analytes.

QuEChERS

The acronym “QuEChERS” stands for “quick, easy, cheap, effective, rugged, and safe” extraction methodology. This technique uses a small amount of organic solvent

compared to many other extraction techniques. The extraction is performed in two main steps: solvent extraction via vigorous shaking, and quick dispersive solid-phase extraction for purification of the extract. QuEChERS is considered the method of choice for food analysis as it combines several sample preparation steps into one, and extends the range of analytes recovered compared to older, more tedious extraction techniques [21]. QuEChERS was employed as a green sample preparation procedure in many applications, such as extraction of pesticide residues in different target crops [22] and improvement of the extraction yields of incurred pesticide residues from crops [23]. In addition, seven pharmaceuticals were isolated from bivalves by QuEChERS, followed by LC-MS/MS [24]. A wide range of environmental contaminants were detected in human blood samples, combining QuEChERS with LC-MS and GC-MS methods [25]. A sample of opiates, amphetamines, and cocaine metabolites in whole blood was prepared by QuEChERS prior to LC-MS/MS analysis [26]. Recently, QuEChERS procedures were employed for full isolation of tetrahydrocannabinol and its metabolites from whole blood samples and then detection by GC-MS/MS [27].

Solid-phase microextraction (SPME)

SPME is an efficient and straightforward sample preparation technique. It was developed by Pawliszyn and Belardi in 1989 [28]. SPME is compatible with GAC principles as it eliminates the need for solvents and integrates sampling, analyte extraction, enrichment, and sample introduction into a single step. The principle of SPME is based on partitioning of analytes between an extraction phase and the sample matrix. A fiber coated with a polymeric stationary phase is placed directly in the sample (DI-SPME) or in its headspace (HS-SPME) for a certain time. Analytes partition into the extraction phase until equilibrium between the fiber coating and the sample is reached, unless the user terminates the sampling earlier. After the extraction is completed, desorption of the concentrated analytes takes place by transferring the SPME fiber into an analytical instrument where the analysis is performed. The main advantages of SPME are its simplicity, low cost, short sample preparation time, elimination of the solvent disposal costs, and good limits of detection, reliability, selectivity, and sensitivity. However, it also has some drawbacks which should be taken into consideration to avoid poor results. Good understanding of the process is fundamental for proper method development. In addition, the fiber is fragile and may be easily damaged during handling. The coating itself deteriorates with repeated usage; hence, implementation of appropriate quality assurance/quality control (QA/QC) measures is critical.

SPME has been employed routinely in a combination with gas chromatography (GC) and gas chromatography–mass spectrometry (GC-MS). It is successfully applied as a green technique for the extraction of volatile and semivolatile organic compounds from complex sample matrices [29]. SPME has also been used in combination with high-performance liquid chromatography (HPLC) and liquid chromatography–mass spectrometry (LC-MS) to analyze thermolabile or poorly volatile compounds which are not amenable to GC or GC-MS [29].

Complex food mixtures include a wide range of organic compounds with different volatilities and polarities, usually present at trace levels in complex matrices. Many other conventional sampling methods require large sample volumes, long sample preparation times, and the use of toxic organic solvents. SPME eliminates these drawbacks and can be successfully used for the determination of impurities or other additives, and determination of natural active constituents of food commodities. Numerous reviews addressed the applications of SPME as a sample preparation technique (e.g., [30–32]).

Microextraction by Packed Sorbent (MEPS)

MEPS performs the same function as SPE, but with some significant differences. The principle of MEPS is based on sample collection by a sorbent (a bed or a coating material of the inner surface of a chromatographic column). Analytes are extracted from the sorbent with a suitable solvent, and the sample is introduced into a chromatographic system. The sorbent bed can be easily regenerated by washing with a solvent. The main advantages of the MEPS technique are that it significantly decreases the required solvent volume (10–50 μL), it works with smaller sample volumes than standard SPE (as low as 10 μL), the extraction time is short (about 1 min), and the energy consumption is minimal. Consequently, this technique obeys GAC principles. MEPS can be fully automated and performed online using the same syringe at all stages, including sample processing, extraction, and injection steps. MEPS is widely applied as a sample preparation method for many analytes, including drugs of abuse (opiates, cocaine, and amphetamine) in human hair [33] and plasma [34], different metabolites in urine [35], as well as clozapine, risperidone, and their active metabolites in urine samples [36].

Stir-Bar Sorptive Extraction (SBSE)

The principle of SBSE is based on sorptive extraction, just like SPME. The main difference is the volume of the sorptive phase, which is much higher in SBSE. The analytes are absorbed by a thick film of a polymer (e.g., PDMS) coated on a magnetic stir bar. The extraction is dependent on the partitioning coefficient of the solutes between the polymer coating and the sample matrix. SBSE is a green solventless sample preparation technique when thermal desorption is applied for analyte desorption. It has been widely employed as a sample preparation method for many analytes including organic pollutants in water samples [37].

Solid-Phase Nanoextraction (SPNE)

The principle of SPNE is based on strong affinity of target analytes toward gold nanoparticles. Aqueous samples (~500 μL) are mixed with colloidal gold solution. The analytes quantitatively bind to the surface of gold nanoparticles and then centrifugation is done to recover the nanoparticles. SPNE is rapid, easy to use, and requires very small volumes of organic solvent for the detection and determination of trace levels of compounds in complex matrices. It has been adopted as a green sample preparation methodology in some applications including determination of

polychlorinated biphenyls in environmental waters [38] and polycyclic aromatic hydrocarbons in drinking water samples [39].

9.2.2.3 Liquid Extraction Techniques

Single-Drop Microextraction (SDME)

The principle of SDME, also called liquid–liquid microextraction (LLME), is based on analyte extraction into a microdrop of solvent suspended from the tip of a conventional microsyringe or PTFE rod. The analytes diffuse into the droplet, and the microdrop is retracted into the syringe and then injected into a chromatographic injector. SDME consumes a very small volume of the solvent (1–2 μL); hence, it is considered a green method of sample preparation. SDME is a sample preparation method for many analytes [40], including organic compounds in environmental matrices [41], phenol derivatives in soft drinks and dairy products [42], and BTEX compounds (benzene, toluene, ethylbenzene, and xylenes) in water samples [43].

Liquid-Phase Microextraction (LPME)

Liquid-phase microextraction can be performed in three modes:

- Dynamic LPME, in which a small amount of solvent in a microsyringe is used for the extraction of the analytes, enriching them and then injecting them into a chromatograph;
- Two-phase hollow fiber (HF) LPME, in which the analytes partition into immobilized organic solvent present inside a porous polypropylene capillary tube that is placed in contact with the sample;
- Three-phase HF-LPME, in which the analytes are concentrated in a third phase inside the lumen of the capillary after crossing the organic solvent embedded in the pores of a semipermeable membrane.

LPME consumes a negligible amount of organic solvent, uses a relatively low sample volume, and reduces waste generation. Thus, it is considered a green sample preparation method. LPME has been used as a sample preparation method for numerous analyte/sample combinations, including antidepressants in vitreous humor [44], cocaine and its derivatives in hair samples [45], pesticides in environmental water [46], and food analysis [47].

Supported Liquid Membrane Extraction (SLME)

The principle of this technique is the same as three-phase HF-LPME. SLME is based on the difference in concentration of the analytes between the donor and acceptor phases. In order to adjust the concentration gradient between these two phases, solutes must exist in two forms, e.g., non-ionic in the donor phase (to be easily extracted into the membrane) and ionic in the acceptor phase, where they should be irreversibly trapped. This can be achieved by adjusting the pH in both aqueous phases. After the extraction is completed, the acceptor phase is transferred

to the analytical instrument [48]. SLME lessens the volumes of solvent consumed, so it is considered a green technique. SLME is employed for the extraction of many analytes such as pesticides in water [49], heterocyclic aromatic amines in human urine [48], metals from wastewater and process streams [50], Black B dye from simulated textile wastewater [51], basic drugs from human plasma [52], and phenols in water samples [53].

Microporous Membrane Liquid–Liquid Extraction (MMLLE)

The principle of this technique is the same as two-phase HF-LPME. The MMLLE technique can use the same types of membranes as SLME (e.g., hydrophobic membranes made of PTFE). The MMLLE technique is based on the partitioning of the analytes between the aqueous and the organic phase, which means that the separation is controlled by the concentration gradient across the membrane. In MMLLE, the acceptor phase is a water-immiscible organic solvent, which fills the pores of the hydrophobic membrane. The hydrophobic, mostly uncharged, compounds are easily extracted from the aqueous phase to the organic phase. However, they cannot be backextracted to the aqueous phase as in the SLME technique. The extract is organic and can be analyzed by any analytical method. MMLLE is considered complementary to SLME, as it allows extraction and enrichment of compounds which cannot be extracted by SLME [48]. MMLLE reduces consumption of reagents; hence, it is a green technique. MMLLE has been employed for the extraction of many analytes from complex matrices, including organotin compounds [54], pesticide residues in red wines [55], and sulfonylurea herbicides in water samples [56].

Dispersive Liquid–Liquid Microextraction (DLLME)

In this technique, a three-phase system consisting of the sample, a high-density extraction solvent, and a disperser solvent (which should be miscible with both phases) is used. A mixture of the disperser and extraction solvents is added to the aqueous sample by a syringe, forming a cloudy solution. After the extraction process is completed, the cloudy solution is centrifuged, and the high-density extracting phase is collected in the lower part of a conical glass test tube and is taken for analysis with a microsyringe. The main advantages of DLLME are its high enrichment factor, high recovery, good repeatability, and small sample volumes. It offers large area of contact between the aqueous phase and the solvent, resulting in rapid transfer of analytes from the aqueous phase to the extraction phase. DLLME was employed for the extraction of many analytes including aryloxyphenoxypropionate herbicides in water [57], phthalate esters in commercial beverages [58], and in soybean milk [59], and the analysis of milk and dairy products [60].

One of the improvements on standard DLLME involves the use of ionic liquids (IL) as the extraction solvent instead of toxic chlorinated solvents. This technique is called IL-DLLME. As ionic liquids are considered green solvents, IL-DLLME is considered a green method of sample preparation as it eliminates the use of toxic solvents. DLLME with ionic liquids can also be performed without using a dispersive solvent, e.g., ultrasounds were used to disperse ionic liquid in a water sample [61].

In another procedure, the sample added to ionic liquid was heated until homogenous liquid was obtained. Then, it was cooled, and the ionic liquid containing the analytes was centrifuged. This technique is called temperature-controlled ionic liquid dispersive liquid-phase microextraction. IL-DLLME technique was used for the extraction of analytes such as copper in natural waters [62], polycyclic aromatic hydrocarbons (PAHs) in water samples [63], organophosphorus pesticides in wheat [64], organophosphorus pesticides in environmental samples [65], and chlorophenols in honey samples [66].

9.2.2.4 Membrane Extraction

Membrane extraction uses a non-porous membrane which can be in a liquid or a solid phase (polymer impregnated with a liquid), placed between two other phases, usually liquid, but sometimes gaseous [67].

Supported Liquid Membrane Extraction (SLME)

This technique was classified again under membrane extraction techniques. The principle and application of this technique were discussed previously in the liquid-phase microextraction (LPME) section.

Microporous Membrane Liquid–Liquid Extraction (MMLLE)

This technique was also classified again under membrane extraction techniques. The principle and applications of this technique were discussed previously in the liquid-phase microextraction (LPME) section.

Membrane Extraction with a Sorbent Interface (MESI)

MESI technique is fully compatible with GC due to its gaseous acceptor phase. In MESI, a non-porous polymeric membrane is used for the extraction of analytes from a gas or a liquid phase. The analytes from the sample partition into the membrane. They are then removed from the inner membrane surface by a stream of gas flowing inside the module and transferred to a sorbent, where they undergo enrichment. The concentrated analytes retained in the trap are released by thermal desorption and introduced by a stream of carrier gas into the GC column [67]. MESI is solventless technique and provides a semicontinuous analysis; hence, it obeys the GAC principles. MESI has been applied for the extraction of analytes such as benzene, toluene, ethylbenzene, and xylenes (BTEX) in water [68], volatile organic compounds (VOCs) in human breath [69], as well as aromatic hydrocarbons in air, soil, and water [70].

Membrane-Assisted Solvent Extraction (MASE)

The principle of MASE is based on the transfer of organic compounds in the aqueous sample across a non-porous polymeric membrane to a small volume of organic solvent. The solvent should be immiscible with water, able to dissolve the analytes

well, and it should not pass back through the membrane into the aqueous sample. The extraction takes place at an elevated temperature, leading to accelerated transfer of analytes into the organic solvent. The extracted concentrated analytes are analyzed by GC. MASE reduces consumption of solvents; hence, it is a green technique. MASE has been applied for the extraction of analytes including organic compounds in industrial wastewater, organophosphorus pesticides in water samples [71], and tetramine in food [72].

Microdialysis sampling

Microdialysis sampling is a well-known method for enrichment of low-molecular-weight hydrophilic analytes. In this technique, a probe with a semipermeable membrane is placed in the sample. An electrolyte solution is pumped through the probe using a syringe pump, causing analyte concentration gradient between the perfusate and the surrounding medium. Due to the gradient, analytes diffuse into the probe. The concentrated analytes coming from the probe (dialysate) are then analyzed by an appropriate analytical method. Microdialysis sampling requires smaller samples and consumes lower solvent volumes compared to standard LLE. It has been employed for the extraction of analytes such as cytokines, proteins, and metabolites in wound fluids [73], alachlor and its metabolite in microbial culture medium [74], as well as aniline and 2-chloroaniline in industrial wastewater [75].

Thin-Film Microextraction (TFME)

The principle of TFME is the same as in SPME, except that a thin film of the extracting phase is used instead of a coated fiber [76]. It is a green solventless extraction method that has been applied for the extraction of polycyclic aromatic hydrocarbons (PAHs) in waters [77].

9.2.2.5 Extraction with Alternative Green Solvents

Ionic liquids (ILs)

ILs are non-volatile, thermally stable (up to ~300 °C) liquids which dissolve organic and inorganic compounds; therefore, they are used as alternatives to traditional organic solvents. ILs are considered green solvents which do not emit toxic vapors to the environment. However, they might pose environmental burden when they are disposed of. ILs have been used in many extraction techniques such as supported liquid membrane extraction [78], liquid–liquid microextraction [79], liquid-phase microextraction of polycyclic aromatic hydrocarbons [80], and dispersive liquid–liquid microextraction (DLLME) [81].

Supercritical Fluid Extraction (SFE)

SFE facilitates the extraction of organic compounds from solid samples. SFE can be accomplished in both static and dynamic modes. In the static mode, the sample

and solvent are mixed together and kept for a certain time at a constant pressure and temperature. In the dynamic mode, the fluid flows through the sample continuously. The extracted analytes can be collected by depressurizing the supercritical fluid and sorbing the analytes into a solvent or a solid phase, or transferring them to an online chromatographic system. The most common supercritical fluids include carbon dioxide, nitrous oxide, ethane, propane, n-pentane, ammonia, and sulfur hexafluoride. CO_2 is the most popular due to the lack of corrosive and explosive characteristics. SFE minimizes or completely eliminates the use of organic solvents. SFE has been employed for the extraction of analytes such as petroleum hydrocarbons (PHCs) in a contaminated sand [82].

Subcritical Water Extraction (SWE)

Subcritical water extraction is also called hot water extraction (HWE), or pressurized water extraction (PWE). In SWE, superheated water is used as the extracting solvent. Water below the supercritical state ($T_c = 374$ °C, $P_c = 218$ atm) can achieve very selective extractions of polar compounds at lower temperature. Moderately polar and non-polar organic pollutants can be extracted at higher temperatures. SWE is a green technique as it eliminates the use of organic solvents, and most of the fluid phases are recyclable. SWE has been applied for the extraction of compounds from biological/environmental systems [83], yttrium and europium from waste cathode-ray tube phosphor [84], pesticides in soil [85], isoflavones from herbal plants [86], and oil and tea saponin [87].

Natural Deep Eutectic Solvents (NADES)

NADES are recent green alternatives introduced by Verpoorte and co-workers in 2011. They are mixtures of cellular components such as sugars, amino acids, alcohols, organic acids, and choline derivates [86]. NADES are typically formed by mixing a hydrogen-bond donor (HBD) and a hydrogen-bond acceptor (HBA) molecule, resulting in a marked reduction of the melting point of the mixture. It is noteworthy that according to the chemical nature of the components attached to amine, alcohol, ketone, aldehyde, and carboxylic groups, these groups behave as hydrogen-bond donors or acceptors as well. NADES are biodegradable, safe, reusable, cheap, and available. Also, they possess high solubilization ability, negligible volatility, adjustable polarity, and a wide range of liquid state. However, NADES have some limitations, including high viscosity, which slows down the mass transfer in the processes of dissolution or extraction [88]. To overcome the high viscosity caused by the presence of the extensive hydrogen bonding, van der Waals, and electrostatic interactions between the components, water is added to NADES during the preparation [21, 28, 31, 32] or afterward, as a diluent [61]. In addition, water can be used to adjust NADES selectivity and polarity. NADES have been applied for the extraction of analytes such as anthocyanins in grape skin [89], isoflavones [61], alkaloids [47], vanillin [90], and extraction of environmental pollutants [91].

9.2.2.6 Assisted Extraction Techniques

Microwave-Assisted Extraction (MAE)

In MAE, microwave energy is used to enhance the extraction process. MAE principle is based on heating of the system due to the absorption of microwaves by polar molecules, resulting in heating of the solvent in contact with a sample for the extraction of analytes from the sample matrix into a solvent or an aqueous solution. In MAE, high-throughput sampling can be obtained compared to ultrasound-assisted extraction, especially when it is applied under pressurized conditions in closed systems. However, MAE is only applicable to thermally stable compounds due to the high temperature applied during the extraction process [18]. MAE has been applied among others for the extraction of organochlorine pesticides in plants [92] and polychlorinated biphenyls (PCBs) from environmental samples [93].

Ultrasound-Assisted Extraction (USE)

In this technique, ultrasonic energy is used to facilitate extraction of analytes from solid samples via ultrasonic vibration and cavitation to ensure good contact between the sample and the solvent and good matrix penetration under locally pressurized conditions. USE reduces solvent consumption and saves time and energy compared to conventional Soxhlet extraction; hence, it can be considered a green extraction technique. Example applications include extraction of heavy metals from environmental samples [94] and vitexin from edulis leaves [95].

Pressurized Liquid Extraction or Pressurized Fluid Extraction (PLE or PFE)

In this method, also known as accelerated solvent extraction (ASE), the extraction is performed at high temperature and pressure above the atmospheric pressure boiling point of the solvent. The elevated temperature increases solubility and diffusion rate of the analytes and reduces the viscosity and surface tension of the solvent. Elevated pressure enhances the penetration of the extractant into the matrix pores. PLE is considered a green technique as it reduces the solvent consumption, allows the use of ecofriendly solvents such as ethanol and methanol, and accomplishes rapid and efficient extraction in a shorter time with reduced energy usage. Sample applications of PLE include extraction of active phytopharmaceuticals [96], organic contaminants in environmental and food samples [97, 98], and pesticide residues in tuber crops [99].

9.3 Green Liquid Chromatography

Liquid chromatography consumes large volumes of organic solvents. For example, a very simple chromatographic separation with a conventional LC column (4.6 mm i.d., 15–25 cm in length, packed with 5 μm particles) operated 24 h a day at a flow rate of 1 mL/min produces about 1500 mL of waste daily. This volume of waste could

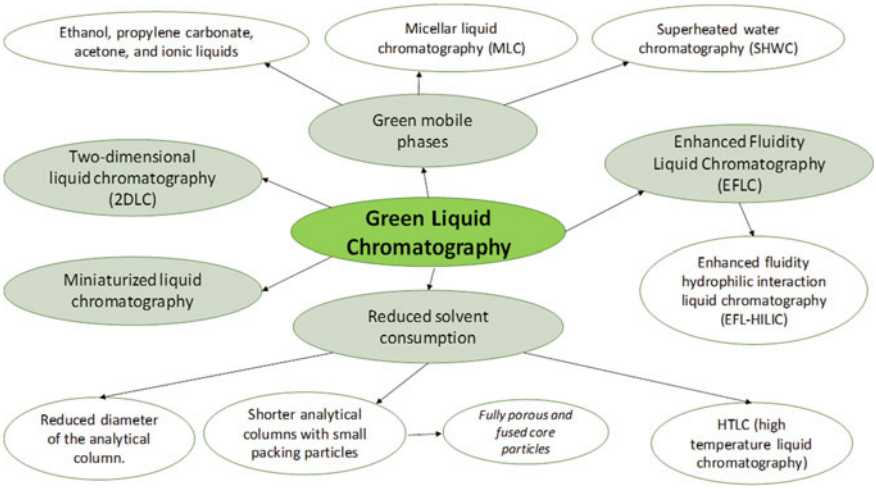

Fig. 9.1 Green approaches to liquid chromatography

be considered negligible if compared to the amount of wastes generated by a large industrial company; however, some companies use dozens of liquid chromatographs in their laboratories, resulting in the production of large volumes of toxic wastes every day. Thus, elimination, or at least a significant reduction of the amount of toxic solvents used for LC separations is preferred to protect the environment. There are several strategies to make LC methodologies greener such as (i) reducing mobile phase consumption and (ii) using ecofriendly mobile phases. Figure 9.1 shows different pathways for greening liquid chromatography.

9.3.1 Reduction of Solvent Consumption

A good strategy to reduce the volume of organic solvents consumed, and consequently the organic wastes produced, is to optimize column-related parameters such as the diameter and length of the analytical column, stationary phase particle size, and mobile phase temperature.

9.3.1.1 Reducing the Diameter of the Analytical Column

When the internal diameter (i.d.) of the column is reduced, the mobile phase flow rate is also reduced, resulting in a significant reduction of mobile phase consumption. In order to maintain the same linear velocity when the column i.d. is reduced, the flow rate has to be lowered according to Eq. (1):

$$F_{\text{reduced}} = F_{\text{conventional}} \left(\frac{\text{i.d.}_{\text{reduced}}}{\text{i.d.}_{\text{conventional}}} \right)^2 \quad (1)$$

The most commonly used LC columns with i.d. ranging from 3.0 to 5.0 mm (conventional LC column) allow flow rates of 300–10,000 μl/min, resulting in consumption of significant amounts of the mobile phase. LC columns with an internal diameter (i.d.) from 2.1 to 3.0 mm (called narrow-bore LC columns) allow flow rates of 200–1000 μl/min and can be easily used with conventional equipment with little modification. These narrow-bore LC columns lower solvent consumption and increase mass sensitivity [3].

If the internal diameter ranges from 2.1 to 1.0 mm, the columns are called microbore. When the i.d. ranges from 0.1 to 1.0 mm, the columns are classified as capillary LC columns. Finally, if the i.d. ranges from 0.025 to 0.1 mm, which offers lower flow rates and significant mobile phase volume reduction, these columns are called nanocapillary LC columns. The flow rates employed in the microbore LC range from 50 to 400 μL/min, in capillary LC range from 0.4 to 200 μL/min, while those of the nano-LC range from 2.5×10^{-5} μL to 4.0×10^{-3} μL/min [3]. Nanocapillary LC is considered a nearly solvent-free method. Reduction of the column i.d. often increases the analytical sensitivity (especially when UV, fluorescence, and electrospray ionization mass spectrometry detectors are used) owing to the lower dilution of the solutes in the mobile phase, resulting in the production of more concentrated bands at the detector. On the other hand, reducing the column i.d. dramatically reduces the sample capacity, which is the most important limitation of this approach.

The advantages of using reduced diameter LC columns in green chromatography are illustrated in Fig. 9.2, which shows how capillary LC can be used to achieve fast separation with decreased solvent consumption. In this example, only 39 μL of solvent was consumed in the separation of an alkylbenzene mixture on a 300 μm i.d. capillary LC column, while 12 mL was required when the separation of the same mixture was performed on a conventional column of 4.6 mm i.d. [100]. Examples of microbore LC applications include drug analysis [101–103], protein and peptide analysis [104], hormone analysis [105, 106], toxin analysis [107, 108], and inorganic analysis [109]. Capillary columns have been applied among others for drug analysis [110], environmental analysis [111], nucleotide analysis [112], flavonoid analysis [113], and pesticide analysis [114]. Sample applications of nanobore columns include biosample analysis [115], drug analysis [116], enantiomeric separation [117], flavonoid analysis [118], and lipid analysis [119].

9.3.1.2 Using Shorter Analytical Columns with Small-Particle-Size Packing Materials

The reduction of column length with concomitant use of packing materials with smaller particle sizes leads to fast and efficient separations in LC. Column efficiency is dependent on column length and the packing materials' particle size according to Eq. (2):

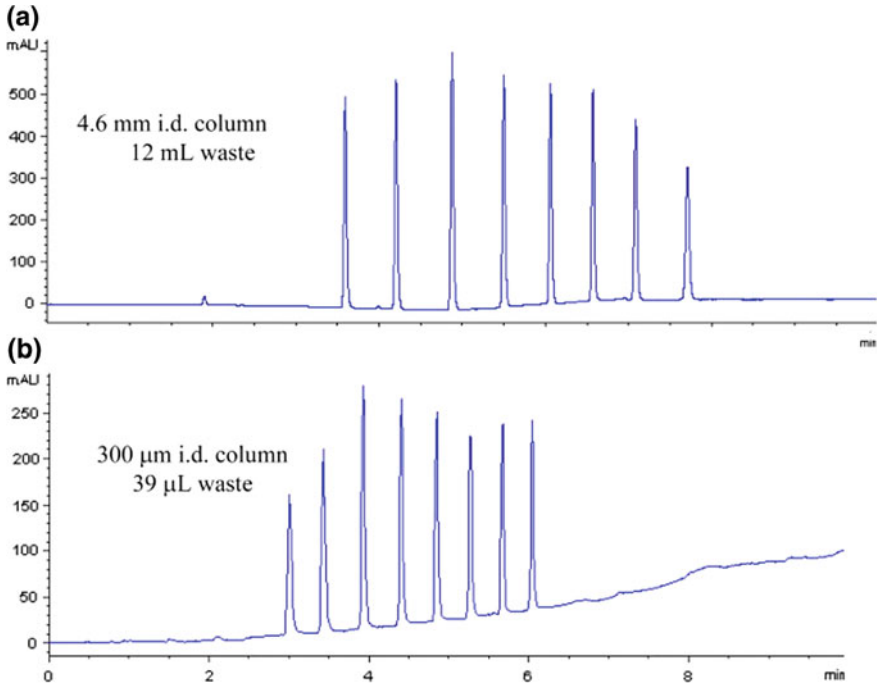

Fig. 9.2 Chromatograms of an alkyl benzene mixture separated on **a** a conventional LC column (4.6 mm i.d.) at a flow rate 1.5 mL/min; 12 mL of solvent was required per analysis; and **b** capillary LC column (0.3 mm i.d.) at a flow rate of 6 µL/min; only 39 µL of solvent was consumed per analysis. Chromatographic conditions: gradient elution: 50–95% acetonitrile in water over 5 min, and then 95% for 1 min. Agilent SB-18, 150 mm, 3.5 µm particle size. UV detection at 220 nm. Reprinted from Ref. [100] with permission from Elsevier

$$N_{\mathrm{eq}} = \frac{\mathrm{L}}{2 \cdot d_{\mathrm{p}}} \tag{2}$$

where L is length of the column, d_p is the packing material particle diameter, and N_{eq} is the number of theoretical plates.

When the particle size is decreased by a factor of two at constant flow rate, the pressure drop generated by the column increases by a factor of four. Consequently, standard HPLC instruments typically cannot be used with small-particle columns due to excessive back pressure. As particle size reduction cannot be implemented without instrumental modifications, ultraperformance LC (UPLC, also called UHPLC) instruments were introduced to provide higher pressures (up to 1200 bar) than conventional HPLC systems while minimizing extracolumn band broadening. The advantages of UHPLC methods are reducing the analysis time and reducing the waste generation, which makes the separation greener. UPLC found numerous applications, examples of which are described in Ref. [120].

9.3.1.3 New Packing Material Technologies

The use of new packing material types is a promising trend toward greener separations. Fused-core particles (also called superficially porous or core shell particles) [121] approximate the performance of sub-2 μm fully porous particles, but without inducing comparably high backpressures. Consequently, columns packed with such particles can usually be used with standard HPLC instruments [122]. Fused-core technology uses silica particles consisting of a solid inner core of a 1.7 μm o.d., with a bonded porous outer shell of 0.5 μm thickness ($d_p = 2.7$ μm). This packing material provides high separation efficiencies due to enhanced mass transfer, low internal porosity, smaller diffusion distances, and narrow particle size distribution. Columns packed with superficially porous particles can be used for greening LC with standard HPLC instruments (400 bar maximum pressure). For example, fused-core particles were compared to fully porous sub-2 μm particles in the analysis of a mixture of sulfonamides at two different column temperatures [122]. The chromatograms shown in Fig. 9.3 illustrate the possibility of using superficially porous particles as an alternative to sub-2 μm fully porous particles in terms of speed and efficiency. In addition, the separation was faster at elevated temperature.

Monolithic columns offer an alternative to packed columns, with the goal of overcoming the compromise between column pressure drop and efficiency of separation. A monolith is a porous rod structure characterized by larger macropores and smaller mesopores. These pores offer large number of channels (thus high permeability) and high surface area for separation. Monolithic columns allow the use of high mobile phase flow rates with low pressure drop, resulting in shorter analysis times compared to conventional HPLC [123]. However, unless the column diameter is reduced, this does not lead to solvent savings.

9.3.1.4 Elevated Temperature

High-temperature liquid chromatography (HTLC) was introduced in 1969. In HTLC, liquid chromatographic separation is performed at temperatures higher than ambient, but lower than the critical temperature [124]. Elevated temperature is a popular strategy to make HPLC greener and to decrease solvent consumption. In comparison to other experimental parameters, such as mobile phase pH and composition, changing temperature during the method development stage is much easier. Using higher temperature in LC requires some instrumental modifications, such as preheating the mobile phase before entering the column and cooling it after eluting from the column (with most detectors), supplying a column with a thermostat, and using thermally stable stationary phases [125]. Elevated temperature in HPLC offers many benefits, especially for users of conventional systems (400 bar). Elevated temperatures decrease the viscosity of the mobile phase, resulting in a reduction of column backpressure, which in turn allows using higher flow rates, longer columns, or using columns packed with small particles providing higher efficiency separations [126]. There are many other benefits arising from using higher temperature, such as

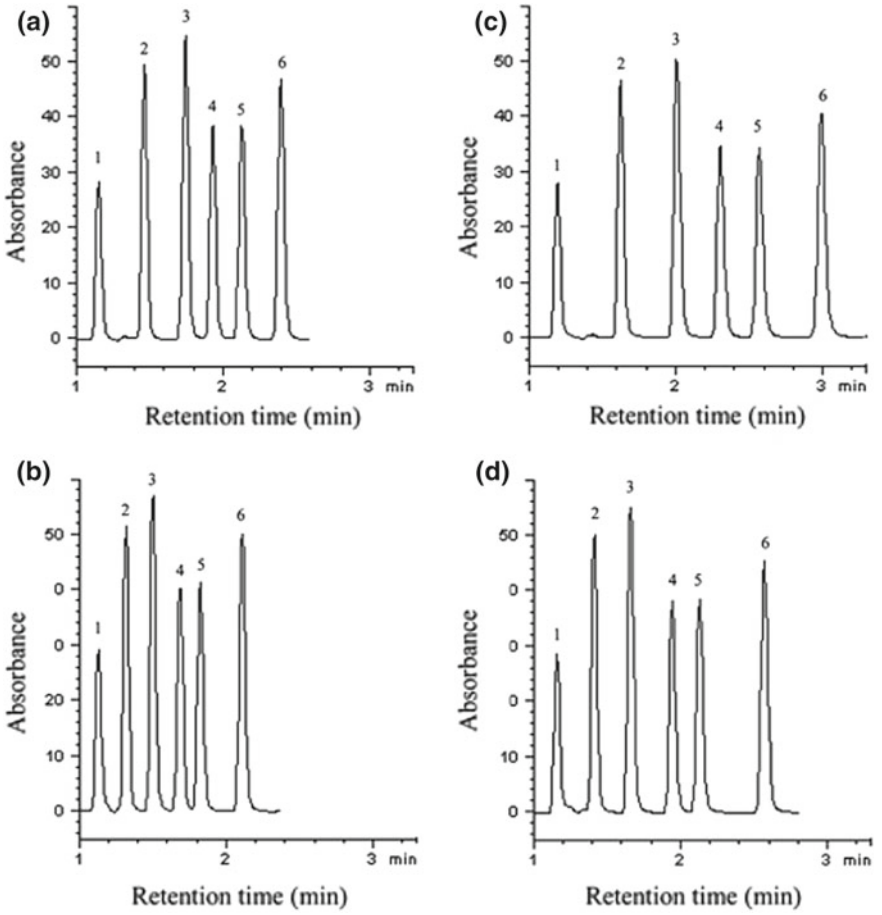

Fig. 9.3 Chromatograms of sulfonamides separated on 150 mm × 4.6 mm columns at a flow rate of 1.2 ml/min; **a** fused-core Kinetex® C18 column (2.6 μm) at 30 °C; **b** fused-core Kinetex® C18 column (2.6 μm) at 60 °C; **c** sub-2 μm Zorbax StableBond C18 column (1.8 μm) at 30 °C, and **d** sub-2 μm Zorbax StableBond C18 column (1.8 μm) at 60 °C. The mobile phase: water with 0.5% acetic acid: acetonitrile (75/25, v/v). Detection: UV at 254 nm. Peak identification: 1—uracil, 2— sulfanilamide, 3—sulfacetamide, 4—sulfapyridine, 5—sulfamerazine and 6—sulfamethazine. Reprinted from Ref. [122]

decreasing the polarity of ethanol and water so they can be used as green ecofriendly mobile phases in LC analysis, decreasing secondary interaction of analytes with silica improving peak symmetry, enhancing mass transfer from the mobile phase to the stationary phase allowing the use of higher flow rates without efficiency loss, and development of new, temperature-responsive stationary phases which contribute to green chromatography.

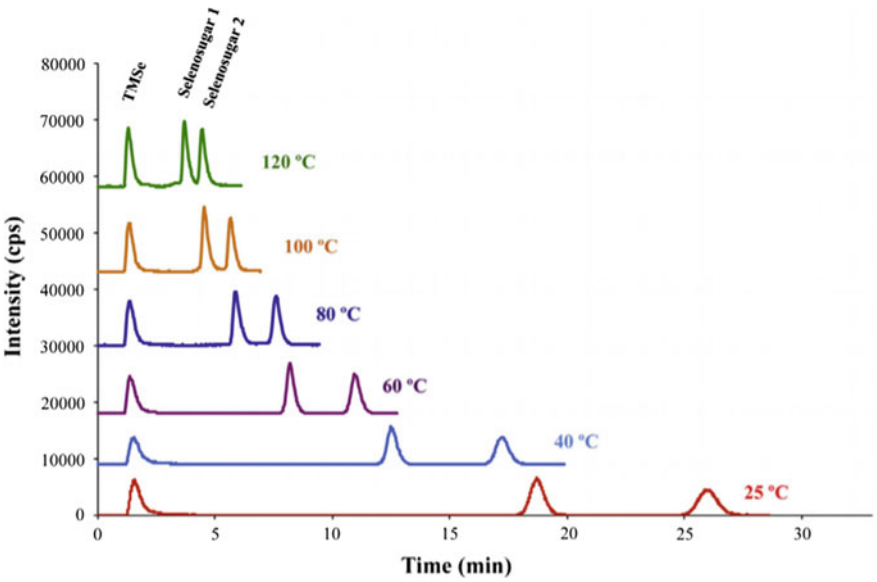

Fig. 9.4 Effect of the column temperature on the chromatographic separation of trimethylselenonium ion and selenosugars 1 and 2. Column: Hypercarb (100 mm × 4.6 mm, 5 μm); mobile phase: ultrapure water + 2% (v/v) methanol; flow rate: 1.0 mL/min. Reprinted from Ref. [127] with permission from Elsevier

Since HTLC leads to reduction of organic solvent consumption and shorter analysis times, it is often adopted as a green technique for routine HPLC analysis. The use of HTLC has been reported in many publications. For instance, high-temperature liquid chromatography (HTLC) and inductively coupled plasma–mass spectrometry (ICP-MS) were applied for the determination of selenium metabolites in urine samples [127]. Selenosugar 1, selenosugar 2, and trimethylselenonium ion were efficiently separated, and the analysis time decreased markedly by increasing the column temperature. Figure 9.4 shows the effect of the column temperature on the chromatographic separation and the analysis time. Table 9.1 summarizes examples of recent applications of HTLC.

Although elevated temperature offers many benefits in liquid chromatography, it also has some limitations. For instance, decomposition of thermally labile compounds might occur at higher temperatures. In addition, thermal stability of the stationary phase should be considered. For example, silica-based columns under RP conditions should not be heated to higher than 60 °C in most cases, especially with acidic or basic buffered eluents. Because of these drawbacks, the characteristics of the stationary phases and the analytes must be considered before applying HTLC [142].

Table 9.1 Recent applications of HTLC

Analytes	Matrix	Column	Temperature (°C)	Detector	References
Pharmaceutical compounds	Wastewater	HILIC Pinnacle DB Cyano (2.1 mm × 50 mm, 1.9 μm)	70	UV detector	[128]
Anti-inflammatory drugs and antibiotics	Wastewater	Zorbax SB C18 (150 mm × 4.6 mm, 1.8 μm)	80	UV detector	[129]
Pharmaceutical drugs	Hair	Waters ACQUITY HSS C18 (150 mm × 2.1 mm, 1.8 μm)	60	TQ-MS	[130]
Drugs of abuse	Urine	ACQUITY HSST3 (100 mm × 2.1 mm, 1.8 μm)	50	TQ-MS	[131]
Steroids	Pharmaceutical gel	XBridge BEH300 C4 (2.1 × 50 mm, 3.5 μm)	80–160	Photodiode array detector	[132]
Multiclass pharmaceuticals	Surface water	ACQUITY HSST3 (150 mm × 2.1 mm, 1.8 μm)	50	TOF-MS	[133]
Arsenosugars	Biological samples	ZirChrom-SAX (150 mm × 4.6 mm, 5 μm) Hypercarb (100 mm × 4.6 mm, 5 μm)	40–140	HTLC-ICP-MS	[134]
Artificial sweeteners	Beverages	Shodex ETRP1 (150 mm × 3.0 mm, 4 μm)	110–150	HTLC-MS	[135]

(continued)

Table 9.1 (continued)

Analytes	Matrix	Column	Temperature (°C)	Detector	References
Metals and alcohols' content	Alcoholic beverages	Hamilton polymeric reversed phase (100 mm × 4.1 mm, 5 μm)	80–175	ICP-MS	[136]
Clodronate	Human serum	Supelco Ascentis MS C18 (100 mm × 2.1 mm, 3 μm)	50	UV	[137]
Intact proteins	Bovine pancreas, heart, and milk; horse heart; chicken eggs	Dionex ProSwift RP-2H (50 mm × 4.6 mm, –[a]) and Dionex ProSwift RP-4H (250 mm × 1 mm, –)	120	Evaporative light scattering detector	[138]
Cyclosporin and tacrolimus	Blood	Waters ACQUITY UPLC C18 (10 mm × 2.1 mm, 1.8 μm)	55	TQ-MS	[139]
Sulfonamides	Wastewater and surface water	Zorbax SB C18 (150 mm × 4.6 mm, 1.8 μm)	60	UV	[140]
Ritonavir and related compounds	Tablets	Waters ACQUITY BEH Shield RP18 (100 mm × 2.1 mm, 1.7 μm)	50	UV	[141]

[a] (–): Information not available

9.3.2 Using Green Mobile Phases

Acetonitrile/water and methanol/water mixtures are the most popular and typical mobile phases used in HPLC. Acetonitrile has low acidity, minimal chemical reactivity, low boiling point, low viscosity, and low UV cutoff (190 nm) [89]. Acetonitrile and methanol are miscible with water; therefore, they are ideal solvents for RPLC [143]. However, both acetonitrile and methanol cause acute and chronic toxicity to aquatic life [100]. The latter has lower toxicity and lower disposal costs; hence, it should be selected over acetonitrile as a mobile phase whenever possible. According to the GAC principles, it is mandatory to search for alternative green mobile phases to protect the environment.

9.3.2.1 Superheated Water

Water is the greenest alternative to all organic solvents in liquid chromatography. It is safe, non-flammable, non-toxic, inexpensive, and recyclable. The main limitation of using pure water as a solvent in analytical procedures is the poor water solubility of many hydrophobic organic compounds. Using pressurized hot water (also referred to as subcritical water or superheated water) is a direct way to greening liquid chromatography. This approach to separation has been called superheated water chromatography (SHWC). In SHWC, liquid water is used under elevated pressure at temperatures between the atmospheric boiling point and the critical temperature of water (374 °C) [144]. By increasing the temperature and pressure of water, the polarity of superheated water markedly decreases and becomes similar to those of other organic solvents (methanol or ethanol), resulting in enhanced solubility of organic analytes. SHWC was adopted as a green technique in many applications. For example, superheated water was used at different temperatures for the separation of the standard paraben solution [145]. The separation was performed faster at higher temperature. At 180 °C, the separation was done in 10 min as shown in Fig. 9.5. This study confirmed that SHWC is an ecofriendly alternative to conventional HPLC methods in terms of efficiency and speed. Many other applications have been documented, including analysis of pharmaceutical compounds [146, 147], hormones [148], and enantiomer separation [149].

9.3.2.2 Ethanol

Due to environmental hazards related to the use of acetonitrile as a mobile phase in RPLC, more ecofriendly alternative solvents have been introduced such as ethanol. Ethanol is a natural product with properties similar to acetonitrile and methanol, but offers some advantages including lower toxicity, volatility, and disposal costs. It has been successfully used with water as a mobile phase to substitute methanol and acetonitrile in RPLC without compromising separation efficiency [150], However,

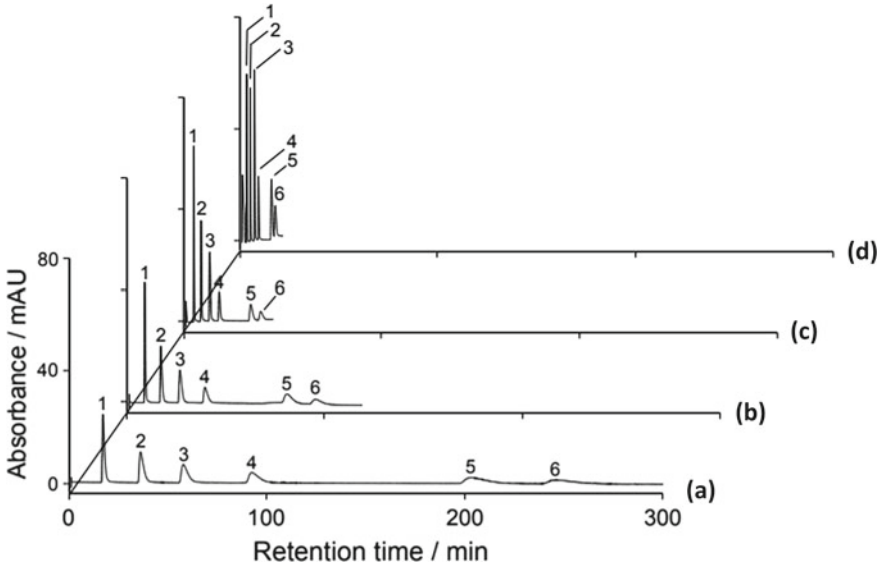

Fig. 9.5 Chromatograms obtained from SHWC separation of the standard paraben solution at column temperatures of: **a** 120 °C, **b** 140 °C, **c** 160 °C, and **d** 180 °C. Chromatographic conditions: ZirChrom DiamondBond-C18 (150 mm × 2.1 mm, 3 μm) column; mobile phase flow rate 0.5 mL/min; UV detection at 254 nm. Peak identification: 1—methylparaben, 2—ethylparaben, 3—isopropylparaben, 4—propylparaben, 5—isobutylparaben, and 6—butylparaben. Reprinted from Ref. [145] with permission from John Wiley and Sons

the higher backpressure induced by ethanol due to its higher viscosity hinders its use as a mobile phase with conventional HPLC systems (400 bar). To avoid this backpressure problem, UPLC instruments and/or high mobile phase temperatures could be used. Ethanol has been used as a green organic modifier in numerous applications achieving highly efficient separations. Table 9.2 summarizes recent applications of ethanol as a green organic modifier in the analysis of various analytes in different matrices, mainly pharmaceutical preparations.

