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### Correlation of the Surface Charge Characteristics of Polymers with Their Antithrombogenic Characteristics

S. Srinivasan<sup>a</sup>; P. N. Sawyer<sup>a</sup>

<sup>a</sup> Electrochemical and Biophysical Laboratories of the Vascular Surgical Services, Department of Surgery and Surgical Research, State University of New York, Brooklyn, New York

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## **Correlation of the Surface Charge Characteristics of Polymers with Their Antithrombogenic Characteristics**

S. SRINIVASAN and P. N. SAWYER

*Electrochemical and Biophysical Laboratories of the Vascular Surgical Services, Department of Surgery and Surgical Research, State University of New York, Downstate Medical Center, Brooklyn, New York 11203*

### **SUMMARY**

A knowledge of the structure of the double layer is essential in the investigation of reactions at an interface between two dissimilar media. This aspect is briefly presented in respect to charge separation and potential distribution in the interfacial region. The types of reactions that can occur at solid-solution interfaces (electron transfer, electrosorption, and electrophoretic deposition) are discussed. The electrokinetic methods for determination of surface charge characteristics of insulator materials in electrodes are reviewed. Thrombosis on the blood vessel wall and on prosthetic materials is an interfacial chemical reaction. The evidence for an electrochemical mechanism of thrombosis on conducting materials is outlined. Under normal conditions, the blood vessel wall is negatively charged. Injury or atherosclerosis makes it less negatively or even positively charged. With decrease of pH, there is an increase in the surface charge density of the blood vessel wall with an isoelectric point at a pH of about 4.5. Materials treated chemically so as to introduce negatively charged groups (sulfonate, carboxylate, heparinized, anionic ioplex) tend to be antithrombogenic while positively charged surfaces (cationic Ioplex, quarternary ammonium group) are thrombogenic. A useful criterion for antithrombogenic polymer materials is that their surfaces must have a uniform negative charge.

## 1. INTRODUCTION

Thrombosis is an interfacial reaction occurring at the blood vessel wall-blood or prosthetic material-blood interface. In general, there is an electric potential drop across solid-electrolyte interfaces, and this potential drop influences the rates of reactions which occur at such interfaces. The potential variation across solid-electrolyte interfaces depends significantly on the surface charge characteristics of the solid. Over the past 18 years considerable evidence [1, 2] has been obtained to show that the occurrence or nonoccurrence of thrombosis depends on the surface charge characteristics of the blood vessel wall, blood cells, and prosthetic materials. The aim of the present paper is to correlate the surface charge characteristics of polymer materials, which are obtained from electrokinetic techniques, with their antithrombogenic characteristics. Before dealing with this subject, however, a brief survey is made of the following topics: 1) the structure of the double layer at solid-electrolyte interface, 2) types of reactions which occur at solid-electrolyte interfaces, 3) electrokinetic methods for determination of surface charge characteristics of insulators materials, 4) evidence for an electrochemical mechanism of thrombosis, and 5) structure of the double layer at the blood vessel wall-electrolyte interface under various conditions.

## 2. STRUCTURE OF THE DOUBLE LAYER AT SOLID-SOLUTION INTERFACES

### i. Its Origin: Charge Separation at an Interface Between Two Dissimilar Media

An electric double layer nearly always exists at any interface between two dissimilar media and almost invariably when one of the phases is an electrolyte solution [3]. It arises basically because of a separation of opposite charges across the interface as seen in Fig. 1, which is an illustration for the case of a solid-solution interface. A knowledge of the structure of the double layer at the solid-solution interface is particularly important since there is a variety of reactions that occur at such types of interfaces; the thrombosis reaction at the blood vessel wall or on prosthetic materials is a good example [1, 2]. The solids may be broadly divided into three groups: conductors, semiconductors, and insulators. The structures of the double layers at the interfaces of an electrolyte

