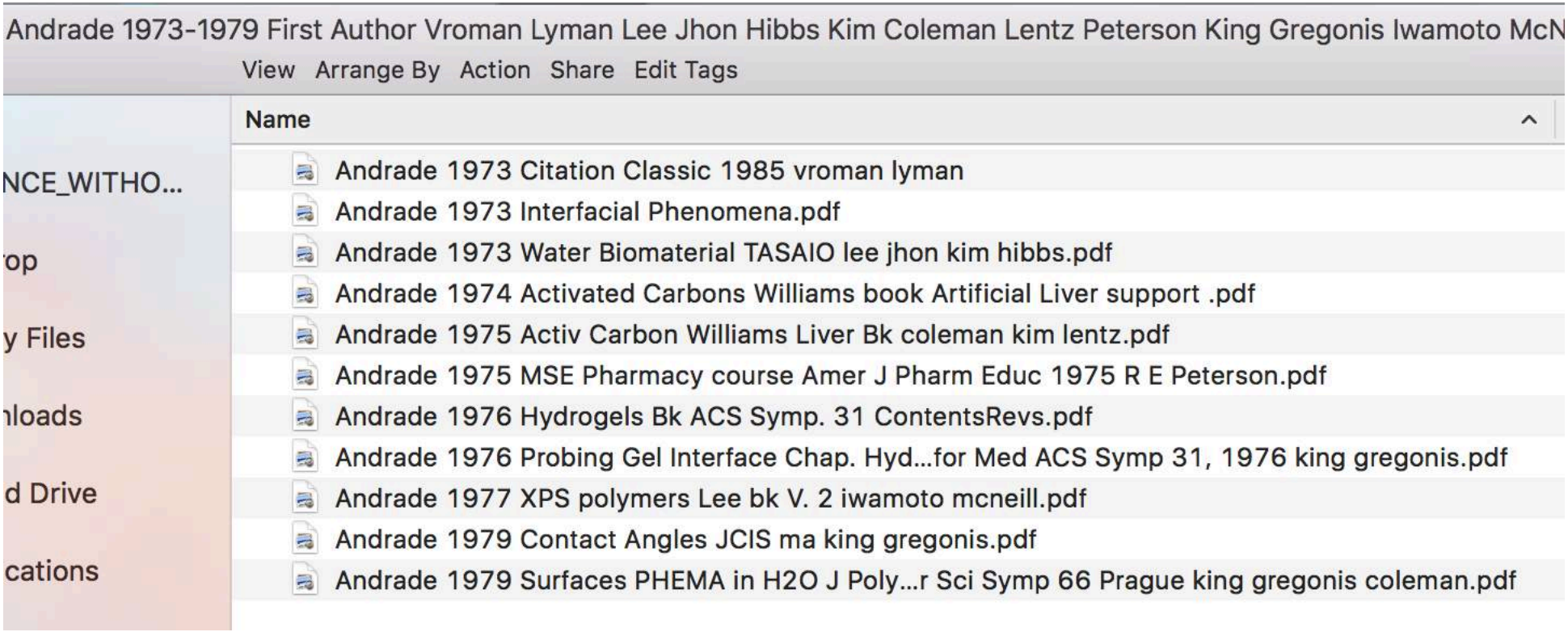
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Andrade J D. Interfacial phenomena and biomaterials.
Med. Instrum. 7:110-20, 1973.
[Colleges of Engineering, Medicine, and Pharmacy, University of Utah, Salt Lake City, UT]

This paper reviewed basic surface and interface science and applied it to the question of the "biocompatibility" of synthetic materials used in medical devices. It formulated the minimum interfacial free energy hypothesis and developed the relationship and correlations between more commonly known surface parameters and the interfacial free energy between polymers and aqueous solutions. [The *SCI*® indicates that this paper has been cited in over 80 publications since 1973, making it the most-cited paper published in this journal.]

J.D. Andrade
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September 23, 1985

This paper was my first serious effort at attempting to apply the basic principles of surface and interface science to the questions and problems in the implant biomaterials field.

D.J. Lyman, University of Utah, had been invited to present a paper at the Seventh Annual Meeting of the Association for the Advancement of Medical Instrumentation in Las Vegas in April 1972. He couldn't accept and suggested that I give the paper. I jumped at the chance, and the organizers of the meeting kindly agreed to let a young, unknown assistant professor give an "invited" talk. I remember the meeting well. Others on the program included Larry Hench, John Autian, and Vincent Gott, all well-known biomaterials scientists.

The fact that the paper has been modestly cited is perhaps because it was the first comprehensive review and presentation of basic surface-science principles applied to protein adsorption, cell adhesion, tissue reaction, and general "biocompatibility." It is, frankly, still a reasonably good introduction to the subject.

The major scientific contribution of the paper was the formulation of the minimum interfacial free energy hypothesis. This is a very simple concept and argues that, as the interfacial free energy between two phases goes to zero, interfacial processes are minimized. Basically, one attempts to "eliminate" the interface. Highly water-swollen aqueous gels were being considered for medical device applications, and the hypothesis provided a rational means to study and interpret their interfacial behavior.

The concept was generated about five years earlier in stimulating discussions with Paul Predecki, professor of materials science at the University of Denver, Colorado. Paul was my PhD thesis supervisor and was very instrumental in formulating the early ideas. So was Leo Vroman (Brooklyn VA Hospital), who was a consultant to our NIH contract on coagulation-resistant surfaces. In fact, it was Vroman's delightful book, *Blood*,[1] (which my wife, Barbara, and I literally stumbled across in a rustic and cozy Denver public library in 1967) that really stimulated my interest in blood-materials interactions.

The major problem with the interfacial free energy hypothesis is the measurement. Although we and others have struggled with this problem over the years, the measurement of solid-liquid interfacial free energies is still very unsatisfactory.

Our group is now attempting to understand surface motions and dynamics in the hopes of more completely assessing the role of interfacial free energies in polymer-biological solution processes and particularly in protein adsorption. Our more recent thoughts on this and related areas are included in two recent books.[2,3]

1. **Vroman L.** *Blood*. Garden City, NY: Natural History Press, 1967. 178 p.
2. **Andrade J D**, ed. *Surface and interfacial aspects of biomedical polymers*. New York: Plenum, 1985. 470 p.
3. ·····, ed. *Protein adsorption*. New York: Plenum, 1985. 345 p.

ANDR-4

Research

Interfacial phenomena and biomaterials[1-3]

J. D. ANDRADE, PH.D. Colleges of Engineering, Medicine, and Pharmacy, University of Utah, Salt Lake City, Utah 84112.

ANDRADE, J.R. *Interfacial phenomena and biomaterials.* Med. Instrum. 7: 110-120, 1973—The surface properties of medical implants have been widely investigated and speculated with respect to their biological interactions. There are no surface reactions in biomaterials and implant medicine; there are interfacial reactions and interactions. The object of study must be the interface. A brief survey of the material-aqueous system interfacial properties of a variety of materials is presented. Dispersion and polar contributions to the interfacial free energies are determined and discussed, and protein adsorption data is presented and analyzed. The role of interfacial properties on cell adhesion and tissue reactions is discussed. The concept of the minimal interfacial free energy interface is presented, as well as a discussion of methods for producing aqueous gel interfaces. The effect of gel interfaces on protein adsorption, cell adhesion, and foreign body reaction is analyzed. Reviews of surface science and of the foreign body reaction are also presented.

biocompatibility; blood; surfaces; interfaces; cells; tissue reactions; protein adsorption; implants; hydrogels; coatings

Introduction

BLOOD COMPATIBILITY, THROMBORESISTANCE, TISSUE COMPATIBILITY, foreign body reaction, protein adsorption, hemolysis, platelet adhesion, tissue ingrowth and adhesion, and biocompatibility are common terms in present-day bioengineering, attesting to the critical importance of interface-dependent phenomena in modern medicine. In considering the general biocompatibility or, perhaps less naively, the *"biotolerability"*[4] of materials, four levels must be considered: (1) *the molecular level*, within the 3 to 15 A range (the effects of water, water structure, ions, and small solutes); (2) *the macromolecular level*, from 10 to several hundred A (proteins, polysaccharrides, and micelles); (3) *the cellular level*, in the micron range, generally from 2 microns in diameter (platelets) to over 20 microns (large tissue cells); and (4) *the tissue level*, from 0.1 mm and greater in extent (collections of cells, tissues, etc.).

This brief review will examine some of the macromolecular, cellular, and tissue levels of non-living surface-living system phenomena. Before continuing, however, the concept of surface and interface must be discussed, along with some requisite background material.

Concept of Surface and Interface (4)

Surfaces. A surface is a discontinuity and is defined wherever a phase terminates. The phase may terminate at a vacuum or at the surface of another phase. The surface formed where two phases meet is an *interface*. Five common interfaces are known: solid-gas, solid-liquid, solid-solid, liquid-gas, and liquid-liquid.

A "free" or "ideal surface" is the interface produced by a solid or liquid with a vacuum. Such a surface can be represented by a surface energy, a measure of the unsatisfied bonding capacity of the surface (Fig. 1). The surface energy may be a result of unsatisfied primary or secondary bonds. The surface energy caused by secondary bond interactions can be calculated by using dipole-dipole and London dispersion potential expressions (28).

The term "surface tension" is often used in describing a surface. The surface atoms in any condensed phase are in an asymmetric force field, resulting in an attraction towards the bulk (Fig. 2). In many condensed phases, particularly liquids, it is possible to visualize some of the surface atoms being displaced into the bulk, resulting in a surface deficient of atoms. The atom-depleted surface is then in tension, a phenomenon termed "surface tension." A manifestation of this condition is the tendency for the surface area to be reduced. Not all materials exhibit a surface tension; the non-deformability of many solids precludes development of a surface tension, except at high temperatures. Thus, solids may have a minimal or even zero surface tension.

To quote N. K. Adam (1):

> Hence every surface molecule is subject to a strong inward attraction, perpendicular to the surface. This inward attraction causes the surface to diminish in area, because the surface molecules are continually moving inwards more rapidly than others move outwards to take their places; the number of molecules in the surface is therefore continually diminishing, and the contraction of the surface continues until the maximum possible number of molecules are in the interior; i.e., until the surface is the smallest possible for a given volume, subject to the external conditions or forces acting on the drop.

Surface tension is surface free energy. Work must be expended in order to extend a liquid surface, i.e., molecules must be brought from the interior to the surface against the inward attractive forces. Surface energy is a measure of the inward attractive force—the residual bonding capacity. Surface tension incorporates surface energy and surface entropy, i.e., the changes induced in the order or structure of the surface. Thus, surface tension and surface free energy are equivalent, although the latter is certainly the preferred terminology. The units of surface tension are dynes/cm, and units of surface free energy are ergs/cm^2, which are equivalent.

Interfaces. The free surface is a very important concept and is often a good approximation of solid-gas or liquid-gas interfaces. However, one is

[1]Portions of this paper were presented at the Seventh Annual Meeting of the Association for the Advancement of Medical Instrumentation, Las Vegas, Nevada, April 25, 1972, and at the Conferences on Adhesion, Polymer Conference Series, June 1971 and June 26, 1972, University of Utah, Salt Lake City, Utah.

[2]Portions of this work were supported by Contract AT(11-1)-2147 from the U.S. Atomic Energy Commission, Division of Applied Technology, and by Grant GK 29382 from the National Science Foundation.

[3]Reprint requests to Joseph Andrade, Ph.D., College of Engineering, Division of Materials Science and Engineering, The University of Utah, Salt Lake City, Utah 84112.

often interested in interfaces between condensed phases: solid-solid, solid-liquid, or liquid-liquid.

In the interface of Figure 3, γ_A represents the surface free energy of the free surface of Phase A, and similarly for γ_B. The terms $\gamma_{A(B)}$ (the effect on A due to the presence of B) and $\gamma_{B(A)}$ (the effect on B due to the presence of A) serve to reduce the free energy at the interface. Thus, we can say that the interfacial free energy, $\gamma_{AB} = \gamma_A - \gamma_{A(B)} + \gamma_B - \gamma_{B(A)}$ How these terms can be approximated will be discussed later.

The presence of B partially satisfies the unsatisfied bonding of A and vice versa. The unsatisfied bonding capacity at the interface is known as the interfacial energy, and γ_{AB} is known as the interfacial tension or interfacial free energy.

The work of adhesion at an interface is a measure of the interphase bonding and is defined as:

$$W_{AB} = (\gamma_A + \gamma_B) - \gamma_{AB} \tag{1}$$

or

$$W_{AB} = \gamma_{A(B)} + \gamma_{B(A)} \tag{2}$$

The work of cohesion (W_c) of a single phase can be defined analagously by considering Figure 4. We see that

$$W_c = 2\gamma_A \tag{3}$$

It is clear that the interfacial tension between two identical phases must be zero, i.e., $\gamma_{AA} = 0$, and an interface does not exist.

Interface Interaction Specificity (28). The existence of a number of different types of forces across an interface, depending on the phases present, leads to the concept of interfacial specificity, i.e., only certain forces are common to both phases and can thus interact. If the dipole moment of Phase A is zero, then dipole-dipole interactions across the interface clearly are zero, regardless of the value of the dipole moment of Phase B.

Many years ago, Berthelot hypothesized that the attractive constant, a_{12}, in the Van der Waals equation of state for gases could be related as a geometric mean:

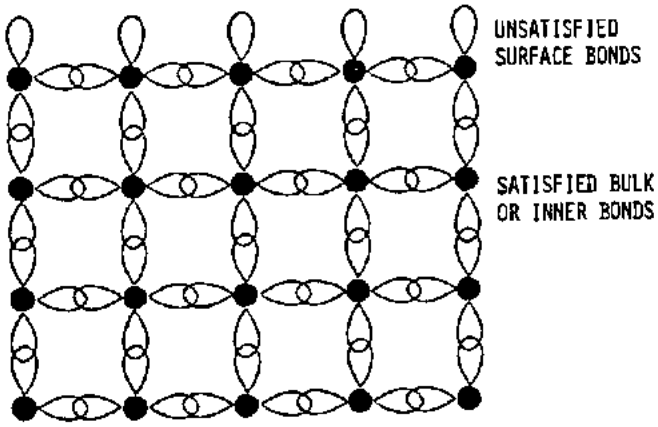


FIG. 1. A schematic illustration of the unsatisfied bonding capacity at a free surface.

$$a_{12} = \sqrt{a_{11}\, a_{22}} \tag{4}$$

If a_{11} and a_{22} are known (the attractive constant for 1-1 and 2-2 interaction), a_{12} could be calculated as the geometric mean. Because a is a measure of intermolecular attraction, Good and Elbing (31) stated the following:

Let

$$\Delta F_{12}^a = \sqrt{\Delta F_1^c\, \Delta F_2^c}$$

where ΔF_{12}^a is the free energy of adhesion between Phases 1 and 2, and ΔF_1^c, ΔF_2^c are the respective free energies of cohesion (equivalent to the work of cohesion discussed earlier).

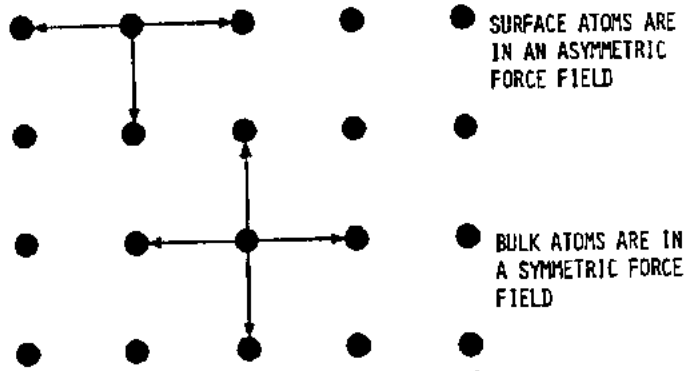


FIG. 2. The asymmetric nature of the forces exerted on surface atoms.

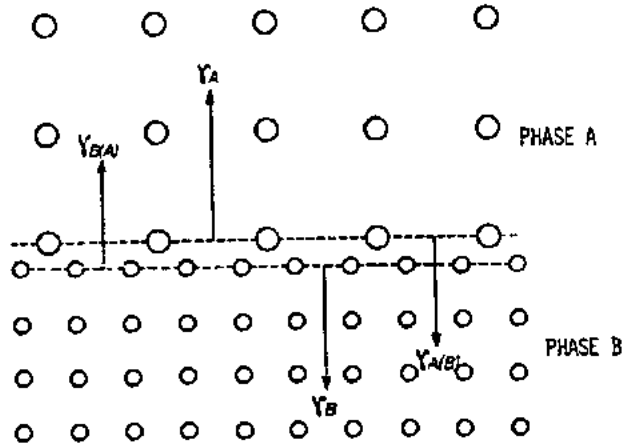


FIG. 3. Hypothetical interface between two phases, A and B (from Ref. 28).

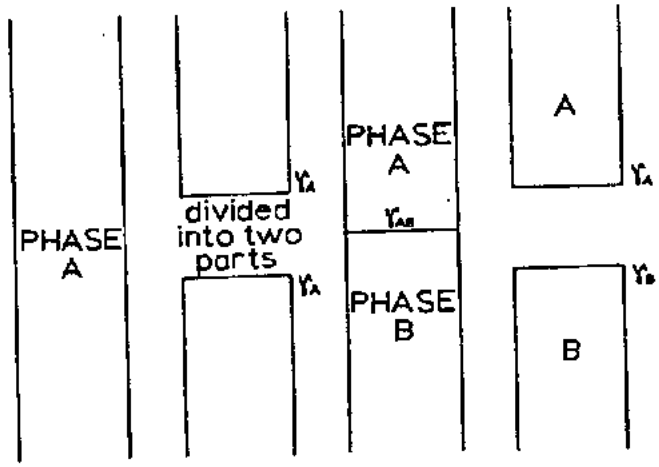


FIG. 4. Work of cohesion (on the left): $W_c = 2\gamma_A$; work of adhesion (on the right): $W_{AB} = \gamma_A + \gamma_B - \gamma_{AB}$.

JOSEPH D. ANDRADE has been involved in biomaterials and bioengineering related work for the past 6 years. Since January 1969, he has been associated with the University of Utah, Division of Materials Science and Engineering and Division of Artificial Organs in the Colleges of Engineering and Medicine, respectively. He is an associate professor in both the Colleges of Engineering and Pharmacy and holds the rank of assistant research professor of surgery in the College of Medicine. Professor Andrade conducts an active research program in the areas of biomaterials, artificial kidneys, and enzyme electrodes. Dr. Andrade team-teaches a sequence of courses on biomaterials with Professor Donald J. Lyman at the University of Utah. His main extracurricular interest is the so-called energy crisis, particularly the proliferation of coal-fired electrical generating plants in the Southwestern United States.

TABLE 1. *Critical surface tensions of various polymeric solids (77)*

Polymeric Solid	γ_C Dynes/cm at 20°C
Polyhexafluoropropylene	16.2
Polytetrafluoroethylene	18.5
Polytrifluoroethylene	22
Poly(vinylidene fluoride)	25
Poly(vinyl fluoride)	28
Polyethylene	31
Polytrifluorochloroethylene	31
Polystyrene	33
Poly(vinyl alcohol)	37
Poly(methyl methacrylate)	39
Poly(vinyl chloride)	39
Poly(vinylidene chloride)	40
Poly(ethylene terephthalate)	43
Poly(hexamethylene adipamide)(6/6 Nylon)	46

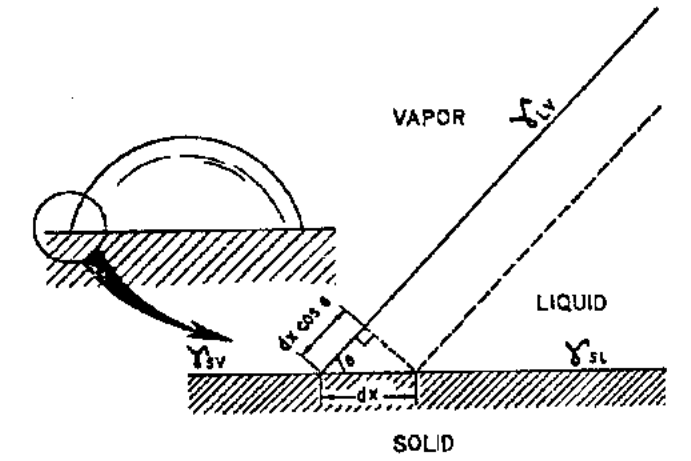


FIG. 5. The contact angle.

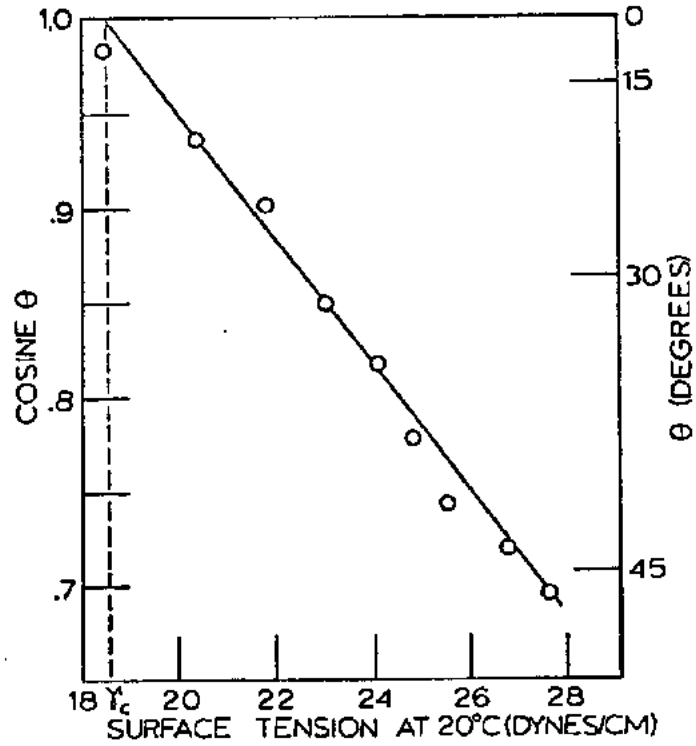


FIG. 6. Wettability of polytetrafluoroethylene by n-alkanes, intercept at $\cos\theta = 1$ indicates γ_c (redrawn from Ref. 77).

However,

$$\Delta F_1^c = 2\gamma_1 \qquad \text{(See Equation 3)}$$

$$\Delta F_2^c = 2\gamma_2$$

$$\therefore \quad \Delta F_{12}^a \simeq 2\sqrt{\gamma_1\gamma_2}$$

However,

$$\Delta F_{12}^a = \gamma_1 + \gamma_2 - \gamma_{12}$$

$$\therefore \quad \gamma_{12} \simeq \gamma_1 + \gamma_2 - 2\sqrt{\gamma_1\gamma_2} \tag{5}$$

A more accurate expression would be

$$\gamma_{12} = \gamma_1 + \gamma_2 - 2\phi\sqrt{\gamma_1\gamma_2} \tag{6}$$

where ϕ can vary from 0.5 to 1.15 and can be calculated from intermolecular force considerations (31). If the bonding in Phases 1 and 2 are similar, $\phi \simeq 1$; if the bonding is dissimilar, $\phi \gtrsim 1$.

Fowkes (28) postulated that the interfacial energy may be considered as a number of terms, each due to a single type of intermolecular force:

$$\gamma = \gamma^{\text{dispersion}} + \gamma^{\text{dipole}} + \gamma^{\text{metallic}} + \ldots \tag{7}$$

He then considered systems where only *one* force type could act across the interface. Consider mercury-hydrocarbon:

$$\gamma_{Hg} = \gamma^{\text{dispersion}}_{Hg} + \gamma^{\text{metallic}}_{Hg}$$

$$\gamma_{\text{hydrocarbon}} = \gamma^{\text{dispersion}}_{\text{hydrocarbon}}$$

He then stated that

$$\gamma_{12} \simeq \gamma_1 + \gamma_2 - 2\sqrt{\gamma_1^d\gamma_2^d} \tag{8}$$

But $\gamma_1^d = \gamma_1$ for the hydrocarbon. As γ_1, γ_2, and γ_{12} are well known, one can solve for γ_2^d, which for Hg is about 200 ergs/cm². Fowkes (28) has considered many other systems and has found that his results are in excellent agreement with experimental and calculated data.

More generally, one may state that

$$\gamma_{12} = \gamma_1 + \gamma_2 - 2\sqrt{\gamma_1^d\gamma_2^d} - 2\sqrt{\gamma_1^p\gamma_2^p} - 2\sqrt{\gamma_1^m\gamma_2^m} - \ldots \tag{9}$$

where γ_1^p is the polar contribution to the surface free energy of component 1, and γ_1^m is the metallic bonding contribution.

Thus,

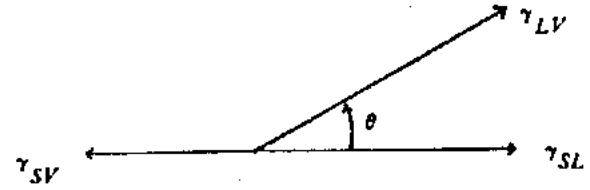
$$\gamma_{12} = \gamma_1 + \gamma_2 - 2\sum_i \sqrt{\gamma_1^i\gamma_2^i} \tag{10}$$

where i = dispersion, polar, metallic, etc.

Contact Angle and Wettability. Another basic expression necessary for an understanding of surface phenomena is the Young-Dupree or contact angle equation. Consider a drop of liquid on a solid substrate. Consider the tangent to the drop surface at the region of *S*, *L*, and *V* equilibrium (Fig. 5) where the interfacial energies are represented by: γ_{SV} (solid-vapor), γ_{SL} (solid-liquid), and γ_{LV} (liquid-vapor). Let there be a small displacement, dx. Then $(dG)_{T,P,n} = \gamma_{SV}\,dx - \gamma_{SL}\,dx - \gamma_{LV}\,dx\cos\theta$; at equilibrium $dG = 0$, or

$$\gamma_{SV} = \gamma_{SL} + \gamma_{LV}\cos\theta \tag{11}$$

This is the contact angle or wettability equation and is Adamson's fourth basic equation of surface chemistry (2). It can also be obtained by considering γ as a surface tension and performing a static force balance:



If the contact angle is 0, the liquid is completely spreading or completely wets the substrate. The contact angle is a very useful inverse measure of wettability.

Critical Surface Tension, γ_C. Zisman perhaps has done more than anyone else in characterizing the surface properties of polymers, largely by use of the contact angle (77). Extensive studies of the contact angle of a variety of liquids on clean, low energy polymer surfaces revealed a linear relation between $\cos\theta$ and γ_L (Fig. 6) for a homologous series of organic liquids. The intersection of the line with $\cos\theta = 1$ occurred at a certain value of γ_L, which Zisman called the critical surface tension for wetting, γ_C, for that particular series of liquids. Even for non-homologous liquids, the points fell on a straight line or within a fairly narrow band (Fig. 6).

The γ_C values derived from such plots correlate very well with the chemical nature of the polymer surface. The γ_C values of typical polymers of interest are tabulated in Table 1.

The critical surface tension, γ_C, is a "... useful empirical parameter whose relative values act as one would expect of γ_{SO}, the specific surface free energies of the solid. (77)" The correlation between γ_C and γ_{SO} is often extremely good (54).

Chemical and Structural Nature of Polymer Surfaces. Zisman's γ_C-surface composition relationships utilize the "... usually reasonable assumption that the surface composition of the solid polymer was the same as that of the horizontally oriented polymer molecule. (77)" However, many of these polymers are crystalline, and different faces of a single crystal or a lamella will have different surface energies.

It has been well documented (6, 66) that different faces of polymer crystallites will have strikingly different surface energies; thus, the surface energy of a crystalline polymer is not only a function of its chemical nature but is also a function of how the molecules are oriented.

Surface energy is also a function of density, i.e., the number of surface groups per unit area. A crystalline surface would be expected to have a higher surface energy than an amorphous one, due to density considerations alone. In fact, Roe (58) has shown that γ_C is proportional to the fourth power of the amorphous density for polyethylene. Schonhorn (65) has proposed that one must distinguish between γ_S^a (amorphous), γ_S^{ac} (amorphous-crystalline), and γ^c (crystalline) in the surface equations. He concludes that, for apolar polymers, $\gamma_S^a = \gamma_C = \gamma_{LV}$, where γ_{LV} is the surface tension of the liquid polymer melt, but that γ_S^{ac} and γ_S^c may be quite different. Schonhorn and Ryan (66) prove this point by measuring the wettability of polymer single crystals.

Schonhorn's conclusion that $\gamma_S^a = \gamma_C = \gamma_{LV}$ essentially states that the surface region of a typical polymer is an amorphous, liquid-like zone, with little or no crystallinity, which is in agreement with Lee et al. (41).

Polymers are usually cast or molded against low-energy surfaces that tend to reduce sticking. As the polymers crystallize, the low molecular weight or impurity species are rejected from the growing crystal. A polymer crystal thus tends to be surrounded by uncrystallized material, which is probably why γ_C and other surface properties are not particularly sensitive to crystallinity or bulk density (41, 65). If the polymer is cast against a high energy substrate, which can furnish many heterogeneous nucleation sites, its surface properties are different from those of conventionally formed polymers, which Schonhorn (64) has demonstrated. He studied the surface properties of both crystalline and non-crystalline polymer surfaces prepared by melting on both high energy (gold) and low energy (nitrogen gas) substrates. A portion of this data is given in Table 2. It is clear from Table 2 that γ could be made to double by casting on gold. Similar results have now been obtained for polytetrafluoroethylene (67) and perfluorinated ethylene-propylene (FEP) copolymer (32).

No evidence of oxidation or any other chemical changes in the surface could be detected. The great differences in wettability may be attributed partly to increased surface density due to crystallinity of the surface zone. The high energy substrate is believed to provide nucleation sites that result in transcrystallinity. Schonhorn has published a photograph (64) that strikingly documents the transcrystalline phenomenon.

TABLE 2. *Surface properties of polymers nucleated against gold substrates (64)*

Polymer	Bulk Density	$(\gamma_C)_{N_2}$	$(\gamma_C)_{Au}$
Polyethylene	0.95	35	69.6
6/6 Nylon	1.14	46	74.4
Polychlorotrifluoroethylene	2.12	31	58.9
Polypropylene (isotactic)	0.90	29	39.5
Polypropylene (atactic)	0.86	29	28.0

TABLE 3. *Surface and interfacial data for polymer and other surfaces (derived from References 12 and 47 and Equations 13 and 14)*

Surface	γ_{SO} ergs/cm	γ_{12} ergs/cm^2	W_{12} ergs/cm^2
Glass	170.0	20.4	222.4
Water	72.8	0.0	145.6
6/6 Nylon	39.5	5.1	107.2
Polyvinylidene chloride	38.5	5.4	105.9
Polystyrene	38.0	5.6	105.2
Polytrifluorochloroethylene	38.0	5.6	105.2
Polyethylene terephthalate	37.5	5.8	104.5
Polymethyl methacrylate	36.5	6.2	103.1
Polyvinyl chloride	35.0	6.9	100.9
Polyethylene	33.5	7.6	98.7
Paraffin	25.0	12.5	85.0
Polytetrafluoroethylene	24.0	13.2	83.6
Silastic®	21.0	15.6	78.2
Polyhexafluoropropylene	19.5	17.0	75.3
Air	0.0	72.8	0.0

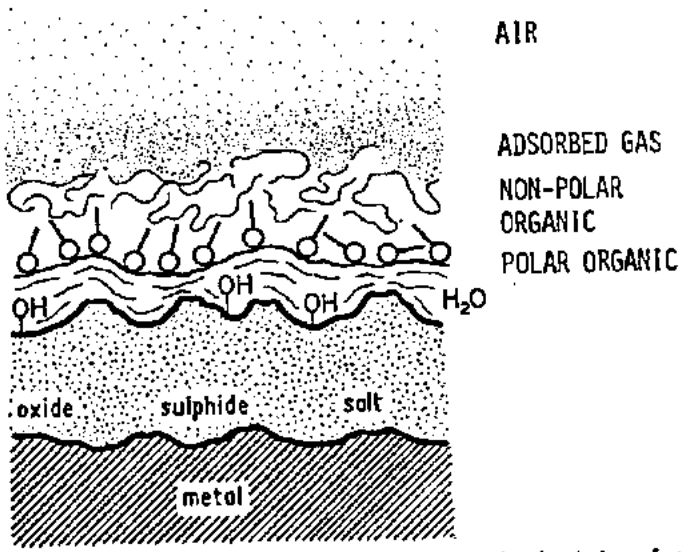


FIG. 7. Hierarchy of spontaneously adsorbed layers on a metal surface (redrawn from Ref. 24).

Perhaps the reason for Schonhorn and Ryan's observation of increased wettability accompanying increasing surface tension of the mold material rests more in the area of epitaxy than in transcrystallinity.

In summary, the surface free energy of a polymer depends on: (1) the chemical nature of the surface, i.e., the types of chemical bonds and atoms present on the surface; (2) the density of the surface, which is a measure of the number of chemical bonds or atom groupings on the surface (64-67); (3) the crystallinity and orientation of the surface, with specific reference to epitaxy and crystallite orientations (64-67).

Interfacial Hierarchies. The theme of this section is taken from a figure in an article by Eirich (24) (Fig. 7). A high energy metal surface in contact with normal atmospheres is covered with a series of layers, each serving to reduce the surface free energy of the surface. The inner layers may consist

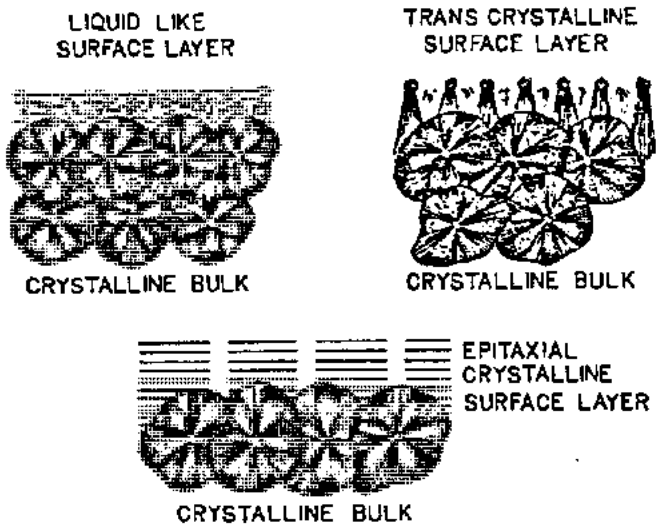


FIG. 8. Some possible interfacial hierarchies for crystalline polymers.

of primary bonds, such as an oxide or sulphide on a metal, followed by strong polar bonds, such as water or OH^- adsorption. The hierarchy continues until the final surface is a relatively low surface energy, non-polar organic. The hierarchy of Figure 7 naturally assumes that all the species illustrated are present in sufficient concentration. To "coat" or interface convert a surface is, according to Eirich (24), to " . . . establish a different hierarchy of adsorbed layers which has to compete with, and stand up against, the natural order."

