JOURNAL OF APPLIED POLYMER SCIENCE VOL. 19, PP. 1885–1892 (1975)

Hydrogels of Crosslinked Poly(1-glyceryl Methacrylate) and Poly(2-hydroxypropyl Methacrylamide)

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Synopsis

Two hydrophilic polymer networks of different crosslinking density and varying reference degree of swelling were prepared from 2,3-dihydroxypropyl methacrylate (glyceryl methacrylate) and N-(2-hydroxypropyl)methacrylamide. They were characterized by swelling and compression measurements, and the Flory-Huggins interaction parameters were determined. The results reveal the importance of hydrophobic forces in the physical properties of poly(1-glyceryl methacrylate). Poly(2-hydroxypropyl methacrylamide) gels do not exhibit the presence of these specific effects.

INTRODUCTION

Hydrophilic methacrylate polymers, in particular poly(2-hydroxyethyl methacrylate) (PHEMA) first developed by Wichterle and Lim[1,2] in 1955, are currently in use as biomedical materials.[3,4,5] These PHEMA gels have been shown[6,7,8] to have limited water compatibility. However, materials of high water compatibility are more desirable for biomedical materials, not only because of their capability of filling cavities in organs or tissues after implantation of unswollen gel, but also because they allow easier transport of physiologic fluids through the implants. In order to achieve high swelling in aqueous media, we have prepared and investigated two other hydrogels: poly(1-glyceryl methacrylate) (PGMA) and poly(2-hydroxypropyl methacrylamide) (PHPMD). Both have potential usefulness in medical applications requiring higher swelling than is achievable with PHEMA.

PHEMA gels are also of theoretical interest because of their amphiphilic nature. In hydrogen bonding solvents (especially in water), a certain amount of diluent-induced ordering exists, which is of importance for the study of structure–property relations.[7,8,9] Thus, it seemed worthwhile to investigate how changes in the amphiphilic nature of PGMA and PHPMD are reflected in the physical properties of the gels with respect to PHEMA.

EXPERIMENTAL

Preparation of Monomers

Glyceryl Methacrylate (2,3-Dihydroxypropyl Methacrylate). Refojo has described[10] the synthesis of glyceryl methacrylate (GM) by hydrolysis of glycidyl

methacrylate. Since by this method the final product may contain some epoxy-type residues which are harmful from the biomedical point of view, we have decided to obtain GM by hydrolysis of 2,3-isopropylidene glyceryl methacrylate (IPGM). IPGM was obtained by reaction of methacryloyl chloride (1 mole) (Aldrich Chemical Co., Inc., Milwaukee, Wis.), with 2,2-dimethyl-1,3-dioxolane-4-methanol (1.2 moles) (acetone ketal of glycerine, Aldrich Chemical Co., Inc.) in the presence of pyridine (1.1 moles) and ether (250 ml) at 0–5°C. After separation of pyridine hydrochloride, the ether solution was washed with diluted sulfuric acid, followed with 10% NaOH, and finally with water. The pure IPGM (0.85 mole) obtained by evaporation of ether was subsequently stirred with 0.3*N* hydrochloric acid (200 ml) at room temperature for 5 hr to hydrolyze. IPGM is immiscible with water; but as the reaction proceeds, its solubility increases. When the hydrolysis is complete, the reaction mixture is homogeneous. Next, the mixture was completely neutralized with 10% NaOH and saturated with sodium chloride. GM was extracted with four 150-ml portions of ether. The ether extracts were dried over sodium sulfate and evaporated on a rotating evaporator at room temperature. GM (0.4 mole) is a viscous hydroscopic fluid, and its purity was checked by IR spectra.

N-(2-Hydroxpropyl) Methacrylamide. N-(2-hydroxypropyl) methacrylamide (HPMD) was obtained by reaction of methacryloyl chloride (1 mole) with 2-aminopropanol (2 moles) (Aldrich Chemical Co., Inc.) in the presence of triethylamine (1 mole) in dry acetonitrile at 0–5°C. After separation of hydrochlorides and evaporation of solvent at room temperature, a very viscous liquid is obtained. The monomer (0.6 mole) was purified by recrystallization from methanol, mp 67°C. Inspection of IR spectra indicates that the amount of 2-aminopropyl methacrylate in the product is negligible.

