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Permeation of Water Through Some Hydrogels

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Synopsis

The permeability to water and the average pore radius of transparent hydrogels from glyceryl methacrylate (GMA), 2-hydroxyethyl methacrylate (HEMA), propylene glycol monoacrylate (PGMA), and a polyelectrolyte complex were determined. The transport process was found to be a predominantly viscous flow in the polyelectrolyte complex and in the more dilute GMA hydrogels (74–94% water), but in HEMA hydrogel (40% water), and PGMA hydrogels (40–60% water), diffusion seemed to play a more important part in the movement of water through the gel. These hydrogels are potentially useful for surgical implants in the cornea. A comparison is made with the flow conductivity of the corneal stroma at normal hydration.

INTRODUCTION

Transparent hydrophilic polymer networks (hydrogels) synthesized from glyceryl methacrylate (GMA) (2,3-dihydroxypropyl methacrylate) and containing at equilibrium variable amounts of water, can be prepared by varying the degree of swelling at the time of network formation, or by varying the density of crosslinks.[1] Likewise, 2-hydroxyethyl methacrylate (HEMA) and propylene glycol monoacrylate (PGMA) can be polymerized to obtain transparent hydrogels. In HEMA and PGMA hydrogels the amount of water at equilibrium is limited by the relative insolubility of the polymer in water.[2] Hydrogels of this type have been proposed for certain medical uses by Wichterle and Lim.[3] Their transparency and softness makes them particularly interesting in the field of ophthalmology.

Artificial corneas partially or totally buried within the corneal stroma have been reported in the medical literature.[4] Poly(methyl methacrylate) is the material most commonly used for these implants,[5,6] although a great variety of materials have been tested unsuccessfully. A buried implant made of transparent silicone rubber[7] offers advantages in treating certain corneal diseases. However, all of these materials are impermeable to water; therefore, it seemed desirable to obtain materials with improved properties for the manufacture of corneal implants. Hydrogels seemed to offer many of the desired properties.

The permeability of hydrogels to water and to metabolites is an important property to be investigated in regards to their potential use as implants

in surgery. If the permeability of an implant is similar to the permeability of the surrounding tissues, assuming the tissue reaction and the polymer stability to body fluids are good, it is expected that such an implant, not interfering greatly with the metabolism of the tissue, would be well tolerated by the body. The flow of water across the corneal stroma has been investigated by Hedbys and Mishima,[8] using an apparatus similar to that used by White[9] for determining the permeability of acrylamide polymer gels. In this report the permeability characteristics of some hydrophilic gels are described, and a comparison is made with the permeability of corneal stroma at normal hydration.

EXPERIMENTAL

Permeability Measurements

The permeability apparatus described by Hedbys and Mishima[8] was used. The film holder consists of two identical, round, porous stainless steel plates in solid steel rims, separated by a brass ring. The film was placed on one of the porous plates, separated from it by filter paper in such a way that the relatively soft gel film would not come in contact with the stainless steel porous plate in the down-flow side of the cell. The resistance of the filter paper to water flow is negligible, and it protects the gel film against deformation under pressure. The spaces between the film and the brass ring were filled with lacquer; the second porous plate was placed over this, and then the cell was sealed with lacquer. The cell was clamped between two glass chambers filled with distilled water. Air pressure, measured on a U-tube mercury manometer, was applied to the water in one chamber. Connected to the water chamber on the other side was a calibrated capillary tube for measuring flow rates. The measurements were carried on with the apparatus immersed in a constant-temperature water bath at 25°C.

The rate of flow was determined by timing the movement of the meniscus along the calibrated capillary. About four determinations were made at each of four different pressures. The rate of flow was plotted against the pressure gradient. A straight line passing through the origin was obtained. In the cases where a leak existed, the points fell in a curve, in which instances the experiments were discarded.

Membranes

The films were cast from aqueous solutions of the monomers and redox catalyst, between two glass plates separated by a rubber gasket. After polymerization in the oven at about 65°C., the films were washed in distilled water for several weeks. Circular sections of the equilibrated films were then cut, by using a 16-mm. diameter corkborer. One of the sections was used in the permeability cell, and at least three others were employed to determine water content.

