Surface Modifying Additives for Biomedical Polymers

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Many synthetic polymers have characteristics which make them useful as biomedical materials (Table 1). One reason for this is the wide range of properties available from man-made polymers. The chemistry of the repeat unit, the shape of the molecular backbone, and the existence and concentration of intermolecular bonds among the millions of molecules that make up the polymer sample all influence ultimate properties [1]. Additional property variations are possible in polymers with more than one kind of repeating unit [1, 2]. Copolymers, terpolymers, and even multipolymers are possible in which the properties of more than one polymer type are combined to produce a unique material. The arrangement of the different repeat units in copolymers allows further property variations. The overall concentration of each monomer is also a major determinant of the properties of copolymers, but unless one monomer is used in great excess over the other, the resulting properties can be quite different from either homopolymer.

In graft and block copolymers, particularly when graft or block length is high, some of the properties of the two homopolymers are retained. For instance, a hard, high-melting block can be copolymerized with a soft rubbery block. With the proper arrangement of the blocks, the resulting copolymer can be a thermostatic elastomer. At room temperature, the liquid-like soft blocks are strengthened and reinforced by the hard blocks or segments. At elevated temperatures, the hard blocks soften and flow to permit thermoplastic processing. Upon cooling, the original structure reforms. The thermostatic polyurethanes, an important class of biomaterials, have this block, or segmented, structure. Many interesting polymers can be made by combining one hard block with two or three different soft blocks. These polymers are block terpolymers or block multipolymers. They can have interesting permeability properties [3] and biocompatibility [5], both of which can be tailored over a wide range by varying block chemistry and concentration.

In addition to the structural factors mentioned, the shape of a polymer's molecular weight distribution (Fig. 2) and its average molecular weight can have a significant effect on polymer properties. If we were to fractionate a typical polymer sample according to chain length, we might find that the low molecular weight homologues were waxes or even liquids, while the high molecular weight fractions were tough and viscous, even at elevated temperatures. The macroscopic properties we measure and assign to polymers are really the weighted averages of the properties of the various polymer fractions that are present in the sample.

![Figure 1. Some possible structures for AB copolymers.](image1)

![Figure 2. Typical polymer molecular weight distribution.](image2)

**CURRENT BIOMEDICAL POLYMERS**

Virtually all of the polymeric biomaterials in clinical use today are industrial polymers that were adopted for use in medical applications. As evidence accumulates that a new material is reasonably safe, it may be used in other medical devices. Eventually, its use is accepted by government regulators and the medical community and it becomes known as a biomaterial. Silastic® silicone rubber from Dow Corning (Midland, MI) is a good example of this evolution. The silicones were originally developed for high-temperature electrical coil insulation. Following the success of the silicone rubber hydrocephalus shunt, other medical applications were found, and medical grade Silastics® were introduced.

The Jarvik VII artificial heart is constructed from Lycra® spandex elastomer (sold by Ethicon, Inc. Somerville, NJ under the name of Biomer® segmented polyurethane). Lycra® was developed to replace natural rubber thread in textiles. It is widely used in pantyhose, underwear, and stretch fabrics.

Although the life-threatening consequences of inadequate biocompatibility in an artificial heart are well appreciated, lack of biocompatibility is seldom implicated when complications occur with simple acute devices such as vascular catheters. In fact, all blood and tissue contacting devices could probably benefit from improved biomaterials. Clotting, inflammatory...

