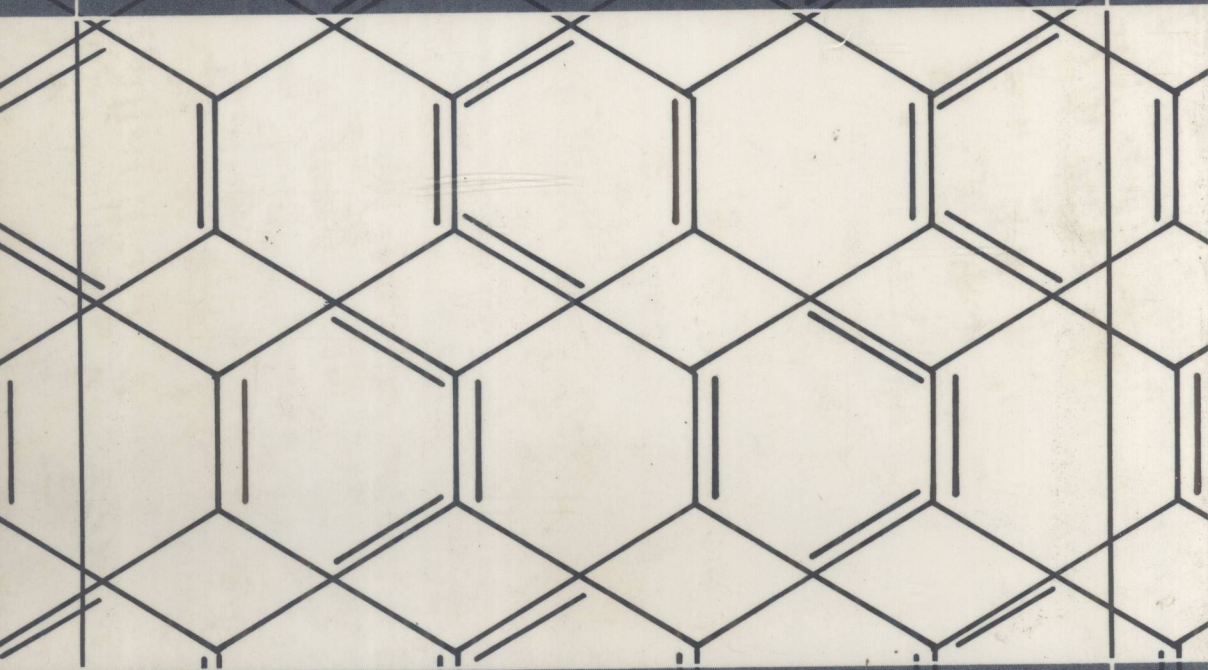
PROGRESS IN BIOMEDICAL POLYMERS



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PROGRESS IN BIOMEDICAL POLYMERS

PREFACE

This book is derived from a Symposium held during the 196th National Meeting of the American Chemical Society, in Los Angeles, and sponsored by the Division of Polymeric Materials: Science and Engineering. This Symposium was a follow-up of two earlier ones (Dallas, 1980 and Chicago, 1985) which have been published in book form, by Plenum Press, as "*Biomedical and Dental Applications of Polymers*" (C. G. Gebelein and F. F. Koblitz, Eds., 1981) and "*Advances in Biomedical Polymers*" (C. G. Gebelein, Ed., 1987). Many changes have occurred in the field of biomedical polymers during this interval and some of these are reflected in the present book. One important, not necessarily obvious, change occurs with the book's authors. Many of these scientists have entered this field during the past decade.