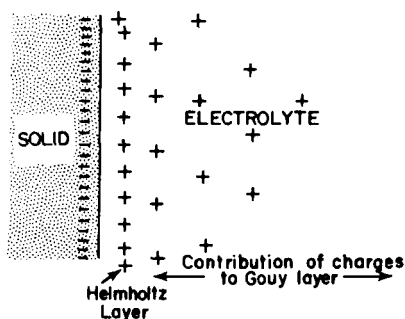


Fig. 1. A typical charge distribution at a solid-electrolyte interface.

with a conductor and with a semiconductor have been extensively investigated [4]. An advantage of studying such types of interfaces is that the double layer characteristics across these interfaces can be easily varied by changing the potential of the metal or the semiconductor by using a suitable polarization circuit. Since the present paper deals with the interfaces across insulator (e.g., polymers)-solution interfaces, the other types of interfaces will not be further considered here. The double layer characteristics at insulator-solution interfaces depend markedly on the chemical nature of the surface of the insulator material, for example, on the polar groups present on the surface and on the occurrence of specific adsorption on the surface from species in solution.

## ii. Potential Variation across Double Layer; Compact Layer and Diffuse Layer Potentials

Due to the separation of charges across the solid-solution interface (Fig. 1), one should expect a potential drop across the interface. The potential drop depends on a number of factors (the surface charge density, the concentration of the electrolyte, the presence of specific adsorption, etc.) for which several theories have been proposed [4]. The most accepted is the one in which there is a sharp, nearly linear potential drop starting from the surface of the solid to the first layer of ions on the solution side nearest to the solid, followed by an exponential decay of the potential to the bulk of the solution where there is electrical neutrality (i.e., number of positive ions is equal to the number of negative ions, unlike the region closer to the interface, vide Fig. 1). The potential variation across a typical interface is depicted in Fig. 2.

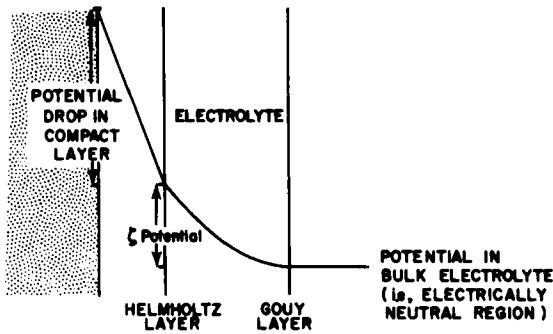


Fig. 2. A typical potential distribution across a solid-electrolyte interface. Diagram also shows position of Helmholtz and Gouy layers.

### iii. Zeta Potential across an Insulator-Solution Interface

In the case of insulating solid-solution interfaces, the region where there is an exponential variation in potential with distance out into the solution is important. The potential in this region is referred to as the zeta potential. It is the potential which can be derived from electrokinetic measurements [3]. Ideally, one would like to obtain the total potential drop across the solid-solution interface but this is practically impossible except in dilute solutions under which conditions the contribution of the zeta potential to the total potential drop across the interface becomes more and more important till in very dilute solutions it is nearly 100%.

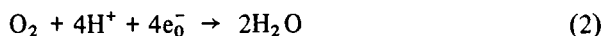
A knowledge of the zeta potential across insulating solid-solution interfaces is, however, very useful because when comparing a series of solids in the same electrolyte, the higher the zeta potential, the higher is the magnitude of the surface charge density of the solid and vice versa. One may use the convention that when the solid has a negative surface charge density, the zeta potential is negative.

## 3. TYPES OF REACTIONS AT SOLID-SOLUTION INTERFACES

### i. Conducting Solid-Solution Interfaces

There are basically three types of reactions that can occur across conducting solid-solution interfaces: 1) electron transfer, 2) electrosorption, and 3) electrophoretic deposition. As an example of the first type, one

may consider the corrosion of a metal (M) which occurs according to the two partial reactions:



The potential-dependent adsorption of organic compounds (e.g., hydrocarbons, alcohols, amines) on metals serves as an example of the second type of reaction. The adsorption-potential curves are usually parabolic. The reason for this behavior is that adsorption of these compounds on the solids occurs by the displacement of adsorbed water molecules from the surface [5]. Due to the fact that water has a relatively high dipole moment, it is not so easily displaced at potentials which are increasingly negative or positive from the potential of zero charge. The electrostatic interaction between the water molecules and the solid is least at the potential of zero charge and increases in either direction [6]. Hence the adsorption of the organic compound is maximum at the potential of zero charge and decreases in both directions with potential. Electrophoretic deposition of colloidal particles on solids (e.g., electrophoretic painting of the bodies of cars) occurs only in the presence of intense electric fields in solution. Such situations are rarely encountered in biological environments.