9.3.2.3 Propylene Carbonate

Propylene carbonate (PC) is a polar aprotic solvent that has been used in chromatographic analysis as a green alternative to acetonitrile without compromising the separation efficiency. PC offers various advantages over acetonitrile such as a lower toxicity, higher biodegradability, and lower capacity to bioaccumulate, resulting in easy disposal of its waste [170]. PC also has higher boiling point and flashpoint temperature than those of acetonitrile; consequently, the risk of accidental fires is minimized in chemical laboratories. However, PC has two major drawbacks. Firstly, it is not completely miscible with water, which is why a third solvent, such as methanol or

Table 9.2 Recent applications of ethanol as a green mobile phase

Analytes	Column	Mobile phase	Temperature (°C)	Detector	References
Statins in hydro-alcoholic solutions	ODS-AQ YMC C18 (50 mm × 4.6 mm, 3 μm)	Ethanol/25 mM formic acid (pH 2.5) (50:50, v/v)	40	UV (238 nm)	[151]
Dextromethorphan and its impurities	ACQUITY BEH C18 (50 mm × 2.1 mm, 1.7 μm)	Ethanol/10 mM ammonium formate (pH 4.7)	38	UV (280 nm)	[152]
Prednisolone in tablets	Phenomenex C18 (150 mm × 4.6 mm, 5 μm)	Ethanol/water (30:70, v/v)	50	UV (254 nm)	[153]
16 active pharmaceutical ingredients	XBridge BEH Shield RP18 (50 mm × 4.6 mm, 2.5 μm)	Ethanol/20 mM acetate buffer (pH 4.85)	33.7	UV (210 nm)	[154]
Diltiazem in topical formulations	C18 column (250 mm × 4.6 mm, 5 μm)	Ethanol/H_3PO_4 (pH 2.5) (35:65, v/v)	50	UV (240 nm)	[155]
Phenylephrine, paracetamol, and guaifenesin in tablets	Onyx Monolithic C18 (100 mm × 4.6 mm)	Ethanol/phosphate buffer (pH 7)	25	UV (220 nm)	[156]
Ampicillin in injection powder	Zorbax C18 (150 mm × 4.6 mm, 5 μm)	Ethanol/water (40:60, v/v)	25	UV (210 nm)	[157]
Clidinium/chlordiazepoxide; Phenobarbitone/pipenzolate in coformulated pharmaceuticals	Zorbax SBC18 (75 mm × 4.6 mm, 3.5 μm)	Ethanol/water (50:50, v/v)	25	UV (210 and 220 nm)	[158]

(continued)

Table 9.2 (continued)

Analytes	Column	Mobile phase	Temperature (°C)	Detector	References
Chlorphenoxamine/caffeine/chlorotheophylline in coformulated pharmaceuticals	Polaris SI (50 mm × 4.6 mm, 3 μm)	100% ethanol	25	UV (220.4, 270.4, and 276.4 nm)	[158]
Mebeverine and sulpiride in coformulated pharmaceuticals	Zorbax SBC18 (75 mm × 4.6 mm, 3.5 μm)	Ethanol/water (94.5:5.5, v/v)	25	UV (220 nm)	[158]
Permethrin isomers in pharmaceutical cream	C18 column (150 mm × 4.6 mm, 5 μm)	Ethanol/H_3PO_4 (pH 3.0) (67:33, v/v)	30	UV (215 nm)	[159]
Cefepime in lyophilized powder for injection	Luna C18 (250 mm × 4.6 mm, 5 μm)	Ethanol/water (55:45, v/v)		UV (258 nm)	[160]
Dapsone in pharmaceutical formulations	C18 (150 mm × 4.6 mm, 5 μm)	Ethanol/formic acid (pH 3) (10:90, v/v)		UV detection	[161]
Ertapenem in injection powder	Zorbax Bonus-RP (150 mm × 4.6 mm, 5 μm)	Ethanol/0.1% formic acid (20:80, v/v)		UV (297 nm)	[162]
Daptomycin in lyophilized powder	Zorbax C18 (150 mm × 4.6 mm, 5 μm)	Ethanol/water (55:45, v/v) pH 4.5 with glacial acetic acid	25	UV (221 nm)	[163]

(continued)

Table 9.2 (continued)

Analytes	Column	Mobile phase	Temperature (°C)	Detector	References
Telmisartan, hydrochlorothiazide, amlodipine in tablets	Inertsil ODS-3 C18 (250 mm × 4.6 mm, 5 μm)	Ethanol/20 mM phosphate buffer pH 7 (70:30, v/v)	25	UV (240 nm)	[164]
Lansoprazole enantiomers	CHIRALPAK IC-3 (100 mm × 4.6 mm, –[a])	Ethanol/water (50:50, v/v)	40	UV (210 and 280 nm)	[165]
Caffeic acid in emulsions	C18 XDB Waters (250 mm × 4.6 mm, 5 μm)	Ethanol/acetic acid (pH 2.5) (40:60, v/v)	25	UV (325 nm)	[166]
Rifaximin in tablet	Eclipse Plus C18 (150 mm × 4.6 mm, –)	Ethanol/0.1% acetic acid (52:48, v/v)		UV (290 nm)	[167]
Capecitabine in human plasma	C18 (150 mm × 4.6 mm, 5 μm)	Ethanol/formic acid (pH 3) (55:45, v/v)	50	UV (310 nm)	[168]
Quetiapine in rat plasma	ACQUITY BEH C18 (50 mm × 2.1 mm, 1.7 μm)	Ethanol/water/formic acid (80:20:0.1, v/v/v)	40	MS/MS detection	[169]

[a] (–): Information not available

ethanol, must be added to enhance the miscibility. Ethanol is preferred because of its green characteristics. Secondly, PC is characterized by higher density and viscosity compared to standard solvents, which induce high backpressure in chromatographic systems. Using ethanol as the ternary solvent with PC increases the backpressure markedly. This problem can be avoided by using UPLC and/or increasing the temperature of the mobile phase to decrease its viscosity. PC/methanol mixtures have been used as a green alternative to acetonitrile in most HPLC applications involving PC [171–175]. PC/ethanol/water mobile phase was also adopted as an alternative to acetonitrile/water in some pharmaceutical applications without compromising separation performance or changing elution order of the analytes [170, 176, 177]. Figure 9.6 demonstrates the possibility of using PC/ethanol as alternative organic modifiers to acetonitrile in RPLC for the separation of compounds having acidic, neutral, and basic characteristics without sacrificing the separation performance nor changing the elution order of the analytes. In addition, an ion-pairing liquid chromatography (IPLC) method was developed for the separation of betaxolol-related impurities at 70 °C. The chromatograms shown in Fig. 9.7 show that the analysis time could be decreased by 25% when PC/ethanol was used instead of acetonitrile as organic modifiers with no detrimental impact on resolution, efficiency, or peak symmetry.

9.3.2.4 Acetone

According to the classification by Snyder et al. [178], acetone belongs to the same group as ACN. Although they have similar viscosities (0.33 mPa for ACN and 0.31 mPa for acetone at 25 °C) and other physicochemical properties, such as solubility and miscibility with other solvents, acetone is less toxic and easily biodegradable, and therefore can be used as a green alternative to acetonitrile in some RPLC applications.

In comparison to acetonitrile, acetone is characterized by much higher UV cutoff (340 nm), which severely limits its use as a mobile phase with UV detectors. Furthermore, it is highly volatile and difficult to be pumped. However, recent developments in MS- and aerosol-based detectors in liquid chromatography offer new opportunities to use acetone in RPLC. Funari et al. investigated the possibility of substituting acetonitrile with acetone as the mobile phase in the analysis of complex plant extracts with double detection by UV and corona-charged aerosol detector (CAD). The separation efficiency, the number of detected peaks, and peak capacity were similar for both solvents using the CAD detector [179]. In addition, ACN was replaced with acetone in the analysis of peptides by HPLC/MS [180, 181]. However, as UV detectors remain the most popular choice in many HPLC applications, acetone is not considered the favorite green alternative to acetonitrile in RPLC.

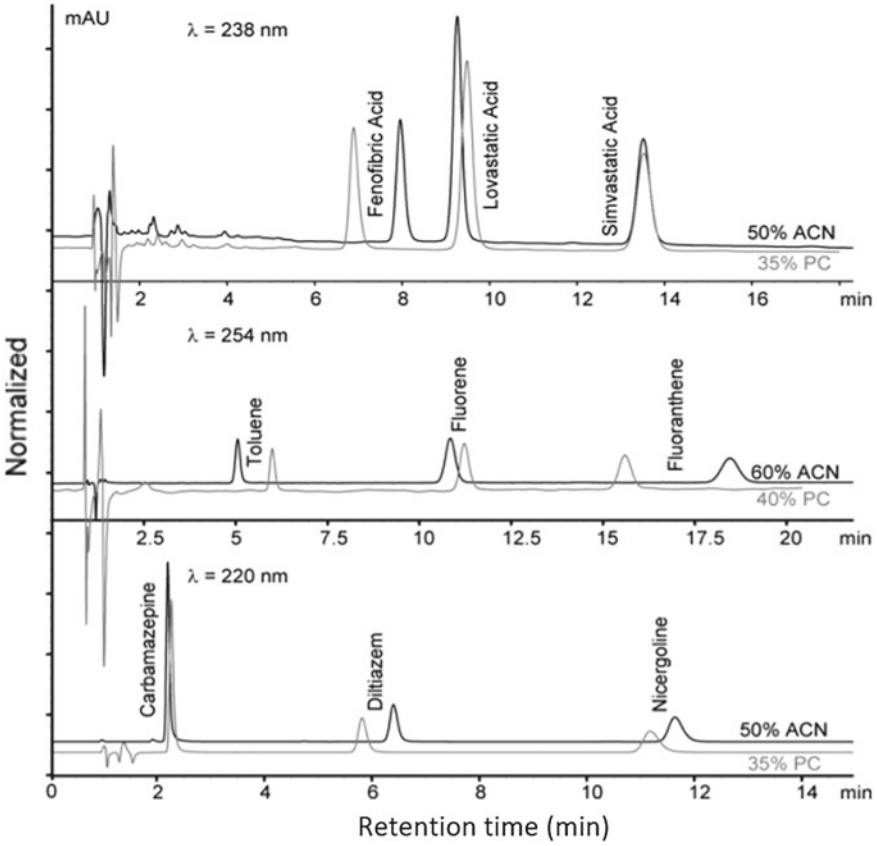

Fig. 9.6 Chromatograms demonstrating the possibility of using PC/ethanol as alternative organic modifiers to acetonitrile in RPLC in the separation of some compounds having acidic, neutral, and basic characteristics. Chromatographic conditions: Purospher® RP-C18 column (75 mm × 4 mm, 3 μm); flow rate: 0.5 mL/min; column temperature 25 °C. Reprinted from Ref. [170] with permission from Elsevier

9.3.2.5 Ionic Liquids (ILs)

Ionic liquids (ILs) or room-temperature ionic liquids (RTILs), composed of various organic cations and inorganic or organic anions, are effectively molten salts that remain liquid at ambient temperatures [182]. ILs are widely used as extraction solvents in sample preparations, as surface-bonded stationary phases in ion exchange and as mobile phase additives in LC [183]. ILs are recyclable, produce smaller amounts of waste, dissolve both organic and inorganic compounds and catalysts, have low vapor pressure, and are non-flammable and miscible with water and organic solvents. However, they are expensive and hazardous to the aquatic environment.

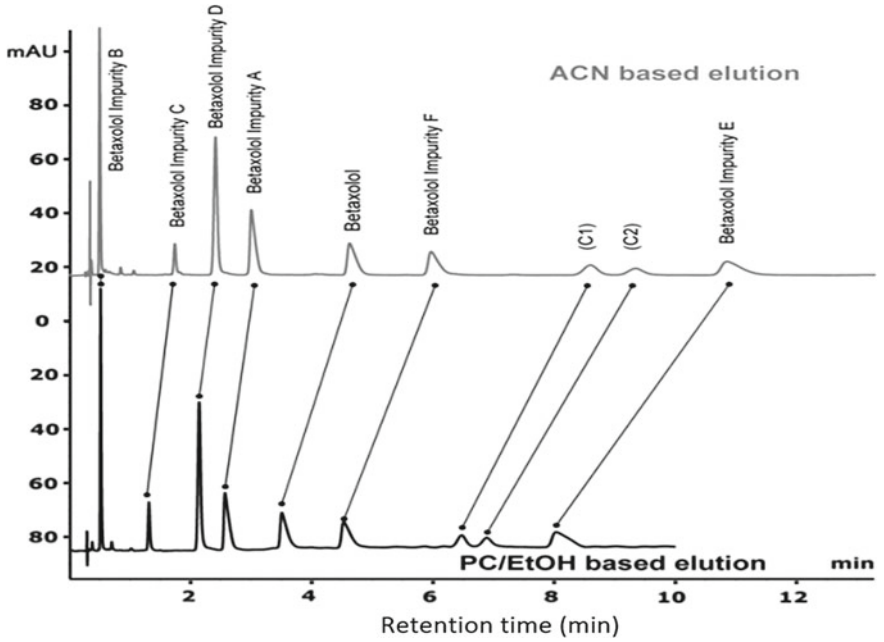

Fig. 9.7 Separation of betaxolol-related impurities by ion-pairing liquid chromatography (IPLC) using PC/ethanol as organic modifiers to replace acetonitrile in the mobile phase. Chromatographic conditions: Zorbax SB-C18 column (50 mm × 4.6 mm, 1.8 μm) at 70 °C with a flow rate of 2 mL/min and UV detection at 273 nm

The use of ionic liquids as mobile phase additives in liquid chromatography has gained a great interest as a way to make LC greener. They are usually added in a small amount to reversed-phase mobile phases as a silanol-blocking agent to enhance the separation of basic compounds. Indeed, ILs can suppress interactions between anionic free silanol of the stationary phase and the positively charged compounds at low pH, which are the main cause of peak tailing and peak broadening. Larger amounts of ILs can also be added to an aqueous mobile phase as an organic modifier instead of conventional organic modifiers. ILs have been used among others as mobile phase additives in RPLC for the analysis of pharmaceutical compounds, including antidepressants in urine samples [184], β-lactam antibiotics [185], β-blockers [186], fluoroquinolones in bovine, ovine, and caprine milk [187], thiamine (vitamin B1) [188], ephedrine [189], and recently urazamide in pharmaceutical preparations [190].

9.3.2.6 Supercritical Fluids

Supercritical fluids (SFs) are considered environmentally friendly solvents in chromatographic separations. The most popular SF used as a mobile phase in supercritical fluid chromatography (SFC) is carbon dioxide. It is non-flammable and non-toxic and

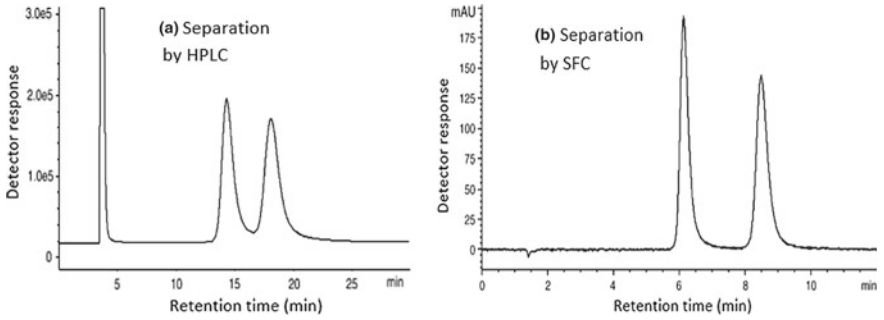

Fig. 9.8 **a** Enantiomeric HPLC separation of pantoprazole. Separation performed at 35 °C; mobile phase: 75:25 hexane/2-propanol at a flow rate of 1 mL/min. **b** Enantiomeric separation of pantoprazole by SFC. Separation performed at 35 °C, 20 MPa; mobile phase: 25% 2-propanol at a flow rate of 2 mL/min. Column: CHIRALPAK AD, 250 mm × 4.6 mm, packed with the 3,5-dimethylphenylcarbamate derivative of amylose, coated on 10 μm silica gel support. Reprinted from Ref. [197] with permission from Elsevier

has low disposal cost. Supercritical CO_2 is also characterized by high solubilizing power, very low viscosity, and high diffusivity, leading to efficient and quick separations. Supercritical fluid chromatography (SFC) typically utilizes carbon dioxide (critical temperature 31.1 °C, critical pressure 72.9 atm) as the mobile phase. In most applications, organic modifiers, e.g., methanol, are added to CO_2. Modifiers increase mobile phase polarity and density, which increases the solubilizing power of the fluid, especially for polar compounds. They also help with stationary phase deactivation, leading to improved peak shapes. SFC has the potential to replace HPLC in some pharmaceutical applications, e.g., enantiomeric separation of antiulcer drugs [191]. In this application, although both SFC and HPLC in general could provide good enantioselectivity, SFC provided remarkable benefits in terms of the mobile phase flow rate, resolution, analysis time, and reduced consumption of hazardous organic solvents. Figure 9.8 illustrates the separation of pantoprazole enantiomers by HPLC and SFC, respectively. The latter could achieve resolutions higher than 2, and the retention times were markedly shorter than those obtained by HPLC.

Recently, SFC has been re-gaining popularity not only because of its greener character, but also because of wider availability of commercial instrumentation, including accessories that convert a standard HPLC system to one with SFC capability. SFC columns are similar to those used in NP-HPLC. However, in order to improve the selectivity of separations, specific stationary phases such as 2-ethyl pyridine have been developed. SFC has a wide range of applications, including chiral separations [192, 193], analysis of pharmaceuticals [194, 195], plasticizers in medical devices [196], and polymers [195]. The years 2014–2018 have witnessed a great expansion of SFC use in bioanalysis applications [197], forensic applications [198, 199], drugs of abuse [200–202], lipidomic analysis [203, 204], analysis of natural products [205–207], food science [208–211], contaminants in food [212–219], environmental analysis [220–228], and cosmetic analysis [229, 230].

9.3.2.7 Enhanced Fluidity (EF) Mobile Phases

EF liquid mixtures are organic solvents or organic–aqueous solvents mixed with high proportions of liquefied gases, such as carbon dioxide. These subcritical solvents share the positive attributes of both supercritical fluids (fast diffusion rates and low viscosities) and commonly used liquids (high solvent strength). EF liquid mixtures are used as green mobile phases for the separation of moderately polar to polar compounds in LC. These mixtures offer many advantages including the ability to tune the polarity by changing the pressure, lower pressure requirements to maintain a single phase, improving chromatographic separation efficiency, and shortening the analysis time. In addition, the lower viscosity of EF liquids enables the use of longer capillary columns (1 m or more) to achieve efficient separations [231]. These solvent properties provide enhanced efficiency for NPLC, RPLC, HILIC, and size exclusion separations, and make EFLC more selective and efficient than conventional HPLC or SFC. EFLC was applied among others for chiral separations [232], separation of inulin fructans from chicory [233], and protein analysis [234].

9.3.3 Green Hydrophilic Interaction Liquid Chromatography (HILIC)

HILIC is a variant of NPLC, in which the separation is performed by partitioning between a water-enriched layer adsorbed on the surface of a polar stationary phase and the mobile phase. These mobile phases contain higher amount of organic solvents such as methanol or acetonitrile; therefore, HILIC is generally considered a non-green mode of separation. In order to make HILIC a green separation technique, ecofriendly solvents were introduced to replace acetonitrile and methanol. For instance, amino acids and catecholamines were separated by using a water/ethanol mixture as the mobile phase, and this method demonstrated that the ecofriendly ethanol can successfully substitute acetonitrile in HILIC [235]. Recently, certain proportions of EFL, e.g., carbon dioxide, were added to mobile phases to increase the diffusivity and decrease the mobile phase viscosity, leading to efficient separations in a shorter time. This technique, known as enhanced fluidity hydrophilic interaction liquid chromatography (EFL-HILIC), has been used for the separation of analytes such as nucleosides and nucleotides [236, 237], and oligosaccharides [238]. The features of EFL-HILIC are illustrated by the analysis of oligosaccharides [238] shown in Fig. 9.9. It has been shown that the addition of CO_2 to a mobile phase composed of methanol/water allows replacing acetonitrile/water mobile phases in HILIC separations.

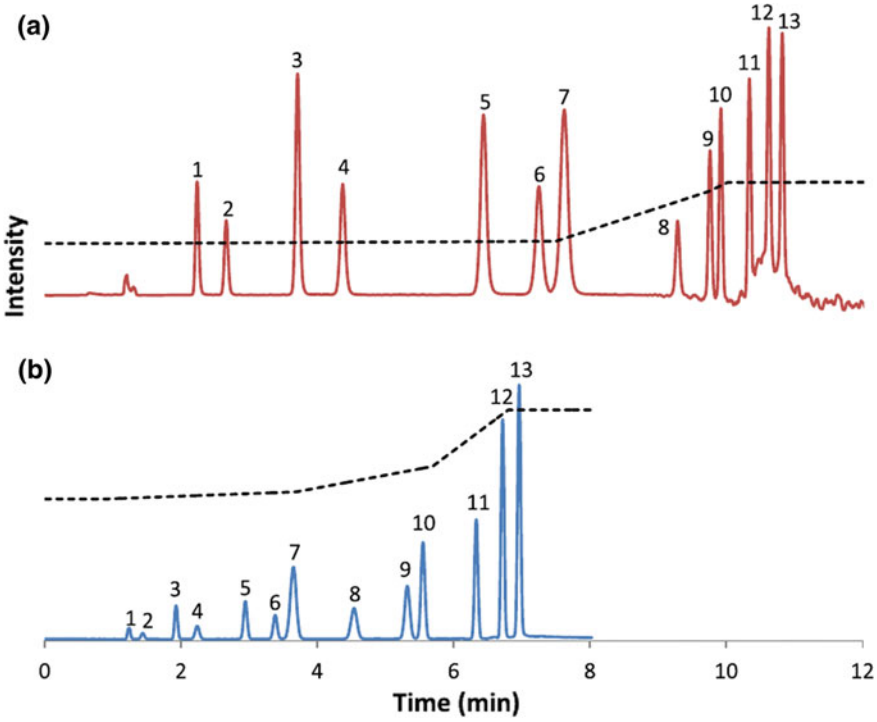

Fig. 9.9 Separation of 13 oligosaccharides by HILIC using two mobile phases: **a** A: ACN:H2O; B: H2O, 0.2 vol% TEA, 80 °C, flow rate: 1.5 mL/min, and **b** A: MeOH:H2O:CO_2; B: 82.5:17.5 MeOH:H_2O, 3 vol.% TEA, 90 °C, flow rate: 2.5 mL/min. Peak identification: (1) fructose, (2) glucose, (3) sucrose, (4) maltose, (5) melezitose, (6) raffinose, (7) maltotriose, (8) isomaltotriose, (9) maltotetraose, (10) stachyose, (11) maltopentaose, (12) maltohexaose, and (13) maltoheptaose. Reprinted from Ref. [238] with permission from Elsevier

9.3.4 Micellar Liquid Chromatography (MLC)

Micellar liquid chromatography is an RPLC mode in which the stationary phase is non-polar, and the mobile phase is an aqueous solution of a surfactant at a concentration above the critical micellar concentration (CMC) [239]. In MLC, a surfactant is added to the mobile phase forming a pseudo-stationary phase into which compounds can partition. The retention and separation of analytes depend on the differential partitioning between the three phases: stationary phase, bulk solvent, and the micellar pseudo-phase.

MLC has been considered an interesting technique for GAC due to the advantages it offered. Firstly, it uses mobile phases consisting mainly of aqueous solutions of a surfactant and a small proportion of an organic modifier (3–15%, v/v). In addition, the micellar mobile phases are less toxic, non-flammable, safe to work with, and do not generate hazardous wastes owing to biodegradability of the surfactants [240].

For instance, sodium dodecyl sulfate (SDS), the most popular surfactant used in MLC, is a fatty alcohol sulfate which is aerobically degraded. However, in order to enhance MLC separations, it is necessary to add an organic modifier to the aqueous solution of micelles, such as propanol, butanol, or pentanol. These modifiers are less toxic than acetonitrile and methanol [241]. Micelles possess a great solubilizing ability allowing the direct injection of drugs in complex matrices (biological fluids and dosage forms) without prior sample treatment other than filtration. Furthermore, MLC is compatible with conventional HPLC instruments in analytical chemistry laboratories, so there is no need for instrumental modifications.

Due to all previously mentioned advantages of MLC, it is used as a green alternative to RPLC in the analysis of numerous analytes in different matrices. Table 9.3 summarizes recent applications of MLC.

Table 9.3 Recent applications of MLC

Analytes	Column	Mobile phase	Detector	References
Nicotine in formulations and biological fluid	Kromasil C18 (250 mm × 4.6 mm, 5 μm)	0.15 M SDS + 6% n-pentanol (v/v) with 0.01 M NaH_2PO_4 and 0.001 M KCl, pH 6.0	Electrochemical detector at 0.8 V	[242]
Tamoxifen in plasma	Kromasil 5 C18 (150 mm × 4.6 mm, 5 μm)	0.15 M SDS + 7% n-butanol (v/v), pH 3.0	Fluorescence (260 nm/380 nm)	[243]
Nelfinavir in tablets	LiChrospher C18 (–)[a]	0.5 M Tween 20 + 2% n-butanol (v/v) with H_3PO_4, pH 4.2	UV (249 nm)	[244]
Opium alkaloids in pharmaceutical preparations	Kromasil C1 (150 mm × 4.6 mm, 5 μm)	0.10 M SDS + 5% n-butanol (v/v) with H_3PO_4, pH 2.5	UV (280 nm)	[245]
Penicillin antibiotics in formulations and in urine	Zorbax C18 (150 mm × 4.6 mm, 5 μm)	0.11 M SDS + 6% n-propanol (v/v) with 0.01 M NaH_2PO_4, pH 3.0	UV (210 nm)	[246]
Zidovudine derivatives in aqueous and simulated gastric and intestinal fluids	Phenomenex Synergi Fusion-RP 80 (250 mm × 4.6 mm, 4 μm)	0.05 M SDS + 1% n-butanol (v/v) with 0.01 M NaH_2PO_4, pH 3.0	UV (267 nm)	[247]

(continued)

Table 9.3 (continued)

Analytes	Column	Mobile phase	Detector	References
Tamoxifen and endoxifen in plasma	Kromasil C18 (150 mm × 4.6 mm, 5 μm)	0.15 M SDS + 7% n-butanol (v/v), pH 3.0	Fluorescence (260 nm/380 nm)	[248]
Tricyclic antidepressants in pharmaceutical formulations	Zorbax C18 (150 mm × 4.6 mm, –)	0.02 M Brij-35 with citric buffer, pH 3.0	UV (254 nm)	[249]
Lamivudine and seven derivatives in simulated gastric and intestinal fluids	Kromasil C18 (250 mm × 4.6 mm, 5 μm)	0.15 M SDS + 4% n-butanol (v/v) with 0.01 M KH_2PO_4-Na_2HPO_4 buffer, pH 7.0	UV (272 nm)	[250]
Sildenafil in oral suspensions and tablets	ACE 5 C18–AR (50 mm × 4.6 mm, 5 μm)	0.0082 M SDS with acetate buffer, pH 4.0	UV (298 nm)	[251]
Serotonin reuptake inhibitors in plasma and urine	Kromasil C18 (150 mm × 4.6 mm, 5 μm)	0.075 M SDS + 6% n-butanol (v/v) with 0.01 M NaH_2PO_4, pH 7.0	Fluorescence detection Excitation wavelength (236, 295, and 230 nm) and emission wavelength (310, 350, and 305 nm) for citalopram, paroxetine, and fluoxetine, respectively.	[252]
Tizoxanide in human urine and plasma	Chromolith® C18 (100 mm × 4.6 mm, –) NUCLEODUR MN-C18 column (150 mm × 4.6 mm, 5 μm)	0.1 M SDS + 8% n-propanol (v/v) with 0.3% TEA and 0.02 M H_3PO_4, pH 4.0	UV (240 nm)	[253]
Flavoxate in tablets	BDS Hypersil phenyl (250 mm × 4.6 mm, 5 μm)	0.15 M SDS + 15% n-propanol (v/v) with 0.3% TEA and 0.02 M H_3PO_4, pH 2.5	UV (325 nm)	[254]
Abacavir, lamivudine, and raltegravir in human plasma	Kromasil C18 (150 mm × 4.6 mm, 5 μm)	0.05 M SDS, pH 7.0	UV (260 nm)	[255]

(continued)

Table 9.3 (continued)

Analytes	Column	Mobile phase	Detector	References
Diltiazem, metoprolol, and isosorbide in human serum	Pinnacle II Cyano (150 mm × 4.6 mm, 5 μm)	0.0415 M SDS + 10% n-propanol (v/v) with 0.02 M NaH_2PO_4, pH 7.0	UV (225 nm) [256]	[256]
Felodipine in tablets and human plasma	Shim-pack CLC-C18 (250 mm × 4.6 mm, 5 μm)	0.085 M SDS + 6.5% n-pentanol (v/v) with 0.025 M phosphate buffer, pH 7.0	Fluorescence (240 nm/440 nm)	[257]
Eight β-blockers in urine samples	Zorbax Eclipse × DB-C8 and Zorbax Eclipse × DB-C18 (150 mm × 4.6 mm, 5 μm)	0.10 M SDS + n-propanol (from 0 to 30% (v/v) in 15 min)	UV (225 nm)	[258]
Darunavir, ritonavir, emtricitabine, and tenofovir in human plasma	Kromasil C18 (150 mm × 4.6 mm, 5 μm)	0.06 M SDS + 2.5% n-pentanol (v/v), pH 7.0	UV (214 nm)	[259]
Six β-blockers	Zorbax Eclipse C18 (150 mm × 4.6 mm, 5 μm)	0.02 M Brij-35 and 0.15 M SDS with 0.01 M NaH_2PO_4 and HCl, pH 3.0	UV (225 nm)	[260]
Three oxicams in gel and suppositories	C8 (150 mm × 4.6 mm, 5 μm)	0.15 M SDS + 10% n-propanol (v/v) with 0.3% TEA and 0.02 M H_3PO_4, pH 3.0	Time-programmed UV detection	[261]
Ofloxacin and flavoxate in biological fluids	BDS Hypersil phenyl (250 mm × 4.6 mm, 5 μm)	0.15 M SDS + 15% n-propanol (v/v) with 0.3% TEA and 0.02 M H_3PO_4, pH 2.5	UV at 325 nm	[262]
Ascorbic acid, pseudoephedrine, and ibuprofen in tablets	ODS C18 (150 mm × 4.6 mm, 5 μm)	0.03 M SDS + 8% 1-propanol (v/v) with 0.3% TEA and 0.02 M H_3PO_4, pH 3.0	UV (260 nm)	[263]
Tamoxifen and its main metabolites in plasma	C18 column (–)	0.08 M SDS + 4.5% n-butanol (v/v), pH 3.0	Fluorescence (260 nm/380 nm)	[264]
Free ampicillin in human serum albumin	RP-8 endcapped (125 mm × 4.0 mm, 5 μm)	0.06 M CTAB + 20% ACN (v/v), pH 7.4	UV (254 nm)	[265]

(continued)

Table 9.3 (continued)

Analytes	Column	Mobile phase	Detector	References
Esomeprazole, leflunomide, and ibuprofen in human plasma and tablets	Shim-pack VP-ODS (150 mm × 4.6 mm, 5 μm)	0.1 M SDS + 10% n-propanol (v/v) with 0.3% TEA and 0.02 M H_3PO_4, pH 3.5	UV (285 nm)	[266]
β-adrenoceptor antagonists in pharmaceutical formulations	Zorbax Eclipse × DB (150 mm × 4.6 mm, 5 μm)	0.15 M SDS/15% 1-propanol at pH 3 and 0.15 M SDS/0.05 M Brij-35 at pH 3	UV (225 nm)	[267]
Angiotensin-converting enzyme inhibitors, and hydrochlorothiazide in tablets	C18 (150 mm × 4.6 mm, 5 μm)	0.012 M SDS + 10% n-propanol (v/v) with 0.3% TEA and 0.02 M H_3PO_4, pH 3.6	UV (210 nm)	[268]
Terephthalic acid impurities	C18 (100 mm × 2.1 mm, 3.5 μm)	Acidic 1% sodium dodecyl sulfate (SDS) solution	UV (240 nm)	[269]
Axitinib, lapatinib, and afatinib in plasma	Kromasil C18 (150 mm × 4.6 mm, 5 μm)	0.07 M SDS + 6.0% n-pentanol (v/v) with 0.01 M phosphate salt, pH 7.0	UV (260 nm)	[270]

[a] (–): Information not available

9.3.5 Two-Dimensional Liquid Chromatography (2DLC)

Multidimensional liquid chromatography is a technique in which a combination of more than one separation mechanisms is applied to the same sample, resulting in enhanced resolution, peak capacity, and separation efficiency. 2DLC is sometimes regarded a green ecofriendly technique as in some implementations it fulfills most of GAC principles.

2DLC can be performed in two modes [271]:

- Heart-cutting: Selected fraction(s) collected from the first-dimension (^{1}D) effluent are subjected to the separation in the second dimension (^{2}D). It is applicable when only a few components of the sample need additional separation.
- Comprehensive two-dimensional liquid chromatography: The entire effluent from ^{1}D is divided into small fractions, each of which is injected into ^{2}D for further separation. The separation selectivity is determined by the stationary and mobile phases used in the first and the second dimensions, so the compatibility between

them is necessary. This mode is applicable when a large number of complex sample components need further separation. The transfer of fractions between the two dimensions can be performed on- or off-line.

Online two-dimensional liquid chromatography can be considered a "green" technique because in many cases a single run could be sufficient to separate sample components of interest. This results in the reduction of solvent consumption and waste generation when compared to the off-line mode.

Different approaches have been proposed to make 2DLC greener. One approach is to accelerate the separation in the second dimension by increasing the mobile phase temperature, using shorter columns [272], fully porous sub-2 μm particles or superficially porous particles [273]. Another approach to make 2DLC more ecofriendly is to replace hazardous solvents like acetonitrile and methanol with more benign biodegradable solvents, e.g., ethanol, especially in the first dimension. The main reason for using acetonitrile and methanol in 2DLC is the low UV cutoff of both solvents. However, in 2DLC, low UV cutoff is not necessary in the first dimension of the system, allowing the use of other ecofriendly solvents. Another approach to make 2DLC "greener" is using temperature programming in the first dimension, allowing reduction of the amount of the organic modifier used in ^{1}D separation and focusing the analytes injected into the second-dimension column [274].

2DLC is being used for the analysis of many types of complex samples. In the recent years, LC × LC methods have been developed and applied to separate polymers [275, 276], natural products [277], and in proteomics [278]. Many applications were done in food analysis [279], including citrus juices [280] and whole grain bread extracts [281]. Other applications included phenolic acids and flavonoids [282], and pharmaceutical samples [283].

9.4 Green Aspects of Gas Chromatography

Gas chromatography (GC) is a technique used for the analysis of volatile and semivolatile compounds. To make gas chromatography more ecofriendly, several approaches have been proposed. Firstly, the choice of the carrier gas has to be considered. Helium (He) is the most popular carrier gas used in GC due to its advantageous chromatographic characteristics (high efficiency at relatively high linear velocity, high diffusivity, low viscosity, inertness, non-flammability, safe handling, etc.). On the other hand, helium is a non-renewable resource, and the world's reserves are close to being depleted. Nitrogen (N_2) can also be used as a carrier gas in GC. However, its optimal linear velocity is low compared to helium or hydrogen, resulting in longer analysis times; hence, nitrogen is the least desirable carrier gas for GC. From the chromatographic point of view, the best carrier gas in GC is hydrogen. It has the highest optimum linear velocity of the three common carrier gases compared here, resulting in shorter analysis times and efficient separations. Hydrogen is considered the best carrier gas when samples contain compounds eluting over a

wide range of temperatures at constant pressure. The main concern with regard to hydrogen is safety, as it is its flammable and may form explosive mixtures with air when its concentration exceeds the lower explosive limit (LEL). It should be pointed out, however, that barring a catastrophic failure, it is unlikely that hydrogen accumulates in a confined space to the extent that LEL is exceeded because H_2 has the highest diffusivity of all gases. Safety concerns can be further alleviated by the use of hydrogen generators, so that the use of gas cylinders can be avoided.

Another approach to make GC greener is to increase sample throughput and shorten the analysis time by using shorter columns with smaller internal diameter. Such columns increase the linear velocity of the carrier gas, resulting in faster separation without the loss of efficiency. The main limitations of this approach include small sample capacity of narrow diameter columns, which might easily lead to column overloading, and the high pressures required to drive the carrier gas through the column at the desired linear velocity.

The next possibility to make GC greener is to use low thermal mass (LTM) technology. LTM GC is considered a green technique as resistive heating of a GC column allows increased column heating rates (up to 1800 °C/min) and reduction in power consumption by a factor of 200 compared to standard GC ovens [284]. Fast heating and cooling rates allow high sample throughput, leading to high efficiency separation. However, the LTM technology has its drawbacks. First, the host oven should be kept at elevated temperature all the time to avoid cold spots, which negates the advantage of reduced power consumption by the module itself. In addition, if the host oven is at higher temperature than the LTM GC module, thermal conditioning of the LTM GC is necessary prior to the analytical work, as impurities that come from the carrier gas or stationary phase decomposition products could accumulate in the module.

Stearns et al. introduced another technology based on direct resistive heating of nickel-clad fused silica GC columns [285]. This direct resistive heating method can achieve heating rates as high as 800 °C/min. The column also cooled from 360 to 40 °C in less than 1 min. The power consumption was less than 70 W for a 5 m column when heating to 350 °C at 800 °C/min was applied. The advantages offered by the resistively heated nickel-clad fused silica column make it ideal for fast GC analysis or portable instruments. This technology is considered green because of low power consumption, rapid heating and cooling, and high reliability [285].

Comprehensive two-dimensional gas chromatography (GC × GC) has received a great deal of interest owing to the ability of this technique to analyze very complex mixtures of volatile and semivolatile organic compounds, high peak capacity, high resolution and efficiency. GC × GC allows better separation of analytes in complex matrices than conventional one-dimensional gas chromatography, while utilizing the same volumes of reagents, the same sample volume, and requiring the same or slightly longer time for separation. In addition, GC × GC allows the separation of target analytes in complex samples with little to no sample preparation, resulting in significant time and reagent savings [286]. Therefore, GC × GC is considered "greener" if compared to one-dimensional gas chromatography. A two-dimensional GC system is achieved by combining two columns of different selectivities in series

through a special interface called a modulator [287, 288]. The modulator is the most critical component of any GC × GC system. It traps the first-dimension column effluent and injects it into the second-dimension column at regular intervals. It also must provide a narrow injection bandwidth to the second-dimension column to maximize the separation performance of the system.

GC × GC modulators can be classified into thermal and flow modulators. In thermal modulation, the analytes are trapped into the stationary phase at low temperature, while at the end of each modulation period, the capillary is heated rapidly to release the analytes into the second-dimension column. Cold and hot gas streams are typically used in thermal modulation for cooling and heating the capillary column [287, 289]. The main drawback of this technique is the need for cryogenic agents (liquid CO_2 or N_2), which are difficult to handle and expensive. In addition, the use of liquid cryogens compromises the characteristics of GC × GC as a benign separation technique.

Differential flow modulators are an alternative to thermal modulators. In these modulators, the effluent from the first-dimension column is collected in a sampling loop (or loops) and flushed at a very high flow rate to the second-dimension column by an auxiliary stream of carrier gas. These types of modulators do not require cryogenic agents; thus, they are considered more economical and greener that thermal modulators that use cryogenic agents. However, the sensitivity of GC × GC with differential flow modulators is usually worse than that with thermal modulators due to lack of band refocusing in the modulator.

Recently, a new type of thermal modulator has been developed as an alternative to cryogenic modulators. These modulators are known as consumable-free modulators (CFMs) [290, 291]. They focus the analytes at ambient temperatures eliminating the need for cryogenic agents or other consumables, which makes them greener.

9.5 Miniaturization in Chromatography

Miniaturization of analytical instrumentation is a recent trend that presents many advantages, such as space savings and minimization of the overall scale of analytical system. Miniaturized separation systems produce less waste, require fewer consumables, reduce energy consumption, and often improve method sensitivity compared to full-size separation systems. These positive attributes make miniaturized separation systems "green." For instance, as discussed earlier, using shorter columns with reduced diameter allows using lower mobile phase flow rates, resulting in a reduction of solvent consumption compared to traditional methods. Also, if concentration-dependent detectors are used such as UV detectors, lower flow rates help reduce dilution of the analyte in the mobile phase, leading to improved detection sensitivity. In addition, miniaturized systems require a smaller amount of a sample, which is very beneficial in some research areas, including forensic and biomedical sciences. Moreover, microscale sample preparation techniques (SPME, MEPS, SPNE, LPME, etc.) are usually used with miniaturized systems, saving larger amounts of solvents.

According to GAC principles, miniaturization offers the advantage of instrument portability, which facilitates on-site analysis. Portable chromatographs are classified into [292]:

- Compact chromatographs, which weigh 10–25 kg. They help reduce costs, materials, energy consumption, and space.
- Chip-based chromatographs, which weigh 0.2–3 kg. Typically used in on-site analysis, they allow very fast analysis and are fully self-supporting, but have restricted analytical capabilities.
- Micro-chromatographs, which weigh less than 0.2 kg and are used for space investigations. They offer many advantages, such as automated analysis, resistance to impact and shaking, but they have very limited capabilities.

Chip-based separation systems consume very little chemicals and energy. They are often as small as a coin, easily portable, and might become inexpensive when mass produced. Examples of applications of such systems include enantiomer analysis [293], glycopeptide profiling [294], and analysis of volatile compounds [295].

9.6 Summary

Protection of the environment is the main goal for many researchers these days. Chromatographic methodologies have the potential to be more benign at all steps of the analysis, starting from sample preparation to separation and final determination. An ideal green chromatographic method should avoid using any consumables and should be implemented in an online mode without prior sample preparation. However, sample preparation is necessary in most cases. Hence, green miniaturized and solventless sample preparation procedures should be adopted whenever possible to reduce solvent consumption. Gradual replacement of the present analytical methods by green ones is expected in the future.

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Chapter 10
Flow Injection Analysis Toward Green Analytical Chemistry

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Abstract Green analytical chemistry has brought new goals in the development and application of analytical methods. The flow injection methods meet some of these goals: reduction of chemical waste generation, reduction of the use of harmful reagents and solvents, and increase the security of analysts. Simple equipment, great repeatability, controlled dispersion, reproducible signals, and high sample throughput are the basic advantages of flow injection methods of analysis. Development of FIA leads to the well-established concepts: sequential injection analysis (SIA), lab-on-valve (LOV), and also multi-syringe, multi-commuted, and combined flow systems. The recent literature points to the efforts of analysts to develop green analytical methods by adapting classical methods to flow conditions or developing completely new methods based on flow analysis. This chapter will briefly describe flow systems and evolution of these systems with the aim of achieving the goals of green analytical chemistry. Some recent examples of reduction of the use of toxic chemicals, replacement of reagents, and reduction of waste are reviewed.

Keywords Green analytical chemistry · Flow injection analysis · Sequential injection analysis · Lab-on-valve · Lab-on-chip · Multi-commutation · Miniaturization

10.1 Introduction

Sustainable development is represented as a path to everything that is good and desirable in a community, [1] and "sustainable" becomes a term that draws attention

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J. Płotka-Wasylka and J. Namieśnik (eds.), *Green Analytical Chemistry*,
Green Chemistry and Sustainable Technology,
https://doi.org/10.1007/978-981-13-9105-7_10

to the importance of any field of human activity, to which it is added. The sustainable development concept was founded in 1987 through the report *Our Common Future* [2]; it was explained and critically considered in various scientific papers [1, 3–5]. Sustainability principles can be applied in chemistry as well, to form a framework, in which the negative impact of harmful and toxic chemicals on environment and people is solved. In the context of sustainability, chemists get the possibility to solve a large number of global problems concerning pollution, but also to contribute to the positive public opinion on chemistry and its role in modern researches.

Environment monitoring is unimaginable without the analytical chemistry. Analytical methodology must especially maintain its high quality through accuracy, precision, and sensitivity, and the method needs to be as environmentally acceptable as possible. Finally, analytical chemistry must be recognized for being a crucial discipline of chemistry, pointing at the fact that analytical chemistry is not just a simple tool for other chemists to use, but a continuously developing research area with large implications for the future well-being [6].

Green analytical chemistry, developed within the green chemistry, recognizes the significant role of flow method of analysis in the process of "greening" the analytical methods through the reduced sample and reagent consumption, through automation and minimization, analytical waste management, operator safety, and energy saving.

10.2 Flow Injection Methods of Analysis—Short Development Overview

Because of the need to increase the effectiveness, science and technology development directs its researches in the field of analytical chemistry toward the development of selective and sensitive methods that enable a large number of analyses in a short period of time, with reduced amount of reagent and sample consumption. In that way, analytical chemists had been taking care of sustainability, before it became a global trend. This kind of requests accelerated the development of automated methods that allowing the basic steps of the analysis to be taken (sampling, sample dilution, determination of analyte, measurement results processing) without an intervention of the analyst.

Many reviews on development and modern trends can be found in literature, as well as the classification of the flow methods of analysis. Development overview of the basic flow systems and some of their modern descendants is given in this chapter.

