Development of Blood-Compatible Elastomers. V. Surface Structure and Blood Compatibility of Avecothane Elastomers

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Summary

The Avecothane 51 elastomer, a member of a series of proprietary materials best characterized as polyurethane/poly(dialkylsiloxane) block copolymers, displays considerable hemocompatibility without any incorporated anticoagulants. In the form of intra-aortic balloons, the elastomer was implanted in several thousands of cardiac patients without intolerable hematologic effects. Hemocompatibility has been assumed to result from a predominantly dispersion-type surface force field whose intensity fluctuates within small domains, maintaining adsorbed blood proteins in an unstable state. The relative hemocompatibility of films, which were obtained from a prepolymer solution cast on substrates impenetrable to the solvent, is a function of the effective surface molecular structure. This can vary as a function of preparative conditions (temperature and rate of evaporation), and has been correlated with an anisotropic distribution of the silicone component in cured films. The concentration of this component in surface layers was quantified independently by IRATR spectroscopy and electron-microprobe analysis, giving consistent results. An IRATR index, which is computed from the ratio of absorptivities measured at 13.00 and 12.62 μ and is inversely proportional to the relative silicone content of surface layers, was found to correlate with the apparent hemocompatibility determined by different in vitro methods. Optimized reproducible hemocompatibility is attained by strict process controls.

INTRODUCTION

The development of various types of implantable and/or extracorporeal circulatory assist devices has been pursued at an accelerating rate over the past decade since these prostheses can provide therapeutic benefits to patients which would be otherwise unattain-
able. In one or another of their parts, all of these blood pumps require flexible blood contact surfaces provided by elastomers.

To be useful in actual short- or long-term implantations without inducing any intolerable hematologic effects under clinical conditions; i.e., in the ultimate performance test of any prosthetic material, candidate elastomers have to comply with a set of requirements which is one of the most stringent ever specified for materials. In addition to adequate bulk properties, such as tensile strength, elasticity, and fatigue resistance, the surface of elastomers which qualify for circulatory assist devices has to be not only passively but also "dynamically" hemocompatible \textit{in vivo}. This implies that the initial effective surface molecular architecture of candidate elastomers, viz., the surface-number density and spatial arrangement of various moieties directly in contact with blood, which are the physical determinants of hemocompatibility, must be resistant to possible enzymatic attacks and stress-induced rearrangements of polymeric chains. This prerequisite is well exemplified by the fact that, at 100 beats/min, i.e., the typical heart rate of a cardiac patient, the elastomer can be subjected to about $10^8$ stress/strain cycles in only 1 week of implantation.

A substantial number of hemocompatible materials has been suggested, encompassing a wide spectrum of rationales for surface structure and preparative methods. These include approaches that rely on the deposition of various types of coatings (viz., ionically or covalently attached anticoagulants, grafted synthetic gels, macromolecular substances of natural origin, etc.) to improve the hemocompatibility of materials which possess the desired mechanical properties but are not sufficiently compatible with blood. At present, however, there are only a few of these materials which proceeded past the developmental stage, and even fewer have reached the level of the ultimate performance test of being employed in circulatory assist devices used safely in patient care.

In reality, the routine clinical application of an elastomer in a circulatory assist device imposes a set of additional requirements, inasmuch as the molecular engineering techniques which were applied in developing the hemocompatible surface structure of that material have to be transposed to production scale with reasonable economy. First, the synthesis and purification of the elastomer should be reproducibly performable at levels substantially larger than bench-scale
preparations without deteriorating quality. Secondly, the processes involved in the fabrication of prosthetic devices should not alter the desired surface molecular architecture responsible for hemocompatibility, particularly in the critical areas of the blood-contact surface. Thirdly, each operation in the overall process should be subjectable to some relevant quality-control procedure with relative ease since, upon implantation, the material as well as the device made of it cannot cause any detrimental effects to the host.

