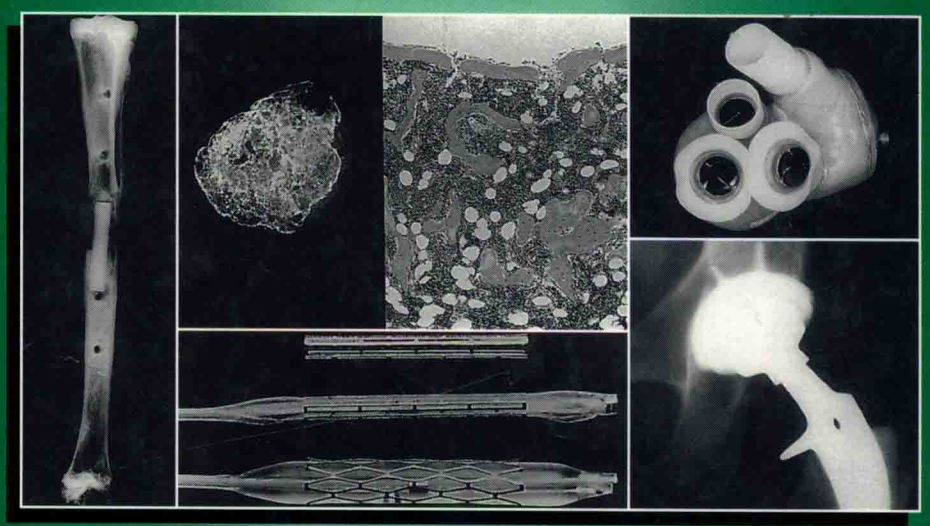
Human Biomaterials Applications



Edited by
Donald L. Wise, Debra J. Trantolo, David E. Altobelli, Michael J. Yaszemski, and **Joseph D. Gresser**

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Human Biomaterials Applications

Preface

Overall, *Human Biomaterials Applications* has a specific focus on biocompatible materials used in or on the human body. Such so-named "biomaterials" range from biopolymers used in controlled-relesase drug delivery systems, to biopolymeric plates used in bone repair, to case studies on specific orthopedic devices. Note that basic science, engineering, and medical experience are each necessarily integrated into the contents of this book. As a result, scientists, research engineers, and physicians are among those who are chapter authors as well as coeditors.

The reference text that *Human Biomaterials Applications* constitutes will embrace the use in or on the human body of polymers, metals, and so on. The book is organized by the type of biomaterial application, in the following sections: I. Selected Biomaterials and Biocompatibility Studies; II. Case Studies of Orthopedic Biomaterials; III. Specific Biomedical Applications of Biomaterials; and IV. Functional Biomaterials. This organized format allows the reader to focus on a specific application of interest.

As noted above, *Human Biomaterials Applications* addresses polymers as well as metals and other materials that are used in or on the human body. For example, topical chapters on biopolymers might include controlled-release drug-delivery systems, bone repair cements and resorbable fixtures, synthetic burn-wound coverings/dressings, and so on. Integral to chapters on these applications of biomaterials will be discussions on quality control using a variety of instrumentation, such as gel permeation chromatography (GPC), thermal gravimetric analysis and differential scanning calorimetry (TGA/DSC), and high performance liquid chromatography (HPLC), although much of the quality control work will be defined within the chapters on the particular biomaterial application.

The readers of *Human Biomaterials Applications* will have broad and various specialty backgrounds, but will be quite focused in their own applied work. Materials scientists and materials engineers will be interested in reading those biomaterials applications concerned with properties, performance, and use. Design criteria will be important, because the research engineer is going to be concerned with the selection process for given tasks. The academic physician and practicing surgeon will be concerned with materials behavior, toxicology, and biocompatibility, and will want to see these aspects presented in a readily accessible form. As a result, each chapter provides details satisfying to professional colleagues interested in biomaterials in general.

