Modification of the Dynamic Swelling Behavior of Poly(2-hydroxyethyl methacrylate) in Water

B. G. KABRA,[1] S. H. GEHRKE,[1,*] S. T. HWANG,[1] and W. A. RITSCHEL[2]

[1]Department of Chemical Engineering, University of Cincinnati, Cincinnati, Ohio 45221 and [2]Division of Pharmaceutics and Drug Delivery Systems, University of Cincinnati Medical Center, Cincinnati, Ohio 45267

SYNOPSIS

The equilibrium and dynamic swelling behavior of glassy polymers immersed in solvents can be modified by controlling the history of the polymer sample, which includes prior swelling and the drying method, or by copolymerization with other monomers. In this paper, the swelling kinetics in water of ionic hydrogels of 2-hydroxyethyl methacrylate copolymerized with potassium 3-sulfopropylmethacrylate and/or ethylene glycol dimethacrylate have been studied at 23°C. The dimensional changes of a swelling polymer sheet can be controlled through incorporation of anisotropic stresses in the initially dry, glassy polymer. These anisotropic stresses do not affect the swelling kinetics as long as the sample is partially glassy. However, differences in the initial stresses cause sharply different swelling kinetics once the polymer becomes entirely rubbery, due to differences in dimensional changes. Increasing the percentage of ionic comonomer in the polymer increases the equilibrium degree of swelling and the water sorption rate without changing the time for equilibration or the swelling transport mechanism. In contrast, increasing the percentage of cross-linker in the polymer not only reduces the degree of swelling and water sorption rate, but also increases the equilibration time and shifts the water transport mechanism from Fickian diffusion to anomalous transport.

INTRODUCTION

The equilibrium and dynamic swelling behavior of poly(2-hydroxyethyl methacrylate) (PHEMA) hydrogels has been studied by many researchers because of PHEMA's importance in biomedical applications.[1-6] Control of these properties is particularly important for polymer-mediated drug delivery devices and hydrogel absorbents. The kinetic response depends both upon the history of a given gel sample and its chemical composition. Although the properties of glassy polymers are well known to be history-dependent, the effect of history on swelling kinetics has been little studied. Franson and Peppas found that repeated cycles of swelling and drying caused the degree of swelling to increase with each cycle without affecting the swelling rate or transport mechanism.[2] Modification of the swelling behavior of PHEMA by copolymerizing 2-hydroxyethyl methacrylate (HEMA) with other comonomers, including cross-linkers, has been more extensively studied. Copolymerization with a monomer more hydrophobic than PHEMA will reduce its degree of swelling at equilibrium, whereas the degree of swelling increases upon copolymerization with a more hydrophilic comonomer. The effects of both hydrophobic and hydrophilic comonomers on the dynamic swelling of HEMA-based copolymers has been studied.[2-4] The rate at which equilibrium is reached increases with an increase in the fraction of hydrophilic monomer. Copolymerization with these comonomers affects not only the swelling behavior of the copolymer but can also cause substantial changes in other properties like the glass transition temperature (T_g). The swelling behavior of PHEMA can also be modified through control of the cross-link density. Increasing the percentage of cross-linker in the copolymer reduces the degree of swelling while affecting the swelling kinetics in a complex manner.[7,8] The swelling rate of the polymer decreases

* To whom correspondence should be addressed.

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with increasing cross-linker, as increased cross-linking decreases both solvent diffusivity and the relaxation rate of the polymer chains. Also, the transport mechanism shifts from simple diffusion control to anomalous transport (relaxation-influenced sorption). Similar effects of the cross-linking on swelling kinetics have also been observed for the polystyrene–cyclohexane system.[9,10]

Thus, the use of hydrophilic or hydrophobic comonomers or cross-linkers to control the swelling behavior of PHEMA is complex because such copolymerization alters all the copolymer's physical and chemical properties, not just the swelling. In contrast, modification of the swelling behavior of PHEMA by copolymerization with ionic comonomers is potentially much easier to control, since significant changes in the swelling degree occur even at low levels of comonomer: low enough that other properties like T_g are largely unchanged. Use of a strong acid salt as the comonomer will largely eliminate any pH-dependence. Although the equilibrium swelling behavior of ionic copolymers of HEMA has been studied, dynamic swelling studies have not been carried out.[11,12] In this work, we investigated the equilibrium and dynamic swelling behavior in water of cross-linked and uncross-linked copolymers of HEMA and potassium 3-sulfopropylmethacrylate (PSPMA) at 23°C. The effect of sample history (prior swelling and method of drying) was also studied, with special attention paid to the effects on the sorption kinetics caused by unusual dimensional changes.