WORKING HYPOTHESIS FOR THE DEVELOPMENT OF INHERENTLY NONTHROMBOGENIC ELASTOMERS

The nonthrombogenic nature of these elastomers is to be attained without the presence of any incorporated or surface-bound anticoagulant, or the introduction of any surface groups that would give rise to a negative charge in contact with blood or plasma. Thus, a working hypothesis defining the selection of components for these materials requires that the macromolecules employed in them should not only allow for a set of desirable bulk physical properties, but should also give rise to a specific surface molecular structure whose characteristics can be defined by considering the physicochemically distinguishable phases of the interaction which occurs between a polymeric surface and normal blood. Based on diffusion kinetics and the known volume-number densities and diffusion constants of plasma proteins and cellular blood components, it has been shown that the “primary population” which settles on and is in direct contact with any surface, can be expected to be composed of proteins rather than of the cellular components. This theoretical result is valid whether the diffusion kinetic considerations are applied to stationary or to the more complicated case of moving blood, and is also consistent with experimental observations. It is known from desorption kinetics that the mean residence time as well as the rate of removal of an adsorbate are related to a parameter describing the fluid mechanical conditions prevailing near the surface, and exponentially related to the normalized binding energy or the energy barrier an adsorbate has to pass to become disengaged from the surface. Thus, it follows from both the diffusion and desorption kinetic considerations that a polymeric blood-contact surface is likely to be “primed” by adsorbed plasma proteins; also, to be hemocompatible,
it has to interact with the same proteins as to minimize their binding energy, which is dependent on the surface molecular structure.

The major factors contributing to the adsorptive capacitance of an uncharged polymeric surface can be related, in principle, to a) the effective surface-number density of sites available for H-bonding and hydrophobic bonding, and b) the mean energies involved, respectively, in each type of these bonds. Thus, a possible way of attaining hemocompatibility of polymeric surfaces is to satisfy the requirement of minimizing the binding energy of plasma proteins which form the “primary population” of the surface. Since H-bonds generally involve energies substantially greater than that of hydrophobic bonds, the effective surface-number density of accessible H-bonding sites has to be minimized. By incorporating a variety of groups into the surface, which are capable to interact with plasma proteins via van der Waals-London type forces only, a force field can be established whose main component is of the dispersion type and whose intensity fluctuates as a function of locus. Under these conditions, it can be expected that plasma proteins placed into such a force field will be in an energetically unstable position. In the present work, the combination of poly(ether urethanes) with organosiloxanes to form block structures has been assumed to meet the requirement for bulk physical properties as well as that of a randomized dispersion force field.

DEVELOPMENT AND PROPERTIES OF AVCOTHANE ELASTOMERS

For potential use in various types of blood pumps, in 1967, a series of proprietary elastomers, which can be best characterized as polyurethane/poly(diethylsiloxane) block copolymers, were introduced and given the name Avcothane (registered trademark of Avco Corp.). Since the urethane/silicone ratio may be varied within relatively broad limits, and both poly(ester urethanes) and poly(ether urethanes) can be utilized, this versatility allows for elastomers which can have a range of desired physical and technological properties in addition to hemocompatibility. At present, the most “patient-tested” and hence the most developed member of the series is the Avcothane 51 elastomer, which is composed of a poly(ether urethane) (90%) and poly(dimethylsiloxane) (10%). Some of the
TABLE I

Typical Properties of Acothane Elastomers

<table>
<thead>
<tr>
<th>ASTM No.</th>
<th>ACOPTHANE 51</th>
<th>Q</th>
<th>PEU*</th>
</tr>
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<tbody>
<tr>
<td>Density (g/cm³)</td>
<td>D-1505</td>
<td>1.09</td>
<td>1.05</td>
</tr>
<tr>
<td>Tensile Strength (psi)</td>
<td>D-382</td>
<td>6200</td>
<td>4700</td>
</tr>
<tr>
<td>Ultimate Elongation (%)</td>
<td>D-382</td>
<td>980</td>
<td>1500</td>
</tr>
<tr>
<td>Indentation Hardness (Shore &quot;A&quot;)</td>
<td>D-2240</td>
<td>72</td>
<td>63</td>
</tr>
<tr>
<td>Gravés Tear Resistance (lb/in.)</td>
<td>D-1004</td>
<td>490</td>
<td>----</td>
</tr>
<tr>
<td>Dielectric Strength (volts/mil)</td>
<td>D-149</td>
<td>1500</td>
<td>----</td>
</tr>
<tr>
<td>Lee-White Clotting Time (min)</td>
<td>N. A.</td>
<td>45-65</td>
<td>45-65</td>
</tr>
</tbody>
</table>