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PART I

BIOMATERIALS AND BIOCOMPATIBILITY STUDIES

1

Biomaterials and Their Biocompatibilities

Luigi Ambrosio, Gianfranco Peluso, and Patricia A. Davis

1. Introduction

Biomedical implants are used to resolve pathologies that cannot be corrected either by the natural healing process or traditional surgical intervention. Successful use of implants requires materials exhibiting specific characteristics particular to the application. Prosthetic implants must fulfill two criteria. The first is biocompatibility. That is, the material from which we construct the implant must not elicit an adverse response once inside the body. The second is demonstration of appropriate functional characteristics. The implant must perform as the tissue for which it substitutes. Efforts to satisfy the latter criterion in terms of mechanical properties led to the investigation of structural biomaterial composites. Since portions of the human body are composite structures, a progression toward the use of composite materials for application in the human body is natural.

1.1. Composite Materials

High strength fibers that reinforce a polymer matrix describe some composite materials. The matrix protects the fibers. The kinds of fibers used for these composites vary. They range from glass to polymer to carbon fibers. Fibers are more resistant than ordinary polymeric materials. Once embedded, they improve the strength of the matrix. The strength is at a maximum in the direction of the fibers' orientation. Opportunistic placement of fibers in particular directions increases the strength of the composite, permitting multiaxial mechanical support.

A major problem encountered using fibers in composites is their inclusion into the matrix during preparation. The matrix must protect the fiber surface from abrasion and from contact with the environment. The method used to place the fibers into the matrix can affect the matrix–fiber interface properties and the final properties of the composite system.

Continuous fiber composites are prepared by a process called lamination. Laminate properties can be defined as a function of fiber orientation in each layer with respect to the laminate axis. The relative orientation of each layer to the others is defined by using macromechanics (Fig. 1). The properties of a layer, such as volumetric composition, geometric properties, fiber layout, and fiber material, are determined by micromechanics theory *(1)*.

Micromechanical analysis (Fig. 1) accounts for the nonhomogeneous nature of the layer. Still, it ignores the internal structure of the

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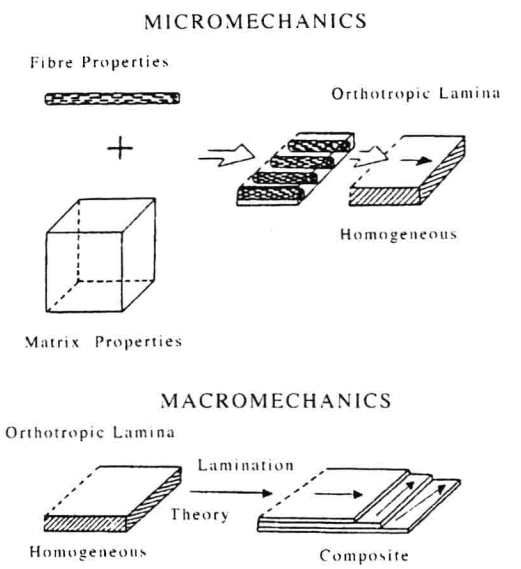

Fig. 1. Micromechanical and macromechanical analysis.

fiber and the matrix. However, it approximates the geometry of the packing. We simplify the calculation and obtain engineering stiffness expressed as the average properties of the layer. Macromechanical analysis uses this engineering stiffness. This analysis ignores the microstructure of the layer. Macromechanics considers each layer as a homogenous material with properties that differ in the directions parallel and perpendicular to the fibers, referred to as orthotropic materials. Various orientations of orthotropic layers construct the structural element. We use the classical theory of laminar plates to figure out the forces of single layers. Thus, the load conditions imposed on the structure determine the orientation of the layers.

Micromechanics and the theory of lamination link the mechanical properties of the constituents and that of the composite *(2)*. Figure 2 shows the calculations for determining the mechanical properties of a laminate. Incorporation of high strength fibers into a polymeric matrix provides for materials that are lighter, more rigid, and more resistant than traditional structural materials. Controlled properties permit for the construction of materials that satisfy the requirements of specific applications successfully and effectively.