A relatively low energy polymer surface will have a less complex hierarchy as it begins as a polar or non-polar organic surface. The polymer surface, however, can have structural or morphological variations, particularly in the case of semi-crystalline polymers. One could postulate the structures presented in Figure 8.

In addition to variation in surface structure resulting from simple casting on various mold surfaces, processing methods such as spinning, extrusion, and injection molding will lead to various surface structures that must be expected to influence the surface properties.

Commercial polymer surfaces may contain mold-release agents as well as plasticizers and perhaps other additives. Polymer surfaces may also be chemically different from their bulk because of surface oxidation, hydroxylation, or carboxylation under certain process conditions. Even in the case of non-crystalline polymers, some orientation influence of casting substrates and processing conditions can be expected.

It is therefore apparent that a polymer interface can be a complex hierarchy of structures and molecular types, varying from the bulk material through the solid polymer interfacial zone to the actual outer surface, which may contain adsorbed water, polar and non-polar organics, and gases.

General Correlations

There has been substantial interest and activity in relating the surface properties of materials to complex biological phenomena, particularly thrombus formation. Salzman recently authored a complete, concise review on the subject (62). Blood freshly withdrawn from an animal into a glass test tube clots more quickly than in a paraffin-coated or silicone-treated tube. These general observations led to the establishment of Lambert's Rule in the field of blood coagulation, which states, " . . . the coagulation time was inversely proportional to water wettability. (62)" A number of other investigators have proposed analagous relationships. In 1965, Lyman et al. (47) claimed to have found a correlation between the surface free energy, γ_{SO}, of hydrophobic polymer surfaces and their thrombus-inducing properties. This conclusion was later refined (44, 45) to " . . . platelet adsorption increases with increasing critical surface tension." Bischoff (12) has postulated a relationship between the work of

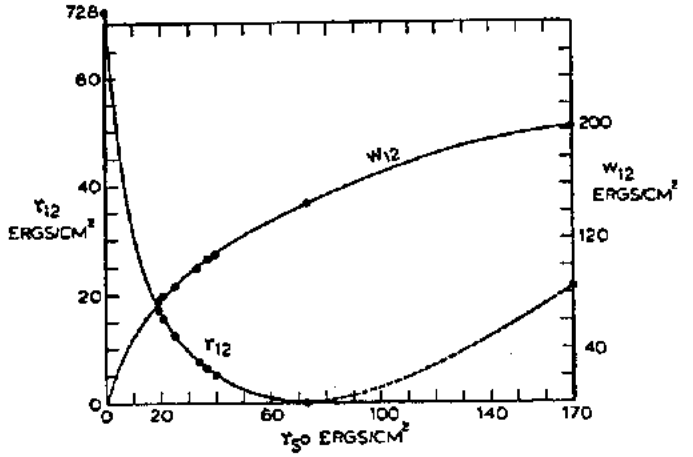


FIG. 9. γ_{12} and W_{12} for water and various surfaces plotted against γ_{SO} (see Table 3).

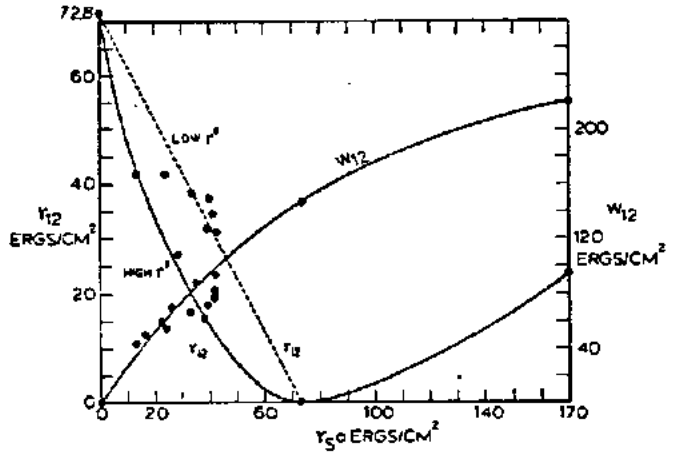


FIG. 10. The data of Table 4 plotted against γ_{SO}.

TABLE 4. *Surface and interfacial parameters for various surfaces (derived from References 28 and 36 and Equation 15)*[a]

Surface	γ_{SO}	γ^d	γ^p	γ_C	γ_{12}	W_{12}
Glass	170	80	90	—	23.8	219.0
Water	72.8	21.8	51.0	—	0	145.6
6/6 Nylon	41.3	33.6	7.8	46	20.2	94.0
Polyvinylidene chloride	41.3	38.2	3.2	40	31.0	83.1
Polystyrene	40.6	38.4	2.2	33	34.5	78.9
Polyvinyl chloride	39.6	38.1	1.5	39	37.3	75.1
Polyethylene terephthalate	39.5	36.6	2.9	43	31.6	70.6
Polyethylene	32.4	31.3	1.1	31	38.0	67.2
Polytrifluoro chloroethylene	26.9	23.8	3.1	31	29.0	70.7
Paraffin	23.7	23.2	0.5	15-22	41.7	54.8
Polymethyl siloxane	22.1	20.5	1.6	24	34.5	60.4
Polytetra-fluoroethylene	15.6	14.5	1.0	18.5	38.3	50.0
Polyhexafluoro propylene	12.4	11.7	0.7	16.2	41.5	43.7
Air	0	0	0	0	72.8	0

[a] All values in ergs/cm²

adhesion at the polymer-blood interface and coagulation time. Baier (7) has suggested that Zisman's critical surface tension, γ_C, data for polymers can be related to their biocompatibility properties, concluding that polymers with a γ_C of about 25 dynes/cm are the most biocompatible. Blackshear has postulated that different protein-surface interaction mechanisms are evident with surface energies $\gtrsim$ 30 ergs/cm² (13). This author has suggested that the interfacial free energy may be the more important surface property of interest (3-6). This concept will be discussed in further detail here.

Three major parameters must be considered: (1) γ_S is the surface free energy of the polymer or other surface being considered; (2) γ_{SW} is the interfacial free energy between the surface and the water; (3) W_{SW} is the work of adhesion between the surface and water. It has been established that

$$\gamma_{SW} \simeq \gamma_S + \gamma_W - W_{SW} \tag{12}$$

The work of adhesion, W_{SW}, is a measure of the interfacial attraction or bonding between the surface and the liquid medium. The interfacial free energy is a measure of the unsatisfied surface energies at the interface.

The surface free energy or surface tension of water or saline solution is approximately 73 ergs/cm². According to the Lyman et al. (44-47) or Baier (7) criteria, such a surface would be bioincompatible; yet it is common knowledge that such is not the case.

A hypothetical surface with a free energy of zero would be ideal according to the correlation of Lyman et al. (44-47). Such surfaces, termed air or nitrogen, are well known. Blood in contact with an air surface does thrombose; indeed the air-blood interface is usually considered, especially by Lyman et al. (47), to be highly thrombogenic. Baier claims a range of γ_C equal to 20 to 30 dynes/cm may be optimum, yet the polymers in Table 1 are all thrombogenic. Thus, it must be concluded that the Lyman, Baier, and Lambert correlations are not generally valid; neither the surface free energy nor γ_C are the controlling surface parameters.

If it is assumed that the first thing a solid plunged into blood "sees" is water or saline, then the interfacial free energy and work of adhesion between the surface and the aqueous solution can be calculated. It is these quantities that will be involved in subsequent molecular adsorption and cellular adhesion phenomena. These interfacial quantities can be readily calculated using Equation 9 if the components of the surface energy are known.

In 1965, Lyman et al. (47) calculated the surface free energy of polymers from contact angle data, using the assumption that the intermolecular interactions between the liquid and contacting surface are similar in nature. This is a weak assumption because water obviously has a very high polar interaction, whereas many of the polymers they considered did not. What their assumption essentially means is that we can approximate γ_{12} by

$$\gamma_{12} \simeq \gamma_1 + \gamma_2 - 2\sqrt{\gamma_1 \gamma_2} \tag{13}$$

and

$$W_{12} \simeq 2\sqrt{\gamma_1 \gamma_2} \tag{14}$$

Using a value of γ_{H_2O} = 72.8 ergs/cm² and the γ_{So} values as calculated by Lyman et al. (47), the data in Table 3 can be generated.

Figure 9 is a plot of the surface energy, γ_{So}, versus γ_{12} and W_{12} between the surfaces of interest and water. It is clear that γ_{12} goes through a minimum at $\gamma_{So} \simeq 73$ ergs/cm², which means that when water contacts water, there is no interface and the interfacial free energy is zero. The work of adhesion for this example is simply 2 γ_{H_2O}, or the work of cohesion for water. W_{12} is a continuously increasing function (as defined by Equation 14. Because it is known that air and glass surfaces are both quite bioincompatible, W_{12} is not a very satisfactory function to attempt to correlate with biocompatibility. Teleologically, γ_{12} is a much more satisfactory parameter to use because it shows both air and glass to be "bad" and water to be "good".

These calculations have been quite crude because Equations 13 and 14 have been assumed to be valid, i.e., the binding in water and in the polymer are of the same type. This is obviously not the case, and the more general expression, Equation 9, should be used. Fortunately, the dispersion and polar components of the surface energy for a variety of polymer surfaces have been tabulated (36). Table 4 presents this data. W_{12} and γ_{12}, for a water interface, where

$$\gamma_{12} = \gamma_1 + \gamma_2 - 2\sqrt{\gamma_1^d \gamma_2^d} - 2\sqrt{\gamma_1^p \gamma_2^p} \tag{15a}$$

and

$$W_{12} = \gamma_1 + \gamma_2 - \gamma_{12} \tag{15b}$$

The γ_{12} and W_{12} data are plotted against γ_{So} in Figure 10. These curves are more refined versions of those presented in Figure 9.

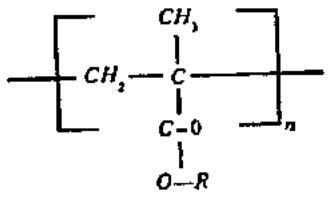
Note that the curves of Figure 10 are quite similar to those of Figure 9. As expected, W_{12} increases as γ_{So} increases. γ_{12} again passes through a minimum at $\gamma_{So} = \gamma_{water} = 72.8$ ergs/cm². For γ_{So} values less than 60, there are apparently two crude curves, representing those polymers with a substantial polar contribution (the lower curve) and those polymers with a very small polar component (the higher curve). The range of γ_{So} from about 65 to 100 ergs/cm² is not available with readily available materials. In order to test the hypothesis that minimal interfacial free energy may be correlated with optimum biotolerability, we must prepare surfaces with energies such that their water interfacial energies are less than approximately 5 ergs/cm².

A very hydrophilic surface with a high water content, such as an aqueous gel (hydrogel), might be suitable. Consider a polymer with a γ_c of 30 to 35 ergs/cm² (say polymethyl methacrylate) and assume that a material consisting of a network or matrix of the polymer surrounded by water could be produced. If this hypothetical hydrogel contained about 70% water, its γ_{12} would probably be less than 10 ergs/cm². If the gel contained about 90% water, the γ_{12} would probably be less than 3 ergs/cm². Such gels can be and have been produced and are indeed most promising as biocompatible and blood-compatible biomedical materials (56, 57, 75).

In 1959, two Czech scientists reported on the development of polyhydroxyethyl methacrylate (PHEMA) as a material for medical applications (75). The gel is stable in the physiological environment and seems to be extremely biocompatible. It has been studied extensively in Europe and, to a limited extent, in the United States (5, 6, 43, 57, 68, 75).

The acrylic gels are compatible with many types of biological tissue, including blood (68). Refojo and Yasuda (57) have conducted extensive studies on the hydroxethyl and glyceryl methacrylate gels. Wichterle and Lim (75) have proposed many medical applications for such gels. These materials are quite stable in aqueous solutions and do not suffer from hydrolysis, as do many other gel systems. Unfortunately, the mechanical properties of gels in general are usually poor.

The common Hydron® materials are based on acrylic acid esters, particularly the esters of methacrylic acid. The resulting polymer is represented as:



If R is $-CH_3$, the polymer is polymethyl methacrylate (Plexiglas or Lucite) and is hydrophobic. If R is CH_2-CH_2-OH, the polymer is polyhydroxyethyl methacrylate (poly-HEMA), also called Hydron® - S (43). If R is $-CH_2-\underset{OH}{CH}-\underset{OH}{CH_2}$, the polymer is polydihydroxypropylmethacrylate, used in opthalmology (57).

Water or alcohol interacts strongly with the -OH groups. The last two polymers are alcohol soluble and have no mechanical properties in water solution. These polymers can be readily cross-linked, however, to form stable three-dimensional networks that form gels in aqueous solutions, hence the generic name *hydrogels*.

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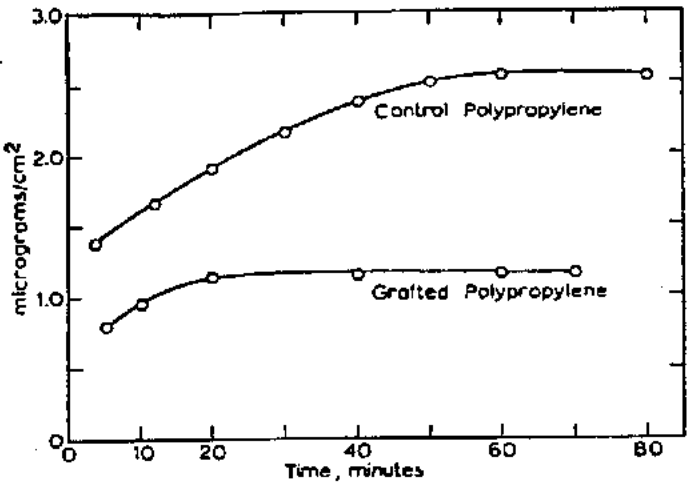

FIG. 11. Preliminary albumin adsorption data onto hydrogel-grafted and ungrafted (control) polypropylene (see text and Ref. 40 for details).

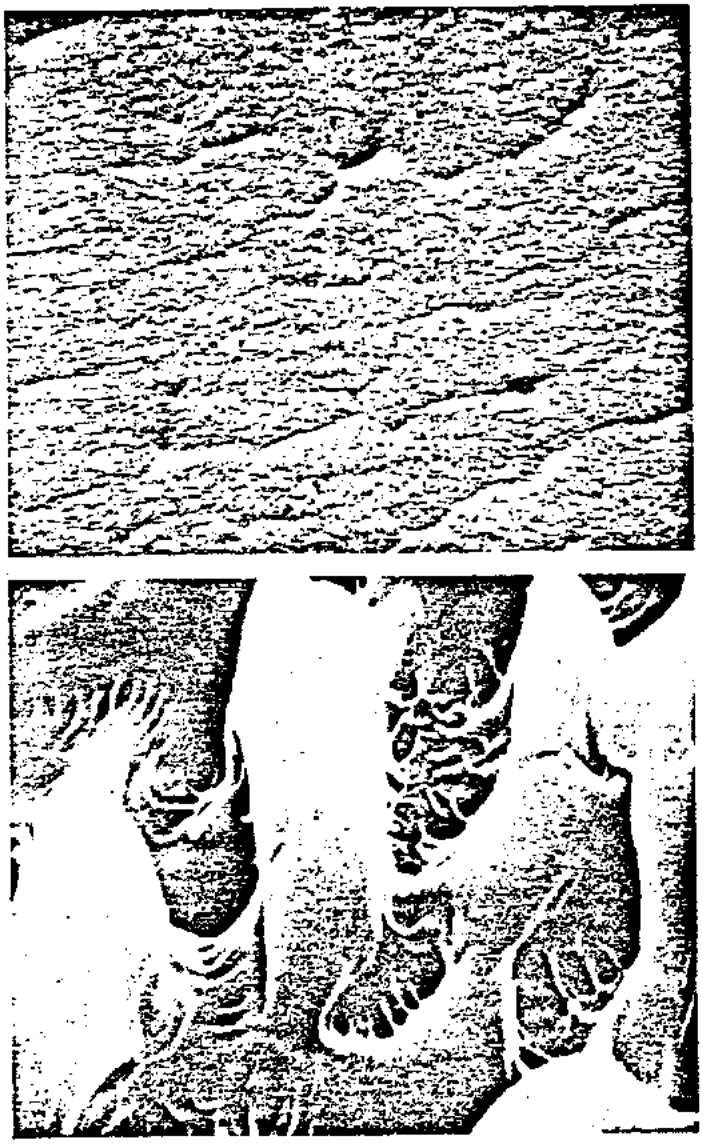

FIG. 12. *A* Scanning electron micrograph (SEM) of control polypropylene surface, 5,000X original magnification; *B* 5,000X SEM of 15% HEMA-grafted surface (1.0 Mrad) (see Ref. 40 for details).

One may use ethylene dimethacrylate, tetraethylene glycol dimethacrylate and many other compounds as cross-linking agents. Different cross-linkers and various degrees of cross-linking lead to a wide variety of properties. Commercial Hydron® is cross-linked with ethylene dimethacrylate to yield a gel containing 40% water with the ability to transmit molecules up to about 8,000 MW (43).

Protein gels are also biologically compatible under certain conditions. Fibrinogen and fibrin have been used in some cases (18). Lightly cross-linked gelatin (49) and suitable modified collagen materials (60) have been shown to be blood compatible. The biological response to these materials, however, is highly dependent on their molecular configuration. Protein gels are susceptible to enzymatic attack and are often unstable in the biological environment.

Many other gel-forming systems are known (20). Some of these, such as poly (N-vinyl pyrrolidone), are biologically compatible. Polyvinyl pyrrolidone has been used as a plasma expander (30). Many water-soluble polymers have been approved for use in foods and food packaging materials (20).

The problem of poor mechanical strength of gels may be circumvented by utilizing the unique biological compatibility of gel only at the surface of the device, perhaps as a simple coating (40). Theoretical evidence indicates that a neutral interface of the order of 100Å in thickness and having a high water content should not adsorb compounds from an aqueous solution (3). Such surfaces can be expected to be biocompatible (6).

Thus far, surface charge and surface potential have been totally ignored in the discussion. The ionic interactions at an interface can be incorporated by adding the appropriate charge-charge, charge-dipole, and charge-induced dipole terms to Equations 9 and 10. Charged surfaces can lead to specific interactions, however, which may modify the interface significantly. One can anticipate a complex interfacial hierarchy in many systems (Fig. 8). The hydrogen-bonding capacity of the surface is obviously of major importance in its interactions with water. This contribution has been lumped into the γ^p term in the previous calculations and tables, probably a significant error. A separate term should be utilized for the hydrogen-bonding interactions. The importance of this interaction has been documented by Nyilas (53) in his development of the Avcothane copolymer.

It is therefore clear that interfaces with minimal interfacial free energies can be designed. It is hypothesized that such interfaces will not greatly perturb the local bioenvironment and should thus be compatible or tolerable to the host tissues, including blood. Maloney *et al.* (49) presented a similar hypothesis in 1969. Although they did not consider interfacial free energy per se, their hypothesis and conclusions are essentially the same as the minimal interfacial free energy hypothesis.

At this stage in its development, the minimal interfacial free energy concept cannot be correlated directly to blood compatibility or to tissue reaction. Qualitatively, the concept is satisfying and seems to be on a firmer foundation than the correlations previously proposed between biocompatibility or blood-compatibility and surface properties.

The Molecular Level

There has been relatively little interest in studying biocompatibility at the molecular level. Perhaps the most significant consideration is the structure of water itself, particularly interfacially induced structures (23). There is growing evidence and awareness of the important role of water structure in biological systems (23, 69). Water structure and so-called "hydrophobic bonding" is of major importance in the mechanical and physical properties of some hydrogel systems (34, 56). Therefore, such structuring can be expected to affect the interfacial free energy and biological compatibility of such gels (6).

The role of solute ions in determining or affecting biocompatibility has not been thoroughly studied. The ubiquitous presence of Na^+, Cl^-, K^+, Ca^{++}, and other ions should hint that they may be important. There has been some interest in the role of Ca^{++}, and its influence in blood coagulation is well known. Leonard (42) claims that calcium ions may serve as bridges between the surface and certain biological interactions. Rappa-

port (55) has discussed the role of ion exchange capacity of solid surfaces, especially K^+, in cell and tissue culture work. The complexation and interaction of such ions with proteins is well known.

The role of ions and other low molecular-weight solutes in the modification of water structure and in the change of local electrostatic interactions through dielectric constant and other changes (19) might also be speculated.

The Protein Level

There has been much interest in and work on the adsorption of plasma constituents, especially proteins, onto a variety of surfaces. Some of the key groups in this area have been Falb et al. (25), Vroman et al. (72-74), Salzman et al. (63), Brash and Lyman (14, 15), Baier et al. (8, 10), and others. A number of models have been proposed for macromolecule adsorption from solution, and extensive reviews are available (27). The great bulk of the work on protein adsorption has concentrated on purified plasma proteins with the objective of elucidating blood coagulation phenomena. A case has been made for the role of interfacial free energy and solvent (water) effects on protein adsorption from solution onto polymer surfaces (3, 5, 6).

Studies of protein adsorption onto aqueous gel surfaces are in progress (40). Preliminary adsorption data for a polypropylene surface and a hydrogel-grafted polypropylene surface are presented in Figure 11. The washing solution was phosphate-buffered saline (pH 7.4) with no protein present (irreversibility assumed). These data utilized a 5-mg % (mg/100 ml) solution of radio-iodinated (I^{125}) human serum albumin (RIHSA).* The proteins used were checked for purity and homogeniety by high resolution acrylamide gel electrophoresis. Almost all of the radioactivity is associated with the albumin band. The run was carried out at 37°C. An adsorption apparatus that completely eliminated all air-solution interfaces was utilized. The solid samples were counted by liquid scintillation. The grafted polypropylene sample contained about 4.5mg/cm² (gross area) of fully hydrated polyhydroxyethyl methacrylate; the equilibrium water content of the graft was about 70% (40).

The data of Figure 11 lend further, though preliminary, evidence to the minimal interfacial free energy approach for minimizing protein adsorption (3, 5, 6, 40). This is surprising because the grafted surface has a much greater surface area (Fig. 12,*A*) than the ungrafted control (Fig. 12,*B*), and the data of Figure 11 do not take into account true surface area. Thus, the amount of protein adsorbed per unit of *true* area for the grafted sample would in reality be much less than reported in Figure 11.

It is interesting to compare the data of Figure 11 with those for Silastic®† rubber grafted under similar conditions (Fig. 13). In this case, the equilibrium water content was much lower, about 20% (40). It is clear from Figure 13 that the degree of protein adsorption is reduced only slightly in the grafted sample. These data indicate the important role of water content and thus of interfacial free energy in affecting protein adsorption.

The Cellular Level

The interaction of cells with surfaces has been studied and speculated upon since the beginning of cell culture work. In 1921, Fenn (26) considered the role of interfacial tension between a cell and a solid substrate in cell adhesion phenomena and phagocytosis. Mudd and Mudd (51, 52) also considered interfacial tensions in cell-cell interaction. Until recently, this early work was largely ignored. Van Oss and Gilman (70) recently studied the surface and interfacial free energy aspects of phagocytosis. Interfacial free energy was specifically considered in a paper by Van Oss et al. (71). There is thus a growing interest in interfacial free energy as an important parameter in fundamental cell-cell and cell-substrate interactions.

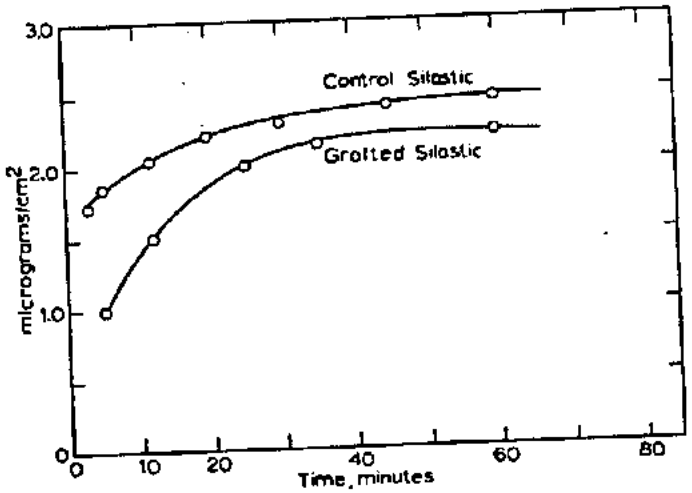

FIG. 13. Preliminary albumin adsorption data onto hydrogel-grafted and ungrafted Silastic® rubber (see text and Ref. 40 for details).

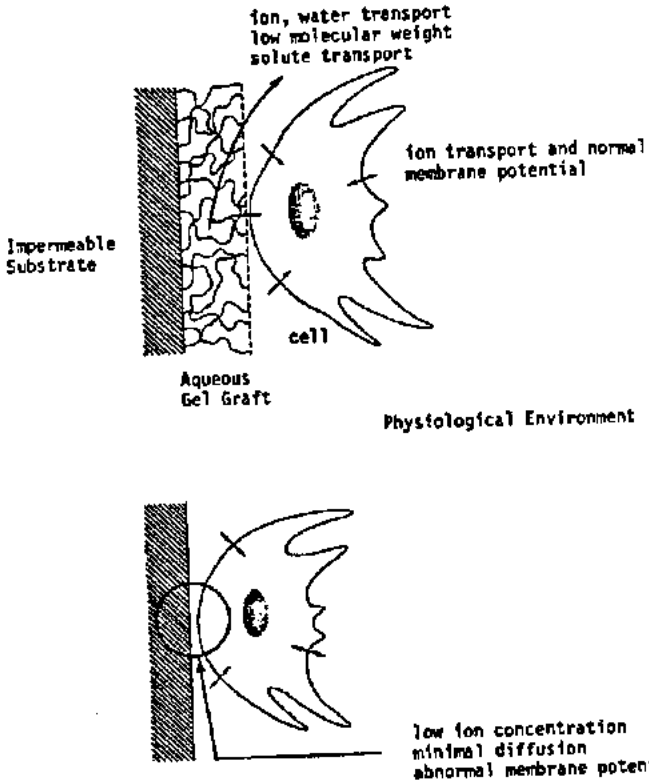

FIG. 14. A schematic diagram of the interface between a cell and a gel surface (upper) and between a cell and an impermeable substrate (lower).

The interaction of blood-formed elements with artificial surfaces has been of great interest, particularly platelets and red blood cells. The remainder of the discussion will concentrate on platelets, infamous for their ability to adhere to surfaces. Red blood cells tend to adhere to surfaces to a much lesser degree than platelets, though their interactions with artificial surfaces are believed important in sub-lethal hemolysis and gross hemolysis (11, 13). Data is also available on white cell-surface effects (38).

Platelet interactions with artificial surfaces have been reviewed by Salzman (61, 62). The general conclusion is that existing correlations of platelet adhesion with surface properties are not very satisfactory (29). Lyman et al. (44, 45) claim that the degree of platelet adhesion is directly related to critical surface tension. There does seem to be a crude correla-

*Abbott Laboratories, North Chicago, Illinois.

†Registered trademark of Dow Corning Corporation, Midland, Michigan.

tion, although Lyman's data support Baier's $\gamma_C \simeq 25$ dynes/cm optimum more than it supports a direct γ_C relation. A case cannot be made for or against a γ_{12} correlation, as Lyman's surfaces were restricted to the γ_C range from approximately 16 to 43 dynes/cm. For those surfaces for which data is available in Table 4, the γ_{12} values fall between 30 and 40 ergs/cm^2. The real test of the γ_{12} argument may lie in the range from about 0 to 10 ergs/cm^2, corresponding to approximately 60 to 100 ergs/cm^2 for γ_{SO}. Unfortunately, very little platelet adhesion data is available for hydrogel surfaces.

Platelets do not adhere to normal vessel intimas (61). There is evidence that the vessel wall is hydrophilic and perhaps of a hydrogel nature (6, 72). One can determine γ_C values of dehydrated intima using hydrocarbon and polar organic liquids (9). Perhaps such data have some significance in that they can be used to indicate the γ^d and γ^p contributions to the surface energy of the vessel wall. Placing water, however, on a fully hydrated vessel wall produces total wetting both in vitro and in vivo (6, 9). Baier et al. concluded from their study that "the blood vessel intima is an intrinsically low-surface-energy lipoprotein lining with an outermost layer of predominantly hydrocarbon composition. (9)" The implication is that such a surface with a γ_C of 25 to 30 dynes/cm should exhibit blood compatibility. The quotation may be true, but the implication is highly misleading because it ignores the fact that regardless of what the dehydrated intimal components are, the intima itself is a hydrophilic gel under normal conditions. Water, therefore, must play a role in the biocompatibility of the vessel wall. If the conclusions of Baier et al. are correct, the role it plays may involve substantial hydrophobic structuring (6, 19). The author has argued (6) that the interfacial free energy between the intima and blood is relatively low, and that this is one of the reasons for its optimum blood tolerability.

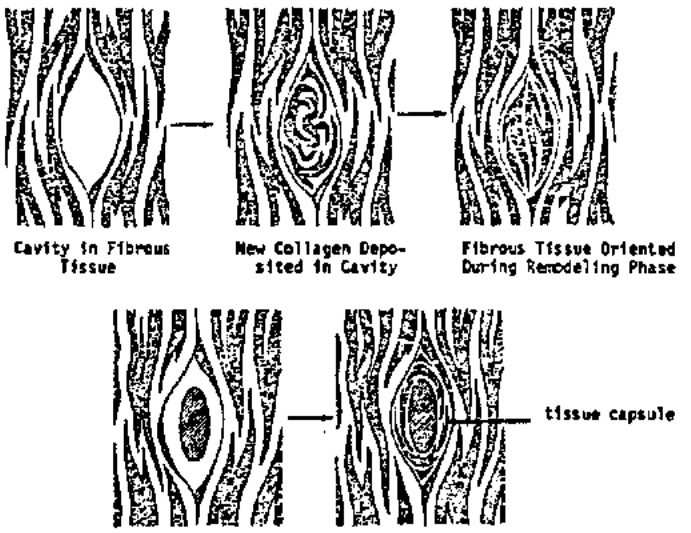

FIG. 15. *A*, The tissue response to a cavity; *B*, the tissue response to an inert impervious implant (redrawn from Ref. 33).

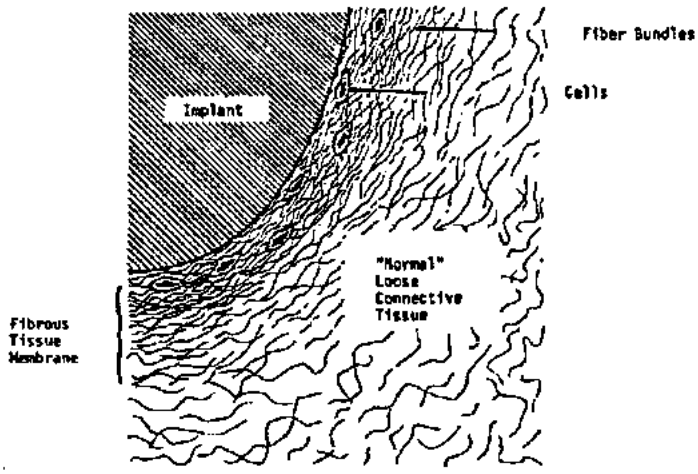

FIG. 16. The fibrous tissue "membrane" adjacent to a relatively large impervious implant.

Lyman et al. (46) have shown that adsorbed albumin films (if undenatured) exhibit very little platelet adhesion. Albumin is readily soluble in water and can form good gels; albumin on a surface may also be a hydrogel.

The extensive platelet drops observed with bubble and membrane oxygenators (both with high interfacial free energies) are in contrast to those observed in systems containing hydrogel surfaces, such as cellophane dialyzers, and hydrogel-coated adsorbents (5). There is thus some evidence to indicate that interfaces of low energy may be tolerable to platelets.

Figure 14 represents the interaction of a cell with a gel interface as contrasted with a non-gel interface. Clearly, ionic and low molecular-weight solute equilibria and interactions between the cell and the surrounding medium cannot occur when the cell is in contact with or very near an impermeable substrate. The gel interface will permit H_2O, ion, and small solute permeation and transport, however, thus probably minimizing any upsets produced by the presence of an interface. Assuming the gel surface has minimal water structuring properties and is un-ionized, and further assuming that it is not particularly chemically reactive, minimal cell adhesion to such a surface would be expected. If for some reason cells were in contact with the gel interface, minimal perturbations of the interfacial properties of the cell membranne itself, such as its surface charge and trans-membrane potential, would be expected. Some of these considerations have been discussed by Rappaport (55).

The Tissue Level

The typical surgical implant today is a relatively inert, stable, static structure placed in a dynamic, living environment. Regardless of how inert the material is, it is still a static discontinuity in a dynamic, living system and will, by its very presence, seriously perturb this system. This perturbation or effect on the surrounding tissue is called a "foreign body reaction" (FBR) (16).

In order to implant a device, an incision, or wound, is made. Whenever tissue is damaged, the organism attempts to repair the damage and restore continuity to the damaged structure. This response is called wound healing. Thus, wound healing and the FBR often occur simultaneously (16).