The membrane thickness was measured by placing it between two plastic films of known thickness (shim stock, The Artus Corporation, Englewood, N. J.) and measuring the total thickness with a precision micrometer, taking precaution not to compress the membrane. Several measurements were made of each specimen, which then were averaged. The membrane thickness was obtained by subtracting from the average value the thickness of the two plastic films.

Per cent of water, and the specific water content[10] of the membranes were determined in the standard way. Circular membranes of known thickness and diameter were blotted between tissue paper, placed in weighing bottles, and weighed before and after drying to constant weight. Three samples were used for each type of membrane, and the results were averaged. The amount of water in the hydrogels was expressed as per cent water in the hydrogels (w/w).

Glyceryl methacrylate (GMA) monomer was prepared and purified as described elsewhere.[1] In some batches of GMA monomer there were some crosslink-forming impurities, originating perhaps by the disproportionation of monoester molecules into difunctional, or even trifunctional, monomers. Membranes containing at equilibrium variable amounts of water were made, in general, by varying the concentration of GMA monomer in the aqueous polymerization mixture. In a few instances, in order to control better the amount of water in the membrane, a crosslinking agent, tetraethylene glycol dimethacrylate (TEGDMA), was added to the GMA monomer solution. TEGDMA is a commercial product (The Borden Chemical Company, Philadelphia, Pa.) which was used without further purification. Ammonium persulfate, 6% aqueous solution, and sodium metabisulfite, 12% aqueous solution, were used as redox initiator in the polymerization. GMA membranes for the permeability measurements were prepared as it is indicated in Table I.

2-Hydroxyethyl methacrylate (HEMA) is a commercial product (The Borden Chemical Co., Philadelphia, Pa.) which was redistilled before use.

TABLE I
GMA Membranes

GMA, vol.	n_D^{25} GMA	H_2O, vol.	TEGDMA, vol.	12% $Na_2S_2O_5$, vol.	6% $(NH_4)_2S_2O_8$, vol.	H_2O in hydrogel, %
1	1.4620	1	—	0.1	0.1	94.2
1	"	1	0.02	0.1	0.1	83.2
1	"	1	0.03	0.1	0.1	76.1
1	"	1	0.05	0.1	0.1	73.9
1	1.4670	2	—	0.1	0.1	87.7
1	1.4680	0.5	—	0.1	0.1	80.3
1	"	1.0	—	0.1	0.1	85.1
1	"	1.5	—	0.1	0.1	88.8
1	"	2.0	—	0.1	0.1	89.2
1	"	2.5	—	0.1	0.1	93.6

The preparation of transparent HEMA hydrogels was described previously.[2] The membranes used in these experiments were prepared as shown in Table II. After the membranes were cast, the ethylene glycol in the gel was exchanged by distilled water. The films equilibrated in water were used for the permeability measurements.

TABLE II
HEMA Membranes

HEMA, vol.	H_2O, vol.	Ethylene glycol, vol.	12% $Na_2S_2O_5$, vol.	6% $(NH_4)_2S_2O_8$, vol.	H_2O in hydrogel, %	Appearance
3	1.5	0.3	0.1	0.1	53.8	Hazy film
1	0.5	1.0	0.1	0.1	38.7	Clear film

Propylene glycol monacrylate (PGMA) is a commercial product (Celanese Chemical Co.) and it was used as such without further purification. Transparent hydrogels from PGMA were reported previously.[2] The preparation of membranes for permeability measurements (Table III) was carried as previously described for HEMA membranes.

TABLE III
PGMA Membranes

PGMA, vol.	H_2O, vol.	Ethylene glycol, vol.	TEGDMA, vol.	6% $(NH_4)_2S_2O_8$, vol.	12% $Na_2S_2O_5$, vol.	H_2O in hydrogel, %
3	1	1	0.05	0.1	0.1	62.6
3	1	1	0.20	0.1	0.1	41.2

The polyelectrolyte complex used in these experiments is a transparent membrane, permeable to water and electrolytes. It is commercially available as Ioplex (Amicon Corporation, Cambridge, Mass.). These membranes are synthesized by reacting linear water-soluble ionic polymers of opposite electrical charge such as poly(vinyl trimethyl ammonium) and poly(styrene sulfonate).

RESULTS

The equation[9,11] used for calculating the permeability coefficient K was

$$K = VL\eta/tA\Delta P \tag{7}$$

where V is the volume of water (in milliliters), having a viscosity η (in poises), flowing through a sample of thickness L (in centimeters) and area A (in square centimeters), in a given time t (in seconds), under a pressure difference ΔP (in dynes/square centimeter) resulting in a value for K in square centimeters.

