Dynamic Swelling Behavior of pH-Sensitive Anionic Hydrogels Used for Protein Delivery

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ABSTRACT: There have been many attempts to use anionic hydrogels as oral protein delivery carriers because of their pH-responsive swelling behavior. The dynamic swelling behavior of poly(methacrylic acid-*co*-methacryloxyethyl glucoside) and poly(methacrylic acid-*g*-ethylene glycol) hydrogels was investigated to determine the mechanism of water transport through these anionic hydrogels. The exponential relation $M_t/M_\infty = kt^n$ (where M_t is the mass of water absorbed at time t and M_∞ is the mass of water absorbed at equilibrium) was used to calculate the exponent (n) describing the Fickian or non-Fickian behavior of swelling polymer networks. The mechanism of water transport through these gels was significantly affected by the pH of the swelling medium. The mechanism of water transport became more relaxation-controlled in a swelling medium of pH 7.0, which was higher than pK_a of the gels. The experimental results of the time-dependent swelling behaviors of the gels were analyzed with several mathematical models. © 2003 Wiley Periodicals, Inc. J Appl Polym Sci 89: 1606–1613, 2003

Key words: hydrogels; drug delivery systems; diffusion

INTRODUCTION

When a hydrophilic, crosslinked polymer network is brought into contact with a compatible penetrant (e.g., water), the penetrant enters the polymer network, and this results in a swollen gel phase (hydrogel). If a solute (drug) is incorporated into the glassy polymer network, the solute is released.[1–3] There have been many efforts to make use of this process of water penetration and subsequent solute release in polymer materials for controlled drug delivery systems. Swellable polymers have received considerable attention for the oral delivery of therapeutic proteins because they show the ability to release drugs at a zero-order rate and to target proteins to specific sites, such as the upper small intestine, which extends their biological activity.[4–12]

In swelling-controlled-release systems, drug transport through the polymer network is controlled by the relative ratio of the polymer relaxation occurring as the polymer network absorbs water and the drug diffusion across the associated water concentration gradient.[13,14] In these systems, the polymer relaxation by penetrant sorption plays an important role in drug release. Therefore, many studies of the transport mechanism and penetration rate of the penetrant in polymeric materials have been performed.[15–17]

In this work, we used two crosslinked copolymers, poly(methacrylic acid-*co*-methacryloxyethyl glucoside) [P(MAA-*co*-MEG)] and poly(methacrylic acid-*g*-ethylene glycol) [P(MAA-*g*-EG)], to determine the mechanism of penetrant transport through anionic hydrogels. Anionic hydrogels are three-dimensional polymer networks that are capable of swelling by absorbing large amounts of water or aqueous solvents, and their swelling behavior can be dependent on changes in external environmental conditions, such as the pH, ionic strength, solvent composition, and temperature. In particular, anionic hydrogels exhibit a drastic change in swelling that depends on the environmental pH change; this makes them suitable candidates for oral protein systems.[18–23] This pH-responsive swelling behavior is due to ionization of the functional groups in the gels, which depends on the pH of the surrounding medium. This ionization significantly affects the penetrant transport mechanism of the polymer networks.[16,24] In anionic hydrogels, an increase in the degree of ionization contributes to electrostatic repulsion between charged groups and, therefore, swells the gels to a high degree. Then, highly swollen hydrogels contain large amounts of unbound water, which allows greater solute release.

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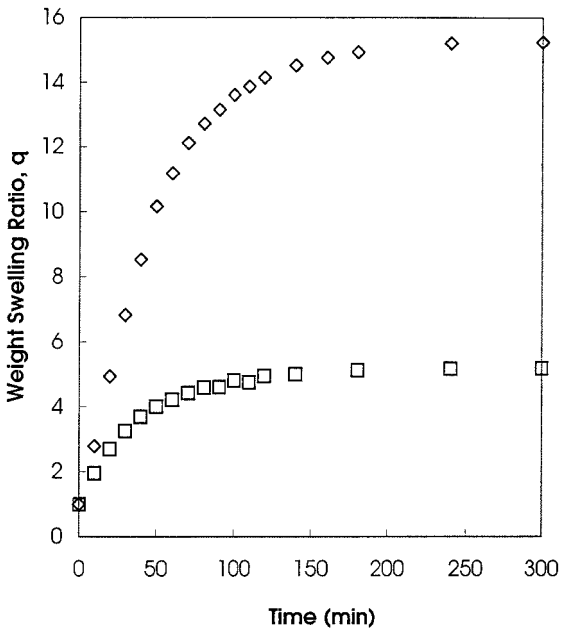

Figure 1 Dynamic swelling of P(MAA-*co*-MEG) samples with 1:1 MAA/MEG swollen in buffered solutions with (□) pH 2.2 and (◇) pH 7.0 at 37°C.