The dynamic swelling properties of a polymer includes the solvent sorption rate, the rate of approach to equilibrium swelling, the solvent front velocity, and the transport mechanism controlling solvent sorption. The solvent sorption rate indicates the solvent uptake per unit time and is directly related to the equilibrium swelling degree of the polymer. The rate of approach to equilibrium can be characterized by a diffusion coefficient in the case of a Fickian transport mechanism. The velocity of the solvent front, which separates the inner unswollen, glassy region from the outer swollen, rubbery region is important in drug delivery applications and in characterizing the transport mechanism. The transport mechanism, which indicates the relative importance of diffusion and relaxation, is typically determined by fitting sorption data (for short times or $M_t/M_\infty \leq 0.6$) to the empirical expression[2-5]

$$M_t/M_\infty = Kt^n \qquad (1)$$

Here, M_t is the mass of solvent absorbed at time t, M_∞ is the mass sorbed at equilibrium, and K is a rate constant characteristic of the polymer–solvent system. For a slab, a value of $n = 0.5$ indicates Fickian diffusion and a value of $n = 1$ implies Case II (relaxation-controlled) transport; values of n between these limits define anomalous transport. A value of n greater than 1 defines Super Case II transport. For ordinary diffusion, Fick's law is the appropriate constitutive equation for the mass transfer flux, and a mutual diffusion coefficient can be defined relative to the polymer-fixed frame of reference.[13,14] For a plane sheet, the diffusion coefficient D can be calculated from the following equation[14]:

$$M_t/M_\infty = 1 - \sum_{n=0}^{\infty} \{8/(2n+1)^2\pi^2\} \times \exp\{-(2n+1)^2\pi^2(Dt/L^2)\} \qquad (2)$$

where t is time and L is the initial thickness of the sheet. Although this equation is readily evaluated using a spreadsheet program, it is instructive to examine the short-time limiting expression as well[14]:

$$M_t/M_\infty = (4/\pi^{0.5})(Dt/L^2)^{0.5} \qquad (3)$$

The appearance of the dimensionless time group (Dt/L^2) in these equations indicates that a plot of M_t/M_∞ vs. $\sqrt{t}/L$ will yield a single master curve (referred to as a "diffusion plot") that is independent of sample dimension and initially linear. The thickness dependence is a valuable means of identifying the transport mechanism, since Case II transport will scale with t/L and anomalous transport may have a complex dimensional dependence.

EXPERIMENTAL

Materials

Ophthalmic grade 2-hydroxyethyl methacrylate (Polysciences) was further purified by vacuum distillation at 67°C and 3.5 mmHg. Cuprous chloride was added to the distillation flask to inhibit polymerization during the distillation. The top and bottom 20% fractions were discarded. The middle 60% was stored in a dark glass bottle at 4°C prior to polymer synthesis. Potassium sulfopropylmethacrylate (PSPMA) (Polysciences), ethylene glycol dimethacrylate (EGDMA) (Aldrich), and benzoyl peroxide (Aldrich) were used as received. PSPMA and 0.5 wt % of the initiator benzoyl peroxide were

dissolved in the purified HEMA; in some cases, EGDMA was also added to the solution. The solution was deaerated in a vacuum desiccator at 3 mmHg for 15 min. The polymerization mold consisted of two polypropylene plates separated by a silicon rubber gasket and held together by clamps; the solution was injected into the mold through a hole in one of the polypropylene plates. The mold was then put into a vacuum oven (NAPCO, Model 5831), and polymerization was carried out at 60°C and 25 mmHg for 24 h. The thickness of the glassy polymer sheet obtained was equal to the thickness of the silicon rubber gasket.

The glassy polymer sheet was then swollen in distilled water and cut into smaller square portions with a razor blade; the aspect ratio (length : thickness) was kept greater than 10 so that one-dimensional transport could be assumed. Most swollen samples were dried in the vacuum oven at 60°C and 10 mmHg for 24 h. Samples could also be dried at constant area using an electrophoresis gel dryer (Bio-Rad, Model 543); drying took 24 h at 60°C and 5 mmHg.

