TISSUE ENGINEERING INTELLIGENCE UNIT 6

Patrick Vermette, Hans J. Griesser, Gaétan Laroche and Robert Guidoin

Biomedical Applications of Polyurethanes

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UNIT 6

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Chapter 1

PREFACE

Polyurethanes form a large family of polymeric materials with an enormous diversity of chemical compositions and properties. They have found wide spread application in a number of technological areas and a range of commodity products, such as polymers for clothing (Lycra® being a well-known example), automotive parts, footwear, furnishings, construction, and in paints and coatings for appliances. The wide range of properties that can be achieved with polyurethane chemistry also attracted the attention of developers of biomedical devices who saw promise in, for instance, the mechanical flexibility of these materials combined with their high tear strength. Thus, polyurethanes were tried in a number of biomedical applications, as discussed in this book. However, a number of drawbacks quickly became apparent, most importantly their unexpected lack of stability in the living host environment. Early studies were mostly done with "available" polyurethanes developed for quite different uses; hence, in retrospect, their failure to meet the requirements of biomedical applications may not be altogether surprising. The clinical findings of adverse consequences with early polyurethanes led to a large number of studies aiming to elucidate the reasons for polymer degradation in the biomedical environment, and the synthesis of customized polyurethanes guided by biomedical considerations. This work is still continuing; promising improved materials have been developed and are now undergoing detailed testing, and this raises the possibility of commercialization in the near future of the "ultimate" biomedical polyurethane(s) optimized for specific biomedical requirements.

Another avenue towards improving the biomedical performance of polyurethanes, which is of more recent origin than synthetic approaches, comprises the application of surface modification or coating technologies. This type of approach has been featured in a substantial number of studies. It offers the promise of enabling use of an "available" polyurethane whose biomedical response has been improved by the alteration of its surface chemistry.

The literature on the development and evaluation of polyurethanes intended for biomedical applications is enormous and, on account of its multidisciplinary nature, spread over a wide range of primary scientific and applied technological journals. Biomedical polyurethanes also are featured in many patents. Of course the subject of biomedical polyurethanes has been covered in many reviews, as well as an excellent book (Lelah MD, Cooper SL. *Polyurethanes in Medicine*. Boca Raton, FL: CRC Press, 1986); these previous surveys of the field, or parts thereof, are invaluable in conveying the history and status (at the time) of progress on applying polyurethanes to various biomedical applications. Yet, the field has over the last few years continued to progress rapidly, and several conceptually new polyurethanes have recently become available for detailed clinical testing. In addition, the application of surface modification and coating techniques, the use of polymer additives and their effects on the biological response of polyurethanes and the development of novel biostable polyurethanes were surveyed only very briefly in the most recent book (Lamba NMK, Woodhouse KA, Cooper SL. *Polyurethanes in Biomedical Applications*. Boca Raton, FL: CRC Press LLC, 1998) dedicated to these materials.

Hence, we perceived a need for an up-to-date text, and we hope that the present work will meet this need and convey information to both the novice and the expert in the field.

While presuming some background knowledge of biomaterials science, for the reader who is a relative novice to the field we present and discuss a number of concepts that are relevant to biomedical polyurethanes, in the hope of conveying the multifaceted task that faces the developers of improved biomedical materials. Such materials must meet a diverse number of criteria, some of which may be poorly defined. Of course some of these issues, such as the question of what is "biocompatibility" and how one assesses it, applies to other classes of biomedical materials as well. An exhaustive discussion of all aspects of biomedical requirements, tests, and responses obviously is beyond the scope of this work, and the reader is encouraged to consult standard textbooks on biomaterials science, such as:

- Ratner BD, Hoffman AS, Schoen FJ, Lemons JE, Eds. *Biomaterials Science: An Introduction to Materials in Medicine*. San Diego: Academic Press, 1996.
- Von Recum AF, Ed. *Handbook of Biomaterials Evaluation*. New York: Macmillan, 1986.
- Silver FH, Doillon C. *Biocompatibility: Interactions of Biological and Implanted Materials, Vol 1—Polymers*. New York: VCH Publisher, 1989.

One challenge we faced in writing and editing this book is the wide range of technological fields that apply to the development and testing of biomedical materials. We approached this challenge by assembling editors and authors from diverse technological backgrounds — and geographical locations. Only once did the four editors meet in one room to assess whether the contents might end up forming a cohesive unit. Nor did we have an opportunity to meet all contributors in person in the course of writing. However, modern communication technology has eliminated the obstacles of geographical location, and all of us are richer for the experience of collaborating on his book across oceans, different mother tongues, and different cultural backgrounds. There were misunderstandings, delays, and mishaps, but above all an overriding sense of goodwill and collaboration that so much characterizes the international community of scientists.

A further challenge in writing and editing this book lies in the vague nature of some of the terminologies used by many researchers. A prominent example is the term "biocompatibility". Innumerable biomaterials publications declare the development of biocompatible materials, and polyurethanes are well represented in this. Why, then, is development and testing still ongoing? If those publication titles were to be true in their literal meaning, the challenge of developing the "ultimate" biomedical polyurethane would appear to have been solved long ago; as a corollary, there would be no need for this book. It is also regrettable that many researchers fail to acknowledge that "biocompatibility" requirements may differ considerably for different biomedical applications. Thus, a polyurethane that performs well in one host body location may be unsuitable for another biomedical purpose. Likewise, a number of publications report "blood-compatible (or hemocompatible) polyurethanes". Why is it, then, that these materials have not led to the fabrication of "perfect" cardiovascular devices and efforts are continuing on improving the hemocompatibility of these materials? Is it perhaps because informed researchers and device manufacturers realize the true value of such claims based on tests that do not fully replicate

the real in vivo requirements? Regrettably, though, this situation leads to confusion for novices and should be addressed.

Language is a wonderful communication tool but needs to be used with precision. The term "biocompatible" means exactly that, i.e., *full* compatibility with *all* requirements; it does not mean "almost biocompatible" or "more compatible than polymer X". It is a pity that so many researchers use loose, ill-defined terminology instead of bringing precision to their reports and declaring an improvement in performance in this-and-that application as measured by this-and-that test. While of course such details are contained in the body of reports, the use of unqualified, broad, imprecise statements in abstracts and conclusions sections should be discouraged.

Having said this, we admit to using in this book terminology that is not always well defined or implicitly clear in its meaning. Some terms have widely accepted usage in the field, and we do rely in many instances on an implicit understanding of the contents and limits of such usage. We beg the reader's indulgence for such compromises and any confusion and uncertainty we may bring about with our writing.

We hope that this book will prove to be of value to readers from various technical backgrounds. Research and development of biomedical materials requires the expertise of materials scientists, engineers, chemists, clinicians, surface scientists, biologists, and others, pooled into a collective effort. It is difficult to structure a text such that it addresses the needs of such a diverse audience and starts at realistic levels of pre-existing knowledge. Those who have worked in the biomaterials field for a while may wish to skip many sections, while others will undoubtedly feel that we left out some useful background information. We do hope that every reader will derive some benefit.

Editing this book has been a challenging but most rewarding task. We thank all the contributing authors for their efforts and timeliness; it has been a pleasure working with you. We also express our sincere thanks to the reviewers who graciously consented to donate their time for the careful review of draft Chapters and whose suggestions, much appreciated by the authors, led to substantial improvements. We wish to acknowledge partial financial support by the *Fonds pour la Formation des Chercheurs et l'Aide à la Recherche* (Fonds FCAR, Québec, Canada), the Cooperative Research Centre for Eye Research and Technology, (Sydney, Australia) and the National Sciences and Engineering Research Council of Canada (NSERC, Canada). Finally, we thank our loved ones for their understanding and patience during the hours we spent on this book. It is to them that we dedicate this work.

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January 2000

Chapter 1

Synthesis, Physicochemical and Surface Characteristics of Polyurethanes

Martin Castonguay, Jeffrey T. Koberstein, Ze Zhang, and Gaétan Laroche

1.1 Introduction

This Chapter constitutes the starting point that will bring the reader to the other subjects discussed in this book as, for example, the biological response and biostability related to polyurethanes (PUs) are primarily driven at the first steps with their Synthesis and processing. Many literature reviews have been published about the synthesis, phase separation, mechanical, chemical, and surface characteristics of polyurethanes. However, it was the authors' feeling that the concepts lying behind these subjects were often presented as having something to do with black magic. First, the synthesis of polyurethanes is most of the time described as a presentation of the various soft segments, hard segments and chain extenders that are currently used for the preparation of theses polymers. In the present Chapter, many efforts were put in presenting the experimental steps required to obtain polyurethanes, as well as the problems that may be encountered during the synthesis. Second, the importance of selecting the appropriate constituents and postsynthesis thermal treatments are also emphasized in relationship with the mechanical and chemical properties that are expected. In connection with this section, we have also compared the mechanical characteristics of PUs with other currently used biomedical polymers. Finally, the nature of the polyurethane composition implies a wide diversity of surface characteristics, which in turn, are of prime importance when dealing with an eventual use of PUs as biomaterials. Therefore, the means that should be put forward to modulate the PUs surface composition as well as its significance with the biological response are presented.

1.1.1 Why Are Polyurethanes Different from Other Currently Used Polymers?

Most of the polymers manufactured in industry possess a fairly simple chemical structure as they are synthesized from one or two monomers therefore leading to the formation of homopolymers or copolymers. Examples of these polymers are poly(ethyleneterephtalate) (PET), poly(tetrafluoroethylene) (PTFE), poly(styrene), poly(ethylene), poly(propylene), poly(butadiene), etc. On the other hand, polyurethanes possess more complex chemical structures that typically comprise three monomers: a diisocyanate, a macroglycol (which is an oligomeric macromonomer) and a chain extender. Because of the three "degrees of freedom" that are

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available when considering the synthesis of a polyurethane, one may obtain a virtually infinite number of materials with various physicochemical and mechanical characteristics. Due to this unique composition, the structure of polyurethanes is quite different from that of other polymers. In fact, PU elastomers usually show a two-phase structure in which hard segment-enriched domains are dispersed in a matrix of soft segments. The hard segment-enriched domains are composed mainly of the diisocyanate and the chain extender, while the soft segment matrix is composed of a sequence of macroglycol moieties. For this reason, polyurethanes are often referred as segmented block copolymers. This particular molecular architecture, as well as the intrinsic properties of each ingredient used for the synthesis of polyurethanes, explained the unique characteristics of this class of materials when compared to other polymers.

Despite what is claimed in the literature, polyurethanes found a niche in biomedical applications mainly because of their interesting mechanical properties rather than for their biological response. Indeed, most of the studies related to the use of polyurethanes as biomaterials state that they are both "biocompatible" and "hemocompatible" despite the fact that several publications have clearly demonstrated that PUs degrade in the human body (Chapter 5) and are not more blood compatible (Chapter 4) than the other materials currently used in vascular surgery. However, it is clear that polyurethanes are characterized by unique mechanical properties that may be very useful for particular applications, especially when fatigue resistance is required.

1.2 Chemistry

1.2.1 Polyurethane Structure

Polyurethane is the general name of a family of synthetic copolymers that contain the urethane moiety in their chemical repeat structure (Fig. 1.1).

Since polyurethane was first synthesized in 1937 by Otto Bayer and co-workers,[1] it has achieved a variety of applications including elastomers, foam, paint, and adhesives. Such diversity of applications originates from the tailorable chemistry of polyurethanes, i.e., the chemical composition of polyurethanes can be tailored, by choosing different raw materials and processing conditions, to accommodate many specific requirements. As a family of biomaterials, polyurethanes are most frequently synthesized as segmented block copolymers. In the following, we are going to focus on the basic chemical reactions, raw materials, and synthesis of segmented polyurethanes.

1.2.2 Basic Chemical Reactions

Segmented polyurethanes can be represented by three basic components in the following general form:

$$P\text{-}(D(CD)_n\text{-}P)_n$$

Where P is the polyol, D is the diisocyanate and C is the chain extender. Polyol, or the so-called soft segment, is an oligomeric macromonomer comprising a "soft" flexible chain terminated by hydroxyl (-OH) groups. The chain extender is usually a small molecule with either hydroxyl, or amine end groups. The diisocyanate is a low molecular weight compound that can react with either the polyol or chain extender, leading to the interesting segmented structure illustrated above. In linear polyurethanes, the three components have a functionality of two. If a branched or crosslinked material is desired, multifunctional polyols, isocyanates, and sometimes chain extenders can be incorporated into the formulation. Due to the statistical nature of the copolymerization, polyurethanes have both a distribution in total molecular weight and a

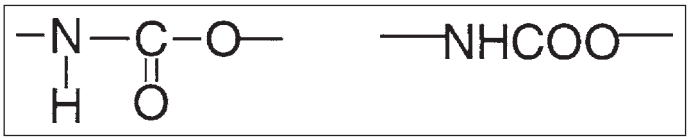


Fig. 1.1. Urethane linkage.

distribution in the hard segment sequence length, those copolymer sequences denoted as $D(CD)_n$, that follow essentially a most probable distribution.

The principle chemical reaction involved in the synthesis of polyurethanes is the urethane-forming reaction, i.e., the reaction between isocyanate and hydroxyl groups (Fig. 1.2a).

Because this is a nucleophilic addition reaction, it is catalyzed by basic compounds such as tertiary amines and by metal compounds such as organotin. Urethane formation is actually an equilibrium reaction; the presence of catalyst therefore also increases the rate of the back reaction at high temperatures.

Another important basic reaction is the chain extension reaction which occurs between chain extender (diol or diamine) and isocyanate. When a diol is used as chain extender, urethane will be formed according to Figure 1.2a while urea will be formed according to Figure 1.2b if diamine is used.

Isocyanate not only reacts with primary amine, but can also react with secondary amine such as the N-H in urethane or urea groups, even though the rate of reaction is much lower compared with that of the primary amine. The nucleophilic addition nature of the reaction with the secondary amine remains the same and so the chemical structure of the products (allophanate and biuret, with respect to the reaction with urethane and urea) can be easily predicted according to Figure 1.2. Allophanate or biuret formation leads to branching and crosslinking and is favored when excessive isocyanate is present.

In addition to the above two basic reactions, the reaction of water with isocyanate must also be mentioned. Because isocyanate is so active, it reacts with active or acidic hydrogen almost instantly. This two-step reaction with water has become the most important side reaction that should be avoided or minimized, except if a foam or high urea content is desired (Fig. 1.3).

The amine groups formed during the second step will further react with remaining isocyanate to produce urea groups. The carbon dioxide formed (Fig. 1.3b) can be used to produce a polyurethane foam. The net effect of this reaction on the ratio of reactants is the consumption of one unit of isocyanate and the formation of one amine group. Further reaction of the amine group with an isocyanate leads to the formation of an urea.

1.2.3 Raw Materials

Segmented polyurethane is composed of three raw material reactants: polyol, diisocyanate, and chain extender (diamine or diol). The final properties of the polyurethane produced are largely dependent on the chemical and physical nature of these three building blocks.

1.2.3.1 Polyol

Conventional polyols are usually a polyether (with a repeating structure of -R-O-R'-) or a polyester (with repeating structure of -R-COO-R'-), with chain ends terminated by hydroxyl groups. Unlike diisocyanate compounds and chain extenders, a polyol is oligomeric with a molecular weight normally ranging from a few hundred to a few thousand. At room temperature, polyols can be liquid or solid (wax-like), depending on the molecular weight. Due to their aliphatic structure and low intermolecular interaction,

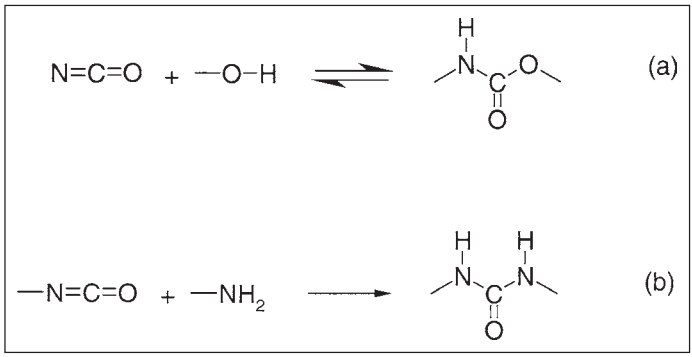


Fig. 1.2. Chain extension reaction occurs between chain extender (diol or diamine) and isocyanate. When a diol is used as chain extender, (a) urethane will be formed, while (b) urea will be formed if diamine is used.

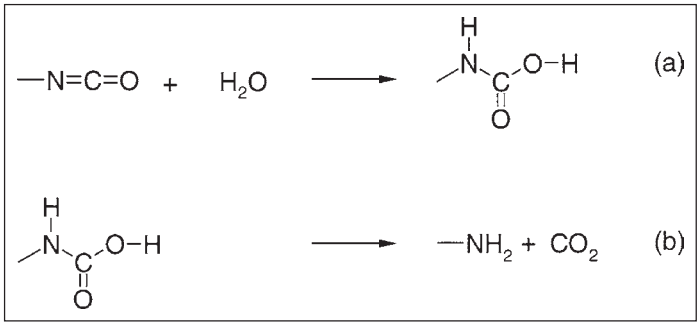


Fig. 1.3. The reaction of water with isocyanate must also be considered. Because isocyanate is so active, it reacts with active or acidic hydrogen almost instantly. This two-step reaction with water has become the most important side reaction that should be avoided or minimized, except if a foam or high urea content is desired.

particularly the abundant ether bonds, polyol molecules rotate and bend easily and are therefore soft materials. Consequently, the polyol sequence of polyurethane-segmented block copolymers is referred to as the soft segment. New polyol soft segment materials including polyalkyl,[2] polydimethylsiloxane[3] and polycarbonate[4] have also been developed to fulfil the critical and specific requirements intrinsic to biomedical and industrial applications. The chemical structures of four types of representative polyols are illustrated in Figure 1.4. Other types can be easily found in the literature. Some novel polyols are presented in Chapter 6.

1.2.3.2 Isocyanate

The most important isocyanate used in polyurethane manufacture is diisocyanate, containing two isocyanate groups per molecule. These two functional groups work to join together (by chemical reaction) two other molecules (polyol or chain extender) to form a linear chain. When the functionality is greater than two, a branch site is formed between the molecules, leading to network or crosslink formation. Diisocyanate can be either aromatic or aliphatic, as represented by 4,4'-diphenylmethane diisocyanate (MDI) and hydrogenized MDI (HMDI). Another

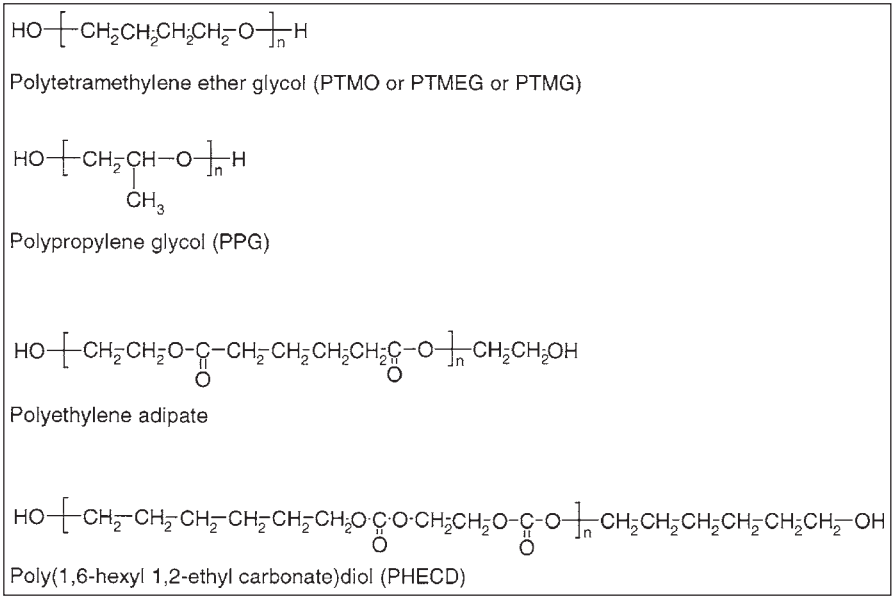


Fig. 1.4. Macroglycols used for the synthesis of biomedical-grade polyurethanes.

equally important (or even more important in industry) diisocyanate compound is toluenemethyl diisocyanate, or TDI, which is also aromatic in nature. The chemical structures of these three types of diisocyanate compounds are shown in Figure 1.5. A myriad of additional diisocyanates can be found in literature.[5,6]

Because of the ring structure of the diisocyanates and the strong intermolecular interactions such as hydrogen bonding among urethane groups that form following the reaction of isocyanate with chain extender, the segments that contain isocyanate and chain extender are more rigid than polyol, are typically glassy at room temperature and therefore are called hard segments.

1.2.3.3 Chain Extender: Diamine or Diol?

The direct reaction of polyol with diisocyanate produces a soft gum rubber with poor mechanical strength. The properties can be drastically improved by the addition of chain extender. The role of the chain extender is to produce an "extended" sequence in the copolymer consisting of alternating chain extenders and diisocyanates. These extended sequences, or hard segments, act both as filler particles and physical crosslink sites to increase mechanical strength. A polyurethane-urea is obtained when a diamine is used while a polyurethane results when the diol is used. Two commonly used chain extenders are showed in Figure 1.6.

1.2.4 Synthesis of Segmented Polyurethanes

Polyurethanes may be polymerized by a variety of techniques that produce different materials. In the laboratory, solvent is usually used to reduce the viscosity and promote the formation of high molecular weight copolymers. The polymerization often follows a two-step procedure:

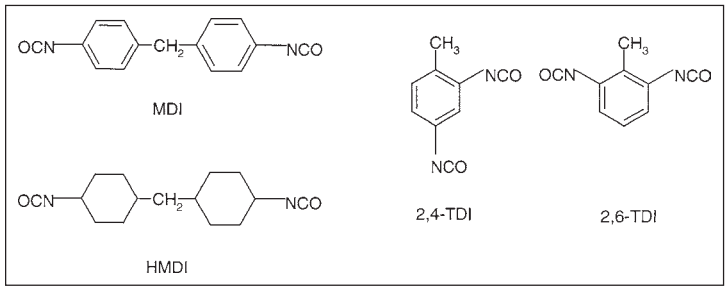


Fig. 1.5. Diisocyanates used for the synthesis of biomedical-grade polyurethanes.

Fig. 1.6. Chain extenders commonly used for the synthesis of biomedical-grade polyurethanes.

First, an isocyanate end-capped "prepolymer" is formed by the reaction of polyol with excess diisocyanate; then the chain is extended to high molecular weight through the reaction of residual isocyanate functionality with added chain extender. Commercial polyurethanes are usually prepared without solvent either by a similar two-step procedure forming first the prepolymer or by the so-called "one-shot" process in which all three monomers are mixed simultaneously. Alternatively, bulk polymerization can be accomplished by reaction injection molding (RIM), in which a stream of diisocyanate and one of polyol with chain extender is rapidly combined by impingement mixing directly before entering a mold cavity.

1.2.4.1 Laboratory Synthesis

The laboratory synthesis of polyurethane is usually carried out in a three-neck glass flask and a common set-up is illustrated in Figure 1.7. The inlet has three functions: connection to vacuum line, introduction of nitrogen gas, and adding reactants. The speed of reactant addition needs to be regulated. The reaction should be performed under nitrogen atmosphere in order to protect from moisture and oxygen. Efficient stirring is very important to ensure uniformity of the reaction and a narrow distribution of molecular weight, particularly in the chain extension step.

In the classic two-step solution phase synthesis of polyurethane composed of MDI, PTMO, and BD, the following procedures are commonly adopted:

1. Set-up of the reactor according to Figure 1.7. A predrying of glassware is recommended. The reactor is vacuumed and then purged with nitrogen gas. A slight positive nitrogen pressure is kept in the reactor. A simple method of keeping positive nitrogen pressure is to make a connection of the reactor to a balloon inflated with nitrogen gas.
2. Preparation of the reactants. It is strongly recommended that all of the reactants be purified before the synthesis. Polyol should be dried with strong agitation at 100-120°C under 0.1 torr for at least one hour to ensure the water content is less than 0.03%.

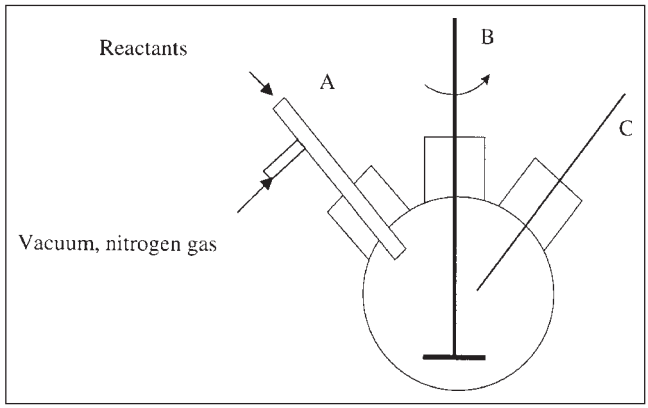


Fig. 1.7. Laboratory set-up for the synthesis of polyurethanes. A: Inlet; B: Stirrer; C: Thermometer; D: Three-neck glass flask.

Distillation can be used to purify the chain extender and the isocyanate. The distillation of isocyanate should be carried out under reduced pressure to avoid the self-addition reaction of isocyanates at elevated temperature. Solvent should also be freshly distilled or treated with metallic sodium to remove traces of water.

3. Adding isocyanate compound to the reactor. The temperature of the reactor is kept at a predetermined temperature, for example at 70°C.
4. Adding polyol to the reactor. The polyol should be slowly introduced under constant agitation. Once the addition is completed, the reaction is maintained at 70-80°C with agitation for 2-3 hours to complete the reaction.
5. Predetermined amount of purified solvent is added to the reactor. The temperature of the reactor is reduced to 40-60°C. The solvent will reduce the viscosity of the polyurethane and maintain effective agitation in the next chain-extending step. The amount of solvent can be calculated based on the desired final concentration of the polyurethane solution, for example, 20% wt/v.
6. Adding chain extender. Chain extender should be slowly added under vigorous agitation. The reaction is kept at 40-60°C until completion. At this stage, significant increase of viscosity and temperature will be noticed and efficient agitation is extremely important. Completion of the reaction is indicated by the attainment of constant viscosity or by the residual isocyanate index.
7. Terminate of the reaction by introducing chain-terminating agent such as methanol.
8. Store the polyurethane solution in dark-colored container and preferably under sub-ambient temperature.

The high viscosity of the solution usually indicates success of the synthesis. By contrast, a poor viscosity, or the formation of gel (crosslink) indicates failure of a synthesis.

The major advantage of solution synthesis is the relative ease in controlling the reaction. However, it is less frequently used in industry than in academic institutions, because of the high cost and inconvenience involved with the use of solvent. In industry, two types of bulk polymerization are commonly used. In the two-step method, the prepolymer (the product of isocyanate with polyol) is first prepared; then chain extender is directly added to the reactor with vigorous agitation without introducing solvent. When the viscosity of the product has reached a certain degree, it is poured out of the reactor and cured at elevated temperature. In the one-shot method, all ingredients are simply mixed together. More advanced techniques, such as reaction injection molding (RIM), can be used for one-step bulk polymerization and pellet extrusion (Chapter 2).

1.2.4.2 Calculation of the Reactants

The calculation of reactant ratio for the synthesis of segmented polyurethane is straightforward: the total number of isocyanate groups should be equal to or slightly higher (by experience) than the number of hydroxyl groups, including both the polyol and chain extender. A typical formulation often in the literature, would be a ratio of isocyanate to polyol to chain extender of 2:1:1, which is based on the following two idealized reactions in the two-step method:

$$\text{Step 1: } 2n(\text{MDI}) + n(\text{Polyol}) \longrightarrow n(\text{MDI-Polyol-MDI})$$

$$\text{Step 2: } n(\text{MDI-Polyol-MDI}) + n(\text{Diol}) \longrightarrow (\text{MDI-Polyol-MDI-Diol})_n$$

However, because of the bifunctional nature of the reactants, they not only react with each other but also react with the products. Consequently, products with a general form like MDI(Polyol-MDI)_i will be found at the end of step 1. The larger the product becomes, the less chance by which it will react with a new reactant. Therefore, the value of i will follow a statistic distribution with the highest possibility at i = 1. The exact distribution not only depends on the reactivity between reactants, between reactants and different products, but also largely depends on the experimental parameters of each particular synthesis system, such as stirring. For the same reason, plus the consideration of the excess of isocyanate, the products at the end of step 2 will take a general form like:

$$[\text{MDI(Polyol-MDI)}_i\text{-Diol-(MDI-Diol)}_j]_k\text{-MDI}$$

Due to the difficulty in keeping the reactants completely free of moisture, the amount of isocyanate is often slightly higher than the theoretical ratio. This ratio is empirically determined. In the following example, the isocyanate index (NCO:OH) is 1.02, i.e., the excess of isocyanate is 2%. In industry, excess isocyanate is also used to introduce certain degree of crosslinking, which is desirable for improved mechanical strength, since it leads to the formation of allophanate and biuret branch points.

Example:

One mole of MDI: 250 g; one mole of PTMO-1000: 1000 g; one mole of BD: 90 g. With the ratio of MDI:PTMO:BD = 2.04:1:1, the ratio of reactant weights in grams: 510:1000:90.

In industry, polyurethanes are often categorized according to their hardness. While thermal history or processing will have significant influence on their mechanical properties, when the chemistry of the isocyanate, polyol, and chain extender has been determined, the hardness of polyurethane mainly depends on the overall hard segment content (the weight percentage of the isocyanate and chain extender in the formula) and the molecular weight of the soft segment. The hard segment content can be adjusted, for example, by changing the ratio of polyol to chain extender. In the above example, an increase of BD ratio, for example from 1-1.5 (so the PTMO ratio will decrease from 1-0.5), will significantly increase the hardness of the polyurethane. On the other hand, an increase in soft segment length will normally produce polyurethanes with low hardness and high extensibility.

1.3 How to Control Physicochemical and Mechanical Properties of Polyurethanes?

As described above, polyurethanes are made from three different chemical species that all influence the characteristics of the polymer. Keeping in mind the various molecules that may be

used for the synthesis of polyurethanes, the following section will focus on clarifying the effect of some isocyanates, macroglycols, and chain extenders on the properties of the final material.

1.3.1 Effects of Diisocyanate Monomers

1.3.1.1 Mechanical Characteristics

Because of the strong tendency of rigid aromatic moieties to pack efficiently and the presence of hydrogen bonding between isocyanate-derived groups (urethanes and ureas), isocyanate segments tend to self-organize to form semi-crystalline phases within the polymer macromolecular assembly. Each type of diisocyanate has a different intrinsic ability to form such microphase structures. As the elasticity of the polymers depends on their degree of crystallinity and the degree of hard segment segregation, it is clear that the selection of the diisocyanate monomer will be one of the key parameters that influence polyurethane mechanical characteristics. Many authors have tried to correlate mechanical properties of polyurethanes with the structure of the hard segments, macroglycols and chain extenders used to synthesize them. Among them, Schollenberger has perhaps achieved the most success in this respect, as detailed in a book Chapter published 30 years ago.[7]

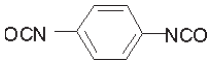
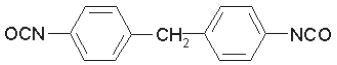
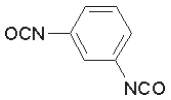
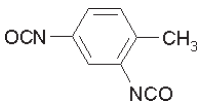
Table 1.1 reproduces data on structure/properties of polyurethanes published by Schollenberger that demonstrates how mechanical characteristics can be manipulated through the appropriate selection of hard segments. This may be illustrated through the variation of the modulus at 300% elongation for polyurethanes synthesized under similar conditions but with different types of diisocyanates. As may be seen in Table 1.1, where the modulus of polyurethanes synthesized with polytetramethylene adipate, 1,4-bis (2-hydroxyethoxy) benzene and different diisocyanates are shown in decreasing order, the polymer containing 1,4-PDI is by far the more rigid with a modulus of 3400 psi. This result may be attributed to the compact, rigid, and highly symmetric nature of 1,4-PDI. On the other hand, 4,4'-MDI presents a structure very similar to the 1,4-PDI one. However, free rotation of the two phenyl moieties is allowed because of the presence of the methylene group joining the two aromatic rings. For this reason, 4,4'-MDI develops a three-dimensional structure rather than the in-plane structure as depicted in Table 1.1, that impedes efficient molecular packing. 1,3-PDI is no less rigid or compact than 1,4-PDI; however, its symmetry is lower leading to less efficient molecular packing. Finally, the structure of 2,4-TDI is similar to that of 1,3-PDI with the exception of the addition of one methyl group. The asymmetry caused by this additional moiety leads to steric hindrance between polyurethane chains and less efficient packing.

1.3.1.2 Chemical Relevance

Diisocyanates used for the synthesis of medical-grade polyurethanes may be divided into two classes: aromatic and aliphatic. In practice, manufacturers involved in the synthesis of medical-grade polyurethanes use primarily MDI despite the observation that this monomer leads to a potentially carcinogenic degradation product, namely methylene diamine (MDA). It should be pointed out that no cancer was reported in patients implanted with polyurethane devices, however. Apparently manufacturers prefer to work with a fairly safe material made with MDI rather than using other aromatic diisocyanates. The carcinogenicity issue of degradation products from other diisocyanate-based polyurethanes has not been thoroughly examined.

Nevertheless, a solution to the potential carcinogenic effect of MDA has already been proposed, that is the use of a hydrogenated version of MDI, HMDI, for the synthesis of biomedical-grade polyurethanes. The gain from minimizing the potential carcinogenic effect

Table 1.1. Effect of diisocyanate structure on the 300% modulus of some polyurethanes[A]

Diisocyanate	300% modulus (MPa)
1,4-phenylene diisocyanate 	23.4
4,4'-diphenylmethane diisocyanate (MDI) 	13.1
1,3-phenylene diisocyanate 	9.7
2,4-toluene diisocyanate 	2.1

[A] Polymers made of 2.5 parts of diisocyanate, 1 part of poly(tetramethylene adipate) and 1.5 part of 1,4-bis(2-hydroxyethoxy) benzene.

of the degradation products comes at the expense of the mechanical and in vivo characteristics that are poorer than for the aromatic version of the polyurethanes. Aromatic-based diisocyanates, as mentioned above, present a fairly rigid molecular structure due to delocalization of the π electrons throughout the aromatic rings, therefore impeding rotation of the C-C bonds. On the other hand, the cyclohexane moieties of aliphatic-based diisocyanates are highly flexible as they experience reversible boat to a chair conformational changes. As mentioned above, such flexibility within the structure of the diisocyanate is detrimental to hard segment ordering and cohesion.

Polymers made from aromatic diisocyanates also tend to yellow upon exposure to light at ambient conditions as they form di-quinones, which act as chromophores. While manufacturers of MDI-based polyurethanes claim that the biological response and mechanical characteristics are not affected by this transformation, this subject is far from being well documented in the scientific literature.

1.3.2 Effects of Macroglycols

1.3.2.1 Mechanical Characteristics

As observed for their diisocyanate counterpart, macroglycols used to synthesize polyurethanes influence the mechanical characteristics of the final products. In the same manner as what has been described above, mechanical properties of polyurethane are driven by the ability of the macroglycol moieties to pack themselves in closer molecular arrangement. This behavior is illustrated in Table 1.2, which shows the effect of ester macroglycol structure on the mechanical properties of polyurethanes made of MDI (two equivalents), the macroglycol (one equivalent) and butanediol (one equivalent). Again, the modulus at 300% of elongation is used as a probe of the rigidity of the materials investigated. The highest modulus is observed for the PU synthesized with poly(tetramethylene adipate) glycol, the macroglycol that presents the best structural regularity relative to the other polymers. This behavior finds its explanation in the model proposed by Blackwell and Lee that demonstrates that MDI model compounds packed in such a way that the $(CH_2)_4$ diol chain extender fit perfectly between the MDI units to maximize their packing.[8]

1.3.2.2 Chemical Relevance

Aside from mechanical property considerations, the choice of one macroglycol over another resides in the resistance of such macroglycol toward hydrolysis and chemical degradation. Polyester-urethanes were the first to be used in biomedical applications because these polyurethanes possess good mechanical properties due to the ability of the ester groups to form hydrogen bonds. The rapid hydrolysis of ester groups, a reaction which is considered by most chemists as being the cornerstone of organic chemistry, was initially overlooked during the development of biomaterials. Biomaterial scientists discovered that the hydrolytic stability of polyurethanes could be improved by the use of polyether-based materials because ether groups can be cleaved only in a strong acidic environment. Ethers may however be readily oxidized in air to lead to the formation of peroxides. This latter mechanism may explain the inadequate stability of polyether-urethanes upon in vivo implantation. Nevertheless, the chemical stability of polyether-based is by far superior to that of polyester-based urethanes. Examples of the effects of hydrolysis for both polyester-urethanes and polyether-urethanes made of MDI (two equivalents), butanediol (one equivalent) and various macroglycols are presented in Table 1.3, demonstrating the superior stability of polyether-urethane toward hydrolysis.

New macroglycols are being introduced with the aim of improving the in vivo chemical stability of biomedical grade polyurethanes (see Chapter 6). Among them, the carbonate-based macroglycols have been a clear focus of the biomaterial research community in the 1990s. They are purported by their manufacturers to be more biostable than their polyester and polyether counterparts. While, from a purely chemical point of view, the carbonate moiety should be more prone to degradation than the ether groups, no comprehensive comparative study on the relative stability of polyether and polycarbonate toward hydrolysis has appeared. Only in vivo implantations have been performed wherein it was demonstrated that polycarbonate-urethanes seem to be more stable than polyether-urethanes. This result may also indicate however that the in vivo degradation mechanism is not only related to hydrolysis.

Table 1.2. Effect of macroglycol structure on the 300% modulus of some polyurethanes[A]

Macroglycol	300% modulus (MPa)
Poly (ethylene adipate) glycol	6.2
Poly (tetramethylene adipate) glycol	9.0
Poly (hexamethylene adipate) glycol	8.3

[A] Polymers made of 2 parts of diphenylmethane-4,4′-diisocyanate, 1 part of macroglycol and 1 part of 1,4-butanediol.

Table 1.3. Effect of macroglycol structure on the hydrolytic stability of some polyurethanes[A]

Macroglycol	Type	Tens. strength (N)	Elongation at break (%)	300% modulus (MPa)
Poly(ethylene adipate) glycol	Polyester	40	119	100
Poly(hexamethylene adipate) glycol	Polyester	30	131	75
Poly(oxytetra-methylene) glycol	Polyether	88	105	110
Poly(oxypropylene-1,2) glycol	Polyether	88	100	112

[A] Polymers made of 2 parts of diphenylmethane-p,p′-diisocyanate, 1 part of macroglycol and 1 part of 1,4-butane diol; mechanical properties retained after 21 days in H_2O at 70°C.

1.3.3 Effects of Chain Extenders

1.3.3.1 Mechanical Characteristics

Although the chain extender is a short molecule, its chemical structure can also have a profound influence on the mechanical properties of polyurethanes. As shown in Table 1.4, the modulus at 300% of elongation for polyurethanes made of MDI (2 equivalents), poly(tetramethylene adipate) glycol (1 equivalent) and various types of chain extenders, vary as a function of the chain length of the glycol. The modulus increases with the number of methylene groups from two to four methylene groups while it decreases when the glycol contains six—(CH_2)—moieties. Again, this result has been explained by modeling studies performed by Blackwell et al.[8] They showed this length of chain extender led to near optimal packing of diisocyanate residues leading to a more ordered hard segment microdomain.

In addition to the length of the chain extender moiety, its relative concentration with respect to the macroglycol content is also a key parameter to control the mechanical properties of the polymer. Generally speaking, high equivalent ratio of chain extender leads to an increase of hard segment content, therefore producing polyurethanes that are harder, stiffer and stronger.[9]

Table 1.4. Effect of glycol structure on the 300% modulus of some polyurethanes[A]

Glycol	300% modulus (MPa)
Ethylene glycol	6.9
Trimethylene glycol	8.3
Tetramethylene glycol	9.0
Hexamethylene glycol	7.6

[A] Polymers made of 2 parts of diphenylmethane-4,4′-diisocyanate, one part of polytetramethylene glycol and one part of glycol.

1.3.3.2 Chemical Relevance

Despite the fact that most polyurethanes used for biomedical applications are made with a diol as chain extender, the search for different mechanical characteristics has led to use of diamine chain extenders for the synthesis currently described as PEUU (polyether-urethane-urea). The urea groups provide an additional N-H functionality within the polymer chain that increases the degree of inter-urethane hydrogen bonding. N-H groups on the urea linkages and those of the urethane groups act as the hydrogen bond donors while carbonyl groups, and to a smaller extent ether functionalities, are hydrogen bonds acceptors.[9] The additional intermolecular hydrogen bonds provided by the urea groups increase the cohesive density of the hard microdomains. Despite the fact that hydrogen bonds are considerably weaker than covalent linkages, their great number is responsible for the fact that polyurethane-ureas behave much like thermosets rather than thermoplastics.

1.4 Thermotropic Behavior of Polyurethanes

As mentioned above, the physicochemical and mechanical properties of polyurethanes are largely affected by the aggregation state of the polymer chains. Indeed, the selection of a given set of isocyanate, macroglycol and chain extender depends on the particular crystallinity and degree of microphase separation that is desired. The microdomain structure of polyurethanes however is highly dependent on the thermal history of the polymer. Surprisingly, this important aspect of polyurethane processing has often been neglected by scientists dealing with biomaterial applications. In fact, most papers investigating the thermal transitions observed with polyurethane samples failed to mention their thermal history. Thermal history effects alone may be the true origin of observed phenomena that are attributed to in vivo or in vitro aging of the polymer.

Thermal history effects have been studied extensively, and the literature documents a wide variety of different thermotropic behaviors for polyurethanes. Pioneering work by Cooper et al reported three endothermic transitions for polyurethane made with methylene diisocyanate and butanediol after a thermal cycle that consisted of heating above the melting point, slowly cooling under pressure to room temperature and then annealing at a temperature below the melting point.[10,11] The lowest temperature endotherm, observed between 60 and 80°C was assigned to the disruption of short range order of hard segments microdomains while endotherms observed at higher temperature were attributed to the disruption of long-range (between 120 and 190°C) and microcrystalline order of the hard segments (above 200°C).

Koberstein et al performed a number of thorough studies on the effect of the temperature on the microphase structure of polyurethanes. It is clear that the endothermic response of polyurethanes depends on the procedure for sample preparation as well as the details of subsequent conditioning as clearly demonstrated in Figure 1.8 (experiments were performed on compression molded samples).[12] Region I is characteristic of a low incubation temperature near the hard segment glass transition where a non-crystalline microphase structure predominates. The high-temperature melting endotherm in region I (Peak I) is associated with a microphase separation transition to the disordered state that is nothing else than the dissolution of the microphase structure. Conditioning the sample in region II results in a more crystalline sample and leads to the appearance of two high temperature endotherms. Studies performed using both differential scanning calorimetry and small angle x-ray scattering demonstrated that the first endotherm is due to a partial disordering of the microdomain structure while complete disordering occurred during the second endotherm.[13]

Jacques pointed out that melt crystallization using different thermal cycles might give rise to different molecular organization.[14] Indeed, crystallization is possible in region III in the case where T_c is approached from a lower temperature. For example, quenching a polyurethane sample from the melt and reheating it to a higher temperature (lower than T_m) gives rise to easier crystallization and to structures with melting points that are significantly higher than those obtained by quenching directly down to T_c from the homogeneous melt temperature. This behavior found its explanation in the fact that crystal nuclei may remain after the former thermal cycle and seed the crystallization at higher T_c.

Blackwell and Lee,[8] demonstrated the existence of polymorphic crystal transitions in MDI/BD-based polyurethanes. They found that initial crystallization tend to form contracted crystal structures while annealing and stretching the sample promoted the formation of extended crystal polymorphs which had a lower melting point and presented a structure consistent with an all-trans conformation of the BD residue.

The literature illustrates that sample preparation method is of paramount importance when dealing with the crystalline structure, and consequently the thermotropic behavior, of polyurethanes. Briber and Thomas[15] demonstrated two crystalline polymorphs for MDI/BD-based polyurethane solvent cast at 145°C. The first crystal type was intrinsically disordered while the second one was more ordered and melted at higher temperatures.

The above-mentioned data illustrate that the thermal history of polyurethanes is a major parameter to be considered when dealing with the physicochemical properties of this family of polymers. Unfortunately, only a few publications dealing with the characterization of biomedical polyurethanes make mention of the polymer thermal history.

1.5 Comparison of Mechanical Properties of Biomedical Polyurethanes with Other Biomedical Grade Polymers

Table 1.5 lists the mechanical characteristics of different polymers currently used in the biomedical market. As already pointed out, the mechanical properties of polyurethanes are highly dependent on several parameters that govern their microphase separation. As may be seen in Table 1.5, the tensile strength of polyurethanes is variable, with values ranging from 25-62 MPa, while their elongation goes from 355-800%.[7] On the other hand, the other polymers listed in Table 1.5 present a tensile strength ranging between 100 and 3000 MPa and an elongation at break 100 and 1000%.[16] It is therefore clear that polyurethanes exhibit totally different mechanical characteristics as compared to most of the other biomedical grade polymers. In particular, polyurethanes exhibit much higher elasticity than most of the other polymers considered. One of the most important considerations in choosing a biomaterial, however, should be the mechanical properties of the part of the body that has to be replaced.

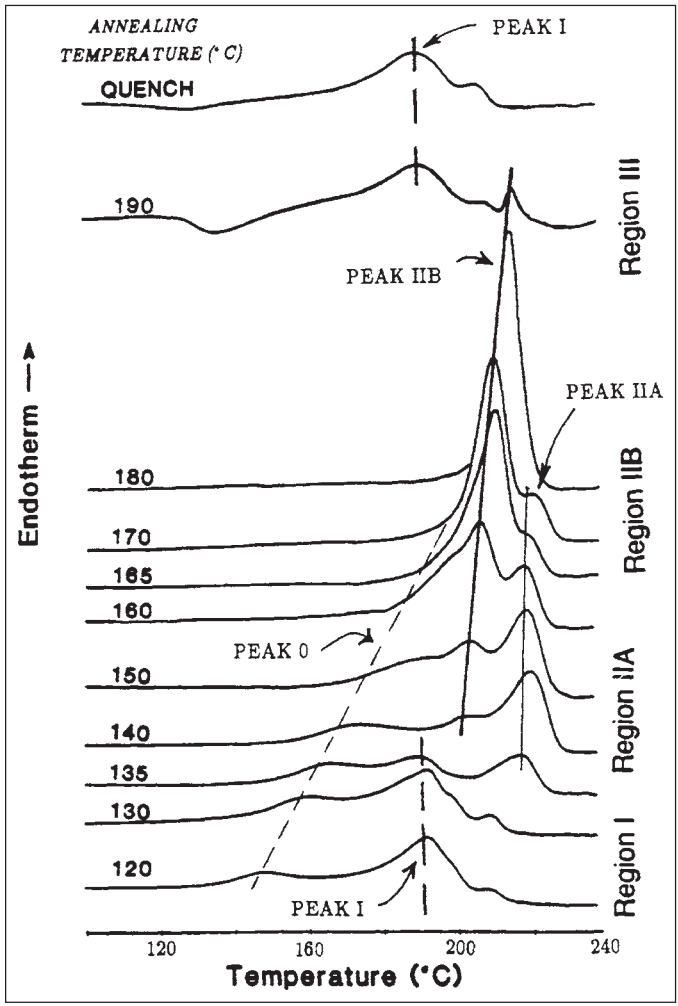


Fig. 1.8. DSC thermograms (40°C/min) of MDI/BD/PPG polyurethane after melt crystallization at the indicated temperature. The specimen contains 60% by weight of the hard segment (reprinted with permission from Koberstein J and Galambos A, Macromolecules, 1992; 25:5618-5624). Copyright (1992) American Chemical Society.

Unfortunately, this appears not to be current practice. For example, arterial prostheses are made from a variety of materials without careful consideration of the need for appropriate mechanical characteristics. Indeed, arterial prostheses manufacturers present tensile strength and elongation at break data for their raw materials even though the most important mechanical property for this application should be the compliance (which is a measure of the radius deformation of a tube submitted to an internal pressure (dr/dP) of the material under a tubular form). Current materials are chosen primarily on the basis of their biostability and biological response (purely based on «surface» characteristics) without paying much attention to the match/mismatch of their mechanical properties with respect to those of the native arteries. This results in part because a compromise between the intrinsic limitations of materials from a mechanical

Table 1.5. Mechanical properties of some biomedical-grade polymers

Polymer	Tensile modulus (MPa)	Elongation at break (%)
Low density polyethylene	140-300	200-900
High density polyethylene (HDPE)	700-1400	100-1000
Ultra high molecular weight polyethylene	100-700	200-500
Polypropylene	1100-200	100-600
Polyethyleneterephtalate (PET)	3000	50-300
Polytetrafluoroethylene (PTFE)	410	200-400
Polyurethanes*	25-62	355-800

* Refers to polyurethanes presented in Tables 1.1 to 1.3.

point of view, the difficulty to balance the body/material physiological parameters (host response) and the clinical demands is very hard to attain. Consequently, materials as different as PET, PTFE and polyurethanes have all been considered in the fabrication of arterial prostheses.

1.6 Surface Characteristics of Polyurethanes

In the previous pages of this Chapter, it was shown that polyurethanes are not homogeneous materials at the nanometer scale. A microphase segregation process leads to the formation of a two-microphase structure with regions enriched in either hard or soft segments. This segregation is thermodynamically driven by unfavorable interactions between polar urethane and relatively nonpolar macroglycol segments. The heterogeneous morphology of polyurethanes is perturbed at an interphase where the chemical composition and morphology ultimately attained is a balance between bulk and interfacial interactions. When the environment surrounding the polymer surface is hydrophobic such as polyurethane-air, the nonpolar components of the polyurethane segregate preferentially to the interphase. If the interphase is with a biological fluid such as blood, the polyurethanes polar components adsorb preferentially in the interphase. This section will discuss how the surface composition is influenced by the composition of the polymer and the environment to which the polymer is exposed. A short discussion will also be given on the time-scale of the segregation process.

1.6.1 Causes of the Surface Segregation Phenomenon

The surface segregation phenomenon is caused by the difference in surface energy between components in a multiconstituent polymer system.

At equilibrium, the total energy of a system, that is the bulk chemical potential times the total volume plus the surface energy times the surface area, must be at a minimum. Surface segregation occurs for multiconstituent system because preferential adsorption of the lowest surface energy component can decrease the surface energy. The segregation of this component comes at an energy cost required to remove it from the bulk phase. The balance of this latter exchange of chemical potential and the surface tension reduction associated with surface segregation dictates the final surface composition attained by the system. Thermodynamics of surface segregation has been treated by several authors.[17]

The same type of interactions are at play at the polyurethane interface. Because the host response is largely, if not completely in some cases whereas mechanical requirements are not an important feature, determined by the surface composition of the material to which blood (or any other biological fluid) is exposed, it is clear that the actual surface composition is a parameter of paramount importance. The word "surface" is defined here as the first few atomic layers at the surface of the material. The composition of these top atomic layers is not the same as that in the bulk of the polymer, and it cannot be accurately predicted from it because of surface segregation phenomena and impurities.[18] The dual character of polyurethane (polar hard segment and nonpolar soft segment) and the fact that nonpolar soft segments have some mobility at body temperature because their glass transition temperature is below 0ºC have profound effects on the surface composition of polyurethanes. Because of this mobility of the soft segments, the surface composition of segmented polyurethanes can change in order to find the composition (or the hard/soft segments ratio) that will minimize the interfacial free energy. This unique phenomenon will depend on the environment to which polyurethane is exposed. In brief, polyurethanes will have a higher proportion of polar hard segments at the interface when the environment is polar (e.g., water or blood) and more nonpolar soft segment at the surface when the environment is nonpolar (e.g., air or vacuum). Conversely, and more importantly for the understanding and control over the surface composition of segmented polyurethanes, the extent of surface rearrangement upon contact with a given environment, like blood, will depend on the composition and molecular architecture of the polyurethane. The degree of crosslinking, as well as compositional parameters such as soft segment average molecular weight along with hard and soft segment composition and ratio will affect the polyurethane surface composition as discussed in the following paragraphs.

1.6.2 Effects of Number Average Molecular Weight of Soft Segments

In order to separate the effects of the number average molecular weight from the effect of the hard segment/soft segment ratio, it is important when varying the number average molecular weight to keep the hard segment weight percentage as constant as possible by adjusting the molar ratios of the hard segment/extender/soft segment. Ex vivo AV and AA shunt tests performed with polyether-urethanes composed of a MDI hard segment, a PTMO soft segment (Mw=1000 or 2000) and a 1,4-butanediol chain extender showed that for comparable hard segment weight percentage the platelet adhesion density on the PTMO-1000 polyether-urethane was clearly lower than that observed on the PU with a soft segment composed of PTMO 2000.[19]

1.6.3 Effects of Chemical Composition of Soft Segments

Some studies have shown that the chemical nature of the soft segment has an effect on the surface composition of polyurethanes: for polypropylene glycol and polytetramethylene oxide the surface is enriched in the soft segment with respect to the bulk composition whereas in the case of polyethylene glycol (PEG, also known as polyethylene oxide, PEO) the opposite is observed, that is, there is a lower concentration of the soft segment at the surface. Polyethylene glycol is known to be a more polar polymer and therefore it shows a smaller tendency for surface segregation when exposed to air or vacuum[20-22] but will segregate to the surface in hydrophilic (polar) environments. In fact, contact angle measurements show that the surface free energy at the polymer-air interphase increases in the order of PDMS, PTMO, hard segment (when MDI-BD) and PEO.[22] In the same study, the phenomenon of surface segregation of PEO under hydrated states was observed by ESCA, where it leads to a decreased N/C ratio for the water-equilibrated polyurethane when compared to the same PU equilibrated in air.

However, PUs with less hydrophilic soft segments, such as PTMO and PDMS, had a surface enrichment in their hard segments after equilibration in water. All these results are in agreement with the aforementioned increase in surface free energy: PDMS<PTMO<MDI-BD hard segment<PEO. Finally, the study showed that phospholipid sorption is enhanced on the more hydrophilic water-equilibrated PEO-rich surfaces than on hydrophobic surfaces such as those of PUs containing PTMO or PDMS as the soft segment.[22] In summary, the component (soft or hard segment) with the lower surface energy is enriched at the polymer interphase[23] when the environment is air or vacuum and the component of a higher surface energy segregates to the surface when the environment is more polar, like water or blood. However, the segregation of one segment or another is not necessarily complete, and some fraction of the other segment may still be present on the surface. For example, a polyurethane with a PTMO soft segment was analyzed by secondary ion mass spectrometry and there was evidence of the presence of hard block at the outermost surface, even if soft segment segregation to the surface had occurred.[21]

1.6.4 Effects of Hard Segment/Soft Segment Ratio

The fact that polyurethane surface composition depends upon the nature of the environment with which it is in contact must not overshadow the fact that the surface composition is also influenced by the bulk composition of the PU itself. The influence of the hard/soft segment ratio has been thoroughly studied. The surface of a polymer blend composed of BioSpan-S® (BS, a polyurethane capped with PDMS) and a phenoxy base polymer (BP) is almost completely covered by the BS component at bulk concentrations as low as 1.7 wt% when the blend polymer is exposed to air. This occurs because BioSpan-S® has the most hydrophobic character of the two-component blend.[24] However, when the bulk concentration of BS drops below 0.17 wt%, BS becomes undetectable on the surface. This shows that there is a lower bulk concentration limit (0.17 wt% here) below which the concentration of the lower interfacial energy component becomes too small for that component to be able to cover the surface. Conversely, there is a high bulk concentration limit (1.7 wt% here) above which the surface is completely covered with the component of lower interfacial free energy. The surface composition does not change at composition above this limit.

The hard/soft segment ratio of the PU surface obviously has important effects on the biological response of PUs. For example, in polyether-urethanes (PEU) made from polytetramethylene oxide (PTMO, number average molecular weight 1000 or 2000) and various hard segments, it was found that the higher hard content PEU had a more hydrophilic surface. This indicates higher hard segment enrichment at the air-polymer interphase, while ex vivo canine shunting tests showed that the extent of platelet adhesion is less when the PEU contains a lower fraction of hard segment.[19] The ex vivo environment however is not a polymer-air interphase, and interfacial reorganization may have occured in these tests.

1.6.5 Influence of the Fabrication Process on Surface Composition

In the case where the film is produced by evaporation of a solvent (solution casting), the film interacts with a substrate on one side (glass for example) and usually air on the other side. This leads to different interfaces and therefore different polyurethane surface compositions on the two sides of the film. For example, polyurethane with a PPG soft segment has more PPG on the air-facing side of the film than on the glass-facing side of it.[23]

1.6.6 Surface Composition Changes Induced by the Measurement Technique

The various results presented above have demonstrated that PU surfaces reorganize when exposed to different environments. Vacuum in an ESCA (XPS) spectrometer is the most non-polar medium that can exist and the PU surface will rearrange to expose the segment with the lowest interfacial energy. However, these conditions are very different from those of the polymer-blood interphase found in most of the biomedical applications. A technique called freeze-dried ESCA analysis was developed to provide a better way of measuring the surface composition under conditions that are closer to the conditions experienced by polyurethanes in the human body, i.e., at a PU-blood interface where the PU is interacting with a polar liquid. The technique can be briefly described as follows: the PU sample is hydrated, frozen at -160°C and then the ice layer is removed by sublimation at -60°C and $1x10^{-6}$ Torr. With this procedure, the PU surface rearranges to its equilibrium composition for a PU water interface and when water sublimates at -60°C to expose the PU surface for ESCA analysis it is assumed that surface rearrangement (in reaction to the high vacuum conditions for ESCA analysis) does not occur because the sample is below the glass transition temperature of soft segments. This technique has shown that at the PU-water interface there is migration of the hard segment to the surface upon hydration. Angle-dependent ESCA studies can probe different depths in the sample and the results have shown that the rearrangement is occurring only near the surface (< 2 nm).[25]

1.6.7 Polyurethane Surface Composition as a Function of Time after an Environmental Change

The time scale required for surface reorganization upon changing the environment to which PUs are exposed has been measured by infrared and visible sum-frequency spectroscopy.[26] The polyurethane studied had PDMS grafted on as end groups and the hydrophobic PDMS groups were shown to be enriched or depleted from the surface depending on whether the PU was exposed to water or air, respectively. The time needed for the surface to reequilibrate with its environment was faster when a hydrated PU was dried (3 hours) rather then when a dry polyurethane was hydrated (25 hours). The sum-frequency generation technique has the advantage of being able to analyze the PUs while they are under hydrated conditions. The results of this study offer a reasonable explanation for the observed discrepancy between results from classical ESCA studies (not hydrated state) and those from contact angle measurements (hydrated state). The time scale of the surface restructuring going from air to water environment (25 hours) must also be considered.

1.7 Conclusion

This Chapter puts in evidence all the complexity that surrounds polyurethanes regarding their synthesis and the attainment of appropriate physicochemical properties and surface characteristics. First, it is obvious that a judicious choice of diisocyanate, macroglycol, and chain extender must be made in order to get a polyurethane with the desired properties. In addition, once the polymer constituents have been chosen, the molecular weight of the macroglycol moieties still has to be determined. Finally, the thermal history of a polyurethane sample has also to be considered as being a driving force when dealing with its intrinsic characteristics. Taking into account all these degrees of freedom, it is now easier to understand how difficult it

can be to attain polyurethane formulations with reproducible properties. Even easier to understand are the discrepancies between results coming from laboratory to laboratory while dealing with polyurethane materials that are poorly characterized in one or another of these degrees of freedom. This phenomenon is probably at the origin of the difficulties encountered by scientists faced with the problem of developing polyurethanes for biomedical applications.

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CHAPTER 2

Commercial Production of Polyurethanes

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2.1 Introduction

As discussed in the preceding Chapter, polyurethanes (PUs) involve relatively complex chemistry and synthesis procedures compared to other conventional polymers used in biomedical applications. To meet the task of engineering PU-based devices and implants that fulfil the requirements of a particular application, understanding how devices and implants are commercially produced is imperative. What process equipment companies need to manufacture PUs products? How materials can be shaped in their end-used configuration? What sterilization process could be applied to PU-based products? Although a general overview of the physicochemical properties of model PUs (laboratory-scale) was highly important for the scope of this book (Chapter 1), the answer to these questions is also mandatory. To begin with, this Chapter provides a review of the commercial polyurethanes that have been used in biomedical applications. A detailed history of PU materials, including both biomedical and industrial chronology, highlights the importance of this family of polymers in medicine. Some key events are retraced but the chronology is necessarily incomplete due to the breadth of the field. We believe that it is very important to summarize how and more importantly why PU technology evolved over time. Special care has been taken to retrace the main events of PU history which originate mainly from the scientific literature and/or patents rather than from personal communication. The present Chapter also provides terminology for some commercial PUs, their chemistry and major companies involved in the field. The main processing methods for converting PU raw materials to configured articles are discussed, together with a general overview of the key parameters that dictate the quality of the final products. We refer the reader to other appropriate polymer literature (such as Szycher's *Handbook of Polyurethanes*, CRC Press, Boca Raton, 1999) for further technical information. In addition, this Chapter covers sterilization processes for PU devices and components. Finally, a list of commercial polyurethanes used in biomedical applications is provided (Table 2.4).

2.2 History

Biomedical grade polyurethanes have an interesting story which is difficult to retrace for a number of reasons, including the use of trade names for similar compositions and the very large

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variety of very different compositions of matter that have been and continue to be referred to generically as polyurethanes. Polymer science and technology have developed in parallel with modern medicine, so it is interesting to see how the PU industry has responded to advances in biomedical science and its changing requirements. Until recently, most PU materials used medically were polymers originally designed for non-medical applications. Device developers adopted them as biomaterials due to the empirical findings of some pioneering researchers and the lack of availability of medical-grade analogues. Recently a few small commercial firms have begun to specialize in designing new families of polyurethanes that have the potential to replace the original commercial formulations. Some of these firms offer new materials which appear to provide relatively improved performance in certain applications. Confusion continues, however, because of the use of trade names to describe nearly identical materials, and claims of novelty that are not based on fact. Table 2.1 summarizes more than 60 years of polyurethane research, development and applications.

2.2.1 General Chronology

In the late 1930s, the textile industry realized that nylon polyamides discovered by Carothers[1] had the potential to become an important fiber-forming material. Because worldwide patents were held by E.I. du Pont de Nemours & Co. (Wilmington, DE, U.S.) (thereafter called DuPont in the text), some German groups began a search for different routes to produce material with similar properties. In 1937, Professor Otto Bayer and his team discovered the reaction between aliphatic diisocyanates and aliphatic diols[2,3] which led to the formation of linear polymers of high molecular weight. These polymers, named thereafter polyurethanes, which had useful properties for the production of plastics and fibers, were commercialized in Germany under the tradenames of Igamid U (plastics) and Perlon U (fibers) in 1942.[1,4] Perlon U, however, never gained acceptance as a competitor to nylon in the American market.

Nevertheless, DuPont became interested in this new family of polymers and began working in 1942 on isocyanates. While an early DuPont patent disclosed the use of diisocyanates,[5] Lieser, from Germany, issued the first American patent concerning diisocyanate reactions in 1941.[6] Within a short time, many patents were approved concerning polyurethane technology.[7-9] The development of other polyurethanes was actively pursued in Germany during World War II. Farbenfabriken Bayer (thereafter called Bayer in the text), a branch of the former I. G. Farbenindustrie (Leverkusen, Germany), expanded their work to include promising variations such as rigid foams, adhesives, and coatings.

2.2.1.1 Polyester-Urethane

In many countries, commercial firms entered into license agreements to make new polyurethane systems. The first British companies to produce polyurethane were Kay Bros., Dunlop Co., Volcrêpe Ltd. and Sorbo Ltd..[10] In the United States, an association of DuPont, Monsanto, Goodyear Aircraft Corp., and Lockheed Aircraft Corp. developed, in the period of 1946-48, techniques for the production of rigid foam similar to the Bayer systems. Interest in isocyanates and polyurethanes grew gradually in the United States with the introduction of PU elastomers (1950) and flexible foams (1952) by Bayer. In their early years, polyurethanes were characterized by their good properties but high prices.

The arrival of flexible polyurethane foams with high strength and low densities insured large-scale production of PU materials and their precursors. Between 1952-1954, Bayer developed a diisocyanate-polyester flexible foam suitable for the continuous commercial production of Moltopren. To introduce this system and other PU technologies to the American market, Bayer and Monsanto joined together in 1954 to form the Mobay Chemical Company.

Table 2.1. History of polyurethanes

Date	Events
1937	Discovery of PU synthesis reaction by Otto Bayer's team.[2,3]
1938	First patent application on diisocyanate reaction by Rinke et al granted in 1950.[9]
1941	First American patent on diisocyanate reactions by Lieser.[6]
1942	German commercialization of Igamid U and Perlon U.[4]
1947	First polyester-urethane rigid foams.[1]
1952	First flexible polyester-urethane.[134]
1954	Lycra® patent by Langerak.[135]
1957	Polyether-urethane foams commercially available.[1]
1958	Polyester-urethane foam used in breast implant by Pangman. First biomedical application.[11,12]
1958	Use of polyester-urethane Ostamer™ for bone fixation by Mandrino and Salvatore.[13,14]
1959	Estane® VC thermoplastic polyester-urethane patented by Schollenberger and commercialized by B.F. Goodrich Co..[46,136]
1960	American patent for Lycra® awarded to Steuber (DuPont).[34]
1961	Thermoplastic Polyurethane Estane® VC (B.F. Goodrich Co.) as a vascular elastomer component.[15-17]
1967	Lycra® introduction in medicine by Boretos and Pierce.[35,36]
1971	Avcothane™ patent awarded to Nyilas (Avco).[137]
1972	Biomer™ (Lycra® T-126) researched by J. W. Boretos.[138]
1977	Extrudable Biomer™ patent awarded to Gilding and Taylor (Ethicon Corp.).[139]
1977	Introduction by Upjohn Chemical of Pellethane™ 2363 family.[45,46]
1978	MDA released from MDI-based polyether-urethane (published by Baxter-Travenol).[49]
1977-78	Second generation of polyurethane. Thermoplastic moldable aliphatic HMDI/PTMO-based polyether-urethane Tecoflex® introduced by Szycher et al.[53,140,141]
1981	Degradation of polyether-urethane reported by Parins et al..[19,47]
1982	Implantation of the first artificial heart using Biomer™ and Avcothane™ as polymer components.[17]
1984	Thermoplastic extrudable polyether-urethane Tecoflex® patented by Szycher.[142]
1991	Commercial withdrawal of Biomer™.[53]
1992	Restricted use of Pellethane™ by Dow Chemical Co..[54,55]
1992/1993	Corethane™ American patent awarded to Pinchuk.[64,65]
1999/2000	Elast-eon™ family developed by Elastomedics Pty Ltd (see Chapter 6).

Developments in coatings, elastomers, and adhesive materials, using polyesters as the principal flexible component or soft segment, were therefore gradually introduced.

2.2.1.2 Polyether-Urethane

Despite their remarkable properties, polyester-based systems remained at that time too expensive for general applications. In order to reach broader markets, the use of cheaper resins was developed by American companies. Polyethers derived from propylene oxide and castor oil were used to partially replace the more expensive polyesters in certain urethane systems. The commercial entry in 1957 of urethane-grade polyether polyols derived from propylene oxide brought a major change in PU technology and market potential. The use of polyether glycols gained importance due to their greater range of properties, their hydrolytic stability and their lower prices. In 1955, DuPont started marketing a flexible foam based upon poly(tetramethylene ether) oxide (PTMO), Teracol 30,[1] which they abandoned due to high production costs. Gradually, companies such as Dow Chemical Co., Union Carbide Ltd., Wyandotte Co., and others began manufacturing polyether-urethanes as foam, adhesives, coatings, and elastomers.

Polyurethane science has continued to advance to include a wide variety of reactants and processing methods, and it is now one of the most diverse fields within polymer science. The commercial potential for biomedical polyurethanes, however, is very small compared to most industrial markets. Although improved technology now exists for tailoring polyurethanes to some specific medical applications, most industrial research is aimed at the large volume non-medical market. In the United States, for example, research and development of novel polyurethanes is performed primarily by small firms with support from the government or those device manufacturers interested in assuring the supply of polymers needed to manufacture their new or existing products.

2.2.2 Commercial Polyurethanes for Biomedical Applications

Polyurethane materials were first introduced in biomedical applications in the late 1950s. Pangman described in 1958 a composite breast prosthesis covered with a polyester-urethane foam.[11,12] This polyester-urethane foam was soon found to be susceptible to hydrolysis and severe in vivo degradation. Mandrino and Salvatore also used, in 1958, a rigid polyester-urethane foam called Ostamer™ for in situ bone fixation.[13,14] Three years later, the application of polyester-urethane Polyurethane Estane® VC (B.F. Goodrich Co. now called BF Goodrich Specialty Chemicals, Cleveland, OH, U.S.) was proposed by Dreyer et al[15-18] to be used as components for heart valves and chambers, and aortic grafts. In the mid-1960s, Cordis Corp. (Miami, FL, U.S.) started to commercialize polyester-urethane diagnostic catheters.[19]

Scientists, in their quest for the ideal biomaterial, were attracted by these early materials.[14,20-30] Unfortunately, the first cardiovascular applications of these ester-based materials gave poor results.[16,18,31,32] When investigations revealed that polyester-urethanes were hydrolytically unstable,[18,33] polyurethanes, in general, were thought to be unsuitable as implantable biomaterials. That is, the huge family of polymers referred to generically as polyurethanes was indicted because of the poor performance of a single, albeit industrially important, subclass. This could be explained by the poor level of understanding at the time, which lumped all polyurethanes together as a single class of materials. This is now known to be a very inaccurate generalization, based in part on the success of the more hydrolytically stable polyether-urethanes. These more stable polymers restimulated interest in polyurethanes as biomaterials. As the potential hydrolysis of ester moieties was a well-established concept at that time, why was the hydrolysis of polyester-urethanes has not been anticipated by manufacturers?

In 1954, textile chemists at DuPont developed Lycra® spandex as a high-performance alternative to natural rubber in elastic thread. The patent was awarded to Steuber in 1960.[34] With its outstanding properties, including its degradation resistance (e.g., during laundering) Lycra® was quickly adopted by the textile industry. Lycra® is a so-called segmented polyether-urethane-urea. It was first introduced as a biomaterial in 1967 by Boretos and Pierce[35,36] who first obtained "buckets" of the polymer in solution directly from the DuPont spinning line that produced Lycra® spandex yarn. This material was first used as the elastomeric components of a cardiac assist pump and its arterial cannulae.[37,38]

The year 1971 marked the arrival of the earliest polyurethane specifically designed for medical uses; Avcothane-51™ (AVCO-Everett Research Laboratory, Everett, MA, U.S.), which was a polyurethane/silicone hybrid. In 1972, Biomer™, a version of Lycra® T-126 produced by Ethicon Corp. (Somerville, NJ, U.S.) under a license from DuPont was made available. Both Avcothane™ and Biomer™ are synthesized in and fabricated from solution, e.g., by dipping, spraying or casting, and are not extrudable or moldable. Nevertheless, as the first "real" biomedical polyurethanes, these two polymers were studied intensively.[28,39-45] Avcothane™ was used clinically in the first intra-aortic balloon pump (IAB) starting in about 1971. It is still in clinical use today in IABs, but it is now called Cardiothane-51® by its current owner, Arrow International (Reading, PA, U.S.). Biomer™ components were used in the "Jarvik Heart", the first artificial heart implanted in 1982.[17] Avcothane™ and Biomer™ appeared at that time to possess a combination of thromboresistance, biostability and flex life that was sorely needed to make cardiac assist devices safe and efficacious. Prior to their introduction virtually no other polymers had the required property profile, a factor which impeded progress in the development of IABs, ventricular assist devices and the artificial heart during the 1960s. In 1977, Upjohn Chemical (North Haven, CT, U.S.) commercialized the first medical grade thermoplastic polyether-urethane: the Pellethane™ 2363 series.[45,46] It was first used in an implantable device as the catheter for the Avco™ IAB, the development of which began while it was still an experimental material.

While the device industry was using polyurethanes as a critical device-component, ongoing studies were done on the toxicity and in vivo stability. In vivo hydrolysis was already known to take place with polyester-urethane. Parins et al[19,47] were the first (1981) to publish on the degradation of Pellethane™ 2363-80A. Thereafter, Lemm[48] reported on the relative stability of various polyurethanes. Polyether-urethanes were recognized later to be susceptible to oxidation.

Another major focus of attention has been the potential carcinogenicity of PU materials. In 1978, a publication by Baxter-Travenol reported that methylene dianiline (MDA) was released in some steam autoclaved Texin® blood bags.[49] In the 1980s, a debate took place in the medical community which got hotter in 1988 when Blais,[50] from the Canadian Ministry of Health (Ottawa, ON, Canada), focused attention on a silicone gel-filled breast prosthesis covered with polyester-urethane foam (namely Même prosthesis). His concern was confirmed by Batich and Williams[51] and Guidoin et al.[52] Researchers have therefore turned their efforts onto stability and toxicity issues. The concern of carcinogenicity is still under debate, although no human cases of polyurethane-induced cancer have ever been reported.

In the early 1990s, some suppliers modified their policy regarding the manufacture and sale of medical-grade polyurethanes. This was a direct result of the product liability problems encountered by producers of Teflon®, polyurethane, and particularly silicone raw materials (used in breast implants). In 1991, DuPont and Ethicon Corp. decided to end Ethicon's manufacture and sale of Biomer™.[53] Pellethane™, now owned by Dow Chemical Co. (Midland, MI, U.S.), was restricted to implantation periods that do not exceed 29 days in 1992.[54,55] During 1979 Thoratec Laboratories Corp. (Pleasanton, CA, U.S.) anticipated these events and began developing a segmented polyurethane known as BPS-215, as a replacement for Biomer™ in the Pierce-Donachy ventricular assist device (VAD) (a descendant of the first VAD to use

polyether-urethanes). BPS-215 is a functional equivalent for Biomer™, but not an identical chemical match. In 1991, The Polymer Technology Group (Berkeley, CA, U.S.) developed so-called clone polymers, identical in composition to the original materials. One example is BioSpan® segmented polyurethane which is substantially equivalent to Biomer™ in polymer composition, stabilizer content, and physico-chemical properties. This approach is attractive to existing device manufacturers because it constitutes a change in vendor, rather than a change in material. This facilitates approval of the change by regulators like U.S. Food and Drug Administration (FDA) (Rockville, MD, U.S.), who would require much more extensive testing to support a material change in a clinical device. Ironically, the development of BPS-215 and BioSpan® occurred early in the clinical application of VADs and artificial hearts. As a result many more clinical implants of these devices have used the substitute polymers rather than the "original" polymers they replaced.

Segmented polyether-urethanes based on PTMO soft segments remained the materials of choice for chronically-implanted blood pumps due to their excellent flex life in flowing blood. However, other chronically-implanted devices and prostheses have specific requirements which have stimulated the development of new compositions of matter. Pacemaker leads, in particular, have caused the softer grades of certain polyether-urethane insulation materials to degrade via the soft segment. This has been shown to occur by metal ion oxidation (MIO) or environmental stress cracking (ESC) (see Chapter 5). Experienced manufacturers like Medtronic (Minneapolis, MN, U.S.) have tried to prevent this problem by using harder grades and/or by carefully controlling processing conditions, e.g., to reduce residual stresses in fabricated parts. Several investigators have proposed the use of alternative soft segments to overcome these problems. One approach is based on removing or minimizing ether or ester bonds. Another technique combines stable, hydrophobic polydimethylsiloxane (PDMS) with polyether or polycarbonate soft segments in the PU backbone and/or as end groups. The use of PDMS covalently attached to PU backbone has been published by Pinchuk et al in 1988.[56] Ward proposed the end-group approach, based on his experience with Avcothane-51™. Recently, Gunatillake and Meijs, focusing on the first approach, reported on the development of a series of polyurethanes with improved biostability incorporating a high level of siloxane segments into both hard and the soft segments.[57-62]

One soft segment offered as an alternative to PTMO has been successfully commercialized. It is based on aliphatic polycarbonate from hexamethylene and ethyl carbonate monomers. In fact, aliphatic polycarbonate-urethanes offered by Szycher as Chronoflex® "biodurable polyurethanes", proved to be inferior in biostability to the aromatic analogues originally introduced by Pinchuk. Pinchuk's Corethane™ PUs from Corvita Corp. (Miami, FL, U.S.) (now Bionate® polycarbonate-urethanes) was patented for biomedical use in 1992.[63-66] However, prior to their proposed use as biomaterials, polycarbonate-urethanes were in commercial use as oxidatively stable elastomers and coatings. They represent an alternative to polyether-based PU biomaterials when oxidation is the primary mode of degradation. When copolymerized with silicone polyols, polycarbonate-urethanes appear to combine the hydrolytic stability of PTMO-based polyurethanes with the oxidative stability of the polycarbonate soft segment. These polyurethanes have recently been patented by The Polymer Technology Group (Ward RS, The Polymer Technology Group, personnal communication). Meijs and Gunatillake developed a series of macrodiols with fewer ether linkages than PTMO. Polyurethanes based on these macrodiols, poly(hexamethylene oxide) (PHMO), poly(octamethylene oxide) (POMO) and poly-(decamethylene oxide) (PDMO), offered significantly improved stability over their PTMO counterparts.[67-71] Coury et al[72,73] from Medtronic introduced biostable polyurethanes based on dimer acid soft segments, which to date have not been commercialized. Currently,

improved in vivo biostability via various surface (see Chapter 7) and bulk modifications is being actively investigated by a number of groups. The main classes of polyurethanes for chronic implantation, however, continue to be the thermoplastic polyurethanes based on PTMO or polycarbonate soft segments. They currently have the most history and the most extensive documentation on file with the FDA.

2.3 Manufacture of Polyurethane

Polymers can be categorized into two broad groups: thermoplastics and thermosets. Thermoplastics are defined as materials capable of being repeatedly softened by heat and hardened by cooling. Thermosets, on the contrary are set into permanent shape by chemical crosslinking which occurs during or after forming. Once a thermoset has been hardened into the desired shape, the process is generally irreversible. In the case of polyurethanes, the distinction is not always clear and depends on the type of crosslinking between the molecules. The segmented polyurethanes are technically thermoplastics, but some hard segments (generally polyureas) can have a cohesive energy density that is too high for traditional thermoplastic processing. They are generally processed by solution-based method to avoid degradation that could occur during extrusion or injection molding, for example.

Usually we refer to polyurethanes as elastomers. One way to distinguish between these is with the average molecular weight between crosslinks. In the case of polyurethane this parameter is approximately 1000 g/mol for a thermoset, 5000 for an elastomer, or 25000 g/mol for a thermoplastic, respectively (Table 2.2).[1] This molecular weight is usually controlled by using different chain extenders, which are made of urea or urethane linkages, depending on the specific chain extender used. In general, chain extenders are active hydrogen containing compounds, mostly difunctional. Typical examples are water, glycols, diamines, and amino-alcohols. Diamine chain extenders give high bond attraction between substituted urea linkages and usually lead to thermoset materials. On the other hand, thermoplastic polyurethanes are mainly produced by using linear diols as chain extenders. For biomedical applications, 1,4 butanediol, 1,6 hexanediol, and ethylene glycol are mostly used.[74]

2.3.1 Classification of Polyurethane Materials

It can be useful to classify PU materials by their rigidity, density or porosity. A classification based on rigidity distinguishes polyurethanes by their crosslinking characteristics whereas the density/porosity classification differentiates polyurethanes using the final density of the end-use product.