The rapid development of automated method of analysis started in the 1950s, at the time when the results of clinic tests started being used for diagnostic purposes, and the demand for laboratory tests increased. By solving this problem, developing a system for continuous flow analysis with air segmentation, segmented flow analysis (SFA) (Fig. 10.1a), the foundation for development of modern flow analysis techniques was set. In his paper from 1957 [7], Skeggs described this technique as an automated continuous colorimetric method. Samples are successively taken into the flow of

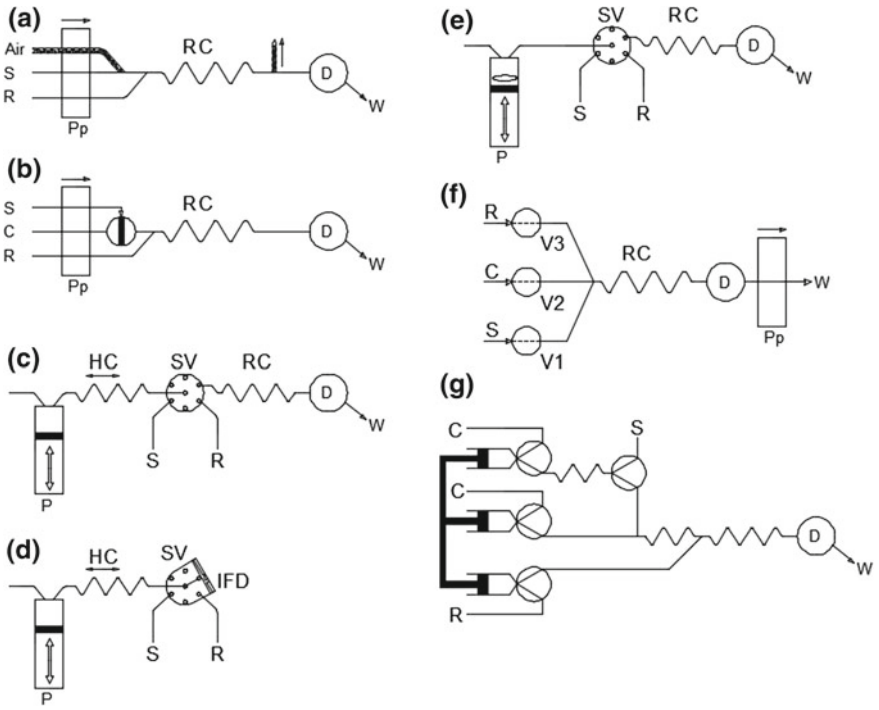

Fig. 10.1 Flow analysis technique manifolds. **a** Segmented flow analysis (SFA), **b** flow injection analysis (FIA), **c** sequential injection analysis (SIA), **d** lab-on-valve (LOV), **e** lab-in-syringe (LIS), **f** multi-commuted flow analysis (MCFA), **g** multi-syringe flow analysis (MSFA); S—sample; R—reagent; C—carrier; Pp—peristaltic pump; P—syringe pump; SV—selection valve; RC—reaction coil; HC—holding coil; IFD—integrated flow detector; Vi—solenoid valves; D—detector; W—waste

suitable solution using a pump, and they are segmented with air bubbles and directed to a small dialyzer to remove any interference. After that the dialysis samples are mixed with reagents' flow to get a colored product. Color intensity is recorded by colorimeter, equipped with a flow cell. Timely air bubbles entering into the flow is the most significant part of this procedure because it enables sample separation and prevents signal overlapping. However, it is indispensable to remove air bubbles before measuring.

In the 1970s, Ružička and Hansen [8] presented the new concept of the continued flow analysis based on injecting the sample into the carrier flow without air segmentation, flow injection analysis (FIA).

In the past period, FIA enriched significantly the development of analytical chemistry, which resulted in printing more than 18,000 papers, numerous monographs and about a hundred dissertations. The application of FIA in analytical chemistry enabled the usage of numerous new procedures for analytical signal developing, which were inapplicable in classic procedure of sample analysis. Simple apparatus, repeatable

injection of well-defined sample volume, controlled dispersion, and reproducible signals, as well as a high throughput are the basic advantages of analyte determination by using flow injection analysis.

FIA has been developing and leaning on the following three cornerstones, since the very beginning [9]:

(a) Reproducible injecting or inserting of the well-defined volume of sample solution to the continuous flow of carrier or reagent (if the carrier is not a reagent, i.e., if it does not develop any signal in reaction with analyte, reagent is added by using another line in the flow system).
(b) Reproducible and precise timing of sample zone manipulation from the injection point to the detection point with controlled sample dispersion.
(c) The analyte forms a concentration gradient provided by a transient and reproducible signal on detector.

Analytical signal obtained by using the selected detector is always the result of two kinetic processes that occur simultaneously: physical process of the sample zone dispersion and chemical process of signal developing in reaction between analytes and reagent [9].

FIA system (Fig. 10.1b) is composed of peristaltic pump, injection valve, detector, and tubing, through which sample, reagent (and carrier), flows with a selected flow rate. The pump impels one or more "flow lines" through narrow tubing toward detector. In a flow line, there can be a reagent, solvent (or some other medium, e.g., a buffer), and a sample. Small sample volumes are injected into flow by injection valve. In the flow to detector, the sample gets mixed with the reagent in a reaction loop due to the controlled dispersion and during that a product of reaction is generated and then determined on the detector. Detector response is in a form of a peak, i.e., concentration gradient.

A breakthrough made by FIA systems refers primarily to analysis speed, repeatability, and robustness. However, the continuous flow, which enabled all this, also brought a constant reagent or solvent consumption—which is undesirable for laboratories with a large number of samples and is not environmentally friendly.

Because of the accentuated need for developing environmentally friendly methods, sequential injection analysis (SIA) was developed and described in 1990 [10]. SIA system is a completely computer-controlled, multi-position selection valve, and syringe pump is used (Fig. 10.1c). Unlike the FIA system, a holding coil is added to the SIA system. Furthermore, SIA system can have only one flow line, which in some applications can be a disadvantage.

The specific quality of SIA system is improved and controlled sample and reagent dispersion, caused by flow reversal in holding coil.

SIA system operation (flow speed, injection volumes, aspiration sequence of solutions) is fully computer-controlled. Some steps of the flow method have to be planned and written into programmable procedure. By changing the basic chemical reactions, on which the method is based, or by applying the new method, the construction of the SIA system is not changed; only programmable procedure is changed. This feature

of the SIA system is a huge advantage comparing to FIA that has to be constantly redesigned for each change in the application of a new method. SIA advantages are reflected in reducing both reagent consumption and waste generation.

Ten years later (2000), a new approach in automated analysis based on flow was described. It additionally reduced reagent consumption to the micro- and sub-microliter level, l-on-valve (LOV) (Fig. 10.1d). LOV retained all SIA system advantages. The peculiarity of the new generation is the solid part integrated to the multi-selection valve that enables repeatable micro-fluidic manipulation. It is designed as a micro-canal system, connected with selection valve inputs, functioning together as a little laboratory for sample processing, that is where the name *lab-on-valve* comes from. Many different reactors and detectors can be fitted into (optic fibers as spectrophotometric detector or potentiometric sensors). Besides additional reagent consumption reduced to micro- and sub-microliter level, what has to be emphasized is compactness, robustness, and the possibility of conventional pump and valve application [11].

Special application of LOV is the SI-LOV system with bead injection (SI-BI-LOV). Suspension of beads is injected and retained in the flow cell or column. This kind of flow cell gives a range of application possibilities depending on beads' characterization: It can be used for separating, pre-concentrating, as a renewable reagent and so on. It is important to add that the solid-phase chemistry was introduced to the flow analysis with development of this kind of system, and therefore, the basic advantage is possibility of simple automated renewing of active beads' surface.

Flow-batch-analysis (FBA) system, originated from the combination of peristaltic pump and solenoid valve or from sequential injection analysis with mixing/reaction chamber, to which certain reagent and sample volumes are brought, mixed, and brought to the detector by the flow, or the detector is inserted in the chamber. This kind of system offers certain improvements in the procedure of calibration, dilution, and titration. Combination and number of solenoid valves being used and programmed depend on complexity and needs of the method [12].

Continued to FBA, a system called lab-in-syringe (LIS) (Fig. 10.1e) was developed and applied, and it is consisted of the combination of FBA and SIA. In this system, the loop is omitted, as the role of mixing liquids is taken over by syringe's void. It is ideal for downscaling and different extraction approaches' automation, e.g., liquid–liquid micro-extraction [13].

The combination of the best features of FI and SI methodologies is achieved by integrating injection port with the reagent and sample confluence point, using central input on LOV manifold. Two syringe pumps are connected with thermostated holding coils to LOV. Flow cell, situated also around LOV system, enables analytical signal recording. This kind of system, programmable Flow Injection (pFI), can function as a sequential injection or flow injection system, and two modes can be programmed: stop in holding coil (SHC) and stop in flow cell (SFC). Furthermore, this system enables stopping the flow, the possibility of reverse flow, and different flow rate. The basic advantage is simpler optimization of programmable procedure, the reduced reagent and solvent consumption, improved sensitivity because of the programmed stopping the flow [14].

One of very interesting approaches offering a new dynamics in flow methods' development is the use of commutation device, e.g., solenoid two-way or three-way valves. Commutation device can be applied in the flow system always when there is a need for redirecting sample or reagent flow, multiple injecting, stopping the flow, the use of more detectors, simultaneous determining of more analytes, adding or removing reagent column, and so on [15]. These systems introduce the multi-commutation approach, multi-commuted flow analysis (MCFA) (Fig. 10.1f). MCFA system is consisted of multi-canal peristaltic pump and a set of three-way solenoid valves. Solenoid valves can strategically be situated into this flow system, depending on method. All analytical steps are controlled by software. The concepts of flow injection analysis or sequential injection analysis can be achieved by integrating the solenoid valve in flow system [16, 17].

Furthermore, the multi-syringe flow analysis (MSFA) (Fig. 10.1g) is composed of four-injection two-way pumps, on whose heads there are solenoid valves. MSFA is based on combination of FIA, SIA, and MCFA bringing the advantages as well as improvements of these techniques to analytical chemistry: parallel operation of more flow lines, robustness, solenoid valve application, simultaneous both sample and reagent injecting that improves mixing and enhances sample throughput [18, 19].

Multi-pumping flow system uses solenoid micro-pumps that enable reproducible solution delivering in microliter volumes.

10.3 Designed to Be Green

The concepts defined by green chemistry through its twelve principles are well known today [20]. Green analytical chemistry (GAC) has adapted these twelve principles to the needs of analytical chemistry [21, 22]. There are various papers giving a critical review of significant and fast acceptance of green chemistry principles in developing new methods and technologies that can be applied to analytical laboratories.

The most important principles of GAC that are connected to the green methods, based on the application of flow methods of analysis, are prevention of waste generating, safer chemicals usage, a design for energy efficiency, real-time analysis, and safer chemistry for increased safety for the operator.

The application of these principles, in the majority of cases, improved the basic analytical performances of the method as accuracy, precision, and sensitivity.

The flow methods of analysis enable a total or partial automation of certain steps in preparing reaction solution and sample pre-processing, measuring the accurate reagent and/or analyte volumes, simple manifold, robustness, reduced exposure of the analyst to the chemicals and enhanced safety.

Minimizing and automation, following the green flow methods of analysis, mean the reduction of toxic chemicals consumption and energy efficiency through enhancing the speed of analysis. Considering the basic characteristics of flow systems, it is clear to expect some methods that replace toxic solvent with the less hazardous

ones or the application of completely benign reagents or natural reagents and very small number of direct methods and techniques that do not request any solvents and reagents.

FIA in developing the analytical methods brings in greater sample throughput, but one disadvantage as well—the continued reagent consumption even then when a sample has not been processed. There are alternatives offered for solving this problem: to deliver the reagent along the flow line or even better to inject a certain reagent amount to the sample flow, when the sample consumption is not limited.

The green application of FIA system has particularly improved with the usage of solid-phase reagent along with the all combinations it allows. A solid support inside the flow cell can enable separation or pre-concentration of analytes and reduced reagent consumption, and it can improve sensitivity and selectivity of the method. The development and application of the solid-phase extraction (SPE), solid-phase micro-extraction (SPME), and liquid–liquid micro-extraction (LLME) can be coupled with SIA or with LOV systems, as well as with the systems based on multi-commutation.

SIA is the robust descendant of the FIA system. All SIA improvements derive from the sequential injection pump and selection valve, they are reflected in reducing the reagent consumption to a microliter level or less, and the same goes for the waste reduction. They can be applied in combinations with different detectors and for the determination of analyte in different matrices.

Versatility and additional minimizing are achieved through the usage of LOV. LOV is ideal for fitting in different columns for separation and pre-concentration or columns with immobilized reagent. The most often detectors integrated into the LOV, similarly as into the SIA, are: fiber-optic, spectrophotometric, fluorometric, or electroanalytic. The application of this system in the future will be even greater along with the developing of 3D printing. Furthermore, LIS is also a successful example of extraction chamber minimizing that "moved to the empty space" of the syringe pump and enabled organic solvent saving and automation of the extraction process. The last described examples of modern flow systems development show that manifold and flow detector minimizing are equally important for GAC.

Multi-commutation principles offer a different approach in solving automation problems in analytical chemistry. Reagent consumption is comparable to the reagent consumption in SIA. SIA is more robust system, and it can be recommended in solving problems like reagent saving, but multi-commutation offers the possibility of a faster and more sensitive analysis.

Multi-syringe flow analysis (MSFA) is a technique that uses a multi-syringe burette incorporated into the flow system. Managing the liquids' flow by this system application enables applying well-known methods in an environmentally more acceptable way or it enables a development of completely new green analytical methods. The basic principle that enables this kind of approach is the possibility of reagent and solvent volume reduction in different steps of analytical procedure.

10.3.1 The Application of Reagents from Nature

Natural reagents generated from the extracts of certain plants can be an excellent replacement for chemicals with an aim of promoting the so-called lab in nature. Innocuous reagents from nature in combination with the advantages of the flow methods of analysis are the great combination that can be used for educative purposes, but also for improving the method features with an aim of their "greening." Natural extracts of plant tissues, leaf, or blossom can be used for determining, most often, metal ions in samples of different origin.

Water extracts of blossom and roots of some plants can be used as indicators in the process of determining acetic acid in wine vinegar. For determining the acidity, lab-on-chip system with the possibility of using two detectors is optimized: lab-on-chip with the web camera (LOC-CMOC) as a detector or with the fiber-optic reflective absorption probe detector (LOC-RA). For method with LOC-RA, the detection time and flow rate are controlled, and this enables the fast analysis and reduced reagent consumption. With the usage of other detector, web camera, the color change can be recorded in the real time. Analytical signal generated by this detector is the time of continued migration needed for the sample and reagent zone to achieve, by diffusion, a certain distance proportional to acid concentration [23].

Acetic acid in vinegar samples can be determined by acid–base titration using the SIA system, but this time the indicator is turmeric extract (*Curcuma domestica*) rich in curcumine, and natural reagent is the hydrated lime, the natural base. Traditionally prepared reagent from the nature is titrated by the acetic acid sample, and the color change of the indicator is followed at 455 nm. Linearly increasing the analyte concentration decreased the absorbance. Optimally chosen conditions of SIA system application enable the sample frequency 45 h^{-1} [24].

The simple FIA system with fiber-optic detector with Z-cell has been used for determination of Fe ions. The method was based on reaction between Fe ions and polyphenols from green tea extract. The optimized FIA system enables sampling rate of 180 injections h^{-1} and detection limit of 0.05 ppm of Fe(III) ion [25].

For determining Fe(III), *Phyllanthus emblica* Linn. extract has been used. The method is based, like in the previous example, on forming complexes between Fe(III) and tannin extracted from plants. Absorbance measured at the wavelength of 570 nm and linearity is achieved in the concentration range between 0.50 and 20.0 mg L^{-1}. The developed FIA method has been satisfactorily applied to the determination of iron(III) in real samples (pharmaceutical preparations, groundwater, and tap water), and the results are in good agreement with those obtained by ICP-OES [26].

The green SIA method for spectrophotometric determination of Al(III) ions is optimized. The method is based on the reaction of forming complexes between Al(III) ions and flavonoids extracted from heartwood of *Ceasalpinia sappan* Linn. This method also enables very low limits of determination 0.072 mg L^{-1} and sampling rate of 128 injections h^{-1} [27].

Anthraquinone compound extracted from the root of the plant *Morinda citrifolia* in reaction with Al(III) ions gives a reddish complex that absorbs on 449 nm. This reaction is used for the FIA method for determination of Al(III) ions in tea [28].

Astilbin, the natural reagent, is isolated from the root of *Smilax china* L. with the usage of SIA, and spectrophotometric detector can be used for simultaneous determination of Mn and Fe ions in natural water. Both ions together with reagents form complexes with different reaction rate. It is possible to determine these ions, without previous separation, by spectrophotometric kinetic monitoring of complexes at a wavelength of 440 nm. A throughput of 12 samples h^{-1} was obtained with detection limits of 0.05 mg L^{-1} Fe(III) and 0.20 mg L^{-1} Mn(II), respectively [29].

For determining the antibiotic doxycycline in pharmaceuticals, leaves' extract is used to prepare a natural reagent with Fe(III) ions. The plants chosen are rich in Fe ions, and characteristic for the climate in which the research is done. Optimal conditions of FIA system with spectrophotometric detector are determined, as well as the basic analytical features. Under the optimal conditions, it is possible to determine doxycycline in the concentration of 5–250 $\mu g\ mL^{-1}$ with a sample throughput of 36 h^{-1} [30].

As a source of Fe ions in preparing natural reagents, a soil rich in these ions can be used. Based on this fact, the reverse FIA is optimized with spectrophotometric detector for determination for antibiotics ciprofloxacin in pharmaceuticals by the usage of Fe ions, extracted from the soil. The concentration rate achieved is 0.5–50 $\mu g\ mL^{-1}$ and sample throughput of 46 samples h^{-1} [31].

Sequential injection analysis with spectrophotometric detector is used for determining benzoyl peroxide (BP) by bleaching the β-carotene extracted from the soft tissue of a pumpkin. All variables that can significantly change the analytical signal are optimized. The limit of determination of 9.4 mg L^{-1} and the analysis frequency 9 h^{-1}, both were achieved under the optimally chosen: flow, incubation time, reagent and sample volumes [32].

Polyphenol oxidase enzyme (PPO) extracted from the crude avocado extract (*Persea americana*) is used for determination of isoproterenol in pharmaceuticals. The separated enzyme is immobilized on the controlled pore silica (CPS) reactor. The enzyme reactor is fitted into the simple, sensitive, and fast FIA system with UV-Vis detector. The procedure is based on the oxidation reaction of this drug with immobilized PPO. The absorbance is measured at 492 nm, and the linearity in concentration rates from 1.23×10^{-4} to 7.38×10^{-4} mol L^{-1} is achieved. This is a very interesting example of a "green" problem solution: innocuous reagent and reduced reagent consumption. Silica is one of the best choices for support employed to immobilize enzymes, considering the enzyme instability, handling problems, and extracting the enough amounts for batch conditions.

Overviewing the application of natural reagents in analytical purposes, there is an impression of creative and interesting chemistry—and besides for developing the green methods, the application of these reagents is very important for teaching the green analytical chemistry. However, sometimes the natural materials are limited to a climate or a season. The detection limits and linear ranges are probably constrained by higher blank values originating from the reagents themselves and the limitation of the

detection systems used. The eventual instability due to the external impacts is reduced to the least possible measure because of the closed flow system. The advantages of these reagents application come from the fact that they ideally correspond to the requests for waste reducing and handling with safe chemicals. Regardless of the above-mentioned downsides, great green analytical methods can be designed with coupling flow systems and reagent from nature [34] (Table 10.1).

10.3.2 Reagentless Procedures

The reagentless method is the only one that is a better solution for developing the green method than the application of natural reagents and the reduced amounts of hazardous solvents. Forming falling drops is used in developing the reagentless method for ethanol determining in red wine. The drop formed between radiation source (LED) and phototransistor (Pht) affected the intensity of the radiation beam, thus permitting the drop growth to be monitored by the photometer. Under the optimized conditions, FIA is used for ethanol determining at a concentration rate of 1–30% (v/v) with a sampling rate of 50 determinations h^{-1} [35].

SIA system in combination with a near-infrared LED photometer is optimized for simultaneous and real-time determination of sugar, color, and dissolved CO_2 in soft drinks. The difference in refractive index and the manipulation with the schlieren effect enabled the sugar determining. The dissolved CO_2 is determined after collecting in the acceptor's current by measuring in the contactless conductivity detection [36].

Photoreactor is often successfully joined with the flow methods of analysis to enable oxidation or photodegradation of analytes. A method for indomethacin determining through the application of SIA with photoreactor is suggested. After the photochemical reaction, the analyte was fluorometrically determined at hydrodynamic conditions. The use of the photoreactor and fluorimetric detector allowed the linear concentration range to be extended and sensitivity to be increased, making it possible to apply the system not only to the indomethacin concentrations in pharmaceutical formulations but also to dissolution tests [37].

Electroanalytical techniques are by its nature, in the majority of cases, harmless for the environment, as they often enable the direct analyte determination without adding reagents or hazardous solvent consumption. Different versions of mercury working electrodes bring a shadow over green concept of electroanalytical techniques. However, instead of the mercury working electrode, a carbon or bismuth working electrode is used. The application of biosensors brings of course more points in this race in greening. With this observation, electroanalytical technique coupled with flow analysis systems gives a lot of possibilities in developing new methods.

Sequential injection monosegmented flow analysis is suggested by the application of anodic striping voltammetry with bismuth film electrode (BiFE). Under the optimal conditions, Cd and Pb were determinates in the concentration range 10–100 $\mu g\ L^{-1}$.

Table 10.1 Examples of the application of reagent from nature in flow-based procedures

Analyte	Reagent	Source	Sample	Note	References
Acetic acid	Dyes extracted from flowers and roots	Butterfly pea flower (*Clitoria ternatea*), orchid flower (*Dendrobium Sonia*), beet root (*Beta vulgaris* subsp. vulgaris)	Vinegar	Simple FIA setup, with lab-on-chip using modified web camera (LOC-CMOS) detector; and LOC with fiber-optic reflective absorption probe detector (LOC-RA)	[23]
Acetic acid	Curcumin and natural base	Turmeric (*Curcuma domestica*) and hydrated lime	Vinegar	Acid–base titration using a sequential injection (SI) system with spectrophotometric detector	[24]
Fe^{3+}, Fe^{2+}	Polyphenols	Green tea (*Camellia sinensis*)	Pharmaceutical	Flow injection analysis with FI-LED photometer	[25]
Fe^{3+}	Thanins	*Phyllanthus emblica* Linn	Pharmaceutical	FIA with spectrophotometric detector	[26]
Al^{3+}	Homoisoflavonoid: brazilin, brazilein	*Ceasalpinia sappan* Linn	Pharmaceutical, water, beverage	SIA with spectrophotometric detector	[27]
Al^{3+}	Anthraquinone	*Morinda citrifolia*	Tea	FIA with spectrophotometric detector	[28]
Fe^{3+}, Mn^{2+}	Astilbin	*Smilax china* L.	Groundwater	SIA for simultaneous spectrophotometric determination of iron and manganese	[29]
Doxycycline	Fe^{3+}	*Senna alata* (L.) Roxb, *Polygonum hydropiper* L., *Diplazium esculentum* (Retz.)	Pharmaceutical	FIA with spectrophotometric detector	[30]

(continued)

Table 10.1 (continued)

Analyte	Reagent	Source	Sample	Note	References
Ciprofloxacin	Fe^{3+}	Soil	Pharmaceutical	Reverse FIA with spectrophotometric detector	[31]
Benzoyl peroxide	β-carotene	Pumpkin (*Cucurbita moschata* Decne)	Product for acne treatment	SIA with spectrophotometric detector	[32]
Isoproterenol	Polyphenol oxidase	Avocado (*Persea americana*)	Pharmaceutical	FIA with spectrophotometric detector	[33]

The method is inexpensive, with low reagent consumption, sensitive, and reproducible, with the possibility of determination of 12 samples h^{-1} [38].

The combination of biosensors and flow systems offers selectivity, additional minimizing, reduced chemical consumption, and reduced sample amounts, and of course it improves method sensitivity. The classic biosensor is the one for glucose determination. Amperometric biosensor for glucose determination is often based on immobilized enzyme glucose oxidase. Here is the example of amperometric sensor for glucose based on chemisorptions of glucose oxidase to the hybrid biocomposite nanomaterial made of carbon and platinum. Biosensor is integrated into the flow injection system. Detection of hydrogen peroxide oxidation peak produced by the reaction between glucose oxidase and glucose can be used to indirectly determination of glucose. Under the optimal conditions, glucose can be determined in pharmaceuticals and food with a sample throughput of 200 h^{-1} and with detection limit of 15 $\mu mol\ L^{-1}$ [39].

Glucose oxidase can be chemisorpted on Au seeds decorated on magnetic core Fe_3O_4 nanoparticles and then immobilized on screen-printed carbon electrode bulk-modified with manganese oxide (SPCE). SPCE is integrated into the FIA system for determination of H_2O_2 oxidated with MnO_2 and Fe_3O_4. This amperometric sensor is mechanically robust with reproducible response to the concentration change of H_2O_2 [40].

10.3.3 Green Analytical Methods with Reduced Reagent Consumption or Reduced Waste Amount

Sequential injection analysis (SIA) in combination with LOV gives the opportunity of the reduced solvent and reagent consumption to the microliter level, the simplicity in handling, and enhanced sample throughput. The μSI-LOV method has been

developed for biparametric Cd and Pb determining with the application of spectrophotometry. It is a challenge to observe both metals in potentially polluted water with different interferences. Selective determination of both metals using the same reagent, dithizone, and at the same wavelength is possible at different pH values. Under the optimal conditions achieved, LOD for Cd and Pb were 34 $\mu g\ L^{-1}$ and 56 $\mu g\ L^{-1}$, respectively. The consumption of both, sample and reagent, for one measurement is 20 μL, and sample throughput achieved is 55 h^{-1} [41].

Similarly, the application of fully automated μSI-LOV system is optimized for biparametric Fe and Cu determination at ppb levels. This time a non-toxic reagent for Fe determination was used for biparametric determination, 3-hydroxy-4-pyridinone chelator, functionalized with a polyethylene glycol chain (MRB12) to improve water solubility. The combination of non-toxic reagent and LOV automation system resulted in a simple, fast, and green method. Additional improvement is the enhanced sensitivity, LOD for Fe is 15 $\mu g\ L^{-1}$ and for Cu it is 18 $\mu g\ L^{-1}$. Furthermore, a total waste volume for determination is 695 μL for Fe and 813 μL for Cu [42].

Less toxic or non-toxic reagent selection together with the combination of flow system gives the possibility of low consumption and generation of low amount of non-toxic waste. Methods for Fe ions determinations in water are based on formation colored complex with non-toxic bidentate and hexadentate 3-hydroxy-4-pyridinone (3,4-HPO).

The μSI-LOV method, based on reaction of complexation with bidentate ligand, enables detection limits of 7 $\mu g\ L^{-1}$ and eluent consumption of 350 μL. It is a sustainable alternative for Fe determination in natural water with the possibility of the eventual improvement of detection limits after pre-concentration [43].

The application of hexadentate ligand enables the forming of complex at stoichiometry that gives the possibility for additional reduction of reagent consumption. A column for extraction using a solid phase is additionally fitted into the SIA system to remove the matrix and achieve the speciation after the reduction Fe(II) with H_2O_2. Besides the commonly used flow cell (FC), a liquid waveguide capillary cell (LWCC) that considerably improves the sensitivity has also been used. The dynamic concentration ranges were 0.1–2 $mg\ L^{-1}$ with the FC and 0.005–0.1 $mg\ L^{-1}$ with the LWCC. This method can be considered environmentally more acceptable because of the non-toxic reagent for complexing and the reduced consumption of other chemicals that are common for this kind of methods [44].

Two new thiazolylazo dyes have been suggested recently as possible reagents for spectrophotometric determination of copper(II) in water samples in the form of a chelate complex. Based on this reaction, an optimized flow method for determining Cu(II) ions in tap water and river water has been developed by the application of SIA system. The applied reagents are poorly soluble in water, so in this kind of methods, an organic solvent, like toluene, is often used. However, by the application of surfactant, like Triton X-100, which is optically transparent, stable, and relatively non-toxic, the solubility of organic compounds in water is increased. Furthermore, considering the molar absorption coefficient, the need for pre-concentrating is avoided. The suggested procedure, unlike the common one, does not request extraction using a relatively big

volume of organic solvent. The application of SIA reduced the ligand consumption by twelve times. In addition, a single determination of copper(II) on a SIA manifold is completed in only two minutes [45].

Chromogenic reagents and organic solvents were not used in the proposed SIA method for determination of Cr(VI) in steel alloys, sewage sludge, and wastewater. The method was based on the detection of a blue unstable intermediate compound resulting from the reaction of Cr(VI) with hydrogen peroxide (H_2O_2) in acidic medium. The common reagents, chromogenic reagents and organic solvent, for determination of Cr(VI) are replaced by H_2O_2 and H_2SO_4, whose products after reaction are environmentally friendly. Absorbance is measured at 583 nm by the application of spectrophotometer equipped with the Z-type flow cell. The achieved limit of detection is 0.16 $\mu g\ mL^{-1}$ with the sample throughput 80 h^{-1} and with generating 145 μL of waste for one determination. The results are comparable to those generated by the application of AAS as well as with certified value of Cr(VI) in a standard reference material [46].

Spectrophotometric determining of Fe ions in the environment is enabled by the reversible binding of Fe ions from the sample to the reagent 1-(2-thiazolylazo)-2-naphthol, immobilized to the C18 silica support. The green, sensitive, and selective method with the detection limit of 15 $\mu g\ L^{-1}$ and the analysis frequency of 25 samples h^{-1} is developed. Eluent, buffer and steps of Fe(III) ions reduction has been performed with non-toxic chemicals, and along with the reduced reagent and sample consumption. The waste amount is reduced at 3.6 mL for one determination [47].

Interestingly, reverse FIA (rFIA) system can be used for developing of green method that will reduce the reagent consumption according to the concept and principles of GAC. The so-called reverse FIA (rFIA) is based on injection of reagent into flow of sample, and besides the reduced chemical consumption, the method sensitivity is enhanced as well. Reverse FIA system for multi-parametric determining (Mn(II), Fe(II), Cu(II), and Fe(III)) is optimized and applied on these principles, along with the application of multi-optical sensor with four diodes for radiation emission. Peristaltic pump is used for sample/reagent flow. Multi-syringe pump is used for injection control [48].

Similarly, the reverse FIA with spectrophotometer, which has the possibility of simultaneous change of wave lengths, can be applied for sequential determining of some nutrients NO_2^-, NO^{3-}, PO_4^{3-}, Fe^{2+}, Fe^{3+}, and Mn^{2+} in natural water. The procedure is software-controlled with enhanced precision, reduced reagent consumption. Also, wide linear dynamic range and a good sample throughput were accomplished [49].

The optimization of pFI method of Fe determination at ppb level in the seawater is described. SHC method enables the sampling frequency of 90 h^{-1} and LOD 3.1 ppb. SFC method enables the sampling frequency of 40 h^{-1} and LOD 0.57 ppb. This method can be considered green because of the reduced reagent consumption [50, 51].

The methods for determination of chloride can demonstrate that flow analysis technique improves and simplifies the development of green analytical procedures. The standard method for chloride determination requests the consumption of a highly

toxic reagent $Hg(SCN)_2$. But it is possible to reduce the consumption of this reagent without decreasing analytical performances of the method. FIA system with solid-phase reactor (SPR) was developed and used for determination of chloride. SPR was prepared by toxic reagent immobilization on an epoxy resin bead. This method reduced the consumption of $Hg(SCN)_2$ by 400% without decreasing the analytical features. The analytical procedure is simple and enables the routine water sample analysis with sampling frequency of 100 h^{-1} [52].

However, the possibility of green methods application is developed, e.g., based on redox reaction with $K_2S_2O_8$ and the effect of UV radiation, when chlorine is generated, which discolors the methyl orange solution. The applied flow system with photoreactor is consisted of solenoid micro-pumps and valves. Finely, obtained results demonstrated enhanced sensitivity and precision. Consumption of chemicals and also time needed for photo-conversion were reduced. Sample throughput achieved is 75 h^{-1} [53].

The flow methods of analysis based on MSFA principles will dominantly develop in direction of minimal reagent and solvent consumption in the steps of sample pre-processing. Multi-syringe system controlled by solenoid valves and fitted into the flow injection system with spectrophotometric detector is adjusted to chlorine determining by application of the common reaction system $Fe/Hg(SCN)_2$. By the optimization procedure, the reduced toxic reagent consumption is achieved and the sample throughput is 130 h^{-1} [54].

Micro-sequential injection lab-on-valve (μSI-LOV) system is developed for determining the degree of pectin esterification (DE). Under the optimally selected conditions, the system is adjusted to spectrophotometric titration of samples/standards with mix-reagent (bromothymol blue pH indicator and NaOH). This method under the flow conditions is based on the same reaction as commonly used batch titration procedure. The presented method requires remarkably low consumption of sample and reagents and is thereby environmental friendly, and enables DE determining at LOD 0.057% (w/v) and sample throughput 15 h^{-1} [55].

Online SPR with cerium(IV) trihydroxyhydroperoxide (CTH) in the flow conditions is applied for oxidation of folic acid, in order to be determined in the form of highly fluorescent product. The optimal conditions were selected to develop simple and sensitive green analytical procedure including online pre-column derivation combined with SPEn. It has been developed for the routine quality control and dosage form assay of folic acid at a very low concentration level [56].

Micro-flow injection system is designed and fabricated by etching the polymethyl methacrylate (PMMA) by using laser ablation techniques and a sealed polydimethylsiloxane (PDMS) as a top plate. A part of this μFA is homemade micro-flow cell with light-emitting diode (LED) as a light source and a USB 2000 spectrometer as detector. The determination is based on the yellow complex absorbance that is generated in reaction Fe(III) ions and norfloxacin. Under the optimal conditions, LOD at 0.12 and LOQ at 0.45 mg L^{-1} are achieved. Besides its advantage in minimizing the use of sample and chemical reagents and diminutive waste generation, reasonably economic, it can also provide a good sample frequency of 45 h^{-1} [57].

Spectrophotometric method for speciation of Fe(II)/Fe(III) and Cr(VI)/C(III) is suggested and developed. For these determination of metal ions in artesian water a common reagent, 1,10-phenanthroline was used. The determination has been performed using lab-in-syringe system. Using calibration method with adding of standard and coupling oxidation step with complex formation, Fe(II) and Fe(III) determination has been successfully achieved without separation [58].

Minimizing with an aim of chemicals saving in combination with automation aiming at repeatability, improved sensitivity, enhanced user safety, simple handling, and reduced laboratory costs are the basic interests in analytical green methods development. It is proved that all these concepts can be achieved by the combination of direct-immersion single-drop micro-extraction and automated lab-in-syringe technique together with spectrophotometric Z-form cell. The applicability of this system is shown on Pb determination in water based on a common reaction with dithizone. Solvent volume for extraction and reagent is considerably reduced in relation to the previous published dispersive liquid–liquid micro-extraction (DLLME) methods. Also the sensitivity is improved because of pre-concentration [59].

Online SIA method is developed and optimized for determination thallium in traces, using flame atomic absorbance spectrometry (FAAS) together with the previous dispersive liquid–liquid micro-extraction (SI-DLLME). The extraction step aiming at thallium pre-concentrating is based on the application of environmentally friendly ion liquid as an extraction solvent. Flow system includes selection valve and three micro-syringe pumps. This kind of procedure allows analysis with low consumption of organic solvents. The system is fully programmed and closed. The possibility of contamination is reduced and micro-analysis is enabled [60].

Modular 3D print device is designed, fabricated, and then applied. It has a disk form, and it integrates features for oxidation, solid-phase extraction, and Fe ion complexation. This 3D device is fitted into a multi-syringe flow analysis (MSFA) system and directly connected with the flow line toward the spectrophotometric detector. The 3D print device replaced typical elements of flow networks, made of tubing and discrete elements, showing improved performance. The developed 3D print device is highly robust, and suitable for application to real samples, as showed for the Fe determination on certified reference materials, and comparison with ICP-OES [61].

Multi-commuted flow system with spectrophotometric detector is designed and based on the slow reaction between iodate and p-aminophenol (PAP) in an acid medium. It takes 40 min for this reaction to reach equilibrium; however, reproducible detector response is achieved with sample frequency of 70 h^{-1}. Multi-commuted system with six six-way solenoid valves with parallel reaction coils is used for achieving stopped flow conditions and zone trapping, which has finally resulted in improved sample throughput compared to the previously described methods. Under the optimally selected conditions, the sample zone dispersion is controlled and by the application of micro-pumps, the zone mixing is improved and reagent consumption and waste generating reduced (1.05 mg PAP and 0.7 mL of waste per determination). LOD achieved is 8.2×10^{-6} mol L^{-1}. This method is applied to table salt analysis [62].

The multi-commuted system for "green" determination of chloride was developed. The possibility of improved mixing in pulsed flows and long path-length spectrophotometry are used to reduce reagent consumption and minimal waste generation. Chlorine was determined in natural water at LOD of 6.8 $\mu g\ L^{-1}$ and with sample frequency 60 determinations h^{-1} [63].

Multi-commuted flow system with the closed-loop strategy with LED photometer is optimized and applied for cadmium determination in water. A sample circulation is enabled by this system, which has additionally improved the method sensitivity along with the application of the long optical path length of the flow cell (200 mm). This method is based on dithizone application with the addition of surfactant Triton X-100. The surfactant enhances the solubility of dithizone in water, and the organic solvent application is avoided. This method's LOD is 3.0 $\mu g\ L^{-1}$, reagent consumption per determining is 4 μg, and sampling rate is 43 h^{-1} [64].

Multi-syringe flow analysis (MSFA) offers many advantages in developing green methods of analysis: simplicity, speed, improved sensitivity, and reduced costs. MSFA is a combination of some good features of FIA and SIA systems, a huge number of analyses in a short period of time, robustness, and reduced reagent consumption at the same time. When monolithic flow conductor device, called chip, was integrated in MSFA, with the complete software system control and online data processing, we get an ideal tool for kinetic-catalytic method, chip-MSFA. The automated kinetic-catalytic spectrophotometric method for cobalt determination is developed. The method is based on the catalytic effect of Co in the oxidation of hydroxybenzoic acid by H_2O_2 in basic media. All reagents and samples are simultaneously propelled into the chip to achieve an efficient mixing. The reaction product is monitored at 482 nm. Under the optimal conditions, the LOD achieved is 0.02 $\mu g\ L^{-1}$ and the injection throughput is 68 h^{-1} [65].

In a similar way, using chip-MSFIA system, Mn(II) can be determined in water samples without any special extraction and separation steps. Method is based on the catalytic effect of Mn(II) on the auto-oxidation reaction of succinimidedioxime (SIDO). Reagents and the sample were simultaneously dispensed to the chip for their complete mixing, heating, and measurement. The proposed method is highly sensitive, selective, and simple for tracing Mn(II) determination at LOD 0.33 $mg\ L^{-1}$ and with an injection throughput of 22 injections h^{-1} [66].

A portable device for the simultaneous determination of chloride, fluoride, pH, and redox potential in a chip-based multi-pumping flow system is developed using the advantages of flow techniques with potentiometric detection. The main idea of this design is to perform several analyses (four in the case here presented) simultaneously using only one chip with ion-selective electrodes (ISEs). This system was applied successfully to water samples getting a versatile system with an analysis frequency of 12 samples h^{-1} [67].

Considering the fact that in group of classic methods of analysis, titration procedures are often used, it is interesting to apply a multi-commuted system in an analysis based exactly on acid–base titration. The method of spectrophotometric titration is developed, but fully automated employing a homemade syringe pump for fluid propulsion and solenoid valves for solution handling. At the end of the flow

system, there is a homemade LED-based photometer with the appropriate electronic interfaces. Under the optimal conditions achieved, the linear dynamic range is from 0.036 to 0.176 mol L^{-1}. This method is applied to the fruit juice, vinegar, and wine samples [68] (Table 10.2).

The development and application of 3D printing device bring new possibilities in minimizing certain flow system devices that leads to better automation as well as to the integration of analysis procedures.

Erkal et al. showed integration possibilities of commercially available electrodes with 3D-printed rigid, reusable fluidic devices and applied them to neurotransmitter detection, measuring oxygen tension in a stream of red blood cells. The electrode fitting is removable and reusable. This device has a simple design and can be applied/shared in/with different laboratories [69].

Furthermore, a 3D printing technology is used for creating a LOV unit and used for lead and cadmium determining in fresh or brackish water. Lead was selectively extracted on TrisKem Pb resin and eluted with ammonium oxalate. Cadmium was pre-concentrated on Amberlite® IR 120 and selectively eluted with potassium iodide. These two metals were detected with Rhod-5N fluorescent reagent. The LOD achieved is 0.20 μg L^{-1} for cadmium and 0.17 μg L^{-1} for lead. All analysis pro-

Table 10.2 Examples of green analytical methods with reduced reagent consumption or reduced waste amount in flow-based procedures

Analyte	Sample	GAC strategy	References
Cd^{2+}, Pb^{2+}	Polluted water	Selective both metal determining using μSI-LOV, and the same reagent at the same wavelength is possible at different pH values	[41]
Fe, Cu	Natural water	The combination of non-toxic reagent and μSI-LOV spectrometry	[42–44]
Cu(II)	Tap water, river water	Reduced consumption of organic solvent by addition of relatively non-toxic surfactant, Triton X-100. SIA spectrophotometry	[45]
Fe^{2+}/Fe^{3+}	Water	Reversible binding of analyte from the sample to the reagent, immobilized to the C18 silica support	[47]
Mn^{2+}, Fe^{2+}, Fe^{3+}, Cu^{2+}	Natural water	Multi-reverse FIA with the multi-optical sensor	[48]

(continued)

Table 10.2 (continued)

Analyte	Sample	GAC strategy	References
NO_2^-, NO^{3-}, PO_4^{3-}, Fe^{2+}, Fe^{3+} Mn^{2+}	Natural water	rFIA technique with a variable wavelength spectrophotometer	[49]
Fe^{3+}	Water	The reduced reagent consumption by using pFA approach with two variants: stop in holding coil, stop in flow cell	[51]
Cl^-	Water	FIA with the a solid-phase reactor (SPR) with immobilized reagents	[52]
Cl^-	Urine and natural water	MPFA system with photo-induced oxidation of analyte	[53]
Cl^-	Mineral, tap water and well water	MSFA system for than 100-fold decrease in used $Hg(SCN)_2$ amount	[54]
Degree of pectin esterification	Pectin samples	μSI-LOV for low consumption of sample and reagents	[55]
Folic acid	Pharmaceutical	Online pre-column derivation combined with SPEn integrated in FIA with fluorescence detection	[56]
Fe^{3+}	Water	Homemade micro-flow cell integrated in μFA with light-emitting diode (LED) reduces chemical/reagent consumption with low chemical waste release	[57]
Pb	Water	Lab-in-syringe automation of direct-immersion single-drop micro-extraction for reduced chemical consumption	[59]
Th	Spiked environmental samples	Environmentally acceptable ion liquid as a extraction solvent in SI-DLLME with FAAS	[60]

(continued)

Table 10.2 (continued)

Analyte	Sample	GAC strategy	References
Fe	Water	Integrated 3D device in MSFA with spectrophotometric detector. 3D device in disk form integrates features for oxidation (speciation), solid-phase extraction, and Fe ion complexation	[61]
IO_3^-	Table salt	MCFA with six solenoid valves with parallel reaction coils is used for achieving the improved zone mixing and reagent consumption and waste generating reduced	[62]
Cd	Water	MCFA in the combination of the closed-loop facility and long optical path length of the flow cell allows improved sensitivity and low volume of waste generated	[64]
Co	Water and pharmaceuticals	Chip-MSFA with spectrophotometric detector used for determination of Co based on catalytic effect of Co in the oxidation of hydroxybenzoic acid by H_2O_2 in basic media	[65]
Cl^-, F^-, pH, and redox potential		Chip-based MPFS with ion selective electrodes for reduced sample consumption and waste generated	[67]
Acidity	Fruit juice, vinegar, and wine samples	Waste and reagents minimization with MCFA for photometric acid–base titration	[68]
Cd, Pb	Water	Waste and reagents' minimization with MSFIA-LOV for fluorescent determination	[70]

cedures are integrated in LOV unit, which opens new perspectives for the design of more complex LOV systems [70].

10.4 Concluding Notes

Flow systems became the acknowledged tool in developing green methods. Market needs and technology developments have defined the development of flow method of analysis in the past and will certainly be in the future. The trend of minimal chemical consumption will lead to miniaturization of fully programmed devices incorporated in the flow system. Search for the benign and less harmful chemicals will mark the development of green analytical chemistry and will be applied in flow analysis method.

Laboratories in nature, on-valve, in-syringe, or on-chip will be more applied in future. The bead injection approach in combination with LOV will be more applied with an aim of sample pre-processing or reagent immobilizing.

In a laboratory and on a field, the development of robust and portable flow systems with various adapted detectors will be significant for environment monitoring. The new generation of portable devices will be based on lab-on-chip flow systems. The need for fast and automated techniques coupled with separation techniques and pre-processing techniques for samples of different origins is already noticeable. Also, multi-commuted systems could more often be combined with integrated micro-devices. The application of lithography carving techniques and 3D printers is expected in these devices developing [71].

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Chapter 11
Remote Monitoring of Environmental Pollutants

Jacek Gębicki and Bartosz Szulczyński

Abstract Atmospheric air quality is one of the key factors influencing human health. Air quality evaluation is not an easy task as the atmosphere is a complex system subjected to continuous changes in time. Observed progress in the development of measurement devices and technologies is fundamental for acquisition of more reliable information about condition and quality of atmospheric air. Unfortunately, this process leads to an increase in the monitoring and air quality evaluation cost, which limits their widespread application. Accordingly, there is a search for new, cheap, alternative methods of information acquisition about air quality in the field of both new chemical sensors and sensor matrices. The technologies are developed, which allow monitoring of hardly accessible and dangerous for human placed where air pollution occurred. Moreover, the paper presents and discusses current measurement tools utilized for atmospheric air quality evaluation. The development trends connected with atmospheric air monitoring were also presented.