Glass transition measurements were made using a Perkin–Elmer differential scanning calorimeter (Model DSC 7) in conjunction with a Perkin–Elmer TAC 7 instrument controller and a Perkin–Elmer 7500 professional computer. The sample was heated at a rate of 20°C/min from 30 to 200°C. The glass transition temperature was then determined from the thermogram using the Perkin–Elmer TAS 7 software package.

Swelling Measurements

Dynamic swelling measurements were made primarily by gravimetric means. The polymer sample was immersed in excess deionized water (Fisher Scientific) at 23°C for a period of time, then removed after an appropriate interval, blotted free of surface moisture with filter paper (Whatman No. 40), weighed using a Mettler analytical balance (Model AE 200, accuracy ±0.0001 g), and then returned to the water. This procedure was repeated until the sample attained constant weight. This simple technique yielded excellent results as the amount of time spent out of the solvent was negligible and the blotting could be done reproducibly, within 3%.

In some cases, solvent front movement was also measured. The polymer sample was immersed in water and held under a stereomicroscope (Olympus, Model SZH-ILLD) with a clip such that the edge of the sample was seen; the moving solvent front was observed under polarized light. The distance moved by the front with time was measured using a digital Filar eyepiece (LASICO, Los Angeles, CA) in conjugation with a processor (LASICO, Model XM). This system was also used to measure dimensional changes in samples.

RESULTS AND DISCUSSION

Effect of Sample History

Poly(HEMA-*co*-PSPMA) may contain residual initiator, unreacted monomer, and a diffusible sol fraction. The presence of these materials adds to the osmotic swelling pressure of the polymer until they diffuse out, thus altering the swelling kinetics observed. Also, for use in drug delivery systems, polymers must be free of such impurities. These impurities can be leached from the polymer sheets by swelling them in water. Thus, it is necessary to determine if leaching cycles have an effect on subsequent swelling behavior. Therefore, poly(HEMA-*co*-PSPMA) with 3 wt % PSPMA was removed from the mold, allowed to swell to equilibrium in water, dried in a vacuum oven, allowed to swell again, redried, and then allowed to swell for the third time. Figure 1 indicates that swelling kinetics do not change significantly over three swell/dry cycles. The equilibrium swelling degree does fall by 6% between

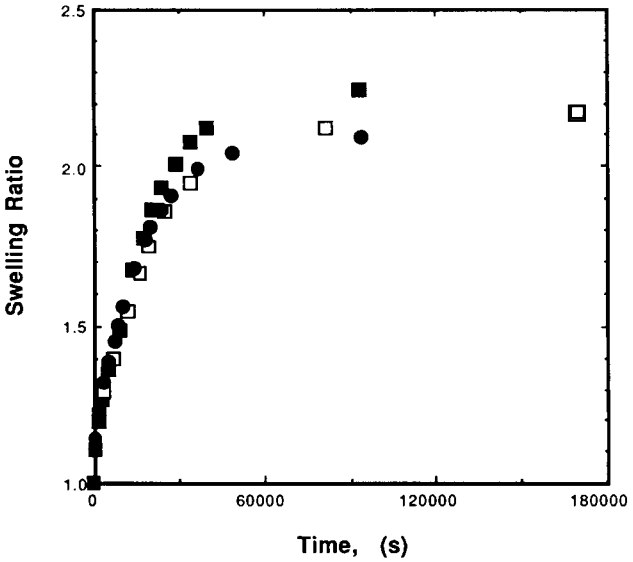


Figure 1 Water sorption rates of initially glassy poly(HEMA-*co*-PSPMA) with 3 wt % PSPMA after repeated cycles of swelling and drying in a vacuum oven. The sorption rate is not a function of cycle number. (■) First swelling; (□) second swelling; (●) third swelling.