A gross incision is not required for a wound-healing response. Any damage or insult to tissue or cells will produce a response. Thus, in order to understand the FBR, a working knowledge of wound healing (48, 59) is necessary.

Wound Healing. The surgical trauma produced during most implantations results in a wound-healing response. If the surgeon changed his mind and decided *not* to implant a foreign body, he would still be faced with a complex series of processes designed to heal the wound site. The wound-healing process begins with bleeding, if vessels have been severed, followed by blood clotting, edema formation, influx of white cells, macrophages, and finally influx of repair cells, the fibroblasts, which produce collagen, the structural matrix of most animal tissues. Finally, the wound will remodel in response to applied stresses and attain maximal strength. The net result is that the vacant or damaged region is filled with new fibrous tissue (Fig. 15,*A*). In the presence of an inert implant, the same process occurs, i.e., there is a tendency to fill the space with connective tissue, which results in an encapsulation of the implant (Fig. 15,*B*). The implant is then naively said to be "encapsulated," "walled off," or "rejected" by the body. This is a metastable condition. If the implant could somehow be abruptly removed without surgical trauma, tissue would tend to fill in the gap until continuity was restored. This is what is observed with some of the newer absorbable sutures.

For relatively large and impervious implants, the FBR leads to a fibrous tissue layer near the implant. The fiber bundles are usually oriented parallel to the implant surface. It is this oriented fibrous tissue that is often termed the "encapsulating membrane" or capsule (Fig. 16).

Chemical Factors. Unfortunately, most implants are not truly inert. If the implant produces noxious chemical or mechanical stimuli, an irritation is produced which exists as long as the noxious stimulus is present. This condition usually persists long after the initial stimulus of the implantation. Any chronic irritation of the tissues leads to inflammation and results in a fibrous tissue response. The "reaction" to the foreign body is now a composite of the response to the inflammatory stimuli and the natural tendency towards encapsulation. The result is a more intense reaction, the intensity of the reaction being more or less proportional to the degree of chemical or mechanical irritation (16, 17).

The chemical stimulus can be a result of ions evolved during the corrosion of implanted metals or of monomer or catalyst residues in polymers leaching into the tissues, as well as plasticizers, antioxidants, and other additives. It may also be due to impurities or filler material in the polymer, mold-release agents, or machining oils. Virtually any chemical or material that can make its way to the tissue-implant interface can result in some degree of chemical stimulus to the tissue.

The inflammatory reaction is basically the neutrophil-macrophage-edema phase of the wound healing response (16). The tissue exhibits extensive cellularity. If the irritation is not excessive, it will result in a greater amount of fibrous tissue and a thicker capsule. Laing et al. (39) have shown that for a large variety of metals implanted in rabbit muscle, three basic reactions could be differentiated: (1) *mild*—a collection of cells and fibrous tissue adjacent to the implant followed by a region of fibrous tissue (Fig. 16); (2) *moderate*—a zone of free inflammatory cells adjacent to the implant, then a thin encapsulating fibrous tissue-cell membrane, followed by normal connective tissue; (3) *severe*—tissue necrotic (dead) immediately adjacent to the implant, followed by an inflammatory response and a thick fibrous capsule. The fibrous membrane thickness could be correlated with the degree of implant corrosive activity. The thickness varied from 2 to 8 microns for a mild reaction to more than 1,000 microns (1 mm) for a very severe response. There was a correlation between membrane thickness and ion concentration, as well as between thickness and ion toxicity.

Mechanical Factors. Movement of an implant with respect to adjacent or surrounding tissue will produce a mechanical cellular irritation, thus provoking a tissue response. Generally, the greater the degree of movement, the thicker the capsule formed. The fibrous tissue in the capsule is often oriented in the direction of movement of the implant.

A study comparing several different implantation sites concluded that muscle shows the greatest reaction (16, 76), possibly because of the extension and contraction movements invariably present in muscle, which would produce mechanical irritation. In the case of a rod implant, the ends of the rod generally exhibited a greater FBR than the center. This result is attributed to the increased mechanical trauma of the tissue at the ends of the rod.

Geometrical Factors. The size and shape of the implant with respect to the cells and surrounding tissue is another factor in the FBR. A large implant will be sensitive to mechanical trauma. The greater the mechanical trauma, the thicker the capsule. The thicker the fibrous capsule, the more difficult it is to nourish the inner layers adjacent to the implant. A thick, dense capsule may outstrip its blood supply. The deeper layers adjacent to the implant may degenerate and even calcify. The degeneration products may provoke an additional tissue response, thus compounding the problems. The main conditions necessary for permanence seem to be the unimpaired nutrient supply of the tissue surrounding the implant.

In general, the larger the solid structural unit of the implant, the greater a barrier and discontinuity it is, the thicker the capsule that forms, and the poorer the blood supply to the inner layers. Small implants generally exhibit thin capsules with good blood supplies and are, therefore, much more stable implant systems.

Thin fibers, 30 to 50 microns in diameter, of most materials are very well received in tissue, resulting in a thin fibrous capsule, a good blood supply, and good cellularity. They produce a stable "tissue-fabric." Davilla has shown that, for a variety of inert materials, the diameter of the fiber has a greater influence on the FBR than the type of material (21, 22). Davilla's work establishes a satisfactory explanation for the success of velours, felts, weaves, knits, and other textile structures in implant applications.

Interfacial Factors. The very presence of an interface between the implant and the surrounding tissue serves to permit a variety of phenomena that may be important in the FBR. Some of these factors have been speculatively discussed by Kordan (37).

Adsorption processes will occur at the interface. Protein adsorption is rapid and perhaps irreversible; the adsorbed protein may appear altered or structurally different to its solution neighbors. The presence of the implant grossly changes the local dielectric environment, thus affecting local intermolecular interactions. It is possible that cell membranes very near or touching an implant will have their membrane potential altered by the lack of physiological ions at the implant interface. The implant surface may carry a residual surface charge or dipole orientation. Local crystallinity or lattice orientations on the implant surface can affect the FBR, as can surface defects and localized surface states.

Kordan (37) stated that ". . . new and unnatural surface phenomena are invariably brought into being between the implanted plastics and the intact cells nearest the site of the implanted polymers." With proper polymer surface engineering, those interfacial phenomena can be controlled. The tissue reaction to hydrogel surfaces has been studied, and the reactions have been extremely mild. There seems to be an inverse correlation between the extent of gel graft and the tissue reaction. The extent of tissue reaction through the water content and perhaps thickness of the hydrogel surface should be controllable.

Conclusions

Interfacial free energy is important, and probably more important than critical surface tension, surface free energy, or even work of adhesion. It must be realized, however, that there is not just one single interface in the systems of interest; there are interfaces, each with its interfacial free energy. There are interfacial hierarchies, just as there are free surface hierarchies (Fig. 8). Furthermore, the hierarchy will be in dynamic equilibrium with its substrate and the external environment. There is no such thing as a stable "conditioned" surface that the blood or the tissues "see." The hierarchy seen at $t = 1$ minute may be different from the one observed at $t = 1$ hour, 1 day, or even 1 year.

The best way to solve a surface or interface-induced problem may be to eliminate the interface, i.e., produce a system whose interfacial free energy is zero.

The gel surfaces described certainly do not have zero interfacial energies, and they certainly are not the complete answer. They do provide a somewhat new approach to a now old and tired problem.

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WATER AS A BIOMATERIAL

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"Blood compatibility" is a term often used in the bioengineering and artificial organ literature. There is no generally agreed definition of the term, there certainly is no generally accepted standard test with which to quantitate it, and it is doubtful that even a conceptual consensus exists as to its meaning.

We say that the vascular endothelium is blood compatible and most prostheses are not blood compatible. The blood incompatibility of artificial prostheses has generally been related to local hemodynamic phenomena and to local interfacial interactions between the implant and the blood.

A number of surface science parameters have been proposed to correlate with blood compatibility, including the surface charge[1], surface free energy[2], work of adhesion[3], and critical surface tension[4]. Though crude correlations do exist with certain subsets of materials, there has been little or no general correlation between surface properties and blood compatibility, which has prompted some researchers to conclude that surface properties are inconsequential[5]. A good deal of the problem may be due to our preoccupation with materials and implants and thus our subconscious emphasis on the "surface" properties of those implants.

Surfaces do not exist - neither in engineering nor in biology. Interfaces exist. The phenomena to be considered are interfacial phenomena[6], not merely surface phenomena.

The properties of an interface are obviously related to and dependent on the "surface" properties of the 2 adjacent phases. There is an interaction or an adhesion between the 2 phases[7], thus the surface properties of phase A at the A-B interface may be grossly different from the surface properties of A at the A-air interface - particularly if one or both of the phases are liquids, gels, or easily deformable solids. Nevertheless, there are a number of methods by which the interfacial energy can be approximated[6-8]. Procedures are available for obtaining the dispersion, and polar (or non dispersion) contributions to the interfacial adhesion, and thus to the interfacial free energy[9-11]. Most methods depend on the measurement of a solid-liquid-vapor contact angle, which is not very physiologic. The technique of Hamilton[10] allows one to directly determine the interfacial polar binding in situ by the measurement of the n-octane/saline/solid contact angle.

WATER

In order to understand blood interfacial phenomena, we must consider the nature of blood or plasma. Blood plasma is a solution which contains 90% water. There are many synthetic hydrogels which can contain more water than plasma. Water is commonly considered to be a passive medium or mileau in which biochemical reactions and physiological processes occur. This may be an incorrect assumption. Our group and others are considering a different set of assumptions - that water plays important roles in many biological processes, particularly at interfaces[12].

The structure of water, in bulk, at interfaces, and in gels, has been well reviewed[12-14]. The role of water in biological processes is also receiving extensive consideration and study[12,15-17]. Water appears to play an important role in membrane permeability and intracellular structure[18-21], in cancer[22], in the biocompatibility of hydrogels[13], in the structure, function, and molecular biology of proteins[23-25], in the mechanism of anesthesia[26], in cryobiology and cryoprotection[27,28], in the structure and function of viruses and antibiotics, in muscle contraction[29], in the mechanism of action of some steroids[30], in radiation damage and radiation protection[31], and even in platelet aggregation[32]. Many more examples are available[12]. Much of the evidence is somewhat circumstantial, but there is so much of it, sweeping over so many fields, that it must be more than mere artifact or coincidence.

PLASMA

A simplified view of blood plasma is presented in Table I. Each water molecule cannot be much farther than 100 Å from a protein. Each water molecule is within 17-20 Å of the center of an ion[33]. When one considers the amount of water involved in the hydration shell of proteins, the amount of water structured due to hydrophobic bonding, and the water of hydration of electrolytes, it is clear that a significant proportion of the water in blood may bear little resemblance to "bulk" water. Water in hydrogels can be considered as bulk water, interfacial water, and water of hydration (called, x, y, and z water, respectively)[13]. It is highly probable that similar arguments hold for blood.

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TABLE I

BLOOD PLASMA - A SIMPLIFIED VIEW

Component	Wt. %	"Average" Molecular Weight	"Average" size, A	Millimoles cc	No. of Molecules Per Protein	Molecules Per $(500A)^3$ Zone
Protein	7	100,000	40 x 200	7×10^{-4}	1	52
Organics	2	150	10	0.133	190	10,000
Electrolytes (as NaCl)	1	58	"Point"	0.170	240	12,500
Water	90	18	3.1	50	70,000	3,700,000

Note that each hypothetical protein has a volume of the order of 150,000 A^3; the solution volume per protein is of the order of 2,500,000 A^3/protein - which can be considered as a solution layer about 100 A thick around each protein molecule. Thus each water molecule or solute molecule is probably no farther than 100 A from a protein surface. These are very crude calculations; they serve to illustrate the gross numbers and magnitudes involved.

THE ENDOTHELIAL SURFACE

The inner surface of most of the vascular system consists of a single layer of thin polygonal cells, endothelial cells, which form a tight smooth surface. The cells are generally about one micron thick. The intercellular junctions are about 100-200 Å wide and probably serve as pores[34]. Sawyer and his group have outlined a model for the vascular wall interface[35], containing negatively charged pores on the order of 20 to 50 Å in diameter and having an electrical double layer approximately 10 Å thick with a zeta potential in the 10 to 15 millivolt range. They suggest that the surface charge is essentially neutralized at about 10 Å into the solution. The negative surface charge of cells and the consequent double layer result in a concentration of cations, including calcium and hydrogen, leading to an interfacial pH and pCa significantly different from that in the bulk[36], possibly affecting pH or pCa-dependent reactions.

It is generally agreed that intact, normal endothelium is blood compatible. It is, therefore, of interest to consider the nature of the endothelial surface, that outermost structure which directly contacts and interfaces with blood.

The interface between cells and the extracellular environment has a very low interfacial tension[19,21,36,37]. There is some question as to the relationship between the measured tensions and true interfacial tension or interfacial free energy[36,38]. It is generally agreed that the cell/medium interfacial tension is in the 1-3 dynes/cm range, but can be as low as 0.1 dyne/cm for certain cell types[19,21]. This low interfacial tension was one of the major reasons for the development of the Harvey-Danielli model of cell membranes; it was obvious that the lipid bilayer could not directly interface with extracellular fluid (if it did the interfacial tension would be in the 10-20 dynes/cm range, much higher than observed[36]); thus an outer protein coat was postulated, based on interfacial tension studies with proteins at oil/water interfaces[39]. There are many other ways by which interfacial tensions could be minimized[40].

There has been a wide variety of evidence for the existence of carbohydrate-rich coats on the outer surfaces of cells, intimately connected with the plasma membrane itself. In 1962, Brandt[41] considered the so-called "extraneous coats" of cell membranes quite seriously and by indirect evidence established the existence of the coats and their importance in cell phenomena, including pinocytosis, water transport, and membrane selectivity. A recent text on biological electron microscopy[42] clearly points out the existence and importance of the cell coat. Extensive reviews are available on the outer cell coat[43-47], generally concluding that it is a carbohydrate-rich structure, covalently attached to the plasma membrane and extending out into the extracellular aqueous phase[45]. Glycolipids are probably also present in the interior regions of the coat, perhaps directly interfacing with the plasma membrane (Figure 1). The cell coat may be somewhat collapsed and perhaps denser in the vicinity of the plasma membrane. The oligosaccharide moieties in the outer regions of the coat are probably highly extended into the outer aqueous solution (Figure 1), has been observed on over 50 different cell types[47], and may be present on all cells[44]. The coat is obviously the outermost layer or barrier between the cell and its environment and must be expected to play a fundamental role in cell interfacial phenomena. Its common nature is not to imply that it is the same from cell to cell or even on the same cell at different times. The coat is important in antigenic properties and may react specifically with its environment[44,45]. The thickness of the coat is not well known; estimates indicate it may extend out 300 Å or more[46]. Its thickness is very important in cell adhesion phenomena[48]. It is likely that the coat may not be homogeneous and may vary in local charge, thickness, and composition. The evidence for the existence of carbohydrate-rich cell coats is convincing, though there is still some disagreement[49].

It is clear that a carbohydrate-rich layer would be highly hydrated and gelatinous, and would probably have a very low interfacial energy. It is difficult to imagine how one can obtain an interfacial energy of one dyne/cm or lower in water without postulating that the "solid" side of the interface is very highly hydrated. It is evident that proteins in the surface layer are in a gel-like state[21]. The same must be true for the carbohydrate-rich cell coat. Nonspecific adsorption, once the interfacial energy is in the 0.2 - 2 dyne/cm range, is very weak and probably highly reversible[50,51].

The presence of water on both sides of the interface is not sufficient for a low interfacial tension. The ice-water interface is a good example, exhibiting an interfacial tension of about 22 dynes/cm[52]. It is how the water is structured and oriented at the interface which is important[13] and not necessarily how much water[53] (though one can expect some correlations between the amount of water in a gel and its structuring)[13]. It is probably not a coincidence that carbohydrates contain large amounts of hydroxyl groups, known to minimally perturb the structure of water[54,55], particularly in certain conformations of the molecule[55,56]. The same may be true for the backbone oxygens in peptides and proteins[25].

It has been suggested by one of us[6] that interfacial tensions at implant/tissue or implant/blood interfaces of the order of 5 dynes/cm or lower are probably biocompatible. However, it is possible that interfacial tensions in the several dyne/cm range are biologically significant and can function as driving forces for various phenomena; for example, cell sorting[57]. If so, such energies might also be important in blood compatibility.

The interfacial properties of the normal intima are obviously of interest. It is highly likely that it, too, is carbohydrate-rich and probably highly gelatinous. The question of the wettability or non-wettability of the intima has been considered by Vroman[58], concluding that "... the endothelium was wettable, wettable for blood"[58]. Vroman also noted that he injected "... oil into the plasma space, and the oil stayed round, telling me that it did not want to coat the endothelium, that it would rather have the plasma do that..."[58]. Comparing this experiment with our earlier discussion of cell interfacial tension and the Hamilton method[10] for determining the polar contribution to the interfacial adhesion, it is clear that Vroman showed the endothelium had a very low interfacial tension against blood. This is to be contrasted with the conclusion reached by Baier and De Palma[59] from critical surface tension and infrared spectroscopy of the inner surface of dehydrated blood vessels. They concluded that the inner surface had a critical surface tension of about 25 dynes/cm, thus substantiating the Baier hypothesis for blood compatible surfaces[4]. They further suggested that the inner surface of blood vessels consists largely of methyl groups. This is in contrast to the wealth of evidence for the carbohydrate nature of the cell surface, for its low interfacial tension, its gelatinous nature, and its wettability. Their conclusions are probably due to the depth of penetration of the infrared beam and perhaps to collapse and/or restructuring of the intimal surface upon dehydration. Even the "fully hydrated" surface may be significantly different from the same surface immersed in H_2O, due to the influence of the air/gel interface. This is not to say that "free surface" parameters are not important - they most certainly are, though one must be careful to not overextend them.

PLATELETS AND RED BLOOD CELLS

Platelets are known to stick or adhere to damaged endothelium, collagen, fibrin, and many "foreign" surfaces. They are not generally known to stick to intact endothelium or other blood cells and probably not to most undamaged cells. Although the exact basis of these phenomena are not well known, it is certainly reasonable to expect that the outermost carbohydrate coat of the platelet must play a major role. White[60] has noted that the platelet surface is the most sensitive portion of that cell's anatomy. The platelet membrane has the remarkable capacity of being able to transform from a non-sticky to a sticky state. It does contain a coat on the order of 150 to 200 Å thick which is believed to be largely carbohydrate material. White says that the exterior coat is the layer in which platelet stickiness develops[60]. The available methods for establishing the existence of polysaccharides and carbohydrate substances at the electron microscopic level have demonstrated the existence of cell coats on human blood platelets[61]. The coat is important in the mechanism of adhesion of various substances to the platelet surface and is evidently involved in platelet adhesion and platelet aggregation. Behnke considers the coat as a functional structural element of the cell membrane itself[61]. Behnke further suggests[61] that the characteristic gap observed between neighboring platelets in aggregates may be due to the presence of the coat preventing direct contact between the plasma membranes. A similar intercellular space is present between adhering endothelial cells[34]. It is known that this space is occupied by a substance containing glycoproteins, and it is speculated that this substance acts as an adhesive or cementing substance. It appears that the coat substance may also be involved in adhesion in platelet aggregates. Behnke's photo micrographs clearly document the existence of an outer cell coat on the human platelet.

The red blood cell membrane is perhaps the most studied membrane in all of membrane biology. A glycoprotein has been extracted from the red blood cell membrane which is believed to be located entirely on the exterior surface of the intact red cell. The protein apparently contains a lipophilic zone which is continuous with and adheres to the lipophilic region of the plasma membrane and then a highly hydrophilic zone containing the sialic acid residues which extends out into the aqueous environment[62].

It is thus clear that both the platelet and the red cell contain carbohydrate-rich coats, though the coats differ greatly in terms of sialic acid density, saccharide composition, and probably in thickness. The platelet is apparently uniquely equipped to adhere to foreign surfaces, including damaged endothelium or the subendothelium, and to adhere to other platelets and aggregate, under the proper stimuli, yet it must not adhere under normal conditions. The red cell's function is non-adherence. Both cell types are apparently free to contact the damaged vessel wall or foreign surface, but only the platelet can stick. This unique behavior must rest, at least in part, in the platelet membrane. There must be a delicately balanced mechanism which can readily sense and induce platelet sticking when necessary. It has been suggested that the induction of platelet aggregation may be related to a change in the local water organization in the vicinity of aggregating agents[32] and, by extension, in the vicinity of the damaged vessel wall. Abdulla's "entropic trigger" mechanism[32] is very intriguing; a related mechanism involving ordered water is believed, at least in part, responsible for the elasticity of elastin[63]. It could be that the high sialic acid surface density of platelets[64] potentiates the mechanism. Such a suggestion need not be incompatible with the glucosyl transferase - glycoprotein model of platelet adhesion[65].

THE MINIMUM INTERFACIAL ENERGY HYPOTHESIS

Why do cells have such low interfacial tensions? Why are cell surfaces highly hydrophilic and gelatinous? Biochemistry and physiology appear to be dependent on specificity and coexistence. Platelets, red cells, endothelium must all coexist and not interact, yet they must respond nearly instantaneously and react in their own specific way under the proper stimuli. Nature's problem is to design a system which is highly non-reactive, i.e. "biocompatible", and yet capable of highly specific and subtle interactions. Fortunately, our problem is to design a surface which, when placed in blood, will exhibit a non-reactive interface. A non-reactive interface means one which will not be involved in adsorption or adhesion phenomena, in double layer formation, or in highly adverse water interactions. A highly gelatinous, high water content, interfacial zone, appears to meet these requirements - particularly if the gel is not charged and its dipole character is such that local water bonding is not greatly perturbed. Such a gel should exhibit a very low interfacial energy with blood or other physiological fluid. Such a gel should be blood compatible. This "minimum interfacial energy hypothesis" has been suggested a number of times[6].

A carbohydrate gel, say an uncharged polysaccharide, might be suitable. A highly hydroxylated synthetic gel might also be suitable. Our group has chosen to use synthetic, biologically stable, methacrylate-based gels, containing side chain hydroxyl groups which impart hydrophilicity. These materials are often called synthetic hydrogels and are being considered for medical use[66,67]. Their relatively poor mechanical properties can be circumvented by properly attaching them to a suitable substrate[53,68,69]. The most popular of these gels has been the polyhydroxyethyl methacrylate (PHEMA), one form of which is called Hydron® [67]. The blood compatibility of hydrogels has not been extensively studied, though the results to date are encouraging[53].

The consideration of hydrogels for medical use has been intuitive. The gel is more like the natural vessel, it is soft and pliable, it gives, it is non traumatic to protein and cells, it is more natural, etc. These are all intuitive expressions of what we have tried to outline here and elsewhere[6]. There has been a general impression that the compatibility of a gel interface should increase with its water content[53]. Our own view on this subject is in the literature[6]. More recently the role and organization of water in the gel and particularly on its surface has been considered[13] - not the organization of water at the gel/air interface, but the organization of water at the gel/water interface.

If one applies the Hamilton test[10] to the endothelium[70], one finds that the polar interfacial energy is at a minimum. The oil or octaine drop beads up to form a nearly perfect sphere[58]. If one applies the same test to the surface of a bulk 40% water PHEMA gel[70], the angle is about 150°, indicating a small but detectable interfacial energy. The critical surface tension of these gels is about 47 dynes/cm[71], yet their interfacial energy is quite low, though perhaps not as low as the endothelium or monolayers of cells in culture[70]. A radiation-grafted HEMA gel on an inert substrate also exhibits an octane/water contact angle of about 150°[70], indicating that a thin grafted layer probably has interfacial properties similar to that of a conventionally polymerized gel. Though such gels appear to be blood compatible, their surface may not be optimum. If we indeed want a minimum interfacial free energy situation, with little or no adverse interfacial water structuring, then conventional PHEMA gels may not be optimal. There is substantial evidence that the water in such gels is organized and structured[13,61,72]. The ion conductivity data for PHEMA gels is a function of the water content of the gels. A plot of the activation energy for ion conduction against percent water (Figure 2) shows distinguishable slopes, indicating that "x, y, and z water" may exist in synthetic hydrogels[13]. These results are verified by thermal expansion data and by differential scanning calorimetry studies[72]. Low water content PHEMA gels (20% water) consist of highly organized water which exhibits no phase transition in the vicinity of 0° C. Higher water content gels (40% water) appear to contain primarily y and z water[13,72].

As blood may contain relatively structured water, a certain degree of interfacial water structuring may be desirable for optimum compatibility.

We do not completely understand the role of the surface charge of the endothelium in blood compatibility - perhaps the double layer ion concentrations and the local water of hydration may play important roles. We have also totally ignored flow effects. It may well be that the synthesis of flow and surface effects may rest in the endothelial boundary layer, in the electrical double layer in the vicinity of the shear plane, and in the effect of flow on interfacial water organization.

CONCLUSIONS

1. Cells exhibit very low interfacial tensions with the extracellular environment.
2. The interfacial properties of cells are highly dependent on their carbohydrate-rich outer "coat," including red cells, platelets, and normal vascular endothelial cells.
3. The outer cell coat is most likely hydrophilic, gelatinous, extended out into the solution, and probably of very high water content. It could be considered as an uncrosslinked, water soluble macromolecular solution - concentrated and immobilized at the cell interface.
4. Blood plasma can be considered as a 90% water solution - each water molecule probably within 10-20 Å of non-water bonding influences, such as ions, proteins, etc. Thus it is reasonable to suspect that plasma water bears little relationship to the properties of pure water.
5. Water is now known to be structured, organized, and influenced by a variety of solutes and surfaces, including many hydrogels.
6. The structure of water is of importance in a wide range and variety of biological phenomena; it is reasonable to hypothesize that it may also play a role in cardiovascular interfacial phenomena.
7. Synthetic surfaces which can coexist with blood with a low interfacial energy and whose interfacial water is not significantly different from plasma water merit extensive study as blood compatible surfaces.
8. Parameters which characterize only the free surface properties of a material, such as surface charge, surface energy, surface tension, and critical surface tension, should be used conservatively and with great caution until bio- and blood-compatibility is much more clearly understood. It is doubtful that such parameters can be used to screen materials for their biocompatibility.
9. Fluid dynamics may significantly affect the interfacial properties and must be considered in any complete treatment of interfacial blood compatibility.
10. Water is the most concentrated biochemical in blood and in tissues. It merits much more extensive consideration in biochemical and physiological processes.

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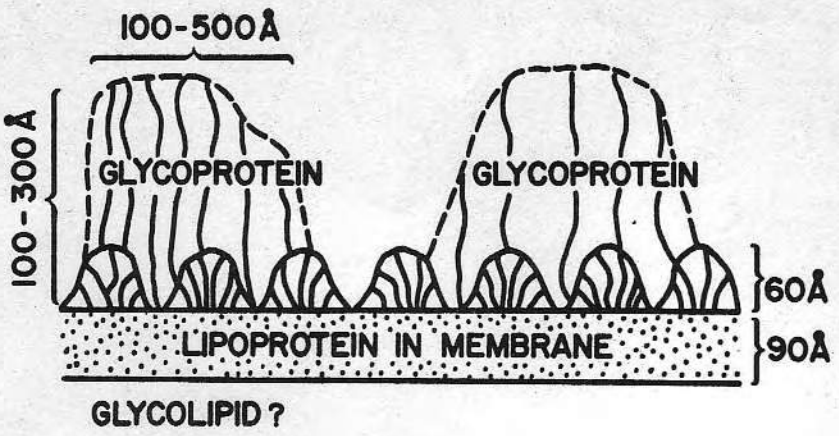

Figure 1. A model of the surface carbohydrate structure of the red cell membrane. Note the extension of the glycoproteins into the aqueous phase. The oligosaccharide portions (not shown) may be even more extended. The outer structure is obviously highly hydrated and very "loose"(46).

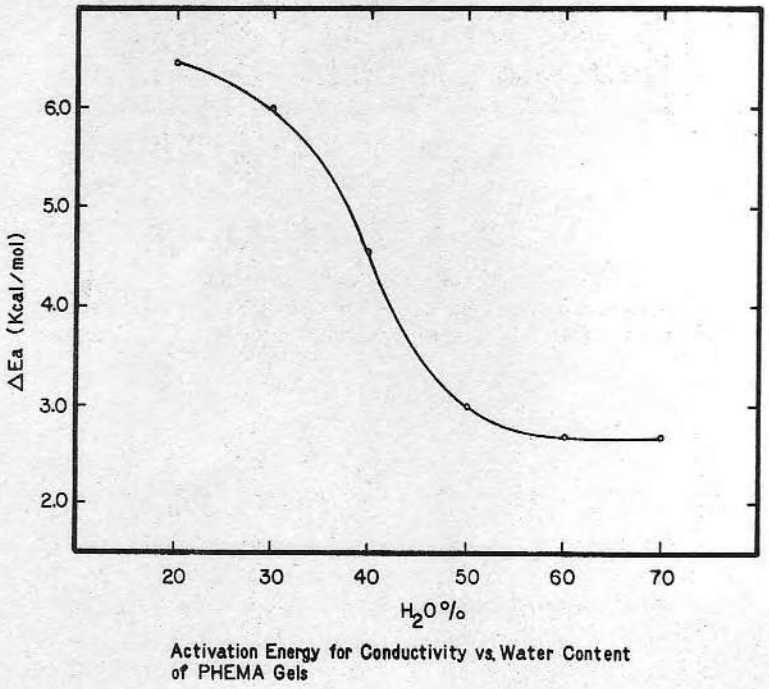

Figure 2. Activation energy for ion conduction of polyhydroxyethyl methacrylate hydrogels (1% ethylene dimethacrylate cross-linker) plotted against gel water content. Note that the curve can be considered to be made up of 3 parts(13).

The Coating of Activated Carbons for Optimal Blood Compatibility

J D ANDRADE, D L COLEMAN, S W KIM and D J LENTZ

Sorbent haemoperfusion has been studied for the past 25 years for the removal of endogenous and exogenous toxins (see Chang, 1972a for reviews). Most of the work in the last decade has focused on two general classes of sorbents: (1) activated carbon (see Andrade et al, 1972a for a review) and (2) polymeric adsorbents (see Rosenbaum, 1972 & 1974 for reviews). The major application of sorbent haemoperfusion has been in three areas: (1) treatment of uraemia; (2) acute drug overdose, and more recently (3) treatment of hepatic failure.

PROBLEMS WITH UNCOATED CHARCOAL

Activated carbon has been the most studied adsorbent, because of its broad adsorption spectrum, its high surface area and capacity, and its ready availability. There are, however, two major problems associated with direct haemoperfusion over activated carbon: carbon microparticles (micro-emboli), and blood compatibility. The microparticles are in part due to the highly porous nature of activated carbon, which makes it inherently fragile. The microparticles present on the carbon surface are readily seen on scanning electron micrographs (Figure 1) and the carbon is obviously rough, and susceptible to abrasion and further fracturing. Another factor is the ash content and ion exchange capacity of some carbons, which can lead to electrolyte changes.

Haemoperfusion of columns of uncoated activated carbon generally results in acute thrombo- and leucocytopenia, and also sludging and channelling which leads to pressure gradients and often reduced clearances. Relatively high heparin doses are generally used for haemoperfusion of uncoated activated carbon. Such blood incompatibility is a common characteristic of most high surface area particulate systems, due to high surface area to blood volume ratios, relatively long blood residence times, and generally poor local haemodynamics.

The microparticle problem can be greatly reduced by proper selection and washing of the carbon (Andrade et al, 1972a, b; Van Wagenen et al, 1974).

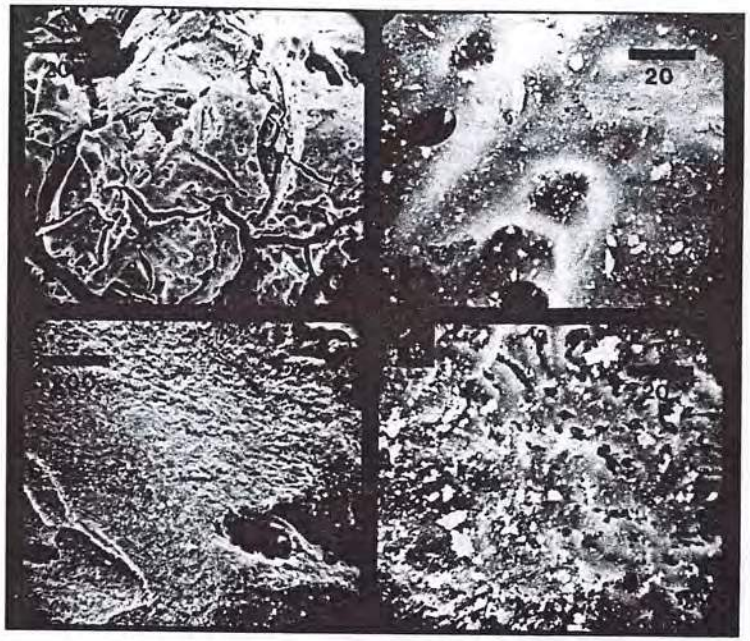

Figure 1. Scanning electron micrographs of Witco 517 (Witco Chemical Co, New York, N Y, U S A) and Fisher (Fisher Scientific Co, Fairlawn, N J, U S A) granular activated carbon. The Witco material is on the top (a & b), the Fisher on the bottom (c & d). The bars on a & c represent 200 microns, those on b & d represent 20 microns. The micro-particles present on the surface are evident, particularly at the higher magnification. (From: R Van Wagenen et al, 1974).

By proper design of the washing procedure the carbon can be cleaned of soluble ash and electrolytes. Coating or encapsulation of the carbon is usually done to further reduce the microparticle problem and to impart the needed blood compatibility.