In addition, the two earlier symposia and books contained many papers on the artificial heart, related cardiovascular polymeric materials, and artificial organs. Although much new research in these areas is included in this volume, the total content is smaller than in the previous volumes, reflecting a shift in biomedical polymer emphasis. On the other hand, six of the thirty seven papers in this book deal directly with ophthalmic polymer applications. While ophthalmic polymers are hardly a new biomedical endeavor, the past decade has seen renewed emphasis on these applications and several new companies and materials are currently available. Likewise, the area of diagnostic polymers has matured greatly in the past decade, spurred on no doubt by the AIDS problem, and a pair of papers in this area are included in this book. All in all, the papers presented in this book continue the quest for restoring the health and quality of life depicted many years ago by King David when he said, "*I will praise Thee; for I am fearfully and wonderfully made; marvelous are Thy works, and my soul knoweth right well.*" (Psalm 139:14). In a world where problems and pain often seem more common than blessings and helping hands, it is good to see scientists trying to improve our lifestyle.

The major emphasis in this book, as a whole, is on new polymeric biomaterials. The potential range of applications for these new biomaterials spans the entire breadth of the biomedical polymer field, including surgery, dental cardiovascular, orthopedic and medication uses. This book is subdivided into four sections for the convenience of the reader. These sections are: (1) *OPHTHALMIC POLYMER APPLICATIONS*, (2) *SURGICAL, DENTAL AND DIAGNOSTIC APPLICATIONS*, (3) *POLYMERIC BIOMATERIALS*, and (4) *CONTROLLED RELEASE AND BIOACTIVE POLYMER APPLICATIONS*. Naturally there is some overlap because these areas are inter-related.

Our book opens with six papers on ophthalmic polymers. The first three papers come from a biomaterials company and are concerned directly with the manufacture, testing and chemistry of contact lens polymers (Meyers, Harvey and Bowman). This is followed by a pair of papers treat-

ing problems in the surgical handling of the intra-ocular lens (IOL) implants (Goldberg, et al.). The final paper in this section describes a new artificial corneal prosthesis (Jacob-LaBarre and Caldwell), which may restore sight to some blind people. Although the total volume of ophthalmic polymers consumed in any year is small, the uses are critical in an aging population. It is encouraging to see new companies developing ophthalmic materials, as well as new researchers entering this field.

The second section considers a variety of applications. The first two papers (Brauer and Lee, and Tseng, Hyon and Ikada) discuss two different types of tissue adhesives for use in surgery. The next pair of papers (Cranin, et al., and Habal) describe some clinical facial surgery applications. The following paper, by Okada and Ikada, considers a collagen-based percutaneous implant and the paper by Yannas et al., deals with nerve regeneration via a collagen-containing system. These are followed by a trio of papers on dental applications. The first (Antonucci, et al.) covers the synthesis and properties of some new fluorinated polymers, while the second (Stansbury and Bailey) describes potential dental applications for the spiro orthocarbonate monomers, which expand on polymerization. The third paper (Tesk, et al.) considers the application of the Weibull statistical analysis method with dental materials. The Weibull method is also considered in the paper by Azhar, et al., but the main theme there is on an enzymatic diagnosis system for blood glucose levels. The final paper in this section (Kesler, et al.) considers diagnostic polymers for steroid analysis.

Section three is the largest subsection with fourteen papers on several types of polymeric biomaterials. The lead-off paper describes some recent research in elastomeric polypeptides from the laboratories of Urry, while the second paper briefly delineates the biomedical applications of a new thermoplastic elastomer (Deisler, et al.). The following five papers deal with potential cardiovascular applications of polymers. Benson, et al., addresses the reduced elasticity caused by the interaction of calcium ions with the poly(urethanes) most commonly used in artificial hearts and other cardiovascular applications. Two papers consider the modification of the surface properties of poly(urethanes) by grafting techniques (Wrobleski, et al.) and by inclusion of a fluorinated copolymer (Takahara, et al.). Griesser, et al., also considers surface modification, via plasma grafting, for poly(tetrafluoroethylene) polymers, which are now popular vascular replacement polymers. The final cardiovascular related paper (Kambic, et al.) involves the surface modification of the polymers with a crosslinked gelatin protein.