We studied the dynamic swelling behavior of the anionic hydrogels to investigate the effect of the pH of the swelling medium and copolymer compositions on the penetrant transport. Emphasis was given to the dependence of the penetrant transport mechanism on the ionization of the functional groups in the polymer networks. In addition, the time-dependent swelling behavior of the polymer networks was analyzed with several mathematical models.

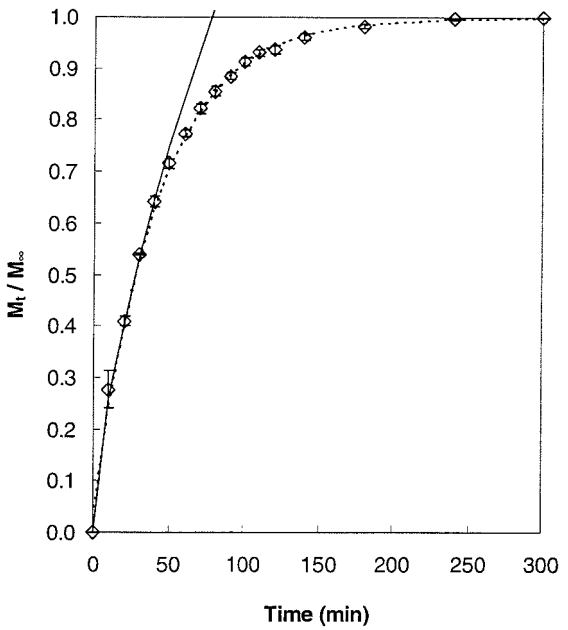

Figure 2 M_t/M_∞ of P(MAA-*co*-MEG) samples with 4:1 MAA/MEG swollen in a pH 2.2 buffer solution at 37°C: (◇) experimental data, (—) eq. (2), and (…) eq. (4) (average ± standard deviation, $n = 3$).

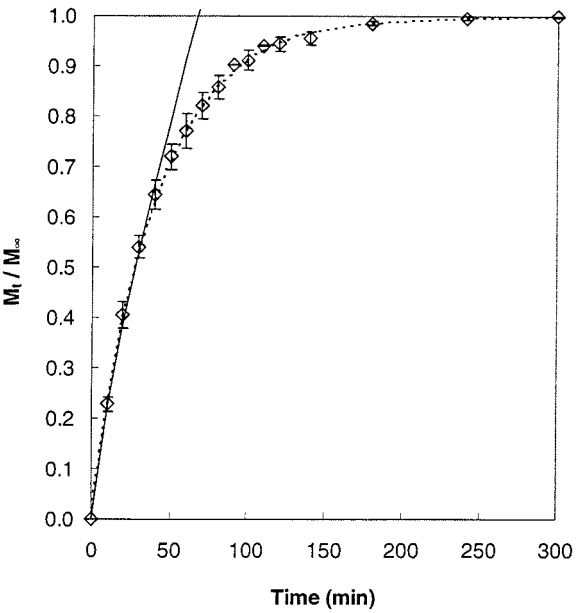

Figure 3 M_t/M_∞ of P(MAA-*co*-MEG) samples with 1:1 MAA/MEG swollen in a pH 2.2 buffer solution at 37°C: (◇) experimental data, (—) eq. (2), and (…) eq. (4) (average ± standard deviation, $n = 3$).

EXPERIMENTAL

Hydrogel synthesis

The copolymer of methacrylic acid (MAA) and 2-methacryloxyethyl glucoside (MEG), designated

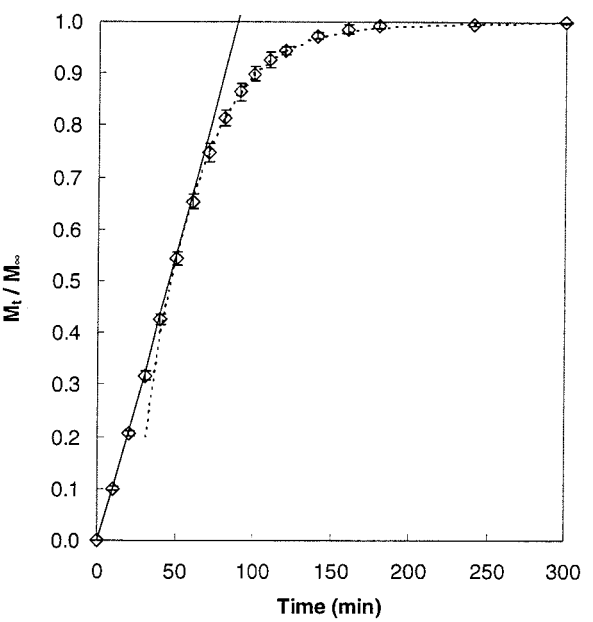

Figure 4 M_t/M_∞ of P(MAA-*co*-MEG) samples with 4:1 MAA/MEG swollen in a pH 7.0 buffer solution at 37°C: (◇) experimental data, (—) eq. (2), and (…) eq. (4) (average ± standard deviation, $n = 3$).