Keywords Air monitoring · LIDAR · Drones · Analyser · Chemical sensors · Electronic nose

11.1 Introduction

In many countries, economic and industrial development significantly contributed to increased emission of atmospheric air pollutants. Industrial and municipal plants, such as landfills, wastewater treatment plants and other fields of human activity, including transportation or energy generation, produce a substantial amount of hazardous substances with varying physical and chemical properties. Harmful impact of these compounds on natural environment can result from both properties of particular chemical compounds and mutual amplification of negative properties of different

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J. Płotka-Wasylka and J. Namieśnik (eds.), *Green Analytical Chemistry*,
Green Chemistry and Sustainable Technology,
https://doi.org/10.1007/978-981-13-9105-7_11

chemical compounds interacting with each other [1, 2]. Protection of ambient air from pollutants encounters serious problems. First of all, high dynamics of the atmosphere, which is the main route of pollutants, transfer and exchange between the remaining elements of the environment. Secondly, large exposure of humans, fauna and flora, as they cannot be isolated from pollution, it is possible in case of water or soil contamination. Among thousands of air pollutants, some substances are emitted by anthropogenic sources and these are treated as characteristic pollutants [3, 4]. This group engulfs:

- Gaseous pollutants, including gases and vapours of the chemical compounds such as volatile organic compounds, carbon oxides (CO and CO_2), sulphur oxides (SO_2 and SO_3), nitrogen oxides (NO_x), ammonia, fluorine, aromatic and aliphatic hydrocarbons, their chlorine derivatives, phenols and so-called oxidants which are secondary pollutants created via photochemical, radical and catalytic reactions of the substances polluting the air (ozone, NO_2, formaldehyde, acrolein and organic hyper oxides),
- Solids, including inorganic and organic particles (suspended dust) with different sizes of grains and different chemical compositions, for example fly ash, carbon black, dust generated during cement production, metallurgical dust, compounds of lead, copper, chromium, cadmium, nickel or other heavy metals,
- Liquids in the form of droplets, for instance acids, bases and solvents,
- Biological pollutants, namely micro-organisms—viruses, bacteria and fungi, the type and number of which depart from natural composition of air microflora.

The sources could be divided with respect to way of pollutants spreading:

- Point, for example stacks,
- Linear (transportation routes and sewage channels),
- Surface (open reservoirs and landfills).

Each emitter (emission source) is characterized by technical parameters deciding about pollutants spreading—the most important of them are:

- Emission magnitude (amount of substance emitted in a unit of time),
- Type of emitted pollutants.

Figure 11.1 schematically presents spreading of primary and secondary pollutants in atmospheric air.

Apart from the technical parameters of the emitters, spreading of pollutants is influenced by meteorological conditions: air temperature, wind direction and velocity as well as atmospheric precipitation [5–7]. The pollutants introduced to the atmosphere, which remain there in unchanged form, are named primary pollutants. Chemical reactions and physical processes, which occur between the pollutants and atmosphere constituents, lead to the formation of the secondary pollutants.

Evaluation and control of ambient air quality are not an easy task. Air is very complex system, subjected to continuous changes. A progress in measurement methods is fundamental for acquisition of more reliable and useful information about air condition and quality. Obviously, this progress leads to an increase in cost of air quality

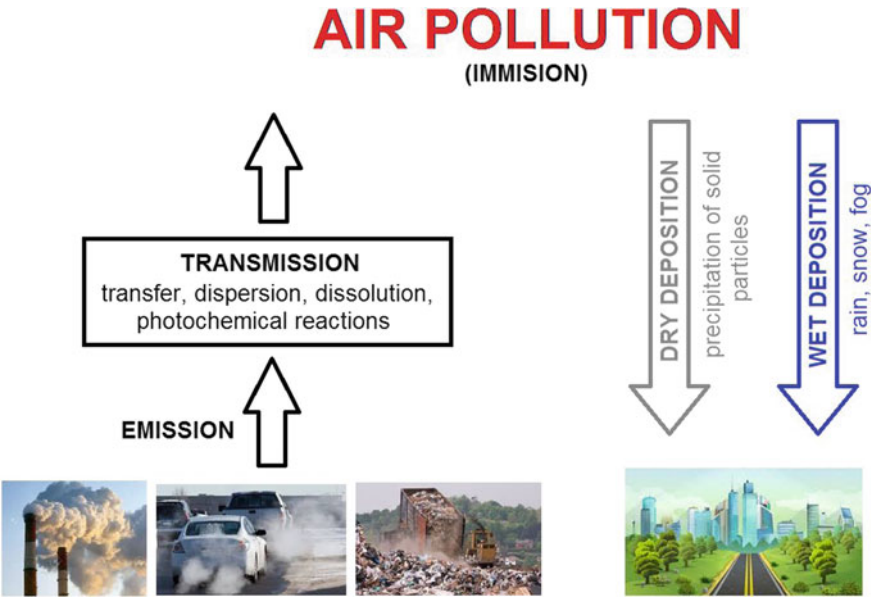

Fig. 11.1 Scheme of pollutants spreading in air

evaluation and monitoring, which significantly limits their widespread application. Environmental monitoring is a series of actions aimed at environmental protection starting from hazard identification, through measurements of pollution level, finishing with evaluation of effects and preventive measures [8–10]. Execution of the measurements in defined time intervals allows tracing the changes and their tendencies as well as predicts their effects. In such environments as soil or water, where spreading rate of contaminants is relatively low, environmental monitoring is carried out "in situ" or the measurements are performed in laboratory. Such a system is insufficient in case of atmospheric monitoring, even when the measurement can be done at the sampling site. Air is the main and very fast medium of pollutant transfer, and lack of possibility of isolation from atmospheric pollutants exposes the entire biosphere to the hazard. When hazardous chemical or biological factor is released to atmosphere, a few kilometre ranges of detection system provide a few minute time margins to launch alarm and protection. That is why remote monitoring systems are employed for ambient air. These systems are equipped with different sensitive apparatuses capable of hazard detection from a distance of a few kilometres, detection and concentration measurement and fast data transfer [11, 12].

11.2 Systems of Remote Atmospheric Air Monitoring

There are two main systems of remote atmospheric air monitoring:

- Remote monitoring (LIDAR and drones).
- Detection and the hazard site and data transfer (analysers, sensors, sensor matrices).

11.2.1 LIDAR

Remote detection of pollutants is accomplished with optical instruments, such as the light detection and ranging (LIDAR). LIDARs can measure atmosphere components such as: dust, fog, clouds of sulphuric acid droplets formed from SO_2, sulphur, nitrogen, carbon oxides, oxygen and ozone. Remote detection does not require entering polluted region if it is hardly accessible. The simple version of the air quality measurement LIDAR is the scattering LIDAR (schematically presented in Fig. 11.2a). A source of electromagnetic radiation is a pulse laser sending short and strong impulses of such wavelength, which is not absorbed by natural gas components of the atmosphere [13, 14]. An optical system directs a radiation beam from the laser towards desired target. The radiation encounters different obstacles, dust and aerosol and undergoes scattering in all direction, also backwards; hence, a fraction of it returns to the sources. Returning fraction of the scattered radiation, named echo, is collected by a telescope and is directed to a detector, which measures its intensity. A detector of light intensity is a photomultiplier or a photodiode. An electronic system of the LIDAR synchronizes the measurements and is controlled by a computer. Location of the laser beam scattering source is identified by measurement of time between triggering of the impulse and return of scattered light. Intensity of the returning beam depends on a concentration of the factor causing scattering.

LIDARs are also used for selective detection of gas pollutants in atmospheric air [15, 16]. This approach utilizes a phenomenon of absorption of radiation having particular wavelength by pollutants. These are differential absorption LIDARs (DIAL). A scheme of DIAL operation is shown in Fig. 11.2b. There are two laser beams, the first with the wavelength absorbed by the measured gas (λ_1) and the second with slightly different wavelengths, but not absorbed or hardly absorbed by the measured gas (λ_2), which serves as the reference beam. If there is no absorbing substance of the beams' path, intensity of scattered radiation will change in time in an identical way. The presence of the absorbing substance in scattering cloud will result in lower intensity of the absorbed beam. Typical range of the DIAL is 10 km. Measurement of NO_2 and O_3 content in upper layers of the atmosphere employs the LIDARs, which take advantage of fluorescence phenomenon. Laser of the fluorescence LIDAR emits the impulses of electromagnetic radiation of the wavelength absorbed by the measured substance (usually from the UV range), which stimulates its fluorescence. The radiation emitted by the substance is focused by a telescope and directed to a detector.

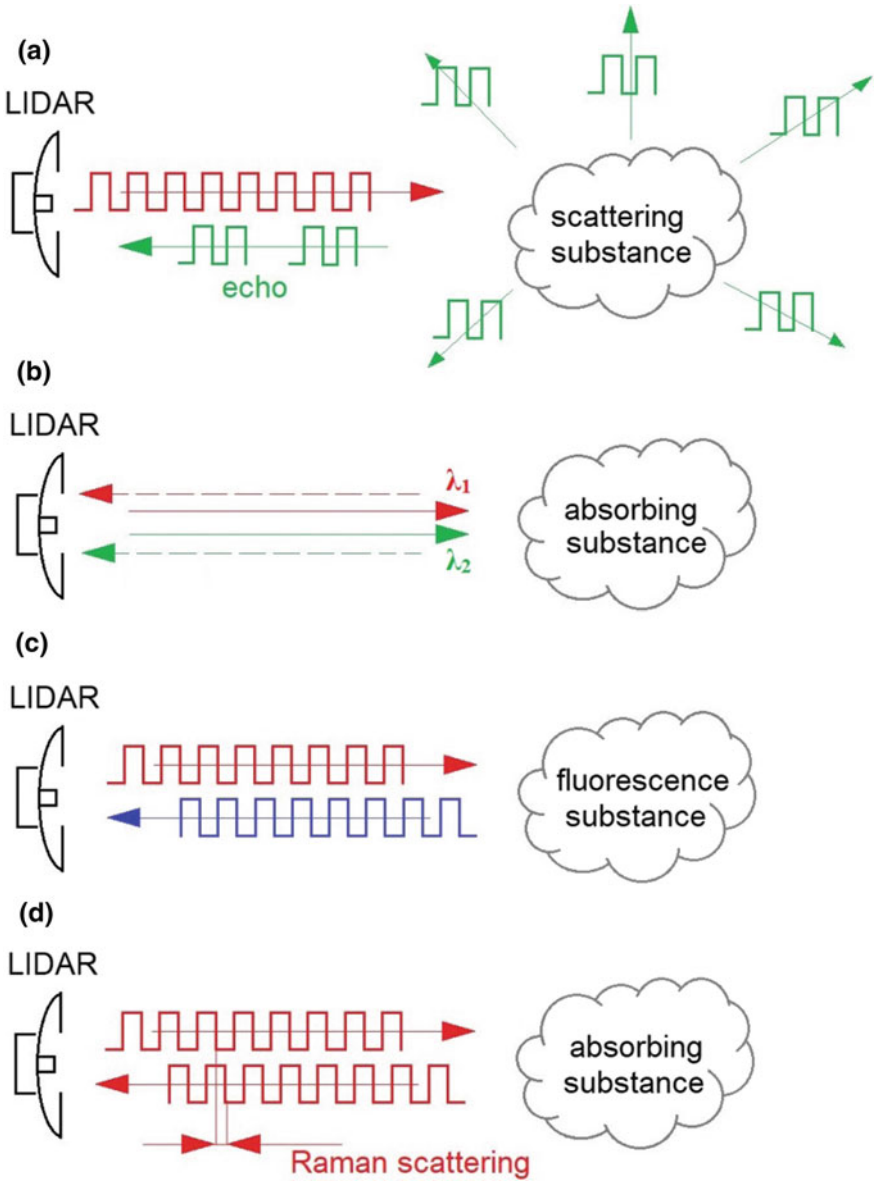

Fig. 11.2 Scheme of LIDAR operation, **a**-scattering, **b**-absorbing, **c**-fluorescence, **d**-Raman scattering

Fluorescence spectra or wavelength, at which the maximum occurs, is characteristic for particular substances and is the basis of their identification. A scheme of fluorescence LIDAR operation is shown in Fig. 11.2c. Raman LIDARs are used for selective detection of gases. Scattering of the radiation on gas particles is accompanied by a wavelength shift (Raman phenomenon), which is characteristic for a given substance. Laser sends the impulses of defined wavelength, and detector collects the radiation only of the wavelength shifted with respect to the wavelength of laser impulses. The Raman LIDARs are not sensitive, and they are utilized to the identification of the gases, which are present in atmosphere in high concentration, such as H_2O, CO_2, O_2 and N_2. The monitoring range of the Raman LIDAR amounts to hundreds of metres. A scheme of Raman LIDAR operation is shown in Fig. 11.2d.

11.2.2 Drones

Drones—unmanned aerial vehicles (UAVs)—thanks to measurement devices, cameras and air sampling containers on board, can provide precise information about pollutant distribution in atmosphere, which allows detailed analysis of air composition in particular layers of the atmosphere [17, 18]. Drones can be useful as far as photographic documentation is concerned, which is indispensable for evaluation of potential localization of emission sources, monitoring of large areas and investigation of integrity of gas transmission pipeline as similar facilities. Air sampling can be accomplished over municipal or industrial regions. Different emission sources can be monitored, from stacks to municipal landfills. Drones can provide monitoring hardly accessible and dangerous for human locations, where air pollution occurred. They can be equipped with passive tele-detection sensors—cameras operating in infrared, optical sensors and active tele-detection devices—LIDAR lasers. Drones can be used for measurement of pollutants such as: ozone, carbon monoxide, nitrogen dioxide, sulphur dioxide, hydrogen sulphide and methane [19, 20]. Drones equipped with dedicated device and container make it possible to collect samples for evaluation of dust pollution originating from individual heating systems and transportation sources. Application of laser counters enables continuous monitoring of suspended dust, including PM1, PM2.5 and PM10. Small size, low mass, low power demand and low cost of drones make them well suited for these tasks [21]. Propellers (hexacopters and octocopters), schematically illustrated in Fig. 11.3, occurred to be the most practical for into-air emission as they offer an opportunity to perform measurements close to the emitter, in so-called suspension.

In case of these drones, the bigger number of propellers means higher weight of the carried loads, better stability of flight and easier manoeuvring. Drones differ in size, aerodynamic lift, offering different capabilities and modes of operation. These factors influence carried load, speed, altitude and range. Mass of the equipment influences on increased energy consumption could result in range reduction and limitation of the collected air samples. Vision cameras mounted on drones provide imaging of air quality via creation of 3D model and its verification as well as real-time

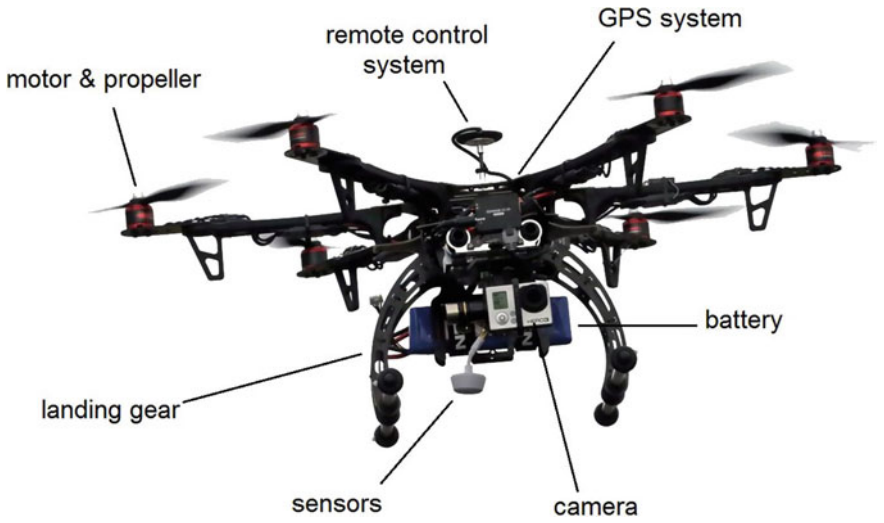

Fig. 11.3 Schematic structure of a drone with measurement instruments

analysis. Additionally, recording of air temperature and humidity allows calculation of dispersion also in blaze or cloud. Data from on-board measurement and recording devices are transmitted to the tablet where they are stored and the operator has online insight into measured and recorded values. Another method of data transfer from the measurement devices in drones is transmission to mobile telephones with Android operational system, where these data are immediately displayed. During its flight, drone records its GPS position, altitude, temperature, humidity and all monitored pollutants in defined time intervals. Moreover, drones can be equipped with GPRS and Wi-Fi communication function. GPRS is utilized for data transmission to the drone information management system (DRIMS). Secure online system allows remote monitoring or even control over airborne laboratory and storage as well as processing of collected data. Drone also connects with the ground station using Wi-Fi protocol. Both ground stations and cloud servers implement DRIMS software, and they can record data from many operating drones simultaneously. The benefits stemming from the air quality investigation using drones include relatively low cost of purchase and exploitation of the measurement equipment, flexibility in sensor selection, equipment specification and possibility of drone model adjustment. Drones shorten the time necessary for collection of the desired information, increase safety of the personnel performing the measurements, provide repeatability of measurements via numerous flights over the same region and offer the possibility to perform measurements in radiologically, biologically, chemically hazardous environments or where volcanic gases are present [22]. Disadvantages of application of drones to air quality evaluation engulf: limited time of flight duration, relatively low load-carrying capacity, limited availability of dedicated sensors and on-board measurement equipment. Moreover, there is a lack of universal, complete legal regulations concern-

Table 11.1 Exemplary commercially available drones for control and monitoring of atmospheric air quality

Company	Model/platform	Detected pollutions	Additional features
SciflyTech	AirSense 100	CO, SO_2, VOCs, NO_2, O_3 and NO_2, PM10, PM2.5	– Automated flight planning – Real-time pollution mapping
Scentroid	DR300	CO_2, CO, Cl_2, H_2, HCl, HCN, PH_3, H_2S, organic solvents, CH_4, NO, NO_2, O_2, VOCs, SO_2, NH_3, O_3, formaldehyde, PM10, PM2.5	– Sampling system – Radiation monitoring
United Systems	SOWA	PM2.5, PM10, VOCs, formaldehyde, HCl, HCN	– Temperature, humidity, pressure measurement – LTE or Wi-Fi communication – HD camera
HiveUAV	Hive	LIDAR, air quality sensors	– Thermal imaging – HD camera – Honeycomb software
Aretas Aerial	Octocopter V1000	PM2.5, PM10, VOCs, formaldehyde, O_3	– Radiation monitoring – Temperature, humidity, pressure measurement – Noise monitoring – LIDAR

ing utilization of drones in environmental protection. Accordingly, it is necessary to create integrated, coherent system of information exchange. Table 11.1 presents exemplary commercially available drones together with the information about their measurement and detection parameters.

11.2.3 Analysers

In the monitoring system of remote type, detection of hazard on site and remote data transfer, point analysers are applied. These are devices, which provide sample collection, detection of pollutants, basic processing and data transfer. Moreover, the analysers must fulfil additional requirements connected with long-term operation without supervision from the personnel. Such situation implies the following:

- Applied sensors or detectors must be characterized by high stability of indications, or there must be periodical automatic recalibration during their operation cycle.
- Particular elements of the analysers must reveal high level of reliability.

Table 11.2 Reference methodologies for measurement of basic atmospheric air pollutants together with admissible level of each substance in atmosphere averaged over time unit

Analyte	Reference	Admissible level averaged over time unit
Nitrogen dioxide Nitrogen oxides	EN 14211 standard chemiluminescence method of nitrogen monoxide and dioxide concentration measurement	200 $\mu g/m^3$—1 h
Sulphur dioxide	EN 14212 standard fluorescence UV method of sulphur dioxide concentration measurement	350 $\mu g/m^3$—1 h
Ozone	EN 14625 standard method for ozone concentration measurement using UV photometry	120 $\mu g/m^3$—8 h
Carbon monoxide	EN 14626 standard method for carbon monoxide concentration measurement using non-dispersive infrared spectroscopy	10 mg/m^3—8 h
PM10	EN 12341 standard gravimetric method for measurement of mass concentration of the fractions PM10 or PM2.5 suspended dust	50 $\mu g/m^3$—24 h
PM2.5		25 $\mu g/m^3$—year

- The analysers operating in a continuous mode provide vast amount of information, which must be evaluated; hence, the analysers must contain a device for data transfer to a monitoring centre, for conversion of the sensor/detector signal to the final result form and for potential preliminary reduction of the information.

In case of fundamental atmospheric pollutants, such as nitrogen oxides, sulphur dioxide, carbon monoxide, ozone or suspended dust PM2.5 and PM10, legal regulations enforce suitable reference methodology. Table 11.2 presents basic information about the reference methodologies for continuous monitoring of atmospheric air pollution together with admissible values of mean concentration related to time unit.

11.2.3.1 Measurement Method for NO and NO_2

A method of nitrogen monoxide (NO) concentration measurement is based on a chemiluminescence phenomenon, which is energy emission in the form of light due to chemical reaction. Nitrogen monoxide reacting in a gas phase with ozone produces excited non-stable molecule of nitrogen dioxide (NO_2), which returns to

its ground state emitting the radiation of the wavelength from 600 nm to 3000 nm, with the maximum at 1200 nm. Radiation intensity is proportional to concentration of nitrogen monoxide [23]. The reactions occur according to Eqs. (1) and (2):

$$NO + O_3 \rightarrow NO_2^* + O_2 \tag{1}$$

$$NO_2^* \rightarrow NO_2 + h\upsilon \tag{2}$$

In the chemiluminescence method, determination of nitrogen dioxide concentration is possible only after its conversion to nitrogen monoxide and NO concentration measurement as presented above. In this case, magnitude of radiation emission is proportional to the sum of NO concentration formed from NO_2 and NO contained in the analysed air sample. Concentration of nitrogen dioxide is calculated based on a difference between emission magnitude for sample, which crossed the converter, and the magnitude of emission for the sample, which was not subjected to conversion. Measurements of both emissions can be performed simultaneously or alternately. Accordingly, one can distinguish at least three fundamental designs of the analysers:

1. Analysers with two reaction chambers and two radiation emission detectors. Measurement of emission magnitude for the sample without NO_2 conversion and for the sample after NO_2 conversion occurs in the same time.
2. Analysers with two reaction chambers and one radiation emission detector. In the same time, both chambers are supplied with air samples without NO_2 conversion and after NO_2 conversion. Measurement of radiation emission occurs alternately thanks to application of special, often rotating, diaphragm.
3. Analysers with one reaction chamber and one radiation detector. The reaction chamber is alternately supplied (using electro-valve) with air sample without NO_2 conversion and next the sample after NO_2 conversion. Radiation emission measurement occurs in accordance with sample supply cycle.

Figure 11.4 presents a scheme of NO and NO_2 analyser comprised of two reaction chambers and two detectors.

11.2.3.2 Measurement Method for SO_2

A method for sulphur dioxide concentration measurement is based on fluorescence in UV phenomenon [24]. Molecules of sulphur dioxide, subjected to ultraviolet radiation of the wavelength 200–220 nm, are excited to energetically non-stable forms, which return to the ground state, emitting the energy in the form of light of the wavelength 240–420 nm, which can be illustrated with the following reactions (3) and (4):

$$SO_2 + h\upsilon \rightarrow SO_2^* \tag{3}$$

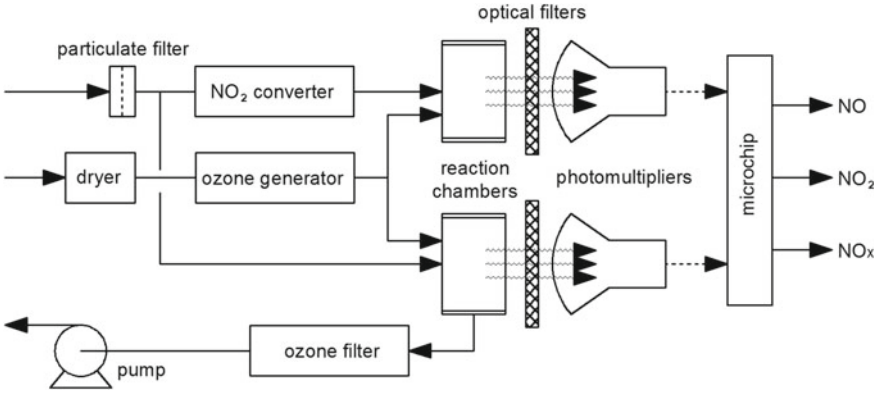

Fig. 11.4 A scheme of NO and NO_2 analyser with two reaction chambers and two radiation emission detectors

$$SO_2^* \rightarrow SO_2 + h\upsilon \tag{4}$$

Intensity of fluorescent radiation $h\upsilon$ is proportional to sulphur dioxide concentration, which is described by Eq. (5):

$$I = k \cdot C \tag{5}$$

where: I is intensity of fluorescent radiation, k is coefficient of proportionality and C is concentration of sulphur dioxide.

After passing through the band-pass filter, emitted radiation is converted into electrical signal using a detector (e.g. photomultiplier), which is schematically presented in Fig. 11.5.

11.2.3.3 Measurement Method for O_3

Measurement of ozone concentration is based on photometry in UV method [25]. Molecules of ozone absorb UV radiation at the wavelength of ca. 250 nm, and the magnitude of that absorption is proportional to concentration. This dependency can be described with Eq. (6):

$$\frac{I}{I_0} = e^{-klc} \tag{6}$$

where: I is intensity of UV radiation after passing through investigated sample, I_0 is intensity of UV radiation after passing through the sample without ozone, k is absorption coefficient, l is optical path length and c is ozone concentration.

Figure 11.6 presents a scheme and principle of operation of ozone analyser.

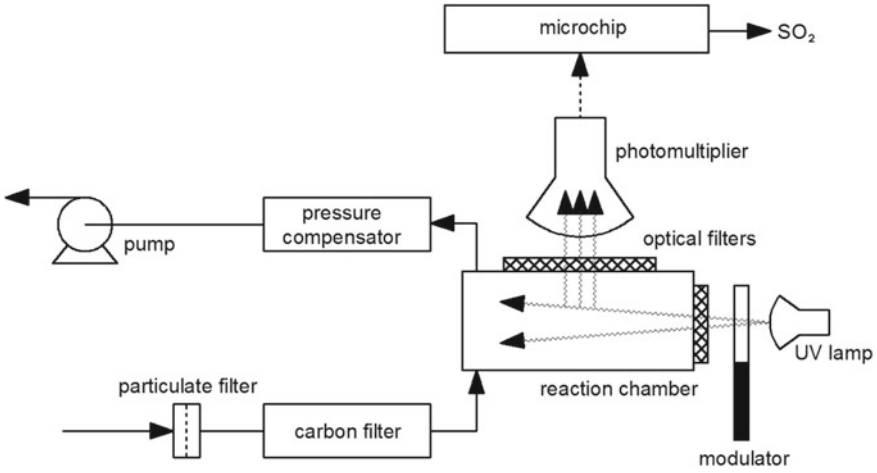

Fig. 11.5 A scheme of SO_2 analyser

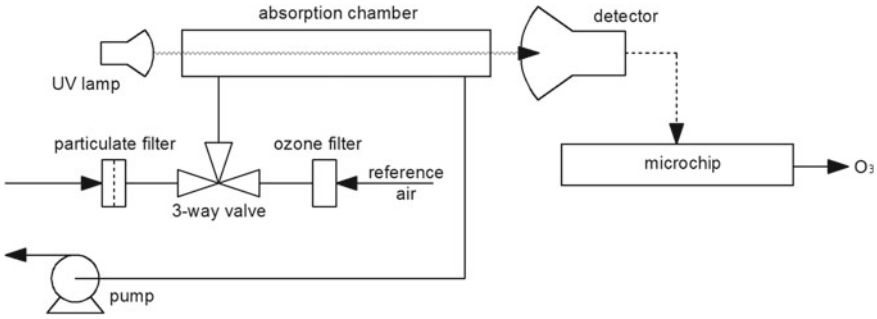

Fig. 11.6 Scheme of ozone analyser

11.2.3.4 Measurement Method for CO

Measurement of carbon monoxide concentration is performer using selective infrared spectroscopy [26]. Attenuation of infrared radiation (IR) in a measurement chamber is a measure of carbon monoxide concentration according to the Lambert–Beer law. There are two technical solutions of the analysers, which limit the problems with drift, sensitivity and stability caused by infrared radiation absorption also by other molecules comprised of two different atoms (especially: carbon dioxide, water vapour, nitrogen oxides as well as hydrocarbons). The main solutions include:

- Measurement of infrared radiation absorption for the wavelength characteristic for carbon monoxide—ca. 5 μm,
- Two-chamber analysers employing a chamber filled with pure air (drift compensation),
- Analysers with rotary wheel (GFC system).

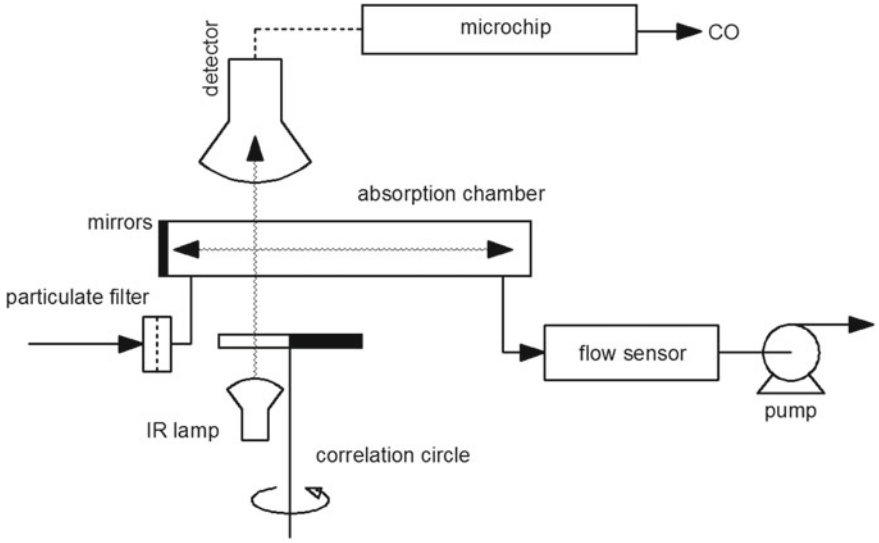

Fig. 11.7 Scheme of CO analyser with the rotary correction wheel

The analysers with rotary wheel, often termed correction wheel, is the solution most frequently applied in the analysers for continuous measurement of carbon monoxide concentration in atmospheric air. A correlation wheel contains a filter filled with nitrogen (not absorbing IR radiation) and a filter filled with carbon monoxide. The wheel is placed between the infrared radiation source and the absorption chamber where its absorption by carbon monoxide molecules occurs. IR radiation reaches the absorption chamber alternately through the filter with nitrogen and through the filter with carbon monoxide. The IR radiation passing through the carbon monoxide filter reaches the absorption chamber lacking in the CO characteristic wavelength; hence in the absorption chamber, only the radiation characteristic for other molecules naturally present in examined air samples is absorbed. Passing through the nitrogen filter, the entire radiation reaches the absorption chamber where attenuation originates from carbon monoxide as well as from other molecules naturally present in the air sample. CO concentration in the sample is calculated based on a difference between both signals. Figure 11.7 depicts a scheme and principle of operation of carbon monoxide analyser with the rotary correction wheel.

11.2.3.5 Measurement Method for PM10 and PM2.5

A reference method for measurement of suspended dust PM10 and PM2.5 concentration is the gravimetric method [27]. The measurement is performed with the samplers, into which the air is sucked for 24 h with constant flow rate. Dust fraction is deposited on a filter. Knowledge of the mass of deposited PM10/PM2.5 dust on

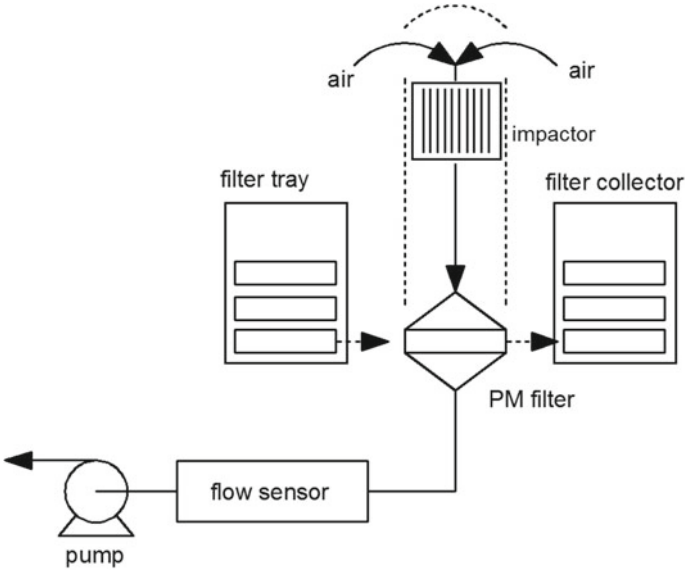

Fig. 11.8 Scheme of sequential sampling of suspended dust PM10/PM2.5

the filter and volume of sucked polluted air allows determination of PM10/PM2.5 dust concentration. One of the most important elements of the sequential sampler of PM10 or PM2.5 dust is a separation head, which makes it possible to separate fractions of the suspended dust and to sample the particles of suitable aerodynamic diameter. Figure 11.8 presents a scheme of sequential system for suspended dust PM10/PM2.5 collection.

In case of measurements of suspended dust PM10/PM2.5, the information about concentration level is known after a few days. It is caused by the fact that after 24 h the filters are transferred to the laboratory fulfilling required temperature and relative humidity conditions. There the filters are subjected to conditioning process, and then they are weighed several times until desired measurement uncertainty is achieved. Such situation causes that the information about suspended dust concentration is not available in real time but with certain time delay. There is a need for dust analysers working in online mode. In order to implement a device for automatic measurement of suspended dust for air quality evaluation, the measurement method utilized in it must be accepted as equivalent to the reference method. In this case, it must be revealed that the device fulfils the equivalence requirement and the results of measurements must be presented to the European Commission and accepted by it. Currently, three methods of suspended dust PM10/PM2.5 measurement are employed:

- Quartz microbalance method,
- β radiation attenuation method,
- Optical method (light scattering).

Measurement of Suspended Dust Using Quartz Microbalance

The measurement is performed in a continuous way using an oscillatory microbalance. Dynamics measurement systems continuously collect measured air and direct it alternately directly on a measurement filter or via cleaning filter, which effectively removes aerosols from the sample at suitable temperature. The measurement filter is alternately supplied with an air sample with dust and the air cleaned on the filter. When the air with dust is passed through the filter, the device measures mass increment of sum of volatile and non-volatile components. When the clean air is passed through the filter, the device determines mass of volatile components contained in collected dust. The filter vibrates with characteristic frequency, which changes upon dust deposition. Dust deposited on the filter increases mass of the vibrating system, thus decreasing frequency of vibrations. Concentration of suspended dust in air is determined using calibration frequency, dust mass and sample volume.

Measurement of Suspended Dust Using β Radiation Attenuation Method

A principle of operation of the analyser relies on attenuation of β radiation passing through the filter with deposited PM10 dust. In this device, β radiation is a stream of electrons with the energy from 0.01 to 0.1 MeV. They are emitted by radioactive source of low activity. The most frequently utilized are isotopes of krypton ^{85}Kr or carbon ^{14}C. Dust concentration measurement utilizes differential approach. A measurement cycle starts from determination of the reference value, which means β radiation absorption by pure filter. Air sampling time amounts from 30 min to 24 h (depending on the method of concentration determination); after that time, irradiation is repeated. Intensity of passing radiation is most frequently measured with Geiger–Muller metre. Dust deposited on the filter causes attenuation of electron stream. Difference in radiation before and after air sampling is proportional to amount of retained dust and thus to its concentration in air.

Measurement of Suspended Dust Using Light Scattering

A principle of analyser operation is relatively simple. A steam of air containing dispersed particles flows through the area illuminated with laser beam. The particles scatter the laser beam, which is then collected by an optical system and focused on a detector, most frequently photodiode. Each passing particle corresponds to one impulse of scattered light and thus to one current impulse of the detector. Suitable positioning of the optical system provides measurement of the particles characterized with given aerodynamic diameter. Concentration of suspended dust is calculated via conversion of the number of particles determined in unit of time to mass in a unit of volume.

Nowadays, also miniaturized particle counters (optical sensors) are employed as the measurement tools for determination of suspended dust PM10/PM2.5 concen-

tration. Unfortunately, a drawback of these sensors is insufficient quality of obtained results. Commercially available PM10/PM2.5 sensors exhibit different metrological characteristics, dimension and price. It results in the fact that potential customers do pay attention to quality and reliability of the results. A fundamental mistake is a priori assumption that the data provided by the sensor manufacturer ensure high quality of obtained results. It is often not true, and in order to accept particular sensor as the one characterized by high enough quality of results with defined measurement uncertainty with respect to the reference method, it is necessary to execute "side-by-side" field tests with the reference method or the analysers fulfilling the equivalence requirements. Based on these tests and using suitable statistical tools proposed, for instance in EU guidelines, it is possible to state if a given sensor follows the requirements for results of defined quality and measurement uncertainty. Commercially available sensors often do not possess such documentation confirming executed test and reliable determination of measurement uncertainty with respect to the reference method.

11.2.4 Chemical Sensors

A fundamental part of every analyser is a chemical sensor defined as "a device converting chemical information into analytically useful signal". The analytically useful signal can take different forms of energy: mechanical, electrical, magnetic or chemical as well as the form of heat and radiation. Nevertheless, the most frequently utilized signal is electrical one. The sensors are characterized by many advantages such as low production costs, simple design and possibility of miniaturization as well as relatively good metrological parameters including [28]:

– High accuracy and precision,
– High sensitivity,
– Low limit of detection and quantification,
– High selectivity,
– Wide measurement range,
– Short response time.

Combination of the sensors with different methods of data analysis, based on pattern identification, gives a possibility of elaboration of modern measurement systems.

Two basic parts can be distinguished in the structure of chemical sensors:

- Receptor part characterized by relatively high selectivity with respect to particular analyte,
- Transducer part generating analytically useful signal.

The sensors can react to the formation of chemical substance, changes of light reflection coefficient, change of mass, alteration of magnetic or electric field, change of colour, etc. Due to mechanism of detection reaction of the sensor, they can be

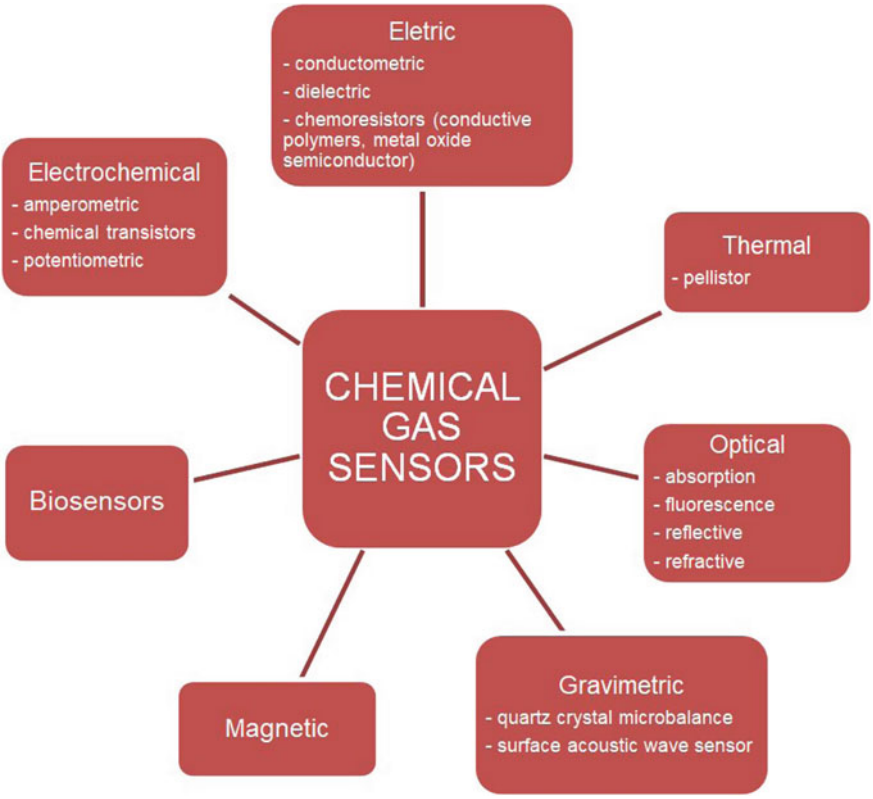

Fig. 11.9 Classification of chemical sensors for measurement of gaseous compounds

divided into the following groups. Figure 11.9 schematically presents the information about basic groups of chemical sensors including the types of sensors within particular group [29].

Widespread application of the chemical sensors to air quality monitoring is limited by still insufficient limit of detection parameter. Concentration level of many pollutants present in atmospheric air is below 1 ppm. Such situation results in the fact that there are not many sensors, which can fulfil these requirements. In case of commercially available chemical sensors, potential customers mainly focus on high selectivity and low limit of detection [30]. Figure 11.10 schematically illustrates different types of commercial chemical sensors ranked according to their limit of detection. The information presented in this figure reveals that only electrochemical, photoionization and metal–oxide–semiconductor sensors exhibit LOD parameter below 1 ppm.

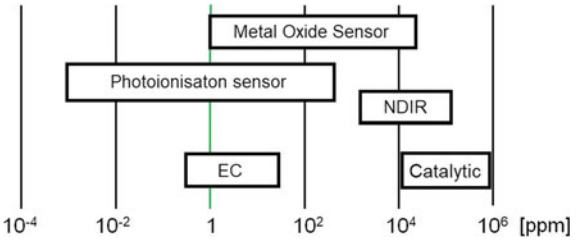

Fig. 11.10 Characteristics of commercial chemical sensors with respect to their limit of detection

11.2.4.1 Electrochemical Sensors

Principle of operation of these sensors consists in a diffusion phenomenon of analyte molecules through a membrane and internal electrolyte towards working electrode surface, which is suitably polarized with respect to the reference electrode. On the working electrode, electrochemical oxidation or reduction of the analyte molecule occurs, and the counter electrode experiences the reaction providing electron balance. The signal of the sensor generated electric current, which is proportional to analyte concentration in the vicinity of the sensor. The internal electrolyte, being reaction environment, is most frequently aqueous solution of strong acids and bases, with the possibility of doping with different aprotic solvents enhancing analyte solubility in the internal electrolyte [31–35]. Figure 11.11 schematically depicts design and principle of operation of the electrochemical sensor.

11.2.4.2 Metal–Oxide–Semiconductor Sensors

Operation principle of these sensors is based on diffusion of analyte molecules to receptor surface of the sensor, chemisorption and change of resistivity of the recep-

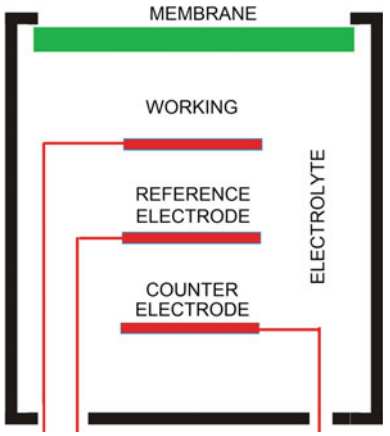

Fig. 11.11 Scheme of electrochemical sensor in a three-electrode version with the measurement electrode, counter electrode and reference electrode

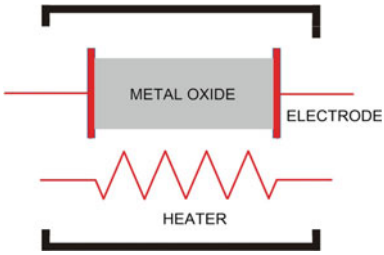

Fig. 11.12 Scheme of MOS-type sensor

tor element depending on the character of semiconductor constituting receptor layer. Detailed mechanism of signal generation in the metal–oxide–semiconductor sensors is a complex process, involving numerous phenomena such as diffusion and chemisorption, gas desorption, catalysed chemical reactions, electric conductivity of semiconductors and surface electron phenomena [36, 37]. Sensitivity and limit of detection of the sensor depend mainly on: receptor layer thickness and catalytic particles entrained in this layer (Pt, Pd, Ag, Au, V, Ru, Rh, Ti, Co, In, and different types of oxides) and temperature of the receptor layer. Sensor signal is strongly dependent on the receptor element temperature, because this parameter has an impact on the most important stages of the measurement process [38–40]. Typical operation temperature of these sensors is in the range 500–900 K. Suitable temperature is provided by electric heaters. Schematic design of the MOS-type sensor is shown in Fig. 11.12.

11.2.4.3 Photoionization Sensors

This type of sensors is most commonly used for volatile organic compounds, and it is characterized by the lowest value of LOD among aforementioned sensors. Manufacturers of these sensors recommend them as the best ones for detection of trace amounts of pollutants. Operation principle of photoionization sensors is based on ionization of neutral molecules of chemical compounds, which are within the ultraviolet range of induction lamp [41–43]. Ionization process in case of PID sensors is caused by electromagnetic radiation with suitably selected photon energy (wavelength from 10 to 400 nm). Formed ions are directed between two polarized electrodes. In the electric field generated by electrometer, ions travel towards the electrodes causing a flow of current, which is then converted into voltage signal. This signal is proportional to concentration of the compounds subjected to ionization. A scheme of the photoionization sensor is presented in Fig. 11.13.

Table 11.3 presents exemplary commercially available electrochemical, metal–oxide–semiconductor and photoionization sensors characterized by LOD below 1 ppm. The table also contains advantages and disadvantages of application of these sensors to monitoring and control of atmospheric air quality.

