Solute and Penetrant Diffusion in Swellable Polymers: X. Swelling of Multiethylene Glycol Dimethacrylate Copolymers

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Synopsis

The swelling behavior of copolymers containing 2-hydroxyethyl methacrylate and various multiethylene glycol dimethacrylates was examined at 25°C. These highly crosslinked copolymers show some hydrophilic behavior due to the hydroxyl groups of HEMA. Analysis of the swelling data indicates an anomalous water transport in the network, which depends on the degree of crosslinking attained according to the dimethacrylate comonomer molar fraction in the copolymerization feed. Thermomechanical analysis data were used to further characterize the network structure.

INTRODUCTION

The growing popularity of various types of hydrogels, such as those produced from the reaction of multifunctional methacrylates, for use in drug delivery devices has prompted an abundance of current and ongoing research in this area.[1] Hydrogels are water-swollen polymeric networks produced from various hydrophilic homo- or copolymers.[2] Hydrogels may be held together by ionic or covalent bonds and may be noncrystalline or semicrystalline depending on the crosslinked character of the network.[3-6] Controlled release from such hydrogels may be achieved by incorporation of a bioactive agent within the polymer matrix and subsequent release of the agent into a solvent under a variety of rate-limiting mechanisms.

In this work, we concentrate on the properties and uses of crosslinked homo- and copolymers of multifunctional dimethacrylates with hydroxyethyl methacrylate. Such swollen networks have been identified as excellent candidates for controlled release devices because of their inertness, biocompatibility, and ease of regulation of drug release by variation of the crosslinking density. Finally, a wide range of such monomers is available which may be tailored to the type of drug (hydrophilic or hydrophobic) and to the release requirements.[7,8]

Specifically, the properties and characteristics of the above class of acrylates have been examined as they pertain to use in swelling-controlled release (SCR) devices,[9-11] including variables related to their dynamic and equilibrium swelling behavior in various solvents, their crosslinking density, and details of their preparation and crosslinked structure.

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SCR systems are solvent-activated polymeric drug release matrices. Release from these systems is based on solute diffusion and macromolecular relaxations within the polymer matrix.[9] The matrix is initially loaded with drug by absorption from a drug solution during which time the matrix also swells, depending upon its compatibility with the solvent being used, as well as on the degree of matrix crosslinking and on the drug molecular structure. The solvent is subsequently removed from the matrix, resulting in a dry, glassy, polymeric matrix, usually in the form of microspheres, cylinders, disks or small irregular particles. Solute release from the matrix is accomplished as the polymer is placed in an aqueous environment. A solvent penetrates the polymer (usually with a visible front having a velocity dependent on the structure) and a simultaneous mechanism of swelling of the matrix and transport (release) of dissolved drug out of it occurs.[9,12]

The time-dependent swelling characteristics of the polymer are of vital importance in these SCR systems. Release behavior from these systems varies from time-dependent (Fickian) to time-independent or zero order release, which, incidentally, is the most desirable and controllable release behavior.[13-15]

Polymers used with SCR systems include poly(ethylene-co-vinyl alcohol), poly(vinyl alcohol) and its copolymers, poly(vinyl alcohol-co-N-vinyl-2-pyrrolidone), poly(2-hydroxyethyl methacrylate-co-methyl methacrylate), and multifunctional methacrylates and their copolymers with 2-hydroxyethyl methacrylate (HEMA).[9,12,16]

The advantages of SCR systems[9] over other methods of controlled release include:

(i) ease of preparation of such polymers;
(ii) possibility of conventional pharmaceutical preparative techniques;
(iii) possibility of release of both short and long half-life drugs;
(iv) attainment of zero order release.

The present work concentrates on these copolymers of multiethylene glycol dimethacrylates mostly to show that highly crosslinked methacrylate structures exhibit strong relaxational phenomena during water transport (swelling) through them.

EXPERIMENTAL

Materials and Fabrication

The polymers for these studies were prepared according to common methods for free-radical copolymerizations. Ethylene glycol dimethacrylate (EGDMA), diethylene glycol dimethacrylate (DEGDMA), triethylene glycol dimethacrylate (TrEGDMA), and tetraethylene glycol dimethacrylate (TeEGDMA) monomers (Polysciences, Warrington, PA) were distilled and copolymerized in molar fractions of 1.0, 0.7, and 0.5 with 2-hydroxyethyl methacrylate (HEMA) in molar fractions of 0.0, 0.3, and 0.5, respectively. Azobis-isobutyronitrite (AIBN) (Aldrich Chemical Co., Milwaukee, WI) was added at 1 mol % as an initiator. The reactions were carried out in 7 mL

polypropylene vials sealed with paraffin and agitated in a water bath at 40°C for 6 h and 60°C for an additional 12 h.