Polymerizations

Poly(1-glyceryl Methacrylate). Polymerizations of GM were carried out in aqueous solutions using $2.5 \times 10^{-2}M$ ammonium persulfate as an initiator at 55°C in glass tubes for 48 hr. The crosslinking agent, ethylene glycol dimethacrylate (EGDM) (K and K Lab, Inc., Plainview, N.Y.), was distilled before use. The weight ratio of water to monomer in the reaction mixtures ranged from 0.15 to 1.0, and the weight ratio of crosslinker to monomer ranged from 0.0 to 0.03.

Poly(2-hydroxypropyl Methacrylamide). Polymerizations of HPMD were carried out at 50°C for 48 hr using $2.5 \times 10^{-2}M$ ammonium persulfate as an initiator and a methanol–water (1:1 by weight) mixture as a solvent. Again, EGDM was used as the crosslinker. The ratio of solvent to monomer in the reaction mixtures ranged from 0.6 to 1.15, and the weight ratio of crosslinker to monomer varied from 0.01 to 0.04.

In both cases, the reaction mixtures were degassed prior to polymerization. After polymerization, the transparent gels were removed by breaking the tubes.

Swelling and Compression Measurements

The gels were repeatedly extracted with water at room temperature and 50°C, followed by equilibration in water at 25°C. The swollen-state volume, V_s, was determined by weighing blotted samples first in air and then in water. The samples were then dried to constant weight, w_2. The partial specific volume of

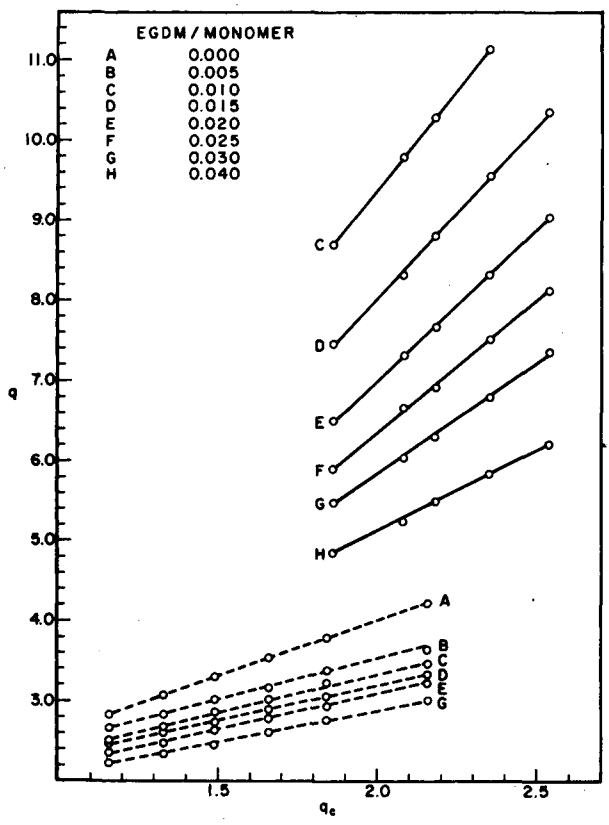

Fig. 1. Swelling degrees, q, for PGMA (dotted line) and PHPMD (solid line) gels vs. degree of dilution prior crosslinking, q_c, for varying amounts of crosslinking agent.

the polymers, $\bar{v}_2 = 0.7217$ for PGMA and $\bar{v}_2 = 0.7821$ for PHPMD, were taken from the plot of average specific volume of swollen gels, $\bar{v}$, versus weight fraction of solvent in the gels, g_1, since $\bar{v}_2 = \bar{v} - g_1 \times (\delta\bar{v}/\delta g_1)$.[11] The plots are linear in the range of interest, and thus the partial specific volumes do not depend on the concentration of solvent in the gels. The volume degree of swelling, $q = V_s/w_2 v_2$, obtained in this way is shown in Figure 1.