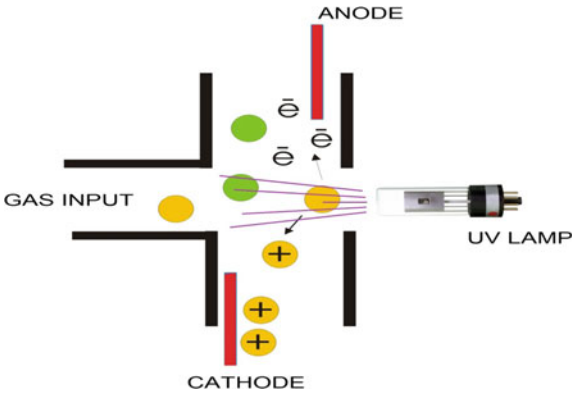

Fig. 11.13 Scheme of photoionization sensor design

Table 11.3 Comparison of advantages and disadvantages of commercial chemical sensors utilized for control of air quality characterized by LOD below 1 ppm

Manufacturer	Sensor type	Advantages	Disadvantages
Unitec Srl	Electrochemical	High sensitivity, relatively good dynamic properties; time constant of achieving 90% of response magnitude to a step change of measured gas concentration is typically shorter than 60 s; low energy consumption	Medium selectivity, dependence of signal on operation temperature, relatively big dimensions
Environmental Sensors Co.			
The Canary Company Pty Ltd.			
Drager Safety			
App-Tek International Pty Ltd			
AlphaSense			
Aeroqual	MOS	High sensitivity, low influence of temperature on sensor signal, low dependency of signal on humidity, short response time, fast regeneration, long lifetime, small dimensions, low price	Low selectivity, high operation temperature, high energy consumption, sensitivity to sulphur compounds and alcohols
Unitec Srl			
Figaro Engineering Inc.			
MOCON Baseline Series	PID	Limit of detection at ppb level, small size, mainly VOC detection	Low selectivity, ionization of only certain volatile chemical compounds, short lifetime of the lamp ionizing
AlphaSense			
Ion Science			
Industrial Scientific			
RAE Systems			

11.2.5 Sensor Matrices

One of the current problems connected with atmospheric air quality is odour. It is usually a mixture of organic and inorganic odorous compounds, characterized by different olfactory thresholds. Depending on duration time and frequency of manifestation, they can have a negative impact on human health causing, for instance, depression, nausea, difficulties in breathing, irritation of eyes and respiratory system, headaches [44, 45]. A reference method for odour measurement is dynamic olfactometry where human nose is a sensor. Application of this method requires trained personnel, laboratory with suitable temperature, relative humidity and noise-level parameters. Air samples polluted with odorous compounds are sampled at source and transported to the laboratory for determination of odour concentration. This method possesses certain disadvantages in the form of lack of online measurements. Arrival of the personnel can occur after odour nuisance episode, which obviously renders precise measurement and determination of odour nuisance peaks [46–48]. It seems that sensor matrices, often named electronic nose instruments, can be an alternative in this field. These matrices are comprised of two basic elements: chemical sensor block and numerical method set (so-called chemical image identification block), employed to analysis of the signals acquired from particular sensors [49, 50]. The chemical sensors contained in the matrices can be characterized by limited selectivity, which is a drawback in case of individual sensors that should exhibit high selectivity. In case of the sensor matrix, this feature becomes advantage due to integral element of the matrix design, which is the chemical image identification block. Such connection of both elements results in improved universal character of the sensor matrices. Figure 11.14 schematically depicts design elements of a sensor matrix being an analogue of human sense of smell.

Electrical (semiconductor) and gravimetric sensors are most frequently utilized chemical sensors in the sensor matrices. Number and type of applied chemical sensors depend on target environment of the sensor matrix [51–53]. Branches of human activity where sensor matrices are employed cover large field, including safety [54–56], environmental pollution [57–59], medicine [60–62], work safety regulations [63], food industry [64–66] and chemical industry [67, 68]. Figure 11.15 schematically shows major and minor types of chemical sensors utilized in electronic nose instruments.

Despite significant application potentialities of the sensor matrices, lack of suitable legal regulations enabling their application to atmospheric air monitoring regarding odour nuisance caused that the sensor matrices (electronic nose instruments) are only used for evaluation of air quality in municipal landfills and wastewater treatment plants. Table 11.4 presents exemplary information about application of the sensor matrices to air quality evaluation in the vicinity of sewage treatment plants and municipal landfills [69–79]. Moreover, this table contains the information about type of electronic nose utilized, chemical sensors employed and data analysis method.

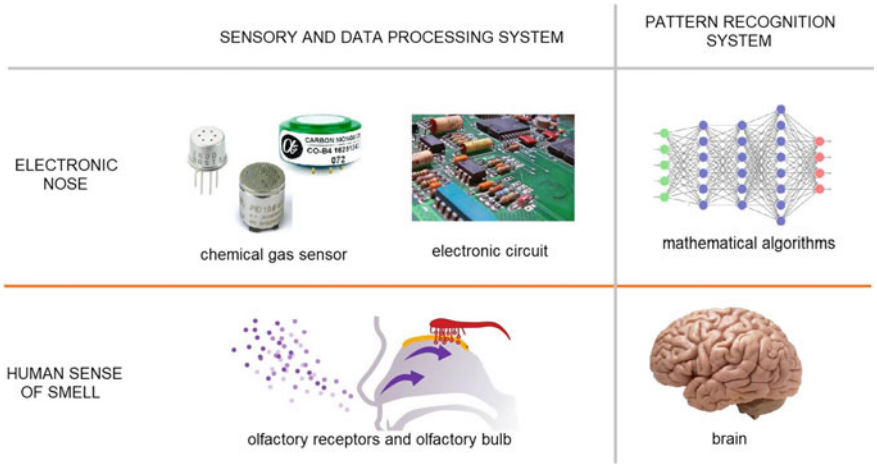

Fig. 11.14 Schematic representation of operation principle of electronic nose together with its natural counterpart

Fig. 11.15 Types of the sensors utilized in design of sensor matrices (electronic nose instruments)

Table 11.4 Examples of the use of electronic nose devices for the assessment of air quality around municipal landfills and sewage treatment plants

Source of malodours	Type of sensors/name of electronic nose	Data analysis method
Landfill	16 tin oxide	Multilayer perceptron (MLP) networks
Landfill site	3xEOS835	nd
Waste disposal and landfill areas	6 to 8 tin oxide sensors	Linear regression
Wastewater treatment plant	FOX3000	Principal component analysis (PCA), relative sensorial odour perception (in short: rSOP) and the relative fingerprint
	eNOSE 5000	Principal component analysis (PCA)
	Neotronics Scientific Ltd. model D;	Artificial neural network (ANN)
	Pen-2	Partial least squares (PLS) and principal component analysis (PCA)
	5× e-nose; 6 MOS	Partial least squares (PLS)
	EOS25, EOS28, EOS35	Principal component analysis (PCA) and linear regression
Landfill	MOS	Principal component analysis (PCA)

nd no data

11.3 Future Perspectives of Atmospheric Air Remote Monitoring

In remote monitoring of atmospheric air, one can apply any measurement method, provided it fulfils the situation-specific requirements concerning sampling and data acquisition frequency as well as limit of quantification. Five main goals can be distinguished:

- Air quality control and its conformity with the standards; in this case, it is required to use the analytical method precisely defined in a standard.
- Detection and determination of contribution of particular emitters; designed system must provide the results precisely attributed to time, space and meteorological conditions.
- Investigation of the effects of pollutant impact on the environment, including types of effects, which can be correlated with the measurement results (e.g. with the results of epidemiological investigations).

- Investigation of background and its trends involving geographical and seasonal conditions as well as application of the method with low limit of detection.
- Investigation of the processes occurring in the atmosphere.

The aforementioned goals determine organization of the monitoring system. The methods of atmospheric air pollutant measurement engulf a wide range of devices, from cheap chemical sensors for measurement of single-component gases to expensive analysers operating in online mode. Selection of suitable device is a key factor in identification of the hazards connected with atmospheric pollution. A progress in chemical sensor technology resulted in shifting of the limit of detection below 1 ppm for some of these sensors. It seems that this trend is going to be maintained because new design and material solution are still being introduced on the market [80–83]. Despite the fact that spectroscopic methods are the reference ones for continuous monitoring of atmospheric air, the chemical sensors can constitute a complement and provide preventive action where continuous, high-quality measurement is required. Another undisputable feature of the chemical sensors, as compared to other devices utilized in air quality control, is the possibility of miniaturization and relatively low production cost. This situation enables application of scattered measurement network comprised of the chemical sensors located over particular area. Also in case of the sensor matrices, proper selection of the sensors and data analysis methods can result in common utilization of these devices for quality control of the air polluted with the compounds of high odour nuisance. They can play the role of supporting devices, or in certain conditions they can substitute the reference method [84]. Due to gradual approach of the city agglomerations to municipal plants, the residents of these areas become more frequently exposed to odour nuisance. The mentioned devices can operate in online mode informing about potential hazards. However, the sensor matrices and drones carrying various sensors need respective legal regulations in order to implement the standards yielding their widespread application. Changing legal regulations aimed at increased health care, work safety and strict admissible levels of emission in the vicinity of industrial plants show that protection of atmosphere from pollution became one of the most important elements of ecological policy in the European Union [85].

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Chapter 12
Comparative Greenness Evaluation

Marta Bystrzanowska, Aleksander Orłowski and Marek Tobiszewski

Abstract Greenness of analytical procedure is multivariable aspect as many greenness criteria should be taken into consideration. On the other hand, modern analytical chemistry offers dozens of analytical procedures, based on different sample preparation and final determination techniques that are used for the determination of a given analyte in a given matrix. For such complex decision-making processes, multi-criteria decision analysis tools are applied as a systematic approach to deal with complex decisions. Multi-criteria decision analysis can be treated as green analytical chemistry comparative metric tool if criteria of assessment describe procedures greenness. In this contribution, we present the results of ranking of seven analytical procedures that are used for the determination of benzo[a]pyrene in smoked food products. The results of TOPSIS, AHP, PROMETHEE application indicate that the first rank is scored by microwave-assisted extraction followed by high-performance liquid chromatography with spectrofluorometric detection, indicating this procedure as the greenest alternative. The contribution describes a step-by-step approach to the application of three multi-criteria decision analysis tools as green analytical chemistry metrics systems.

Keywords Greenness assessment · Analytical procedure assessment · MCDA, Multi-criteria decision analysis · TOPSIS, AHP, PROMETHEE

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J. Płotka-Wasylka and J. Namieśnik (eds.), *Green Analytical Chemistry*,
Green Chemistry and Sustainable Technology,
https://doi.org/10.1007/978-981-13-9105-7_12

12.1 Comparative Greenest Evaluation

The main role of analytical chemistry is being a control tool in chemistry. Therefore, it allows to obtain information about chemical substances (qualitative and quantitative analysis), their occurrence in the environment, food, products, materials, or organisms. It allows to support the development of chemical engineering and production technology of many chemicals. Every system of chemical analysis can be divided into several steps, as it is presented in Fig. 12.1 [1]. After sample collection, analysis begins with pre-treatment of the sample for further separation into components. Then, the components have to be detected in a way that ensures proper quantification of the separated compounds and gives some necessary characteristics and unique data for the identification step.

There is a lot of different analytical procedures for analytes determination in real samples, including a wide range of possible methods for sample pre-treatment, methods of separation, types of detectors, and way of identification. Primarily, the choice of proper analytical procedure depends on the nature of analyte(s) and matrix, aim of the analysis, and also the quality of metrological factors of the procedure (expected accuracy, precision, and sensitivity). Unfortunately, there is no universal procedure for samples analysis, even if the same analytes and the same matrix are taken into account. Selection of an appropriate methodology may be dictated by metrological and technical issues, as well as economic and environmental factors. Selection is not only a matter of analytes and matrix or sample form aspects. Therefore, choosing the best procedure is not so easy. Additionally, during procedure development, it is also compulsory to choose the proper reaction conditions or select the right reagents, solvents, etc. The situation is getting more and more complicated, so the decision-making process is much more demanding at the same time. It is necessary to introduce any system of evaluation that will allow you to analyze the problem and help in making the right choice/decision.

Many methods for assessing the greenness of procedures are well-known in analytical chemistry. It is worth-mentioning National Environmental Methods Index (NEMI), where its pictogram is colored green if reagents used for the procedure are not hazardous, persistent bioacumulative and toxic or corrosive or produce no significant amounts of wastes [2]. This is a remarkable approach because it is pioneering metric system for green analytical chemistry. Unfortunately, the result of the analysis is qualitative only. Therefore, it is not possible to obtain measurable information on hazards, only very general view. Gałuszka et al. [3] presented another green analytical chemistry metrics solution of Analytical Eco-Scale. Its idea is based on the original

Fig. 12.1 General scheme of an analytical procedure [1]

study of Eco-Scale invented by Van Aken [4]. The assessment procedure involves more environmental impact parameters and presents penalty point system evaluation. Therefore, each procedure initially gets 100 points. If it differs from ideal one, then it gets some penalty points, which are subtracted from the base value. The higher the total score, the greener analytical procedure is. The penalty points may be given for the type and amount of reagent that may cause environmental problems, the amount of energy consumed by the electrical devices and also the way of waste treatment (lack of recycling). The result of scoring is easy to read and provides quite clear comparisons of the different analytical methodologies. Unfortunately, the score does not carry any information about the structure of the hazards and assessment procedure is conducted in semi-quantitative way. One of the latest proposals is Green Analytical Procedure Index (GAPI) constituted by Płotka-Wasylka [5]. It is a combination of NEMI and Analytical Eco-Scale, with the incorporation of new aspects. This tool allows to evaluate an entire analytical methodology, from sample collection to final determination. An assessment is presented by five pentagrams (four pentagrams for each step of analytical methodology) used to evaluate and quantify the environmental impact and colored from green through yellow to red, reflecting low, medium and high environmental impacts, respectively. The proposed approach of assessment can be a good semi-quantitative tool for laboratory practice and educational purposes. The results are presented in a legible manner and clearly indicate the weakest points in analytical procedure. Unfortunately, it is difficult to compare analytical procedures with each other which parameters are similar.

As for every analyte and sample matrix, there are at least few (sometimes dozens) of analytical procedures available, and analyst can take advantage of this fact. There are tools originating from managerial science and practice that are called multi-criteria decision analysis programs. They perfectly deal with the comparison of many alternatives (such as analytical procedures) described by few assessment criteria. What is interesting, it was proved that analytical procedures can differ in the area of environmental impact, the differences in metrological criteria are insignificant [6]. In other words, the analyst can potentially select a greener analytical procedure, without deterioration of required analytical performance.

12.2 MCDA

12.2.1 General Information About MCDA

As mentioned above, the solution to this multiobjective problem of green analytical procedure selection may be the application of multi-criteria decision analysis (MCDA) approach. This is a group of methods that allow to evaluate a large amount of data including many criteria (parameters of evaluation) and many alternatives (possible options in decision problem) [7]. The most important advantage is the possibility of assessing weight values to criteria that reflects decision-makers' pref-

erences. These are also methods, where assessment may be improved by dividing all of the criteria into some separate groups. It means that comparison could be much more systematic and comprehensive. For instance, while analyzing different analytical procedures, it is possible to describe them by several scenarios (different points of view during evaluation—groups of parameters). These, for example, can be metrological, environmental, and economic points of view. It is a tool for comparative assessment that allows to rank given options and select the best solution. Currently, the use of evaluation methods, such as the MCDA methods, is increasingly desirable. It is due to the development of chemical sciences, as well as the fact that the differences between the various procedures are often insignificant, but the expectations of stakeholders are increasing. The reason to use MCDA may be also the availability of these tools as a commercial software. MCDA constitutes the group of mathematical models based on different algorithms. They are providing a framework for collecting, storing, and processing all relevant information to support complex decision process [8]. As a result, making the decision is more traceable and transparent. MCDA provides a useful tool for decision aid in the field of multiple objectives, for the use of different types of data and the involvement of different stakeholders together with their preferences. It allows to conduct more comprehensive analysis. The most important advantage is necessity of describing decision problem by numerical values and getting final results also as numerical values. It is possible to easily create a ranking and select the best solution, without much of subjective approach. Another feature is the fact that MCDA methods cope very well when there are some conflicting criteria. It means that problem may involve both benefit and cost criteria at the same time. But first of all these methods could be used for analysis where there is a large number of criteria and alternatives, and also evaluation should be done according to different perspectives, and additionally, there is a need to take into account the decision-makers' preferences. It is possible due to giving relative importance by assessing proper weights to criteria. In a brief, MCDA methods allow to prepare the ranking of a finite set of alternatives in terms of a finite number of decision criteria to find the best solution among all possible options.

The most popular methods are *Technique for Order of Preference by Similarity to Ideal Solution (*TOPSIS*)*, *Analytic Hierarchy Process (*AHP*), and Preference Ranking Organization Method for Enrichment Evaluations (*PROMETHEE*)*. Their application is characterized by different mathematical algorithms; therefore, they may differ in, for instance, manner of assessing weights to criteria.

The reason for their popularity in various applications may be fact that these methods are used in commercial computer software as Expert Choice, D-Sight, M-MACBETH, Super Decisions, Web-HIPRE, etc. Calculations using software are rather not labor-intensive and time-consuming. Moreover, some parameters are calculated automatically, so the number of procedure stages is minimized. In addition, most of the programs allow to present obtained results in the form of clear charts and diagrams.

12.2.2 Application MCDA in Chemistry

MCDA is willingly used to deal with complex problems including management, business, engineering, and science areas [9]. Due to some ecological or environmental management problems that are of complex nature, there is a significant growth in interest of MCDA application in environmental field [10]. Unfortunately, the use of these tools in chemical sciences is rather scarce. However, there is a significant increase in the application of MCDA methods in chemistry from the year 2010, what was presented in Fig. 12.2.

The constant increase of interest in the quality and control of individual environment's components, and food industry products from the chemical point of view, has forced the development of analytical procedures. At the same time, their multiplicity and diversity have become a huge problem when choosing the right analytical procedure for a given purpose. Therefore, it is not surprising that other tools need to be used, especially those that allow for quick and comprehensive evaluation. In analytical chemistry, MCDA methods are usually used to select the best procedure, or the most appropriate reagents, solvents, etc., for a given analytical goal. The examples of their application are presented in Table 12.1.

12.2.3 Steps for the MCDA Analysis

As it was previously mentioned, there are lots of different MCDA tools, based on various mathematical algorithms. However, despite their mechanisms, the general procedure is similar and it consists of several steps that they lead to the final solution of the decision problem. The general scheme of MCDA operation is presented in Fig. 12.3 [33].

The first task is proper definition of the problem, and construction of the main aim of evaluation, and then choosing groups of stakeholders taking part in decision process. Quite often it is single decision maker (DM). The next step is the identification of possible alternatives, which will be the subject of reflection; they are the potential options to reach the aim of MCDA analysis, stated in the first step. Then,

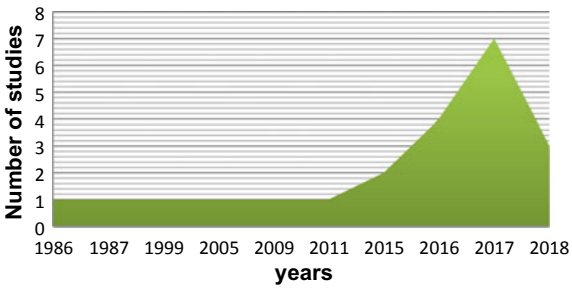

Fig. 12.2 Trends in MCDA application in the area of chemical sciences

Table 12.1 Application of MCDA methods in analytical chemistry

Author and year	MCDA method	Area of application	References
Smilde et al. (1986)	Pareto-Optimality	P	[11]
Smilde et al. (1987)	Pareto-Optimality	P	[12]
Eagan et al. (1999)	AHP	P	[13]
Khan et al. (2005)	AHP	P	[14]
Li et al. (2009)	TOPSIS	P	[15]
Perez-Vega et al. (2011)	AHP	M	[16]
Tobiszewski et al. (2015)	TOPSIS	M	[17]
Tobiszewski et al. (2015)	PROMETHEE	P	[18]
Bigus et al. (2016)	TOPSIS	M	[19]
Serna et al. (2016)	SCI, AHP, DEMATEL	P	[20]
Jędrkiewicz et al. (2016)	PROMETHEE	P	[21]
Tobiszewski et al. (2016)	PROMETHEE	P	[22]
Nikouei et al. (2017)	PROMETHEE II	M	[23]
Tobiszewski et al. (2017)	TOPSIS	M	[24]
Hicks et al. (2017)	MAVT	M	[25]
Xu et al. (2017)	AHP	P	[26]
Gadge et al. (2017)	TOPSIS	P	[27]
Cinelli et al. (2017)	ELECTRE	P	[28]
Chalabi et al. (2017)	SMART	P	[29]
Jędrkiewicz et al. (2018)	TOPSIS	P	[30]
Kadziński et al. (2018)	ORDREG	P	[31]
Bigus et al. (2018)	TOPSIS	P	[32]

M Material selection: solvent, derivatization agents, reagents
P Procedure selection and reaction's conditions

the set of criteria is defined, which determine the requirements for the most suitable option. They must be relevant to describe properly the differences in alternatives in reaching the main aim of analysis. One of the most important parts of whole process is weighting of criteria, which reflects DMs' preferences. It could be realized by conducting surveys among the experts or directly assessed by DMs. The weighting of criteria should reflect DM's opinion of differences in criteria importance. Then, there is a moment for consideration on MCDA algorithm that should be selected and applied. The last step is interpretation of given results and choosing an appropriate alternative.

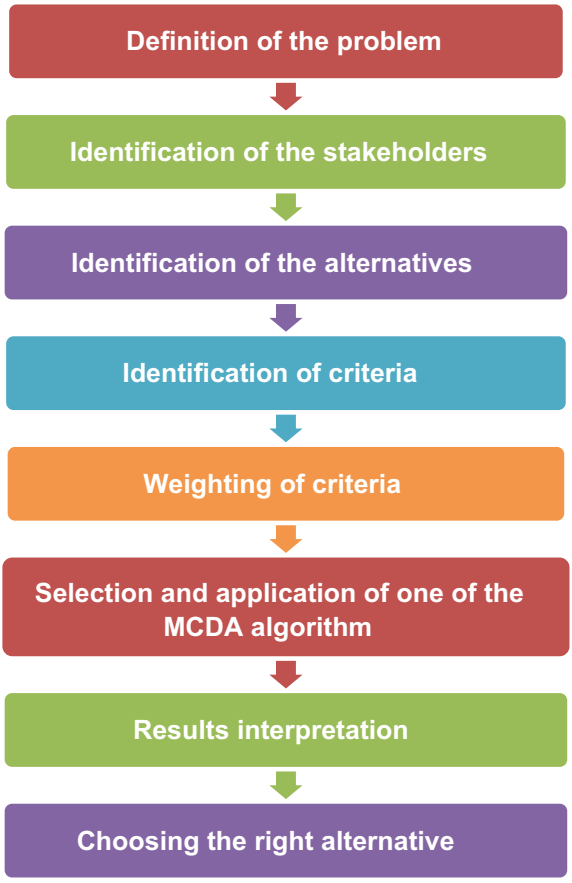

Fig. 12.3 General steps for MCDA methods [33]

12.2.4 Algorithms Descriptions in a Brief

MCDA reflects a group of various evaluation approaches, based on different mechanisms. The models indicated above, such as TOPSIS, AHP, and PROMETHEE are only examples of MCDA methods. These are methods that are more universal, so they may be applied to solve various decision-making problems. On the other hand, there are also some methods that have been created particularly for one specific problem and are not useful for others. Regardless of the type of method, the aim is to make decision-making process more systematic by conducting comparisons without bias and finally to make up a conscious decision. Procedures for the particular method's application may sometimes seem to be complex and are not the main subject of this chapter. Therefore, it was decided to present only the basics of those three algorithms, which are used for the evaluation in this case study.

12.2.4.1 TOPSIS Algorithm

Technique for Order Preference by Similarity to Ideal Solution (TOPSIS) was developed by Hwang and Yoon in 1981 [34]. Its mechanism is based on the selection of alternative, which has the shortest distance from the positive ideal solution in a geometrical sense. In other words, its algorithm allows to allocate the ideal and negative ideal solutions, then place the rest of the alternatives between them. As a result, it leads to obtain the ranking of alternatives and choose the best option. Only basic information about TOPSIS algorithm is presented here. More details are available in the articles describing its fundamentals [35, 36].

The input data is the matrix consisting of n alternatives, described by m criteria. The algorithm of TOPSIS can be presented in several steps as presented below:

(1) Construction of normalized decision matrix

$$r_{ij} = x_{ij} \div \sqrt{\sum x_{ij}^2},\ i = 1, 2, \ldots, m \text{ and } j = 1, 2, \ldots, n \tag{12.1}$$

where x_{ij} and r_{ij} are original and normalized scores in decision matrix, respectively.

(2) Construction of the weighted normalized decision matrix

$$v_{ij} = r_{ij} \times w_j,\ i = 1, 2, \ldots, m \text{ and } j = 1, 2, .., n \tag{12.2}$$

where w_j is the weight of the criterion j and $\sum_{j=1}^{n} w_j = 1$

3) Determination of positive ideal (A^*) and negative ideal (A^-) solutions

$$A^*=\left\{\left(\max_i v_{ij} | j \in C_b\right), \left(\min_i v_{ij} | j \in C_c\right)\right\}=\left\{v_i^* | j = 1, 2, \ldots, m\right\} \tag{12.3}$$

$$A^- = \left\{\left(\min_i v_{ij} | j \in C_b\right), \left(\max_i v_{ij} | j \in C_c\right)\right\} = \left\{v_j^* | j = 1, 2, \ldots, m\right\} \tag{12.4}$$

(4) Calculation the separation measures for each alternative

$$S_i^* = \sqrt{\sum_{j=1}^{m} \left(v_{ij} - v_j^*\right)^2}\ j = 1, 2, \ldots, m \tag{12.5}$$

$$S_i^- = \sqrt{\sum_{j=1}^{m} \left(v_{ij} - v_j^-\right)^2}\ j = 1, 2, \ldots, m \tag{12.6}$$

(5) Calculation the relative closeness to the ideal solution

$$C_i^* = \frac{S_i^-}{S_i^* + S_i^-}, i = 1, 2, \ldots, m \text{ and } 0 < C_i^* < 1 \tag{12.7}$$

(6) Arrangement of scenarios in order of closest to ideal to furthest from ideal—creation of a ranking

The alternative with C_i^* closest to 1 is the best preference among the possible alternatives.

Calculations involving TOPSIS application are performed in Excel program (Microsoft 2010).

12.2.4.2 AHP Algorithm

The AHP technique was developed by Saaty [37]. The most characteristic is the presentation of given problem by hierarchical structure. There are several levels constituting of the main goal, criteria, sub-criteria, and alternatives. Components are organized gradually from the most general to the more detailed and hence placed from the upper to lower part of the hierarchy, respectively. AHP mechanism is based on pairwise comparisons, and it means that elements from different levels are compared in pairs. Therefore, it is possible to assess relative preference with respect to each of the elements at the next and higher level. The preference intensity between elements is estimated according to Saaty's Fundamental Scale [38]. It is linear and bipolar scale that consists of nine possible numeric values. Degrees of the scale and its description are presented in Table 12.2.

Table 12.2 Pairwise comparison scale based on Saaty's Fundamental Scale [39, 40]

Intensity of importance	Definition	Explanation
1	Equal importance	Two activities contribute equally to the objective
3	Moderate importance of one over another	Experience and judgment slightly favor one activity over another
5	Essential or strong importance	Experience and judgment strongly favor one activity over another
7	Very strong importance	An activity is strongly favored and its dominance demonstrated in practice
9	Extreme importance	The evidence favoring one activity over another is of tile highest possible order of affirmation
2, 4, 6, 8	Intermediate values between the two adjacent judgments	When compromise is needed

Degree of advantage of one element over another may be determined as follows:

- Value 1 means, that element A is of the same importance as B
- Value 9 means total advantage A over B.

Odd steps are usually used, however, intermediate values as 2, 4, 6, and 8 are also possible. The determination of the advantage of one of the elements is based on the so-called axiom of reciprocity–reverse system. Therefore, if object A has a strong advantage over object B (A = 5B), then B will be 5 times weaker than A (1/5A = B).

More detailed description of AHP theory is available in references [41–43]. According to them, AHP algorithm can be briefly described in several steps as stated below:

(1) Building the hierarchical structure model—defining the main goal of the analysis, criteria or sub-criteria and alternatives
(2) Establishing a pairwise comparison matrix of the criteria.

$$A_{i,j} = \frac{W_i}{W_j} i, j = 1, 2, 3, \ldots, n \tag{12.8}$$

where $A_{i,j}$ is the weight exchange value of the pairwise comparison of element e_i and e_j, and W_i and W_j are the relative weights among elements.

Establishing the degree of relative importance among the elements of a particular level is conducted by pairwise comparisons with respect to a specific element in the upper level. It means that criteria are compared with respect to the goal, then sub-criteria (if they are defined) are compared with respect to the criteria, and finally, alternatives are compared with respect to each sub-criteria or criteria. Preference functions are described with nine-point scale proposed by Saaty as described above [39].

(3) Normalization of the pairwise comparison matrix—derivation of the eigenvector and maximum eigenvalue

$$AW = nW \tag{12.9}$$

The principal eigenvector W (normalized vector) of the matrix A states priorities of criteria [42, 44]. The value of maximum eigenvalue $\lambda_{\max}$ determines the strength of consistency among comparisons. It equals the number of order.

$$AW = \lambda_{\max} W \tag{12.10}$$

The Perron-Forbenius rule, the following relative weight can be derived:

$$\lambda_{\max} = \left(\frac{1}{n}\right)\left(\frac{W_1'}{W_1} + \frac{W_2'}{W_2} + \ldots + \frac{W_n'}{W_n}\right) W_i, W_j = 1, 2, 3, ..., n \tag{12.11}$$

$$W' = AW \tag{12.12}$$

(4) Determination of the consistency of the pairwise (consistency index and consistency ratio)

$$\mathrm{CI} = \frac{\lambda \mathrm{max}}{(n-1)} \tag{12.13}$$

This difference of value between λ_{max} and n is used to judge the degree of consistency. If the consistency index ≤ 0.1, the consistency level is satisfactory.

$$\mathrm{CR} = \frac{\mathrm{CI}}{\mathrm{RI}} \tag{12.14}$$

Consistency ratio (CR) allows to check the correctness of comparisons—it is calculated to determine inconsistencies in the evaluation. If the consistency ratio ≤ 0.1, it means that the evaluation within the matrix is acceptable, if more than 0.1 the judgments are untrustworthy and the assessment is valueless or must be repeated. Precise values of random index (RI) may be found in [45].

(5) Evaluation of alternatives according to the identified priorities

For AHP calculations, Super Decisions software was selected to be applied. It was developed by Thomas Saaty [46], the developer of AHP tool.

12.2.4.3 PROMETHEE Algorithm

PROMETHEE is the non-parametric outranking method for a finite set of alternatives developed by Brans and Vincke [47]. In general, it is based on positive (domination one alternative over other) and negative preference flows for each alternative in the valued outranking relation. It allows to rank the alternatives according to the DM's preferences by assessing appropriate weights [48].

Actually, the name PROMETHEE is used for the family of few outranking methods that consist of PROMETHEE I (for generation of partial ranking), PROMETHEE II (generation complete ranking of alternatives), PROMETHEE III (ranking based on interval), PROMETHEE IV (ranking partial/complete when a set of viable alternatives are continuous), PROMETHEE V (for problem with segmentation constraints), and PROMETHEE VI (that is used for human brain representation). In the presented paper, PROMETHEE II is applied, which is based on pairwise comparison of alternatives along each criterion.

More details of the PROMETHEE II mechanism is presented in [47]. In a brief, its algorithm consists of several steps as follows [49]:

(1) Determination of deviations based on pairwise comparisons

$$d_j(a,b) = g_j(a) - g_j(b) \tag{12.15}$$

where $d_j(a,b)$ is the difference between the evaluations of a and b on each criterion.

(2) Application of the preference function

$$P_j(a,b) = F_j\left[d_j(a,b)\right] \; j = 1, .., k \tag{12.16}$$

where $P_j(a,b)$ is the preference of alternative a in regard to alternative b on each criterion, as a function of $d_j(a,b)$.

(3) Calculation of an overall or global preference index

$$\forall a, b \in A, \pi(a,b) = \sum_{j=1}^{k} P_j(a,b) w_j \tag{12.17}$$

where $\pi(a,b)$ of a over b (from 0 to 1) is the weighted sum *p(a,b)* for each criterion, and w_j is the weight associated with *j*th criterion.

(4) Calculation of outranking flow—The PROMETHEE I partial ranking

$$\phi^+(a) = \frac{1}{n-1} \sum_{x \in A} \pi(a,x)(4) \text{ and } \phi^-(a) = \frac{1}{n-1} \sum_{x \in A} \pi(x,a) \tag{12.18}$$

where $\phi^+(a)$ and $\phi^-(a)$ is the positive/negative outranking flow for each alternative.

(5) Calculation of net outranking flow—The PROMTHEE II compete ranking

$$\phi(a) = \phi^+(a) - \phi^-(a) \tag{12.19}$$

where $\phi(a)$ is the net outranking flow for each alternative.

In this case study, PROMETHEE algorithm is used as commercial computer software—VisualPROMETHEE software.

12.3 Case Study

12.3.1 PAHs in Smoked Food Products

Polycyclic aromatic hydrocarbons (PAHs) constitute a large class of organic compounds, which are composed of two or more fused aromatic rings in linear, angular, or cluster arrangements [50]. Primarily, they are formed through incomplete combustion or pyrolysis of organic matter and during various industrial processes. However, PAHs are also formed as a result of food thermal preparation methods (grilling, roasting, and smoking). Sander et al. [51] proved that there

are over 660 different compounds that belong to the PAH group and additionally some of them are mutagenic and carcinogenic [52, 53]. Exposure to PAHs occurs mainly by inhalation of air and by ingestion of food or drinking water [54, 55]. Thus, food may be contaminated by PAHs from air, dust, and soil. However, most of PAHs in food is formed during industrial processing and food preparation such as smoking, roasting, baking, drying, frying, or grilling [56]. Scientific Committee on Food (SCF) concluded that 15 PAHs show clear evidence of mutagenicity/genotoxicity in somatic cells in experimental animals in vivo [57]. This group of compounds is formed by: benz [*a*]anthracene, benzo[*b*]fluoranthene, benzo[*j*]fluoranthene, benzo[*k*]fluoranthene, benzo[*ghi*]perylene, benzo[*a*]pyrene, chrysene, cyclopenta[*cd*]pyrene, dibenz[*a,h*]anthracene, dibenzo[*a,e*]pyrene, dibenzo[*a,h*]pyrene, dibenzo[*a,i*]pyrene, dibenzo[*a,l*]pyrene, indeno[1,2,3-*cd*]pyrene, and 5-methylchrysene. Smoking is one of the oldest methods of food preservation and is still widely used in fish and meat processing. In Europe, about 15% of the total quantity of fish for human consumption is available in the form of cold- or hot-smoked products [58]. The formation of PAHs during smoking depends on: type and composition of wood, type of generator, oxygen accessibility, temperature, and time.

For analysis in this case study, benzo[a]pyrene (BaP) was selected to be controlled. It is due to the fact that it is the most commonly studied and has shown various toxicological effects in experimental animals, with the most critical effects being genotoxicity and carcinogenicity. Therefore in 2004, European Union introduced BaP as a marker of the carcinogenic PAH in food with maximum limits in certain foods in the EU [59]. Maximum levels for BaP in a number of food types including smoked meat and fish was established by European Commission in 2005 [60]. According to the regulations, maximum level of BaP in smoked meat and smoked meat products cannot exceed 5 μg/kg [61]. Due to the properties and adverse influence of PAHs on environmental and human health, as well as common occurrence in food, there is a strong necessity for their continuous monitoring.

The main techniques used for the PAH determination in food matrices involve gas chromatography coupled with mass spectrometry and high-performance liquid chromatography with fluorescence detection. Analytical procedures for PAH determination also include some sample preparation techniques that are successfully applied, for instance, Soxhlet extraction, solid-phase extraction, and liquid–liquid extraction, pressurized liquid extraction and QuEChERS, etc. Comparison of various procedures is presented in [62]. Regardless of the chosen method, reliable results are needed. To aid the decision-making process in the selection of the greenest or more widely the best analytical procedure, dedicated tools are needed. Generally, the selection depends on the aim of the analysis and DM's preferences. Hence, the necessity to use MCDA tools is justified.

12.3.2 Steps of MCDA Analysis

12.3.2.1 Main Goal of Analysis

In this specific case study, main aim of the analysis is finding the best analytical procedure for PAH determination in smoked products such as meat and fish from the point of view of a green analytical chemistry approach. The assessment takes mainly environmental or greenness parameters into account but also some metrological factors. In other words, the most suitable procedure is going to be appropriate for that kind of real samples (analytes, matrix, concentration level) in terms of good analytical performance and is eco-friendly at the same time.

12.3.2.2 Alternatives

Alternatives are the subject of considerations. These are different possible options that may reach the stated goal. In the presented case, alternatives constitute analytical procedures for PAHs determination in smoked products. Examples of possible alternatives are summarized in Table 12.3.

The data is collected by searching the scientific articles databases. Selected analytical procedures use different extraction methods, as a form of sample preparation for analysis, as well as various determination techniques and various detection methods. These analytical procedures are used successfully, as exemplified by numerous publications.

12.3.2.3 Criteria of Assessment

Criteria are factors that allow to make an evaluation of a given problem and describe alternatives. In case of selection of the best analytical procedure for PAH determination in smoked products, environmental and metrological parameters are taken into account. Technical evaluation of analytical procedure is based on limits of detection (LOD) and precision, expressed as coefficient of variance (CV). However, according to the main aim of the analysis, most of the parameters are related to the environmental assessment. The amount of sample needed to perform analysis, as well as the total time needed to perform analysis are taken into account. The time is also connected with another factor—number of procedural steps. This criterion is very important, and it influences the time needed and also energy, reagents consumption, as well as occurrence of any potential errors and analytes losses during the operations. According to 12 Principles of Green Chemistry formulated by Anastas and Warner [70], amount and characteristics of reagents and solvents are also included in evaluation. These two last criteria are designated on the basis of a set of information, for instance, amount, type, and hazards character (signal word and pictograms) of each reagent. It should also be noted that regardless of the MCDA method chosen,

Table 12.3 Analytical procedures of PAH determination in smoked meat and fish

	Analyte	Matrix	Analytical methodology	Abbreviation	References
1	BaP	Smoked fish	Accelerated solvent extraction-Gas Chromatography-Mass Spectrometry	ASE-GC-MS	[63]
2		Cold-smoked fish (mackerel)	Liquid–Liquid Extraction-Gas Chromatography- Mass Spectrometry	LLE-GC-MS	[64]
3		Cold-smoked fish (salmon)	Liquid–Liquid Extraction-High-Performance Liquid Chromatography-Fluorescence detection	LLE-HPLC-FLD	[65]
4		Smoked meat	Solid-Phase Extraction-Gas Chromatography-Flame ionization detector	SPE-GC-FID	[66]
5		Smoked meat	Microwave-assisted extraction-Reversed-Phase High-Performance Liquid Chromatography-Spectrofluorimetric Detection	MAE-RP-HPLC-FLD	[67]
6		Smoked fish	Microwave-assisted extraction-Dispersive Liquid–Liquid Micro-extraction-Gas chromatography–Mass Spectrometry	MAE-DLLME-GC-MS	[68]
7		Smoke-cured fish products	Soxhlet extraction-Gas Chromatography–Mass Spectrometry	Soxhlet-GC-MS	[69]

all the criteria must be expressed numerically or easily transformable into calculable units. If not, there is necessity to change them into numerical values. So, the information on reagents in the form of safety pictograms is used. The reagents evaluation according to approach from Analytical Eco-Scale [3] is proposed. Penalty points are given depending on reagents volume from 1 to 3 points (<10 mL—1 point, 10–100 mL—2 points, >100 mL—3 points). Whereas hazardous character is determined by a number of pictograms multiplied by points for signal wording (danger—2 points, warning—1 point). On the other hand, solvent evaluation is based on calculations proposed by Tobiszewski and Namieśnik [71]. Score for each solvent is product of multiplication of solvent volume (mL) and total analytical hazard value (taHV). taHV parameter is estimated according to algorithm related to oral toxicity, inhalation toxicity, carcinogenicity, other hazardous effects, aquatic acute toxicity, aquatic chronic toxicity, biodegradability, hydrolysis, bioconcentration, and hazard value related to the volatility.

An important element of the analysis is also the definition of the preference functions for criteria used in evaluation, what is presented in Table 12.4. The desirable dependencies for given criteria should be determined: "The higher, the better" or "The lower, the better", etc. These preference functions are correlated with 12 Principles of Green Analytical Chemistry proposed by Gałuszka et al. [72].

As stated before, one of the most important advantages of MCDA methods is making an evaluation according to the DM's preferences. It means that there is a possibility to judge which criteria influence the most on the main goal and how strong this impact is. MCDA tools allow to rank given options in accordance with pro-environmental or technically beneficial or economically advantageous approach. This is done by assigning appropriate weights to all criteria. In this particular case study, as MCDA is used for greenness assessment, most of the criteria are related to greenness, so they represent environmental parameters. However, due to the fact that analytical procedures are subject of consideration, also metrological parameters are taken into account. The weights assigned to all criteria are equal; as a result, their impact on the main goal is the same.

Table 12.4 Preference function for applied set of criteria

Criterion	Unit	Preference function
LOD	[μg/kg]	The lower the better
CV	[%]	The lower the better
Amount of sample	[g]	The lower the better
Time of analysis	[min]	The lower the better
Score for solvents	[points]	The lower the better
Score for other reagents	[points]	The lower the better
Number of procedural steps	–	The lower the better

12.3.3 Input Data

All the data values are taken directly or indirectly from indicated above (Table 12.3) scientific papers. As it was mentioned earlier, all parameters for evaluation should have numerical values. So if not, transformation them into calculable units is obligatory. This step is shown in Sect. 3.2.3 *Criteria*. The set of data prepared for the analysis with MCDA tools is presented in Table 12.5.

According to defined preference functions (Table 12.4), in Table 12.5, the best and the worst values for each criterion are marked with bold and italicized values, respectively.

12.3.4 TOPSIS Analysis

Some basic information about the TOPSIS method and its algorithm are described in Sect. 2.4.1 *TOPSIS algorithm*. According to previous sub-sections evaluation involving TOPSIS tool is applied using Excel program (Microsoft 2010). Analysis begins

Table 12.5 Dataset for case study of PAH determination in smoked products

	Analytical methodology abbreviation	LOD [μg/kg]	RSD [%]	Amount of sample [g]	Time of analysis [min]	Score for solvents	Score for other reagents	Number of procedural steps
1	ASE-GC-MS	0.3	*23*	10	**76**	1050	**0**	**6**
2	LLE-GC-MS	0.24	7.89	10	782.35	5446.7	8	7
3	LLE-HPLC-FLD	0.25	17.48	**1**	225	2527.11	4	8
4	SPE-GC-FID	0.1	8.75	*30*	255.25	21896.8	8	*11*
5	MAE-RP-HPLC-FLD	**0.066**	**7.6**	2	100	6659.64	**0**	**6**
6	MAE-DLLME-GC-MS	0.21	8.7	**1**	*1498.43*	**55.27**	*9*	7
7	Soxhlet - GC-MS	*1*	10	10	1489.5	*22061.4*	4	7

Table 12.6 Final ranking of analysis involving TOPSIS method

Alternatives	Similarity to ideal solution
MAE-RP-HPLC-FLD	0.885
LLE-HPLC-FLD	0.761
ASE-GC-MS	0.714
LLE-GC-MS	0.629
MAE-DLLME-GC-MS	0.613
SPE-GC-FID	0.463
Soxhlet-GC-MS	0.377

with defining main aim, as well as set of criteria and set of alternatives. Then, weighting the criteria must be provided. In this case study, all of them are characterized by the same importance. It means that all of the values are equal (0,1429…). According to TOPSIS algorithm, it is necessary to find the best and the worst value within each criterion (max or min)—determination of positive/negative ideal solution. Then, rest options are allocated between these two extreme values. Obtained results of the analysis, ranking of analytical procedures for PAH determination, are shown below in Table 12.6.

In TOPSIS method, final score is a value that determines similarity to ideal solution. It is because chosen alternative must have the shortest distance from the positive solution and furthest from the ideal solution of the geometric point by using the Euclidean distance (determination of the relative proximity of the optimum solution alternative).

12.3.5 AHP Analysis

As it was previously mentioned, analysis involving AHP method is conducted using SuperDecisions software. The first step is defining main aim, set of criteria and set of alternatives and then constructing the hierarchical structure of a given problem. The scheme for the hierarchy model is presented in Fig. 12.4.