BIOCOMPATIBLE COATING OF ACTIVATED CHARCOAL

The coatings studied to date are shown in Table I. Some coatings are strong and apparently excellent in minimising microparticles, while others are very blood tolerable but perhaps less effective with respect to reducing microemboli. While a fairly complete study exists on the evaluation of commercial activated carbons (uncoated) and on the selection of an optimum carbon (for the parameters

TABLE I. Coating of Activated Carbon for Medical Applications

Coating	Investigator	Year**	Institution	City
Albumin, Adsorbed	Coleman & Andrade	1974	U of Utah	Salt Lake City
	Herbert et al*	1964	Mt Sinai Hosp.	New York
Albumin, Adsorbed on Cellulose Nitrate	Chang	1969	McGill	Montreal
Albumin, Cross-linked	Andrade et al	1971	U of Utah	Salt Lake City
	Coleman & Andrade	1974	U of Utah	Salt Lake City
Cellulose Acetate	Yatzidis	1966	Univ.of Athens	Athens
	Rosenbaum et al	1968	Temple Univ Med School	Philadelphia
Cellulose Triacetate, deacetylated	Denti et al	1973	SORIN	Saluggia (Italy)
Cellulose Nitrate (Collodion)	Chang	1968	McGill Univ	Montreal
	Rietema & Van Zutphen	1972	Tech Hoge School	Eindhoven
Dextran, Adsorbed	Herbert et al*	1965	Mt Sinai Hosp.	New York
Haemoglobin, Adsorbed	Lau et al*	1965	Mt Sinai Hosp.	New York
Heparin Complexed Cellulose Nitrate	Chang	1967	McGill	Montreal
Hydroxyethyl Cellulose	Davis et al	1974	So Research Inst	Birmingham (USA)
Methacrylate Co-polymer***	Gilchrist et al	1974	Strathclyde Univ	Glasgow
Nylon	Chang	1966	McGill Univ	Montreal
Polyhydroxyethyl methacrylate	Andrade et al	1971	U of Utah	Salt Lake City
	Willson et al	1973	King's College Hospital	London
Unidentified*** Acrylic Polymer	Fennimore et al	1974	Smith & Nephew Research Ltd	Harlow, Essex

*For clinical assay applications
**Year of first report or for unpublished work, year of our first knowledge of the work
***Reported in this volume

evaluated) for haemoperfusion applications (Van Wagenen et al, 1974), no comparable study exists for a range of different coatings and only a limited number of coatings have been thoroughly evaluated (Andrade et al, 1971; Chang, 1972a, 1974; Fennimore et al, 1974; Gilchrist et al, 1974). Clearly a detailed comparative

study of a large variety of potential coating systems is needed, with emphasis on fine particle production, permeability and mass transfer properties, and blood tolerability. Appropriate protocols are readily available (Andrade et al, 1972a; Chang, 1972a; Chang, 1974; Fennimore et al, 1974; Van Wagenen et al, 1974). Such a broad study is essential before extensive commercial development and clinical application is carried out, with what may well prove to be less than optimum systems.

The characteristics of an 'ideal' coating system are:

1. The coating must be strong enough to eliminate all fragmentation and generation of carbon fines (microemboli).
2. The coating must be freely permeable to the toxins of interest.
3. The coating must be blood tolerable, particularly with respect to the adhesion of blood cellular elements.
4. The coating must permit good flow and low pressure drops in the column, i.e. coated particles must not adhere or aggregate in the column.
5. The coating must be readily sterilisable, be non-toxic and non-pyrogenic.

A suitable coating, particularly albumin coatings and certain hydrogel coatings, can dramatically improve the blood compatibility. Other materials exhibit excellent blood compatibility (Bruck, 1972, 1974) but have not been used for sorbent encapsulation.

THE ALBUMIN AND HYDROGEL HYPOTHESES

It is generally accepted that protein adsorption is the first discernible event in foreign-surface-induced coagulation and thrombosis, followed by platelet adhesion and perhaps aggregation, and then – depending on the degree of anticoagulation – fibrin formation and true coagulation.

Lee & Kim (1974) and Kim et al (1974) have proposed a mechanism for platelet adhesion to surface-adsorbed protein. This mechanism is based on platelet enzyme-adsorbed glycoprotein complexes which result in platelet adhesion to the interface. Of the common plasma proteins, surface adsorbed gammaglobulins and fibrinogen can participate in such complexes, but adsorbed albumin cannot, as it lacks the required carbohydrate acceptors (see Kim et al, 1974). Thus a surface which fails to adsorb gammaglobulins, fibrinogen or certain other glycoproteins should be thromboresistant. A surface which preferentially adsorbs albumin rapidly *and* maintains an adsorbed albumin film in equilibrium with plasma should not be able to participate in the enzyme complexes and should therefore be thromboresistant.

The Lee and Kim model (1974) is basically an extension of a general mechanism of intercellular and cell substrate adhesion proposed by others (Roseman,

1970; Bosmann, 1971; Jamieson et al, 1971). If one accepts this model, then a number of approaches to thromboresistant surfaces become obvious:

1. Produce a surface which does not adsorb protein. This is the basis for the minimum interfacial free energy or hydrogel hypothesis (Andrade, 1973; Andrade et al, 1973).
2. Produce a surface which selectively rapidly adsorbs albumin from plasma and maintains the adsorbed albumin film. This may be an explanation for the apparent blood tolerability of certain polyether urethanes.
3. Pretreat the surface with adsorbed albumin or produce an immobilised or covalently bonded albumin film. This is the albuminated surface approach which has been suggested and applied by many investigators.

We will consider each of these approaches briefly.

Minimum Interfacial Energy

Interfacial adsorption is largely dependent on interfacial free energy. It is observed and commonly accepted that interfacial adsorption decreases as the initial interfacial free energy decreases (Davies & Rideal, 1963; Andrade, 1973). Thus, the essence of the minimum interfacial free energy hypothesis is that if one can produce a prostheses/plasma interface of minimal, ideally zero, initial interfacial energy, then adsorption phenomena will be minimised or virtually non-existent. If proteins, particularly certain glycoproteins (Lee & Kim, 1974) cannot be adsorbed, then platelet adhesion cannot occur (Kim et al, 1974) and the interface is thromboresistant.

How Does One Achieve a Low Interfacial Free Energy?

We have discussed the answer to the question previously (Andrade 1973; Andrade, et al, 1973). Briefly, the 'solid' side of the interface must be as similar to plasma as possible, especially in terms of the intermolecular interactions present. This means that the 'solid' must contain water and electrolytes, and perhaps low molecular weight solutes as well.

A hydrogel surface partially satisfies these criteria. A loosely cross-linked aqueous gel will equilibrate with plasma constituents (Bruck, 1972, 1973), particularly water, ions and low molecular weight solutes. The gel solution interfacial free energy will depend on the nature of the equilibration, partitioning of various solutes in the gel, organisation of water in the gel (Jhon & Andrade, 1973) and in the plasma (Andrade et al, 1973), and the interface electrical potentials present (even for 'uncharged' gels). The interfacial free energy should determine subsequent interface adsorption processes, speaking of course in a general surface chemistry sense.

A variety of synthetic and natural aqueous gel systems are available. Though

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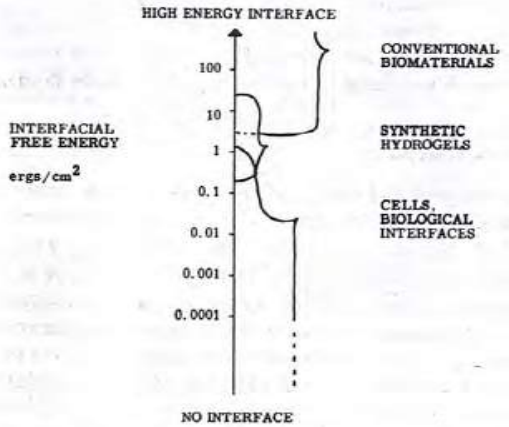
We have previously reviewed the nature of cell/solution interfaces with emphasis on interfacial properties of endothelium, red cells and platelets (Andrade et al, 1973). It is now generally accepted that the outer cell surface is a carbohydrate-rich zone, actually glycoprotein of high carbohydrate content, extending from the classical cell membrane into the extracellular phase. This zone is obviously very hydrophilic, perhaps gel-like in nature, of high water content, and exhibits a very low interfacial tension (Andrade et al, 1973). In addition, the carbohydrate-rich zone contains most of the sialic acid residues, largely responsible for the negative surface charge of the cell. Thus nature has managed to interface most cells with extracellular solutions in such a way as to provide a very low interfacial energy.



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One approach to prevent the desorption of pre-adsorbed albumin is to chemically attach the albumin to the substrate (Andrade, 1970) or to crosslink the adsorbed film and in effect encapsulate the material (Andrade et al, 1971). Glutaraldehyde cross-linked albumin exhibits thromboresistance for longer periods than adsorbed albumin (Coleman & Andrade, 1974) but only short-term studies have been made to date.

DISCUSSION

We have presented a preliminary rationale for the apparent blood tolerability of albumin-coated and hydrogel-coated adsorbents. There are certainly many other blood tolerable materials (Bruck, 1974) which we have not considered and which may not fit the rationale presented. This is not surprising for there may be more than one mechanism for the adhesion of platelets to foreign surfaces. The purpose of the hypothesis is to help the design of future experiments which should lead to a more complete understanding.

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DISCUSSION

THE CHAIRMAN: In relation to one thing which Dr Andrade mentioned, I would like to point out that not all hydrophillic materials are blood compatible, so that the presence of water alone does not ensure blood compatibility. We have a number of polyurethanes which take up water to 90% of their weight and are not blood compatible. Furthermore a number of other materials exist which do not contain water and which are blood compatible.

The other question is why do you not study acrylamides? In contrast to hema, they do not seem to have any kind of deleterious effects on platelets.

DR J D ANDRADE (USA): I would question that hema does. It depends a great deal on the purity of the preparation, the methacrylic acid content, and so forth. Gels are very subtle systems. I do not mean to imply that water is a

controlling force in gels but it plays a very important role. It is probably one term in a multiparameter equation for which we do not yet even know the other terms. My aim with gels is to minimise, or better eliminate, all protein adsorption to the surface. Such a system is certainly going to involve water, as well as the matrix of the gel network in its interactions with other solutes. It is also going to involve the ionic equilibria, and the interface junction potentials which exist if the gel itself is uncharged, because of ion partitioning and so forth, plus a variety of other factors. With respect to non-gels being blood compatible, I tried to indicate that if the material for some reason or other preferentially binds albumin, or absorbs albumin very rapidly and keeps it there, this will make it blood tolerant. This is very similar to Dr Baier's rationale. He says that blood tolerable materials recruit a protein, which he says has a critical surface energy (γ_c) of 25 ergs/cm which then confers blood tolerability on it. Whether or not all this will hold up with further experience I do not know.

PROFESSOR T M S CHANG (Canada): I would just point out that Dr Andrade's first reference to the use of carbon with albumin adsorbed directly to it was an in vitro analytical study of vitamin adsorption. This does not prevent embolism. The system we have used since 1969 for haemoperfusion is activated charcoal granules coated with polymer to prevent particle embolism and a second coating of albumin for blood compatibility.

DR J D ANDRADE (USA): Adsorbed albumin on carbon is indeed fairly blood tolerable, in our experience probably more so even than the coated hydroxyethyl methacrylate material. Gluteraldehyde crosslinked is blood tolerable. What Dr Chang says with respect to the mechanical properties of adsorbed albumin is of course entirely correct: it will have no effect whatever on particulate matter.

ARTIFICIAL LIVER SUPPORT

Proceedings of an International Symposium on Artificial Support Systems for Acute Hepatic Failure 2nd and 3rd September 1974

Edited by
ROGER WILLIAMS and
IAIN M MURRAY-LYON

PITMAN MEDICAL

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The Coating of Activated Carbons for Optimal Blood Compatibility

J D ANDRADE, D L COLEMAN, S W KIM and D J LENTZ

Sorbent haemoperfusion has been studied for the past 25 years for the removal of endogenous and exogenous toxins (see Chang, 1972a for reviews). Most of the work in the last decade has focused on two general classes of sorbents: (1) activated carbon (see Andrade et al, 1972a for a review) and (2) polymeric adsorbents (see Rosenbaum, 1972 & 1974 for reviews). The major application of sorbent haemoperfusion has been in three areas: (1) treatment of uraemia; (2) acute drug overdose, and more recently (3) treatment of hepatic failure.

PROBLEMS WITH UNCOATED CHARCOAL

Activated carbon has been the most studied adsorbent, because of its broad adsorption spectrum, its high surface area and capacity, and its ready availability. There are, however, two major problems associated with direct haemoperfusion over activated carbon: carbon microparticles (micro-emboli), and blood compatibility. The microparticles are in part due to the highly porous nature of activated carbon, which makes it inherently fragile. The microparticles present on the carbon surface are readily seen on scanning electron micrographs (Figure 1) and the carbon is obviously rough, and susceptible to abrasion and further fracturing. Another factor is the ash content and ion exchange capacity of some carbons, which can lead to electrolyte changes.

Haemoperfusion of columns of uncoated activated carbon generally results in acute thrombo- and leucocytopenia, and also sludging and channelling which leads to pressure gradients and often reduced clearances. Relatively high heparin doses are generally used for haemoperfusion of uncoated activated carbon. Such blood incompatibility is a common characteristic of most high surface area particulate systems, due to high surface area to blood volume ratios, relatively long blood residence times, and generally poor local haemodynamics.

The microparticle problem can be greatly reduced by proper selection and washing of the carbon (Andrade et al, 1972a, b; Van Wagenen et al, 1974).

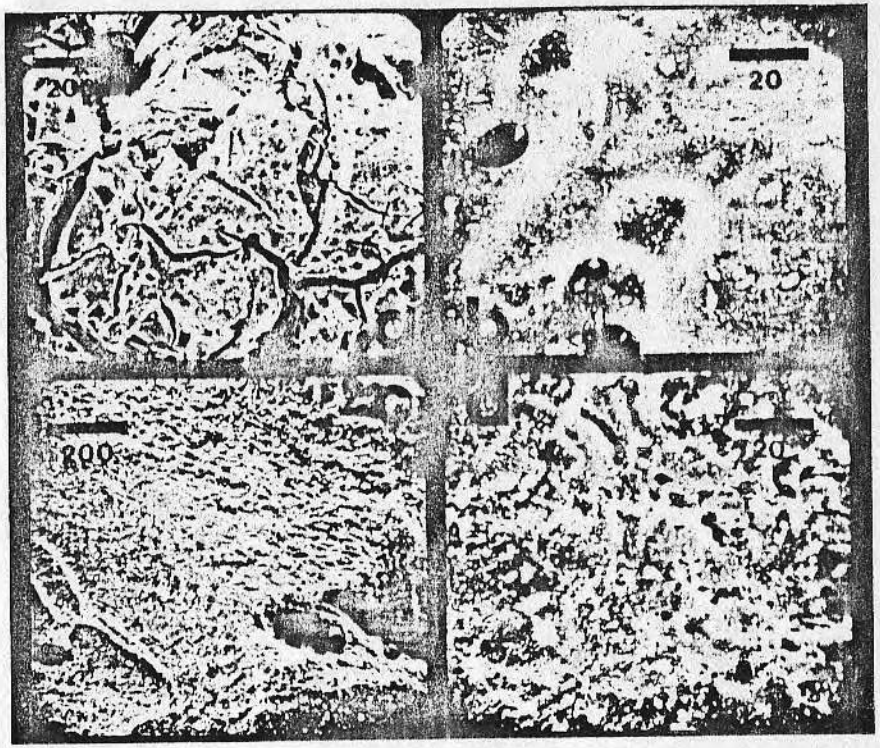

Figure 1. Scanning electron micrographs of Witco 517 (Witco Chemical Co, New York, N Y, U S A) and Fisher (Fisher Scientific Co, Fairlawn, N J, U S A) granular activated carbon. The Witco material is on the top (a & b), the Fisher on the bottom (c & d). The bars on a & c represent 200 microns, those on b & d represent 20 microns. The micro-particles present on the surface are evident, particularly at the higher magnification. (From: R Van Wagenen et al, 1974).

By proper design of the washing procedure the carbon can be cleaned of soluble ash and electrolytes. Coating or encapsulation of the carbon is usually done to further reduce the microparticle problem and to impart the needed blood compatibility.

BIOCOMPATIBLE COATING OF ACTIVATED CHARCOAL

The coatings studied to date are shown in Table I. Some coatings are strong and apparently excellent in minimising microparticles, while others are very blood tolerable but perhaps less effective with respect to reducing microemboli. While a fairly complete study exists on the evaluation of commercial activated carbons (uncoated) and on the selection of an optimum carbon (for the parameters

TABLE I. Coating of Activated Carbon for Medical Applications

Coating	Investigator	Year**	Institution	City
Albumin, Adsorbed	Coleman & Andrade	1974	U of Utah	Salt Lake City
	Herbert et al*	1964	Mt Sinai Hosp.	New York
Albumin, Adsorbed on Cellulose Nitrate	Chang	1969	McGill	Montreal
Albumin, Cross-linked	Andrade et al	1971	U of Utah	Salt Lake City
	Coleman & Andrade	1974	U of Utah	Salt Lake City
Cellulose Acetate	Yatzidis	1966	Univ.of Athens	Athens
	Rosenbaum et al	1968	Temple Univ Med School	Philadelphia
Cellulose Triacetate, deacetylated	Denti et al	1973	SORIN	Saluggia (Italy)
Cellulose Nitrate (Collodion)	Chang	1968	McGill Univ	Montreal
	Rietema & Van Zutphen	1972	Tech Hoge School	Eindhoven
Dextran, Adsorbed	Herbert et al*	1965	Mt Sinai Hosp.	New York
Haemoglobin, Adsorbed	Lau et al*	1965	Mt Sinai Hosp.	New York
Heparin Complexed Cellulose Nitrate	Chang	1967	McGill	Montreal
Hydroxyethyl Cellulose	Davis et al	1974	So Research Inst	Birmingham (USA)
Methacrylate Co-polymer***	Gilchrist et al	1974	Strathclyde Univ	Glasgow
Nylon	Chang	1966	McGill Univ	Montreal
Polyhydroxyethyl methacrylate	Andrade et al	1971	U of Utah	Salt Lake City
	Willson et al	1973	King's College Hospital	London
Unidentified*** Acrylic Polymer	Fennimore et al	1974	Smith & Nephew Research Ltd	Harlow, Essex

*For clinical assay applications
**Year of first report or for unpublished work, year of our first knowledge of the work
***Reported in this volume

evaluated) for haemoperfusion applications (Van Wagenen et al, 1974), no comparable study exists for a range of different coatings and only a limited number of coatings have been thoroughly evaluated (Andrade et al, 1971; Chang, 1972a, 1974; Fennimore et al, 1974; Gilchrist et al, 1974). Clearly a detailed comparative

study of a large variety of potential coating systems is needed, with emphasis on fine particle production, permeability and mass transfer properties, and blood tolerability. Appropriate protocols are readily available (Andrade et al, 1972a; Chang, 1972a; Chang, 1974; Fennimore et al, 1974; Van Wagenen et al, 1974). Such a broad study is essential before extensive commercial development and clinical application is carried out, with what may well prove to be less than optimum systems.

The characteristics of an 'ideal' coating system are:

1. The coating must be strong enough to eliminate all fragmentation and generation of carbon fines (microemboli).
2. The coating must be freely permeable to the toxins of interest.
3. The coating must be blood tolerable, particularly with respect to the adhesion of blood cellular elements.
4. The coating must permit good flow and low pressure drops in the column, i.e. coated particles must not adhere or aggregate in the column.
5. The coating must be readily sterilisable, be non-toxic and non-pyrogenic.

A suitable coating, particularly albumin coatings and certain hydrogel coatings, can dramatically improve the blood compatibility. Other materials exhibit excellent blood compatibility (Bruck, 1972, 1974) but have not been used for sorbent encapsulation.

THE ALBUMIN AND HYDROGEL HYPOTHESES

It is generally accepted that protein adsorption is the first discernible event in foreign-surface-induced coagulation and thrombosis, followed by platelet adhesion and perhaps aggregation, and then – depending on the degree of anticoagulation – fibrin formation and true coagulation.

Lee & Kim (1974) and Kim et al (1974) have proposed a mechanism for platelet adhesion to surface-adsorbed protein. This mechanism is based on platelet enzyme-adsorbed glycoprotein complexes which result in platelet adhesion to the interface. Of the common plasma proteins, surface adsorbed gammaglobulins and fibrinogen can participate in such complexes, but adsorbed albumin cannot, as it lacks the required carbohydrate acceptors (see Kim et al, 1974). Thus a surface which fails to adsorb gammaglobulins, fibrinogen or certain other glycoproteins should be thromboresistant. A surface which preferentially adsorbs albumin rapidly *and* maintains an adsorbed albumin film in equilibrium with plasma should not be able to participate in the enzyme complexes and should therefore be thromboresistant.

The Lee and Kim model (1974) is basically an extension of a general mechanism of intercellular and cell substrate adhesion proposed by others (Roseman,

1970; Bosmann, 1971; Jamieson et al, 1971). If one accepts this model, then a number of approaches to thromboresistant surfaces become obvious:

1. Produce a surface which does not adsorb protein. This is the basis for the minimum interfacial free energy or hydrogel hypothesis (Andrade, 1973; Andrade et al, 1973).
2. Produce a surface which selectively rapidly adsorbs albumin from plasma and maintains the adsorbed albumin film. This may be an explanation for the apparent blood tolerability of certain polyether urethanes.
3. Pretreat the surface with adsorbed albumin or produce an immobilised or covalently bonded albumin film. This is the albuminated surface approach which has been suggested and applied by many investigators.

We will consider each of these approaches briefly.

Minimum Interfacial Energy

Interfacial adsorption is largely dependent on interfacial free energy. It is observed and commonly accepted that interfacial adsorption decreases as the initial interfacial free energy decreases (Davies & Rideal, 1963; Andrade, 1973). Thus, the essence of the minimum interfacial free energy hypothesis is that if one can produce a prostheses/plasma interface of minimal, ideally zero, initial interfacial energy, then adsorption phenomena will be minimised or virtually non-existent. If proteins, particularly certain glycoproteins (Lee & Kim, 1974) cannot be adsorbed, then platelet adhesion cannot occur (Kim et al, 1974) and the interface is thromboresistant.

How Does One Achieve a Low Interfacial Free Energy?

We have discussed the answer to the question previously (Andrade 1973; Andrade, et al, 1973). Briefly, the 'solid' side of the interface must be as similar to plasma as possible, especially in terms of the intermolecular interactions present. This means that the 'solid' must contain water and electrolytes, and perhaps low molecular weight solutes as well.

A hydrogel surface partially satisfies these criteria. A loosely cross-linked aqueous gel will equilibrate with plasma constituents (Bruck, 1972, 1973), particularly water, ions and low molecular weight solutes. The gel solution interfacial free energy will depend on the nature of the equilibration, partitioning of various solutes in the gel, organisation of water in the gel (Jhon & Andrade, 1973) and in the plasma (Andrade et al, 1973), and the interface electrical potentials present (even for 'uncharged' gels). The interfacial free energy should determine subsequent interface adsorption processes, speaking of course in a general surface chemistry sense.

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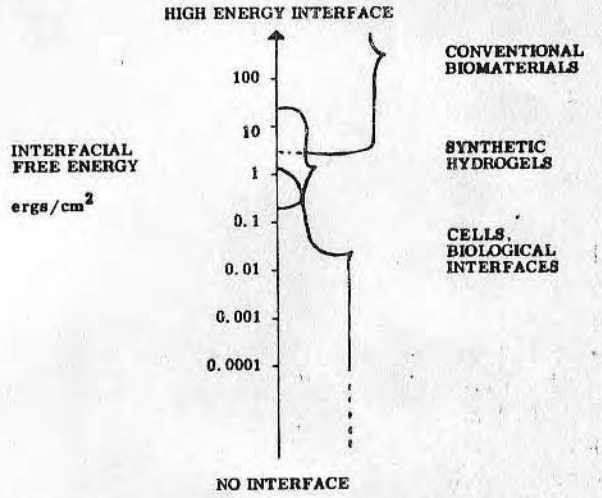

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DISCUSSION

THE CHAIRMAN: In relation to one thing which Dr Andrade mentioned, I would like to point out that not all hydrophillic materials are blood compatible, so that the presence of water alone does not ensure blood compatibility. We have a number of polyurethanes which take up water to 90% of their weight and are not blood compatible. Furthermore a number of other materials exist which do not contain water and which are blood compatible.

The other question is why do you not study acrylamides? In contrast to hema, they do not seem to have any kind of deleterious effects on platelets.

DR J D ANDRADE (USA): I would question that hema does. It depends a great deal on the purity of the preparation, the methacrylic acid content, and so forth. Gels are very subtle systems. I do not mean to imply that water is a

controlling force in gels but it plays a very important role. It is probably one term in a multiparameter equation for which we do not yet even know the other terms. My aim with gels is to minimise, or better eliminate, all protein adsorption to the surface. Such a system is certainly going to involve water, as well as the matrix of the gel network in its interactions with other solutes. It is also going to involve the ionic equilibria, and the interface junction potentials which exist if the gel itself is uncharged, because of ion partitioning and so forth, plus a variety of other factors. With respect to non-gels being blood compatible, I tried to indicate that if the material for some reason or other preferentially binds albumin, or absorbs albumin very rapidly and keeps it there, this will make it blood tolerant. This is very similar to Dr Baier's rationale. He says that blood tolerable materials recruit a protein, which he says has a critical surface energy (γ_c) of 25 ergs/cm which then confers blood tolerability on it. Whether or not all this will hold up with further experience I do not know.

PROFESSOR T M S CHANG (Canada): I would just point out that Dr Andrade's first reference to the use of carbon with albumin adsorbed directly to it was an in vitro analytical study of vitamin adsorption. This does not prevent embolism. The system we have used since 1969 for haemoperfusion is activated charcoal granules coated with polymer to prevent particle embolism and a second coating of albumin for blood compatibility.

DR J D ANDRADE (USA): Adsorbed albumin on carbon is indeed fairly blood tolerable, in our experience probably more so even than the coated hydroxyethyl methacrylate material. Gluteraldehyde crosslinked is blood tolerable. What Dr Chang says with respect to the mechanical properties of adsorbed albumin is of course entirely correct: it will have no effect whatever on particulate matter.

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A Materials Science Course for Pharmacy Students[1]

To the Editor:

Containers, packaging materials, drug administration devices and synthetic and natural polymers play very important roles in modern pharmacy. Most pharmacy curricula do not provide students with any background in the area of containers and synthetic polymers. It is imperative that pharmacy students and pharmacists be aware of the advantages and disadvantages of materials and their potential for interacting with drugs or otherwise affecting safety or efficacy.

A number of standard pharmacy texts contain chapters dealing with polymers (plastics) in pharmacy (1, 2). Autian (1, 3) pioneered much of the research dealing with the use of plastic materials in pharmacy and is largely responsible for alerting the pharmacy community to the importance of plastic materials in modern pharmaceutical practice and technology. The *U.S. Pharmacopeia* contains information on glass and plastic containers (4). There is a growing awareness of the need for testing and control of containers (5) and of drug-plastic interactions (6), the leaching of potentially toxic additives from plastic containers (5, 6) and the problem of particulate matter in parenteral preparations (7). The relatively new and growing area of controlled and sustained drug release pharmaceuticals and devices (8) is largely dependent on sophisticated polymer technology.

Drugs come into contact with materials at various stages of synthesis and manufacture, purification, sterilization, packaging and administration to the patient. Some of the equipment and materials involved in these processes include stainless steel kettles, glass kettles and containers, plastic and metal packaging materials, plastic and glass syringes, metal needles, rubber stoppers, *etc.* These varied materials can interact with drugs *via* the processes of adsorption, leaching, corrosion, or even direct catalysis or chemical bonding. In addition, plastic materials may absorb or partition drugs into the bulk plastic.

Therefore, it is important for a modern pharmacy curriculum to provide students with at least an introduction to those aspects of materials science and engineering which are important in modern pharmacy, with emphasis on plastic materials.

The Department of Applied Pharmaceutical Sciences (College of Pharmacy) and the Department of Materials Science and Engineering (College of Engineering) of the University of Utah have instituted a two-quarter course, three credit hours per quarter, for junior/senior pharmacy students called *Materials Science in Pharmacy*. The course was taught on an experimental basis during the winter and spring quarters, 1974, to about 30 students. It was offered again in 1975. The course has been well received and is now an elective course in both pharmacy and engineering for advanced undergraduate and graduate students.

The only prerequisites for the course are at least junior-level standing and at least concurrent registration in a physical pharmacy or physical chemistry course.

The first half of the course provides the basic materials science background. Major emphasis is placed on polymeric materials with secondary emphasis on glass and metal materials. Though crystal and molecular structures are briefly covered, they are not emphasized. Most of the time is spent on questions related to materials stability and degradation, including the role of additives in polymers.

The second quarter emphasizes surface properties of materials and drug/materials interactions, particularly sorption processes and permeability. The leaching of polymer additives and ions from metals and glasses is discussed, with considerations of toxicity aspects. The nature of aqueous polymer solutions and gels is treated in detail because of the importance of binders, thickening agents, jellies, and gels in pharmacy. Brief discussions of pharmaceutically-active polymers, microencapsulation, controlled drug-release and extracorporeal pharmacy are also presented.

COURSE OUTLINE

A detailed outline of course topics for this two-quarter sequence follows:

1. Role of Materials in Pharmacy

Packaging, containers, binders, fillers

[1] Presented to AACP Section of Teachers of Pharmacy, New Orleans LA, November 1974, and to the American Society for Engineering Education, Troy NY, June 1974.

Materials for drug preparation and characterization
Materials for drug delivery
Materials for drug sterilization and purification
Materials for drug attachment and immobilization

2. Nature of Materials Science and Engineering

Chemical bonding
Metals, ceramics, polymers
Packing, crystallinity, non-crystalline structures
Defects
Strengthening mechanisms
Mechanical behavior

3. Nature of Polymeric Materials

Monomers and polymerization
Chain reaction polymerization (addition)
Step reaction polymerization (condensation)
Vinyl and vinylidene compounds
Bonding in polymers — molecular models
Molecular weight distributions — number average and weight average
Linear and branched polymers
Block and graft polymers
Co-polymers — monomer reactivity
Thermosetting and thermoplastic materials
Cross-linking; 3-D networks
Impurities — monomer, initiator, low molecular weight material
Tacticity — atactic, isotactic, syndiotactic
Polymer crystals — degree of crystallinity
Physical properties — optical properties, permeability, thermal behavior
Chemical properties — biodegradability, surface properties, impurities and additives
Mechanical Properties
Processing and fabrication
Typical commercial polymers:
- Polyethylene
- Polypropylene
- Polystyrene
- Polyvinylidene Cl (Saran®)
- Polymethyl methacrylate (Plexiglas®)
- Polyethylene terephthalate (Mylar®, Dacron®)
- Polyhexamethylene adipamide (6/6 Nylon)
- Polydimethyl siloxane (Silastic® rubber)
- Polyisoprenes (natural and synthetic rubbers)
- Polybutadienes
- Polyurethanes
- Polyvinyl chloride
- Polytetrafluoroethylene (Teflon®)
- Polytrifluorochloroethylene
- Epoxy resins

Polymer additives:
- Plasticizers
- Stabilizers
- Antioxidants
- Processing aids
- Fillers
- Others

4. Nature of Inorganic Glasses

Ceramic materials in general
Silica (SiO_2) bonding
Crystalline forms of SiO_2
Amorphous SiO_2 (glass) — silicate structures
Glass-forming agents
Commercial glasses
- Soda lime
- Borosilicate

Physical properties of glass — optical, thermal
Mechanical properties of glass
Chemical properties of glass
- Solubility and corrosion
- Ion exchange
- Ion-sensitive glasses
- Gel structure of glass surfaces

Fabrication of glass

5. Nature of Metal Alloys

Solid solutions
Multiphase solid structures — grains, grain boundaries
Phase diagrams for metal alloys
Aluminum and alloys
Allotropic transformations
Iron system — stainless steel
Cobalt system
Titanium system
Corrosion
Oxide nature of metal surfaces
Fabrication of metals
Heat treating

6. Processing and Fabrication

Casting
Coatings and adhesives
Extrusion — general
Film and sheet — laminates
Tubing and shapes
Fibers
Molding — injection, blow, vacuum, other
Other considerations

Second Quarter:

1. Nature of Polymer Solutions and Gels

Criteria for polymer solubility
Solubility parameter and cohesive energy density
Shape of polymer molecules in solution
Phase separation in polymer solutions
Measuring molecular weight and size
Water soluble polymers — uncharged
- Polyvinyl pyrrolidone
- Polyvinyl alcohol
- Polyacrylamide
- Polysaccharides
- Polyethylene glycols
- Polyhydroxyalkyl methacrylates
- Cellulose and derivatives

Water soluble polymers — charged (polyelectrolytes)
- Proteins
- Mucopolysaccharides
- Sodium carboxymethylcellulose
- Polystyrene sulfonates
- Others

Properties of polymer solutions
- Rheology — viscosity

Polymer gels
- Sol-gel transformations
- Gelation on cooling
- Gelation on heating
- Cross linked gels — noncovalent
- Cross linked gels — covalent

Water structure and aqueous systems

2. The Surface Properties of Materials

High energy surfaces — metals and glasses
Low energy surfaces — polymers
The chemical nature of polymer surfaces
Contact angles, critical surface tension

Surface charge
Interfaces — general
Solid/aqueous solution interfaces
Interfacial energy
Interfacial charge
Adsorption from solution

3. Drug/Materials Interactions

Adsorption from solution
Drug reactions with surface species
Drug solubility in polymers — adsorption
Effect of materials on drug analyses

4. Toxicology of Materials

Leachables from plastics
Heavy metal ions — metal alloys
Ions from glasses
Surface residues
Particulate matter
Biocompatibility

5. Drug Delivery Sytems

Solubility
Biodegradeability
Controlled release systems
Sustained release systems
Microencapsulation
Soluble polymers as drugs and drug carriers
Extracorporeal pharmacology

6. Summary and Miscellaneous

Reference sources
Current research
Polymer — materials analyses

TEXTS AND REFERENCE MATERIALS

The present required text is Rodriguez's, *Principles of Polymer Systems* (9). A variety of readings and reserve books are utilized (1-13).

An extensive set of notes and teaching aids is being developed for the course. The development of a laboratory for the course is being seriously considered.