The polymer samples used in the equilibrium and dynamic swelling studies were prepared by slicing thin disks (approximately 0.3 mm) from the bulk polymer cylinders using a Buehler diamond-grit saw. Rough edges were smoothed using a diamond grinding wheel and all samples were rinsed in acetone following grinding.

The samples used in the thermomechanical analysis studies were prepared by cutting rough samples from the polymer disks previously prepared. The edges were rounded using a sharp razor to give a facial surface area of equivalent size to the probe tip (0.6207 mm^2).

Swelling Studies

The dynamic and equilibrium swelling studies were carried out at 25 ± 2°C. Dry polymer disks were initially weighed in both air and *n*-heptane. The disks were immersed into separate vials containing buffered distilled water (pH 7.0) and were removed at 0.5–2.0-h intervals, blotted dry, weighed in air, and placed again into the vials. After equilibrium swelling was reached (approximately 7 days), the samples were removed, weighed in both air and heptane, and allowed to dry in air for 24 h. The samples were then dried in a vacuum oven for an additional 24 h and weighed in both air and heptane to give the final dry weight.

Thermomechanical Analysis

Strain vs. time and strain vs. temperature data were taken using a thermomechanical analysis system (Model TMS-2, Perkin-Elmer, Norwalk, CT). Polymer discs with parallel surfaces were placed in the sample chamber. The strain probe was lowered and centered on the sample and the entire sample chamber was lowered into a high temperature furnace. All studies were performed by equilibrating the samples at 225°C, and then recording changes in width of the sample as a function of time under a continuous force of 50 g. Strain vs. temperature studies were performed in a similar manner with the exceptions that the samples were equilibrated at 25°C then heated at 10°C/min from 25°C to temperatures above the observed glass transition temperature (typically < 320°C). A constant force of 50 g was applied to these samples during the study period. Experiments at 10, 20, 30, and 40 g were also performed on selected samples.

RESULTS AND DISCUSSION

Equilibrium and Dynamic Swelling Studies

Analysis of the equilibrium and dynamic swelling characteristics of all copolymer compositions was performed. Trends in these characteristics were found to be due to both the composition of HEMA comonomer as well as to the molecular weight of the multiethylene glycol dimethacrylate used. Figure 1 illustrates the dynamic swelling behavior of P(HEMA-co-TrEGDMA) copolymers with varying HEMA compositions. In this figure the ratio of the

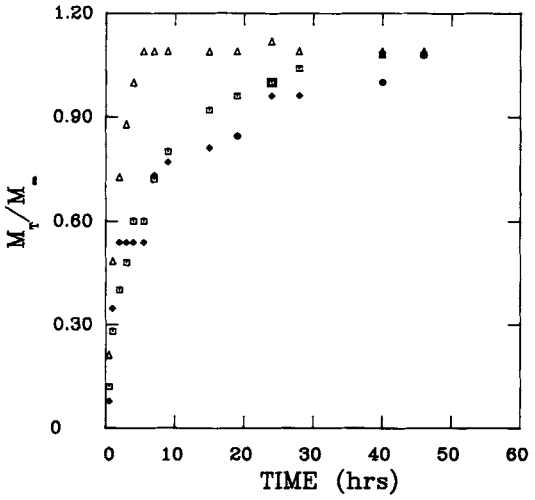

Fig. 1. Normalized water uptake of three P(HEMA-co-TrEGDMA) copolymer networks at 25°C as a function of time. The networks contained 0 (◇), 30 (□), or 50 mol % (△) HEMA.

mass of penetrant uptake at any time, M_t, to the mass of penetrant uptake at equilibrium, M_∞, is shown as a function of time. The copolymer with 50% HEMA appeared to rise to its equilibrium uptake value in under 10 h while the lower concentrations required more than 40 h to reach equilibrium.