Then pairwise comparisons based on nine-point Saaty's Fundamental Scale are conducted. Comparisons between pairs of elements are made, first for criteria with respect to the main goal, then for alternatives with respect to each criterion. Similar evaluations are conducted for alternatives with respect to each criterion. It is done to establish, which element is smaller/bigger and estimate how many times (multiples). For this purpose, calculations using Microsoft Excel are made. In Fig. 12.5, the sheet for pairwise comparison among possible analytical procedure with respect to *Score for solvent* using Super Decision software is presented as an example. The

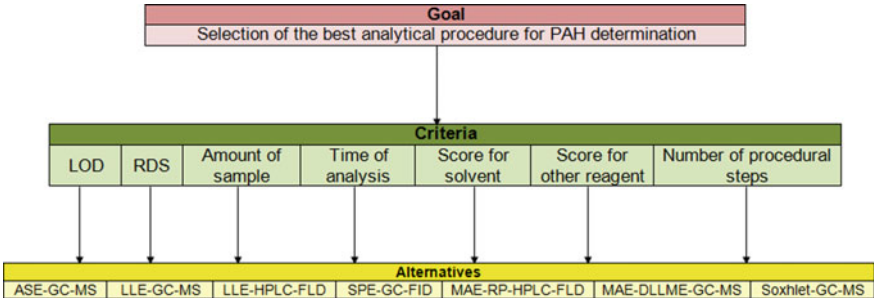

Fig. 12.4 Hierarchical structure of AHP model for the selection of best analytical procedure for PAH determination

Node comparisons between alternatives (analytical procedures) with respect to *Solvent score*																		
ASE-GC-MS	>=9.5	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	>=9.5	LLE-GC-MS
ASE-GC-MS	>=9.5	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	>=9.5	LLE-HPLC-FLD
ASE-GC-MS	>=9.5	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	>=9.5	SPE-GC-FID
ASE-GC-MS	>=9.5	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	>=9.5	MAE-RP-HPLC-FLD
ASE-GC-MS	>=9.5	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	>=9.5	MAE-DLLME-GC-MS
ASE-GC-MS	>=9.5	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	>=9.5	Soxhlet-GC-MS
LLE-GC-MS	>=9.5	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	>=9.5	LLE-HPLC-FLD
LLE-GC-MS	>=9.5	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	>=9.5	SPE-GC-FID
LLE-GC-MS	>=9.5	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	>=9.5	MAE-RP-HPLC-FLD
LLE-GC-MS	>=9.5	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	>=9.5	MAE-DLLME-GC-MS
LLE-GC-MS	>=9.5	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	>=9.5	Soxhlet-GC-MS
LLE-HPLC-FLD	>=9.5	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	>=9.5	SPE-GC-FID
LLE-HPLC-FLD	>=9.5	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	>=9.5	MAE-RP-HPLC-FLD
LLE-HPLC-FLD	>=9.5	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	>=9.5	MAE-DLLME-GC-MS
LLE-HPLC-FLD	>=9.5	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	>=9.5	Soxhlet-GC-MS
SPE-GC-FID	>=9.5	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	>=9.5	MAE-RP-HPLC-FLD
SPE-GC-FID	>=9.5	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	>=9.5	MAE-DLLME-GC-MS
SPE-GC-FID	>=9.5	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	>=9.5	Soxhlet-GC-MS
MAE-RP-HPLC-FLD	>=9.5	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	>=9.5	MAE-DLLME-GC-MS
MAE-RP-HPLC-FLD	>=9.5	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	>=9.5	Soxhlet-GC-MS
MAE-DLLME-GC-MS	>=9.5	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	>=9.5	Soxhlet-GC-MS

Fig. 12.5 Alternatives comparison results on nine-point scale in terms of "solvent score" criterion

reason to build the hierarchical structure is to simplify the analysis to make it more understandable.

An important step during the AHP analysis is to check the Consistency Index (CI) and Consistency Ratio (CR) values. These parameters are calculated to determine any inconsistencies in the evaluation. They provide information about the judgments—their trustworthiness. In other words, they measure how consistent the judgments have been relative to large samples of purely random judgments. It is desired to obtain the consistency index/consistency ratio values of ≤ 0.1. In our case study the inconsistency values for all comparisons are smaller than 0.1, so the consistency level is satisfactory and evaluation within the matrix is acceptable.

Finally, evaluation of alternatives according to the priorities identified is performed. As a result, ranking of possible options is done, together with finding the

Name	Graphic	Ideals	Normals	Raw
ASE-GC-MS		0.782	0.194	0.097
LLE-GC-MS		0.429	0.107	0.053
LLE-HPLC-FLD		0.571	0.142	0.071
SPE-GC-FID		0.359	0.089	0.045
MAE-RP-HPLC-FLD		1.000	0.249	0.124
MAE-DLLME-GC-MS		0.613	0.152	0.076
Soxhlet-GC-MS		0.268	0.067	0.033

Fig. 12.6 Final results of analysis involving AHP as MCDA tool

best options. Results of AHP analysis using SuperDecisions Software are presented in Fig. 12.6.

Scores of analysis using SuperDecisions Software are estimated by three different values: Raw, Normals, and Ideals. The Raw column is read directly from the Limit Supermatrix, while the Ideals are obtained by dividing the Raw values by the largest raw value. Therefore, the Normalized values are obtained from Raw values by summing and dividing each by the sum. On the other hand, the Normals column presents the results in the form of priorities. Usually, this value is a way of reporting the final resolution.

12.3.6 PROMETHEE Analysis

In Sect. 2.4.3, *PROMETHEE algorithm* mechanism and algorithm of this tool are explained. In this case, Visual PROMETHEE Software is applied for analytical procedures evaluation. First task is defining main aim, set of criteria, and set of alternatives. Then, assessing appropriate weight for criteria is done. For PAH determination in smoked products, it is estimated to be equal as it is presented in Fig. 12.7.

In accordance, using Visual PROMETHEE Software, it is necessary to choose the best value within each of criterion—minimum (MIN) or maximum (MAX)—depending on DM's preferences. Preference functions for applied set of criteria are presented in Table 12.4 (Sect. 3.2.3. *Criteria of assessment*). The main advantage of this software is the possibility of making an assessment for different types of PROMETHEE method, not only for PROMETHEE II. Obtained result as a complete ranking of alternatives is summarized in Fig. 12.8.

Phi, Phi+, and Phi− are the scores of PROMETHEE analysis as the preference flows: the net flow, the positive (or leaving) flow, and the negative (or entering) flow, respectively. They are computed to consolidate the results of the pairwise compar-

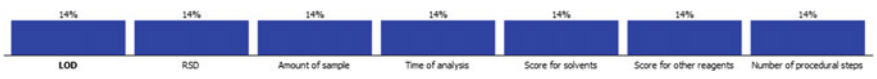

Fig. 12.7 Assess weight values for given criteria

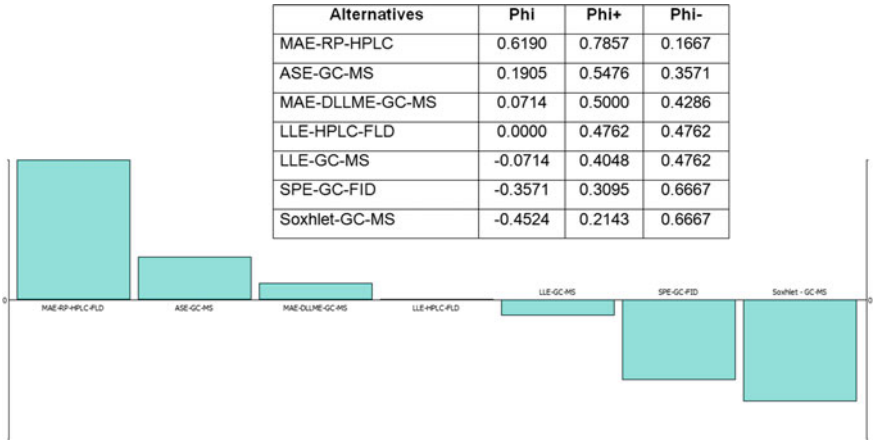

Fig. 12.8 Final results of analysis involving PROMETHEEII as MCDA tool

isons of the actions and to rank all the actions form the best to the worst one. The larger Phi+ and the smaller Phi− the better. The net preference flow is the balance between the positive and negative preference flows, and it takes into account and aggregates both of them into a single score.

12.3.7 Comparison of Obtained Result and Conclusions

In the case study of choosing the best analytical procedure for PAH determination in smoked meat and fish products, three MCDA methods are applied. TOPSIS, AHP, and PROMETHEE algorithms are used, and their results are summarized in Table 12.7.

Undoubtedly, the best analytical procedure for PAH determination in smoked meat and fish is that one based on high-performance liquid chromatography with spec-

Table 12.7 Comparison of obtained results with TOPSIS, AHP, PROMETHEE

Rank	TOPSIS		AHP		PROMETHEE	
	Alternatives	Similarity to ideal solution	Alternatives	Normals	Alternatives	Phi
I	MAE-RP-HPLC-FLD	0.885	MAE-RP-HPLC-FLD	0.249	MAE-RP-HPLC-FLD	0.619
II	LLE-HPLC-FLD	0.761	ASE-GC-MS	0.194	ASE-GC-MS	0.191
III	ASE-GC-MS	0.714	MAE-DLLME-GC-MS	0.152	MAE-DLLME-GC-MS	0.071
IV	LLE-GC-MS	0.629	LLE-HPLC-FLD	0.142	LLE-HPLC-FLD	0.000
V	MAE-DLLME-GC-MS	0.613	LLE-GC-MS	0.107	LLE-GC-MS	–0.071
VI	SPE-GC-FID	0.463	SPE-GC-FID	0.089	SPE-GC-FID	–0.357
VII	Soxhlet-GC-MS	0.377	Soxhlet-GC-MS	0.067	Soxhlet-GC-MS	–0.452

trofluorometric detection, preceded by microwave-assisted extraction. It is worth looking at Table 12.5 with input data again. As can be seen, MAE-RP-HPLC-FLD procedure is characterized by the most desired criteria values in response to other options (the most similar to the preferred ones). In all analyses using different algorithms, the lowest places in the ranking are for Soxhlet-GC-MS and SPE-GC-FID procedures. Their low positions in the ranking are due to high score for solvents. It means that highly toxic and hazardous solvents are used, involving their high volumes. In case of procedure with pre-treatment including Soxhlet extraction over 300 mL of dichloromethane is used. On the other hand, procedure based on solid-phase extraction needs over 200 mL of n-hexane. Additionally, Soxhlet-GC-MS is characterized by the highest value for limit of detection, which is additionally not preferable. If we have a closer look at SPE-GC-FID, the highest amount of sample and number o procedural steps are significant problems. It makes the procedure more time-consuming, as well as less eco-friendly. The consumption of reagents and water, energy is much greater in this case. The possibility of analytes losses and making mistakes is also greater. Thus, it potentially affects the result of the analysis and its reliability.

The biggest differences between the different MCDA methods are visible for ranks from 2 to 5. The differences in ranks are due to different algorithms applied. It should be also clearly noted that in all three cases of MCDA tools application the numerical scores are within considerably narrow ranges. It is an implication that analytical procedures ranked at positions 2–5 are not very different. Moreover, ranking positions depend strictly on assessed weight values for criteria of evaluation. If we change the weights of importance, the results could also change. In this particular case study, analysis involved metrological and environmental criteria, which influence on the main aim is estimated as equal. It is done to reconcile two aspects: green analytical chemistry and analytical performance at the same time.

12.4 Summary

Many chemical decision problems are characterized by interdisciplinary nature. They can be evaluated from the point of environment, economy, metrology, technology, feasibility, etc. They taking into account many criteria, many alternatives, and various groups of stakeholders with different preferences. Finding a balance between all components and elements may be difficult. It is a reason for MCDA application. These tools allow the users to solve complex problems in a technically valid and practically useful way. MCDA is used to combine multioutput information into a single value that is easy to be compared with other possibilities. The use of different MCDA methods leads to different results, what is caused by the use of different algorithms.

Based on the three different algorithms used, it was found that the greenest and analytically most sound procedure for PAHs determination in smoked meat and fish is high-performance liquid chromatography with spectrofluorometric detection,

preceded by microwave-assisted extraction. On the other hand, the worst solution is using gas chromatography coupled with mass spectrometry with Soxhlet extraction.

It is worth noting that despite various algorithms, the results of analyzes are very similar. This correlation may indicate the correctness of the analyses carried out by means of various methods. Thus, it can be concluded that the choice of the MCDA tool is of minor relevance in this case.

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Chapter 13
Quantitative Assessment

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Abstract The main trends in the development of analytical chemistry are the determination of increasingly lower concentrations of analytes in samples with complex matrix composition (trace analysis). While the obtained analytical results must be reliable, which means that they must accurately (truly and precisely) reflect the actual content of analytes in a representative sample of the material object under study. However, it is an extremely difficult and complicated task, which is a great challenge for analysts. Therefore, it is becoming increasingly important to pay attention to the problem of quality assurance and quality control (QA/QC) of the obtained results. This chapter provides information on QA/QC systems. The terms for quality of the results—its relevance and consequences, uncertainty estimation, traceability, measurement errors (types and effects)—are also described.

Keywords Quality assurance · Quality control · QA/QC · Uncertainty · Measurements errors · Traceability

13.1 Introduction

The possibility of wide access to various types of information facilitates not only political decisions, but also economic and technological decisions (related to the control of processes of production of various types of consumer goods). As a result, a new type of market in which information is traded has been created. Analytical information about tested material objects is a specific type of information. This information is usually obtained not from the analysis of the whole object, but from the analysis of appropriate samples. In order to meet the growing demand for analytical information, more and more intensive work is underway to develop new methodological and apparatus solutions, so that analytical results are a source of as much information

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J. Płotka-Wasylka and J. Namieśnik (eds.), *Green Analytical Chemistry*,
Green Chemistry and Sustainable Technology,
https://doi.org/10.1007/978-981-13-9105-7_13

as possible, in other words, so that the results are as informative as possible. It can therefore be concluded that all directions of development of analytical chemistry can be reduced to one—the aspiration to obtain as comprehensive analytical information as possible.

In analytical chemistry, a very broad spectrum of measurement methods and techniques is used. Table 13.1 presents only their basic classification of modern methods of chemical analysis. One of the basic development directions of analytical chemistry is the desire to determine increasingly lower concentrations of analytes in samples with a complex matrix. This type of task poses a great challenge to analysts and requires attention to quality control and quality assurance (QC/QA) of the obtained results [1].

The quality assessment system usually consists of the following elements:

– tracking and evaluation of the precision of the results obtained by periodical analysis of control samples;
– evaluation of trueness by:
  - analysis of samples of certified reference materials (CRM),
  - comparison of the results obtained with the results obtained for the same sample using the reference method,
  - carrying out analyses of samples after the standard addition,
    – carrying out interlaboratory comparative tests (intercalibration),
    – use of control cards,
  - application of an appropriate system of auditing.

In order to ensure the quality of analytical results, it is necessary to verify the reliability of the measuring instruments used and to check the extent of applicability and calibration of the analytical procedures used.

13.2 The Quality of the Results—Its Relevance and Consequences

Accurate environmental analytical measurements are developed for various purposes, for instance, determination of the environmental fate (transformation and transport) of a chemical substance or determination of the xenobiotic concentration in the environment. These processes provide to obtain data necessary to ensure the quality of the environment, environmental risk assessments or in some cases for regulatory purposes as well as public health [2].

Quality is a relative concept: either “high” or “low” in absolute terms, but rather adequate or not suitable sense of the extent to which a product, process or service meets the requirements previously set by the objective or client [3]. Quality has been a constant objective in analytical chemistry since many years, but today it is a popular term due to the implementation of quality assurance rules in analytical laboratories [4].

Table 13.1 Basic classification of modern methods of chemical analysis

Classification parameter	Types of analytical methods	Explanation
The way of relation with the current SI measurement system (traceability)	Primary methods	Used for the direct measurement of quantities described in the SI system
	Ratio methods	A classic example is the isotopic dilution mass spectrometry technique (IDMS)
	Secondary methods	
The principle of measurement	Absolute methods	Methods based on the measurement of quantities such as mass, volume, time, electrical charge—in principle do not need to be calibrated
	Relative methods	Methods based on the principle of comparing signals from the analyte present in the standard sample and in the test sample—the calibration step is necessary
Testing of the sample	Direct methods	A suitable measuring device (sensor) is placed directly in the tested object in order to obtain analytical information (pH measurement, electrical conductivity measurement)
	Indirect methods	In most cases because of: – very low levels of analyte concentrations – the complex composition of the matrix and the presence of interferents make it necessary to prepare the sample properly, the measurement of the amount (concentration of the analyte) is carried out in an appropriate extract

(continued)

Table 13.1 (continued)

Classification parameter	Types of analytical methods	Explanation
Type of analytical information	Methods for the determination of momentary concentrations of analytes in a tested material object	Methods used to study the quality of the environment and to determine individual exposure
	Methods for the determination of time-weighted concentrations for the sampling period	
Places where analytical information was obtained about the material object under examination	In situ measurement methods	For this purpose, appropriate mobile laboratories or mobile or portable control and measurement devices are used
	Laboratory methods	
The way of obtaining analytical information	Methods based on the use of devices with direct reading of the quantity/concentration of the analyte	Methods typically used in field studies to quickly obtain analytical information (often semi-quantitative)
	Methods with preliminary sample preparation and calculation of the concentration/quantity of the analyte based on the results of measurements carried out in the laboratory	
Method of collecting a representative sample	Sedimentary methods	A sample of the analytes is collected as a result of the process of free migration of the analyte to the collecting surface
	Insulation methods	The sample is collected in a vessel (sampler) of defined volume
	Aspiration methods	The sample of the analytes is taken by passing a stream of the medium through a trap (e.g. a sorption tube)
The level of automation	Manual methods	Most of the operations and activities (both in the field and in the laboratory) related to sample preparation are carried out manually

(continued)

Table 13.1 (continued)

Classification parameter	Types of analytical methods	Explanation
	Automatic methods	All activities including sampling and sample preparation operations are carried out with a suitable instrument
	Monitoring methods	Specific variant of automated methods. The equipment used in monitoring studies must have the following characteristics: – the ability to obtain information in real time or with a slight time delay – possibility of continuous measurements – long period of so-called autonomous work

The main task of the analytical chemical laboratory is to provide information on the chemical composition of material systems, commonly regarding the identity and/or quantity of one or more relevant components in samples taken from these materials. The quality of scientific information shall generally be assessed in accordance with international standards for objectivity, integrity, reproducibility and traceability [3]. Chemical analysis of any material can be defined as a chain of decisions, actions and procedures. The diagram in Fig. 13.1 shows the cyclical nature of many analytical chemistry processes and operations. As with any chain, the strength of the chain of relations in terms of chemical analysis depends on the strength of its weakest link. In general, the weakest links in the analytical process are not those progressive parts that are considered as components of chemical analysis, i.e., chromatographic separation of mixtures or spectrometric detection, but rather those stages of the analytical process which take place outside the analytical laboratory, such as the selection of materials to be sampled, the preparation of a sampling action plan and the selection and use of techniques and equipment necessary for taking samples and their transport, maintenance and storage.

If the analytical laboratory is not responsible for the sampling stage, the quality management system does not consider these weak links in the analytical process. If, in addition, the sample preparation steps (extraction and cleaning of extracts) have not yet been carried out properly, the use of even the most modern analytical instruments and complex computer techniques cannot improve the situation and the analytical results do not represent any value. It is therefore necessary that the quality control and quality assurance of analytical results cover all stages of the analytical process. This process must be an integral process for which checking the extent of applicability of the analytical method (validation) is only one, albeit a very

important, step [5]. In order for the laboratory to be able to provide customers with reliable and reproducible results, it is necessary to perform systematic calibration of analytical instruments and to subject the so-called validation of entire analytical procedures. The term "validation" refers to the determination of the characteristics of the method, which correspond exactly to what was previously understood by the term "applicability range of the method" (specificity, selectivity, accuracy, precision, repeatability, limit of detection, measuring range, linearity range, etc.). In order to control the quality of the laboratory's work, the samples of reference materials are treated and determined in the same way as the actual samples. Comparison of the result obtained with the actual content of the analyte in the sample of the reference material provides a basis for drawing conclusions as to the reliability of analytical work carried out in a given laboratory.

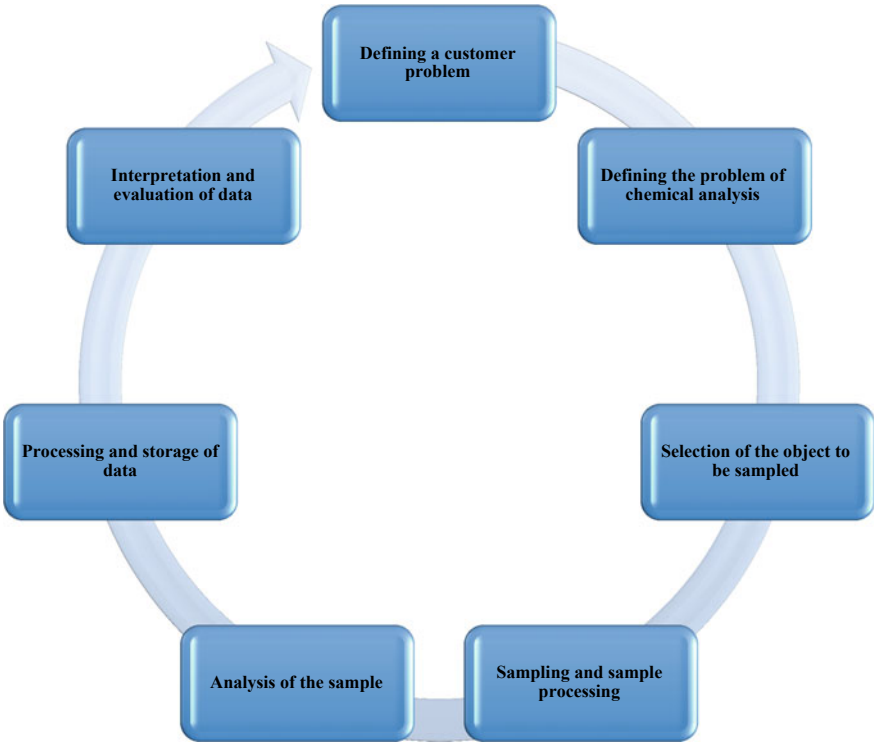

Fig. 13.1 Schematic presentation of the cyclic character of many processes and operations in the field of analytical chemistry (based on [3])

13.3 Measurement Errors

One of the criteria that characterise the quality of the obtained measurement result is its accuracy which is defined as the degree of agreement between the obtained measurement result (single!) and the actual value (expected). On the other hand, the degree of compliance of the result of the determination (as an average value calculated from a series of measurements) with the expected value is called trueness (correctness) [6, 7].

Errors are a consequence of the accuracy (trueness and precision) of the analytical procedure used to obtain the measured quantity and can be characterised as the difference between the expected values and the values obtained from the determination. This difference is due to different errors. There are three types of errors: gross, random and systematic (constants and variables) [1]. There are also classifications of errors where they are divided by how the error values of the measurement result are given and by sources of error (Table 13.2) [1].

The total error of a single measurement result can be divided into three components, as described in the following equation:

$$d_{x_i} = x_i - \mu_x = \Delta x_{\text{sys}} + \Delta x_i + \delta x_i \tag{1}$$

where d_{xi}—total measurement result error,
x_i—the value of the result of the measurement,
Δx_{sys}—bias,
Δx_i—random error of single measurement,
δx_i—gross error.

There are many ways of detecting results with gross errors. Each of these methods can be used under certain conditions. After elimination of results with gross errors, the correctness of the final result (which is usually the average value of a series of measurements) is affected by systematic and/or random errors. Determination of systematic errors is one of the ways of determining the correctness of the analytical procedure [1].

Depending on the conditions in which a series of measurements was obtained, the repeatability or precision of the results obtained under the same measurement conditions, usually expressed by means of repeatability standard deviation, variance, relative standard deviation or coefficient of variation, may be discussed. Intermediate precision, i.e. the precision of results obtained in a given laboratory in a long-term measurement process, is a more general concept than repeatability. There is also a concept of reproducibility, which expresses the precision of results obtained by different analysts in different laboratories using a given measurement method [1].

Table 13.2 Classifications and characteristics of the main types of errors [1]

Criterion	Error type	Equation/Description
Manner of presenting a determination result	Absolute	$d_{x_i} = x_i - \mu_x$ x_i—value of a measurement result μ_x—expected (true) value
	Relative	$\varepsilon_{x_i} = \frac{d_{x_i}}{\mu_x}$
Source of errors	Methodological	–
	Instrumental	–
	Human	–
Type of error	Gross (δx_i)	An error due to a one-off effect of a transient cause which causes the measurement result to deviate significantly from the mean value (deviating result). The gross error is characterised by the following properties: – is the result of a one-off effect of a transient cause – occurs only with some measurements – is a random variable, however, with an unknown distribution and an unknown expected value – is the easiest to detect and therefore to eliminate – takes both positive and negative values (unlike in the case of systematic error) – the reason for its occurrence may be, e.g. a mistake in reading the indications of a measuring instrument or a mistake in calculations
	Systematic (Δx_{sys})	An error which, when multiple measurements of the same value of a certain quantity are made under the same conditions, remains unchanged or changes as a function of a certain parameter according to a known law. Its value is the difference between the actual value (expected) and the average value of the measurement results when the number of measurement results is infinite. This type of error cannot be calculated without knowing the real value or the value conventionally accepted as real. Systematic errors, which should be small, determine accuracy. They are also a component of uncertainty. This type of error can be a feature of a single measurement or analytical process, in which case it is referred to as bias There are two types of systematic error: – a constant whose value does not depend on the analyte content level—a_{sys} – a variable whose value depends (mostly linearly) on the content level of the analyte—$b_{\text{sys}}\ \mu_x$ The systematic error determines the dependence: $\Delta x_{\text{sys}} = a_{\text{sys}} + b_{\text{sys}}\ \mu_x$

(continued)

Table 13.2 (continued)

Criterion	Error type	Equation/Description
	Random (Δx_i)	1. An error resulting from typical experimental variations the value of which decreases when the same analyte is determined repeatedly in samples of the same material or when the same measurement is taken a certain number of times; it is impossible to calculate the same error for a single result or to predict its mark; despite a small value, these errors are the basis for calculating precision and are a component of the uncertainty of analytical results 2. The difference between the result of measurement and the mean of the results of a large number of repeated measurements of the same quantity to be measured

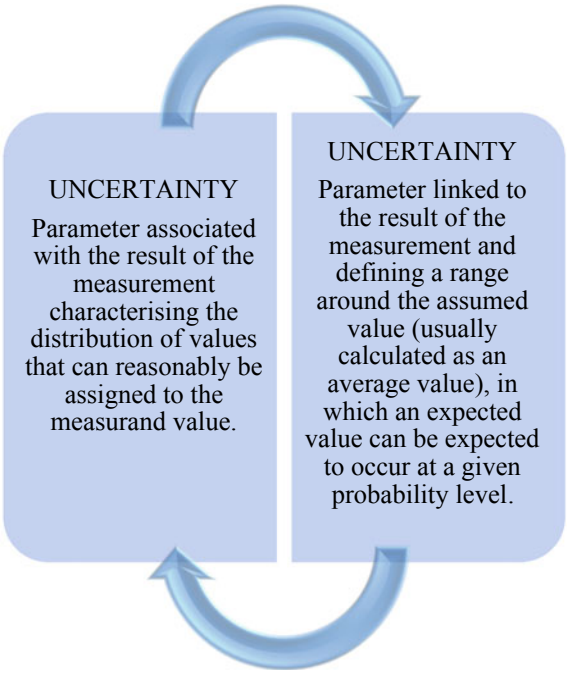

Fig. 13.2 Definitions of the uncertainty

13.4 Uncertainty

Uncertainty and traceability are key features of any result of the analysis. It is therefore necessary to estimate the uncertainty for each measurement result and to document its traceability. Definitions of the uncertainty term are given in Fig. 13.2.

Uncertainty exists at every stage of the measurement procedure. Estimating the uncertainty of an analytical result is an added value that increases the reliability of the result and allows the quality of the result to be determined. The certainty of the analytical result depends on the uncertainty of all stages of the analytical procedure with which it is obtained. The uncertainty of the result of the analysis is a component of the uncertainty of all individual stages of the analytical process [8–10]. The decisive parameter affecting the uncertainty of the result of the determination is the one for which the uncertainty is highest. It is therefore necessary to specify the sources and types of uncertainty for the individual steps of the analytical procedure and more specifically for each quantity to be measured [11, 12].

Estimating the uncertainty of the analysis result means that it is possible to determine a range around the mean value (the result of the determination is usually presented as an arithmetic mean), within which the expected value should be found. The width of this interval depends on:

– the uncertainties associated with the equipment, accessories, reagents, standards, reference materials, etc., are used during the analytical procedure,
– the uncertainty associated with the person performing the determination, associated with and dependent on his or her experience and skills,
– the level of probability with which this range is determined.

Before estimating the uncertainty of the result of the analysis, it is necessary to identify the sources of standard uncertainties that will make up the complex uncertainties. According to a report presented by EURACHEM in 1995, there are several sources of uncertainty for quantitative analysis:

– incomplete determination of the analyte,
– sampling,
– non-quantitative extraction/enrichment process,
– contamination of the sample during sampling and sample preparation for analysis,
– personal error related to the reading of analogue instruments,
– awareness/imperfect measurement of the influence of environmental conditions on the analytical procedure,
– uncertainty of instruments designed for mass and volume measurement,
– instrument resolution or detection limit,
– values assigned to measurement standards and reference materials,
– constants and other parameters obtained from external sources that are used in the calculations,
– approximations and simplifications provided for measurement procedures,
– random error.

There are many ways to estimate the uncertainty of measurement. The consequence of the uncertainty of measurement is the notation (“rounding”) of the measurement result. When calculating the complex uncertainty of measurement based on standard uncertainties, the right of transfer (propagation) is used, and the consequence of which is to increase the influence of the highest value on the final value. The most

Table 13.3 Description of the methods for estimating the uncertainty of measurement [11, 12, 14]

Method	Description
Bottom-up	This approach ("from detail to the whole") is time-consuming and labour-intensive. Where this method is used, all sources of uncertainty must be identified, standard uncertainties must be calculated and the right of propagation must be used to calculate the value of the complex uncertainties. This approach to uncertainty estimation must be supported by a graphical representation of the impact of the individual standard uncertainties on the complex uncertainties using the Ishikawa diagram
Fitness for purpose	Method of uncertainty estimation based on the mathematical relationship between the measurement result and the uncertainty value; the method is much easier and less time-consuming than a bottom-up approach; in this method, the estimated uncertainty value for a given level of content (as a relative value) can be used for measurements made at other levels
Top-down	Method ("from the general to the detail") using mainly the precision of the results obtained; data derived from interlaboratory studies shall be used; the theoretical basis of this approach lies in the fact that for most measurements the main uncertainty component is that resulting from the dispersion of results due to their non-repeatability
Validation-based	Method of uncertainty estimation based on inter- or within laboratory validation process (precision, trueness, calibration, limit of detection and robustness)
Robustness-based	Method of uncertainty estimation based on robustness tests from interlaboratory tests

commonly used methods of estimating the uncertainty of measurement are presented in Table 13.3. The final result of the analysis therefore consists of:

- determination of the measured value and its unit,
- the result with the expanded uncertainty value ($y \pm U$, including units for y and U),
- the value of the *k-factor* for which the expanded uncertainty has been calculated.

An estimation of the uncertainty of the analytical result is a necessary and crucial step in the process of obtaining it. Without the uncertainty of the result, the determination cannot even be treated as a result from a metrological point of view [13]. This is because the value of the uncertainty of the result of the analysis allows for it:

- confirmation of its robustness,
- defining and documenting its quality,
- comparison of the result obtained with limit values, standardised values or reference values.

For this reason, the time and costs incurred in estimating the uncertainty are compensated by obtaining reliable analytical results, the interpretation of which in turn leads to information on the objects under investigation.

13.5 Traceability

Comparison of measurement results only makes sense if they are presented in the same units of measurement or in relation to the same scale. The issue of traceability has arisen with the first human measurements, while the term "measurement traceability" itself is constantly evolving and has many meanings in different contexts [4]. Several definitions of the term "measurement traceability" have been presented. In quality management systems—Fundamentals and vocabulary, ISO 9000:2015, the measurement traceability has been defined as: ability to track the fate, application or location of a unit by pre-recording the results of the determinations. While in international vocabulary of metrology—basic and general concepts and associated terms—VIM [7], the measurement traceability is described as property of the result of a measurement or a standard unit of measurement which can be linked to specific references generally to national standards or international units of measurement, through a continuous chain of comparisons, with a specified uncertainty [7, 15].

Every day, a huge number of chemical analyses are carried out, and each of them is characterised by its own requirements for the quality of the obtained result. The most important parameter of a reliable measurement result is its measurement traceability with a given standard of known metrological characteristics. Ensuring measurement traceability is therefore achieved by comparing a given property to a higher-level standard [16].

The International Committee for Weights and Measures (abbreviated CIPM from the *French Comité international des poids et mesures*) is the world's leading organisation for ensuring measurement traceability, the objective of which is to establish the measurement traceability for *SI* units. It is known, however, that not all measurements may refer to *SI* units, in which case, according to the recommendations of the Consultative Committee for Amount of Substance (CCQM), measurement traceability is determined with internationally recognised, preferably certified, reference materials.

In the measurement of chemical quantities, apart from the calibration of the measuring instrument, the result of each measurement depends on the type of sample and the way the analytical procedure is carried out. Chemical measurements usually require a special procedure to prepare the sample for analysis, which involves the need to take a representative portion of the tested material, as well as, e.g. dissolution or mineralisation and extraction of the sample. This means that in chemical measurements the concept of accuracy is difficult to define and the concept of traceability is much more difficult to implement. In the case of the chemical measurements, the biggest problem is to ensure the measurement traceability of the entire analytical process. For this reason, the validation of the entire measurement procedure and the assessment of the influence of sample components on the final measurement result are a very important element ensuring the quality of chemical measurement results [17].

The requirements to ensure measurement traceability apply both to physical operations (weighing and measuring liquids) and to the use of chemical standards and

CRM so that measurement traceability can be ensured throughout the analytical procedure. In addition, the use of CRM in chemical measurements, where they have a function similar to the standards of the international measurement system, allows the transfer of the value of a given quantity between different laboratories and its independent repetition in different laboratories. It is necessary to use reference standards for which measurement traceability can be demonstrated and for which the uncertainty is known. Reference materials play an extremely important role here, and it is through their use that a link to standards can be ensured—measurement traceability and thus global traceability of measurements can be achieved. For trace analysis, matrix and CRM are required to meet the measurement traceability requirement for a typical analytical procedure [18].

Ensuring measurement traceability, which is equal to ensuring the reliability of measurements, is an element of analytical chemistry, which is currently given special importance. Therefore, in order to obtain a complete overview of the measurement traceability, it should always be considered in the following aspects: the measurement traceability of analytical results, the measurement traceability of the standards used, the measurement traceability of the instrument used and the measurement traceability of the analytical methods (procedures) used [19].

13.6 Calibration

Calibration study is considered a necessary part of the validation of the method. According to one of the dictionaries, the calibration is "to determine, rectify or mark graduations of" [20]. Calibration is also referred to as "a model attempting to predict the value of the independent variable when only the dependent variable is known" [21]. For an analytical chemist, it is obvious that each analytical process includes a calibration step. In this sense, appropriate calibration in instrumental analysis is a basic prerequisite for chemical analysis, particularly in those areas where traceability is required for compliance and acceptance. The method of calibration itself depends on factors such as [22]:

- type of measuring device,
- number of samples,
- possibility of preparation of standards with a wide range of concentrations to check an entire measurement range,
- required accuracy of determination,
- sample matrix complexity,
- allow ability of sample composition changes.

A well-planned calibration step combined with an appropriate statistical analysis of the results makes it possible to obtain information not only about the type of response of the calibrated instrument or measurement points that lie outside the calibration curve, but also important data concerning the model equation linking the output

signal to the measured value and the limit of detection of the calibrated measuring instrument [1]. There are several ways to classify specific calibration techniques. There are two major groups of calibration approaches: external and internal. The description of the following methods is summarised in Table 13.4.

Calibration is therefore an integral and indispensable part of the analytical procedure. The purpose of calibration is to minimise measurement errors, i.e. to control

Table 13.4 Description of the calibration methods

Method		Description
External calibration *(standard samples are measured independently from real samples)*	**Single-point method**	Two measurements are carried out: for the standard mixture and for the sample. The content of the analyte in the real sample is calculated using the proportional relationship between the signals of the standard sample and the real sample
	Bracketing solution method	It is necessary to take three measurements: one for the real sample and two for samples of standard solutions in which the content of the analyte is, respectively, larger and smaller than the content of the analyte in the test sample
	Multipoint calibration method	Classical calibration curve method where the dependence $S = f(c)$ a linear form $S = a + bc$ shall be determined
Internal calibration *(standard is usually added to the real sample and analysed together)*	**Standard addition method**	Measurements are carried out on the sample itself and then on the sample with the addition of a standard. The advantage of this method is the minimal influence of the matrix composition on the measurement result, because both samples (real and with the addition of a standard) are determined in a matrix with a very complex composition

(continued)

Table 13.4 (continued)

Method		Description
	Internal standard method	Known amount of a compound, different from the analyte is added to the unknown sample, and internal standards are used when the detector response varies slightly from run to run because of hard to control parameters

and ensure the quality of the results obtained. Calibration also plays an important role at the stage of developing new analytical procedures and verifying their scope of applicability.

13.7 Summary

The problem of assurance and quality control of measurement results is mainly related to insufficient information concerning the tools applied during the process and the way in which they are used. Above all, the statistical tools underpinning metrology should be mentioned. The results of analytical measurements are a kind of "product" of the work of a chemist-analyst.

As with any of the products manufactured, the analytical result is also required to be of high quality. In addition, in the case of the quality of the analytical result, there is a cumulative quality requirement: the quality of each product is defined as the result of comparing the value obtained from the measurement with the reference value, which is the normalised value or the expected value. Therefore, in order for the result obtained from the measurement to be comparable (reliable, accurate) with the reference value, it must be documented and its high quality must be maintained. In order to be able to conclude on the quality of the tested products, the quality of the analytical measurement results must be ensured first.

It should be stressed that the basic and necessary parameters that characterise the analytical result are traceability and uncertainty. An analytical result without documenting its traceability and/or without an estimated value of uncertainty instead of characterising the material object may be a source of disinformation. These two parameters are the basic requirements for a reliable measurement result.

The values of errors and uncertainty strongly depend on the level of analyte content (concentration). Usually no acceptable, as a too high, values of these parameters in the case of analyte content on the percentage level can be satisfying for trace analysis.

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Chapter 14
QuEChERS—A Green Alternative Approach for the Determination of Pharmaceuticals and Personal Care Products in Environmental and Food Samples

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Abstract The widespread environmental distribution of pharmaceuticals and personal care products (PPCPs) is well-recognized, and the number of recent studies reflects the continuing interest and high level of research activity on the presence of PPCPs in the environment and food. In order to quantify their low environmental levels, sensitive and selective analytical methodologies are required. Recently, significant effort has gone into determining their concentrations in environmental matrices, with special attention to environment-friendly practices and the development of so-called *Green Analytical Chemistry* (GAC) methods. GAC is one of the most active areas of research and development in Green Chemistry and represents a real challenge for environmental analytical chemists. Its objective is the introduction of new techniques and methodologies able to minimize the environmental and occupational hazards involved in all stages of chemical analysis, allowing faster and more energy-efficient methods without compromising performance criteria. To accomplish the goal of GAC, the QuEChERS (Quick, Easy, Cheap, Effective, Rugged and Safe) method was introduced. As a result of the inherent advantages of the QuEChERS having "*Green Chemistry*" characteristics, the method has expanded rapidly to include the extraction of different groups of contaminants from various matrices and emerged as a green alternative to traditional sample preparation steps. This chapter deals with the application of the QuEChERS approach as a "*green*" sample preparation technique for determining PPCPs residues in environmental and food matrices

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J. Płotka-Wasylka and J. Namieśnik (eds.), *Green Analytical Chemistry*,
Green Chemistry and Sustainable Technology,
https://doi.org/10.1007/978-981-13-9105-7_14

and highlights major trends in its development. A brief explanation of the analytical technique used is provided together with a discussion of the experimental features of the studies reviewed.

Keywords Green Analytical Chemistry · QuEChERS · PPCPs · Environmental samples · Food samples

14.1 Introduction

Human activities that have an ecotoxicological impact on the environment are at the center of many research fields, such as chemistry and environmental science. Numerous methodologies have been developed to analyze various compounds or classes of compounds in different kinds of environmental samples. Sometimes, however, the analysis of environmental samples leads to a contradictory situation causing negative impacts on the environment and humans [1]. This is due to the generation of excessive chemical waste, and the use of high amounts of reagents that can be more toxic than the chemical species being determined, affecting not only the environment but also the safety of the operator due to exposure to hazardous materials. Therefore, there is an urgent need to combine sustainability with scientific and technological evolution [2].

During the last three decades, greener alternatives in multistep preparations have been sought, with the aim to reduce time and cost of analysis without affecting the analytical characteristics of the method in terms of efficiency and accuracy [3]. What is remarkable is that this could also minimize errors involved in each stage of the analytical process, since method uncertainty is affected by the number of steps in the method. As such, the more automated a workflow, the higher the reproducibility.

This idea of green chemistry came about in 1991, during a special US Environmental Protection Agency (USEPA) program, where the primary importance of the need to find environmentally friendly techniques in science was raised [4]. In the aftermath, the rapid development of green chemistry in analytical laboratories has led to what is now termed "Green Analytical Chemistry" (GAC) [5].

Since GAC is now well established, it can be characterized as an emerging branch of analytical chemistry, applicable, and motivating not only in the academic sphere but also in industry, and through its adoption promises improvements in the quality of life in developed and developing countries [2, 6].

The GAC approach is comprised of twelve principles [7] that should be followed during the development of environmentally friendly green analytical methods and form the so-called backbone of GAC (Fig. 14.1), and include (1) the reduction, replacement, detoxification, or elimination in the use of solvents, reagents, preservatives, and of course hazardous substances (2) minimization of energy consumption, (3) simplification in the management of analytical waste, and (4) establishment of a safer environment for the operators and the environment [8].

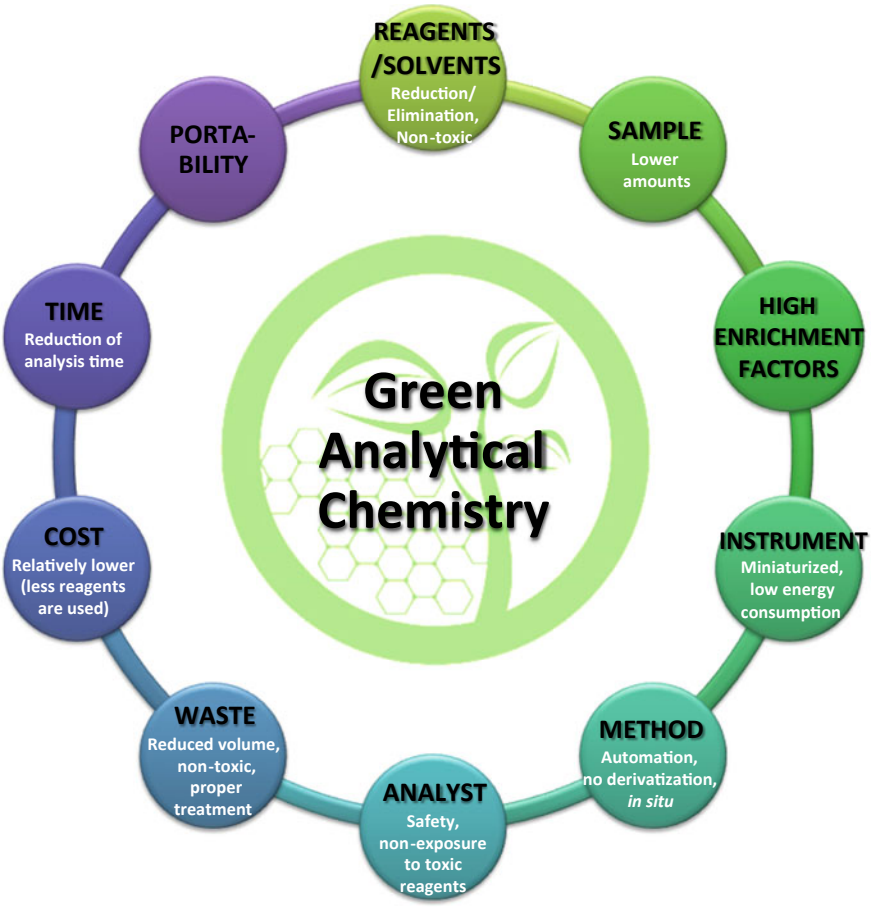

Fig. 14.1 A schematic "backbone" for the Green Analytical Chemistry (adapted from Gałuszka et al. [7])

The extent of "greening" a method can be easily assessed thanks to the so-called ecological scale which uses a score of between 0 and 100 to categorize the "greenness" of the method [2, 9]. The methods are categorized accordingly:

- excellent green analysis (>75 points);
- acceptable green analysis (>50 points); and
- inadequate green analysis (<50 points).

The "side effects" of conventional analytical chemistry are gradually being lost by adopting various steps, with the reduction or elimination of toxic solvents and reagents being the simplest and miniaturization and automation being the more challenging ones [2].

Following these "principles," novel and environmental-friendly sample preparation techniques have gradually replaced conventional ones and combined with liquid chromatography (LC) and gas chromatography (GC) coupled to mass spectrometry have become the method of choice for the separation and quantification for many analytical purposes. While significant effort has gone into sensing, direct measurement of untreated samples, on-line treatment of waste and automation, the miniaturization of procedures and instrumentation is key to achieving GAC [10]. As such, both sample pretreatment techniques and instrumentation that tend to be smaller or even portable are gaining popularity.

14.2 QuEChERS in PPCP Analysis

Over the last decade, modern sample preparation techniques based on GAC have begun to receive attention for monitoring PPCP residues in environmental and food samples, with the aim of combining sample extraction, purification, and enrichment. Among the different eco-friendly analytical configurations, QuEChERS (Quick, Easy, Cheap, Effective, Rugged and Safe) is one of the most promising in achieving the principles and goals of GAC for the extraction of PPCPs from complex environmental and food matrices. Accordingly, this technique is expected to have the most pronounced development in the future. What follows is a brief description of developments in the QuEChERS approach relevant to environmental and food analysis and applications coupled to chromatographic analysis with emphasis on studies published during the last five years (Tables 14.1 and 14.2).

14.2.1 QuEChERS—General Information

The QuEChERS method was first published by Anastassiades et al. in 2003 as an alternative to conventional extraction techniques (Fig. 14.2) for determining pesticides residues in fruit and vegetables with high water content [11].

It was first conceived in 2001 for the determination of veterinary drugs in animal tissues but its ability to extract non-polar and mainly basic pesticides from plants, led the authors to conduct an exhaustive study of its potential as a multiresidue method. As a result, a streamlined method was presented for the first time in 2002 at the EPRW (European Pesticides Residues Workshop) in Rome [12], as a promising tool for a green and affordable multiresidue method. As depicted in Fig. 14.3, the "*original*" method has been modified to enlarge both the target analyte and commodity (matrix) group.