CONCLUSIONS

A course for pharmacy students which provides them with an adequate knowledge and awareness of materials (particularly polymers) and the application of materials in the pharmaceutical industry has been developed at the University of Utah. While many of the topics in this course are comparable to those in courses which use the classical dosage form-approach, the emphasis is different. Materials-related problems are discussed. The students are provided with sufficient background to enable them to participate actively in the solution to materials-related problems.

A modern pharmacy curriculum must consider the role of materials, particularly polymers, in the pharmaceutical sciences. Initial informal course evaluations expressed by students are favorable and lend support for continuation of this sequence.

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An Exercise in the Use of the Secondary Literature: Introduction to the Use of the de Haen *Drugs in Use* and *Drugs in Research* Systems

To the Editor:

A major goal of contemporary pharmacy education is concerned with equipping the future pharmacist with the necessary knowledge and/or skills required to allow him to practice effectively as a member of the health care team. Providing drug information to patients and to members of the health care team continues to be an accepted role of the pharmacist. This function until recently was concerned only with product information; however, today, we now consider drug information also to involve other considerations. In order for the future pharmacist to research the literature more fully for complicated drug information requests, he must be familiar with the secondary literature.

The effective utilization of the secondary literature is stressed in institutional pharmacy, a senior-level course at The University of Toledo College of Pharmacy. Utilization of the secondary literature was originally communicated to the student *via* lecture. This included an explanation of *Index Medicus, Medlars, Iowa Drug Information Service, International Pharmaceutical Abstracts (IPA), Excerpta Medica: Pharmacology and Toxicology*, and the de Haen *Drugs in Use* and *Drugs in Research* systems.[1]

The *Drugs in Use* system selectively searches over 400 professional journals, both domestic and foreign, providing over 6,000 re-

[1] Paul de Haen Inc., 11 West 42nd Street, New York NY 10036.

Hydrogels for Medical and Related Applications

Joseph D. Andrade, EDITOR
University of Utah

ACS SYMPOSIUM SERIES **31**

AMERICAN CHEMICAL SOCIETY
WASHINGTON, D. C. 1976

CONTENTS

Donald H. Ford and Doris H. Clouet, *Editors*

Tissue Responses to Addictive Drugs

New York NY: Spectrum Publications Inc. (distributed by Halsted Press), 1976. xx + 704 pp., 206 figs., 120 tbls. $50.00

This book is the proceedings of a workshop of the International Society for Neuroendocrinology held at the Downstate Medical Center, State University of New York, June 1975. The book is comprised of 42 manuscripts which were contributed by 93 authors. Most of the research groups from the United States which have major involvement in the study of the mechanisms of opiate action, tolerance, and addiction are represented. There is a minimum of contributions from foreign researchers. The manuscripts are each well referenced and the book contains a complete and useful index.

The subject matter of the book is a multidisciplinary coverage of the effects of the opiates on brain and other tissues. The first five manuscripts deal with the disposition of opiates within the brain. A number of the contributions survey the evidence for the existence of specific receptors in nervous tissue for opiates. The methods of studying opiate receptors which are discussed include stereospecific receptor binding, photoaffinity labeling, and pharmacological discrimination.

The roles of various brain amines, the cyclic nucleotides, the prostaglandins, and protein synthesis in opiate action and addiction are discussed in a number of the manuscripts. Other major portions of the book deal with the effects of the opiates on neonates and on peptide hormonal release from the pituitary gland.

Most of the manuscripts are well written and serve as useful introductions and/or overviews into many of the currently active areas of opiate research. The pace at which research in this field has advanced is demonstrated by the fact that only one manuscript referred to the enkephalins, and the endorphins were not reported. Thus, this book does not represent the current state of opiate research; but, the book does discuss much of the science and experimental technique that have made possible the rapid advancement in this area.

The book will be useful for the student or new researcher who is attempting to become familiar with the many aspects of opiate research. The cost of the book makes it prohibitive for inclusion in most personal libraries; however, the subject matter and quality of the volume are sufficient to warrant inclusion in institutional libraries which provide services to researchers in the health sciences.

David S. Fries
University of the Pacific

Joseph D. Andrade, *Editor*

Hydrogels for Medical and Related Applications (ACS Symposium Series: 31)

Washington DC: American Chemical Society, 1976. xiv + 359 pp.,-127 figs., 56 tbls. $21.75

Hydrogels have many attractive features for a number of biomedical applications including the design of drug delivery systems. These are polymeric materials which are insoluble in water but which retain a significant amount of water in their network structures. Their interfacial free energies tend to be low. A combination of a 'wet' internal surface, low interfacial free energy, and the occasional presence of surface charges makes them much more compatible with biological fluids than most insoluble materials which can be used for coating purposes or for the construction of devices of various kinds and implants. Hydrogels also have useful permeability characteristics which can be modified by structural alteration.

The present symposium volume has been edited with care by Joseph D. Andrade and appears to be the first of its kind. It contains 24 articles. After a lucid, introductory chapter, the book is divided into two parts. The first part contains 13 chapters and is concerned primarily with bulk properties of synthetic hydrogels, particularly methacrylate derivatives. The topics covered include swelling pressures and their relations to water activity, effect of water on the osmotic and viscoelastic behavior of gels, permeability characteristics of hydrogels and diffusion through gel membranes, chemical and analytical aspects of hydrogels, and their thermal behavior. One chapter deals with some connective tissue components.

The second part of the book has 10 chapters on interfacial properties of hydrogels, and includes discussions on their wettability, surface electrical properties, water sorption, co-graft polymerization induced by radiation, and the formation of fibrous capsules. Some blood compatibility studies are also reported. I found this emphasis on interfacial properties refreshing. Throughout the book, the applications of many different theoretical and experimental techniques are illustrated.

As might be expected of the proceedings of a symposium, all the chapters are not of uniform quality. I found all of them of some interest, however, and some highly thought provoking. Many of the authors are reputable scholars in the field. Occasionally some overly enthusiastic claims are made regarding the resemblance of hydrogels to biological tissues and their biocompatibility, but these do not detract much from the overall quality of the book. I recommend it highly as a review of the many different kinds of experimental and theoretical approaches currently being used to understand and characterize hydrogels and to adapt them for biomedical applications.

Pasupati Mukerjee
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A. DeBruin

Biochemical Toxicology of Environmental Agents

Amsterdam, The Netherlands: Elsevier/North-Holland Biomedical Press (distributed by Elsevier/North-Holland Inc., New York NY), 1976. x + 1,544 pp., 123 figs., 57 tbls. $130.75

Biochemical Toxicology of Environmental Agents is a difficult book to review. At first, one is almost overwhelmed that one individual could organize and write a 1,500-page book consisting of 42 chapters and about 13,000 literature citations from 1,100 journals. The author, himself, commented on having to correct, insert, and rewrite chapters as new publications appeared. Any single-author work of this size requires very good organization on the part of the author. Dr. De Bruin has done this admirably. The material is well presented including a balanced use of tables.

Is this book a textbook, a definitive reference work, or a review? It is partially a textbook, but because of the wide scope of topics that are covered, it is more of a comprehensive review of the current status of biochemical toxicology of agents encountered in the environment. The literature is covered through 1975.

Most chapters follow the same general format. There is an introduction of the topic and, where necessary, biochemical pathways are shown. The remainder, and usually the majority, of the chapter covers specific topics. Thus halogenated hydrocarbons, alcohols, ketones, aldehydes, nitro compounds, aromatic compounds, organo-metallic compounds, and ionizing radiation will be discussed in terms of the biochemical topic being covered in a particular chapter. In other words, don't look for a complete chapter on pesticides. Instead, pesticides will be mentioned in nearly every chapter.

The 42 chapters are grouped together by broad biochemical topics. Chapters 1-8 cover the metabolism of foreign compounds. These chapters are complete and detailed. There are separate chapters on occupational agents, pesticides, chemical carcinogens, hepatic microsomal enzymes, and synergism and antagonism between com-

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Joseph D. Andrade, *Editor*

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J. D. Andrade, ed., Hydrogels for Medical and Related Applic, ACS Symp. Series 31, 1976

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Probing the Hydrogel/Water Interface

JOSEPH D. ANDRADE, ROBERT N. KING, and DONALD E. GREGONIS

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The interfacial properties of gel/water interfaces are important in the biomedical applications of hydrogels, particularly in the areas of blood compatibility, tissue compatibility, and cell adhesion. The gel/water interface may also be important in the interfacial chemistry of cell membranes (1).

Very little information is available on gel/water interfaces. Many of the classical surface chemical methods involving solid/liquid interfaces are inapplicable to the gel/liquid interface, because the "solid" is highly deformable and, in general, the liquid is highly diffusible in the solid. Gels, by definition, are not sols so classical liquid-liquid interface techniques are not generally applicable.

Gel/liquid interfaces are thus experimentally and theoretically somewhat frustrating. Nevertheless, they are of such great practical and scientific importance that they merit careful study.

Silberberg has considered the gel/solvent interface, largely in a theoretical sense (2,3).

The objective of this paper is to consider a variety of experimental methods which can provide information on gel/water interfaces. Much of the discussion will be brief and perhaps shallow - but that is largely the present state of affairs with regard to gel/liquid interfaces.

Topography - Structure

The first "measurement" which should be made on a surface is gross examination, followed by microscopic examination. Is the surface rough? Does it have an apparent structure or morphology? Is there any apparent orientation? Such questions must be answered before any subsequent surface characterization can be meaningful as virtually all surface characterization techniques are surface roughness or topography dependent. Although a variety of techniques are available for measuring the topography of hard solid surfaces (4), they are largely inapplicable to gel surfaces.

Clean copy NOT MA

Optical microscopy is very useful (5) and can be used to study in situ surface topography using phase or interference contrast or with water immersion optics. Often, however, one requires higher magnification and must resort to the scanning electron microscope (SEM) or to the transmission electron microscope (TEM).

Simple air drying of the gel followed by metal coating ofte shows substantial differences in gel topography. Figure 1 shows a series of radiation-grafted poly(hydroxyethyl methacrylate) (PHEMA) coatings on polypropylene (6). The gross differences in topography are quite evident and strongly affect the surface or interfacial characterizations.

Air drying is seldom adequate for studying gel surfaces, particularly for less rigid gels. Most gels exhibit gross changes in structure and shape during drying and transformation to the xerogel state. Though a variety of techniques are available for examining delicate biological structures by SEM and TEM most generally involve fixation or cross-linking steps, followed by dehydration, and critical point drying from Freon or liquid CO_2 (7). We would prefer to avoid such procedures with gels.

The most accepted and common method of observing highly deformable gels is by freeze-etching. The sample is rapidly froze often in liquid Freon, and fractured under liquid nitrogen. The fracture surface can then be directly observed in a cold stage or cold stub-equipped SEM or it can be replicated cold and the replica examined by SEM or TEM (7,8).

Cluthe has examined radiation cross-linked poly(ethylene oxide) (PEO) gels containing 1 to 10% polymer (9) by freeze etch replication. He showed that the structures observed from embedded and sectioned gels were similar to those of the freeze-etch replicated samples. He observed and discussed "cellular" structures for the PEO gels. He also noted that the "fibrillar" structures observed in the TEM by others may result from air drying artifacts.

Blank and Reimschuessel (10) recently reviewed various gel structure theories and presented photographs of polyacrylamide, poly(ethylene oxide), and poly(vinyl alcohol) gels. They considered the liquid phase in the gel in terms of free liquid, capillary or pore retained liquid, and polymer adsorbed liquid, i.e., a three-layer model. This is similar to the "X, Y, Z" water hypothesis of gel water (11). The solid phase was considered in terms of a cellular or micellar theory and a fibrillar theory (also called the "brush-heap" theory (9)). Their photographs clearly document roughness on the 10 micron level in most of the gels examined. High resolution studies on the structure of gelatin gels are also available (12,13). Geymayer has reviewed the problems involved in high resolution studies of freeze etched gels, including cooling rates, segregation and aggregation of diffusible solutes, and instrumentation (14).

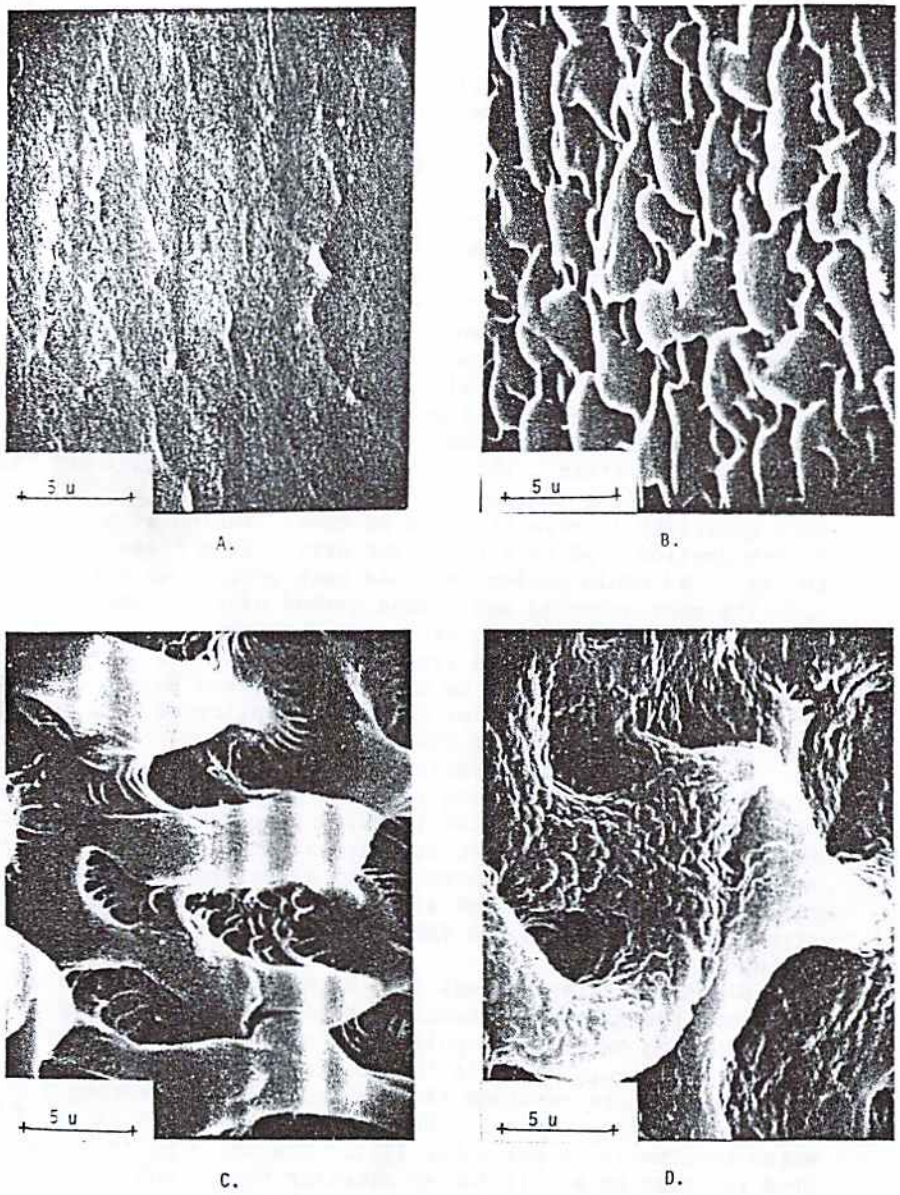


Figure 1. SEM photos of HEMA grafts on polypropylene (original magnification, 3150 ×). (A) Control; (B) 15% HEMA, 0.25 Mrad; (C) 15% HEMA, 1 Mrad; (D) 20% HEMA, 0.5 Mrad.

We have carried out some very preliminary studies of PHEMA gels using freeze-etch SEM techniques. These studies are too premature to make any conclusions as to gel surface or bulk structure, but they do permit some conclusions about experimental methodology.

One can freeze dry a sample and observe it directly in the SEM at ambient temperatures (Figure 2a). This is generally unsatisfactory due to charging. One can freeze-dry, coat the sample at ambient temperature, and observe at ambient temperatures (Figure 2b). One can freeze the sample and observe it at liquid nitrogen temperatures (charging is not a serious problem as ice is a fair conductor); the sample can be slowly warmed and the ice sublimes away revealing the structure (Figure 2c). The sample of Figure 2c was mounted as indicated in Figure 3.

It is clear, even for a fairly rigid, highly cross-linked PHEMA gel, of relatively low water content, that air drying or freeze drying and ambient temperature examination may not reveal the 'real' structure. Freeze etching certainly has artifacts also, but at this stage it appears to be the method of choice for synthetic aqueous gels (14).

A more reliable procedure than outlined in Figure 3 is to place the sample onto a temperature controlled stage. Such stages are available for most SEM's. The samples can be observed frozen, freeze-etched, micromanipulated, and, if desired, coated under controlled temperature conditions.

Figure 4 is a sequence of photographs of a 70% H_2O - 30% PHEMA opaque gel, mounted and fractured under liquid nitrogen and examined in the ETEC Bio-SEM (ETEC, Inc., Hayward, California). The topography observed may be related to the rate of freeze etching.

We have not examined transparent gels - studies are in progress. Matas, et.al., however, reported some SEM studies of hydrophilic contact lenses (15). Surface scratches and roughness could be readily seen - no apparent bulk structure or porosity could be seen.

The surface roughness of the gels can be determined by stereo pair SEM photographs and stereophotogrammetric analysis (16).

Contact Angle Methods

Contact angle methods are widely used for measuring surface tensions or free energies of liquids and, less rigorously, of solids. Interfacial tensions can often be obtained by contact angle methods.

The traditional techniques for measurement of contact angles rely on determination of the static liquid profile encountered at the three-phase line (TPL) of the solid, a liquid, and a second fluid which may be liquid or vapor. These include (17) (a) the tilting plate method, (b) the sessile drop method,

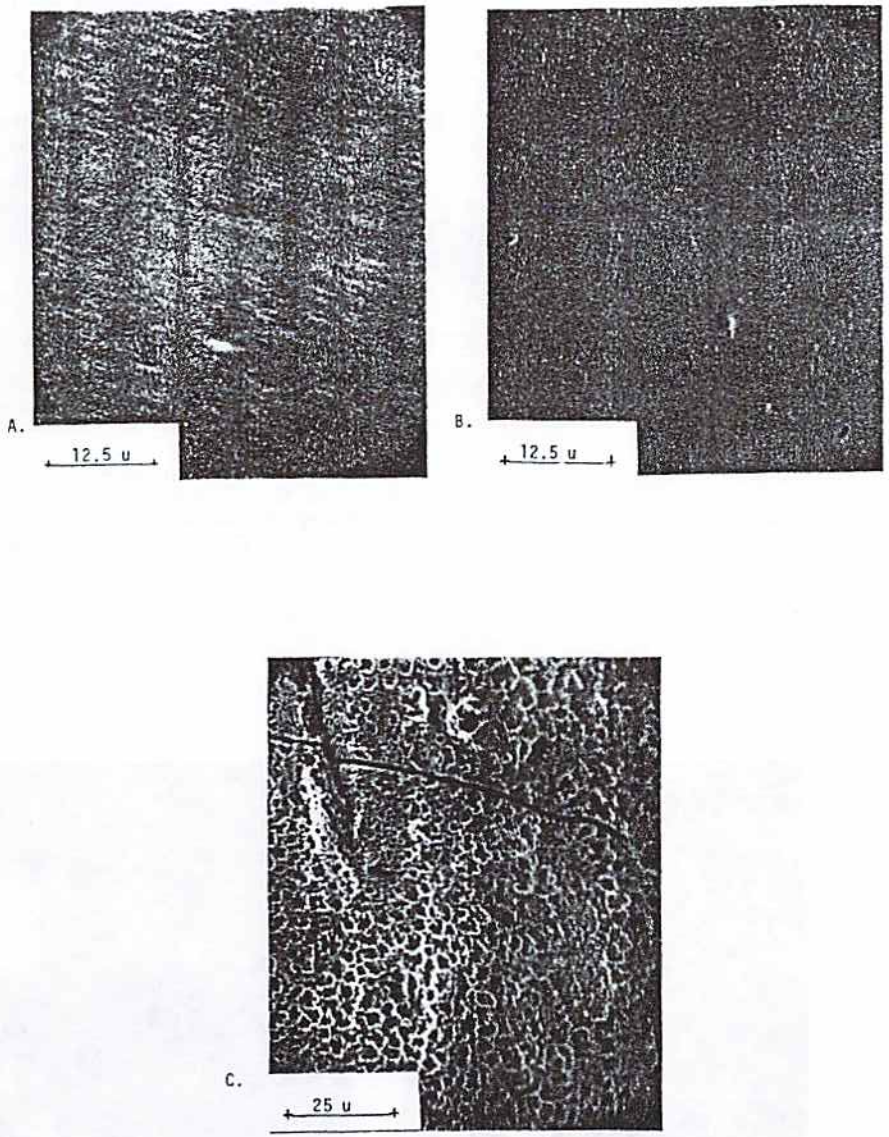


Figure 2. A PHEMA gel containing 7.5% ethylene glycol dimethacrylate crosslinker. The gel is opaque and contains 38.1% wt water. (A) Freeze-dried, stored ambient, and examined ambient; (B) freeze-dried, coated ambient, and examined ambient; (C) frozen; freeze etched; examined cold.

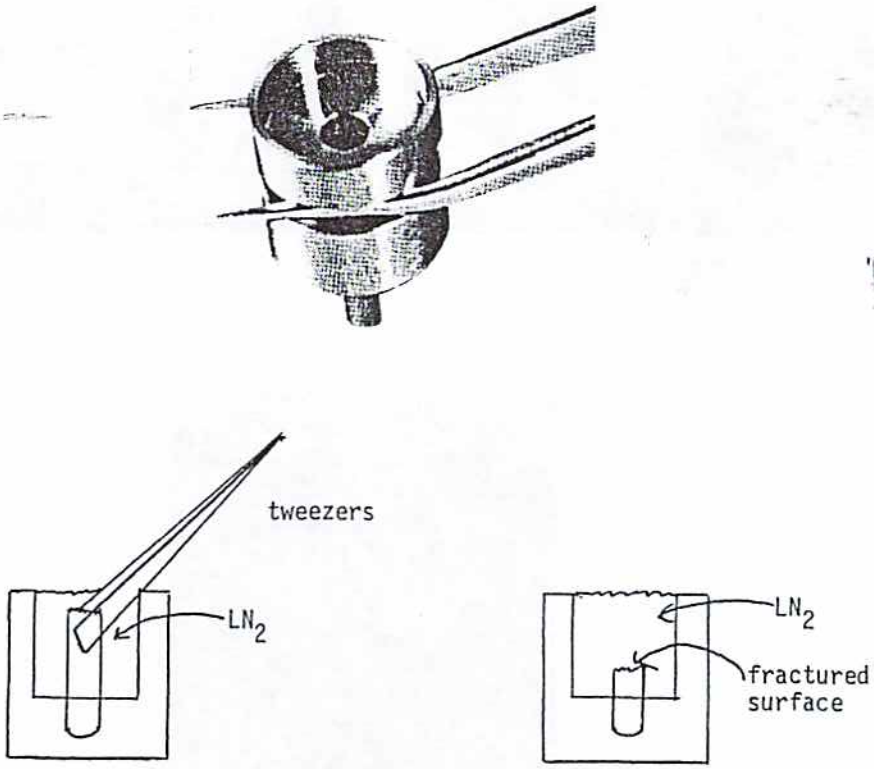
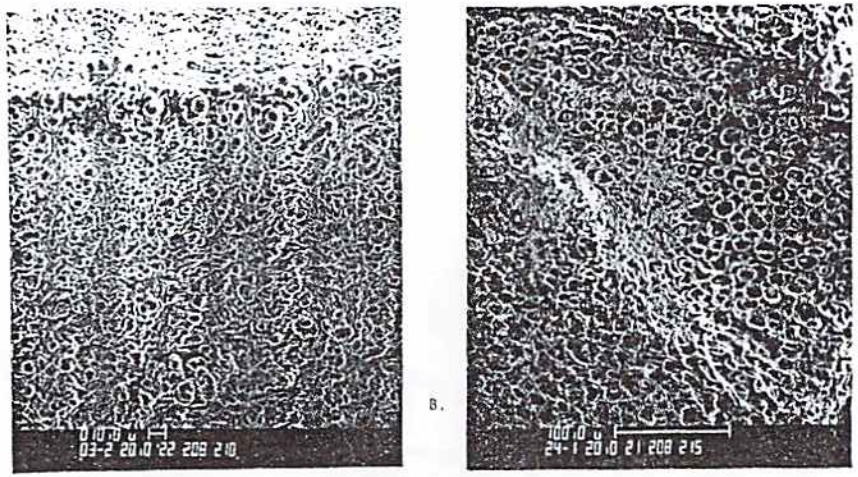


Figure 3. Cold stub and method of mounting and fracturing gel samples for freeze etch SEM examination



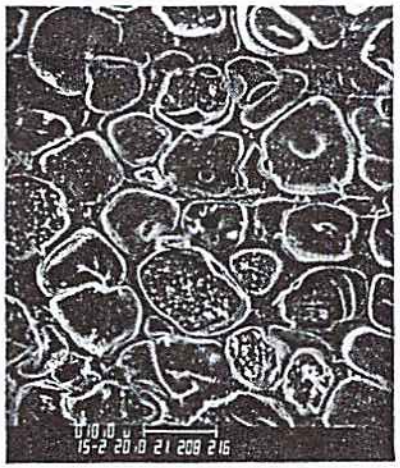


Figure 4. 30% PHEMA–70% water opaque gel freeze fractured in LN_2 and observed in the ETEC BioSEM before and during freeze etching. (A) Initial fracture surface and mold surface (top) showing ice crystals due to improper sample handling during fracture and admission to the SEM. (B) A groove produced by the micromanipulator. A cylindrical or cellular morphology is evident in the newly fractured zone. A similar but more random or disturbed morphology is evident outside of the micromanipulated zone. (C) Higher magnification of the micromanipulated zone showing "cells" which appear to be rupturing due to freeze etching.

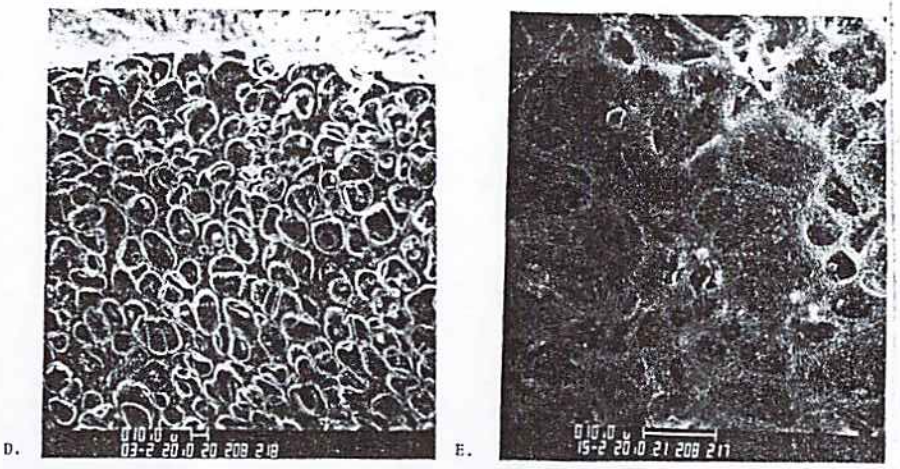


Figure 4. (D) A view of original fracture surface after extensive freeze etching (same areas as (A)). Note similarity with B and C. (E) A view prior to complete freeze etching. Note similarity to those regions of (B) outside the micromanipulated zone. All photos courtesy of ETEC, Inc., Hayward, Calif. All samples uncoated.

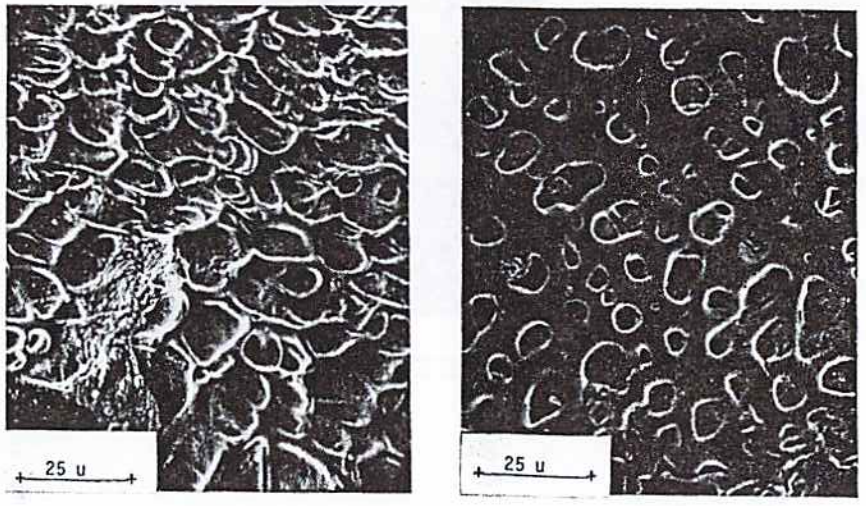


Figure 5. The same as in Figure 4. (A) Examined via the method of Figure 3. (B) Freeze-dried, coated ambient, and examined ambient.

(c) the captive bubble (sessile bubble) method, (d) the drop dimension method and (e) the Wilhelmy plate method. These methods have been adequately described elsewhere (17-20) and have been extensively used to investigate a large number of three-phase systems.

All of the above methods essentially rely on the classical contact angle or Young-Dupree equation:

$$\gamma_{SV} = \gamma_{SL} + \gamma_{LV} \cos\theta_e \quad , \qquad (1)$$

where: γ_{SV} = solid/vapor interfacial tension

γ_{SL} = solid/liquid interfacial tension

γ_{LV} = liquid/vapor interfacial tension;

θ_e = equilibrium contact angle.

Several basic assumptions are inherent in this equation. The liquid must be considered incompressible, fluid, and coherent (25). Fluidity means that the application of a shear stress to the liquid must be accompanied by a shear strain, provided the stress is maintained beyond the molecular relaxation time. Coherence implies that the liquid resists a tensile stress until the stress magnitude is sufficient to cause rupture. The surface tension of a liquid is macroscopic evidence of coherence.

The solid surface in contact with the liquid must be considered smooth, homogeneous, isotropic and, most importantly, non-deformable, i.e., rigid in the sense that stress gradients at the TPL are insufficient to deform it significantly.

Equation 1 assumes that thermodynamic equilibria, at all three interfaces (solid/liquid, liquid/vapor, and solid/vapor), have been attained (21-24).

The kinetic interpretation relies on the measurement of dynamic contact angles and observation of the resultant contact angle hysteresis. The kinetics of surface wetting (or non-wetting) make use of the fact that the liquid/vapor interface will change its shape and total area as needed under the influence of the underlying surface in order to maintain a constant curvature at equilibrium. This directly results from the Laplace equation of capillarity (17):

$$\Delta P = \gamma_{LV} \left(\frac{1}{R_1} + \frac{1}{R_2}\right) \quad , \qquad (2)$$

where: ΔP = pressure differential between the concave and convex sides of the interface;

γ_{LV} = liquid/vapor interfacial tension; and

R_1, R_2 = principle radii of curvature.

Differences in ΔP from region to region over the interface correspond to gradients in hydrostatic pressure within the underlying bulk liquid, and therefore tend to cause motion in directions which will diminish these gradients. Such motion or yielding of the interface to meet the Laplacian ΔP requirement is nearly always accompanied by a displacement of the TPL which causes an instantaneous change in the shape and/or area of the liquid/vapor interface. The dynamic contact angle is an instantaneous measure of the angle between the liquid/vapor interface and the solid/liquid interface while the TPL is moving.

Dynamic contact angles may be measured by either spontaneous spreading or forced spreading of a liquid on a surface. In the spontaneous spreading method, the contact angle is observed as a function of time and of distance traversed by the TPL as a drop of liquid spontaneously spreads and approaches the equilibrium contact angle. In this case the driving force is the extent to which the γ_{SV}, γ_{SL}, and $\gamma_{LV} \cos\theta_{inst.}$ are imbalanced. In forced spreading, the liquid/vapor interface is moved relative to the solid surface at a series of constant velocities by application of an external force. At each velocity the contact angle reaches a steady state value and a relationship between the TPL velocity and contact angle is thus established. In this case the driving force in which the TPL undergoes displacement is the result of a pressure-curvature imbalance (25).

The importance of dynamic contact angle measurements lies in the phenomenon of contact angle hysteresis, i.e., the ability to change the observed contact angle of a liquid on a surface without subsequent displacement of the TPL. This may be exhibited on many surfaces by measuring the instantaneous contact angle while, for example, increasing and decreasing the size of the sessile drop. Comparison of the resulting curves of advancing and receeding contact angles in the case of most surfaces will show that a hysteresis loop is formed. The most common types of non-ideality are either a homogeneous but geometrically rough surface or a geometrically smooth but heterogeneous surface (19). One may also have both heterogeneities and surface roughness. Practically speaking then, both surface roughness and/or surface heterogeneity, both of which give rise to contact angle variations, can be the major undetected cause of contact angle hysteresis. Swelling, absorption, and molecular reorientation at the interface can also lead to apparent hysteresis (26).

The gel surface may be capable of molecular reorientation during dynamic contact angle measurements, as has been suggested (28).

The gel/liquid interface poses still further deviations from ideality which have yet to be considered. In addition to possibilities of surface roughness and surface heterogeneity, the typical gel surface is extremely deformable. Thus in the case of contact angle characterization of the gel surface, the vertical components of surface tension should cause appreciable

distortion in the gel surface at the TPL and could cause gross misrepresentations of the angular measurements. This effect would thus significantly influence dynamic measurements and thus contact angle hysteresis. The contact angles of liquids at deformable solid surfaces have been theoretically treated by several investigators (23,27), but have yet to be experimentally applied to the surfaces of gel systems.

Interface Potentials

Ideally we would like to be able to probe the electrical double layer at gel/solution interfaces. Perhaps the most straightforward way is to use electrokinetic methods (29,30) generally electrophoresis (31), streaming potential (32), or electroosmosis (29). Such measurements allow one to calculate the potential at the shear plane - the zeta potential - given a number of assumptions.

