BIOMEDICAL POLYMERS

POLYMERIC MATERIALS AND PHARMACEUTICALS FOR BIOMEDICAL USE

Edited by
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Akio Nakajima

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PREFACE

This volume is based upon selected papers from the symposium on "Polymeric Materials and Pharmaceuticals for Biomedical Use" presented April 4–6, 1979 at the First Joint Congress of the American Chemcial Society and the Chemical Society of Japan in Honolulu, Hawaii. This cooperative Japan–US conference afforded a unique opportunity to bring together polymer and biomedical scientists working in the growing field of biomedical polymer science. The seventeen chapters in this volume are substantially expanded and updated from the original papers. They represent a sampling of diverse topics in this still-young area of science. Most important, presented here is significant new work from Japan where there is now a major research interest in the health-related aspects of polymer science.

In view of the unique international character of the symposium and this volume, some further comment on the evolution of Japanese biopolymer research seems most appropriate. In 1957, the Research Association for Artificial Organs was founded in Japan, mainly by clinicians; but in 1963, this association was renamed and reorganized as the Japan Society for Artificial Organs involving not only medical but also materials scientists. Under the auspices of this society, the Second International Symposium for Artificial Organs was held in Tokyo in 1977 attracting more than 160 papers from all over the world. The Society of Polymer Science—Japan and the Society of Materials Science—Japan have also set up committees on medial polymers and biomaterials, respectively. These committees have been active through symposia and meetings to connect the concepts and methodologies in various disciplines such as medicine, dentistry, chemistry, pharmacy, and engineering. The Japan Society for Biomaterials was also formed at the end of 1978.

Most significant has been recognition of the importance of fundamental research in this interdisciplinary field by the Ministry of Education of Japan. A special research project "Fundamental Studies on Biomedical Polymer Materials" was funded in 1977 with a budget of $1,000,000 per year. Today, more than 80 scientists are involved in this project from the medical and polymer fields. The progress of this three-year project will be published (in Japanese) during 1980. Other ministries of the Japanese Government, such as International Trade and

Industry, are also now actively promoting research and development with projects in Life Sciences.

In organizing the original symposium and especially in producing this volume, it has been our intention to provide a balanced view of the biomedical polymer field that will be of value to that wide scientific audience working in chemistry, physics, biology and medicine and who ultimately contribute to advances in health care. The topics covered therefore range from *polymer implant and prosthetic materials to tissue–polymer interfaces* to *polymeric drugs* to *polymers in agriculture* to *biopolymer synthesis.*

In many respects this volume is related to *"Polymeric Drugs"* by (Donaruma and Vogl, eds. Academic Press, 1978), except that we have attempted to add the important dimension of a more comprehensive overview of fundamental and applied studies in the synthetic and natural biopolymer field. In so doing, it is our hope that some research reported here may stimulate new approaches to the solution of such key problems as: (1) physical, chemical, and surface properties that most influence physiological acceptance in soft or hard tissue or in contact with blood; (2) *in vitro* methods to provide good correlation with *in vivo* blood compatability or implant acceptance; (3) polymer molecular weight and structural influence upon drug pharmacology for polymer-drug conjugates; (4) mechanisms for tissue, metablite, bacteria, or blood cell adhesion to polymer surfaces.

It is a special pleasure to acknowledge the warm personal interaction and collaboration between the coeditors that was fostered by our mutual desire to produce a worthwhile work. Indeed, we hope it will be possible to maintain continuing scientific ties in the future between Kyoto University and the University of Florida. We are of course greatly indebted to the authors in Japan, Canada, Australia, and the United States for their fine contributions and for their excellent cooperation. We hope they will be pleased with the product of our joint efforts. Finally, a special expression of gratitude must go to Terry Elston and Alice Holt who typed so much of the next and helped with so many important details.

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BIOMEDICAL POLYMERS
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CHEMICAL, PHYSICAL, AND MECHANICAL ASPECTS OF BLOOD COMPATIBILITY[1]

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INTRODUCTION

For the most part, *in vivo* results of implanted polymers do not correlate well with the results of *in vitro* and *ex vivo* testing of biomedical polymers. Poor surface characterization of the polymer, lack of appreciation of the effect of fabrication variables on changing surface structure, as well as poor experimental test design have all contributed to this situation. However, a major factor in this lack of correlation has been the almost total neglect of the role of mechanical properties on *in vivo* implant performance.

This paper presents some of our studies and thoughts on how the chemical and physical properties of a polymer must be balanced with its mechanical properties for the development of a small diameter vascular prosthesis.

PLATELET ADHESION TO POLYMER SURFACE

One of the first observable events that occurs as blood comes in contact (*ex vivo* or *in vivo*) with a polymer surface is platelet adhesion to that surface. Many reports (1,2) on platelet adhesion and its relationship to the thrombogenic

1 *This work has been supported by the National Science Foundation, Grant DMR 76-83681, Polymer Program and the National Institute for General Medical Sciences, Grant GM 24487-02.*

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nature of a polymer surface indicated a general lack of correlation. This appears to result from variables such as the effect of an air interface and blood flow rates. Also, since most materials studied were thrombogenic, excessive exposure times resulted in the surfaces having rather similar platelet adhesion. By using a simple *ex vivo* flow-through cell filled with saline to avoid air interfaces coupled with short exposure times, we were able to demonstrate a direct relationship between the number of platelets adhering to a polymer surface and the tendency of the polymer surface to form a clot (3,4). Later studies using sheep as the source of whole blood (5) supported our earlier human blood studies. We observed no difference in platelet adhesion between venous and arterial blood at equal flow rates. Heparinization of the animal also did not affect this initial platelet adhesion. Analysis of this data using a model for convective diffusion in laminar flow showed deviations from a pure diffusion model (5). This indicates that platelet adhesion is not due to diffusion alone, but that the surface nature of the polymer does play an important role in initial platelet adhesion.