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**TABLE 1**

Properties That Make Polymers Useful as Biomaterials

<table>
<thead>
<tr>
<th>Property</th>
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<tbody>
<tr>
<td>Low Fabrication Cost</td>
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<tr>
<td>Low Materials Cost</td>
</tr>
<tr>
<td>Wide Range of Mechanical Properties Available</td>
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<tr>
<td>Relative Biocompatibility</td>
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<tr>
<td>Wide Range of Transport Properties Available</td>
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<tr>
<td>Optical Transparency</td>
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<tr>
<td>High Strength-to-Weight Ratio</td>
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<tr>
<td>Good Flex Life</td>
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<tr>
<td>Good Abrasion Resistance</td>
</tr>
<tr>
<td>Versatile Component Assembly</td>
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<tr>
<td>Ease of Compounding</td>
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<tr>
<td>Good Aesthetics</td>
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response, and infection in even the simplest devices can result in sudden death or irreversible damage to the patient. We must, however, acknowledge that economic constraints always exist, and that new biomaterials should not add complexity to the production process or significantly increase raw materials cost. Furthermore, the cost of organizing and maintaining a fully-staffed biomaterials development and manufacturing group is very high. For the materials manufacturer who sees a relatively small market (and big potential liability) in biomedical uses of his product, it may not make sense to offer his polymer as a biomaterial. As a result, few really new biomedical polymers are ever commercialized.

DEVELOPMENT

There is good experimental evidence that the blood-materials interactions that occur at a smooth surface are only affected by the constitution of the outer few molecular monolayers of the polymer [4]. This means that as long as the polymer does not contain any leachable impurities, the chemistry of the bulk polymer, which is distant from the biological interface, does not affect in vivo performance. For this reason, investigators concentrate on the surface region.

We can define at least two levels of understanding in applied biomaterials science (Fig. 3). On one level, we try to understand the relationship between the measured surface chemistry and the in vivo response of the material. This task is difficult because of the limitations of existing surface analytical instruments. A higher level of understanding is necessary before we can develop functional relationships between in vivo response and the chemistry of the bulk polymeric material. If we can understand how easily made changes in bulk composition can change the surface chemistry of a polymer, we can use this knowledge to control in vivo response.

1. In Vivo Response = f(Surface Chemistry)
2. In Vivo Response = f(Bulk Chemistry)
   a. Level 1
   b. Surface Chemistry = f(Bulk Chemistry)

Figure 3. Levels of understanding in biomaterials science.

The study of polymer surface chemistry is complicated by the fact that many commercially available polymers contain additives or impurities that are surface-active (Table 2). A surface-active agent, or surfactant, is capable of migrating to an interface and populating that interface at a concentration that is much higher than its average concentration in the bulk phase. Extremely surface-active materials can have nearly 100 percent concentration in a surface, even if their initial bulk or average concentration in the polymer is in the parts per million range. This is analogous to the effect a detergent has on the surface tension and surface chemistry of water.

<p>| TABLE 2 |</p>
<table>
<thead>
<tr>
<th>Surface-Active Contaminants That May Be Present in Polymers</th>
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</thead>
<tbody>
<tr>
<td>Polymerization Surfactants</td>
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<tr>
<td>Catalysts</td>
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<tr>
<td>Solvents</td>
</tr>
<tr>
<td>Stabilizers</td>
</tr>
<tr>
<td>Plasticizers</td>
</tr>
<tr>
<td>Internal Lubricants</td>
</tr>
<tr>
<td>Anti-Blocking Additives</td>
</tr>
<tr>
<td>Degradation Products</td>
</tr>
<tr>
<td>Processing Equipment Lubricants</td>
</tr>
<tr>
<td>Silicones</td>
</tr>
</tbody>
</table>

Trying to interpret the surface analysis of a polymer contaminated with an unknown substance is very difficult. In the absence of sensitive surface analysis, a sample's biological response may be wrongly assigned to the base polymer when it is, in fact, largely due to a contaminant. Processing or thermal history variations can lead to variability in in vivo performance if differences in the amounts of additive or impurity in the surface are produced.

This subject may seem to be one of minor importance in the development of new biomedical polymers, but it is so common that it often makes a major determinant of biological response. The news is not all bad, however. It is possible to design surface-active molecules and intentionally add them to a base polymer for the purpose of improving biocompatibility.