2.3.1.1 Rigidity

We can classify PU as flexible, semi-rigid or rigid.[75] The type and degree of crosslinking will determine this aspect: flexible polymers are much less crosslinked than rigid ones. Crosslinking is controlled by the amount and the functionalities of the polyols used (diols vs triols, etc). The important parameter is the average molecular weight per branch point.[1] Average values are 400-700, 700-2500 and 2500-20000 g/mol for rigid, semi-rigid, and flexible PU, respectively (Table 2.2). Flexible PUs are made generally from adipic acid polyesters, dimer acid polyesters, or polyethers. More rigid ones are composed from castor oil and derivatives, polyesters of high hydroxyl content, polyethers or dimer acid polyesters.[75,76]

Table 2.2. General characterization of polyurethane materials

Polymer characteristics		
Class		
(average Mw between crosslinks)	Thermoset	1000 g/mol
	Elastomer	5000 g/mol
	Thermoplastic	25000 g/mol
Rigidity		
(average Mw per branch points)	Rigid	400-700 g/mol
	Semi-rigid	700-2500 g/mol
	Flexible	2500-20000 gmol
Density	Very light	50 kg/m^3
	Light	50-200 kg/m^3
	Medium	200-500 kg/m^3
	Heavy	500-700 kg/m^3
	Superheavy	> 700 kg/m^3
Porosity		
(average diameter of cells)	Solid	< 0,01 μm
	Microporous	0,01-1 μm
	Macroporous	1-100 μm

2.3.1.2 Density and Porosity

Another possible classification of PU materials is via the final density of the piece.[77] Generally, polymers can be classified into five categories (Table 2.2): very light ($\rho < 50$ kg/m^3), light ($50 < \rho < 200$ kg/m^3), medium ($200 < \rho < 500$ kg/m^3), heavy ($500 < \rho < 700$ kg/m^3), and superheavy ($\rho > 700$ kg/m^3). On the other hand PU products can be characterized by the porosity. The denomination depends on average diameters of the pore size (Table 2.2):[77] 1-100 μm (usually ellipsoidal), the material is called macroporous; 0.01-1 μm (usually spherical), the material is called microporous and below 0.01 μm, it is referred to as a solid. It is important to note that the morphology of the final product can vary from the center (core) to the edge (skin).[78] This can be controlled by heat and mass transfer at the surface of the free product or at the wall of the mold depending on the processing tools.[76,78] This may introduce variable properties like density and permeability across the section of the final product.

2.3.2 Methods of Preparation

There are three methods for the preparation of PUs:[75,76,79,80] one-shot method,[81] prepolymer method, and quasi-prepolymer method. In general, the prepolymer method and the quasi-prepolymer method are regrouped under the names "two-step methods" or "two-step polymerization". In the one-shot method, all the ingredients (polyol, poly-isocyanate, catalyst and chain extenders, etc) are mixed simultaneously and the resulting mixture is directly allowed to polymerize. In the prepolymer method, the polyol is prereacted with an excess of

poly-isocyanate. This prepolymer is then mixed with the rest of the ingredients during processing. In the quasi-prepolymer (partial prepolymer) method, a part of the polyol is mixed with the poly-isocyanate and the rest of the polymer and other constituents are mixed as a second phase. The streams thus obtained are finally mixed together at the end.

In general, the one-shot method is used for the preparation of flexible PU, while the prepolymer and the quasi-prepolymer are used for more rigid PU. The choice of the method depends on different factors such as the viscosity of the mixture during processing, the time of reaction and heat transfer limitations.[80] PU formation is a highly exothermic process. The one-shot method is mainly used with highly viscous component since viscosity will decrease as the amount of heat increased. For a better control of the temperature, the prepolymer method is more suitable since the total amount of heat will be distributed in two successive steps. For the quasi-prepolymer method, the mixing of the components is a little different and usually leads to a lower viscosity mixture. This is particularly suitable for molding or casting operations involving complex geometries.

2.3.3 Processes

Since PUs are generally elastomers, they can be supplied in various forms: castable liquids or thermoplastic pellets (millable gums).[82] This is a great advantage over several polymeric systems since they can be processed by thermoplastic and/or thermoset (or rubber) equipment. It is not our intention to give a detailed description of all PU processes described below. Therefore, only general guidelines for biomedical PU production are given in order to differentiate the processes. For a more exhaustive description, the reader is referred to a more general polymer processing literature[83-85] or special technical dictionaries.[79,86]

The choice of the process can have a dramatic influence on the final properties of the PU materials. An example is surface properties. As discussed in Chapter 1, PU are formed of hard and soft segments (crystalline and amorphous-enriched phase, respectively). Segment mobility and polarity will affect how the material interacts with its surroundings. It has also been shown that the method of fabrication influences mechanical and chemical properties as well as the biological response due to surface concentration of the soft segments. Lelah et al[40] found that the surface concentration of the soft segment increases in the following order: extruded, cast and solvent evaporation, for example.

In addition, manufacturing of polymer products inevitably leads to the emergence of residual stresses. Residual stresses are stresses remaining in a part that has been chilled quickly during or after molding, extrusion or forming. They are created because there was not enough time, for the stresses created during processing, to relax while the material was still soft. Over time, high residual stresses can be responsible for structural problems like warping, shrinking, and fissuring. This is especially true near defects in a piece or in the vicinity of stress concentrators like holes, cuts or sharp angles. Residual stresses can be relieved to some extent by a suitable curing regime or by annealing.[87] Annealing relieves the residual stresses in a polymer by heating it to predetermined temperature, keeping it at this temperature for a preset period of time, and slowly cooling it down as a suitable rate. In the case of PU, a temperature between 100-150°C should be applied for a period of 1-3 hours, preferably under a nitrogen atmosphere to prevent exposure to moisture and oxidation.[88] Moreover, it is important to note that PUs absorb water. Moisture content must be kept as low as possible, particularly in melt processes. High moisture levels are known to give poor surface characteristics.[89] In general, soft materials are processed at lower temperature than hard materials. In the following section, we will present a list of the most likely used PU processing techniques. They are listed in three categories: machine molding, liquid molding and other processes.

2.3.3.1 Machine Molding

Machine molding methods have been widely used to produce biomedical PU devices and implants. In machine molding methods, a piece is made by filling a mold using a machine under pressure. Machine molding includes mainly injection molding, blow molding, and compression molding. Injection molding is a procedure where a heated material is forced by pressure to fill a mold in a single shot action. Clamping pressure should be more than 3.2 MPa in order to avoid flashing. Each resin has a preferred temperature profile for processing. Keeping in mind that PU degradation is initiated at as low as 150ºC, Walder[89] reported that aliphatic PUs injected around 170ºC may remain in the barrel for 30 minutes without any physical degradations. However, aromatic PUs injected at 220°C, started to yellow within 5 minutes. At these temperatures, dwell time should not exceed 5 cycles to avoid thermal degradation. Nevertheless, cycle times are mainly dependent on the design, thickness, and size of the part, and also on the type of resin used. Typical conditions are also given elsewhere.[74] Moreover, manufacturers recommend the use of surface impregnated mold release agents for long production runs with PU systems.

Reaction injection molding (RIM) is a process involving the mixing of two reacting streams by high-pressure impingement followed by an injection into a closed mold at low pressure.[90,91] The main advantages of RIM over coventional injection methods are large scale production, low energy use, and low equipment cost. Derivatives of this technique are: Reinforced Reaction Injection Molding (RRIM) and Structural Reaction Injection Molding (SRIM). In RRIM, the reinforcement is injected along with the reactants, while for the SRIM, the reinforcement is already placed into the mold before injecting the reaction mixture. Due to the charge in the reacting polymer streams, the major difference between RRIM and SRIM is the injection pressure. RRIM generally operates between 7-20 MPa while SRIM operates at a 20-30 MPa level.[91] The reactants are dispensed at low temperature (15-40°C), while the mold walls are set initially around 65°C.[92] The total cycle time is at least between 1-4 minutes for foams and 20-60 seconds for elastomers.[79]

Blow molding is a method of fabrication in which a hollow tube of hot polymer (parison) is extruded and placed in a mold where an air pressure is applied inside the tube forcing the plastic against the surface of the mold by compression giving its final shape. The operating conditions are similar to injection molding described above, with an air pressure around 600 kPa. Cycle time is between 10 and 60 seconds. Usually, the injection temperature is just a few degrees over the melt point T_m or over the glass transition temperature T_g of the hard segments. Compression molding is a process where a piece is formed under pressure and heat using a hydraulic press by introducing a predetermined amount of material into an open mold. For PU applications, a minimum of 50 tons of load is recommended and heating capacity of 145°C is also needed for the majority of applications.[93] Typical molding conditions are a temperature of 116ºC and a pressure of 14 MPa (10-20 MPa) for a duration of 30 minutes.[94]

2.3.3.2 Liquid Molding

Liquid molding techniques use liquid reactants or solvents in the processing. A list of solvents specific to PUs are given in Lamba et al.[45] The most common solvents are N,N'-dimethylacetamide (DMAc), tetrahydrofuran (THF), and methylene chloride. THF, which is flammable and a peroxide generator, dissolves most PUs and is easily removed from the material. Methylene chloride, which is a very volatile and inflammable ozone depleting agent, dissolves some PUs and is easy to remove. DMAc, which may be a hard solvent to remove is commonly used for less soluble PUs. Other solvents may be used such as dimethylformamide, N-methylpyrrolidone, cyclopentanone, cyclohexanone, dioxane and

chloroform.[95] A comprehensive review of solvent characteristics was given by Szycher.[88] Liquid molding techniques include casting, embedding and molding (potting) and solvent molding. However, highly crosslinked polymers will not dissolve to form a mobile solution.

Casting involves the formation of a piece by pouring the premixed reacting liquid in a mold where it is converted into a solid. In general, the mold is preheated to a minimum of 50°C and left there for around 30 minutes. After curing (several hours at a temperature around 100°C), the piece is removed from the mold and the process is repeated. A variation of casting is slab forming where the reacting liquid is poured on a conveyor belt for continuous production. The final product must then be cut into the desired shape. Embedding is similar to casting. The technique refers to the enclosure of a foreign object which will be permanently surrounded and protected by the polymer. The final product is then retrieved from its mold after curing. Processing conditions are also similar, but cautions must be given to the characteristics of the embedded piece. Molding (potting) is very similar to embedding and casting. Unlike the casting process, in potting the mold becomes an integral part in the final product for structural purposes.

Solvent molding (dipping) involves the formation of a polymer film on a male mold by dipping it into a solution or a dispersion. The final product is thus obtained by evaporation of the solvent leaving a single polymeric object. The purity of the solution and the cleanness of the surface are major factors in order to obtain good pieces. The viscosity of the solution must also be carefully set. There are three techniques mainly used for PU applications: vertical dipping, rotating mandrel and rotating plate.[93] In the vertical dipping technique, a mandrel is slowly immersed into the solution in order to obtain a film by retrieving it and allowing it to dry. A number of such dips are required until the desired thickness is reached. There can be non-uniformities due to gravity pulling on the solution while retrieving. This can be overcome by inverting the mandrel at each dip. In the rotating mandrel, the process operation is similar to vertical dipping, but the mandrel is placed in a horizontal position and rotates slowly. Usually, the mandrel is removed after two complete rotations and the resulting film is then allowed to dry. While the two precedent techniques are used to make cylindrical parts, the rotating plate method is used for film and sheets. A disc of appropriate shape is simply used instead of a cylindrical mandrel.

2.3.3.3 Other Processes

Other processes that could not be placed in any of the two preceding categories are extrusion, elastomers methods, fiber spinning, and spinning. Extrusion involves the heating and mixing materials by means of helical screws into a barrel and forcing the molten mixture through an orifice into its final shape. This is a continuous process. For PU processes, a minimum ratio of screw length over screw diameter (L/D) of 24 is needed.[74] In general, a value of 30 for the L/D ratio is recommended.[89] Since PUs are highly heat sensitive, the temperature and time of processing must be carefully determined. Aliphatic PUs are extruded at lower temperature compared to aromatic PUs. Typical conditions are given for several biomedical PUs.[88,96] In general, a temperature profile between 150 and 180°C is used for a throughput of 60-70 kg/hr.[94]

Elastomer methods are used for more elastic or rubbery materials and generally used to produce sheet or thin film (Table 2.3). They include banbury, calendering, and roll mill. Fiber spinning is the process of forming fibers from extrusion dies (spinnerets). The process can be made in three different states: melt, dry or wet. The filament obtained is then stretched and wound on a barrel operating at a higher linear velocity than the extruder exit speed giving orientation and strength. A variation of this technique is filament winding where the filament is applied in a predetermined way on a mandrel forming mats or woven pieces. Spraying is a process similar to paint spraying. Liquid streams are pumped either mechanically or

Table 2.3. Processes for the fabrication of polyurethane devices and implants depending on the end-used configuration

	Foam/ 3D piece	Tubing	Coating	Adhesive	Fiber	Sheet	Film
			Machine molding				
Injection molding	X						
Reaction injection molding (RIM)	X						
Blow molding	X						
Compression molding	X						
			Liquid molding				
Casting	X		X	X		X	
Embedding	X						
Molding (potting)	X						
Solvent molding (dipping)		X	X	X			
			Others				
Extrusion	X	X			X	X	X
Banbury						X	
Calendering						X	
Roll mill						X	
Fiber spinning		X			X		
Spraying	X	X	X	X			

pneumatically into mixing heads. The mixing can be mechanical or by impingement. Finally a compressed air stream forces the reactants through the small orifices of a spraying gun at high pressure forming an atomized cloud that can be applied onto the desired surface.

It is clear that some processes mentioned above are not used in processing biomedical polyurethane products. Casting, extrusion, and solvent molding (dipping) are the most popular processes used in the commercial production of biomedical polyurethanes. Writing standard operation protocols that would lead step-by-step to the production of polyurethane-based implants and devices is not an easy task, since most of the processing conditions are based on empirical findings. In fact, each polyurethane system (e.g., difference in composition and/or configuration) possesses its own requirements that dictate the processing conditions. In addition, most of the studies reporting, for example, on stability and biological response of commercial polyurethanes fail to mention the processing history of these materials. This could explain, at least in part, some of the discrepancies found in the literature in terms of the biological response and stability issue of some commercial materials.

2.3.4 Configurations

Polyurethane materials can be found in several day-to-day applications. Here we have selected the more likely configurations to be found in medicine. Each piece must be processed so as to confer its own set of mechanical properties which are dependent on the solicitation

(stress-strain) and the environment (physical and chemical).[95] Table 2.3 lists possible processes that can be used for the following configurations.

2.3.4.1 Tubing

PU tubing in biomedical applications can be formed by three techniques:[45] extrusion, solvent molding, and fiber methods. When using extrusion techniques, care must be given to the temperature since PUs can degrade due to long residence time of the polymer into the extruder. While extrusion is the primary choice for making tubing, solvent methods can also be very suitable in order to produce nonporous tubings. Generally, tubings are produced onto a polymer mandrel (usually polyethylene or polyvinylchloride-based materials) which becomes part of the tubing or onto a metal mandrel which is removed later on. Particular attention must be given in order to completely remove residual solvent, which can directly affect the performance of the end-use products. This can be done by drying the tubing via a gas stream, low heat, or by vacuum. In general, products are finally washed with water in order to ensure the removal of solvent traces. However, special care should be taken when washing the polymer with water, since it can lead to some side reactions. For these reasons, the solvent must be carefully chosen.[97] In order to build up more thick parts, the procedure can be repeated many times until the desired thickness is obtained. Porous tubings, on the other hand, can be produced by fiber methods. Filament obtained by fiber spinning can be woven or knitted into cylindrical parts. Filament winding can also be used directly by adaptation of the rotation pattern of the winding mandrel. Fiber methods have for advantage that the porosity, pore size, and orientation can be controlled by the translation and the rotational speed of the mandrel.[98] Other methods like lamination and spraying can be used and are described elsewhere.[45,95]

2.3.4.2 Coating

Polyurethane coatings can be used to modify interfacial properties of some biomaterials.[99,100] They can have a wide range of application due to their flexibility, toughness, excellent electrical insulating properties, and good adhesion.[80] While solvent methods and classical spraying are usually used, plasma spraying is gaining interest.[101-103] The processing is similar to the methods already described.[45] In the solvent method, the choice of the solvent is again very important. Only a few solvents are suitable for PUs. For practical and economical reasons, the concentration of polymer should be high in order to use the least amount of solvent. It is also a compromise between processing (high viscosity) and final properties (solvent removal). Nevertheless, the most important parameter in coating is the preparation of the surface to be coated. The surface must be cleaned and the wettability can be improved by an etching process (liquid or plasma). Other techniques including hot-melt deposition, fluidized bed and surface modifying additives (SMA) are described elsewhere.[45]

2.3.4.3 Foams

PU foams are mainly produced by the reaction of water with isocyanate which gives carbon dioxide.[82] The preparation of PU foams involves the formation of gas bubbles in a liquid which is polymerizing followed by the growth and stabilization of those bubbles as the polymer solidify.[1,79,80] The formation of foams involves three important steps: the colloidal aspect of bubble nucleation (solubility controlled), the dynamics of bubble growth (diffusion controlled) and solidification plus curing leading to the final product (heat and mass transfer). Beside the poly-isocyanate, polyol, water and catalyst, foam formation possibly requires the presence of additives which include nucleating agents and secondary blowing agents, surfactants, and others

(see Chapter 3). Again the effects of these components on the biological response have not been elucidated yet and should be carefully assessed.

2.3.4.4 Fiber, Sheet and Film

Fibers are produced mainly by extrusion and fiber spinning; the method being dependent of the isocyanate and the chain extender used. In special cases, a solvent reacting technique can be used as described by Lamba et al.[45] This method is known to give fibers of irregular cross section. Once the fiber is produced, different pieces can be woven or knitted using textile machinery. A more complete description of particular applications, formulations, and processes of PU fibers can be found in the literature.[80]

Two important techniques are mainly used to produce PU sheets: extrusion and casting. Both methods are continuous and require final forming equipment for dimensional setting. In the case of casting, this is done on a conveyer covered with Mylar, Teflon® or glass sheets for nonadherence reasons.[101] The pour method is called slabstock forming and can be done using two procedures: the transverse or the through methods.[79] They differ only by the way the reacting mixture is poured. In the transverse method, the mixture is deposited evenly by a transverse mixing onto the moving conveyer. In the through method, the mixture is deposited evenly and directly onto the moving conveyer. After a certain curing distance on the conveyer, the final step involve cutting the material into the desired shape. Laminating techniques can also be used to produce sheet of multilayer having different properties.[45,75,77] Films are simply sheets not exceeding 0.25 mm in thickness. They are made principally of rigid urethane and are used mainly for packaging or as surface modifier for water vapor permeability control. Gas permeability decreases when crosslinking increases and depends on the type of PUs (e.g.,polyether > castor oil > polyester).[80] Films are mainly produced by solution casting. The polymer must be completely dissolved to make a clear solution in order to obtain films that are clear and free of bubbles. When using a dipping process, the key to obtain a consistent thickness is to control the viscosity of the solution and the solids' concentration. While viscosity control the thickness of the wet coating, the solid concentration control the thickness of the dry coating.[89]

2.3.5 Sterilization

The ability of being sterilized while keeping its integrity is an essential requirement for all medical polymers. Sterilization is defined as a process leading to the destruction or the elimination of microbial life. The are three main categories of sterilization processes: heat, gas, and radiation. The parameters and the efficiency of a sterilization process are mostly dependent on the process and not on the material. If a material is not suitable under the parameters of the selected process, another sterilization process has to be chosen. Modifying the parameters would have a direct effect on the sterilization efficiency. There are two ways to determine the efficiency. First, when it is appropriate for the device, it could be immersed in a liquid microbiological culture media. If the device is sterile, no microbial growth would be observed. The second alternative, more efficient and common, is the determination of the sterility assurance level (SAL).[104] The SAL is defined as the probability of no more than one in a million that the implant will remain nonsterile. The technique consists of the bioburden determination,[105] which is the number of viable microorganisms on the implant prior to sterilization, followed by fractional-run sterilization studies to determined graphically the exposure time require to achieve a 10^{-6} SAL.

2.3.5.1 Heat Sterilization

2.3.5.1.1 Dry Heat

Dry heat is a very effective bacteria-killing process, which consists of the oxidization of the organic constituents of the cell. Dry-heat sterilization requires a 2-hour exposure at 160-180°C.[106] Nevertheless, its use is restrictive since it is known to cause distortion in low-softening-point polymers such as for polyurethane materials.

2.3.5.1.2 Steam Heat (Autoclave)

It has been the most widely used method for the sterilization of medical instruments. Steam sterilization is an accurate process for the majority of surgical instruments, surgical dressings, fluids, and other absorbent materials. The sterilization is done in a pressurized chamber with saturated steam at 15 psi (121°C) for 15-30 minutes.[106] The process should be used with caution when it is applied to polyurethanes. Residual stress in the devices and aggressive chemicals onto polymer surfaces can modify, in combination with the heat and moisture, materials properties. They can even enhance polymer hydrolysis.

2.3.5.2 Gas Sterilization

2.3.5.2.1 Ethylene Oxide

Ethylene oxide (EO), an effective bactericide and a gas harmless to most plastics, is an alternative for heat and moisture sensitive materials. Active at low temperature, it can diffuse easily into materials needed to be sterilized, even through sealed plastic wrapping. When using EO sterilization technique, five important parameters must be controlled including gas concentration, moisture, time, temperature and aeration time. Due to its high toxicity and explosive tendency, pure EO is normally mixed with CO_2, O_2, N_2 or a nonozone-depleting chlorofluorocarbon-like compound, before being injected in the partially-vacuumed chamber to a final EO concentration ranging between 600-1200 mg/l. Moisture, helping the gas permeation through the material, is maintained between 40-90%. The required sterilization time, which depends upon the size, density and composition of the product, can range from 2-48 hours for a typical temperature range of 30-50°C.[104] Higher temperature allows better gas diffusion but combined with EO may alter materials' properties. Aeration time is a crucial factor in EO sterilization. Insufficient aeration may allow the presence of residual EO and its by-products within the material matrix.[107] The residual chemical products may irritate skin and mucous membranes and even cause chemical burns as EO reacts with human proteins. It has been reported that blood hemolysis[108] or adverse hemolytic reactions[109] have been caused by residual EO. The sterilization process manufacturers recommend at least three, but preferably five days of aeration for sterilized polymer tubing. Depending on the implantation site and the implant size, the FDA has recommended a permissible residual EO level of 5-250 ppm.[104]

2.3.5.3 Radiation Sterilization

Radiation sterilization is an interesting alternative for polymers which are sensitive to heat, moisture, or ethylene oxide. The advantages of radiation sterilization are: fewer process variables (dose rate, exposition time), needlessness of aeration and the possibility to sterilize different materials hermetically sealed at the same time. Radioactive emissions bombard the cells causing ionization of the molecules. However, during the sterilization of polymers, radiation causes an excited state releasing free radicals, which may cause crosslinking or chain

scission. Discoloring, yellowing and loss of clarity are phenomena that could occur during polyurethane sterilization. Additives like "antirads" may absorb energy or accept free radicals, which can minimize the radiation effects before damage occurs.[110] Again the use of additives should be carefully justified.

2.3.5.3.1 Gamma Radiation

The process is commonly done at temperatures under 38ºC with a 2.5 million-rad dose (2.5 Mrads). Usually, 1.5 Mrads is sufficient to kill most microbes. Lower doses will have fewer negative effects like discoloration and embrittlement. The emission of gamma rays is usually obtained from cobalt 60 but cesium 137 may also be used. Materials exposed to cobalt 60 or cesium 137 will not be radioactive after the sterilization because gamma rays have no mass. The accuracy of gamma-ray sterilization is independent of the thickness or the density of the materials. Polymers can support multiple sterilization cycles. Because the effect of radiation is cumulative, polyurethane can withstand radiation up to 1000 Mrads.[110]

2.3.5.3.2 Electron-Beam Sterilization

The Gamma-ray sterilization consists of raising the energy level of the electrons to an excited state.[110, 111] Electron-beam (E-beam) sterilization is based on the addition of external high-energy electrons. In this process, electrons are provided by a cathode tube. The electrons are accelerated in vacuum by electrostatic forces or microwaves, increasing the energy and the penetration ability. Unlike the gamma-ray process where rays travel through the material in all directions, the E-beam electrons are accelerated in a single direction. The doses used in this process are 100 times stronger than gamma sterilization.[110] This implies a shorter exposition time in the range of minutes compared to several hours with the gamma treatment. Another advantage of the E-beam sterilization is, contrary to the continuous gamma decay, E-beam can be turned on and off as desired. The process also allows easier control of the dosage than with EO. A shorter exposure time for the E-beam process assures a higher production and the possibility of less damage of the material. On the other hand, E-beam sterilization induces an increase of the material temperature between 10-20˚C. To avoid this temperature increase, the energy of the E-beam may be decreased. This technology, which can only sterilize the surface to a few-inch depth, may be inappropriate for thick or dense objects.

2.3.5.4 Other Sterilization Processes

Implants may be sterilized in hospitals by immersion in an aqueous glutaraldehyde solution as an extreme alternative for heat and post-EO-aeration sensitive polymers. In order to obtain acceptable sterilization results with this technique, meticulous manipulation and relatively long immersion times are needed.[104] Other new technologies such as gaseous chlorine dioxide,[112] low-temperature gas plasma, vapor-phase hydrogen peroxide, and machine-generated X-rays have been examined for potential new sterilization applications.

Vapor-phase hydrogen peroxide (VPHP)[113,114] was developed as an alternative sterilization technique. After good results for the sterilization of glass, stainless steel and polyethylene, VPHP technology has been used for the sterilization of polymers. The process consists of preheating the material under vacuum followed by the addition of the VPHP generated by heating a peroxide solution. After the sterilization, the material has to be aerated with air to remove H_2O_2. Although some authors claimed that VPHP sterilization does not enhance polyurethane degradation, too little is known to draw firm conclusions. Cytotoxicity has been reported and associated to the residual H_2O_2. A sufficient aeration seemed to inhibit the adverse

effects of the H_2O_2 but, again, further work has to be done to validate the aeration time needed for the removal of residual peroxide.

Gas plasma sterilization[113,115] is a dry, low-temperature process. A plasma is created by exposing a monomer's vapor to an electromagnetic field created by microwave or radio frequency discharge. A variety of charged and uncharged excited chemical species will react and therefore kill microorganisms. For example, H_2O_2 vapor can be used as the substrate gas (Sterrad® system, Advanced Sterilization Products, a division of Johnson & Johnson Medical, Irvine, CA, U.S.). Sterrad® has been reported by Advanced Sterilization Products to be an adequate alternative to heat-and-moisture sensitive items (Advanced Sterilization Products, personnal communication). For example, this company reported that polyurethanes remain unchanged after 100 sterilization cycles. However, they failed to mention the chemical composition of the polyurethane system and the test methods used to study polyurethane degradation. In addition, further studies are warranted to characterize the effect on surface properties.

2.3.5.5 Selection of the Sterilization Process for Polyurethanes

Since polyurethanes are a wide family of polymers, the selection of the sterilization technique may be adequate for one polyurethane and inadequate for another. Therefore, in order to make a proper selection of the sterilization process, we must consider the efficiency, toxicity, and severity of the sterilization process. Sterilization is a major concern to make suitable a material for biomedical applications. Manufacturers should be aware of the duality between toxicity and severity when selecting the sterilization technique. Physical and chemical alterations should be also minimized. Guidelines and procedures were developed as practices by the industry in conjunction with the Association for the Advancement of Medical Instrumentation (AAMI) and the European Committee for Standardization (CEN).[116] Concerted efforts toward global harmonization have been undertaken to establish agreement between European and American groups.[116]

Although it has been stated that no MDA was produced during a "normal-length" steam heat sterilization,[117-120] this technique, nevertheless, must be considered as a potential cause of PU hydrolysis. Indeed, Shintani has shown that MDA may be released with other hydrophilic compounds.[121] On the other hand, autoclave sterilization appears suitable for thermoset polyurethanes, which can more easily withstand pressure, heat, and moisture conditions. It is our opinion, however, that any polyester-urethanes should avoid autoclaving because of their susceptibility to hydrolysis.

Despite the long time required for the aeration of EO-sterilized products, this process is the most advantageous one for the sterilization of polyurethane materials. Shintani reported that EO sterilization produced the smallest amount of potentially toxic compounds, in comparison with autoclaving and gamma-ray sterilization.[121] However, manufacturers have to assure that residual EO will be under acceptable levels. Despite the encountered problems concerning toxicity and aeration, this process is probably the best alternative to autoclaving sterilization.

Gamma-ray sterilization is widely used for some biomedical materials such as polyethylene, polyesters, polystyrene, polysulfone, and polycarbonate. However, since chain scission, crosslinking,[120] and deterioration of the mechanical properties[110,122,123] of polyurethanes have been reported, this technique should be avoided with most PUs. MDI-based polyurethanes are also susceptible to release MDA products. Earlier results have demonstrated that gamma sterilization produces more MDA than steam sterilization.[118,119,121] Another drawback of this technique is the high capital costs associated with establishing an in-house sterilization operation.

Table 2.4. Commercial polyurethanes for biomedical applications

Trade Name	Composition Hard/Soft/ CE	Notes and Applications	Processing / sterilization	Ref.
		Applied Biomedical Corp. (Danvers, MA, U.S.)		
Angioflex®	MDI / PTMO / BD-PDMS	Thermoplastic polyether-urethane Trileaflet heart valves, artificial heart blood pumping diaphragms	Solution casting	19, 143
		Arrow International		
Cardiothane®-51 (Avcothane™ 51)	MDI/ PTMO/ BD-PDMS	Thermoplastic aromatic polyether-urethane polydimethylsiloxane copolymer Artificial hearts, intra-aortic balloons, blood conduits	Solution casting	45, 127, 143
		Bayer Corp.[a]		
Texin® 5186	No available info	Thermoplastic aromatic polyester-urethane No plasticizers Flexible tubing, film, catheters, connectors	Extrusion, injection molding a EO, dry heat, radiation	(see note)
Texin® 5250 5270 5275 5286	No available info	Thermoplastic aromatic polyether-urethane No plasticizers	Blow molding, extrusion, injection molding	a

Table 2.4. Continued

Trade Name	Composition Hard/Soft/ CE	Notes and Applications	Processing / sterilization	Ref.
		Flexible tubing, film, catheters, connectors, seals, gaskets bushings, housings.	Dry heat, EO, radiation	
Texin® 5290	No available info	Thermoplastic aromatic polyether/polycarbonate urethane No plasticizers Anesthetic connectors, seals and gaskets, flexible tubing, film, extruded profiles, catheters	Blow molding, extrusion, injection molding Dry heat, EO, radiation	a
Texin® 5590	No available info	Thermoplastic aliphatic polyether-urethane No plasticizers Tubing, catheters, connectors, various medical devices	Extrusion, Injection molding Autoclaving, boiling water, dry heat, EO, radiation	a
		Becton Dickinson Polymer Research (Sandy, UT, U.S.)		
Vialon	MDI/ PTMO/ BD	Thermoplastic aromatic polyether-urethane Catheters	No available info	45
		BFGoodrich Specialty Chemicals[b]		
Estane® 5701	No available info	Thermoplastic polyester-urethane	Extrusion, melt coating,	45

Table 2.4. Continued

Trade Name	Composition Hard/Soft/ CE	Notes and Applications	Processing / sterilization	Ref.
			solution coating	
		Cardiovascular, wound dressings		
		Cardiac Control Systems, Inc.[c]		
Surethane™	PTMO/ MDI/ ED	Thermoset aromatic polyether-urethane-urea	Solvent casting, coating	19, 45
		Purified Lycra®	Autoclaving, EO	
		Antioxidant as additives		
		Coating for cardiac pacing and defibrillation leads		
		CasChem, Inc.[d]		
Biothane®	Non-tolylene diisocyanate (Vorite™) (MDI usually)/ Castor oil-based polyols (Polycin™)	Thermoset aromatic (usually) polyether-urethane	Casting, potting	17
		Catalysts as additives	Autoclaving, EO, radiation	
		Adhesive, coating, kidney dialyzers and blood oxygenators component, catheters		
		CT Biomaterials[e]		
ChronoFlex® AL	HMDI/ polycarbonate/ BD	Thermoplastic aliphatic polycarbonate-urethane	Extrusion	45
ChronoFlex® AR	MDI/ polycarbonate diol/chain extender	Thermoplastic aromatic polycarbonate-urethane	Dipping, solvent casting	e (see note)

Table 2.4. Continued

Trade Name	Composition Hard/Soft/ CE	Notes and Applications	Processing / sterilization	Ref.
ChronoFlex® C	No available info	Thermoplastic aromatic polycarbonate-silicone-urethane	Extrusion	e
Chronothane™ P	No available info	Thermoplastic aromatic polyether-urethane	Casting, extrusion, injection molding, sheet extrusion	e
			Gamma ray	
Hydrothane™	No available info	Hydrophilic thermoplastic aromatic or aliphatic polyester-urethane	Casting, extrusion, injection molding, sheet extrusion, casting	e
		Dow Chemical Co.[f]		
Isoplast® 2510	MDI/ POEOP/ HD	Thermoplastic aromatic polyether-urethane Acrylic polymer modifier concentrate 6-10%	Blow molding, extrusion, injection molding	f (see note)
Isoplast® 2520	MDI/ CHDM	Thermoplastic aromatic polyether-urethane Acrylic polymer modifier (10%), color concentrate (0-5%)	Blow molding, extrusion, injection molding	f
Isoplast® 2530	MDI/ HD	Thermoplastic aromatic polyurethane Additives < 2%	Blow molding, extrusion, injection molding	f
Isoplast® 2531	MDI/ PTMO/ CHDM/ HD	Thermoplastic aromatic polyether-urethane Additives < 2%	Blow molding, extrusion, injection molding	f

Table 2.4. Continued

Trade Name	Composition Hard Soft/ CE	Notes and Applications	Processing / sterilization	Ref.
Isoplast® 2532	MDI/ CHDM	Thermoplastic aromatic polyurethane Additives < 2%	Blow molding, extrusion, injection molding	f
Isoplast® 2540 NAT	MDI/ POEOP/ HD	Thermoplastic aromatic polyether-urethane Acrylic polymer modifier concentrate (2-6%), glass fiber (30-60%)	Blow molding, extrusion, injection molding	f
Isoplast® 2560 NAT	MDI/ POEOP/ HD	Thermoplastic aromatic polyether-urethane	Blow molding, extrusion, injection molding	f
Pellethane™ 2363	MDI/ PTMO/ BD	Thermoplastic aromatic polyether-urethane Additives < 2%	Extrusion, injection molding, solution casting, thermoforming	19, 45, 143
		Tubing, connectors, fittings, catheter components, tensioning ligatures and transdermal drug delivery patches	Dry heat, EO, gamma radiation, electron beam	
		Ethicon Corp.		
Biomer™	MDI/ PTMO/ ED	Thermoset aromatic polyether-urethane-urea	Solution casting	4, 19, 40, 45, 72, 139
	MDI/ PTMO/ Water	Thermoplastic aromatic polyether-urethane-urea	Extrusion	

Table 2.4. Continued

Trade Name	Composition Hard/Soft/ CE	Notes and Applications	Processing / sterilization	Ref.
		Bladders, chamber coatings, catheters		
		Thoratec Laboratories Corp.		
BPS-215 SPU	MDI/ PTMO/ ED	Thermoset blend of aromatic polyether-urethane-urea and minor amount of amphipathic segmented multipolymer, SMA-300	Casting	19, 144
		VADs, grafts Used clinically in the Pierce-Donachy ventricular assist device		
		Polymedica Industries (Woburn, MA, U.S.)		
Mitrathane™	MDI/ PTMO/ ED	Hydrophilic thermoset aromatic polyether-urethane-urea	Casting, precipitation techniques, spinning	19, 45, 145
		Vascular grafts		
		The Polymer Technology Group[g]		
Bionate® PCU (previously known as Corethane™)	MDI/ HMEC/ BD	Thermoplastic aromatic polycarbonate-urethane	Compression molding, extrusion, injection molding	g (see note)
		Leads, grafts, stents	EO	
BioSpan® SPU	PTMO/ MDI/ ED-CHDA mixture	Thermoset aromatic segmented polyether-urethane-urea Antioxidant and a copolymer of decyl	Casting, dipping	45

Table 2.4. Continued

Trade Name	Composition Hard/Soft/ CE	Notes and Applications	Processing / sterilization	Ref.
		methacrylate and diisopropylaminoethyl methacrylate as additives Film, coating, adhesive VADs, urological implants, leads		
BioSpan-D® SPU	PTMO/ MDI/ ED-CHDA mixture	Hydrocarbon-modified BioSpan® Oligomeric hydrocarbon end groups covalently bonded Stabilizing additives	Casting, dipping	g
BioSpan-F® SPU	PTMO/ MDI/ ED-CHDA mixture	Fluorocarbon-modified BioSpan® Oligomeric fluorocarbon end (-CF_2, -CF_3) groups covalently bonded Stabilizing additives	Casting, dipping	g
BioSpan-P® SPU	PTMO/ MDI/ ED-CHDA mixture	Polyethyleneoxide-modified BioSpan® Polyethyleneoxide (PEO) end groups covalently bonded Stabilizing additives	Casting, dipping	g
BioSpan-S® SPU	PTMO/ MDI/ ED-CHDA mixture	Silicone-modified BioSpan® Oligomeric polydimethylsiloxane end groups covalently bonded Stabilizing additives	Casting, dipping	g
BioSpan-SP® SPU	PTMO/ MDI/ ED-CHDA mixture	Silicone-polyethyleneoxide modified BioSpan®	Casting, dipping	g

Table 2.4. Continued

Trade Name	Composition Hard/Soft/ CE	Notes and Applications	Processing / sterilization	Ref.
		Hydrophilic PEO and hydrophobic polydimethylsiloxane end groups covalently bonded		
BioSpan-C® (previously known as Coromer®)	MDI/ HMEC/ ED	Thermoset aromatic segmented polyether/polycarbonate urethane-urea Stabilizing additives Film, coating, adhesive VADs, urological implants, leads	Casting, dipping	g
BioSpan-SC®	MDI/ HMEC/ ED	Silicone-modified BioSpan-C® Oligomeric polydimethylsiloxane end groups covalently bonded Stabilizing additives	Casting, dipping	g
		Thermedics, Inc.[h]		
Tecoflex®	HMDI/ PTMO/ BD	Thermoplastic aliphatic polyether-urethane Tubing,blood pump diaphragms, adhesive, sheet, film fiber, catheters, wound dressings	Extrusion, injection molding, solution casting	19, 45, 140-143, 146
		Toyobo Co. (Osaka, Japan)		
Toyobo ™5	MDI / PTMO/ PD	Thermoset aromatic polyether-urethane-urea	No available info	19, 45, 143

Table 2.4. Continued

Trade Name	Composition Hard Soft/ CE	Notes and Applications	Processing / sterilization	Ref.
		LVAD		
		Elastomedics Pty Ltd		
Elast-eon™ 1	Polyhexamethylene oxide (PHMO), aromatic polyurethane	Improved environmental resistance over PTMO polyurethanes 80A-75D (Shore)	Extrusion, injection molding, solvent casting, compression molding	67-71
Elast-eon™ 2	Siloxane based macrodiol, aromatic polyurethane	Biostability indistinguishable from Pellethane™ 55D, Additives free 80A-75D (Shore)	Extrusion, injection molding, solvent casting, compression molding	57, 59-61
Elast-eon™ 3	Siloxane based macrodiol, modified hard segment, aromatic polyurethane	Flexibility approaching that of silicone, biostability indistinquishable from Pellethane™ 55D, additives free 650A-80 A (Shore)	Extrusion, injection molding, solvent casting, compression molding	61, 62
Elast-eon™ 4	Modified aromatic hard segment polyurethane	Rigid material with high heat distortion temperature, additive free 55 to 85D (Shore)	Extrusion, injection molding, solvent casting, compression molding	147

a: Polymers Division, Marketing Communications Group, Bayer Corp., personnal communication, 1998.
b: BF Goodrich Specialty Chemicals, personnal communication, 1998.
c: Bertolet RD, Cardiac Control Systems, Inc., personnal communication, 1998.
d: Harlett B, Caschem, Inc., personnal communication, 1998.
e: Dorren SJ, CT Biomaterials Div. of Cardiotech International, personnal communication, 1998.
f: Nash P, Dow Chemical Co., personnal communication, 1998.
g: Troconis I, The Polymer Technology Group, personnal communication, 1998.
h: Voltero MA,Thermedics, Inc., personnal communication, 1998.

2.4 Conclusion

Commercial polyurethanes available for biomedical applications are difficult to list due to chaotic comings and goings in the market and due to the lack of organizations that control it. While some polyurethanes have only changed their commercial name since they were first marketed, others have been retrieved for some or all medical applications. Our processes to retrace biomedical polyurethane have reinforced what history has shown. Polyurethanes listed in Table 2.4 are commercial PUs that we have been able to retrace. Many other polyurethanes such as polyurethanes made in university and/or research laboratories mentioned only once in the literature have not been included.

The present Chapter also shows how commercial PUs can be made. The selection of the appropriate processing conditions and sterilization techniques for polyurethane materials has been reviewed. It should be pointed out that manufacturing conditions of polyurethanes influence the properties of the end products. In addition, variability is a major concern that should be addressed for commercial polyurethanes.[124] These variations may alter surface characteristics and therefore affecting considerably the interaction between the device and the human body. Physico-chemical properties and the service life of implants risk being altered by these variations. Batch-to-batch variations in the composition of commercial PUs have been observed and reported to be mainly associated with the presence of processing aids, contaminants, and/or unreacted reagents that have the ability to migrate within the polymer matrix. Tyler et al[125,126] have found differences in lots of Biomer™ and Lelah[40] has reported silicone contamination on extrusion grade Biomer™ that was attributed to the presence of a polydimethylsiloxane additive. Iwamoto reported a silicone-concentration variability on balloon pump surfaces.[127] Belisle et al[128] have detected amino-compound fragments probably added during the processing in order to enhance the polymer stability. Polydimethylsiloxane (PDMS), which may have been added as a lubricant, has been also found on catheter surface.[129] Moreover, nonessential chemical species were found in some PU materials.[130] Low molecular weight materials such as polyether groups concentrated near the surface, have been found into polyurethanes.[131] Continuous production of polyurethane materials should be favored over batch production in order to assure a better homogeneity between lot-to-lot production. Precautions should also be taken during handling and intermediate steps between processing and end-use applications. In addition, physical variations can be enhanced during polymer processing and sterilization. Microbubbles[132] and small cracks[133] can be observed following the manufacturing processes. These alterations can initiate and accelerate degradation and must therefore be overcome. It is thus of paramount importance to standardize the conditions of manufacturing in order to minimize any possible alterations.

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CHAPTER 3

Additives in Biomedical Polyurethanes

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3.1 Introduction

In the preceding Chapter, industrial production of polyurethanes (PUs) was covered. The main industrial processes and sterilization techniques that apply to biomedical polyurethanes were discussed. However, the issue of using polymer additives during the preparation of commercial polyurethanes must also be covered. In fact, polymers are usually mixed with one or several additives to produce plastics for target end-use application. Additives are normally incorporated into a monomer solution or a polymer during polymer synthesis, compounding, melt processing and molding, and production operations of plastics articles.[1] Their use can be simply to improve manufacturing operations or to affect specific property enhancement or modification in order to meet specific requirements fundamental to the technological end-use. In fact, the "additives" terminology is descriptive of their primary function: antioxidants, heat and light stabilizers, processing aids, impact modifiers, fire retardants, fillers and coloring agents. Alternatively, some of the additives can be made an integral part of the polymer macromolecular structure by grafting or copolymerization.[2] Additives are, therefore, essential ingredients of a polymer formulation in the production of an end-use product. For biomedical applications, the biological response of additives should receive no less attention than that of the polymer substrate. This Chapter aims to review briefly the use of additives in polymers, with particular emphasis on their use in the production of polyurethanes that are destined for biomedical applications and their potential effects on the biological response of the mammalian host body.

3.2 Classification of Plastics' Additives

The classification used in this Chapter is based on the general requirements that dictate the use of additives to facilitate the manufacturing process, to modulate physical and chemical properties of the final product and to improve polymer stability. This somewhat arbitrary method of classification provides a simple framework for discussing the use of additives in PUs. However, not all the additives mentioned in the following section may be used for making biomedical PUs. In the absence of detailed reports on the manufacturing processes of PU materials, a general reference to some of the additives in common use in the plastics industry is included here with the aim of identifying those additives which are most relevant to the manufacture of biomedical PUs.

Biomedical Applications of Polyurethanes, edited by Patrick Vermette, Hans J. Griesser, Gaétan Laroche and Robert Guidoin.

3.2.1 Additives Used as Processing Aids

Most fabrication processes involve an initial melting of the polymer powder or granules followed by forming, molding, or extruding processes to produce the final product. These processes and fabrication methods often involve the application of high shear to a polymer resin at elevated temperature. Under these conditions the polymer undergoes extensive deformation and is subject to extreme levels of stress during the various stages of melting and mixing in a processing machine. The ease with which polymer fabrication can be accomplished depends on the physical and chemical properties of each plastic material, in particular on its melt viscosity and its resistance to heat and oxidation during processing. The adverse effects of processing can be reduced through the use of additives known as processing aids which include:[3]

- accelerators: to accelerate the rate at which the cure reaction occurs;
- blowing agents: to generate gas in order to expand or "foam" the polymer;
- compatibilizers: to improve mixing between polymer melts;
- diluents: to modify resin viscosity;
- defoaming agents: to trap gases during compounding;
- exotherm modifiers: to modulate process parameters including temperature or pressure;
- lubricants: to prevent a polymer from sticking to the machinery and reduce friction between polymer particles;
- nucleating agents: to promote or control the formation of spherulites in crystallizable polymers;
- wetting agents: to generate uniform dispersion in a polymer matrix without agglomeration.

Additives can be also used to facilitate handling and packaging. These include:[1,3]

- antiblocking agents: to prevent plastics from sticking together and improve film clarity by preventing condensation;
- antistatic agents and slip agents: to eliminate surface electrical charges responsible for dust pick-up on polymers.

Some additives used during the fabrication of plastics, including lubricants, can cost many times more than the raw materials. This cost, however, is generally offset by energy savings and the ease of large scale manufacturing associated with their use in addition to improving material properties of the finished product (see below).

3.2.2 Additives Used to Modulate Physico-Chemical Properties of the End-Use Product

Additives that fall into this category are mainly used to modulate mechanical properties, e.g., strength, ductility, and flexibility, as well as other physical properties such as color, fire resistance, and smoke formation. For example, some polymers such as poly(vinyl chloride), PVC, which is processed with thermal stabilizers (necessary for all PVC applications) but without plasticizers, will yield to a rigid product. The incorporation of a plasticizer in the formulation will result, however, in the formation of a product with a degree of flexibility that is ideal for cable and wire coating and insulation applications. Furthermore, as some biomedical plastics are colored to some extent, it is important to take into consideration the use of coloring agents. Plastics can be colored using two main methods. The surface can be painted or printed after processing, or coloring agents can be incorporated before or during processing. From a biomedical point of view, additives may also be seen as surface modifying agents (SMA) that may drive the biological response. It is in this context that additives can be incorporated "free" within the structure of the polymer and/or can be bound to the polymer structure. This latter subject is discussed in Section 3.3.4 of the present Chapter. Additives that are used to modulate properties of

the final product may include: curing agents, fibers, fillers, impact modifiers, microspheres/ microballoons, odor modifiers, optical brightners, peroxides, and smoke suppressants.

3.2.3 Additives Used to Improve Polymer Stability

This category of additives is probably the most relevant to the manufacture of additives used for making biomedical-grade PUs.[1,3-5] Polymer stabilization is crucial to both the fabrication (processing, sterilization, handling, packaging, and storage) cycle and product performance and durability. Antioxidants, heat and light stabilizers and antifogging agents are the major additives that exert important effects on the short- and long-term in-service performance of polymer artefacts.

3.3 Additives Used in Biomedical-Grade Polyurethanes

Additives known to be added to the formulation of biomedical-grade PU can be grouped into four categories: antioxidants, lubricants, plasticizers, and additive functional groups.

3.3.1 Antioxidants (AOs)

The performance of a polymer can be adversely affected by oxidative degradation that takes place during the different stages of polymer fabrication and subsequent exposure to aggressive biological and technological environments (Chapter 5). Polymer oxidation can be accelerated by many factors that include oxygen concentration, sunlight, radiation, heat, ozone, atmospheric pollutants, water, enzymes, mechanical stress, adventitious metal and metal ion residues from the polymerization step or from processing machines. To better appreciate the use of antioxidants and their mechanisms of action, the salient features of polymer oxidation are presented here.

Oxidative degradation of polymers occurs both in vitro, during thermal processing and environmental exposure, and in vivo, through an autooxidative free radical chain reaction process, Figure 3.1. This process involves the generation of free radicals, which become involved in propagation reactions that lead to the formation of hydroperoxides. Termination reactions finally result in the elimination of free radicals from the autooxidizing system. Hydroperoxides, the primary products of autooxidation, are inherently unstable to heat, light and metal ions and decompose readily to yield further radicals (see Fig. 3.1) which would continue to initiate the chain reaction. Hydroperoxides, and their decomposition products, are ultimately responsible for the changes in molecular structure and molar mass of the polymer which are manifested in practice by the loss of mechanical properties and by changes in physical properties of the polymer surface, e.g., loss of gloss, yellowing and cracking.

It is important, therefore, to inhibit the process of oxidation, and this can be achieved by the incorporation of low levels of antioxidants (e.g., 0.01-0.5 %wt./wt.) normally added during the fabrication stage. Antioxidants are classified according to the way by which they interrupt the overall oxidation process: chain breaking (CB), sometimes referred to as primary AOs, and preventive antioxidants, sometimes referred to as secondary AOs (see Fig. 3.1). CB antioxidants act by removing the propagating radicals, R* and ROO*. They are further subdivided into chain breaking donor (CB-D) antioxidants which are capable of reducing ROO* to ROOH, and chain breaking acceptor (CB-A) antioxidants which oxidize the alkyl radicals. Examples of CB-D antioxidants include hindered phenols and aromatic amines[6] whereas CB-A antioxidants include quinones and stable free radicals, e.g., stable nitroxyl radicals. Preventive antioxidants act by interrupting the second oxidative cycle by preventing or inhibiting the generation of free radicals. The most important preventive mechanism is the decomposition of hydroperoxides

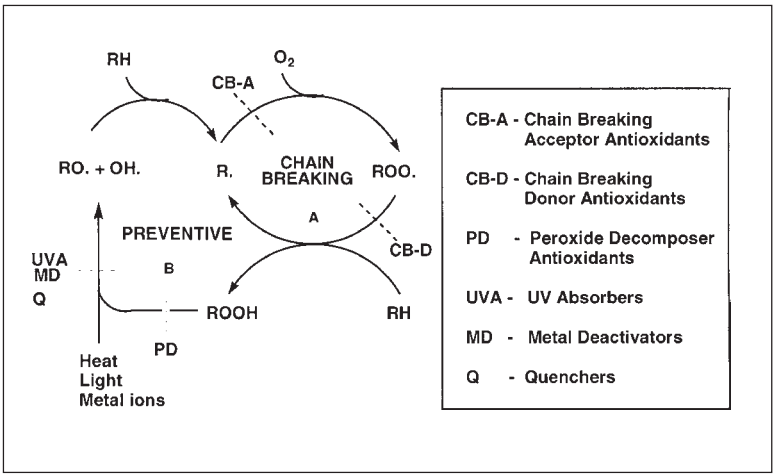

Fig. 3.1. Oxidative degradation processes and antioxidant mechanism.

(PD) by a nonradical process. Examples of peroxide decomposers include phosphorus-containing antioxidants[6] (e.g., phosphite esters) and sulfur-containing antioxidants (e.g., thiodipropionates). Other stabilizers that act by a preventive mechanism include metal deactivators, photo-antioxidants, UV absorbers and nickel complexes.[6] The use of a combination of antioxidants sometimes leads to a positive synergistic effect in which the level of protection afforded by the combination is greater than the total sum of effects exerted by the individual components (when used separately under exactly the same conditions and total concentration).[7] For example, a three component synergistic mixture containing a peroxide decomposer, a UV absorber and a radical scavenger may be an ideal solution for the protection of PUs, but its use in biomedical applications must first be fully justified.

The above discussion clearly indicates the importance of antioxidants in polymers including biomedical-grade PUs. However, it is not only important to consider the protective effects of antioxidants on the PU substrate during manufacture and post manufacturing steps (e.g., the different methods of sterilization treatment of medical artefacts) but also their biological response during in vivo use. To gain an insight into the key role played by antioxidants in the protection of PU material a basic understanding of the degradative processes in PUs is essential.

Thermal oxidation of PU is governed by the behavior of the hard segment (containing the urethane units) and the soft segment (comprising the polyols). The urethane unit is relatively stable towards thermooxidation albeit moderated by the nature of substituents in both the hard and soft segments, e.g., aromatic isocyanates confer greater stability than aliphatic ones whereas polyether diols reduce thermal oxidative stability. Thermal degradation of PU, in an oxygen deficient environment, starts in the urethane part whereas thermooxidation takes place in the ether part of the PU macrostructure. In the presence of oxygen, therefore, oxidation of PU proceeds in a typical free radical chain mechanism, similar to that shown in Figure 3.1. The thermal decomposition of the hydroperoxide (which is accelerated by traces of metal ion impurities, e.g., copper, iron) formed from the polyether segment results in the formation of different chain scission products, see Figure 3.2, resulting in a rapid decrease in molar mass.[8,9] Stabilization of PUs can be achieved either by incorporating the antioxidants during processing/fabrication stage or during synthesis, e.g., to stabilize the precursor polyol against autooxidation

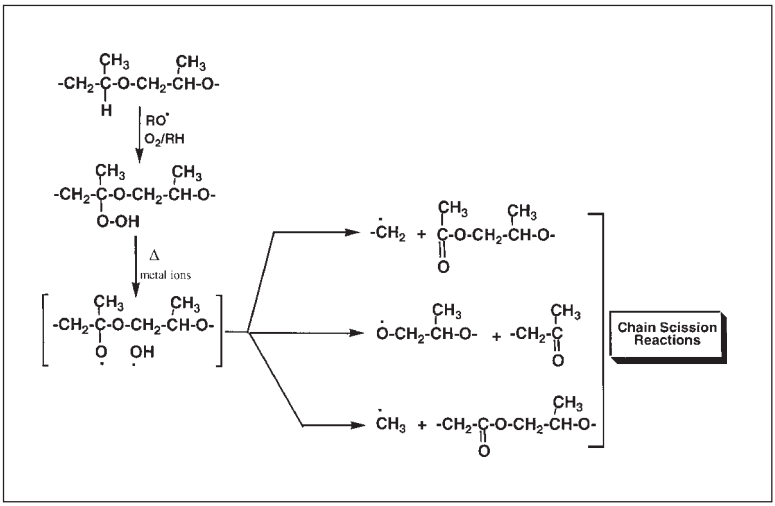

Fig. 3.2. Thermal decomposition of hydroperoxides formed in polyether segment of PU.

during storage and synthesis by preventing discoloration arising from exothermic reactions and scorching.

Photochemically initiated oxidation of PUs proceeds by a similar free radical chain reaction involving hydroperoxides, and their thermal and photolytic breakdown products. Under photooxidative conditions, both aliphatic and aromatic parts of a PU structure are susceptible to free radical attack. For example, MDI-based PUs photooxidize (due to the ease of hydrogen abstraction) forming hydroperoxides giving rise to highly colored conjugated quinone imide-type products (see Fig. 3.3).[8,9] Aliphatic isocyanate-based PUs often yield less coloration than the corresponding aromatic PUs because of the absence of products absorbing above 400 nm. A PU soft segment containing a polyether macrodiol is less stable toward photooxidation than a polyester one of a similar molar mass.

It is clear, therefore, that PU requires both thermal and UV stabilization which can be achieved by the use of radical scavengers, e.g., phenolic AOs or hindered amines (HALS), and UV absorbers, e.g., benzotriazoles and hydroxybenzophenones. Synergistic combinations of all three types of AOs (e.g., hindered phenol, high molar mass HALS and benzotriazole) should offer effective stabilization for PUs.

Hydrolytic degradation of PUs is known[8,9] to occur autocatalytically at the (amide) urethane linkage leading to more or less important chain scission (see Fig. 3.4) and rapid reduction in molar mass concomitant with loss of mechanical properties. Indeed, hydrolysis of commercial PUs gives rise to their precursor monomers, which is a cause for concern because of toxicity issues. The hydrolytic degradation process is accelerated by acids and proteolytic enzymes (hydrolases) which may target the amide bond. The biochemical environment of a living tissue or organism may also cause an oxidative degradation leading to the formation of peroxidized intermediates or products. PU-based implants or medical devices could be adversely affected by oxidative stress associated with their use in such an aggressive environment resulting in the reduction of their longevity and projected benefits.

Degradation of PU material by high energy radiation, following post processing treatment of medical artefacts for sterilization purposes, is also expected to proceed by a free radical chain mechanism initiated by gamma radiation,[10] albeit at different rates due to the higher

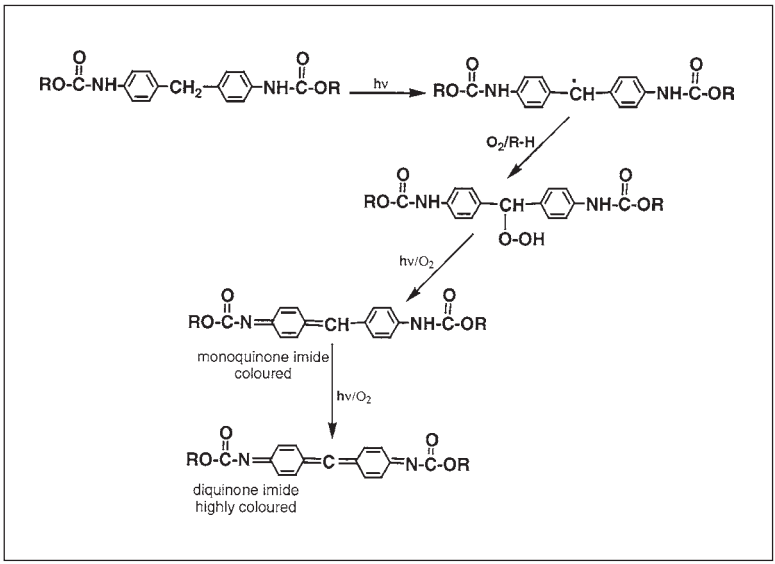

Fig. 3.3. Photoxidation reactions of MDI-based PU.

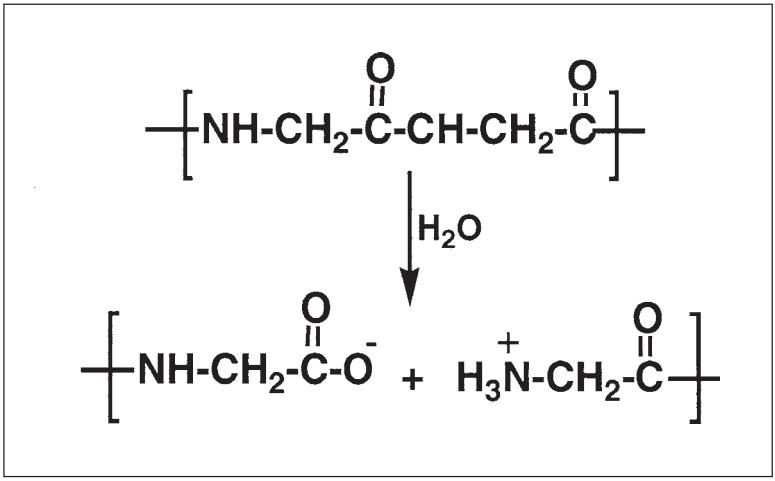

Fig. 3.4. Hydrolytic degradation of PU backbone.

rates of radical generation by the high energy radiation. The mechanism of inhibition of oxidative degradation is expected to be similar to that shown (see Fig. 3.1) for thermooxidation.

The use of antioxidants in PUs intended for biomedical applications should also take account of other physical factors such as their solubility, migration, blooming and loss from the polymer, especially under an abrasive and aggressive service environment.[6] The levels of toxic and cytotoxic responses developed by the use of these antioxidants, alone and in the presence of

other additives in the polymer formulation, must be clearly assessed both in terms of their intrinsic chemical activities and the physical factors mentioned above.

There are many examples in the literature[4,5] that refer to the use of antioxidants in PUs for biomedical applications. These include Tinuvin 328, Tinuvin P, Tinuvin 622, Tinuvin 765, Chimassorb 944, Chimassorb 81, Irganox 245, Irganox 1010 and Irgafos 168 (see Fig. 3.5 for structures). Antioxidants used for the photostabilisation of PU elastomers for maxillofacial use include[7] AM-340, Sanduvor EPU, Syntase-62, Syntase-1200, Uvinul D-49 (Uvinul 3049), Uvinul N^~539 (Uvinul 3039), Tinuvin 770, Eastman RMB, and USP-111 ZnO (see Figure 3.5 for structures).

Toxicological information concerning the use of Tinuvin P has been reported in the literature. Indeed, allergic contact dermatitis from Tinuvin P used in a face cream was reported by Cronin[11] as well as several cases of contact allergy to Tinuvin P used in plastics.[12-15] Moreover, Björkner and Niklasson[13] showed that a patient's gingivitis was healed completely when the gold filling and all composite dental fillings were replaced by materials not containing Tinuvin P. The maximum level of Tinuvin P tolerable in dental restorative materials was found to be 0.09%. Toxicological investigations were also carried out on Chimassorb 944, Tinuvin 622 and Tinuvin 770 by Ciba-Geigy Corporation.[16] Cytokine expression and macrophage activity were characterized, by administering, via intraperitoneally the additives mentioned above. Ciba-Geigy Corporation[16] reported that one of the test compounds, Chimassorb 944, was more toxic to mice following intraperitoneal administration than the other test additives. In terms of immunohistochemistry, there were no obvious differences in the distribution of macrophage surface markers except for the high dose of the most toxic compound, Chimassorb 944. On the other hand, it was found that, for lower dose (representing 1% of a quoted rat oral LD_{50}), cytokine gene expression was significantly inhibited for both Chimassorb compounds but was normal or slightly inhibited for both Tinuvin compounds. These differences were magnified for a longer period of exposure in mice, where both Chimassorb compounds induced a significant inhibition of cytokine gene expression whereas cytokine expression was normal or slightly inhibited with both Tinuvin compounds. Therefore, their investigations showed that the compounds showing no effect were Tinuvins 622 and 770 and the compounds showing effect were Chimassorbs 119 and 944. However, these results did not indicate a clear and consistent separation in the responses of the aforementioned Chimassorbs and Tinuvins. In another study, Ciba-Geigy Corporation[17] evaluated neurological effects of Tinuvin 770, whereas Tinuvin 770 was administrated orally to rats by gavage at different daily doses (600, 1000 and 2000 mg/kg) for a 28-day period. All animals subjected to a 2000 mg/kg/day dose died between days 2 and 17. Two male rats of the 1000 mg/kg/day-group died on days 5 and 28. No mortalities occurred following the 600 mg/kg/day-dose. Ptosis of eyelids, muscular hypotonia and rough coat were observed in all dosed groups. Sedation, brownish eye discharge and kyphotic carriage were reported for the 1000 and 2000 mg/kg/day-groups. Chimassorb 81 were also investigated by Ciba-Geigy Corporation[18] whereas albino guinea pigs were submitted to intradermal injections (into the neck region) and closed patch exposure over the injection sites one week later; 65 and 60% of the animals showed skin reactions following the 24 and 48 hour-exposures, respectively. Chimassorb 81 was, therefore, classified as moderate to strong skin sensitising (contact allergenic) potential in albino guinea pigs. However, observations made on animals should be carefully interpreted. For example, mouse tissue is 50 times less responsive to Sydney Funnelweb Spider (*Atrax robustus*) venom than tissue from humans or monkeys.[19] In addition, Underhill[19] found that adult mice were unaffected by *A. robustus* venom, while the venom of this Australian spider is lethal to human. A worker could mistakenly judge this spider to be harmless when examining the LD_{50} toxicity of its venom on mice!

Synergistic effects were found[7] when a combination of UV absorbers was used to enhance polymer photostability. For example, a combination of Tinuvin 328 and Uvinul D-49 in

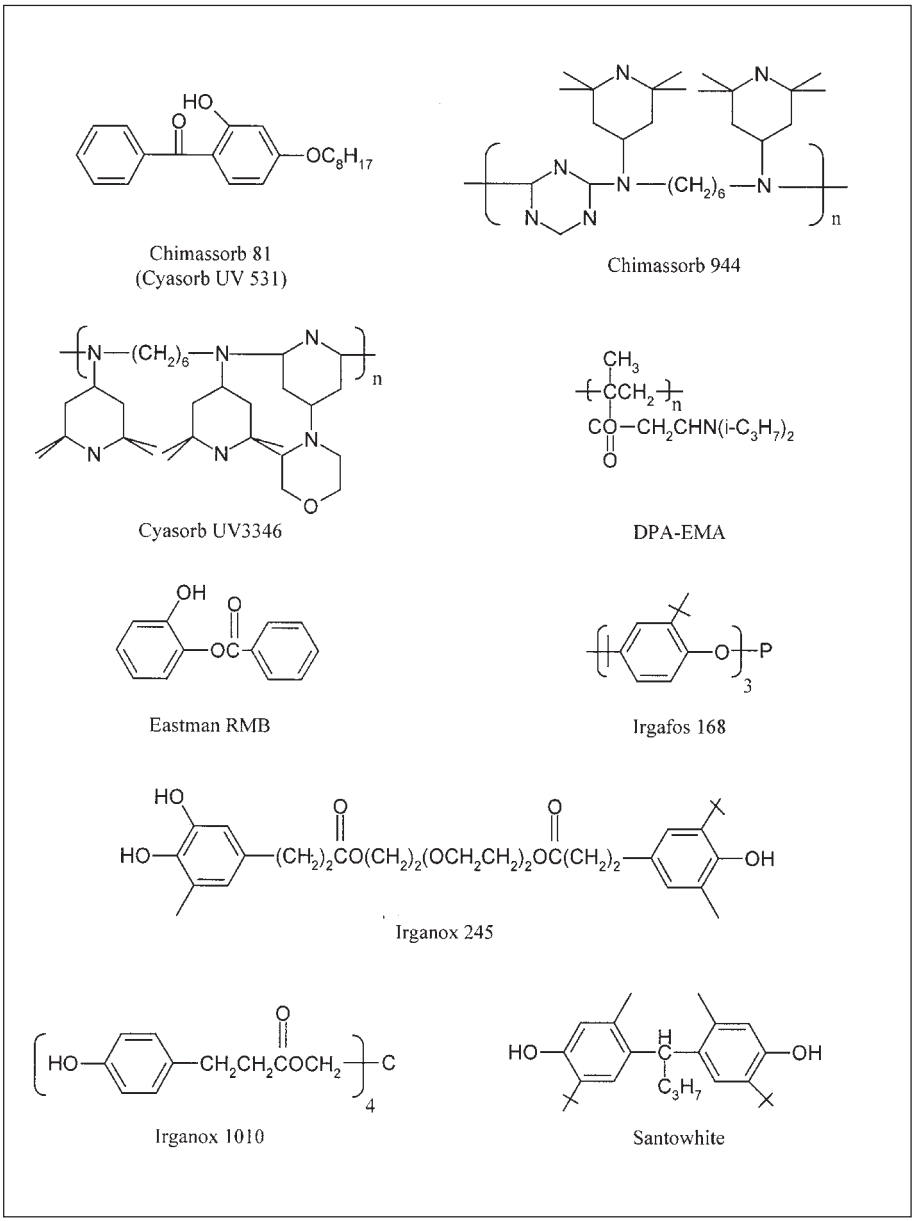

Fig. 3.5. Chemical structures of antioxidants and stabilizers.

Calthane ND 2300 (an aliphatic polyether-urethane, PEU) extended the stage of complete melting to 96 hours instead of 72 hours when Uvinul D-49 alone was used. It was also found that the incorporation of an antioxidant and an UV stabilizer in the formulation resulted in considerable improvement in the photostability of the matrix. For example, the addition of an antioxidant such as Irganox 1010 (a thermal antioxidant) to Calthane ND 2300 that was

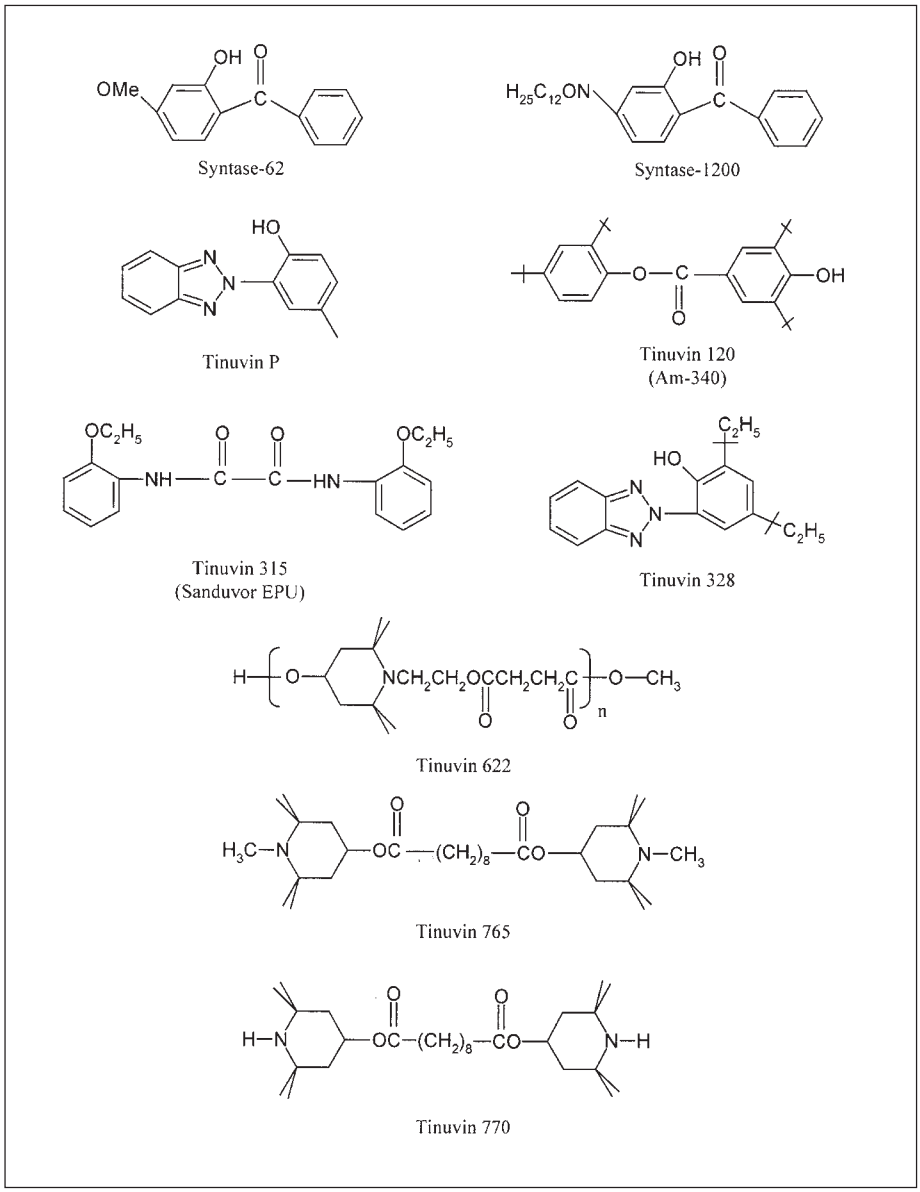

Fig. 3.5, continued.

already embedded with Tinuvin 315 (or Sanduvor EPU) stabilizer, doubled the photo UV life-aging of the system from 72 to 144 hours. In addition, Chu and Fisher[7] reported that a combination of Tinuvin 328 and Irganox 1010 extended the induction time for the appearance of a slight tackiness to 226 hours compared to 120 hours for Tinuvin 328 alone. It was concluded that although the incorporation of UV stabilizers enhanced the UV resistance of PUs, the problem of tackiness resulting from UV aging was not solved satisfactorily although

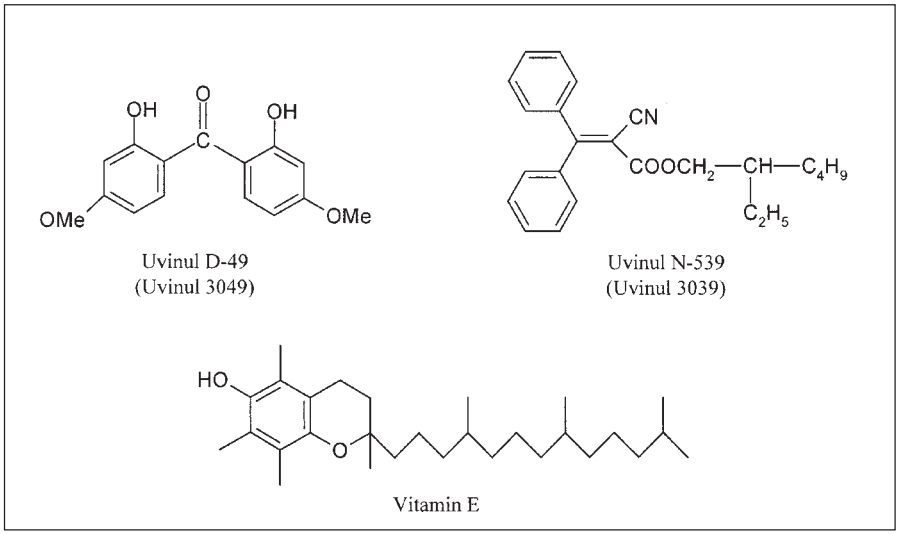

Fig. 3.5, continued.

the phenomenon of yellowing was significantly improved.[7] However, the apparent improvement in color observed by Chu and Fischer[7] may be explained by the low concentration of color-contributing species (absorbing above 400 nm) formed and not as a consequence of the efficiency of the stabilizers used.

It is well known[8,9] that aliphatic-based PUs are susceptible to photooxidative degradation as is indicated by the tackiness observed.[7] The most promising UV absorbers were shown to be Tinuvin 770, and the combination of Tinuvin 328, ZnO, and an antioxidant. However, Chu and Fischer[7] suggested that, even if a certain UV absorber is proven to be successful in a specific PU system, it does not necessarily mean that it will be equally useful for other PU systems. Indeed, when Tinuvin 120 (or AM-340) was incorporated in aliphatic PEU, tackiness was not observed until 250 hours of UV aging. However, the same UV stabilizer in Calthane ND 2300 (an aliphatic polyester-urethane) did not prevent partial melting after 192 hours. Furthermore, Calthane ND 2300 systems with Tinuvin 328 showed complete melting after exposure for 300 hours, while a PEU system containing Tinuvin 328 showed only slight tackiness. As discussed above these observations are further demonstrations of the general characteristics of PUs toward both thermo- and photo- oxidation which show great variations with the nature and type of the initial formulation used, e.g., isocyanates, polyols, extenders, catalyst residues and metal ion impurities.

In another study, Chu and Fischer[20] investigated the effect of some UV stabilizers on the mechanical properties of Calthane ND 2300. Tinuvin 328, Tinuvin 770, and Irganox 1010 were shown to be highly compatible with some PU systems and offered good UV stability. While both the tensile strength and modulus of elasticity decreased with increasing UV exposure, the rate of decrease, however, was greater for the specimens containing UV stabilizers alone. Again, the incorporation of the antioxidant (Irganox 1010) in the system appears to contribute to the thermal stabilization of the oxidatively sensitive soft segment (polyether diol) of Calthane ND2300, hence the marked improvement observed under photooxidative conditions.

Zhao et al[21,22] investigated the effects of Santowhite, Tinuvin 328, and Cyasorb UV 3346 on the fatigue lifetime and ultimate tensile stress of a PTMO/MDI/ED-based PU (see Fig. 3.5 for chemical structures of the AOs). The incorporation of a combination of these additives into

the polymer formulation was shown to result in the elimination of the effects of water and a reduction of the papain-mediated effect on the fracture stress of the polymer substrate. Moreover, Zhao et al[21,22] and Marchant et al[23] showed that the use of antioxidant and/or UV absorbers improves the fatigue lifetime of PTMO/MDI/ED-based PUs exposed to papain. For example, after an incubation period of one month with papain, unstabilized PU failed after 165 cycles whereas the stabilized system (containing Santowhite and Tinuvin 328) failed after 264 cycles; a combination of Cyasorb UV 3346 and Tinuvin 328 failed after only 190 cycles.[21-23] It is interesting to note here that papain, a proteolytic enzyme, is capable of hydrolyzing the PU backbone. The effects of UV stabilizers and/or antioxidants as reported above are intriguing since these additives are not known to interfere with hydrolytic processes. Other reasons, however, may be offered to explain more satisfactorily the above observations. The first is that these antioxidants may interfere with the activity of the site-specific hydrolase in question so as to inhibit or attenuate its hydrolytic attack on the urethane linkage. To test this proposition the activity of the papain enzyme should be checked to ascertain its level throughout the period of the experiment. Secondly, it is possible that these antioxidants are initially shielding the PU substrate from hydroxyl-mediated degradation reactions that are not under the control of the specific enzyme used. In vivo experiments[24,25] have indicated that PEUs are attacked by oxidative chemicals released from activated inflammatory cells during environmental stress cracking. It is plausible to surmise, therefore, that the free radical scavenging ability of the phenolic antioxidant used in the above experiment (i.e., Santowhite) may be partly responsible for shielding the polyether soft segment from oxidative attack in addition to any possible inhibitory effect on the enzyme. This assertion appears to be justifiable in the light of the improvement observed in the fatigue lifetime for this formulation.

Richards et al[26] used pyrolysis mass spectrometry to determine the structure of an additive present in the commercial PUs, Biomer™ and Lycra® spandex (see Chapter 2 for formulation). Their study identified the additive as poly(2-diisopropyl aminoethyl methacrylate), DPA-EMA (see Fig. 3.5 for structure). Richards et al[26] further reported that this additive formed a second phase in the polymer which was insoluble in DMAc (N,N-Dimethylacetamide), and accounted for approximately 7% (wt./wt.) of the total polymer. Moreover, Tyler et al[27] reported variations between two lots of the commercial (PEU) Biomer™ which were attributed also to the presence of DPA-EMA. Tyler and Ratner[28] studied also the influence of lot-to-lot variations on in vitro enzymatic and oxidative degradation of the PEU. It was found that PEU-containing DPA-EMA showed retarded enzymatic, and accelerated oxidative degradation processes compared to the lot without the additive. It was suggested that the surface-active DPA-EMA additive might form a protective coating that reduces the susceptibility of the PU to enzyme-catalyzed hydrolysis. Indeed, their data supported the hypothesis that enzyme-catalyzed hydrolysis, initiated at the surface of the polymer, may be reduced by coating the PU with an inert layer. In contrast, the extent of oxidative degradation after 24 hours in the lot containing DPA-EMA was enhanced. Tyler and Ratner[28] further suggested that DPA-EMA may be reacting with hydrogen peroxide to form highly polar charged groups that would alter the surface characteristics of PEU and increase its capacity to swell.