Perhaps the biggest problem is the assumption involving the nature of the fluid dynamic boundary layer in such studies and the position of the shear plane. Even if the gel surface is perfectly smooth, we still have the problem of defining an interface position for a gel consisting of highly mobile segments and chains at the interface (2,3). The shear plane could be outside the interfacial zone, within the zone and free draining, or within the interfacial zone and non-free draining, as discussed by Brooks (33), and others (34). These same problems are present in viscometric or rheologic characterization of gel/liquid interfaces.

One must be particularly careful with streaming potential and electroosmosis measurements with respect to other fluid dynamic assumptions, particularly entrance effects and the establishment of parabolic flow profiles (35).

One can also obtain surface potential information using gel/air measurements, such as with a vibrating reed electrostatic millivoltmeter (36). These methods are commonly used to characterize monomolecular films at the liquid/air interface (37), including synthetic polymers (38). Such methods cannot be easily applied to the gel/solution interface, however.

The interpretation of gel/solution electrokinetic data is far from straightforward. One must of course consider a classical treatment in terms of fixed charges on the polymer "surface" and double layer counterions. In addition, the gel will absorb and partition ions from solution, even if the gel is largely "uncharged" in terms of fixed polymer charges, (this will be discussed later). If ions are partitioned between the gel and the solution, interface potentials will result which will, of course, influence electrokinetic measurements (39).

Adsorption of Polymers

One can study the adsorption of polymers at gel/water interfaces. Much of the work in this area has involved plasma protein adsorption (40-42). We have discussed the protein adsorption behavior of gels previously, in terms of interfacial free energies and water structure considerations (1).

One can obtain information on the nature of gel/water interfaces by adsorbing gel molecules on other substrates and then characterizing the adsorbed polymer/water interface. A large literature on polymer adsorption is available, including the study of water-soluble polymers (43).

The theories of colloidal particle stabilization by adsorbed non-ionic polymers via entropic and enthalpic repulsion (44,45) may be useful in understanding gel/protein and gel/cell interactions.

Effects of stereoregularity on interfacial behavior have been observed in poly(methyl methacrylate), poly(isopropyl acrylate), poly(2-vinyl pyridine 1-oxide) and other polymers (46,67).

The adsorbed layers can then be characterized by the instrumental techniques discussed in this paper.

Partitioning

Gels are very subtle probes of their environment. They will partition ions and other solutes and swell or deswell in response to their solution environments. Of particular importance to their surface properties is ion partitioning in the gels, which may significantly influence interfacial potential and interfacial tension studies.

Ion partitioning in gels has been observed for cellulose (47), cross-linked dextrans (48,49), poly(hydroxyethyl methacrylate) gels (50), and others. Of particular interest to us is the ion concentration profile of the gel/solution interface. Ideally we would like to know the concentrations in the electrical double layer, in the gel/water interfacial region, and in the sub-interfacial zone, perhaps to 1 or 2 microns below the surface. Such measurements are difficult to make by conventional techniques. One approach is to rapidly freeze the gel/water interface, fracture it, and perform an electron microprobe analysis or energy dispersive analysis of x-rays (EDAX) in the SEM using a cold stage to maintain the sample below -130°C to avoid ice crystallization and consequent ion segregation (51). Unfortunately the spatial resolution is limited to 0.1 to 1.0 micron or larger, making a high resolution interfacial region profile very difficult.

Microautoradiography of frozen samples is also possible, but is plagued by technical difficulties. More speculative methods of measuring concentration profiles will be discussed later.

Probing the Outermost Zone

There are very few methods with which to probe the outermost part of the gel/solution interface. We have already discussed the problems with contact angle measurements. Most optical spectroscopy methods, particularly IR, probe a zone of the order of microns in depth (next section). Although ellipsometry can ideally measure a film thickness of a few Angstroms (52), it may be difficult to apply to gels because of the lack of significant refractive index differences between the gel and the surrounding solution.

A variety of techniques are available for directly examining the nature of the surface itself. Only a limited number of these can be discussed here - see Reference 53 for the others. The two techniques most promising for polymeric and biological samples are electron spectroscopy (often called ESCA - electron spectroscopy for chemical analysis) and secondary ion mass spectroscopy (SIMS). Both techniques involve high vacuum environments. The sample must be frozen in liquid nitrogen, generally at T < -130°C. Experience with such methods on aqueous and biological samples is very limited at present.

ESCA was developed largely by the efforts of Siegbahn and his collaborators in Sweden (54). ESCA is based on the precise measurement of the kinetic energy of electrons ejected from the sample by the action of incident radiation, usually x-ray or UV. The binding energy of the electron prior to ejection (E_B) is obtained from the measured kinetic energy (E_k):

$$E_B = E_{h\nu} - E_k - C \quad ,$$

where $E_{h\nu}$ is the energy of the monoenergetic excitation radiation (commonly Mg Kα, 1254 eV), and C is an instrument constant, which is readily determined experimentally. The high precision of the E_k measurement allows one to not only identify the elements present in the surface but also to identify their oxidation state. The photoelectron spectra can be shifted by up to 10 eV, depending on the oxidation state of the element (54,55).

Modern ESCA instruments sample an area of the order of several mm^2. The volume sampled depends on the photoelectron escape depth for the sample. The escape depth is of the order of 5 to 15 A over the energy range of interest for most metals (58). Data for polymers and low density solids are not readily available, though escape depths of the order of 50 to 100 A are generally accepted (58). The sampling depth can be decreased by decreasing the angle the escaping electrons make with the sample surface. This procedure is commonly called the "glancing angle" technique (59). A nondestructive depth profile over the 0-50 A range in polymers can be obtained by intensity ratios of emitted electrons of different kinetic energies (58).

The SIMS technique utilizes a focused ion beam which is rastered or scanned across the surface, sputtering off the outer 0 to 15 or so Angstrons of the surface and analyzing the sputtered ions by a very sensitive mass spectrometer. All elements and their individual isotopes can be detected. An elemental or isotopic image of the surface can be obtained with better than one micron resolution. The interface can be progressively ion-etched away and reanalyzed, providing a compositional analysis into the sample with about 100 A depth resolution. SIMS is in reality a destructive technique, as the ion beam continually sputters away the outer surface.

The SIMS method has been extensively applied to inorganic samples (56). Very limited application to biological samples is also underway (57).

The qualitative interpretation of ESCA spectra is relatively straightforward. Depth profiling of organics, using ESCA or SIMS, however, is speculative at this time and requires a great deal of empirical calibration work before it can be very useful.

Probing the Subsurface Zone

The most common method is the use of multiple internal reflection infrared spectroscopy (60). Some depth dependence is available using different angles of incidence, though the distance probed is in the micron range. Careful studies have given monolayer sensitivities of known monolayers deposited directly on the internal reflection elements (IRE's).

The recent development of Fourier transform infrared spectroscopy (FT-IR) (61) overcomes many of the intensity and sensitivity limitations of conventional dispersive infrared spectroscopy, particularly for aqueous solutions (62,63). FT-IR can also be used in the multiple internal reflection mode (64). To our knowledge FT-IR has not yet been applied to gel/solution interface studies, however.

Raman spectroscopy should be very useful in characterizing gel/solution interfaces directly, as water is an ideal solvent for Raman studies (65).

Elemental analysis of the subsurface zone can be accomplished by energy dispersive analysis of x-rays in the SEM, as previously mentioned, or by the more accurate wavelength dispersive analysis of most electron microprobes (51). Subsurface penetration is in the micron region and can be adjusted somewhat by varying the incident electron beam energy. Again the sample must be rapidly frozen to liquid nitrogen temperatures and maintained below -130°C for analysis (51).

Further Discussion

Other techniques are available for study of the gel/water or gel/solution interface. Most solid surface characterization

techniques (55) can, in principle, be applied to the frozen gel surface. Practically all of the microscopic and histologic techniques used for the study of cell surfaces can also be applied, including selective fixatives, stains, etc. (7). Some of the methods used in the study of liquid/liquid interfaces (17,66) can be applied to gel interfaces. We have also ignored many techniques which are generally applicable only for high surface area systems.

We have discussed primarily those techniques with which we are familiar or which we are considering to apply to the study of gel/solution interfaces.

Conclusions

A variety of methods are available for the study of gel/solution interfaces.

Direct in situ methods include:

1. rheologic or viscometric analysis
2. ellipsometry
3. contact angles
4. electrokinetics
5. infrared spectroscopy
6. Raman spectroscopy
7. optical microscopy

Dry gel/air interface methods include:

1. infrared spectroscopy
2. scanning, transmission, and optical microscopy
3. surface potential
4. contact angles
5. ESCA
6. SIMS

Frozen gel surfaces can be studied by:

1. scanning, transmission, or optical microscopy
2. electron microprobe or EDAX
3. ESCA
4. SIMS

and many of the other methods.

These methods permit one to probe the gel/solution interface with respect to:

1. interface energetics
2. interface potentials
3. interface chemical groups and orientations
4. interface structure or morphology
5. interface elemental composition

The subsurface zone can be analyzed for:

1. interface chemical groups and orientations
2. interface elemental composition

In addition, soluble gel molecules can be studied as adsorbed films at solid/liquid interfaces or liquid/air interfaces.

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Abstract

The experimental characterization of gel/water interfaces is briefly discussed. Interfacial characteristics discussed include topography/morphology, interfacial tension or free energy, interface potential, adsorption, partitioning, the chemical nature of the gel surface, and the nature of the subsurface region. Techniques briefly discussed include microscopy, contact angle methods, electrokinetic methods, surface potentials, infrared spectroscopy - including Fourier transform and Raman, x-ray photoelectron spectroscopy (ESCA), and secondary ion mass analysis (SIMS). Most of these techniques are discussed in suggestive and speculative terms as so few have been applied to the gel/water interface. A variety of techniques are available for studying the gel/water interface either in situ or in the frozen state.

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17

Elimination of Electroosmotic Flow in Analytical Particle Electrophoresis

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Interest in surface coatings which will markedly reduce or eliminate the zeta potential at a chamber wall stems from the practical issue of eliminating electroosmotic flow during electrophoresis. In a closed cylindrical glass electrophoresis chamber containing an electrolyte the negative charge at the glass wall results in an increase in concentration of cations close to this surface. Application of an external electrical field results in movement of fluid near the wall (electroosmosis) toward the cathode and a concurrent forced return flow through the center of the tube. It can be shown from hydrodynamics that there is a cylindrical envelope (stationary level) in the chamber where no net flow of fluid occurs during electrophoresis. Figure 1 illustrates the general features of laminar electroosmotic fluid flow for a closed cylindrical tube including the parabolic fluid flow profile, regions of electroosmotic flow, return fluid flow and location of the stationary level.

In analytical particle electrophoresis true electrophoretic velocities of particles may be measured at the stationary level while velocities determined elsewhere in the chamber will be comprised of contributions from both electrophoresis and electroosmosis. In preparative applications of electrophoresis the boundary of a concentrated suspension (sample) becomes paraboloidal in contour as a result of electroosmosis of the suspending medium in the chamber. The non-planar sample distribution introduces difficulties in separating or resolving particle populations which differ in electrophoretic mobility. In analytical particle electrophoresis the presence of electroosmotic flow requires that measurements be carried out at the stationary level. Since this level is infinitely thin electroosmotic flow will always contribute to experimental error.

The wall charge in electrophoresis chambers arises from either the ionization of surface charge groups or as a consequence of redistribution of ions from the suspending medium (adsorption or desorption). The wall charge may be reduced or eliminated by:

a) use of adherent or adhesive films (1).

Characterization of Metal and Polymer Surfaces

Volume 2 Polymer Surfaces

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XPS Studies of Polymer Surfaces for Biomedical Applications

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Several examples are presented on the use of XPS to study polymer surfaces intended for biomedical applications. These studies include the apparent segregation of nitrogen-rich (polyurethane) and silicon-rich (polydimethylsiloxane) components in a block copolymer due to fabricating and curing conditions; the study of "treated" and untreated polystyrene cell culture dishes; and the examination of the surface of PVC films and catheters. This work is preliminary and must not be considered definitive at this stage. It does serve, however, to indicate the applications of XPS to biomaterials surface science.

INTRODUCTION

The surface and interfacial properties of polymers are important in a variety of biomedical applications, particularly in blood-contact applications. Polymer surface-induced mechanisms appear to be important in coagulation and thrombosis, the two interrelated processes in blood "clotting". Assuming a pure polymer, with no leachable toxic or biochemically active products, the major interfacial interaction appears to be adsorption of plasma proteins. The plasma protein adsorption properties seem to correlate with the materials long term blood "compatibility".[1]

A number of surface properties have been proposed to correlate with blood compatibility. These are tabulated in Table 1.[2-11]

As is evident from Table 1, most investigators have considered only one surface property. Very little work has been done in attempting to measure a spectrum of surface properties and look for

TABLE 1. SURFACE CHARACTERIZATION OF MATERIALS FOR BLOOD COMPATIBILITY CORRELATIONS*

General Class	Surface Property	Measurement	Investigator	Year	Reference
Surface Energetics	Wettability	Visual Observation	Lampert	1931	2
	Surface Free Energy, γ_s	Contact Angles	Lyman	1965	3
	Critical Surface Tension, γ_c	Contact Angles	Baier	1972	4
	Work of Adhesion	Contact Angles	Bischoff	1968	5
	Interfacial Free Energy	Contact Angle and Intermolecular Force Calculations	Andrade	1973	6
	Wettability Spectrum	Contact Angle and Intermolecular Force Calculations	Nyilas	1975	7
Charge or Potential	Zeta Potential	Streaming Potential	Ross, Mirkovitch, et. al. Sawyer, et.al.	1953	8
	Charge	Ion Interactions	Hubbard & Lucas	1960	9
	Conductivity	Bulk Conductivity	Bruck	1973	10
Surface Chemistry	Functional Groups	Direct Synthesis	Falb		2
	Functional Groups	MIR-Infrared Spectroscopy	Baier	1970	11
Cleanliness	Impurities	"Teflon Test"	Baier	1970	11

*This is a very brief, summary table. The references given are representative and not intended to be complete.

their correlation, if any, with protein adsorption and/or blood compatibility, though R.E. Baier and his collaborators[11,12] have pioneered in the use of a variety of surface characterization tools for biomedical material surface.

Although the surface chemistry of polymers is of great interest for biomedical applications, the only technique which has been routinely applied is multiple internal reflection (MIR) infrared (IR) spectroscopy. The MIR method, however, samples of the order of a wavelength, or in the micron range for the conventional infrared spectrum[13]. Thus, MIR-IR is in reality a bulk method or a method for monitoring the subsurface zone[14], though with spectral subtraction techniques true surface sensitivity can be attained.

X-ray photoelectron spectroscopy (XPS) has been used for polymer surface characterization; a number of recent comprehensive reviews are available[15,16](and this symposium). The application of XPS to the study of freeze-etched hydrogels has been suggested[14]. A recent book is available.[17]

The work reported here is preliminary in nature; it is basically a feasibility study. Although we are using XPS as only one of a battery of surface characterization tools, only XPS studies are reported here. No attempt is made in this paper to correlate XPS results with biological properties, although a correlation matrix between surface properties and biological behavior is being sought.[18]

MATERIALS AND METHODS

Polyvinyl chloride (PVC) catheters were obtained from local commercial sources; "treated" polystyrene tissue culture dishes were from Falcon Plastics, Inc.; Avcothane-51 polyether urethane-polydimethylsiloxane block copolymer[19] was obtained from a commercial balloon sold for cardiac-assist applications.

The data reported were obtained on the following instruments: 1) duPont Instruments Model 650B photoelectron spectrometer using MgKα radiation; 2) the GCA/McPherson ESCA 36 (MgKα); 3) the Physical Electronics Ind. (PEI) ESCA/Auger electron spectrometer; and 4) the Hewlett-Packard 5950B instrument, which utilizes monochromatic Al Kα 1,2 radiation. Samples were generally mounted on double-stick tape, run at 10^{-7} to 10^{-9} torr vacuum at ambient temperatures, and charging shift referenced to the C-1s line. Some samples were mechanically mounted without tape or Indium foil (PEI; GCA/McPherson, Hewlett-Packard).

RESULTS AND DISCUSSION

Avothane-51 is a synthetic elastomer that is widely used for blood-contact applications. Developed by E. Nyilas of the Avco-Everett Corporation, it is a polyether urethane/polydimethylsiloxane copolymer[19,20]. Its blood compatibility is reported to be due to a very low H-bonding capacity at the surface[21], which is highly dependent on the fabrication/dipping/drying conditions[20]. Nyilas has concluded, based on MIR-IR data[20] that "... the distribution as well as the orientation of the silicone component of Avcothane-51 in the solid films of this elastomer is anisotropic. It is this anisotropic distribution that induces the differences between surface molecular structures and the different biological effects ..." (Reference 20, page 80,83).

The variable surface properties are probably due to different ratios of siloxane and urethane components at the surface. This is a good problem for XPS as the N-1s line can be attributed only to the urethane component while the Si-2p line can be attributed only to the silicone component. An Avcothane-51 cardiac-assist balloon was examined. The outer surface of the balloon is designed and fabricated for optimal blood compatibility, while the inner surface never sees blood. Inner and outer (blood-contact) surfaces were examined in the duPont, Physical Electronics, Ind. and GCA/McPherson XPS instruments. The "outer" (blood) surface had a N-1s signal which was clearly evident in fast survey scans on all three instruments. No N-1s signal was evident in survey scans for the "inner" surface. Figure 1 gives the N-1s and Si-2p data taken on the duPont 650B electron spectrometer, corrected to a C-1s line of 285.5 eV. Clearly the "blood compatible" surface contains both urethane and siloxane while the "blood incompatible" surface is largely siloxane.

The use of a higher resolution instrument, such as the Hewlett-Packard 5950B, permits one to distinguish the higher binding energy polyether urethane carbons from those in the polydimethyl siloxane component.

A commercial polystyrene petri dish was examined (Figure 2) and showed the presence of surface oxygen, probably due to oxidation, and silicon, perhaps due to mold release agents. The commercial "treated" dish (probably corona discharged) showed the absence of silicon and a much more intense O-1s signal, as expected (Figure 2). Such surfaces are commonly used for *in vitro* cell culture. The surface properties of the substrate material are known to play an important role in the morphology and the properties of the cell culture.[22] A residue of organic biochemical matter remains on a surface after cells have been cultured on it and then removed. This material has been called cell exudate or substrate-attached material[23]. XPS analysis of the substrate-attached material may

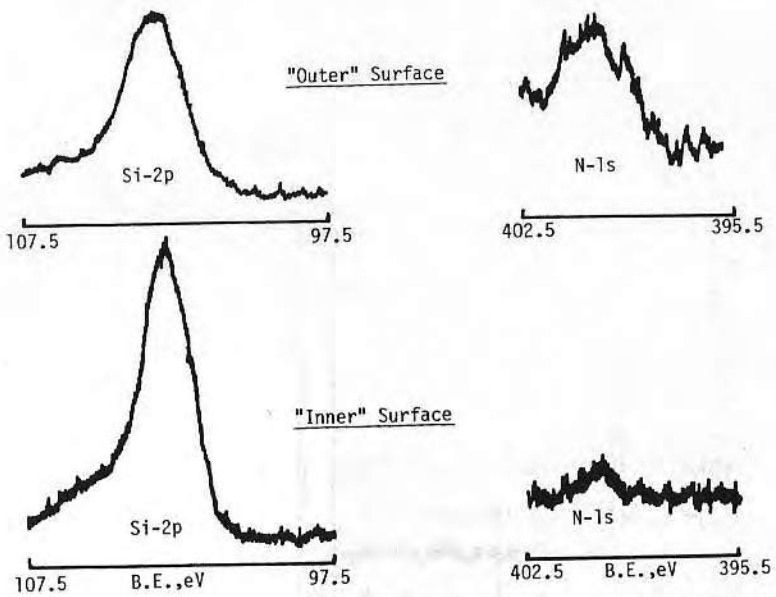

Fig. 1. Avothane-51 cardiac-assist balloon examined in duPont 650B using MgKα. Spectra were charge-corrected to the C-1s line at 285.5 eV. Note that the outer or "blood compatible" surface shows a higher polyurethane content (N-1s) than the inner surface. Note also the change in the Si-2p intensity for the two surfaces. Silicon spectra contained at sensitivity of 500 counts/sec/vertical distance at 0.2 eV/sec scan rate. Nitrogen spectra obtained at sensitivity of 100 counts/sec/vertical distance and 0.05 eV/sec scan rate.

be very important in characterizing cell exudates and cell-substrate interactions[24].

Catheters are tubular devices used to provide access to an animal or patient, generally in the vascular system, to sample blood, administer nutrients or drugs, etc. Little is known about the surface nature of commercial catheters.

Polyvinyl chloride (PVC) is commonly used as a tubing and catheter material. It is highly plasticized, generally with phthalates or adipates. As PVC is susceptible to dehydrochlorina-

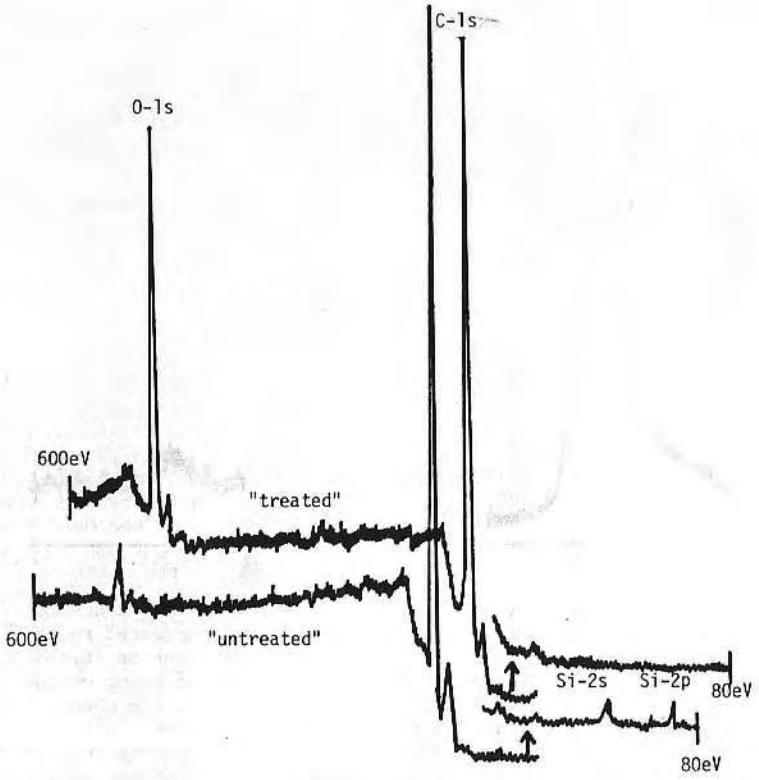

Fig. 2. XPS spectra of a commercial polystyrene cell culture dish, as received. The lower spectrum is for the untreated dish, showing the presence of surface oxidation (O-1s) and silicon (Si-2s, 2p), perhaps due to a mold release agent. The upper spectrum is for the treated, highly wettable dish, showing the absence of silicon and much more extensive surface oxidation. These spectra were obtained on the PEI XPS with MgKα - no charge corrections have been applied.

tion at processing temperatures, it is generally heat stabilized with various metal salts of fatty acids and epoxidized oils. Further, it is known that the presence of phthalate at the surface produces high platelet adhesion, which may be responsible for the

relatively poor blood compatibility of common PVC[25].

XPS examination of a pure PVC film (cast from N,N-dimethylformamide solution) produced the spectrum in Figure 3. The relatively pure film, prepared under ambient conditions, shows fairly substantial surface oxygen probably due to oxidation. The spectrum of a commercial PVC catheter is given in Figure 3. Comparison of the two spectra clearly shows the much higher level of surface oxygen in the fabricated material. One must be cautious in such analyses due to the probable presence of a surface layer of plasticizer in the commercial material. A problem with PVC is the apparent radiation "damage" under x-irradiation, leading to a progressive loss in intensity of the Cℓ lines. The decrease in Cℓ-2p intensity appears to be linear with x-ray exposure for at least the first 30 minutes in the duPont 650B XPS. We detected no such effects in the Hewlett-Packard instrument even after 2 hours of x-ray exposure.

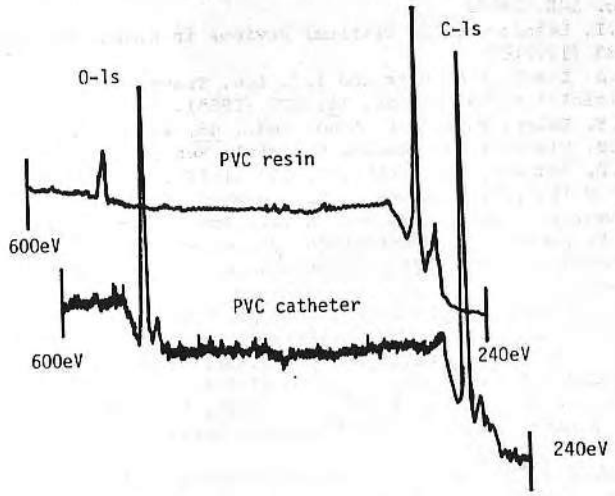

Fig. 3. XPS spectra (MgKα) of a PVC film cast from DMF (upper spectrum) and a commercial PVC catheter (lower spectrum) clearly show evidence of oxygen atoms at the surface. Note the greater degree of oxidation in the catheter material. Upper spectrum obtained on duPont 650B; lower spectrum is from the PEI instrument. The Cℓ-2p lines are intentionally omitted.

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Contact Angles at the Solid–Water Interface

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The study of polymer–water interfaces by contact angle methods can be accomplished directly at the polymer–water interface. Using two water-immiscible liquids or a liquid and a vapor, one can deduce the dispersion and polar components of the hydrated solid surface free energy and the solid–water interfacial free energy. The theory is presented and a numerical analysis procedure is developed to solve the equations in the general case. The special case of *n*-octane and air is also presented. Data and results are given for poly(hydroxyethyl methacrylate-methoxyethyl methacrylate) copolymers of varying composition and equilibrium water contents. The results show that the hydrophilic component dominates the polymer–water interfacial properties, even at relatively low hydrophilic component compositions. The method presented should be useful for the study of polymer–water interfaces, particularly for hydratable or mobile polymers which can reorient to equilibrate differently with a water environment than with the air or vapor environment commonly used in contact angle studies.

INTRODUCTION

Relatively mobile interfaces will organize or structure themselves so as to achieve the lowest possible interfacial tension or interfacial free energy. This phenomenon is well known for liquid–liquid interfaces, and it is becoming more well known for solid–liquid interfaces. Contact angle studies and, more recently, X-ray photoelectron spectroscopy clearly show the ability of solids to rearrange their surface structures in response to their environment (1). This is a relatively slow process in the case of rigid solids, such as polyethylene and other rigid polymers, and one has to go to elevated temperatures to see the effect (2). In the case of highly mobile systems, such as aqueous gel networks, the process is relatively rapid and easy to detect, for example, by an advancing and receding contact angle experiment (3).

If one is interested in characterizing the interfacial properties of highly mobile solids, it is important that the characterization be done in the environment of practical interest or relevance. Our studies concentrate on the polymer–water interface and in particular the interface between aqueous gel networks and aqueous solutions (4). We are particularly interested in probing the polymer surface interfacing with, and fully equilibrated with, an aqueous solution of interest. For these reasons we prefer to use contact angle techniques which utilize water-immiscible liquids to probe the solid–water interface directly. Other studies which have utilized such methods include those of Hamilton, utilizing octane as a probe of the polymer–water interface (5), and Tsunoda *et al.*, utilizing nitrobenzene as a probe of polymer–water interfaces (6). A large number of groups have utilized the measurement of the contact angle of a water droplet at the polymer–hydrocarbon interface. These include Tamai *et al.* (7), Bargeman (8), Matsunaga (9), and Holly and Refojo (10). Often two different apolar liquids are used, and this has been commonly called the two liquid technique of determining the surface free energy components of polymeric solids (7, 9).

We have previously shown how air bubbles and *n*-octane droplets at the polymer–water interface can be used to derive the interfacial free energy and surface free energy components of fully hydrated solids (4). In this paper we develop the method of analyzing the data more fully. We assume that the following experimental quantities are known: the surface tension of the water-immiscible phase; the dispersion and polar components to the surface tension of the water-immiscible phase; the surface tension and dispersion and polar components of the water phase saturated with the water-immiscible phase; and the saturated water–water-immiscible liquid interfacial tension. These quantities are readily measurable and generally available in the literature. The only experimental quantity which need be measured directly is the contact angle itself, which is always measured through the water phase. In the case of the captive air bubble at the polymer–water interface, the angle measured is in essence a water-receding contact angle.

It is imperative that the solids be ultraclean and very well extracted. Any water-extractable components which can affect the solid–water interfacial tension, the oil–solid interfacial tension, or the oil–water interfacial tension will lead to results which are very difficult to interpret. Simple straightforward tests are available to test for the presence of surface active extractables from the solid substrates (11–13).

Theory

Consider the contact region among a solid, water, and a third phase immiscible with water (Fig. 1), which could be air or another liquid. The contact angle, θ, is given as the angle from the solid phase through the water phase. The interfacial free energy between two phases can be estimated from the surface free energy of the component phases. Depending on the system, three approximations have been used as given in the following equations (14):

$$\gamma_{12} = \gamma_1 + \gamma_2 - 4\left(\frac{\gamma_1^d\gamma_2^d}{\gamma_1^d + \gamma_2^d}\right) - 4\left(\frac{\gamma_1^p\gamma_2^p}{\gamma_1^p + \gamma_2^p}\right) \quad [1]$$

(harmonic mean equation)

$$\gamma_{12} = \gamma_1 + \gamma_2 - 2(\gamma_1^d\gamma_2^d)^{1/2} - 4\left(\frac{\gamma_1^p\gamma_2^p}{\gamma_1^p + \gamma_2^p}\right) \quad [2]$$

(geometric–harmonic mean equation)

and

$$\gamma_{12} = \gamma_1 + \gamma_2 - 2(\gamma_1^d\gamma_2^d)^{1/2} - 2(\gamma_1^p\gamma_2^p)^{1/2} \quad [3]$$

(geometric mean equation)

where the superscripts d and p refer to the dispersion and polar components, respectively, γ refers to the interfacial tension, and the subscripts 1 and 2 refer to the two phases of interest.

Equation [1] is reported to be the best (14) approximation for organic liquids, polymers, water, etc. Equation [2] is reported to be best for high energy systems, such as mercury, glass, metal oxides, graphite, etc. Equation [3] is said to be unsatisfactory in general (14), though this is the most widely used expression in the literature. We chose to use the first approximation for our work along with Young's equation for nondeformable solids.

Considering Fig. 1, with air as the probing

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fluid, we have:

$$\gamma_{SV} = \gamma_S - \pi_e = \gamma_{SW} + \gamma_{WV} \cos \theta_{air}. \quad [4a]$$

With octane or another water-immiscible fluid as the probe liquid, we have:

$$\gamma_{SV} = \gamma_S - \pi_e = \gamma_{SL} + \gamma_{WL} \cos \theta_L \quad [4b]$$

where subscript L refers to water-immiscible liquid and subscript V refers to water vapor. π_e is the water vapor equilibrium spreading pressure. We chose to use water vapor spreading pressure in Eq. [4b] since the surface is fully equilibrated with water at the instant the octane drop or air bubble is applied. The θ measurement is made at that instant. The quantity to be obtained from the experiment is γ_{SV}, the fully water-equilibrated solid surface free energy.

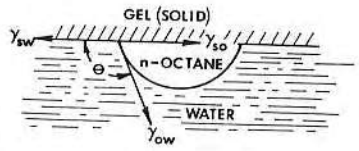

FIG. 1. The three phase equilibria between a solid, water, and a water-immiscible liquid or vapor. γ_{WL}, γ_{WV}, γ_{LV}, and θ can be directly measured. Note that γ_{LV} for a captive air bubble is assumed to be zero. See text.

We now use the interfacial tension approximations:

$$\gamma_{SL} = \gamma_{SV} + \gamma_{LV} - 4\left(\frac{\gamma^d_{SV}\gamma^d_{LV}}{\gamma^d_{SV} + \gamma^d_{LV}}\right) - 4\left(\frac{\gamma^p_{SV}\gamma^p_{LV}}{\gamma^p_{SV} + \gamma^p_{LV}}\right) \quad [5]$$

$$\gamma_{SW} = \gamma_{SV} + \gamma_{WV} - 4\left(\frac{\gamma^d_{SV}\gamma^d_{WV}}{\gamma^d_{SV} + \gamma^d_{WV}}\right) - 4\left(\frac{\gamma^p_{SV}\gamma^p_{WV}}{\gamma^p_{SV} + \gamma^d_{WV}}\right). \quad [6]$$

Here, γ_{LW} and θ are known quantities and γ_{SW} is the parameter to be calculated, as well as γ^d_{SV} and γ^p_{SV}. As before, V refers to water vapor. Combining Eqs. [4, 5, 6], one obtains:

$$\gamma^d_{SV}\left(\frac{\gamma^d_{WV}}{\gamma^d_{SV} + \gamma^d_{WV}} - \frac{\gamma^d_{LV}}{\gamma^d_{SV} + \gamma^d_{LV}}\right) + \gamma^p_{SV}\left(\frac{\gamma^p_{WV}}{\gamma^p_{SV} + \gamma^p_{WV}} - \frac{\gamma^p_{LV}}{\gamma^p_{SV} + \gamma^p_{LV}}\right) = \frac{\gamma_{LW} \cos \theta + \gamma_{WV} - \gamma_{LV}}{4} \equiv K. \quad [7]$$

There are two unknowns, γ^d_{SV} and γ^p_{SV}, in this equation. Since the value of K depends on the liquid used, by selecting two liquids one would have two equations for solving these two unknowns through a numerical method. The values of γ_{SW} can then be calculated using Eq. [6] with $\gamma_{SV} = \gamma^d_{SV} + \gamma^p_{SV}$.