## ii. Insulating Solid-Solution Interfaces

A number of methods are available for the study of reactions across conducting solid-solution interfaces. Unfortunately, this is not the case when dealing with reactions across insulating solid-solution interfaces. One may now wonder whether the same types of reactions as across conducting solid-solution interfaces can occur across insulating solid-solution interfaces. The adsorption reaction can obviously occur. There is considerable evidence for this in colloidal chemistry [3] and it has been shown that adsorption depends markedly on the zeta potential (the only measurable electrochemical parameter in these cases) across the insulator-solution interface. As for electron transfer, it is very difficult to visualize such types of reactions here, because the insulator cannot act as a donor or acceptor of electrons (vide Reactions 1 and 2) and at the same time permit migration of electrons within the solid. There is, however, the possibility that species adsorbed on insulators may induce electron conducting properties to the solid. Alternatively, if very thin layers (a few mono layers) of insulating

solids are deposited on conducting substrates, electron transfer reactions may occur across interfaces of these solids with solution.

#### 4. EVIDENCE FOR AN ELECTROCHEMICAL MECHANISM OF THROMBOSIS

There is considerable evidence for an electrochemical mechanism of thrombosis. Most of it has been obtained from work on conducting solids. Since details of these investigations have been published elsewhere [1, 2], only a few summarizing remarks will be made here. From experiments carried out on a number of metals and also on some metals with variation of the potential across the double layer at the metal-blood interface, one is able to conclude that there is a critical thrombogenic potential ( $\approx 0.100$  mV vs the normal hydrogen electrode). By a determination of current-potential relations on metal electrodes in blood and in blank (control solution, e.g., saline) solutions, it was shown that blood is electrochemically active in a certain region of potential above this critical potential [7]. The weight of thrombus deposited on a metal electrode is linearly related to the quantity of electricity passed across the metal-solution interface. Adsorption of some blood coagulation factors (e.g., fibrinogen, thrombin) on metal electrodes (Hg, Pt, Au) was shown to be a potential-dependent phenomenon [8]. The adsorption maximum is at potentials positive (anodic) to the critical thrombogenic potential. It is a striking observation that Hageman factor, which is supposed to initiate the blood coagulation mechanism [9], does not adsorb on platinum and on mercury over a wide range of potentials\* in which there is significant adsorption of fibrinogen and thrombin. Fibrinogen polymerizes to fibrin at anodic potentials; at low anodic potentials fibrin strands are formed whereas at high anodic potentials amorphous powders are deposited on electrodes [10]. Evidence for an electrochemical mechanism of thrombosis on the blood vessel wall is presented in Section 6. Before dealing with this topic it is worthwhile to review briefly the methods used to characterize insulator-solution interfaces (Section 5).

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\*As obtained by a comparison of the double layer capacities across metal-solution interface as a function of potential in solutions which contain or do not contain Hageman factor.

## 5. METHODS FOR THE DETERMINATION OF THE DOUBLE LAYER CHARACTERISTICS AT INSULATOR-SOLUTION INTERFACES

### i. General

There are four methods for the determination of the double layer characteristics at insulator-solution interfaces: streaming potential, electroosmosis, electrophoresis, or sedimentation potential measurements [3]. Since these techniques have been extensively treated in the literature, they will be presented only briefly in the following subsections.