In one experiment the permeability of cellophane swollen in water was determined. Cellulose dialysis tubing was allowed to equilibrate in distilled water for a few weeks prior to the permeability measurements. The permeability coefficient found, 10.44×10^{-16} cm.^{2}, is somewhat smaller than the value found by Madras et al.[11] $K = 15.51 \times 10^{-16}$ cm.^{2}, for uncoated cellophane swollen in water at 25°C.

The permeability coefficients obtained for the hydrogels that were studied here are compiled in Table IV.

TABLE IV
Permeability Coefficients of Hydrogels

Hydrogel	H_2O, %	$K \times 10^{15}$, cm.^{2}
Cellophane	57.6	1.044 ± 0.010
Polyelectrolyte complex	66.6	8.18 ± 0.15
HEMA	38.7[a]	0.075 ± 0.006
"	53.8[b]	0.094 ± 0.012
PGMA	41.2	0.087 ± 0.024
"	62.6	0.28 ± 0.03
GMA	73.9	1.46 ± 0.07
"	76.1	2.21 ± 0.04
"	80.3	4.65 ± 0.06
"	83.2	6.08 ± 0.06
"	85.1	6.09 ± 0.52
"	87.3	11.55 ± 0.51
"	87.6	6.55 ± 0.20
"	88.8	14.79 ± 0.32
"	89.2	19.96 ± 0.61
"	93.6	42.04 ± 2.69

[a] Clear film.
[b] Hazy film.

The average pore radius and its relation to the permeability coefficient is expressed by an equation given by Ferry:[10]

$$r = \sqrt{8K/S} \tag{2}$$

where r is the average pore radius (in centimeters), K is the permeability coefficient, and S is the specific water content. This equation has been used often to calculate the pore size of membranes; for example Madras et al.[11] used it to compute the pore radius for cellophane, and White[9] applied it in the determination of the average pore radius in acrylamide polymer gels.

This equation is based on the following assumptions:[10] (*1*) the water flows through parallel cylindrical capillaries of circular cross section; (*2*) the rate of flow of water is governed by Poiseuille's law; (*3*) the total volume of pores represents the total volume effective in filtration; i.e., all the capillaries are open to the surface, and there is no immobilized water lining the walls of the pores. In general, these assumptions make the calculated

values of pore radius (Table V) appear too small.[10] From an analysis of the extent to which the above assumptions are justified, Elford and Ferry[12] concluded that an error in the average pore diameter of not more than 25% is incurred when this equation is applied to membranes of porosities greater than 20 mμ. As expected, for the same type of hydrogel, the pore size increases with increasing water content (Table V).

TABLE V
Average Pore Radius for Hydrogels

Hydrogel	H_2O, %	Pore radius, mμ
HEMA	38.7	0.40 ± 0.13
PGMA	41.2	0.45 ± 0.10
"	62.6	0.63 ± 0.21
GMA	80.3	2.17 ± 0.59
"	83.2	2.62 ± 0.26
"	85.1	2.39 ± 0.69
"	88.8	3.70 ± 0.54
"	89.2	4.58 ± 0.78
"	93.6	6.23 ± 1.57
Polyelectrolyte complex	66.6	3.64 ± 0.49

DISCUSSION

In their study of the flow of water in the corneal stroma, Hedbys and Mishima[8] made use of eq. (1). They did not include in their formula the viscosity factor, because it was not known if the viscosity of the fluid moving in the corneal stroma was that of water or whether dissolved macromolecules (proteins and polysaccharides) accompany it and increase its viscosity. k is then a constant called the flow conductivity and is dependent on the viscosity of the moving fluid and the structure of the membrane. The values for the flow conductivity of corneal stroma at normal hydration as found by Hedbys and Mishima[8] and those for hydrogels are summarized in Table VI. The corneal stroma has a structure composed basically of collagen fibrils (20% by weight) of about 300 A. in diameter[13] lying parallel to one another in the lamellae of the stroma. The rest of the tissue is made up of an aqueous fluid in which is dispersed about 5% by weight of protein and mucopolysaccharides, called the ground substance of the cornea.[14] Hedbys and Mishima[8] suggested that the ground substance provides the resistance to the water flow through the stroma, while, at the normal hydration of the cornea, the collagen fibrils do not interfere greatly with the movement of water. The ground substance of the stroma may be considered as a hydrophilic gel, with about 95% water, strengthened by the collagen fibrils. The effective area of flow, correcting the area occupied by the collagen fibrils at normal corneal hydration, was given by Hedbys and Mishima[8] at about 0.75 of the total area of flow. Using the corrected area, a value of 18.1×10^{-13} cm.^{4}/sec.-dyne for k is obtained.