The hydrophilicity of the matrix due to the HEMA content caused more rapid penetrant uptake as well as a higher equilibrium swelling as a function of time, as illustrated in Figure 2, where the mass of penetrant uptake, M_t, per unit mass of polymer, M_p, is plotted vs. time. The P(HEMA-co-TrEGDMA) copolymer with 50% HEMA was the most hydrophilic and absorbed nearly double the water quantity at equilibrium with respect to the lower HEMA compositions.

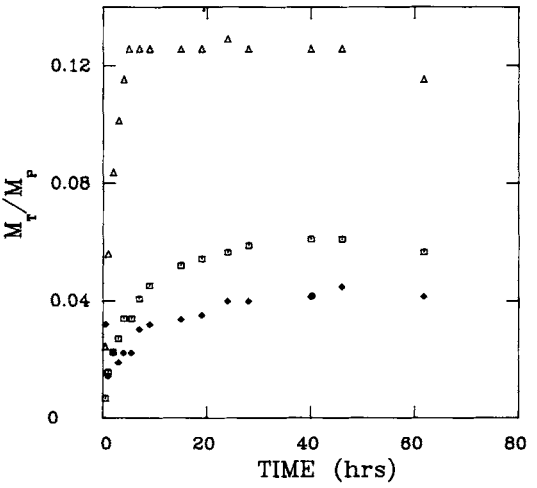

Fig. 2. Water uptake per dry polymer weight (g/g) for three P(HEMA-co-TrEGDMA) copolymer networks with 0 (◇), 30 (□), and 50 mol % (△) HEMA, at 25°C.

TABLE I
Exponent n of Eq. (1) for Various Copolymers

Copolymer	HEMA mole fraction	n
P(HEMA-co-DEGDMA)	0.00	0.41 ± 0.03
	0.30	0.59 ± 0.02
	0.50	0.59 ± 0.07
P(HEMA-co-TrEGDMA)	0.30	0.63 ± 0.02
	0.50	0.89 ± 0.04

To quantify this swelling behavior, the swelling results were analyzed using eq. (1) which has been previously discussed by Ritger and Peppas.[13] Table I illustrates the calculated n values and associated statistics for water transport into various copolymer composition according to eq. (1).

$$M_t/M_\infty = kt^n \tag{1}$$

The values of n indicate that water transport in these crosslinked copolymers was a relaxation-coupled process, since the exponent n was greater than 0.50. The statistical analysis indicated the 95% confidence intervals. It is obvious that a non-Fickian transport behavior was observed as the percentage of HEMA in the copolymer increase from 0 to 50%. It is obvious that increase of the HEMA content or associated decrease of the DEGDMA or TrEGDMA content led to lower crosslinking and, therefore, significant relaxation. Similarly, for the same HEMA content (e.g., 0.50), Table I indicates that copolymers containing the longer ethyleneglycol unit (e.g., TrEGDMA instead of DEGDMA) showed a greater deviation from the Fickian mechanism, or stronger relaxational behavior.

Since the thickness of the various polymer samples tested varied, a comparison of the level of water uptake vs. the normalized time, $t^{1/2}/\delta$, where δ is the initial polymer sample thickness, was also made for water transport in the P(HEMA-co-TrEGDMA) samples (Fig. 1 vs. 3) This comparison indicated a comparable swelling behavior of the different HEMA compositions, and less of a difference in initial water uptake rates. However, the equilibrium uptake values still increased with increasing HEMA content.

Figures 4 and 5 show similar trends in the water uptake behavior of P(HEMA-co-EGDMA) for varying concentrations of HEMA. However, the pure PEGDMA polymer reached an equilibrium water uptake level in under 5 h, while copolymers containing HEMA required more than 20 h to achieve equilibrium. From Figure 5 it is clear that water transport in copolymers with higher HEMA concentration resulted in substantially higher equilibrium levels of water uptake per unit mass of polymer.