POLYMER SURFACES

Certain block and graft copolymers can add additional complexity to the relationship between surface chemistry and bulk chemistry. Solids and liquids try to minimize interfacial energy [4]. This is the same driving force that causes low energy surface-active impurities to migrate to the air-facing surface of a polymer. Since air is a low-energy fluid, the interface between air and the polymer will have the lowest energy when the polymer surface also has a low energy. Migration of the surfactant to the polymer surface succeeds in lowering polymer surface energy and, therefore, overall interfacial energy. This effect is thought to minimize the activation of blood constituents for coagulation, cell adhesion, and other adverse biological processes.

In many block and graft copolymers, another mechanism for interfacial energy minimization exists. By reorientation of the surface molecular layers, one of the blocks or grafts can preferentially populate the surface. For instance, when brought to equilibrium in air, a block copolymer of the type shown in Fig. 4 will have a surface that is mostly comprised of the so-called soft block or low surface energy block. It is even possible that none of the more polar, hard segment will be present in the polymer surface. A polymer put into the blood stream is exposed to the more polar, aqueous environment of the blood. The polymer may then attempt to reorient its polar blocks toward the surface in order to minimize the energy of the blood-polymer interface.

Figure 4. Surface segregation of one block in a copolymer.

Thus, the design and manufacture of new biomedical polymers must take into account the possible migration of surface-active species and the reorientation of the surface layer that may occur in different environments. For many polymers, it is helpful to imagine a dynamic, liquid-like surface (albeit of very high viscosity) instead of a rigid, unchanging surface that is fixed forever at the time it is fabricated.

SURFACE MODIFYING ADDITIVES

With the complexities discussed, how can we develop new biomedical polymers in a systematic way? All biomedical polymer applications have requirements that can be divided into bulk property and surface property categories. An elastomer for an artificial heart, for instance, must have good...
bulk mechanical properties such as flex life, toughness, flexibility, and processability. This same polymer must also have a surface which does not cause blood to clot or the adjacent tissue to become inflamed.

In many classes of polymers, the relationship between the molecular variables and the bulk properties is fairly well understood. A systematic, if somewhat empirical, process may be used to achieve the desired bulk properties. In the case of surface properties, their relationship to the variables that can be manipulated by the materials scientist is less well known, and is clouded by the influence of the over-present impurities. However, even if a precise functional relationship were known between surface properties and first-order molecular variables, another problem would still exist: the chances are remote that an optimum in both surface and bulk properties could be found at a single molecular structure and molecular weight.

This basic dilemma of biomaterials development has often led device manufacturers to use surface treatments or coatings applied after the device or component is fabricated (Fig. 5). The method we have employed involves a simple

A. Bulk Properties = f (Molecular Structure / Molecular Weight)

B. Surface Properties = f (Molecular Structure / Molecular Weight)

Optimum A ≠ Optimum B

Solution: Coating
Grafting
Surface Treatment
Lamination
Controlled Release
BLENDING
* Surface Modifying Additives

Figure 5. Surface Modifying Additives (SMA) can provide an effective solution to the dilemma of biomaterials development: The simultaneous optimization of surface and bulk properties.

The blending step before fabrication of the surface. This approach takes advantage of two mechanisms by which condensed phases of matter minimize their interfacial energy: the migration of species from the bulk to the surface and the reorientation of surface molecules (Fig. 6).

The process begins with the synthesis of novel copolymers and terpolymers that we call surface-modifying additives or SMAs [5-10]. A small amount of SMA is blended with the base polymer before device fabrication. During and after fabrication, the SMA migrates to the surface in high concentration. This dramatically changes the outermost molecular monolayers, which comprise the region we believe determines biocompatibility. The SMAs are relatively high molecular weight copolymers that are at least partially compatible with the base polymer. Both factors help the SMA to remain permanently anchored to the base polymer. As with many surfactants, so little of the SMA is required to achieve the desired change in surface chemistry that the original bulk properties are preserved.

