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Polyelectrolyte Complexes: Permeability to Water and Potential Uses in Ophthalmology*

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Synopsis

Complexes from poly(vinylbenzyltrimethylammonium chloride) and polystyrenesulfonate are transparent, water-insoluble materials which offer interesting possibilities in ophthalmology for contact lenses and surgical implants. The permeability to water of a series of neutral polyelectrolyte complex membranes was determined. The measurements were carried out at relatively low pressure gradients (20–900 mm. Hg). The results are in good agreement with previously reported data obtained at higher pressures (6.9 atm. and higher). The refractive index of the complexes was also determined, and apparently a linear relationship exists between the refractive index and the amount of water in the complex: 70% water, n_D 1.40; 45% water, n_D 1.48; 35% water, n_D 1.51. A polyelectrolyte complex membrane 0.09 mm. thick containing 60% water at equilibrium swelling will have a similar permeability to water as the endothelium of the cornea (1.55×10^{-11} cm.^{3}/sec.-dyne) at 35°C. The same membrane, but with a thickness of 0.03 mm., will have a permeability similar to that of the whole corneal stroma (4.9×10^{-11} cm.^{3}/sec.-dyne). At 0.21 mm. thickness the membrane will have a permeability similar to that of the epithelium (0.67×10^{-11} cm.^{3}/sec.-dyne).

INTRODUCTION

Polyelectrolyte complexes, made by reacting poly(vinylbenzyltrimethylammonium chloride) with sodium polystyrenesulfonate, are insoluble in water because of their ionically crosslinked structure.[1] Complexes containing excess polycation or polyanion, as well as a neutral polysalt, can be obtained containing various amounts of water at equilibrium swelling. Recently Michaels[2] reviewed the properties and uses of these materials, mentioning also their potential use as tissue substitutes in the human body. Because polyelectrolyte complexes are transparent, flexible, and highly permeable to water and to the microsolutes found in the body fluids, their use, particularly in ophthalmology, offers certain interesting possibilities: Contact lenses and corneal implants are some of the more obvious possible applications.

A surgical implant made of a synthetic material with physical characteristics similar to the tissue in which it is to be implanted will, if the material

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is not affected by the body fluids, have a good chance of being tolerated by the body. Intralamellar water-impermeable membranes interfere with water flow across the cornea.[3] Permeability then may well be an important criterion for tolerance of artificial corneal implants. Polyelectrolyte complexes are homogeneous nonporous gels and resist penetration by fibrous tissue and cells. Therefore, implants made of these materials should remain transparent in the cornea. Experimental implants of polyelectrolyte complexes in animals were carried out in conjunction with laboratory determinations of some pertinent properties and partially support the above arguments. Details of the animal experiments will be reported elsewhere.

Permeation of water through polyelectrolyte complexes was reported before.[2] The data were obtained on operating at 100 psi (6.8 atm.) and higher pressure across the membrane. Under these conditions, compression of the membrane resulting in a decreased permeability is a likely possibility. To determine whether it is possible to use these materials in corneal surgery, it was judged desirable to determine the permeability to water under essentially the same conditions used previously to determine the water permeation through the corneal stroma.[4] We have previously reported[5] the permeability of a polyelectrolyte complex membrane as compared with a series of non-ionic hydrogels and with the corneal stroma at normal hydration. It was found at the time that this membrane possessed a remarkably higher permeability to water than non-ionic hydrogels having similar water content at equilibrium swelling. From this finding it seemed that it would be possible to make corneal implants with a water permeability similar to the corneal stroma, without having to use the greatly hydrated (ca. 87–90% H_2O) non-ionic hydrogels.[6,7] Of course, the higher the water content in a hydrogel, the weaker the tensile strength of the material, and the more difficult it is to manipulate.

EXPERIMENTAL

Materials

The homogeneous polyelectrolyte complex membranes used in these experiments were all neutral, varying only in the water content at equilibrium swelling. These experimental membranes were obtained through the courtesy of Amicon Corporation (Lexington, Mass.). Similar membranes are now commercially available from Amicon Corporation.