1.2. Composite Biomaterials Preparation

The ideal prosthesis must exhibit two fundamental requirements in terms of both mechanical and biological efficacy. The first requirement is that the mechanical property be equal to that of the tissue for which it substitutes. The second requirement deals with elevated physiochemical stability *in situ*. We discern mechanical projections using the micromechanical analysis and lamination theory described earlier. We get physiochemical stability by controlling processing techniques.

Preparation of composite prostheses comes about by different technical processes. They vary with respect to the physiochemical characteristics of the material and the geometric structure of the final product. The physical parameters involved are many because various chemical reactions usually take place during manufacturing. Chemical reactions, such as the curing process, produce the final properties of the materials.

The principle technologies of preparing composite materials are: laminating process, filament winding, and resin transfer molding. Fundamental variables that control such processes are pressure, temperature, and time. For example, a composite material with an epoxy base resin and carbon fibers was used to prepare some prostheses for bone repair (Fig. 3).

We prepared these prostheses using a processing technology similar to a laminating process with a silicone mold. To obtain the mold, we filled a metallic tub with liquid silicone around the prosthetic model. We removed the model after the silicon cross-linking process. Then, we filled the mold with preimpregnates by a predetermined sequence. Afterward, it was transferred to an oven to initiate the cure process. During this process, silicone expands and in doing so develops a pressure sufficient for compressing the material into its final geometry *(3)*. The resin used

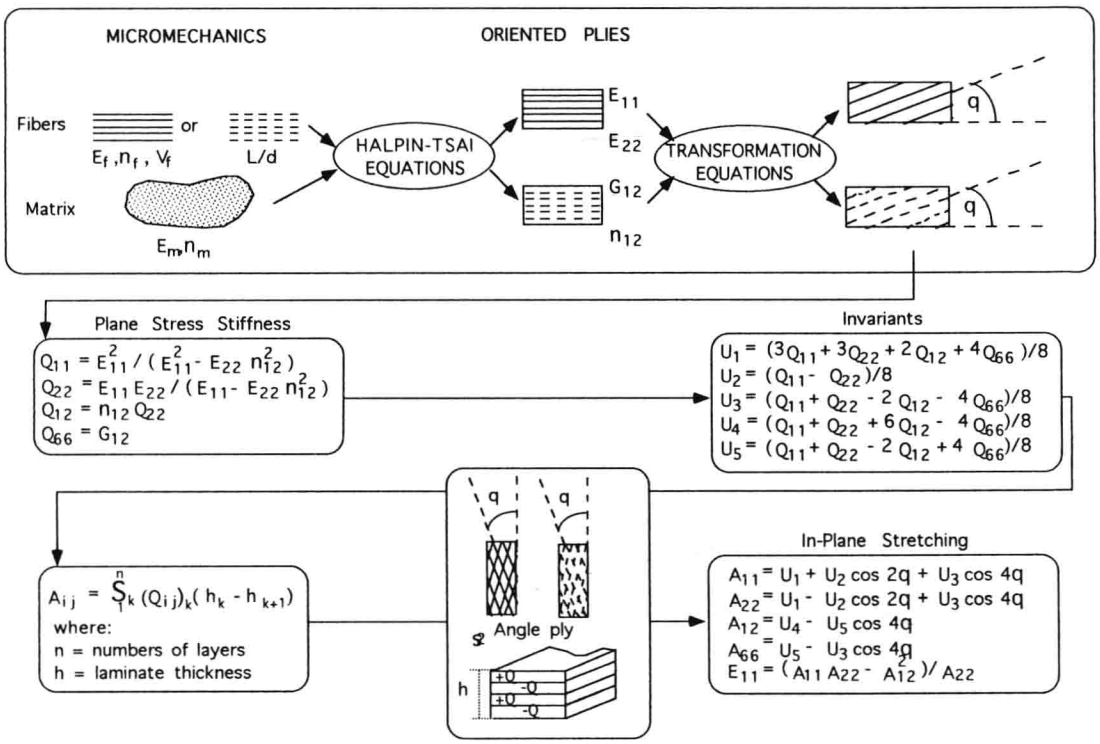

Fig. 2. Typical calculation for determining a laminate's mechanical properties.