The effect of using vitamin E, a biological antioxidant (see Fig. 3.5 for structure), in PUs was investigated by Schubert et al.[29] Biaxially strained polyether-urethane-urea (PEUU) specimens with and without vitamin E were tested in vivo. Vitamin E was found to improve the biostability of the PEUU by inhibiting oxidation and crosslinking of the polyether soft segment.[29] Indeed, neither pitting nor cracking were observed in vitamin E-containing PEUU specimen of a 10-week old implant compared to a control (without vitamin E) which ruptured as a result of extensive pitting and cracking. Their results also suggested that vitamin E had improved the biological response of the PEUU in vivo as indicated by the lower leukocyte counts obtained in the exudate of vitamin E-containing PEUU compared to the control. More-

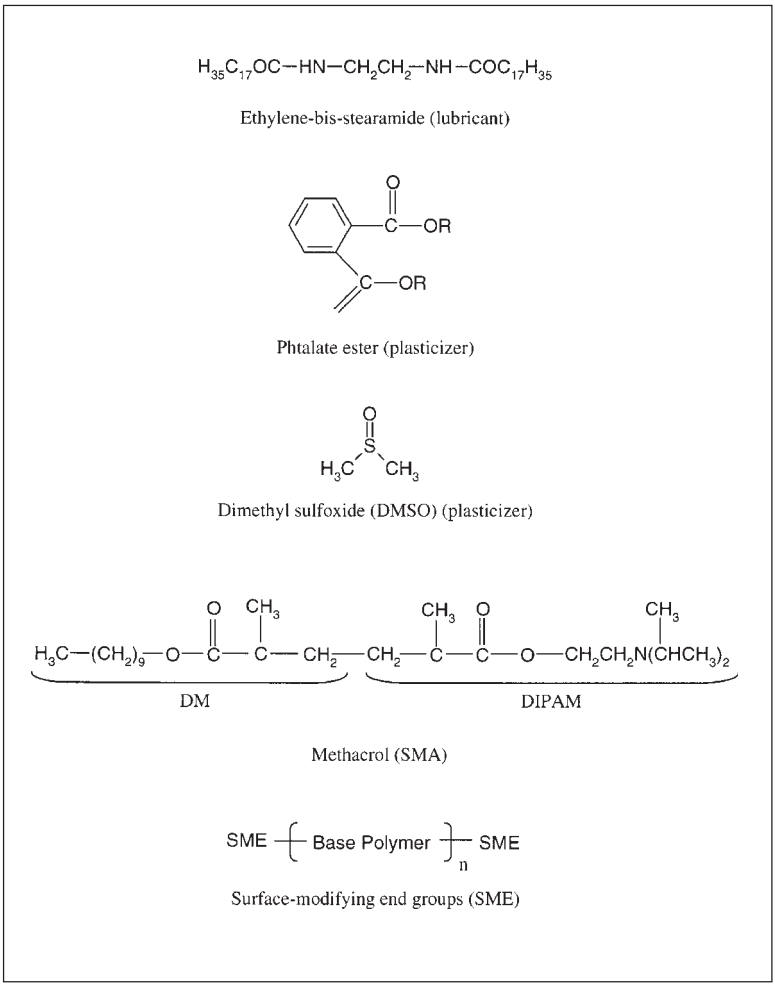

Fig. 3.6. Chemical structures of non-antioxidant additives.

over, fewer activated cells were found to adhere to PEUU containing vitamin E compared to the control.

The discussion above clearly indicates the imperatives of using antioxidants in polymer formulations. Their use, however, in thermoplastic PUs (elastomeric PUs) for biomedical applications is ill-defined and further work is needed to establish their function in the retention of yield stress and elastic modulus under the influence of in vivo stress and aggressive environment. Furthermore, low molecular weight antioxidants could interfere with enzyme activity, as well as exerting indeterminate effects as a result of diffusion into, and interaction with, the immediate environment. Even "acceptable" additives may be extracted into the in vivo environment causing a change in the property of the material and would raise further concerns relating to their effect on tissues and necrosis. At best, therefore, biomedical application should seek polymers that either do not require the use of additives or could be satisfied by the use of the few well-characterized additives. Other end-use specifications, e.g., sterilization,

would impose further restrictions on the available range of additives for use in biomedical applications. The small volume need of the biomedical arena means that supply is limited to the available manufactured product lines, hence the need for an approved list of additives that could assist and stabilize PU materials during processing and post-processing treatments and to withstand the in vivo service environment. To maintain the clinical performance of PUs for extended periods, antioxidants can be essential ingredients for the longevity of medical implants. This requirement must be balanced against the sacrificial nature of antioxidants and their transformation products, and their biological response at the optimum effective concentration levels. Unfortunately, there are no clear strategies available for selecting an appropriate antioxidant, or an additive in general, for a given application. The establishment of a database which incorporates all chemical, physical, spectroscopic, toxicological and immunologic information is the first strategic step toward developing scientifically-based protocols for the screening and selection of additives for human contact applications in general, and for biomedical applications in particular. The onus is on the scientific community, the polymer and polymer additive industry to initiate and coordinate these efforts and establish an objective strategy of selection and use.

3.3.2 Lubricants

PU chain molecules are highly viscous in the melt phase and tend to stick to metal surfaces of a processing machine, hence the need for lubricants for melt processing of PUs. The main function of a lubricant is to decrease internal and external friction by improving flow characteristics of the plastic during processing.[30,31] Most lubricants are surfactants that are usually amphiphilic molecules, i.e., they possess a hydrophobic tail and a hydrophilic head group.[30] Therefore, at the polymer/metal interface, the hydrophilic head of the surfactant will have a strong affinity toward the metal, which is obviously more hydrophilic than the polymer.

Lubricants are described arbitrarily as "internal" or "external" lubricants depending on their mechanism of action. Internal lubricants are mostly soluble in the polymer melt and work "internally" by facilitating the movement of the polymer chains against each other during processing. In fact, an "internal" lubricant should exhibit only weak interactions with the polymer chains since this will help the macromolecules to arrange themselves in the direction of flow and slide by each other creating a "ball bearing" effect. In this way, an internal lubricant reduces intermolecular friction, thus reduces the polymer melt viscosity and improves its rheological characteristics.[30,31]

External lubricants are largely insoluble in the polymer matrix. They work "externally" by migrating to the surface of the polymer melt during processing and act, therefore, as lubricants between the polymer melt and the processing equipment. However, since the bond strength between the polymer and the lubricant is generally weak, it would be expected that, under conditions of high shear rates (as experienced during extrusion or injection molding), the efficiency of a lubricant is considerably reduced if it was "squeezed-out" of the polymer melt. In view of the high level of stress experienced by a thin layer of a polymer melt undergoing shear during processing, it is imperative that the polar groups of the lubricant adhere strongly to the processing equipment to ensure stability of the boundary layer. The best lubricants to achieve this requirement are those containing a polar group that would react chemically with metal surfaces.[30] Thus, the lubricant will provide external lubrication by covering the surface of the processing equipment and, therefore, reduce the friction between the polymer and the contacting metal surface of a processing machine.[30,31]

Determining whether a material acts as an "internal" or "external" lubricant is not an easy task. It can be done, however, by determining the effect of the lubricant on the fusion, mill stick times and melt viscosity of the polymer compound/formulation. Internal lubricants will not significantly affect fusion or mill stick times of polymer melts but will lower their melt

viscosities. In contrast, external lubricants will increase both the fusion and mill stick times but will not significantly lower the compound melt viscosity.[31] Needless to say, however, essentially all lubricants in use exhibit both "external" and "internal" lubricating characteristics. The following classification that is based on types of chemical compounds is more informative:[31]

1. amides,
2. hydrocarbon waxes,
3. fatty acids esters,
4. fatty acids, and
5. metallic soaps.

An important conceptual point in understanding the implication of lubricants in PU materials was clearly established by Ratner and Paynter[32] when they reported that the surface of PUs was different from that of the bulk. It is well known that phase segregation and domain formation observed in PUs is an important cause of the difference between surface and bulk composition (see Chapter 1). However, another possible cause may reside in the fact that low molecular weight lubricant molecules tend to aggregate on the surface of PUs. In fact, Ratner and Paynter[32] showed that methanol and acetone, both nominally non-solvents for PUs, readily extracted surprisingly large amounts of material from PUs; analysis of the extracts revealed the presence of species that had lower molecular weight than the initial Pellethane™ material. They found, using FT-IR spectroscopy, that the low molecular weight extract in methanol was largely composed of polyether, with some urethane-link character, which can be attributed to unreacted precursor monomers or oligomers (see Chapter 1). They also found, among the other extracts, amide-rich materials that were attributed to the lubricant used during extrusion of PU tubing. Further interesting observations concerning PU surfaces and lubricants have come from XPS studies. Ratner and Paynter[32] found, for the unextracted Pellethane™ tubing, an XPS peak at 288 eV (from the C1s) indicative of the presence of amides. On the other hand, methanol-extracted Pellethane™ showed instead a peak at 289.2 eV indicative of urethanes. This suggested that extruded Pellethane™ tubing may have a surface which is not made up of PU, but that of an amide (an ethylene-bis-stearamide-based compound, see Figure 3.6 for structure). Moreover, Ratner et al[33] reported that adding Advawax® 240 to PUs transformed the surface into a highly hydrocarbon-rich environment. Further work by Briggs[34] has supported this conclusion; he observed the presence of an amide-lubricant on the surface of Pellethane™ materials which was identified as ethylene-bis-stearamide by secondary ion mass spectrometry (SIMS). Ethylene-bis-stearamide has been reported to have a good balance of "internal" and "external" lubricating properties.[31] Special care must be taken, however, in choosing this material since different blends of Advawax® are available commercially (ex. Morton International Inc.).

Further investigations by Ratner and Paynter[32] have shown that, for hydrocarbon-rich surfaces which were associated with the use of the stearamide lubricant during extrusion of PU, the in vivo platelet consumption was low. Indeed, hydrocarbon-rich surfaces appeared to be responsible for the subsequent reduction in platelet consumption. Ratner et al[33] postulated that a hydrocarbon environment at the surface may contribute to improved compatibility by reducing calcification and degradation. Bandekar and Sawyer[35] investigated the effect of a bis-amide wax on the adhesion and activation of human platelets, using a group of Pellethane™ samples with varying amounts of wax. That investigation led to the conclusion that the presence of bis-amide processing wax affected the hemocompatibility properties of the Pellethane™ samples. Indeed, it was found[35] that platelet activation increased with the amount of wax. These observations, however, appear to contradict the earlier findings of Ratner and Paynter.[32] Careful assessment of those two studies reveal fundamental differences in experimentation. In fact, Bandekar and Sawyer[35] evaluated the platelet adhesion and activation using an in vitro procedure while Ratner and Paynter[32] characterized the platelet consumption using an

arterio-venous (AV) shunt implanted in baboon. Furthermore, Bandekar and Sawyer[35] characterized the "surface" additive composition and concentration using FT-IR/ATR technique spectroscopy which is not a "true" surface characterization technique, while Ratner and Paynter[32] used XPS that probes a depth of approximately 30-50 Å. Generally speaking, in vivo investigations offer more realistic evaluation than those performed in vitro. However, further investigation is still needed to better understand the biological response of additives used in the manufacture of PUs.

Hari and Sharma[36] also studied the effect of external lubricants on protein adsorption. They used PPO/MDI/ED-based PU that was rubbed uniformly with two well-known lubricants: calcium stearate and a medical grade silicone emulsion. The protein used was a mixture of albumin, fibrinogen and γ-globulin. They showed that fibrinogen adsorption was encouraged by the presence of calcium stearate and silicone on the surface whereas albumin adsorption was discouraged. The general assertion being made here is that synthetic materials that favor the lowering of fibrinogen adsorption would also exhibit lower platelet adhesion and should afford better blood compatibility.[37]

3.3.3 Plasticizers

Plasticizers are generally used to improve the degree of flexibility by lowering the glass transition temperature (Tg) of polymers. When the polymer is heated in the presence of a plasticizer, an intimate mix of polymer and plasticizer is formed in the melt. On cooling of the melt, plasticizer molecules develop specific weak interactions (van der Waals forces) with the polymer chains. These plasticizer molecules are, therefore, relatively mobile and are able to migrate easily to the surface, with subsequent loss to the contact environment coupled with the loss of material flexibility. Leaching of plasticizer molecules become even more severe in applications which require the use of PU elastomers in tubings for transporting hydrophobic fluids. Since plasticizer molecules usually possess relatively long alkyl chains, they screen the polymer chains from each other, thereby preventing them from "re-forming" the chain-chain interactions that give the unplasticized polymer its rigidity.[38] Plasticizers are typically organic liquids.[1,38] The most widely used are phtalate esters (see Fig. 3.6 for structure). While various phtalates have been studied over the years, investigations on the plasticizer di(-2-ethylhexyl)phtalate, DEHP, has been performed more thoroughly. This is the most widely used plasticizer for medical tubing and plastic intravenous bag (IV)[39] and has often been considered as a model compound for plasticizers.

The effects of incorporating some of the plasticizers in Estane 5740-070 has been investigated by Cooper et al[40] which included Carbowax 200, Aroclor 1248 and DMSO (see Fig. 3.6 for structures). It was shown that the soft polyester segments were preferentially plasticized by the less polar Carbowax, as indicated by a shift of the Tg toward lower temperatures. Moreover, they found that the plateau modulus was mostly affected by the incorporation of the highly polar DMSO whereas the other plasticizers had little effect on the plateau modulus.[40,41]

In an attempt to elucidate the biological response of plasticizers, Cadogan[42] reported that phtalates generally possess a low degree of toxicity for oral, dermal and intraperitonial uses. Some animal testings have shown that plasticizers do not irritate skin or mucous membranes and do not cause sensitization whereas other studies, carried out on different mammalian species, have indicated that some phtalates may cause, in some cases, adverse effects on the liver and reproductive systems. In fact, Cadogan[42] indicated that while phtalates caused peroxisome proliferation in rat and mouse liver cells, they showed no such effects in humans, marmosets and guinea pigs. Recent[42-46] in vivo testing showed that most of the phtalates and other plasticizers produce no estrogenic activity. In 1986, EPA, the American Environmental Protection Agency[39] listed DEHP as a "probable human carcinogen". In a decision made by the European

Commission,[47] DEHP should not be classified or "labeled" as a carcinogenic and irritant substance, while IARC, the International Agency for Research on Cancer[48] had previously classified DEHP as "possibly carcinogenic to humans". It is clear that issues of toxicity and benefits attributed to DEHP have remained unresolved, and it may be "prudent" to seek alternative plasticizer molecules for use in PUs that are intended for biomedical use.

3.3.4 Additive Functional Groups

It is generally accepted that the surface characteristics of synthetic-based materials are crucially important when considering their interaction with the biological environment. The biological response of a synthetic material is, therefore, closely linked to the surface texture and surface composition of the material. However, since physical/mechanical considerations normally dictate the acceptability of a polymer for a particular application, its bulk properties must also be thoroughly examined. Designers of medical devices would ideally like to have independent control of the chemistry of the surface region of any polymer chosen for its bulk characteristics.[49] To be able to optimize the surface chemistry of a material while leaving the bulk properties intact, certain strategies had to be formulated (see below). In reality, most synthetic polymers used in biomedical applications have been developed for their bulk properties and processability, while little or no consideration at all has been paid to their surface properties which are primarily responsible for instigating the biological response. This has led to the development of different surface treatments and coatings that have been tentatively applied to biomedical-grade PUs (Chapter 7). However, an alternative approach to modulate the surface properties of PU materials is to use additives with specific surface functionality. In fact, some researchers began to study polymers and polymer compounds that would develop the desired surface chemistry, and possibly eliminate the need of post-fabrication surface treatment (such as plasma treatments and plasma polymerization) and, perhaps, simplify the manufacture of device components. As a result, surface-modifying additives (SMA) have been proposed as well as the more recent developments of surface-modifying macromolecules (SMM) and surface-modifying end groups (SME). It should be noted that SMEs are not strictly additives since they are not incorporated free within the polymer matrix, but rather they are coupled to the polymer backbone.

3.3.4.1 Surface-Modifying Additives (SMA)

Surface-modifying additives are components which, when added in low concentrations (approximately 1%) to a material during fabrication, will spontaneously rise to, and dominate, the surface.[50] The driving force to concentrate the SMA at the surface, after its blending with the polymer, is basically energetic: the SMA should reduce the interfacial energy. It has been shown that the surface properties of a polymer can be modified through the addition of small amounts of a second polymer that is surface active in the base polymer.[51,52] To do this, two factors must be taken into account. Firstly, the magnitude of the difference in interfacial energy between the system with and without the additive at the surface will determine the strength of the driving force leading to a SMA-dominated surface. Second, the chain mobility of the bulk material and the additive molecules within the bulk will determine the rate at which the SMA reaches the surface or, if it will get there at all. The amount of additive required to achieve complete surface modification is crucial. It is a delicate balance between having a necessarily small but sufficient amount of additive so as not to affect adversely the bulk property of the base polymer, and to maintain complete surface coverage of the polymer artefact. Complete surface saturation was reported to be generally achieved at a bulk concentration of less than 1% (wt./wt.) of the "additive" polymer.[53] However, very little investigations have been carried out

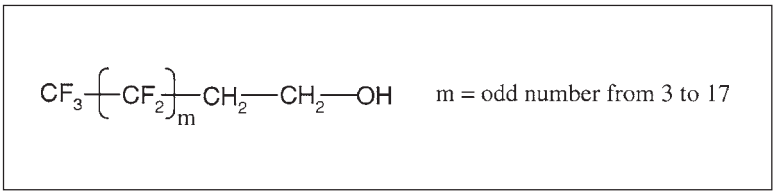

Figure 3.7. Chemical structure of monofunctional fluorinated alcohol (BA-L).

on this particular concern. There is still some controversy concerning the assumption that "surface saturation" can be achieved using polymer additives (SMA, SMM or SME).

Although surface activity is a key parameter in determining whether or not an additive is suitable for a particular application, there are other important requirements to consider too. Generally speaking, SMAs are diblock copolymers that have a structure which is amphiphilic, that is, certain groups or segments will have attraction for the major polymer component of the blend, while other portions of the molecule will have little attraction for the base polymer, which is of lower polarity. In fact, the block that is more soluble in, or compatible with, the bulk material should anchor the other block which has the required surface property but is incompatible with the bulk material. A sufficient period of curing and/or annealing is generally required to affect migration of the "additive" polymer to the surface. As indicated by Ward et al,[53] the low solubility of the "additive" as a whole is important in promoting surface activity. Indeed, the efficiency of the "additive" as a surface-modifier increases as its solubility in the base polymer decreases. Since most of the polymers are melt-processed, additives must generally have equal or greater thermal stability than that of the base polymer to survive the polymer forming operations such as injection molding and extrusion, and during some sterilization processes.

Brunstedt et al[54] have studied protein adsorption on a series of additives that were dispersed in, or coated on, polyether-urethane-urea (PEUU). The additives used were the antioxidant Santowhite (see Fig. 3.5 for structure) and Methacrol® 2138-F, an antifoaming agent (see Fig. 3.5 for structure). Methacrol® is a copolymer of diisopropylaminoethyl methacrylate (DIPAM) and decyl methacrylate (DM). XPS and contact angle studies have revealed that PEUUs containing Methacrol®, and a mix of Methacrol® and Santowhite, were capable of significant dynamic surface reorientation. These findings suggest that Methacrol® is surface active whereas Santowhite is largely surface inactive. Moreover, Brunstedt et al[54] found that the presence of Methacrol® reduced the adsorption of proteins when compared to the control (no additive). The effect of Methacrol® in reducing protein adsorption was most apparent for the adsorption of factor VIII. On the other hand, fibrinogen adsorption on PEUU stabilized with 0.0% DM and 4.8% DIPAM increased by 33% when the same PEUU was stabilized with 4.8% DM and 0.0% DIPAM. Similar observations were reported for IgG, factor VIII and Hageman Factor (Factor XII). However, a reduction in protein adsorption only is not necessarily indicative of a better surface, i.e., it might not improve the clinical performance of the material.

However, in some cases, additives that are normally used as lubricants or plasticizers are also surface-active compounds and have been considered also as surface-modifying additives (SMAs). For example, as mentioned previously, both Briggs[34] and Ratner and Paynter[32] have reported the presence of ethylene-bis-stearamide (a lubricant) on the surface of the Pellethane™ material. Should we consider ethylene-bis-stearamide as a biomedical-grade SMA? And, if so, would it have a beneficial or detrimental effect inside the human body? In view of the conflicting findings of Ratner and Paynter[32] and Bandekar et al[35] between platelet activation and the presence of ethylene-bis-stearamide (as discussed above), we must examine further the implications of its use within the overall mechanisms of biological response. The suitability or other-

wise of ethylene-bis-stearamide, and other SMAs, for biomedical applications cannot be easily addressed. These molecules were primarily designed to facilitate polymer processing: the long term effects of their use as SMAs, and the way they modulate the biological response of PU materials must be further investigated.

Even though some SMAs may have beneficial effects on the mechanical properties and/or biological response of some PU materials, their limitations should be noted. A major limitation to their use is that of leaching. For example, Ratner et al[33] found that Advawax® was easily extracted from the material after exposing the polymer to water. Leaching of SMAs might result in the loss of the protective coating of the polymer but, more importantly, their release into a living organism environment is of great concern as it may induce undesirable systemic and/or local tissue response. Furthermore, using a polymeric SMA as a minor ingredient requires also due care and attention to the manufacturing methods employed. For example, with methods that involve dipping a mandrel into a polymer solution, the SMA can inadvertently be selectively removed from the dipping bath. The consequence of such an uncontrolled loss of SMA from the solution could lead to non-uniform coverage of the surface of the material and, in extreme cases, to incompatibility of the material with the host environment. To overcome some of these limitations, two other approaches have been advocated: the surface-modifying macromolecules (SMM) which have been introduced by Santerre's group and the surface-modifying end groups (SME).

3.3.4.2 Surface-Modifying Macromolecules (SMM)

In an effort to produce a material that can be blended with PU materials, to achieve different surface chemistry of the PU while leaving the bulk phase relatively unchanged, Santerre's group[55] developed the surface-modifying macromolecules (SMMs) method. SMMs are known to contain two segments which differ in their compatibility with the base polymer. The polymer segment with the lower compatibility with the base polymer (PU) provides a driving force for the migration of the SMM toward the surface, whereas the more compatible part of the SMM acts as a linker to the base polymer via noncovalent interactions and physical entanglements.[55,56] It was anticipated that by tailoring SMMs to the base polymer the final polymer formulation will carry the SMM chemistry at or close to its surface, thereby effecting the desired biostability and biological response.[55] Tang et al[55] reported that because of their amphiphilic nature, SMMs would not only migrate towards the surface of the polymer mixture but also stabilize themselves within the PU.[55]

In an attempt to stabilize polyester-urethane-urea, Tang et al[55,56] combined SMMs containing 1,6-hexanediisocyanate (HDI) to the base formulation of the PU. This particular diisocyanate was selected principally because other diisocyanates, such as TDI and MDI, are suspected to have potentially carcinogenic effects in the human body. The second segment was made using two polyols of similar molecular weight of 1000 namely, polypropylene oxide (PPO) and polytetramethylene oxide (PTMO). SMMs were synthesized similarly using the prepolymer method. The final step was different, however, in that chain extension was not performed. Instead, the prepolymer was end-capped by a monofunctional fluorinated alcohol (BA-L) (see Fig. 3.7 for structure).[55,56]

Using XPS analyses, Tang et al[55,56] found that all mixtures of 5%-SMM in PLC/TDI/ED-based PU showed an increase in the fluorine content towards the surface suggesting surface enrichment of SMM to a depth of about 10 nm from the surface. Indeed, XPS data clearly indicated that the tails of the SMM reside at the surface of the PU. However, as clearly reported in Chapter 1 of this book (Section 1.6, Surface characteristics of polyurethanes), it is fairly well anticipated that the hydrophobic moiety of the SMM would be detected by XPS, since the vacuum used in XPS is a non-polar environment. Tang et al[55] also reported that SMMs gener-

ated a non-wettable surface similar to that of Teflon®. It should be pointed out, again, that surface reorientation can take some time (see Chapter 1, Section 1.6.7); the time needed for the surface to reequilibrate with its environment could be up to 25 hours when a dry polyurethane is hydrated. Therefore, it would have been interesting to compare contact angle over time. Differential scanning calorimetry (DSC) of a mixture of SMM and the PU showed that, at 5% (wt./wt.) SMM in the base polymer, the additive had no detectable effect on the PU structure. Tang et al[56] reported also that these fluorine-containing macromolecules can possibly provide a masking effect on the functional groups contained within the various segments of the PU, which would otherwise be susceptible to hydrolytic enzymatic degradation. In fact, they found that some SMMs were able to enhance the hydrolytic stability of a polyester-urethane-urea exposed to cholesterol esterase (CE), while other SMMs resulted in the generation of more degradation products. These observations clearly indicate that the effects of SMMs are not universal and a preliminary assessment of the compatibility of the substrate would be required first. It is clear from the above discussion that the most important difference between SMA and SMM lies in the macromolecular size of the latter.

3.3.4.3 Surface-Modifying End Groups (SME)

Surface-modifying end groups (SMEs) were designed to overcome some of the limitations of SMAs. For PU systems, end groups are coupled (see Fig. 3.6) to the backbone polymer during synthesis via a terminal isocyanate group.[53,57,59] The use of different end groups could allow the formation of different surface chemistries and might enable to some degree the attainment of surface characteristics normally associated with hydrocarbons, silicones and fluorocarbons.[53,59]

Ward[50] claimed that the use of oligomeric end groups, at typical concentrations, can presumably leave the original polymer backbone intact while increasing the overall molar mass. He also suggested that surface modification via oligomeric SMEs can be easily adapted to the synthesis of any polymer that can incorporate a low molecular weight, monofunctional end group. In fact, it was suggested that SMEs are expected to have a slight negative effect on processability[53] whereas certain end groups can even enhance processability by facilitating the wetting and spreading of the base polymer on mandrels or substrates to be coated. Some SMEs can also enhance processability by improving factors such as mold release, mold filling, surface smoothness, coalescence of water-based emulsions, and adhesion to substrates.

Since SMEs can greatly influence the surface or interfacial layer of a medical device, they may be helpful also in enhancing the biostability and biological response of the base polymer by providing a more stable interface to the body. Ward et al[53] postulated that, in principle, some surface-related properties may be influenced by SMEs. For example, they found a correlation between the nature and molecular weight of SME and the water contact angle when SME was added to Biomer™ (MDI/PTMO/ED). In fact, polymers incorporating different hydrophobic end-groups, e.g., hydrocarbon, silicone and fluorocarbon, showed increased water contact angle relative to the pure PU system.[53,58] Again sufficient time is required in order to allow reorientation of the polymer chains before contact angle measurement. In addition, hydrocarbon-based SMEs gave tensile strengths that were little better than fluorocarbon-based SMEs; both however gave better values than the silicone-based SMEs. On the other hand, the ultimate elongation and initial modulus were all very similar for the different SMEs prepared.[53,58] These findings show that SMEs could influence the mechanical properties of the base polymer and are currently under further investigation to examine their potential for improving the biostability of implants.[59] The reader is referred to Chapter 6 of this book for further details.

3.4 Conclusion

The study of additives for biomedical applications is an important field of endeavor in which the analytical chemist is frequently called upon to separate, identify, determine and characterize the multitude of additives in commercial polymer formulations. The analytical methods and skills needed are not within the scope of this Chapter but interested readers should consult other works such as *Manual of Plastics Analysis* (Plenum Press), *Plastics Additives: An A-Z Reference* (Chapman & Hall), or *Finishes in Textiles: Identification* (AATCC Test method 94-1992).

This Chapter provides some direction as to the role of additives in the field of biomedical applications of PU. It is not yet clear, however, whether or not additives have a beneficial or detrimental effect on the biological response and biostability of the base material. For example, it can be presumably postulated, as suggested by Vermette et al,[60] that some of the additives may provide a shield against the biological attack. However, this claim remains unsubstantiated. Moreover, the question of leaching of additives into the biological media needs to be fully addressed because of possible negative physiological and immunological responses of the host organism which, in turn, would adversely affect both the short and long term success of a device or an implant. Further investigations into the use of additives for the production of biomedical-grade PUs is necessary to satisfy these demanding requirements. A proper understanding of chemical and physical properties of additives, their effect on the mechanical properties and behavior of the polymer resin, and the combined additive-resin effect(s) on the host organism would pave the way for a better understanding of the needs and requirements of future medical devices and implants for the wide range of applications open to PU elastomers.

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Chapter 4

Biocompatibility of Polyurethanes

Yves Marois and Robert Guidoin

4.1 Introduction

In the last 50 years, the development and the conception of biomaterials used for the construction of prostheses and medical devices has expanded very rapidly. A wide variety of biomaterials are now commonly implanted in the human body for the treatment of various diseases such as heart failure, atherosclerotic diseases, aortic aneurysm, ear dysfunction and cataracts. They are also used to augment tissue, namely, bone, muscle, skin and breast either after trauma or for cosmetic reasons. Biomaterials are the basic constituents of prostheses or implants which are designed to restore and support functions of organs and tissues as well as substitute and consolidate tissue, ligamentous, articular and osseous structures. They also can be used to stimulate the repair and healing of nerves, tissues and wounds in a precise and predetermined timeframe or for a period of time exceeding the life expectancy of the recipient.

The type of application, the organ function which needs to be restored, and the time of implantation are important factors dictating the choice between a material requiring long-term stability or one that will be bioresorbed. All biomaterials must meet a number of criteria and satisfy necessary requirements to comply with those of regulatory agencies for clinical use. The materials used in the design of prostheses and implants must be purified, constructed and sterilized using conventional methods. They should not contain impurities, initiators, additives, stabilizers, emulsifiers or coloring leachables that would cause in vivo reactions. This is further discussed in Chapter 3.

Biomaterials must exhibit mechanical, physical, or electrical properties for their application. Surface properties are also important and should be accounted for by any investigator (see Chapter 7). Surface characteristics that should be considered are hydrophilicity, charge, polarity and energy, heterogenous distribution of functional groups, wettability, water absorption and chain mobility. As well, morphological or topographical aspects including texture, smoothness and roughness should be accounted for.

However, all these properties may be modified under a physiological environment because they will be subjected to the following components: the duration of implantation, the temperature of the body and the pathological conditions at the implant site. Biomaterials must maintain thier biostability and biofunctionality during implantation in order to avoid graft failure. In other words, the function of the organ or tissue must be guaranteed and the materials must maintain their mechanical, chemical and structural properties for long-term use.

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Finally, any biomaterial and its degradation products, if biodegradable, should not induce any deleterious reactions or disturb the biological environment. This requirement has been described under the general heading of biocompatibility. Section 4.2 will discuss how the use of the word has been collectively employed to describe a number of in vitro or in vivo tests, both simple and complex, in order to label any given material as biocompatible. However, this terminology is often excessive, inaccurate and misleading. At present, there is a need to clarify the definition of biocompatibility, as several authors consistently overuse the word, creating intolerable confusion. The use of the word needs to be brought back into a better perspective.

4.2 Biocompatibility

4.2.1 Definition of Biocompatibility

The selection of the materials used in the construction of prostheses and implants is basically focussed on their ability to maintain mechanical, chemical and structural integrity and on various characteristics which allow this function to substitute any organ or tissue properly and exhibit safe, effective performance within the body. For a number of years, biocompatibility has been defined as the ability of a material to perform with an appropriate host response in a specific application. Under this definition, which appears relatively ambiguous and vague, any material used satisfactorily in orthopedic surgery may be, for instance, inappropriate for cardiovascular applications because of its thrombogenic properties. Another widely used material may have deleterious effects if used under stress-strain conditions because of wear particles generation. Biocompatibility is by no means a measurable entity. One may simulate observing the biocompatibility of a material by comparing its behaviour to reference materials in standardized experimental conditions.

In a clinical context, the behaviour of autologous grafts or tissues becomes the gold standard for any given material to be considered biocompatible. In fact, biocompatibility is a complex notion which has to be interpreted as a series of events or interactions happening at the tissue/material interface whose outcome must be satisfactory or optimal. These interactions are influenced by intrinsic characteristics of the materials but also by the confrontational circumstances namely, the biological site destined for implantation, and most of all, the inflammatory setting induced by the surgical act and maintained by the presence of the material. In the last few decades, considerable progress has been made regarding the tissue/material interactions upon implantation which allowed the identification of materials and surface characteristics which are more biocompatible. Scientists are now elaborating new strategies to facilitate the integration of various prostheses and implants to their respective organ or tissue sites by proposing new bioactive and biocooperative materials.

4.2.2 Biocompatibility Tests

A few decades ago, it was generally thought that biomaterials destined for implantation had to be chemically inert and consequently were believed to play no major role in any physiological process. However, it has recently become very clear that materials which stimulate prosthetic incorporation in the tissue offer considerable advantages and are likely to be more successful than those that do not heal satisfactorily. With the development of sophisticated analytical techniques, progress has been made to elucidate which molecular or cellular responses are critical in host/material reactions and what surface characteristics and/or polymer chemistry are important in mediating these reactions toward host tolerance. It is only through local tissue response that a dynamic interaction will occur between activated inflammatory cells and

the secretion of cytokines to stimulate angiogenesis, smooth muscle cells and fibroblast proliferation and collagen production in a cascade of events leading to the encapsulation and satisfactory healing of prostheses or implants.

With the increasing number of synthetic materials being introduced into the field of medicine, there is an increasing demand for more discriminating tools to evaluate their safety and efficacy. Any severe reactions by the host toward the biomaterial will probably result in failure. Consequently, the need for standardized methods and protocols for assessing the biological response of materials has never been greater. A list of tests being used to assess the biological response of materials is shown in Table 4.1.

At present, a variety of different types of cell culture methods are frequently used. They involve in vitro studies which may assess the morphology, cytotoxicity, or secretory functions of different cell types (usually those that will be in contact with the material during implantation). This may be achieved by either a direct or indirect contact assay, or by adding a diluted extract from the biomaterial to the culture medium. Other types of tests determine various cell functions such as cell membrane integrity, replication, phagocytosis, the production of reactive oxygen species, secretion, activation, chemotaxis, and chemokinesis.

Blood contact assays have been developed and include tests investigating the adhesion or activation of blood cells, proteins, and macromolecules such as those found in the complement or coagulation cascades. Other biocompatibility tests have been tentatively proposed and involve analytical testing or observations of physiological phenomena, reactions or surface properties attributable to a specific application such as anti-bacterial surface testing, protein adsorption characteristics, calcification or mineralization processes.

In spite of this plethora of possible test methods, the protocols currently required by North American and European regulatory agencies for the evaluation of biocompatibility do not incorporate such quantitative test procedures aimed at determining the nature and intensity of cellular reactions (Table 4.1). Only qualitative assessments are recommended, and these involve the estimation of acute toxicity through the gross microscopic examination of tissue, which relies on the subjective expertise of investigators in identifying cell morphology and the severity of the reaction. While such toxicity testing is essential, this method alone should not be used when evaluating the biocompatibility of a material. Before claiming the biocompatibility of one given biomaterial, one must perform a series of tests requiring the evaluation of cell compatibility, toxicity, mutagenicity as well as additional in vitro tests for a specific application which will guarantee the function and inocuousness of the device. It is generally accepted that in vitro tests are essential prior to conducting in vivo trials. Such preliminary screening tests are quick to perform, reproducible and inexpensive. While recognizing that their main limitation is their relative simplicity compared to the complex interactions that occur in vivo, their sensitivity in discriminating between biocompatible and nonbiocompatible materials (with proper control materials) can be used to reject unsatisfactory materials before performing in vivo implantation studies. Thus, there is a need to find the most appropriate and sensitive in vitro tests which correlate well with the in vivo response.

In order to determine the biocompatibility of materials used in the construction of synthetic vascular prostheses, we recently attempted to establish a direct correlation between such in vitro results and the in vivo healing of arterial grafts. The usefulness of six different in vitro tests in predicting the in vivo healing performance of vascular grafts was evaluated in those grafts known to exhibit a variety of different healing responses as observed during previous in vivo trials in a canine thoraco-abdominal bypass model. The results were able to demonstrate that some in vitro tests, namely, polymorphonuclear cell (CD_{18}) and lymphocyte (IL-2) receptor expression assays, direct contact assay using endothelial cells and an extract dilution assay on mouse fibroblasts were useful in predicting the in vivo behaviour of vascular prostheses. Of particular interest were the uncleaned arterial grafts which had shown poor healing in previous

Table 4.1. Test methods used to evaluate biological response

Test Methods Used To Evaluate Biological Response

FDA tests	**In Vitro Testings**				**In Vivo Testings**	
	Cell culture		Blood response	Others	Tissue compatibility	Implantation
Implantation	Type of cells	Tests	Coagulation tests	Bacterial adhesion	Subcutaneous	Subcutis
Hemolysis	Fibroblasts	Replication	Complement	Protein adsorption	Intramuscular	Blood
Acute systemic toxicity	Monocyte	Proliferation	Platelet adhesion and activation	Calcification	Intraperitoneal	Bone
Pyrogenicity	Macrophage	Adhesion	Fibrin(ogen) adhesion and activation	Mineralization		Cornea
Mutagenicity	Endothelium	Density	Erythrocytes			Reproduction
	Osteoblast	Morphology	SEM observations			Heart
	Urethelial cells	Phenotype				Arteries
	Gingival cells	Receptor expression			• Wound healing	
	Epithelial cells	Secretion molecules			• Graft healing	
	Reproductive cells	mRNA expression			• Inflammation	
					• Exudate	
					• Enzymes	
					• Cell receptor expression	
					• Cell secretion molecules	
					• mRNA expression	
					• Blood tests	
					• In situ hybridization	

in vivo studies and induced elevated expression of CD_{18} and IL-1 receptors. These grafts caused poor endothelial cell migration and viability and generated a cytotoxic response from fibroblasts in an extract dilution assay.[1]

4.3 Blood Compatibility of Polyurethanes

4.3.1 Decade 1970-1985

With the pioneer work of Boretos in the late 1960s [2] and of Lyman early 1970s,[3] who both claimed the blood compatibility of polyurethane-urea polymers, these elastomer materials have since been widely used for biomedical applications such as the artificial heart,[3] intra-aortic balloons,[4] pacemaker leads,[5] heart valves,[6] and hemodialysis membranes.[7] It was soon realized that blood compatibility was intimately related to their microphase separated structure composed of hard and soft segment domains.[8,9] The first significant studies on the blood response characteristics of polyurethanes (PUs) were reported in the early 1980s.[10] The first emphasis was put on the effect of chemical composition with the studies of da Costas et al on a series of segmented polyurethanes of various surface composition using three different polyethers as soft segments, namely, polytetramethylene oxide (PTMO), polypropylene oxide (PPO), and polyethylene oxide (PEO), and two diisocyanates, 2,4-toluene diisocyanate (2,4 TDI) and 4,4'-diphenylmethane diisocyanate (MDI). Using a simple homemade in vitro test system, the platelet retention index of various PTMO, PPO and PEO synthetized PUs showed lower indexes for PEO-PUs as compared to PTMO-PUs, PPO-PUs or hard segment analogs.[11] The relationship between blood response and hard/soft segment concentrations was further confirmed with Biomer™[12] and other studies which showed that the hard segments of PUs were highly thrombogenic in platelet retention experiments.[13] Two reasons were proposed to explain the high thrombogenicity of hard segments: first, the high crystallinity of the polymers and second, they exhibit surfaces with strong hydrogen bonding. Merrill et al suggested that surface mobility may play a role in the interaction of polymers with biological systems.[13] Using scanning electron microscopic techniques, Takahara et al also demonstrated that the platelet adherence and morphology on PU films was significantly modified by the size and characteristics of the microphase separation in the polymer.[14]

In an attempt to reduce the thrombogenic potential of polyether-urethanes (PEUs), Lelah et al investigated the effects of ionic domains on platelet and fibrinogen deposition at the surface of PEUs.[15] On the hypothesis that negatively-charged surfaces show better blood compatibility, they chemically modified their chain extender N-methyldiethanolamine (MDEA) into zwitterionomer, anionomer, and cationomer-type polyurethanes as compared to neutral PEUs. As expected, cationization of PEUs increased their acute thrombogenic potential in terms of platelet and fibrinogen adhesion whereas zwitterionic surfaces (positive and negative charges) were shown to be more thromboresistant than anionomeric surfaces. They explained their results by the embedding process of positive ions in the bulk and the preferential presence of negative ions exposed at the end of the short side chain on the surface. Another explanation was also given for this phenomenon. Lelah et al suggested that a synergistic effect of both charges (zwitterionomer-PEUs) on protein adsorption created a favorable surface for improved blood compatibility.[15] Although not frequently discussed, one may have to take into consideration the effect of the isoelectric point (pI) of the protein and pH of the environment (to determine the net charge of the protein), as well as the zeta potential of the PU surface (to determine the net charge bearing on the polymer's surface) when designing these experiments.

It was also during the 1980s that the concept of hydrophilicity of polyurethanes was first discussed. Hydrophilicity describes a surface characteristic promoting water absorption in the

polymer which has been associated with blood response. An optimization of the hydrophobic-hydrophilic ratio as surface modification has been shown to improve blood compatibility by reducing platelet adhesion.[14,16,17]

Lelah et al have also examined the hydrophilic status of their ionized polyurethanes and found contrasting results. In contrast to neutral more hydrophilic PEUs, the slightly hydrophilic cationomer PEU exhibited greater platelet and fibrinogen uptake than its neutral parent PEU. They finally concluded that the simple concept of hydrophilicity alone should not be used to correlate with blood responses.[12] In fact, microporous vascular grafts made of hydrophilic polyether-urethane-urea (PEUUs) were shown to induce a low level of hemolysis in vitro but exhibited a high rate of occlusive thrombosis in vivo.[18-20]

4.3.2 Chemical, Morphological, and Structural Modifications (Decade 1988-1998)

In the late 1980s, a number of studies investigating various chemical, morphological and structural modifications to PUs have shed some light on the blood response induced by these polyurethanes. Newly developed and innovative methods of synthesis and surface modifications such as chemical incorporation, grafting, and coating techniques were attempted with the aim of increasing blood compatibility of polyurethanes.

4.3.2.1 Extraction Methods

Extraction methods on some polyurethane block copolymers have been found to improve the blood compatibility of an experimental polyurethane-urea material containing higher proportions of soft segment than Biomer™. This high soft segment polymer was precipitated and extracted with methanol prior to recast from solution. The ex vivo platelet deposition levels on the extracted surface were significantly lower than that of the nonextracted material.[21] Biomer™ submitted to the same extraction process gave similar results. However, Lelah et al were unable to determine if the extraction process modified the platelet response by removing low molecular weight oligomers from the block copolymer or if extraction removed low molecular weight additives.[21]

The results of another study examining the solvent cast and acetone-extracted Biomer™ indicated that the presence of an extractable fraction, when removed, also improved the compatibility of the material.[22] This study was followed by that of Grasel et al who investigated the effects of extraction on the blood response of a standard polyurethane block copolymer containing no additives, stabilizers, or processing aids.[23] Three well-known extraction media were retained, namely, methanol, toluene and acetone. The blood response of the nonextracted and extracted polyurethanes coated on polyethylene tubings was tested in a canine ex vivo shunt experiment by measuring ^{111}In-labelled platelets and ^{125}I-labelled fibrinogen deposited on the surface. Results showed no significant difference in both platelet and fibrinogen deposition following extraction in either media. As extracted Biomer™ was previously shown to have improved blood compatibility,[21] these results were attributed to a difference in chemistry (Biomer™ having urea functionality) or to the presence of an unknown agent in Biomer™.

4.3.2.2 Chemical Composition

In recent years, the chemical composition of PUs was modified by several investigators with the intention of improving blood compatibility and discovering which factors influence most blood contacting responses. One method was to synthetize PUs or segmented polyether-urethane-ureas with highly hydrophilic soft segments. Producing PEUUs with MDI

and PTMO, Takahara et al introduced long hydrophilic side chains with sodium sulfonate of various concentrations or methoxy end groups into the PEUU soft segment. Results demonstrated that platelet and fibrinogen uptake was lower with the least concentrated sulfonated PEUU whereas long side chain diol containing methoxy end group PEUU was more thrombogenic than a PEUU having a comparable concentration of sodium sulfonate groups.[24] Further investigations on the influence of the chemistry of polyol on blood interactions were carried out by the group of Cooper. They investigated different PUs containing various polyol constituents PEO, PTMO, polybutadiene (PBD), hydrogenated-PBD (HPBD) and polydimethylsiloxane (PDMS), as well as all interesting materials with favourable blood-contacting properties. These PUs were prepared by conventional two-step solution polymerization. Using a canine ex vivo shunt experiment, PU-coated polyethylene tubings were tested for short term platelet and fibrinogen deposition. PEO-based PU was found to be more thrombogenic than nonpolar HPBD-based PU with PDMS-based PU being the least thrombogenic.[24] The results with PEO were found to be similar to those published by Okkema et al,[25] but were in contrast to those reported by da Costas et al[11] whose platelet counting method might be arguable in terms of reproducibility and accuracy. The relatively good results observed with PDMS-based PU were imparted to the hydrophobic nature of the polymer surface. Here again, the authors concluded that the initial rate of platelet adhesion increased with an increase in hydrophilicity of the various polyol used in the synthesis of the PUs, thus, confirming that the blood compatibility of polyurethanes may depend on a combination of factors including microphase separation, surface heterogenicity, and surface hydrophilicity.[24]

In a poorly reported study, Affrossman et al studied the effect of molecular weight (Mw) variation of different soft segments on the blood response of two series of PEUs synthesized with PEO or PTMO while the hard segment (MDI) and the chain extender (not stated) were kept constant. In a questionable in vitro blood chamber experiment, they reported data on platelet behaviour for PTMO polyurethanes while omitting those of the PEO polyurethanes. They found no significant difference between PTMO-based polyurethanes of molecular weight ranging between 650 and 2000 Mw and provided no substantial conclusion.[26]

Other investigators developed innovative sulfonated polyurethanes on the basis that functional groups incorporated in the PU may impart some degree of anticoagulant activity or as others reported, heparin-like character or activity. These polyurethane materials have been shown to display varying degrees of antithrombotic activity.[27-30] Santerre et al synthesized sulfonated PUs having various sulfur contents (1.4-3.1%) and containing lysine or aspartic acid. Thrombin time experiments showed no significant heparin-like properties to sulfonated PUs with lysine or aspartic acid although an increase in thrombin time was shown for those sulfonated PU with increased sulfonate content.[31] Their findings were in contrast to those reported for sulfonated polystyrene resins.[32]

More recently a novel blood-compatible polymeric material, 2-methacryloyloxyethyl phosphorylcholine (MCP), was investigated for its surface blood compatibility properties by blending in PU. Ishihara et al have incorporated various MCP polymers copolymerized with cyclohexyl methacrylate or 2-ethylhexyl methacrylate (EHMA) into Tecoflex® 60 using the same solvent. Following incubation in whole blood or platelet rich plasma (PRP), platelet adhesion was assessed by scanning electron microscopy (SEM). Examination of photomicrographs revealed a reduced adhesion of platelets at the surface of PU-MCP membranes with MCP composition as low as 5 wt.%. The authors suggested that a reduction of plasma protein adsorption on PU-MCP membranes might explain their results.[33,34]

With the aim of developing polyurethane biomaterials which are more stable in vivo, PUs were prepared without polyester soft segments. Li et al introduced new PUs based on cholesterol and phosphatidylcholine analogous moieties. Polybutadiene (PBD), polyisoprene (PIP), hydrogenated-PIP (HPIP) glycols were used as polydiol soft segments in a conventional two-step

solution polymerization procedure using MDI and two additional chain extenders as hard segments.[35] Qualitative results of platelet deposition after 60 min of incubation in PRP and viewing under SEM revealed that the apparent number of platelets as well as the morphological changes were the lowest for HPIP-PU while maintaining excellent mechanical properties. The hydrophobic nature of the hydrocarbon-based polydiols was the only argument used by the authors to explain their results.

In a second study, Li et al were interested in blending phospholipid diols with long chain alkyl groups (C_{16} to C_{20}) because of their claimed blood compatibility, excellent mechanical properties, and nonether soft segment composition. PUs were synthesized using the previously investigated HPIP and four different phospholipid diols as polyols with MDI and BD as hard segments. Again, the apparent number of platelets and their morphological changes after incubation in PRP for 60 min were assessed by SEM. The results showed a better trend of low adherent platelets on phospholipid PUs as compared to PU alone or BioSpan® as controls. The authors suggested better blood compatibility properties for HPIP-based phospholipid PUs with saturated long chain alkyl groups (C_{16}, C_{18}, and C_{20}) and claimed their potential for wide biomedical applications.[36]

Finally, in a recent study, a solution polymerization was used to prepare PU and α-hydroxyethyl methacrylate (HEMA)-terminated PU (HPU) interpenetrating polymer networks (IPNs), with PU based on two different polyether-type polyols of various Mw.[37] Different wt.% of HPU were used in the preparation of IPNs and tested for their blood response. A relative index platelet adhesion (RIPA) was used as a hemocompatible parameter. The amount of whole blood platelets was calculated on PU membranes and compared to that of glass plate in a ratio of adhered platelet on PU/adhered platelet on glass. Results showed lower platelet adhesion with IPNs containing 25 wt.% of HPU and interpreted as an optimal hydrophilic/hydrophobic domain ratio induced by changes in surface soft segments to hard segment ratio. XPS analysis confirmed these results by showing that RIPA correlated well with the surface O/N and C-O-C ether group ratios.

4.3.3 Surface Modifications of Polyurethanes

In the last decade, a number of surface modifications have been proposed to improve the antithrombotic properties of polyurethanes bearing in mind that the primary factor in determining the blood compatibility of any materials is the material surface chemistry. The methods include coating or impregnation processes, photo-chemical immobilization reactions and various grafting techniques using surface derivatization or oxidation, ionization, or polymerization.

4.3.3.1 Grafting Techniques

In a chronic ex vivo arterio-venous shunt experiment, McCoy et al studied six different materials simultaneously in terms of radiolabelled platelet deposition and SEM viewing.[38] A sulphonated PEU and a C_{18} alkyl grafted derivative of PEU were compared to the same PEU, Biomer™, low density polyethylene (LDPE), and PDMS as controls. The results demonstrated that the alkyl grafted C_{18} PEU was the most thrombogenic of all materials in terms of platelet deposition. Their findings were in disagreement with those of Grasel et al[39] and Li and Nakaya[36] although the platelet adhesion test differed slightly. Again, sulfonated PEU materials appear to exhibit nonthrombogenic behaviour as previously reported.[15,27,28]

The blood response toward sulphonated grafted polyurethane surfaces obtained by surface derivatization was further assessed in vitro and in vivo. The oxidizing properties of Cerium (IV) ions were used to graft 2-acrylamido-2-methylpropane sulphonic acid (AMPS) on Pellethane™. In a series of blood incubation tests, AMPS-PU was shown to reduce the

generation of fibrinopeptide A, β-thromboglobulin and C_{3a} as well as decreasing the adherence of platelets and neutrophils in vitro. However, conflicting results were observed in vivo as a greater amount of adherent thrombus formation and increased attraction of macrophages to the material were observed with AMPS-PU. Although confering heparin-like characteristics to AMPS derivatization grafting on biomaterial surfaces, the authors expressed caution in extrapolating in vitro results to the in vivo situation.[40]

In another oxidation reaction, this time by ozone and peroxides adsorption, a surface-grafted polymerization of acrylamide and dimethylacrylamide (DMAA) on polyether-urethane was attempted by Inoue et al and further evaluated by ex vivo arterio-venous shunt and in vivo by catheter tube implantation in the inferior vena cava of rabbits.[41] Their findings revealed that the DMAA-grafted PU surface exhibited less clot formation than the nongrafted surface. They suggested that the better blood compatibility of the DMAA-grafted PU may be due to weaker interaction of the grafted material with the blood components as frequently reported for other materials.[42,43]

Phosphorylcholine groups were also attached to polyether-urethane surfaces by a photo-chemical method using UV irradiation. As previously reported by Ishihara et al,[33] phosphorylcholine adsorbed PEU surfaces exhibited prolonged clotting times and reduced platelet adhesion with increased concentrations of phosphorylcholine at the surface compared to unmodified PEU surfaces.[44] Photo-oxidation should be carefully assessed before using UV irradiation of PU materials.

Finally, Saito et al[45] have recently reported the grafting of photo-reactive alpha-propylsulphate-poly(ethylene oxide) (PEO-SO_3) on PU surfaces via a photo-chemical technique. Using a flow-controlled chamber method, they showed anti-factor X_a activity on the grafted surface as well as reduced platelet adhesion compared to unmodified PU surface. Their study confirms previously reported studies showing the benefits of PEO and of SO_3 in improving the blood compatibility of PU surfaces.[45]

4.3.3.2 Heparin Immobilization

For the past three decades, many investigators have focussed on the development of antithrombogenic polyurethanes by immobilizing heparin either by chemical reaction of functional groups contained in a spacer and introduced in the PU backbone or by a grafting method on graft polymerization of functional groups. Reviewing all the research with heparin would be fastidious and only recent innovative approaches will be discussed here. Through the years, surfaces bearing ionically bound heparin have encountered major difficulties, namely, temporary anticoagulant activity and elution from the surface which may jeopardize long term applications. Heparinizable PUs may be obtain by different methods. First, a chain extension reaction may be performed with chain extenders containing amine on hydrolizable ester groups in their backbone or side chain. Heparin may then be covalently bound by coupling reactions between the free hydroxyl or amine groups on heparin and the free isocyanate group on an hydrophilic spacer such as PEO.[46,47] A second approach consists in the introduction of spacers such as diamine diisocyanate[48] or poly (amino-amine)[49] onto the urethane linkage and subsequent heparinization of the PU by the dipping technique. Among the strategies that increase the immobilizing site, graft polymerization may be an effective method using functional group grafting by oxygen plasma glow discharge followed by graft polymerization. Heparin-immobilized PUs have been prepared by coupling reactions of NH_2 and COOH functional groups with heparin,[50] and more recently with acrylic acid,[51] and acryloylbenzothiazole (AB).[52] Results of the blood compatibility of heparinized-PUs by functional group grafting demonstrated lower activation of platelets and plasma proteins which leads to reduced thrombus formation as compared to nonheparinized functional group grafted PUs. Peripheral blood mononuclear

cells were also shown to adhere less and secrete lower tumor necrosis factor after contact with heparinized PUs. Authors acknowledged that their results with AB grafted on PU surfaces were not promising with regard to blood contact applications. Moreover, the residual bioactivity of heparin was found to be approximately 25%, slightly higher than those reported elsewhere.[47,49,53]

4.3.3.3 Immobilization of Antithrombotic Molecules

Other novel approaches to achieve blood-compatible PUs besides albumin and heparin are the coating or chemical immobilization of various antithrombotic drugs[54] or molecules such as urokinase derivatives,[55] prostacyclin,[56] ADPase,[57] dipyridamole,[58] glucose,[59] and more recently hirudin[60] or silver atoms.[61,62] However, some of these studies have been anecdotal without any in vivo or clinical follow-ups while others are still under development or currently under investigation.

4.4 Biocompatibility of Polyurethanes

In vitro and in vivo biocompatibility studies investigating various polyurethanes for a wide range of applications have focussed on the cellular, enzymatic, and tissue responses to the material. These interactions between cells and synthetic materials have been the subject of extensive research because of the implication of biomaterials on substituting and maintaining organs or tissue functions. In vitro testing procedures are a fundamental part of any material evaluation. They include cytotoxicity tests which investigate the effect of extractables from the biomaterial on cell morphology, viability or function. Direct contact assays using fibroblasts or endothelial cells are also frequently used for the determination of the cellular response toward biomaterials. Among the cell type used for these tests, the fibroblast and endothelial cells are the most commonly used for cytotoxicity tests. Other types of cells may be used and include the neutrophil, lymphocyte, monocyte, epithelial cell as well as specific cells which will be in contact with the biomaterial upon implantation for different applications such as the skin, the blood, the tympanum, and the cornea.

In vivo studies have also been developed to assess the cellular or tissue responses of polyurethanes either subcutaneously, intramuscularly, or intraperitoneally. Again, other implantation sites such as those receiving the implant may be recommended and include the cardiovascular system (artificial heart,[63] vascular grafts,[64-68] stents,[69] sink hole valves,[70] and catheters[41]), the middle ear (tympanic membrane[71]) and the eye (intraocular lenses[72]), the esophagus,[73] ureteric,[74] and biliary tract[75] stents and endoprostheses.

4.4.1 In vitro Biocompatibility Testing of Polyurethanes

The biocompatibility of polyurethanes has been assessed in vitro using various cell culture techniques. For the last two decades, the group of Anderson at Case Western Reserve University has been involved in elucidating the cellular interactions with biomaterials especially those induced by a segmented polyether-urethane, Biomer™. Their studies also included various polymers for comparison purposes. Results demonstrated that Biomer™ induced low monocyte reactivity in terms of interleukin-1 (IL-1) secretion which was found to be similar to PDMS.[76] However, Biomer™ was unable to stimulate fibroblast proliferation.[77,78] These studies were able to confirm the biocompatibility of Biomer™, but also indicated that the intensity of the fibrotic or healing response was low. These findings may have a serious impact on the biofunctionality of prostheses or implants made of Biomer™ upon implantation. In other words, a biocompatible polymer does not necessarily mean that the healing of the device will be optimal and satisfactory.

When reviewing the literature on the in vitro biocompatibility testing of polyurethanes, we found only a limited number of papers describing the biocompatibility of well characterized polyurethanes.[79-82] Other studies reported the compatibility testing of polyurethane devices including catheters,[61,83] stents,[74,84] tympanic membranes,[85] and artificial heart[86] without any detailed description of the chemistry involved in the fabrication of the biomaterial. Most of these studies report good biocompatibility of polyurethanes in general.

When conducting biocompatibility studies on PUs, one must include appropriate control materials or materials with clinical relevance for a specific application. In a vascular application, various polyurethane vascular grafts were compared for cytotoxicity and endothelial cell behaviour using organotypic culture assays. A polyester-urethane arterial graft, Vascugraft® was shown to promote the growth of a continuous monolayer of endothelial cells equivalent to that observed with polytetrafluoroethylene vascular grafts, Impra® and Goretex®,[87] whereas a Tecoflex®-based polyurethane vascular graft exhibited no cell proliferation.[88] Furthermore, a hydrophobic polyether-urethane-urea graft was found to exhibit superior cell migration characteristics than those observed with a hydrophilic graft of similar chemistry, but having different surface texture.[87,88] None of the biomaterials tested were shown to release cytotoxic contaminants. The authors recognized that the surface characteristics of a biomaterial may have a potential effect on cell behaviour.

In another study, Ertel et al reported on the intrinsic toxicity of various materials including a polyether-urethane.[80] Following evidence that no toxic leachables were released from any of the materials investigated, they suggested that the toxicity generated by most of their materials could be attributable to surface morphology or chemistry.

Investigating a number of vascular grafts having different chemistry and surfaces, we have recently been able to identify to some extent which type of chemistry or structure may generate optimal cell growth using an organotypic culture technique.[89] It was found that woven polyester structures showed greater cell growth than polyurethane or PTFE structures having porous structures. As previously reported, textured porous surfaces as opposed to smooth surfaces have been shown to stimulate both cell growth and metabolism. Moreover, cell adhesion is said to be regulated by substrate wettability, surface charge, and roughness.[90,91]

The effect of the surface of prosthetic devices on cell behaviour was further confirmed by Sank et al who found that polyurethane foam such as those found in breast implants are a poor substratum for fibroblast attachment and proliferation when compared to smooth or textured silicone surfaces.[92] In contrast, endothelial cells showed slightly better proliferation properties on the PU surface. Lee et al also suggested that there are two crucial factors which should be considered when determining cell attachment and proliferation properties at the surface of a polyurethane. The first factor is the surface morphology which may be regulated by dispersion of hard segment phase in the polymer and second, the hydrophilic property which is induced by high chain mobility at 37ºC for instance.[81]

At this time, there is no real consensus as to the best surface characteristics to promote optimal cell behaviour on polyurethanes. These elastomers possess attractive chemical and mechanical properties and exhibit relatively good biocompatible characteristics. However, extrapolating in vitro results to the in vivo situation should be done with proper caution.

4.4.2 In vivo Biocompatibility Studies of Polyurethanes

In the last three decades, a substantial amount of in vivo studies has been published on various polyurethanes used in the construction of the artificial heart, heart valves, pacemakers, vascular grafts, stents, endoprostheses and catheters. Although many studies confirmed the excellent mechanical properties and favourable biofunctionality of these devices, only a few reports have been concerned with the chemical stability (oxidation) and the degradation

(mineralization, environmental stress-cracking) of segmented PUs. Consequently, a number of modifications have been attempted to reduce mineralization and oxidation, stabilize the hydrophobic-hydrophilic domains, increase the resistance to degradation and enhance the mechanical properties through innovative polymer synthesis. Recently published, more significant papers which compare PUs of various chemical composition or modification will be reviewed to assess those exhibiting good compatibility after implantation.

As reviewed by Coury et al,[93] it was only during the 1980s that calcification, environmental stress-cracking, and oxidation phenomena in vivo were brought to the attention of scientists involved in the synthesis of PU elastomers and devices. The first interest was in the segmented polyether-urethane Biomer™ frequently used in several biomedical applications. Biomer™ was found to be relatively stable with implantation time [94,95] although some microscopic defects at the surface were reported.[96] It was also demonstrated that Biomer™ induced low inflammatory reactions in vivo.[94,97,98]

A few years later, a study by Zhao et al brought new evidence that adherent macrophages and foreign body giant cells (FBGC) may be involved in the chemical degradation and stress-cracking phenomena.[99,100] The authors demonstrated that the presence of localized surface cracking on a PEU cast film was produced under adherent FBGC (see Chapter 5).[100]

In a more detailed study which included three different Pellethane™ PEUs with varying weight percent in hard segment as well as one PEUU and other materials as controls, Anderson's group indicated, using a theoretical analysis,[101] that an increase in Pellethane™ weight percent of hard segment, surface hardness, and hydrophobicity resulted in an increase in total protein adsorption, density of adherent macrophages participating in FBGC formation and subsequent FBGC density. They suggested that implant surface properties influence the inflammatory response shortly after implantation and modulated further cell activation and proliferation. On the other hand, they recognized that their model was not able to generate any correlations between the materials studied and cell fusion kinetics.[102] In a study on aliphatic polyurethane Tecoflex®-based membranes, Lindner et al demonstrated that an increase of plasticizer weight percent in Tecoflex® membranes corresponded to an increase in the inflammatory reaction shortly after implantation. When compared to PVC, Tecoflex®-based membranes were shown to elicit a greater chronic inflammatory response. The authors suggested that the plasticizer released during the course of implantation might have triggered the inflammatory response.[103]

More recently, the effect of surface charge on the inflammatory response of polyether-urethane was investigated by William's group. In their experiment, the net charge of PEU was modified by introducing different concentrations of sulphonate ionic groups in the PEU backbone giving a range of negative charge. After intramuscular implantation in rats, they reported that the response to PEU was largely inflammatory and that the net surface negative charge had a significant effect on the acute inflammatory response (> 1< 2 weeks) by reducing neutrophil invasion and macrophage activation.[104]

With the view to stabilized PEUs, antioxidant additives such as synthetic compounds Santowhite® and Irganox® have been conventionally incorporated in the polymer (see Chapter 3). However, it has been recognized that the use of these compounds may compromise the biological response if too concentrated or if their oxidation degradation products have undesirable toxicity. The use of a natural antioxidant vitamin E was recently investigated in a PEUU elastomer for surface degradation characteristics, chemical stability and inflammatory response in a cage implant exudate study. It was shown that vitamin E prevented surface cracking and chemical degradation up to five weeks in vivo. However, after 10 weeks, an estimated 18% chemical degradation was observed for the PEUU with vitamin E whereas 82% chemical degradation was reported for the PEUU without antioxidant. Leukocyte count and adhesion studies revealed that the inflammatory response was lower on the PEUU with vitamin E than on the PEUU without antioxidant.[105]

In recent years, a number of modifications or substitutions of the soft segment component have been attempted in order to enhance the biostability and biocompatibility of segmented PUs. Changes to the soft segment chemistry may include substitution of polyether segments with polybutadiene, polydimethylsiloxane, polycarbonate, and other aliphatic hydrocarbon segments. Incorporation of PDMS in PUs was shown to exhibit good blood compatibility, low toxicity, good thermal and oxidative stability, low modulus, and anti-adhesive properties (see Chapter 6). Studies have also confirmed that polycarbonate soft segment was more stable than polyether soft segment. With studies lacking findings on the biostability and biological response of these modified PUs, Mathur et al recently reported the effects of chemical composition variation of the soft segment on the chemical stability, the rate of degradation and the inflammatory response to modified PUs. Two unmodified polyether-urethanes, one PDMS modified PEU, and two polycarbonate-urethanes were investigated. Results demonstrated lower cell densities and adhesion on PDMS-PEU than on unmodified PEU. These findings were attributed to the hydrophobic nature of PDMS end groups. Polycarbonates showed slightly less macrophage attack as compared to PEUs. In a similar fashion, the biodegradation rate of PDMS-PEU was also less extensive than those of unmodified PEUs. Again, the authors suggested that PDMS might provide a shield against oxygen radicals secreted by inflammatory cells and consequently reduced the rate of biodegradation. In addition, it was found that only a minor amount of biodegradation was seen on polycarbonate-urethanes as compared to unmodified PEUs and PDMS-PEU, thus confirming the oxidative stability of the carbonate linkage.[106]

Nair et al[107] have also studied the effect of hydrophilicity on tissue response to polyurethane interpenetrating polymer networks (IPNs). They found that highly hydrophilic polyurethane-polyvinyl pyrrolidone or, in contrast, highly hydrophobic polyurethane-poly(methyl methacrylate) IPNs elicited inert responses in vivo. The authors concluded that the relative hydrophobicity or hydrophilicity of polymer surfaces is an important factor determining tissue compatibility. They also found that interfacial energy had no correlation with tissue responses whereas an interfacial energy near zero has been shown to be a requirement for blood compatibility. More recently, Hunt et al further investigated the effect of changing the hydrophilicity of polyurethanes on the in vivo biological response.[104] They obtained a relatively narrow range of hydrophilicity (42-67 contact angle degrees) from various polyurethanes prepared with PEO, PTMO, PHMO, POMO, and PDMO as macrodiols and MDI as hard segment constituents. After intramuscular implantation, the acute and chronic inflammatory responses were evaluated by counting specific cell types and quantifying cytokines released from these cells. Although they state that the decrease of hydrophilicity increases macrophage population, the data reported by Hunt et al on macrophage ED-2 and MHC III cellularities clearly showed that the more hydrophobic PDMO-based PU was less reactive than the other materials particularly during the acute phase of inflammation (> 1 week < 1 month).

In conclusion, the effect of hydrophilicity, net charge, antioxidant incorporation, and chemical composition on the hemocompatibility, biocompatibility or biostability of PU surfaces is still under debate and requires clear and well-designed studies to bring quantifiable and reproducible parameters that will discriminate between polyurethanes of various chemical composition, structure and morphology.

4.5 Effect of Protein Adsorption on Polyurethanes

One final thought regarding the hemocompatibility and biocompatibility of polyurethanes is to review the effects, potential benefits or drawbacks of protein adsorption on PU surfaces. Upon implantation, one of the first events which occurs is the adsorption of proteins onto polymeric surfaces. Plasma proteins which adsorbed to the surfaces of biomaterials include

albumin, hemoglobin, thrombin, fibrinogen, fibronectin, complement components, and immunoglobulins (IgG). The composition of the adsorbed proteic layer is strongly dependent on the structure and composition of the polymers.[108,109] Surfaces precoated with plasma proteins have shown that certain proteins influence the hemocompatibility,[110] affect cellular interactions, and promote bacterial colonization and infection of devices.[111] In fact, in the mid 1970s, albumin was recognized as an effective molecule for surface passivation as opposed to fibrinogen or fibronectin which were shown to promote thrombus formation. Albumin was also shown to have preferential adsorption characteristics onto segmented polyurethanes. When exposed to blood, albuminated PU surfaces were found to be less thrombogenic by masking the substrate from the blood's host defense activation mechanisms.[112] The hemocompatibility of albuminated polyurethanes was further reported by several investigators.[112-116] On the other hand, recent studies have suggested that reduced plasma protein adsorption on polyurethane surfaces might lead to reduced thrombogenicity[34] and also reduced bacterial adhesion.[11,117,118] With the intent of suppressing protein adsorption on PU surfaces, investigators have modified their polymers by incorporating PEO chains,[119] poly(vinyl pyrrolidone),[111] or negatively-charged sulfonate group bonding.[28,29] Other surface modifications were also attempted to reduce protein adsorption and cell adhesion on PU by blending amphiphilic polymer[120] or incorporating polymeric molecules with polar groups such as phospholipids[34,121] or phosphorylcholine.[122]

In evaluating the cellular reactions or the biological responses of various biomaterials including polyurethanes, several authors have argued that inflammatory cells are the predominant components of cell/biomaterial interactions and that the intensity and duration of the inflammatory response at the tissue/implant interface determine the biocompatibility of biomedical polymers. While intending to elucidate these interactions, a limited number of studies have looked at the intimate relationship between blood proteins and various cells involved in the inflammatory response of biomaterials in terms of chemotaxis, proliferation, and activation. One of the most interesting and perhaps surprising results obtained by Anderson's group was the greatest activation of monocytes in terms of IL-1 secretion by various materials including Biomer™ which were precoated with albumin.[123] Other blood proteins such as fibronectin, fibrinogen, IgG, and hemoglobin demonstrated reduced IL-1 activation on the material surfaces. The variability of their results was imparted to the differential protein adsorption properties of the polymers. In a follow-up study, they reported that albumin preadsorbed on Biomer™ suppressed fibroblast activity in a polymer-dependent manner.[124] From this study, it appears that the fibrous encapsulation is a complex response which involves the polymer, proteins, and the biological environment.

In contrast, Hasper et al investigated the cellular reactions to silicone and polyurethane by measuring IL-8 and MIP-1a secreted by monocytes as well as P-selectin and platelet derived growth factor (PDGF-AB) released by platelets following in vitro incubation. Their results revealed that a Pellethane™ 2363 used in the production of the Berlin Heart pumps and cannulas activated the complement cascade and platelets but showed lower monocyte activation compared to silicone. By pretreating the PU and silicone surfaces with albumin, they demonstrated reduced monocyte activation (IL-8) for both types of surfaces and concluded that albumin treatment could be useful in preventing inflammatory and thrombotic complications during the initial circulating support.[86]

These studies clearly show that at this time there is no real consensus regarding the advantages or drawbacks of protein adsorption with biomedical polymers. There is compelling evidence to suggest that among plasma proteins, albumin may be beneficial to blood contacting surfaces, such as polyurethanes, by reducing platelet and bacterial adhesion. On the other hand, albuminated surfaces may have a propensity to activate monocytes and inhibit fibroblastic proliferation. These findings attest to the complex interactions between proteins and blood or tissue environments occurring after implantation. With the next century, the real challenge

for the biomaterial scientist will be to develop polymers and structures with optimal mechanical and physical properties, biocompatibility, hemocompatibility, and biostability which can be used when constructing devices destined to replace vital organs and other tissues, thus improving and prolonging human beings' lives.

4.6 References

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Chapter 5

Biomedical Degradation of Polyurethanes

Patrick Vermette, Stéphane Lévesque, and Hans J. Griesser

5.1 Introduction

5.1.1 Purpose and Content of this Chapter

As discussed in the preceding Chapter, polyurethanes (PUs) generally show relatively acceptable biological responses, which have frequently led to statements that they are biocompatible. However, many researchers have pointed out a need for improved performance in some applications, such as for some cardiovascular products where currently available materials exhibit excessive protein and platelet adsorption. Secondly, initial expectations of long service life of PU-based devices were frustrated, since another major shortcoming is the degradation that has been reported to occur with PUs in a variety of implant situations. There exist many reports of stress cracking and reduction in performance—in some cases even device failure—from various laboratories, and this situation has led to the withdrawal from the market of some PU-based devices. Pacemakers are a well-known example. These reports have led to a large body of work on how this biomedical degradation of PUs is initiated and progressed, and how it might be overcome. Analysis of the causes and mechanisms of biomedical degradation has proved very challenging, which is not surprising given the enormous complexity of biological environments and the finely tuned, multiple defence mechanisms that the human body has evolved to combat the intrusion of foreign materials.

This Chapter reviews reports on the degradation, both in vivo and as studied by in vitro models, of various commercial and experimental PUs. Also included in this Chapter is discussion of some approaches towards mitigating or overcoming the problem, since many studies describe both the problem and attempts towards a cure. Discussion of synthetic routes towards biostable PUs continues in Chapter 6. Since the performance and stability of polymers is influenced not only by the conditions of the end-use application, but also by the way a polymer has been manufactured, the issue of degradation initiation in the course of the manufacturing process is also discussed.

In summary, the literature is somewhat confusing and there can be found apparent contradictions. Some of the discrepancies in the literature may perhaps be attributable to variability in the synthesis of a particular PU and/or variability in the manufacture of a particular device from a given PU. Space and information available does not permit us to discuss possible reasons for all the major discrepancies. Nor do we aim to cite comprehensively; there is a fair

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degree of duplication in concepts guiding some of the studies, and at times even the execution of studies, which has led us to omit some reports. Also, reports that are descriptive only of macroscopic manifestations of degradation often are insufficiently instructive for advancing molecular understanding; this has also led us to omit some reports. Finally, some excellent reports that are cited and discussed in other Chapters of this book also bear on this Chapter and could also have been included here, but were not for the sake of avoiding partial duplication. We trust the reader to make appropriate connections.

A serious difficulty in the study of PU degradation and improvement, probably more important than material or device reproducibility, is the absence of standardized, universally accepted tests that could be recommended or prescribed in order to evaluate the stability of PU materials and devices. Results can, however, markedly depend on the physical configuration (size, shape, flexibility, etc) of the implant and on the implantation conditions. These factors influence the outcome by affecting the severity of inflammatory/host defence reactions which, inter alia, strive to digest or occlude materials recognized as foreign. Also, in vivo calcification of biomedical devices is often found to occur at flexing or moving parts.[1,2] At present, the best, least ambiguous test appears to be the expensive and time-consuming option of implantation into test animals such as sheep. A compounding factor is, of course, that as materials of putatively improved stability become available, it becomes progressively more expensive and time-consuming to test them. Regrettably, accelerated tests have often been ambiguous, although some have provided important information on mechanisms. Thus, it is difficult at present to be confident in assessing by in vitro predictive methods a PU material as stable and appropriate for use in long-term implants.

5.1.2 Biocompatible PU—What Does It Mean?

First, allow us to be provocative: why the need for this review when a number of reports have claimed that they have found a particular PU to be biocompatible? Isn't the problem solved and this review thus merely of historical interest? We submit that this is not so. The term "biocompatible" means exactly what it says; it does not mean "more or less biocompatible" or "a bit better than material X". As for other polymeric materials used or intended for use in long-term implanted biomedical devices, the human body has proved to be a very challenging environment for PUs. The human body has evolved a finely tuned, complex system of defenses against intrusion and injury, and these defense reactions unfortunately and invariably are activated by biomedical implants. The mechanisms will not be discussed in this Chapter (a good overview can be found in refs. 3 and 4) but basically for the purposes of this Chapter it suffices to say that in tissue contact, phagocytosis attempts to digest foreign material, or, if this is frustrated, to encapsulate the foreign body. Thus, specialized cells secrete a variety of digestive enzymes at the implant interface. The cardiovascular system differs in that blood coagulation attempts to seal off any perceived "leakage", but the resultant clot formation on cardiovascular implants again can be likened to walling off the injury as in encapsulation by collagenous scar tissue. In summary the activation of cellular defense mechanisms leads to vigorous biomolecular, enzymatic attack. These enzymes are of course designed to combat "natural" materials such as viruses, bacteria, wood splinters, and various other intrusions and injuries, rather than the well-intended insertion of synthetic polymeric implants. The human body is not equipped with biological recognition (e.g., antigen/antibody) for synthetic materials such as polymers, and thus the defense is nonspecific and apparently comprises a range of biological pathways. If we, for simplicity, consider attacking enzymes as falling into two classes: oxidative and proteolytic/hydrolytic, then we can stipulate that a suitable biomedical polymer should be resistant against both modes of attack. One might expect a polymer such as polytetrafluoroethylene (PTFE), which is chemically relatively very unreactive and requires extremely vigorous conditions for

chemical reaction, to be able to withstand such biological attack modes (although experience now teaches us that such assumptions should be tested even when they seem very reasonable!). But would we, or should we, expect PUs to withstand such degradative cellular/enzymatic attack?

A further reason is that "biocompatible" can contain different requirements depending on the implant. Resistance to biodegradation and blood compatibility is the most frequently discussed; others, such as resistance to bacterial colonization, apply to some applications. What is the point and merit of using the term "biocompatible" in an unqualified way unless/until all the potential biological requirements and responses have been assessed and found to be met?

While polyurethanes certainly have met some of the biomedical performance requirements for some applications, a broad, unqualified claim of biocompatibility is not warranted. The occurrence of degradative attack is in itself a manifestation of bio-incompatibility. If a material were available now that is "biocompatible" in the literal meaning of the word, the impetus for a fair part of current biomaterials research would disappear. So let us focus now on the question of how much progress has been made in addressing but one of the key biomedical requirements on PUs for a number of applications, that of resistance to degradation in the biomedical environment.

5.1.3 Some Terminology

Owing to the apparent complexity of the biological defense pathways and resultant interactions leading to implant degradation, there is a basic multidisciplinary body of ideas that must be involved in order to appreciate interpretations of degradation testing in vivo and in vitro and to appreciate assumptions and limitations inherent in the various tests. Complications caused by the insertion of medical devices derive from materials-tissue interactions that include both effects of the implant on the host tissues and effects of the host on the implant.[3,4] Interpretation of polymer degradation in an in vivo environment requires understanding of responses to injury by the host body, mechanisms of which include inflammation, wound healing, and foreign body responses, which are activated to maintain homeostasis.[3,4] The same mechanisms that have evolved specifically to rid living organisms of invading foreign substances[5] unfortunately are also activated by biomedical implants and appear to compromise the stability of some materials, with polymer erosion and loss of material.[6] This is not limited to biomedical PUs.[7] It is also important to acquire an appreciation of molecular biology and biochemistry concepts, such as to relate the influence of cells and/or cellular components, water, enzymes, and other high- and low-molecular compounds, and their synergies and interactions, to PU degradation.

Stability has been defined as the "quality, state or degree of being resistant to chemical change or to physical disintegration".[8] This is, however, not an intrinsic property; some environmental conditions have the ability to affect the integrity of a polymer. Thus, the recognition that PUs are susceptible to attack under certain conditions offers an avenue to investigate molecular mechanisms of biodegradation. However, as for biocompatibility, one needs to clarify and qualify the meaning of the term biodegradation. It has been used frequently, but often to mean different things. As stated by Williams,[9,10] in the context of biomedical polymers biodegradation can be defined as structural or chemical changes in a material that are initiated or accelerated by the vital activity of the biological environment. The emphasis on the key role of a living host organism/metabolism expresses that biodegradation is not just degradation of the material by an aqueous phase of extracellular fluid or other chemical/biochemical fluids not regulated by metabolic processes. This does not mean, however, that the study of PU degradation in other potentially damaging environments would be unable to generate data and conclusions of significance to biological/physiological degradation, but one needs to be keenly aware of assumptions, limitations, and potential pitfalls.