Figure 2 shows the temperature dependence of swelling. The data were obtained by measuring the length of a gel rod immersed in water at different temperatures T. The lengths were taken cathetometrically, and the q values were calculated using the formula

$$q_T = q_{25}(l_T/l_{25})^3.$$

Because of the friability of the gels, unilateral compression measurements are the most convenient way to obtain their moduli. Cylindrical samples of 1.2 cm in diameter and 1 cm in height were compressed between two Teflon plates. The top plate was fitted with a motor-driven micrometer and the initial dimensions were measured by means of a cathetometer. The force was measured by an inductive transducer attached to a carrier wave amplifier and recorder.[12] All measurements were taken at 25°C. The 5-min modulu, G, were determined by a least-squares computer fit to the equation

$$\sigma = G[(L/L_0)^2 - (L_0/L)].$$

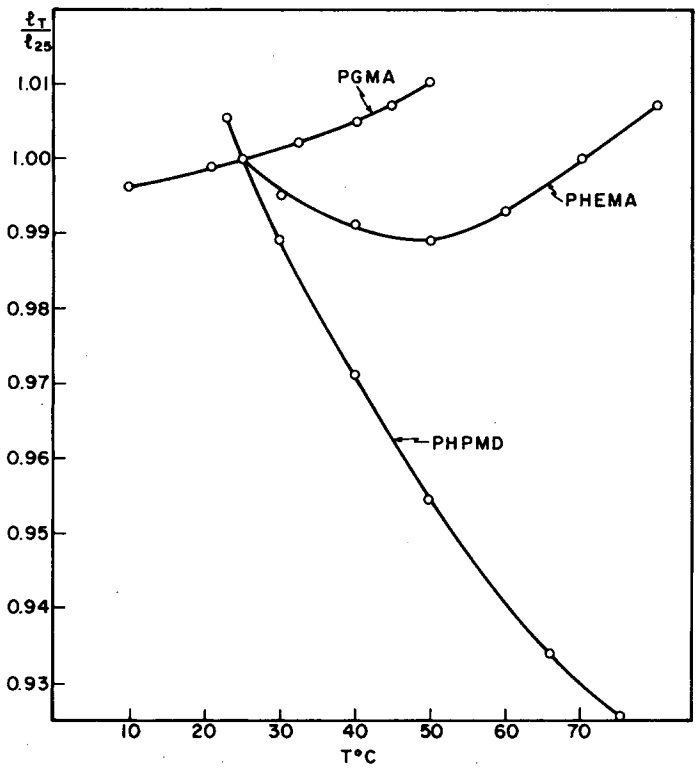

Fig. 2. The swelling of PGMA (q_{25} = 2.86) and PHPMD (q_{25} = 5.48) gels in water as function of temperature; plotted as length relative to length at 25°C. Data for PHEMA are taken from Warren and Prins.[9]

In the above equation, σ stands for the true stress (force per unit area of a strained cross section); L and L_0 are heights of the samples in compressed and uncompressed state, respectively; and G is given by[13]

$$G = RTq_0^{-2/3}q^{-1/3}\nu^*$$

where ν^* is the number of moles of physically effective network chains per cubic centimeter of dry volume; and q_0 is the reference degree of swelling at which the chains are unstrained. We take $q_0^{-2/3} = 0.5q_c^{-2/3}$, with q_c standing for the degree of dilution prior to crosslinking.[14] Compression measurements results are presented in Figures 3 and 4.

From swelling and compression measurements, the Flory-Huggins interaction parameter χ is obtained from[13]

$$\nu^*\bar{V}_1q_0^{-2/3}q^{-1/3} - 0.5\nu^*\bar{V}_1q^{-1} + \ln(1 - q^{-1}) + q^{-1} + \chi q^{-2} = 0.$$

In this equation, $\bar{V}_1$ is the partial molecular volume of the solvent. The values of the interaction parameter are presented in Figure 5.