### ii. Streaming Potential Techniques

When an electrolyte flows through a narrow tube of an insulator material, a potential ( $E$ ) develops across the ends of the tube. This potential is linearly dependent on the pressure drop ( $P$ ) in the tube, as given by

$$\zeta = 4\pi\eta KE/DP \quad (3)$$

where  $\zeta$  is the zeta potential, and  $\eta$ ,  $K$ , and  $D$  are the viscosity, specific conductivity, and dielectric constant, respectively, of the electrolyte. Thus, from the slope of the  $E$ - $P$  relation, one can calculate the zeta potential across the insulator-solution interface.

### iii. Electroosmosis Techniques

A convenient way of obtaining the surface charge characteristics for porous materials is by using electroosmosis techniques. Here, the rate of transfer of fluid flow,  $v$ , in the presence of an applied electric current ( $i$ ) across the membrane yields information on the zeta potential at the material-solution interface according to the equation:

$$\zeta = 4\pi K\eta Av/Di \quad (4)$$

where  $A$  is the cross sectional area of the membrane.

### iv. Electrophoresis Techniques

Electrophoresis techniques are valuable and simple for yielding information on the zeta potentials across colloidal particles-solution interfaces. In



electrophoresis there is the migration of these colloidal particles in an electric field (E). By measuring the electrophoretic mobility ( $v$ ), one can calculate the zeta potential by using the equation:

$$\zeta = 4\pi\eta v/DE \quad (5)$$

#### v. Sedimentation Potential Techniques

A second method available for obtaining the zeta potentials across colloidal particles-solution interfaces is by measurement of sedimentation potentials. The sedimentation potential is defined as the potential which arises between two reversible electrodes, vertically separated apart in a tube containing the electrolyte, through which the colloidal particles are allowed to fall under gravity. The sedimentation potential (E) is related to the zeta potential by:

$$E = Dr^3(\rho - \rho')ng\zeta/3\eta K \quad (6)$$

where  $g$  is the gravitational constant,  $\rho$  and  $\rho'$  are the densities of the particle and of the solution, respectively,  $l$  is the distance between the electrodes,  $r$  is the radius of the sedimenting particles, and  $n$  is the number of such particles in solution per unit volume.

## 6. STRUCTURE OF THE DOUBLE LAYER AT THE BLOOD VESSEL WALL-ELECTROLYTE INTERFACE UNDER VARIOUS CONDITIONS

### i. General

Before presenting the correlations of the surface charge characteristics of synthetic polymers with their antithrombogenic characteristics, the behavior of the blood vessel wall-electrolyte interface in respect to its electrochemical characteristics under various conditions will be briefly reviewed. It will be ideal if one can synthesize polymer materials with the electrochemical properties (e.g., surface charge, ion transport, ion absorption and desorption) of the blood vessel wall itself. The work which is discussed in the next few subsections is found in great detail in previous articles [1, 2, 11].

## ii. Normal Wall

Streaming potential and electroosmosis techniques reveal that the blood vessel wall is negatively charged under normal conditions. The former technique has been used both *in vivo* and *in vitro*, whereas only *in vitro* measurements were made with the latter. Zeta potentials across the blood vessel wall-blood (or electrolyte having the same ionic composition as blood) are in the region of  $-8$  to  $-12$  mV.

## iii. Effect of Injury

Injury to the blood vessel wall causes a reduction in the magnitude of its negative charge density and quite often even a reversal of its sign. Injury is generally accompanied by thrombosis. There is apparently little change in the surface charge density of progressively increasing atherosclerotic walls until the maximum degree of atherosclerosis is reached, at which point there is a marked decrease in the magnitude of the zeta potential.

## iv. Effect of pH

With decreasing pH, the zeta potentials across blood vessel wall-solution interfaces become less negative until at a pH of about 4.5 the zeta potential becomes zero (iso-electric point) and below a pH of 4.5 the zeta potentials are positive (i.e., the blood vessel wall becomes positively charged). One may speculate that this behavior is caused by the increasing specific adsorption of hydrogen ions as the pH is lowered.

## v. Effect of Drugs

Antithrombogenic drugs (e.g., heparin, chondroitin sulfate) increase the negative charge density of the blood vessel wall while thrombogenic drugs (e.g., polyquarternary, protamine) have the opposite effect and in several cases have even caused a reversal in the sign of the surface charge [12]. Since antithrombogenic compounds generally have some strong negatively charged groups while thrombogenic compounds have positively charged groups, specific adsorption of these entities on the blood vessel wall is indicated.