TABLE VI
Flow Conductivity of Corneal Stroma and Hydrogels at 25°C.

Hydrogel	H_2O, %	$k \times 10^{13}$, cm.⁴/sec.-dyne
Corneal stroma at normal hydration	77–79	13.6
Cellophane	57.6	1.168 ± 0.002
Polyelectrolytes complex	66.6	9.16 ± 0.17
HEMA	38.7[a]	0.084 ± 0.007
"	53.8[b]	0.105 ± 0.013
PGMA	41.2	0.097 ± 0.005
"	62.6	0.32 ± 0.03
GMA	73.9	1.64 ± 0.08
"	76.1	2.48 ± 0.05
"	80.3	5.21 ± 0.07
"	83.2	6.81 ± 0.07
"	85.1	6.82 ± 0.58
"	87.3	12.93 ± 0.57
"	87.6	7.33 ± 0.23
"	88.8	16.56 ± 0.36
"	89.2	22.34 ± 0.69
"	93.6	47.04 ± 3.02

[a] Clear film.
[b] Hazy film.

This value of k is in agreement with the value of k for a GMA hydrogel with about 90% water.

The structure of a hydrogel, and not only its water content, has undoubtedly a strong influence on its permeability. For example, the polyelectrolyte complex membrane has an appreciably larger permeability than the acrylic hydrogels with the same water content. It is evident that the structure of the polyelectrolyte complex is different from that of the acrylic hydrogels. Of course, the same family of hydrophilic gels will increase its permeability to water with increasing water content.

White[9] has shown that the permeability of a gel with a relatively low density of crosslinks depends on the amount of polymer in the gel and is independent from the amount of crosslinks in the network. The gel consists of a random intertwining of polymer chains that are occasionally crosslinked, in such a way that the formation of pores is controlled primarily by the concentration of polymer chains, and is relatively little affected by the amount of crosslinks. GMA monomer as used in these experiments is not of uniform purity, as it is found by the different gelling characteristics of the diverse batches. This is probably due to the presence in the monomer of some crosslinking forming impurities, such as diesters and triesters which are produced easily by disproportionation of GMA. In the cases where relatively concentrated gels could not be easily obtained by polymerization of different monomer dilutions, crosslinks

were introduced by adding to the monomer solution different amounts of a bifunctional monomer (TEGDMA). Within the range that these TEGDMA crosslinks were introduced in the polymer network, it is not expected that they will affect its permeability, which will be determined mainly by the amount of polymer in the hydrogel. It is known that bifunctional monomers, such as TEGDMA, when copolymerized will not be utilized completely in establishing crosslinks.[15-17] Assuming that all the crosslinks in the network are introduced by TEGDMA, and that all TEGDMA molecules act as crosslinkers, it can be calculated that the monomer mixture GMA–TEGDMA (1:0.02) will produce approximately one crosslink per every 100 GMA units in the polymer, while a mixture like GMA–TEGDMA (1:0.05) will give one crosslink per about 40 GMA units, which undoubtedly would affect slightly the pore size of the membrane.

TABLE VII
Calculated Diffusion Coefficients from Permeability of Hydrogels

Hydrogel	H_2O, %	$D \times 10^5$, cm.²/sec.
HEMA	38.7	3.08 ± 0.15
PGMA	41.2	3.89 ± 0.20
"	62.6	7.76 ± 0.84
GMA	80.3	88.59 ± 0.11
"	82.5	132.80 ± 1.23
"	85.1	109.85 ± 9.39
"	88.8	265.00 ± 5.54
"	89.2	386.71 ± 1.18
"	93.1	750.32 ± 47.76
Polyelectrolyte complex	66.6	255.75 ± 4.62

Whether the permeation of hydrogels by water is a viscous or diffusive type of transport can be analyzed by calculating a coefficient of diffusion, as used by Ticknor[18] for cellophane membranes, and comparing it with the self-diffusion of water. The difference between both mechanisms is whether the molecules move in groups as in viscous flow, or whether they move individually in a random movement as in the diffusive type flow. In general, it seems that the permeation of membranes by liquids involves both a viscous and a diffusive flow mechanism.[9,18] The gradient in hydrostatic pressure would lead to viscous flow, while the gradient in chemical potential, due to the gradient in hydrostatic pressure, would lead to diffusive flow. White[9] found that in acrylamide polymer gels the transport process was predominantly viscous flow in the more dilute gels, while diffusion became more important in the more concentrated gels.