DISCUSSION

Inspection of the swelling data (Fig. 1) shows that both PGMA and PHPMD swelling is governed by polymerization conditions in the usual fashion, i.e., the

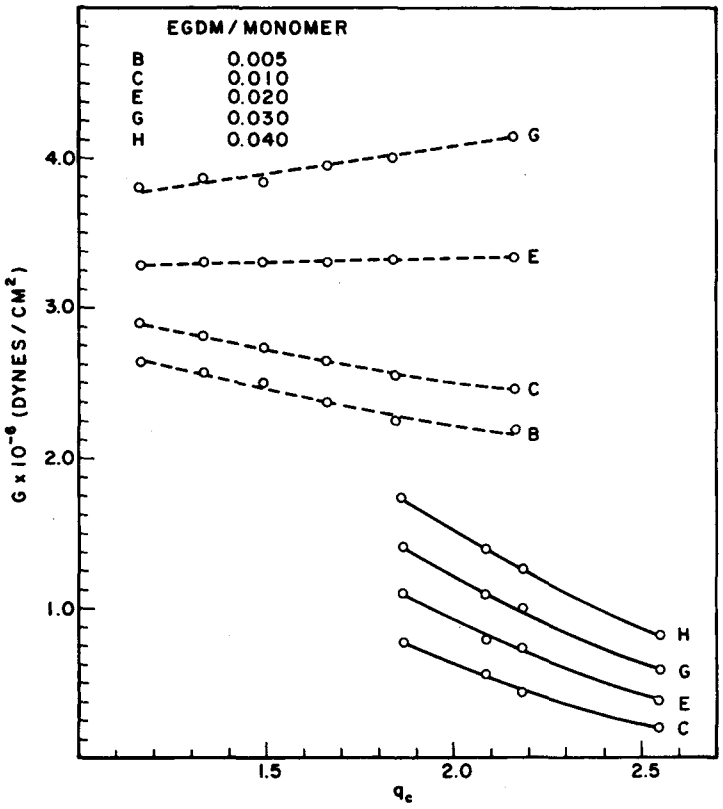

Fig. 3. Moduli, G, of PGMA (dotted line) and PHPMD (solid line) gels vs. degree of dilution prior to crosslinking, q_c, for varying amounts of crosslinking agent.

degree of swelling decreases with increasing concentration of crosslinking agent and with decreasing amount of solvent during polymerization. This dependence is especially pronounced for PHPMD, which is in sharp contrast with PHEMA gels where swelling is independent of polymerization conditions and $q = 1.85$.[8]

PGMA gels obtained by polymerization of the monomer without crosslinking agent are not soluble in any available solvent. Their swelling degrees depend on polymerization conditions similar to the gels obtained with EGDM. In other words, their behavior is typical of crosslinked networks. Presence of the crosslinks (in gels without EGDM) can result from chain transfer between growing radicals and inactive polymer molecules leading to branching reactions. Apparently, branch formation is very frequent, with the growing branching to some extent terminated by combination thus producing an insoluble crosslinked network. Such a process of network formation becomes less probable in diluted reaction mixtures; and, as Refojo reports,[10] if monomer concentration is less than 5%, a water-soluble polymer is obtained instead of a gel. In the case of PHPMD, we found similar effects although crosslinking due to combination of branchings is remarkably smaller. In fact, it is so small that it is difficult to obtain reliable swelling degrees for the gels by the method used in this work. If the concentration of HPMD in the reaction mixture is smaller than 20%, a viscous solution of linear polymer is obtained.