* Represents a typical poly(ether urethane), presented only for comparison.
** Solvent-cast film of polymer purified by reprecipitation.
N. A. = Not applicable.

typical physical properties of solvent-cast films of this material, as determined according to applicable ASTM methods, have been listed in Table I. Another member of the series having a similar composition but a different urethane component, Acothane Q (which has somewhat different physical properties and is more extensible than Acothane 51), has been recently developed. However, the in vivo performance of the Acothane Q in various applications has not as yet been tested as thoroughly as that of Acothane 51.

The completely cured Acothane 51 elastomer is only partially soluble in any known solvent, although it still retains some thermoplastic properties inasmuch as it is heat- or ultrasonically scalable, for example. Thus, one of the most feasible methods of obtaining films or sheets of this elastomer whose surfaces are hemocompatible immediately after curing is by the way of solvent-casting a prepolymer solution under clean room conditions. Dissolved in a 2:1 mixture of absolute tetrahydrofuran and dioxane, a typical prepolymer solution contains about 12.5% (by wt) solids which is composed of a mixture of a relatively high molecular weight poly(ether urethane) and a poly(dimethylsiloxane) having a relatively medium molecular weight, and at least three reactive acetoxyl end groups per chain. During the preparation of the prepolymer, a fraction of the silicone component becomes covalently coupled to the urethane since the prepolymer solution does not undergo any phase separation over
extended periods of time (viz., 6 months), which would be expected in the absence of such bonding. Upon the evaporation of solvents from a liquid film, the curing process results in the formation of a matrix of a crosslinked polyurethane/silicone copolymer, in which small domains of the silicone homopolymer are dispersed. In Figure 1, at a magnification of 180,000, a transmission electron micrograph displays a typical bulk structure of the elastomer composed of two distinct but interwoven networks of chain bundles which are interspersed with nodules assumed to be domains of polysiloxane homopolymer. As a result of their relatively greater mean Z-number, the domains relatively rich in silicon atoms appear whiter than the background.

**IN VIVO PERFORMANCE OF AVCOTHANE 51 IN SHORT- AND LONG-TERM IMPLANTATIONS**

Since the introduction of the intra-aortic balloon pumps (IABP's) made by this laboratory, the Aveothane 51 elastomer has been the standard building material of these temporary cardiac assist devices. In cases of noncomplicated refractory cardiogenic shock secondary
to myocardial infarction, IABP counterpulsation treatment is administered for about 4.5–5.5 days,\textsuperscript{3,4} with the patients treated with relatively small doses of heparin and relatively medium doses of low molecular weight Dextran for added anticoagulative protection. However, the tail of the distribution curve of this type of patients extends to about 14 days, with an increasing number of recent cases which have reportedly involved periods in the range of 30–44 days. An increasing fraction, viz., about 40% of the total patient population treated by Aveothane 51 IABP's, includes cases requiring cardiac assistance under postoperative conditions. For these patients whose IABP treatment averages about 9–11 days, the administration of any heparin during at least the first 5–7 postoperative days is completely unfeasible given their condition, since this would interfere with the overall healing process. Although a large number of human implantations were performed under quite diversified clinical conditions (i.e., about 8000 cases by the end of 1974, in a total of 360 hospitals in the U.S. and abroad) and a significant fraction of the cases dealt with quite complicated postoperative patients, there has been no reported case so far in which either the fatigue failure of the IABP would have caused a fatality, or the \textit{in vivo} performance of the Aveothane 51 elastomer would have led to clinically intolerable hematologic damage.