The "diffusion coefficients" were calculated from the permeability coefficients by the equation:[18]

$$D = RTK/\epsilon\bar{V}\eta \qquad (3)$$

where D is the "diffusion coefficient" (in square centimeters/second), R is the gas constant (8.314×10^7 ergs/°C.-mole), T is the absolute temperature (298°K.), K is the permeability coefficient, ϵ is the fractional void volume (for which the specific water content was used, both values being approximately equal), $\bar{V}$ is the molar volume (18 cm^3/mole), and η is the viscosity (0.8937×10^{-2} poise). It is obvious that for GMA hydrogels, within the range of hydrations studied, the calculated "diffusion coefficients" (Table VII) are very much larger than the self-diffusion coefficient 2.8×10^{-5} $cm.^2$/sec. of water (at 25°C.).[19] The same is evident for the polyelectrolyte complex membrane. In these hydrogels the net water transport can be considered to be primarily under a viscous flow mechanism. For HEMA and PGMA hydrogels the calculated "diffusion coefficient" is of the same order of magnitude as the self-diffusion coefficient for water, indicating that in these hydrogels diffusion may contribute greatly to net water transport. In addition, it was suggested by Ticknor[18] that the size of the capillaries would determine whether the flow was predominantly viscous or diffusive; viscous flow of water across a hydrophilic membrane would predominate if the capillary radius were much larger than the radius of the water molecule (1.5 A.).[20] If, on the other hand, the capillary radii were less than approximately twice the radius of the water molecule, diffusive flow would be controlling. The average pore radius of HEMA and PGMA is of an order of magnitude of twice the radius of the water molecule, which again seems to indicate that in these hydrogels diffusion may contribute greatly to net water transport. The pore radii of the rest of the hydrogels studied here are so much larger compared to the radius of the water molecule, that in them viscous flow would predominate.

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Résumé

On a déterminé la perméabilité à l'eau, et le rayon moyen des pores d'hydrogels transparents de méthacrylate de glycéryle (GMA), de 2-hydroxy méthacrylate d'éthyle (HEMA), de monoàcrylate de propylène-glycol (PGMA) et d'un polyélectrolyte complexe. On a trouvé que le processus de transport est avant un écoulement visqueux dans le polyélectrolyte complexe et dans les hydrogels de GMA plus dilués (74–94% d'eau), mais dans les hydrogels d'HEMA (40% d'eau) et ceux de PGMA (40–60% d'eau), il semble que la diffusion joue un rôle plus important quant au mouvement de l'eau à travers le gel. Ces hydrogels pourraient être utiles en vue de l'implantation chirurgicale dans la cornée. On a fait une comparaison avec la conductivite à l'écoulement du stroma de la cornée à degré d'hydration normal.

Zusammenfassung

Die Wasserpermeabilität und der mittlere Porenradius von transparenten Hydrogelen aus Glycerylmethacrylat (GMA), 2-Hydroxyäthylmethacrylat (HEMA), Propylenglykolmonoacrylat (PGMA) und einem Polyelektrolytkomplex wurden bestimmt. Der Transportprozess erwies sich im Polyelektrolytkomplex und in den verdünnteren GMA-Hydrogelen (74–94% Wasser) vorwiegend als viskoses Fliessen, im HEMA-Hydrogel (40% Wasser) und in den PGMA-Hydrogelen (40–60% Wasser) schien jedoch die Diffusion eine wichtige Rolle für die Bewegung des Wassers durch das Gel zu spielen. Diese Hydrogele sind potentiell für chirurgische Hornhauteinpflanzungen brauchbar. Ein Vergleich mit der Durchströmbarkeit des Hornhautstroma bei normaler Hydratation wird durchgeführt.

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