Permeability Measurements

The permeability apparatus has been previously described.[4,5] The rate of flow was determined four times at each of four different pressures. The pressure gradients used in the experiments varied for each membrane. With the most permeable membrane, a pressure across the membrane as low as 20 mm. Hg was used in order to get a slower and more easily measur-

able rate of flow. With the least permeable membrane, higher pressures were used (600–900 mm. Hg). The average of the rate of flow at each pressure was plotted against the pressure gradient as a straight line passing through the origin (Fig. 1).

Refractive Power of Polyelectrolyte Complexes

The refractive index of the membranes at 25°C. was measured by using a Valentine precision refractometer. The wet membrane (0.04–0.10 mm. thick) was blotted of superficial water immediately prior to the measurements, then was placed directly on the prism and attached to it by a slight amount of residual superficial moisture. The determinations were carried out by using the standard technique for the refractive index of liquids. The polyelectrolyte complex membrane showed very little contrast between the dark and the light portions of the field, and the intersection line was rather diffuse. Ten to fifteen readings were taken for each membrane, and the average of these readings was taken as the refractive index for the respective membrane. Two or three different pieces of each membrane were used in the determinations with good agreement between them. There seems to be a linear relationship between the refractive index and the amount of water in the membrane at equilibrium swelling (Fig. 2).

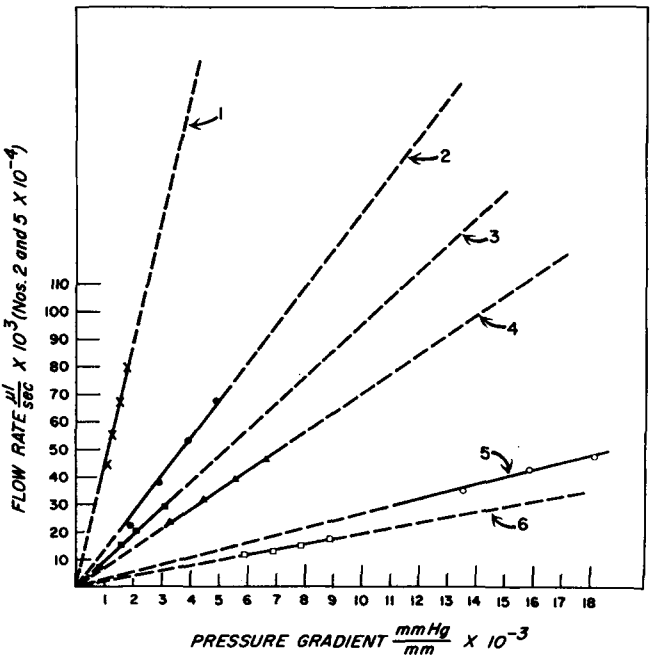

Fig. 1. Flow rate across 78.5-mm.^{2} polyelectrolyte complex membranes vs. pressure gradient for various membrane thickness and hydration: (*1*) 0.093 mm., 75%; (*2*) 0.102 mm., 55%; (*3*) 0.065 mm., 66.6%; (*4*) 0.09 mm., 67%; (*5*) 0.044 mm., 42%; (*6*) 0.101 mm., 55%.