## 7. EFFECT OF CHEMICAL OR ELECTRICAL TREATMENT OF INSULATOR MATERIALS ON THEIR SURFACE CHARGE CHARACTERISTICS

### i. Chemical Treatment

**a. Sulfonation, Carboxylation.** Tubes of Teflon were chemically treated so as to introduce varying concentrations of negatively charged groups (e.g., sulfonate, carboxylate) on the surface. As described in Section 6, one of the essential criteria for a nonthrombogenic surface, like the blood vessel wall itself, is a uniformly negatively charged surface. The untreated, sulfonated, and carboxylated surfaces were provided by the American Cyanamid Co. The zeta potentials for a typical group of untreated, sulfonated and carboxylated Teflons are presented in Table 1. The sulfonated Teflons, as expected, have the most negative zeta potential, the carboxylated come next, and the untreated Teflon has the least negative value.

**b. Heparinization.** Heparin is one of the strongest known antithrombogenic compounds. It significantly increases the negative charge density of the blood vessel wall (Section 6). Due to its marked antithrombogenic character, several groups or workers attempted to bond heparin to different types of polymer surfaces. One of the main problems with this treatment is that the heparin-polymer bond is not strong, and this results in the loss of heparin from the surfaces of implanted prostheses. Members of the Battelle Memorial Institute have been successful in attaining a higher degree of the strength of this bond to surfaces in the following manner. Quarternary ammonium salts are first bonded to the surfaces. These will make the surfaces positively charged. The heparin is then bonded to these positively charged surfaces. Zeta potentials, as obtained from streaming potential measurements on untreated, quarternized, and heparinized silicone rubber tubes are shown in Table 1. It may be a surprising observation that the heparinized surfaces have a lower negative surface charge density than the untreated silicone rubber tubes. This may be due to the fact that the silicone rubber itself has negatively charged groups on the surface. There are, however, cases where heparinization of other types of polymers make the surface more negatively charged than the untreated surfaces.

c. **Ioplexes.** Anionic, cationic, and neutral Ioplexes (Ioplex is the trade name for a polyelectrolyte complex) have been provided by the Amicon Corp. Zeta potentials of these membranes in Krebs solution as obtained from electroosmosis measurements are presented in Table 1. As may be predicted, the cationic Ioplexes are positively charged and the anionic ones are negatively charged. The neutral Ioplexes have a small positive surface charge.

## ii. Electrets

Electrets were prepared by the American Cyanamid Co. from Teflon tubes by first employing a thermal treatment followed by electrification using an applied potential of 4.4 to 6.0 kV across the walls of the tubes. The streaming potential-pressure relation of electrets has only a slightly higher slope than that of the untreated Teflon surface. Under this intense electric field, however, the surfaces become quite uniform in respect to surface charge, which is one of the requirements for a nonthrombogenic surface. The zeta potential at the electret-Krebs solution interface is found in Table 1.

## 8. THE IN VIVO BLOOD COMPATIBILITY OF CHEMICALLY AND ELECTRICALLY TREATED INSULATOR MATERIALS

The materials, on which surface charge characteristics were determined (Section 7), were fabricated into tubes of approximately 3 cm length and 1 cm i.d. and implanted as vascular prostheses in the canine thoracic inferior vena cava (TIVC) of dogs. Unless the dogs died in shorter periods of time, they were sacrificed 2 weeks after implantation, and the tubes removed and examined for thrombus deposition. The results of these experiments are also presented in Table 1. It is clearly seen from these results that the positively charged tubes are thrombogenic. In the case of the chemically (with sulfonate, carboxylate, heparin groups, or anionic Ioplexes) or electrically (electrets) treated tubes, which have a negative surface charge density as shown by streaming potential or electroosmosis measurements, minimal thrombus formation was found at the junctions of the prostheses with the recipient vessels. There are several possible reasons for this junctional thrombus formation [13]: pockets of low flow area at the junctions of the solid tubes (with