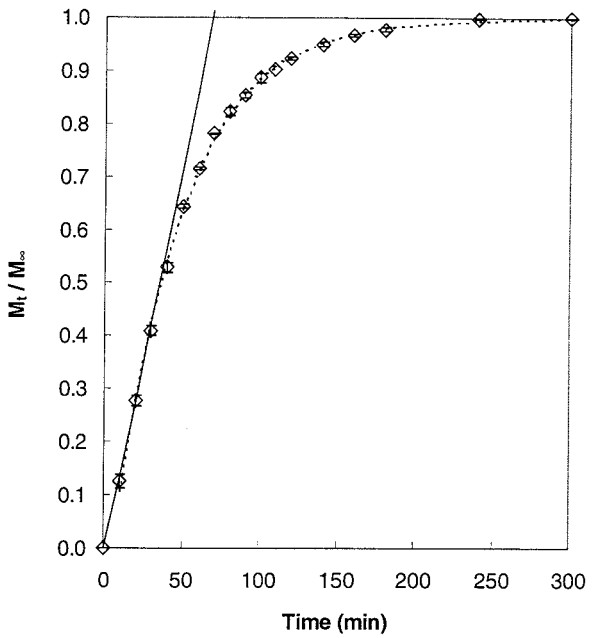

Figure 5 M_t/M_∞ of P(MAA-*co*-MEG) samples with 1:1 MAA/MEG swollen in a pH 7.0 buffer solution at 37°C: (◇) experimental data, (—) eq. (2), and (…) eq. (4) (average ± standard deviation, $n = 3$).

P(MAA-*co*-MEG), and the copolymer of MAA and poly(ethylene glycol) monomethyl ether monomethacrylate (PEGMA), designated P(MAA-*g*-EG), were prepared by free-radical photopolymerization. MAA (Polysciences, Warrington, PA) was distilled under vacuum before use to remove an inhibitor, whereas MEG (Polysciences) and PEGMA (Polysciences) were used as received. Tetra(ethylene glycol) dimethacrylate (TEGDMA; Polysciences) was used as a crosslinking agent without further purification.

To initiate the reaction, we used 1-hydroxycyclohexyl phenyl ketone (Irgacure 184, Ciba–Geigy, Hawthorne, NY) as a UV-light sensitive initiator. Monomers with feed compositions (molar ratio) of 1:1, 1:2, 1:4, and 0:1 MEG/MAA for P(MAA-*co*-MEG) hydrogels and of 1:1 ethylene glycol (EG)/MAA for P(MAA-*g*-EG) hydrogels with various molecular weights of PEGMA (300, 500, and 1100) were mixed. In each set of monomer mixtures, TEGDMA was added in the amount of 1.2 mol % of the total monomers. The initiator was added in the amount of 0.1 wt % of the total monomers, and then these mixtures were diluted to 60 wt % of the total monomers with a 1:1 (w/w) mixture of ethanol and water. After the complete dissolution of the monomers, crosslinking agent, and initiator, nitrogen was bubbled through the mixture for 15 min for the removal of dissolved oxygen that would act as an inhibitor for the reaction. The mixture was cast between glass slides to form films. The mixture was exposed to UV light (intensity = 15.0 ± 0.5 mW/cm^2) for 30 min in a nitrogen environment.

Synthesized hydrogel films were cut into disks 1 mm thick and 1 cm in diameter. The disks were placed in deionized water for 7 days, with the water changed every 12 h for the removal of any unreacted monomers, crosslinking agent, and initiator. Then, the disks were dried in air for 1 day and placed in a vacuum oven at 25°C until their weight remained constant within 0.1 wt % over 24 h. The hydrogel disks were stored in a desiccator for future use. The kinetics of such polymerizations have been discussed extensively.[25–27]

Dynamic swelling experiments

To determine the dynamic swelling behavior, we weighed and placed dried hydrogel disks in phosphate citrate buffer solutions with pH values of 2.2 and 7.0 at 37°C. The ionic strength of each buffer solution was adjusted to 0.5*M* by the addition of potassium chloride. The disks were taken out of the buffer, blotted for the removal of surface water, and weighed at specified time intervals

The swelling of the network can be expressed by the weight swelling ratio q:

$$q = \frac{W_s}{W_d} \tag{1}$$

where W_s is the weight of the swollen hydrogel and W_d is the weight of the initially dried hydrogel.