5.2 Methods for the Assessment of Polyurethane Degradation

One purpose of this section is to help appreciate the relevance of the major test methods and how they can be utilized to combat PU degradation. The various methods can provide information on different aspects of the problem, and therefore the selection of method(s) to be applied to the characterization of the biodegradation of a PU material depends on the purpose of the study, the intended application(s) of the material, and the time scale over which stability of the material is desired. Limitations of techniques also suggest that, in many instances, no single technique will be available to give full and unambiguous information.

The methods have been grouped into five subdivisions. These are somewhat arbitrary and there is some overlap. Other techniques for polymer characterization[11,12] may also be useful in many instances and we refer the reader to these texts and other appropriate polymer literature for further information. In this overview of methods in this section, only a few selected references are cited with the aim of illustrating a typical use of the particular method for the study of PU degradation. The aim of this section is to convey what information can be gained. It will be in later sections of this Chapter that we will discuss the information acquired with particular PUs and the insights that these analysis methods have provided on PU biodegradation.

5.2.1 Macroscopic Characterization

Macroscopic characterization methods provide information on "bulk" properties such as mechanical performance. Techniques that can provide this type of information include mechanical testing, permeability testing, electrical testing, and color measurement.

Mechanical properties occupy a position of prime importance among the physical properties of PU materials, not only because they define to a large extent the scope for potential applications of a particular PU, but also because they have been the most used property for assessment of the degradation of PU materials. The two aspects are, of course, closely related: the specific elasticity of a given PU may make it particularly suitable for an application such as a small diameter vascular graft, but of course any significant, degradation-induced change in elastic properties may render the device unsuitable for the application. The preeminent position of mechanical properties in PU materials specification and degradation testing relates to the mechanical requirements placed on these materials in a large proportion of biomedical device applications. However, often too much emphasis is placed on comparing values of mechanical properties measured before and after degradation, with insufficient information on the relevance of the measured losses in comparison with the requirements on the mechanical properties and their acceptable range. Partly this may be because the minimum and maximum values of mechanical properties acceptable in specific end-use requirements are often ill defined. Thus, it is often unclear how much degradation-induced decrease in mechanical properties can be tolerated.

Tensile elongation and tensile modulus have been the most widely studied properties for the evaluation of the stability of PU materials. Tensile testing, in a broad sense, is a measure of the ability of a material to withstand tensile forces and thus to determine to what extent the material stretches before breaking.[11,12] Since changes in tensile properties have been found to be useful measures of the extent of polymer chain degradation, the relative stability of PUs is often compared on the basis of tensile strength, elongation, and tensile modulus. Thus, tensile properties have been used to rank PUs in terms of their relative susceptibility to degradation.[13,14] Tensile testing, however, does not reveal information on the pathways of degradation and the concurrent use of other test methods, which may include DSC, GPC, XPS (or ESCA), and SEM, is indicated to arrive at an understanding of what drives the observed tensile results.[13] Moreover, a substantial amount of polymer chain cleavage reactions is required until

measurable changes in tensile strength result. Hence, tensile testing is unsuitable for early detection of biomedical degradation. For example, Brandwood et al[15] found that a PU based on PTMO/MDI/BD implanted subcutaneously in sheep for periods of 6 months showed no significant changes in the tensile properties, but SEM examinations revealed a significant extent of surface cracking. Thus, although tensile testing is useful for detecting bulk degradation, its insensitivity during the early stages of degradation makes it impractical for use in the development of PUs intended for long-term applications. Moreover, because some materials, including PUs, are very sensitive to the rate of applied strain, the data obtained by standard tensile testing may possess limited predictive ability for applications involving loads, and their application rates widely different from those applied in the test method.[11,12]

An increasing number of workers recognize the importance of understanding in detail the behavior of biomedical polymers under long-term loading. Such behavior is described in terms of creep properties. When a polymer is subjected to a constant load, it deforms quickly to a strain consistent with its stress-strain modulus, and then continues to deform slowly with time until rupture or yielding causes failure. The degree of creep depends upon several factors, such as the chemical composition and method of manufacture of a polymer, the amount of load, temperature, and time.[11,12] Assessment of creep can be useful to determine the effect of the aging environment on the life of a PU-based device, as it is more sensitive to smaller changes than tensile testing. For the same reason, creep can also be useful for probing for variability in the manufacture of a PU material, since relatively small differences in the material (e.g., crystallinity, degree of crosslinking, lamellar orientation, etc) affect the creep behavior of materials.[11,12]

Another important test method for evaluating material stability is stress relaxation. Stress relaxation refers to the decay in stress with time when a polymer sample or a component is held at constant strain.[11,12] This is in contrast to creep measurements, where a fixed amount of load is applied to a specimen and the resulting deformation is measured as a function of time. Superior oxidative stability of polyester-urethanes over polyether-urethanes was demonstrated by stress relaxation data recorded with samples held in air and nitrogen atmospheres at 130°C.[16,17] Nevertheless, characterization of the stress relaxation behavior of PUs has been used to a surprisingly small extent, even though a number of biomedical applications impose some strain on the PU material, and it would thus seem that the use of stress relaxation data would be appropriate and might characterize the relative degradation and usefulness of materials. For example, very low stress relaxation is required of materials used to make some types of sutures, which may be required to hold constant strain for a long period. If the suture material suffers an excessive decrease in stress under constant deformation, the suture may fail prematurely.

The characterization of fatigue life is also a test method that has been used to determine the stability of PUs since some devices can be subject to cyclic loading due to flexing, stretching, or twisting. Such cyclic loading eventually causes mechanical deterioration by progressive fracturing that eventually leads to complete failure. Fatigue life is defined as the numbers of cycles of deformation required to bring about failure of the test specimen under a given set of oscillating conditions.[11,12] The failures that occur from repeated application of stress or strain are well below the apparent ultimate strength of the material. At high stress levels, materials tend to fail at relatively low numbers of cycles. At low stresses, however, the materials can be stressed cyclically for long periods of time and the failure point can be difficult and time-consuming to establish; also, under those conditions reproducibility may be poor since small variations in materials synthesis and manufacture may be amplified. Although mechanical properties are usually associated with bulk properties rather than surface phenomena, cyclic loading experiments appear to relate to some extent also to surface defects.[11,12] For PUs, this is exemplified in a study by Marchant et al[18] who reported that following treatment with the enzyme papain, no evidence of chemical degradation was detected by GPC and IR spectroscopy, but the fatigue life was affected.

The mechanical properties of polymers are, however, dependent not only on the molecular weight of the polymer chains, and the crosslink density: a number of other factors come into play as well. Additives can act as plasticizers; thus, for instance diffusive loss of additives to the surrounding medium can render a polymer more brittle. Water also acts as a plasticizer and hence its sorption into biomedical PUs is of importance. Diffusive transport of lower molecular weight degradation products also has the potential to affect the mechanical properties, and it would therefore be useful to understand the spatial distributions (over time), the diffusion rates, and the overall effects of such breakdown products. Finally, oxidative degradation of polymers typically is not spatially homogeneous due to reaction-terminated diffusion of oxygen into the polymer. Hence, the mechanical properties that can be measured represent an overall assessment of what in reality is a complex, spatially inhomogeneous polymeric material. The weakest points/spots/areas in a sample do, however, exert a disproportionate influence and act as initiation sites for failure. One way to probe for spatial effects is via the study of diffusion parameters of various molecules in these polymeric materials.[19] In addition, assessment of the permeability characteristics of PUs is directly relevant to biomedical membrane applications including membrane oxygenation and wound dressings. The transport of small molecules in polymers is strongly dependent on the polymer microstructure and morphology, and the nature of the penetrant.[20] Hence, Variability in manufacturing that may affect the sizes and distribution of soft and hard segments may affect the permeability of lower molecular weight species and thereby the rate and spatial distribution of biomedical degradation.

The sorption and transport of water/atmospheric moisture into PUs and resultant effects on mechanical and electrical properties have been recognized and studied. Stokes et al[21] found that Pellethane™ 2363-80A and 2363-55D showed decreased tensile strength and increased elongation on water sorption; the electrical property of volume resistivity also was altered as a result of moisture absorption. The finding of reduced mechanical strength is consistent with water acting as a plasticizer. Moisture absorption was found to be largely reversible.[21] The solubility of additives in solvents and biological fluids can also be a consideration in affecting the service life of a biomedical device as some additives can be extracted by solvents as well as by biological fluids.[22] Thus, sorption of water and loss of plasticizing additives have counteracting trends on mechanical properties, and therefore there clearly is a potential for such effects not to become measurably manifest due to their counterbalancing contributions, at least in the earlier stages of biodegradation.

Combination of well-suited mechanical properties and excellent electrical insulation has led to application of some PUs as pacemaker lead insulators. An insulator must possess a sufficient dielectric strength to withstand the voltage applied, a high resistance to prevent leakage of current, and must maintain integrity under the particular environmental conditions. The dielectric strength of an insulating material is defined as the maximum voltage required to produce dielectric breakdown and is expressed in volts per unit thickness. Given that sufficient initial dielectric strength can be obtained with appropriate PUs, the key issue is whether this can be maintained over an extended service life. Changes to the chemical composition, such as the introduction of additional polar groups upon oxidation and changes to the molecular weight upon oxidative and/or hydrolytic reactions, will affect the dielectric properties adversely. Moreover, water sorption will decrease the dielectric strength. Thus, it is important to monitor the time dependence of the dielectric strength under realistic service conditions and define the time to failure.

As PUs appear suitable for cosmetic applications, such as maxillofacial surgery,[23-25] it is important to characterize the color stability of PU materials exposed to appropriate environmental conditions. In some instances this can be done simply by visual assessment by a trained observer.[26] To improve on such qualitative observations, quantitative colorimetric measurements can be done using a spectrophotometer, but it appears that trained human observers

can better detect subtle changes in hue. For example, Turner et al[23,24] reported that some PUs used to make maxillofacial prostheses exhibited slight color changes when evaluated by a human observer, but no statistically significant differences in color upon aging were detected by standard numerical evaluation. Standard numerical descriptions of colors, which enables assessment of their stability, have been established by the International Commission on Illuminants,[11] in terms of "value", "hue", and "chroma". It is thus possible to perform comprehensive examination of the color stability.

5.2.2 Microscopic Characterization

We shall discuss as microscopic properties, those that fall between macroscopic bulk properties and molecular structural characterizations, realizing the arbitrary nature of such distinctions. Included are thermal analysis methods and optical analyses such as refractive index, light transmittance, haze, and photoelastic properties. The average number of monomer units per chain, or degree of polymerisation, may also be included under this heading. This is usually converted to, and quoted as, molecular weight and its polydispersity.

Differential scanning calorimetry (DSC) is commonly used to identify crystalline and amorphous phases, bulk microphase separation, and the various types of thermal transitions. Any of these properties may be useful indicators of the progress of biodegradation of PUs. Measurement of the glass transition temperature (Tg) has been an important indicator of PU degradation. The Tg is defined as the temperature at which a material loses its glasslike, more rigid properties and becomes rubbery and more flexible. Takahara et al[13] reported, for example, that the Tg of a PBD(2000)/MDI/BD-based PU increased after exposure to an oxidative environment. This increase was attributed to restriction of molecular motions due to crosslinking. Meijs et al[27] reported that DSC analysis of the four thermal transitions of a polyether-urethane (PEU) showed that degradation induced by hydrogen peroxide was associated with greater order in the hard domain and greater mobility in the soft domain. While DSC may provide useful information on the degradation of PU materials, it must be kept in mind that it is a bulk characterization technique and may therefore be not sensitive to early stages of degradation.

For the characterization of PU biodegradation on the basis of changes in the molecular weight and its polydispersity, a method commonly used is gel permeation chromatography (GPC), also referred to as size exclusion chromatography (SEC). This method has potential due to its sensitivity for detecting changes in the weight average molecular weight (Mw) and the number average molecular weight (Mn) earlier than some of the methods discussed above. It is useful for comparative purposes to show sample degradation and batch-to-batch variations. For instance, Ratner et al[28] found that Estane® treated with H_2O_2 and copper underwent extensive crosslinking, causing a substantial increase in Mw. GPC analysis can be very useful to determine whether chain scission or crosslinking is the more important consequence of polymer oxidation reactions. Chain scission pathways generally result in reduced strength and creep resistance, while crosslinking is usually associated with an increased modulus of elasticity. However, Ratner et al[28] found that the observed changes in GPC chromatograms sometimes amount to slight changes in the peak shape. The effects seen in the GPC chromatograms are often subtle, especially in the early stages of degradation. This is not surprising since GPC is essentially a bulk characterization technique by averaging over a large number of polymer chains; molecular weight changes occurring mainly in near-surface layers are superimposed on much unaltered polymer material.[29] Thus, the use of statistical analysis is greatly beneficial in assessing the significance of slight changes in Mw and Mn.[28] Moreover, GPC is a method that requires samples of known molecular weight and similar molecular architecture for calibration.

Since most plastics placed under internally or externally applied stress and viewed through polarized light exhibit optical stress gradients, photoelastic properties can be used by research-

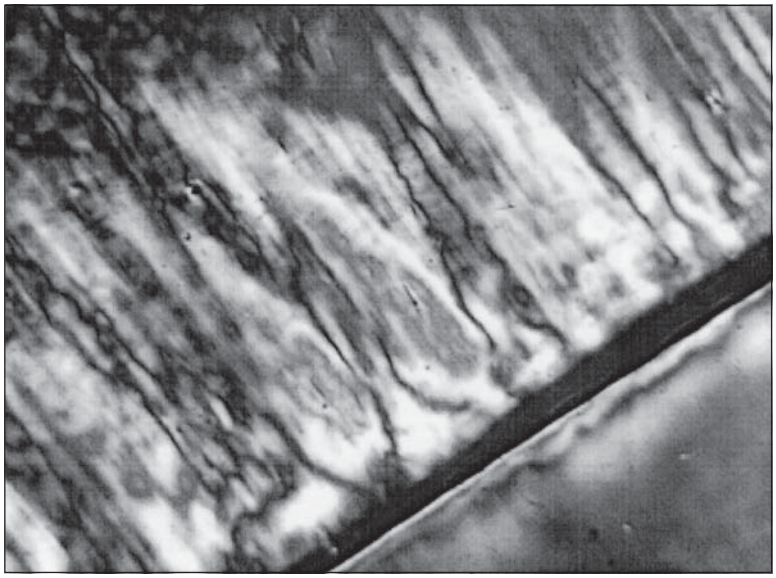

Fig. 5.1. Polarized light microphotograph of a polyurethane sample showing residual stress.

ers and process engineers for determining residual stress as well as the degree of orientation in polymeric parts. Useful information can be obtained through such analysis regarding the location of stress concentration. Residual stress sites can act as initiation sites for attack, and the presence or absence of such sites, as well as the effectiveness of manufacturing and annealing procedures, can conveniently be assessed using optical methods. Polarized light microscopy offers a method for rapid assessment of residual stress (Fig. 5.1). While this approach has been used to study effects of molding, annealing, and machining on the polymer structure and homogeneity, it has been little used for characterizing degradation of PU materials.[11] The refractive index, luminous transmittance, and haze also can be used to detect surface imperfections, density changes, or inclusions that produce light scattering, and thereby are properties that are potentially useful for assessment of the stability of PU materials.[11] For example, Sturdevant[30] showed that the percentage light transmittance through the polymer was useful to determine the extent of radiation-induced changes in the clarity of PUs.

5.2.3 Characterization of the Molecular Structure and Composition

Methods to describe those attributes that are characteristic of individual polymer chains, including their chemical compositions, are mainly spectroscopic techniques such as infrared (IR) spectroscopy. The various modes of IR spectroscopy enable the probing of polymer compositions to different depths. A number of other spectroscopic methods are also available, and together these methods can provide an assessment of the depth distribution of degradation-induced changes to the chemical composition of polymer chains. This is particularly important from our point of view since degradation appears in most cases to start in surface layers and then progressively move inwards into the polymer bulk.

Fourier transform infrared (FT-IR) spectroscopy has been applied by many researchers to the study of PU degradation as it provides detailed chemical information from the observed vibrational bands. It can reveal specific chemical information as well as in some cases an assess-

ment of the orientation of structures. For example, Bernacca et al[31] reported that FT-IR spectroscopy indicated the involvement of the polyether soft segments in the calcification process. In another study, Chawla et al[32] reported on the basis of FT-IR/ATR spectra that some portions of an explanted pacemaker lead had suffered extensive localized damage. They found that the C-H bands in the 3000-2800 cm^{-1} spectral region, the carbonyl stretch band at 1730 cm^{-1}, the 1368 cm^{-1} band assignable to CH_3, and the peak at 1105 cm^{-1} due to C-O-C group all showed decreased intensity after explantation.[32] This finding indicated that the degradation process involved the polyether components. One of the main advantages of using FT-IR spectroscopy for characterizing PU degradation is that it does not require a high vacuum environment, which may cause polymer surfaces to rearrange.[33] With a probe depth of the order of 0.1-2 μm, depending on the particular mode and the wavelength, FT-IR is not a bulk analysis technique given the thickness of PU components in typical biomedical devices. It can thus potentially detect degradative changes earlier than the above bulk analysis methods can. However, the sensitivity of FT-IR for detecting surface-localized, early-stage compositional changes does not match that of the extremely surface-specific spectroscopic method of XPS, which probes to a depth not exceeding 10 nm and, with angle-dependent analyses, can even be used to characterize compositional changes over the outermost 10 nm of a polymer.

5.2.4 Surface Characterization

As discussed in Chapter 1, the surface layers of polymers such as PUs may differ compositionally from the bulk as polymer chains are mobile and can rearrange in response to interfacial forces.[33] Moreover, environmentally induced degradation usually starts in surface layers. Hence, analysis of surface layers and comparison with the bulk chemistry is important. Also, since it is increasingly recognized that the biomedical performance and degradation of polymers in biomedical devices is a function not only of the bulk properties, but particularly of the nature and the topography of the surface, detailed characterization of polymer surfaces is critical not only in terms of their chemical composition but also in terms of surface topography. The mechanisms of degradation may vary with the specific bulk and surface characteristics, respectively, and thus may not be identical throughout the material's depth. It is also likely that lower molecular weight degradation products produced in surface layers can diffuse into the surrounding biological medium, whereas degradation products produced in the bulk are more likely to remain within the polymer (at least until diffusion has allowed them to cover sufficient distances). Hence, the surface layers may be less plasticized by lower molecular weight degradation products than deeper regions; this may be (one of) the reason(s) for the observed stress cracking being more severe in surface layers.

In nonpolar environments (air, vacuum) hydrophobic chain segments accumulate preferentially at the surface whereas in polar environments hydrophilic groups are energetically favored at the interface.[33] Therefore, complete characterization of biomedical PU surfaces requires the use of many techniques to compile the information needed, and at least one method needs to be able to provide information on the surface structure adopted in a hydrated aqueous environment. Freeze-hydration has been developed explicitly for this purpose, but it is still a rather challenging technique and experimentally demanding. The methods of interest for characterizing surface-related aspects of PU degradation may include surface topography methods (SEM, AFM), surface energy and surface tension techniques, and surface spectroscopic methods (XPS, SIMS).

Scanning electron microscopy (SEM) has often been used to perform characterization of the surface topography of PU materials that have been explanted. In fact, SEM images have been commonly used to assess the extent of surface crack formation on PU samples. One advantage of SEM is its wide range of magnification, with modern field emission (FE-SEM)

instruments offering resolution of ~ 7 nm, and, at the other extreme, excellent low-magnification (~20x) images. A large depth of field allows study of rough and curved samples. This feature makes SEM particularly useful for examining degradation with large objects.[32] A drawback, however, is the difficulty in obtaining accuracy in the vertical (z-) scale; thus, surface images are often used in a qualitative depth fashion. Depth information, such as the depth of cracking, can be obtained with SEM cross-sectioning methods; skilled operation of microtomes is necessary particularly with relatively soft polymers. The vacuum nature of SEM entails dehydration of samples, which may affect their surface topography relative to the one expressed in contact with biomedical environments. The method of so-called "environmental SEM" aims to reduce this issue but it is still necessary to work at reduced pressure to avoid excessive electron scattering. Also, resolution is much inferior in "environmental SEM". On the other hand, liquid cell AFM can be used for characterizing the surface topography of biomedical materials whose surface layers may be affected, e.g., by swelling, on interaction with water.

Atomic force microscopy (AFM) excels in providing extremely high lateral resolution and accuracy in the vertical scale (height or depth of features). It does not, however, possess the ease of zooming in and out that SEM offers. Initially the range of AFM scan heads was quite small, allowing only small sample areas to be assessed, which raises the need for multiple scans in order to assess whether an image is representative. Larger scan heads have become commercially available, and this also allows rougher surface topographies to be assessed with reliability. One limitation of AFM can be that steep features are not reproduced faithfully due to finite curvature of the imaging tip, whose side rather than tip can first contact a steep slope or abrupt step. Sharp tips have become available but the operator still needs to be aware of potential imaging artefacts. In particular for imaging the steep-sided, deep surface cracks shown by SEM with degraded PU samples, one must expect that cracks may not be reproduced faithfully but appear as troughs with less sharp edges than is really the case. If necessary, this can be corrected mathematically, but it would appear to be simpler to acquire a parallel SEM image for qualitative assessment of the severity of this issue.

Another potential artefact in AFM can arise from excessive sample/tip interactions; an excessive applied force leads to distortions of the polymer surface topography in the course of imaging. The use of tapping mode is advisable with soft polymer surfaces. AFM can also be performed on samples in contact with liquid environments by the use of liquid cells; this is particularly important for characterizing surfaces that may swell to considerable extents in biological media but in normal air investigations might present a compacted surface. AFM should be very suitable for the characterization of surface-related degradation but has been little used to date for this.

To establish a good chemical-mechanistic understanding of biomedical PU degradation, the chemical composition of the surface is required. In fact, interactions between a polymer and a host body, and the immune response attack on the implant, are directly and often markedly affected by the surface chemistry. There are many different surface and interfacial parameters (e.g., chemical structure, orientation and mobility of groups within the topmost atomic layers) that may play a role in the stability of PU materials.[35]

Interfacial tension, which is a measure of the degree of interaction between two phases at their common boundary,[35] can provide a "first line" characterization of chemical changes on polymer degradation. Contact angle methods are the most commonly used way of measuring surface energy and wettability. Since the depth of analysis of this technique is reported to be approximately 0.3-2 nm, it probes the surface region that will interact with the surrounding environment. For example, Pike et al[36] monitored the in situ stability over time of PDMS-PUU polymer surfaces using dynamic contact angle analysis, finding that the PDMS-PUU surfaces were altered by long-term exposure to water and showed a time-dependent increase in hysteresis. The water-stored polymers became more hydrophilic over time. The dynamic contact

angle results were consistent with XPS data. In performing contact angle measurements, however, a number of concerns must be addressed to obtain meaningful data.[35] A major concern is that surface-active low molecular weight compounds can interfere markedly with the measurements but this can go unrecognized. Partially oxidized PU chain fragments are likely to be surface active, mobile, as well as enriched in surface layers (due to attack progressing inwards from the surface layers); hence their interference in surface energy determinations must be considered. Such lower molecular weight material can also be leachable, due to solubility in probe liquids, and induce time dependence and irreproducibility into the measurements, as well as contaminate the probe liquids. Contact angle measurements can be of limited use for assessing the degree of degradation since they do not provide detailed chemical information and, while they tend to show at first an increasing surface polarity on oxidation, they then change much less as oxidation proceeds from, for instance, hydroperoxides to carbonyls. A further limitation of contact angle measurements is that effects due to changing surface topography—such as cracking—are superimposed on chemical surface changes. Finally, the interpretation of contact angle data in terms of dispersive and polar components, or in the form of a Zisman plot, has become questionable. As understanding of intermolecular forces progressed and interfacial interactions are described in terms of various forces rather than the simplistic surface energy pictures used before new methods such as the surface force apparatus (SFA) became available, it has become clear that the older contact angle interpretations have neglected some forces of relevance. It appears much preferable to use a surface force apparatus and/or a modified-tip AFM in the force mode to directly access selected interfacial forces rather than trying to disentangle them from contact angle data. The only significant advantage of contact angle measurements is equipment cost. We no longer use contact angle measurements for quantitative interpretations, only for qualitative detection of changes that then are assessed by chemically more informative, more specific assay methods. Dynamic wetting measurements may be more informative than static contact angle measurements but care in interpretation is still needed.

For probing PU degradation mechanisms, there exists a range of spectroscopic techniques that can be used to probe surface chemistry and structural modifications. Among these, XPS has been very popular for the analysis of biomedical polymer surfaces and has also been used to monitor PU biodegradation. Its high surface specificity and sensitivity allows very early detection of attack starting at surfaces. For example, Marchant et al[18] reported that while no chemical degradation could be observed by GPC and IR spectroscopy for PEUU treated with papain, changes in the polymer surface composition were detected by XPS analysis. Their findings comprised an increase in the C-C component of the C1s signal and a decrease in the C-O component for enzyme-treated samples, suggesting a reduction in surface ether linkage content. Another major feature of XPS in the characterization of materials degradation is that it enables construction of depth profiles over the outermost few polymeric layers, by varying the photoelectron takeoff angle.[33,35] Additional work, including chemical tagging reactions, is required to characterize PU surfaces properly after in vivo or in vitro degradation, in order to discern chemical groups that cannot be differentiated spectroscopically.

Although more complex in instrumentation and analysis, SIMS is capable of providing the most detailed information on the bonding structure of PU surfaces. However, SIMS appears not to have been applied so far to the study of PU degradation.

To enhance the understanding of early-stage PU degradation, clearly surface analyses are very powerful. There are, however, some concerns that must be addressed. One is that biological molecules, particularly proteins but also lipids in many instances, adhere tightly to many polymer surfaces. The problem therefore arises: how does one clean an explanted material surface from biomolecules that interfere with XPS and SIMS analyses, yet avoid the simultaneous removal of PU material from surface layers, such as lower molecular weight fragments

that would probably provide useful clues to the degradation chemistry? Unfortunately the XPS C1s spectra of proteins and PUs have a fair degree of similarity, making it difficult to assess whether a surface cleaning protocol, such as trypsin digestion of surface-bound proteins, is sufficient but not excessive. We encountered this hurdle in (unpublished) work and were not able to acquire interpretations with confidence.

In addition, since the high vacuum environment used in the spectrometers (XPS, SIMS) may cause polymer surfaces to be different from those adopted in polar, aqueous environments, caution should be used in such analyses (see Chapter 1). Ideally, XPS and SIMS analyses of freeze-hydrated samples[35] should be performed. One must remember that a high vacuum environment is not a biological solvent! A further challenge arises from surface-located additives and contaminants, which may at times be difficult to recognize. A major issue in surface analysis is avoidance of surface contamination from fingerprints, packaging materials, handling tools, laboratory air, and other possible sources.

5.2.5 Analysis of Degradation Products

Apart from the characterization of the polymer itself, there is also interest in the analysis of the degradation products. As reviewed earlier by Griesser,[33] characterization of PU material surfaces after exposure to incubation solutions, such as water and water+papain, showed only small surface changes, such as a reduction in ether groups. In many instances chemical changes on PU surfaces are small and insufficient to provide detailed mechanistic information. This may be due to prompt diffusive removal of the degradation products from the surface, thus continually exposing a fresh PU surface for renewed attack. It appears reasonable to assume that oxidized lower molecular weight fragments from PU degradation would be more soluble in aqueous media and therefore able to solubilize into the surrounding host environment. Alternatively, it may be that the surface cleaning protocols applied prior to analysis removed layers of such PU fragments and exposed a largely intact PU material.

It therefore appears very promising to study the PU degradation products not in situ but after their isolation from the remaining polymer material. Thus, Labow et al[37] were able to evaluate the neutrophil mediated degradation of PUs using a C-14 radiolabelling technique. Although no effect of neutrophils on the polymer were detected by SEM, indicating that degradation had not progressed to stress cracking, radiolabelling proved useful for detection of degradation products. Model PU systems were used, as this approach cannot be easily adapted to assess in vivo degradation.

In earlier work to detect TDAs in TDI-derived PU foam, Guthrie and McKinney[38] developed a TLC/fluorimetric technique claimed to be sensitive to 1 ppm. Later, Batich et al[39] used a GC-MS technique that also enabled identification of TDA produced under acid, alkaline, or high temperature degradation conditions. Although these findings have raised the concern of possible in vivo release of some potentially toxic degradation products, particularly aromatic amines which are known to be powerful carcinogens, verification of the in vivo validity of the concern, and full characterization of the range of degradation products generated by the biological degradation of PUs, are still required. Detection and analysis of the full range of degradation products is critical not only to the toxicological evaluation of implanted PUs, but also to improved understanding of the pathways of biodegradation. Therefore, in studies aiming to provide further information on degradation products and concentration levels for the various products, a number of methods have been developed to isolate and chemically analyze PU degradation products. For instance, Wang et al[40] have developed an analytical method for the isolation of degradation products, the method including steps for sample preparation, separation of analytes by reverse-phase high-performance liquid chromatography (HPLC), and identification of compounds by tandem mass spectrometry (MS-MS). This technique has been shown to be

sensitive to concentrations close to nanogram levels. However, while most useful for the study of in vitro degradation of PUs, applicability to in vivo degradation is still to be verified, since methods for sample preparation involving removal of adhering tissue and/or protein layers may interfere by removing some of the PU degradation products from surface layers. There appears to be a need for further research towards developing reliable ex situ and in situ analytical techniques for the detection of degradation products. Moreover, improvements to highly sensitive methods are required for reliable and accurate detection of products produced during the early stages of biodegradation, with the dual aims of improving understanding of the early steps involved in biodegradation and designing a method for the detection of the onset of degradation before performance decreases potentially critical to the viability of the biomedical device have resulted.

5.2.6 Summary

A wide range of analytical techniques has been applied to the study of the degradation of PU materials both in vitro and after retrieval from in vivo usage. These techniques have provided much useful information on particular PUs, as will be reviewed below. However, as our brief review of these methods has aimed to show, each technique has particular strengths and limitations, and for detailed study of PU biodegradation it is necessary to utilize a range of methods concurrently and to apply an appreciation of their potential and their limitations when interpreting results. It is not possible—nor useful—to recommend a particular "toolkit" of techniques most appropriate to further study of PU degradation; clearly there is a need for improvements in both resolution and sensitivity of many methods. Particularly challenging is the development of sample preparation methods for PU devices retrieved from in vivo usage, since the removal of adhering biological material and debris can interfere with analytical methods and lead to loss of some of the degradation products and/or other information on the in vivo biodegradation mechanisms. Nevertheless, much useful information has been acquired by applying particular methods to specific questions regarding PU biodegradation, and these results will be reviewed in the remainder of this Chapter.

5.3 Influence of Manufacturing Process on Polyurethane Stability

As for other polymers, variables in the manufacturing process can have an influence on the stability of polyurethanes. Indeed, excursions from appropriate manufacturing conditions may substantially decrease the material's stability. In addition, sterilization methods may sow seeds of degradation. This section addresses how the stability of PUs may be related to fabrication, sterilization, storage and handling.

5.3.1 Influence of Fabrication Process

Phase segregation, crystallinity, the sizes of domains, surface topography, and the surface chemical composition of a polymer are among the properties that may be affected by the fabrication process (extrusion, molding, casting, etc). For example, injection molded specimens and extruded materials may contain compressive surface stresses that can play a major role in the generation of microcracking of PU parts.[41] If the polymer chills too quickly on the mold surface while molten polymer is still entering the cavity, evidence of a type of molding defect called "cold flows" may originate on the surface of tensile specimens; an example is reproduced in Figure 5.2.[42] In addition, Coury et al[41] reported that films prepared by compression molding may acquire surface texture due to irregularities of the mold surfaces. Other

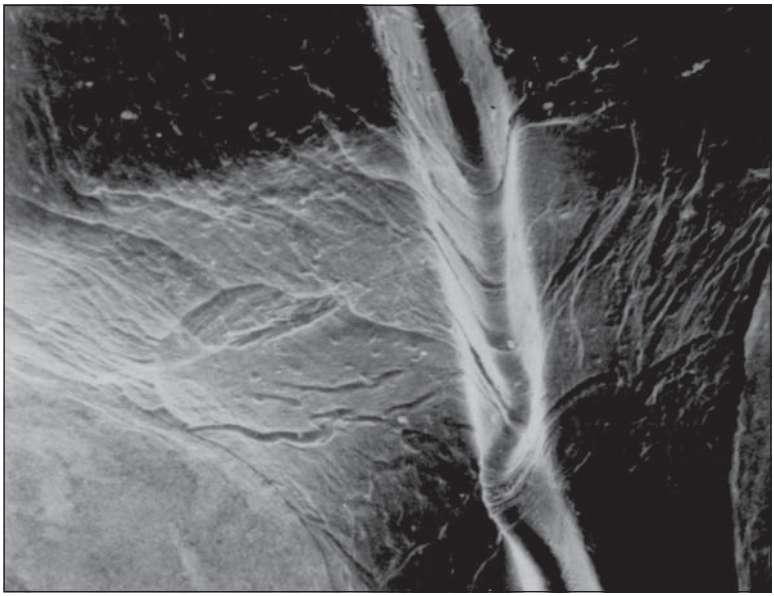

Fig. 5.2. If a polymer chills too quickly on the mold surface as molten polymer is still entering the cavity, "cold flows" (a molding defect) can form on the surface of the finished polymer. Reprinted with permission from: Stokes KB. Polyether polyurethanes: biostable or not? Journal of Biomaterials Applications 1988; 3: 228-279.

preparation methods, such as solvent casting, reproduce the texture of the substrate on the "mold" side and may lead to smooth or rough texture on the "air" side.[41]

5.3.1.1 Thermal Degradation

Among the parameters that affect the integrity of PU materials, the fabrication temperature occupies a prominent position. Obviously, a minimum process temperature is defined by the requirements of molding or extrusion; on the other hand, excessive temperature leads to thermal damage. Thus, a compromise must be sought and the process temperature well controlled. While PUs generally possess relatively good thermal stability,[16, 17] urethane and urea groups can be subject to some extent of thermal decomposition during the fabrication procedure. Decomposition of urethane groups can take place in a variety of ways. The main mechanism depends strongly on the nature of the substituents on the N and O atoms.[16,17] Urethanes of many commercially available isocyanates and primary and secondary alcohols start to decompose in the temperature range 150-200°C; the onset degradation temperature of urethane bonds depends on the type of isocyanate and glycol used.[43] Aliphatic isocyanates produce urethanes with generally higher thermal stability. Accordingly, the dissociation temperature of the three commercially available isocyanates TDI, MDI and HMDI increase in the order TDI < MDI < HMDI. Allophanate and biuret groups are reported to degrade at lower temperatures (approximately 100°C).[16,17] Other components of the PU structure also affect the thermal stability. Generally, polyester-urethanes exhibit higher thermal stability than polyether-urethanes.[16,17,43] Yet, comparison of these onset temperatures for thermal decomposition with the processing temperatures commonly used in extrusion and molding suggests that some thermal degradation must be expected for most, if not all, commercial polyurethanes.

5.3.1.2 Influence of Moisture

Moisture during processing has a marked detrimental effect and requires careful control. In places with relatively high humidity, it is very difficult to produce good quality PUs unless appropriate precautions are taken but this can be expensive. Coury et al[41] indicated that protection from moisture absorption preserved the shelf life of PU solution, and that moisture absorption during solvent evaporation in a humid environment can cause hazing and blistering of films. In addition, loss of adhesion to substrates may occur due to moisture absorption. Hydrolysis reactions not only affect the mechanical strength and subsequent resistance to degradation, but may also lead to low molecular weight compounds that pose safety risks. Shintani[44] reported that MDA was detected in nonsterilized materials due to the fact that MDI, a starting reagent, is sometimes used in excess during PU fabrication, and rapidly converted to MDA in a moist atmosphere. With increasing concern about the health risks associated with MDA in polyurethanes, such reactions must be stringently avoided.

5.3.1.3 Influence of Liquids

Strong acids and bases are generally detrimental to PUs due to their initiation of chemical degradation reactions, but certain solvents, specifically solvents such as toluene, acetone, methyl ethyl ketone, and ethyl acetate, also affect the properties of polyurethanes adversely.[45] However, even with solvents that are not harsh to the chemistry of PU material and do not dissolve PU, other adverse phenomena might take place. For example, when a solid PU is placed in contact with such solvents, extraction and desorption of additives, such as plasticizers and stabilizers, can occur. Additives and/or unreacted products can be extracted by solvents.[22]

Each solvent used complicates the fabrication process not only because it eventually requires removal but also because it may contain or attract impurities as well as participates in undesirable chemical reactions.[41] The solvents DMF and dimethylacetamide, used for dissolving Biomer™ and Pellethane™, very likely contain amine-type impurities, such as dimethylamine and tertiary amines. This is a concern because secondary and tertiary amines may catalyze the hydrolysis of allophanate, biuret, urethane, and urea linkages.[41] Among the consequences of these chemical changes may be a decrease of the solution viscosity, changes in the molecular weight distribution, and changes in the mechanical properties of the polymers. DMF and dimethylacetamide should therefore be used dry and amine-free. Moreover, the ether-based solvents THF and dioxane are susceptible to oxidation to peroxides and further degradation products.[41] Such species may induce oxidative chain reactions, which lead to scission or discoloration in PEUs. These hygroscopic ether-based solvents should be kept dry and free of oxygen before and during use. Furthermore, Nair[46] reported considerable decreases of thermal properties if PUs suffer from swelling due to solvent exposure; crosslinks formed by the urethane links may be disrupted if the extent of swelling is too high.

5.3.2 Degradation During Sterilization

5.3.2.1 Degradation During Thermal Sterilization

Steam sterilization by autoclaving has traditionally been very widely used for biomedical instruments.[46] Accordingly, a number of studies have addressed the question whether this procedure causes any damage to polyurethanes. Mazzu and Smith[47] did not detect any traces of MDA after extruded Pellethane™ 2363-80AE had been sterilized for 30 minutes using a standard autoclave at 125°C, nor when the same material had been treated for 5 hours with a dry heat sterilization technique at 125°C. MDA was detected only after longer durations (90 and

180 minutes) of steam autoclaving, indicating that both steam and prolonged thermal exposure are necessary to cause measurable release of MDA, which most likely originated from hydrolysis reactions.[47] They also found that the molecular weight of Pellethane™ 2363-80AE decreased linearly with increasing duration of autoclaving. In contrast, Shintani[44] reported no molecular weight changes of the same PU formulation following autoclave sterilization. This apparent contradiction may be due to a difference in sample thickness, with the progress in hydrolysis from the surface to μm levels not measurably affecting the weight of thick samples. In addition, Shintani and Nakamura[48] reported that the amount of MDA detected in thermosetting PUs after autoclave sterilization (121°C for 30 minutes) was the same as that before autoclaving. They concluded that their PU samples were stable towards autoclaving-induced hydrolysis reactions. These studies suggest that at least some thermosetting PUs, if properly manufactured, should be sufficiently stable so that release of MDA and other potentially toxic degradation products is not accelerated by the standard autoclaving sterilization procedure.

5.3.2.2 Degradation During Ethylene Oxide Sterilization

Ethylene oxide (EO) gas sterilization is also widely used to sterilize PU-containing biomedical devices, but surprisingly the detailed chemical molecular effects of EO exposure of PUs are insufficiently clarified. Abraham et al[49] reported that EO-sterilized BioSpan® series PUs, which are thermosetting materials, showed higher ultimate tear strength values than nonsterilized samples. In addition, GPC measurements showed that EO sterilization produced a measurable reduction in the average molecular weight of BioSpan® materials. Moreover, SEM micrographs of BioSpan® PUs sterilized with EO showed extensive surface pitting. On the other hand, EO sterilization did not exert any significant effects on the molecular weights and their distributions of ChronoFlex® materials, and the surface of these samples appeared unaffected in SEM.[49] No MDA was detected following EO sterilization of Pellethane™ 2363-80AE.[47] Therefore it appears that EO treatment appears not to affect the integrity of some PUs, but we note that it has been reported to interact with additives present in PU formulations.[49] Possible effects of EO on additives and plasticizers require further investigation.

5.3.2.3 Degradation During Radiation Sterilization

Exposure of polymers to high energy radiation invariably creates radicals inside the material; these radicals can then react with O_2 dissolved in the polymer (or in-diffusing from the atmosphere if the polymer was degassed prior to radiation sterilization), and some radicals will react with other radicals. The addition of O_2 leads to peroxy radicals which, by abstracting hydrogen, convert to hydroperoxides or, by combining, convert to peroxides. These metastable groups can dissociate with time or upon thermal activation, regenerating radicals that again participate in various reaction cycles. The net result is the production of various oxidative groups, chain scissions, and crosslinks; that is, the polymer becomes more polar and more heterogeneous. Clearly, radicals that serve as seeds of oxidative chain reactions are produced during radiation sterilization. As this is an unavoidable consequence of high energy radiation treatments, the question becomes whether the reactions thus initiated in the PUs occur to an extent that leads to unacceptable consequences, perhaps by interacting and amplifying biologically induced degradation reactions, or by providing sites for attack by biological agents such as oxidative enzymes.

Shintani and Nakamura[50] reported that gamma-ray irradiation produced MDA in MDI-based PUs. MDA formation was attributed to the radiation cleaving urethane linkages proximal to terminal free amino groups. They also found that MDA formation increased with increasing irradiation dose according to a second-order regression equation. MDA was found

to form at amounts of a few ppm at 10 Mrad irradiation intensity, while at 2.5 Mrad intensity the amount was less than one ppm. This indicated that the susceptibility to MDA formation was borderline; although 2.5 Mrad of intensity is the officially approved level for sterilization of medical devices, some microorganisms such as *Bacillus pumilus* and *Clostridium botulinum* can survive this treatment and consequently require higher irradiation levels for satisfactory sterilization; 6 Mrad intensity is recommended for devices that have to be disinfected from these pathogens.[50] Another study found that the elution of MDA and other low molecular weight compounds from irradiated material increased with increasing irradiation dose.[44] The molecular weight distribution as well as the ultimate tear strength of gamma-ray irradiated PTMO/MDI/BD-based PUs decreased linearly with increasing irradiation dose.[44]

Radiation sterilization of polyurethanes should therefore be considered with caution and its effects thoroughly documented for a new material.

5.3.2.4 Other Effects

The level of degradation caused by sterilization seems to vary with the combination of sterilization method and the chemical components of PU polymers; especially important is thought to be the polyol portion.[51] Shintani reported that sterilization produced higher amounts of MDA from PUs fabricated with smaller molecular weight polyols than from PUs fabricated from larger molecular weight polyols.[51] While the number of reliable studies is far less than the variety of polyurethane formulations, however, no general rules can be given with any confidence. Each PU should be tested thoroughly. As a starting point, for PUs EO treatment may be preferable to other sterilization methods, as it seems to cause less change in the properties of the materials.[49,51] It would appear that gamma-ray sterilization is most likely to produce MDA and other low molecular weight compounds.[51]

5.3.3 Influence of Storage and Handling on Polyurethanes

Degradation of biomedical PU materials and devices during storage (shelf life) has been a concern for years. As mentioned by Coury et al,[41] the storage of PU raw materials and the storage of finished PU devices contain some common features and some distinct issues. Polyurethane pellets (which is how e.g., Pellethane™ and Tecoflex® are commonly supplied) should be protected from moisture and ultraviolet radiation.[41] While slow hydrolysis may occur on storage, water moisture in pellets probably exerts its most adverse effects during high temperature processing where it can lead to a marked extent of various fast hydrolytic reactions. PU materials supplied in solution form must also be protected from moisture as well as ultraviolet radiation. Coury et al[41] reported that moisture during curing produced an intractable skin inside a Cardiothane® 51 container.

Finished polyurethanes are susceptible to harsh environmental conditions. Pellethane™ 2363-80A films exposed to outdoor weathering showed severe degradation of tensile properties over a 6-month exposure. Pellethane™ 2363-55D was more resistant than Pellethane™ 2363-80A under the same conditions.[41] This can be rationalized by the fact that the extent of photodegradation of PUs generally decreases with increasing polymer stiffness and crystallinity.[52] Deng et al[53] reported very similar stress-strain curves of a polyester-urethane exposed to various conditions: aged for 2 days under no or low prestrain (0% and 20%) in two environments (25°C and 85°C in air). In contrast, for polyester-urethane elastomer samples aged while exposed to high strain levels (200% and 400%), the behavior of the stress-strain curves was strongly influenced by the aging environment. Aging under high strain caused a substantial increase in the brittleness of the materials. Albrecht and Zehendner[54] compared the natural aging of a rigid PU foam at 23°C over 5 years with the aging over 25 and 39 weeks at 70°C. It

was observed that the 70°C storage for 25 and 39 weeks represented a lower level of aging than 5 years storage at 23°C.

Storage considerations for the finished components must also address retention of dimensional characteristics, sterility and cleanliness.[41] As recommended by Coury et al[41] the parts should be placed in fixtures and containers, which apply low stress. Storage temperature should be moderate to prevent mechanical set. Devices in their storage and shipping containers should be run through a qualification protocol to assure that the package provides protection from UV radiation and microbial and other contamination. PUs, while extremely tough, are subject to mechanical damage if aggressively handled. For example, some surgical equipment can acutely damage PU components.

5.4 Biodegradation of Polyurethanes

In this section, we review pertinent literature on the manifestations and mechanisms of biodegradation during in vivo usage of biomedical polyurethanes. This Chapter does not, however, detail how biodegradation influences the clinical performance of PU-based devices; this subject is discussed in Chapter 8 of this book.

Analysis and interpretation of in vivo degradation data needs to take into account that it is often difficult to perform experiments with an adequate level of control over the many variables that may influence the performance and longevity of the device. An example is the analysis of explanted pacemakers, which had been in use for varying periods of time and for which detailed records were not available since it had not been anticipated that the need for failure analysis would arise. There is also the issue of biological variability between subjects. When performing in vivo experiments with test animals such as dogs or sheep, some compromises may also be required in order to meet the needs of both the pathologist and the materials scientist.[55,56]

Another critical but difficult issue is the preparation of retrieved samples for analyses. The complete removal of anchoring tissue, cellular material, adsorbed blood clots, or other proteinaceous layers from retrieved medical devices is necessary for studying changes to bulk and particularly surface properties of PUs. Following explantation, however, medical devices are usually fixed with formaldehyde or glutaraldehyde, which causes the tissue to become crosslinked and tightly attached to the device. Fixed tissues thus are usually difficult to fully remove from implants, and the cleaning procedure may introduce artefacts in the analysis of the cleaned explanted material. For example, if the tissues are not completely removed, it may not be possible to assess biodegradation-induced alterations of the surface chemistry and mechanical properties of the materials or, if measured, these may be difficult to interpret.[55,56] Only descriptions on the macroscopic scale, such as changes in dimension, color, cracking and fissuring, can be reliably done if residual anchored tissue, lipids and/or proteins are still present.

In order to examine the chemical details of degradation of explanted devices, anchoring tissues must be removed. Attempts have been made to remove these tissues from medical devices by using for example sodium bicarbonate, bleaching agents, or pancreatin.[55,56] However, these cleaning procedures have been shown in some instances not to completely remove the fixed tissues sufficient for analysis of the PU surface by surface-sensitive analytical methods. Other techniques which include strong acidic and alkaline conditions have been therefore investigated. Although some techniques can be effective in removing anchoring tissue, it must be considered that they can also be too harsh on the PU and lead to damage of the material.[55,56] For instance, Zang et al[55,56] reported that strong acidic and alkaline conditions, used to clean vascular prostheses, reduced the carbonate group content near the surface of Vascugraft® prostheses and reduced the molecular weight and urethane content of the material. In addition, the same studies found that the use of elevated temperatures (near boiling point) resulted in major

changes to the microporous and microfibrous morphology of the PU vascular graft. Thus, it is recommended that control "cleaning" experiments should be carried out on virgin material under the same conditions as on explanted devices in order to distinguish between effects of implantation and those of the cleaning agent.

5.4.1 Degradation During In Vivo Applications

5.4.1.1 Pacemaker Lead Insulators

In 1986, Pirzada et al[57] reported on the first long-term follow-up of a unipolar PU coated electrode in patients. They mentioned that surface cracking leading to insulation failure was relatively uncommon and, when observed, occurred mainly at the suture site. However, only macroscopic characterizations were performed, and chemical changes would have gone undetected.

Some years later, Chawla et al[32] examined by light microscopy, SEM, and FT-IR spectroscopy explanted PU cardiac pacing leads that had developed early electrical malfunction. They reported that all explanted leads exhibited some damage to the PU insulation. In visual inspection, the most evident damage was the presence of cracks in the insulation. Additionally, most of the explanted leads had opaque areas with rough and frosty surfaces. Samples of explanted lead insulation showed evidence of physical damage at 30x and 300x SEM magnifications. The damage was in the form of transverse bands of erosion or dissolution alternating with less degraded zones. Furthermore, the insulation adjacent to the electrode showed cracks and erosion. Material shrinkage appeared to have further damaged the sheath at its junction with the electrode tyne, suggesting that stress or stretching accelerated the degradation. Moreover, the study found by FT-IR that for the explanted leads the 3000-2800 (C-H bands), 1730 (C=O), 1368 (CH_3), and 1105 (C-O) cm^{-1} regions had decreased in intensity compared to those for the reference PU tubing, suggesting degradative changes in the polyether components.

Explanted leads from human patients have also been reported to be frequently damaged at the inner insulation, sometimes with degradation to the inner surfaces of the outer tubing (coaxial lead conductor) (Fig. 5.3).[58-60] Stokes et al[58-60] reported that the appearance of the degraded polymers ranged from soft and gummy material with no color development to amber or even nearly black, brittle chunks. These degraded areas were, however, relatively small, affecting only a few millimeters of the 58-cm long device. A decrease of PTMO ether content was also observed in explanted leads. In addition, Stokes et al[58-60] reported that cubic crystals were sometimes found at or near the site of degradation. These were reported to be composed of silver and chlorine, suggesting that metal had been released from conductor coils and entered into contact with PU parts, playing a role in its biodegradation. Indeed, the concentration of transition metals in PU lead insulation explanted from human patients appeared to increase with implantation time even when there were no clear signs of bulk degradation. Nickel was present on the luminal surface of the PU insulation at and near degradation sites, while silver, cobalt, iron, and chromium were seen occasionally.[58-60] Various metals and alloys appeared to have differing influences on the biodegradation: the severity of damage done to Pellethane™ 2363-80A in vivo was in the order Co >> Fe, MP35N > DBS, Mo, Ag > 304SS, Cr, Ti > Elgiloy > Ni > Pt. Thus, the presence of metals at or near the degradation sites of PU parts coupled with corrosion of metallic parts provides strong evidence that these materials can be involved in the polymer degradation process.

Following a one-year subcutaneous implantation in rabbits, Pellethane™ 2363-80A tubing over cobalt mandrels experienced severe degradation; cracking completely through its entire thickness at metal contact points in three out of five specimens.[58-60]

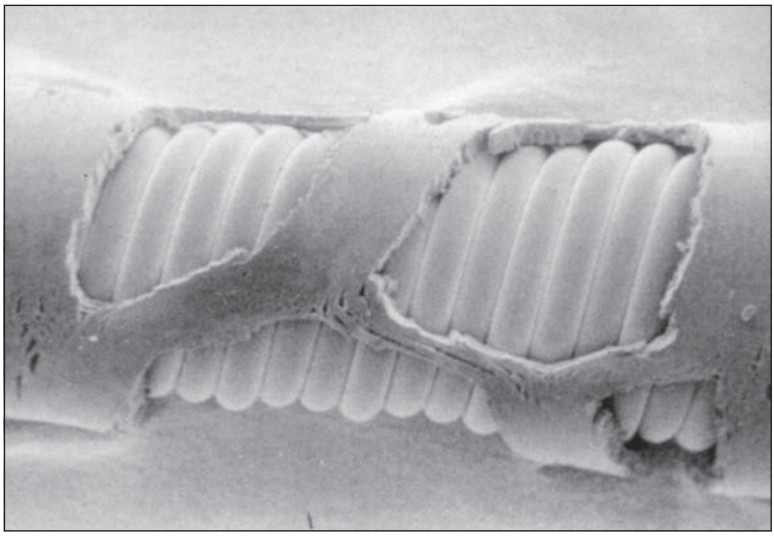

Fig. 5.3. An early cardiac pacing lead explanted 14 months after implantation. Residual stress in the insulation resulted in cracks perpendicular to the long axis of the device. Magnification 14x. Reprinted with permission from: Stokes KB. Polyether polyurethanes: biostable or not? Journal of Biomaterials Applications 1988; 3: 228-279.

5.4.1.2 Heart Valves

In animal trials, PU valves have been shown to succumb mostly to calcification, thrombosis, or mechanical failure. Mackay et al[61] reported that early PU valves had not performed well in durability tests, with failure occurring within less than 100 millions cycles, the equivalent of approximately 2.5 years cycling at physiological rates. In contrast, more recent prototype PU valves made of Lycra® 156C successfully completed more than 400 million cycles (equivalent to ~10 years in vivo operation) and some PEUU valves exceeded 800 million cycles without failure (equivalent to more than ~20 years of clinical function).[61] Comparison with similar valves fabricated from a PEU material suggested that the PEU valve was likely to fail sooner than a valve made of PEUU.

In addition, Mackay et al[61] reported that calcium deposits tended to accumulate in regions of stress concentration and in proximity to surface defects. Both calcium and phosphorus were present in the adherent calcified plaque-like material on the leaflet surfaces. Morphologically, two distinct types of calcification were observed: one was associated with the PU surface or the interface between the leaflet surface and micro-thrombi or fibrous sheath; the other was characterized by calcification associated with degenerated cells. Hilbert et al[62] reported that calcification related to alterations in the physico-chemical properties of the PU may develop independent of surface thrombotic material, fibrous sheath formation, and the degeneration of cells. Calcium deposits are generally attached to microbubbles, which have been observed on the PU leaflet. In addition, the surfaces of nonmoving parts showed no evidence of thrombus formation or calcification.

5.4.1.3 Vascular Prostheses

Much research effort has centered on the development of artificial blood vessels, particularly small diameter vascular grafts, and polyurethanes have attracted attention because of their suitable mechanical properties. However, because of the intended long duration of such implants, the question of biostability becomes crucial to the success of such a device. The biostability of a microporous hydrophilic vascular prosthesis made from Mitrathane® presents an interesting example. Mitrathane® is a PTMO/MDI/ED-based PU. Paynter et al[63] reported that after six months (the longest implantation period investigated) all of the implanted grafts were occluded by thrombosis and were degraded to varying degrees on the external surface. It was further concluded that the gross in vivo surface degradation of Mitrathane® prostheses, observed after six months, could not have been caused by simple chemical hydrolysis alone, as the polymer was found to be stable when immersed in water at 37°C for at least 11 months. Following 15 days of implantation in mice, Maurin et al[64] observed small fissures in fragments of implanted Mitrathane® and suggested that they may be a consequence of swelling and deswelling. The reader is referred to Chapter 8 for further details on PU-based vascular prostheses.

5.4.1.4 Breast Implants

The use of PU materials for the reconstruction of the female breast has over the years spawned considerable debate. In this context, we are not concerned with the question of mechanical suitability, viz., the resistance to rupture due to mechanical stress; but mostly the question of biological attack onto the integrity of the PU material is the subject of this section, although of course such biodegradation may weaken the resistance towards mechanically induced rupture. The most noticeable manifestation of insufficient biocompatibility of breast implants is the formation of a capsule around the implant. However, whereas the capsules formed around silicone breast implants consisted almost entirely of connective tissue, the capsules formed around PU-covered silicone breast reconstruction prostheses indicated a foreign body reaction.[65,66] Interestingly, some workers found that following explantation the PU foam was missing; only the basal layer of the foam was still observed by SEM.[65,67] This indicates removal of substantial amounts of material by biodegradative processes. It was also reported that the foreign body reaction (in the form of granulations) sometimes continued even after removal of the implant.[65] This may suggest that some PU material or breakdown products were still present at the implantation site. In a case report, Slade and Peterson[67] mentioned that in one patient there was an almost complete disintegration of the PU foam cover over a 9-year period. In another investigation, Smahel[68] removed PU-covered implants from patients between 3-36 months after implantation. He noted in each case that the PU had fragmented. Furthermore, Sinclair et al[69] reported that 52% (39 of 75) of retrieved PU-covered breast implants showed an extent of reduction in structural and mechanical integrity such as to make intact foam unretrievable. They also mentioned that there was a significant negative association between the duration of implantation and the likelihood of retrieving intact PU foam. Moreover, they found some fracture lines and fissures in the structure even in specimens removed within 5 days after implantation. Histological sections of the capsules from implants in which intact foam was recovered enzymatically showed typical triangular appearance of the structure. Foam was present in more than half of the capsules.

On the other hand, Szycher and Siciliano[70] reported very different conclusions, finding that PU foam cover had undergone only very slow bioresorption, even after 9 years of human implantation. They reported that they were able to recover some intact PU foam from a 9-year implant. Moreover, they claimed that the "foam fragmentation" observed by other investiga-

tors may have been due to a misinterpretation of the intricate open-celled structure of the PU foam.

Thus, the literature is contradictory, but it would appear that the scope for biodegradation of the PU foam cover needs to be carefully ascertained when proposing new PU materials for this application.

5.4.1.5 Gastric Bubbles

Some PU materials, such as aromatic-based polyester-urethanes, have been also used in the fabrication of gastric bubbles. These devices have been used as a temporary adjunct to diet and behavior-modification therapy for obesity.[71] When implanted, gastric bubbles are floating freely in the stomach, where they are directly exposed to gastric juices, which possess a pH of ~ 1.2. With such a low pH the scope for acid-catalyzed degradation exists and hence these conditions of implantation must be considered as very hostile compared to other end-use applications. Dillon and Hughes[71] reported that five PU gastric bubbles had undergone severe degradation following four months implantation in humans. They found that consequent upon exposure to the gastric fluid the PU materials of these gastric bubbles had suffered a 39-55% decrease in average molecular weight, a 9°C decrease in the glass transition temperature, the disappearance of soft segment crystallinity, and a broadening of the hard segment melting region.

5.5 Biological Activity Involved in Polyurethane Biodegradation

What are the biological agents of the host body that may cause biodegradation of PUs? It appears that the act of implantation activates the host's defense system, which sees the introduction of the biomedical device not as the intended beneficial act but as a breach of the body's integrity. Mammalian metabolisms have evolved a variety of host defense mechanisms to combat the intrusion of a foreign entity. In excellent reviews, Williams[9,10] suggested that the biological defense activity of the host might involve enzymatic attack and active cellular digestion. Proteolytic enzymes fulfil a key role in the removal of protein-based intrusive entities, and digestion of material by macrophages is a nonspecific defense reaction. More recently, oxidative enzymes have been considered as major agents of biodegradation. However, other contributions may also exist.

There has been consideration of a possible contribution by bacteria in, for example, the degradation of sutures in an infected wound. Too little is known of this subject, however, to draw firm conclusions and assess questions such as the ability of bacteria to utilize the nutritional potential of the carbon content of organic polymers.[9,10] Lipid solubilisation of some components of a polymer may also be a potential contribution in the biodegradation of PU materials; extraction of low-molecular-weight material has been postulated to be an important concern in the initial processes of degradation[22] as such extraction makes a material more brittle (low molecular weight materials acting as plasticizers) and thus more vulnerable to cracking from residual stresses. Lipids can also interact with some enzymes.[22] In addition, Takahara et al[72] reported that phosphatidylcholine and cholesterol were not only adsorbed onto the surface of PU but also absorbed into PU. Degradation of the tensile properties and the fatigue life by lipid sorption was observed for some PU formulations.[73,74] All of these, and possibly many other factors not yet considered, may contribute to the phenomenon of biodegradation.[9,10] Apparently, the biodegradation of PU materials results from complex interactions between the material and the host organism.

This complexity makes it not only difficult to unravel the biological and chemical pathways of biodegradation, it also raises the question of what an appropriate accelerated in vitro

test for the biodegradation of PUs should be based on. To appreciate the relevance of the various accelerated tests used to study the biodegradation of PUs, it is essential to briefly review cellular interactions with PUs.

The implantation of any foreign material in soft tissue initiates, regardless of the tissue or organ into which it is implanted, an inflammatory response.[3,4] The predominant cell type present in the inflammatory response varies over time after the injury.[3,4] In general, the inflammatory response is characterized by an early acute phase, which is dominated by polymorphonuclear leukocytes (PMNs) and a later, chronic phase controlled by mononuclear cells, such as macrophages and lymphocytes.[3,4,75] For example, in the exudate around Biomer™ implants, the acute phase of the inflammatory response was still prevalent at 4 days, with PMNs remaining the predominant cell type around the implant.[76] At 7 and 21 days, however, mononuclear leukocytes, which include macrophages and lymphocytes were predominant and reflected a change in the inflammatory response from acute to mildly chronic. These events, in general, apply to most biomedical materials, but may vary in intensity and duration depending on polymer surface properties.[77] Activation of the inflammatory cells may occur following adhesion of the cells to the surface of synthetic materials and/or through a nonadhesive mechanism.[78,79] Both adhesive and nonadhesive events between the cells in the exudate and the materials surface may therefore participate in the polymer degradation.

Considering the short lifetime of PMNs (hours to days), it might be tempting to conjecture that extensive biodegradation occurs mainly because of macrophages attempting digestion of the material, since these cells have a lifetime of days to weeks. However, interestingly, Williams[9,10] reported that nylon specimens implanted in one rat for a total of ten weeks showed slight degradation compared to a nonimplanted control, while specimens continuously reimplanted every week for the same total of ten weeks showed much greater degradation. Silk sutures, on the other hand, showed the reverse situation, with reimplanted specimens exhibiting less degradation than those maintained in a single animal. These experiments would indicate that the nature of the material determines whether the stability of a material is affected by the acute phase of the inflammatory response (dominated by PMNs) or by the chronic phase where macrophages and lymphocytes dominate.

Marchant et al[80] reported leukocyte adhesion and spreading along with the presence and growth of multinucleated foreign body giant cells (FBGCs) on Biomer™ samples. Although PMNs were dominant in the exudate at 4 days, the adherent leukocytes were reported to be predominantly macrophages. Hence it seems that macrophages rather than PMNs and lymphocytes preferentially adhered to the PU materials. More recently, Zhao et al[81] implanted prestressed Pellethane™ 2363-80A in rats under three different conditions, which were: (i) an intense inflammatory reaction, (ii) a normal inflammatory reaction, and (iii) a suppressed inflammatory reaction. The normal inflammatory condition caused severe cracking or rupture of the PEU specimens as early as 5 weeks following implantation. Chain cleavage along with a reduction in the molecular weight of the material was evident. Interestingly, however, neither surface cracking nor polymer chain degradation was found with the same materials implanted with a severe inflammatory response over 15 weeks. Although the severe inflammatory response caused an increased concentration of macrophages, Zhao et al[81] reported that the natural functions of the phagocytic leukocytes were destroyed, resulting in premature death of these cells before they could adhere to the foreign body surface. In this case the material was protected from degradation by the loss of cellular viability. On the other hand, no cracking was observed with prestressed specimens in the presence of the suppressed reaction, even after 10 weeks implantation. In fact, the few adherent cells found on the polymer surface did not exhibit any phagocytic function. Thus, the results of Zhao et al[81] demonstrate that cracking or rupture of PUs is associated with macrophage adhesion.

In another investigation, Zhao et al[82] reported that at 5 and 10 weeks post-implantation, some isolated frosty areas, which occupied 20-40% of the total sample areas, were evident under an optical microscope. Under SEM, those frosty areas consisted mainly of micro-cracks with some pitting. Interestingly, while cracking and pitting were found in the areas where FBGCs had resided on the 5-week implant (Fig. 5.4) and 10-week implant (Fig. 5.5), no cracking or pitting was found in the areas without adherent cells. FBGCs are formed during the inflammatory reaction by the fusion of activated macrophages that adhere to the surface of the implant.[83,84] FBGCs became a dominant feature of cell adhesion on PU with increasing implantation time. It thus appears that the adherent cells may isolate the polymer surface areas they are in contact with and release products which may include active oxygen species, hydrogen peroxide, and/or hydrolytic enzymes, all of which may be capable of attacking the polymer surface underneath the cell membrane. Page et al[78] reported that most enzymes are released rapidly, frequently within 4-6 hours, and in large quantities. Up to 80% of the total enzyme content within a cell may be released extracellularly after macrophages are exposed to any of a large number of inflammation-inducing substances. The enzyme released appeared to include acid hydrolases, such as cathepsins, glycosidases, acid phosphatase, aryl sulfatase, and others. In addition to acid hydrolases, stimulated macrophages may synthesize and secrete several other enzymes, which operate at neutral pH. These include collagenase, elastase, plasminogen activator, and lysosymes. It should be noted that macrophages vary considerably with regard to their levels of cellular proteins and enzymes, depending on their site of origin and the stimuli to which they have been exposed.[78,79] Interestingly, Henson found that the amount of lysosomal enzymes released during phagocytosis was dependent on the size of the polymer article, with larger particles inducing greater amounts of release of enzymes.[85]

5.6 Pathways of Polyurethanes Biodegradation

5.6.1 Hydrolysis

Polyester-urethanes were the subject of much early effort but their stability proved insufficient, and thus most of this class of materials has been removed from the market for long-term applications. Hence, discussion of the hydrolytic degradation of these materials may seem to be of historical interest only. However, with the increasing interest in tissue engineering and the resultant desire to produce controllable degradable scaffold materials, which have a tolerable inflammatory response, the lack of hydrolytic stability of polyester-urethanes may turn from a drawback into an attractive feature. The rich variety of polyester-urethane compositions may allow fine-tuning of degradation rates over a considerable range.

The aliphatic ester linkages in polyester-urethanes are known to be susceptible to hydrolytic degradation.[86] It has been observed that polyester-urethanes degrade and become fragmented within months as a result of hydrolytic decomposition; the kinetics of hydrolysis can be described in terms of a first-order reaction with an average induction period of 7 days.[87] The biomedical environment adds an extra factor to the degradation process as indicated by the fact that the kinetics of scission of polyester-urethanes were about 10 times greater than for the same materials aged in a 50% relative humidity atmosphere.[88] At elevated temperatures, on the other hand, such as during extrusion or injection molding, some PEUs are susceptible to rapid hydrolysis by H_2O if not properly dried. Whereas PUs based on PTMO, poly (hexanediol-1,6-carbonate), and poly(butylene-1,4-adipate) are known to possess good hydrolytic stability, much faster degradation was observed for PUs containing poly(ethylene adipate), poly(diethylene glycol adipate) or poly(alkylene tartrate).[87] The same study also reported that under moderately acidic conditions, PUs synthesized from aromatic diisocyanates are less stable

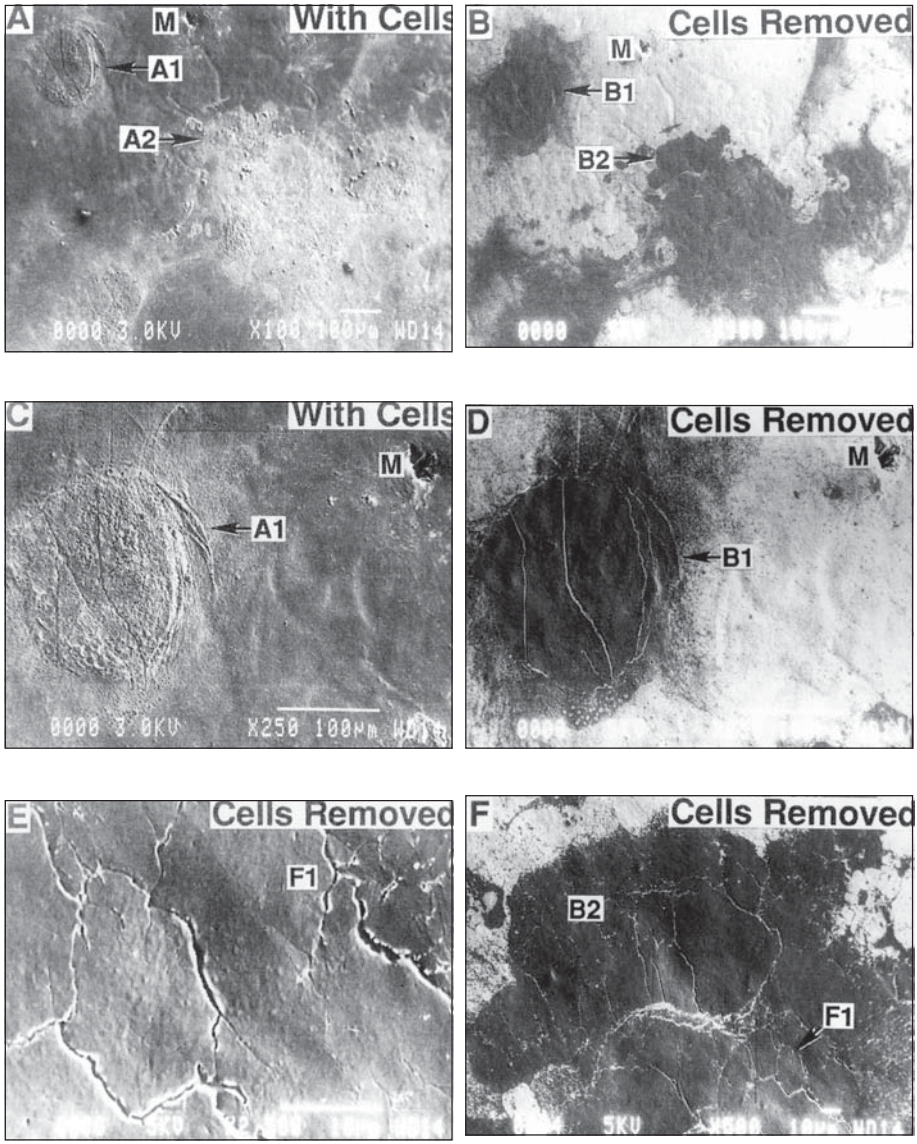

Fig. 5.4. SEM analysis of cracking of polyurethane due to cell adhesion during 5 weeks implantation. (A) specimen prior to removal of FBGC cell areas marked A1 and A2, original magnification x100. (B) same area as in (A) after removal of cells, showing footprints of the FBGCs corresponding to: B1 to A1 and B2 to A2; original magnification x100. (C) Area A1 with cells, original magnification x250. (D) Area B1 after cell removal, showing cracking of the polymer surface and at the cell perimeter; original magnification x250. (E) Cracked area F1 after cell removal, original magnification x2500. (F) Area B2 after cell removal, F1 cracked surface area under FBGC; original magnification x500. M = pinhole marker. Reprinted with permission from: Zhao Q, Topham N, Anderson JM et al. Foreign-body giant cells and polyurethane biostability: In vivo correlation of cell adhesion and surface cracking. J Biomed Mater Res 1991; 25: 177-183.

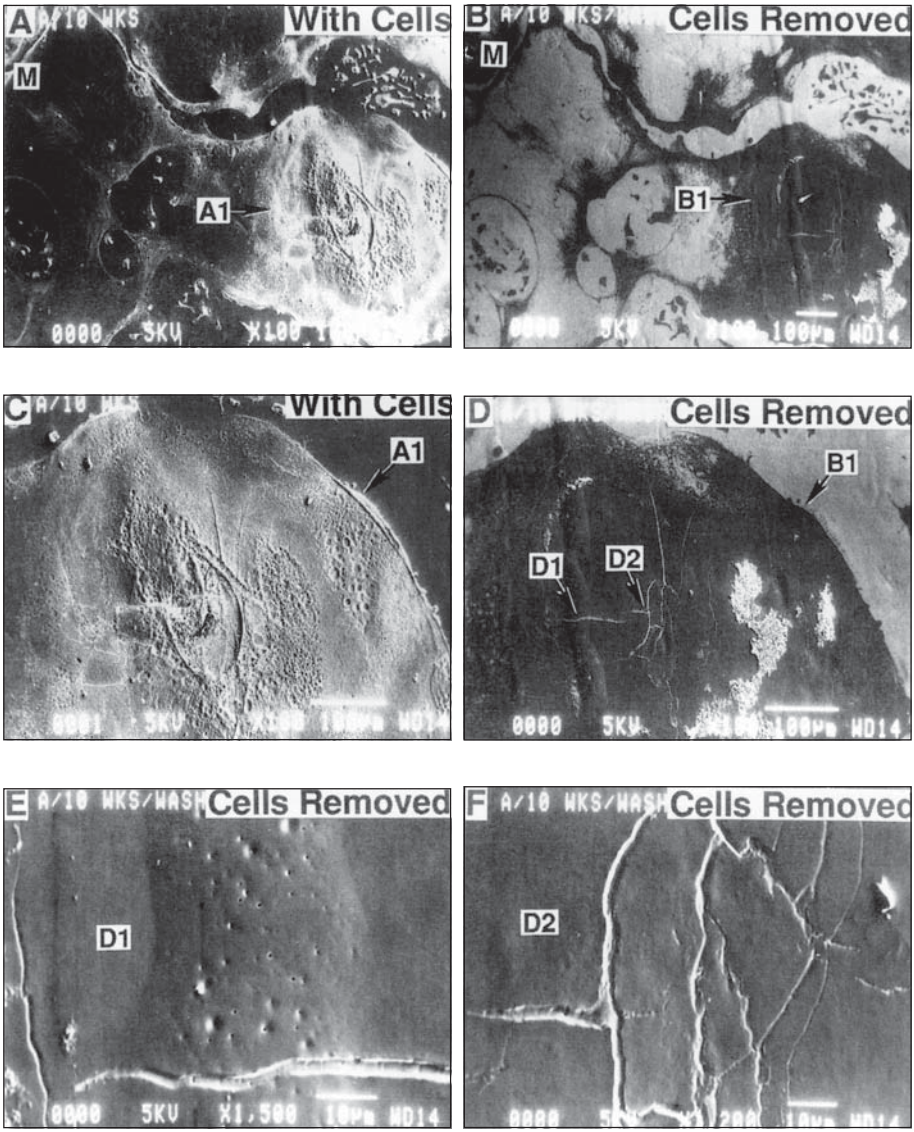

Fig. 5.5. SEM analysis of cracking of polyurethane due to cell adhesion during 10 weeks implantation. (A) specimen prior to removal of FBGC cell area A1, original magnification x100. (B) same area as in (A) after cell removal, showing footprints of the FBGCs; original magnification x100. (C) Area A1 with cells, original magnification x180. (D) Area after cell removal, D1 = cracked surface area under the FBGCs, D2 = another area of cracking under the same area of FBGCs; original magnification x180. (E) Area D1 (after cell removal) showing cracking and pitting of the polymer, original magnification x1500. (F) Area D2 (after cell removal) showing cracking of the polymer; original magnification x1200. M = pinhole marker. Reprinted with permission from: Zhao Q, Topham N, Anderson JM et al. Foreign-body giant cells and polyurethane biostability: In vivo correlation of cell adhesion and surface cracking. J Biomed Mater Res 1991; 25: 177-183.

than those containing aliphatic diisocyanates. Lai[89] found that PU hydrogels derived from polyether-based prepolymers and hydrophilic monomers had questionable hydrolytic stability if they were prepared in nonpolar solvents, but surprisingly the PU hydrogels were hydrolytically stable if prepared in the absence of solvent. This might be due to the strong association of the hydrophilic monomer with the polar portion of the urethane prepolymer in nonpolar solvent.

As discussed by Williams[9,10] the in vivo performance, especially hydrolysis, of biomedical polymers in general obeys these rules, which of course are in agreement with well-established chemical principles:

- polymers with minimal water absorption and no hydrolysable bonds are not expected to be degraded in aqueous environments. PTFE is an obvious example.
- polymers displaying water absorption, but no hydrolysable bonds may swell and absorb species, but are unlikely to degrade. Acrylic polymers (polymethylmethacrylate) are examples.
- polymers with limited water absorption but with hydrolysable bonds may be mostly hydrolysed near the surface, but with minimal bulk degradation. Certain aromatic polyesters are examples.
- Polymers, which are hydrophilic, water absorbing, and hydrolysable are predisposed to degrade severely. Certain polyamides and aliphatic polyesters are examples, as are the polylactides.

Hydrocarbon and fluorocarbon polymers are stable towards hydrolysis, while polymers containing heteroatoms (the most important of which are O and N) in polar groups (involving C-N or C-O bonds for instance) can be susceptible to hydrolysis and other forms of degradation.

The propensity of PUs for hydrolysis is mainly associated with the hydrolytic instability of ester groups.[87] The hydrolysis resistance of PUs thus is expected to increase if the accessibility of water to the ester groups is reduced for instance by the presence of adjacent hydrophobic segments.

5.6.2 Oxidation

The polyether segment of PU materials is thought to be the structural element that is most susceptible to oxidative attack, whereas it is highly resistant to hydrolysis. It is well known that C-H bonds adjacent to ether groups are susceptible to homolytic bond cleavage by radical reactions. Thus, the presence of radicals or potentially radical-forming species, such as peroxides and hydroperoxides, must be avoided. The detailed mechanisms of oxidative attack in the biomedical environment have not yet been fully elucidated, but it appears reasonable to surmise that the same mechanisms apply as in the oxidative degradation of a number of polymers in other applications. The oxidative degradation of polymers has been studied extensively, most prominently so for polyolefins. Polyethylene for instance has been found to degrade by complex schemes of radical-induced oxidative chain reactions and reaction cycles, which in part regenerate radicals for further autocatalytic progress of the degradation. The initial steps are thought to comprise the formation of carbon-centered radicals, for example by mechano-chemical chain scission or by UV exposure. These radicals rapidly react with in-diffusing (or dissolved) atmospheric oxygen (O_2) to produce peroxy radicals. The peroxy radicals can decay by several reactions, some of which generate a new radical, such as the abstraction of a hydrogen atom from a C-H bond by the peroxy radical. Moreover, the hydroperoxide group thus formed is metastable and can decay spontaneously to form oxy radicals (C-O·) which then undergo further radical reactions, such as abstraction of a H atom from C-H to form hydroxy groups. When C-O abstracts a H atom from a C-H bond, however, a new carbon-centered radical is formed and the destructive sequence begins anew. There are

also chain branching reactions and thus the concentration of radicals generally increases with time, accelerating degradation.[52,58,59,86]

It is therefore most important to avoid the introduction of radicals in the fabrication and processing of polyether-containing materials, to avoid providing the seeds for initiation of oxidative reaction cycles. However, evidently the biomedical environment then can initiate analogous degradation reactions; it stands to reason that the in vivo degradation of polyether segments would follow analogous chemical pathways as those known in vitro. The initiation of these pathways in vivo is (if introduction of radicals prior to implantation is minimized or excluded) in all likelihood assignable to host defense reactions involving attempted digestion of the apparent "intruder" (the implant) by oxidative enzymes that produce oxidative radical species.

Initiation of oxidation can be random or site specific. Random initiation is more probable in hydrocarbon polymers such as polyethylene or polypropylene. However, initiation in PEUs tends to be site specific;[13,58,59,86] hydrogen atoms adjacent to carbonyl and ether groups are more easily abstracted by free radical reactions.