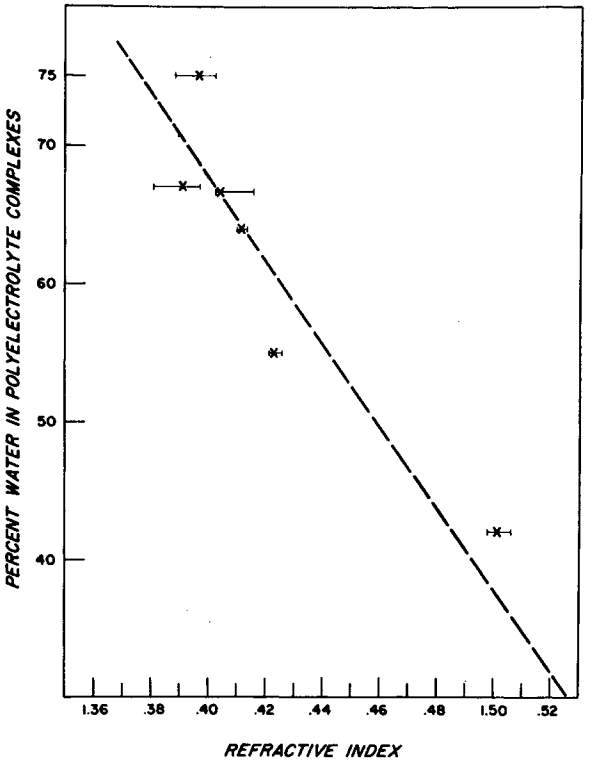

Fig. 2. Refractive index of neutral polyelectrolyte complex membranes. The means and extremes of 10–15 determinations of the refractive index at 22°C. of each membrane are represented.

RESULTS AND DISCUSSION

The volume V (in cubic centimeters), flowing in time t (in seconds) through a microporous membrane of area A (in square centimeters) and thickness L (in centimeters) under a pressure gradient P (in dynes/square centimeter) may be expressed as

$$V/t = K(A/\eta)(\Delta P/L)$$

where η (poises) is the viscosity of the permeant, and K (in square centimeters) is the permeability coefficient.[8] While a model of solution diffusion through these membranes may be more applicable,[2] for consistency with other ophthalmological permeability studies, this viscous flow model has been employed.

The permeability P (in cubic centimeters per second-dyne) or hydraulic conductivity, of a membrane is given by the equation $P = (K/\eta L)$. The product PL is the flow conductivity per unit thickness (in cm.^{4}/sec.-dyne).

The results (mean values ± standard error of mean) are tabulated in Table I. For most membrane types, identified by the water content at

equilibrium swelling, two or three pieces were used independently for the permeability measurements. The results found for different pieces of the same material were in good agreement with each other, which is proof of absence of leaks in the system or imperfections in the membranes. The per cent of water in the membranes was determined in the standard way: blotting between tissue paper and weighing before and after drying to constant weight. With thin membranes, the error of this method is obvious. The plot of the refractive index versus hydration (Fig. 2) is very useful to correct any markedly erroneous results of the hydration obtained gravimetrically.

TABLE I
Permeability of Water-Swollen Polyelectrolyte Complexes at 25°C.

H_2O in the membrane, %	Membrane thickness, mm.	$P \times 10^{11}$, cm.³/sec.-dyne	$PL \times 10^{14}$, cm.⁴/sec.-dyne	$K \times 10^{16}$, cm.²
42	0.044	0.57 ± 0.0022	2.50 ± 0.010	2.23 ± 0.0089
"	"	0.27 ± 0.028	1.21 ± 0.12	1.08 ± 0.11
55	0.102	1.22 ± 0.049	12.50 ± 0.51	11.17 ± 0.45
"	"	1.45 ± 0.054	14.85 ± 0.55	13.27 ± 0.49
"	0.101	1.88 ± 0.023	18.97 ± 0.24	16.95 ± 0.20
60	0.070	1.53 ± 0.022	10.70 ± 1.53	9.56 ± 0.14
"	"	1.61 ± 0.27	11.30 ± 1.91	10.09 ± 1.70
"	0.066	1.93 ± 0.030	12.74 ± 0.20	11.38 ± 0.18
64	0.064	17.41 ± 0.035	111.41 ± 0.23	99.57 ± 0.20
66.6	0.065	14.08 ± 0.0026	91.60 ± 1.72	81.80 ± 0.015
67	0.090	6.87 ± 0.46	61.79 ± 4.12	55.22 ± 3.68
"	"	7.61 ± 0.084	68.49 ± 0.76	61.21 ± 0.68
75	0.097	29.51 ± 0.47	286.34 ± 4.59	255.90 ± 4.10
"	0.093	45.43 ± 1.13	422.47 ± 10.54	377.56 ± 9.42
"	"	43.47 ± 1.99	404.27 ± 18.49	361.29 ± 16.52