The next three papers in the third section involve orthopedic polymer applications, and all three involve different biodegradable polymers for potential use as bone plates. The first paper (Tunc and Jadhav) considers high strength poly(lactides); the second paper (Vanderbilt, et al.) uses a polyamide derived from a spirobibutyrolactone; the third paper (Horton, et al.) utilizes a poly(ester-amide) material. Hirano, et al., considers some biomedical uses for chitosan, while Penczek and Klosinski detail their research on some novel poly(phosphates) related to natural polymers. Wang examines cell growth on poly(vinyl alcohol) derived hydrogels which can be used as wound dressings. The final paper in this section (Blass) describes potential biomedical uses of an old plastic, poly(vinyl chloride), which is made with new kinds of plasticizers.

The last section contains six papers on controlled release and bioactive polymeric systems. The first two papers show zero-order kinetic release profiles with cleavable polymeric drugs, even though the nature of the polymers and drug agent are markedly different. Gebelein, et al., compares the release profiles for 5-fluorouracil from a polymeric drug

(zero order) and a monolithic system (not zero order), while Ghosh describes the release of nalidixic acid from polymeric drug systems. Jansen, et al., discusses the release of antibiotics from poly(urethane) systems and Favero, et al., considers the release of norgestomet from poly(silicones), to maintain pregnancy in cows. The final two papers consider bioactive organometallic polymers. Carraher, et al., details the biological activity of some palladium derivatives against several kinds of cancer, while Siegmann, et al., covers related information for platinum containing polymers.

We wish to thank the officers of the Division of Polymeric Materials: Science and Engineering, American Chemical Society for sponsoring the symposium from which this book is derived. Naturally, we thank the authors for their fine research papers. We give a special note of thanks to N. Doddi, a non-author who chaired the ophthalmic polymer session. We also thank our wives and families for their special assistance during the time this book was being developed. All of the manuscripts were typeset by CG Enterprises. Finally, we wish to give thanks to our God, without His support nothing of lasting value can occur.

Charles G. Gebelein and Richard L. Dunn

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POLYMERIC BIOMATERIALS

CONTACT LENS MATERIALS: THEIR PROPERTIES AND CHEMISTRIES

Thomas B. Harvey, III, William B. Meyers, Lyle M. Bowman

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The use of poly(methyl methacrylate) (PMMA) in corneal contact lenses led to the popularization of the contact lens in the early 1950s. PMMA is lighter than glass, clear, rigid, and relatively inert biologically. Its largest failing as a contact lens material is its lack of oxygen permeability, and a variety of materials have since been developed to overcome the oxygen deprivation problem that arises with PMMA lenses. More modern contact lens materials have much higher oxygen permeability than PMMA, and most of these materials fall into one of two categories: (1) soft hydrogels, or (2) rigid gas permeable. The chemical compositions and physical properties of both types of materials will be discussed.

INTRODUCTION

The use of poly(methacrylate) (PMMA) in corneal contact lenses led to the popularization of the contact lens in the early 1950s. PMMA is lighter than glass, clear, rigid, and relatively inert biologically. Its largest failing as a contact lens material is its lack of oxygen permeability. The cornea of the eye satisfies most of the oxygen needs by the absorption of oxygen directly from the atmosphere. When a PMMA contact lens is in place, some of the oxygen demand may be supplied by an exchange of tear fluid behind the lens, but for many individuals this is not a sufficient amount of oxygen to promote good corneal health.

DISCUSSION

Two basically different approaches to overcoming the oxygen barrier problem have been tried. One approach has been to make polymers which are much more hydrophilic than PMMA and thus absorb water to become hydrogels. In this case, the oxygen permeates very readily through the aqueous portion of the hydrogel and thereby supplies the oxygen needs of the cornea in an adequate manner. The other approach has been to make the solid polymer itself more oxygen permeable. This has been accomplished primarily by the introduction of siloxane groups, in one form or another, into the polymer.