The blood interfacial phenomena, if any, which are induced by the Aveothane 51 elastomer implanted as the main body of the IABP, are obviously a function of the hemodynamic conditions of pumping as well as that of the molecular structure of the blood-contact surface of the balloon. The \textit{in vivo} hematologic effects of Aveothane 51 IABP's in humans, representing a widely diversified group in terms of their clinical conditions, have been subjected so far to two series of statistical analyses. Although the results of these studies have been described elsewhere in detail,\textsuperscript{7,8} a brief summary can be given as follows. In both analyses, the changes observed in various hematologic parameters during IABP treatment were statistically evaluated and compared to the changes in the same parameters which were monitored in control groups consisting of patients who had similar cardiac conditions but not as severe as to require circulatory assistance. While platelet levels were found to be somewhat affected by the combined material surface and hemodynamic effects of the assist device, the particular conditions of the
patients appeared to have an effect on platelets of at least equal magnitude. In nonassisted control patients, platelet levels during cardiogenic shock were found to decrease in proportions which are about equal to that observed in the IABP-treated cases. The set of balloon-assisted patients showed two distinct patterns: platelet levels steadily decreasing with increasing pumping time, and platelet level changes displaying the "platelet tide" (i.e., recovery after initial decrease). Both of these patterns occurred with about equal frequency. The absence of any detrimental in vivo effects of Avcothane 51 IABP's under highly critical conditions is illustrated in Figure 2. In this diagram, the absolute platelet counts of two groups of patients are compared as a function of postoperative pumping or observation time. The members of both groups underwent one of the following surgical interventions: coronary artery bypass graft (CABG), mitral valve replacement (MVR), or aortic valve replacement (AVR). A group of 21 cases required IABP assistance, while the condition of the control group consisting of 16 patients was not as severe to require the same. As seen from Figure 2, the recovery of platelet levels in the assisted patients is not significantly different in spite of their more severe general condition.

![Variation of Platelet Levels in Post-Op Patients with and without IABP Assistance](image)

**Fig. 2.** Postoperative variation of platelet levels in patients who underwent either coronary artery bypass graft (CABG), mitral valve replacement (MVR), or aortic valve replacement (AVR) surgery.
In terms of erythrocyte counts and plasma hemoglobin levels, no significant degree of hemolysis could be detected in the IABP-assisted patients. Leukocyte counts in patients having somewhat subnormal levels at the beginning of pumping returned to normal; in other cases, however, there were no significant changes. Fibrinogen, one of the plasma proteins most sensitive to foreign surfaces, showed levels increasing from subnormal to normal as a function of pumping time. The overall in vivo performance of Acothane 51 balloons appears to be consistent with the state of the surface of recovered devices, showing only the presence of occasional adherent platelets upon examination by scanning electron microscopy.

In addition to implantable IABP’s, representing its most extensive application, the Acothane 51 elastomer has been employed as the main blood-contact surface of various types of extracorporeal circulatory assist devices which are currently under development. Another significant application, recently reported by Kolff and co-workers, involves the accomplishment of sustaining an experimental animal for 78 days with an implanted total artificial heart whose blood-contact surfaces were made essentially of the same elastomer. It is noteworthy that, following postimplantation recovery, the hematologic parameters of the animal were at normal levels up to about 5 days prior to termination.

CORRELATIONS BETWEEN PREPARATIVE CONDITIONS, SURFACE MOLECULAR ARCHITECTURE, AND HEMOCOMPATIBILITY

Although the in vivo performance of Acothane 51 blood-contact surfaces which has been documented above is indicative of a considerable degree of nonthrombogenicity, the apparent hemocompatibility is a function of the effective surface molecular structure, i.e., the type and surface-number density of groups actually exposed. In turn, the effective surface structure can vary as a function of the preparative conditions, despite the fact that the bulk composition of the starting material used, i.e., that of the prepolymer solution is constant.

