

Glyceryl Methacrylate Hydrogels

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Synopsis

Hydrophilic three-dimensional polymer networks (hydrogels) were prepared from glyceryl methacrylate (2,3-dihydroxypropyl methacrylate). The solubility of poly(glyceryl methacrylate) in water permits the preparation of transparent hydrogels containing variable amounts of water at the equilibrium stage. This is accomplished by varying the degree of swelling at the time of network formation, and by varying the density of crosslinks. The temperature dependence of swelling of the hydrogels in water and in 0.9% sodium chloride solution, was determined. There exists a linear relationship between the refractive index and the per cent of water in the hydrogel. These hydrogels are potentially useful in ophthalmology.

INTRODUCTION

The use of crosslinked hydrophilic polymers for the manufacture of surgical implants and contact lenses has been proposed by Wichterle and Lim.^{1,2} When three-dimensional hydrophilic polymers are equilibrated in water or in aqueous solutions, hydrogels with very attractive properties for medical uses are obtained. These hydrogels may be particularly useful in the field of ophthalmology because they are soft, easily cast to any shape, and can be made transparent. The permeability of hydrogels to water and to low molecular weight water-soluble substances is a very important property when they are considered for use as prostheses to be placed in close contact with living tissue. If the permeability of the implant is similar to the permeability of surrounding tissue, it is expected that the implant will not interfere greatly with the metabolism of the tissue. In surgery, it is also important to use only those polymers that are not contaminated with low molecular weight impurities; these impurities could be harmful if they should diffuse from the polymer into the tissue. For this reason, it is advantageous to use gels rather than plastics. Gels are easier to purify prior to implantation owing to the freer diffusion of the impurities from the swollen molecular network of the gel.

Dreifus and Klenka³ studied the irritability of various kinds of acrylic

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hydrophilic gels, ionizable basic and acid polymers, polymers containing amide groups, and polymers containing hydroxyl groups to ocular tissue. They found that the implants of neutral nonionizable polymers showed the least irritation to the tissues.

The polymerization of solutions of water-soluble monomers is a convenient way to obtain hydrogels with a given shape. If the conditions of solubility are maintained during the polymerization process, the hydrogel is homogeneous both physically and optically. If the solubility decreases during the polymerization, then the polymer will separate from the solution, and an opaque, spongy hydrogel will be obtained. Both transparent and opaque hydrogels from 2-hydroxyethyl methacrylate and propylene glycol monoacrylate were studied by Refojo and Yasuda.⁴ The maximum amount of water which can be maintained in transparent hydrogels depends on the hydrophilicity of the monomer and was found to be 40% for 2-hydroxyethyl methacrylate gels and about 50% for propylene glycol monoacrylate gels at room temperature. In these hydrogels a relatively large part of the gel volume is occupied by the solid network structure, hence, the velocity of diffusion of water and water-soluble low molecular weight substances is hindered by the disperse phase. Greater permeability should be obtained in hydrogels with increased water content, therefore the preparation of hydrogels from glyceryl methacrylate (2,3-dihydroxypropyl methacrylate) was contemplated.

Glyceryl methacrylate can be prepared by acid hydrolysis of a dioxolanoalkyl methacrylate, e.g., isopropylidenglyceryl methacrylate.⁵ The dioxolanoalkyl methacrylate can be synthesized by the method of Fegley and Rowland.⁶ An alternative way to prepare glyceryl methacrylate is that of Iwakura et al.⁷ They showed that in the hydrolysis of glycidyl methacrylate (2,3-epoxypropyl methacrylate) in aqueous nitric acid, the opening of the epoxy ring occurred rather rapidly, but the hydrolysis of the ester was not perceived. In this work the last of the two procedures was used to obtain glyceryl methacrylate mainly because the epoxy derivative is a commercially available product.

EXPERIMENTAL

Glyceryl Methacrylate

Commercial glycidyl methacrylate (100.0 g.) (The Borden Chemical Company, Philadelphia, Pa.), distilled water (150 ml.), and concentrated sulfuric acid (0.25 ml.) were stirred for six days. During the experiment the reaction flask was kept in a water bath at 24–29°C. No additional inhibiting agent was added to the reaction mixture other than the amount present in the commercial glycidyl methacrylate.