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Hydrogels

In hydrogels, the oxygen permeability follows a semi-logarithmic relationship when plotted against the water content.[1] The data can be described by Equation 1, where P = the permeability [(mL (STP) cm)/ (cm^2·sec·cmHg)] and H = the percent hydration.[2]

$$P = (2.4 \times 10^{-10})(e^{0.0443H}) \qquad \text{(Equation 1)}$$

Figure 1 shows the correlation between the percent hydration and the oxygen permeability for several lens hydrogels. Hydrogels made of lightly crosslinked poly(hydroxyethyl methacrylate) (PHEMA) were commercialized as soft contact lenses in the early 1970s. These PHEMA lenses had sufficient oxygen permeability for daily wear, and were more comfortable than PMMA lenses. Nevertheless, their lack of rigidity meant that they could not correct astigmatism as readily as could PMMA lenses.

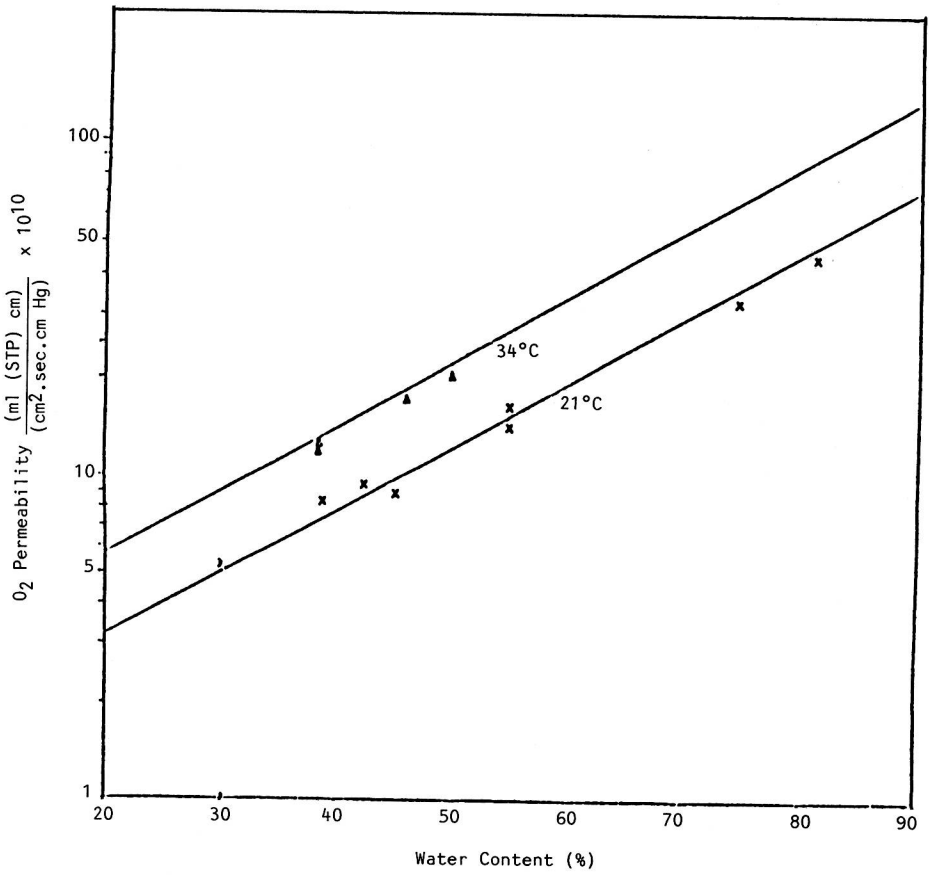


Figure 1. Oxygen permeability as a function of water content. The 21°C data were taken from reference 3. The line at 34°C is from the equation obtained from reference 2, while the data at 34°C were obtained in the Sola Ophthalmics Laboratories.