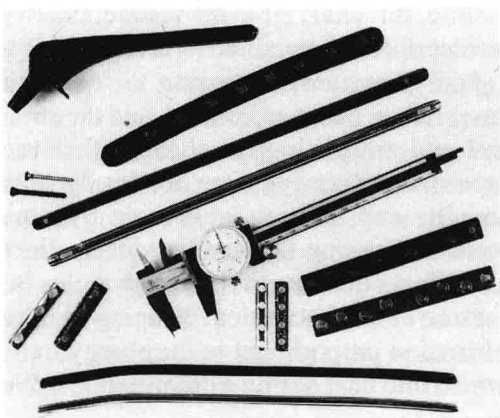

Fig. 3. Composite prostheses for orthopedic applications.

was tetraglycidi-amino-diphenylmethane (TGDDM) and di-amino-diphenyl-sulfone (DDS). The carbon fibers preimpregnated with under-reacted epoxy matrix made up the remaining material. To avoid processing problems, the matrices were mixed complexes of epoxy resin, hardener, catalyst, and diluent.

Curing of reactive prepolymer involves the transformation of monomers to oligomers, that is, from a liquid to a solid. Growth and branching of the polymer chains start in the liquid state and lead to a solid network after the gel point. This network is insoluble with a characteristic glass transition temperature.

The cure process of composite materials is a fundamental phase in the construction of composite prostheses. Incomplete cross-linking reaction can lead to migration of low-mol-wt materials (monomers and/or solvent) into the surrounding tissue. This causes inflammation and mechanical property degradation *(4)*.

1.3. Physiochemical Characterization of Biomaterials

After the synthesis of a biomaterial, it is necessary to advance to the phase of physio-

chemical characterization of the composite. For this objective, we use different methods to verify the presence of reactive groups on the surface of the polymer. The morphology, the remaining reactive agents, and the mechanical properties are other verifiable parameters.

1.3.1. Thermal Analysis

We use differential thermal analysis to study the thermal properties of materials. It gives a range of information about the parameters and characteristics of the material. Examples are glass transition temperature, melt temperature, crystallinity, the presence of possible solvents, and the extent of crosslinking reaction of thermoplastic materials. Knowledge of these properties is essential for both the selection of the type of processing or conditions of manufacturing. Also, complete physical characterization of the material is necessary for defining its use.

1.3.2. Infrared Spectroscopy

We use infrared spectroscopy to identify molecules and the types of bonds inside the polymer structure. Chemical bonds give absorption bands whose frequency depends on the nature of the bonds. Infrared spectroscopy unequivocally identifies molecular groups with characteristic absorption bands. The interpretation of an infrared spectrum is not as easy as it may seem. In fact, some bands can obscure others. Also, superposition of bands that shift because of structural characteristics can be mistaken for bands of a totally different group. Therefore, for exact interpretation, we use unshifted bands to determine structural characteristics. This technique identifies the chemical structure of materials and points out the presence of unreacted monomer.

1.3.3. Scanning Electron Microscopy (SEM)

An often used instrument for analyzing the morphological structure of materials is the SEM because of rapid and easy sample preparation. SEM analysis allows one to obtain information about the structure and interaction between fiber and matrix of a composite. This analytical technique yields information about the type of fracture, the deformation of materials, and the presence of microvoids in the system. Such information is fundamental for the optimum use of the material.

We use techniques other than those just described to understand the physical state and characteristics of materials. The most important among these are gel permeation chromatography (GPC), nuclear magnetic resonance (NMR), and X-ray diffraction.