Glycidyl methacrylate is immiscible with water, but as the reaction proceeds, solubility is increased until a clear solution is obtained. As the reaction product, glyceryl methacrylate, is formed, it codissolves the unreacted glycidyl methacrylate.

The reaction mixture was neutralized with 10% sodium hydroxyde and then extracted with five 100-ml. portions of ether. The ether extract was washed with three 20-ml. portions of distilled water, then this aqueous solution was washed again with 50 ml. of ether. The combined ether extracts were dried with anhydrous sodium sulfate. The ether was then evaporated in a rotating evaporator with the rotating flask kept in a cool water bath. The residue from the ether extract, 18.8 g., was mainly glycidyl methacrylate which could be used to prepare more glyceryl methacrylate.

The aqueous extract from the ether solution was saturated with sodium chloride. The glyceryl methacrylate separated out as an oily layer above the saturated saline solution. The oily material was dissolved in methylene chloride. The organic solution was dried with anhydrous sodium sulfate and evaporated, without heating, by using the same procedure described above for the concentration of the ether extract. The residue from the evaporation, 11.6 g., was a viscous, clear liquid, mainly glyceryl methacrylate.

The aqueous reaction medium, previously extracted with ether, upon saturation with sodium chloride separated into two layers. The organic layer was taken up with methylene chloride and the solution, after being dried by anhydrous sodium sulfate, was evaporated in the rotating evaporator by using a cool water bath under the rotating flask. The yield was 71.6 g. of glyceryl methacrylate. Sometimes the residue contained some gelled polymer which was separated by dissolving the monomer in ether and filtering the insoluble polymer.

Glyceryl methacrylate is a hygroscopic liquid. When a drop of it is placed in the prism of the refractometer, the refractive index changes rather quickly from about n_D^{25} 1.4620 to the more stable value n_D^{25} 1.4710.

The elemental analysis was made from a sample dried and sealed under vacuum.

Calculated for $C_7 H_{12} O_4$: C, 52.5%; H, 7.5%. Found: C, 52.6%; H, 7.7%.

Bulk Polymerization

Glyceryl methacrylate was polymerized at 65°C. with the use of benzoyl peroxide (0.7%) as initiator. The polymer was transparent, hard, and brittle, and adhered tenaciously to the walls of the glass polymerization tube. It swelled in water to a transparent hydrogel containing 75% water at equilibrium at room temperature. Polymerized without an initiator at 65°C., it yielded a similar polymer that swelled in water to a translucent hydrogel containing 71% water. Polymerization of glyceryl methacrylate with 0.03% tetraethylene glycol dimethacrylate at 65°C., without an initiator, yielded a polymer with similar characteristics. The hydrogel was translucent and contained, as expected, less water at equilibrium (63%) than the other hydrogels, owing to the increase in the amount of crosslinks in the polymeric network.

Swelling measurements were made in the standard way. The gel was immersed in water at room temperature until reaching the equilibrium-swollen condition. The equilibrated gel was then withdrawn, surface-dried, and weighed. Two and sometimes three samples were taken for each experiment, and agreement was generally within less than 1%. The average value was taken in each case.

Polymerization in Water Solution

Polymerization of glyceryl methacrylate in water solution with redox initiator afforded transparent hydrogels containing, upon equilibration, variable amounts of water, depending on the initial dilution of the monomer solution (Fig. 1). If the solution of the monomer in water was diluted

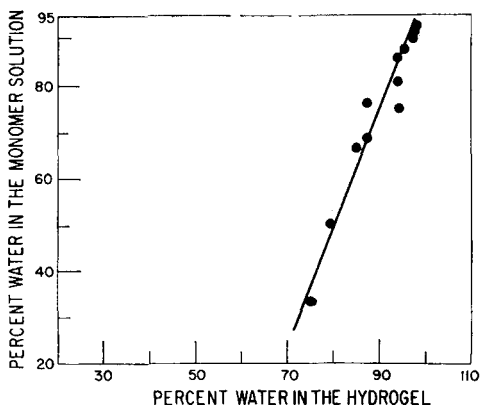


Fig. 1. Effect of the amount of water in the monomer solution upon the amount of water in glyceryl methacrylate hydrogels.