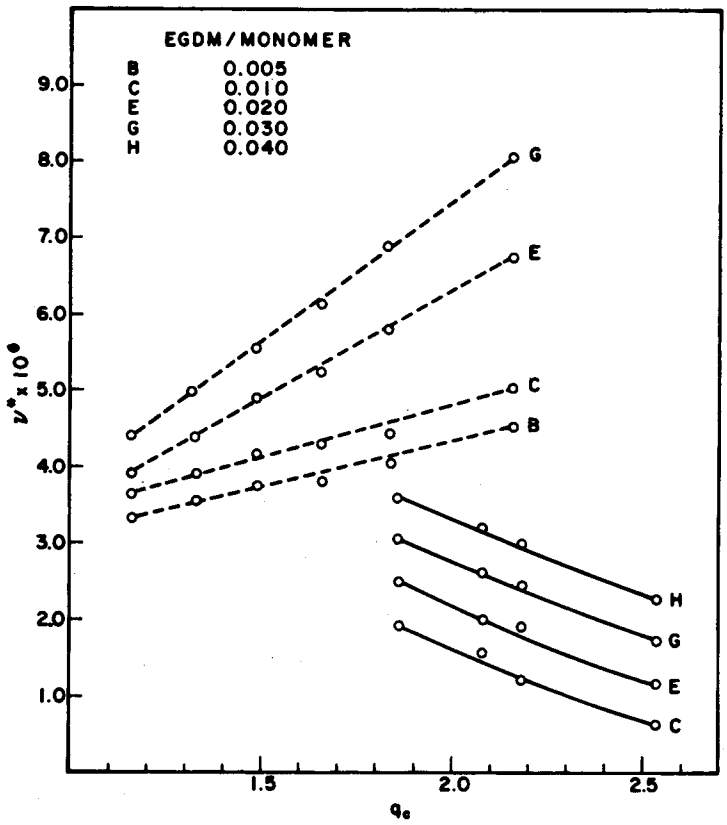

Fig. 4. Number of moles of elastically effective network chains per cubic centimeter of dry polymer network, ν^*, for PGMA (dotted line) and PHPMD (solid line) gel vs. degree of dilution prior crosslinking, q_e, for varying amounts of crosslinking agent.

There are remarkable differences in the temperature dependence of swelling for the gels under consideration (Fig. 2). For PGMA, swelling is an endothermic process (as originally observed by Refojo[10]); while for PHPMD, the reverse is true. For PHEMA, the sign of the enthalpy of dilution, ΔH_{dil}, depends on temperature where, below $T = 55°C$, ΔH_{dil} is negative. In spite of the favorable enthalpy of dilution, the swelling is limited. Therefore, one has to conclude that entropy of dilution, ΔS_{dil}, is negative. This decrease in entropy can be explained by the pronounced structuring of water upon solvating hydrophobic groups[15] and apparently disappears above 55°C. This decrease in entropy can be minimized by the grouping of hydrophobic parts of polymer chains.[9] Since the swelling degrees are higher and temperature dependence is monotonic, one could conclude at a first glance that, in the case of PGMA and PHPMD, the hydrophobic forces are not operative. In fact, this is not exactly the case. A deeper insight into the nature of intermolecular interactions can be obtained by analyzing the changes in partial molar enthalpy of dilution of the water, $\Delta \bar{H}_{1,dil}$. The $\Delta \bar{H}_{1,dil}$ values can be found assuming that the excess of partial molar free energy of dilution of the solvent, $\Delta \bar{G}_1^e$, is $RT\chi_q^{-2}$. Then, $\delta(\Delta \bar{G}_1^e/T)/\delta T = -\Delta \bar{H}_{1,dil}/T^2$. Appropriate values for varying values of q were taken from Figure 5. The data found in this way are presented in Table I.

TABLE I
Partial Molar Enthalpy of Dilution of the Water for PGMA and PHPMD

	$\Delta\bar{H}_{1,\text{dil}}$, cal/mole					
	20°C	30°C	40°C	50°C	60°C	70°C
PHEMA[a]	—	−19	−12	−3	+7	+13
PGMA	+22	+27	+38	+46	+60	—
PHPMD	—	−48	−48	−54	−49	−55

[a] Values for PHEMA are taken from Warren and Prins.[9]