1.3.4. Mechanical Characterization

The complete mechanical characterization of a prosthesis is accomplished using mechanical and viscoelastic analysis. Measurement of the elastic and viscoelastic components of the modulus characterizes the material. Also, knowledge of the values of resistance to deformation and fatigue is important in selecting a material.

1.3.4.1. Dynamic Mechanical Analysis (DMA)

Dynamic mechanical study of the properties of a material constitutes a principal method for analyzing its viscoelasticity. Besides dynamic parameters, it is possible to find the glass transition region, the degree of crosslinking, phase separation, and the structural and morphological changes that take place with processing. One obtains dynamic modulus and loss modulus from dynamic mechanical testing. Dynamic modulus reflects the stiffness of a material. Loss modulus is a measure of the mechanical damping or internal friction proportional to the energy transformed into heat during a deformation cycle.

1.3.4.2. Mechanical Analysis

Mechanical testing measures the material's ability to resist a particular loading (tensile, compressive, bending). The material's response is in terms of ultimate strength and deformation. Characteristic parameters that one extracts from the stress-strain curve are:

1. Elastic modulus: the slope of the linear part of the stress-strain curve. It is usually called Young's modulus.

2. Secant modulus: the relationship between force and deformation at any point along the stress-strain curve.
3. Strain-at-break: the strain the material sustains immediately before rupture.
4. Ultimate strength: the maximum force supported by the material.
5. Rupture strength: the force the material supports immediately before rupture.

Values of force and deformation at the yield point are of particular importance in the mechanical characterization of polymeric materials. We define the yield point as the value of stress where the material changes from prevalent elastic to plastic response. In plastic response, deformation becomes permanent and is no longer reversible on removal of the load.

We categorize materials in terms of their strength, strain-at-break, and elastic modulus. These parameters are tied to the physical properties of the material and processing conditions. The properties are molecular weight, degree of crystallinity, and amount of crosslinking.

1.3.4.3. Fatigue Testing

The durability of a material is an important parameter for planning a prosthesis. Fatigue tests give an idea of durability under cyclic loading. Fatigue testing of materials for biomedical applications is not well defined. It is very difficult to correlate fatigue results with in vivo performance. This is because there is still much unknown about the interactions among cells, tissues, and the material. Yet, fatigue testing can indicate the material's performance once implanted.

2. Biocompatibility

2.1. Introduction

We perform various tests to evaluate the biocompatibility of potential prosthetic materials. The greater part of these experiments allows for quick evaluation of the risks involved with the use of a specific material. We carry out experiments in vitro or in animals. Many materials might satisfy the biomechanical requirements. For example, the tensile qualities of certain artificial tendons are better than those found in natural tendons; however, some may show little or no biocompatibility once implanted.

We base this approach to discussing today's biocompatibility testing methods on the priority of testing. We present biocompatibility tests in the order in which we perform them.

2.2. Blood Compatibility

Interactions of various blood components with biomaterials—cellular and/or plasmatic—begin at implantation. Therefore, it is extremely important that hemostatic activities, such as thrombosis, are not altered immediately following surgery. It is necessary that the biomaterial does not interfere with coagulation nor with the factor that regulates it.

In practice, a material must not cause certain events, such as adhesion, platelet aggregation, blood coagulation, obstruction of blood flow for fibrin or cell deposit, and depletion of electrolytes. The latter two properties are not considered absolutely indispensable. Under certain conditions, it may be fundamental to have composites at one's disposal that activate hemocoagulative processes or, on the contrary, that inhibit them.

Therefore, it is useful to study the basic hemocompatibility of a material. We also study the potential clinical use in animal models or with blood. Still, mammalian species show differences, not only in the quantity of circulating plasma and cellular components, but also in coagulative and fibronectin response.