**Table 1.** Correlations of the Surface Charge Characteristics of Some Chemically and Electrically Treated Polymers with Their Antithrombogenic Characteristics

| Material                   | Institution providing material | Surface active group or compound | Zeta potential of material in Krebs solution (mV) | Results of implantation of tubes in canine TIVC |
|----------------------------|--------------------------------|----------------------------------|---|---|
| Untreated Teflon (control) | American Cyanamid              | —                                | -9.5  | Thrombus formation in tube in over 50% of cases |
| Carboxylated Teflon        | American Cyanamid              | Carboxylate                      | -14.0   | Junctional thrombus formation                   |
| Sulfonated Teflon          | American Cyanamid              | Sulfonate                        | -19.5   | Junctional thrombus formation in few cases      |
| Teflon electret            | American Cyanamid              | Polar impurity in Teflon         | -11.0   | Junctional thrombus formation in few cases      |

|                             |                   |                      |       |  |
|-----------------------------|-------------------|----------------------|-------|--|
| Untreated silicone rubber   | Battelle Memorial | —                    | -21.2 | Junctional thrombus formation  |
| Quaternized silicone rubber | Battelle Memorial | Quarternary ammonium | +15.9 | Thrombus formation in tube   |
| Heparinized silicone rubber | Battelle Memorial | Heparin              | -15.9 | Junctional thrombus formation  |
| Neutral Ioplex              | Amicon            |                      | +4.9  | Thrombus formation in tube   |
| 0.5 Cationic Ioplex         | Amicon            |                      | +15.6 | Thrombus formation in tube   |
| 0.5 Anionic Ioplex          | Amicon            |                      | -7.8  | Small amounts of thrombus formation in tube. Problem of separation of inner layers |

thickness of walls ranging from 0.5 to 1 mm) with the porous recipient vessels, change in the electrochemical characteristics from solid tube to recipient vessel, nonporous nature of solid tubes which does not permit active ion transport, etc. The inner surfaces of the uniformly\* negatively charged tubes were free of any thrombus deposits. There were some mechanical problems with the anionic Iplexes, mainly connected with the separation of the inner layers of the tube wall. Of the negatively charged surfaces examined, the sulfonated Teflon and heparinized silicone rubber surface are the most promising.

### 9. THROMBOGENIC NATURE OF NONUNIFORMLY CHARGED SURFACES

From the work presented in Section 8 as well as in previous papers on the testing and evaluation of materials in respect to their blood compatibility and the correlation of this property with the surface charge characteristics of the materials [1, 2], one may conclude that the positively charged surfaces are thrombogenic while the uniformly negatively charged surfaces tend to be anti-thrombogenic. There are, however, several instances where one finds that surfaces exhibiting markedly negative zeta potentials are thrombogenic. One example is glass. Some untreated glass surfaces have an even more negative zeta potential than the corresponding siliconized glass surfaces. The latter surfaces are considerably more nonthrombogenic than untreated glass surfaces. A possible explanation for the thrombogenic behavior of untreated glass is that its surface charge is rather nonuniform. Siliconization makes the glass surface quite uniform in respect to surface charge. Though electrokinetic methods are quite valuable in determining the surface charge characteristics of materials, these methods only yield the net value of the surface charge density. It is not possible to discriminate between local sites. A second example of the influence of nonuniformly charged surfaces catalyzing thrombosis is in the case of the more corrodible metals which are contaminated with surface impurities (e.g., oxides, adsorbed organic species,) [15]. It is necessary to find methods for the characterization of surfaces [16] in respect to surface contaminants.

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\*Evidence for the uniform negative surface charge density of chemically treated (sulfonated, carboxylated) tubes was obtained by isotope labelled techniques [14]. From the method of preparation, it is obvious that electrets possess a uniform negative surface charge density.

The necessity of finding methods for the preparation and characterization of uniformly negatively charged surfaces, which tend to be antithrombogenic, is amply demonstrated in this article.

### ACKNOWLEDGMENTS

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