Polyelectrolyte complex membranes do show some compaction under pressure; this is particularly noticeable when operating under a relatively low pressure. Most membranes showed evidence of gradual compression under relatively low pressure (20–80 mm. Hg) as it is shown in Figure 3. The rate of flow decreased in successive measurements carried out while the pressure was maintained constant. In all cases, a steady-state rate of flow was eventually obtained within 1 hr. No such decay in flow rates could be observed in the time span of measurement when measurements were made under constant higher pressures (100–900 mm. Hg), so obviously demonstrated that the membranes were quickly compressed to a more stable state. Most of the water present at saturation in polyelectrolyte membranes is bound as water of hydration of the ionic sites,[2,9] and only the "free" water within the polymer network would be easily squeezed out of the gel when it is compressed. The observed compression is, therefore,

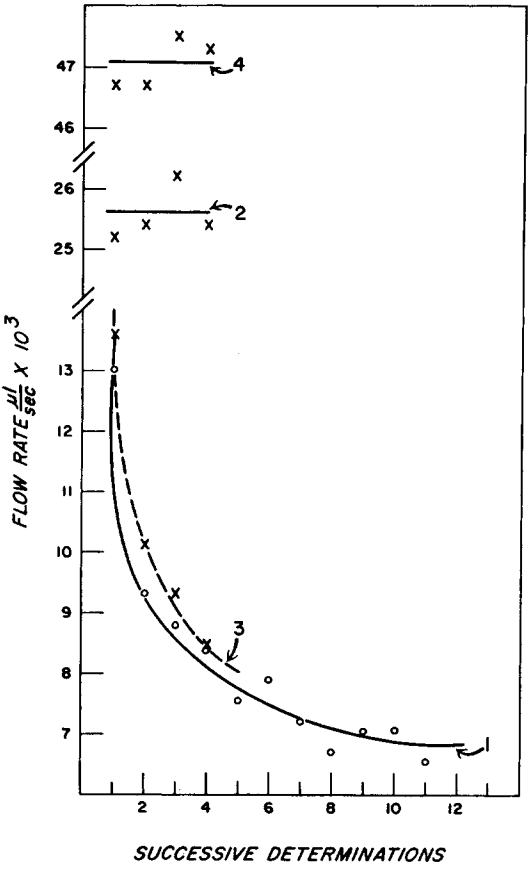

Fig. 3. Compaction under pressure of polyelectrolyte complex membranes at various membrane thickness, hydration, and pressure: (*1*) 0.064 mm., 68%, 50 mm. Hg; (*2*) 0.064 mm., 68%, 140 mm. Hg; (*3*) 0.097 mm., 75%, 40 mm. Hg; (*4*) 0.090 mm., 67%, 600 mm. Hg.

believed to result from a displacement of some of the free water in the membrane.

In spite of the above observed compression of the membranes, the steady-state flow rates obtained in this work agree well with the data reported previously by Michaels,[2] which were obtained operating at substantially higher pressures across the membrane (6.8 atm. and over). A plot of the log permeability coefficient versus per cent water in the polymer is given (Fig. 4) including both sets of data.