TABLE I
Parameters n and k_1 of Eq. (2) for P(MAA-*co*-MEG) Hydrogels with Various Molar Ratios of MEG and MAA and Swollen in pH 2.2 and 7.0 Buffer Solutions at 37°C (Average ± Standard Deviation, $n = 3$)

Sample MEG/MAA (molar ratio)	n		$k_1 \times 10^2$ (min^{-n})	
	pH 2.2	pH 7.0	pH 2.2	pH 7.0
1:1	0.79 (±0.04)	1.05 (±0.07)	3.61 (±0.24)	1.18 (±0.30)
1:2	0.69 (±0.04)	1.06 (±0.07)	5.02 (±0.69)	1.03 (±0.21)
1:4	0.67 (±0.03)	1.05 (±0.01)	5.43 (±0.43)	0.91 (±0.04)
0:1	0.72 (±0.01)	1.05 (±0.03)	5.20 (±0.04)	0.71 (±0.09)

TABLE II
Parameters A and k_2 of Eq. (4) for P(MAA-*co*-MEG) Hydrogels with Various Molar Ratios of MEG and MAA and Swollen in pH 2.2 and 7.0 Buffer Solutions at 37°C (Average ± Standard Deviation, n = 3)

Sample MEG/MAA (molar ratio)	A		$k_2 \times 10^2$ (min^{-1})	
	pH 2.2	pH 7.0	pH 2.2	pH 7.0
1:1	0.96 (±0.03)	1.12 (±0.03)	2.41 (±0.24)	2.27 (±0.05)
1:2	0.96 (±0.02)	1.52 (±0.08)	2.45 (±0.13)	2.89 (±0.16)
1:4	0.95 (±0.00)	1.93 (±0.17)	2.35 (±0.12)	2.94 (±0.18)
0:1	0.99 (±0.00)	4.90 (±0.94)	3.12 (±0.30)	3.61 (±0.13)

RESULTS AND DISCUSSION

Dynamic swelling behavior of P(MAA-*co*-MEG) hydrogels

In previous studies,[28,29] we observed that P(MAA-*co*-MEG) networks exhibited pH-responsive swelling behavior and that the carboxylic acid groups of MAA became ionized at higher pH values than pK_a of the polymer (pH ~ 5).

To investigate the time-dependent swelling behavior of P(MAA-*co*-MEG) hydrogels, we performed dynamic swelling studies. The P(MAA-*co*-MEG) disks with various MAA and MEG compositions were tested in pH 2.2 and 7.0 buffer solutions. Figure 1 presents the q values of 1:1 MAA/MEG P(MAA-*co*-MEG) in pH 2.2 and 7.0 buffer solutions at 37°C as a function of time.

At pH 7.0, the amount of absorbed water in the polymer network was larger than that at pH 2.2 at the same time point. As the pH of the swelling medium was above pK_a of the gel, which was about 5 in these hydrogels, the ionization of the carboxylic acid groups of poly(methyl methacrylate) (PMAA) in the gel occurred. That resulted in a more hydrophilic polymer network and contributed to the higher water absorption.

The portion of the water absorption curve with a fractional water uptake (M_t/M_∞) less than 0.60 was analyzed[30] with the following equation:

$$\frac{M_t}{M_\infty} = kt^n \tag{2}$$

where M_t is the mass of water absorbed at time t, M_∞ is the mass of water absorbed at equilibrium, k_1 is a characteristic constant of the hydrogel, and n is a characteristic exponent describing the mode of the penetrant transport mechanism.

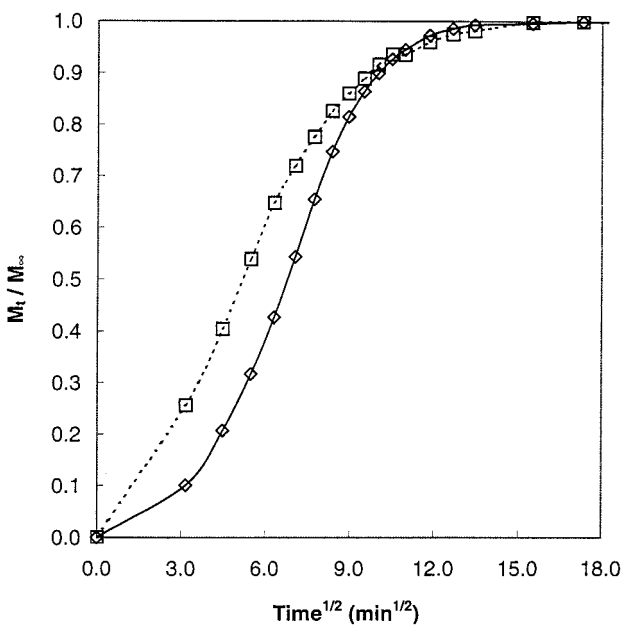

Figure 6 M_t/M_∞ of P(MAA-*co*-MEG) samples with 4:1 MAA/MEG as a function of the square root of time swollen in (□) pH 2.2 and (◇) pH 7.0 buffer solutions at 37°C.