more than 5%, no gel formed; instead a water-soluble viscous polymer was obtained. Ammonium persulfate, 12% aqueous solution, and sodium metabisulfite, 6% aqueous solution, were used as redox initiator for the polymerization. To the solutions containing up to 75% water there was added 0.1 ml. of each salt/ml. of monomer; to the rest of the solutions there was added 0.1 ml. of each salt solution/0.5 ml. of monomer. The polymerization was carried out in 1.5×10 cm. test tubes, heated in an oven at 51°C. for 3 hr. and then overnight at 60°C. When the polymerization was complete, the gels were removed by breaking the glass tubes and were allowed to equilibrate in distilled water.

Degree of Swelling and Amount of Crosslinking

Glyceryl methacrylate was polymerized in water solution with tetraethylene glycol dimethacrylate (TEGDMA) as the crosslinking agent, with the use of persulfate-bisulfite redox initiator. TEGDMA is a commercially available monomer (The Borden Chemical Company, Philadel-

phia, Pa.), and it was used without further purification. To 50% solutions of glyceryl methacrylate in distilled water and 0.1 ml. of each of the persulfate and the bisulfite solutions/ml. of monomer (see under polymerization in water solution), was added increasing amounts of TEGDMA. The polymerization was carried out at 65°C., yielding transparent gels which remained transparent upon equilibration in distilled water at room temperature. The amount of water found in the equilibrated hydrogels is inversely proportional to the amount of crosslinking agent added to the monomer solution (Fig. 2).

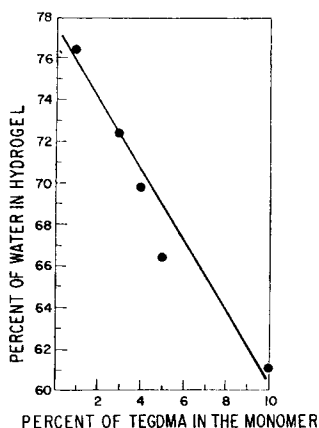


Fig. 2. Effect of crosslinking on the water content in glyceryl methacrylate hydrogels.

Hydrogels of Copolymers of Glyceryl Methacrylate and Glycidyl Methacrylate

Glycidyl methacrylate is insoluble in water, but it is codissolved in water when it is mixed with glyceryl methacrylate. Commercial glycidyl methacrylate, without further purification, was used in these experiments. To solutions containing 0.5 ml. of glyceryl methacrylate, 3.3 ml. of distilled water, 0.1 ml. of 12% ammonium persulfate, and 0.1 ml. of 6% sodium metabisulfite, were added increasing amounts of glycidyl methacrylate. Up to 14% glycidyl methacrylate per glyceryl methacrylate in the above aqueous solution formed clear solutions; 20% glycidyl methacrylate per glyceryl methacrylate yielded a turbid aqueous solution at room temperature. The polymerizations were carried out at 64°C. for 6 hr. The gels are transparent except for those containing 14 and 20% glycidyl methacrylate per glyceryl methacrylate, respectively; these present some white opaque spots through the hydrogels. The presence of glycidyl methacrylate in the copolymer seems to decrease the number of crosslinks in the network, subsequently increasing the amount of water in the hydrogel. This effect reaches a constant value with copolymer containing above 2% glycidyl methacrylate per glyceryl methacrylate in the monomer solution (Fig. 3).