The relatively good stability of PUs towards conventional chemical oxidation reagents might suggest that in the in vivo degradation of PUs, noncatalyzed oxidative degradation might be a pathway of minor importance. Also, the available oxygen concentration is low in the in vivo environment. Yet, oxidative enzymes exist and are involved in host defense reactions. Also, it does not require much oxygen to account for the observed rates of degradation in vivo. Thus, oxidative reaction cycles, whether induced by radicals produced during manufacture or by oxidative enzymes, appear capable of leading to in vivo degradation. Oxidative reactions can be much accelerated when catalyzed by transition metal ions, enzymes, light, heat, mechanical stress and, of course, combinations of these factors. The next two sections review two oxidative degradation pathways that have been observed in vivo. These are environmental stress cracking (ESC) and metal ion oxidation (MIO). The difference between ESC and metal ion oxidation is somewhat subtle and can lead to confusion. While both pathways involve oxidative reactions that degrade the average molecular weight of the polymer and thereby its desirable mechanical qualities and ultimately its integrity, the damage to the surface and some of the factors involved appear to be quite different.

5.6.2.1 Environmental Stress Cracking (ESC)

PEU materials are known to be susceptible to a degradative phenomenon involving crack formation and propagation (see Fig. 6.2). For instance Phillips et al[90] reported that micro-fissures appear visually as a frosted area on an otherwise translucent surface. This is usually found in areas of devices where the stress level on the polymer is high. However, the fissures may also appear even if no additional stress has been placed on the polymer. This micro-fissure phenomenon is believed to be a result of residual polymer surface stress, which may have been introduced during fabrication of the device and not sufficiently reduced by annealing. The depth of these surface fissures has been determined to be only 10-15 microns after 3 years of implantation.[90] Typically, devices for which PEUs exhibit this phenomenon, commonly called ESC, are used under low rates of mechanical loading and plastic deformation.[86] Thus, ESC is thought to be not simply a mechanical fracture phenomenon, but the generation of such crazed cracks is assigned to a combination of mechanical stress (residual and/or external) and exposure to some chemical environments.

Different mechanistic hypotheses have been proposed for this pathway of degradation; however, none have been fully satisfactory. ESC evidently involves oxidation of the surface layers of the polymer, generally manifested by the decrease of soft segment ether concentration relative to that of the urethane ether.[86] As ESC appears to be promoted by the presence of cells

adjacent to the PEU-containing implant, it appears reasonable to invoke cellular interactions that cause surface oxidation, as opposed to the process of bulk oxidation which is important in MIO (see below). However, oxidation of the surface of the polymer appears to be insufficient by itself; evidently residual stress is also necessary to produce ESC.[84] ESC appears to be related to the ether content; resistance to ESC increases as the ether content decreases (and hardness increases).[86] In addition, polycarbonate-urethanes have been reported to be generally more resistant to ESC than polyether-urethanes. Stokes et al[86] also reported that the performance of polyether-urethanes can be improved if extruded optimally and the device is annealed, but do not exclude the possibility that subsequent stress may be imposed during implantation. If the latter conjecture indeed applies, the problem of ESC may not be controllable by careful manufacture and annealing processes; surgical handling may also need to be improved. Careful assessment, for instance by sensitive electron spin resonance (ESR) spectroscopy, of the question of radicals introduced during manufacture appears warranted.

The chemical composition of PEUs obviously can be expected to affect the rates with which radical reactions, once initiated, and mechanical stresses cause ESC. For example, Hergenrother et al[91] found by SEM that H_{12}MDI-based PUs were more susceptible to surface cracking than MDI-based PUs. The former materials also manifested more pronounced changes in the molecular weight.

5.6.2.2 Metal Ion Oxidation (MIO)

Transition metal ions are known to be capable of interacting with the auto-oxidative radical reaction cycles, leading to an acceleration of degradation. This has led to the inclusion into the polymer of metal chelating additives in applications such as polyethylene insulation for copper cables. In some biomedical devices likewise, oxidative degradation catalyzed by metal ions may be a contributing mechanism. In fact, implanted PEU devices that contain metallic components may be subject to bulk oxidation catalyzed by corrosion products of the metallic components.[21,58-60] MIO results in the appearance of deep brittle cracks typical of a high rate of loading and does not require mechanical stress to be present.[86] Since metallic components are involved in MIO, it can be presumed that while it ultimately leads to bulk oxidation, the process starts from the interface between the metallic part and the PU, and propagates into the PU. Unlike ESC, MIO does not require cellular interactions. The oxidation potential of an ion depends on its environment and what it is dissolved in or ligated with.[21,59] Effective chelation with an additive within the polymer can largely remove this destructive potential, but in the biomedical device industry such additives are not normally used. The hard segment has been considered a likely site for interaction between PEUs and metal ions.[92] It contains a number of potential sites for metal ion interactions/complexation, such as the amide and ester groups and the carbonyl oxygen.[92] The PEU soft segment is another potential site for metal ion interactions, with crown ether-like structures known to ligate many metal ions. However, the soft segment has less variety in potential binding sites than the hard segment. Whether the hard or soft segment predominates in metal ion interactions leading to MIO, however, has not been experimentally established. The interactions may be more complex than just complexation of ions; Thoma et al[92] have reported that interaction between metal ions and PU materials cause changes in the morphology of the polymer.

5.6.3 Enzymatic Degradation

Even though enzymes are designed for highly specific interactions with particular biological substrates, some appear capable of recognizing and acting upon "unnatural" substrates such as PU polymers. Smith et al[93] found that enzymes are capable of altering polymer structure. A

mechanistic model for the attack by hydrolytic enzymes on PUs has been proposed by Santerre et al.[94] It comprises: 1) water and electrolytes contact the PU and begin to interact with its surface; 2) the surface layers of the PU material undergo motions that lead to "restructuring", a process which entails the rearrangement of segments and chemical structures such as to present a chemical surface composition that minimizes the interfacial energy between the PU surface and the aqueous environment; 3) adsorption of enzymes occurs; 4) adsorbed enzymes react with one or several susceptible bonds at or near the surface. Depending on the formulation, PUs possess one or several types of vulnerable chemical groups that may be available for cleavage by hydrolytic enzymes. These may include urea, urethane, ester, and carbonate groups. Oxidative enzymes are likely to attract primarily the C-H bond adjacent to an ether linkage; these groups are known to be vulnerable to oxidative attack.

Since enzymes are normally substrate specific, their ability to induce PU degradation is surprising. Perhaps the adsorption of an enzyme at the infinite (on the molecular scale) synthetic surface causes conformational changes in some enzymes that then enable them to act on a wider variety of chemical structures than they would normally be capable of attacking. Alternatively, the foreign body response may release enzymes with broad band activity in order to attack and digest the intruding material.

Enzymatic degradation of PU materials has been discussed in terms of oxidative or hydrolytic modes of attack. For example, in the presence of an electron donor and oxygen, oxidative enzymes such as horseradish peroxidase may catalyze the generation of hydrogen peroxide, which is an oxidant.[95] Enzymes producing superoxides are also known to be involved in metabolic and immune defense pathways. However, most studies have concluded that enzymatic attack onto PUs occurs by hydrolytic enzymes rather than oxidative enzymes. Wang et al[96] reported that the chemical structure of two identified products isolated from PCL/TDI/ED exposed to cholesterol esterase (a hydrolytic enzyme) indicated that the ester bonds of the polymer were most susceptible to cleavage. However, this is not a surprising result given this enzyme's task of cleaving alkyl esters, and it needs to be verified whether this route is also important in vivo. The observed lack of stability of polyester-urethanes is consistent with attack by esterases, but it is not clear how important this mechanism would be in polyether-urethanes.

Wang et al[96] observed that the two identified products made up approximately 55% of the release of TDI segments. Since no TDA was detected, one can conclude that the urethane and urea linkages of TDI segments are relatively resistant to hydrolysis by cholesterol esterase. In another investigation, Bouvier et al[34] reported that the soft segment rather than the hard segment of Pellethane™ 2363-80AE appeared most susceptible to enzymatic degradation by trypsin.

Thus, while there appears to be a reasonable case for the involvement of enzymes in the in vivo degradation of PUs, much further study is still needed in order to clarify the molecular biochemical pathways and detailed action routes. In particular interactions between various enzymes, hydrolytic swelling, metal ions, and in-built stresses in the polymer are little understood and likely complex.

5.6.4 Mineralization/Calcification

Calcification (i.e., the deposition of calcium-containing apatite mineral) occurs with a wide spectrum of cardiovascular and noncardiovascular medical devices. In fact, calcification is the leading macroscopic cause of failure of most bioprosthetic heart valves, and it limits the functional lifetime of experimental mechanical blood pumps and polymeric heart valves, including those made with PU parts.[97]

It is important to note that calcification is a normal, physiologic event in the formation of bone, dentin, and tooth enamel. Although calcareous deposits are unusual in functional soft

tissues,[97] calcification occurs on biomaterials when they are implanted into the circulatory system or in certain instances when these same materials reside within connective tissues. Schoen et al[97] reported that in general, the determinants of mineralization include factors related to both host metabolism and the implant structure and chemistry. Mineral nucleation and growth can be observed within the boundaries of the biomaterial, involving its originally implanted constituents (intrinsic), or are associated with elements or tissue not initially implanted such as thrombus, adherent cells, or pseudointima (extrinsic). On smooth-surfaced blood pump bladders, as in trileaflet polymeric heart valves, most deposits were clearly related to an extrinsic calcification mechanism.

It appears that there are similarities between physiological and pathological calcification. For example, the mineral deposited initially in both normal and pathological calcification is almost always a poorly crystalline form of hydroxyapatite, $Ca_{10}(PO_4)_6(OH_2)$, often substituted in carbonate.[97] A second feature common to virtually all forms of calcification is crystal formation on cell membranes, usually in the form of extracellular vesicles. Fisher et al[98] reviewed some factors that must be taken into account when interpreting calcification of biological valves and elastomer PUs. These include mechanical damage, penetration and absorption of blood components, calcium complexation with some functional groups within the material, removal of calcification inhibitors, protein interaction with calcium which may transport calcium phosphate to the material, cell fragments and/or mitochondria of damaged cells may enhance deposition of calcium phosphate, and the age of the patient. Interestingly, Fisher et al found that PU extracts (from methanol and chloroform) calcified to a greater degree than bulk PUs. The tendency of PU to calcify may be more related to the presence of small molecular weight oligomers and/or additives than to the bulk polymer itself. These lower weight materials may be better able to act as ligands for calcium ions or salts.

Calcium-containing deposits have been frequently associated with surface defects, which perhaps originated during fabrication or degradation. Calcification apparently does not occur as readily on defect-free regions of devices.[31] This may relate to the fact that surface defects are high energy sites that are known to be able to initiate adsorption of ions, proteins, and other molecules, and thus act as nucleation sites for crystal growth. Surface defects may in principle occur both on soft and hard segment parts of PUs, but findings by Bernacca et al[99] by FT-IR spectroscopy suggest involvement of the hard segment components in calcification of a PEUU, in contrast to PEU, in which it appeared that the soft segment ether components were more likely to be involved.

Another important factor seems to be the age and the species of the animal used to evaluate biomaterials-associated calcification. The calcium turnover in a young, growing animal differs from that in an adult one, which may result in an earlier and faster calcification of circulatory devices. The loading and number of flex cycles per unit time may also vary with the age of the animal. The implant site can also affect the rate of calcification. Bernacca et al[99] found that PEUU samples calcified to a much lesser degree in a subcutaneous rat implant model than in a bovine pericardial implant site.

As discussed above, biomaterial-associated calcification is a complex mechanism, which is linked to even more complex metabolic phenomena. It is therefore very difficult to determine whether calcification is a pathway of PU degradation or simply occurs as a result of PU degradation, or perhaps even is a molecularly completely separate phenomenon. Nevertheless, calcification can be a cause of device failure.

5.6.5 Others

Since PU materials have been widely used for pacemaker lead insulators, there exists the possibility that electrical discharges can alter the dielectric properties of the insulating sheath

materials. When an insulating material is composed of two or more different phases or contains dispersed macroscopic regions, space charge buildup may occur at the macroscopic interfaces as a result of a difference in the conductivities and dielectric permittivities of the materials comprising the interfaces. The collection of space charge at the interfaces leads to field distortions and possibly to a dielectric loss. Interfacial polarization may result from a number of causes. Since water has a finite solubility in biomedical PUs such as those used for pacemaker lead insulators, it can assist in producing interfacial polarization effects. A number of studies have reported that the interfacial loss is dependent on the quantity of water present.[100-102] Dielectric loss in commercially available polymers may also result from ionic conduction when traces of catalysts or other ionic impurities are present in the materials.

In addition, when materials are exposed to an electrical stress such as in pacemaker lead applications, "treeing" may also occur. Treeing is an electrical prebreakdown phenomenon, which is well-known in polyethylene cable insulation. The term is applied to a type of microscopic damage, which progresses through a dielectric section under electrical stress. Local variations in properties and field strength reinforce localized damage, which progresses along field lines. Its path often resembles the form of a tree, which is thought to be the result of microscopic local electric discharges. One may liken the phenomenon to miniature lightnings striking within the material wherever a path of least resistance is present. Although the voltage used in pacemaker leads does not generally exceed 5V, it has been reported that treeing may start and progress at low electric stress in the presence of moisture without a detectable partial discharge.[100-102] Water absorption, polymer morphology, local defects in the structure or chemical composition, and mechanical stresses are thought to play important roles in the mechanism and the generation of treeing. The microphase-segregated structure of PUs is likely conductive to the establishment of the dielectric conditions involved in treeing. It is also possible that initial degradation could enhance the conditions that lead to treeing. However, little is currently known about treeing in PUs, and it is difficult at this time to extrapolate how much of a concern this particular aspect is in biomedical applications of PUs when they are used adjacent to metallic conductors. More investigation is warranted in order to assess this particular concern.

Photodegradation by UV irradiation may also occur with PU materials. While degradation usually is taken to indicate a decrease in mechanical properties and eventually in integrity by the occurrence of chain scissions, light-induced changes can also involve crosslinking reactions, which tend to increase the brittleness of a polymer. The events are similar to those that occur upon γ-irradiation. Photodegradation occurs following activation of polymer macromolecules by the absorption of photons of light by chromophores in the polymer.[52] Photodegradation can be accelerated by heat, mechanical stress, some organic solvents, various chemicals, and water.[52]

As reviewed by Rabek,[52] photo-oxidative degradation is usually initiated by the abstraction of hydrogen from methylene ($-CH_2-$) groups. Aromatic diisocyanate-based PUs are generally less stable towards exposure to light than those made with aliphatic diisocyanates. The stability of different PUs is believed to follow the order: MDI < TDI < HMDI

As the hard segment content of the PU is increased, the photodegradation efficiency is lowered. The extent of degradation upon photolysis of PUs decreases with increasing polymer stiffness and crystallinity.[52]

5.7 Accelerated Testing Models

As the in vivo degradation mechanisms are not fully understood at the molecular level, the criteria for a successful in vitro predictive test are not well established. Many studies have proposed and used various tests and models, but as yet there is no consensus on the most meaningful test method for the predictive accelerated in vitro testing of candidate PU based

biomaterials. Moreover, as more biostable polyurethanes are being developed, the concomitant increases in duration of in vivo implantation required to assess their useful service life become prohibitive, and accelerated model studies become essential. This quandary has led a number of workers to utilize specific tests designed for their particular purposes. However, standard test methods specifically designed to evaluate biomedical materials are highly desirable for meaningful comparison of materials.

As various degradation tests have been used to mimic the in vivo PU degradation, it is challenging to assess their utility and assess reported test outcomes. This lack of standardization creates difficulties for design engineers, product developers, and clinicians. The key to overcoming this is to develop standardized test methods for evaluation of the stability of biomaterials and common terminology. Unfortunately, the insufficient fundamental molecular understanding of in vivo degradation mechanisms hampers this effort, and the fact that the literature contains substantially more description of how rather than why PUs degrade does not help the situation. It is therefore challenging to provide an authoritative assessment of published test results and appropriate interpretation of data (Fig. 5.6).

5.7.1 Accelerated Tests for Hydrolysis

Tables 5.1 and 5.2 list various test methods for the hydrolytic degradation of various PUs and results obtained, for commercial and experimental materials. They indicate that most PEU materials are stable towards simple hydrolysis (incubation in H_2O or buffer solution). Nevertheless, some PUs can be susceptible to hydrolysis upon exposure to water or buffer. For example, Cardiothane® 51, Estane® 58810, Estane® 5714F1, and Pellethane™ 2363-80A all showed changes in the molecular weight (Mw and Mn) following a four-day incubation in water at 85°C.[103] In addition, PTMO/MDI/BD-based PU showed a decrease in toughness following a 30-day exposure to water at 75°C.[13] Meijs et al found that hydrolytic degradation occurred when Pellethane™ 2363-55D was aged at 100°C in water.[27] As reviewed by Fambri et al[87] earlier studies had shown that the tests are sufficiently accelerated at 70°C so that differences in hydrolytic stability can be observed in a reasonable period of time, such as within 10-30 days.

5.7.2 Accelerated Tests for Oxidation

Oxidative test conditions used by various workers and results obtained are also listed in Tables 5.1 and 5.2. The relative susceptibility to oxidation of some PEUs has been examined for instance in 0.1N silver nitrate ($AgNO_3$) at 90°C for 35 days.[58,59] All of the PUs with high ether contents displayed severe degradation of mechanical properties (UTS, elongation at break, and modulus (100%)). In another study, 0.1N silver nitrate solution at 75°C was used to determine the resistance to oxidative degradation of some PU materials.[13] As expressed by Takahara et al,[13] the purpose of their study "was not so much to duplicate the oxidative environment of implanted devices, but to categorize PUs for their relative susceptibility to oxidative degradation". However, if the real-life oxidative environment is not duplicated well enough in terms of its essential features, the applicability of such comparative testing remains open to question.

Hydrogen peroxide has also been used to determine the stability of PUs towards oxidation. For example, Biomer™ was found to undergo changes in molecular weight (Mw and Mn) after only a one-day exposure to a 5% H_2O_2 solution at 37°C (Table 5.1). Furthermore, Meijs et al[27] showed that treatment of Pellethane™ 2363-80A with 25% hydrogen peroxide for 24 hours at 100°C was a convenient method for assessing oxidative stability; such exposure resulted in a significant decrease in the ultimate tear strength (UTS). External strain or internal processing stress appeared not to accelerate peroxide induced degradation. The mechanism of

Table 5.1. Degradation of commercial polyurethanes

Materials	Incubating Media		Conditions		Observations	Ref.
	Media	Conc	Temp (°C)	Time of aging (days)		
Avcothane 51	Cholesterol, lipid solution strained	**	37	30	Stiffness ↑, tensile strength ↑ and ductility ↓ (fatigued and nonfatigued).	74
Biomer	H_2O		37	1	No changes in Mw, Mn, and surface chemistry {FTIR, XPS}.	104, 109
				30-180	No substantial changes in Mw, Mn and fatigue life. Little change in surface chemistry {FTIR-ATR}. No changes in stiffness, tensile strength, and ductility.	108
			85	4	Porosity enlarged and dynamic mechanical properties changed. No changes in ductility, stiffness, tensile strength, Tm, and Tg.	14
	PBS	pH 7.3	37	180	No changes in tensile strength and ductility.	15
	Borate buffer	pH 10	37	7	No changes in ductility, stiffness, tensile strength, Tm, and Tg.	14
			60	4	No changes in ductility, stiffness, tensile strength, Tm, and Tg.	14
	K_3PO_4	pH 7.6	37	30-180	No substantial changes in Mw, Mn, and fatigue life. Little change in surface chemistry {FTIR-ATR}. No changes in stiffness, tensile strength, and ductility.	108
	Cysteine, EDTA	0.05 M, 0.02 M, pH 6.2	37	30-180	No substantial changes in Mw, Mn, and fatigue life. No changes in stiffness, tensile strength, and ductility.	108
	NaCl, $CaCl_2$, K_2HPO_4, barbital buffer strained, metallic or plastic	100 mM, 1.7 mM, 1.7 mM, pH 7.4	37	2.5, 5	No calcification in the absence of metal ions (plastic components), no relation between the calcification degree and the magnitude	125

continued

Materials	Incubating Media Media	Conc	Conditions Temp (°C)	Time of aging (days)	Observations	Ref.
	components used in the experimental set-up				of the bending strain. Calcification ↑ with metal (strained) and metal contaminants in deposits (metallic components). Phosphate deposits ↑ with time or number of loading cycles.	
	Cholesterol, lipid solution strained	**	37	30	Stiffness ↑ (non-fatigued), no substantial stiffness differences when fatigued compared to nonfatigued. Tensile strength and ductility ↓ (fatigued and nonfatigued).	74
	Phosphatidylcholine, cholesterol, NaN_3	0.25%, 0.1%, 0.02%	37	28	Weight ↑ and toughness ↓.	73
	$AgNO_3$	0.1 M	75	30	Toughness large ↓, Mw ↓, microcracking. Oxidation of the soft segments {XPS}. Tm related to PTMO oligomer.	13
			90	35	Ductility ↑, tensile strength ↓, and stiffness ↓.	59
	$AgNO_3$, lactic acid sodium salt	0.1 M, 0.1 N	75	30	Toughness ↓, oxidation of the soft segments {XPS}. Tm related to PTMO oligomer.	13
	H_2O_2	5%	37	1	Different mechanisms and degradation rates between lots. Mw and Mn ↓, MDI/PTMO ratio ↓ {FTIR}, surface N/C ratio changed {XPS}	94, 109, 126
		25%	100	1	Tensile strength and ductility ↓.	27
		30%	37	1	Mw and Mn ↓, MDI/PTMO ratio ↓ {FTIR}. Surface N/C ratio changed.	104. 126
	Leucine aminopeptidase	?	37	1	Different mechanisms and degradation rates between lots.	109
	Papain	?	37	1	Different mechanisms and degradation rates between lots.	109
		80 U/ml	37	14	Weight ↑ and Mw small ↑. N surface concentration ↑ {XPS}. No substantial changes to toughness and stiffness.	73

continued

Materials	Incubating Media Media	Conc	Conditions Temp (°C)	Time of aging (days)	Observations	Ref.
		100 U/ml	37	30-180	Mn and fatigue life ↓, papain surface adsorption, urethane/urea moieties ↓ {FTIR-ATR}. No changes in stiffness, tensile strength, and ductility.	108
	Urease	100 U/ml	37	30-180	Mw ↑, urease surface adsorption. Hard segment ↓ {FTIR-ATR}. No changes in stiffness, tensile strength, and ductility. No substantial changes to fatigue life.	108
'Biostable' PUR	Phosphatidylcholine, cholesterol, NaN_3	0.25%, 0.1%, 0.02%	37	28	Weight ↓. No changes to toughness.	73
	$AgNO_3$	0.1 M	75	30	No changes in toughness and surface composition {XPS}.	13
	$AgNO_3$, lactic acid sodium salt	0.1 M, 0.1 N	75	30	No changes in toughness and surface composition {XPS}.	13
	Papain	80 U/ml	37	14	Small ↓ in weight and toughness ↓. No substantial changes to stiffness.	73
Cardiothane 51	H_2O		85	4	Mw and Mn ↓. No changes in ductility, stiffness, tensile strength, Tg, Tm, and dynamic-mechanical properties.	14
	Borate buffer	pH 10	37	7	Mw and Mn ↓. No changes in ductility, stiffness, tensile strength, Tg, and Tm.	14
			60	4	Mw and Mn ↓. No changes in ductility, stiffness, tensile strength, Tg, and Tm.	
	$AgNO_3$	0.1 M	90	35	Exposed material became too weak to test.	59
Corethane 80A	PBS	pH 7	37	28	No MDA release. Surface content of silicone additives ↓ {XPS}.	22
	Phosphatidylcholine	1 mg/ml	37	28	No MDA release. Large ↓ in surface content of silicone additives {XPS}.	22
	CH_3COOH	0.5 N	70	30	No changes to tensile strength.	127

continued

Materials	Incubating Media Media	Conc	Conditions Temp (°C)	Time of aging (days)	Observations	Ref.
	HNO_3	0.5 N	37	7	No changes to tensile strength.	127
	H_2O_2	3%	70	30	No changes to tensile strength.	127
	H_2O_2, $CoCl_2$ in glass wool pre-strained	1.63 M, 0.05 M	37	7-98	No cracking.	107
	Cholesterol esterase	40 U/ml	37	28	No MDA release; MDA recovered from PU following methanol extraction. Surface content of silicone additives ↓ {XPS}.	22
	Cholesterol esterase, phosphatidylcholine	40 U/ml, 1 mg/ml	37	28	No MDA release. Surface content of silicone additives ↓ and lipid adsorption {XPS}.	22
Corethane 55D	CH_3COOH	0.5 N	70	30	No changes to tensile strength.	127
	HNO_3	0.5 N	37	7	No changes to tensile strength.	127
	H_2O_2	3%	70	30	No changes to tensile strength.	127
	H_2O_2, $CoCl_2$ in glass wool pre-strained	1.63 M, 0.05 M	37	7-98	No cracking.	107
Estane 58409	H_2O_2 cast on glass, Ag, Au, Cu	3%	37	1, 7	No substantial weight ↓. Mw ↑ with magnitude varying with the substrate.	28
	α-chymotrypsin cast on glass, Ag, Au, Cu	?	37	1	No substantial weight ↓ and no substantial Mw changes.	28
	Leucine-aminopeptidase cast on glass, Ag, Au, Cu	?	37	1	No substantial weight ↓ and no substantial Mw changes.	28
	Papain cast on glass, Ag, Au, Cu	?	37	1, 7	No substantial weight ↓ and no substantial Mw changes.	28
Estane 58810	H_2O		85	4	Mw and Mn ↓. No changes in stiffness, ductility, tensile strength, and dynamic mechanical properties.	14

continued

Materials	Incubating Media Media	Conc	Conditions Temp (°C)	Time of aging (days)	Observations	Ref.
	Borate buffer	pH 10	37	7	Mw and Mn ↓. No changes in stiffness, ductility, and tensile strength.	14
			60	4	Mw and Mn ↓. No changes in stiffness, ductility, and tensile strength.	14
Estane 5714 F1		H_2O	85	4	Mw and Mn ↓. No changes in stiffness, ductility, tensile strength, and dynamic mechanical properties.	14
	Borate buffer	pH 10	37	7	Mw and Mn ↓. No changes in stiffness, ductility, and tensile strength.	14
			60	4	Mw and Mn ↓. No changes in stiffness, ductility, and tensile strength.	14
Med Adhere 2110	$AgNO_3$	0.1 M	90	35	No changes in tensile strength, ductility, and stiffness.	59
Microthane	Cholesterol esterase	4 U/ml	37	10	Release of degradation products.	112
Pellethane 80A	Anhydrous atmosphere		100	1, 14	No substantial changes to mechanical properties.	27
	H_2O		85	4	Mw and Mn ↓. No changes in stiffness, ductility, tensile strength, and dynamic mechanical properties.	14
			100	1, 4, 14	No Mw changes. Tensile strength ↓.	27
	PBS	pH 7.3	37	180	No changes in tensile strength and ductility.	15
	Borate buffer	pH 10	37	7	No substantial changes in Mw and Mn. No changes in stiffness, ductility, and tensile strength.	14
			60	4	No substantial changes in Mw and Mn. No changes in stiffness, ductility, and tensile strength.	14
	Citrated plasma		37	7	Protein adsorption.	106

continued

Materials	Incubating Media Media	Conc	Conditions Temp (°C)	Time of aging (days)	Observations	Ref.
	$AgNO_3$	0.1 M	90	35	Tensile strength and ductility ↓. No changes to stiffness.	59
	H_2O_2	25%	100	1, 4, 14	Tensile strength, ductility, weight, Mw, Mn, and soft segment {FTIR-ATR} all ↓. Yellowing, cracking, surface and bulk chain cleavage. Hard segment surface concentration ↑ {FTIR-ATR}.	27
	H_2O_2 cast on glass, Ag, Au, Cu	3%	37	1	No substantial changes to weight and Mw.	28
	H_2O_2 conductor coils made of pure metals or alloys	3%	37	180	Moisture on surface, gas generation (Co, Ag, Pt). Discoloration (Co, Cr, glass, 304 SS, DBS), yellowing (Mo), and red-brown coloring (Fe). Coil corrosion (Mo, Co, Fe, DBS), cracking (Mo, DBS, CR), pitting (Elgiloy, glass, MP35N, Ag, DBS), degradation and PU disintegration (Co), In contact with Mo, soft segment bulk concentration ↓ {FTIR}. Tensile strength ↓ (with MP35N, Elgiloy, Cr, DBS, 304SS, glass, iron, Teflon). Ductility ↓ with Co, Mo, > Cr, DBS, and ↑ with 304SS, glass, Fe, Ti, Ni, Pt. Toughness changed: T_{Co}, $T_{Mo} < T_{MP35N}$, $T_{Elgiloy} < T_{CR}$, T_{DBS}, $T_{304SS} < T_{glass}$, T_{Fe}, T_{Teflon}, T_{Ag}, $T_{Ti} < T_{Ni}$, T_{Pt}.	58, 59
	H_2O_2, $CoCl_2$ in glass wool pre-strained	1.63 M, 0.05 M	37	7-98	Cracking to breakage, both with and without acetone extraction or annealing.	107
	H_2O_2, $CoCl_2$ strained	10%, 0.1 M	50	10	Isolated open cracks and brittle microcracking. Soft segment surface concentration ↓ {FTIR}. Nonhydrogen-bonded urethane carbonyl ↓ and appearance of new bands {FTIR}. Mn and Mw ↓.	106

continued

Materials	Incubating Media Media	Conc	Conditions Temp (°C)	Time of aging (days)	Observations	Ref.
	H_2O_2, $CoCl_2$ human plasma pre-treated {37°C, 7D},	10%, 0.1 M	50	10	Cracking similar to in vivo and strained varying with human plasma composition. Soft segment surface concentration ↓ {FTIR}. Non-hydrogen-bonded urethane carbonyl ↓ and appearance of new bands {FTIR}. Mn and Mw ↓.	106
	α-chymotrypsin cast on glass, Ag, Au, Cu	?	37	1	No substantial changes to weight. Mw ↑ when cast on Au.	28
	Leucine-amino-peptidase cast on glass, Ag, Au, Cu	?	37	1	No substantial changes to weight. Mw ↑ when cast on Ag, Au.	28
	Papain cast on glass, Ag, Au, Cu	?	37	1	No substantial changes to weight and Mw.	28
Pellethane 80AE	PBS	pH 7	37	14	No release of degradation products.	113
				28	No MDA release. Surface content of silicone additives ↓ {XPS}.	22
	$CaCl_2.2H_2O$	9 mM	37	30, 2*15, 3*10	No substantial differences in calcification between unstrained and pre-strained PU (cast from THF or DMF) (15 days). Calcification increasing with frequency of reincubation (cast in THF or DMF). No substantial differences in calcification when pre-treated with serum (for 30 days). Reduced calcification when 1,1-hydroxyethylidene bisphosphonic acid incorporated in PU.	121
	$CaCl_2.2H_2O$,	3.87 mM,	37	30, 2*15,	Porosity ↑ with time of incubation (over 15, 30 days), both for plain and porous materials.	121
	K_2HPO_4	2.32 mM		3*10	Thickness of plain films ↑ over 30 days, leading to increased calcification.	

continued

Materials	Incubating Media Media	Conditions Conc	Temp (°C)	Time of aging (days)	Observations	Ref.
	Phosphatidyl-choline	1 mg/ml	37	28	No MDA release. Surface content of silicone additives ↓ {XPS}.	22
	CH_3COOH	0.5 N	70	30	No changes to tensile strength.	127
	HNO_3	0.5 N	37	7	Tensile strength ↓.	127
	H_2O_2	3%	70	30	No changes to tensile strength.	127
	Cholesterol esterase	40 U/ml	37	14	MDA release.	113
				28	No MDA release. Surface content of silicone additives ↓ {XPS}.	22
	Cholesterol esterase, phosphatidyl-choline	40 U/ml, 1mg/ml	37	28	No MDA release. Surface content of silicone additives ↓ and lipid adsorption {XPS}.	22
	Trypsin	300 followed by 4500 U/ml	37	60	No substantial surface chemical changes after 30 days {FTIR-ATR, XPS}.	34
			25	90	No substantial changes in the ratio of soft-to-hard segments {FTIR-ATR}. ↑ in the relative content of hard segments on the surface {XPS}. Ether linkage content ↓. Changes in the molecular weight distribution {GPC}.	34
Pellethane 90A	H_2O_2	25%	100	1	Tensile strength ↓. No changes to ductility.	27
Pellethane 55D	PBS	pH 7.3	37	180	No changes in tensile strength and ductility.	15
	$AgNO_3$	0.1 M	90	35	Tensile strength and ductility ↓. No changes to stiffness.	59
	H_2O_2	25%	100	1	Tensile strength ↓ and ductility ↑.	27
	H_2O_2, $CoCl_2$ in glass wool pre-strained	1.63 M, 0.05 M	37	7-98	Cracking to breakage (with or without acetone extraction), no cracking if annealed.	107

continued

Materials	Incubating Media Media	Conc	Conditions Temp (°C)	Time of aging (days)	Observations	Ref.
	H_2O_2 conductor coils made of pure metals or alloys	3%	37	180	Cracking, reduced soft segment concentration (in contact with Co, Mo) {FTIR}. Tensile strength ↓ (Elgiloy < Co ≤ Cr < Mo) whereas tensile strength ↑ with Ni. Ductility ↓ (DBS, Cr < Co < Mo) and ↑ with Pt, Ni. Toughness ↓ ($T_{Mo}<T_{Co}$, $T_{Cr} < T_{DBS} < T_{304SS}$, $T_{Elgiloy} < T_{MP35N}$, T_{glass}, T_{Fe}, T_{Teflon}, T_{Ag}, $T_{Ti} < T_{Ni}$, T_{Pt}).	58, 59
Tecoflex EG80A	PBS	pH 7.3	37	180	Ductility ↓. No change to tensile strength.	15
	$AgNO_3$	0.1 M	90	35	Tensile strength, ductility and stiffness ↓.	59
	H_2O_2	25%	100	1	Tensile strength and ductility ↓.	27
Tecoflex EG60D	H_2O_2	25%	100	1	Tensile strength and ductility ↓.	27
Tecothane 80A	CH_3COOH	0.5 N	70	30	No change to tensile strength.	127
	HNO_3	0.5 N	37	7	Tensile strength ↓.	127
	H_2O_2	3%	70	30	Tensile strength ↓.	127
	H_2O_2, $CoCl_2$ in glass wool pre-strained	1.63 M, 0.05 M	37	7-98	Cracking to breakage (with or without acetone extraction).	107
Toyobo TM5	Cholesterol, lipid solution strained	**	37	30	Ductility (fatigued) ↓; ductility ↑ and tensile strength ↓ (nonfatigued). Stiffness ↓ (fatigued or nonfatigued). No substantial differences in tensile strength when fatigued compared to non-fatigued.	74

**: NaCl (9.00 g/l), glucose (1.00 g/l), urea (0.25 g/l), alanine (0.15 g/l), glutamine (0.15 g/l), glycine (0.15 g/l), triolein (4.50 g/l), cholesterol (1.00 g/l), cholesterol palmitate (1.50 g/l), lecithin (2.50 g/l), sodium azide (0.20 g/l).

continued

Table 5.2. Degradation of model polyurethanes

Materials			Incubating Media		Conditions		Observations	Ref.
Soft	**Hard**	**Chain Extender**	**Media**	**Conc**	**Temp (ºC)**	**Time of aging (days)**		
PCL	TDI	ED	PBS	pH 7	37	15	Increased release of degradation products when cast as films compared with tubes.	128
PCL Mn: 1250	TDI SMMs added	ED	Cholesterol esterase	0.1 U/ml	37	15	Substantial release of degradation products for PU without SMM. Decreased release when adding SMM to PU, varying for different SMMs.	114
PCL 1 Mn:1250	TDI 2.2	ED 1.2	PBS	pH 7	37	7	No substantial release of degradation products.	96
						18	No substantial release of degradation products.	117
			Cathepsin B	0.020 U/ml	37	28-30	No increased release of degradation products compared to buffer. However, weight ↓, and evidence of surface degradation, due to acetate buffer.	115
			Carboxyl esterase	0.2,	37	≈17	No surface alterations.	117
				0.4, 0.8 U/ml			Release of degradation products dependent on enzyme activity (0.8 ≈ 0.4 > 0.2).	
			Carboxyl esterase with PMSF	0.4 U/ml	37	≈17	≈90% inhibition of release of degradation products with PMSF.	117
			Cholesterol esterase	0.048 U/ml	37	28-30	Release of degradation products. No substantial enzyme-dependent weight changes and no cracking.	115
				0.1 U/ml	37	21	Release of several degradation products including derivatives of	116

continued

Materials			Incubating Media		Conditions		Observations	Ref.
Soft	Hard	Chain Extender	Media	Conc	Temp (°C)	Time of aging (days)		
							diisocyanate segment and chain extender segment, and TDA. Radiolabel release ↑ with time. Enzyme adsorption (after 3 hrs). No surface cracking.	
				0.2 U/ml	37	7	Release of degradation products, including TDA derivatives. No TDA release. No surface degradation.	40, 96
				0.05, 0.1, 0.2, 0.4 U/ml	37	≈18	Release of degradation products dependent on enzyme activity (0.4 ≈ 0.2 > 0.1 > 0.05). No surface alterations.	117
			Cholesterol esterase with PMSF	0.1 U/ml	37	≈2	≈50% inhibition of release of degradation with PMSF.	117
			Collagenase	0.91 U/ml	37	28-30	No increased release of degradation products compared with buffer. No substantial enzyme-dependent weight changes and no cracking.	115
			Horseradish peroxidase	0.5 ng/ml	37	21	No substantial release of degradation products, no substantial surface pitting.	116
			Xanthine oxidase	0.00012 U/ml	37	28-30	No increased release of degradation products compared with buffer.	115
PEO Mn:1000	MDI	BD	Phosphatidyl-choline	0.25%	37	1-4 hrs	High lipid absorption both at the surface and in the bulk.	72
			Phosphatidyl-choline, cholesterol	0.25%, 0.1%	37	1-4 hrs	Lipid absorption both at the surface and in the bulk.	72

continued

Materials			Incubating Media		Conditions		Observations	Ref.
Soft	**Hard**	**Chain Extender**	**Media**	**Conc**	**Temp (°C)**	**Time of aging (days)**		
PEO 1 Mn:1000	MDI 3	BD 2	H_2O		75	10, 30	Toughness ↓.	13
			$AgNO_3$	0.1 M	75	30	Large ↓ in toughness and Mw ↑. No micro-cracking. Small ↓ in Tg. Oxidation of soft segments {XPS}.	13
			$AgNO_3$, lactic acid sodium salt	0.1 M, 0.1 N	75	30	Large ↓ in toughness and small ↓ in Tg. Oxidation of soft segments {XPS}.	13
			Phosphatidyl-choline/choles-terol, NaN_3	0.25%, 0.1%, 0.02%	37	28	Weight ↑. No changes in toughness.	73
			Papain	80 U/ml	37	14	Weight, tensile strength, stiffness, toughness, Mw, and hard segment surface concentration {XPS} all ↓. Papain adsorption.	73
PEO-PPO 0.75-0.25 Mn:1000-1000	TDI 2.2	ED 1.2	Cathepsin B	0.020 U/ml	37	28-30	No increased release of degradation products compared to exposure to buffer solution. Weight ↓, ridges, no cracking, both with and without cathepsin.	115
			Cholesterol esterase	0.048 U/ml	37	28-30	As above.	115
			Collagenase	0.91 U/ml	37	28-30	As above.	115
			Xanthine oxidase	0.00012 U/ml	37	28-30	No increased release of degradation pro-ducts compared to exposure to buffer solution. Ridges, no cracking.	115

continued

Materials			Incubating Media		Conditions		Observations	Ref.
Soft	**Hard**	**Chain Extender**	**Media**	**Conc**	**Temp (°C)**	**Time of aging (days)**		
PEO-PTMO 0.5-0.5 Mw:1000-1000	TDI 2	ED 1	Cholesterol esterase	0.1 U/ml	37	21	No substantial release of degradation products, no surface cracking. Enzyme adsorption (after 3 hrs).	116
			Horseradish peroxidase	0.5 ng/ml	37	21	No substantial release of degradation products, no surface cracking.	116
PTMO 1 Mw: 1000	TDI 2	ED 1	Cholesterol esterase	0.1 U/ml	37	21	No substantial release of degradation products, no surface cracking. Enzyme adsorption (after 3 hrs).	116
			Horseradish peroxidase	0.5 ng/ml	37	21	No substantial release of degradation products, no surface cracking.	116
PTMO Mw:1000	MDI	BD	PBS	pH 7.3	37	180	No changes in tensile strength and ductility.	15
			Phosphatidyl-choline	0.25%	37	1-4 hrs	Lipid absorption both onto the surface and into the bulk.	72
			Phosphatidyl-choline, cholesterol	0.25%, 0.1%	37	1-4 hrs	Lipid absorption both onto the surface and into the bulk.	72
			Cholesterol esterase neutral buffer pretreatment	80 U/ml	37	126	Release of degradation products.	118
			Cholesterol esterase fibrinogen pretreatment	80 U/ml 1 mg/ml	37	126	Release of degradation products delayed by Fg pretreatment.	118
			Cholesterol esterase neutral buffer pretreatment with SMMs	80 U/ml	37	126	Decreased release of degradation products, varying between the various SMMs.	118
			Cholesterol esterase fibrinogen pretreatment, with SMMs	80 U/ml 1mg/ml	37	126	As above; no substantial influence of Fg pretreatment.	118

continued

Materials			Incubating Media		Conditions		Observations	Ref.
Soft	**Hard**	**Chain Extender**	**Media**	**Conc**	**Temp (°C)**	**Time of aging (days)**		
PTMO 1 Mw:1000	MDI 2	BD 1	Cholesterol esterase	0.1 U/ml	37	21	No substantial release of degradation products, no surface cracking.	116
			Horseradish peroxidase	0.5 ng/ml	37	21	No substantial release of degradation products, no surface cracking.	116
PTMO 1 Mn: 1000	MDI 3	BD 2	H_2O		75	10, 30	Toughness ↓.	13
			$AgNO_3$	0.1 M	75	30	Large ↓ in toughness, Mw ↑ and micro-cracking. Small ↓ in Tg. Oxidation of soft segments {XPS}.	13
			$AgNO_3$, lactic acid sodium salt	0.1 M, 0.1 M	75	30	Toughness ↓. Small ↓ in Tg. Oxidation of soft segments {XPS}.	13
			Phosphatidyl-choline, cholesterol, NaN_3	0.25%, 0.1%, 0.02%	37	28	Lipid sorption, weight ↑, toughness and Tg ↓.	73
			Papain	80 U/ml	37	14	Small ↓ in weight and small ↑ in Mw. Toughness, Tg, and hard segment surface concentration {XPS} all ↓.	73
PTMO 2.5 Mn:2000	MDI 3.5	ED 1	H_2O		25	30	Soft segment surface concentration {XPS} ↓ and degradation of ether moieties {FTIR}. Methanol extraction revealed low Mw degradation products.	110
			Papain	12.5 U/mg	25	30	No changes in Mw, Mn, and bulk chemistry. Soft segment surface concentration {XPS} ↓ and degradation of ether moieties {FTIR}. Methanol-extractable low Mw products, including possibly MDA.	110

continued

Materials			Incubating Media		Conditions		Observations	Ref.
Soft	Hard	Chain Extender	Media	Conc	Temp (°C)	Time of aging (days)		
PTMO 2.5 Mn:2000 with or without Santowhite (0.83%) and Tinuvin 328 (0.21%)	MDI 3.5	ED 1	H_2O		25	14,28	Minimization of changes in physical properties by the use of additives: without additives, tensile strength and fatigue life ↓, whereas no substantial changes in tensile strength and fatigue life with additives. Reduction in surface ether content {XPS} when no additives present.	18, 111
			Cysteine, EDTA	0.05 M, 0.02 M, pH 6.5	25	14,28	Without additives, tensile strength and fatigue life ↓, whereas no substantial changes in tensile strength and fatigue life with additives.	18, 111
			Papain	42 U/ml 75 U/ml	25 25	28 14, 28	Same as above. Reduced changes in physical properties by the use of additives: tensile strength ↓, fatigue life ↓ with additives < without additives. Reduction in surface ether content {XPS} when no additives present. Methanol-extractable low Mw products, including possibly MDA.	18,111 18, 111
PTMO 2.5 Mn:2000 with or without UV 3346 (0.5%) and Tinuvin 328 (0.5%)	MDI 3.5	ED 1	H_2O		25	14, 28	Without additives, tensile strength and fatigue life ↓, whereas no substantial changes when additives present in PU.	111

continued

Materials			Incubating Media		Conditions		Observations	Ref.
Soft	**Hard**	**Chain Extender**	**Media**	**Conc**	**Temp (°C)**	**Time of aging (days)**		
			Cysteine, EDTA	0.05 M, 0.02 M, pH 6.5	37	14, 28	As above.	111
			Papain	42 U/ml	37	28	As above.	111
				75 U/ml	37	14,28	↓ in tensile strength and fatigue life with additives < without additives.	111
PHMO Mw:650	MDI	BD	PBS	pH 7.3	37	180	No changes in tensile strength and ductility.	15
POMO Mw:1685	MDI	BD	PBS	pH 7.3	37	180	No changes in tensile strength and ductility.	15
PDMO Mw:1270	MDI	BD	PBS	pH 7.3	37	180	No changes in tensile strength and ductility.	15
PDMS Mn:1920	MDI	BD	Phosphatidyl-choline	0.25%	37	1-4 hrs	Lipid absorption both onto the surface and into the bulk.	72
			Phosphatidyl-choline, cholesterol	0.25%, 0.1%	37	1-4 hrs	Lipid absorption both onto the surface and into the bulk.	72
PDMS 1 Mn:1350	MDI 4.5	BD 3.5	H_2O		75	10, 30	No changes in toughness.	13
			$AgNO_3$	0.1 M	75	30	No changes in toughness. and surface composition {XPS}. No microcracking. Mw ↑.	13
			$AgNO_3$, lactic acid sodium salt	0.1 M, 0.1 M	75	30	Toughness ↓. Carbonyl moieties ↑ {XPS}.	13
			Phosphatidyl-choline, cholesterol, NaN_3	0.25%, 0.1%, 0.02%	37	28	Weight ↓; disintegration. Lipid sorption.	73
			Papain	80 U/ml	37	14	Weight ↓ and Mw small ↑. No toughness changes.	73
PBD 1 Mn:2000	MDI 5.3	BD 4.3	$AgNO_3$	0.1 M	75	30	Large ↓ in toughness. Tg and O surface content {XPS} ↑. No microcracking.	13

continued

Materials			Incubating Media		Conditions		Observations	Ref.
Soft	Hard	Chain Extender	Media	Conc	Temp (°C)	Time of aging (days)		
			$AgNO_3$, lactic acid sodium salt	0.1 M 0.1 M	75	30	Large ↓ in toughness. O surface content {XPS} ↑.	13
			Phosphatidyl-choline, cholesterol	0.25%, 0.1%	37	28	Weight ↑ and toughness ↓.	73
			Papain	80 U/ml	37	14	Weight, toughness, Mw, hard segment surface concentration {XPS} all ↓.	73
HPBD 1 Mn:2100	MDI 6.7	BD 5.2	$AgNO_3$	0.1 M	75	30	No toughness changes. Small ↑ in Mw. No microcracking. Oxidation of soft segments {XPS}.	13
			Phosphatidyl-choline, cholesterol, NaN_3	0.25%, 0.1%, 0.02%	37	28	Weight ↑. No substantial changes to toughness.	73
			Papain	80 U/ml	37	14	Weight ↓, small ↑ in Mw. No changes to toughness, surface composition {XPS}.	73
PCN 1 Mn:1000	HDI 3	BD 2	Phosphate buffer	pH 7	37	42	Water uptake < 1%.	119
			Cholesterol esterase	400 U/ml	37	70	Release of small amount of degradation products.	119
PCN 2 Mn:1000	HDI 3	BD 1	Phosphate buffer	pH 7	37	42	Water uptake < 1%.	119
			Cholesterol esterase	400 U/ml	37	70	Release of degradation products.	119
PCN 2 Mn:1000	MDI 3	BD 1	Phosphate buffer	pH 7	37	42	Water uptake < 1%.	119
			Cholesterol esterase	400 U/ml	37	70	Release of degradation products.	119
PCN 2 Mn:1000	HMDI 3	BD 1	Phosphate buffer	pH 7	37	42	Water uptake ≈ 2%, deformation after 2 weeks.	119
			Cholesterol esterase	400 U/ml	37	70	Release of degradation products.	119

continued

Materials			Incubating Media		Conditions		Observations	Ref.
Soft	**Hard**	**Chain Extender**	**Media**	**Conc**	**Temp (°C)**	**Time of aging (days)**		
PTAd 1.5 Mn:2010	MDI 7.1	ED 5.5	Air strained		25	2	Increasing strain led to no substantial degradation of ester moieties {FTIR} but stiffness and ductility ↓, tensile strength ↑.	53
					85	2	Increasing strain and temperature led to degradation of ester moieties {FTIR} and reduced stiffness, tensile strength, and ductility.	53
			H_2O strained		85	2	Increasing strain led to degradation of ester moieties {FTIR} and reduced stiffness, tensile strength, and ductility.	53
PPG Mw:625 cast on glass, Ag, Au, Cu	MDI	ED	H_2O_2	3%	37	1, 7	No substantial changes to weight. Mw ↑ when cast on Au, Cu.	28
			α-chymotrypsin	?	37	1	No substantial changes to weight and Mw.	28
			Leucine-aminopeptidase	?	37	1	As above.	28
			Papain	?	37	1, 7	No substantial changes to weight. Mw ↑ when cast on Au, Cu.	28
PPG Mw:2000 cast on glass, Ag, Au, Cu	MDI	ED	H_2O_2	3%	37	1	No substantial changes to weight. Mw ↓ when cast on Ag.	28
			α-chymotrypsin	?	37	1	No substantial changes to weight and Mw.	28
			Leucine-amino-peptidase	?	37	1	No substantial changes to weight. Mw ↑ when cast on Au.	28
			Papain	?	37	1, 7	No substantial changes to weight. Mw ↓ when cast on glass.	28

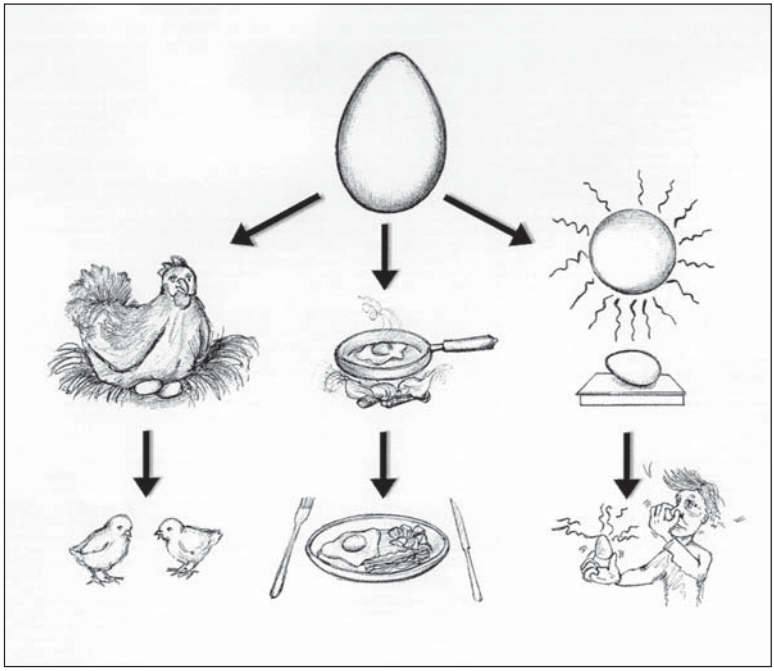

Fig. 5.6. Pitfalls from accelerated test models should be recognized.

peroxide attack is less clear; while Meijs et al[27] found that the polyether soft segment was susceptible to rapid degradation, Tyler and Ratner[104] found a correlation between the hard segment content and the extent of degradation, for Biomer™ treated with both 5% and 30% hydrogen peroxide at 37°C for 24 hours, suggesting that the hard segment was being attacked in the degradation process. In addition, Tyler and Ratner[104] reported that changes in the average molecular weight varied from a decrease of 55.8% to an increase of 3.9%. This suggests that there may be a number of mechanisms by which hydrogen peroxide can react with PUs, including the generation of additional crosslinks.

The relevance of hydrogen peroxide exposure to the prediction of in vivo degradation needs to be discussed. It is thought that some cells secrete peroxidic molecular species such as superoxides as part of the immune defense reactions. Although it is not known what the concentration of hydrogen peroxide might be under macrophages in vivo, the concentration of hydrogen peroxide in in vitro tissue cultures has been measured as approximately 10^{-5} M. However, when macrophages are stimulated by certain chemicals, the hydrogen peroxide concentration has been reported to increase by 25-fold or more.[59] In addition, it is not known how the concentration of hydrogen peroxide varies with time. However, since auto-oxidation is a "self-sustaining" mechanism, once initiated it may progress in the absence of external oxidative initiators (provided of course that oxygen molecules are available to continue adding to radicals); the biological initiator oxidant thus may only be necessary for a relatively short period.[59] Hypochlorus acid (HOCl) has been also used to categorize PUs for their relative susceptibility to oxidation. Pellethane™ 2363-80A was degraded by 10 mM hypochlorus acid at 25°C. Sutherland et al[105] reported that PEU incubated with HOCl developed damage manifestations analogous to those displayed by in vivo stress cracked implants. FT-IR/ATR analysis of

HOCl-treated PEU revealed that the ether linkages were being attacked. It should be noted that hypochlorus acid is one of the most reactive oxidants produced by PMNs.[105]

5.7.2.1 Accelerated Tests for ESC

Zhao et al[106] found that oxidizing a prestressed Pellethane™ 2363-80A specimen in an aqueous solution of 10% hydrogen peroxide and 0.1 M cobalt chloride ($CoCl_2$) caused isolated cracks and brittle microcracking, but without crack propagation. However, when the specimens were pretreated with human plasma prior to $H_2O_2/CoCl_2$ exposure, the cracking was ductile, with large open cracks interconnecting and propagating across the surface along a direction transverse to the applied stress. Interestingly, the morphological pattern of the in vitro stress cracking (7-day human plasma + 10-day oxidation) was very similar to that observed after an in vivo 70-day exposure. The sample treated with human plasma plus $H_2O_2/CoCl_2$ was more cracked than the in vivo samples. Thus, it is clear that the human plasma acts as a catalyst for oxidation; α_2-macroglobulin was identified as a plasma component responsible for promoting stress cracking.[106]

Later, Zhao et al[107] reported that the accelerated test system described above had some limitations. These included sample flotation, uneven cracking near the sample-air interface, and exposure of the material to higher temperature (50°C) than that of body temperature (37°C). The pretreatment with human plasma was therefore substituted by the addition of glass wool. The samples were embedded in glass wool and incubated in a $H_2O_2/CoCl_2$ solution at 37°C. The glass wool- $H_2O_2/CoCl_2$ accelerated test also closely reproduced in several weeks the in vivo stress cracking phenomenon that is typically observed over months of implantation in an animal model, thus meeting one requirement of an accelerated test.

5.7.2.2 Accelerated Tests for MIO

In order to determine which metals accelerate the oxidative degradation of PUs, Stokes et al[58,59] immersed sealed Pellethane™ 2363-80A and 2363-55D tubing samples containing the conductor coil alloys in 3% hydrogen peroxide at 37°C for a period of 180 days. At the end of the 6-month experiment, the polymers were almost completely disintegrated over the cobalt mandrels. In addition, severe corrosion was observed on the mandrels made of cobalt. The tubing from the molybdenum samples was severely cracked from the lumen side outward, progressing almost, but not completely, through the wall. The tubings tested in the presence of cobalt or molybdenum showed a significant loss of PTMO ether. All tubing samples had liquid droplets on their lumen surfaces within 3 days. In addition, all the tubing swelled due to gas pressure.

5.7.3 Accelerated Tests for Enzymatic Degradation

Enzymatic attack on PUs has been well studied in vitro; Tables 5.1 and 5.2 list a variety of enzymatic degradation tests that have been applied to various PUs. Both hydrolytic and oxidative types of enzymes have been reported to be important in inducing degradation although some enzymes have been reported to be less effective than expected. Enzymes that have been reported to attack PU to some extent are papain,[28,73,108-111] cholesterol esterase,[22,40,96,112-119] urease,[108] trypsin,[34] phospholipase,[33] and carboxyl esterase.[117] Enzymes are likely to degrade PUs by different pathways. For example, it has been proposed that papain hydrolyses urethane and urea linkages while urease attacks urea linkages only. In addition, Phua et al[108] reported that papain was more effective in degrading Biomer™ samples than urease. Trypsin has been also found to have the ability to induce degradation in PEU, the soft segment being most

affected, particularly the CH_2-O bond of the ether linkages.[34] Moreover, cholesterol esterase (CE), which is known to catalyze the hydrolysis of fatty acid esters of cholesterol,[103] has been shown by Santerre et al to attack PUs.[94,95,115,116] CE has been identified as an intracelullar enzyme in a variety of animal tissues and has also been found in monocytes as they rapidly differentiate into macrophages around implantation sites.[103] Results from CE incubation experiments showed that the polyester-urethane material, PCL/TDI/ED, showed a significant increase in release of radiolabel, while PTMO/TDI/ED, PTMO-PEO/TDI/ED, PTMO/MDI/ED, and PTMO/MDI/BD showed no increase in release of radiolabel.[95] In addition, the surfaces of all polymers investigated in that study showed no signs of cracking or fissuring by SEM.

On the other hand, leucine aminopeptidase,[2,17] α-chymotrypsin,[17] cathepsin B,[31] collagenase,[31] xanthine oxidase,[31] and horseradish peroxidase[28] were reported to have little or no effect on PU stability. For example, Ratner et al[28] found that papain, leucine aminopeptidase, and α-chymotrypsin used in high concentrations caused small changes in molecular weight. Indeed, although evidence of degradation was found as a result of enzymatic attack, the majority of changes in molecular weight remained under 20% and was often subtle. They also reported that, in general, metal substrates (Ag, Au, Cu) examined had little effect on the rate of enzymatic degradation.

It is not clear whether demonstration of the ability of an enzyme to attack PU in vitro can be extrapolated to conjecturing that this enzyme, or a related enzyme, does play a role in degrading PUs in vivo. It is important to recognize that enzymes are unstable, their activity decreasing with time, at a rate dependent upon conditions of storage.[93] Therefore, most enzymatic incubation solutions need to be replenished daily in order to maintain the initial enzyme activity in the solution. Replenishing is, however, only appropriate if the mechanistic model of enzymatic degradation proposed by Santerre et al[94] is valid. On the other hand, if enzymes are adsorbed tightly onto the PU surface and denaturate, they may form an inactive layer that shields the material from further attack, and replenishment of enzymes in the solution would have no effect. Moreover, special care should be used when comparing enzyme activity between studies. Generally, enzyme activity is expressed in Units/ml; and unit definition depends upon the condition of assay and the substrate used.

5.7.4 Accelerated Tests for Calcification

In an excellent report, Bernacca et al[120] reviewed various accelerated in vitro test methods for assessing the calcification of biomaterials. The accelerated tests include: heparinized plasma, high concentration of calcium in salt solution, physiologic concentration of calcium and phosphate with collagen matrix, and physiologic concentration of calcium and phosphate in salt solution (static and dynamic). Heparinized plasma has the advantage of approximating the biologic fluid environment without the cellular components of blood, but has the disadvantages of requiring frequent replacement and requires the addition of antimicrobial agents and heparin. The effects of added heparin and antibiotics on calcification are unknown. As mentioned by Bernacca et al,[120] heparinized plasma is a complex mixture, making it difficult to pin-point those factors critical to the calcification process. On the other hand, the use of high calcium content may lead to calcium deposition due to simple precipitation.

A dynamic in vitro method was also developed by Bernacca et al[120] to study the calcification process. The test apparatus consists of a modified Rowan Ash fatigue tester. The test fluids were different simple salt solutions containing approximately physiological concentrations of calcium and phosphate. This system allowed complete heart valves to be calcified under controlled conditions and with sufficient control to permit study of the early stages of calcification. Calcification was induced even in the absence of cells, that is, outside the body. Dynamic in

vitro tests produce generally greater calcification than static in vitro tests, supporting the idea that mechanical stress contributes to calcification.[120] Golomb and Wagner[121] examined calcification on PU films immersed in human serum for 2 hours prior to incubation in a metastable solution of calcium phosphate. Interestingly, bioprosthetic tissue specimens treated using their protocol calcified in a similar fashion to those explanted from animals (Fig. 5.7).

5.7.5 Summary

As reported by Bernacca et al and Fisher et al,[98,122] test methods for the study of biomedical polymer degradation may be divided into two main groups, in vivo and in vitro, and each group subdivided into dynamic and static tests. Dynamic in vivo systems include study of human explants and implantation of intact devices into large animals, such as cattle, sheep, dog, or baboon. Static in vivo tests include usually subdermal or intramuscular implantation of materials into smaller animals, such as rats or rabbits. On the other hand, static in vitro tests are carried out in small sample vials to study at a more fundamental level biological interactions with the material. Dynamic accelerated in vitro test methods are mainly used to investigate the engineering performance of materials and devices. In general, in vitro systems are simpler, cheaper, and more easily controlled than in vivo systems. They also possess the advantage of eliminating the inherent variability of living systems. However, in vitro tests may omit critical elements present in living biological systems that may act synergistically. Static test systems can be used to study small numbers relatively quickly, but cannot give information regarding the response of the material to mechanical stress. Moreover, in vivo studies generally produce rather heavily degraded material, making the study of the early stages of the degradation process difficult.[98,122]

5.8 Conclusion

In this Chapter we have reviewed studies and experimental data on factors that affect the stability of biomedical PU materials. Their stability in biological environments can be affected by the manufacturing process (i.e., extrusion, sterilization, storage, and handling) as well as by the cellular and/or noncellular components of the mammalian body. Clearly, PUs may suffer from mechanical degradation, thermal degradation, hydrolysis, oxidation, enzymatic attack, and/or photodegradation. These mechanisms of degradation may act alone or synergistically. For example, it has been found that external or internal strain may act synergistically with some cellular and/or noncellular components to cause surface cracking.

The weight of evidence from numerous studies is not unambiguous but suggests that in general the soft-segment domain of PEUs is the likely site of biological attack, and that this attack occurs by the action of oxidative enzymes secreted by cells that aggregate at the implantation site as a result of the wound response. At a molecular level, the attack probably occurs at the macrodiols CH_2 groups adjacent to the oxygen atom of the ether linkage. In some cases, the hard-segment domain was reported to be involved in the degradation process. Metal ions, mechanical stress, and hydrolytic pathways can also play a role, and there is scope for interaction with oxidative mechanisms of biodegradation.

It is also not clear to what extent the observed degradation is caused by the biological environment, or whether radicals produced during extrusion, sterilization, or other processing steps prior to implantation are important as well. Experimentally, it has often been observed that samples of nominally identical material composition can show considerable variation in in vivo degradation testing. Variability in the manufacturing processes, such as in an annealing step, may induce considerable variability in the vulnerability of a PU material to degradation. However, this is not easy to separate from the variability inherent in living test systems, and it

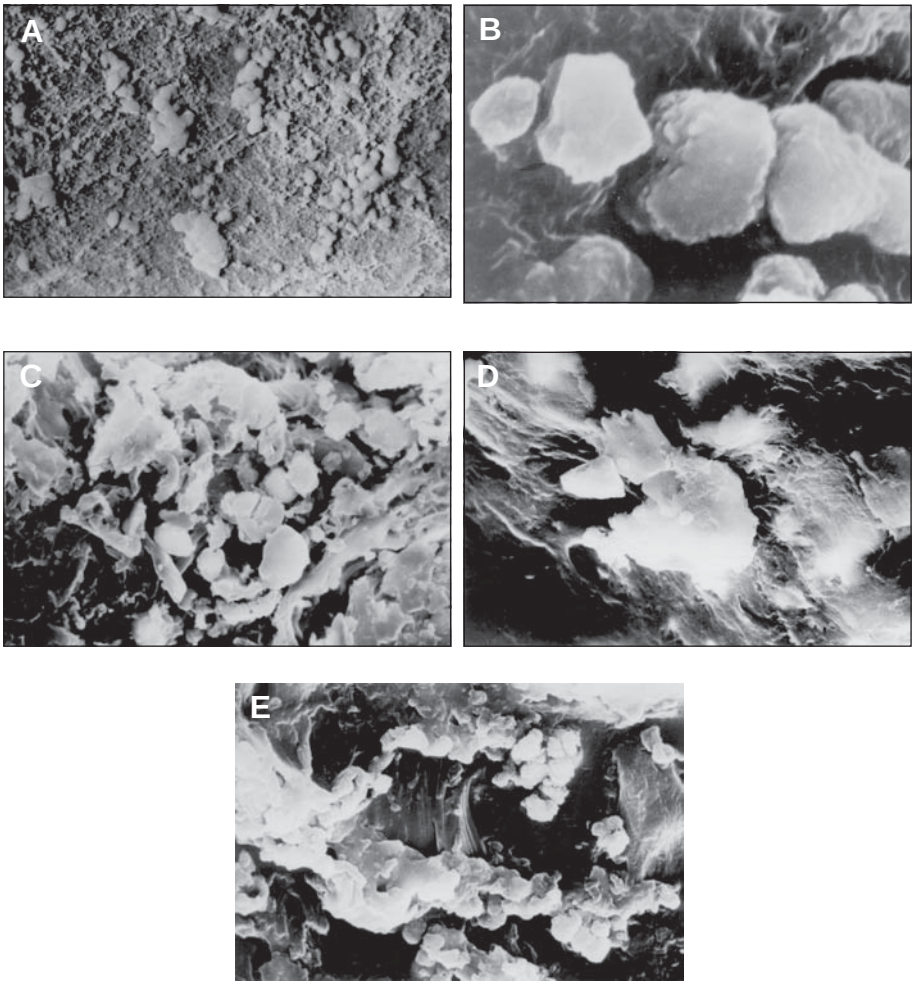

Fig. 5.7. SEM analysis of calcification of bioprosthetic heart valve tissue after 14 days in vitro (A-C) and in vivo (D and E). (A) surface of bioprosthetic tissue covered with plaque-like calcium deposits; (B) and (C) tissue cross-sections. (D) surface and (E) cross-section of explanted tissue. Reprinted with permission from: Golomb G, Wagner D. Development of a new in vitro model for studying implantable polyurethane calcification. Biomaterials 1991; 12: 397-405.

is thus not clear to what extent effects induced in manufacturing and processing are superimposed on the biologically driven degradation. There is evidence for the latter in for instance a study that observed significantly different degradation rates and mechanisms for two Biomer™ lots.[109,123] Thus, while the PU formulation is an important parameter in determining the mechanism and rate of degradation of a PU material and has received much attention, other factors must be considered and their importance addressed when developing and testing PU formulations intended to be more biostable.

Additives can also play a role. This may not always be considered to a sufficient degree, since PU formulations developed in the laboratory may be tested without incorporated addi-

tives, but for processing one then needs to provide additives such as slip agents whose effects on biodegradation may not be predictable. For example, a polymer contained DPA-EMA (an ultra-violet-stabilizing additive) underwent a slower enzymatic degradation process and faster oxidative degradation compared to a lot prepared without the additive. Thus, it appears that the presence of additives in PU materials may be a key component in determining the pathways and rates of degradation. For many additives used to make PUs it has not been established yet whether the additive has a beneficial or detrimental effect on the stability and performance of the material (see Chapter 3).

It is well established that the degradation of a PU material may considerably affect both the mechanical performance of the device and its biological responses. The time scale for a material to be intolerably damaged can vary considerably. A material may be suitable for short term application such as catheters and extracorporeal circulation apparatus, but not for long term implant usage such as vascular grafts, heart valves, and pacemaker lead insulators. The clinical relevance of PU degradation obviously depends both on the material and the application. In general, it is advisable to avoid any treatment or usage which causes hydrolysis or oxidation of aromatic PUs, since degradation products are suspected to be carcinogens.

Although there is a considerable amount of published data on the biomedical stability of a wide range of PUs (Tables 5.1 and 5.2), comparison of results from different laboratories is often difficult. Protocols for synthesis, processing, and testing vary substantially; in sparticular the absence of widely accepted standardized tests for accelerated degradation and calcification is a serious drawback. Even for commercial PU samples there can be substantial variability between lots. End-use product testing must not be neglected; too much emphasis is placed on testing laboratory formulations rather than finished products. In parallel, such samples must be thoroughly characterized by a range of analytical techniques, including surface spectroscopic methods. This is particularly relevant as "real-life" PU samples typically have surfaces that are "contaminated" by slip agents or other processing additives, environmental adventitious molecules such as hydrocarbons or organosilicon compounds, or additives transferred from packaging materials. Yet, it is at the surface of a PU material that biological responses are triggered and degradation by enzymatic attack takes place. Therefore, in the absence of detailed data on what the outermost molecular layers of the material under study really comprise, erroneous conclusions may be drawn regarding correlations between composition of a PU and the observed biological responses including in vivo degradation. Surface-localized additives or contaminants may substantially alter the way a PU interacts with the biological host environment and thereby not only affect biological response but also degradation, as it appears reasonable to surmise that the adsorption, activity, and deactivation by denaturation, of attacking degradative enzymes will be a function of the particular surface chemistry. Many interpretations in the literature that were based on the theoretical PU formulations may be in error due to unrecognized effects from additives and contaminants. On the other hand, one may argue that such surface-chemical effects might only play a role in the early stages of degradation, before much bulk damage occurs; yet, a retardation of surface attack may translate into slower bulk damage and the longer service life could then wrongly be ascribed to the PU formulation rather than retarded degradation by surface-localized low molecular weight molecules. These considerations are supported by a study that showed a slip agent, bis-ethylene-stearamide, to be present on a commercial PU formulation.[124] Those studies suggest that the good biocompatibility of that particular formulation may be related to the surface presence of that additive. This illustrates that thorough characterization of the surface chemical composition, as well as of the bulk composition, is required for interpretation of biological responses and, we conjecture, the rates and mechanisms of in vivo degradation of a PU material. In addition, other important factors such as synthesis and processing conditions, sterilization, storage, handling, and the test system all must be well controlled and characterized.

Thus, many variables appear to be involved in the in vivo degradation of biomedical PUs, and the effects of some of them are still rather incompletely understood. Unrecognized variables (such as surface composition/additives) may be at least in part responsible for some of the contradictions in the literature. Detailed characterization of the test materials by a wide range of analytical methods, close control of processing parameters, and well-defined test systems are essential for acquiring reliable data and an improved understanding of the molecular pathways of biomedical degradation of PUs.

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Chapter 6

Developments in Design and Synthesis of Biostable Polyurethanes

Pathiraja A. Gunatillake, Gordon F. Meijs, and Simon J. McCarthy

6.1 Introduction

Synthetic elastomers are frequently the materials of choice for the construction of implantable medical device componentry. To function effectively, the chemical and mechanical properties of the polymer must be suitable for the intended application. The polymer must also have characteristics that impart good biological compatibility with the surrounding environment. In the case of long-term implants, this includes resistance to premature failure or degradation by mechanical or chemical means.

The attractiveness of polyurethanes for medical implants is largely due to their excellent mechanical properties (Chapter 1) and relatively good processability. They exhibit high tensile strength and elongation, excellent tear strength and abrasion resistance. Their chemical make-up also offers substantial opportunities for synthetic polymer chemists to tailor structure to meet specific property requirements.[1-5]

The use of polyurethanes for medical implants was first suggested by Boretos and Pierce in 1967.[6] Since their introduction many different polyurethanes have been evaluated for their stability in the biological environment using both in vitro and in vivo test procedures (Chapter 5). It is now known that many polyurethanes degrade in the biological environment.[7-10] Many interrelated factors influence the biostability of polyurethanes. These factors include chemical structure and associated polyurethane morphology, mechanical properties, manufacturing, processing and fabrication conditions, and implantation procedures and device specific factors.[7] The chemical composition is a key determinant of biostability.

Polyurethanes used in early implant applications were those developed for non-medical uses. However, during the last 15 years several research groups have focused on developing improved polyurethanes with chemistries that achieve a combination of good mechanical properties, processability, and resistance to degradation. The intention of this Chapter is to provide the reader with a short review of current understanding of the relationships of polyurethane structure and morphology with biostability, and a review of recent advances in design and synthesis of new polyurethanes with improved biostability. The reader is referred to Chapters 1 and 2 in this book for details of polyurethane chemistry.

Biomedical Applications of Polyurethanes, edited by Patrick Vermette, Hans J. Griesser, Gaétan Laroche and Robert Guidoin.

6.2 Biostability and Polyurethane Structure

Polyurethane elastomers are prepared by reacting three components—a diisocyanate, a macrodiol, and a chain extender. The macrodiol forms the "soft" segment of the polyurethane while the diisocyanate and the chain extender in combination form the "hard" segment. Polyurethanes exhibit two-phase micro-domain morphology resulting from solubility differences between the soft and hard segments. The chemical composition of the two domains and the associated morphology affect the stability of the polyurethane in the biological environment.

6.2.1 Soft Segment Structure

Polymer biostability is of crucial importance for long-term implants. It was recognised early that polyester-urethanes were not suitable for long-term medical implants due to poor hydrolytic stability.[2,3,7] This problem has been largely eliminated by the use of polyether macrodiols. Poly(tetramethylene oxide) (PTMO) (see Fig. 6.1) is the most common macrodiol in conventional medical formulations. However, PTMO-based polyurethanes are susceptible to oxidative degradation.

PTMO-based polyurethanes can degrade when implanted for long periods. The degradation appears as surface or deep cracking, stiffening, erosion or deterioration of mechanical properties, such as flex fatigue resistance (Fig. 6.2). This deterioration may ultimately lead to implant failure. Biodegradation may also result in the leaching of toxic products from the device. The problem of polyurethane biodegradation limits potential development of long-term artificial hearts, valves and small bore vascular grafts.[7] Biodegradation of polyurethanes has been observed with its use in pacemaker leads.

The mechanism for biologically induced degradation of polyurethanes has been the subject of much investigation. The results have been summarised in a number of review articles.[8,11-18] Although the exact mechanisms are not fully understood, it is widely held that oxidative pathways involving either environmental stress cracking (ESC) or transition metal ions, such as cobalt, play an important role.

ESC requires a chemical agent and some level of stress. Stress can result from inappropriate handling (residual stress) or alternatively, it can result from external loading (e.g., flexure while in use or from compression from suturing). It is likely that the biological chemical agents derived from the host implant response are oxidative and that susceptible functionalities such as abstractable methylene hydrogens adjacent to oxygen in PTMO macrodiol are the point of attack.[8,19,20] Szycher demonstrated that softer polyurethanes (containing greater fraction of PTMO) are more prone to stress cracking.[8,19] A predominantly oxidative mode of degradation is consistent with improved resistance in the presence of antioxidants[21] and also similarity between in vivo and in vitro failure when an in vitro oxidative model is used.

As mentioned previously, the degradation of polyurethanes in the biological environment has largely been reported as surface or deep cracking, stiffening, erosion or deterioration of mechanical properties, such as flex life. Unambiguous quantitation of surface and bulk chemical changes in explanted biomaterials is generally difficult due to limitations in analytical techniques and the difficulty associated with biological residues that contaminate sample surfaces. However, McCarthy et al[22] have applied a novel technique, combining cryomicrotomy and FT-IR microscopy to study subtle chemical changes associated with degradation of implanted materials. The study included analysis of three commercial polyurethanes, Pellethane™ 2363-80A, Tecoflex® EG80A and Biomer™, explanted after 18 months subcutaneous implantation in sheep. The degradation of the polyurethanes under these conditions was associated with severe oxidation of the aliphatic polyether soft segment, hydrolysis of the urethane bond joining hard to soft segment (in all three materials), and significant hydrolysis of aliphatic

$$HO\,(CH_2)_4\text{—}[O\,(CH_2)_4]_n\text{—}O\,(CH_2)_4OH$$

Fig. 6.1. Chemical structure of poly(tetramethylene oxide) (PTMO).

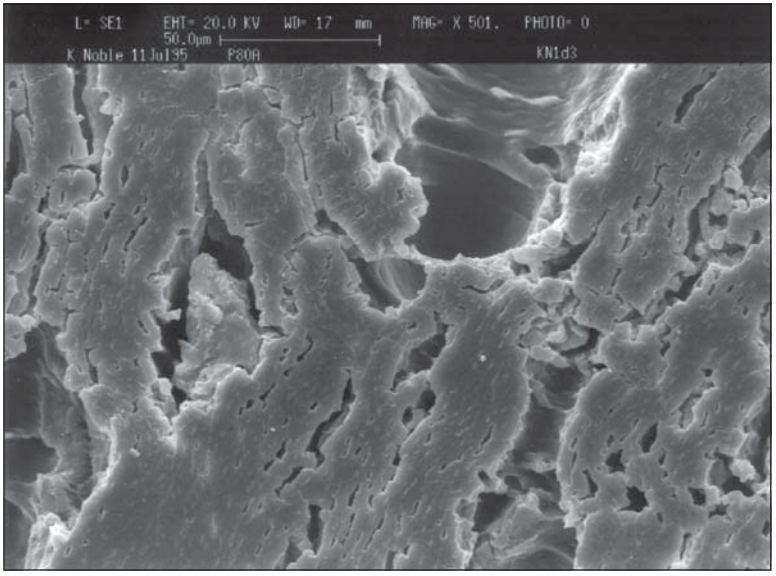

Fig. 6.2. Electron micrograph showing severe degradation by environmental stress cracking (ESC).

hard segment in Tecoflex® EG 80A. Oxidative change in the polyether soft segment was reflected in a significant loss of ether (1112-1115 cm^{-1}) and methylene absorbances (2937-2776 cm^{-1} and 1369-1363 cm^{-1}). The hydrolysis of the hard segment junction interphase region is reflected in the loss of nonhydrogen-bonded carbonyl absorbance (1740-1718 cm^{-1}), urethane C-N absorbance (1231-1222 cm^{-1}), and urethane C-O-C absorbance (1080 cm^{-1}) and in the appearance of amine absorption (near 3300 cm^{-1}). Hydrolysis of the Tecoflex® hard segment was reflected in significant loss of hydrogen-bonded-carbonyl absorbance (1702 cm^{1}).

6.2.2 Hard Segment Structure

Although there are a vast number of potential combinations of diisocyanates and chain extenders to form the hard segment of polyurethanes,[3-5] only relatively few have been used in medical implants. Due to ease of handling, its symmetric structure, high reactivity and purity, 4,4'-methylenediphenyl diisocyanate (MDI) is the most frequently used diisocyanate along with the chain extender 1,4-butanediol. Low molecular weight diamine chain extenders such as ethylenediamine are commonly used in polyurethane-urea formulations. Aliphatic diisocyanates such as hydrogenated MDI (H_{12}MDI) and trans-cyclohexane diisocyanate have been used occasionally.[9-10]

The hard segment chemical structure and content significantly influence the biostability of polyurethanes. Several researchers[11,23-26] have reported that polyurethanes based on aromatic diisocyanates are more biostable than their aliphatic counterparts. Stokes[23] has shown

Pellethane™ 2363-55D, which is based on an aromatic diisocyanate MDI to exhibit little stress cracking compared to Tecoflex® EG-60D based on the aliphatic diisocyanate H_{12}MDI. The results were confirmed by Szycher.[24] In another study, Chris et al[25] also demonstrated that aliphatic polyurethanes experience severe stress cracking when implanted in rabbits. Hergenrother et al[26] showed that polyurethanes based on H_{12}MDI exhibited significantly greater stress cracking and molecular weight reductions compared to MDI based polyurethanes. The greater stability of aromatic diisocyanate based polyurethanes compared to aliphatic may be attributed mainly to their ability to form hard segment crystalline order resulting from molecular symmetry and strong intermolecular attractions through π-electron interactions. Polyurethanes based on cycloaliphatic diiscoyanates such as H_{12}MDI have low hard segment crystallinity due to the configurational isomers present.[7]

For these reasons, biomedical polyurethanes are generally formulated to have hard segments based on the aromatic diisocyanate MDI.