Figures 6 and 7 indicate overshooting of the equilibrium value of water uptake which occured with water transport in copolymers of P(HEMA-co-TeEGDMA) with molar fractions of 0.30 HEMA. This maximum in water transport was followed by a gentle decline back to the true equilibrium value. Such overshooting phenomena have been thoroughly analyzed as a function of polymer crosslinking density and geometrical characteristics by the swelling

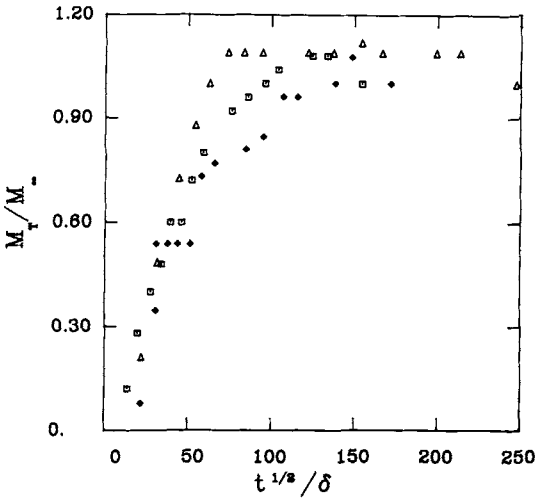

Fig. 3. Normalized water uptake of three P(HEMA-co-TrEGDMA) copolymer networks at 25°C as a function of $t^{1/2}/\delta$. The networks contained 0 (◇), 30 (□), or 50 mol % (△) HEMA.

samples by Peppas and Urdahl.[17] Comparison of the uptake of penetrant per unit polymer mass vs. time for various copolymers containing 30% HEMA and 70% of a dimethacrylate (Figs. 6 and 7) indicated that the water transport overshooting phenomenon was most prominent with copolymers containing the TeEGDMA moiety. This behavior may be due to the increased mobility of the copolymer chains in the case of the less highly crosslinked P(HEMA-co-TeEGDMA) polymer networks. Indeed, incorporation of the larger molecular weight crosslinking agent TeEGDMA results in a loosely crosslinked network structure. The same water transport behavior was observed for diffusion studies in pure polymeric networks of PTeEGDMA which seemed to be less

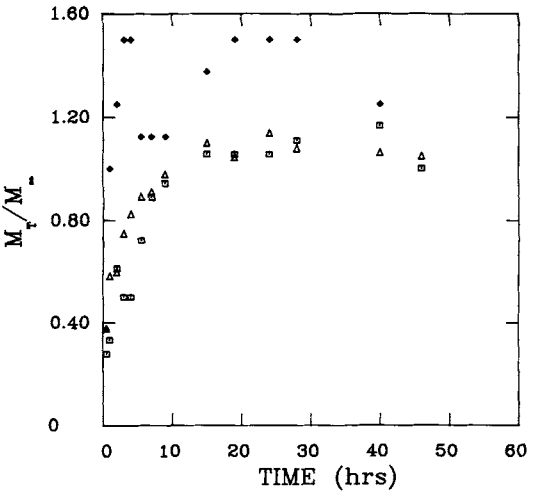

Fig. 4. Normalized water uptake of three P(HEMA-co-EGDMA) copolymer networks at 25°C as a function of time. The networks contained 0 (◇), 30 (□), or 50 mol % (△) HEMA.

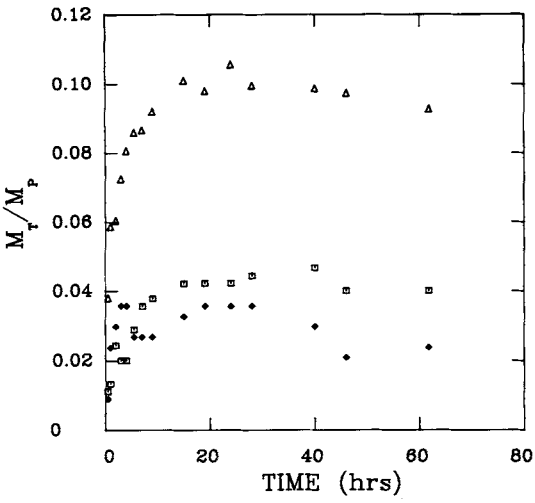

Fig. 5. Water uptake per dry polymer weight (g/g) for three P(HEMA-co-EGDMA) copolymer networks with 0 (◇), 30 (□) and 50 mol % (△) HEMA, at 25°C.

crosslinked and absorbed more water at equilibrium than PTrEGDMA, PDEGDMA and PEGDMA (Fig. 7).