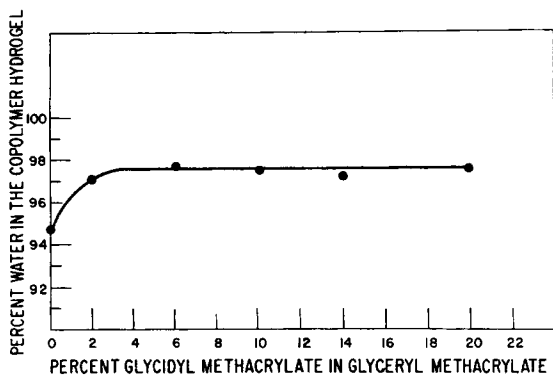


Fig. 3. Glyceryl methacrylate-glycidyl methacrylate copolymer hydrogels.

Influence of Temperature on Swelling of Glyceryl Methacrylate Hydrogels

A solution of glyceryl methacrylate (1 volume), distilled water (2 volumes), 12% ammonium persulfate (0.1 volume), 6% sodium metabisulfite (0.1 volume) was polymerized at 65°C. for 4½ hr. in several 1.5 × 10 cm. test tubes. The resulting gel was cut into pieces about 1 cm. long and allowed to equilibrate in distilled water for about two months. Then two or three pieces were equilibrated at each one of several temperatures during

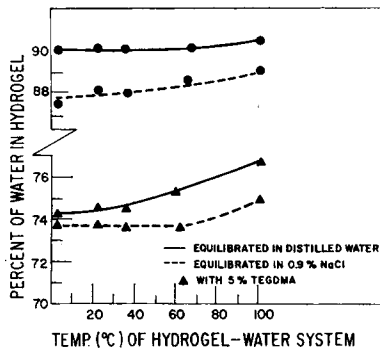


Fig. 4. Effect of temperature on water content in glyceryl methacrylate hydrogels.

five days. The water was determined in the standard way. The amount of water in the hydrogel increases by raising the temperature. This effect was more marked when the number of crosslinks in the polymer network was raised by adding to a solution of the monomer in the same proportions described above, 5% TEGDMA per glyceryl methacrylate (Fig. 4).

When instead of distilled water 0.9% sodium chloride solution (isotonic with blood and tears) was used for the equilibration of the gel, the amount of water in the hydrogel was lowered 1-2% in relation to the gel equilibrated in distilled water (Fig. 4).

Refractive Power of Glyceryl Methacrylate Hydrogels

The refractive index was measured by using a Valentine precision refractometer and employing the technique for testing solid specimens. The hydrogel, with two surfaces as close as possible at right angles to each other, was blotted of superficial water immediately prior to the measurement, then was placed directly on the prism, using no attaching liquid. The border line was not always very sharp because it was difficult to have both surfaces of the hydrogel intersecting at sharp edges. Nine to twelve determinations were made for each hydrogel, and good agreement to the third decimal point was obtained. There is a linear relationship between the refractive index and the per cent of water in the hydrogel (Fig. 5).

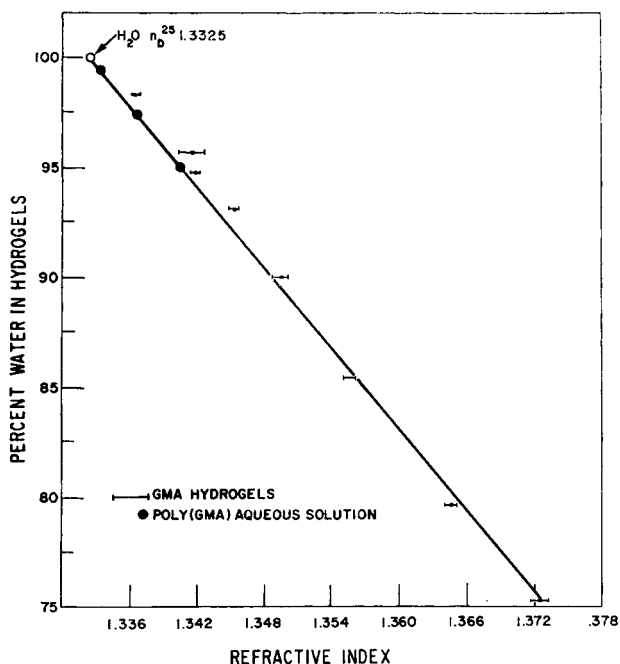


Fig. 5. Refractive index of glyceryl methacrylate hydrogels and of poly(glyceryl methacrylate) aqueous solutions.