In our initial studies on platelet-polymer interactions, a dipping technique had been used in which the polymer surface was moved through a blood/air interface. Heavy platelet adhesion was observed on all surfaces. Since proteins are known to spread and denature at a blood/air interface, it was suspected that a denatured protein layer had been coated on the polymer surfaces by a Langmuir-Blodgett transfer and caused the heavy platelet adhesion (3,6). These observations led us to examine the effect of a native protein layer on platelet adhesion. When uncharged, hydrophobic polymers were coated with an adsorbed native layer of plasma proteins, initial platelet adhesion was reduced (7) (Table I). However, platelet adhesion intensified on the fibrinogen and γ-globulin coated surfaces at longer exposure times, but not on the albuminated surfaces (8). Thus, an adsorbed layer of native albumin appears to pacify a thrombogenic polymer surface. This concept was further supported by experiments in which a membrane oxygenator circuit was albuminated (9) and by albuminated polystyrene (in the form of Gott-rings) which was an non-thrombogenic as a heparinized surface (7,10).

Studies by Mustard et al. (11,12) on platelet adhesion, aggregation and release reactions by polystyrene latex also showed the importance of the adsorbed plasma protein coating in causing platelet aggregation and release of constituents to occur. In model studies, Glynn et al. (13) showed that the γ-globulin fraction to be most active with albumin and

TABLE I

PLATELET ADHESION TO VARIOUS SURFACES

Surface	*Platelet Adhesion*[b]		
	1 Min.	*3 Min.*	*5 Min.*
Teflon FEP	*5.4*	*18.5*	*Clot*
Teflon FEP/Albumin[a]	*0.1*		*0.1*
Silastic Rubber	*4.6*		
Silastic Rubber/Albumin[a]	*0.2*		*0.5*
Silastic Rubber/Fibrinogen[a]	*1.3*		*3.7*
Silastic Rubber/γ-Globulin[a]	*1.3*		*6.1*

[a] *Films were precoated with protein using precise adsorption techniques (17).*

[b] *Mean number of platelets adhering to 20,000 μ^2 surface area after exposure to whole blood in flow through cell (3,7).*

fibrinogen showing little effect. While our results on the effect of fibrinogen is in contrast with that shown by Glynn et al. (13), it is consistent with those of Massina and Luscher (14) using polylysine complexed with fibrinogen.

These results do support the potential role of platelets and the preformed plasma protein coating on the polymer surface in the *in vivo* initiation of coagulation . Thus, the ideal nonthrombogenic polymer should be one showing little or no platelet adhesion.

PROTEIN ADSORPTION TO POLYMER SURFACES

It has been shown by us and others (15) that under an adhering platelet there is a protein layer. This layer must form *in situ* as blood flows over the polymer surface. The formation of a protein layer is not unexpected since the concentration of proteins in blood is much larger than platelet concentration and protein diffusion is greater than platelet diffusion (16). Since the data on platelet adhesion to surfaces precoated with proteins show the influence of the protein on platelet adhesion, differences in the thrombogenecity of noncoated polymers must relate to the nature of the protein layer formed *in situ*. For example,

a few of the factors influencing the nature of this protein layer include how well the proteins cover (or mask) the polymer surface, differences in the overall composition of the adsorbed protein layer, and whether or not the proteins are structurally altered on adsorption. It is to this "protein modified" polymer surface that the platelets adhere, and this is in turn dependent on the chemical and physical surface properties of the polymer.

Early studies to assess the amount of protein adsorption onto various polymer surfaces were concerned with determination of protein adsorption isotherms under static conditions using grating infrared spectroscopy with internal reflectance techniques. The data in Table II was obtained (18) using this method for three reference polymers (Teflon FEP, Silastic Rubber, and a block copolyether-urethane-urea from our laboratory). Figure 1 shows the adsorption of albumin onto these polymers as a function of solution concentration. The adsorption isotherms are essentially Langmiur type as indicated by the linearity of the $1/a$ versus $1/c$ curves (Fig. 2) according to the relationship (19):

$$\frac{1}{a} = \frac{1}{a^{\infty}} + \frac{1}{a^{\infty}\, bc}$$

where a^{∞} is the amount of protein adsorbed ($\mu g/cm^2$), at saturation; a is the amount adsorbed at any time t; b equals K_1/K_2 where K_1 and K_2 are the rate constants of adsorption and desorption respectively; and c is the concentration of protein in solution at equilibrium.

Based on these and other static adsorption data, two trends could be noted in the relationship of protein adsorption to the thrombogenicity of the polymer surface: (a) as the amount of protein adsorbed increased, thrombogenicity decreases; and (b) as the fibrinogen to albumin concentration ratio increases, the thrombogenecity increases. Thus the polymers tested may be grouped as follows:

Increasing Thrombogenicity ←

Teflon FEP Silastic Rubber Copolyether-Urethane-Urea
Polystyrene
Polyethylene

Increasing protein adsorption →

Increasing Fibrinogen/Albumin Ratio ←