The development of the full potential of nonthrombogenic properties, which depends on the attainment of a specific surface molecular structure, is a function of the rate of the removal of solvents from
the liquid film of the prepolymer solution. In the presence of solvents having fixed vapor-pressure characteristics, for a liquid film cast on a substrate which is impenetrable to the solvents (or on a "nonsink"-type substrate), the rate of solvent removal is equal to the rate of evaporation, which is a function of a) the effective temperature of the liquid film at the gas interface, b) the temperature of the gas phase above the liquid film, and c) the rate and nature of the gas flow in the vapor phase. On substrates penetrable to the solvent, the rate of solvent removal is greater than the rate of evaporation. Upon exposing a liquid prepolymer film on an impenetrable substrate

![Graph](image)

Fig. 3. Measured rate of evaporation of liquid Avcothane 51 prepolymer solution films as a function of computed "skin" layer thickness. Air flow ~210 cm/min; air temperature ~23.5°C.
under ambient conditions, in about the first 2 min of drying, a semi-solid, gel-like layer or "skin" is formed on the top of the air-facing surface (AFS) while the rest of the film underneath remains liquid. As a result, the evaporation rate for the remainder of the drying becomes diffusion-controlled. A typical rate of "skin" formation of a liquid film dried on a "nonsink"-type substrate is illustrated in Figure 3.

After the completion of drying and curing, the two sides of the resulting solid film of the Aveothane 51 elastomers, which has been obtained under the conditions described above, have different surface molecular structures. Among others, this is demonstrated by the fact that the IRATR (or FMIR) spectra of the two sides are not identical, particularly in the range of 11.0–14.0 μ, as shown in Figure 4. The AFS side where the "skin" was initially formed displays a doublet at 12.26 and 13.00 μ, respectively, while the substrate-facing surface (SFS) where the liquid film solidified last shows only a single peak at 12.62 μ and the peaks displayed by the AFS side appear

![Fig. 4. Typical infrared attenuated internal reflectance spectra of the substrate-facing side (SFS, left) and air-facing side (AFS, right) of cured Aveothane 51 elastomer films.](image_url)
only as shoulders. If the reactive poly(dimethylsiloxane) component used in the prepolymer is separately converted into a homopolymer, the IRATR spectrum of this material will display a strong absorption band, peaking at 12.82 μ as is shown in Figure 5. Thus, the IRATR spectrum of the SFS side is a composite envelope of the spectrum of the AFS side and that of the poly(dimethylsiloxane) homopolymer. The comparison of these IRATR spectra indicates that the distribution of the silicone component in the solid films of the Avothane 51 elastomer is anisotropic. However, by means of the IRATR spectral characteristics, the corresponding surface molecular structures can be quantified in terms of a parameter denoted as the IRATR index. This parameter can be computed by dividing the optical absorptivity at 13.00 μ by that measured at 12.62 μ. Since, in a typical SFS spectrum, % T (12.62 μ) < % T (13.00 μ), the IRATR index of this

Fig. 5. Infrared attenuated internal reflectance spectrum of the pure silicone component of Avothane 51.
type of surface will be $\leq 1$. For a typical AFS side whose spectrum displays a relative minimum at 12.62 $\mu$, the inverse will be true; hence, the IRATR index of this surface will be $\geq 1$.

The correlatability of the IRATR index with the anisotropic distribution of the silicone component in solid films of the Aveothane 51 elastomer and with the resulting difference in surface molecular structure has been verified by an independent method. This has involved subjecting Aveothane 51 surfaces, which had different but well-defined IRATR indices, to electron-microprobe analysis and determining the silicon atom concentration in surface layers having identical areas. A direct linear relationship displayed in Figure 6 has been found between the silicon atom count and the inverse of the IRATR index, as the latter quantity should, by its definition given above, be inversely proportional to the concentration of siloxane.

![Graph](image.png)

Fig. 6. Correlation between surface silicone content as determined by electron microprobe analysis and the inverse IRATR index of Aveothane 51 elastomer films.
chains in the surface layer of the cured elastomer penetrated by the infrared beam. In view of the fact that the depth of penetration of the electron-probe beam is roughly comparable to that of the infrared beam, the correspondence between the silicon count and IRATR index appears to be quite satisfactory.