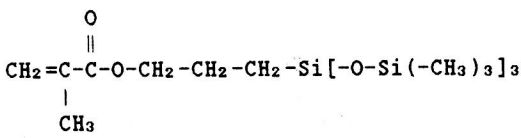
A crosslinked copolymer of MMA and glyceryl methacrylate (GMA), with the same water content as PHEMA, is also used for daily wear contact lenses. This MMA/GMA copolymer has a higher elastic modulus than PHEMA, and thus provides better visual acuity than PHEMA.

These materials with 40% water do not generally provide enough oxygen transmission for extended wear, and the desire for extended wear contact lenses led to the development of higher water content materials having about 45-80% water. These materials came on the scene in the early 1980s and allowed a sufficient oxygen supply to the cornea even during sleep. There are some trade-offs however. These high water content materials are softer, have lower tear strengths, lower elongation at break, and a greater tendency to accumulate waste deposits during extended wear. Because the high water content materials are softer than the lower water content lens hydrogels, the lenses must be made thicker to retain mechanical integrity. One drawback to the increased thickness is that the full gain of oxygen transmission cannot be realized.

In order to get these higher water contents, new polymers were required. Typical copolymers have been made from HEMA, MMA, methacrylic acid (MMA), n-vinylpyrrolidinone (NVP), diacetone acrylamide (DAA) and ethoxyethyl-methacrylate (EEM) in various combinations.

Rigid Gas Permeable Lenses (RGPs)

The first gas permeable material to find use in contact lens applications was cellulose acetate butyrate, which was introduced for this application in the late 1960s. This material had up to 100 times the oxygen permeability of PMMA, but suffered from insufficient dimensional stability, and was supplanted in the early 1980s by the so-called silicone/acrylate gas permeable materials. Most of these copolymers gain their permeability from the incorporation of tris-(trimethylsiloxy)-silypropyl methacrylate (TRIS) into a copolymer with MMA or with MMA and dimethyl itaconate. The structure of TRIS is shown below. Through most of the range studied, the amount of oxygen permeability shows a semi-logarithmic relationship to the percent of TRIS present in the copolymer, as shown in Figure 2.



TRIS

The amount of TRIS that can be usefully incorporated is limited by the decreasing hardness and wettability of the copolymers that contain increased amounts of TRIS. The wettability of these copolymers may be improved by the use of a wetting comonomer such as MAA. Permeabilities of these copolymers have steadily increased in recent years until extended wear rigid lenses are now available. Other recent advances in this area include the introduction of fluorinated monomers which further enhance oxygen permeability and improve the surface properties of the lenses.

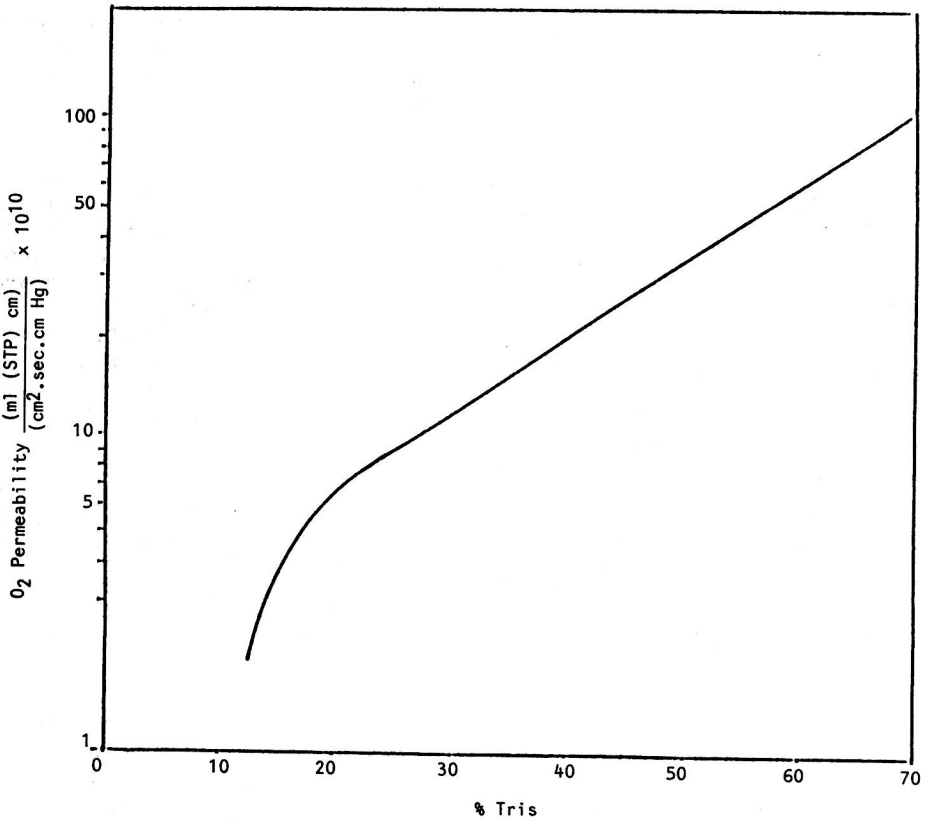
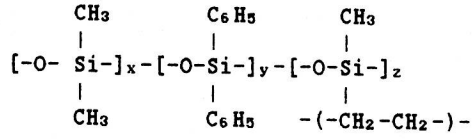