The objective of the QuEChERS developers was not only to create a cheap and environmentally friendly method but also an efficient extraction technique that results in few interferences (pigments, lipids, sugars, fatty acids, etc.), safe for instrumentation and makes it easier to distinguish analytes from endogenous components.

Table 14.1 Summary of the most recent applications of QuEChERS for the determination of PPCPs in environmental samples (2015–2018)

Target analytes	Sample matrix (amount)	QuEChERS				Detection of analytes			Method performance			Ref.
		Solvent	Salts	Clean-up step	Final extract	Detection system	Column	Mobile phase	(%) R	LOD	LOQ	
47 ECs: antibiotics, NSAIDs, lipid regulators, antimicrobials, antidiabetics, analgesics and PPCPs	soil, sediment (1 g)	10 mL ACN	6 g $MgSO_4$, 1.5 g NaCl, 1.5 g $C_6H_5Na_3O_7$* 2 H_2O, 0.75 g [HOC(COOH) $(CH_2COONa)_2$ 1.5 H_2O	Aliquot: 1 mL Sorbents: 150 mg $MgSO_4$, 50 mg PSA, 50 mg C_{18}	1 mL H_2O/MeOH (70/30)	UHPLC–QqQ MS/MS	Kinetex XB-C_{18} 100A, (50×2.1 mm, 1.7 μm)	ESI (-): (A) MeOH, (B) H_2O (both with 2.5 mM NH_4F) ESI (+): (A) MeOH, (B) H_2O (both with 2.5 mM NH_4F and 0.1% FA)	9 – 98	n/a	10 – 40 ng g^{-1}	[13]
9 musks, 6 sunscreens, carbamazepine, and several PAHs, PCBs, OCPs	sediment (2 g)	10 mL EtOAc/ toluene (75/25)	4 g $MgSO_4$, 1 g NaCl, 0.5 g [HOC(COOH) $(CH_2COONa)_2$ 1.5 H_2O, 1 g $C_6H_5Na_3O_7$* 2 H_2O	Aliquot: whole extract Sorbents: 1200 mg $MgSO_4$, 400 mg PSA, 400 mg C_{18}	1 mL EtOAc/toluene (75/25)	GC–MS	HP-5 MS UI (30 m×0.25 mm, 0.25 μm)	-	77 – 131	0.01-3.18 ng g^{-1}	0.05 – 1.91 ng g^{-1}	[14]
9 parabens	sludge (10 g)	10 mL ACN (1% FA)	4 g $MgSO_4$, 1 g NaCl	Aliquot: 2 mL Sorbents: 150 mg $MgSO_4$, 50 mg chitin	2 mL ACN (1% FA)	LC–MS/MS	Kinetex C_{18} (3×50 mm, 2.6 μm)	(A) H_2O, (B) ACN/MeOH 50:50	62 – 119	1. 5 –3 ng g^{-1}	5 – 10 ng g^{-1}	[15]
19 PPCPs	sewage/	10 mL	0.2 g NH_4Ac	no clean-up	0.5 mL MeOH	LC–	Zorbax SB	(A)H_2O,	73 –	0.001–	0.002–	[16]

(continued)

Table 14.1 (continued)

Target analytes	Sample matrix (amount)	QuEChERS				Detection of analytes			Method performance			Ref.
		Solvent	Salts	Clean-up step	Final extract	Detection system	Column	Mobile phase	(%) R	LOD	LOQ	
(antibiotics, analgesics, psychiatrics, b-blockers and parabens)	surface water (10 mL)	ACN (1% HAc)			(pH= 6.5, NH_4OH)	MS/MS	C_{18} (4.6×50 mm, 1.8 µm)	(B) MeOH (both with 0.1% FA)	125	0.167 ng mL^{-1}	0.25 ng mL^{-1}	
8 antibiotics, 6 other drugs	sewage sludge/soil (5 g/6 g)	QuEChERS was used for clean-up		Aliquot: n/a Sorbents: 70 mg NaOAc, 280 mg Na_2SO_4, 100 mg EDTA	diluted with H_2O (pH=2.6) up to ≈1/16 1/20 (5% organic solvent)	UHPLC–MS/MS	BEH C8	(A) H_2O (B) ACN (both with 0.1% FA)	50 – 140	n/a	0.1 – 180 µg kg^{-1}	[17]
immunosuppressive drugs and metabolites	sediments (5 g)	15 mL ACN (2% FA)	9 g $MgSO_4$, 3.2 g NH_4Ac	no clean-up	0.5 mL MeOH/H_2O (10/90)	LC–MS/MS	Kinetex RP-18 (100×4.6 mm, 2.6 µm)	(A) H_2O (B) ACN (both with 0.2% FA)	102 – 104	0.048 – 0.133 ng g^{-1}	0.15 – 0.25 ng g^{-1}	[18]
carbamazepine, flumequine, thiabendazole	soil (2 g)	10 mL ACN	6 g $MgSO_4$, 1.5 g NaOAc	Aliquot: 5 mL Sorbents: 125 mg PSA 150 mg C18, 750 mg $MgSO_4$	0.1 mL ACN/H_2O (10/90)	LC/QqLIT-MS/MS	Zorbax Eclipse Plus C18 (150×4.6 mm, 5 µm)	(A) ACN (B) H_2O (both with 0.1% FA)	70 – 77	0.02–1.3 ng g^{-1}	0.04–2 ng g^{-1}	[19]
11 psychiatrics/ metabolites	sediment (5 g)	15 mL ACN (2% NH_4OH)	4 g $MgSO_4$, 1 g NaCl	Aliquot: 12 mL Sorbents: 150 mg PSA, 900 mg $MgSO_4$	0.5 mL H_2O/ACN (50/50)	UHPLC–MS/MS	Cortecs UPLC C18+ (100×2.1 mm, 1.6 µm)	(A) H_2O (0.1% FA) (B) ACN	47 – 110	0.01–2.08 ng g^{-1};	0.04 – 6.94 ng g^{-1}	[20]
synthetic musks	beach sand (5 g)	3 mL ACN	2.4 g $MgSO_4$, 0.75 g NaOAc	Aliquot: whole extract	0.5 mL ACN	GC–MS	J&W CP-Sil 8 CB	-	60 – 127	0.79 – 38 pg	n/a	[21]

(continued)

Table 14.1 (continued)

Target analytes	Sample matrix (amount)	QuEChERS				Detection of analytes			Method performance			Ref.
		Solvent	Salts	Clean-up step	Final extract	Detection system	Column	Mobile phase	(%) R	LOD	LOQ	
(5 nitro, 5 polycyclic and 1 macrocyclic)				Sorbents: 180 mg $MgSO_4$, 60 mg PSA, 30 mg C18			(50 m× 0.25 mm, 0.12 µm)			g^{-1}		
73 OMCs: analgesics, antibiotics, lipid regulators, psychiatrics, β-blockers etc., and suspect screening of 1300 ECs	soil (1 g)	10 mL ACN (1% HAc)	5 g $MgSO_4$, 1.5 g NaOAc	Aliquot: 5 mL Sorbents: 750 mg $MgSO_4$, 125 mg C_{18}	0.1 mL ACN/H_2O (10/90)	LC–QTOF-MS	Poroshell 120 EC-C_{18} (50×4.6 mm, 2.7 µm)	(A) H_2O (0.1% FA) (B) ACN	70 – 120	n/a	0.1 – 5 ng g^{-1}	[22]
7 NSAIDs and metabolites	sludge (1 g)	15 mL H_2O /ACN (1/2)	2 g NaCl 2 g $MgSO_4$	SPE clean-up	2 mL of the extract	LC–ESI–MS/MS	Strata-X/PFP	(A) H_2O (B) ACN	36 – 76	0.065 – 6.7 ng g^{-1}	0.22 – 22 ng g^{-1}	[23]

* stands for ×

n/a not available; *ACN* acetonitrile; *EtOAc* ethyl acetate; *FA* formic acid; *HAc* acetic acid; *MeOH* methanol; *NH_4F* ammonium formate; *NH_4Ac* ammonium acetate; *PSA* primary secondary amine; *ECs* emerging contaminants; *NSAIDs* non-steroidal antinflammatory drugs; *OMCs* organic microcontaminants; *PPCPs* pharmaceuticals and personal care products

Table 14.2 Summary of the most recent applications of QuEChERS for the determination of PPCPs in food samples (2015–2018)

Target analytes	Food matrix (amount)	QuEChERS				Detection of analytes			Method performance			Ref.
		Solvent	Salts	Clean-up step	Final extract	Detection system	Column	Mobile phase	%R	LOD	LOQ	
14 veterinary drugs (sulfonamides, benzimidazoles, macrolides, β-lactams, amphenicol, anisole, piperidine)	milk (10 g)	10 mL ACN (0.01 % HAc)	4 g $MgSO_4$	Aliquot: 2 mL Sorbents: 150 mg $MgSO_4$, 50 mg lab-made chitosan	n/a	LC–MS/MS	XTerra C_{18}, (50×3 mm, 3.5 μm)	(A) H_2O (B) ACN (both with 0.1% FA)	62 – 125	0.3 – 16.6 μg kg^{-1}	1 – 50 μg kg^{-1}	[24]
24 macrolides and metabolites	bass (Lateolabrax) (1 g)	5 mL ACN/H_2O (84/16) (0.1 M EDTA)	1g NaOAc, 0.25 g K_2CO_3, 0.25 g $NaHCO_3$	Aliquot: 1 mL Sorbents: 32 mg Z-Sep+ 75 mg PSA, 0.25 g Na_2SO_4	0.2 mL extract, 0.3 mLMeOH, 0.5 mL 8 mM NH_4F)	UHPLC–Q-Orbitrap MS	Hypersil Gold Q C_{18} (100×2.1 mm, 1.9 μm)	(A) H_2O (B) MeOH (both with 0.1% FA and 4mM NH_4F)	81 – 107	0.12 – 3.61 μg kg^{-1}	0.20 – 6.02 μg kg^{-1}	[25]
14 steroid hormones and 1 metabolite	chicken, pork and beef (1 g)	4 mL ACN	0.8g $MgSO_4$, 0.2 g NaCl	Aliquot: 1.25 mL Sorbents: 50 mg Al_2O_3, 50 mg Florisil	1.25 mL ACN	UHPLC–Orbitrap MS	Zorbax Eclipse Plus C_{18} (100×2.1 mm, 1.8 μm)	(A) H_2O (0.1% FA) (B) MeOH	70 – 103	n/a	1.0 μg kg^{-1}	[26]
87 veterinary drugs	honey (5 g)	10 mL EtOAc	-	Sorbents: 5 g Na_2SO_4, 0.2 g C_{18}, 0.2 g PSA	0.1 mL (0.15 mL MeOH, 4.75 mL	nanoLC–HRMS	EASY-Spray PepMap® C_{18} (75×150 mm, 3 μm)	(A) H_2O (B) ACN (both with 0.1% FA)	70 – 120	n/a	n/a	[27]

(continued)

Table 14.2 (continued)

Target analytes	Food matrix (amount)	QuEChERS				Detection of analytes			Method performance			Ref.
		Solvent	Salts	Clean-up step	Final extract	Detection system	Column	Mobile phase	%R	LOD	LOQ	
					H_2O)							
4 parabens and 10 UV filters	human milk	2.5 mL ACN	150 mg $MgSO_4$, 150 mg NaCl	Sorbents: 250 mg PSA, 50 mg C_{18}, 25 mg $MgSO_4$ Aliquot: 2 mL	0.1 mL ACN/H_2O (70/30)	UHPLC–MS/MS	Gemini C_{18} (100× 2 mm, 3 μm)	(A) ACN/H_2O (10/90) (B) ACN/H_2O (90/10) (both with 0.1% FA)	87 – 112	0.1 – 0.2 ng mL^{-1}	0.3-0.6 ng mL^{-1}	[28]
sulfonamides and their metabolites	salmon (1 g)	5 mL ACN/H_2O (84/16) (1% HAc)	1g $MgSO_4$, 0.1 g NaOAC	Sorbents: 45 mg Z-Sep+, 32 mg PSA 0.25 g Na_2SO_4	0.2 mL extract, 0.3 mL MeOH, 0.5 mL 8 mM NH_4F)	UHPLC–Q-Orbitrap	Hypersil Gold aQ C_{18} (100 ×2.1 mm, 1.9 μm)	(A) H_2O (B) MeOH (both with 0.1% FA and 4mM NH_4F)	83 – 109	0.04 – 1.34 μg kg^{-1}	0.07 – 2.33 μg kg^{-1}	[29]
26 pharmaceuticals (anorexics, stimulants, anxiolytics, antidepressants and laxatives)	plant food supplements (0.5 g)	10 mL ACN	4 g $MgSO_4$, 1 g NaCl	Aliquot: 1 mL	0.5 mL extract diluted in 1 mL ACN/H_2O (10/90)	UHPLC–MS/MS	Kinetex C_{18} (150× 2.6mm, 1.7 μm)	(A) H_2O (0.1% FA) (B) ACN	70 – 120	0.01 – 2.94 μg L^{-1}	0.02 – 9.80 μg L^{-1}	[30]
7 β-agonists	muscle and viscera (5g)	1 mL ACN (1% HAc)	6 g $MgSO_4$, 1.5 g NaOAc	Sorbents: 900 mg $MgSO_4$ 150 mg PSA 150 mg C_{18}	diluted with 1 mL ACN/H_2O (9/1) for muscle and ACN for viscera	LC–MS/MS	Zorbox SB-C_{18} (150× 4.6 mm, 5 μm)	(A) H_2O (B) MeOH (5 mM NH_4Ac)	70 – 120	n/a	1.0 μg kg^{-1}	[31]

(continued)

Table 14.2 (continued)

Target analytes	Food matrix (amount)	QuEChERS				Detection of analytes			Method performance			Ref.
		Solvent	Salts	Clean-up step	Final extract	Detection system	Column	Mobile phase	%R	LOD	LOQ	
15 sulfonamides, 14 fluoroquinolones, 4 macrolides, 3 nitroimidazoles,4 tetracyclines, dapsone and trimethoprim	honey (2 g), royal jelly (1 g)	10 mL ACN (1% HAc)	4 g Na_2SO_4, 1 g NaCl	Aliquot: 4 mL Sorbents: 900 mg Na_2SO_4 50 mg PSA 150 mg C18-EC	0.3 mL extract with 0.7 mL H_2O (2 mM NH_4F, 0.1% FA)	LC–MS/MS	Poroshell 120, EC-C_{18}, (100×2.1 mm, 2.7 μm)	(A) H_2O (2 mM NH_4F, 0.1% FA) (B) MeOH	80 – 118	0.14 – 3.81 ng g^{-1}	honey: 0.50 – 9.70 ng g^{-1} royal jelly: 0.58 – 12.68 ng g^{-1}	[32]
80 veterinary drugs (benzimidazoles, β-lactams, lincosamides, macrolides, nitromidazoles, quinolones, sulfonamides and trimethoprim, tetracyclines, triphenylmethane dyes, amphenicols, nonsteroidal estrogens and steroid hormones)	fish tissues (1 g)	5 mL (ACN/MeOH:H_2O, 3:1:1) (1% HAc)	without salting-out	no clean-up	1 mL	LC–Orbitrap MS	UPLC BEH C_{18} (100×2.1 mm, 1.7 μm).	(A) H_2O (0.1% FA) (B) MeOH	61 – 110	n/a	0.25 – 25 μg kg^{-1}	[33]
sulfonamides and 5 acetylated metabolites	baby foods (5 g)	15 mL ACN (1% HAc)	6 g $MgSO_4$, 1.5 g NaOAc	Aliquot: 4 mL Sorbents: 900 mg $MgSO_4$ 150 mg PSA 150 mg C18	0.8 mL	UHPLC–Orbitrap-MS	Hypersil Gold aQ (100 ×2.1 mm, 1.9 μm)	(A) H_2O (0.5 mM HAc and 1 mM NH_4F (B) MeOH (0.2 mM HAc)	61 – 86	0.03 – 0.17 μg kg^{-1}	0.10 – 0.55 μg kg^{-1}	[34]

(continued)

Table 14.2 (continued)

Target analytes	Food matrix (amount)	QuEChERS				Detection of analytes			Method performance			Ref.
		Solvent	Salts	Clean-up step	Final extract	Detection system	Column	Mobile phase	%R	LOD	LOQ	
nitroimidazoles, nitrofurans and chloramphenicol	chicken, muscle, egg (2 g)	10 mL hexane 15 mL EtOAc	n/a	n/a	diluted in 1 mL (5% MeOH and 0.1% FA)	UHPLC–MS/MS	BEH C_{18} (50×2.1 mm, 1.7 µm)	(A) H_2O (B) ACN (both with 0.1% FA)	87 – 117	0.02 – 0.2 µg kg^{-1}	0.1 – 0.5 µg kg^{-1}	[35]
47 ECs: antibiotics, NSAIDs, lipid regulators, antimicrobials, antidiabetics, analgesics and PPCPs	fish (3.25 mL)	10 mL ACN	6 g $MgSO_4$, 1.5 g NaCl, 1.5 g $C_6H_5Na_3O_7$ * 2 H_2O 0.75 g [HOC(COOH) (CH_2COONa)21.5 H_2O]	Aliquot: 1 mL Sorbents: 150 mg $MgSO_4$ 50 mg PSA 50 mg C_{18} Aliquot: 4 mL	dissolved in 1 mL H_2O/MeOH (70/30)	UHPLC–MS/MS	Kinetex XB-C_{18} 100A (50×2.10 mm, 1.7 µm)	ESI (-): (A) MeOH (2.5 mM NH_4F) (B) H_2O (2.5 mM NH_4F) ESI (+): A) MeOH (2.5 mM NH4F) (B) H_2O (2.5 mM NH_4F) (both with 0.1% FA)	38 – 104	0.08 – 0.98 ng g^{-1}	5 – 30 ng g^{-1}	[13]
23 antibiotics and some of their metabolites	seafood (clam, mussel, fish)	10 mL ACN	6 g $MgSO_4$, 1.5 g NaOAc	Sorbents: 900.2 mg $MgSO_4$ 149.9 mg PSA 149.9 C_{18}	1 mL MeOH	UHPLC–QqLIT MS/MS	HSS T3 (50×2.1 mm, 1.8 µm)	(A) ACN (B) H_2O (both with 0.1% FA)	30 – 70	0.01 – 0.31 ng g^{-1}	0.02 – 1.03 ng g^{-1}	[36]
16 β-lactams	chicken muscle (2 g)	5 mL ACN (0.1 % FA)	QuEChERS extraction tube	Sorbents: QuEChERS cleanup tube	2 mL ACN/H_2O (10/90)	UPLC–Q-Orbitrap-MS	HSS $T3C_{18}$ (100× 2.1 mm, 1.7 µm)	(A) H_2O (B) ACN (both with 0.1% FA)	83 – 112	0.01 – 0.35 µg kg^{-1}	0.03 –.16 µg kg^{-1}	[37]

(continued)

Table 14.2 (continued)

Target analytes	Food matrix (amount)	QuEChERS				Detection of analytes			Method performance			Ref.
		Solvent	Salts	Clean-up step	Final extract	Detection system	Column	Mobile phase	%R	LOD	LOQ	
UV-filters and estrogens	Eastern crayfish, Red swamp crayfish, Eastern oyster, Hooked mussel (0.05 g)	5 mL ACN	2.5 g $MgSO_4$, 1 g NaCl	Aliquot: 2.5 mL (submitted to SPE)	0.5 mL MeOH (0.1% NH_4OH)	LC–MS/MS	XBridge C_{18} (150× 2.1 mm, 2.5μm)	(A) H_2O (B) MeOH (both with 0.1% NH_4OH)	>80	0.2 – 2 ng g^{-1}	0.7 – 6.7 ng g^{-1}	[38]
nitrofuran metabolites and nitroimidazole residues	honey	10 mL ACN	4 g $MgSO_4$ 1 g NaCl	-	1 mL MeOH/H_2O (1:9) (5 mM NH_4F)	LC–MS/MS	ZORBAX Eclipse XDB C_{18} (150×4.6 mm, 5 μm)	(A) MeOH/H_2O (1:9) (5 mM NH_4F) (B) MeOH	91 – 105	0.12 – 0.74 μg kg^{-1}	0.21 – 1.27 μg kg^{-1}	[39]
182 organic contaminants (PPCPs, veterinary drugs and pesticides)	fish fillet (10 g)	10 mL ACN	4 g Na_2SO_4 1 g NaCl	Aliquot: 1 mL Sorbents: 150 mg of Na_2SO_4 125 mg C18 25 mg PSA	1 mL ACN	LC–QTOF/MS/MS	Zorbax Eclipse Plus C_{18} (50×2.1 mm, 1.8 μm)	(A) H_2O/MeOH (98:2) (B) MeOH (both with 0.1% FA and 5 mmoL NH_4F)	70 – 120	5 – 25 μg kg^{-1}	1.5 – 7.5 μg kg^{-1}	[40]
625 multiclass food contaminants: (426 pesticides, 117 veterinary drugs and pharmaceuticals, 42 food packaging contaminants, 10 perfluoroalkyl substances, 21 mycotoxins, 9	baby food containing meat and vegetables (10 g)	10 mL ACN (0.1 % HAc)	4g $MgSO_4$, 1g NaOAc	Aliquot: 5 mL Sorbents: 750 mg $MgSO_4$ 250 mg PSA	3 mL ACN (20% MeOH)	UHPLC–Q-TOF	Zorbax (RRHD) Eclipse-Plus C_{18} (50×2.1mm, 1.8 μm)	(A) H_2O (B) ACN (both with 0.1% FA)	n/a	n/a	n/a	[41]

(continued)

Table 14.2 (continued)

Target analytes	Food matrix (amount)	QuEChERS				Detection of analytes			Method performance			Ref.
		Solvent	Salts	Clean-up step	Final extract	Detection system	Column	Mobile phase	%R	LOD	LOQ	
nitrosamines, 9 sweeteners												
10 (NSAIDs)	milk (5 g)	10 mL ACN (5 % HAc)	-	Sorbents: 1 g $MgSO_4$ 150 mg C_{18}	0.5 mL ACN (0.1 %FA)	HPLC–MS/MS and LC Q-Exactive Orbitrap	Kinetex Biphenyl (100 × 2.1 mm, 2.6 μm)	(A) H_2O (B) ACN (both with 0.1% FA)	78 – 97	0.4 – 1.5 μg kg^{-1}	0.8 – 1.9 μg kg^{-1}	[42]
90 veterinary drugs (14 families: lincomycins, macrolides, sulfonamides, quinolones, tetracyclines, b-agonists, b-lactams, sedatives, b-receptor antagonists, sex hormones, glucocorticoids, nitroimidazoles, benzimidazoles, nitrofurans, and the others)	royal jelly (1 g)	20 mL ACN (5% HAc)	2 g NaCl, 2 g Na_2SO_4	Aliquot: 10 mL Sorbents: 200 mg NH_2	1 mL H_2O (25% ACN)	UPLC–QTOF-MS	UPLC BEH C_{18} (100× 2.1 mm, 1.7 μm)	(A) H_2O (0.1% FA) (B) ACN	70 – 120	0.06 – 6.0 μg kg^{-1}	0.21 – 20 μg kg^{-1}	[43]
veterinary drugs, ergot alkaloids, plant toxins and other	poultry, swine, cattle, horse and lamb feed (2 g)	5 mL ACN (1% HAc)	4g $MgSO_4$, 1g NaCl, 1g $Na_3C_6H_5O_7$, 0.5g	-	0.5 mL ACN/H_2O (1/3)	UHPLC–HRMS	Hypersil Gold (100× 2.1 mm, 1.9 μm)	(A) H_2O (0.1% HAc) (B) MeOH/ACN (90/10) (0.1%	80 – 120	n/a	< 12.5 μg kg^{-1}	[44]

(continued)

Table 14.2 (continued)

Target analytes	Food matrix (amount)	QuEChERS				Detection of analytes			Method performance			Ref.
		Solvent	Salts	Clean-up step	Final extract	Detection system	Column	Mobile phase	%R	LOD	LOQ	
			$C_{12}H_{18}Na_4O_{17}$					HAc)				
77 compounds (polar pesticides, PPCPs, PBDEs, PCBs, PAHs, OCPs)	fish, muscle and breast milk (10 g)	10 mL ACN	4 g $MgSO_4$ 1 g NaCl	Aliquot: 5 mL	0.3 mL (GC–QqQ-MS/MS) 0.1 mL MeOH/H_2O (2/8) (LC–QTOF-MS/MS)	GC–QqQ-MS/MS and LC-QTOF-MS/MS	ESI (-): XDB-C_{18} (4.6× 50 mm, 1.8 μm) ESI (+): XDB-C_{18} (2.1×100 mm, 1.8 μm)	ESI (-): (A) H_2O (1% MeOH) (B) MeOH (10% H_2O) (both with 5 mM NH_4Ac) ESI (+): (A) H_2O (B) MeOH (both 0.1% FA)	70 – 120	n/a	LC-QTOF-MS/MS: 0.2 – 9 μg kg^{-1}	[45]
14 sulfonamides	fish tissue (1 g)	5 mL ACN (or MeOH) (1% FA)	-	Aliquot: 1 mL Sorbents: C_{18}	1 mL extract	LC–ESI–MS/MS	ZORBAX SB-C_{18} (150×4.6mm, 5 μm)	(A) H_2O (5 mM NH_4Ac and FA) (B) MeOH	80 – 93	0.43 – 1.22 μg kg^{-1}	1.27 – 3.71 μg kg^{-1}	[46]
90 veterinary drugs	milk (2 g)	20 mL ACN (1% HAc)	1 g NaCl 2 g Na_2SO_4	Aliquot: 10 mL Sorbents: 100 mg C_{18}	1 mL H_2O (25% ACN)	UPLC–QTOF-MS	BEH C_{18} (100×2.1 mm, 1.7 μm)	(A) H_2O (0.1% FA) (B) ACN	73 – 122	0.03 – 5.20 μg kg^{-1}	0.10 – 17.30 μg kg^{-1}	[47]
fluoroquinolones	poultry muscle and kidney (2 g)	10 mL H_2O/ACN (80/20) (5% HAc)	4 g Na_2SO_4, 1 g NaOAc	Sorbents: 50 mg PSA 50 mg C_{18}	2 mL H_2O (0.1% FA)	LC–TOF-MS and LC–MS/MS	SB C_{18} (100×3.5 mm, 2.1 μm)	(A) H_2O (B) MeOH (both 0.1% FA)	83 – 114	n/a	n/a	[48]

* stands for ×

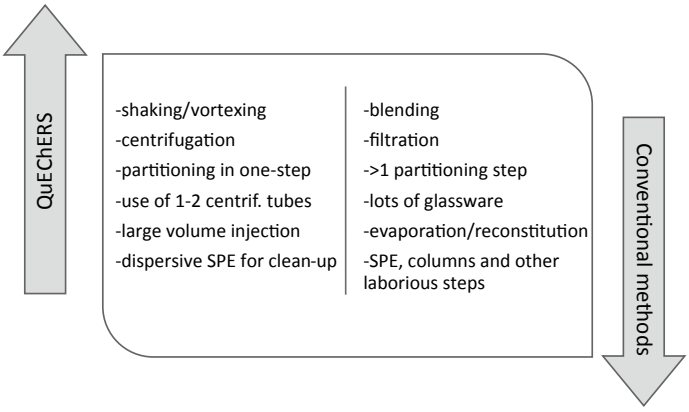

Fig. 14.2 QuEChERS compared to conventional extraction methods

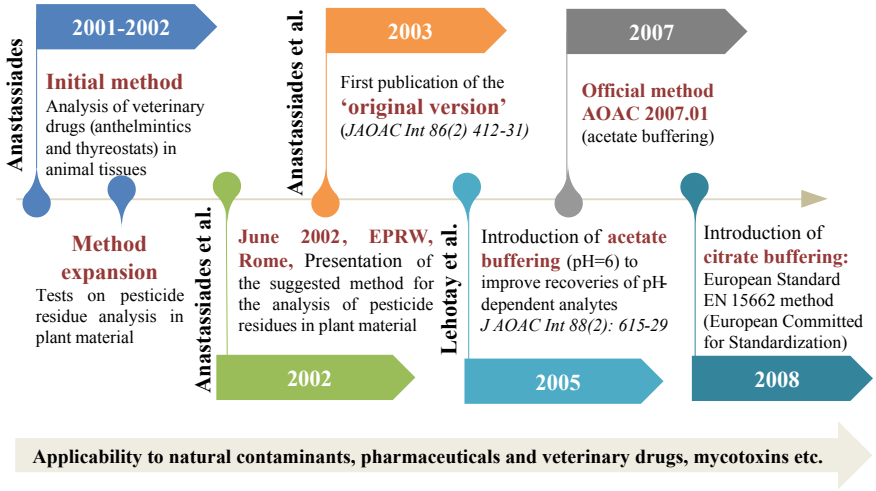

Fig. 14.3 The evolution of the "*official*" QuEChERS method

According to Lehotay et al. [49], the original QuEChERS was to be a flexible "template" that could be modified for different applications so as to be considered as a universal method. A large number of studies employing QuEChERS for environmental, food and clinical analysis specifically targeting pharmaceuticals, veterinary drugs, perfluorinated compounds, polycyclic aromatic hydrocarbons, alkaloids, mycotoxins, and many other compounds have been published [13, 50].

The method is based on two sequential steps: a solid–liquid (buffered) partitioning with a salting-out effect followed by a clean-up using dispersive solid-phase extraction (d-SPE) (Fig. 14.4). Both steps are applied separately in order to analyze a large number of compounds in different matrices. However, combining both steps

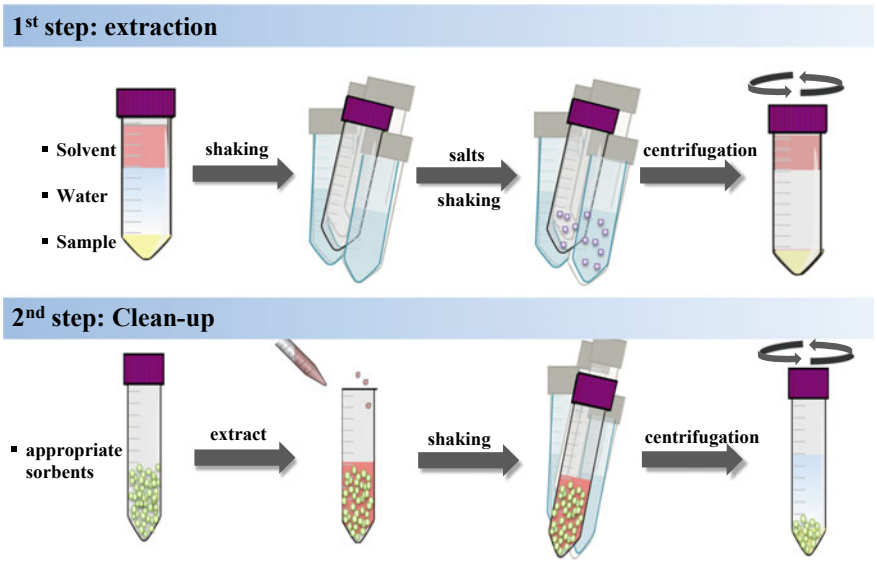

Fig. 14.4 Visualization of QuEChERS working steps

in a single method quickly became attractive for multiresidue analysis evidenced by the number of publications involving QuEChERS not only for pesticide analysis but also for various ECs in environmental matrices and food [14–21, 51–70].

In addition, although designed to extract non-polar ($\log K_{ow} > 4$) pesticides from vegetables with a high water content matrix, it has now been expanded to include a broad range of semi-polar or non-polar pesticides in complex environmental and food matrices. Sometimes the whole process is applied as a clean-up step following another sample preparation technique [19].

14.2.1.1 Modifications of the Original QuEChERS

The original QuEChERS method was able to extract many multiclass analytes in a variety of matrices. However, in multiresidue methods, there is always the need to increase recoveries, restrict matrix effects, and avoid instrumentation blockage or contamination. In this context, the original method has been modified either in the first step (LLE) by changing the extraction solvent, using mixtures or modifiers, adapting sample pH, or during the second clean-up (d-SPE) step by using various sorbents depending on the interfering compounds (Fig. 14.5).

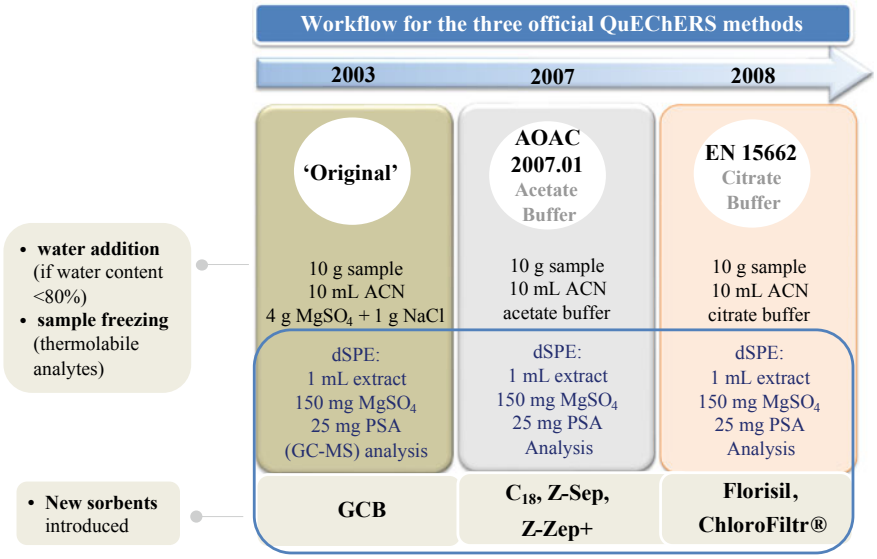

Fig. 14.5 Workflow for the three official QuEChERS methods and the most frequently used clean-up sorbents

Extraction Solvent

The most common extraction solvent used in QuEChERS is acetonitrile (ACN) [18, 71]. In some cases, however, the structure of target analytes or the nature of the analyzed matrix requires a different solvent. As such, ACN is occasionally mixed with methanol (MeOH), dichloromethane (DCM), hexane, acetone, and more rarely is totally replaced by methanol, acetone, or hexane.

The addition of water to the sample is also important. This step precedes the addition of the extraction solvent and allows the method to be used with matrices that have a lower water content (<80%). Its purpose is to weaken the interactions between the matrix and the pores of the matrix to enhance partitioning.

Adjustment of Sample PH

The first step of QuEChERS is based on LLE, which means that ionizable compounds may remain in the aqueous phase; this is very much dependent on pH. For this reason and to avoid reduced recoveries and poor accuracy, modified versions of QuEChERS are pH-oriented.

The modifications made to the QuEChERS method focus on improving the recoveries of pH-dependent analytes. Hence, the introduction of buffering salts was of great importance. Among the modified methods, two have been established as official methods according to international standard organizations, namely the AOAC

2007.01 method (AOAC International) [71], which uses acetate buffering and the EN 15662 (the European Committee for Standardization, CEN) [72] that uses citrate buffering. In both cases the pH is buffered at around 5 to prevent the degradation of pH sensitive compounds. As for EN 15662, the function of PSA in the clean-up step is stronger than in AOAC 2007.01, where the strong buffering capacity of acetate affects the efficiency of PSA leading to clean-up problems [73]. These two methods, however, are no longer considered solely for pesticide analysis and buffering with either formate or phosphate-buffered saline has been proposed. Regarding the protection of pH-dependent compounds that suffer from degradation at pH 8 (the pH of the extracts after purification), the addition of different concentrations of formic acid in ACN (from 0.1 to 5%) is efficient. This adjusts the pH to 5 and allows the long-term storage of samples prior to injection [74].

Addition of Salts

The addition of salts is intended to remove excess water from the organic layer ($MgSO_4$) and enhance the salting-out effect (NaCl). However, in case salts enter the organic layer and then deposit as a solid in the instrumentation, the latter could be affected irreversibly. To overcome this, the use of ammonium chloride and ammonium formate has been also reported [75, 76]. Formate adapts the pH to the desirable value without affecting the instrumentation, while ammonium formate and ammonium salts improve the ionization of analytes.

Freezing-Out Step

Since the addition of $MgSO_4$ to the acetonitrile sample system is exothermic, thermolabile analytes may be degraded and subsequently lost. To prevent this, the addition of cold water during the rehydration step or freezing the sample before extraction have been suggested [77]. The latter is used in the clean-up step when sorbents other than PSA and C_{18} are used. This step involves freezing the extract for 1–2 h before and after clean-up to precipitate out lipids avoiding the need to add extra sorbents [78]. Using dry ice is also suggested as a way to reduce analysis time.

Clean-up Sorbents

Interferences derived from the matrix, such as endogenous components or co-extractive compounds can be an important obstacle during analysis, leading to false results. With a view to obtaining cleaner extracts (as free as possible of interfering compounds), various clean-up sorbents other than PSA have been tested. The selection of the appropriate sorbents is based on the selective removal of co-extractives and their compatibility with the instrumental analysis method.

The combination of PSA with C_{18} is of primary importance especially in the analysis of samples with high lipid content. C_{18} helps to remove lipids without affecting analyte recovery by retaining polar analytes. Moreover, C_{18} on its own has been reported as a clean-up sorbent [22]. Graphitized carbon black (GCB) has also been added to the clean-up sorbent to remove pigments (chlorophyll) from colored matrices—although it can result in the loss of some planar analytes [65]. In several studies, GCB is also used together with PSA and C_{18} [79, 80]. An alternative to GCB for colored samples is ChloroFiltr®, a polymer-based sorbent designed to remove of chlorophyll without losing planar analytes [81].

In the case of non-polar analytes, the use of Florisil or Alumina is also an option [82–84]. More recently, successful lipid removal has been achieved using zirconium oxide-based materials [85]. The attractiveness of these new materials as sorbents is their high efficiency without any loss in analyte recovery. When zirconium oxide is combined with Si, it is commercially referred to as Z-Sep and when C_{18} is added, it is commercially known as Z-Sep+. In other cases, albeit more rarely, diatomaceous earth, polymer sorbents such as styrene-divinylbenzene (SDB) and SAX (a strong anion exchange sorbent) [86] and recently nanomaterials and magnetic nanoparticles have been reported [87–89]. The advantage of using nanomaterials is in their high extraction capacities resulting from their large surface areas.

It is noteworthy that $MgSO_4$ which is used in parallel during clean-up to remove any residual water remaining after extraction can be replaced by $CaCl_2$ on condition that the target analytes do not include polar compounds. This reagent allows for good clean-up, possibly better than "*conventional*" clean-up [90]. Lastly, although rarely used, the use of SPE after QuEChERS extraction is preferred when the clean-up sorbents negatively affect recovery. However, this option reduces the simplicity of the method and extends analysis time.

14.2.1.2 Application of QuEChERS in PPCP Analysis

Environmental Samples

From an analytical point of view, the analysis of PPCPs in solid environmental matrices remains a challenge due to their low levels and the strong interactions between the analytes and other sample components present in complex matrices. A number of various extraction techniques have been applied to the recovery of PPCPs from solid environmental samples such as soil, sediments, and sludge [14–21, 23, 62–64]. Although, QuEChERS has seldom been adopted the number of studies using QuEChERS is increasing (Table 14.1) and several modified versions of the method have been applied with good results for the extraction of non-polar, medium polar, and polar PPCPs, including non-steroidal anti-inflammatory drugs (NSAIDs) (i.e., ibuprofen etc.) [91], antibiotics (i.e., sulfonamides, quinolones, tetracyclines, etc.) [19], natural and synthetic hormonal steroids (estrogenic and androgenic compounds) [92], and other classes of PPCPs. Among these antibiotics and NSAIDs are the most commonly analyzed classes of compounds. For example, QuEChERS was used to

extract 31 substances including hormonal steroids, veterinary and human drugs in soils [92]. The authors found that QuEChERS could effectively extract multiple classes of pharmaceuticals from soils in the low ng g^{-1} concentration range, achieving recoveries for most of the target compounds (e.g., sulfonamides, carbamazepine etc.) comparable with ultrasonic extraction [93] or PLE [94]. The methodology was applied to real soil samples collected in the several areas of France, confirming the presence of SAs and human drugs (carbamazepine, ibuprofen) in soils that had received different treatments with manure and sludge, respectively.

In most cases, modified QuEChERS protocols have been used. The modifications usually focus on the parameters affecting extraction efficiency and the matrix effects like the amount of sample used, the sorbents required in the clean-up step, and the volume of water added during extraction. Besides these, still other, even more dramatic modifications have been made, such as the inclusion of ultrasonic-assisted extraction to improve extraction efficiency [19]. Concerning the extraction step, pH adjustment with different acids such as acetic [18, 25, 65, 91], formic [15, 20, 75], ascorbic, or citric acid [22, 95, 96] is usually performed; buffers or bases can be used as well [14, 97]. With respect to the clean-up step, C_{18} and PSA sorbents in combination with $MgSO_4$ provided the best results for most of the studied compounds and, therefore, it was typically selected as clean-up sorbents. Studies in which the use of C_{18} and PSA sorbents were applied alone have also been reported. Moreover, the desire for even more selective and cheaper clean-up phases have led to the application of various new sorbent material, like Chitin, which is a cheaper alternative to PSA and C_{18} [98].

Although QuEChERS is considered a high-throughput analytical approach, d-SPE involves extra sample manipulation, which compared to the extraction alone, creates some intrinsic limitations of the method. In addition, the challenges posed by matrix effects, especially when ESI-MS detection is employed, should be taken into account to avoid false results. For example, strong matrix effects (−80 to + 251%) have been reported for the determination of NSAIDs (ibuprofen, ketoprofen, diclofenac, and salicylic acid) by Peysson and Vulliet [99]. The authors developed a multiresidue method for screening 136 compounds including 119 pharmaceuticals and 17 hormones in aerobic biological sludge using an optimized QuEChERS protocol with a PSA clean-up step followed by LC-TOF/MS analysis. In the case of naproxen, the matrix effect was so high that its determination was questionable.

To overcome the these issues, a combination of QuEChERS extraction with a fully automatic solid-phase extract purification and pre-concentration, followed by LC-MS/MS was developed for the determination of NSAIDs and their metabolites in sewage sludge [26]. In this interesting report, various commercially available sorbent phases (i.e., silica gel functionalized with octyl or octadecyl groups and a polymeric phase functionalized with N-benzylpyrrolidone groups) were evaluated as a replacement for d-SPE. This approach offers several advantages compared to the QuEChERS method itself, including a reduction in analysis time (about 30 min per sample) and a significant increase in the overall pre-concentration factor. Moreover, high clean-up efficiencies were obtained with low matrix effects for all studied compounds.

Application to Foodstuffs and Animal Feed

Similar to the analysis of pharmaceuticals in environmental samples, determination of trace levels of these compounds in foodstuffs and animal feed presents significant challenges owing to the complex composition of animal tissues and feed including pigment, fat, cellulose, and wax constituents, which may interfere with sample extraction and analysis. Consequently, fast feasible analytical methods are required, especially in food control and safety. In this regard, the QuEChERS approach has been used to determine veterinary drugs in different food matrices including honey, meats, fish etc. and to accurately determine certain families of drugs while at the same time increasing sample throughput and reducing the cost of analysis.

As can be seen in Table 14.2, different versions of QuEChERS based either on the AOAC Official Method 2007.01 or on EN 15662 norms have been used to efficiently extract of target analytes. Depending on the nature of the target compound, pH control/adjustment is usually performed using acids (e.g., formic or acetic) [24, 25], bases (e.g., NH_3) [14], buffer solutions or salts (i.e., sodium acetate, or citrates) [16, 17]. In the majority of the cases, the d-SPE step is performed using various sorbents, such as C_{18}, PSA and GCB and different combinations of all three. In some cases, such as in the extraction of certain animal tissues, shrimp or animal feed, PSA has been used on its own. To enhance the clean-up for complex matrices to effectively remove interferences thereby overcoming existing limitations of traditional QuEChERS dispersive phases, new types of d-SPE sorbents have been applied. For example, d-SPE sorbents (Z-Sep and Z-Sep+) containing zirconia (ZrO_2) have been applied in the monitoring of 127 veterinary drug residues in bovine meat using UHPLC-MS/MS [85]. The obtained results showed that although the performance of the method was improved in terms of precision with the use of Z-Sep+ and Z-Sep+ in hexane, the recoveries for many of the studied veterinary drugs such as tetracyclines, fluoroquinolones, macrolides, and β-lactams were poor due to the strong interaction of the analytes with the sorbents. Alternative sorbents, which are cheaper and environmentally friendlier, like chitosan, have been studied [27]. The application of these materials has proven advantageous for extracting different classes of veterinary drugs (sulfonamides, benzimidazoles, macrolides, β-lactams, amphenicol, and anisole, piperidine) in milk, providing not only good recoveries, but also high efficiency in the reduction of matrix components from the final extract.

So far, antibiotics and, in particular, sulfonamides (SAs) have been the most investigated compounds. However, since a variety of contaminants has been detected in trace-level amounts, research efforts have recently focused on developing methods for the simultaneous determination of multiple classes of drug residues, including, quinolones, tetracyclines, macrolides, benzimidazoles, etc.

Samples of animal origin (e.g. animal tissues, milk, eggs, etc.) are the most commonly analyzed, probably due to the accumulation of in their tissues and the subsequent risk for humans. An interesting example is a study by Abdallah et al. [100], who developed a QuEChERS method for the simultaneous determination of 22 SAs and their metabolites in edible animal (pig, beef, sheep, and chicken) tissues. This report illustrates the advantages of using QuEChERS coupled to high-performance

liquid chromatography–high-resolution mass spectrometry (HPLC–HRMS; HPLC Orbitrap MS) over traditional methods, especially in terms of reliability when identifying SAs and their metabolites in food and minimizing the risk of false positives or negatives. Compared to the traditional LC–MS/MS quadrupole system, the analytical procedure was superior both qualitatively and quantitatively with higher selectivity and sensitivity. The proposed method was validated according to the European Commission Decision 2002/657/EC [101] and shown to be sensitive (LOD: 3–26 g kg^{-1} and LOQ: 11–88 g kg^{-1}), selective and precise (intra- and inter-day precision 1–14 and 1–17%, respectively) and accurate (recovery 88–112%) for determining SAs in animal tissues at low concentration levels.