Polyelectrolyte complex membranes are substantially more permeable to water than non-ionic hydrogels having similar water content at equilibrium swelling.[4] Water molecules in the liquid state are associated by hydrogen bonding in a three-dimensional network. When non-ionic hydrophilic polymers of the poly(glyceryl methacrylate) type are in contact with water, the hydrogen-bonded water is further bound to the hydrophilic

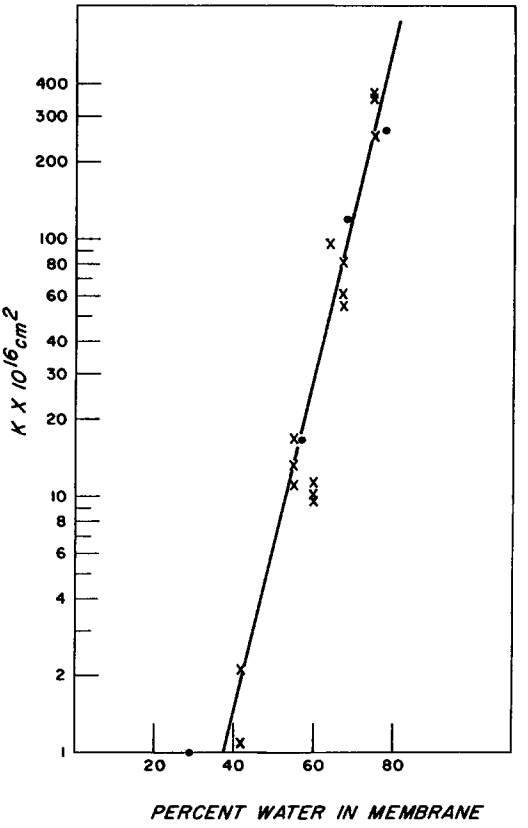

Fig. 4. Permeability coefficients as function of water concentration in neutral polyelectrolyte complex membranes: (×) this work; (●) Michaels' data.[2]

moieties in the polymer. The water molecules, hydrogen-bonded to the polar groups in the polymer, link the hydrophilic residues of the polymer into the quasicrystalline structure of the water in the gel, and there is a consequent reduction in mobility of the water in the gel. The concept of "crosslinking" hydrophilic polymers with water molecules was reported previously.[10] In the polyelectrolyte complex hydrogels most of the water molecules are probably solvating ion pairs by dipole–dipole attraction which results in a "destructuring" of the hydrogen-bonded water network. Some water will form tightly bound hydration shells around cations and anions by ion–dipole attraction, but still a portion of the water is believed to be present as free water within the polymer network.[9] The free water, though indeed associated to some degree in a network structure, would have more fluidity than the highly structured water in the non-ionic hydrogels. Similarly, non-ionic hydrophilic membranes increase significantly in water permeability when they are in a saline medium, perhaps because of the water destructuring influence of the ions in the matrix or because the ions

are associated with the polar groups in the polymer chains by ion-dipole attraction and hinder the formation of hydrogen bonds between the polar groups in the polymer and water.[11] This also would help to explain the relatively high permeability of the corneal stroma, with its polyelectrolyte structure, compared to non-ionic hydrogels with similar water content.[5]

SURGICAL IMPLANT CONSIDERATIONS

The cornea is the transparent window of the eye. It is composed of three principal layers: epithelium, stroma, and endothelium. When the eyelids are opened, evaporation from the tear film surface cause an increase in the tonicity of the precorneal tear film, which induces an osmotic water flow across the cornea from the aqueous to the tear.[12] Also, there is a pressure gradient across the cornea because the normal pressure inside the eyeball is 15–20 mm. Hg above atmospheric pressure. The flow conductivity per unit thickness of the corneal layers at 35°C. was given by Mishima and Hedbys[14] as epithelium, 27; stroma, 1730; and endothelium 7.8×10^{-15} cm.^{4}/sec.-dyne. It would take a polyelectrolyte complex membrane containing about 70% water at equilibrium swelling (n_D = 1.40) to have a permeability to water similar to the stroma. A membrane with about 45% water (n_D = 1.48) would have permeability to water similar to the epithelium, and a membrane with about 35% water (n_D = 1.52) at equilibrium swelling would be similar in permeability to the endothelium. Of course, these comparisons are only valid when the artificial and the natural membranes have the same thickness.