Figure 2. Oxygen permeability of TRIS/MMA copolymers as a function of composition.

Other Materials

The advantages of the high gas permeabilities of silicone rubbers has been taken more directly in the form of silicone contact lens materials of the structure shown below.



The rigidity of these materials can be manipulated by varying the methyl/phenyl ratio, which also affects the oxygen permeability. The materials are very hydrophobic and must be surfaced treated in order to be used as contact lenses. The pure silicone rubber lens materials have never found great acceptance as contact lenses.

A lens material based on perfluoropolyethers gained some attention a few years ago, and is just now becoming a commercial product.

SUMMARY

Since the introduction of PMMA contact lenses, there has been a continuing improvement in compatibility with the ocular environment based on improved materials. Most of these improvements have been based on increasing oxygen permeability for better corneal health.

ACKNOWLEDGMENT

This paper first appeared, in a somewhat modified form, in Volume 59 of the Proceedings of the American Chemical Society Division of Polymeric Materials: Science and Engineering.

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CHARACTERIZATION OF CONTACT LENS PLASTICS

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In the development of contact lens material, characterization of the materials includes measurement of gas transport, and mechanical properties, including the modulus of elasticity, tensile strength, percent elongation and tear strength. Physical properties determined on contact lens plastics include percent hydration, wetting angles, glass transition temperature, percent visible transmission, indentation hardness, refractive index, and percent linear expansion. In addition to polymer measurements, the protein and lipid deposition must be measured to determine biocompatibility in the eye. Each of the measurements must be performed on a finished contact lens which weighs 10 mg at a thickness 0.01 cm. This paper will describe how each of the listed measurements is performed on a contact lens and representative measurements will be given for contact lens polymers. This data will include both rigid gas permeable and hydrogel contact lenses.

INTRODUCTION

In the present contact lens marketplace there currently exist two types of lenses. These are rigid gas permeable (RGP) lenses, commonly called "hard" lenses, and hydrogel lenses called "soft" lenses. All lenses currently in the marketplace are based on methacrylate chemistry. The rigid gas permeable contact lens materials are silicone-methacrylate copolymers and the hydrogel materials are hydrophilic methacrylates with water contents from 38 to 90%. Additionally, some of the newer RGP materials are also fluorosilicone-methacrylate copolymers. The methods for characterization of rigid gas permeable materials and hydrogel materials are often quite different. In this paper we will describe the methods used to characterize both types of plastics. As referenced, hydrogel materials are lathed as dry materials and then hydrated to become the contact lens hydrogel.

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