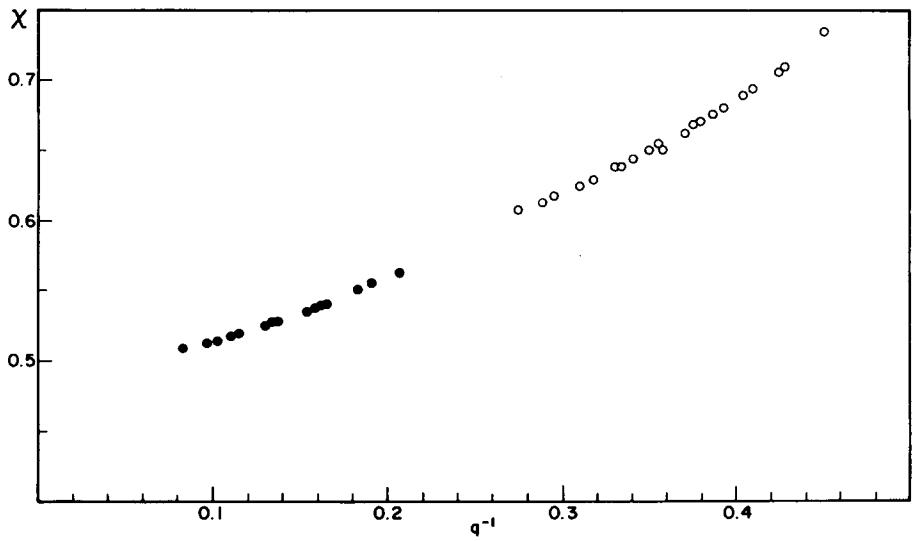

Fig. 5. Flory-Huggins interaction parameter, χ, for PGMA (open circles) and PHPMD (full circles) vs. volume fraction of polymer in the gels, q^{-1}, at 25°C.

Analyzing these data, one should keep in mind that in the case of PHEMA the enthalpy values were obtained in a different way (thermoelasticity), and for PHPMD there is some uncertainty about the value of the Flory-Huggins interaction parameter resulting from the uncertainty in the value of $q_0^{-2/3}$. Polymerization of PHPMD were performed in a mixed solvent while final measurements were taken from the gels equilibrated with pure water. Therefore, reference degree of swelling at the moment of final measurements differs from the value at the moment of polymerization, and the relation between q_0 and q_c is no longer valid. Nevertheless, we believe that we can quite safely draw conclusions from the values since we are not interested in their absolute magnitudes but rather in their trends with temperature. Being interested in relative trends makes also more justifiable the above assumption of $\Delta\tilde{G}^e$ and the neglect of possible temperature dependence of the interaction parameter χ. Table I shows that for the PHEMA gels the enthalpy changes rapidly with temperature. It is a reflection of the disappearance (with increasing temperature) of the increased hydrogen bonding in the hydrophobically structured water.[9] For PGMA, the changes in partial molar enthalpy of dilution of water are again remarkable, and we conclude that hydrophobic forces are operative in the case of these gels. For PHPMD gels, however, the enthalpy is essentially independent of tem-

perature, which suggests that structuring of water does not play an important role in swelling behavior of these gels. In line with these conclusions are swelling results for the gels in mixed solvents, e.g., the PGMA gel of $q = 2.85$ in water and $q = 1.35$ in acetone reaches $q = 4.05$ if equilibrated with a mixture of 50% water–50% acetone. Similar data were obtained for water–tetrahydrofuran and water–dioxane solvents. Such results are typical for systems of amphiphilic nature.[16,17] For PHPMD gels, the swelling degrees in the mixed solvents lie between the values of the pure solvents.

The moduli of PGMA gels (Fig. 3) are remarkably higher than those of PHPMD gels. The moduli decrease with increasing degree of dilution during the polymerization. For PGMA, however, the decrease in gel moduli of small crosslinking density is less pronounced than for PHPMD gels; and in the case of PGMA gels of higher crosslinking density, the moduli even tend to increase. This unexpected behavior might be ascribable to grouping of the hydrophobic parts of network chain as a result of the action of hydrophobic forces. The so-called hydrophobic bonds contribute to the number of ν^*, which in turn affect the value of the moduli. The grouping is more effective for gels with higher water content (easier rearrangements of network chains) and with higher crosslinking density, since EGDM enhances hydrophobicity of the network. These effects are more directly presented on Figure 4. Analysis of the figure should take into account that the uncertainty in $q_0^{-2/3}$ makes the absolute magnitude of the number of elastically effective network chains for PHPMD less reliable than for PGMA.

Swollen PGMA gels are very friable which make them unsuited for load-bearing applications. On the other hand, PHPMD gels are much less friable (especially if prepared as gels of higher crosslinking density) and from that point of view constitute a more promising material for biomedical applications.

The authors greatly appreciate financial support from the National Institute of Health and wish to express their gratitude to Dr. Gerard Hild and Ms. Sachiko Hattori for help in the preparation of IPGM and GM. One of us (W.N.) would like to thank the Technical University of Gdansk, Gdansk, Poland, for the one-year leave of absence.

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Received December 3, 1974