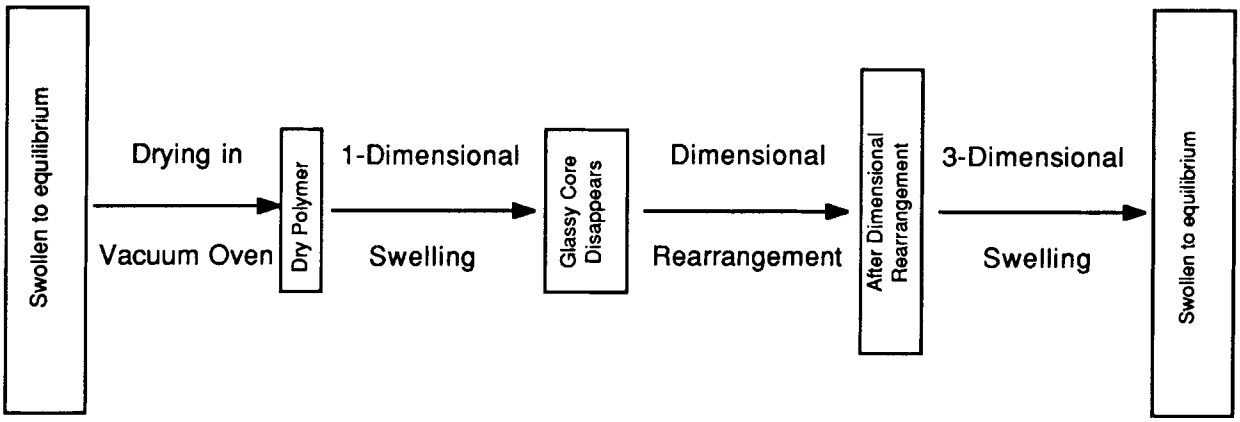


Figure 2 The schematic representation of the dimensional changes that occur upon swelling in a solvent of an isotropically dried (or never-swollen bulk polymerized) polymer sample.

the first and second cycles and by 3% between the second and third cycles. This may be due to the slow loss of soluble materials from the polymer.

Upon drying in the vacuum oven, a swollen polymer sheet shrinks isotropically to a dry, virtually stress-free state. When a sample thus dried is swollen in a solvent, it initially swells only in the direction of diffusion, as the inner glassy core resists expansion in area.[3] Therefore, as long as the glassy core is present, the polymer expands only in the thickness while the area remains constant. This causes anisotropic stress to develop in the sample; it is tensile perpendicular to the direction of diffusion and compressive in the direction of diffusion. Therefore, once the restraining glassy core is gone, the built-up stress is relieved by an expansion in area at the expense of thickness. Although this process takes a finite time, it occurs rapidly with respect to the total swelling time. Once the anisotropic stresses are relieved and the rearrangement of dimensions is complete, the polymer sample swells isotropically until equilibrium is reached. Figure 2 is the schematic representation of these dimensional changes.

These dimensional changes upon swelling can be controlled by introducing anisotropic stress into the initially dry sample. This can be done by swelling the sample to equilibrium, then drying it in a gel dryer—a device designed to dry gel electrophoresis gel slabs without allowing a contraction in area. Thus, a gel dryer-dried sample has an area that is greater and a thickness that is less than the isotropically dried, stress-free sample. Hence, anisotropic stresses must be present in order to maintain these

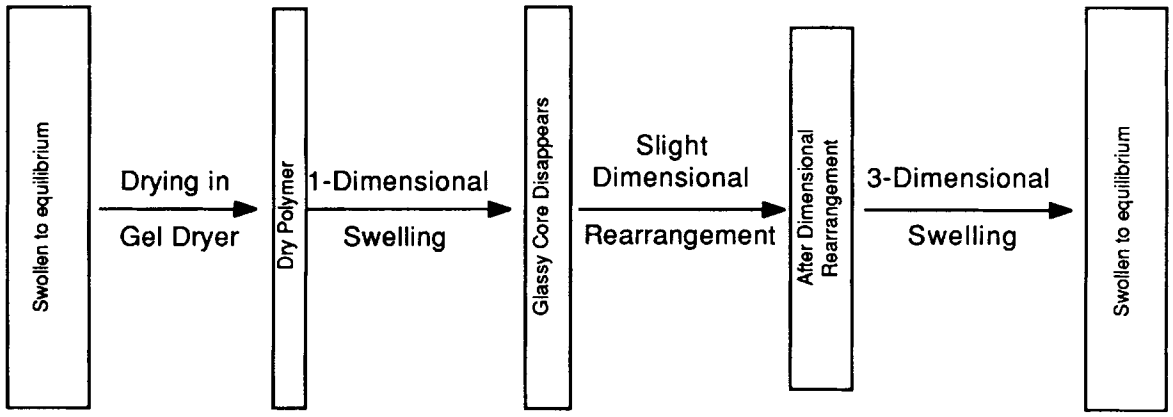


Figure 3 The schematic representation of the dimensional changes that occur upon swelling in a solvent of a polymer sample dried anisotropically at constant area in a gel dryer.

dimensions: stress that is tensile in direction of thickness and compressive in the direction perpendicular to thickness. Only because the dry polymer is glassy does this stress not cause the dimensions to change; upon annealing above T_g, samples dried in this fashion contract in area and increase in thickness, returning to the dimensions of an isotropically dried sample.