Effective surface modifying additives are amphipathic in structure (Fig. 7). That is, they have both polar and nonpolar blocks which may be connected by short hard blocks, allowing them to reorient as their environment changes. We believe that the SMA's surface activity and polar/nonpolar structure are responsible for their ability to improve thromboresistance. Plasma proteins are present at high concentrations in the blood and readily adsorb onto polymer surfaces. The conformational changes in plasma proteins that occur upon adsorption have been implicated in surface-induced thrombosis. Thus, SMAs may improve thromboresistance by minimizing the interfacial energy between the blood and the polymer surface. The reduced energy gradient between the polymer surface and the protein's natural environment in the blood may reduce the tendency for the adsorbing proteins to change conformation and trigger events leading to thrombus formation.

SMAs can improve thromboresistance of many different base polymers in a reproducible and cost-effective way. In addition, the use of surface modifying additives greatly simplifies the development of new biomedical polymers (Fig. 8). Because the SMA determines surface properties independent of the base polymer, the development effort can be divided into two separate parts. In one part, the base polymer is chosen or synthesized to satisfy the bulk property requirements. In another part, the SMA is developed to maximize biocompatibility. To complete the biomedical polymer development, the SMA and the base polymer are literally combined to obtain a material that can satisfy both surface and bulk requirements. Often, the same SMA can be used in several different base polymers, giving each of them the same level of biocompatibility.

The use of SMAs in the production of real biomedical devices is very simple. Before the device is made, the base

![Figure 6. Surface Modifying Additives are uniformly distributed throughout the base polymer prior to surface formation. Once the surface is formed the environment it is exposed to determines the orientation of the SMA which has concentrated there. A simplified SMA structure is used for clarity: O = polar, I = nonpolar block.](image)

![Figure 7. Molecular structure of one class of Surface Modifying Additives. This SMA is a 'solid surfactant'. It has the polar/nonpolar or amphipathic structure of an aqueous liquid surfactant, but is actually a film-forming solid, due to the presence of the short hard segments and overall SMA molecular weight. CED = Cohesive Energy Density.](image)

![Figure 8. The use of Surface Modifying Additives (SMA) can simplify the process of developing new biomedical polymers by separating the tasks of optimizing surface and bulk properties.](image)
polymer is blended with SMA and (re)formed into pellets. Alternatively, a base polymer dissolved in a solvent can have SMA added to it. After addition of the SMA, the base polymer is then processed (e.g., molded, extruded, or cast) in the usual way to make the device. The surface modification generally develops spontaneously, but surface migration may also be accelerated by storage at elevated temperature. Since no post-fabrication coatings or surface treatments are required, rejects from these operations are eliminated and incremental expense is minimized. The process is reproducible and can easily be monitored with simple contact angle measurements or other methods of surface analysis.

CONCLUSIONS

We hope to see the widespread use of surface modifying additives in a variety of blood and tissue contacting devices. Our first clinical application of SMA’s is in the Pierce-Donachy Ventricular Assist Device (i.e., artificial heart), which has shown excellent thromboresistance [11]. The SMAs can be used in a variety of existing base polymers and thus represent a practical way to improve the biocompatibility of a variety of existing devices without the expense of developing entirely new materials.

Although we need controlled studies to prove it, we believe that an across-the-board improvement in the biocompatibility of biomedical devices and prostheses will lead to a reduction in patient morbidity which could significantly reduce the cost of health care.

REFERENCES


Robert S. Ward received the BS in chemical engineering from the Lowell Technological Institute, Lowell, Massachusetts in 1971, and studied engineering management at Northeastern University, Boston from 1975 to 1978. Until recently, he was president of Mercor, Inc., a wholly-owned subsidiary of Thoratec Laboratories. At Mercor, Mr. Ward supervised the development of a family of high flex-life polyurethaneureas, high moisture-vapor-permeable wound dressings and textile coatings, shape-memory thermoplastics, and a novel method of polymer surface modification which significantly reduces platelet uptake of blood contacting biomaterials.

Prior to joining Thoratec in 1979, Mr. Ward was Director of Research at Avco Medical Products, the first manufacturer of Intraventricular Balloon Pumps. While at Avco, Mr. Ward performed structure property/studies on Avothane-516 which led to his development of several new biomaterials.

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