DISCUSSION

First-order factors which influence the swelling of a given network polymer in a given solvent were expressed by Alfrey and Lloyd⁸ as: the density of crosslinks, the affinity of the swelling solvent for the polymer segments, and the degree of swelling at the time of network formation. Poly(glyceryl methacrylate) is water-soluble when prepared in a sufficiently dilute aqueous solution. Very dilute solutions avoid the formation of crosslinks between the growing macromolecules. The solubility of poly(glyceryl methacrylate) in water permits the preparation of transparent hydrogels

containing variable amounts of water at the equilibrium stage; this is accomplished by varying the degree of swelling at the time of network formation, and by varying the density of crosslinks.

Polymerization of glyceryl methacrylate in bulk or in not too dilute aqueous solutions yielded water-insoluble polymers with variable swelling power, indicating the formation of crosslinks between the macromolecular chains. Glyceryl methacrylate, as prepared in this work, seems to be a pure compound, as indicated by its elemental analysis. It is unlikely that crosslinks forming impurities are present in the monomer, but it is conceivable that some difunctional, or even trifunctional, monomers may be formed by the disproportionation of some monoester molecules. A more likely impurity in the monomer is glycidyl methacrylate, which could be visualized producing crosslinks during the polymerization by virtue of its epoxy ring. As it is well known for gel systems,⁹ the amount of liquid found on swelling glyceryl methacrylate hydrogels is inversely proportional to the extent of crosslinking in the network (Fig. 2). Nevertheless, residual glycidyl methacrylate in the glyceryl methacrylate does not seem to be the cause of network formation, since the addition of glycidyl methacrylate to aqueous solutions of glyceryl methacrylate and polymerization of the mixtures thereof yielded hydrogels which at equilibrium held even more water than the gels prepared under the same conditions but without the addition of glycidyl methacrylate (Fig. 3). Considering that glycidyl methacrylate is insoluble in water, the added epoxy groups cannot contribute to the affinity for water by the polymer segments. The increase in water content in glycidyl-glyceryl methacrylate copolymer hydrogels could be explained by a lowering in the density of crosslinks in the network, since the degree of swelling at the time of network formation was practically constant. The epoxy groups in the polymer chains might hinder the formation of interchain hydrogen bonds, in this way facilitating the penetration of water by relaxing the network.

The equilibrium swelling of glyceryl methacrylate hydrogels formed in a swollen state depends upon the degree of swelling which existed at the time of network formation (Fig. 1). This contrasts with homogeneous 2-hydroxyethyl methacrylate hydrogels⁴ which exhibit relatively constant swelling in water regardless of the initial dilution and the number of crosslinks, undoubtedly due to the poor affinity of the swelling solvent, water, for the polymer segments. In general, the relaxed volume of the equilibrated glyceryl methacrylate network is larger than the volume at which it was formed. Polymers obtained in the dry stage, xerogels, have a more compact structure than polymer networks prepared in solution; they swell in water, reaching hydration equilibrium with smaller amounts of water than the hydrogels prepared in the swollen state. The chances of crosslinks formation by chain transfer increases as the concentration of growing chains increases. Mechanical entanglement of the molecules may also have some influence in decreasing the amount of water found in the gels prepared in the more concentrated state.

Swelling of glyceryl methacrylate hydrogels is an endothermic process, as indicated by the fact that increasing the temperature promotes swelling^{10a} (Fig. 4). Some gels, such as propylene glycol monoacrylate hydrogel,⁴ behave in the opposite way; they swell markedly when the temperature is decreased, suggesting that swelling is an exothermic process. In still other hydrogels, it seems that the swelling is an exothermic or an endothermic process depending on the temperature of the system; it was observed⁴ that a hydrogel from 2-hydroxyethyl methacrylate showed swelling by decreasing the temperature below 60°C. and again by increasing the temperature above that point.