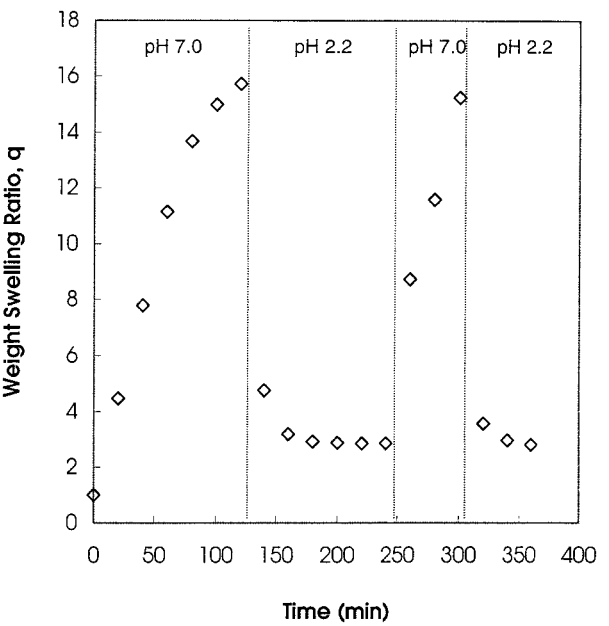

Figure 7 Dynamic swelling/deswelling behavior of P(MAA-*co*-MEG) samples with 4:1 MAA/MEG. The samples were placed in a pH 7.0 buffer solution at t = 0 min, in a pH 2.2 buffer solution at t = 120 min, in a pH 7.0 buffer solution at t = 240 min, and in a pH 2.2 buffer solution at t = 300 min,

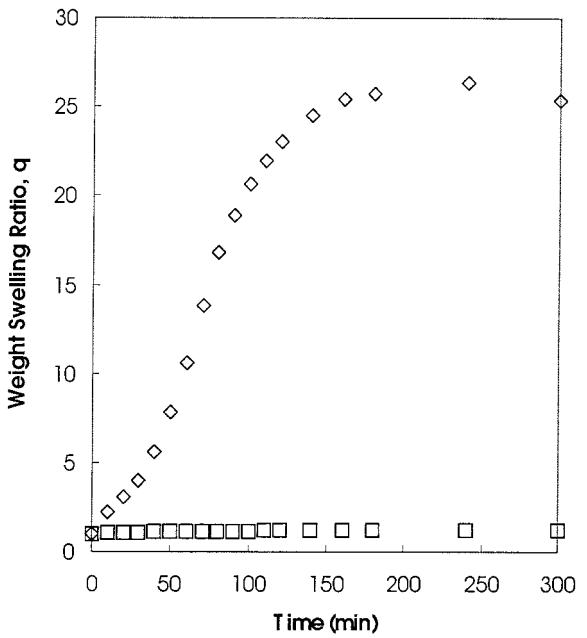

Figure 8 Dynamic swelling of P(MAA-*g*-EG) samples with a PEGMA molecular weight of 300 (1:1 EG/MAA) swollen in (□) pH 2.2 and (◇) pH 7.0 buffer solutions at 37°C.

For a film, $n = 0.5$ indicates Fickian diffusion, $n > 0.5$ indicates non-Fickian or anomalous transport, and $n = 1$ implies case II (relaxation-controlled) transport.

The constants n and k_1 were calculated from the slopes and intercepts of the plots of $\ln(M_t/M_\infty)$ versus $\ln t$ from the experimental data shown in Figures 2–5, and they are given in Table I. The same figures indicate the best fits of the data by the model of eq. (2) (indicated by continuous lines). The values of n at pH 7.0 were around 1, which indicated that the transport mechanism was case II (relaxation control), whereas at pH 2.2, the mechanism was non-Fickian transport.

The dynamic swelling behavior of crosslinked polymers is dependent on the relative contribution of penetrant diffusion and polymer relaxation. In ionic polymer networks, the polymer relaxation is significantly affected by the ionization of the functional groups of the polymer. An increase in the degree of ionization contributes to the electrostatic repulsion between adjacent ionized groups, leading to chain expansion, which, in turn, affects macromolecular chain relaxation. Therefore, the swelling mechanism becomes more relaxation-controlled as gel ionization becomes prominent. This explains why at pH 7.0 P(MAA-*co*-MEG) networks swelled by a relaxation-controlled mechanism. On the other side, at pH 2.2, the ionization was not significant, and there were no interactions between ionized functional groups. Therefore, the overall transport mechanism was not affected as much by relaxation, and the result was a combined non-Fickian (anomalous) transport with n values approaching Fickian (diffusion-controlled) behavior. However, the swelling mechanism of P(MAA-*co*-MEG) showed little dependence on the copolymer compositions at the same pH.