When this gel dryer-dried sample is swollen, it swells only in thickness as long as the glassy core is present, just like the isotropically, vacuum oven-dried sample. Unlike an initially isotropic sample, however, in this case swelling tends to *relieve* stress instead of causing it to build up. Thus, when the glassy core vanishes, only a slight rearrangement of dimensions occurs and in the opposite direction of the ordinary isotropically dried case; that is, the thickness increases slightly at the expense of area (since the sample area at this stage is equal to the fully swollen area). Swelling of the wholly rubbery sample is, again, virtually isotropic. Overall, the net effect is nearly one-dimensional swelling from the dry state to the swollen equilibrium state. The schematic representation of dimensional changes upon swelling of a gel dryer-dried sample is given in Figure 3. Experimentally, these differences in the dimensional changes for the differently prepared samples are demonstrated in Figure 4.

Despite these dramatic differences in dimensional

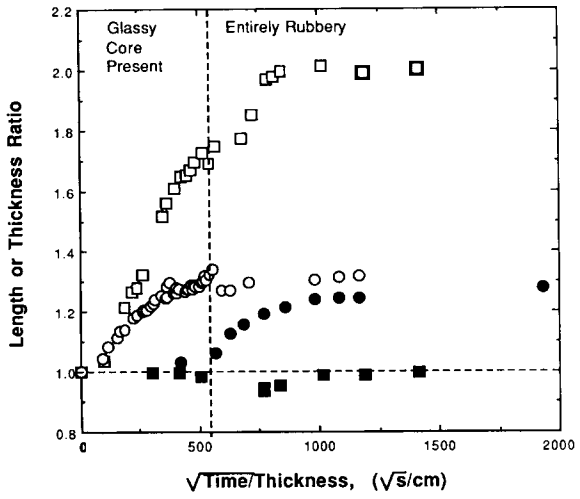


Figure 4 The dimensional changes upon swelling of initially isotropic, vacuum oven-dried and initially anisotropic, gel dryer-dried samples of poly(HEMA-*co*-PSPMA) with 3 wt % PSPMA. (□) Thickness ratio for gel dryer-dried sample; (■) length ratio for a gel dryer-dried sample; (○) thickness ratio for a vacuum oven-dried sample; (●) length ratio for a vacuum oven-dried sample.

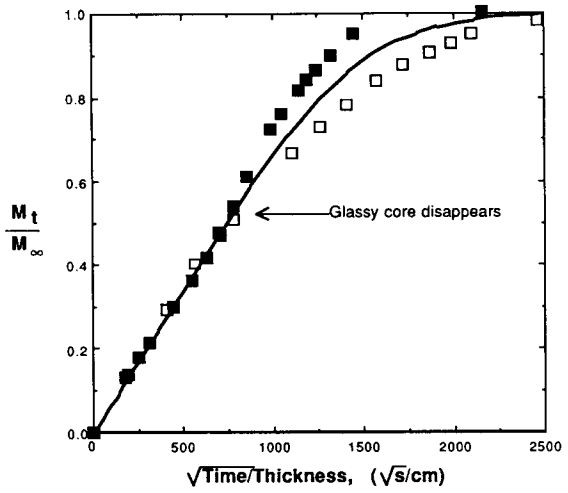


Figure 5 Water sorption rates of poly(HEMA-*co*-PSPMA) with 3 wt % PSPMA, shown on a diffusion plot. Anisotropic stress affects the swelling rate by causing dimensional changes. (□) Gel dryer-dried sample, 1 = 0.85 mm; (■) vacuum oven-dried sample, 1 = 1.33 mm; (---) Fickian diffusion curve with $D = 9 \times 10^{-8}$ cm^2/s.

change, when the sorption data of both vacuum oven-dried and gel dryer-dried samples are plotted on a diffusion plot, the curves for both samples are virtually identical while the glassy core is present, as shown in Figure 5. To this point, they match a classical Fick's law curve with a characteristic diffusion coefficient of $9 \pm 2 \times 10^{-8}$ cm^2/s [obtained by fitting eq. (2) to the sorption data up to the point that the glassy core vanishes]. This characteristic diffusion coefficient is not the rigorous diffusion coefficient defined in eq. (2), since the dimensional changes violate the boundary conditions under which this equation was derived. Nonetheless, this is a useful means of quantifying the swelling rate while the glassy core is present. After the disappearance of the glassy core, the curves separate.