When the chemical activity of water in the hydrogel is modified by some solute, a different amount of water will be found in the gel at equilibrium: 0.9% sodium chloride solution (isotonic with blood and tears) decreases the amount of water in the hydrogel, but the overall shape of the curve is the same; increase of temperature promotes swelling (Fig. 4).

It has been found^{10b} that the refractive index of a swelling gel changes according to the same rules as those which govern the refractivity of homogeneous mixtures of two substances. A linear relationship between refractive index and concentration does not exist in every case; generally the data are represented by a curve, the shape of which is influenced by the way in which the concentration is expressed.¹¹ In glyceryl methacrylate hydrogels containing above 75% water, there appears to be a linear relationship between the refractive index and the per cent of water in the hydrogel (Fig. 5). The scattering of some points may be due to experimental error arising from the difficulty of making gels with two polished faces at right angles and intersecting at a sharp edge.

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References

1. Wichterle, O., and D. Lim, *Nature*, **185**, 117 (1960).
2. Wichterle, O., and D. Lim, U.S. Pat. 2,976,576, March 28, 1961.
3. Dreifus, M., and L. Klenka, *Cs. Oftalmologie*, **15**, 95 (1959).
4. Refojo, M. F., and H. Yasuda, *ACS, J. Appl. Polymer Sci.*, **9**, 2425 (1965).
5. Rohm and Haas Company, Great Britain Pat. 852,384, Oct. 26, 1960.
6. Fegley, V. W., and S. P. Rowland, U. S. Pat. 2,680,735, June 8, 1954.
7. Iwakura, Y., T. Kurosaki, K. Uno, Y. Imai, *J. Polymer Sci.*, **C4**, 673 (1963).
8. Alfrey, T., Jr., and W. G. Lloyd, *J. Polymer Sci.*, **62**, 159 (1962).
9. Jirgensons, B., *Organic Colloids*, Elsevier, New York, 1958, p. 216; H. Staudinger, *Organische Kolloidchemie*, Vieweg, Braunschweig, 3rd Ed., 1950, p. 263 ff.
10. Hermans, P. H., *Colloid Sciences*, Vol. 2, H. R. Kruyt, Ed., Elsevier, New York, 1949, (a) p. 559; (b) *ibid.*, p. 575 ff.
11. Bauer, N., and S. Z. Lewin, in *Physical Methods of Organic Chemistry*, A. Weissberger Ed., Vol. I, Part II, 3rd Ed., Interscience, New York, 1960, p. 1154.

Résumé

On a préparé des réseaux de polymères hydrophiles tridimensionnels (hydrogels) à partir de méthacrylate de glycéryle (méthacrylate de 2,3-dihydroxypropyle). La solubilité du polyméthacrylate de glycéryle dans l'eau permet la préparation d'hydrogels transparents contenant différentes quantités d'eau au point d'équilibre. Ceci est possible en faisant varier le degré de gonflement au moment de la formation du réseau, et en faisant varier la densité des ramifications. On détermine la dépendance thermique du gonflement des hydrogels dans l'eau et en solution contenant 0.9% de chlorure de sodium. Il existe une relation linéaire entre l'indice de réfraction et le pourcentage d'eau dans l'hydrogel. Il est possible que ces hydrogels soient utiles en ophtalmologie.

Zusammenfassung

Hydrophile, dreidimensionale Polymernetzwerke (Hydrogele) wurden aus Glycerylmethacrylat (2,3-Dihydroxypropylmethacrylat) dargestellt. Die Löslichkeit von Poly-(glycerylmethacrylat) in Wasser gestattet die Darstellung von durchsichtigen Hydrogelen mit wechselndem Gleichgewichtswassergehalt. Dies wird durch Variation des Quellungsgrades im Augenblick der Netzbildung und durch Variation der Vernetzungsdichte erreicht. Die Temperaturabhängigkeit der Quellung der Hydrogele in Wasser und in 0.9 %iger Natriumchloridlösung wurde bestimmt. Es besteht eine lineare Beziehung zwischen dem Brechungsindex und dem Prozentgehalt an Wasser im Hydrogel. Diese Hydrogele besitzen eine potentielle ophthalmologische Verwendbarkeit.

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