The previously discussed model, although adequately describing a major portion of the swelling behavior, fails to give an accurate analysis above $M_t/M_\infty = 0.60$. To obtain a better model after 60%, we assumed that for long periods the penetrant sorption was mainly dominated by relaxation of the polymer network and that the sorption process of the polymer by relaxation was first-order. Then, the Berens–Hopfenberg differential equation[31] for the relaxation process could be written as follows:

$$\frac{dM_t}{dt} = k_2(M_\infty - M_t) \tag{3}$$

where k_2 is the relaxation rate constant. The integration of eq. (3) leads to

$$\frac{M_t}{M_\infty} = 1 - A\ \exp(-k_2 t) \tag{4}$$

where A is a constant. In this studies, the constants A and k_2 were calculated from the slopes and intercepts of the plot of $\ln(1 - M_t/M_\infty)$ versus time t at times later than those corresponding to $M_t/M_\infty = 0.60$.

The calculated values of A and k_2 are listed in Table II. The experimental data and the fits with eq. (4) (indicated by dashed lines) are presented in Figures 2–5. The fractional sorption fits with eq. (4) for swelling at pH 2.2 (Figs. 2 and 3) and for the swelling of all hydrogels containing equimolar amounts of MAA and

TABLE III
Parameters n and k_1 of Eq. (2) for P(MAA-*g*-EG) Hydrogels with Various PEGMA Molecular Weights (1:1 EG/MAA) and Swollen in pH 2.2 and 7.0 Buffer Solutions at 37°C (Average ± Standard Deviation, $n = 3$)

Sample molecular weight of PEGMA	n		$k_1 \times 10^2$ (min^{-n})	
	pH 2.2	pH 7.0	pH 2.2	pH 7.0
300	0.50 (±0.07)	1.49 (±0.05)	8.40 (±1.72)	0.08 (±0.02)
500	0.54 (±0.13)	1.47 (±0.10)	7.74 (±2.47)	0.11 (±0.03)
1100	0.47 (±0.02)	1.48 (±0.04)	10.99 (±0.57)	0.14 (±0.06)

TABLE IV
Parameters A and k_2 of Eq. (4) for P(MAA-*g*-EG) Hydrogels with Various PEGMA Molecular Weights (1:1 EG/MAA) and Swollen in pH 2.2 and 7.0 Buffer Solutions at 37°C (Average ± Standard Deviation, $n = 3$)

Sample molecular weight of PEGMA	A		$k_2 \times 10^2$ (min^{-1})	
	pH 2.2	pH 7.0	pH 2.2	pH 7.0
300	0.85 (±0.18)	2.55 (±0.39)	1.46 (±0.36)	2.45 (±0.10)
500	0.96 (±0.11)	2.05 (±0.10)	1.87 (±0.08)	2.30 (±0.32)
1100	0.81 (±0.03)	1.99 (±0.04)	1.94 (±0.13)	2.57 (±0.47)

MEG at pH 7.0), Figure 5 shows nearly the same profile as that recorded experimentally at $M_t/M_\infty < 60\%$.

Plotting the fractional sorption data as functions of the square root of time provides valuable information for distinguishing between Fickian and case II transport mechanisms because the Fickian diffusion curve exhibits a monotonic inflection-free approach to equilibrium, whereas the case II curves are clearly sigmoidal.[15] Figure 6 presents M_t/M_∞ in P(MAA-*co*-MEG) networks as a function of the square root of time in buffers of pH 2.2 and pH 7.0. The difference in the curve shapes between pH 2.2 and pH 7.0 indicate that the swelling mechanism at the high pH value was closer to case II transport than that at the low pH value.

To investigate the reversibility of the swelling/deswelling process of the polymer networks with respect to the environmental pH change, we swelled selected hydrogel samples in a buffer solution of pH 7.0, placed them in a buffer solution of pH 2.2, returned them to a buffer solution of pH 7.0, and finally collapsed them in a buffer solution of pH 2.2. It was necessary for the swelling process to be reversible to ensure that the release of the solute could be initiated and stopped readily. Figure 7 shows the reversible swelling nature of the polymer network, which depended on external pH changes. It is evident from the plot that the swollen networks reverted to relatively collapsed networks whenever the pH decreased below pK_a of the gel and that the deswelling time was faster then the swelling time.