Further comparison of the data of water transport in various copolymers of dimethacrylates at constant HEMA concentrations of 30% (Fig. 6) and 50% (Fig. 8), respectively, indicated a general increase in the rate and equilibrium level of water uptake as the molecular weight of the dimethacrylate increases. It can be seen that the equilibrium level of water uptake was reached in under 20 h for the copolymers containing 50% HEMA, and required more than 40 h for the copolymers with 30% HEMA compositions. Thus, the HEMA content had an important effect on the relative rates of swelling of the dimethacry-

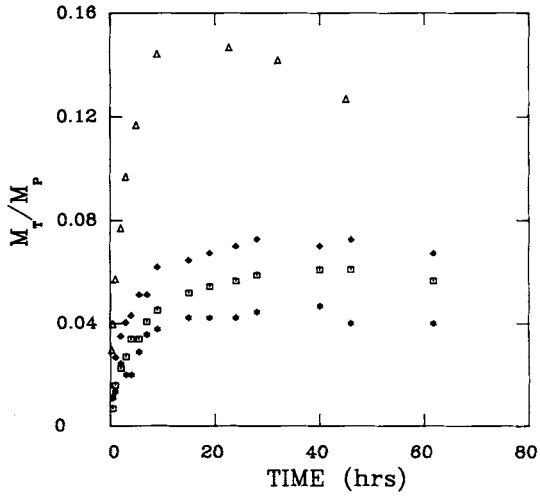

Fig. 6. Water uptake per dry polymer weight (g/g) for four copolymer networks containing 30 mol % HEMA and 70 mol % of one of the following dimethacrylates: (*) EGDMA; (◇) DEGDMA; (□) TrEGDMA; (△) TeEGDMA.

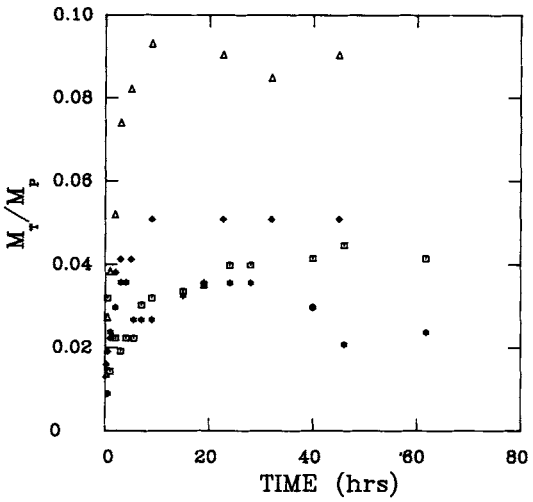

Fig. 7. Water uptake per dry polymer weight (g/g) for PEGDMA (*), PDEGDMA (◇), PTrEGDMA (□), and PTeEGDMA (△) at 25°C.

late-containing copolymers. Furthermore, water transport in P(HEMA-co-TeEGDMA) copolymers is shown to exhibit an overshoot in its equilibrium level of water uptake. Table II shows the equilibrium volume degrees of swelling for copolymers containing varying molecular weight dimethacrylates. For example, for copolymers with 50% HEMA, the degree of swelling varied from 1.105 to 1.160. The greater relaxational ability of the P(HEMA-co-TeGDMA) matrix was the likely reason for the higher degree of swelling of this polymer network.[18]

In summary, then, the concentration of the HEMA copolymer in the dimethacrylate-copolymerized crosslinked polymer samples resulted in both

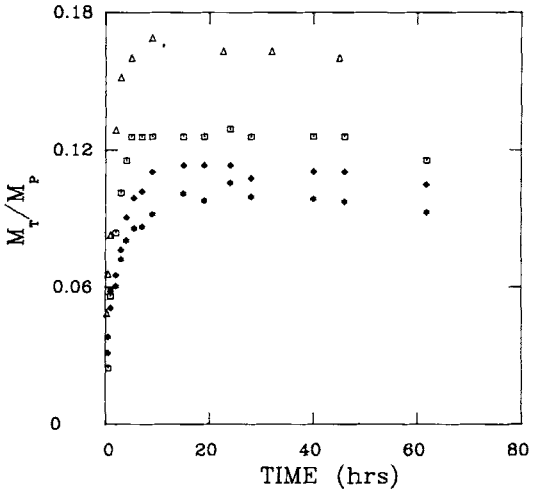

Fig. 8. Water uptake per dry polymer weight (g/g) for four copolymer networks containing 50 mol % HEMA and 50 mol % of one of the following dimethacrylates: (*) EGDMA; (◇) DEGDMA; (□) TrEGDMA; (△) TeEGDMA.