Special Case

We shall first discuss a special case, in which system 1 is octane–water–solid (4, 5), and system 2 is air–water–solid. For octane, $\gamma^p_{LV} = 0$ and $\gamma^d_{LV} = \gamma^d_{WV}$ (5); we assume the spreading pressure for water vapor on liquid octane is zero.

Equation [7] thus reduces to:

$$\gamma^p_{SV} = \frac{K_1\gamma^p_{WV}}{\gamma^p_{WV} - K_1}. \quad [8]$$

For air, $\gamma^d_{LV} = \gamma^p_{LV} = 0$, and Eq. [7] reduces to:

$$\gamma^d_{SV}\left(\frac{\gamma^d_{WV}}{\gamma^d_{SV} + \gamma^d_{WV}}\right) + \gamma^p_{SV}\left(\frac{\gamma^p_{WV}}{\gamma^p_{SV} + \gamma^p_{WV}}\right) = K_2. \quad [9]$$

Here, K_1 and K_2 refer to the value of K from Eq. [7] for octane–water–solid and air–water–solid systems, respectively.

Rearranging Eq. [9] we have:

$$\gamma^d_{SV} = \frac{\gamma^d_{WV}K_2 - \gamma^p_{SV}\{\gamma^d_{WV}\gamma^p_{WV}/(\gamma^p_{SV} + \gamma^p_{WV})\}}{\gamma^d_{WV} - K_2 + \gamma^p_{SV}\{\gamma^p_{WV}/(\gamma^p_{SV} + \gamma^p_{WV})\}}. \quad [10]$$

In terms of the contact angle, the constants K_1 and K_2 take the following form:

$$K_1 = \frac{\gamma_{OW} \cos \theta_1 + \gamma_{WV} - \gamma_{OV}}{4} \quad [11]$$

and

$$K_2 = \frac{\gamma_{WV}(1 + \cos \theta_2)}{4} \quad [12]$$

where θ_1 refers to the solid–water–octane angle, θ_2 refers to the solid–water–air angle, and subscript O refers to octane. Equations [8] and [10] were previously used to calculate the surface properties of fully hydrated aqueous gels (4). A detailed treatment of the relationships between θ_1, θ_2, γ^d_{SV}, and γ^p_{SV} is available (17).

General Use

For any two liquids, designated by subscripts L1 and L2, or a liquid and vapor at the solid–water interface, we may write:

$$\gamma^d_{SV}\left[\left(\frac{\gamma^d_{WV}}{\gamma^d_{SV} + \gamma^d_{WV}}\right) - \left(\frac{\gamma^d_{L1V}}{\gamma^d_{SV} + \gamma^d_{L1V}}\right)\right] + \gamma^p_{SV}\left[\left(\frac{\gamma^p_{WV}}{\gamma^p_{SV} + \gamma^p_{WV}}\right) - \left(\frac{\gamma^p_{L1V}}{\gamma^p_{SV} + \gamma^p_{L1V}}\right)\right] = K_1 \quad [13]$$

$$\gamma^d_{SV}\left[\left(\frac{\gamma^d_{WV}}{\gamma^d_{SV} + \gamma^d_{WV}}\right) - \left(\frac{\gamma^d_{L2V}}{\gamma^d_{SV} + \gamma^d_{L2V}}\right)\right] + \gamma^p_{SV}\left[\left(\frac{\gamma^p_{WV}}{\gamma^p_{SV} + \gamma^p_{WV}}\right) - \left(\frac{\gamma^p_{L2V}}{\gamma^p_{SV} + \gamma^p_{L2V}}\right)\right] = K_2. \quad [14]$$

We again assume the spreading pressures of the liquids used (which must be water-immiscible) are zero. Subtracting Eqs. [14] and [13], we obtain:

$$\gamma^d_{SV}\left[\left(\frac{\gamma^d_{L2V}}{\gamma^d_{SV} + \gamma^d_{L2V}}\right) - \left(\frac{\gamma^d_{L1V}}{\gamma^d_{SV} + \gamma^d_{L1V}}\right)\right] = K_1 - K_2 + \gamma^p_{SV}\left[\left(\frac{\gamma^p_{L1V}}{\gamma^p_{SV} + \gamma^p_{L1V}}\right)\left(\frac{\gamma^p_{L2V}}{\gamma^p_{SV} + \gamma^p_{L2V}}\right)\right]. \quad [15]$$

Notice that the right-hand side of Eq. [15] does not contain γ^d_{SV}. Thus, it can be rewritten into a quadratic expression:

$$Z_1(\gamma^d_{SV})^2 + Z_2(\gamma^d_{SV}) + Z_3 = 0 \quad [16]$$

where

$$Z_1 = 1 - (\gamma^d_{L2V} - \gamma^d_{L1V})/C(\gamma^p_{SV})$$

$$Z_2 = \gamma^d_{L2V} + \gamma^d_{L1V}$$

$$Z_3 = \gamma^d_{L2V}\gamma^d_{L1V}$$

$$C(\gamma^p_{SV}) = K_1 - K_2 + \gamma^p_{SV}\left[\left(\frac{\gamma^p_{L1V}}{\gamma^p_{SV} + \gamma^p_{L1V}}\right) - \left(\frac{\gamma^p_{L2V}}{\gamma^p_{SV} + \gamma^p_{L2V}}\right)\right].$$

Two solutions for γ^d_{SV} can be obtained from Eq. [16] for some assumed value of γ^p_{SV}. One of these solutions is physically unrealistic and can be discarded. For a given γ^p_{SV}, we can say γ^d_{SV} is a function of γ^p_{SV}, or:

$$\gamma^d_{SV} = g(\gamma^p_{SV}). \quad [17]$$

If we write

$$f(\gamma^p_{SV}) = \gamma^d_{SV}\left[\left(\frac{\gamma^d_{WV}}{\gamma^d_{SV} + \gamma^d_{WV}} - \frac{\gamma^d_{L1V}}{\gamma^p_{SV} + \gamma^p_{WV}}\right)\right] + \gamma^p_{SV}\left[\left(\frac{\gamma^p_{WV}}{\gamma^p_{SV} + \gamma^p_{WV}}\right)\left(\frac{\gamma^p_{L1V}}{\gamma^p_{SV} + \gamma^p_{L1V}}\right)\right] - K_1 \quad [18]$$

and substitute Eq. [17] into Eq. [18], we have:

$$f(\gamma_{SV}^g) = g(\gamma_{SV}^g)\left[\left(\frac{\gamma_{WV}^d}{g(\gamma_{SV}^g) + \gamma_{WV}^d}\right) - \left(\frac{\gamma_{L1V}^d}{g(\gamma_{SV}^g) + \gamma_{L1V}^d}\right)\right] + \gamma_{SV}^g\left[\left(\frac{\gamma_{WV}^p}{\gamma_{SV}^g + \gamma_{WV}^p} - \frac{\gamma_{L1V}^p}{\gamma_{SV}^g + \gamma_{L1V}^p}\right)\right] - K_1. \quad [19]$$

For the true value of γ_{SV}^g, the value of $f(\gamma_{SV}^g)$ should be identically zero. For a trial value of γ_{SV}^g, the value of $f(\gamma_{SV}^g)$ will generally be different from zero. Define

$$f'(\gamma_{SV}^g) \equiv \frac{\partial[f(\gamma_{SV}^g)]}{\partial(\gamma_{SV}^g)}. \quad [20]$$

The value of γ_{SV}^g can be obtained from Eq. [19] by using Newton's iterative method with a trial value of γ_{SV}^g, which need not be close to the true value. The next approximated value is related to the previous value by the expression:

$$(\gamma_{SV}^g)_{n+1} = (\gamma_{SV}^g)_n - \frac{f(\gamma_{SV}^g)}{f'(\gamma_{SV}^g)}. \quad [21]$$

When the true value of γ_{SV}^g is reached, $f(\gamma_{SV}^g) \to 0$ and the two successive values of γ_{SV}^g, i.e., $(\gamma_{SV}^g)_n$ and $(\gamma_{SV}^g)_{n+1}$, become equal. After the final value of γ_{SV}^g is obtained, the value of γ_{SV}^d can be calculated from Eq. [16]. The values of γ_{SW} and γ_{SV} can then be obtained from Eq. [6] and the expression:

$$\gamma_{SV} = \gamma_{SV}^p + \gamma_{SV}^d \quad [22]$$

respectively.

MATERIALS AND METHODS

The polymer systems used in this study were poly(hydroxyethyl methacrylate) (PHEMA) and HEMA–MEMA copolymers where MEMA is methoxyethyl methacrylate. Other polymers used are listed in Table I. The preparation of these materials is the same as described previously (4). Surface characterization of the films was again as described (4), including a test for surface-active extractables (12). The contact angle measurements were made in a Rame-Hart contact angle goniometer with an inverted stage, as described in (4). The self-consistent values for the surface and interfacial tensions at 25°C are (in ergs/cm²): $\gamma_{WV} = 72.1$; $\gamma_{OV} = 21.6$; $\gamma_{WV}^d = 21.6$; $\gamma_{OW} = 50.5$ (4). The surface tensions of octane-saturated water and of water-saturated octane are the same as for the pure components.

TABLE I

The Calculated Values of γ_{SW} for Various Hydrophilic Gels and Related Polymers in Octane–Water–Solid and Air–Water–Solid Systems Using the Harmonic Mean Expression[a,b]

Sample[c]	Percentage cross-linker[d]	wt% H_2O	θ_{air}	θ_{octane}	γ_{SV}^d	γ_{SV}^p	γ_{SV}	γ_{SW}
i-PHEMA	1	43	13 ± 1	14 ± 1	21.3 ± 0.5	49.0 ± 0.2	70.2 ± 0.3	0.03 ± 0.01
h-PHEMA	1	39	17 ± 2	22 ± 2	22.2 ± 1.4	46.9 ± 0.6	69.0 ± 0.8	0.1 ± 0.1
P-MEMA	0	2	46 ± 2	74 ± 3	45.1 ± 10.1	23.6 ± 1.4	68.8 ± 8.7	18.7 ± 6.9
P-(25% HEMA + 75% MEMA)	1	18	32 ± 2	55 ± 3	36.3 ± 6.2	32.7 ± 1.5	69.0 ± 4.7	7.9 ± 3.3
P-(50% HEMA + 50% MEMA)	1	23	22 ± 2	37 ± 2	27.1 ± 0.2	41.2 ± 0.9	68.4 ± 0.7	1.6 ± 0.2
P-(75% HEMA + 25% MEMA)	1	33	14 ± 2	27 ± 2	25.3 ± 1.6	45.3 ± 0.7	70.6 ± 0.9	0.6 ± 0.3
PMA	0	~0	52 ± 2	81 ± 1	44.9 ± 6.7	20.5 ± 0.4	65.5 ± 6.3	21.1 ± 4.2
PMMA	0	~0	67 ± 2	90 ± 1	29.7 ± 4.5	16.8 ± 0.4	46.6 ± 4.1	18.4 ± 1.8

[a] Data from Ref. (4).

[b] For octane, $\gamma_{LV}^d = 21.6$, $\gamma_{LV}^p = 0$, $\gamma_{LV} = 21.6$, $\gamma_{LW} = 50.5$; for air, $\gamma_{LV}^d = \gamma_{LV}^p = 0$, $\gamma_{LV} = 0$, $\gamma_{LW} = 72.1$.

[c] i, isotactic; h, heterotactic (see Ref. 4); PHEMA, poly(hydroxyethyl methacrylate); MEMA, methoxyethyl methacrylate; PMA, poly(methyl acrylate); PMMA, poly(methyl methacrylate).

[d] Wt% of hexamethylene diisocyanate.

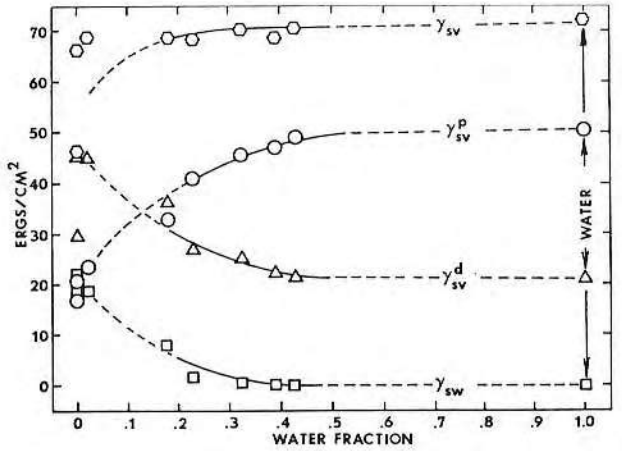

FIG. 2. Plot of the data of Table I. γ_{SV}^d, γ_{SV}^g, γ_{SV}, and γ_{SW} as a function of water fraction of the polymers used. The data at water fraction = 1.0 are for pure water.

RESULTS AND DISCUSSION

Table I presents the calculated values for aqueous gel–water interfaces using octane and air as probes; the error values given are the standard deviation of the measured contact angles. A portion of the data is plotted in Fig. 2 where the interfacial and surface properties are plotted as a function of water content of the solid. Note that even at low compositions of the hydrophilic component (low water contents) the hydrophilic phase tends to dominate the interfacial properties. The result is a rapid drop to near zero in the interfacial energy with increasing content of the hydrophilic component.

The standard deviation of γ_{SV} lies between the standard deviations of γ_{SV}^d and γ_{SV}^g because the values of γ_{SV}^g and γ_{SV}^d do not change independently. In fact, as the values of γ_{SV}^g increase, γ_{SV}^d tends to decrease and vice versa. As a consequence, part of the errors arising from γ_{SV}^d and that of γ_{SV}^g cancel, and the error in γ_{SV} is always smaller than the summation of the errors from γ_{SV}^d and γ_{SV}^g. [See (16) for a more detailed discussion.]

The γ_{SV}^d, γ_{SV}^g, γ_{SV}, and γ_{SW} values in Table I calculated via the harmonic mean approximation of Eq. [1] give values significantly higher than those obtained by using the geometric mean approximation of Eq. [3]. [See (4) for details.]

It is important to note that the γ_{SV} values obtained by this method are often somewhat higher than the normally accepted values for γ_S or γ_C (the critical surface tension) of organic polymers, as the "normal" values are generally determined by advancing contact angles measured in air, which minimizes the influence of the hydrophilic sites. For those studies and applica-

tions where one is primarily interested in polymer–water interfacial properties, which includes virtually all biological applications, the method described here is preferred for characterization purposes.

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SURFACE CHARACTERIZATION OF POLY(HYDROXYETHYL METHACRYLATE) AND RELATED POLYMERS. I. CONTACT ANGLE METHODS IN WATER

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SYNOPSIS

The characterization of the gel–water interface is considered, particularly with respect to obtaining the interfacial free energy between the gel and water, γ_{SW}, utilizing contact angle data. The question of contact-angle-induced deformation of the three-phase region is examined and visual documentation of such deformation is presented. Air in water and octane in water contact-angle data are used to estimate γ_{SV}^{d}, γ_{SV}^{p}, γ_{SV}, and γ_{SW} for the gel–water interface as a function of bulk water fraction in the gel. It is shown that $\gamma_{SW} \simeq 0 \pm 5$ erg/cm^2 when the bulk water fraction is greater than 0.2. All interfacial parameters determined appear to reach a constant value at a bulk water fraction of about 0.4. These results are for poly(hydroxyethyl methacrylate), poly(methoxyethyl methacrylate), poly(dihydroxypropyl methacrylate), and selected copolymers at 25°C in distilled water.

INTRODUCTION

Aqueous gel networks are of considerable interest as blood and tissue interfacing materials and for other biomedical applications [1]. In addition they are of interest as model systems with which to study the gel nature of cell surfaces and membranes [2].

The minimum interfacial free energy hypothesis [2, 3] of protein adsorption and blood compatibility can only be fully tested with hydrogel materials. The hypothesis states that if the gel–water interface has a very low interfacial free energy, then protein adsorption should be very low and highly reversible. The hypothesis is obviously dependent on being able to measure the interfacial free energy and on being able to prepare gels with different gel–water interfacial free energies.

The aqueous-gel–aqueous-solution interface is very difficult to study, as many of the classical assumptions of surface chemistry do not apply. Silberberg [4] has briefly discussed the problem with respect to segment distribution in the interface and hydrodynamic effects (see also ref. 5). We have previously discussed some of the surface and interface characterization methods that may be applicable to the gel–solution interface [6].

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Here we consider the use of contact angle techniques to characterize the gel surface and the gel–water interface. Holly and Refojo [7–10] have also utilized contact angles to probe gel surfaces.

Contact-Angles–Three-Phase Equilibria

Liquid or gas droplets can be used to probe the surface and interfacial free energies of solids. The most common technique utilizes a liquid drop placed at the solid–vapor interface [11, 12]. Referring to Figure 1, let there be a small displacement, dx. Then

$$(dF)_{T,\,V,\,n} = \gamma_{SV}dx - \gamma_{SL}dx - \gamma_{LV}\,dx\cos\theta \tag{1}$$

where F is the Helmholtz free energy, γ is the interfacial free energy related to solid–vapor (γ_{SV}), liquid–vapor (γ_{LV}), and solid–liquid (γ_{SL}) interfaces, and θ is the equilibrium contact angle at the three-phase junction. At equilibrium, $dF = 0$, or

$$\gamma_{SV} - \gamma_{SL} = \gamma_{LV}\cos\theta \tag{2}$$

This is Young's equation, one of the fundamental equations of surface chemistry [11]. There is an implicit assumption in the derivation of eq. (1) — only horizontal displacements are considered. It is assumed that the solid is sufficiently rigid that vertical displacement of the solid is negligible. This assumption is not generally valid for gels.

Now consider the case of three ideally deformable phases in equilibrium, e.g., three immiscible liquids or two liquids and a vapor (Fig. 2). Figure 2(a) can be represented as a triangle, commonly called Neumann's triangle [11, 12], Figure 2(b). The general expression for such a triangle is [13]

$$\frac{\gamma_{23}}{\sin\ \theta_1} = \frac{\gamma_{13}}{\sin\ \theta_2} = \frac{\gamma_{12}}{\sin\ \theta_3} \tag{3}$$

or equivalently [13]

$$\gamma_{12} + \gamma_{23}\cos\ \theta_2 + \gamma_{13}\cos\ \theta_1 = 0 \tag{4a}$$

$$\gamma_{23} + \gamma_{13}\cos\ \theta_3 + \gamma_{12}\cos\ \theta_2 = 0 \tag{4b}$$

$$\gamma_{13} + \gamma_{12}\cos\ \theta_1 + \gamma_{23}\cos\ \theta_3 = 0 \tag{4c}$$

The symbols are defined in Figure 2.

Clearly, Young's equation is just a special case of eqs. (3) and (4c) (refer to Fig. 2(a)) with $\theta_1 + \theta_2 = 180° = \theta_3$.

Contact Angles on Deformable Solids

The problem is: are the angles measured in a conventional contact angle experiment the true *equilibrium* contact angles [13, 14]? Bikerman has questioned the use of eq. (2) with low modulus solids [12]. He demonstrated

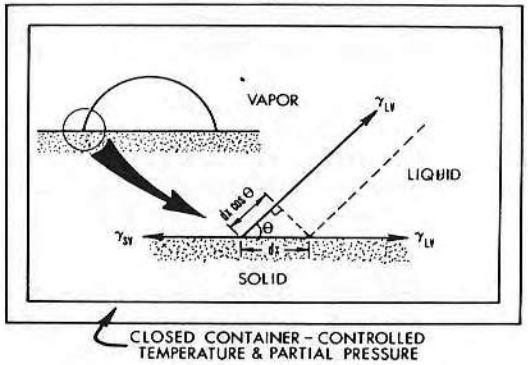


FIG. 1. The contact angle geometry used in deriving Young's equation: $\gamma_{SV} - \gamma_{SL} = \gamma_{LV}\cos\theta$. Symbols are defined in the text.

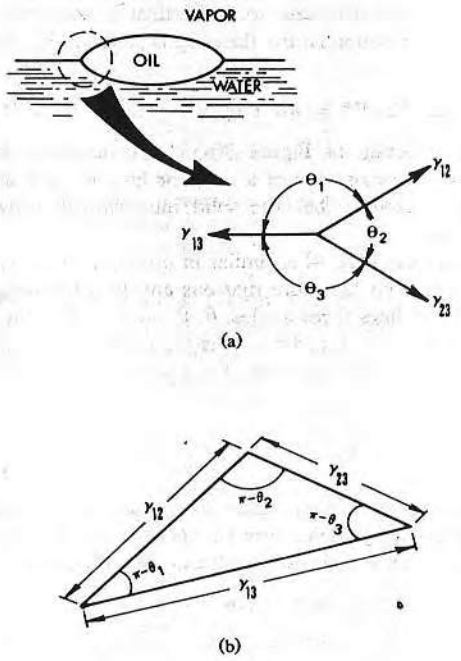


FIG. 2. (a) An oil droplet at a vapor–water interface. All three phases are ideally deformable and achieve the equilibrium configuration shown. (b) Neumann's triangle, presenting in simple form the relationships among the phases (from ref. 13).

that the solid does not necessarily remain planar when in contact with a high surface tension liquid drop [15]. Rigorous treatments of the extent of deformation at the solid–liquid–vapor boundary have been given by Lester [13] and Rusanov [16].

The pressure inside a drop exceeds the external pressure by $2\gamma_{LV}/R$ (assuming the drop is a spherical segment†), where R is the radius of curvature of the liquid–vapor interface and γ_{LV} is the liquid–vapor interfacial tension. (This is the Young–Laplace capillarity equation and is another basic equation of surface chemistry — see ref. 11.) Thus,

$$P = 2\gamma_{LV}/R \tag{5}$$

This pressure is acting vertically downwards on the solid surface within the drop. The stress acting vertically upward at the periphery of the drop is approximately (see Fig. 3(a))

$$2\pi a \frac{t}{2} P^*$$

where a is the drop radius, t is the thickness of liquid–vapor region, $\simeq 10^{-7}$ cm, and P^* is the mean stress due to the vertical component of γ_{LV}. The approximate stress distribution across the drop is given in Fig. 3(b) (ref. 13).

At equilibrium

$$2\pi a(t/2) P^* = \pi a^2 P \text{ or } P^* = (2\gamma_{LV}/R)(a/t) \tag{6}$$

The stress distribution of Figure 3(b) clearly suggests that for highly deformable solids one must expect a ridge or boss to form at the drop periphery. One also expects that the solid immediately below the drop is slightly compressed.

Rusanov's treatment (Fig. 4) is similar in principle to Lester's, though the deformation calculations are more rigorous and lead to much more reasonable numbers. He defines three angles: θ, θ', and θ_0. θ is the contact angle prior to any deformation (Fig. 4(a)), θ' is the apparent or measured contact angle after deformation has occurred (in general $\theta' \leq \theta$, Figs. 4(b), 4(c)), and θ_0 is defined as that contact angle which satisfies Young's equation, i.e.,

$$\cos\theta_0 \equiv \frac{\gamma_{SV} - \gamma_{SL}}{\gamma_{LV}} \tag{7}$$

As our interests in the contact angle are in using it to obtain an estimate of γ_{SL}, θ_0 is operationally useful even though it does not exist in a physical sense. Rusanov utilizes the terms $\Delta\cos\theta$ and $\Delta\cos\theta'$, where

$$\Delta\cos\theta \equiv \cos\theta - \cos\theta_0$$
$$\text{and} \tag{8}$$
$$\Delta\cos\theta' \equiv \cos\theta' - \cos\theta_0$$

†This assumption implies that gravitational effects are negligible, a very good assumption for small drops (see refs. 13 and 16).

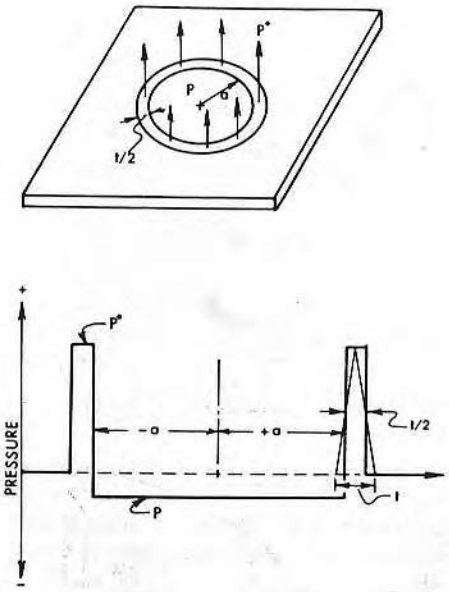


FIG. 3. (a) The drop periphery is modeled as a band of radius a and effective L–V film thickness $t/2$. If P^* is the mean vertical stress at the periphery, then the total vertical force is $2\pi a(t/2)P^*$ (ref. 13). (b) The approximate stress distribution across the drop; P is the stress resulting from the increased pressure inside the drop, i.e., $P = 2\gamma_{LV}/R$, where R is the radius of curvature of the drop (redrawn from ref. 13).

Rusanov treats two conditions: (1) small drops, i.e., $a \leq 1$ mm, where gravitational effects are negligible; (2) very large drops, $a \geq 5$ cm, where gravitational corrections are important, but deformation considerations are simpler and where $\theta \simeq \theta'$. Although large drops are very attractive from the point of view of mathematical analysis, they are impractical for our purposes and for our experimental system. Thus, we shall only discuss the small-drop case.

The equations for vertical deformation are (Rusanov's notation has been changed slightly) (see Fig. 4(c))

$$z_1 = \frac{2(1-\nu^2)\gamma_{LV}}{E}\left[\sin\theta + \frac{(1-2\nu)}{2(1-\nu)}\Delta\cos\theta\right] \tag{9}$$

$$z_2 = \frac{3\gamma_{LV}\sin\theta}{2\pi E}\left[3 - 4\ln 2 + \ln(t/a)\right] \tag{10}$$

where ν is Poisson's ratio $\simeq 0.5$ for the gels of interest; E is Young's modulus or bulk modulus of elasticity $\simeq 1 \times 10^6$ dyn/cm^2 for the gels of interest

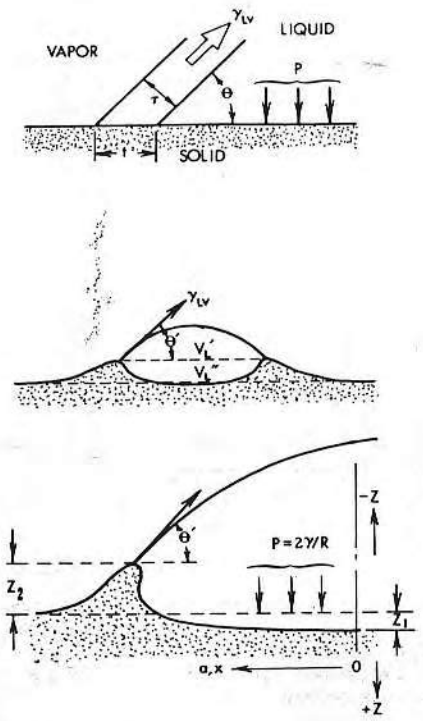


FIG. 4. Rusanov's model for contact-angle-induced deformation (ref. 16). (a) The geometry at the zone of three-phase contact. τ is the thickness of the liquid–vapor interface; t is its intersection with the solid surface, where $t = \tau/\sin\theta$. θ is the contact angle. (b) Exaggerated drop profile after the solid has deformed and equilibrium has been achieved. V_L' is the volume of the portion of the drop above the horizontal line shown; V_L'' is the volume below that line. The contact angle with respect to the horizontal has decreased from θ to θ'. (c) Schematic detail of the deformation in the three-phase region. z_1 is the vertical deformation of the solid inside the drop. z_2 is the maximum height or rise at the drop periphery.

[17], and a is the drop radius in cm. Letting $\nu \simeq 0.5$, $\theta = 90°$, $t = 10^{-7}$ cm, and $a = 0.1$ cm, we get

$$z_1 \simeq +1.5\gamma_{LV}/E \tag{11}$$

$$z_2 \simeq -6.8\gamma_{LV}/E \tag{12}$$

Note that $z < 0$ refers to a tensile deformation, while $z > 0$ refers to a compressive deformation (Fig. 4(c)). Also, z_2 is a function of a, and a may range from 0.05 to 0.2 cm without significantly affecting the coefficient in the z_2 equation (the coefficient would vary from 6.4 to 7.1). For $\gamma_{LV} \simeq 72$ erg/cm^2 and $E \sim 1 \times 10^6$ dyn/cm^2,

$$z_1 \simeq +1\ \mu\text{m}$$

$$z_2 \simeq -5\ \mu\text{m}$$

These results are considerably different from Lester's [13]. Lester's equations lead to deformations in the angstrom range, which he concludes are submicroscopic and not directly observable. From Rusanov's results one would expect to be able to observe the deformations.

Rusanov then calculates the tangential or horizontal displacements, which we call u_1 and u_2. The horizontal displacement at the center is zero, i.e., $u_1 = 0$. The maximum horizontal displacement is at the same point as the maximum vertical displacement, i.e., roughly in the center of the three-phase contact region. Thus

$$u_2 \simeq -\frac{3\gamma_{LV}\Delta\cos\theta}{2\pi E}\,[4\ln 2 - 1 - \ln(t/a)] \tag{13}$$

The negative sign means the displacement is towards the drop center [16].

The expressions for vertical and horizontal displacements permit Rusanov to calculate the general shape of the deformed region and obtain relationships between θ, θ', and θ_0. To do this he utilizes the volumetric relationship shown in Figure 4(b):

$$V_L = V_L' + V_L'' \tag{14a}$$

where V_L is the drop volume. V_L and V_L' are the expressions for the volume of a spherical segment:

$$V_L \simeq \frac{\pi a^3(1-\cos\theta)^2(2+\cos\theta)}{3\sin^3\theta} \tag{14b}$$

$$V_L' \simeq \frac{\pi(a+u_2)^3(1-\cos\theta')^2\,(2+\cos\theta')}{3\sin^3\theta'} \tag{14c}$$

V_L'' is obtained by Rusanov by considering the deformation of the drop:

$$V_L'' \simeq -\pi a^2 z_2 + \frac{2\gamma_{LV}a^2\sin\theta}{E} \tag{14d}$$

Utilizing (14a) as the basic relationship and incorporating (14b)–(14d), (13), and (10), he obtains a relationship between θ and θ' in terms of γ_{LV}, τ, E, and a. He also obtains, using a deformation analysis, a similar relation between θ and θ_0. These two relations permit him to derive an equation relating θ' (the experimentally determinable quantity) to θ_0 (that quantity which satisfies Young's equation). The problem is that his final equation includes two integrals which must be evaluated numerically. Rusanov solved the equations only for the case where $\gamma \simeq 73$ erg/cm^2, $E \simeq 3.5 \times 10^5$ dyn/cm^2, $\tau \simeq 10^{-7}$ cm, and $\gamma_{SV}/\gamma_{LV} = 2$. His results are given in Table I.

TABLE I

Approximate Errors in the Contact Angle when the Gel Is Treated as a Nondeformable System[a]

Θ_o	cos Θ_o	Δ cos Θ'	cos Θ'	Θ'	$\Delta\Theta = \Theta_o - \Theta'$
20.0	.940	0.0180	0.960	16.7	3.3
29.0	.875	0.0265	0.902	25.6	3.4
41.4	.750	0.0330	0.783	38.5	2.9
51.3	.625	0.0335	0.658	48.8	2.5
60.0	.500	0.0315	0.532	57.9	2.1
68.0	.375	0.0270	0.402	66.3	1.7
75.5	.250	0.0230	0.273	74.2	1.3
82.8	.125	0.0160	0.141	81.9	0.9
90.0	0.000	0.0100	0.010	89.4	0.6
97.2	-0.125	0.0030	-0.122	97.0	0.2
104.5	-0.250	-0.0020	-0.255	104.6	-0.1
112.0	-0.375	-0.0060	-0.381	112.4	-0.4
120.0	-0.500	-0.0100	-0.510	120.7	-0.7
128.7	-0.625	-0.0125	-0.638	129.6	-0.9
138.6	-0.750	-0.0135	-0.764	139.8	-1.2
151.0	-0.875	-0.0110	-0.886	152.4	-1.4

[a]These numbers were obtained from Rusanov's data (ref. 16, p. 634), which were calculated assuming the drop radius is 0.1 cm, the liquid is water (γ_{SV} = 73 dyne/cm), $E \simeq 3.5 \times 10^5$ dyne/cm^2, and $\gamma_{SV}/\gamma_{LV} = 2$. As E decreases the error will increase, i.e., $\Delta \cos\theta' = f(1/E)$.

Fortunately, Table I shows that $\theta' \sim \theta_0$ (i.e., within 2°) except when $\theta' < 60°$. Over the range from roughly $15° \leq \theta' < 60°$ the error is about 3°. For $\theta' < 15°$ the error could become considerable. We have not examined the 0–15° range yet.

Demonstration of Contact-Angle-Induced Deformation

Bikerman has shown [15] that a mercury–aqueous-gel interface can produce a deformation ridge on the gel 40 μm high. Though this seems large, the gel modulus was 6×10^4 dyn/cm^2 and γ_{LV} for mercury is roughly 450 dyn/cm. Using eq. (10), we get $z_2 \simeq 0.05$ cm or roughly 500 μm for this system. Thus, Bikerman's observation is within an order of magnitude of Rusanov's treatment. Actually, Bikerman suggests that E in the surface region is greater than 6×10^4 (owing to dehydration of the gel surface). If this is so, E could easily be larger than 6×10^4, which would give z_2 closer to Bikerman's data. Although Bikerman's numbers are reasonable, his treatment has been criticized by Rusanov [18].

We have utilized freeze-etch scanning electron microscopy to examine contact angle drops on polystyrene, poly(hydroxyethyl methacrylate), and several copolymers. These experiments and results are discussed later in the paper.