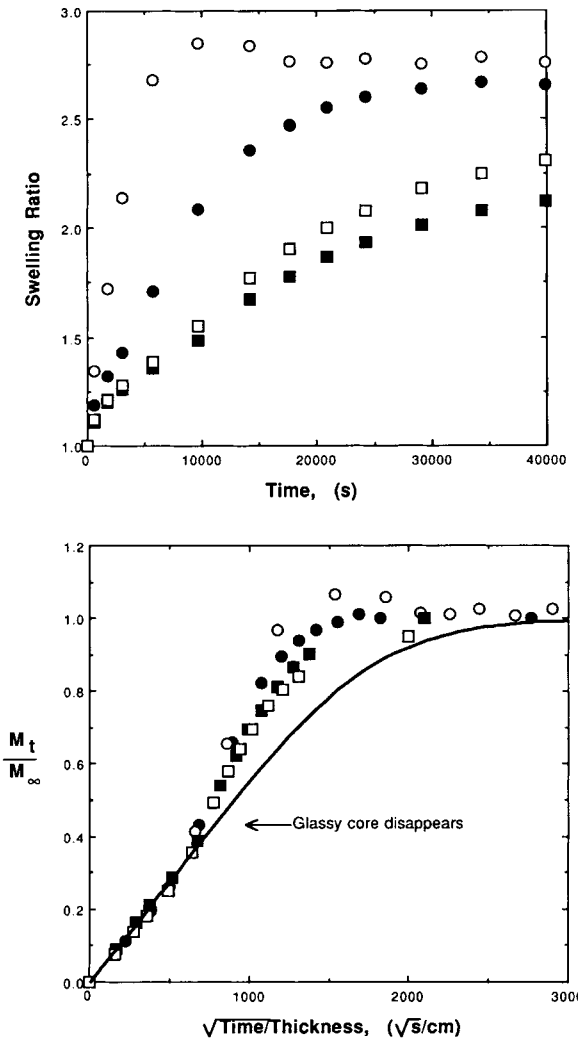
For the isotropic, vacuum oven-dried sample, the experimental data rise above the Fickian diffusion curve: an acceleration in the swelling rate. An acceleration in the swelling rate in the terminal phase of swelling sheets has been termed "Super Case II acceleration."[15-18] Late-stage acceleration has been explained as resulting from the overlap in the middle of the sheet of Fickian precursors to Case II concentration profiles, which then amplify the rate processes controlling the sorption.[15] Another explanation is based on the change in the dimensionality of the process from a constrained, one-dimensional problem to an unconstrained three-dimensional one.[17,18] Here, the data can be explained by carefully considering the effect on the sorption rate that the

dimensional rearrangements after the disappearance of the glassy core will have. For the initially isotropic sample, the dimensional rearrangement causes the thickness of the polymer—the diffusional path length—to decrease and the diffusional area to increase. Both of these effects, in and of themselves, serve to accelerate the sorption rate. Thus, even though the sorption curve deviates from the classical Fickian diffusion curve after the disappearance of the glassy core, there is no need to assume nonclassical diffusive transport mechanisms.

This argument is further supported by the observed deceleration in swelling rate after the disappearance of glassy core for the anisotropic gel dryer-dried samples. As discussed above, in this case, the thickness increases slightly at the expense of area. These effects act to slow swelling, causing the data to fall below the Fickian curve in the terminal phase of swelling. We believe that late-stage acceleration due to dimensional rearrangements should be clearly distinguished from truly non-Fickian transport mechanisms resulting from more complex interactions between polymer relaxation and diffusion.[19] The equilibrium degree of swelling for vacuum oven-dried sample (second swelling) and gel dryer-dried sample (third swelling) were 2.15 ± 0.06 and 2.00 ± 0.06, respectively. The small decline in the degree of swelling upon reswelling may be due to the slow loss of soluble materials from the polymer.