TABLE II
Equilibrium Volume Degree of Swelling of Dimethacrylate-Containing Copolymers of HEMA at 25°C

Copolymer	HEMA mole fraction	Equil. volume degree of swelling
P(HEMA-co-TeEGDMA)	0.00	1.090
P(HEMA-co-TeEGDMA)	0.30	1.060
P(HEMA-co-TeEGDMA)	0.50	1.160
P(HEMA-co-TrEGDMA)	0.00	1.087
P(HEMA-co-TrEGDMA)	0.30	1.060
P(HEMA-co-TrEGDMA)	0.50	1.110
P(HEMA-co-DEGDMA)	0.00	1.030
P(HEMA-co-DEGDMA)	0.30	1.070
P(HEMA-co-DEGDMA)	0.50	1.120
P(HEMA-co-EGDMA)	0.00	1.003
P(HEMA-co-EGDMA)	0.30	1.038
P(HEMA-co-EGDMA)	0.50	1.105

faster rates of water uptake and higher equilibrium degrees of swelling. This was due to the increased hydrophilicity of the networks attributed to the pendant —OH groups of the HEMA moiety. As the molecular weight of the dimethacrylate comonomer increased the matrix became less crosslinked (i.e., the molecular weight between crosslinks increases), resulting in more rotational degrees of freedom in the matrix and a resultant increase in mobility of the polymer chains. The ultimate effect of this increased mobility was an increase in the equilibrium volume degree of swelling and the appearance of an overshoot during swelling.

Thermomechanical Analysis

The purpose of the thermomechanical analysis was two-fold. First, strain vs. temperature studies analysis could be used to determine the glass transition temperature of the polymer network studies. Knowledge of T_g is important in determination and analysis of the swelling characteristics of the particular copolymeric networks. Since water transport and subsequent swelling occur by a lowering of the effective T_g to the experimental temperature, and subsequent transition of an initially glassy matrix to a rubbery matrix, the value of the initial T_g may be an indication of the swellability of the copolymer network.

Table III offers a summary of the glass transition temperatures of dry samples of the various HEMA copolymeric networks. The copolymer glass transition temperatures tended to increase with decreasing HEMA concentrations. In addition, the T_g increased as the copolymer degree of crosslinking increased. Additional studies were performed to determine the effects of stress (0.158, 0.316, 0.474, 0.632, and 0.790 MPa) on T_g. Table III indicates a slight increase in the glass transition under a higher applied stress.

TABLE III
Glass Transition Temperatures of Dimethacrylate-Containing Copolymers of HEMA

Copolymer	HEMA mole fraction	Applied stress (MPa)	Glass transition temperature (°C)
P(HEMA-co-EGDMA)	0.70	0.316	295
P(HEMA-co-DEGDMA)	0.70	0.316	292
P(HEMA-co-TrEGDMA)	0.70	0.316	290
P(HEMA-co-TeEGDMA)	0.70	0.316	280
P(HEMA-co-EGDMA)	0.0	0.316	304
P(HEMA-co-EGDMA)	0.30	0.316	294
P(HEMA-co-EGDMA)	0.50	0.316	296
P(HEMA-co-EGDMA)	0.30	0.158	292
P(HEMA-co-EGDMA)	0.30	0.316	294
P(HEMA-co-EGDMA)	0.30	0.474	295
P(HEMA-co-EGDMA)	0.30	0.632	296
P(HEMA-co-EGDMA)	0.30	0.790	298

In general, the high glass transition temperatures of these networks indicated their low swellability in water. The swelling studies confirmed this prediction since the equilibrium volume degrees of swelling were generally under 1.20 while recent studies by Robert et al.[19] indicated degrees of swelling for pure PHEMA networks greater than 1.50.

The second purpose of the thermomechanical studies was to determine the strain vs. time characteristics of the polymers under a constant loading. Analysis of this compressive stress behavior leads to an elucidation of the mobility of the polymer chains in the matrix and, again, an indication of the potential for swelling of the network based solely on the structural characteristics of the glassy structure. High rates of strain under a constant loading indicated relatively mobile chains in the matrix and possibly a high swelling potential of the matrix.