To calculate the thickness of an artificial membrane having a permeability to water similar to that of a corneal layer per total thickness, divide the flow conductivity per unit thickness of the artificial membrane by the flow conductivity per total thickness of the corneal layer as given by Mishima and Hedbys.[14] These authors assumed the thickness of the corneal layers to be 40, 355, and 5 μ for the epithelium, stroma, and endothelium, respectively. For example, a polyelectrolyte complex membrane 0.091 mm. thick containing 60% water at equilibrium swelling with a flow conductivity per unit thickness (corrected to 35°C.) of $14.14 \pm 1.54 \times 10^{-14}$ cm.^{4}/sec.-dyne, will have a similar permeability to water as the whole endothelium (1.55×10^{-11} cm.^{3}/sec.-dyne).[14] The same membrane, but with a thickness of 0.029 mm., will have a permeability similar to that of the whole corneal stroma (4.9×10^{-11} cm.^{3}/sec.-dyne).[14] At 0.21 mm. thickness the membrane will have a permeability similar to that of the whole epithelium (0.67×10^{-11} cm.^{3}/sec.-dyne).[14] The clinical significance of this is obvious, since it now appears as if some or part of the corneal layers can be surgically substituted by artificial membranes. In some cases of corneal surgery, for example, Dohlman et al.[15] have replaced the endothelium with water-impermeable silicone membranes. The use of a membrane with a similar permeability as the endothelium would be an

obvious advantage in this procedure. Optically, the polyelectrolyte complexes used in this work were not as clear and homogeneous as the methacrylic hydrogels,[6] but more recent samples from Amicon indicate that optical clarity and homogeneity has been greatly improved to the point where there is little difference between the two types of membranes in this respect. A comparison of these two materials at similar water permeabilities shows the polyelectrolyte complexes have higher tensile strength and hence are easier to handle than the methacrylic hydrogels.

There is some evidence in the literature[13] that implants of non-ionizable polymers are less irritating inside the eye than ionizable polymers. On the other hand, the natural polymers forming the body tissues have many ionizable groups. It seems in our experience that polyelectrolyte complexes can be well tolerated by the eye tissues. Unfortunately, the results to date have been inconsistent and indicative of the variable quality of the different samples tested. Nevertheless, materials of standardized purity are now being made by Amicon, and more consistent results should be forthcoming.

Some inconveniences in working with the polyelectrolyte complexes have been observed. In the first place, the membranes cannot be steam-sterilized, since they become brittle during autoclaving, apparently due to partial dehydration. Even heating in water above 60°C. results in morphological changes ranging from opacification to curling of an originally flat membrane. These problems can be overcome by sterilizing the material by high energy irradiation or by chemical means.

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References

1. A. S. Michaels and R. G. Miekka, *J. Phys. Chem.*, **65**, 1765 (1961).
2. A. S. Michaels, *Ind. Eng. Chem.*, **57**, 32 (1965).
3. S. I. Brown and S. Mishima, *Arch. Ophthal.*, **76**, 702 (1966).
4. B. O. Hedbys and S. Mishima, *Exptl. Eye Res.*, **1**, 262 (1962).
5. M. F. Refojo, *J. Appl. Polymer Sci.*, **9**, 3417 (1965).
6. M. F. Refojo, *J. Appl. Polymer Sci.*, **9**, 3161 (1965).
7. C. H. Dohlman, M. F. Refojo, and J. Rose, *Arch. Ophthal.*, **77**, 252 (1967).
8. S. Madras, R. L. McIntosh, and S. G. Mason, *Can. J. Res.*, **27B**, 764 (1949).
9. A. S. Michaels, A. S. Hoffman, and C. A. Gray, paper presented at the 151st Meeting, American Chemical Society, Pittsburgh, Pennsylvania, March 23–26, 1966.
10. M. Kh. Gluzman, G. S. Bashura, and B. I. Dashevskaya, *Vysokomolekul. Soedin.*, **7**, 2024 (1965); *Polymer Sci. USSR*, **7**, 2216 (1955).
11. M. F. Refojo, to be published.
12. S. Mishima, *Arch. Ophthal.*, **73**, 233 (1965).
13. M. Dreifus and L. Klenka, *Cs. Oftalmologie*, **15**, 95 (1959).
14. S. Mishima and B. O. Hedbys, *Exptl. Eye Res.*, **6**, 10 (1967).
15. C. H. Dohlman, S. I. Brown, and E. L. Martola, *Trans. Am. Ophthal. Otolaryng.*, in press.