The Captive Air and Octane Methods

Usually one makes a contact angle measurement by placing a pure liquid droplet on a solid surface in a controlled environment (Fig. 1). There is a problem with aqueous gels and water droplets, however. If one advances a drop of water over a poly(hydroxyethyl methacrylate) [p(HEMA)] surface which has been lightly blotted, the contact angle is of the order of 90° (see ref. 7). If the same drop is then receded, the angle is low, of the order of 20°. Although this may be partly due to the kinetics of gel deformation, Holly and Refojo have suggested that the p(HEMA) surface ". . . is capable of changing its free energy through reorientation of the polymer side chains and chain segments depending on the nature of the adjacent phase" (ref. 7, p. 315).

As we are mainly interested in probing the gel–water interface, rather than the gel–air interface, we have elected to use the captive bubble method [11, 12] (Fig. 5). The advantage of this method is that the gel surface is fully hydrated. In the conventional method one has to worry about the composition of the vapor phase and its interactions with the solid. In the captive bubble technique, the environment is fixed.

From Young's equation we have

$$\gamma_{sv} - \gamma_{sw} = \gamma_{wv} \cos\theta \tag{15}$$

where γ is the interfacial free energy for hydrated-gel–water-vapor (γ_{sv}), hydrated-gel–water (γ_{sw}), γ_{wv} = 72.0 erg/cm^2 at 25°C, and θ is the contact angle for which Young's equation holds, assumed $\simeq \theta'$ here. Although γ_{wv} and θ are known, γ_{sv} and γ_{sw} are both unknowns. ($\gamma_{sv} - \gamma_{sw}$) is commonly called the adhesion tension [7–11].

Hamilton proposed and applied a clever means of getting additional information [19, 20]. Consider a drop of n-octane at a solid–water interface (Fig. 6.):

$$\gamma_{sw} = \gamma_{so} + \gamma_{ow} \cos\theta \tag{16}$$

where the subscript O refers to the octane phase. We write the interfacial tensions in terms of work of adhesion terms, following the treatments of Fowkes [21], Tamai et al. [22], and others [24–27]:

$$\begin{aligned} \gamma_{so} &\simeq \gamma_{sv} + \gamma_{ov} - 2\,(\gamma_{sv}^d\,\gamma_{ov}^d)^{1/2} - I_{so}, \\ \gamma_{sw} &\simeq \gamma_{sv} + \gamma_{wv}' - 2\,(\gamma_{sv}^d\,\gamma_{wv}^d)^{1/2} - I_{sw}, \end{aligned} \tag{17}$$

where γ_{wv}' is the surface tension of octane-saturated water, γ_{sv}^d, γ_{ov}^d, γ_{wv}^d are the dispersion components to the surface free energies of the S, O, and

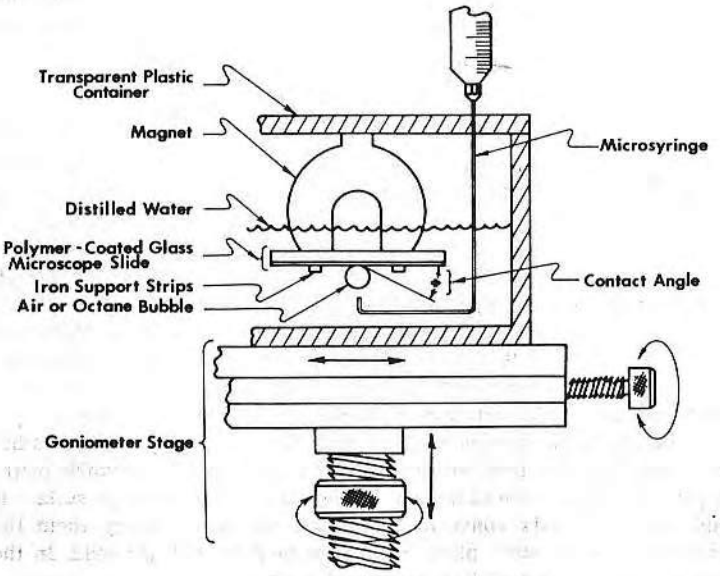


FIG. 5. Apparatus for the captive air and octane measurements.

W phases, and I_{so}, I_{sw} are the nondispersive (polar) interactions at the S–O and S–W interfaces. We have $\gamma_{wv} = 72.1$ erg/cm^2 at 25°C, with $\gamma^d_{wv} = 21.6$ and $\gamma^p_{wv} = 50.5$ erg/cm^2, where γ^p_{wv} is the polar component to the water surface tension. $\gamma_{ov} = \gamma^d_{ov} = 21.6$ erg/cm^2, as octane is completely nonpolar. Combining eqs. (16) and (17), we get

$$I_{sw} = \gamma'_{wv} - \gamma_{ov} - \gamma_{ow} \cos\theta \tag{18}$$

by letting $I_{so} = 0$ (octane has no polar component). γ'_{wv}, γ_{ov}, γ_{ow} are all experimentally known. $\gamma'_{wv} \sim \gamma_{wv}$ (the solubility of octane in water is less than 1 ppm, refs. 12, 23). Thus eq. (18) then becomes

$$I_{sw} \simeq 50.5\ (1 - \cos\theta) \tag{19}$$

As $\gamma_{sw} \simeq \gamma_{sv} + \gamma_{wv} - 2(\gamma^d_{sv}\ \gamma^d_{wv})^{1/2} - I_{sw}$, then γ_{sw} is a minimum when I_{sw} is maximized. $(I_{sw}) = 0$ when $\cos\theta$ 614 1 or $\theta \simeq 0°$; (I_{sw}) max $\simeq$ 101 when $\cos\theta = -1$ or $\theta \simeq 180°$. For a purely apolar surface in water, $I_{sw} \simeq 0$ and θ will be small, indicating a high polar component to the interfacial free energy. For a very hydrophilic surface, θ will approach 180°, indicating a large I_{sw} and a correspondingly low polar component to the interfacial free energy.

A similar technique and analysis has been used by Van der Scheer and Smolders [24] using octadecane as the probe oil. The use of a water drop in octane has been used by Holly and Refojo to probe gel–water interfaces [8, 9].

Thus the octane probe technique gives us an estimate of I_{sw}, the polar work of adhesion at the gel–water interface. The captive bubble method gives us a measure of $\gamma_{sv} - \gamma_{sw}$ from eq. (15). Combining (15) and (17), we have

$$\gamma_{sv} - \gamma_{sw} = 2(\gamma^d_{sv}\ \gamma^d_{wv})^{1/2} + I_{sw} - \gamma_{wv} \tag{20}$$

The left side is known from the captive air bubble experiment. γ_{wv} is known. I_{sw} is known from the octane experiment. γ^d_{wv} is known, so γ^d_{sv} can be calculated. Ideally we would like to get γ_{sw} directly, but that information is simply not available—there are too many unknowns. We will show later how the quantity can be estimated.

MATERIALS

The materials utilized are all polymers of methacrylate esters polymerized by either free radical or anionic initiators. Radical initiation is more versatile as monomer, comonomers, cross-linker, initiator, and solvent are compatible and permit a one-step preparation of the gel. Solvent casting is a desirable method of fabrication—this requires soluble un-cross-linked polymers that are cross-linked by bifunctional reagents after casting. All the materials utilized for the work reported here were prepared by solvent casting.

The monomers utilized are given in Table II. HEMA was given by Hydro Med Sciences, Inc., New Brunswick, New Jersey; it contains 0.04% methacrylic acid, 0.15% diethylene glycol methacrylate, less than 0.02% ethylene dimethacrylate, and 23 ppm of MEHQ. MEMA was obtained from Polysciences, Inc., Warrington, Pennsylvania, and used as received. Gas chromatographic analysis indicates a purity of over 99% for MEMA.

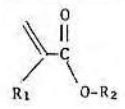
Polymerization is initiated by azobis(methyl isobutyrate) (ABMIB) [28], a derivative of azobisisobutyronitrile (AIBN). ABMIB decomposes to give a radical species which provides a methacrylate end group, thereby avoiding any possibility of artifacts due to initiator chain ends [28].

The polymer films are prepared by solvent casting onto a glass support. The polymers used for solvent casting are prepared by polymerizing monomer at high dilutions. We use 10:1 v/v ethanol/monomer at 60°C for 24 hr with 7.8×10^{-3} mole ABMIB/100 ml of monomer. The ABMIB-initiated polymers polymerized at 60°C have the following tacticities: 0:40:60 iso:hetero:syndio as determined by C^{13} NMR [29, 30].

High syndiotactic material (0:20:80 iso:hetero:syndio) is prepared by uv photolysis at −40°C of the ABMIB-monomer solution in ethanol. Isotactic

TABLE II

Monomers Utilized in this Study : Methoxyethyl Methacrylate (MEMA), Hydroxyethyl Methacrylate (HEMA), Methyl Methacrylate (MMA), Dihydroxypropyl Methacrylate (DHPMA)



R_1=	R_2=	
$-CH_3$	$-CH_2CH_2-OCH_3$	MEMA
$-CH_3$	$-CH_2CH_2OH$	HEMA
$-CH_3$	$-CH_3$	MMA
$-CH^3$	$-CH_2CHOHCH_2OH$	DHPMA

material is prepared by anionic means utilizing a blocked monomer [29]. The HEMA hydroxyl group is blocked with benzoyl chloride to form the benzoyl ester. This is polymerized in toluene with a dibutyl copper lithium reagent, which initiates anionic polymerization without cleaving the benzoyl ester [29]. The tacticity is 80:14:6 iso:hetero:syndio [29, 30]. The benzoate ester is then removed by mild base hydrolysis, which does not attack the more stable methacrylate ester. The isotactic material is isolated by precipitation.

The polymers of dihydroxypropyl methacrylate (DHPMA) are prepared by an indirect route from (2,2-dimethyl-1,3-dioxolane-4-methyl) methacrylate. This monomer is polymerized under the conditions described above. The resulting polymer is concentrated under reduced pressure and the acetone ketal is selectively removed under aqueous acid conditions. The resulting dihydroxypropyl methacrylate polymer is isolated and dried to constant weight in high vacuum.

The materials to be solvent cast are dissolved in dry dimethyl formamide (DMF) to form a 10% w/v solution. The hexamethylene diisocyanate is then added [1% for p(HEMA), 3% for poly (50:50 HEMA-DHPMA), and 5% for p(DHPMA)]. The solution is solvent cast on the aminopropylsilane-treated glass and cured at 60°C for 24 hr. The slides are then vacuum dried at 60°C for 24 hr to remove residual DMF, stored in glass jars, extracted, equilibrated, and used. In the case of p(MEMA), the polymer was solvent cast from toluene onto vinylsilane-treated glass slides. The bonding of the polymer to the glass and polymer cross-linking is done in one step.

For this study the gels are extracted until there is no change in the surface tension of water [31] and until the gels test as nontoxic in sensitive cell culture and inhibition of cell growth assays [32]. For these very thin gel coatings, extraction in three changes of distilled water over a 24-hr period is adequate. The gels are extracted just prior to their use.

The equilibrium water content of the gels was determined gravimetrically by swelling to constant weight in distilled water as a function of temperature. The data reported later are for $T \simeq 25$°C.

METHODS

Electron Spectroscopy for Chemical Analysis (ESCA)

ESCA samples of each lot of gel-coated glass slides are thoroughly dried after extraction and examined by x-ray photoelectron spectroscopy (XPS), a sensitive surface analysis technique [33] which we routinely use as a quality control check.

X-ray photoelectron spectroscopy was done on a Hewlett–Packard 5950B ESCA utilizing monochromatic Al $K\alpha_{1,2}$ radiation at 1487 eV. Fully extracted gels were air dried and then dessicated overnight under a 15-μ vacuum. The samples were mounted in air, inserted into the spectrometer, and analyzed at ambient temperatures in a 10^{-9} Torr vacuum. Power at the x-ray source was 800 W. Instrument resolution in our spectrometer is nominally 0.8 eV or less as measured for the full-width at half-maximum of the C-1*s* line from spectroscopic grade graphite. An electron flood gun operating at 0.3 mA and 5.0 eV supplied a flux of low-energy electrons to eliminate charging artifacts in the resulting spectra.

Wide scans (0–1000 eV) were performed for surface elemental analyses. The only elements assumed to be present on the surface of these materials are C, O, and H (the latter cannot be detected by XPS), and each wide scan was carefully inspected for trace element contamination of the surface. Detailed 20-eV scans of the C-1*s* (275–295 eV) and O-1*s* (520–540 eV) regions were also run for determination of the carbon–oxygen stoichiometry of the surface.

Contact Angles

Static contact angles were measured on a Rame–Hart contact angle goniometer using the immersion chamber in Figure 5. The gel-coated microscope slides were positioned on the magnet and firmly held in place with two iron support strips. The container was filled with doubly distilled water and the top containing the magnet/polymer combination was carefully lowered into the container until the microscope slide was completely immersed. While the gel surface was equilibrating in the container, the goniometer was aligned and focused on the gel–water interface. At this point a microsyringe containing either room air or 99.99% pure *n*-octane (Aldrich Chemicals, Gold Label Octane) was lowered into the water. A bubble or drop volume of $\sim$0.1–0.2 μl was formed on the syringe tip, positioned underneath the gel surface, "snapped" from the tip, and allowed to rise to the polymer/water interface. The apparent air–gel or octane–gel contact angle was then immediately measured (ϕ in Fig. 5). Angles on both sides of each bubble were measured to assure symmetry, and generally five or more air bubbles were measured on each surface, followed by five or more octane bubbles.

Very small bubbles were used in order to minimize gravitational effects. Temperature of the immersion bath was 26 ± 1°C. The angle measured is noted in Figure 5 as ϕ. The measured angles for octane were subtracted from 180° to give the value of θ, in accordance with the derivations and discussion earlier in the paper. For the air bubble case, $\phi = \theta$. See Figures 1, 5, and 6 for clarification.

Liquid surface tensions were measured with a Fisher surface tensiometer using a platinum–rhodium du Nuoy ring cleaned before each use in a dry air radio-frequency glow discharge (Tegal Corp., Richmond, California, Plasmod RFGD apparatus) for 5 min at 300 μ Hg.

Freeze-Etch Scanning Electron Microscopy (SEM)

A small drop of distilled water (~0.1 μl) was placed on the gel–water glass surface. After 3–5 sec. the SEM stub containing the sample and water droplet were placed in liquid nitrogen for several minutes, freezing any deformation induced by the water droplet. The SEM stub, full of liquid nitrogen, was placed in the SEM and the sample chamber evacuated. After about 3 min one could observe the water (ice) droplet on the gel surface. As the sample warms up to ~−100°C, the ice begins to sublime (this is the freeze-etching process) and the ice droplet begins to recede, and eventually disappears after 9 or 10 min (see Figs. 7–9 in Results and Discussion section).

A Cambridge Mark IIA scanning electron microscope was used. Typical operating conditions were 5 KV, 0.175 mA beam current. Sample chamber vacuum was roughly 10^{-5} Torr. All samples were uncoated. The special freeze-etch sample stub was obtained from EM Ventions, Inc., Rockville, Maryland.

Water drops on the gel surfaces were also examined optically using a Nikon Apophot research microscope using reflected light interference contrast at ambient temperature.

RESULTS AND DISCUSSION

Freeze-Etch SEM Studies of Contact-Angle-Induced Deformation of Gels

Figure 7(a) shows a drop of water at the surface of p(HEMA). The gel surface had been lightly blotted prior to applying the drop. After several seconds the sample and its drop were frozen in liquid nitrogen, placed in the SEM, and then observed (see Methods section for details). In Figure 7(b) (11.50 min after inspection) the drop has receded (by subliming in the vacuum of the SEM), exposing the deformation present at the original drop–gel boundary.

Figure 8(b) is a high-magnification view of the original bubble–gel interface after the bubble has receded considerably (time: 6.30 min). A ridgelike

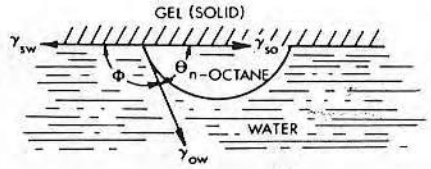


FIG. 6. Drop of n-octane at the gel–water interface. The subscripts denote water (W), octane (O), and gel (S). $\gamma_{SW} = \gamma_{SO} + \gamma_{OW} \cos \theta$.

structure is clearly evident, which may be roughly one micron wide. Figure 8(c) is the bubble profile of a conventional p(HEMA) gel after much of the drop has sublimed off. The oval profile is clearly evident and suggests a uniform depression under the bubble. A similar photo for a high-modulus polystyrene surface exhibits very little evidence of deformation or depression (Fig. 9).

Similar studies utilizing optical microscopy were also performed. The drop–gel junction was clearly observed as the drop receded.

These photos suggest that one can indeed detect water-droplet-induced deformations at gel surfaces and provide visual documentation for the concerns of Bikerman [15], Lester [13], and Rusanov [16]. The features observed in Figures 8 and 9 correspond roughly to the magnitudes of deformation calculable from Rusanov's model [16].

Further freeze-etch experiments utilizing stereo-pair micrographs would enable one to do some quantitative stereogrammetry and measure directly the extents of deformation. Further optical experiments utilizing semiquantitative interference contrast should also permit one to quantitate the extent of deformation.

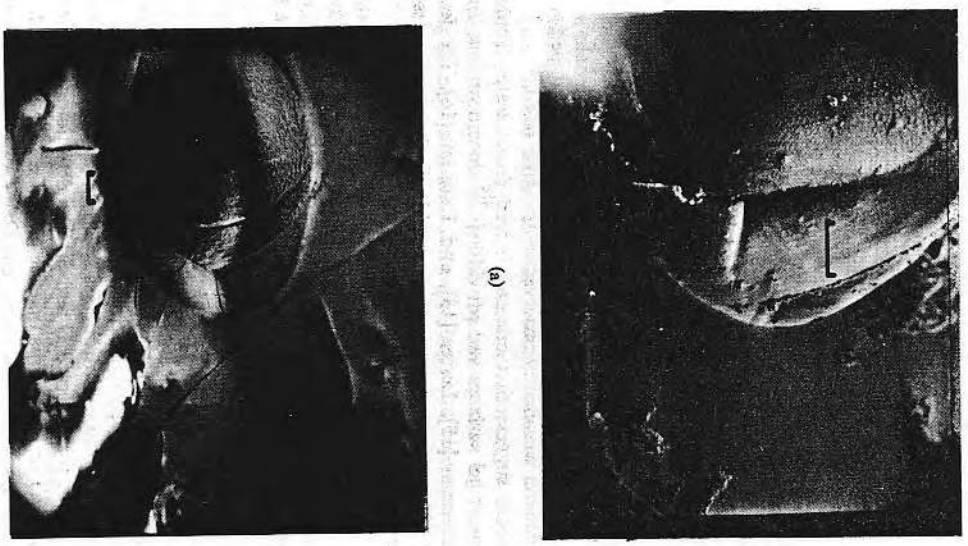
ESCA Studies

The spectrum of the aminopropylsilane-treated (APS) glass clearly shows the presence of nitrogen, confirming the presence of APS on the glass surface. Both APS-glass and control glass spectra show the presence of Na, Ca, and C, as well as the expected O and Si. The detection of Na and Ca with no evidence of Al or B confirms that the glass is a soda-lime type.

The polymer spectra show only C and O, as expected, with a very small amount of Si, probably extracted from the glass or from glassware during preparation. A small amount of N is also seen, probably due to the diisocyanate cross-linker used.

Contact-Angle Studies

The contact-angle data for the various gels are given in Table III. Contact angle and swelling data are for $T \simeq 25$°C, as well as the surface tension data.



(a) (b)

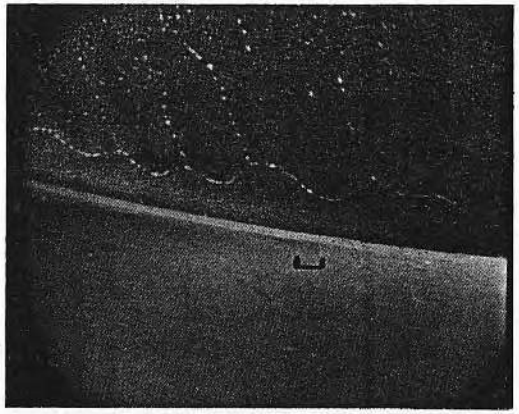
Fig. 7 (a). A drop of water (ice) on a poly(HEMA)-coated glass slide. The drop is on the left, the smooth gel surface on the right. The micrograph was taken 5.5 min after insertion into the SEM. The drop–gel interface is clearly seen. The debris in the right foreground is ice crystals. Bar = 100 μm. (b) Same as top, but a lower magnification and 11.50 min after insertion. The drop has clearly receded. The original drop–gel boundary is clearly visible and indicates substantial deformation at and near the original boundary. Bar = 100 μm.

TABLE III

Contact Angle and Interfacial Parameters for Poly(Hydroxyethyl Methacrylate) and Related Polymers

Gel (a)	% cross-linker (b)	water weight fraction W_f (c)	Θ air (d)	Θ octane (e)	$\gamma_{SV} - \gamma_{SW}$ (f)	I_{SW} (f)	γ_{SV}^d (f)	γ_{SV}^p (f)	γ_{SV} (f)	γ_{SW} (f)
h-p(HEMA)	1	0.39	17 ± 2	158 ± 2	70.0 ± 0.8	97.3 ± 0.7	23	47	70	∿0
i-p(HEMA)	1	0.43	13 ± 1	166 ± 1	71.2 ± 0.3	99.5 ± 0.2	22	49	71	∿0
p(MEMA)	0	0.02	46 ± 2	106 ± 3	50.1 ± 1.9	64.4 ± 2.6	39	21	60	∿10
p(75MEMA - 25HEMA)	1	0.18	32 ± 2	125 ± 3	61.1 ± 1.4	79.5 ± 2.2	33	31	64	∿3
p(50MEMA - 50HEMA)	1	0.23	22 ± 2	143 ± 2	66.8 ± 1.0	90.8 ± 1.1	27	41	68	∿0
p(25MEMA - 75HEMA)	1	0.33	14 ± 2	153 ± 2	70.0 ± 0.6	95.5 ± 0.8	25	45	70	∿0
p(MMA)	0	<0.01	67 ± 2	90 ± 1	28.2 ± 2.4	50.5 ± 0.9	29	13	42	∿14
p(DHPMA)	5	0.55	34 ± 2	144 ± 3	59.8 ± 1.5	91.4 ± 1.5	19	41	60	∿0
p(50HEMA - 50DHPMA)	3	0.45	20 ± 1	158 ± 2	67.8 ± 0.5	67.8 ± 0.5	21	47	68	∿0

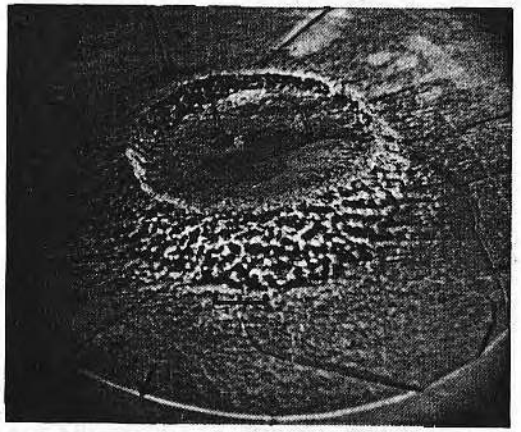
[a] Refer to Table II for abbreviations; h = heterotactic, i = isotactic.
[b] Percent of hexamethylene diisocyanate.
[c] W_f = (W hydrated gel − W dry gel)/ W hydrated gel, where W is weight.
[d] Gel–water–air angle at 25°C (see Fig. 5, $\theta = \phi$).
[e] Gel–octane–water angle at 25°C (see Fig. 5, $\theta = 180 - \phi$).
[f] See text for equations and assumptions; error limits probably of the order of ±5 erg/cm^2.



(a)

(b)

FIG. 8. (a) A 75 HEMA/25 MEMA gel containing a drop of ice (upper). The gel surface is the smooth foreground. Note the presence of a ridge or boss at the junction. This photo was taken 5.20 min after insertion into the SEM. Bar = 10 μm. (b) Same as Figure 8(a), but 6.30 min after insertion. The drop has receded from the original boundary. The contrast has been adjusted to optimally show the ridge or boss at the original gel–ice boundary. The black foreground is the gel. Bar = 10 μm. (c) Same as 8(a) and 8(b), but 8.55 min after insertion. The ice is disappearing rapidly at this point. The curved line in the foreground (arrow) is the original ice–gel boundary. The cracks are probably due to freeze-cracking. Bar = 100 μm.



(c)

FIG. 8. (*Continued from previous page.*)

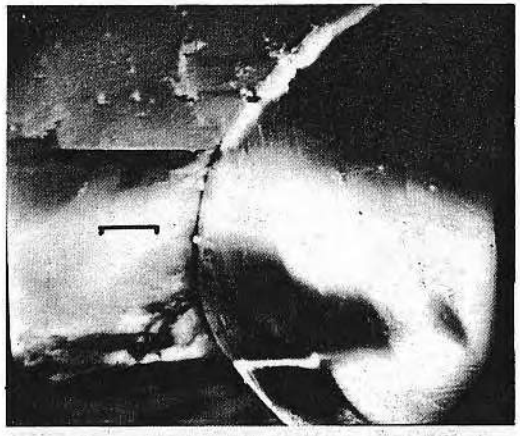
Note that θ_{air} roughly decreases with increasing water content, as expected. θ_{octane} roughly increases with increasing water content showing that the polar interactions across the gel–water interface (I_{sw}) increase with increasing water content, again as expected.

The problem is how to extract an estimate of γ_{sw} from these data. As the quantity cannot be directly determined, we will do our best to crudely estimate it.

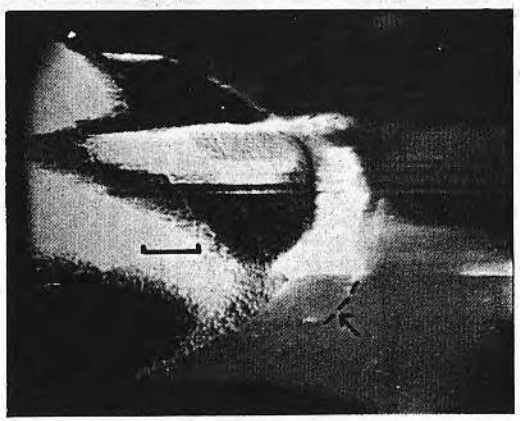
$\gamma_{sv} - \gamma_{sw}$ can be directly determined from the air-in-water contact-angle data via eq. (21). The data (Table III) were obtained using a measured value of γ_{Lv} for water of 72.1 dyn/cm at 25°C.

I_{sw} can be calculated from eq. (18), where $\gamma'_{wv} \simeq \gamma_{wv} = 72.1$ dyn/cm at 25°C; $\gamma_{ov} = 21.6$ dyn/cm at 25°C. Letting $\gamma^d_{wv} = \gamma^d_{ov} = 21.6$ we shall say $\gamma^p_{wv} \simeq 50.5$ dyn/cm. Thus, γ_{ow} must be 50.5 dyn/cm, which agrees with our measured value of 50.6 at 25°C and with handbook [35] values of 50.8 at 20°C. The I_{sw} values presented in Table III were calculated using eq. (19). The trend is similar to that obtained with the $\gamma_{sv} - \gamma_{sw}$ data.

The only related data in the literature are those of Holly and Refojo [7–10]. In the case of those materials that are common to both studies, the θ values agree. We cannot compare our octane data with theirs, as they utilized a water-in-octane system, while we have chosen to use an octaine-in-water method.



(a)



(b)

FIG. 9. (a) Here the water drop was placed on polystyrene, a relatively high modulus material ($E \simeq 3 \times 10^{10}$ dyne/cm^2). The micrograph was taken 4 min after insertion into the SEM. Owing to the low conductivity of the substrate, charging is a serious problem and results in the whitish, washed out regions of the micrograph. Bar = 100 μm. (b) Same as Figure 9(a), but 8.5 min after insertion. Here the ice has receded considerably. The original ice–gel boundary is indicated by an arrow and by the dotted line. If any formation is present, it is of such a magnitude as to not be resolvable at this magnification. Charging is even more severe here. Bar = 100 μm.

We can combine the two sets of data in Table III to obtain another quantity. Solving eq. (20) for γ_{sv}^d, we have

$$\gamma_{sv}^d \simeq \left[\frac{(\gamma_{sv} - \gamma_{sw}) - I_{sw} + \gamma_{wv}}{2 \ (\gamma_{wv}^d)^{1/2}} \right]^2$$

or

$$\gamma_{sv}^d \simeq \left[\frac{(\gamma_{sv} - \gamma_{sw}) - I_{sw} + 72.1}{9.3} \right]^2 \tag{21}$$

Equation (21) is used to estimate the γ_{sv}^d values given in Table III.

Note that eq. (17) is normally written with γ_s and γ_L terms rather than γ_{sv} and γ_{LV}. The difference is the spreading pressure. What is the significance of γ_s and γ_{sv} (where V refers to water vapor) for an aqueous gel? The surfaces we are interested in are those that are fully hydrated and indeed are in equilibrium with water. The "surface" free energy of a gel is highly dependent on its degree of hydration. For these reasons we chose to use γ_{sv} in all equations, arguing that for these polymers γ_s has no physical significance for our experimental conditions.

If we let

$$I_{sw} \simeq 2 \ \ (\gamma_{sv}^p \ \gamma_{wv}^p)^{1/2} \tag{22}$$

then

$$\gamma_{sv}^p \simeq I_{sw}^2 \ \ (4 \ \gamma_{wv}^p) \tag{23}$$

where

$$\gamma_{wv}^p \simeq 50.5 \text{ dyn/cm}$$

Although eq. (22) is a poor approximation for hydrogen-bonded systems, it is useful as a first approximation. We have calculated γ_{sv}^p by eq. (22) and given the results in Table III. Having values for γ_{sv}^d and γ_{sv}^p, we calculate γ_{sv} and, from the $\gamma_{sv} - \gamma_{sw}$ data, calculate γ_{sw}. The values are in Table III.

Although we have made some assumptions in deducing γ_{sv}^d, γ_{sv}^p, γ_{sv}, and γ_{sw}, the results are of considerable interest. First, recall that the experimental data, θ_{air} and θ_{octane}, are taken on fully hydrated gel surfaces immersed in water. There should be no problems with surface dehydration. These are *in situ* measurements. Second, although these results can be affected by distortion effects, as outlined earlier, the distortion-induced changes are roughly comparable to the error limits of the contact-angle measurements for the materials used. Because of the errors and assumptions involved, the γ_{sv} and γ_{sw} values in Table III are probably not better than ± 5 erg/cm^2.

A major concern is the meaning of the quantities γ_s, γ_{sv}, and spreading pressure for gel interfaces. Although we have elected to use γ_{sv}, there is really no rigorous basis for this—the question must be examined in detail. Finally, eq.(22) should be modified considerably for hydrogen-bonded systems. In spite of all these qualifications, the data presented may help serve as a rough guide to point us and others in, we hope, reasonable directions.

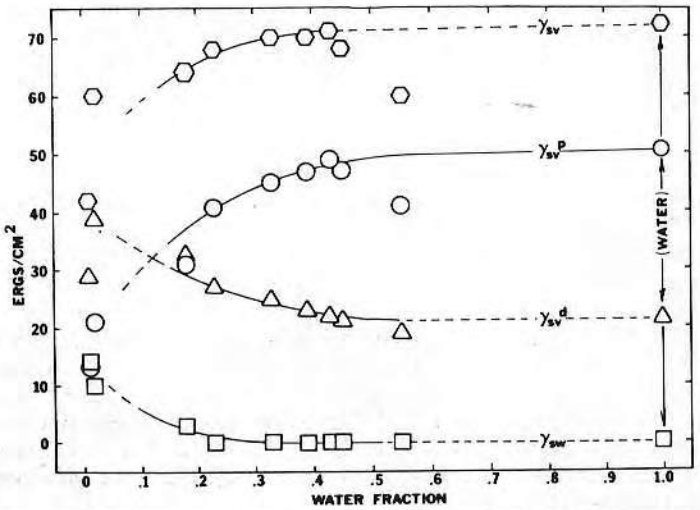


FIG. 10. The surface and interfacial free energy results plotted as a function of bulk water fraction, W_f. The data at $W_f = 1$ are for pure water.

Figure 10 presents γ_{sv}^d, γ_{sv}^p, γ_{sv}, and γ_{sw} as a function of water fraction, W_f. γ_{sv}^d decreases in a roughly linear fashion with W_f until $W_f \simeq 0.4$ and then γ_{sv}^d is probably constant, with a value roughly equal to that of pure water. γ_{sv}^p increases with W_f until about $W_f \simeq 0.4$, at which point $\gamma_{sv}^p \sim \gamma_{wv}^p$. γ_{sv} is roughly constant beyond $W_f \simeq 0.2$, which is of course why γ_{sw} drops to a roughly constant value at $W_f \simeq 0.2$. Perhaps the most surprising result is that γ_{sw} is roughly zero even for water contents as low as $W_f \simeq 0.2$.

CONCLUSIONS

(1) Contact-angle-induced deformation of gels occurs and can lead to relatively large errors in the contact angle, particularly for low-modulus, high-water-content gels. Future studies must consider the effects of such deformation.

(2) Air-in-water and octane-in-water contact angles permit one to probe the gel–water interface in the fully hydrated *in situ* state and to obtain estimates of γ_{sv}, γ_{sw}, γ_{sv}^d, and γ_{sv}^p. The use of other water-immiscible liquids should permit one to determine more reliable estimates of the interfacial properties.

(3) γ_{sw} already approaches zero for $W_f \simeq 0.2$, suggesting that even low-water-content systems may have relatively low interfacial free energies. The work must be extended to include a wider range of W_f values.

(4) As interfacial free energies of the order of 1 erg/cm^2 or even lower may be important, we must be able to measure γ_{sw} to an accuracy of the order of ± 0.1 erg/cm^2. This means that not only must deformation errors be accounted for, but θ itself must be measured much more precisely [14].

(5) As the minimum interfacial free energy hypothesis was formulated mainly for the question of protein adsorption and blood compatibility, one should deal with solutions of physiologic ionic strength buffered to $p\mathrm{H} = 7.4$. Thus γ_{sv} and γ_{sw} should be determined under such conditions.

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