2.2.1. In Vitro Hemocompatibility Evaluation

In vitro methods are the first screenings of materials that are to be used in humans. One test involves contact of the surface of the material with whole blood or its components. Contact occurs for times ranging from 1 s to approx 24 h. Several parameters are evaluated with respect to a control: The time

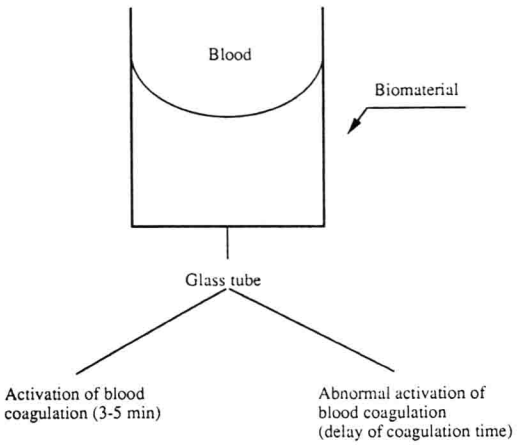

Fig. 4. Interference of a biomaterial on hemocoagulative processes.

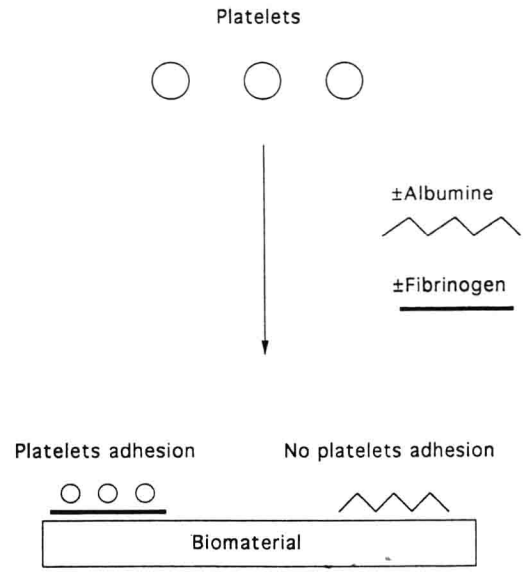

Fig. 5. Platelet adhesion on a biomaterial surface in the presence or absence of fibrinogen or albumin.

required for thrombosis, for formation of prethrombosis, and the time to partial thromboembolism are three such parameters. Others are the release of platelet factors and, finally, the number of free platelets that do not adhere to the material (Fig. 4).

The ability of platelets to adhere to the surface of a prosthesis, to change shape, and to release certain factors, such as serotonin, can be studied under various experimental conditions. Also, materials pretreated for differing degrees of adhesion can be studied. A fibrinogen pretreatment will result in increasing adhesion capability. Decreasing adhesion capability results from albumin pretreatment. A different situation applies for plasma proteins deposited on the material's surface. The selectivity of bonds with certain components (i.e., complement factors) can make the material less compatible by excessive inflammation (Fig. 5). Total protein absorption can be measured by UV-visible spectroscopy and fluorescence, FTIR, immunological technique, radioimmunological technique, circular dichroism (FTIR-ATR), ellipsometry, or contact angle measurement.

One technique is to evaluate qualitatively the bonding of specific proteins to a biomaterial. It measures the residual radioactivity of the material after exposure to a radioactive molecule and suitable successive washings. It is desirable to maintain as much as possible the physiological conditions of blood–material contact. Several methods exist. They involve continual flow of whole blood, platelet-rich plasma, or simple plasma over the surface of the material under investigation (Fig. 6).

A modification of the described methods is a closed system with recirculation. We place the material in a chamber in continuous contact each time with the same aliquot of blood. Under these conditions of controlled blood flow, it is easy to evaluate changes in protein or cellular parameters. Thus, one can follow hematological changes not only at the level of the material, but also directly in the blood. For example, one measures the decrease in the number of platelets.

2.2.2. In Vivo Hemocompatibility Evaluation

It is a given that techniques for in vitro hemocompatibility study allow for an important first screening. In vivo tests are invaluable for understanding if a material affects blood once placed in contact with the compo-