The different characteristics of the effective molecular structure of Avcothane 51 surfaces, which has been established by two independent methods of analysis as given above, were found to result in inducing different effects in blood. In the course of short-term in vitro interactions, modified Lee-White clotting times which have been obtained by using statistical methods and systematically alternated donors, correlate with the IRATR index showing a maximum in the IRATR index range of 1.3–1.6, which is considered to be optimal.

Another evaluation of Avcothane 51 surfaces having different IRATR indices was performed by the Elliptical Cell Method\textsuperscript{13} which, in contrast to the Lee-White method, excludes the blood/air interface and is more sophisticated by measuring surface-induced effects in blood in terms of changes in partial thromboplastin time (PTT) and Stypven time (ST). Changes in PTT values relative to a control indicate the degree to which a contact surface can activate enzymes involved in the coagulation cascade. Changes in ST measure the degree of surface-induced release of thromboplastin material from cellular blood components, chiefly platelet factor 3, which is essentially proportional to the degree of damage inflicted upon platelets. Relative to control, Avcothane 51 surfaces having a mean IRATR index of $1.22 \pm 0.12$ gave a PTT value of $0.96 \pm 0.16$ and an ST value of $0.98 \pm 0.10$, while surfaces having an IRATR index of $0.50 \pm 0.32$ gave PTT and ST values of $0.82 \pm 0.11$ and $0.78 \pm 0.13$, respectively.

In the course of long-term exposures, whole human ACD blood was incubated at 37°C in contact with Avcothane 51 elastomers having either typical AFS surfaces with an IRATR index $\sim 1.4$, or with typical SFS surfaces having an index $\sim 0.8$. After 24 hr, the blood samples were recalcified and subjected to various tests indicative of surface-induced effects. Representative mean values obtained by these tests are listed in Table II. As seen from these data, the typical AFS side of the Avcothane 51 elastomer attains its nonthrombogenic properties by a mechanism which does not involve
TABLE II
Properties and Blood Interfacial Effects of Avcothane-51 Surfaces

<table>
<thead>
<tr>
<th></th>
<th>Air-Facing Side (AFS)</th>
<th>Substrate-Facing Side (SFS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SPECTRAL CHARACTERISTICS</strong></td>
<td></td>
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</tr>
<tr>
<td>IRATR Peaks (μ)</td>
<td>12.26 &amp; 13.00</td>
<td>12.62</td>
</tr>
<tr>
<td>Mean IRATR Index</td>
<td>~ 1.4</td>
<td>~ 0.8</td>
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**IN VITRO HEMATOLOGIC EFFECTS**
(After 24-hour incubation with whole human ACD blood at 37°C)

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<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Mod. Lee-White clotting time (min)</td>
<td>3.8/4.8</td>
<td>&gt; 60/4.8</td>
</tr>
<tr>
<td>(of exposed blood in glass)/Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothrombin time (sec)/Control</td>
<td>18.2/18.3</td>
<td>429/18.5</td>
</tr>
</tbody>
</table>

a selective adsorption or blocking of any of the components of the clotting cascade since, after having been in contact with that surface for 24 hr, the glass clotting and prothrombin times of the blood samples were equal to those of the control. The typical SFS side of the same elastomer induced entirely different effects. Although these results were obtained in interactions with whole blood, the difference between the effects which were exerted by the two sides of the same elastomer on the enzymes of the clotting cascade indicates that the protein adsorptive properties of the AFS and SFS sides are different.

CONCLUSIONS

The results of the work described above indicate that on polymeric contact surfaces, which do not depend on added anticoagulants in attaining nontrombogenic properties and are free of entrapped particulate impurities and other artifacts, the factors influencing the course of surface-induced blood interfacial phenomena are at the molecular level. In the absence of gross surface roughness, for polymers having complex repeat units or for complex copolymers such as the Avcothane 51 elastomer, it is the effective surface molecular structure that is the primary materials factor determinant of these interactions. However, the effective surface molecular structure can vary depending on the preparative conditions employed which, for these reasons, are to be subjected to strict controls should hemocompatibility be reproducibly maintained at optimum levels.
References