Effect of Ionic Comonomer

The degree of swelling (swollen weight/dry weight) of poly(HEMA-*co*-PSPMA) in water at 23°C increases from 1.56 ± 0.06 to 2.74 ± 0.11 as the amount of PSPMA increased from 0 to 8 wt % of the monomer present at the time of polymerization. This increase in swelling is mainly due to the osmotic swelling pressure of the ions in the polymer.[20] The degree of swelling observed substantially exceeds the degrees predicted by current thermodynamic theory of polymer swelling but is consistent with the results observed by Kudela et al. in an equilibrium swelling study of copolymers of HEMA and 2-sulfooxyethyl methacrylate.[12] Figure 6(a) shows that the sorption rate increases as the degree of swelling increases. When these data are replotted on a diffusion plot [Fig. 6(b)], all the samples follow a common curve while the glassy core is present; this portion of the curve can be characterized with a diffusion coefficient of $6 \pm 2 \times 10^{-8}$ cm^2/s. After the disappearance of the glassy core, the experimental data lie above the Fickian curve due to the dimensional rearrangements. The deviation from the Fickian curve increases as the sample thickness decreases; the thinnest sample also exhibited an equilibrium overshoot, something that has been observed by other investigators.[2,10] These results show that the sorption rate of these hydrogels is proportional to the degree of swelling and inversely proportional to square of the thickness. The fact that the distance penetrated by the solvent front increases with square root of time, as shown in Figure 7, is additional evidence of diffusion-controlled transport.



Figures 6 (a, b) Water sorption rates of poly(HEMA-*co*-PSPMA) gels with different amounts of PSPMA given both as swelling ratio (swollen mass/dry mass) against time (a) and on a diffusion plot (b). Increasing the amount of ionic comonomer increases the equilibrium degree of swelling and the water sorption rate without changing the time for equilibration or the transport mechanism. (■) 3 wt % PSPMA, 1 = 1.55 mm; (□) 4 wt % PSPMA, 1 = 1.53 mm; (●) 6 wt % PSPMA, 1 = 1.1 mm; (○) 8 wt % PSPMA, 1 = 0.64 mm; (---) Fickian diffusion curve with $D = 6 \times 10^{-8}$ cm^2/s.

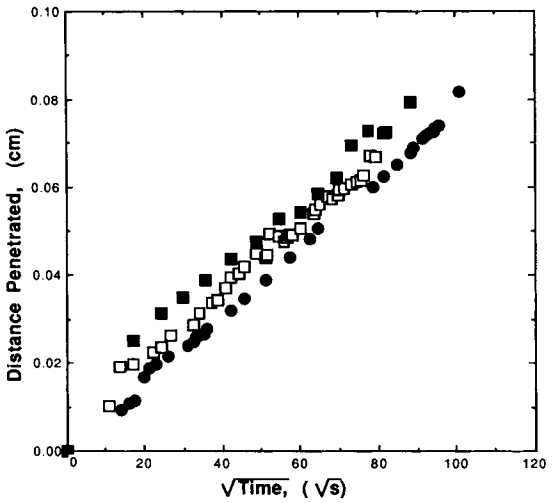


Figure 7 Movement of the solvent front in glassy poly(HEMA-*co*-PSPMA). The linear advance against the square root of time indicates Fickian diffusion. (●) 0 wt % PSPMA, 1 = 1.63 mm; (□) 3 wt % PSPMA, 1 = 1.45 mm; (■) 4 wt % PSPMA, 1 = 1.58 mm.

Thus, the degree of swelling and sorption rate of poly(HEMA-*co*-PSPMA) can be modified in a controlled fashion without altering the rate of approach to equilibrium or the transport mechanism of sorption, simply by adjusting the fraction of the ionic comonomer PSPMA.