Dynamic swelling behavior of P(MAA-*g*-EG) hydrogels

Similar results were obtained for P(MAA-*g*-EG) copolymer hydrogels. It is shown in Figure 8 that the amount of water absorbed in the P(MAA-*g*-EG) networks at pH 7.0 was 20 times larger than that at pH 2.2. An analysis of M_t/M_∞ was carried out with eqs. (2) and (4). The values of n, k_1, A, and k_2 are given in Tables III and IV, as calculated from the experimental results shown in Figures 9–12. The swelling mechanism of P(MAA-*g*-EG) became more relaxation-controlled as the environmental pH changed from 2.2 to 7.0. At pH 2.2, the values of the exponent n were approximately 0.5, regardless of the molecular weight of the grafted poly(ethylene glycol). This indicated Fickian diffusion. At pH 7.0, the values of n were about 1.5. Also, the water transport mechanism of P(MAA-*g*-EG) showed little dependence on the molecular weight of grafted poly(ethylene glycol).

The fits of M_t/M_∞ with eqs. (2) and (4) are shown in Figures 9–12. For the P(MAA-*g*-EG) networks, plotting with eqs. (2) and (4) fitted the experimental data well until $M_t/M_\infty = 70\%$ and from $M_t/M_\infty = 30\%$, respectively.

The fractional sorption data of P(MAA-*g*-EG) as a function of the square root of time in pH 2.2 and pH 7.0 solutions are presented in Figure 13. As we expected, a curve for the pH 7.0 solution indicated that the swelling mechanism was closer to case II transport.

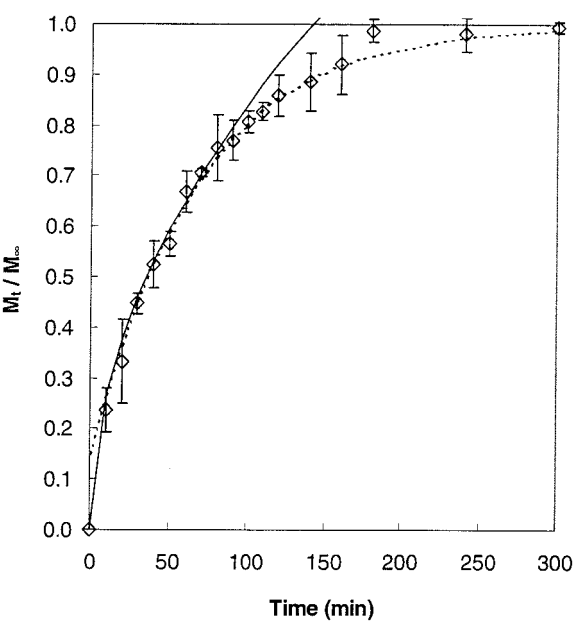

Figure 9 M_t/M_∞ of P(MAA-*g*-EG) samples with a PEGMA molecular weight of 300 (1:1 EG/MAA) swollen in a pH 2.2 buffer solution at 37°C: (◇) experimental data, (—) eq. (2), and (…) eq. (4) (average ± standard deviation, $n = 3$).

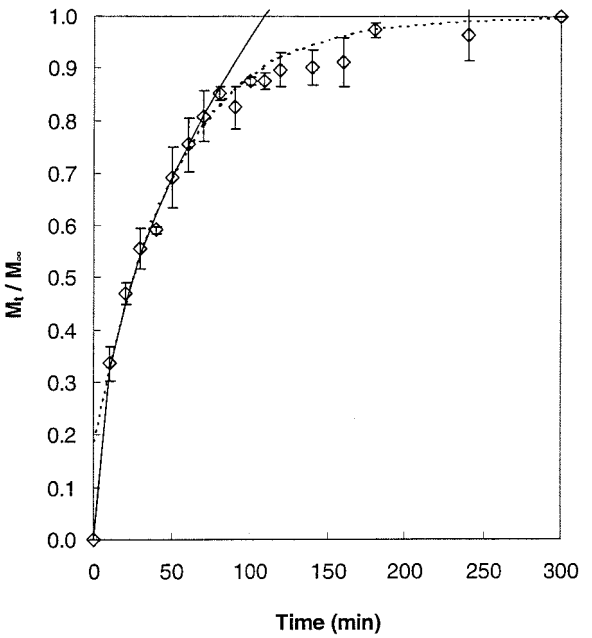

Figure 10 M_t/M_∞ of P(MAA-*g*-EG) samples with a PEGMA molecular weight of 1100 (1:1 EG/MAA) swollen in a pH 2.2 buffer solution at 37°C: (◇) experimental data, (—) eq. (2), and (…) eq. (4) (average ± standard deviation, $n = 3$).