Among other foods (see Table 14.2), plant food supplements, poultry, honey and baby foods have been studied. As an example, a highly sensitive and reliable multiresidue method for determining sulfonamides (12) and their acetylated metabolites (5) in baby foods using UHPLC-Orbitrap-MS system has been developed and validated [37]. The target analytes were extracted using the QuEChERS and ASE methods. Good performance characteristics were obtained by both methods; however, the optimized ASE method gave higher recovery rates for all analytes including better repeatability and reproducibility.

Moreover, applying QuEChERS for the detection of antibiotic residues in honey resulted in cleaner extracts and fewer matrix effects [35, 42, 102]. By using different combinations of sorbent materials in the clean-up step such as C_{18}, PSA, Florisil and NH_2 cartridges satisfactory recoveries were obtained for quinolones, SAs, tetracyclines, and macrolides. In the case of PSA, various polar organic acids, polar pigments, some sugars, and fatty acids are effectively removed, while the recoveries of most analytes increased with the amount of PSA. On the contrary, a reduction in the extraction efficiency was observed for fluoroquinolones when the amount of PSA is 50 mg. C_{18} showed similar clean-up efficiency compared to PSA by removing non-polar interfering substances like lipids. Florisil and NH_2 cartridges were better at analyzing multiple antibiotic residues and can be used to study a wide range of hydrophilic compounds simultaneously.

Additionally, animal feed is also analyzed to ensure its quality and prevent the introduction of contaminants into animals via food ingestion. Lopes et al. [103] used a modified QuEChERS procedure followed by LC-MS/MS to analyze 13 SAs in animal feed. The proposed method was evaluated following the accepted criteria for analytical method validation and quality control (e.g., 2002/657/EC) and proved simple and accurate, providing good validation parameters, such as linearity, LOD, LOQ, and precision.

It is worth mentioning that the ability of the QuEChERS method to extract a variety of compounds with diverse physicochemical properties has stimulated interest in the development of multiresidue procedures for the simultaneous determination of different kinds of compounds with very dissimilar properties in complex matrices. Consequently, to obtain a wide overview of chemicals present in a complex mixture, not only several classes of veterinary drugs can be simultaneously determined, but other contaminant groups (e.g., pesticides, veterinary drugs, and mycotoxins) can be included, increasing the number of compounds to be monitored and the com-

plexity of the analytical problem. In this context, Baduel et al. [21] developed a modified QuEChERS procedure followed by analysis with GC-MS/MS and LC-QTOF-MS/MS for the determination of 77 target compounds in breast milk and fish extracts. These covered a broad activity spectrum, from polar pesticides, pharmaceuticals, and personal care products (PPCPs) to highly lipophilic chemicals such as polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs), and organochlorine pesticides (OCPs). New zirconium dioxide-based sorbents and protein-lipid removal filter cartridges have been tested as alternatives to traditional d–SPE materials demonstrating their high clean-up efficiency for the target analytes. The optimized procedure had good sensitivity (LOQ from 0.08 to 9 $\mu g\ kg^{-1}$), recoveries (70 and 120%), and precision (RSD < 20%). The positive results obtained in this type of application demonstrate the potential of QuEChERS as a general, non-selective procedure, allowing the simultaneous extraction of polar and non-polar organic chemicals. Another interesting work is that of Filigenzi et al. [104] for the determination of 118 compounds, including plant alkaloids, pesticides, and veterinary drugs in milk, bovine muscle and liver tissue and corn silage, using QuEChERS extraction and HRMS. The authors concluded that a combination of generic extraction and chromatographic procedures with full scan HRMS can serve as a useful method for screening complex matrices. The same HRMS system (Exactive Orbitrap), was used by Gómez-Pérez et al. for the determination of more than 350 compounds, including pesticides and veterinary drugs in honey and meat [105]. The authors demonstrated that QuEChERS coupled to Orbitrap MS system is suitable for not only qualitative screening, but also for quantitative analysis providing adequate recovery and precision for most of the studied analytes (>290). Finally, León et al. [13] showed the potential of QuEChERS combined with an Orbitrap mass spectrometer for the accurate mass screening of 77 banned veterinary drugs, mycotoxins, ergot alkaloids, and plant toxins in feed. Based on the outstanding advantages of HRMS like its high resolving power, accurate mass, and full scan data acquisition (with and without fragmentation) allowed the post-target screening of 425 substances including pesticides.

Application to Crops and Vegetables

Several studies have recently demonstrated that plants can take up PPCPs from the growth media when the PPCPs are introduced either by spiking of the medium, from irrigation water, or by sludge application. Therefore, their uptake by crops and subsequent entry into the human food chain are now recognized as an emerging issue in environmental chemistry due to the risk to human health.

The QuEChERS method because of its inherent advantages has also been used to extract PPCPs from plant matrices. For example, Ferro et al. [23], explored the extraction efficiency of QuEChERS to determine carbamazepine and flumequine in lettuces irrigated with recycled water and cultivated under pilot scale conditions. Similarly, Chung et al. [106] used a modified citrate buffered version of QuEChERS to determine the three veterinary antibiotics: chlortetracycline, enrofloxacin,

and sulfathiazole in the roots and leaves of radish (*Raphanus sativus L.*) upon their application to the soil. Similarly, Hu et al. [107] developed a modified QuEChERS method using more acidic extraction conditions to determine 26 antimicrobials in a variety of vegetable matrices, achieving recoveries of between 60 and 98%. More recently, a simple and efficient multiresidue method based on QuEChERS was developed and validated by Martínez-Piernas et al. [25, 108] for the determination of 74 microcontaminants including PPCPs in crops (lettuce, radish, and strawberry) irrigated with treated municipal wastewater. According to their results, a mixture of $MgSO_4$ with C_{18} and PSA gave the best recoveries in all matrices and the cleanest extracts. Under optimized conditions, the method produced good performance characteristics for all the studied matrices, yielding satisfactory recoveries (70–20%) and precision (RSD < 20%) for the majority (84%) of the studied compounds. When applied to the analysis of lettuce and radish crops irrigated with UWW, in order to estimate the potential long-term impact of irrigating crops with treated water, they confirmed the presence of 12 compounds in concentrations ranging from 0.03 and 57.6 ng g^{-1}. Among the detected compounds, N-formyl-4-aminoantipyrine (4FAA) had the highest concentration.

The efficiency of QuEChERS method and its modifications in crops have also been compared with other extraction methods. For example, Chuang et al. [109] compared the performance of QuEChERS extraction in terms of recovery, relative standard deviation (RSD), and method detection limit (MDL) with those of accelerated solvent extraction (ASE) for 11 pharmaceuticals in lettuce and celery. According to the results, both methods were able to achieve reasonable extraction efficiencies for the target compounds. However, the QuEChERS method offers the advantage of a shorter analysis time, reduced sample preparation costs, and the need for lower amounts of organic solvent. Alternatively, lower extraction efficiencies were reported for an unbuffered QuEChERS method for extracting 28 polar contaminants in vegetables irrigated with treated municipal WW, when compared with SLE followed by ultrasounds [110].

14.2.2 Separation and Detection Techniques

Nowadays, PPCP residue analysis is dominated by chromatography coupled to MS. Among the MS techniques, LC-MS is the technique of choice based on the polar and ionic character of the majority of PPCPs. Electrospray ionization (ESI) is the preferred ionization method operating either in positive or in negative ionization mode while atmospheric pressure chemical ionization (APCI) has rarely been used. Most PPCPs, with few exceptions have been ionized in the positive mode, and although good chromatographic response can be obtained by both ionization modes for some compounds (i.e., sulfonamides), the positive mode continues to be the preferred mode because of its ability to simultaneously detect multiple classes of PPCPs. Besides ESI, atmospheric pressure photospray ionization (APPI) has been successfully employed to analyze veterinary drugs (sulfonamides) in honey, resulting in lower matrix effects

and higher signal-to-noise ratios than ESI [111]. Tandem MS (MS/MS) is the most frequent analytical approach since it can provide increased selectivity that helps further distinguish target compounds from potential matrix interferences. Typically, hybrid triple quadrupole (QqQ) analyzers have been widely used for this purpose, which exhibit excellent performance working in the multiple reaction monitoring (MRM) mode. MRM allows monitoring two transitions between precursor and product ions. In general, for each compound, two characteristic MRM transitions are selected under the optimum collision energies with the first one, the most abundant product ion used for quantification and the second for confirmation. Nowadays, new generations of instruments allow ultrafast MRM acquisition speeds and ion polarity switching, which ensures compatibility with ultra-performance liquid chromatography (UPLC), resulting in better resolution, significantly shorter separation times and maximum response simultaneously for a higher number of analytes.

Besides triple quadrupole systems, linear traps, new generation time-of-flight MS (TOF-MS) and hybrid instruments, such as QTOF and Q-linear traps have also been successfully employed for both structure elucidation and screening/quantification of PPCPs and their metabolites in environmental and food samples. Among the most recent innovations in hybrid instruments and HRMS, is the hybrid linear ion trap (LTQ) FT Orbitrap mass spectrometer. The tandem mass spectrometry capability of the linear ion trap (LTQ) and its high resolution and mass accuracy allow high-quality accurate mass MS^n spectra to be acquired enhancing separation of unknown compounds and enable high-throughput workflows. Based on these benefits, a number of applications using QuEChERS as a sample preparation procedure have recently appeared.

Overall, QTOF or Orbitrap/MS systems have several advantages compared to low-resolution MS instrumentation (QqQ/MS or ion trap (IT) mass analyzers) for screening and identifying different PPCPs such as higher sensitivity, mass resolution, and mass accuracy for both precursor (MS) and product ions (MS/MS). The number of applications involving QuEChERS that have steadily increased in recent years is evidence for this. Despite, however, the well-recognized advantages of coupling HRMS with chromatographic techniques, many analysts would benoefit frm other techniques enabling high-throughput analysis, such as ambient mass spectrometry. Among the different ambient ionization techniques, direct analysis in real time (DART) has been probably one of the most frequently used probably because of its commercial availability. DART is a soft ionization technique that does not require a time-consuming preparation step, suffers from fewer matrix effects, requires no solvent or additive use, and results in low adduct formation. Coupling the DART ion source with HRMS analyzers (e.g., TOF-MS, Orbitrap MS) is a powerful approach that has recently received considerable attention [112]. For instance, Martínez-Villalba [113] coupled a modified QuEChERS procedure with HRMS (Orbitrap MS) for the high-throughput analysis of antiparasitic veterinary drugs, namely coccidiostats in feed and benzimidazoles in bovine milk. Their modified protocol consisted of an extraction with ACN or ACN 0.1% (v/v) with NH_3 for feed and milk samples, respectively. The extraction was followed by the addition of a mixture of $MgSO_4$/NaCl (4:1 w/w) and a clean-up step by using $MgSO_4$, C_{18} and PSA. Under optimum conditions, the

target compounds were quantified without the need for an internal standard. Overall, the proposed analytical methodology gave good recovery efficiencies (65–95%) and showed the possibility of quantifying a variety of veterinary drugs at levels established by EU legislation. However, the authors recommended the use of an appropriate internal standard (preferably isotope labeled) in order to compensate for signal variations encountered during repeated sample introduction and to improve method recoveries.

Overall, continued innovation in HRMS and improvements in the MS interface and ionization techniques have enabled new powerful strategies in environmental and foodstuffs contamination assessment and analysis. From this perspective, despite the higher investment costs as compared with low-resolution MS, coupling of new QuEChERS concepts and modifications with HRMS instruments in research or even in routine analysis is anticipated in the near future.

14.2.3 Recovery and Matrix Effect

Among the reviewed QuEChERS applications adapted to the analysis of PPCPs in environmental and food matrices, recovery results varied greatly due to the diversity of chemical classes among the selected PPCPs. In general, the range of recoveries provided by the majority of the studies was good (>60%) for polar and medium polar compounds, since the presence of salts in the medium decreases the solubility of these compounds in the aqueous phase. However, the method is still criticized for not being able to recover all analytes completely and thus the optimization of QuEChERS methods for a variety of environmental and food samples remains challenging for PPCPs owing to their diverse properties, including polarity, solubility, and pKa. In particular, for very polar, acidic or basic analytes QuEChERS might be problematic [80, 114], and if such analytes are within the scope of the analysis, modifications should be made for improving the extraction efficiency.

Regarding matrix effects, although highly selective and sensitive methods (e.g., MS/MS with a triple quadrupole) require less demanding clean-up, matrix effects continue to be one of the most important drawbacks in the extraction process resulting in poor data quality and analytical errors in the quantification of target components. The matrix effect in different QuEChERS applications has been evaluated by comparing the slopes of the calibration curves prepared with or without the matrix such that the matrix effect = (matrix/solvent slope ratio × 100). Positive values indicate signal enhancement due to the matrix, whereas negative results indicate signal suppression of the matrix. In order to mitigate matrix effects, different approaches are applied such as matrix-matched calibration, the standard addition method, and the use of isotopically labeled target compounds. The dilution of the sample extracts and the use of improved chromatography with better separation of the matrix compounds from the analytes (e.g., UHPLC) are often used as alternative options or in parallel. Although all the aforementioned approaches proved to be effective in many cases when correcting for matrix effects, several drawbacks remain, especially in the

case of multiresidue methods for the determination of PPCPs with different physicochemical properties. In such cases, combinations of suitable internal standards and an appropriate sample clean-up have been proposed by many authors for the simultaneous analysis of different compounds. However, it is worth mentioning that the former approach can be extremely costly and is sometimes not feasible because of the lack of available labeled compounds.

14.3 Concluding Remarks and Future Trends

Attention to GAC is growing rapidly, representing a bottleneck in the pursuit of optimum analytical methodologies. Among the different green techniques that follow the principles of GAC, the QuEChERS approach has received considerable attention due to reduced solvent and material consumption, as well as a decrease in time and cost of analysis. It is expected to have the most pronounced development in the future. Overall, the number of QuEChERS methods for determining PPCPs in environmental and food matrices has steadily increased. Fundamentally, these protocols are developed with the aim of improving compatibility with modern analytical instruments including HRMS and other operational features, including simplicity, quickness, miniaturization, automation, reduced costs, and safety.

Although significant progress has already been made in regards to determining PPCPs in environmental and food samples, there remain significant knowledge gaps. On the one hand, existing approaches must be further improved and validated in terms of their applicability; ideally, this should be done using a broad range of sample types, with an emphasis on the simultaneous extraction and subsequent instrumental analysis of several classes of PPCPs in a single run. On the other hand, there remain issues regarding extraction and clean-up. For instance, the latter still constitutes a bottleneck, rendering them labor intensive, and the main source of analytical error. The problem is the selectivity of the analyte in the presence of matrix interferences. As a consequence, certain analytical methodologies do not meet the criteria used in both the enforcement of legislation and assessment of the risk of drug residues to human health and the environment. Further, research is needed to address this limitation together with the development of more advanced and functional materials.

An important future perspective of QuEChERS is its potential automation. Despite its inherent advantages like simplicity, flexibility, and rapidity, the method is still performed manually in the majority of cases. However, in many analytical laboratories, sample throughput has increased considerably and as a consequence, the majority of new analytical methodologies are oriented toward automation. Several systems have been introduced on the market to facilitate sample preparation step. Most involve commercial availability of pre-weighed salts, buffers, and sorbents with the scope to minimize the time devoted to this step. Full automation of QuEChERS formats following sample preparation functions (i.e., liquid dispensing/pipetting, vortex mixing, vial shaking, opening/closing sample vials, addition of solid reagents (salts and buffers), etc.) has been developed by several companies and therefore, automated

coupling with other analytical instrumentation, such as chromatographic MS techniques, is also anticipated in the future. Overall, the percentage of QuEChERS analyses conducted in a semi-automated or full automated fashion is certain to increase in the coming years and, with this trend, the use of this elegant and green sample preparation technique will continue to grow.

Acknowledgements Ms. A. Ofrydopoulou would like to thank the General Secretariat for Research and Technology (GSRT) and the Hellenic Foundation for Research and Innovation (H.F.R.I.) for providing her scholarship through the action "1st Proclamation of Scholarships from ELIDEK for Ph.D. Candidates"—Scholarship Code: 429, as well as the Onassis Foundation for the grant of a doctoral scholarship through the Greek Scholarship Program for Greeks for the academic year 2016/2017.
Ester Heath and David Heath acknowledge the project (ISO-FOOD): "ERA CHAIR FOR ISOTOPE TECHNIQUES IN FOOD QUALITY, SAFETY AND TRACEABILITY," Grant agreement n°: 621329, Duration: 2014–2019.

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Chapter 15
Green Analytical Chemistry: Summary of Existing Knowledge and Future Trends

Justyna Płotka-Wasylka, Agnieszka Gałuszka and Jacek Namieśnik

Abstract Analysis of recent publications in Green Analytical Chemistry shows the current trends and future needs in this area. The main issues are related to search for cheaper, more efficient, more accurate, greener and miniaturized alternatives. Miniaturization is perhaps, the most notable current trend in analytical chemistry. Rapid developments and improvements in instrumentation have led to an impressive range of benchtop technology and portable devices. In addition, an important issue that has been explored by many authors is metrics of Green Analytical Chemistry, such as Analytical Eco-Scale or Green Analytical Procedure Index. Implementation of interdisciplinary methods is an emerging trend in Green Analytical Chemistry. Employment of multicriteria decision analysis, a technique which is used in environmental management, to Green Analytical Chemistry is a very popular and common trend. Another important issue that will determine the future of Green Analytical Chemistry is education and popularization of this concept in the society. This chapter summarizes contemporary problems and gives the future perspectives of Green Analytical Chemistry.

Keywords Trends in Green Analytical Chemistry · Green solvents · Green extraction techniques · Green metrics · Education · Teaching Green Analytical Chemistry

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J. Płotka-Wasylka and J. Namieśnik (eds.), *Green Analytical Chemistry*,
Green Chemistry and Sustainable Technology,
https://doi.org/10.1007/978-981-13-9105-7_15

15.1 Introduction

The importance and scope of use of analytics and bioanalytics are constantly growing due to the need to obtain reliable analytical information about the processes taking place in various material objects of different origins and their composition. At this point, one can ask yourself how many known chemical compounds may be present in the tested samples. The answer to this question can be found in Chemical Abstracts. The relevant data are summarized in Table 15.1. The number of chemical compounds whose basic properties are known is constantly growing.

Two groups of chemists are responsible for this:

- chemists employed in laboratories and industrial facilities where research on new synthesis processes and the production of various types of chemicals on an increasingly larger scale are carried out,
- chemical analysts who develop new analytical procedures and use control and measurement instruments ensuring the ability to detect, identify and quantify an increasingly wider range of analytes at a lower and lower level of content in samples characterized by complex and often variable composition of the matrix.

The increase of the tonnage production and the variety of chemicals produced (in pure form or in the form of appropriate chemical products) makes the human habitat increasingly saturated with chemical compounds. Thus, the immediate human environment is often referred to as a chemosphere. The OECD report provides relevant data and forecasts on the growth in the production of chemicals and the increase in global population growth (Fig. 15.1). According to these data, the manufacturing of chemical products increases by 3% annually when there is a 0.77% increase in population density. Taking the above into account, the need arose to develop a new

Table 15.1 Information on the numbers of existing chemical compounds as well as chemical reactions based on Chemical Abstracts

	02.12.2014	09.09.2015	22.04.2016	17.08.2017	07.08.2018
Number of known chemical substances (organic and inorganic)	65,844,568	66,324,359	66,644,872	67,273,974	67,752,102
Number of known chemical reactions (single-step and multi-step)	76,343,169	82,348,277	88,175,941	100,490,924	110,147,030
Number of chemical compounds available in trade	86,820,549	104,517,210	110,378,650	131,745,000	146,466,171
Number of chemical compounds subject to legal regulations	312,274	344,630	345,575	387,170	389,931

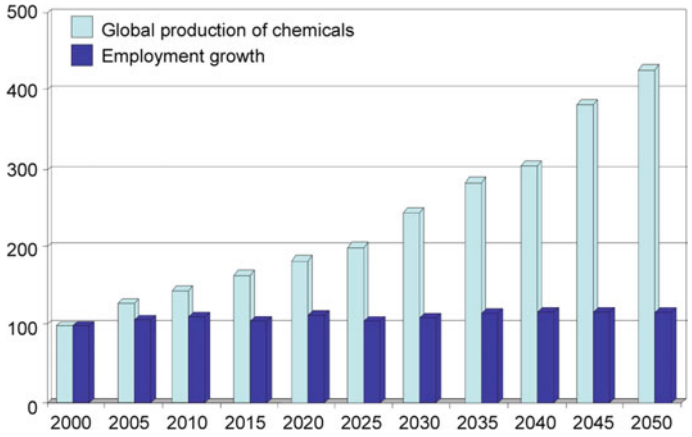

Fig. 15.1 Schematic representation of the relationship between employment growth and production of chemicals based on the OECD report [1]

philosophy regarding meeting the social demand for various types of chemical products. It is related to the implementation of the concept of sustainable development.

When satisfying the consumption needs of the human population, the protection of the environment against degradation and rapacious exploitation must be taken into account, as well as protection of health and life of employees involved in various stages of the process of manufacturing consumer goods. The change in philosophy described above is illustrated on the diagram shown in Fig. 15.2.

This approach to the process of manufacturing consumer goods is described in the form of rules of conduct. Literature provides information on the following principles:

- 12 Principles of Green Chemistry [2]
- 12 Principles of Green Chemical Technology [3]
- 12 Principles of Green Chemical Engineering [4].

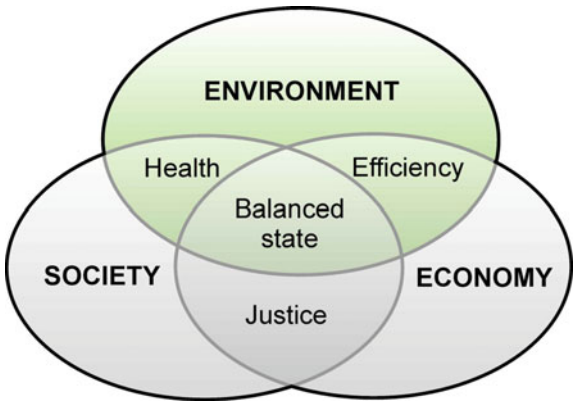

Fig. 15.2 Schematic presentation of the premises constituting the basis for changing the way of activity of chemists and technologists

For the descriptive assessment of activities related to the introduction to the analytical practice of the concept of sustainable development, the 3R concept [5] is used:

- Reduce
- Replace
- Recycle.

Another code of conduct is the ten eco-commandments for earth citizens developed by prof. Menke Gluckert [6].

In addition to these general rules of conduct regarding chemistry and chemical technology, the principles of Green Analytical Chemistry [7] were published, and later also the principles of particular groups of analytical techniques, such as green chromatography or green spectroscopy techniques. The implementation of the principles of green chemistry and Green Analytical Chemistry is the reason why the set of criteria for the selection of analytical methodology, which can be used to perform a specific analytical task, must be expanded. All those who are involved in the development of new methodologies (procedures) are aware that the following criteria should be taken into consideration:

- Accuracy,
- Precision,
- Selectivity,
- Detection limits.

If the principles of Green Analytical Chemistry are taken into consideration, the impact on the environment and human health becomes the fifth parameter in the assessment of the usefulness of analytical procedures [8]. The heart of Green Analytical Chemistry is schematically presented in Fig. 15.3.

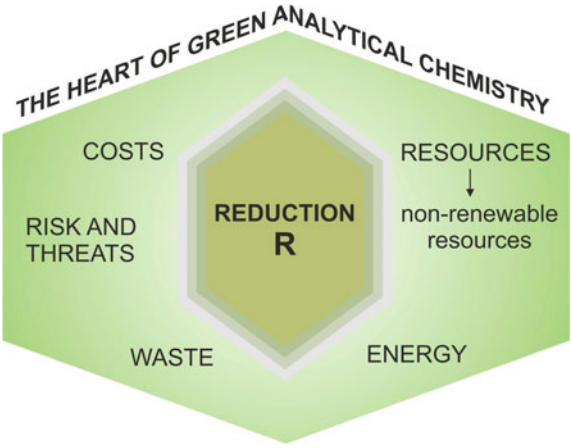

Fig. 15.3 The heart of Green Analytical Chemistry

15.2 Current Trends in Green Analytical Chemistry

Analysis of recent publications concerning Green Analytical Chemistry shows the current trends and future needs in this area. Articles published since 2018 have focused mostly on improvements of analytical procedures aiming at greening the selected steps of the analytical process. These improvements include:

- using an alternative, more environmentally friendly solvents [9–18],
- greening extraction procedures [19–30],
- promoting multi-analyte techniques [31–35],
- reducing reagent volume by application of miniaturized techniques [22, 36–39],
- introducing new components as stationary and mobile phases in chromatography [40, 41],
- eliminating sample treatment [32, 42–46],
- simplifying analytical protocols [47, 48],
- greening sample digestion [49] and derivatization [50],
- using mathematical modelling and chemometrics in greener analytical methods [51, 52].

Some authors have also recently reported on the development of new methods [53–58] or have promoted non-destructive analytical methods [59] and natural reagents [60].

One of the current trends in Green Analytical Chemistry is developing simple and cheap methods for the qualitative and/or quantitative determination of different analytes and parameters that are useful for certain applications. An example of this approach is paper-based analytical devices that can be used in pharmaceutical sciences in gene delivery formulations [61] and determination of amino acids in gym supplements [62]. They can also be used in food chemistry for the determination of antioxidant capacity of tea and vegetable oils [63, 64]. Food adulteration is another area where simple green methods can be employed. Digital images and chemometric tools were successfully used for quantification of fat content in chicken burgers [65]; whereas, liquid–liquid microextraction coupled with mobile phone-based photometric detection was used for the determination of anionic surfactants in milk [66]. Sitanurak et al. [67] proposed using the paper-based device for quantification of hypochlorite in bleach and disinfectants. An interesting green alternative to conventional analytical methods was proposed by Kiwfo et al. [68] who used a noodle-based analytical device as copper (Cu^{2+}) and acid–base assay.

An important issue that has been explored by many authors since 2012 is the metrics of Green Analytical Chemistry. The first tool proposed for the assessment of the greenness of analytical procedures was Analytical Eco-Scale developed by Gałuszka et al. [7]. Both the use and introduction of new metrics were the topic of numerous studies in 2018 [33, 69–74].

Implementation of interdisciplinary methods is an emerging trend in Green Analytical Chemistry. Tobiszewski and Orłowski [75] employed multicriteria decision analysis, a technique which is used in environmental management, to Green Analytical Chemistry. Combining method development in the pharmaceutical analysis

(a quality by design approach) with Green Analytical Chemistry has recently been postulated by Saroj et al. [76].

15.3 Future Directions of Development of New Analytical Procedures and Measuring Instruments

In many research and R&D centres, work is underway to develop new analytical procedures designed for studying various types of material objects. In these procedures, improvements are being made at the stages of detection, separation, identification and quantification of the broadest possible spectrum of analytes. As mentioned before, these new methodological solutions should undergo an assessment of environmental nuisance and impact on the health and life of analytical staff. For this purpose, various tools are used to obtain qualitative or quantitative information about the pro-environmental nature of the proposed methodological solution.

An analysis of literature data might be the basis for distinguishing the development directions of new analytical solutions that to a greater or lesser extent meet the requirements resulting from the principles of Green Analytical Chemistry:

- searching for new non-matrix techniques for preparing samples for analysis,
- introduction of new types of solvents to the analytical practice (the so-called green solvents), the impact of which does not have an adverse effect on either the environment or the health and life of analysts,
- application of additional factors affecting the acceleration of the reaction or the extraction process,
- development of new types of control and measurement devices ensuring the possibility of performing in situ tests (without time delay),
- new solutions in the so-called direct analytical techniques. Such solutions are particularly attractive because the analysis of the tested material does not require any sample preparation. Table 15.2 presents basic information about the different groups of measuring instruments that can be used for direct detection and/or determination of analytes,
- the use of reagents produced from renewable raw materials,
- development of remote measurement techniques (remote sensing). Information on the morphological classification of remote sensing methods is presented in Table 15.3.

In the field of remote sensing techniques, both passive and active devices are used. The latter are equipped with their own sources of radiation, while the operation of the former is based on the use of radiation from external sources (e.g. solar radiation). In practice, active devices have a broader scope of application.

Table 15.4 summarizes information on three analytical techniques equipped with monochromatic radiation sources.

Table 15.2 Basic information on analytical instruments used in direct analyses of different types of samples

Method	Technique	Example of application
Colorimetry	Dry test Wet test	Determination of metal ions in water Determination of metals in vegetables and fruits Determination of nitrates in vegetables
Potentiometry	Ion Selective Electrodes—ISE	Measurement of pH (Glass electrode) Determination of metals in surface water
Activation analysis	(Instrumental) Neutron Activation Analysis—(I)NAA	Determination of metals in environmental samples
Atomic Absorption Spectroscopy	Graphite Furnace Atomic Absorption Spectroscopy—(GFAAS) Quartz Furnace Atomic Absorption Spectroscopy—(QFAAS)	Determination of metals in solid and liquid environmental samples
Inductively Coupled Plasma Mass Spectrometry	Laser Ablation Inductively Coupled Plasma- Mass Spectrometry (LA-ICP-MS)	Determination of major and trace elements in different samples
Infrared Spectroscopy	Fourier-Transform Infrared Spectroscopy (FTIR)	Analysis of samples of different matrix composition
Nuclear Magnetic Resonance Spectroscopy	Nuclear Magnetic Resonance Spectroscopy (NMR)	Analysis of samples of different materials
Emission Spectroscopy	Laser-Induced Breakdown Spectroscopy (LIBS)	Real-time elemental analysis in a wide range of samples
X-ray Fluorescence	Wavelength-Dispersive X-ray Fluorescence (WD-XRF) Energy-Dispersive X-ray Fluorescence (ED-XRF)	Simultaneous determination of many elements in solid and liquid samples
Raman Spectroscopy	Raman Spectroscopy (RS) Surface-Enhanced Raman Spectroscopy (SERS)	Analysis of samples of different matrix composition
Laser-Induced Breakdown Spectroscopy	Laser-Induced Breakdown Spectroscopy (LIBS)	Analysis of chemical composition of different materials
Immunoanalysis	Immunoanalysis (IMA) Enzyme-Linked Immunosorbent Assay—ELISA	Detection and determination of selected dioxins and dioxin-like compounds in environmental samples

(continued)

Table 15.2 (continued)

Method	Technique	Example of application
Fluorescence	Laser-induced fluorescence (LIF) UV light-emitting diode induced fluorescence (UV LED)	Real-time screening of traces of polycyclic aromatic hydrocarbons in surface water and soil samples. A possibility of the use of UV LED in monoaromatic hydrocarbon prospection studies
Ion-Mobility Spectrometry	Ion-Mobility Spectrometry (IMS)	Detection of high energy materials (explosives, propellants) and drugs
Photoelectron Spectroscopy	X-ray Photoelectron Spectroscopy (XPS)	Detection and quantification of all elements except for hydrogen. Determination of types of bonds between elements on the surface of samples
Electron Paramagnetic Resonance Spectroscopy	Electron Paramagnetic Resonance Spectroscopy—EPR (Electron Spin Resonance Spectroscopy—ESR)	Used in solid-state physics for determination of free radicals, in chemistry for studying reaction rates, in biology and medicine for monitoring of spin labelling, in archaeology for dating of tooth enamel
Methods of surface analysis	Secondary Ion Mass Spectrometry (SIMS)	Analysis of surface of different materials (mapping of analytes on the surface of samples)
	Electron Spectroscopy for Chemical Analysis (X-ray Photoelectron Spectroscopy)—ESCA (XPS)	
	Scanning Electron Microscope (Energy-Dispersive X-ray Spectroscopy)—SEM (EDS)	
	Auger Electron Spectroscopy (AES)	
	Ion Scattering Spectroscopy (ISS)	
Mass spectrometry	Direct Analysis in Real Time-Mass Spectrometry (DART-MS)	Analysis of liquid and solid samples
	Selected Ion Flow Tube-Mass Spectrometry (SIFT-MS)	Analysis of gaseous mixtures Determination of volatile compounds
	Desorption Electrospray Ionization Spectrometry (DESI-MS)	Direct analyses of liquid samples Detection of chemical warfare agents
	Proton Transfer Reaction-Mass Spectrometry (PTR-MS)	Real-time simultaneous determination of volatile organic compounds

(continued)

Table 15.2 (continued)

Method	Technique	Example of application
	Membrane Inlet Mass Spectrometry (MIMS)	Determination of volatile compounds that permeate through the membrane in gaseous and liquid samples
	Direct Inlet Probe-Atmospheric Pressure Photo Ionization-Mass Spectrometry (DIP-APPI-MS)	Identification and determination of sample components adsorbed on the surface of a sampler introduced into an ionization chamber.
	Direct Infusion-Mass Spectrometry (DI-MS)	Used in metabolomic studies of liquid samples
	Matrix-Assisted Laser Desorption/Ionization-Mass Spectrometry (MALDI-MS)	Analysis of samples with different matrix composition for determination of biologically active compounds (oligonucleotides, carbohydrates, lipids and others)
	Surface-Enhanced Laser Desorption/Ionization-Time of Flight-Mass Spectrometry (SELDI-TOF-MS)	Analysis of biological material samples (tissues, blood, urine, etc.) for identification of proteins
Remote sensing techniques	Light Detection and Ranging (LiDAR)	Analyses of air samples
	Sonic Detection and Ranging (SODAR)	Measurements of air humidity
Sensor matrix	Electronic nose (e-nose)	Analysis of gaseous samples (air, breath, headspace phase)
	Electronic tongue (e-tongue)	Analysis of liquid samples

Table 15.3 Morphological classification of remote sensing methods

Methods	Passive	Active
Ground	Photographic Photoelectric measurements Correlation spectrometer	Radio measurements LiDAR measurements SODAR measurements
Aerial	Photographic and thermovision Radiometric measurements Correlation spectrometer	SLAR SAR LiDAR measurements
Satellite	Multispectral imaging Microwave measurements Photometric measurements	LiDAR measurements Large-range Radar measurements

Table 15.4 Basic information on monostatic devices with a source of monochromatic radiation

Analytical technique	A brief description of the principle of operation
Differential Optical Absorption Spectroscopy—DOAS	The light radiation beam is directed from the transmitter to the receiver. The length of the optical beam's path is known The intensity of the beam changes due to contact with atmospheric components After returning to the receiver, the beam is directed through a fibre optic cable to the central unit equipped with a computerized spectrometer The computer allows collecting characteristic data on a beam of radiation up to 100 times per second
Differential Absorption LiDAR—DIAL	It is a device in which two laser beams of different lengths pass through a gas cloud (along the same path) If the radiation length of one of the beams is equal to the radiation length best absorbed by a specific component, and the radiation of the second beam is not absorbed at all, the difference in radiation intensity of both beams (after returning to the receiver) is proportional to the amount of the absorbing component
Light Detection and Ranging—LiDAR	It is a pulsed laser system used in a similar way to a radar system. In this case, the return time of the reflected beam of radiation is measured, and on this basis the distance from the cloud of the substance reflecting the radiation or the distance from a fixed obstacle is determined

- development of new procedures for assessing the environmental nuisance and toxicological risk of the activity of chemical analysts.

15.4 Ongoing Challenges and Future Trends in Teaching GAC

Nowadays, many efforts are being made in order to include the GAC concept to education, including the field of analytical chemistry, where twelve GAC principles play the main role. There is no doubt that the understanding and awareness of these principles and other evolving related ideas require special teaching of GAC as part of the curriculum at undergraduate and graduate levels. In fact, making analytical chemistry more environmentally friendly is a basic approach that combines old and

new analytical chemistry ideas and as such, it should be transmitted into the teaching of GAC [77].

Education in Green Analytical Chemistry balances between ethical and chemical aspects; therefore, the main role of teachers is to convince the students that chemistry not only poses a risk for the planet, but also shows great promise for human health care as well as a sustainable environment. Therefore, teaching GAC should be a social responsibility, as it is undoubtedly one of the pillars of modern chemistry [78], and in particular of analytical chemistry [79], which is due to the fact that virtually every area of life today depends on the data obtained and transmitted via chemical research. Analytical chemistry should be socially responsible, because the data and knowledge that it provides affect every element of the reality that surrounds us [77]. Green Analytical Chemistry is an appropriate platform for teaching and promoting social responsibility because it is a social movement itself [80]. If we would like to have analytical chemists who are responsible, socially sensitive, and who would take care of the metrological quality of data and information, we must educate them from the very beginning, from primary school through high school to university. However, it is not a good idea to create separate chapters in chemistry textbooks or to have guest lectures given by humanists. Rather, it should be done by integrating chemical instrumentation and nomenclature with social and ethical themes [81].

An important objective in teaching analytical chemistry is to change the chemistry students' attitude. In addition, the attitude of future generations towards chemistry and its impact on the environment should also be changed. For a long time, some of the green chemistry principles have been included in teaching analytical chemistry, since they are essential for increasing safety and reducing lab costs. However, these efforts were not mandatory; they only depended on the ethical preferences of teachers and lab staff [77]. Therefore, additional efforts should be made to educate teachers about conveying the message of sustainability in analytical chemistry teaching. It should be quite clear that the GAC principles should be an integral part of solving analytical problems, an obligation, and in no case a matter of choice. As pointed out in a recent paper [82], there are several concepts for teaching Green Analytical Chemistry, which are presented in Fig. 15.4.

New ideas in teaching Green Analytical Chemistry include the greening of analytical methods as well as the development of new green methodologies. Safety concerns regarding laboratories and waste have become the reason for developing new ideas of improving the safety in such a working environment and successfully reducing the amount of waste or decontaminating it [77]. Hazard and waste become recognized as design flaws or, more positively, as opportunities for innovation. Experiments can be performed in laboratories that are more comfortable and alluring as well as more economical to maintain [83]. It needs to be stated that analytical chemistry gives the opportunity for innovations in teachings and science, in the context of waste treatment or by using new reagents that increase students' understanding of and sensitivity to the environmental consequences of their scientific choices.

Unfortunately, there are many gaps and areas for improvement in GAC teaching and research. Firstly, the teaching style itself, such as presentations on how to

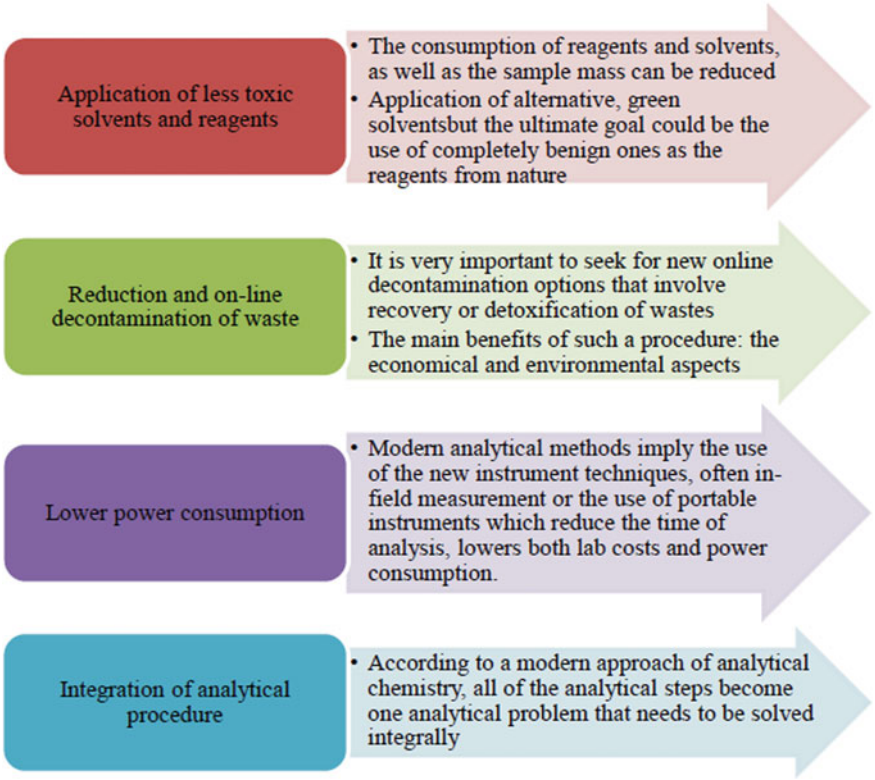

Fig. 15.4 Outline of the studies discussed in the present sub-chapter focused on the use of DES in the extraction and/or digestion/dissolution processes

understand the laws of analytical chemistry, reaction recording style, etc. should be changed. Besides the gaps in education and teaching, there are also ones in the literature and research. The simplest example is that several false "greenness" claims exist in the chemical literature. Many researchers state that a given analytical procedure is green based only on one of the Twelve Principles of Green Analytical Chemistry. Such a proceeding shows a very narrow point of view rather than a multi-dimensional global approach which considers all reagents, materials and energy consumption, as well as the environmental impact of any waste and by-products manufactured. A good example of such a proceeding is a declaration that a given procedure/reaction is "solvent-free" or "solventless". This, undoubtedly, should be changed, and it is the teachers' responsibility to show their students when they can consider a procedure "green".

Widespread success in these and related fields may lead to re-writing undergraduate textbooks as the paradigm shift evolves [82]. Finally, quantification of energy consumption, as well as the costs of an appropriate methodology, has received little attention from both research and teaching perspectives. In addition, several current

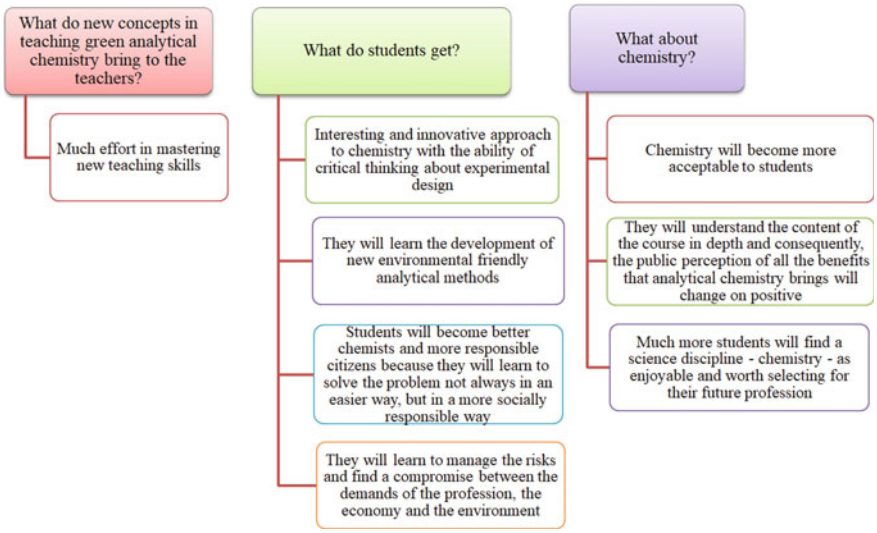

Fig. 15.5 Questions concerning introduction of Green Analytical Chemistry into teaching practice

trends in extraction techniques focused on finding solutions to minimize the use of solvents. Thus, new microextraction techniques are still introduced into analytical practice. These modern methods need to be known for students. Therefore, new textbooks, as well as scholarly materials, will be published in the coming years.

Summarizing the above information, some questions should be asked:

- What do the new concepts in teaching Green Analytical Chemistry bring to the teachers?
- What do students get?
- What about chemistry?

The answers are presented in Fig. 15.5.

15.5 Future Perspectives of Green Analytical Chemistry

A fast progress in Green Analytical Chemistry could not be possible without active participation of analytical chemists in developing new, more environmentally friendly approaches to the analytical process or its phases. Of many different areas of interest in Green Analytical Chemistry, two seems to play a major role in the development of this concept, namely, greening of analytical laboratories and life cycle assessment of reagents and instruments.

Greening of analytical laboratories. Principles of Green Analytical Chemistry set general guidelines for making chemical analysis safer and more environmentally friendly. A successful implementation of these principles on a laboratory scale may

be easier during designing of a new facility, but in the case of existing laboratories, it requires changes which may generate high costs and make the concept of Green Analytical Chemistry a wishful thinking.

A green analytical laboratory can be defined as a laboratory in which Green Analytical Chemistry principles are implemented and constant efforts are being made in order to assure minimum environmental impact through evaluation of the greenness of analytical procedures and selection of the most environmentally friendly options. However, the greening of analytical laboratories can be implemented on different levels of the analytical process, from reagents to methods and procedures to instruments.

From cradle to grave—from reagents to waste. Analytical processes should be perceived similarly to industrial processes in which life cycle assessment is performed. A new approach "from reagent to waste" should be implemented because reagents used in chemical analyses are part of the analytical waste. A green approach to the analytical waste problem is to eliminate it or minimize its amount. More efforts are needed in order to develop methods of recovery of resources from analytical waste. So far, the recovery of americium and plutonium from analytical waste has been performed [84–86]. A possibility of recovering elements other than radionuclides should be examined in the future. Recovery of platinum group elements and rare earth elements seems to be economically viable. A life cycle assessment of analytical instruments should also be adapted to Green Analytical Chemistry.

Another important issue that will determine the future of Green Analytical Chemistry is education and popularization of this concept in the society [77, 82]. This can be achieved through making Green Analytical Chemistry an integral part of a curriculum at different education levels. Simple, but spectacular methods, i.e. those based on smartphone detection, can be presented during science festivals and workshops open to the public. All these efforts will be crucial for a wider interest and continuous progress in Green Analytical Chemistry.

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