6.2.3 Polyurethane Morphology

The polyurethane morphology or micro-domain structure also influences the biostability. Factors such as chemical structure, size, glass transition and melting temperatures, and solubility characteristics of both soft and hard segments as well as their relative proportions can influence the polyurethane morphology. Morphology is also sensitive to thermal processing and handling. It is well known that, despite similarities in chemical composition, commercial polyurethanes Pellethane™ 2363-80A (P80A) and 2363-55D (P55D) have very different biostability; the low modulus P80A is susceptible to severe in vivo stress cracking while P55D demonstrates very good resistance to ESC. In fact, P80A and P55D, respectively are widely used as positive and negative controls to biodegradation in the in vivo evaluation of experimental polyurethanes. In a morphological study involving P80A, P55D and a series of PTMO-based polyurethanes, Martin et al[27] have revealed that the micro-domain morphology of the higher modulus but more stable 55D differed significantly from that of P80A. P55D has a morphology where the hard segment microdomains interconnect as a continuous phase, whereas the hard segment domains of P80A are discrete. This morphological difference appears to be the dominant factor responsible for the observed biostability difference between the two polymers.

6.3 Development of Degradation-Resistant Polyurethanes

The problem of polyurethane susceptibility to degradation, particularly by ESC, has provided stimulus for the development of degradation-resistant polyurethanes. This search for improved polyurethanes has been given renewed urgency with the commercial withdrawal of polyurethanes used for chronic implants by major manufacturers in the early 1990s.

The main strategies have focused on the replacement of PTMO (Fig. 6.1) by some other suitable macrodiol. Studies on the degradation behaviour of both polyester and PTMO-based urethanes have concluded that the susceptible functionalities in these materials are the ester and ether groups, respectively. It is well known that polyester polyol based polyurethanes degrade hydrolytically, while PTMO-based polyurethanes, although stable hydrolytically, degrade oxidatively. Accordingly, research efforts have been focused on developing macrodiols without functional groups susceptible to oxidative and hydrolytic degradation. Various macrodiols investigated to date can be classified into four main groups based on the type of backbone functional group. These groups are ether, hydrocarbon, siloxane and carbonate. Research groups including Coury et al,[28-31] Pinchuk et al,[9,39] and Meijs et al[32-38] have employed such strategies.

6.3.1 Hydrocarbon Macrodiol Based Polyurethanes

Coury et al[28] reported an experimental polyurethane based on a macrodiol derived from predominantly C-18 fatty acids or esters that have been dimerized via Diels-Alder or other coupling reactions. The resulting mixture of diacids or esters is reduced to form a diol. The dimer acids are also reacted with NH_3/H_2 to produce a dimer diisocyanate. The dimer macrodiols (Fig. 6.3) were then reacted with aliphatic diisocyanates such as 1,4-cyclohexane diisocyanate and diol chain extenders to produce all aliphatic polyurethanes. These polyurethanes have been claimed to be biostable[28,29,31] based on in vivo implant experiments. A significant limitation of these polyurethanes is that they are relatively stiff with the modulus of the softest grade similar to that of P55D, which is a harder grade of polyether-urethanes.

Hydrogenated polybutadiene diol and poly(isobutylene) diol have been investigated by several workers[40-43] largely focusing on understanding structure-property relationships. Polyurethanes based on these macrodiols show excellent resistance to UV, thermal and hydrolytic degradation.[42-43] However, these polyurethanes generally exhibit poor mechanical properties compared to their polyether counterparts and are more difficult to synthesize, which may be why they have not received serious consideration for medical implant applications.

6.3.2 Polyether Macrodiol Based Polyurethanes

Meijs and Gunatillake showed that polyurethanes based on MDI, butanediol, and higher macrodiols (e.g., PHMO (Fig. 6.4a); POMO (Fig. 6.4b); PDMO (Fig. 6.4c)) offered significantly improved stability over their PTMO counterparts,[32-36] confirming that the fewer ether linkages in the soft segment improves resistance to degradation under oxidative environments. These macrodiols can be prepared by the acid-catalysed condensation polymerization of the corresponding monomer diols.[44] This polymerisation technique can be easily adapted to prepare macrodiols from diols that do not cyclize easily under acidic conditions, and typically 1,6-hexanediol and other diols of higher molecular weight are suitable.

Martin et al[27,45-46] reported a detailed and systematic study on the effect of the polyether macrodiol structure, ie., methylene to oxygen ratio, on properties and morphology of polyurethanes using techniques such as DSC, DMTA, SAXS, WAXS and FT-IR. Increasing the soft segment CH_2/O ratio caused an increase in stiffness and hardness, and decreased elongation and clarity. Further, the increasing CH_2/O decreased compatibility between the hard and soft segments, producing increased phase separation and hard domain order.

In vivo stability of the polyurethanes was investigated by subcutaneous implantation in sheep using both strained and unstrained test specimens.[34] Polyurethanes that were strained over poly(methyl methacrylate) supports to 250% elongation provided accelerated degradation, the extent of which closely correlated with the results of an 18-month in vivo study with unstrained samples. The degree of cracking or pitting was ranked by SEM examination of up to x1000 after removal of biological debries. It was found that the polyurethanes produced from macrodiols PHMO, POMO and PDMO were significantly more resistant to stress cracking compared with PTMO-based polyurethane control and Pellethane™ 2363-80A, Biomer™ and Tecoflex® EG80A.

6.3.3 Polycarbonate Macrodiol Based Polyurethanes

Pinchuck et al,[9,39] explored the use of polycarbonate macrodiols to develop polyurethanes for long-term medical implants. Polycarbonate macrodiols, based on hexamethylene carbonate (Fig. 6.5a) and copolymers thereof (Fig. 6.5b) have also been claimed to impart good stability,[9,39,47] although there appears to be a softness limitation below which degradation takes

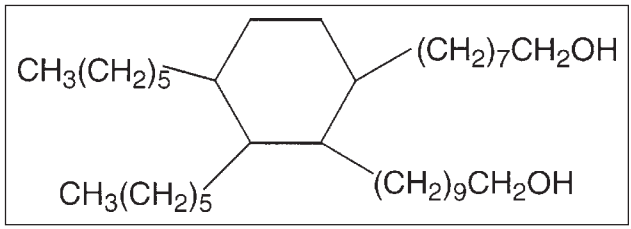

Fig. 6.3. 10-[2,3-dihexyl-6-(8-hydroxyoctyl)cyclohexyl]decan-1-ol.

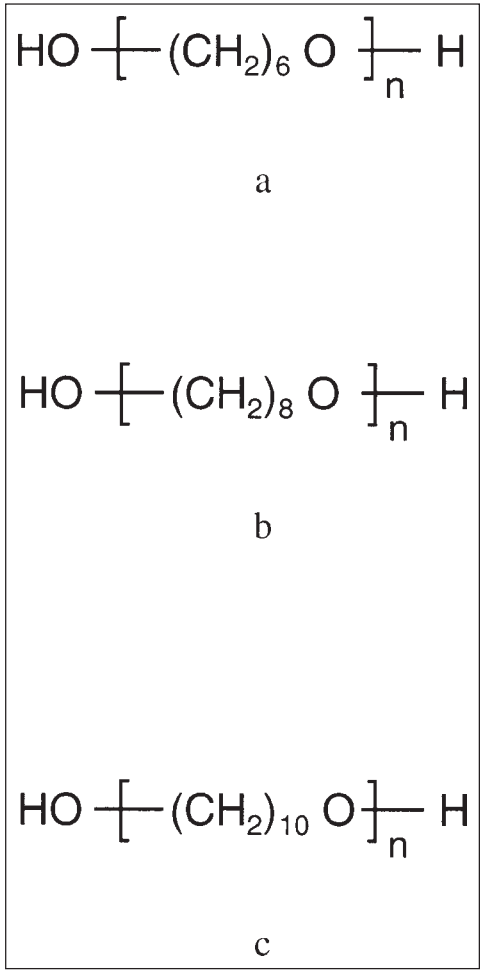

Fig. 6.4. Chemical structure of (a) poly(hexamethylene oxide) (PHMO); (b) poly(octamethylene oxide) (POMO); (c) poly(decamethylene oxide) (PDMO).

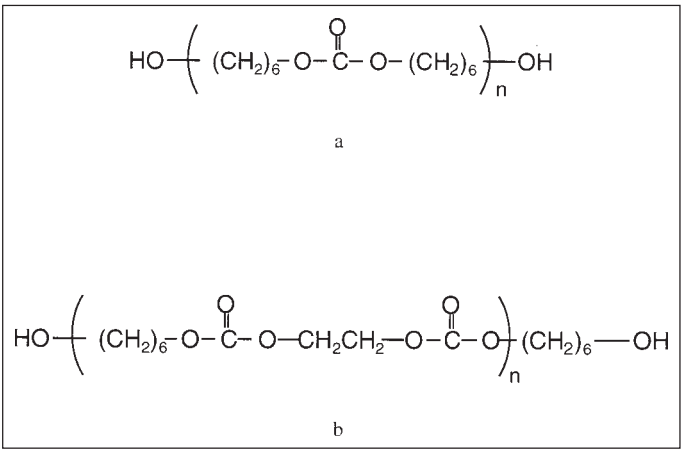

Fig. 6.5. Chemical structure of (a) poly(1,6-hexyl carbonate) diol and (b) poly(1,6-hexyl 1,2-ethyl carbonate) diol.

place. Carbothane™, Corethane™ (now Bionate®) and ChronoFlex® are the trade names of polyurethanes based on these types of polycarbonate diols.

Accelerated in vivo tests carried out in rabbits for up to six months have shown[9] that Corethane™ is significantly more resistant to biodegradation than Pellethane™ 80A. Recent studies[48] on polycarbonate-based aliphatic polyurethane (ChronoFlex® AL80A) samples revealed up to 86% failure (appearance of grooves to shallow cracks possibly associated with a hydrolytic degradation mechanism) in in vivo after 1-year implantation. Although ChronoFlex® AL80A performed better than Pellethane™ 80A, these results create some doubt concerning the long-term biostability of polycarbonate-based polyurethanes.

The relative biostability of polyurethanes prepared from dimer macrodiols (Fig. 6.3), the hexamethylene oxide and analogous macrodiols (Fig. 6.4a and 6.4c) and the carbonate macrodiols (Fig. 6.5a and 6.5b) are yet to be fully ascertained.

6.3.4 Siloxane Macrodiol Based Polyurethanes

The incorporation of poly(dimethyl siloxane) (PDMS) into the polyurethane structure has the advantage of imparting some of the attractive properties of PDMS to polyurethanes. These properties include, high flexibility, low toxicity, excellent thermal and oxidative and hydrolytic stability, and low surface energy. Three main approaches have been reported in the literature to incorporate siloxane segments to the polyurethane structure. One approach has focused on incorporating PDMS as a surface modifying end group.[49-51] Another approach[9] involved covalently binding silicon rubber as a coating material to polyurethanes. A third approach focused on incorporating PDMS in to polymer backbone through the soft segment[31,52-54] as well as the hard segment of the polyurethane structure.[52-53]

Ward et al[50-51] investigated the incorporation of siloxane end groups into the polyurethane structure, by reacting suitable siloxane compounds with the isocyanate terminated polyurethanes. Due to the low surface energy, siloxane groups migrate onto the surface creating a siloxane rich polyurethane surface. Mathur et al[49] showed that a polyether-urethane surface-modified with PDMS provided enhanced in vivo degradation resistance when compared with the uncapped polyurethane.[52-53] FT-IR analysis showed that the PDMS end-caps did not

degrade, but the PTMO soft segments were attacked to reveal pitting and cracking in areas of the specimens under highest strain (test specimens strained to 400%). This may indicate that under high strain, the PDMS surface layer could not effectively protect the oxidatively sensitive bulk of the polyurethane.

Pinchuk et al[9,52-53] developed a composite material (Corplex™) by covalently binding silicon rubber on to a polycarbonate urethane to enhance biostability.

Speckhard and Cooper have shown that synthesis of siloxane-based polyurethanes is not straightforward due to the incompatibility between the highly nonpolar PDMS and the polar urethane segments.[54] Because of the high degree of phase separation, the resulting polyurethanes exhibited very poor mechanical properties. Several techniques have been reported in the literature to synthesize PDMS-based polyurethanes with improved mechanical properties, primarily focusing on increasing interfacial adhesion between PDMS phase and hard domains. These techniques include mixing with conventional polyether (PTMO, PPO) or polyester macrodiols,[55-57] introduction of polar functionality to PDMS,[58-59] use of copolymers of polyethers or polyesters,[60] and hard segment modifications.[61] However, such attempts have achieved only a limited success in incorporating a high level of siloxane segments to the polyurethane structure without significant compromise in mechanical properties.

Focusing on the third approach, Gunatillake et al recently reported on the development of a series of polyurethanes with improved biostability incorporating siloxane segments into both hard and the soft segments.[62-66] The rationale behind this approach is that the incorporation of siloxane segments, as part of the main polyurethane structure should combine the good biostability of siloxane polymers with the excellent mechanical properties of polyurethanes. Significant improvements in mechanical properties were achieved when it was found that a small amount of a second macrodiol when mixed with a siloxane macrodiol would compatibilize the hard and soft segments. This key finding has enabled the synthesis of a new family of PDMS polyurethane elastomers. The compatibilizing effect of the second macrodiol has been demonstrated using thermo-analytical and mechanical techniques. Figure 6.6 shows the change in flexural modulus of a series of polyurethanes with varying amounts of the macrodiol, poly(hexamethylene oxide) (PHMO). The siloxane macrodiol used in this study was α,ω-bishydroxyethoxypropyl polydimethylsiloxane (Fig. 6.7) (Shin-Etsu, Japan) with a molecular weight of 1000. The significant decrease in flexural modulus with only 20% of PHMO is attributed to the compatibilization by PHMO of the siloxane rich soft segment domains and the urethane rich hard segment domains.

Gunatillake et al[62-63] also found that the method of synthesis has a significant effect on morphology and properties of polyurethanes. By appropriate choice of catalysts, both one- and two-step polymerization methods have been successfully adapted for the synthesis of polyurethanes exhibiting good mechanical properties and good processability. In the one-step process, the use of a catalyst such as dibutyltindilaurate was essential to prepare materials with good mechanical properties. The two-step process, on the other hand, could be performed in the absence of catalysts. This is an advantage for biomedical use. The polyurethanes were easily processed using conventional techniques such as extrusion, injection moulding, compression moulding, and solvent casting, offering the advantage of easy fabrication into a variety of devices and prostheses. Due to the presence of the siloxane-rich soft segment, thermal processing requires no processing additives such as bis-ethylene-stearamide waxes, commonly used in conventional polyurethane processing. The siloxane content also contributes to a low degree of post-processing tackiness (antiblocking) which is a serious extrusion line problem in the processing of conventional soft polyurethane elastomers.

Table 6.1 shows the comparative mechanical properties of two grades of these siloxane-based polyurethanes (Elast-Eon™). The properties of the polyurethane are comparable to those of a soft grade of Pellethane™ 2363-80A. Stress-strain curves are compared in Figure 6.8.

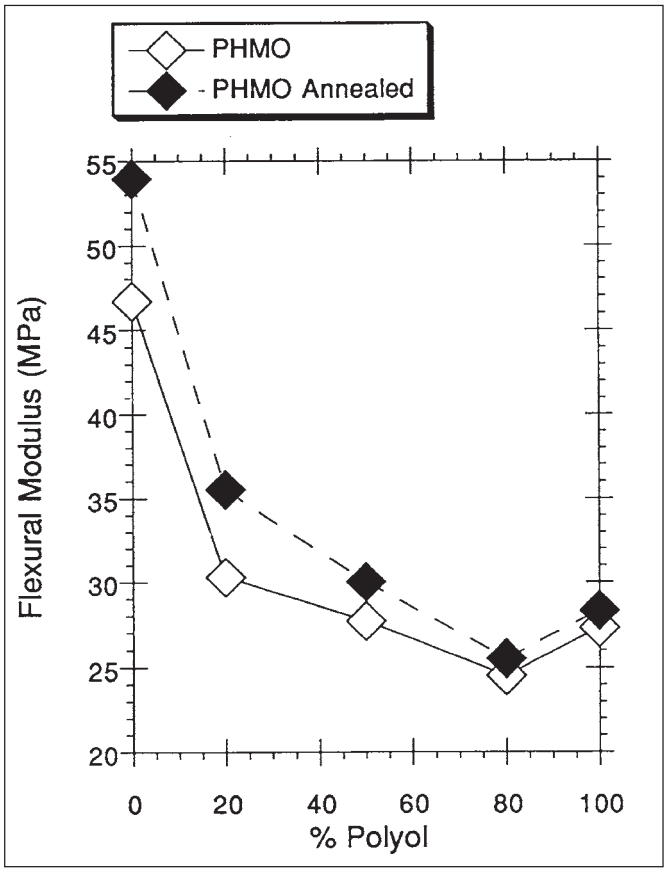

Fig. 6.6. The effect of macrodiol composition on flexural modulus.

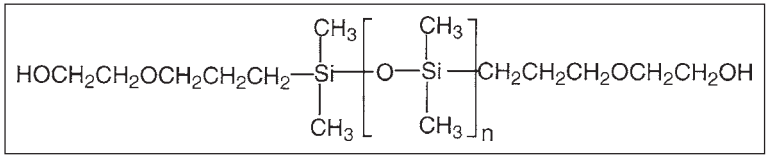

Fig. 6.7. Chemical structure of α,ω-bishydroxyethoxypropyl polydimethylsiloxane.

Gunatillake et al[63] also developed a biostable "soft" grade (Shore 70A) of polyurethane incorporating 1,4-bishydroxybutyltetramethyldisiloxane (Fig. 6.9) as part of the hard segment. This chain extender is used in combination with conventional chain extenders such as 1,4-butanediol. The physical properties of the new polyurethane (Elast-Eon™ 3) are shown in Table 6.1.

The biostability of the new polyurethanes has been assessed by a number of implant experiments using dumbbell shaped specimens in a stressed configuration (250% strain) for three months in sheep.[64-66] In these experiments Pellethane™ 2363-80A and Pellethane™ 2363-55D were used as negative and positive controls, respectively. Results of these experiments

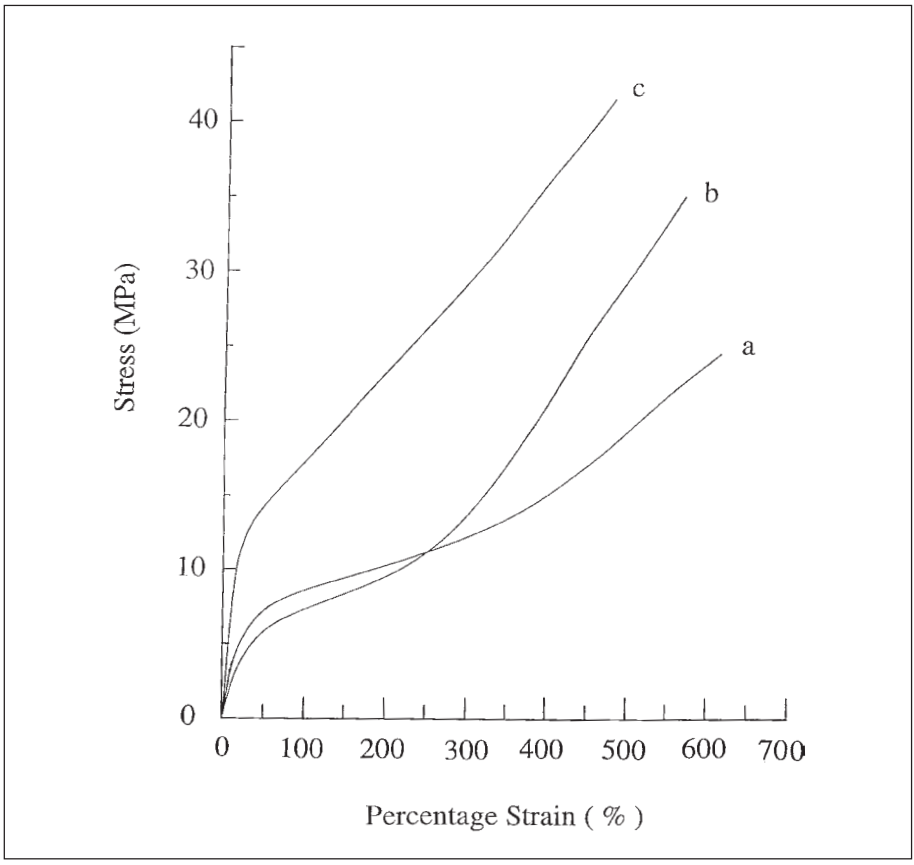

Fig. 6.8. Typical stress strain curves of (a) siloxane-based polyurethane (Elast-Eon™ 2), (b) Pellethane™ 2363-80A, and (c) Pellethane™ 2363-55D.

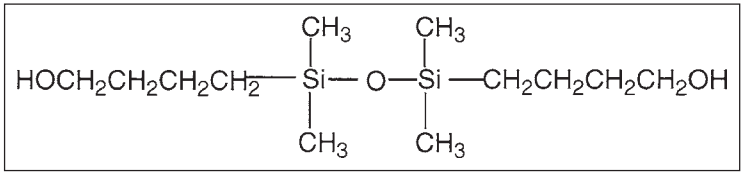

Fig. 6.9. Chemical structure of 1,4-bishydroxybutyltetramethyldisioxane.

have clearly demonstrated that these polyurethanes have superior biostability to that of P80A. Figure 6.10 shows the SEM micrographs of Elast-Eon™ 2, P80A and Elast-Eon™ 3, respectively. In these experiments P55D showed no degradation as evidenced by the absence of any stress cracking. The biostability of the Elast-Eon™ polyurethanes have been confirmed independently by researchers in other laboratories.[68]

Table 6.1. Mechanical properties of polyurethanes

Property	Elast-Eon™ 2	Elast-Eon™ 3	Pellethane™ 2363-80A	Pellethene™ 2363-55D
Shore hardness	84A	70A	82A	55D
Fail stress (MPa)	25.5 ± 1	25 ± 1	33.7 ± 1.8	40.3 ± 1.8
Ult. elongation (%)	460 ± 18	490 ± 11	430 ± 20	328 ± 16
Young's mod. (MPa)	22.5 ± 2	5.0 ± 0.1	13 ± 2	87 ± 10
Tear stren.$(N.mm^{-1})^a$	60 ± 2	57 ± 1	72 (83)	(115)
Stress at 100% E (MPa)	8.3 ± 0.5	5.0 ± 0.1	8(6)	20(17)
Flexural modulus (MPa)	30 ± 1	14 ± 1	35 ± 2	172
Abrasion resistance (mg per 1000 cycles)	40	–	10(20)	(80)

a: Values reported by the manufacturer are reported in parentheses.

6.3.5 Comparative Biostability of Newly Developed Polyurethanes

The relative biostabilities of polyurethanes prepared from dimer macrodiols, polycarbonate, poly(hexamethylene oxide) and siloxane macrodiols have not been reported. In most cases P80A and P55D have been used as positive and negative controls. However, recently Rhodes et al[67] have evaluated the biostability of six polyurethanes. The six polyurethanes included Tecothane™ and Tecoflex® (Thermedics), which were not claimed to be biostable and, four which did make claims to biostability, namely Cardiothane® (Thermedics), ChronoFlex®-AR (CardioTech), Elast-Eon™ 2 and Elast-Eon™ 3 (Elastomedic). The biostability was compared by implanting samples from solvent cast polymer films in rats, subcutaneously for periods of 8 weeks and 6 months. Tecothane™ and Tecoflex® showed degradation at both time periods. The polycarbonate macrodiol based ChronoFlex®-AR showed no degradation in 8 weeks but showed severe degradation after 6 months. The siloxane-macrodiol based Elast-Eon™ 2 and 3 showed no signs of degradation either at 8 week or 6 month time periods.

6.4 Conclusion

Of the several approaches reviewed here, the incorporation of siloxane segments to both soft and hard segments appear to be the most promising approach to develop biostable polyurethanes. Further, this method enables the synthesis of "soft" (low flexural modulus and hardness) polyurethanes without compromising biostability.

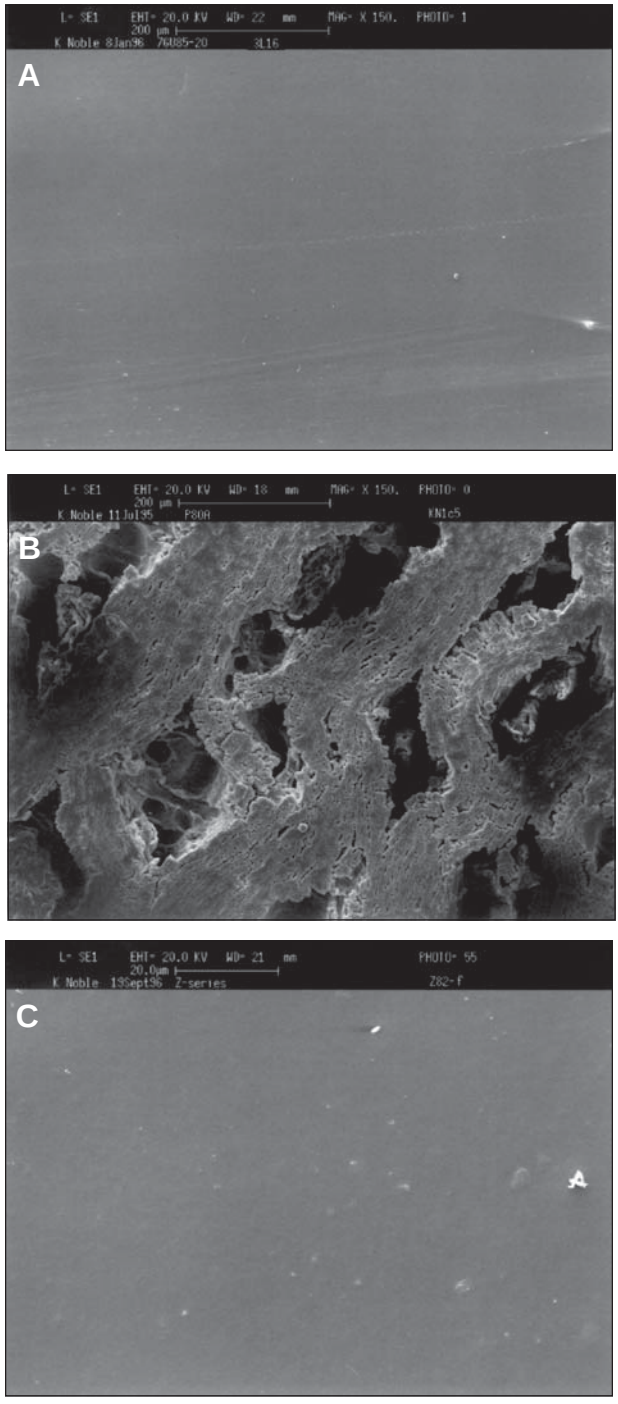

Fig. 6.10. Scanning electron micrographs of explanted (A) Elast-Eon™ 2, (B) Pellethane™ 2363-80A and (C) Elast-Eon™ 3.

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CHAPTER 7

Surface Modification of Polyurethanes

Hans J. Griesser

7.1 Introduction

Why perform surface modification of polyurethanes (PUs) when numerous publications and patents claim "biocompatible" and "blood compatible" PUs? The simple answer is that some claims are exaggerated and others only applicable to specific situations. While the mechanical properties (such as toughness, flexibility, durability, fatigue resistance) of PUs meet requirements, clinical evidence is that there are problems related to PU surface properties. No currently available polyurethane achieves long-term hemocompatibility, and in contact with soft tissue there occurs a foreign body defense reaction involving macrophages etc, as discussed elsewhere in this book. Clearly, the occurrence of adverse reactions to PUs in various biomedical environments attests to their being "bio-incompatible" to varying extents; some appear to promote less severe reactions than others, but all PUs are not integrated into the body in the way the clinician would wish them to be. The aim of many surface modification studies therefore has been to maintain the mechanical properties of PUs while providing a surface with improved biocompatibility. Other studies have aimed to improve cell colonization or degradation resistance by surface modification approaches.

The properties and composition of polyurethane surfaces play an important role in biomedical interactions, such as blood compatibility (see for instance ref. 1), and therefore in the suitability of this class of materials for use in biomedical devices. In the absence of leachable chemical constituents and with appropriate shape (including no sharp edges) and mechanical properties of a device, the biomaterial surface has a large influence on the outcomes of the biological responses to an implant. Hence, it is of great practical interest to analyze, understand, and control the surface composition of biomedical polyurethanes, and thereby interpret and improve their "biocompatibility". The application of surface analytical techniques to the elucidation of the chemical composition of polyurethane surfaces is discussed in Chapter 1; in this Chapter, it will be discussed how the surface properties and hence the "biocompatibility" of polyurethanes can be altered and improved by the application of surface modification methods and thin coatings.

The surface modification of polymers has become a very attractive route towards expanding the use of existing polymers into applications for which they possess suitable bulk properties but inadequate surface properties. Surface modification approaches have thus assumed increasing importance in biomaterials research over the last decade. It is often difficult for the synthetic polymer chemist to design and develop a polyurethane that meets all the requirements

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of the intended application. In these situations, one promising approach is to uncouple bulk and surface requirements; the synthetic chemist focuses on meeting the former (such as modulus) while the surface scientist then independently attempts to optimize the surface properties of the bulk polyurethane, preferably without measurably affecting the bulk properties.

The conventional understanding of surface modification is a separate processing step on the formed bulk solid material. On the other hand, by changes to chemical constituents used in the synthesis of PUs and different synthetic routes, the materials developer often also causes, deliberately or unwittingly, considerable changes to surface properties. In this review, I have chosen to use the term surface modification in a wide sense and include examples of the latter type where synthetic approaches were designed with the explicit aim of achieving specific surfaces and controlling PU surface properties. Methods will be reviewed that have been used to improve the surface properties and biological interactions of commercially available and experimental PUs. The methods used comprise various surface treatments, which introduce various new groups onto polyurethane surfaces, and application of various coatings that mask the underlying PU and determine the interfacial biological responses to the material or implant.

In general, the same surface analysis techniques as discussed in Chapter 1 are applicable to the characterization of modified and coated polyurethanes; where specialized methods have been applied, they will be briefly discussed, but this Chapter assumes a general working knowledge of a range of modern instrumental physico-chemical methods as well as biochemical techniques relevant to biomaterials research. Nor will the biological tests used in the reviewed studies be discussed per se; this Chapter focuses only the outcomes of the biological tests done on modified PUs. For more details on surface analysis techniques as well as the broader principles and terminologies of biomaterials science, and descriptions of biological tests and host responses, the reader should consult standard texts describing surface analysis techniques[2-4] and general biomaterials science texts such as an excellent recent book.[5] Likewise, it is neither feasible nor desirable to present here a detailed discussion of the principles and experimental methodologies of the various surface treatment and coating methodologies that have been applied towards improving polyurethanes. Brief mention will be made of some techniques in combination with the review of pertinent results, but it will be assumed that the reader has consulted, or will be able to consult, specialized texts for thorough discussion of the principles, methods, and instrumentation pertinent to surface treatments, coatings, and surface science.

7.2 Rationale for Surface Modification

The reason why polymer surfaces play a key role in biomedical interactions is that the response of biological media to synthetic materials is dictated, inter alia, by the rapid adsorption of biological entities onto the synthetic surface. Many proteins are designed to be surface active; adsorption at a synthetic surface often activates a specific function and gives rise to signals that stimulate a "walling-off" response—in essence, adsorbed proteins can transmit the message that a nonnatural surface has been located, and the body then tries to wall off and thus isolate the recognized foreign object. This response is seen for instance in the fibrous encapsulation within soft tissue.

Interfacial forces,[6] such as electrostatic forces, emanate from a solid polymer surface and penetrate some distance into the contacting environment, where they give rise to perturbations and hence surface interactions between the polymer and its environment. Interfacial forces, which are a function of the composition and properties (e.g., charge) of the surface layers, therefore govern the adsorption and denaturation of proteins on the surface of a biomedical implant. A key problem in the application of present biomaterials is that the response of the biological medium to synthetic materials is largely uncontrolled and nondiscriminating. Lacking the exquisite specificity characteristic of biological signalling (e.g., antibody/antigen interactions),

nonspecific signals triggered by the uncontrolled surface accumulation of various biological molecules (chiefly proteins but lipids can also be involved) cause adverse interactions that give rise to biocompatibility problems. In blood contact, the catastrophic accumulation of molecular and biological cellular material causes thrombus formation and the clotting of synthetic vascular grafts, for example. In other applications, analogous accumulation of biological material does not replicate a natural tissue. Finally, as degradation in vivo generally proceeds from the surface into the bulk, the chemical composition of the surface layers affect the rates and mechanisms of biodegradation.

The premise behind surface modification is that by changing the chemical composition of the PU surface layers, one can alter the interfacial forces that interact with the biological host medium and thereby mitigate or even prevent adverse biological responses. Ideally, when designing a biomedical device, one would like to be able to independently control the surface chemistry of the material while retaining its favorable bulk characteristics. This would permit the selection of a material for its bulk properties and the tailoring of surface properties for requirements such as thromboresistance or soft tissue integration.

However, it must be recognized at the outset that the various biological media that biomedical devices can be intended to contact can differ quite substantially in their biomolecular composition. For instance, comparing blood and tears, in the latter the positively charged proteins lysozyme and lactoferrin are present in substantial amounts, whereas blood contains predominantly negatively charged proteins, several of which have a strong affinity for surfaces. Accordingly, it may not be feasible to design a single surface modification strategy that will make a PU useful for all biomedical applications. Hence, the requirements of a surface for "biocompatibility" should be defined with respect to the intended end usage, and the surface composition of biomaterials (and the resultant interfacial forces) should be optimized for each individual application. One must realize, therefore, that promising modifications and results reviewed below may not be directly transferable to other applications. Much work and particularly understanding is still required towards designed, controlled optimization of "biocompatibility" for specific devices. Perhaps the word "biocompatibility" should be avoided altogether in favour of more specific terms such as thromboresistance, tissue adhesion, osteointegration, or whatever describes the requirements of a specific intended application. In addition, it should be discouraged for authors to claim "biocompatible" materials after obtaining improved results in one test.

Surface analytical methods occupy a key role in such surface chemistry optimizations and in general in the research and development of materials designed to possess specific surface properties. The analytical methods mentioned elsewhere in this book are well suited to such work since their probe depths are of similar magnitudes to the thickness of the surface layers of modified polyurethanes or coatings that interact with biological fluids. The range of interfacial forces ranges from less than one nanometer for electrostatic forces in saline biological media[6] (e.g., blood) to a few tens of nanometers for van der Waals (dispersion) forces; hence, the biological environment only "sees" a very shallow region of the PU material. Therefore, it is the polymer composition over such depth ranges that should be elucidated by appropriate surface analytical methods when attempting to interpret biomedical responses in terms of polymer chemistry.

The literature on the modification of polyurethanes by surface treatments, by additives, or by the application of coatings is very extensive. Nevertheless, a review is lacking to date; a recent book on biomedical polyurethanes[7] for instance contains only a brief section and few references on the subject of PU surface modification. This Chapter reviews recent work in this expanding field and includes the more important older studies as well. It is, however, neither instructive nor desirable to present an exhaustive overview; computerized searches can easily give the interested reader a comprehensive listing of publications and patents. I have chosen to

illustrate with selected examples the breadth of approaches that have been investigated and the ideas, principles, and results that have been reported. The literature contains some repetition in rationale, approaches, and surface modification chemistries used. Selective discussion is also necessary to keep this review of manageable length and of value to readers.

Before reviewing such studies, however, I wish to discuss some considerations that commonly apply to polymer surface science and analysis studies but usually are not addressed in any detail because either they seem to be assumed to be understood or the authors may not be aware of them. However, while the expert in the field may be well aware of these issues, they can present formidable obstacles to the newcomer. I hope that discussion of some pitfalls will enable newcomers to the field to shorten those painful experiences associated with running into scientifically "trivial" but often nonobvious pitfalls, which are seldom detailed in reports.

7.3 Common Pitfalls in Surface Modification

The surface modification by treatments or coatings, and the analysis of such modified polyurethanes, requires consideration of some fundamental and practical issues that are partly characteristic of all polymers and partly specific to polyurethanes. These issues arise as there are marked differences in structure and properties of polymers compared with metallic and ceramic materials. Accordingly, modification and analysis protocols need to be adjusted and results interpreted based on a thorough understanding of polymer materials science and, if available, also the specific properties of the polyurethane and the modification methodology under investigation.

7.3.1 Variability

7.3.1.1 Variability in the Base Material

Usually, the results of surface modifications are analyzed by comparison with the unmodified base material, using techniques such as air/water contact angle measurements, XPS (or ESCA), and the like. For reliable interpretation of the success of intended modification and coating schemes, and particularly for quantification of surface coverage, it is essential that a reliable, reproducible base material is available. Unfortunately, the surface composition of polyurethanes can depend quite substantially on fabrication conditions, and variability of synthesis and processing conditions can markedly affect the surface chemistry even if the resultant changes to the bulk chemistry and properties are small. For example, temperature affects the chain mobility of segmented PUs and the migration of additives; hence, factors such as the rate of cooling can affect the morphology of materials and the distribution of additives. Thus, relatively small variability in manufacturing processes can lead to batches of nominally identical materials whose effective surface composition may differ significantly. Significant differences in the surface chemistry of two lots of a commercially available PU have been documented,[8] and this possible pitfall should be borne in mind, and assessed by appropriate analyses, prior to undertaking surface modifications.

7.3.1.2 Variability in the Surface Modification

It is important to ensure spatial homogeneity of the surface modification or coating procedure. Variability in the efficiency of modification or the thickness of a coating across a sample may give rise to disproportionate influence of some regions of the sample to observed overall biological responses. This may all sound obvious, but XPS observations showed that samples of

commercial polystyrene tissue culture ware (TCPS and Primaria®) possessed significant lateral variability across a given multiwell plate and variability between plates.[9] This gives cause for concern that biological testing may at times involve variable surface-treated samples.

7.3.2 Surface Contamination

Prior to applying a surface modification methodology, one needs to consider and probe for the possibility that the idealized, intended chemical modification may not be achieved because the modification is not applied to the theoretical polyurethane chemistry but to a surface layer of lower molecular weight species that may be quite different in their chemical composition and response to the surface modification procedure compared with the nominal polyurethane. In fact, the surface of as-supplied polyurethanes often is far from what one may expect it to be from consideration of the theoretical chemical composition. The danger is, in a nutshell, that the surface modification procedure will simply modify the surface contaminants; these low molecular weight species can then wash off or be displaced in the biological medium, thus reexposing an untreated polyurethane surface and leading to the loss of the intended interfacial control. Hence, modern surface analytical tools are indispensable and should be applied with great expertise and a keen awareness of potential interference from contaminants at all steps of polyurethane surface modification and analysis procedures.

We can classify the possible surface contaminants in terms of chemical compounds that are added during the manufacture of the polyurethane ("intrinsic" surface contaminants), and others that accumulate on a PU surface subsequently, adventitiously, and often unsuspectedly from the environment ("extrinsic" surface contaminants).

7.3.2.1 Intrinsic Surface Contaminants

Apart from the possibility of mobile (diffusible) lower molecular weight, polyurethane-like constituents that can arise from, e.g., incomplete curing, polyurethanes can contain, on their surfaces and in their bulk, low molecular weight compounds of chemical compositions quite different from that of polyurethanes. Such compounds can either be surface located as a direct result of how they came to be applied to the polyurethane (e.g., extrusion lubricants), or they can, by virtue of their low molecular weight, diffuse throughout the polyurethane bulk and achieve a finite surface concentration. Some diffusible, bulk-mixed additives can become surface-enriched to considerable extents on account of interfacial energetics; this has been used to advantage (refer Section 7.10 below).

The optimization of properties and viable manufacture of polymers in most cases requires use of additives and processing aids (see Chapter 3). Additives can be antioxidants, plasticizers, pigments, and others added for specific reasons. These additives are usually located throughout the polymeric material but can be present at the surface in significant amounts. Other additives are designed to aid processing, and chemicals such as slip extrusion lubricants are commonly found on commercial polyurethane samples. These intrinsic chemicals are not contaminants in the eyes of the polyurethane manufacturers but to the surface modifier they interfere with the intended modification and hence have the same effect as other contaminants. When a coating is applied, such low molecular weight compounds can provide a weak boundary layer and lead to the facile later delamination of the coating.

Knowledge of the manufacturing process can suggest to a trained surface scientist that such compounds might be present on the surface. For example, the chemical composition of extrusion slip agents is such that they are strongly surface active and therefore one must expect them to have a high affinity for PU surfaces. Nevertheless, it took a surprisingly long time until more than just a few researchers started considering that the observed biological responses

might not entirely be due to the nominal PU formulation but be affected also by low molecular weight compounds of at times quite different chemical composition. This was the case even though early on, XPS analyses often had given results at odds with theoretical expectations, and a SSIMS study then positively identified substantial coverage of the slip agent bis-ethylene stearamide on Pellethane™ surfaces, suggesting that the biocompatibility of this PU might not actually be due to the chemical composition of the material itself, but largely achieved by this processing additive![4] The importance of this "wax" to blood compatibility was examined.[10] This issue is, of course, not limited to PUs but applies equally to many other biomaterials.

For many other additives, their partition between bulk and surface may not be as readily predictable as for slip agents, and their presence on a biomaterial surface may not be suspected by the formulator, who added them for reasons that have nothing to do with the surface (e.g., plasticizers, antioxidants); in fact, their possible presence at and effect on the surface may not be considered. The researcher performing the biological testing may then not receive information regarding surface-located additives, and they may not be considered in the interpretation of observed biological responses. In this regard the paucity of information on additives and processing aids used in the manufacture of commercially available biomedical polyurethanes presents a particularly troublesome problem, since there are many in vivo studies in which such available PUs have been used at face value, without adequate supporting surface analyses to establish what the surface really consisted of.

Additives and processing aids might not be termed contaminants by the PU formulator and processor, but to the surface scientist attempting to modify the PU surface chemical composition, such surface-enriched low molecular weight compounds are effectively contaminants too in that they result in the surface modification procedure achieving an outcome different to that intended and designed on the basis of the nominal, presumed PU surface composition. Accordingly, all such compounds must be removed from the surface by solvent washing or extraction protocols; one must of course then ascertain that the cleaning steps do not substantially affect the PU by, e.g., swelling it. Surface analyses are then needed to verify that the PU surface itself is available for modification studies. Unfortunately, a substantial number of reports on surface modification of PUs have not adequately characterized the composition and cleanliness of the PU material prior to modification, and hence there are many data whose value is dubious. Clearly, it is not instructive to perform biological tests on ill-defined surfaces; ignorance of the detailed surface composition undergoing modification and testing prevents the establishment of valid correlations between surface chemistry and biological responses. Ratner et al has been prominent in advocating detailed surface characterization as being essential for reliable interpretation of bioresponses,[11] but not every biomaterials scientist seems to be heeding this, and some researchers still report biological responses to PUs whose presumed surface composition has not been verified adequately, or at times not at all.

Even if no additives have been used in the synthesis and processing of a PU, one must consider the possible presence of lower molecular weight reaction by-products whose chemical composition may differ from that of the desired bulk PU.

Leachable compounds not only can interfere in surface modification procedures, but also give rise to adverse biomedical effects (see for instance Ref. 12) that may be difficult to disentangle from effects produced by surface modification. For example, application of a coating may reduce the rate of leaching and hence produce a beneficial effect that has nothing to do with the particular coating chemistry.

7.3.2.2 Extrinsic Surface Contaminants

Extrinsic contaminants can reach a polyurethane surface from various adventitious pathways that often are hard to detect and exclude. For instance, packaging materials such as plastic

bags often contain plasticizers that can transfer onto a clean surface.[13] Specific precautions are hence necessary in the storage of clean, freshly fabricated polyurethane sheet or tube material in order to avoid surface contamination. Most plastic bags are unsuitable. Nor is it advisable, unless checked, to wrap clean polymer materials in aluminium foil since many commercially available foils have a thin coating of peanut oil or other vegetable oil; such oils transfer readily. In the author's laboratory, specially cleaned aluminium foil is used. Other suitable storage containers are additive-free "tissue culture" grade polystyrene dishes and bottles.

Other extrinsic contaminants can originate from various sources. Typically there is a finite concentration of hydrocarbon vapour in laboratory atmospheres, and such vapors lead to molecular adsorption onto clean surfaces within rapid time scales unless precautions are used. Particularly troublesome are organosilicone compounds which are used for instance as plasticizers in some brands of laboratory gloves and vial stoppers. Handcreams and shampoos also often contain silicones, which can transfer readily even with skilled analysts via pipette tips and other laboratory utensils. Careful and frequent solvent cleaning of utensils is recommended. Nevertheless, Si is an element that is detected very often in XPS spectra even when it is not nominally part of the analyte surface. The effect of surface modification of such contaminants may be quite different to the intended effect of PU modification. In oxidative surface modifications, silicon oxides can be produced from organosilicones, and such oxides may then be difficult to remove.

Contaminants can, of course, also interfere in the biological evaluation of modified polyurethane surfaces, and it is important to use appropriate sample handling, storage, and testing procedures, as well as to perform control experiments and surface analyses, to guard against the possibility of accumulation of additives and extraneous contaminants in the time period between modification and biological testing.

Surface analysis, particularly by XPS, has been of tremendous value in identifying surface contamination. Some contaminants, however, can be difficult to detect by XPS when their elemental composition is similar to that of the polymer. SSIMS is a most useful complementary technique that can provide unique information.[4]

7.3.2.3 Recommendations–Contamination

In summary, therefore, the surface modification of polyurethanes requires care to avoid problems with contaminants interfering with the intended modification or causing subsequent spot delamination of a coating. Sample surfaces must be rigorously cleaned of adventitious contaminants, processing aids, and surface-accumulated additives in order to ensure reproducible, reliable study and interpretation of surface modifications and the consequent biological responses. One wonders how many studies have been marred by unrecognized surface contamination; perhaps some of the contradictory results in the literature might have been caused by contributions to biological interfacial responses arising from contaminants and/or coating defects induced by contaminants. Rigorous adherence to appropriate protocols of sample preparation (including solvent cleaning steps) and handling is required for the modification step and subsequent surface analyses.

In addition, one needs to consider the possibility that additives and other low molecular weight species (including short polyurethane chains and macrodiols) located inside the polymer might diffuse to the surface after modification and remain at the interface (for reasons of surface energetics and insufficient solubility in the adjacent biological fluid or tissue), thereby altering the intended surface chemistry. Such species can also be expected to diffuse through coatings applied onto polyurethanes. Therefore, unless one can source a polyurethane synthesized and extracted under well-defined conditions that should have removed all low molecular weight material, it is worthwhile prior to commencement of surface modification experimentation to

remove potential sources of surface contamination from the bulk polyurethane material. This can be efficiently achieved by sequential Soxhlet extraction with a polar solvent followed by a nonpolar solvent.

In surface analytical sample preparation procedures it is wise to adopt the philosophy that tools, beakers, etc, all can be a potential source of contamination unless proven otherwise. It is also recommended that surface analyses be performed at various times after surface modification so that effects due to surface reorientation or out-diffusion of additives and other low molecular weight components can be recognized and taken into account when designing protocols for biological assays of modified polyurethanes. Due to possible time dependence of surface properties, it is recommended that a parallel, identical sample should be subjected to appropriate surface analyses at the same time as biological assays are performed.

Finally, supporting surface analyses must be performed by a competent analyst who, in order to be able to recognize potential interference from unforeseen contaminants, has received plenty of information about the sample, its history, handling, and possible components other than the nominal expected polymer surface composition. To ask an analyst to merely provide a set of figures (such as elemental percentages) can lead to key information not being recognized because the analyst may not be aware of what information is being sought and what the composition should be, and the sample provider may not be sufficiently trained in interpreting "raw" surface analysis data. There are a number of examples, even in leading biomaterials journals, of surface analytical data that have not been well interpreted, with the authors obviously having had contract analyses performed but then have not been able to interpret the data fully. Several recent publications contain data suggestive of surface contamination that apparently was not recognized, but to a trained eye the telltale signatures of common contaminants and the deviations from theoretical surface compositions are clear. In my experience, of great value is a feedback loop in which the analyst can discuss with the sample provider during the analysis any unexpected findings and devise (improvise) additional or different analytical routines to adapt to the circumstances and probe further. It is essential to attain the highest possible quality of information about the composition of modified polyurethane surfaces so that biological responses to such surfaces can be interpreted reliably and accurately.

7.3.3 Surface Mobility

The intrinsic mobility of polymer chains[14-16] can cause polymer surface layers to adopt chemical compositions and properties that are quite different from those of the bulk material. This also applies to PUs: XPS[17-19] and SIMS[19] analyses have indeed shown that the surface composition of PUs differs from the nominal bulk composition, an observation which can be rationalized in terms of interfacial energy minimization.[18] The mobility of polymer chains coupled with environmental changes can lead to surface compositions and properties that are time-dependent and dependent on the environment (contacting medium, temperature) that the polymer experiences. Immediately after fabrication, polyurethane surface layers tend not to be in thermodynamic equilibrium, and hence they will "relax" by chain and segmental motions towards attaining a minimal energy situation. Diffusion and reptation of polymer chains also can contribute to the time dependence of polymer surfaces. In addition to random thermal motions, one driving force is the minimization of interfacial energy with the environment. Generally, polyurethanes are brought into contact with air after fabrication, and this forces the polyurethane to attain a surface composition as nonpolar as possible. This takes some time, depending on the rates of motions that can strive towards interfacial equilibrium. The rates depend on factors such as the polymer's thermal transition temperatures, the ambient temperature, diffusion rates of migrating components, and plasticizing effects provided by additives. Solvents can also stimulate the rearrangement of PU surface layers.[20]

As the polyurethane biomaterial is then placed into contact with a physiological medium such as blood or tissue, its surface layers will again undergo motions in order to accommodate the new interfacial situation. In contact with aqueous environments, it is obviously favorable for hydrophilic constituents of the polymer to become enriched at the interface. Thus, polymer chains in the surface and sub-surface layers will have to undergo concerted motions in order to present the lowest energy interface after this change of environment/medium. Such compositional changes in response to changes in the contacting medium can be studied by freeze-hydration XPS,[21] a technique in which a polymer is analyzed in the frozen hydrated state, which is expected to be a good approximation of the polyurethane surface composition adopted in contact with biological media.

It is, however, an unresolved question as to whether an air-stored PU surface indeed adapts to the aqueous environment on biomedical usage. If lipids or hydrophobic residues of proteins were to adsorb sufficiently rapidly (compared with PU surface adaptation motions) at the PU surface, the interfacial energy situation would be quite acceptable, the PU would become shielded from the polar water molecules, and there would be no or little interfacial energy driving force for the PU to change from its nonpolar surface structure.

In addition, polyurethanes show (partial) segregation into "hard" and "soft" segments. Thus, there are a number of interfacial enthalpic factors that will determine the exact chemical composition and microstructure of polyurethane surface layers. One needs to consider enthalpic terms from both the polyurethane/environment interface and the "hard/soft" segment interfaces.

These considerations apply to polyurethane materials in general and are equally important for surface-modified polyurethanes. In general, the mobility of the surface layers is not inhibited as a result of the surface modification procedure. A modified surface again is not in thermodynamic equilibrium, and one may therefore expect that subsequent motions will rearrange the chemical composition of the surface layers towards minimal interfacial energy. This is a particular concern when nondepositing surface treatments are used, in which there is modification of the polyurethane by insertion of small new chemical groups (such as, e.g., sulfonates) over a very shallow treatment depth of only a few nanometers.

Moreover, while it is well recognized that interfacial enthalpic terms affect the chemical composition of a polymer in contact with a medium, much less is known about entropic contributions. However, it is clear that enrichment of one type of chemical structure at the interface creates a chemical potential; unless solubility is limited, there is a driving force towards eliminating concentration gradients. It has been shown that for compositionally graded systems such as surface-modified materials and multilayer structures with thin coatings there is also a contribution from translational entropy to the way in which the chemical constituents arrange themselves for overall surface energy minimization of the total system.[22] Modified polymer chains are akin to a different chemical species compared with untreated polymer chains. Hence, the high concentration of modified chains in surface layers resulting from surface treatments establishes a marked concentration gradient; one can also depict the situation in terms of a chemical potential resulting from a strong concentration profile. This situation leads to a directional driving force: translational motions will drive some of the modified polymer chains into deeper layers, and concurrently unmodified chains migrate towards the surface. These motions alter the entropy of the system and drive towards a new equilibrium which, unfortunately for the surface treatment scientist, consists of surface layers that have lost part of the treatment effects.[23-25]

Even the application of coatings may not prevent such translational entropic dilution. If there is a finite mobility and solubility of the components of the coating and the polyurethane in the other phase, there may be some dilution. Siloxane oligomers and macromolecular chains are particularly notorious for emerging through thin coatings to an air interface. It is hence

advisable to check the surface composition of surface-treated or coated polyurethanes over extended periods of time in order to probe for such effects.

Partial loss of surface treatment effects can occur even when the treated polymer is stored in water,[22,23] even though one might expect polar groups to be energetically favored at the interface when in contact with a polar medium. The reason for the (partial) disappearance of polar groups from the surface even in contact with water has been postulated to be the translational entropy gain associated with reptation of treated chains:[22,23] the presence of a high density of treated chains within a narrow surface region is equivalent to a chemical potential gradient; as in solutions, such concentration gradients are subject to reduction by diffusional motions. In other words, the redistribution of some of the treated chains into the polymer and the concurrent emergence of untreated chains to the surface layers dilutes the concentrations of two chemically dissimilar species of polymer chains.

The mobility of PUs and surface-treated PUs thus may partly or entirely frustrate the efforts of the surface scientist attempting to create a controlled, predictable PU surface for biological testing. On the other hand, the application of coatings may not circumvent the problem either: coatings also typically possess surface mobility and can adapt to the environment, although for some coatings this process can be very slow and beyond the time scale of protein adsorption and exchange processes.[26,27] Such coatings may offer a means of presenting to a biological test a surface that cannot adapt over the time scale within which it becomes covered with proteins and does not differ from that analyzed by standard vacuum spectroscopic methods, thus obviating the need for freeze-hydrated analyses and facilitating detailed characterization of the surface composition and properties. It is not clear how much the mobility of many biomaterials surfaces interacts with the process of competitive protein adsorption (both the polymer surface layers and the various competing proteins trying to adapt in order to minimize interfacial energy) and it is highly desirable to study competitive protein adsorption onto such "immobile" polymer surfaces as a prelude to investigating whether surface mobility matters in vivo.

Given the potentially extended shelf life of some polyurethane-containing biomedical devices, it is important to store samples under realistic storage conditions and perform surface analyses at periodic intervals, so that one can document what the surface composition is at the time of end use. In addition, it is also important to ascertain whether the surface will change under use conditions; slow changes to the surface composition while in contact with the biological medium may have an adverse effect on the device performance, with the "biocompatibility" intended by the surface modification becoming compromised upon the (partial) loss of the modification effects by rearrangement motions in the surface layers. As it is, however, difficult to simulate real-life biological environments, perhaps storage of modified polyurethanes under water may be a way of ascertaining whether the chemical composition of the modified surface layers remains invariant on contact with aqueous media.

Hence, in general, it is not possible to predict what the precise composition of polyurethane surface layers will be under specific circumstances and over time, and it is necessary to perform appropriate surface analyses. The phenomenon of polymer chain mobility and the resultant enrichment of some constituents, the dependence of the composition of polyurethane surface layers on sample history, time, and environment, and the ways in which these factors may affect the long-term stability of the intended results of surface modification procedures all must be taken into account and analyzed. Yet, a substantial fraction of studies have not addressed these issues. Perhaps unrecognized dependence of modification effects on time and environment might account for some of the inconsistent results from biological testing of modified polyurethanes in some studies.

Chain mobility must also be properly appreciated in order to apply appropriate protocols in sample preparation and surface analysis, and avoid erroneous interpretations. The analyst

needs to ascertain that a PU surface is in equilibrium rather than in the midst of adapting to a changed environment. Moreover, the surface compositions determined by vacuum surface analytical techniques may bear little relationship to the effective surface compositions that determine the interfacial interactions when a polymer contacts an aqueous biological medium. Hence, one might draw erroneous interpretations about relationships between surface compositions and performance if the polymer surface mobility/adaptability was neglected. Given the possible marked time dependences in PU surface compositions, the analyst needs to be aware of the effects, their approximate rate constant, and the time lag between surface modification and analysis.

7.4 Surface Modification Types

A wide variety of techniques can be used for the chemical and topographical (etching) modification of preformed, solid PU materials. Broadly speaking, they can be distinguished by the processing equipment used and at the first level divided into methods that use solutions of a modifying reagent ("wet" synthetic chemistry methods) and methods that do not use solvents ("dry" surface modifications) but instead use vapors of reactive chemical compounds. Among the "dry" methods there is a large variety of approaches and equipment. Prominent among these are processes based on vapors activated at low pressure in an electrically driven discharge (low pressure gas plasma, also known as radio frequency glow discharge) for reason of chemical versatility.

Another approach is to use modification of the chemistry during synthesis to achieve specific surface properties or surface chemical groups, such as adding a sulfonated chain extender. Such synthetic approaches may not be considered a surface modification per se, as commonly a surface modification step is understood as a separate step after synthesis and fabrication of a solid bulk polymer piece. There are, however, a number of studies in which synthetic chemical approaches were employed specifically with the intent of modifying surface properties, and surface analytical techniques were used to characterize the results of such synthetic chemistry steps. Some examples of such work will be included as they are instructive in showing that alterations to synthetic procedures can have marked effects on surface properties. Many other studies have investigated PU formulations with various novel components added, and no doubt some of the resultant PUs had different and potentially interesting surface properties. However, most studies employing varying formulations and synthetic procedures have aimed to modify the bulk physical/mechanical properties of PUs or their susceptibility to in vivo degradation (see for instance Chapter 6) rather than their surface properties (although some studies did pay some attention to effects of formulation changes to the surface). Only PU synthesis studies that explicitly targeted specific surface chemistries will be reviewed in this Chapter.

Some PU surface modification strategies have made use of a combination of these types of methods, often by first using a "dry" method to surface activate the PU, or incorporating a constituent during synthesis that gives a desired surface group, and then using a solution of a bioactive molecule to attach a layer with predictable composition and biological response.

The surface topography of a biomaterial can also affect cellular responses.[5] Some of the PU surface modifications reviewed below had topographical effects superimposed on the changes to the surface chemical composition. It is often not straightforward to separate effects arising from topographical changes from those caused by chemical changes.

Generally I will not go into details of the PU that was modified. Many approaches are not limited to a specific PU, although some are not applicable to all PUs. The synthetic chemical approaches and the SMA/SME approaches of course need to be tailored to the PU to be modified, whereas other approaches, particularly those involving the deposition of a plasma polymer coating, would generally seem to be readily transferable to other PUs.

The broader literature on the surface modification of biomaterials contains a number of other approaches that apparently have not been tried on PUs. It is not the purpose of this review to go into discussion of related surface modification/coating technologies that may be useful to PUs; that would be an enormous task. Suffice it to say that a fair proportion of reported coating approaches tried with other substrates seem of promise for the development of improved PUs. Particularly the surface activation of substrates by the deposition of a thin plasma polymer coating that acts as an interfacial bonding layer represents a generic coating technology that usually transfers well to various polymeric and inorganic substrates. The reader whose interest it is to identify promising approaches towards improved PU surfaces should therefore also consult the wider biomaterials literature.

7.5 Synthetic Functionalization with Chemical Groups

A number of studies have applied conventional chemical synthetic approaches specifically to modify PU surface properties, and surface analytical techniques were used to characterize the results of the synthetic chemistry steps. Good examples are two series of papers from Brash's and Cooper's laboratories, both of which report on extensive studies on the incorporation of sulfonate groups into PUs. The well known anticoagulant properties of heparin were thought to be related to the presence of sulfonate groups on this polysaccharide, and the introduction of sulfonate groups into polystyrene surfaces had indeed led to anticoagulant activity.[28] Accordingly, the introduction of sulfonate groups into PU surfaces was done with the aim of analogously improving blood compatibility. Substantial improvements were indeed achieved, although total long-term compatibility remains elusive. It now appears that interpretation of biological interactions must be made in terms more complex than just the presence of some particular chemical surface group, and the PU/blood interactions are incredibly complex and hence a great challenge to control simply by alterations of interfacial forces by surface group substitutions; a bioactive approach (see Section 7.7) may well be required.

The provision of sulfonate groups was achieved by Cooper et al by grafting 1,3-propane sultone to the urethane nitrogen of PU.[29-31] The blood contact response was improved with increasing sulfonate ion content in a polytetramethylene oxide (PTMO) based PU but inferior when the same modification was applied to a polyethylene oxide (PEO) based PU. Ex vivo (canine shunt) platelet adhesion and fibrinogen uptake depended on the sulfonate concentration, with a low amount of sulfonate leading to decreased fibrinogen uptake whereas a high sulfonate concentration led to increased fibrinogen uptake but also reduced platelet adhesion. Thus, clearly, the presence and concentration of sulfonate groups can considerably alter material/blood interactions.

Blends of sulfonated and unsubstituted PUs were found to be superior to the pure sulfonated material.[32] Surface enrichment of the substituted component was revealed by contact angle data and XPS which showed a greater amount of sulfonate groups on the surface of the blended material than on a sulfonated PU with the same overall sulfonate concentration. Canine ex vivo shunt experiments found fewer adherent platelets and less platelet spreading on the blend material compared with sulfonated PU with the same overall sulfonate concentration. The blends also have better physical properties.

The introduction of sulfonate groups into the hard segment of polyether-urethane-ureas was achieved by Santerre et al by the use of a sulfonated diamine chain extender.[33] The resultant material had a high affinity for fibrinogen, whose subsequent desorption was delayed; that is, the Vroman effect was all but eliminated on this surface. Subsequent work[34] suggested that there were specific interactions between sulfonate groups and fibrinogen. Thrombin times of human plasma were also prolonged and depended on the sulfonate concentration, suggesting that sulfonate groups confer a measure of anticoagulant activity on PUs.[35]

The adsorption of fibrinogen is, however, only part of the thrombogenicity issue that faces cardiovascular biomaterials developers. One needs to be very careful in designing and interpreting model protein adsorption studies, since the competitive adsorption from the complex mixture of proteins that exists in blood can markedly alter the picture. For instance, Cornelius and Brash[36] later showed that fibrinogen adsorption onto sulfonated PUs is reduced in the presence of a low concentration of high-molecular weight kininogen (HK), a protein that can exist in single-chain and two-chain forms and is a multifunctional protein that has substantial surface activity and inhibits platelet adhesion on cell-adhesive glycoproteins, inter alia. The comments in that study that HK's role in surface-induced thrombus formation remains an enigma and that it remains to be determined whether surfaces should be designed that are selective for HK or that exclude it, illustrate very nicely the degree of uncertainty that one can face when attempting to rationally engineer biomaterials surfaces at the molecular level for specific purposes.

Carboxylate groups were also incorporated into PUs, by the grafting of propiolactone, and the blood response of the resultant materials compared with sulfonated PUs.[37] The rationale for this approach was derived from observations by Fougnot et al[38] on the anticoagulant behavior of sulfonated and carboxylated dextrans and polystyrene. The surfaces of the materials were analyzed by XPS, contact angles, and a canine ex vivo blood contact test.[37] The latter test showed no statistically significant effect from carboxylate incorporation, whereas sulfonate incorporation significantly reduced platelet deposition and activation, while giving rise to increased fibrinogen deposition, in agreement with the work by Santerre et al discussed above.

The increased fibrinogen deposition raises a concern as preadsorption of this protein onto surfaces significantly increases adhesion of *Staphylococcus aureus* bacteria, as shown on PUs by Baumgartner and Cooper.[39] In a study using base PU and the same material functionalized with sulfonate, quaternary amine, or phosphonate groups (by using glycerophosphorylcholine chain extender), marked differences in bacterial adhesion were found, with a striking result of decreased bacterial adhesion and fibrinogen deposition on the zwitterionic phosphonated PU.[39] Possibly this result is related to the well known anti-adhesive properties of phosphorylcholine (PC) coated surfaces. Other studies with PC coated PU surfaces will be reviewed below in Section 7.8.

Flemming et al[40] similarly modified Pellethane™ by functionalizing it with sulfonate, phosphonate, quaternary amine, and zwitterionic PC groups. In this study, the phosphonated surface was produced by reaction with diethyl bromopropylphosphonate; thus, this phosphonated PU surface is quite different to that produced by Baumgartner and Cooper[39] where glycero-PC was used to generate a "phosphonated" surface (which would be better termed a PC surface). Bacterial adhesion (*Staphylococcus aureus*) onto these surfaces was studied; the phosphonated and the zwitterionic PC surfaces gave the lowest bacterial adhesion (the latter confirms the above results of Baumgartner and Cooper). The effects of fibrinogen and high molecular weight kininogen on bacterial adhesion were also investigated.

In both the above studies, an interesting outcome was the absence of marked beneficial effects from quaternary amine groups, which in an earlier study had been claimed to confer biocidal effects to PUs.[41] Perhaps the type (detailed chemical structure), surface concentration, and the presentation (mobility, etc) of the quaternary amine surface functionalities influence their ability to deter bacterial adhesion.

Other synthetic approaches have also been used specifically to obtain PU surfaces with desired properties. An example is the work of Yoon et al in which a polydimethylsiloxane (PDMS) soft segment was used; surface analysis revealed that the surface was completely covered with this segment.[42] There was, however, strong dependence of the surface properties on casting.

Similar in terms of the synthetic pathways used is work on the introduction of larger chemical entities such as hydrophilic side chains, for instance PEOs, into the soft segment, and block copolymerization to alter surface properties. This will be discussed below.

7.6 Plasma Surface Modifications

Gas plasmas, also known as radiofrequency glow discharges,[43] have in recent years been very popular for the modification of the surface chemistry and properties of PUs and other polymers intended for biomedical applications. This popularity is undoubtedly due to the versatility of gas plasma techniques. Depending on the process vapor, a wide variety of surface chemistries can be produced by plasma-based techniques.

For a description of plasma methods and equipment, the reader is referred to books on the subject.[43,44] For the purposes of the present discussion, I will only briefly draw the distinction between the two main types of interest for PU surface modification, viz., plasma surface treatments and plasma depositions. The former refer to exposure to plasma-activated process vapors that achieve surface modification by the substitution of some of the original chemical bonds or groups on the PU surface with new bonds or groups. The plasma removes atoms or chemical groups by homolytic bond fissions; abstraction of hydrogen atoms by C-H bond fission is particularly common. Onto the resultant carbon-centered radicals, other reactive chemical entities are then attached as they arrive on the surface from the plasma gas atmosphere. For instance, in a plasma struck in an ammonia vapor atmosphere, amine groups can be introduced into polymer surfaces (although other reactions also occur and the effects of ammonia plasma exposure thus are more complex than just an amination of the surface).[23]

Plasma deposition, in contrast, refers to the production by the action of the plasma of a "plasma polymer" coating; activated chemical constituents of the plasma "polymerize" by addition reaction, which can occur both in the plasma atmosphere and on the polymer substrate surface. The net result is the accumulation of a polymeric coating of finite, controllable thickness. The coating is assembled from various chemical species – radicals and ions that are products of ionization, molecular rearrangements, fragmentations, combinations, etc, of the original organic molecules that are fed as a vapor into the plasma discharge. The composition of the plasma phase produced in vapors of organic molecules is exceedingly complex, and accordingly the composition of the coating is also complex; it is related not only to the chemical composition of the feed gas but also to the plasma deposition conditions such as pressure, radiofrequency power, flow rate, and reactor geometry. Moreover, the important role of radicals in the formation of plasma polymer coatings entails that typically, residual radicals become trapped in the forming coating and, presumably due to steric constraints, are not dissipated by covalent bond formation by the time the plasma reactor is vented. These remaining radicals then serve as sites for the slow, continuing post-fabrication oxidation that is observed with the large majority of plasma polymers.[45-47]

Oxidative chemical changes can also be observed after plasma treatments[23] but again not all plasma treatment/polymer combinations lead to ensuing slow oxidative changes to the surface chemistry.[48] When they do occur, however, whether after plasma treatment or plasma deposition, such oxidative chemical changes to surface compositions can continue for extended periods of time[23,45,46] and also can interact with surface-energy-driven rearrangement motions.[26,27] These plasma-induced oxidative reactions thus contribute yet another mechanism for time dependence of polymer surface compositions. Unfortunately many studies employing plasma techniques for the surface optimization of polymers intended for biomedical applications have ignored this effect. It is important to control, and state in reports, the time elapsed between plasma surface modifications and assessments such as surface analyses or biomedical tests.

7.6.1 Plasma Surface Treatments

The plasma modification of PUs has been investigated by a number of workers using various plasma gases. The process—gases air, nitrogen, oxygen, ammonia, water vapor, and carbon dioxide—are commonly used to modify various polymer surfaces including PUs[49] in a wide range of applications, and their ability to create more polar surfaces is well known. A representative early study with biomedical PUs and some of these gases is that of Jansen et al.[50] While there were some changes to the in vitro blood compatibility upon such treatments, it appears doubtful that the large improvements required for long-term patency can be obtained in this way. The same types of process gases have also been used more recently in other work. For example Ito et al[51] reported that after exposure of a PU to an air plasma, the surface became more wettable by water and exhibited "strongly suppressed adhesion of platelets and fibroblast cells" and a slight decrease of in vitro thrombus formation, but also a slightly enhanced activation of adhered platelets and little effect on protein adsorption. Sterrett et al[52] used Ar and O_2 and reported that plasma oxidation led to lower contact angles, as expected, and increased adsorption of albumin, which was unexpected. Surface fluorination in a CF_4 plasma, on the other hand, led to decreased albumin adsorption.[52] Williams et al applied a proprietary plasma treatment to a polyurethane vascular graft to enhance endothelial cell sodding.[53] The plasma treatment "resulted in a chemistry similar to the Primaria surface", which suggests an ammonia or N_2+H_2 plasma atmosphere. Canine implantation of treated and untreated PU grafts indicated that the development of a stable endothelial cell lining appeared to be sensitive to the surface chemistry of the underlying polymer. Modification of a PU in a H_2O plasma led to the addition of oxygen-containing functionalities as well as plasma etching.[54] Finally, a number of studies reported in journals published in the People's Republic of China appear to have been based on the notion that increased hydrophilicity upon such plasma treatments may achieve improved biocompatibility. Certainly the plasma or corona oxidation of polystyrene has been a very successful way of producing laboratory plastic ware for in vitro usage, particularly cell culture. However, by now it is well recognized that hydrophilicity is not the key criterion for in vivo compatibility, particularly as relates to blood contact, since some very hydrophilic polysaccharides and coatings can produce substantial complement activation. Plasma-treated PU surfaces are still synthetic surfaces with no biological mimic or control function at the interface and are less likely to give interfacial responses as good as more sophisticated approaches that aim to deliver bioactive or "stealth" coatings, although the good results obtained by Williams et al[53] may suggest the possibility of success in some applications. Note also that all these plasma treatments produce various surface functionalities and do not allow good control of the interface.

An exception to the general current of using plasma treatments essentially to place more polar groups onto PU surfaces is the study of Giroux and Cooper[55] in which it was aimed to use plasma treatment to introduce sulfonate groups into a PU surface. The idea was, as in the synthetic sulfonation studies discussed in the preceding section, to create a heparin-mimicking sulfonated surface. The plasma treatment approach offered the potential for modification of the surface layers only (the depth penetration of plasma treatments generally is limited to < 100 nm) and hence avoid the changes to the PU bulk properties that inevitably occur when incorporating sulfonate groups by synthetic routes. Sulfur dioxide plasmas produced considerable etching effects on the PU unless short treatment times were used. XPS and contact angle measurements showed that some of the sulfonate groups disappeared from the surface with time; this was assigned to surface mobility. An alternative route was the exposure of the PU to an ammonia plasma followed by reaction with a solution of propane sultone, but this reagent is carcinogenic.

More recent work tends to use plasma treatments as a method for the surface functionalization of PUs prior to the application of another molecular layer or coating. For

example, argon or oxygen plasma pretreatments are popular for creating surface radicals for the initiation of surface radical graft polymerizations; this is a well-known method for grafting acrylic monomers.[56] An example with PU is described in reference 57. In another example, exposure of PU to an argon/water vapor plasma was done in order to load the surface with the antibacterial agent ciprofloxacin.[58] The nature of the surface was not characterized in detail sufficient to state why the antibiotic adsorbed better onto the treated surface.

7.6.2 Plasma Coatings

A wider range of surface chemistries can be produced by the plasma deposition of thin polymeric coatings. By the use of appropriate "monomer" vapors, a wide range of coating surface chemistries and properties can be fabricated, from very hydrophobic to quite hydrophilic and with various desired chemical groups. Another advantage of this approach is that once optimized on one substrate, such coatings can usually be transferred readily onto other polymeric materials. Plasma deposited coatings from the hydrophilic monomers vinyl acetate and N-methyl-N-vinyl acetamide on PU tubing were analyzed and tested for their partial thromboplastin time.[50] The treatments indeed led to more hydrophilic surfaces and prolonged coagulation times. Plasma deposited layers from methane and fluorocarbon/hydrocarbon mixtures gave modified PU surfaces with high contact angles and reduced albumin adsorption;[52] however, in all cases the adsorbed amounts substantially exceeded monolayer coverage, and thus the differences may not be clinically significant.

While the deposition of such coatings offers a relatively convenient and versatile approach towards the surface modification of PUs, the resultant surfaces are, as are the plasma modified surfaces described above, synthetic surfaces that appear to be recognized as such by the host defense system. Assuming that all synthetic solid, rigid surfaces can be colonized by the indiscriminate competitive adsorption of proteins, no such surface will ever be able to produce the desired exquisite specific response inherent in natural systems. The operative word in the foregoing sentence is rigid, in contrast to synthetic hydrogels which may not be recognized as foreign as the host "sees" a fuzzy, very mobile surface with no clear boundary and mostly water, instead of a firm, two-dimensional surface upon which surface active proteins can adsorb. Thus, plasma treatment and coating approaches on PUs have largely been superseded by the fabrication of hydrogel coatings intended to be nonfouling and bioactive coatings that exert specific signals instead of the nonspecific interfacial forces of synthetic solid surfaces; both these approaches are detailed below. However, the plasma methods continue to serve a useful function in providing versatile means of incorporating various desired chemical functionalities onto PU surfaces for the subsequent grafting of nonfouling layers or bioactive molecules. Plasma polymers provide a wider range of surface functionalities, and better control of the surface chemistry, than plasma treatments. On the other hand, process control is more involved. Plasma polymer coatings on PUs have served as interfacial bonding layers in a number of studies, some of which are cited in the following sections, because of their ability to functionalize PU surfaces and adhere tightly to the PU.

But before going on to those topics, it is worthwhile mentioning two plasma-based approaches that explored specific hypotheses instead of just trying to create a chemically different surface. The plasma deposition of perfluorinated coatings was initially developed for Dacron® vascular graft prostheses.[59] However, marked clinical improvements were not observed, and it was subsequently found that proteins in fact adsorb very tenaciously onto such perfluoro-plasma polymer coatings.[60] The fact that platelets were not observed on such coatings was rationalized by their inability to stick to a layer of heavily denatured proteins, but platelet activation occurred nevertheless. Endothelial cells also attached very poorly onto perfluorinated surfaces, on account of the extensive denaturation that adhesive glycoproteins undergo upon strongly irreversible

adsorption.[61] Thus, platelets and endothelial cells do not foul such surfaces but proteins do, and adsorbed proteins stick very tenaciously. Should such a surface be called nonfouling on the basis of observed failure of cell attachment, as has been done for many other surfaces in other studies? Clearly, perfluorinated surfaces are not nonfouling towards all biological material.

Other work found that *Staphylococcus aureus* bacteria could colonize a perfluoro-plasma coating on PU more extensively than they did the uncoated PU,[62] while no platelet adhesion was observed in agreement with earlier work. Thus, it was concluded that the risk of prosthesis-associated infection could be enhanced by the coating.

The initial hypothesis that a perfluorinated coating may be nonfouling in blood contact, in analogy to Teflon® frying pans, thus did not hold, and recent theoretical work[63] has elucidated the physico-chemical basis for this observation: van der Waals interactions between perfluorinated polymers and proteins are repulsive for proteins in cooking oil but attractive for proteins in water. Thus, such a coating is only nonfouling in specific circumstances—again indicating that the general, unqualified use of the term "nonfouling" is inappropriate; it should always be qualified with a description of the circumstances under which it applies.

The other designed plasma coating approach utilizes "glyme" monomers with the intention of producing PEO-like coatings. It has produced coatings with very low protein affinity.[64] The coatings resemble PEO coatings but possess much shorter linear segments.[65] It is believed that these surfaces are not two-dimensional solids in the same way as other plasma polymers, but possess surface chain segments that hydrate and extend some way into solution, thus conferring a steric-entropic barrier to protein adsorption similar to the barrier properties of hydrogel coatings. Thus, these glyme coatings are distinctly different from typical plasma coatings while still offering the same processing convenience (plasma processes lend themselves to automation and computer process control much better than many other coating processes, and the semiconductor industry has long-standing experience with high-throughput, reproducible plasma operation). Glyme coatings may represent a valuable approach towards conferring long-term in vivo patency to PU based devices.

Plasma polymer coatings have also been investigated for their potential to act as a barrier to protect PUs from biodegradation. Typically, plasma coatings are crosslinked and relatively dense. Accordingly, they could be expected not to be permeable to hydrolytic enzymes. McCarthy et al used three different plasma polymers (from toluene, methanol, and siloxane) to coat PUs and tested samples in a subcutaneous sheep implant model.[66] While some reduction in stress cracking was observed, the plasma polymer coatings did not provide effective protection. XPS showed, however, that there was still coating present on the cracked regions. It was thought that the plasma polymer coatings failed to prevent the diffusion of oxidative low molecular weight species, released by macrophages, through the coatings to the PU, but the coatings themselves did not degrade as rapidly as the PU. These results also confirmed the importance of oxidative attack in PU biodegradation.

7.7 Surface Immobilization of Biologically Active Molecules

In principle, the immobilization onto a device surface of a biomolecule with a known biological effect should enable fabrication of biomaterials surfaces that then dictate predictable biological responses to an implant. Although there is an element of a leap of faith in assuming that a surface-bound molecule can still exert a biological role that may be predicated on the mobility and the stereochemical access available to a dissolved molecule in free solution, in fact there have been a number of unequivocal demonstrations of biological activity due to surface-bound molecules. An active biomolecule layer holds promise for circumventing the problems that arise when uncontrolled accumulation of proteins onto PU surfaces induces

adverse biological responses such as platelet adhesion. Obviously, however, a number of requirements must be met.