Résumé

Des complexes de polyvinylbenzyltriméthylammonium et de polystyrènesulfonate sont des matériaux transparents, insolubles dans l'eau, qui présentent des possibilités intéressantes en ophtalmologie pour les lentilles de contact et pour les interventions chirurgicales. La perméabilité à l'eau d'une série de membranes complexes de polyélectrolytes neutres a été déterminée Les mesures ont été effectuées à des gradients de pressions relativement basses (20 à 900 mm de mercure). Les résultats sont en bon accord avec les résultats rapportés précédemment et obtenus à pression plus élevée (6.9 atm. et plus). L'indice de réfraction des complexes a également été déterminé et apparemment il existe une relation linéaire entre l'indice de réfraction et la quantité d'eau au sein du complexe: 70% eau, n_D 1.40; 45% d'eau, n_D 1.48: 35% d'eau, n_D 1.51. Une membrane à base de complexe polyélectrolytique de 0.09 mm d'épaisseur contenant 60% d'eau à l'équilibre de gonflement aura une perméabilité semblable à l'eau que l'endothélium de la cornée (1.55×10^{-11} cm^3 sec^{-1} dyne^{-1}), à 35°C. La même membrane mais à une épaisseur de 0.03 mm aura une perméabilité semblable à celle du stroma de la cornée complète (4.9×10^{-11} cm^3 sec^{-1} dyne^{-1}). A 0.21 mm d'épaisseur, le membrane aura une perméabilité semblable à celle de l'épithélium (0.67×10^{-11} cm^3 sec^{-1} dyne^{-1}).

Zusammenfassung

Komplexe von Poly(vinylbenzyltrimethylammonium) und Poly(styrolsulfonat) bilden durchsichtige, wasserunlösliche Materialien, welche interessante Möglichkeiten in der Ophthalmologie für Kontaktlinsen und chirurgische Implantate liefern. Die Permeabilität einer Reihe von Membranen aus neutralen Polyelektrolytkomplexen für Wasser wurde bestimmt. Die Messungen wurden bei verhältnismässig kleinen Druckgradienten (20–900 mm Hg) durchgeführt. Die Ergebnisse stehen mit früher bei höheren Drucken (6,9 Atmosphären und mehr) erhaltenen Daten in guter Übereinstimmung. Auch der Brechungsindex der Komplexe wurde bestimmt; es besteht offenbar eine lineare Beziehung zwischen dem Brechungsindex und der Menge des Wassers im Komplex: 70% Wasser, n_D 1.40; 45% Wasser, n_D 1,48; 35% Wasser, n_D 1,51. Eine Polyelektrolytkomplex-Membrane von 0.09 mm Dicke mit einem Wassergehalt von 60% beim Quellungsgleichgewicht besitzt eine ähnliche Permeabilität für Wasser wie das Endothelium der Hornhaut ($1,55 \times 10^{-11}$ cm^3 sek^{-1} dyn^{-1}) bei 35°. Die gleiche Membrane, jedoch mit einer Dicke von 0,03 mm, weist eine ähnliche Permeabilität wie das ganze Korneastroma ($4,9 \times 10^{-11}$ cm^3 sek^{-1} dyn^{-1}) auf. Bei 0,29 mm Dicke ist die Permeabilität der Membrane derjenigen des Epitheliums ($0,67 \times 10^{-11}$ cm^3 sek^{-1} dyn^{-1}) ähnlich.

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