The various copolymers prepared in this work were tested in compressive mode. In a set of experiments the temperature was set at 225°C and the compressive strain was measured as a function of time at constant stress of 0.790 MPa. As seen in Figure 9, a sigmoidal compressive curve was obtained for P(HEMA-co-EGDMA), P(HEMA-co-DEGDMA), and P(HEMA-co-TrEGDMA) containing 0.30 mole fraction of HEMA. In all three cases, an inflection point appeared after about 60 min, indicative of a relaxational mechanism in these highly crosslinked networks. However, the copolymer network of P(HEMA-co-TeEGDMA) was rather loosely crosslinked and exhibited a significant compressive strain, as high as 0.53 after 200 min.

A further analysis of the P(HEMA-co-TeGDMA) strain characteristics was performed and the results are shown in Figure 10. Increase of the HEMA content in the TeEGDMA-containing networks result in higher rates of strain and higher ultimate compressive strain at times greater than 200 min. Based on a comparison of the molecular structures of these copolymers, the increase of pendant groups on the TeEGDMA backbone chain due to the higher HEMA concentration may result in lower structural stability or a less ordered

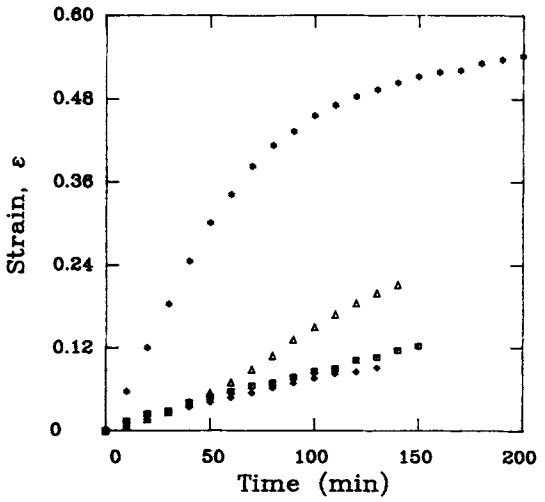

Fig. 9. Compressive strain as a function of time for isothermal compressive creep experiments conducted at 225°C under stress of 0.790 MPa. All copolymer networks contained 30 mol % HEMA and 70 mol % of one of the following dimethacrylates: (△) EGDMA; (□) DEGDMA; (◇) TrEGDMA; (*) TeEGDMA.

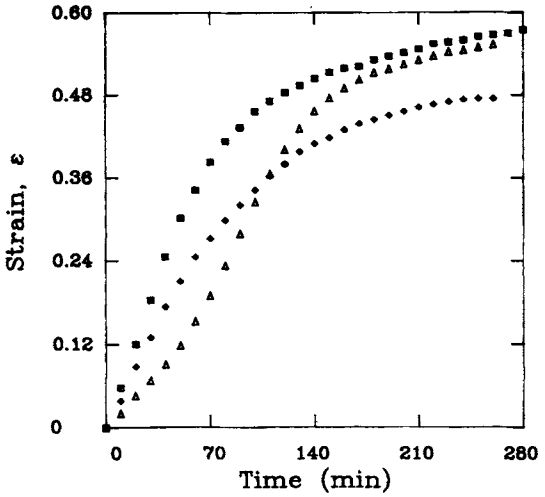

Fig. 10. Compressive strain as a function of time for isothermal compressive creep experiments conducted at 225°C under stress of 0.790 MPa. All studies were with P(HEMA-co-TeEGDMA) containing 0 (◇), 30 (□), or 50 % (△) HEMA.

matrix. This would indicate higher chain mobility within the matrix, and a higher potential for swelling in the higher HEMA concentration samples.

CONCLUSIONS

Both dynamic and equilibrium swelling studies in water may be used to elucidate the potential for zero order solute release of given hydrogel matrices. In the present analysis, various compositions of dimethacrylates and HEMA were studied and their swelling characteristics in water found to be dependent

on both the concentration of HEMA comonomer and the molecular weight of the comonomer/crosslinking agent dimethacrylate.

Thermomechanical analysis indicated higher rates of strain and, therefore, greater chain mobility, in the copolymers containing higher molecular weight dimethacrylates. The concentration of HEMA comonomer was also found to affect the rate of strain, probably through its effect on the molecular structure of the network. The glass transition temperatures of the various copolymers studied here are much higher than for pure HEMA due to the higher degree of crosslinking of the networks. The high glass transitions may also explain the overall low equilibrium volume degrees of swelling exhibited by these hydrogels.

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