Of prime importance is that the surface-immobilized biomolecules are not denatured in the course of the formation of the attached layer. The proximity to a polymer surface, which gives rise to interfacial forces not normally experienced by proteins, can cause structural rearrangements in the protein that can effect denaturation of some of the epitopes. In addition, the method of immobilization can have effects on the efficacy of the attached biomolecules. In many instances bioactive layers have been formed by the covalent attachment of biomolecules onto reactive surface groups. Unless stereospecific reactions can be utilized, clearly it must be expected that a fraction of the surface attached biomolecules are not able to expose their active site to the biological medium for steric reasons. Also, chemical reactions such as glutaraldehyde crosslinking may produce substantial chemical changes in the biomolecules in addition to surface immobilization.

Often the use of a hydrophilic spacer layer between the solid polymer and the bioactive molecule is beneficial in covalent immobilization; reasons probably include increased mobility for exposing the bioactive epitope, and, due to the larger separation (compared with direct immobilization), a reduced strength of the interfacial forces exerted by the polymer upon the bioactive molecules, forces that can induce denaturation of attached proteins. The use of a hydrophilic spacer layer particularly from PEOs has been popular; an early example is the immobilization of heparin onto PU via PEO.[67] A spacer layer is, however, not always necessary; for instance collagen and albumin immobilized via an aldehyde plasma polymer interlayer[68] demonstrated good biological activity.

It may, however, not be necessary to produce a uniform, densely packed monolayer of biologically active molecules on synthetic substrates such as PUs in order to "hide", or "mask", the unfavourable interfacial properties, and markedly alter biological consequences of the synthetic material. Massia and Hubbell have shown that much less than a monolayer of the cell-adhesive glycoprotein fibronectin is required to stimulate good attachment of anchorage-dependent cells.[69] Thus, low amounts of recognition sites may be sufficient for cell colonization as well as platelet adhesion. On the other hand, when attempting to protect PUs against undesirable adhesion of proteins such as fibrinogen, it would appear reasonable to surmise that a fully covering protective layer is required in order to avoid the adsorption of proteins into gaps of the coating.

Another challenge for bioactive coatings is sterilization. Many proteins lose their biological function upon exposure to the main economical sterilization methods available, or, as is often the case for γ-sterilization, there occurs damage to the bulk polymer material. Coatings of small nonnatural peptides that duplicate the biological activity of larger proteins[70] but do not suffer analogous thermal damage on autoclaving may circumvent potential sterilization problems.

Surface-bound biomolecule layers have featured in a large number of studies. The main methods for immobilization of biologically active molecules onto PU surfaces have involved covalent linking by various chemical reactions; however, other approaches, such as self-assembly, have also been used.

7.7.1 Albumin/alkyl Chains

The placement of albumin onto PU surfaces has been the subject of considerable research, for reason of its ability to passivate surfaces in contact with blood against the attachment and spreading of platelets. Platelet membranes do not possess receptors for albumin. The challenges involved in creating a fully passivating albumin layer are, however, enormous. Gaps in the albumin coverage, of sufficient size to allow other proteins to adsorb, reduce effectiveness.[71] Also, a surface-bound albumin layer should not be subject to displacement/exchange effects.

Several strategies have been used in attempts to obtain albumin coverage of PUs. Adsorptive binding from an albumin solution prior to blood contact[72] is problematic due to the likelihood of protein exchange effects on the PU surface; although albumin is a "sticky" protein with high surface activity and hence substantial affinity for synthetic surfaces, it can be displaced by other proteins. Accordingly, studies have either directly coupled albumin covalently onto surfaces or used a surface-bound ligand that can selectively attract and retain albumin with high binding affinity.

The direct covalent linking approach can provide good coverage, as for instance obtained by Beumer et al[68] in the immobilization of albumin via reductive amination onto a plasma polymer interlayer that possessed aldehyde surface groups. The resultant coating has, however, not been tested clinically. One concern with direct covalent immobilization of albumin is that the protein may (partly) lose the conformational flexibility that has been postulated to be essential for its function as a surface passivator.[71] For the same reason, approaches such as crosslinking of albumin layers by glutaraldehyde or γ-irradiation are not promising; their effects on albumin flexibility are likely more severe than when albumin is immobilized by, e.g., reductive interfacial amination onto surface aldehydes. Moreover, covalently attached albumin molecules may in vivo be lost with time due to the actions of circulating proteolytic enzymes. In addition, albumin coating (prior to implantation) approaches require the sourcing of biologically safe protein material, a consideration which has become more acute with the recognition of prion diseases. Moreover, for any coating comprising immobilized proteins, there are issues regarding sterilization and storage/shelf life stability that are not fully resolved in an economically viable fashion.

One approach to attract serum albumin in situ with high selectivity and affinity is to graft alkyl chains onto surfaces, in order to exploit the well-known affinity of albumin for specific lipid structures. PUs containing alkyl surface chains (C-16 and C-18) were fabricated[73-78] and effects on albumin affinity and blood compatibility characterized. The length of the alkyl chain has a substantial effect.[79] Increased albumin retention was achieved and improved short-term blood compatibility in an ex vivo canine shunt model,[76,77] but adhered thrombus was observed after longer-term exposure.[75] On the other hand, using a modified Chandler loop test Haycox and Ratner found no platelet adherence nor activation on a C-18 alkyl derivatized PU surface.[80]

Similarly, Lim et al grafted surfactant-like structures comprising alkyl chains and oligoethylene oxide segments onto PU.[81] XPS showed alkyl enrichment at the surface. A PU with short ethylene oxide segments and terminal C-18 linear alkyl chains gave short-term improvement in blood compatibility but at longer times no benefits resulted.

The reasons for the lack of success are not well established. Perhaps the rather hydrophobic surface (on account of the nonpolar alkyl chains) causes denaturation of proteins other than albumin, proteins that arrive at the surface before albumin has had a chance to form a confluent passivating monolayer. If so, a surface that is hydrophilic and less prone to nonspecific irreversible adsorption of proteins may be more promising. Grasel et al found evidence for surface mobility (reorientation of alkyl chains away from the interface within 24 hours)[76] and this may also contribute to a decrease in the desired specificity for adsorption of albumin.

One alternative albumin attraction approach is based on the observation that this protein also has affinity for Dextran Blue, which is dextran derivatized with a triazine dye. On coupling this compound to a PU surface, Keogh and Eaton obtained reversible albumin adsorption and markedly enhanced clotting times in an in vitro test.[82] Thrombus formation was inhibited during 16 hours of contact. Bacterial adhesion also was reduced, particularly after exposure to albumin.

An alternative approach that achieves selectivity while offering a reasonably hydrophilic surface is to utilize a covalently attached coating of a monoclonal anti-albumin antibody. The challenge is, as for other large proteins, used in the covalent immobilization of bioactive layers

(see below), to define gentle, mild immobilization reactions and conditions for the antibodies. Such a coating has been fabricated and characterized in detail by surface analytical methods,[83] although not on a PU, but the method employs as the first step in the fabrication of the multilayer coating a plasma polymerization step which is readily transferable to various substrates. The coating has since been applied onto PU and is currently undergoing in vivo testing in a sheep model.

7.7.2 Covalent Immobilization

A wide range of reactions that are well established in synthetic organic chemistry can be used to effect covalent interfacial linkage between PU surfaces and biologically active molecules. However, many bioactive molecules, particularly proteins, are structurally fragile and can be denatured when one uses incorrect solvents (including, for some proteins, aqueous solutions with ionic strengths different from the natural tonicity) or reaction conditions such as excessively elevated temperatures. It is therefore advisable to perform covalent immobilization under gentle, aqueous conditions. PU surfaces are, however, not reactive under such conditions and accordingly must be preactivated. This can be done during synthesis, by incorporation of a component that places reactive groups onto the surface, or by the subsequent surface activation of the solid PU material. A number of chemical pathways has been used by various workers in biomolecule immobilization studies onto PUs. The availability of specific reactive groups, such as amines, on the biomolecule often dictate the choice of reaction pathway.

7.7.2.1 Heparin

One molecule of long-standing interest, which has been coated onto various polymeric substrates, is heparin, for reason of its known anti-coagulant function in solution. This coating approach has been the subject of much activity. Coatings of heparin immobilized on PUs by various reaction schemes indeed showed improved blood compatibility in preventing material-induced thrombus formation.[67,84,85]

Whereas for some other biomolecules, such as albumin, adsorptive surface binding appears an option, for heparin it is essential to perform covalent binding since adsorbed heparin is lost from PU surfaces within hours.[86] The reasons are of course the good solubility and the absence of surfactant activity of heparin, properties which cause it to have little affinity for surfaces compared with dissolution into an aqueous medium. Various immobilization schemes have been reported; particularly effective was found to be heparin immobilization via a hydrophilic (PEO) spacer.[67] In that study, both heparin and the PEO spacer were covalently linked via a diisocyanate. Increased heparin coverage by amplification of the surface density of reactive immobilization sites was reported.[87] Narayanan bound heparin onto PU via a polyethylene imine spacer following activation of the PU in a water/oxygen plasma and using a water soluble carbodiimide to effect covalent linkages.[88] Both the outside and inside surfaces of tubes were modified. Lindhout et al attached heparin via carbodiimide onto partially hydrolyzed polyacrylamide that had been grafted onto PU.[89] This heparinized surface markedly delayed the onset of thrombin generation in platelet-rich plasma. Kang et al immobilized heparin via carbodiimide onto carboxylic acid or amine groups generated from a triazole acrylate grafted onto oxygen plasma treated PU.[57]

A different approach was reported by Grainger et al[90] and Park et al[91] in which coatings of heparin-PEO-PDMS or Biomer™-PEO-heparin block copolymers were applied onto substrates including PUs. The hydrophobic block adsorbs well onto substrates while the hydrophilic PEO-heparin blocks can extend into the aqueous environment. For the latter copolymer, following coupling of hydrogenated 4,4'-diphenylmethane diisocyanate (HMDI) to soluble

Biomer™ through an allophanate/biuret reaction, PEO was attached via its terminal hydroxy groups. Remaining hydroxy groups on PEO chains were then reacted with HMDI and heparin coupled onto the resultant isocyanate groups. The resultant terpolymer showed heparin bioactivity. A PEO molecular weight of 3.4 KDa was most effective, as in earlier work[67] for surface-bound heparin immobilized via a PEO spacer.

The mode of action of surface-immobilized heparin is of interest. Ito et al suggested that electrostatic repulsion occurs between platelets and the anionic heparinized surface, rather than physiological action of bound heparin.[92] Protein adsorption studies have shown that surface-bound heparin prevents the adsorption of albumin and fibrinogen[93] and has low affinity for thrombin.[94] Fibronectin[93] and antithrombin III (ATIII),[94] however, bind to this coating; thus, immobilized heparin does not provide an adsorption-resistant coating against all relevant proteins. Hence its mode of action is not akin to that of PEO coatings which can repel various proteins. Experiments such as those of Winterton et al[93] are of importance in assessing whether a surface-attached molecule layer is indeed biologically active and acts in the presumed biospecific way or simply acts to reduce protein adsorption in general, as coatings from PEO and some polysaccharides other than heparin do (see following section on nonfouling surfaces). In fact, heparin can associate with a number of proteins that possess specific heparin binding sites, and in addition the strong ionic character of heparin leads to the nonspecific adsorption of various plasma proteins. Fibronectin is involved in platelet adherence and complement activation; thus, a coating that rejects fibrinogen but not fibronectin may not provide sufficient long-term compatibility. Interactions between proteins can also occur at the interface, such as between fibronectin and ATIII on surface-immobilized heparin on PU.[95] Understanding of such binding interactions is necessary to extrapolate from single-protein model studies to in vivo applications. Yet, many studies only characterize fibrinogen adsorption onto putative blood-compatible coatings. The multiple biological pathways in hemostasis impose on a coating a number of requirements that need to be addressed.

One needs to consider that immobilized heparin may be digested in vivo and therefore the efficacy of the coating may decrease with time. This applies, of course, to all molecules that are "borrowed" from a host's hemostatic, immunogenic, or metabolic pathways. An interesting approach therefore is to use synthetic molecules that can mimic a natural biomolecule. Heparin-like synthetic polymers have been the subject of a number of studies; an example is that of Ito et al in which poly(sodium vinyl sulfonate) was used;[51] this compound was known to be able to activate antithrombin III. This synthetic polymer was immobilized onto PU via an air plasma treatment and graft polymerization. Reduced interactions with proteins and platelets were observed both in vitro and ex vivo.

Ultimately, the definitive test is the intended application. In a detailed study, Gorman et al[96] tested the hypothesis that heparin-coated perfusion circuits reduce thrombin formation and activity, fibrinolysis, and platelet, complement, and neutrophil activation in 20 adults undergoing cardiopulmonary bypass. Various blood assays were performed and tubing segments analyzed after bypass. While heparin-coated circuits showed significantly reduced platelet adhesion, in other assays there was no benefit from the usage of the heparin coating. It was concluded that heparin-coated circuits used with standard doses of systemic heparin reduce platelet adhesion and improve platelet function but do not produce a meaningful anticoagulant effect during clinical cardiopulmonary bypass. Other studies exist which support these indications. Bernacca et al[97] immobilized heparin by a scheme involving activation of urea or urethane groups on the PU surface by HMDI and reaction of the resultant isocyanate groups with the hydroxyl groups of heparin. The heparinized surface was found to be more activating of Factor XII than the control polyether-urethane (PEU). The question is, of course, whether such conclusions apply equally to all heparin coatings or whether it matters how the heparin is applied. The absence of detailed characterization (density, uniformity of coverage, molecular

orientation, molecular structure/architecture of coating) of some if not most reported heparin coatings makes it difficult to speculate on how reliable extrapolation is from one coating to another produced by a different chemical route or a different lab.

As an interesting aside, the findings of Winterton et al[93] also raise the question of why heparin coatings were then applied to biomedical devices such as intraocular lenses (IOLs); if immobilized heparin can mitigate thrombus formation by a specific biological mechanism, it does not follow that it can also prevent the formation of secondary cataracts. To the contrary, the demonstration that fibronectin, a cell-adhesive glycoprotein, can adsorb onto immobilized heparin would suggest that cell colonization can occur onto heparin-coated IOLs via a fibronectin-mediated mechanism; a broadband nonfouling coating would appear a more reasonable choice for the prevention of recolonization by cells. This consideration demonstrates the inherent pitfalls in translating a biomedical coating that is successful in one regard to a different biomedical environment and challenge. Yet, there have been a number of instances where a coating has been translated to a different intended application without regard or apparent understanding of its biological functions and the molecular details of interactions between the coating and proteins of relevance in various biomedical environments.

7.7.2.2 Others

Following the development of their sulfonated PUs, Santerre and Brash developed methods for the covalent linking of amino acids and other organic molecules onto these surfaces.[98] The sulfonate groups, incorporated during synthesis, were subsequently converted to sulfonyl chlorides and these surface groups reacted with amine groups of amino acids. The thrombin times were observed to increase by up to threefold.[34]

The same chemical route was used for the covalent immobilization of lysine onto PU surfaces.[99] The rationale behind this strategy is the attempt to promote selective adsorption of plasminogen (which may provide a fibrinolytic surface layer) from plasma through lysine-binding sites in the plasminogen molecule. The lysine-derivatized PU indeed showed affinity for plasminogen, and there was no Vroman effect (transient adsorption). This suggests that plasminogen has high affinity for this surface. Sulfonated PU (onto which the lysine molecules were immobilized) also showed substantial plasminogen binding, to almost the same extent as the lysine surface. It was hypothesized that lysine may not have been presented in the correct fashion, and that therefore more specific linkage chemistry might be required.

RGD peptides were attached onto PU surfaces by carbodiimide chemistry following carboxylation of the PU.[100] The properties of such coated surfaces were analyzed by variable angle XPS and freeze-hydration XPS in order to assess the orientation and availability of the peptides at the interface. Results were consistent with expectations based on migration/surface enrichment of peptides or PTMO segments in hydrophilic and hydrophobic contacting media. This study provides a good demonstration of the utility of detailed XPS analyses in variable angle and freeze-hydration modes.

The immobilization of collagen via epoxide chemistry was studied using four different bis-epoxide linkers that had been attached onto carboxylated PU surfaces.[101] Epoxides with longer alkyl chains were less effective, which should be expected since these linkers are not well solvated and will tend to remain tightly adsorbed to the PU surface instead of protruding into the aqueous phase where they can more readily react with collagen. The use of hydrophilic linker/spacer molecules has been established practice for exactly this reason for many years. Use of PEO-based bis-epoxides would seem advisable. Bis-epoxides are, however, not ideal anyway for close molecular control of interfacial linkage reactions on account of their tendency to undergo self-reaction at surfaces.[102]

Plasminogen was immobilized onto a PU surface in order to provide a surface coating that could be converted to plasmin, which would then hopefully act fibrinolytically and thereby combat thrombosis.[103] Immobilization was achieved onto aminated PUs by a glutaraldehyde reaction. This raises the question of to what extent the glutaraldehyde reacted by forming crosslinks between amine groups on the same or adjacent protein molecules rather than interfacial bonds between the protein and PU surface amines; to reach surface amine groups, glutaraldehyde has to diffuse through the entire protein layer and hence may well be intercepted substantially by protein amine groups that are not close enough to the surface to form interfacial linkages to the PU. A more selective immobilization chemistry would seem desirable. The covalently immobilized plasminogen surfaces had the same partial thromboplastin times as the controls. Platelet adhesion was increased over a control by immobilized plasminogen but reduced after enzymatic activation of the plasminogen.

The enzyme lumbrokinase was immobilized onto PU in order to combat platelet adhesion.[104] This enzyme is known to be potent in fibrinolysis. Adsorption of fibrinogen was reduced on the lumbrokinase surface compared with a control PU. While platelet adhesion increased at first, it then reduced with time, suggesting that immobilized lumbrokinase digested adsorbed fibrinogen.

Another enzyme that has been covalently immobilized onto PU is glucose oxidase.[105] In that study, the PU surface was activated by the deposition of a thin plasma polymer layer from N-vinyl-2-pyrrolidone followed by borohydride reduction and reaction with 1-cyano-4-dimethylaminopyridinium tetrafluoroborate. The specific activity of surface-bound enzyme was determined. To remove physically adsorbed enzyme, a stringent washing protocol was required.

Thrombomodulin is a potent natural anticoagulant; Kishida et al immobilized it via a partial hydrolysis reaction onto PU in order to develop an antithrombogenic surface.[106] The immobilized amounts were very low, but an effect could be detected.

One potential problem with protein-containing immobilized bioactive layers is associated with the natural proteolytic turnover of proteins, a turnover which may over time ablate a layer of immobilized proteins. Several interesting studies have focused on immobilized pharmacologically active molecules that should not be susceptible to enzymatic attack. A synthetic thrombin inhibitor was equipped with a pendant acrylate functionality so that it could be immobilized by radical graft polymerization onto PU that had been activated by plasma treatment.[107] Covalent grafting avoided the decrease in activity that had been found when the compound was blended with PU. Marked thrombin deactivation and reduced platelet adhesion was obtained. Dipyridamole (a vasodilator) and theophylline were immobilized onto Pellethane™ surfaces using a photoactivated grafting technique.[108,109] In both studies, the grafting moiety consisted of the bioactive molecule at one end and a phenylazido group at the other. Upon UV exposure, the latter group converts to a nitrene group, which is very reactive and was intended to attach to urethane nitrogen atoms. Surface-bound theophylline was found to inhibit surface-induced activation of platelets.[109] Immobilized dipyridamole led in vitro to a decreased number of adhered platelets and less platelet activation by the surface.[110] A short spacer chain increased the activity of immobilized dipyridamole.

It is, however, doubtful whether the immobilization reaction occurred as specifically onto urethane nitrogen groups as proposed by these authors. Nitrene groups are extremely reactive and can insert into just about any bond, including C-H. It is therefore highly likely that at least some of the nitrene groups reacted with other grafting molecules rather than the PU surface. Thus, a crosslinked layer of the photoactive graft molecules can be formed on the surface, with an undetermined density of bonds between the crosslinked layer and the surface. In the worst case scenario, one might envisage an "onion-skin"-like layer where only crosslinks were formed between the graft molecules, and the resultant photograft polymer layer is adsorbed onto the

PU surface noncovalently. Better elucidation of the photoactivated reactions appears essential. Even an investigation with an azido-derivatized fluorescent molecule[111] is not conclusive since conventional chemistry suggests that the nitrene group is able to react with various structural elements (bonds) of the fluorophore.

7.7.2.3 General Considerations

An aspect that has often been ignored in reports on covalent immobilization is the fact that proteins[60,112-114] and other molecules[115] can adsorb quite tenaciously to many surfaces. Nevertheless, when a protein layer is detected after an intended covalent immobilization, it is usually assumed without further study that the interfacial linking reaction has taken place as it should have. However, adsorption by physical (noncovalent) forces can mimic an intended covalent interfacial binding reaction and mask lack of success in forming covalent linkages. It is therefore important to ascertain whether the surface-located molecules are indeed covalently bound or just physisorbed (or a combination of the two, in which case part of the coating can be lost with time).

To probe for the success of intended covalent linkage of biomolecules onto surfaces, washing with urea, SDS, and the like can provide a good indication. A good example is a study by Danilich et al[105] in which the conditions necessary for removal of physically adsorbed glucose oxidase molecules from the solid support were well specified. The use of small probe molecules to perform the same covalent interfacial reaction can be advantageous but some probe molecules also have a tendency to physisorb.[115] Direct assessment of physisorptive versus covalent binding is possible for proteins with a molecular weight of up to 250,000 Da by the technique of surface-MALDI mass spectrometry.[116] This technique provides extremely high sensitivity, being able to detect proteins at surface coverages of the order of a few ng/cm^2, i.e., of the order of 1/100 of a monolayer. The technique is based on the addition of a solution of "matrix" molecules to a layer of proteins on a surface; as the solvent evaporates, the matrix molecules (typically aromatic acids with high near-UV absorption) form crystals into which surface-adsorbed species become embedded.[117] A UV laser is then used for volatilization of the crystals, upon which both matrix molecules and the embedded analyte are extracted and detected in a time-of-flight detector. Adsorbed proteins can be incorporated into MALDI matrix crystals, volatilized, and detected, whereas covalently surface-bound proteins are not detected,[116] because they cannot be incorporated into the matrix crystals forming on solvent evaporation. Thus, the surface-MALDI-MS method has enabled assessment of the success and efficiency of covalent binding of a number of proteins[116] and smaller oligopeptides.[70] If physisorbed proteins are detected among covalently bound proteins, by a reduced (compared with a "control" spectrum recorded with an adsorbed monolayer) MALDI-MS signal, one must consider that desorption/displacement of adsorbed proteins in vivo may produce gaps in the coverage. However, caution and checks are indicated as some proteins are difficult to detect by surface-MALDI-MS; other bioactive molecules such as polysaccharides can also present challenges to detection in a time-of-flight mass detector, perhaps due to low protonation/ionization efficiencies.

But, does it matter whether proteins or other bioactive species are covalently anchored onto a PU substrate or simply physisorbed tightly enough to resist removal by rinsing or washing after the reaction? It may well matter: while physisorbed proteins may resist elution in washing steps after intended immobilization, they may, when placed in the biomedical environment, nevertheless be displaceable by other proteins, from the host medium, that possess higher surface affinity. If a surface-attached layer of biomolecules consists partly or entirely of physisorbed molecules, the intended control over the biological response may thus be lost on account of protein exchange phenomena. Perhaps this may be the reason why some studies with immobilized protein layers have given disappointing results. Any release from the surface

of bioactive molecules also raises concerns about their possible effects in remote sites of the host organism, particularly brain, liver, and kidney tissues.

A second possible pitfall is that the reactive surface groups onto which covalent immobilization is to be done may, in the time lapse between preparing the substrate surface and performing the protein attachment, disappear by surface rearrangement motions or by conversion to other chemical groups incapable of participating in covalent attachment of proteins. Many surfaces show time-dependent compositions. Such effects may go undetected if one does not also simultaneously characterize the polymer surface onto which proteins are to be linked. This issue is most important when using a prior surface treatment step to prepare PU surfaces for the covalent immobilization of biomolecules; the time dependence of the composition of treated polymer surfaces must be considered. As discussed above, surface-modified polymers are inherently in a nonequilibrium state and hence surface rearrangement motions take place which redistribute the attached surface groups into deeper polymer layers and therefore out of reach of interfacial linkage reactions with proteins. Secondly, some surface treatments not only incorporate reactive groups into polymer surfaces but also create radicals that then start oxidative radical reaction cycles. These reactions may convert attached surface groups; for example amine groups can be oxidized to amide groups in such processes. This is particularly the case when using corona discharge treatment and plasma-based methods, as these perform homolytic bond fissions on the polymer surface and thus create various radicals on the treated surface. For instance, plasma-attached amine groups are popular surface groups onto which subsequent solution chemical reactions are performed for biomedical coatings, but few studies have shown appreciation of the fact that amine groups attached from ammonia plasmas not only are subject to loss by reptation, but also oxidize within days to amide groups by radical-induced reactions.[23] Analogous oxidation occurs on the surface of plasma polymer coatings and converts amine groups on alkylamine plasma polymer surfaces to amides.[22,118,119] It is therefore essential that freshly prepared surface-activated surfaces be used for covalent immobilization reactions.[120]

For highly water soluble molecules such as polysaccharides and PEGs (well below the cloud point), the considerations differ as their affinity for surfaces is small (excepting lipopolysaccharides). A thorough water washing step after the covalent coupling may be sufficient to remove most molecules that are not covalently coupled, but for large macromolecules the possibility of entanglement of chains must be considered. Large molecular weight chains that are not linked covalently but are entangled with surface-linked chains may take considerable time to remove. Narayanan[88] used extended (5 days) extraction in phosphate buffered saline for heparin coatings, following which a small increase in the sessile air/water contact angle was observed. Guanidine extraction led to a larger increase in the contact angle. In our work on the covalent coupling of polysaccharides[121] we likewise observed that extended washing can reduce the apparent coverage until a final steady state coverage value is reached.

7.7.3 Self-Assembly

The formation of self-assembled monolayers of alkyl thiol compounds on gold surfaces is well known. Analogously, sulfhydryl-terminated peptides are capable of chemisorbing onto gold surfaces. The high surface density of surface binding sites should thus allow formation of a high surface density of bioactive compounds. Coating a thin layer of gold onto PU and then chemisorbing small peptides with N-terminal cysteine residues, Sun et al[122] confirmed attachment by contact angle and XPS measurements. The peptides, which contained only three or four residues, were selected on the basis of their ability to inhibit thrombin activity in solution. The surface-attached peptides attracted thrombin in vitro with high affinity, and the surface-bound thrombin was effectively inhibited. This approach may have potential as an anti-thrombogenic coating, and its in vivo evaluation should prove of great interest. The

durability in vivo of such a coating should be a focus of attention, since both displacement and enzymatic destruction of the chemisorbed peptides might limit their useful service life. Also, the oxidation of S is known to weaken adhesion of self-assembled monolayers (SAMs) over time.

Films of anti-endoglin antibodies on a PU were coated by the Langmuir-Blodgett method and crosslinked by glutaraldehyde.[123] The authors believed that denaturation was not important but I am concerned that glutaraldehyde often does cause substantial changes to proteins. The obvious test, an endoglin binding assay, was not performed.

7.8 "Non-fouling" Polyurethane Surfaces

An alternative to the "bioactive" approach discussed in the preceding section is the use of "bland" or "stealth" coatings that aim to avoid adverse biomedical consequences by prohibiting the adsorption onto the device of all proteins that induce adverse biological events. Among such "nonfouling" or "anti-fouling" coatings, polyethylene oxide (PEO)/polyethylene glycol (PEG) coatings have occupied the most prominent position, with many studies characterizing their fabrication and biological testing. However, even though for nearly 20 years there have been numerous reports of PEO/PEG[85,124-130] and other coatings as anti-thrombogenic surfaces in vitro, clinical and commercial success apparently has not eventuated yet.

A number of good reviews on nonfouling coatings can be readily found; for a concise update, a very recent review is available which summarizes the key developments in PEO and other nonfouling coatings over the last three years.[131] It also discusses some of the unresolved theoretical and experimental questions surrounding such coatings.

7.8.1 Considerations

Several reasons may contribute to this apparent lack of translating promising coatings to successful devices. One reason may simply be that the in vivo environment may be much more challenging, with a greater diversity of biomolecules that are surface active and may give rise to adsorption phenomena that in vitro tests did not anticipate and replicate. The development of biologically inert surfaces is tested using models that are necessarily a simplification of the complex in vivo metabolic and immune defense systems. It is noteworthy that protein adsorption onto putative nonfouling surfaces has been studied extensively but the possibility that in vivo lipids may play a key role is usually overlooked. How repellent to lipids are the promising coatings showing low protein adsorption?

Another reason is that it is exceedingly difficult with existing techniques for the analysis of surfaces and thin coatings to obtain a good depiction of the coatings produced. For instance, it appears reasonable to assume that not only the chemical composition of a coating affects its biological interactions but also that its thickness (up to a point), density, hydration, microstructure, chain mobility, and other factors matter. These factors are not readily amenable to characterization and may be different for coatings produced from a given starting material under slightly different conditions. The PEO class of coatings is a case in point; the temperature has a marked effect on the coating density[132] but some researchers seem to have failed to realize this. There are contradictions in the literature that may be the result of insufficiently detailed analyses of coatings or insufficiently close control of fabrication parameters. Also, defects in coatings may have gone undetected in many studies and may have caused unrecognized artefacts in biological interactions.

As an example, consideration of data by Inoue et al[133] serves to illustrate potential pitfalls. In that study, acrylamide and dimethyl acrylamide were grafted onto Pellethane™ to densities of 2-120 mg/cm^2. XPS showed, however, spectra comprising both PU and acrylamide components at graft densities of 8 and 26 mg/cm^2. At these graft densities, the thickness of the

grafted layer should greatly exceed the XPS probe depth and no substrate (PU) signals should be detected if the grafted layer had uniform coverage and thickness. The authors failed to recognize the implication of nonuniform coverage in their data. IgG adsorption was reduced by only a factor of 3 under the best graft conditions.

Another is that many studies have used the terms "nonfouling" and "nonthrombogenic" very loosely. A reduction in protein adsorption over a control surface does not entitle the test coating to be called "nonfouling"; a more appropriate term would be "less fouling". The term "nonfouling" should only be used if no measurable adsorption can be detected by the most sensitive state-of-the-art methods, such as surface plasmon resonance, ELISA, time-of-flight secondary ion mass spectrometry, and surface-MALDI mass spectrometry, that can probe in the low ng/cm^2 range. Even then, one needs to realize that these methods have specific limitations and may in some instances not detect protein that is present at higher amounts; thus, careful double-checks are required before claims to nonfouling coatings are made. Sadly, this has been lacking in many studies, and a number of reports on "nonfouling" coatings have not adequately clarified the limitations of their in vitro assays. This is not limited to PUs; the biomaterials literature in general would benefit from enhanced scientific rigor and greater restraint in stating the putative merits of new surfaces. It is essential that clearly defined, sensitive methods and specific terms are used with precision.

There are unsupported assumptions and assertions aplenty in the biomaterials literature particularly when "nonfouling", "nonthrombogenic", and "hemocompatible" coatings are involved. For instance, some authors have described PEO grafts and end-attached polysaccharide coatings as "brush-like". However, a well-solvated macromolecule adopts a random coil configuration and thus an overall spherical shape. Whether by attachment of a macromolecule or by surface grafting, one cannot overcome the limitation that well-solvated macromolecules want to retain that minimum-energy configuration and minimize overlap with each other. Thus, no matter how high the density of surface attachment points is, the result is likely a layer of solvated spheres, not brushes. Moreover, the excluded volume of such attached spheres likely leads to nonoptimal packing density, that is, to small gaps in-between the attached spheres through which small proteins may diffuse and reach the underlying substrate for irreversible adsorption. One simply cannot force well-solvated molecules to attach to a surface in a brush-like structure. Thus it can be rationalized why Österberg et al[134] found nominally "end-attached" dextran not to be superior to "side-on" attached dextran—in both cases the authors probably attached dextran spherical molecules, albeit via different groups.

It stands to reason that the molecules that one wants to yield an antifouling coating want to retain their hydration shell and their entropic freedom by maximal mobility, and thus repel not only proteins but also each other. Yet, this seems to have been unrecognized in some work. The only way to overcome such an energetic limitation against the dense packing of highly hydrated molecules in producing a hydrogel-like coating is to go to marginal solubility conditions such as the "cloud point" of PEO. Under this solution condition, the PEO molecules start to associate and thereby are able to assemble into a denser coating.[132,135] As the coating is then brought back to conditions, i.e., a solution, in which the chains lose their mutual attraction, they want to rehydrate and repel each other. Being crowded, they possess only one direction for expansion on hydration, and they therefore stretch and produce a brush-like coating of elongated, hydrated PEO molecules. With polysaccharides, an analogous condition of reduced solubility with increasing temperature does not exist, and it is therefore debatable whether these materials can produce brush-like coatings rather than coatings consisting of well-solvated random coils.

The analogy with SAMs is fallacious for grafted hydrogel polymers; alkylthiol SAMs are characterized by attractive intermolecular forces between the alkyl chains that bring about this packing, whereas PEO and polysaccharide molecules exert repulsive forces towards each other

under "normal" (25-37°C) conditions and thus do not spontaneously self-assemble. Whether phosphatidylcholine molecules do under the conditions used for the fabrication of such coatings is also a matter of debate. This is in contrast to the work from the groups of Whitesides[136] and Grunze,[137] in which PEO chains were attached to the end of alkylthiol chains and the resultant PEO-alkylthiols used to fabricate SAMs; in this case, the cohesive forces between the self-assembled alkyl chains forced the terminal PEO chains to adopt a densely packed configuration. Clearly, when one attaches a PEO without the alkyl part onto a surface, the driving force for dense packing is not provided and hence the PEO is free to adopt its preferred random coil configuration. I believe that this is the main reason why the excellent protein repellency reported in the studies from the groups of Whitesides and Grunze, respectively, have often not been replicated when attaching PEOs in other ways. The literature suggests that excellent repellency can be produced also by PEO coatings produced by non-SAM routes[132,135] but substantially longer PEO segments are required (with PEO-SAMs very short PEO segments are effective), probably because a much thicker layer of a hydrogel-like structure is required when the specific SAM packing density and chain structure is not provided. Thus, PEO coatings may produce protein repellency in more than one way. These issues, which are still the subject of current research, are discussed in more detail in a recent review.[131]

7.8.2 PEO Surfaces on Polyurethanes

Turning now to some specific studies and experimental results with "nonfouling" or "anti-thrombogenic" coatings on PUs, PEO coatings have shown marked reductions, compared with control PU surfaces, in protein adsorption and platelet adhesion in many studies. An example is that of Desai and Hubbell[130] in which PEOs were incorporated into surface layers using a solvent swelling technique. PEO of molecular weight (MW) 18.5 KDa was better than PEOs of MW 10 KDa and 100 KDa. Brinkman et al studied platelet deposition onto PEO-modified PU.[138] In that study, PEO was covalently attached, either via dicumyl peroxide radical grafting or by the surface graft polymerization of PEO-methacrylate. On both types of PEO surfaces, platelet deposition was almost absent.

Many schemes have been employed to equip PU surfaces with PEOs. The solvent swelling method of Desai and Hubbell[130] is particularly attractive for its simplicity and appears very effective in terms of reducing biological interactions. The adsorption onto PUs of PEO-PPO-PEO triblock copolymers (Pluronics®) is also a simple method for producing PEO-coated PUs but some loss of the PEO with time is observed.[139] Some early studies used block copolymerization to incorporate PEOs into PUs and found the resultant materials to be promising in terms of protein repellency and reductions in platelet adhesion.[125,126] Many other approaches use two-step surface modification methods for producing PEO coatings. Fujimoto et al[140] produced methoxy-PEG methacrylate coatings via an argon plasma surface activation method and radical-induced grafting; reduced, but not zero, adsorption of albumin, IgG, and platelets was obtained. Others have used isocyanate linkage to graft PEO chains;[97,141] by exposing PU to HMDI in toluene, isocyanate groups were introduced, onto which PEO could be coupled.[141] While some improvements in performance result from this PEO coating, the question arises whether increases by 2-3-fold in shunt occlusion times[142] are sufficient indicators of promise for long-term blood compatibility. Freij-Larsson and Wesslén used the same isocyanate chemistry pathway but slighty different conditions, and toluene as the solvent for the second step, to produce PEO grafts on PU.[143] Lee et al[139] found markedly reduced platelet adhesion; in general agreement with much of the literature on PEO coatings, they found longer chains to be more effective and attributed this to enhanced chain mobility. The length of PEO chains was also investigated for instance by contact angle measurements, which on PEO-grafted PU

surfaces reached a value corresponding to pure PEO at a PEO molecular weight of 10 KDa, indicating that longer chains provide more complete coverage.[144]

While many researchers consider PEO coatings promising, contradicting data do exist. Okkema found PU rich in PEO soft segment to be more thrombogenic than PTMO-based PU.[145] Bernacca et al[97] found that PEO-coated PUs (using PEOs of different molecular weights) exhibited extensive protein adsorption on contact with plasma. PEO-coated surfaces also showed reduced complement and platelet activation at short contact times but at longer (> 25 min) blood contact times the coated surfaces were inferior to the control PU. No surface analytical data are provided, and it is therefore not possible to assess whether perhaps the coatings might have been of incomplete coverage, and the need for detailed characterization of a coating prior to interpretation of biological test results is clearly evident.

The introduction of hydrophilic side chains (PEG or sulfonated PEG) into the soft segment led to surfaces enriched in these graft chains, as shown by underwater contact angles.[146] Ex vivo shunt experiments gave results that showed effects from the hydrophilic side chains and the sulfonate group.

It has been claimed that there is a synergistic effect between PEO and sulfonate groups attached onto PUs.[142,147] The clotting times were extended compared with PEO grafts. The reason may be additional repellency by sulfonate groups towards negatively charged proteins. Another study found, however, that for platelet adhesion on modified PUs, an effect from sulfonate groups was additive to that from PEO only when short PEO chains were used.[139]

7.8.3 Other Surfaces

Other surfaces have also shown some promise. Chapman and Valencia[148] and Ruiz et al[149] fabricated modified PUs by the copolymerization of phosphorylcholine (PC) moieties. The more recent data by Ruiz et al showed that the resultant material possessed low—but not zero—affinity for protein adsorption: a reduction of > 80% was observed for the adsorption of fibrinogen and β-globulin, and > 95% for human serum albumin, compared with a SiO_2/TiO_2 waveguide surface. Whether this extent of reduction is sufficient for clinical success is, however, an open question. As it has been contended[150] that fibrinogen adsorption should not exceed 5 ng/cm^2, the in vitro data may not be sufficiently low to meet the putative clinical requirements.

Similarly, Cooper's group[39,151,152] showed PUs containing PC to limit the adherence of neutrophils and bacteria.

PC was also attached onto Pellethane™ surfaces using a photograft technique[153] in which the PC moiety was derivatized with a phenylazido group, which is activated photo-chemically to a nitrene. It was postulated that immobilization reaction occurred specifically with the nitrogen atom of the urethane group of the PU, but as discussed in Section 7.5 for the same reaction with other photoactive moieties, there is, based on conventional chemical principles, doubt whether there is indeed such specificity. Since nitrenes are extremely reactive and are likely to react with other groups including groups on other parts of the same molecule or on other photograft molecules, the reaction can possibly give rise to crosslinked, polymerized photograft layers rather than exquisite molecular immobilization. XPS showed the presence of PC on the photografted surface, but the contact angle of 43° of the grafted surface appears to me to be too high to be consistent with good PC coverage; the layer must be quite patchy. Nevertheless, improved blood compatibility (decreased platelet adsorption and activation and reduced thrombin formation) resulted.

Interestingly, however, the same authors later reported for the same surface that there was little effect on protein adsorption,[154] indicating "that the mere presence of PC groups on a PEU surface is insufficient to suppress protein adsorption". This conclusion should be tempered

by the possibility that insufficient coverage was obtained in that study (gaps, even small, in a coating can have disproportionate effects on interfacial properties) and that a more complete, or better structured layer, may give different results. It is essential to perform state-of-the-art characterization of surfaces and their homogeneity before drawing conclusions about the merits of particular anti-fouling coatings. Indeed, this conjecture is supported by results by the same authors showing that a "biomembrane-like", well-formed PC bilayer markedly suppressed protein adsorption.[154] The authors conclude that "the highly ordered structure of natural phospholipid bilayers seems to be required", but in the light of other studies with PC surfaces an alternative explanation is that a minimum density of coverage of PC is required, and the photograft-PC surface of that study failed to achieve threshold coverage.

The graft polymerization of acrylamide onto PU resulted in reduced protein adsorption and platelet adhesion.[155] Similarly, dimethyl acrylamide was grafted onto Pellethane™.[133] The latter study reported IgG adsorption of ~ 60 ng/cm^2 for coatings from both monomers; however, the uniformity of the coatings is subject to doubt, as discussed above, and it may be that optimally fabricated coatings can offer better performance, given that polyacrylamide is a well-known material with very low protein affinity in separation processes.

Poly(vinyl pyrrolidone) (PVP) is also a material that has been studied for its low affinity for protein adsorption in a number of potential biomedical and membrane applications. A PVP coating on Pellethane™ central venous catheters was found to cause strongly reduced adsorption of fibrinogen and fibronectin as well as reduced bacterial adhesion.[156] Peckham et al tested a PU catheter dip-coated and air-dried with a proprietary PVP-polyacrylic acid copolymer coating and found platelet adhesion to be relatively low, but kallikrein generation was higher than on some other surfaces,[157] indicating a concern regarding activation of the intrinsic coagulation pathway. On poly(ethylene terephthalate) (PET), Desai and Hubbell found PVP incorporated by a solvent swelling method to be inferior to PEO in protein repellency.[130]

Other synthetic hydrogels have also been of interest (and use) in the general biomaterials literature for possible application as antifouling materials or coatings. A hydroxyethyl methacrylate (HEMA)/styrene block copolymer was coated onto the luminal surface of PU vascular grafts[158] and gave good results in a canine in vivo model, with the grafts remaining patent over 3 months whereas the control PU and a PU with a covalently attached PEO layer occluded within 1 month. The HEMA/styrene coated surface also performed better with regard to protein adsorption, with only a monolayer present, whereas the control and the PEO surface had multilayers of adsorbed proteins. The nature of the protein layer also differed, with more albumin and less fibrinogen on the HEMA/styrene coated surface. The HEMA/styrene copolymer was not covalently attached but presumably adsorbed via its hydrophobic polystyrene block.

Polysaccharide coatings are also of interest as antifouling surfaces, and blood contact results obtained for instance with a cellulosic coating on a Teflon® intravenous catheter[159] should be transferable to PU catheters. A glucose layer immobilized via isocyanate chemistry on PU gave promising results in terms of showing the least activating surface among several including two PEO-grafted surfaces.[97] Yet, there was extensive protein adsorption on contact with blood plasma.

Notwithstanding the fact that a pHEMA/polystyrene coating clearly outperformed a PEO coating in the study of Nojiri et al,[158] PEO appears to remain the lead candidate for fabricating coatings intended to be nonfouling. Direct comparisons are unfortunately few and hence it is difficult to assess the relative merits of the various coatings proposed by various authors; differences in coatings between studies are hard to interpret particularly in the absence of standardized testing protocols, and with the paucity of data on surface uniformity. Lee et al[160] produced both a PEO-methacrylate and a poly(N,N-dimethylacrylamide) coating by UV activation, following surface functionalization of the PU by chloromethylation and subsequent

dithiocarbamate reaction. They found the former coating to be more effective at reducing platelet adhesion.

7.9 Coatings for Cell Colonization

Since many anchorage-dependent mammalian cells generally attach reasonably well to PUs, surface modification for improved cell attachment may only be necessary for use with "difficult" cell lines, or for specialized applications. As an example of the latter, Bruil et al modified PU to obtain increased adhesion of leukocytes onto PU films; the aim was to develop filters for leukocyte filtration from blood. Polyethylene imine, a cell adhesion promoting coating, appeared to be useful for this application.[161] The incorporation of sulfonate groups into a PU surface also promoted in vitro leukocyte adhesion.[162]

The endothelialization of vascular grafts by endothelial cell "sodding" has been proposed as a means of improving their blood compatibility. However, PU based grafts do not allow sufficient establishment of a cell lining. Thus, attempts have been made to improve the ability of human endothelial cells to attach and proliferate on PUs. For example, Breuers et al immobilized the pentapeptide GRGDS (a fibronectin fragment) using a multi-step procedure.[163] First, a plasma polymer layer from vinyl acetate was deposited; ester groups of this coating were then saponified and benzoquinone attached; the amine groups of GRGDS then could react with this surface under mild aqueous conditions. Williams et al[53] applied a "Primaria-like" plasma treatment to a PU vascular graft and obtained a well-developed multilayer cell lining. Lin et al[164] grafted RGD-containing peptides covalently onto PU. Two attachment routes were explored. For both, the PU was first functionalized by the addition of ethyl carboxylate groups via a NaH-mediated substitution reaction. Onto this carboxylated surface, a peptide could be anchored directly using carbodiimide chemistry. Alternatively, a peptide with a Fmoc-blocked C-terminus was attached and the blocking group removed after attachment. The two-step route would seem preferable because the Fmoc-blocked peptide cannot undergo carbodiimide-mediated reaction at its C-terminus, which leads to oligomerization of the peptides. The grafted peptide layers led to improvements in the attachment and spreading of cells, and differences between different peptides were observed. In the presence of adhesive serum glycoproteins, however, the differences became much smaller.

Langmuir-Blodgett coated films of anti-endoglin antibodies, crosslinked by glutaraldehyde, were used in an attempt to mediate endothelial cell adhesion on Corethane™ PU.[123] IgG coatings were also produced and showed the same performance. A gelatin coating, however, performed significantly better, raising in my mind the question of the benefit of using the much more expensive anti-endoglin antibody approach.

Huang et al[101] attached collagen onto PU via bis-epoxides and studied the effects on cell growth. Comments on that work are made above in Section 7.7.2.2.

Another reason for equipping a PU with a cell-supportive coating is the desire to produce spatially defined responses. For instance Ruiz et al[149] first incorporated phosphorylcholine into PU in order to produce a nonadhesive surface, onto which cell-adhesive laminin oligopeptides were immobilized. This allowed spatial control of colonization. However, the colonization was not specific to a particular peptide sequence, raising the question of whether the peptide immobilization scheme had simply negated the nonadhesive property of the original surface. Perhaps the cells had been able to colonize the peptide-modified surface regions by the secretion and adsorption of their own extracellular matrix proteins, proteins which managed to adsorb onto laminin oligopeptides regardless of whether a specific cell recognition signal was expressed by the laminin oligopeptide.

Yang et al[165] grafted polyacrylic acid onto PU surfaces and found support of cell adhesion and growth. This is somewhat surprising given the general tendency of hydrogel coatings to be

poor supporters of cell attachment but may suggest a role of carboxyl groups in promoting cell attachment. Another unusual aspect of that work is that grafting was done in the presence of oxygen; normally, molecular oxygen interferes in radical graft polymerization, although earlier surface graft polymerization with ionic monomers also was done without degassing.[166] The structure and properties of the hydrogel coating produced by these authors should be characterized in more detail.

7.10 Surface Modifying Additives and End Groups

While many of the approaches reviewed above comprise a surface modification or coating step that is performed after the PU is synthesized and formed into its end-use shape, a convenient alternative approach is to incorporate into the PU during synthesis an additive or chain end groups that subsequently migrate to the surface and confer desired surface properties. As is implicit in the terminology, the two approaches that have been used comprise the use of a diffusible additive that is surface active, and the use of end groups attached covalently onto PU chains.

7.10.1 Surface Modifying Additives

The surface-modifying additive (SMA) approach[167] is the older and the easier to perform (as discussed in Chapter 3). With suitable additives, only small weight percentages (in terms of the overall bulk formulation) are required to obtain substantial surface coverages, while the bulk mechanical properties are altered little or not measurably with this approach. However, there can be processing disadvantages with SMAs. Another shortcoming of the approach is that long times can be required for surface equilibration. In addition, potential loss of the SMA must be considered; its accumulation in other body parts, particularly vital organs, must be investigated by long-term studies. Finally, if an additive is found to be on the surface when in contact with air or vacuum (as applicable to XPS analysis), there is still the question as to the rate and effectiveness of its disappearance from the surface by migration into the polymer bulk when the polymer is brought into contact with an aqueous environment. The surface enrichment of hydrophobic additives may not be a useful strategy as such SMAs will tend to have unfavorable surface energetics in contact with biological fluids and migrate away from the interface. As fluorocarbon surfaces also tend to denature proteins quite extensively, the utility of fluorinated SMAs must be questioned.

Indeed, some extraction of PEO surface-modifying additives was observed,[139] but nevertheless the SMA-modified PU surfaces showed much decreased platelet adhesion. In that study, PEO-PPO-PEO triblock copolymers (Pluronics®) were used as SMAs. Longer SMA chains were more effective. Sulfonated SMAs were also tried in the light of earlier reports[147] on synergistic effects between sulfonate groups and PEO, but with longer PEO chains the effects from sulfonate groups were not significant. Thus, Lee et al[139] concluded that the mobility of the PEO surface chains was the key property for platelet repellency. The mobility of surface-bound, hydrated PEO chains is generally thought to be an important factor.

Ishihara et al mixed copolymers of 2-methacryloyloxyethyl phosphorylcholine and alkylmethacrylates with PU in a solvent and fabricated samples by evaporation.[168] The aim was to alter the surface properties by providing a surface enriched in the PC moiety, which reduces protein adsorption. For one of the two copolymers, the PC additive attained a good surface coverage as attested by XPS analysis. A small amount of the additive was found to leach out on immersion in water for 10 days. Sonication of the solution gave better dispersion of the additive.[169] On the sample with the PC additive, the amounts of adsorbed albumin and fibrinogen were reduced, and reduced "blood-cell adhesion" was also found. The authors thus claim

incorporation of the PC-SMA to be "an effective method for imparting nonthrombogenicity". I consider this an overstatement; clearly, in this as well as many other studies, the demonstration of reduced protein and platelet adhesion is not sufficient to claim nonthrombogenicity, a claim that would have to be supported by clinical evaluations. "Reduced adverse consequences on in vitro blood contact" would in my opinion be a much more accurate and honest description of the outcome of this and many other PU surface modifications.

The addition of a surface active amphiphilic additive (Methacrol 2138F) also substantially modulated the surface properties of a PU.[170] XPS and contact angle data documented surface enrichment of this additive, and the resultant surfaces exhibited lower protein adsorption. A neat control experiment in that study was the use of a PU coated with the additive, to compare with the PU sample that had been loaded with the additive. Another study showed, however, that Methacrol 2138F was, due to immiscibility, dispersed in discrete domains, and that during implantation this additive leached, leaving behind pits on the PU surface.[171] Another additive, Santowhite powder, was more effective at reducing surface cracking during implantation.

The incorporation into Pellethane™ of an amphiphilic additive, which was a segmented PU containing PEO, was also done with the intention of modifying the surface composition by a SMA approach; high contact angle hysteresis resulted.[172] Fibrinogen adsorption was substantially reduced and the SMA-loaded PU gave protein adsorption equivalent to that of PEO-grafted PU.[173] The additive appeared to be stable towards leaching and extraction. The same group also incorporated a polyacrylic acid based SMA into PU.[174]

The presence of a surface active additive may enhance the mobility of the polymer surface layers and hence their ability to undergo surface reorientation in response to interfacial forces. Enhancement of dynamic surface reorientation was postulated to be an aspect of the function of amphiphilic PEO-poly(methylene-[polyphenyl isocyanate]) and other additives in PU; such additives substantially altered cell colonization and protein adsorption.[175] Dynamic surface reorientation was also postulated to be occurring with the additive Methacrol 2138F.[176]

In principle, a surface-enriched layer of a hydrolytically and/or oxidatively more stable additive can act as a protective layer against biodegradation of PUs. A SMA approach was used in order to reduce the susceptibility of a PU towards degradation by lysosomal enzymes.[177] Some SMA formulations were physically incompatible with the PU and affected surface morphology; in these cases, protection did not result. Fluorinated macromolecular SMAs not only slowed the rate of degradation but also gave reduced levels of fibrinogen adsorption.[178] The authors' suggestion that these surfaces therefore should be anticoagulant seem, however, somewhat premature given that fibrinogen adsorption is only part of the problem of blood compatibility.

In a recent study, the additive dexamethasone inhibited macrophage activation and/or the oxidative burst that leads to stress cracking of PUs.[179] It would appear reasonable to assume that to do so, the additive should be surface-enriched but this remains to be demonstrated.

In a sense, the surface-physical-interpenetrating-network approach of Desai and Hubbell[130] could also be considered a SMA-type approach. However, the additive is, in their method, not added during polymer fabrication but in-diffused into surface layers of a solid base polymer on immersion in a swelling solvent containing the additive. The additive becomes entrapped in the surface layers and substantially modifies surface properties. Particularly with PEOs loaded by this method into PU, protein adsorption and fibroblast adhesion were much reduced.

Some additives that were developed and incorporated into PUs for other reasons can also in principle act as SMAs on the basis of their ability to enrich at the surface, but this is not deemed a deliberate surface modification attempt, and few reliable data are available.

7.10.2 Surface Modifying End Groups

Designed to overcome some of the limitations of the SMA approach, the surface-modifying end group (SME) approach is synthetically more challenging but has been successfully implemented with various end groups that can achieve a desired surface chemistry. PEO chains, silicones, fluorocarbon chains, hydrocarbons, and alkyl sulfonates have been incorporated as terminal groups into various custom PUs with polyether and other soft segments.[180,181] SMEs are surface-active oligomers designed such that during and after component fabrication they should spontaneously self-assemble at the surface of the part and thus affect surface properties. By coupling the oligomeric SME moieties to the ends of linear polymer chains, sufficient mobility is conferred to provide the ability for them to enrich at the immediate surface; contact angle measurements document the changes to the material's surface energy by the SME. The SMEs are coupled onto PU backbone chains via reaction with a terminal isocyanate group. The length of the SME oligomer chain has an effect: for instance octadecyl SMEs are more effective than dodecyl SMEs. The resultant surfaces were characterized by XPS[182] and IR/VIS sum frequency spectroscopy.[183] The latter study also documented environmentally induced changes to the surface, indicating that such surfaces can rearrange in response to interfacial energy changes. The spectroscopic findings were found to correlate with contact angle measurements,[184] thus documenting the motions of the SMEs to and from the surface. On the other hand, Brunstedt et al end-capped PU with diisopropylaminoethyl or decyl moieties, but contact angle analysis and cell colonization suggested that these end groups did not become surface enriched at the hydrated PU surface.[175]

One of the aims of the SME approach was to decrease the susceptibility to degradation of PUs in vivo; as the degradation generally starts from the surface, changes to the surface chemistry are likely to affect biodegradation. In vivo evaluations[185,186] showed increased biostability upon 12 and 18 months intramuscular implantation in rabbits. Over 4 months, full protection was obtained.[186]

Polydimethylsiloxane end-capping of PEU was also observed by Mathur et al[187] to afford a considerable extent of protection against oxidative attack by oxidative radicals secreted by macrophages.

The end-capping of PUs is a synthetic chemical approach rather than what is commonly understood as a surface modification technique, which is usually meant to describe a separate processing step after fabrication of the bulk solid. However, when synthetic approaches are designed with the explicit aim of modifying surface properties, the distinction becomes fuzzy. Also, it is important in such studies that appropriate surface analytical methods are applied to characterize the outcomes.

7.11 Other Surface Modifications

An alternative to the covalent immobilization of biologically active molecules onto PUs, reviewed in Section 7.6, is the controlled release of biologically active entities from an appropriately modified PU. Such an entity can then determine the interfacial responses (until it is exhausted by diffusive loss to the environment). In the simplest approach, a bioactive agent is simply loaded into the PU during formulation or extrusion as an additive, or added afterwards by soaking the PU in a solution of the bioactive agent. This is effective with some molecules and does not require any surface modification procedures; for many other bioactive molecules of interest, however, their solubility in a native PU formulation is insufficient, or other adverse factors exist.

A coating into which the bioactive agent can be loaded to high concentrations is a great asset for this approach. For instance, a surface-grafted copolymer layer of acrylic acid and

acrylamide on PU provides a good matrix for loading the antibiotic agent gentamycin; pacemaker leads thus coated and loaded showed marked improvements in terms of little or no infection when challenged with *Staphylococcus aureus* bacteria, whereas standard leads became heavily infected.[188] This approach thus appears capable of combatting infection-related complications with implants.

This approach is, however, less attractive than the route of covalent immobilization when it comes to obtaining regulatory approval since effects at sites (especially vital organs) remote to the implant must be considered and documented.

Fluoroalkylether structures were incorporated into the PU soft segment by adding fluoropolyether glycol (FPEG) during synthesis.[189] XPS showed enrichment at the PU surface of the low surface energy FPEG, whereas in an aqueous environment the surface layers rearranged.

Han et al grafted perfluoroalkyl chains onto PU with the aim of improving blood compatibility;[190] the premise was that very hydrophobic, perfluorinated surfaces should interact only minimally with blood. However, while chemically inert, perfluorinated surfaces exert strong physical forces that cause tenacious protein adsorption,[60] and the clinical experience with the (perfluorocarbon coated) Atrium® vascular graft has shown that such surfaces may not adsorb platelets but nevertheless exert other adverse consequences. Platelets can be activated without irreversible adsorption. Han et al found an extension of the ex vivo occlusion time from 50 minutes for untreated PU to 130 minutes for the grafted sample. Clearly, much greater improvements must be sought. Interestingly, however, two PEO coatings grafted by the same HMDI-mediated chemistry also gave similar occlusion times.

The grafting of perfluorodecanoic acid chains onto PU surfaces via isocyanate linkage was also used to make samples for subcutaneous implantation into rats for up to 6 months.[191] Surface cracking was, however, worse than on untreated PU and on PU grafted with PEO and sulfonated PEO; the last coating provided the best protection.

Similarly hydrophobic surfaces, as shown by contact angle measurements, were produced by Li et al[192] by including a reactive stearyl phospholipid in the PU synthesis. "Outstanding haemocompatibility" was claimed on the basis of relatively lower platelet adhesion and limited shape change for the adhered platelets compared to poly(vinyl chloride) (PVC). As PVC is, however, a very poor material in contact with blood, the comparison is not impressive and should have been done against a surface such as immobilized heparin or PEO. The clotting time was improved over the controls (99 seconds versus 75 seconds for PVC and 62 sec for glass from platelet poor plasma), but does this really indicate great clinical promise?

Finally, metallized PUs have occasionally been studied. Silver-coated PU catheters were found in long-term implantation in rabbits to display signs of inflammation and tissue reaction comparable to untreated PU.[193] Peckham et al evaluated silver-ion implanted catheters (produced by the Spire Corp.'s Spi-Argent ion beam implantation processes) and found platelet adhesion to be 2-3 times higher than on other PU samples (untreated, and coated by other methods).[157]

7.12 Summary and Conclusions

In summary, a wide variety of surface treatments has been applied to PUs, from one-step methods, such as plasma treatments, to multi-layer coating schemes. It is thereby possible to equip PU surfaces with various chemical functionalities and surface properties. In recent times the trend clearly is towards fairly complex, molecularly engineered surfaces. It appears that such surfaces, designed on the basis of sound knowledge of both biomolecular interactions and surface science, hold promise for the control of interfacial reactions to an implant.

However, one of the difficulties one faces when attempting the rational molecular design of PU surfaces with improved biological responses is that generally the multiple biological requirements of a surface/coating are not sufficiently understood at the molecular level. Thus, it is difficult to molecularly design surfaces on the basis of sound, biologically guided hypotheses. It also often is difficult to design model studies that provide data of relevance to the in vivo situation. For example, many studies have measured fibrinogen adsorption on modified PUs; however, other work has shown that fibrinogen adsorption is affected by the presence of other proteins such as high-molecular-weight kininogen (HK).[36] This points to the importance of considering competitive protein adsorption phenomena; ideally, the adsorption of known and/or putative "good" and "bad" proteins should be studied from multicomponent solutions, ideally full blood, but this is of course exceedingly complex. The recently developed technique of surface-MALDI mass spectrometry[194] provides a tool for analyzing which proteins are successful in the competition for surface sites in adsorption from complex multi-component solutions. This can provide a means of ascertaining whether specific in vitro models are meaningful. However, Cornelius and Brash[36] also point out that it remains to be determined whether surfaces should be designed that are selective for HK or that exclude it, which illustrates very nicely the degree of uncertainty that one can face when attempting to rationally engineer biomaterials surfaces at the molecular level for specific purposes.

Another great challenge is the detailed characterization of the surfaces/coatings produced. For one, highly sensitive surface analytical techniques are based on expensive instrumentation and are not always as accessible as one might wish. Another consideration is that even with state-of-the-art instrumentation it can be difficult to gauge for example whether or not an ultrathin coating is uniformly covering a substrate. Another key issue is the determination of the three-dimensional molecular structure/architecture of coatings/packing density and arrangements of surface-attached macromolecules (e.g., are the grafted molecules arranged as brushes, loops, or random coils?). Methods such as small angle X-ray scattering (SAXS) and near edge x-ray absorption fine structure (NEXAFS) are starting to be applied to biomaterials surfaces to address this question of how much the observed responses are influenced by surface architecture is superimposed on the chemical composition. Further developments in techniques will be of considerable benefit to biomaterials surface science, in the same way that recent developments such as freeze-hydration XPS are. In the meantime, one needs to consider the possibility that a coating might not quite be what the developer designed it to be, and leave open the possibility that artefacts such as microscopic gaps or nonuniformities in some coatings might have contributed to observed biological responses. The literature contains discrepancies in results with similar coatings (particularly for PEOs) and some of these might be due not solely to the coating chemistry but partially to artefacts. More rigorous application of available techniques would, however, be a good start to avoid pitfalls in interpretation and to acquire the maximum possible information on surfaces/coatings of interest for correlation with biological responses.

More rigour in writing would also assist readers of the literature. While some studies probe and report the gaps in our understanding and the complexities of the biological pathways involved in adverse responses to PUs and of the surface/biology interactions, other studies are overly optimistic and simplify matters to a degree that is of concern. To claim "biocompatibility" and "nonthrombogenicity" for a modified surface for example on the basis of reduced adsorption of fibrinogen from an in vitro, single protein solution experiment is clearly inaccurate, scientifically unwarranted, and misleading. To achieve long-term resistance to thrombus formation, evidently a surface must meet other requirements besides reduced in vitro fibrinogen adsorption. Editors of journals should see to it that such terms are not used except when properly justified. There is also the semantic issue of correct usage of the English language: "biocompatible", "nonthrombogenic", and "nonfouling" mean no (i.e., precisely zero) occurrence of adverse events, thrombus formation, and fouling; applying these terms to describe

reduced but not zero occurrence is incorrect usage of language. Moreover, the most sensitive methods known must be applied when assessing fouling before concluding there is none. "Less incompatibility" or "reduced adverse consequences on in vitro blood contact" would in my opinion be much more accurate and honest descriptions of the outcome of many PU surface modifications.

For the materials scientist, the dilemma is that ultimately the real test for a new modified PU surface is the clinical application; yet, it is very difficult to extricate molecular surface design options from observed clinical responses. Molecular biology occupies a central role in the establishment of hypotheses to guide the development of molecularly engineered biomaterials surfaces. Clearly, the next generation of PU surfaces will be developed on the basis of molecular knowledge of biological requirements.

7.13 References

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CHAPTER 8

Biomedical Applications of Polyurethanes

Mylène Bergeron, Stéphane Lévesque, and Robert Guidoin

8.1 Introduction

Polyurethanes (PUs) represent a very broad family of polymers. They have earned an enviable and irreplaceable position within the medical industry. The applications of PUs are limitless. However one should ascertain that PUs are indeed the best materials to manufacture devices for specific applications (Fig. 8.1). We hereby propose a review of some applications which might be incomplete but focus on established successes, disputable results and potential further developments.

The armory of cardiac surgeons would not be as impressive as it is without the outstanding contribution of polyurethanes in intra-aortic balloons, blood sacs for ventricular assist devices (VADs), catheters, pacemaker leads to name the most important. Results of PUs as blood conduits have still not found a niche because of the unresolved lack of long-term resistance to degradation. Breast implants covered with PU foam are part of a scientific controversy. The use of PU in contraception is limited but these materials present some interesting features. Wound dressings and scaffolds for tissue engineering could permit new developments.

8.2 Polyurethanes for Cardiovascular Applications

The requirements of polymeric materials for the manufacture of various cardiovascular devices depend on the intended duration of use, intended method of application, and function. Generally they can be classified into three types of cardiovascular devices, namely transient, interim, and permanent.

- Transient cardiovascular devices are used routinely in emergency situations for periods varying from several days to several weeks. They include the intra-aortic balloon pump, the temporary left ventricular assist device (LVAD) and the biventricular assist device. Once the failing natural heart recovers, the devices are removed.
- Interim cardiovascular devices are used for heart transplant patients awaiting a suitable donor. They include the ventricular assist devices and the total artificial hearts used as bridges to transplantation. These devices can also be applied to heart transplant recipients during a rejection episode with the transplanted heart. They need not be totally implantable as their use is generally intended for less than a month.
- Permanent cardiovascular devices such as totally implantable ventricles, artificial hearts, blood conduits, and blood access, to name a few, are intended for implantation for a

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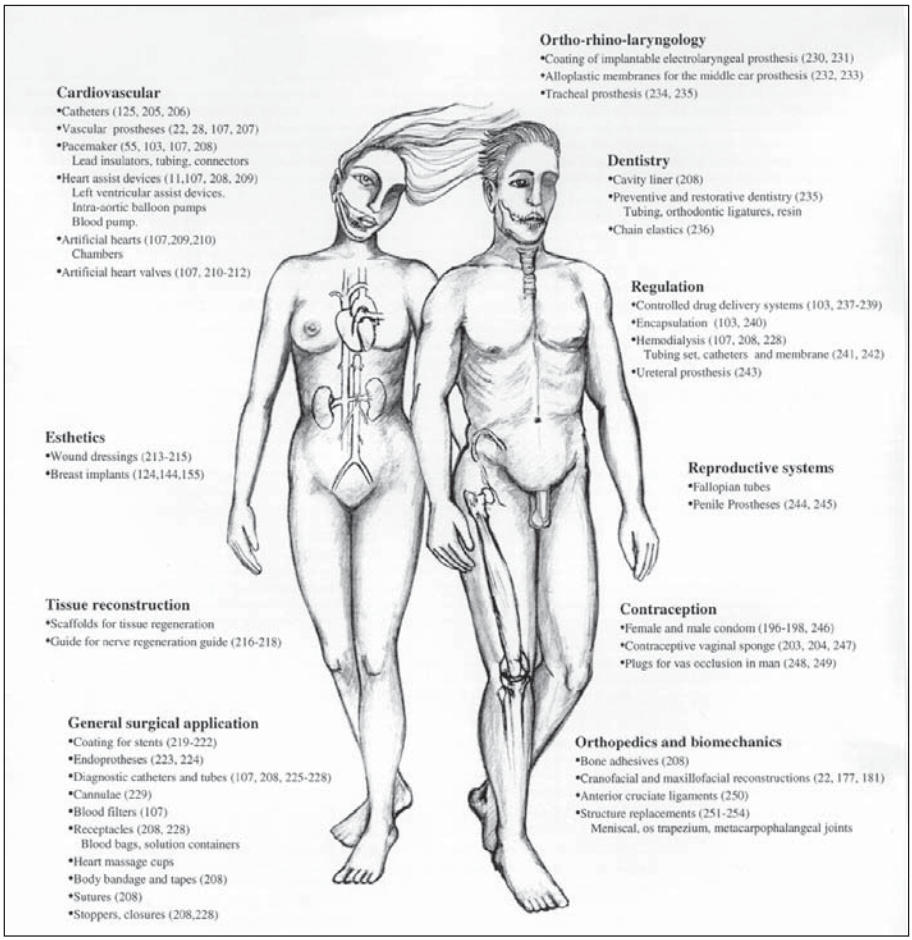

Fig. 8.1. Some polyurethane biomedical applications.

potential duration of two years or more for the ventricles and hearts and for life for blood conduits and blood access. These applications are highly demanding, the long-term stability issue must be raised together with the issues of blood compatibility and physical characteristics.

The success of cardiovascular devices depends on an appropriate selection of polymer, an appropriate know-how of the processing and an appropriate training of the user together with an appropriate clinical evaluation of the patient.

8.2.1 Intra-Aortic Balloon

In the early 1950s, open-heart surgery became a reality thanks to the development of heart and lung machines capable of maintaining cardiopulmonary function.[1] Frequent acute left ventricular systolic dysfunction was a drawback of this procedure. The temporary diversion of excess preload from the heart and its return to the patient by an assist pump could allow for

the recovery of the failing left ventricle.[2] The dependence of the coronary flow on diastolic aortic blood pressure was the basis for the counterpulsation concept.[3-4]

Moulopoulos et al were first to introduce counterpulsation to the circulation assist device by means of intra-aortic balloons (Fig. 8.2).[5] After Kantrowitz et al in 1967, the intra-aortic balloon device became an important circulatory aid in weaning patients from cardiopulmonary bypass.[1] The intra-aortic balloon used in conjunction with an ordinary heart-lung machine has the capability to return the blood to the patients in a pulsatile form,[6] which is achieved by delivering a predetermined volume of gas during the diastole and it is withdrawn during systole.[7] The major advantage of the intra-aortic balloon is the improvement of myocardial oxygen supply,[8] but most advantages are related to the simplicity of this device. For example, it is easier to insert and remove, easier to handle, causes minimal discomfort for the patient, does not require anticoagulation and has a reasonable cost.[9-10]

At present very little information is available concerning the characteristics of polyurethane intra-aortic balloon devices. Our team has conducted a verification to assess the safety of intra-aortic polyurethane balloon devices. Of the 112 devices investigated, macroscopic examination of the balloons revealed no obvious change in either shape or color, and no perceptible abrasions or cracks. However, 61% of the PU intra-aortic balloons were creased, and 40% of the central lumens and 21% of the sheaths showed visible bending flaws. Moreover, residual organic debris was frequently present.[11]

Complications of the intra-aortic balloons are related to catheter insertion with intra-aortic balloon insertion and malpositioning, balloon rupture and entrapment, blood cell destruction, infection, as well as vascular and neurologic injuries.[12] But very few are related to the PU membrane itself which is both enough blood compatible and stable for the duration of the counterpulsation. Some authors found that the device consistently increases coronary flow and decreases tension time index, which enhances the oxygen supply/consumption ratio of the left ventricle. On the other hand, they found that the polyurethane intra-aortic balloon pump does not significantly increase the oxygen supply/consumption ratio in severe cardiac failure.[13,14] In dogs, an increase in the number of platelet microforms due to the fragmentation of the normal-sized platelets has been noted along with the ultrastructural signs of platelet activation, degranulation and alterations of plasma membrane structure. Bolooki found that long term use of intra-aortic balloons with patients resulted in a gradual decrease in red blood cell and platelet count.[12]

Common chemicals such as acetone, ether, and Vi-Drape spray may damage the polyurethane intra-aortic balloon catheter; they cause the polyurethane to stiffen and break. Any contact between these agents and polyurethane intra-aortic balloon catheters should be avoided during dressing changes or repreparation of a sterile operative field. Other chemicals such as isopropyl alcohol do not cause any damage.[14]

Intra-aortic balloon implantation is a well-accepted procedure that permits an increase in pressure of the coronary arteries and a decrease in pressure of the left ventricle. It is an undisputed part of the armory to treat patients after open-heart surgery. The polyurethane balloons are satisfactory and this technology has reached a plateau.

8.2.2 Cardiac Valve

The research on prosthetic valve replacement made with polyurethane began in 1958 with a polyurethane film that was inserted between solid Teflon® fixation rings with semilunar extensions for commissural attachments. Various aortic valve prostheses were developed between 1960 and 1962.[15] The first successful aortic valve replacement with a Teflon®-leaflet valve was performed in April 1960. However, for cardiac surgery, this type of valve was not able to compete with mechanical valves and bioprostheses. The applications were focused on LVAD and

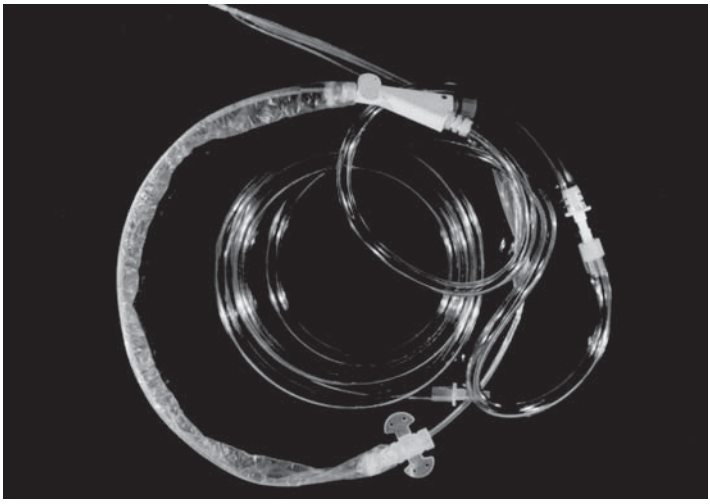

Fig. 8.2. Intra-aortic balloon: (A) gross view

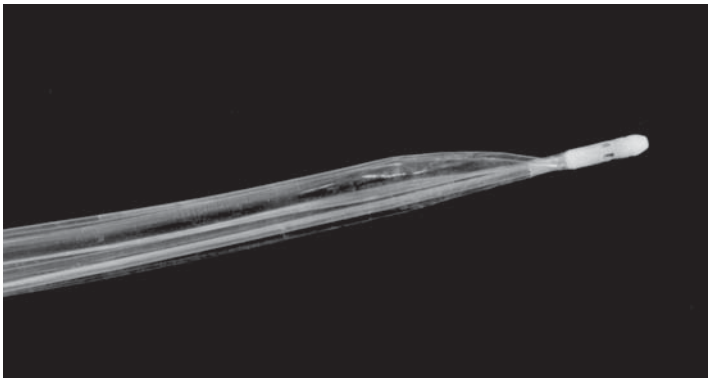

Fig. 8.2. Intra-aortic balloon: (B) detail of a polyurethane balloon.

artificial hearts to replace Björk-Shiley and Hall valves, which were found to induce thrombotic problems and mechanical failures. Their cost is also a contraindication for their selection as artificial devices. To improve these devices, a jellyfish valve was designed and manufactured at low cost. The valve has a simple structure; the center of a thin circular polyurethane membrane is fixed on a polyurethane base plate, which has many holes or slits to reduce flow resistance and help hold the membrane during the diastolic phase. Although it has an annular rather than a central flow, the flow characteristics of the valve are almost the same as that of the Björk-Shiley valve. Regurgitation characteristics of this valve were not evidenced as in the Björk-Shiley valve, with no stagnation point around the membrane, which can be expected to provide good antithrombogenicity.

Pellethane™ is currently the polymer used for the polyurethane tricuspid semilunar valves. The main advantages of PU valves is that they are inexpensive and reliable for a short duration of usage.[16] During the development of an open cell PU leaflet mitral valve, it was thought that when the leaflets were made thin and pliable enough to provide minimal resistance to flow they

would invert during systole, unless artificial chordae tendinae were used to restrict their motion. Once the technique optimized the tension on the chords in the beating heart, complete replacement of the mitral valve became feasible.[17] To increase the durability and decrease the calcification tendencies, a new design of prosthesis (the J-3) was manufactured in a medium open, almost flat shaped position, whereby the stent posts are expanded by a cone-shaped mold. The leaflets have stable closed and open positions. The hydrodynamic evaluation showed minimum pressure drop and very low energy losses compared with other commercially available valves. Very low shear stresses in the flow field downstream of the valve were observed. It was found that in durability tests, prototypes have reached lifetime equivalent to 17 years.[18]

Polyurethane valve prostheses are either constructed from solvent-cast sheets of polyurethane, which are thermally formed into the correct leaflet geometry, or dip-cast valves, which use a stainless steel mold which is dipped into a polyurethane solution to produce the valve leaflets. It was found that the results for the dip-cast valve showed a more uniform distribution of mean axial velocity and Reynolds normal stress resulting from the more circular central orifice produced by the dip-cast leaflets.[18]

A prototype PU trileaflet cardiac valve prosthesis implanted in juvenile sheep for up to 21 weeks led to substantial calcifications in the mitral position compromising the hemodynamic performance and the biomaterial durability. Hoffman et al used a PU tricuspid semilunar valve in the mitral position. Early failures were due to valve tears and calcifications. However mid-term function was good and the authors recommended this valve in temporary cardiac assist devices.[19]

Lo et al have evaluated a new valve design made by dip molding with different PU materials. All explanted valves showed calcification and immobilization, but their results suggest that at least two polyurethanes (Pampul and PUR 1025/1) attain survival times, which are far beyond the lifetime of bioprostheses under the same implant conditions.[20]

Many problems and complications associated with heart valves are related to the dynamic behavior of the valve and the resultant unsteady flow patterns. The generalized correlation between increased turbulence level and the severity of the stenosis is well established. Laser Doppler anemometry measurements were carried out in a pulse duplicator system distal to trileaflet PU prosthetic heart valves installed at mitral and aortic positions. Maximum turbulence level was correlated to the severity of the stenosis. The morphology of the velocity and turbulence waveforms was found to be governed by the stenosis geometry and the valve position (aortic, mitral).[20]

In terms of their hydrodynamic characteristics, PU trileaflet valves showed remarkable in vitro performance in comparison with similarly sized or even larger prosthetic valves. Even though some authors suggested that these prostheses were promising for valve replacement,[16] and some found that the hemodynamic characteristics were very satisfactory with only a small amount of platelets accumulated to the surface of PU material (Avcothane™) , surgeons did not accept these devices for cardiac surgery. The application is therefore restricted to VADs and artificial hearts.

8.2.3 Vascular Prostheses

Although at the turn of the century it was demonstrated that homologous and heterologous artery and veins could serve as arterial substitutes in dogs, and that autologous vein transplants could serve as a suitable arterial replacement in man, most early graft development focused on the use of nonbiologic tubes. In 1952, Vinyon-N was introduced as an innovative concept of a porous fabric arterial prosthesis after the tubes with plain walls had failed. Over the years, stronger and more durable materials such as polyestertetraphthalate (PET) and polytetrafluoroethylene (PTFE) proved to have a sufficient durability. Moreover, because of their outstanding handling characteristics, many investigators tried to develop PU blood conduits

very intensively despite mixed results. Parallel to this development, bovine heterograft and human umbilical cord vein allograft were also used in vascular surgery but are now history.[21]

Polyurethane grafts have a wide range of physical characteristics. It is possible to tailor their pore size, pore density, and compliance simply by changing polyurethane concentration, freezing temperature, and freezing methods (Fig. 8.3).[22] As porosity is an essential component for long term function of small synthetic vascular prostheses,[23,24] it was found that increasing permeability of the vascular grafts was likely to enhance tissue incorporation. Implants with pore sizes between 10 and 45 microns become ingrown with fibrohistiocystic tissue and capillaries, while implants with pore sizes greater than 45 microns are ingrown with organized fibrous tissue and minimal histiocystic response. Thus, microporous vascular prostheses which are minimally ingrown or ingrown with fibrohistiocystic tissue maintain compliance after months of implantation.[24]

Several PU vascular prostheses have reached industrial production as substitutes for small diameter arteries. These include the Corvita®, Thoratec®, Pulse-Tec®, Biomer™, Mitrathane™ (which can be either hydrophilic or hydrophobic) and Vascugraft® prostheses, each having its specific properties. Some of them deserve special attention. The Corvita® prosthesis is composed of polycarbonate-urethane and offers a compliant, low-stress fibrous structure with open communicating inter-fiber spaces (Fig. 8.4). However, it must be sealed to prevent excess blood loss at implantation. The Thoratec® prosthesis is made of polyether-urethane-urea, does not require sealing or preclotting, and offers less space for tissue ingrowth (Fig. 8.5). The Pulse-Tec® prosthesis has the fewest pores on its external surface (Fig. 8.6). Thus, while it does not require preclotting and may prove to be strong enough to resist kinking, its dense external surface may be responsible for delay in tissue ingrowth.