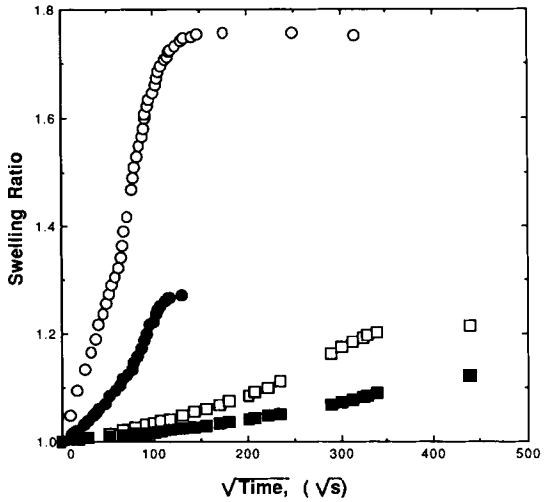


Figure 8 Water sorption rates of poly(HEMA-*co*-PSPMA) with 3 wt % PSPMA and different levels of cross-linking with EGDMA. Increasing the amount of cross-linking reduces the degree of swelling and the water sorption rate, increases the equilibration time, and shifts the transport mechanism from ordinary diffusion to anomalous transport. (○) 0.02 mol fraction EGDMA, 1 = 0.82 mm; (●) 0.12 mol fraction EGDMA, 1 = 0.52 mm; (□) 0.17 mol fraction EGDMA, 1 = 1.49 mm; (■) 0.30 mol fraction EGDMA, 1 = 1.46 mm.

Effect of Cross-Linking

The equilibrium and dynamic swelling behavior of hydrogels can also be modified by varying the degree of cross-linking. From Figure 8, it is readily apparent that increasing the amount of the cross-linker EGDMA in copolymers of HEMA and 3 wt % PSPMA not only reduces the equilibrium swelling degree in water at 23°C, but also the sorption rate and the rate of approach to equilibrium. The increasing deviation of the curves from initial linearity is indicative of increasingly anomalous transport (transport exponents greater than 0.5). This is consistent with results of swelling of cross-linked PHEMA by other investigators.[7,8] Thus, increasing cross-linking density can be used to reduce the degree of swelling of the polymer, in contrast to the effect of the ionic comonomer. In a marked contrast to the effect of ionic comonomer, however, we find that cross-linking not only modifies the degree of swelling and the sorption rate, but also alters the rate of approach to equilibrium and the sorption transport mechanism. From Table I, it is readily apparent that increasing the amount of the cross-linker EGDMA in copolymers of HEMA and 3 wt % PSPMA increases T_g. Thus, increased cross-linking affects the swelling rates in a more complex way than does increased ionic comonomer, since cross-linking also acts to increase the polymer's T_g and alters its relaxational and diffusional characteristics, unlike the ionic comonomer.

CONCLUSIONS

Previous swell/dry cycles have little effect on the swelling kinetics of glassy poly(HEMA-*co*-PSPMA)

Table I Properties of Terpolymers of HEMA, 3 wt % PSPMA, and the Cross-Linker EGDMA

Mole Fraction EGDMA	T_g (°C)	Transport Exponent n
0.00	96 ± 4	0.47 ± 0.02
0.02	97 ± 4	0.49 ± 0.02
0.12	158 ± 5	0.55 ± 0.05
0.17	171 ± 5	0.60 ± 0.05
0.30	190 ± 5	0.68 ± 0.16

Increasing the amount of the cross-linker increases T_g and the transport exponent "n" (95% confidence intervals given).

gels in water. However, the method of drying the swollen samples strongly affects the dimensional changes that occur upon disappearance of the glassy core, which do alter the sorption kinetics. For an isotropically dried sample, swelling while the glassy core is present results in an increase in thickness at constant area. Once the glassy core disappears, the anisotropic stresses that have built up cause the area to increase at the expense of thickness; this causes an acceleration in the swelling rate. If the sample is dried anisotropically, maintaining a constant area, one-dimensional swelling while the glassy core is present relieves stress. Therefore, disappearance of the core increases the thickness slightly at the expense of the area, causing a slight deceleration in the swelling rate. Thus, changes in swelling rates in the terminal phase of swelling can be interpreted without the need to consider nondiffusive transport mechanisms.

The equilibrium and dynamic swelling properties of PHEMA in water can be modified by copolymerization with an ionic comonomer (PSPMA) or cross-linker (EGDMA). An increase in cross-linking reduces the equilibrium degree of swelling, sorption rate, and rate of approach to equilibrium and shifts transport mechanism from Fickian to anomalous at high levels. Thus, cross-linking PHEMA changes its swelling behavior in a complex fashion because cross-linking directly affects many other properties of the polymer besides swelling. In contrast, a small amount of ionic comonomer can be used to increase the degree of swelling without affecting the transport mechanism, which is diffusion-controlled for all the PSPMA copolymers tested, or the rate of approach to equilibrium (characteristic diffusion coefficient $D = 6 \pm 2 \times 10^{-8}$ cm^2/s). As a result, the sorption rate increases in proportion to the degree of swelling and decreases with the square of the sample thickness.

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