Mitrathane™, a polyether-urethane-urea similar to Biomer™, offers three discrete layers in its cross-sectional structure, with the external layer having large pores, and the internal layer having much smaller pores. It exhibits extremely high longitudinal tensile strains and its suture tearing strength was found to be superior to that of the expanded PTFE prosthesis. The radial compliance of the smaller-diameter has been found to be comparable with that of human muscular arterial tissue (Fig. 8.7).[25]

The Vascugraft® prosthesis has open pores that communicate through the thickness of the prosthesis wall. Both the longitudinal and radial compliance of the Vascugraft® prosthesis was found to be superior to that of the reinforced Gore-Tex® graft. In addition, it's bursting strength and suture retention strength exceeds the minimum requirements for small caliber arterial substitutes. The surface properties of the Vascugraft® prosthesis are unique because the polymer contains carbonate groups, which enrich the oxygen content of the surface. Vascugraft® prostheses provide the desired morphology, satisfactory mechanical properties and the appropriate surface characteristics which enable it to provide successful long term performance as an arterial substitute in vivo (Fig. 8.8).[26]

One of the most important anticipated advantages of PU prostheses was the development of a thin layer of endothelial cells on its internal surface. Unfortunately, clinical results differed dramatically from experimental results.[27] This type of prosthesis has many interesting features, such as excellent graft-host healing and good resistance at the suture site.[28] Vascugraft® prostheses in direct contact with endothelium from chick embryo aorta promoted the growth of a continuous monolayer of cells on its surface.[29] Polycarbonate-urethane vascular prostheses were also found to promote luminal endothelialization, induce less chronic intimal proliferation, and produce a significant thinner neointima than ePTFE grafts.[30]

To further improve the thromboresistance of these prostheses, several scientists have added endothelial growth factor,[31] gelatin and fibronectin,[32,33] and ADPase.[34,35] Others have precoated the PU prosthesis with endothelial cells.[36] Galletti et al have combined a biodegradable PU

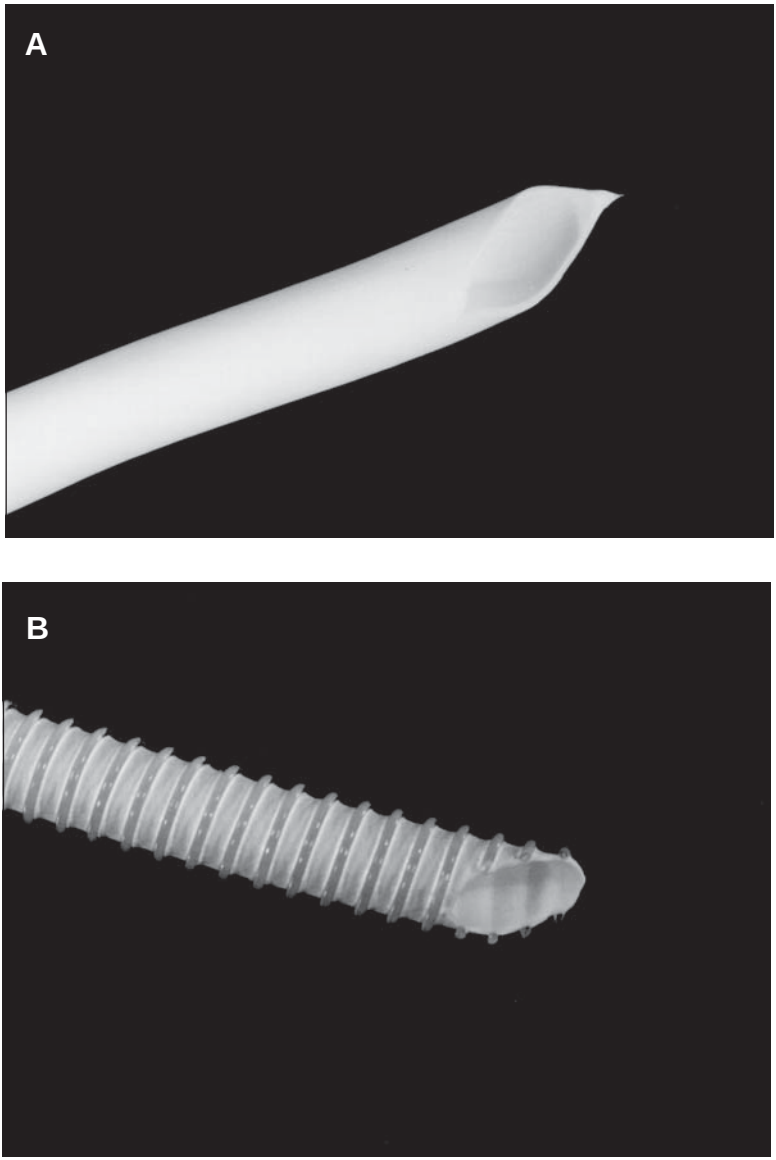

Fig. 8.3. Polyurethane grafts (A) without external support; (B) with external support.

vascular prosthesis with a lipid-rich diet. They found that the essential polyunsaturated fatty acid rich diet is able to prevent thrombosis of the biodegradable PU vascular prosthesis.[37,38]

Polyurethane vascular prostheses offered the potential of superior thromboresistance and reduced anastomotic hyperplasia compared to existing Dacron® and ePTFE alternatives, but have suffered from susceptibility to biodegradation, with resulting mechanical failure. Wilson et al have developed a composite prosthesis, an inner blood interfacing elastomeric porous

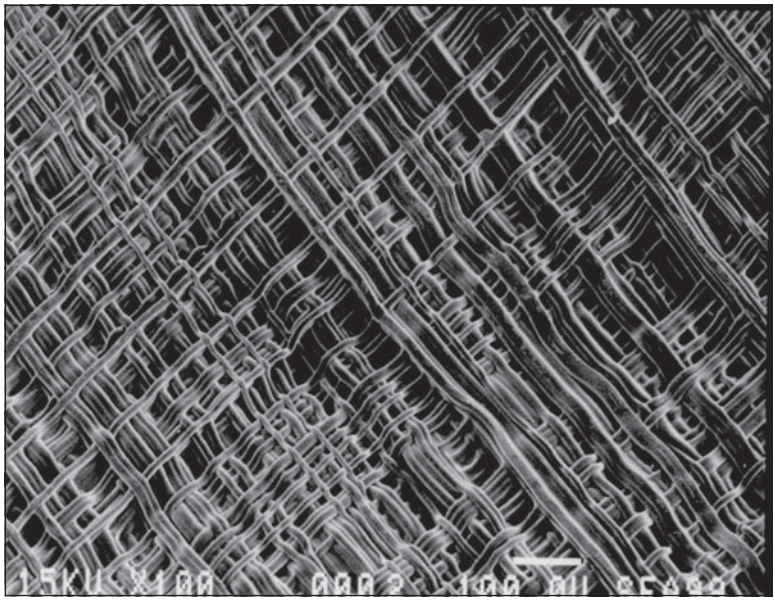

Fig. 8.4. Luminal surface of the Corvita™ prosthesis with open communicating inter-fiber spaces.

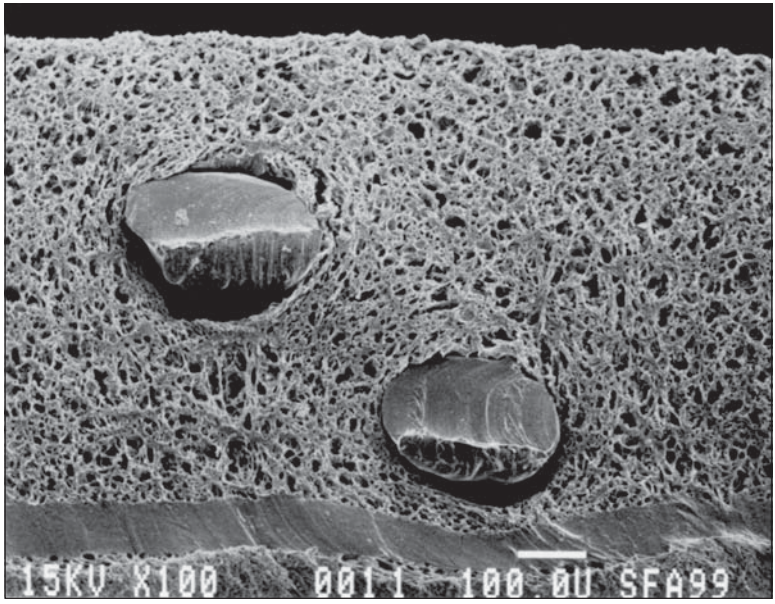

Fig. 8.5. Cross-section of the Thoratec prosthesis with totally impervious walls.

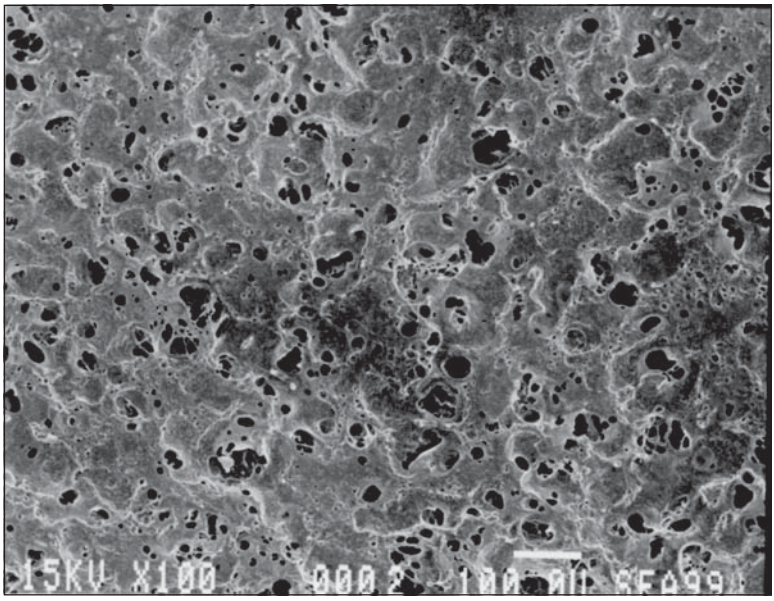

Fig. 8.6. (A) Pulse-Tec prosthesis with few pores on the surface

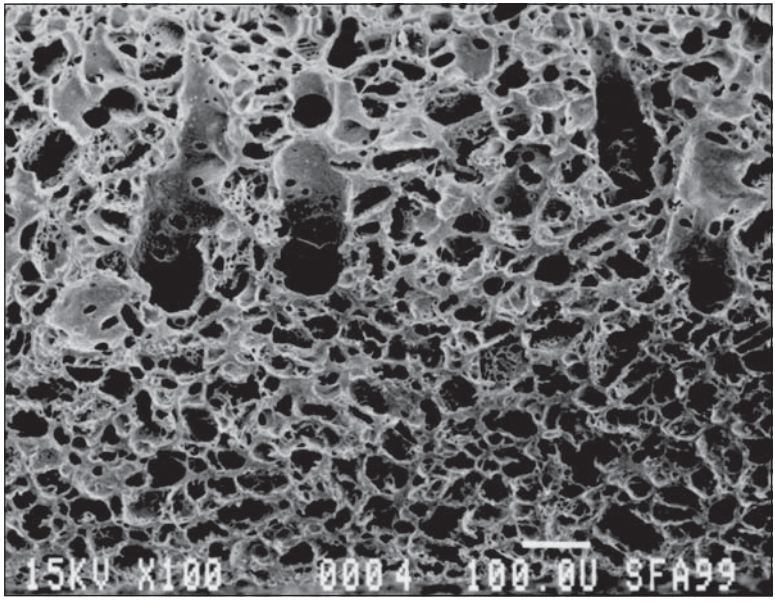

Fig. 8.6. (B) but with a highly porous structures.

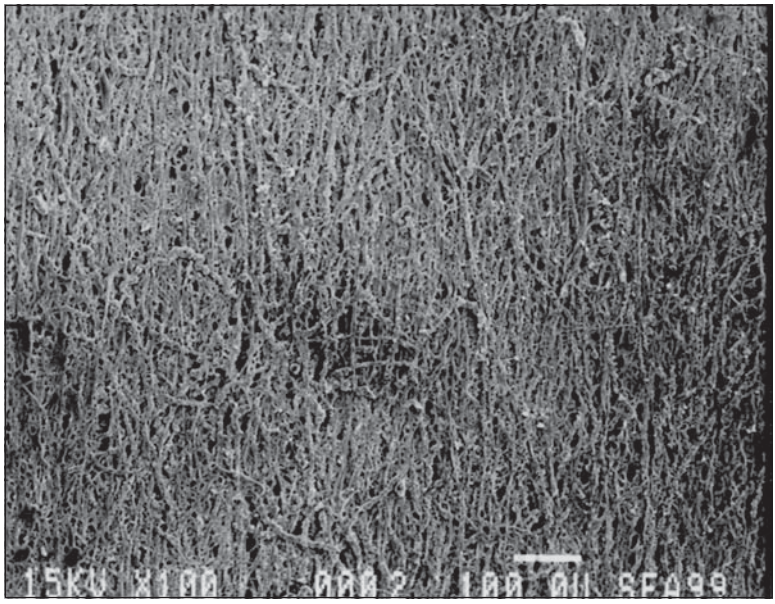

Fig.8.7. (A) Mitrathane™ prosthesis with large pores on the surface

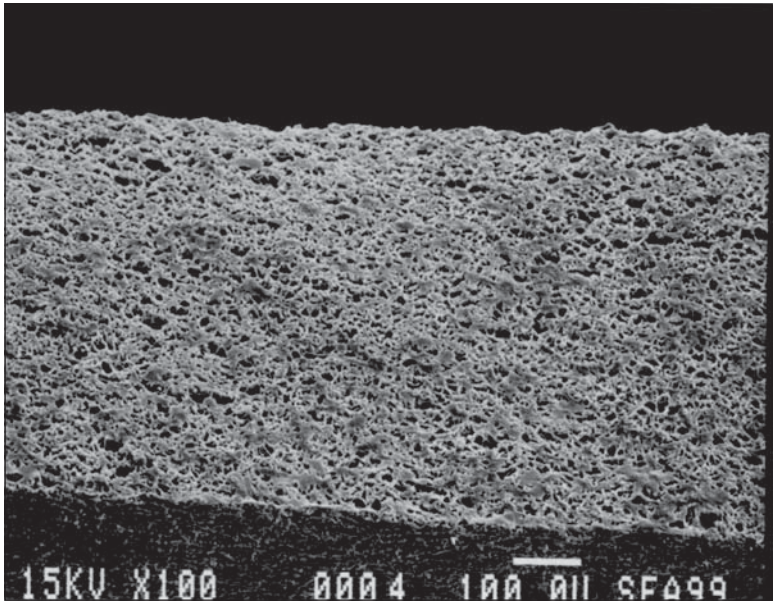

Fig.8.7. (B) and smaller pores in the wall.

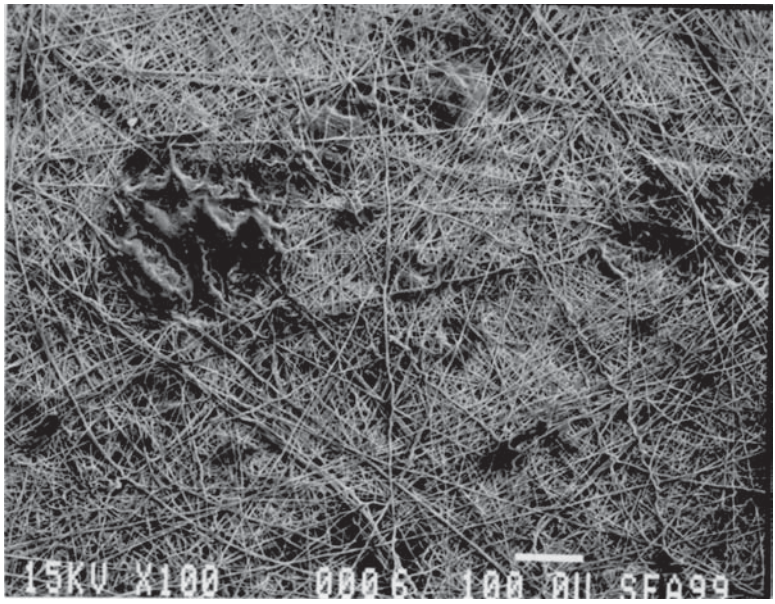

Fig. 8.8. (A) Vascugraft prosthesis with open pores

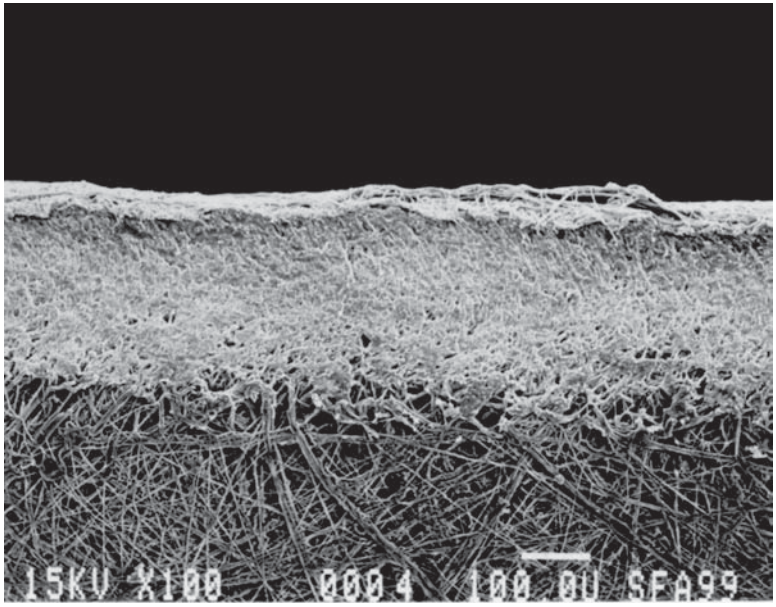

Fig. 8.8. (B) through the thickness of the wall.

membrane made from polyurethane and an outer Dacron® mesh bonded to the inner layer, which guarantees long-term dimensional stability.[39]

The Vascugraft® prosthesis, which must be considered the most stable thoraco-abdominal aorta bypass device in dogs for periods of up to one year, showed evidence of some in vivo damage to the PU microfibres, loss in mechanical properties, and increased microphase separation.[40,41] The carbonate groups that were identified as part of the PU structure of the Vascugraft® prosthesis were found to be susceptible to hydrolysis catalyzed by either collagenase or pancreatin under experimental conditions.[42] This hydrolysis reaction resulted in increased surface hydrophilicity, moisture content and fiber swelling. While these enzymes were responsible for some molecular chain scission, the presence of a buffer was found to increase the molecular weight, enhance the phase separation of the material, and contribute to an improved orientation of the ordered phase along the axial direction of the fibers.

After disappointing clinical results, the manufacturer of this device decided to stop marketing the Vascugraft®. Polyurethane devices that are still commercially available are restricted to AV accesses or as vessel patches.

8.2.4 Leads for Pacemaker

The first pacemaker was implanted in 1959 by an intravenous catheter.[43] This technology has rapidly evolved producing devices that may treat almost all rhythm disturbances. It essentially consists of a power source, electronic circuitry, leads and electrodes.[44] The lead system transports a stimulus to the heart through which the cardiac electrical activity is sensed by the pulse generator.[45] The conductive wire used in the lead system has evolved from a braided spiral to a single monofilar coil to multifilar coils.[46] The 35Co-35Ni-20Cr-10Mo alloy (MP35N) wire has been mostly used as conductive wire since 1977.[47] The role of the insulating material in the lead system is to protect the biologic tissue from the electrical activity.[48]

On their introduction, leads were thought to have an indefinite longevity since no consumable element exists. Lead failures became more evident with the use of lithium batteries as a power source, which have a greater longevity.[44,45] It became apparent that leads can fail through deterioration or loss of insulation,[49-53] conductor fracture,[52] or electrode failure.[53] Leads are insulated mostly with silicone rubber,[54] but other materials have been employed in lead insulation with polyethylene, Teflon®, and a variety of PU formulations.[45]

Polyurethane leads were first implanted in 1978.[55] The first human cardiac PU lead implant used the Pellethane™ 2363-80A insulation. By 1980, more than five models of cardiac leads were released for general medical use by Medtronic.[56]

The majority of permanent PU leads were insulated with Pellethane™ 2363 resins and every company has developed insulating polymers of proprietary composition. When extruded or molded, polyurethanes crystallize; this results in a separation of hard (isocyanate) and soft (polyether) segments that depends on the ratio of hard to soft segment and other factors (see Chapter 1).[56,57]

Polyurethane leads were found to possess properties far superior to silicone rubber, such as tensile strength, hydrolytic stability and fatigue life.[58] It is also well known that polyurethanes have a much better friction coefficient[48,51,59] than silicone, particularly when in contact with blood. Thus PU leads were expected to be easily inserted into smaller veins.[48,59] Segmented copolyether-urethanes were found to be almost as thromboresistant as silicone rubber,[60] and other publications reported that they were less thrombogenic. They were considered to be excellent candidates for use in circular cross-section, blood-contacting implantable devices.[61]

Unfortunately, some failures related to excessive stress during the construction are observed for some specific devices.[56] Polyurethane leads were found to be more sensitive to manipulation than other leads and the removal process alone may actually damage it.[51,62-66] Pirzada et al

suggested that the failure rate was probably underestimated because after insulation failures electrodes would not necessarily be sent back. They may be left in the patient because the removal is extremely difficult and may be associated with complications.[67]

Three mechanisms may be responsible for the in vivo chronic PU lead insulation failure: environmental stress cracking (ESC), metal ion oxidation (MIO), which are well covered in Chapter 5 of this book, and crush injury.

Crush injury can occur during the subclavian introducer technique when the lead is clamped between the clavicle and the first rib.[51,68-70] This possible explanation for insulation failure is not generally accepted. Antonelli et al had found that percutaneous subclavian vein puncture has a negative influence on the performance of PU insulate leads.[57] But most studies performed did not demonstrate a statistically significant difference in time to failure between leads implanted with the subclavian introducer technique and those implanted by the cephalic route. It has been suggested that MIO or ESC were the most likely explanations for the insulation failures.[71-74]

8.2.5 Closure for Atrial Septal Defects

Surgical closure of atrial septal defects has been a safe operation with less than 1% mortality and very low morbidity for the last 4 decades. However cardiopulmonary bypass is not a simple procedure because it requires sternotomy or thoracotomy. The hospital stay is not negligible and the recovery at home takes time. Under these circumstances the development of minimally invasive devices and techniques was undertaken to close small to moderately sized atrial septal defects by catheter.

More than 20 years after the dare-devil era of the two-pieces button in 1954,[75] King and Mills developed a double-umbrella device with a center locking mechanism.[76,77] Rashkind invented a single disk PU prosthesis with six radially arranged struts, three of which supported right-angle barbs.[78] Clinical trials in 19 patients were unfavorable in six cases. This concept was abandoned and Lock et al introduced the Lock-USCI Clam shell made of two facing polyester fabrics squares, each supported by four radially arranged linged arms.[79]

In order to prevent leaks and migration, this concept was revisited with introduction of the Nitinol, a shape memory alloy and manufactured under the trade name of CardioSEAL®. Sideris et al reported closing atrial defects with this buttoned device, which consists of a left atrial disc (occluder) and a right atrial bar (counter occluder).[80] The occluder is a square piece of PU foam whose characteristics are not fully documented.

In the meantime, Babic et al developed the Atrial Septal Defect Occlusion System (ASDOS), which consists of two self-opening umbrellas made of a Nitinol wire frame and a thin membrane of polyurethane (Fig. 8.9). Each umbrella has five arms, which guarantee a round shape in the open position. When joined together, the umbrellas assume a discoid shape in profile and a flower shape in the frontal view.[81] Clinical results were satisfactory[82,83] and the PU plain membrane was fully endothelialized after 3 months of implantation in a pig.[84] In addition to the clinical follow-ups that are now well-documented, it would be of paramount importance to gain further knowledge of the fate of the device itself. Experiments in animals and analysis of explanted devices harvested at reoperation or at autopsy are mandatory.

It would be important to fully assess the ASDOS concept in comparison with other emerging concepts such as the Amplatzer®, a basket-type weave of Nitinol wire that expands to form two facing disks with a waist in between.[85]

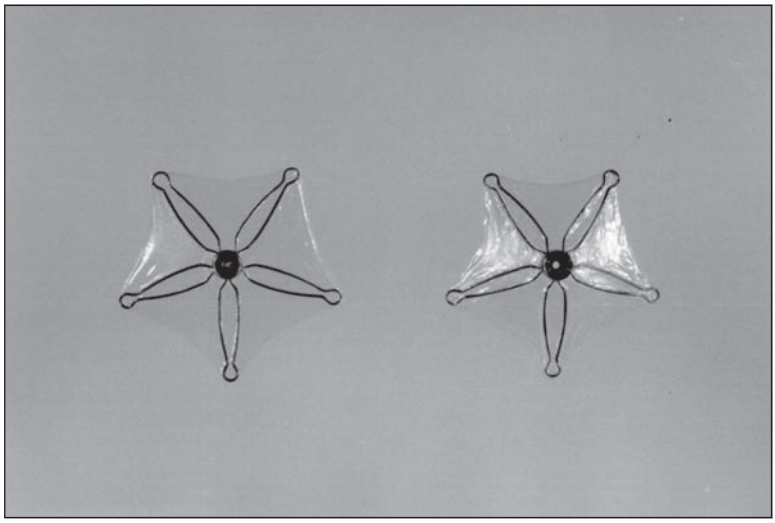

Fig. 8.9. Atrial Septal Defect Occlusion System (ASDOS) for closure of atrial systal defects. It consists of two self-opening umbrellas made of Nitinol wire frame with a thin membrane of polyurethane.

8.2.6 Ventricles for Ventricular Assist Devices and Totally Implantable Artificial Heart

The development of cardiac assist devices and totally implantable artificial hearts has been hampered by the lack of satisfactory polymers able to act as blood-contact surfaces and mechanical functions. As no foreign surfaces can be considered similar to the natural endothelial lining, scientists moved to different concepts, namely, the formation of a pseudointima and the expectation of minimal cellular and/or protein interactions at the surface of the material.[86]

Nowadays, smooth PU surfaces are used in various cardiac assist and replacement devices (Fig. 8.10). The use of this blood contacting surface stems from the desire for there to be no blood coagulation taking place at the interface. However, the selection of the most appropriate polyurethane for long-term application is one of the greatest challenges. Biomer™ has been extensively used for the ventricles in a number of VADs and artificial hearts. Despite insufficient blood compatibility this polymer presents excellent flexure and wear properties. Other polyurethanes have been used, including Avcothane™-51, Elasthane® and Pellethane™ but very few comparisons are available.

In the development of new generations of totally implantable artificial hearts and left ventricular assist devices for long-term use, the selection of an acceptable material to fabricate the ventricles represents a highly challenging problem. First of all, the material must be an elastomer so it can be flexed back and forth during the pumping cycle. Second, the material must not elicit mechanical fatigue over the designated lifetime of the device. Third, the material's surface must have an acceptable low propensity for thrombus formation and the best possible blood compatibility. Fourth, the material must be resistant to calcification. Fifth it must be capable of being easily processed into the complex shape required by the pump design. Sixth, the material must be impervious to water and water vapor to prevent moisture from entering the motor.[86]

In past years, segmented polyether-urethanes were the materials of choice for the fabrication of the artificial ventricles in various artificial hearts and VADs due to their superior flexural

Fig. 8.10. Ventricle of ventricular assist device made of polyurethane: despite weaknesses in blood compatibility, it presents excellent flexure and wear properties.

performance, good blood compatibility, and ease of processing. Since Boretos and Pierce reported the first application of a segmented polyether-urethane in a ventricular assist pump in 1967,[87] such polyether-urethanes have been widely used in various artificial hearts and other circulatory support devices.[88-92] Unfortunately, polyether-urethanes have been found to degrade due to ESC.[93] Such traditional polyether-urethanes, such as Biomer™ and Pellethane™, have therefore been either discontinued or are no longer available for biomedical applications due to their lack of long-term performance and the liability associated with their implantation.[94] In addition, these polyether-urethanes appear to be relatively permeable to water and water vapor. For example, McGee et al found that Biomer™ and Tecoflex® membranes with a thickness of 0.063 cm had water transmission rates of 0.020 and 0.022 g/cm^2, respectively, over a 24-hour period.[95] McMillin also observed water transmission rate of 1022 mg·mm(thickness)/s·m^2 for Biomer™ membrane (0.0366 cm thick) and 375 mg·mm(thickness)/s·m^2 for an equivalent Pellethane™ membrane.[96] These findings support the fact that the moisture passes through a ventricular wall made from polyether-urethane and contaminates the motor housing of devices during long-term use. This in turn adversely affects the reliability of such devices and eventually leads to their failure.[95] As a result, traditional polyether-urethanes could not meet the rigorous requirements of the new generation of totally implantable artificial hearts and VADs. Therefore, it was necessary to identify and select more biostable and impermeable materials for use in fabricating the new generation of ventricles.

The trade names Corethane®, ChronoFlex®, and Carbothane® belong to a new type of commercial polyurethanes. These polymers contain a conjugated carbonate linkage (O-CO-O) in the soft segment that is believed to be more stable than ether linkage (C-O-C) when exposed to biological environments.[97] Pinchuk found that Corethane® films are more biostable than Pellethane™ 2363-80A when evaluated by the Stokes 400% strain test.[98] Reed et al also reported that ChronoFlex® films are stronger than Biomer™ films when exposed to the same Strokes strain test.[99] These studies suggest that polycarbonate-urethanes have significant biostability advantages over polyether-urethanes. However, as discussed in Chapter 6, polycarbonate-urethanes do not possess sufficient resistance to biodegradation required for long term applications.

The use of polycarbonate-urethanes to fabricate ventricles has significant advantages over the use of polyether-urethanes. More recently, other polyurethanes have been developed as potential candidates. Biolon®, a polyether-urethane-urea manufactured by 3M Health Care, is the choice of the Pennsylvania State University Group. The Baylor Heart abandoned polyether-urethane as their pump material for a much stronger polyurethane, a polycarbonate,[100] while the Japanese program has also opted for a segmented polycarbonate, Miractran E980.[101] However, none of today's commercial polycarbonate-urethanes are totally impervious to water vapor transmission. Thus, the severity of the problem of fluid entering those regions of the device where hermetic conditions are mandatory has been reduced but not eliminated. Therefore, additional treatments to these membranes are still required to achieve a completely nonpermeable ventricle for use in a totally implantable artificial heart or VAD.

8.3. Polyurethane for Reconstructive Surgery

8.3.1 Wound Dressings

Wound dressings were introduced to absorb the exudate, a fluid mixture, produced by wounds. Its biochemical and physical composition will vary throughout the healing sequence. Exudate, which may be composed of blood, serous fluids, and highly viscous proteinaceous liquids, is primordial to the wound healing because of its cellular-and-enzymatic-material containing characteristics. Wounds, which may be caused surgically or accidentally, are disruptive in the anatomy or physiology of tissue.[102] They may be acute wounds (cuts, abrasions, incisions, and lacerations), chronic wounds (abrasions, dermal ulcers, and donor sites) or burns (first-degree, second-degree, third-degree burns).[103] The nature of the wound will impact the exudate production and the healing speed. In addition, Winter showed that healing was accelerated when the wound was kept under moist conditions.[104] Dressings should support the healing process while minimizing side effects such as scar formation, infection, and pain.

Polyurethane is often used in wound dressings because of its good barrier properties and oxygen permeability. Dressing shapes and structures are numerous. Commonly PU wound dressings may be semipermeable adhesive films, perforated film absorbent dressings, hydrocolloids, alginate dressings and foams. It can be the only component of the device but it is often used in a multi-component dressing such as hydrocolloid dressings. PU dressings may contain different medicinal agents such as pharmacological active agents, antibacterial agents (chlorohexidine (Opsite® CH) and iodine (Tegaderm® Plus)),[105] topical anesthetics, bacteriostatic agents and antifungal agents. Leg-ulcer dressings may also be impregnated with glycerin, zinc, dermis, or collagen as help-healing agents.[106] Other dressings, principally hydrocolloid dressings, contain both absorbent and gel forming agents. Granuflex® and Bordered Granuflex® contain a dispersion of gelatin, pectin and carboxy-methylcellulose with other polymers. When the wound is malodorous, dressings containing activated carbon such as Lyofoam C® may be used.

The healing process is characterized by an event sequence involving infiltration of cells in which actions and interactions will result in the closure of the wound. Dermal repair can be divided into three overlapping phases (hemostasis and infiltration, proliferation, matrix formation and remodeling).[107-110] By maintaining the moist environment, the dressing fights eschar formation and helps to decrease the re-epithelialization time. Dessication resulting from air exposure creates a deeper zone of necrosis which retards epithelial cell migration and prolongs wound healing.[110] It has been demonstrated that healing of cutaneous injury is improved under moist conditions rather than under dry conditions.[104,111,112] It has been shown that Opsite®, a PU-based wound dressing, used on full thickness inuries, accelerated the inflammatory and

proliferation phases of dermal reapir. The dressing also enhanced contraction, revascularization, and earlier remodeling of the wound. DeConinck et al,[113] using Tegaderm® dressing, reported healing-time reduction and re-epithelialization acceleration in full-thickness wounds. Other mechanisms provided by occlusive dressings may enhance wound healing.[114] Hypoxic wound environment may enhance healing by stimulating fibroblast proliferation and angiogenesis; the local blood-supply O_2 perfusion is sufficient for wound healing.[115] However, ischemic wounds need O_2-permeable dressings.[116] It has been shown that the exudate from occluded wounds contains proteinase, by which lysis action toward hemostasis-step fibrin plug, produces chemotactic factors for macrophage migration and activity.[117]

Fast and favorable re-epithelialization of the wound is the main issue of using wound dressings but effects of the dressing on the host body must also be considered. Many papers report only the action of the dressings.[118-122] In fact, a lack of information has been noted concerning the chemical composition of the polyurethane itself. Since it is well established that the chemical composition of PU materials is of prime importance in determining their biological response and stability, this should be carefully controlled. Moreover, as the exudate is an "aggressive" environment (containing enzymes, macrophages and other potentially harmful chemicals) that can alter the integrity of polymers, the stability of polyurethane should also be examined. These aspects seem to have been neglected in the studies of wound dressings made of polyurethanes. Because the wound is sensitive to its environment, the toxicity and carcinogenic potential of PU degradation products (and plastics' additives) have to be assessed.

8.3.2 Breast Implants

Ivalon, the original Pangman implant introduced in the late 1950s, was made of solid PU foam.[123] Neither the composition nor the chemical characterization of these PU foams were disclosed.[124] These implants often became rock hard and calcified giving unsatisfactory results.[123-125] In 1970, Ashley introduced the Natural-Y breast implant. This device consisted of a silicone-gel implant with an internal Y-shaped septum, to prevent gel migration in response to gravity. They were covered by a thin layer of PU foam (1 mm in thickness) to fix the implant to the chest wall and avoid any further displacement.[126] It was anticipated that in this way ptosis would also be prevented. The implant remained soft for more than a year and a half in 60 patients,[126] but only became popular after Capozzi and Pennisi reported only one case of firmness in 104 breast reconstructions with the PU-covered implants.[127] A new generation of PU-covered implant was promoted: the Même breast implants[128-130] were also made of a silicone bag-gel covered by polyurethane (Microthane) foam (Fig. 8.11).[131] The foam is fixed on a silicone shell with an adhesive to keep the foam intact.

Polyurethane-covered breast implants were popularized as a means of preventing capsular contracture, the most frequent complication with the use of breast implants. They were then recommended for routine use in reconstructive as well as cosmetic augmentation surgery because of the low rate of capsular contracture observed.[126-128,131-133] This high popularity of the PU-covered breast implant was not without controversy. Several complications, both clinical and physico-chemical, were observed when these implants were used. The complications were serious enough to prompt the manufacturer to remove these implants from the market in April 1991.

After the insertion of a breast implant, the foreign material is present in such great quantity that it cannot be removed by phagocytosis because it is anchored by connective tissue which forms around the implant and is called the fibrous capsule.[134] This capsule, a thin membrane that develops at the periphery of the inflammatory zone and grows inward toward the implant,[135] is made of collagen fibers which grow parallel to the surface of the prosthesis. Interspersed within the fibers are various types of cells such as fibroblasts and macrophages,

Fig. 8.11. Même breast implant: the silicone gel prosthesis is covered with polyurethane foam. This foam is fixed on the silicone shell with an adhesive.

which are the most common inflammatory cells found in the capsule.[134] Contracture refers to changes in the shape and softness of the implant and its fibrous capsule. It is essentially the result of remodeling and contraction of the collagen fibers.[135]

Eyssen et al proposed that the interference by the PU polymers with the crosslinking of collagen fibers prevent that tissue from developing its full myofibril contractile force.[136] It was believed that the lack of capsular contracture was due to microencapsulation of particles of PU foam following peripheral degradation and phagocytosis of PU fragments as collagen fibers grew into the foam coating of the implant. The microencapsulation was felt to dissipate the myofibroblast contractile forces.[137,138] Support for this suggestion was derived from histological slides of excised capsules, which showed giant cells surrounding fragments of foreign material within the area of tissue infiltration. This fragmentation and dissolution of the PU foam has been noted to be accompanied by an accumulation of a brown pigment which had a positive reaction for hemosiderin[137] and was felt to be a degradation product of polyurethane.[139]

Several types of complications were observed with PU-coated breast implants. Special surgical care was needed to implant or explant PU breast prostheses. The PU coating produces a high friction coefficient against the patient's breast tissue, so it is practically impossible to "slide" the implant in its place, in contrast to what may be done with the smooth surface implant.[128,140,141] Of greater concern is the difficulty of removing these implants because of tissue ingrowth within the polyurethane covering the implant.[123,142,143] Berrino et al had demonstrated that the removal of the fragments of polyurethane can lead to the sacrifice of large amounts of muscular, subcutaneous or glandular tissue, and that small fragments of polyurethane could be left behind.[142]

Two other clinical complications are breast pain and the presence of hematoma following PU breast implantation. Unesthetic wrinkling of the breast skin was also found to be more common in PU-covered breast implants than in the smooth surface implants.[132,144,145] The skin wrinkles are usually found in the upper quadrant of the breast and is due to the absence of spherical capsular contracture with these implants. The implant does not fill out the upper quadrant because of gel gravity.[132] Rupture of PU breast implant was also reported in the

literature. It was reported that the silicone envelope of the PU-covered breast implant had very low tear strength to ensure softness of the breast.[136]

Infection occurring in PU breast implants was reported by several authors.[130,133,146-151] If infection ensues Hester et al suggested removing all contaminated implants. They said that surgeons must resist the temptation of using antibiotic irrigation to cure the infection.[130] Others have mentioned having unsuccessful treatment using antibiotics and had to remove the implants to cure the infection.[142,147-151]

Another clinical complication is the allergic reaction to the PU implants characterized by an itching rash on the breast approximately 2 to 4 weeks after surgery. The rash and its symptoms disappeared after medical treatment.[136,152,153]

The most important concern with PU breast implants is probably the complications related to physico-chemical degradation of the implant, and more precisely the PU coating.[154-156] Physico-chemical alteration of the polyurethane breast implant seems to take place very early in the implantation process. The disappearance of the polyurethane foam was not accepted by all the scientific community. Szycher and Siciliano had a dissenting point of view about the degradation of the polyurethane foam. They suggested that the polyurethane foam did not disappear but that it is embedded in the fibrous capsule and that it was possible to recover large amounts of polyurethane after enzymatic digestion.[157] This finding is inconsistent with that of Sinclair et al who did not recover intact pieces of polyurethane foam larger than 3 x 3 cm.[158]

One can suggest that the mechanism of PU foam degradation is multifactorial. It would involve several processes such as mechanical stress forces produced during fibrous capsule formation [155,158-162] and enzymatic,[162] oxidative, and hydrolytic processes from surrounding inflammatory cells during the foreign-body reaction.[158-163] It is not only important to know that the body is able to degrade the PU foam, but the most important question that must be answered is what chemical products are going to be released during this biodegradation.

The polyurethane foam which is used to cover the breast implants is a toluene diisocyanate-based polyester-urethane.[124,129] This polyester-urethane is made from 80% 2,4 and 20% 2,6 toluene diisocyanate (TDI).[137,155,164,165] Toluene diamine (TDA) is released from normal hydrolysis of TDI which is known to be sensitive to water and active hydrogen-containing compounds.[124,165] During the late 1960s it was found that TDA is a hepatocarcinogen when fed to rats.[166] TDA was then considered to be inappropriate material for food and cosmetic applications (mainly as hair dyes), and is no longer used for these purposes.[124]

Several authors have shown that the polyurethane foam used in breast implants released TDA.[124,167,168] Luu et al found that the polyurethane foam produces 2,4 and 2,6 TDA continuously in the phosphate buffer extract at 37°C, and at 50°C hydrolysis increased at a rate of 2.5.[168] Residual amounts of TDA were found in the PU foams attached to virgin Même breast implants.[124] Guidoin et al also demonstrated that TDA was produced by alkaline hydrolysis at physiological temperature.[124] Others have found that under physiological conditions the Même implant could release some polyol and 2,4-dimethyl-6-t-butylphenol to the surrounding tissues and that sodium hydroxide, even at the lowest concentrations used, caused the PU foam to decompose and release TDA.[167] At this point several authors raise the question whether the TDA was a residual or a breakdown products of PU foams.[167,168] TDA, whether residual or newly formed from PU foam, will migrate in the patients at a slow but constant rate as long as any PU foam exists.[168]

TDA was not only found in virgin prostheses or in vitro experiments, but it was also found in patients with PU breast implants. Hester et al collected urine and serum samples from 61 patients with polyurethane breast implants. No detectable levels of TDA were found in the serum of these patients, but 2,4-TDA was found in the urine of 48 patients.[164] Chan et al detected TDA in the urine of a patient with PU breast implants as early as 21 days following implantation, while no TDA was found in the urine sample before implantation. They found

that the concentration of 2,4-TDA was always greater than 2,6-TDA. They suggested that the detection of free TDA in the urine provides evidence that 2,4-TDA is a circulating substance in patients with PU-covered breast implants.[169] Sepai et al found degradation products in the urine and plasma of patients up to 2 years following implantation which, according to them, is an indication of the continued degradation of the polyurethane layer. These authors found that the levels detected range from 0.4 to 4 ng/ml in the plasma after implantation.[170]

8.3.3 Maxillofacial Prostheses

Maxillofacial prostheses are used for patients with disfigured or missing facial or body features such as nasal, ear, front, orbital, mandible and cranial vault defects. A good maxillofacial prosthesis must meet some basic requirements: it must have a natural appearance, have a secure and comfortable retention, have a reasonable durability and be compatible with human tissue.[171,172] Several materials have been used to make maxillofacial prostheses. These include silicones, polyvinyls, polymethylmethacrylates, polyethylene and polyurethanes.[173,174] Other materials have also been used.

Most of these materials did not fulfil the basic requirements of a good maxillofacial prosthesis. For example silicones have poor tensile and tear strength. They also have poor adhesion to medical tapes, limited colorability, and they appear cold and lifeless. Vinyl types offer good physical properties, colorability, and appearance; but the major deficiency is the necessity of high-temperature casting. Another drawback is the loss of physical properties with time due to the migration of plasticizers from the host material.[175] When compared to polyvinyls and silicones, PU elastomers best fulfil the requirements of the ideal material for facial prostheses.[172]

The type of polyurethane usually used in maxillofacial surgery is Epithane-3, formally marketed as Dermathane by MIP Industries.[175,176] This material allows prostheses to be lifelike in appearance[176] and the phenomenon of yellowing after exposure to ultraviolet wavelength aging seems to be improved.[175] But since 1978, some studies have centered on an aliphatic polyurethane prepolymer, isophorone. This type of polyurethane shows higher magnitudes in tensile and tear strengths when compared with the commercially available polyurethane, Epithane-3.[174,176]

Polyurethanes have several advantages compared to other materials used. In general, the tear energy necessary for breaking PU elastomers is higher than the other commercially available maxillofacial materials.[177] Furthermore, polyurethanes do not injure the tissues, are hypoallergenic and have a longer longevity (9-18 months) when properly cured and handled. Thus PU elastomers can be used with success in the fabrication of facial prostheses if the casting procedure is done accurately and carefully.[172]

Physical and mechanical behavior of polyurethanes can be altered by variations in the basic composition of the material and by the addition of catalysts.[178-180] Properties of composition with low quantities of isocyanate and no catalyst reached or approximated those parameters proposed as ideal goals to simulate living tissue. When preparing polyurethane materials, proper mixing is essential to avoid entrapment of air and phase separation of the catalyst.[178,179] Also the importance of avoiding contamination by moisture cannot be understated. The presence of moisture during the reaction can completely eliminate the reactivity of the isocyanate groups to the urethane prepolymers.[181] These conditions, which may render the prostheses less durable, are often masked by the addition of colorants in the preparation of a sample for clinical application.[178] However, the effect of plastics' additives on the biological response must be thourougly examined.

One of the most appreciated applications of polyurethane in maxillofacial surgery is when performing cranial vault repair. Several authors were thrilled with the use of polyurethane in this area. The technique consists in combining an alloplastic net with an autogenous bone.[182-184]

One of these prostheses, OsteoMesh, is made of a Dacron® cloth mesh stiffened with polyether-urethane. Bone graft material is placed in the defect, and the Dacron®-urethane implant imposes form on the bone graft material.[185] The repair is ultimately strong and provides good protection for the underlying brain. Furthermore, the combination graft eventually fuses to the surrounding skull thus providing rigid fixation and ultimately good brain protection. Lastly, the operation provides excellent esthetic results.[182-185]

The most serious problems associated with maxillofacial prostheses are: prosthesis discoloration in a service environment, degradation of static and dynamic physical properties of the elastomers, difficulty in repairing the prosthesis and short service lifetime.[186,187] A study evaluated the degradation of different elastomers for facial prostheses exposed to environmental factors. Samples were exposed to ultraviolet radiation (UV), simulated sebum, ozone, chlorine, and nitrogen dioxide, and tested for tear propagation and resistance. The environmental factors affected the polyurethane Epithane-3 the most and the silicones the least.[186] Haug et al have also shown that Epithane-3 was the most affected maxillofacial elastomer by environmental variables such as natural weathering and normal aging.[188]

Another problem with polyurethane is surface coloration which has a tendency to peel off if oily contaminants get on the surface when colors are added or if the patient is not careful when washing the prosthesis.[189]

The assumption of UV stability of aliphatic polyurethanes is questionable (see Chapter 5). The optical properties of maxillofacial prosthetic materials were evaluated after the materials were subjected to the following environmental variables: natural weathering, normal aging, two types of adhesives, two types of cleaning agents and cosmetics. Optical density and color changes were evaluated and all PU elastomers showed changes to these two parameters.[190] It was also found that two types of aliphatic polyurethanes melted completely in less than 2-4 days of UV exposure.[175] Others were unable to complete their study because of the severe degradation of polyurethane after 300 to 600 hours of aging in a UV environment.[186,187,189,192]

Polyurethanes degrade rapidly upon exposure to the UV wavelength range of sunlight. It thus became evident that UV stabilizers must be added to polyurethane to make the materials suitable for maxillofacial prosthetic use. Chu and Fischer tested different UV stabilizers in different PU systems and found that some UV stabilizers do prolong the service life of PU maxillofacial prostheses (see Chapter 3), but they are not completely satisfactory.[175,192] Even though a certain UV stabilizer is successful with a specific polyurethane, it will not warrant its success in other polyurethanes. This complexity makes the task of studying UV stability much more complicated.[175] They concluded that a combination of a UV stabilizer and an antioxidant is the most satisfactory method of increasing the resistance of the materials to UV degradation.[192] Again, the use of plastics' additives must be fully justified.

8.4. Gynecology and Obstetrics

Major applications of polyurethanes in gynecology and obstetrics are directly related to contraception: either as barrier to spermatozoïd migration and/or as spermicide.

8.4.1 Condoms

Condoms represent the oldest form of contraception used by males and the best approach against sexually transmitted diseases. For decades, only natural tissues were available. Thanks to Goodyear and Hancock, who developed the rubber vulcanization process; latex condoms were found to be both reliable and inexpensive. The polyurethane male condoms made of Duron were introduced by Durex in 1994 in the North-American market under the tradename of Avanti®.[193] This material, which seems to be an aromatic polyether-urethane after FT-IR/

ATR spectrum analysis (unpublished data from our group) was found to be stronger than latex and allowed a more sensitive feeling. However, the most positive aspect of this polymer consists in its nonallergic properties.[194] The Avanti® represents an alternative to latex sensitive users. Such PU membranes present the same efficiency as latex in terms of imperviousness to spermatozoïd and viral particles.[195] On top of that those condoms are less sensitive to lubricants and have longer shelf life. Users found them very friendly.[196,197]

The female PU condom was introduced in United States by the Female Health Company in 1993 under the trade name of Reality™.[198] It is also known as the intravaginal pouch. It can be described as a disposable prelubricated loose-fitting PU sheath containing two flexible PU rings.[199,200] The first is located at the closed end of the sheath and anchors the device in place in the vagina. The second ring is at the open end, remaining outside the vagina and covering the labia. FT-IR/ATR spectra show that it is made of an aromatic polyether-urethane (unpublished data from our group). It has many advantages in term of efficiency and resistance. Unfortunately it is not user friendly because it is found to be unappealing and difficult to insert.[201] Erratic results were reported and this device must be considered more as a protection against STDs than a contraceptive.[200-202]

8.4.2 Contraceptive Sponge

These devices made of PU sponge possess a dual action: as a barrier to stop semen and as chemical spermicide agent. They must be inserted only once for limited durations. The probability of toxic shock syndrome (TSS) is very low due to the bacteriostatic properties of nonoxynol-9 used as spermicide. Polyurethane sponge was selected because of its compliance with vaginal tissue.

The Today® sponge was introduced in 1983[203] by Whitchall Laboratories which voluntarily terminated the production in 1995. FT-IR/ATR spectra show that the sponge is made of an aliphatic polyether (unpublished data from our group). The device, impregnated with nonoxynol-9 was shaped like a small doughnut. It was available as the one size fits all sponge capable of releasing about 20% of the spermicide over the first 24 hours after insertion. This device ought to be left in place at least 6 hours after intercourse and provides pregnancy protection within the first 24 hours of insertion.

The second concept of contraceptive sponge, the Protectaid®, was proposed by Axcan Ltd. in 1996 and is still available. That sponge, shaped like a thick disc is impregnated with gel F-5 (a mixture of nonoxynol-9, sodium chlorate and benzalkonium chloride with polydimethylsiloxane as a dispersion agent).[204] Indications and performances do not differ dramatically from the Today® sponge.

8.5 Conclusion

Polyurethanes contribute very significantly to the manufacturing of medical devices. The review of applications and developments hereby proposed for polyurethanes, by no means an exhaustive study, does illustrate well the importance of this family of polymers. Besides the well-accepted application of polyurethane made of plain membranes, there are also future opportunities for development. With their relatively good biological response, performance and ease of manufacture, polyurethanes can be considered the polymer of choice in cardiac surgery for intra-aortic balloon catheters and ventricles. Their use as blood conduits is questionable because of the lack of long-term stability. New developments are likely to come from bioerodible polyurethanes to be used as scaffolds for wound dressings and tissue ingrowth (for example in nerve guidance channels). It is becoming evident that chemists involved in PU synthesis for biomedical applications will have to work more closely with clinicians to tailor the

PU best adapted for specific applications. Polyurethanes are a very broad family of polymers and there are great variations between them. Without them, the armamentarium of medical supplies would not be as complete as it is. Some applications such as breast implants and vascular grafts were or are being abandoned because of unsatisfactory results. However, other applications provide the medical community with indispensable tools such as intra-aortic balloons, ventricular, and pacemaker leads. Future developments are likely to come from tissue engineering with composite and biodegradable polyurethanes (if degradation rate of polyurethane can be pace with accuracy). It is clear that the use of polyurethanes as external scaffold for tissue engineering is still at the developmental stage.

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Chapter 9

The Future of Polyurethanes

Robert Guidoin and Hans J. Griesser

Where would implantology and the biomedical devices industry be today if it were not for synthetic polymeric biomaterials such as polyurethanes? While "natural" biopolymers such as reconstituted collagen have made essential contributions to the viability of some biomedical devices, synthetic polymers have become indispensable and have enabled the fabrication of a wide range of devices that have sustained life or improved the quality of life for millions of patients, as well as facilitated surgical and diagnostic procedures for many years. Synthetic biomaterials have thus made an extremely important contribution to modern health care. Their application is much wider than physicians, patients and the public at large may appreciate, and the need for polymeric biomaterials as components of biomedical devices is certain to increase and broaden in an aging population. Polyurethanes, by virtue of their range of properties, are certain to continue to play an important role among polymeric biomaterials. However, the future of polyurethanes is inextricably linked to various technical and non-technical issues that affect and define the biomaterials scene in general.

Despite the undeniable success of polymeric biomaterials in some applications, the requirements of other applications are currently not fully met with existing biomaterials. Consequently there is a need for further systematic research into biocompatibility and biological host responses to design synthetic polymeric biomaterials, accompanied by the development of novel biomaterials, novel coatings, and devices that are designed based on new knowledge and engineered to meet those challenging requirements. Multidisciplinary teams that can establish effective feedback loops for the rational development of improved biomaterials will no doubt produce materials and engineered devices that will meet the more demanding requirements of long-term device applications in particular.

However, whereas there is a healthy, high-quality body of research being performed at many universities, government research institutions, and a number of industrial laboratories, adoption of the fruits of those research efforts has in recent times been hampered particularly in the United States by disincentives brought about by a legal system that appears to be less interested in noting the undoubted benefits that current, though perhaps imperfect, biomaterials and biomedical devices have brought to so many people. This is accompanied by the high profile of dubious experts and questionable statistics whose scientific unreliability many judges and jurors may find difficult to fathom.[1] Regardless of how reliable or unreliable the scientific evidence against particular devices may be, liability issues over recent years led major companies to withdraw materials and products from supply to manufacturers of implantable biomedical devices. While the withdrawal of a number of large companies from the biomaterials and biomedical devices industries may open up opportunities for emerging smaller players, it remains open to question whether those smaller players will have the technical and financial

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abilities, and the long-term outlook and plans, to implement similar standards of manufacturing quality and product quality controls that larger companies have the resources to apply. Vigilance is needed to ensure that state-of-the-art biomaterials and production methods are applied in the manufacture of biomedical devices, although this may substantially raise the entry price for new suppliers.

Recent efforts to curb excesses in biomaterials-related litigation in the United States[2] may go some way towards mitigating the "biomaterials deficit" and lead to renewed growth in the literally vital biomedical devices industry. The Act[2] is intended to ensure that device manufacturers will have access to the materials and component parts they need to fabricate biomedical devices by providing liability protections to biomaterials suppliers. Such suppliers are granted a broad federal law defense against liability for harm to a claimant caused by an implant, subject only to three narrowly crafted exceptions.[3] Thus, it is intended that biomaterials suppliers should be assured that they will no longer become the focus of any litigation simply because they have "deep pockets". This hopefully will encourage the return of biomaterials suppliers to the biomedical devices market and help ensure that the millions of people who need to rely on implantable devices will have continued access to the technologies needed to save or improve their lives. We expect that this will, inter alia, lead to increased R&D efforts on biomedical polyurethanes.

The usefulness of particular biomaterials cannot be assessed per se, independent of the devices, implants, or other medical supplies that the material forms part of. Criteria for end-use viability comprise much more than simply an appropriate biomaterial; design of the device, mechanical aspects, variability in patient response, and other factors, can all have marked effects. Materials must fulfil specific requirements to establish their effectiveness in relation to a specific device. Biomedical devices can be classified into four categories : those that serve to sustain life or organ viability, to restore or improve functions, to restore or to improve contour, and to contribute to health care delivery.

There is a shortage of precise performance specifications for biomaterials, and this restricts rational, designed clinical advances. Implantology is particularly at risk. Many implants must meet performance criteria for many years and in some cases several decades; artificial blood vessels and joint replacements (hips, knees) are examples. The scope for clinical advances are therefore restricted not only by the issue of the time it takes to assess device performance, but also by a number of criteria:

- Minimization of risk in long-term developments favors selection of existing materials with previous clinical history.
- Developments of new materials and/or improvements of existing materials (both bulk and surface properties) are difficult and costly to document clinically.
- Regulatory authorities are mandated to behave conservatively. This leads to selection of avenues that are likely to be acceptable to regulatory bodies and restriction of some possible experimental approaches, which may reduce the scope for serendipitous discoveries.
- The potential for product liability litigation may limit enthusiasm for progressive approaches of clinicians, engineers and manufacturers in developing new products.

However, the need for increasing numbers and types of biomedical devices will be a feature of societies whose population continues to age. Western societies have provided high standards of health care delivery, but this is costly. More services should be dispensed at lower costs. The last three years particularly have been characterized by budget constraints in many leading economies, and the consequences in the health care systems comprise shorter durations of hospitalization, increasing use of same-day surgery approaches, increases in the number of nursing homes, increasing pressure on re-use of biomedical devices where safe and effective, and pressure for environmentally friendly supplies. The unexpected rise of endovascular devices

was a comforting sign for the future of biomaterials. This new era of implantology was not research driven, but driven by the requirements of MDs.

One can anticipate tremendous developments in the near future of biomaterials that offer improvements in biocompatibility, biofunctionality and biodurability. Based upon their history and their potential, the contribution of polyurethanes is assured. As pointed out by Szycher,[4] medical applications of polyurethane elastomers contribute significantly to the quality and effectiveness of the world's health care systems. Polyurethanes are widely and successfully used in a variety of prostheses, implants and medical supplies, particularly where compliance with soft or cardiovascular tissue is required. In the following, we speculate about the future of this family of polymers in the main applications.

9.1. Cardiovascular Applications

Polyurethanes are considered the materials of choice for blood compatibility. However, while promising results have been achieved with intra-aortic balloons and ventricles for VADs and artificial hearts, scientifically unwarranted extrapolations and unrealistic anticipations have characterized studies towards some other applications. It is time to rethink the concept of a universally biocompatible material. As discussed elsewhere in this book, these are shortcomings of PUs for long term cardiovascular applications; it is in reality the mechanical properties of PUs rather than exceptional blood compatibility that makes this class of materials of great interest for applications such as vascular grafts.

9.1.1 Vascular Grafts for Permanent Implantation

Vascular prostheses made from PUs appeared highly attractive because they could be tailored with a wide range of properties such as wall porosity, compliance, and mechanical characteristics. Initial blood contact was satisfactory. A range of structures was achievable: microporous (communicating or not), interlacing fibrils, plain, without or with polyester support, etc. Handling was superb and many investigators proposed to select PUs for aorto-coronary bypass grafts. However, experimental investigations in animals gave results that were not so encouraging. The thrombosis rates of small diameter grafts were generally poor unless the animals were medicated. The performance of medium diameter arteries was at best equivalent to that of ePTFE grafts: while patency rates did not surpass those of ePTFE grafts, PU grafts degraded quite rapidly after implantation. Under these circumstances, the future of PU-based blood conduits looks unpromising unless recently developed polyurethanes with better biostability can also achieve good patency rates (as a result of probably an additional surface coating step). Caution is, however, mandatory since much blood compatibility research utilizes tests such as whole blood clotting time assays whose predictive power for longer-term implant performance may be very limited indeed. Clearly, to ensure viability of small diameter vascular grafts over many years, considerable breakthroughs in concepts and performance are required, and it is doubtful whether the incremental improvements reported by many researchers in fibrinogen and platelet adsorption, or whole blood clotting times, warrant the substantial investments in clinical efforts needed to assess long-term performance. Given the need for sustained performance over many years, in this application clearly there is a requirement for very marked improvements in performance over existing materials.

9.1.2 Angio-Access

This is a critical application; needle punctures are devastating for the integrity of the vascular wall. PU grafts offer the interesting feature that they can be constructed such that if

they are punctured early after implantation, they do not bleed and the patients recover well. No other polymer has been able to match the performance of the Limino-Brescia fistulae. However, improvements are still desirable.

9.1.3 Pacemaker Lead Insulation

Polyurethanes, along with polyethylene and silicone rubber, are used extensively as insulation for pacemaker leads. Polyurethanes are very attractive because of their relatively good blood compatibility, low coefficient of friction, outstanding flex endurance, and good mechanical strength. However, controversy has arisen about the biostability of polyurethane pacemaker insulation materials, following detection of defects including fissuring and stress-cracking. As discussed in Chapter 5, the reasons are still insufficiently established at the molecular and biochemical levels (although oxidative attack clearly is a key issue), and the development of polyurethanes with well-documented long-term stability is continuing. At present, polyurethanes and silicone rubber are still competing for this application.

9.1.4 Cardiac Valves

The use of cardiac valves made of polyurethanes is restricted to VAD devices and artificial hearts serving as a bridge to transplantation. Those PU valves are unlikely to be suited for long-term implantation because of their propensity to tearing and calcification. For short-term usage, however, they are well suited as they are not expensive and perform satisfactorily from a hemodynamic point of view. At the present state of development, their usage should be restricted to ex vivo devices; implantation would appear to be inappropriate.

9.1.5 Intra-Aortic Balloons

Experience has accumulated over the last 25 years regarding the satisfaction of cardiac surgeons. Currently available intra-aortic balloons are sufficiently blood compatible, flexible, compliant with the host tissues, and have a sufficient durability in case of clinical need for revision within a few weeks. Little improvement is anticipated in this area because a pressing need does not exist: failures are rare. They appear to result from manufacturing defects or friction against a calcified plaque. The market appears to be dominated by one company that appears to satisfy the medical community. We do not anticipate new developments nor the ability of new polymers to compete in this mature niche.

9.1.6 Ventricles for VADs and Total Artificial Hearts

Polyurethanes represent the only family of elastomers that are acceptable for these applications as a result of their flex and endurance capabilities together with their relatively good blood compatibility. As long as these devices are restricted for ex vivo usage and for limited duration, several PU elastomer formulations appear acceptable. However, in implantable devices, the questions of long term durability and water vapor percolation through the membranes must be addressed. Biomer™ is no longer available and Pellethane™ has limitations. It is therefore mandatory to search for innovative polymers that offer biological stability over several years and maintain performance. Some novel polyurethanes presented in Chapter 6 might meet some of the requirements; this needs to be further investigated.

It may not be necessary to formulate a PU to meet all requirements at once; the requirement of imperviousness to water vapour may be addressed with subsequent surface treatments or coatings.

Research in this area is mandatory because the artificial heart potentially offers a solution to the increasingly severe problem of insufficient numbers of hearts from donors. We believe that polyurethane elastomers offer exceptional promise for developments in this field—although progress still hinges on the availability of improved materials—and it is important to support research in this area.

9.1.7 Devices for Interauricular Septal Defects

Although there is a limited size of the market, the non-operative treatment of interauricular septal defect is a challenge. Polyurethane based devices with nitinol reinforcement appear very attractive, but they must compete with polyester umbrellas and nitinol clam-shells. Clinical results to date have not shown a clearcut superiority of any one of these, and further evaluations are necessary.

Nonporous PU has interesting features in term of softness, biological response and durability; and at present it appears to be preferable to porous PU. However, insufficient information is available about the comparison of healing characteristics of the two types.

No major PU development is anticipated to be driven by this area, despite the elegance of the device, because of the low market volume and the presence of competing concepts. There may, however, be scope for application of a novel PU developed for another application.

9.2. Reconstructive Surgery

In reconstructive surgery, polyurethanes are very attractive as transient devices for wound dressings but the PUs tested to date appear to be inadequately stable for permanent implantation. Newer PU materials with improved biostability may offer advantages that remain to be clinically verified.

9.2.1 Wound Dressings

The field of wound dressings is large and diverse. Wounds are caused surgically or accidentally, as in burns and trauma. They can be the result of dermal ulcers or abrasions. They vary in severity from minor scratches to complicated trauma. Wounds are classified in many ways, with or without tissue loss. The physiology of wound healing is now relatively well understood. Wound dressings must achieve:

1. maintenance of a moist wound environment,
2. thermal insulation,
3. compliance of the material, and
4. absorption of the exudate.

The relative importance of these criteria varies strongly with the wound and the clinical indications.

Under these circumstances, it is understandable that a plethora of wound dressings is being developed for specific applications. Polyurethanes are, as a result of their mechanical properties and their versatility, particularly suited where they need to conform to various designs and structures, including porous and laminated dressings.

The performance of wound dressings can be hampered by inappropriate selection of a specific polyurethane. Preference should be given to aliphatic polyurethanes, that is, those using the aliphatic compound HMDI instead of the aromatic MDI in the PU formulation. Some degradation can occur of polyurethanes in the strongly active wound healing environment, with its various enzymes that effect remodelling, and care should be taken that potential products of degradation do not produce any risk of toxicity and/or carcinogenicity.

The future of wound dressings is outstanding and polyurethanes are part of this development. However, we expect that fewer technical concepts for wound dressings will survive in the not too distant future.

9.2.2 Breast Implants

Breast implants for reconstructive or cosmetic surgery are very popular despite the recent controversies and litigations. Failure of silicone gel implants due to silicone migration, encapsulation, calcification and mechanical destruction is well documented, and it appears that the need for better materials is evident even without the additional adverse publicity about silicones allegedly giving rise to asymptomatic long-term tissue responses. The addition of polyurethane foam over the silicone rubber shell appears to reduce capsule formation, but has been stated to lead to TDA release into the patient's urine and milk. Usage is therefore at present limited to silicone rubber prostheses filled with a saline solution.

Despite pioneering work by Szycher to develop a medical textile based on a novel 40-filament fiber melt extruded from a polyurethane elastomer claimed to be "biostable" for breast implant application, the future of polyurethanes in breast implant manufacture must be viewed as being quite uncertain. The situation is severely clouded by the highly public litigations involving silicone breast implants over recent years and the extremely emotional nature of usage of these devices. It is not clear yet what effect, if any, new legislation[2] will have on the development of new breast implant designs that may, at least in experimental stages, incorporate polyurethanes. Clearly, the need for these devices remains but we find it difficult to anticipate developments, and the prospect of large-scale litigations must be a serious deterrent to any future breast implant manufacturer.

9.3. Gynecology and Obstetrics

9.3.1 Condoms

Male condoms made of polyurethane are recommended as an alternative to the cheaper latex based condoms for those who are allergic to latex. However, cost considerations suggest that it is not probable that the market will expand much, despite the advantageous elastomeric features of the PU condoms. The market share of PU-based condoms is small and it is rather doubtful whether the cost of development of novel PU materials for this application would be recouped. More likely is that a PU material developed for another application might find a spinoff home in this market segment.

Female condoms have not gained wide market acceptance as they are not user friendly and do not represent a breakthrough advantage among the mechanical devices for contraception. This, together with cost, probably precludes any further development to which PUs might contribute.

9.3.2 Contraceptive Sponges

This technique of contraception is limited and contraceptive sponges have a restricted availability. Currently available devices comprise a polyurethane foam that is impregnated with spermicides. This foam is usually degradable and has the capacity to liberate TDA, a potent carcinogenic chemical. Owing to the limited time of use, this risk may be limited.

As the market for this type of contraception is shrinking, we do not anticipate a substantial application opportunity for novel PU biomaterials in this area. There appears no rationale to invest in research towards sponges with novel PUs.

9.4. Organ Regeneration in Tissue Engineering

Research in tissue engineering is experiencing an explosive growth as this field is seen as a promising new avenue for the manufacture of replacement organs with improved performance and reduced tendency for rejection, or the repair of injured organs. Polyurethanes are of promise as scaffold materials. Designed biodegradation may be advantageous for controlled regeneration of organs, while biostable PUs may, as a result of their elastomeric properties that can be tailored over a wide range, offer much promise as permanent structural support materials if improved bio-integration (reduced or no foreign body responses such as capsule formation) can be engineered.

9.4.1 Biodegradable Vascular Grafts

The needs are immense for small diameter blood conduits. One approach may be to provide a biodegradable scaffold that promotes the regrowth of natural blood vessels while slowly disappearing. Scaffolds of a composite of polyurethane and polylactic acid base were manufactured and evaluated as biodegradable structures for the development of neovascular structures. Despite initial enthusiasm, animal experimentation did not confirm that it was possible to generate a new artery in this way, and human medical application of these types of grafts has not been considered worth the serious risks involved.

More elegant approaches comprise organogenesis with collagen. Surgeons are increasingly intent on harvesting autologous conduits while homologous veins and arteries are still being investigated. An interesting area for research is xenografting and gene therapy for vascular devices.

The need clearly exists, but there is no proven concept of tissue engineering for vascular application yet. While the cell seeding concept seems to have failed to deliver the expected benefits, the usage of growth promoting factors has brought new in vitro avenues of research that may advance to the stage of clinical trials in the foreseeable future. The possible role of polyurethanes in this field is difficult to predict but the high versatility of this class of materials must make them serious contenders.

9.4.2 Nerve Regeneration

Nerve regeneration via a small conduit is an exciting yet very challenging concept. The ability to entice guided nerve cell regeneration and re-establish nerve communication is not primarily a materials science problem; while a carrier material must fulfill certain functions, success of an implant is much more dependent on close control of biological responses that will most likely have to be engineered with biological signals. This application must be further explored and exciting animal results progressed to evaluation with human nerve regeneration.

9.5. Medical Supplies

9.5.1 Blood Filters

Filters are classified as screen filters and depth filters. The screen filters consist of a mesh that meets the blood flow once and retains blood components larger than the size of the pores. A depth filter presents a structure where the blood meets synthetic surfaces several times. Nylon and/or polypropylene screens are used in the first concept. Polyester wool or polyurethane foam are employed for application in the second concept.

All filters incorporating polyurethane foams have proved to be unsatisfactory for banked blood filtration, dialysis, and extracorporeal circulation filtration. Banked blood filters were rapidly clogged with aggregates while the extracorporal filters cause hemolysis.

As efficient and low cost materials are available for blood filtration, preference is currently given to nylon, polypropylene, and polyester. PUs with markedly improved performance over current PUs would have to be developed for this class of materials to be considered in this application. We note that while polyurethanes have been considered to be relatively blood compatible by many researchers working on vascular grafts, pacemaker insulation, VADs, and artificial hearts, the unsatisfactory performance of this class of biomaterials when used as blood filters raises questions as to what the blood compatibility of PUs really is, and to what extent the blood compatibility is determined by factors additional to the material's properties. Factors such as hemodynamic flow patterns are known to affect thrombus formation in vascular grafts, but the unsatisfactory performance of PUs as blood filters still requires some elucidation, which would seem a prerequisite for the rational design and development of improved polyurethanes for this application.

9.5.2 Catheters

Polyurethane based catheters are of great interest for their mechanical properties and undoubtedly there will be significant developments in this area. Cost considerations suggest high-end usage.

9.5.3 Blood Bags

Blood bags made of PVC have incorporated large amounts of DEHP additive, which is the subject of a long-standing but still unresolved controversy. Blood bags made of PU appear an attractive proposition but again cost is an issue.

9.6. Summary

In conclusion, polyurethanes offer a unique contribution to health care delivery. They comprise a broad family of polymers. On the one hand, this is a great advantage as it is possible to fabricate polyurethanes with diverse properties. On the other hand, it entails the possibility that unwarranted generalizations are made about this family of polymers. For instance, the response of blood to PU surfaces may vary substantially between different PUs. Therefore one must be careful to select the appropriate PU for a particular application.

Clearly, for many applications it will be necessary to develop new custom-designed polyurethanes instead of relying on available commercial types. A number of past successes have been achieved with synthetic materials "borrowed" from other applications, with their initial trials in biomedical applications often supported by little or no rationale except an empirical approach towards evaluating whatever materials happen to be available. Nowadays, however, the development of improved PUs requires a team approach. Guided by well-defined, clear biomedical needs, and improved understanding of biomedical interactions, polymers can be selected and synthesized if necessary, and processed to make prototype medical devices. It is also necessary to achieve better correlations between implantology results and polymer properties. Thus, polyurethanes will be customized and optimized for specific applications, and their performance advantages and limitations understood. The versatility of this class of materials holds the promise that novel, specifically developed polyurethanes will play a key role in many future biomedical devices.

9.7 References

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ABBREVIATIONS

–: decrease
ρ: density
≤: increase
AA: arterio-arterial
AAMI: Association for the Advancement of Medical Instrumentation
AB: acryloylbenzothiazole
AFM: atomic force microscopy
Ag: silver
$AgNO_3$: Nitric Acid
AO: antioxidant
Ar: argon
ASDOS: atrial septal defect occlusion system
ATIII: antithrombin III
Au: gold
AV: arterio-veinous
BA-L: monofunctional fluorinated alcohol
BD: 1,4 butanediol
BS: BioSpan-S®
CB: chain breaking
CB-A: chain breaking acceptor
CB-D: chain breaking donor
CD_{18}: polymorphonuclear cells
CE: cholesterol esterase
CEN: European Committee for Standardization
CHDM: cyclohexanedimethanol
CHDA: cyclo hexane diamine
Co: cobalt
Conc: concentration
Cu: copper
D: diameter
Da: Dalton
DEHP: di(-2-ethylhexyl)phthalate
DIPAM: diisopropylaminoethyl methacrylate
DM: decyl methacrylate
DMAA: dimethylacrylamide
DMAc: N,N-dimethylacetamide
DMF: dimethylformamide
DMSO: dimethylsulfoxide
DMTA: dynamic mechanical thermal analysis
DPA-EMA: poly(2-diisopropyl aminoethyl methacrylate)
DSC: differential scanning calorimetry
E-beam: electron-beam
ED: ethylene diamine
EDTA: ethylene diamine tetraacetic acid
EHMA: 2-ethylhexyl methacrylate
ELISA: enzyme linked immunosorbent/immuno-sorption assay
EO: ethylene oxide

ESC: environmental stress cracking
ESCA: electronic spectroscopy for chemical analysis
ESR: electron spin resonance
FBGC(s): foreign body giant cells
FDA: U.S. Food and Drug Administration
Fe: iron
FE-SEM: field emission scanning electron microscopy
Fg: fibrinogen
FTIR/ATR: Fourier transform infrared spectroscopy in the attenuated total reflectance mode
FT-IR: Fourier Transform infrared spectroscopy
GPC: gel permeation chromatography
H_{12}MDI: 4,4'-methylene biscyclohexane diisocyanate
H_2O: water
H_2O_2: hydrogen peroxide
HALS: hindered amines
HD: hexanediol
HDI: 1,6-hexanediisocyanate or hexamethylene diisocyanate
HEMA: hydroxyethyl methacrylate
HMDI: 4,4'-methylene biscyclohexane diisocyanate or hydrogenated 4,4'-diphenylmethane diisocyanate
HMEC: polyhexamethylenecarbonate
HNO_3: nitric acid
HPBD: hydrogenated polybutadiene
HPIP: hydrogenated polyisoprene
HPLC: high-performance liquid chromatography
HPU: (HEMA)-terminated polyurethane
IAB: intra-aortic balloon pump
IARC: International Agency for Research on Cancer
IgG: immunoglobulin
IL: interleukin
IOLs: intraocular lenses
IPN: interpenetrating polymer network
KDa: kilo-Dalton
L: length
LVAD: left ventricular assist device
MALDI: matrix-assisted laser desorption/ionisation
MCP: 2-methacryloyloxyethyl phosphorylcholine
MD: metal desactivator
MDA: 4,4'-methylene bisphenyl diamine
MDEA: N-methyldiethanolamine
MDI: 4,4'-methylene bisphenyl diisocyanate or 4,4'-methylenediphenyl diisocyanate
MIO: metal ion oxidation
Mn: number average molecular weight
MP35N: 35Co-35Ni-20Cr-10Mo alloy
MS: mass spectrometry
MS-MS: tandem mass spectrometry
MW: molecular weight
Mw: weight average molecular weight
NaCl: sodium chloride
NEXAFS: near edge x-ray absorption fine structure

O_2: atmospheric oxygen
PBD: polybutadiene
PBS: phosphate buffer solution
PC: phosphorylcholine
PCL: polycaprolactone
PCN: polycarbonate
PD: peroxide decomposer
PD: propylene diamine
PDGF: platelet derived growth factor
PDI: phenylene diisocyanate
PDMO: poly(decamethylene oxide)
PDMS: poly(dimethyl siloxane)
PEG: polyethylene glycol
PEO: polyethylene oxide
PEO-SO_3: propylsulphate-polyethylene oxide
PET: poly(ethylene terephthalate)
PEU: polyether-urethane
PEUU: polyuether-urethane-urea
PHMO: poly(hexamethylene oxide)
PIP: polyisoprene
PMNs: polymorphonuclear leukocytes
PMSF: phenylethylsulfonyl fluoride
POEOP: polyoxyethylene-oxypropylene polyol
POMO: poly(octamethylene oxide)
PPG: poly(propylene glycol)
PPO: poly(propylene oxide)
PRP: platelet rich plasma
Pt: platinum
PTAd: poly(tetramethylene adipate) glycol
PTFE: polytetrafluoroethylene
PTMO: poly(tetramethylene oxide)
PU(s): polyurethane(s)
PVC: poly(vinyl chloride)
PVP: Poly(vinyl pyrrolidone)
Q: quencher
Ref: references
RIM: reaction injection molding
RIPA: relative index platelet adhesion
RRIM: reinforced reaction injection molding
SAL: sterility assurance level
SAMs: self-assembled monolayers
SAXS: small angle X-ray scattering
SDS: sodium dodecyl sulfate
SEC: size exclusion chromatography
SEM: scanning electron microscopy
SFA: surface force apparatus
Si: silicon
SIMS: secondary ion mass spectrometry
SMA: surface modifying additives
SME: surface-modifying end groups

SMM: surface-modifying macromolecules
SRIM: structural reaction injection molding
SS: Stainless Steel
SSIMS: static secondary ion mass spectrometry
TCPS: tissue culture polystyrene
TDA: toluene diamine
TDI: 2,4-toluene diisocyanate or 2,6-toluene diisocyanate
Temp: temperature
Tg: glass transition temperature
THF: tetrahydrofuran
Tm: melting temperature
UTS: ultimate tear strength
UV: ultraviolet radiation
VAD(s): ventricular assist device(s)
VPHP: vapor-phase hydrogen peroxide
WAXD: wide angle X-ray scattering
XPS: X-ray photoelectron spectroscopy

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