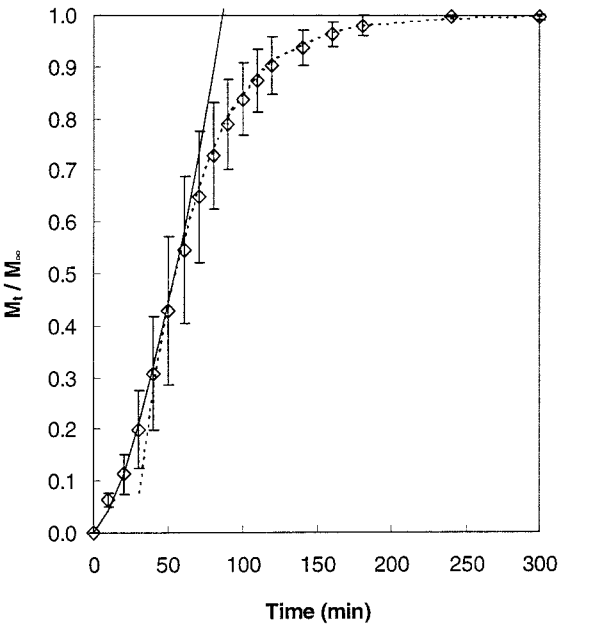

Figure 12 M_t/M_∞ of P(MAA-*g*-EG) samples with a PEGMA molecular weight of 1100 (1:1 EG/MAA) swollen in a pH 7.0 buffer solution at 37°C: (◇) experimental data, (—) eq. (2), and (…) eq. (4) (average ± standard deviation, $n = 3$).

CONCLUSIONS

The water transport mechanism through anionic hydrogels was significantly dependent on the pH of the swelling medium. At a high pH (higher than pK_a of the gel), the water transport was controlled more by polymer relaxation (case II) than by penetrant diffusion. This resulted from the ionization of the carboxylic acid groups on the PMAA of the hydrogels. An increase in the degree of ionization contributed to the electrostatic repulsion between adjacent ionized groups, leading to chain expansion, which, in turn,

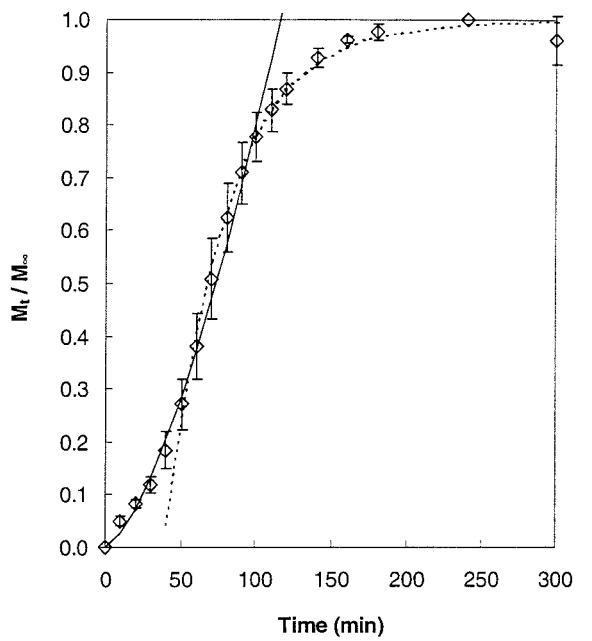

Figure 11 M_t/M_∞ of P(MAA-*g*-EG) samples with a PEGMA molecular weight of 300 (1:1 EG/MAA) swollen in a pH 7.0 buffer solution at 37°C: (◇) experimental data, (—) eq. (2), and (…) eq. (4) (average ± standard deviation, $n = 3$).

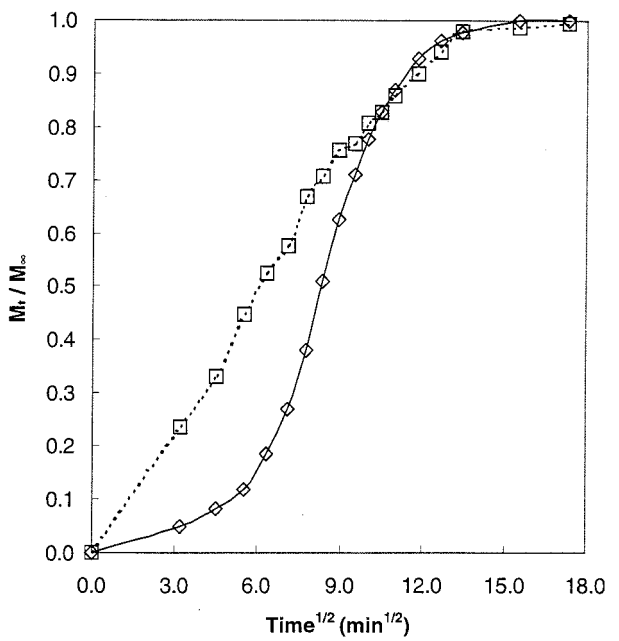

Figure 13 M_t/M_∞ of P(MAA-*g*-EG) samples with a PEGMA molecular weight of 300 (1:1 EG/MAA) as a function of the square root of time swollen in (□) pH 2.2 and (◇) pH 7.0 buffer solutions at 37°C.

affected macromolecular chain relaxation. However, for both P(MAA-*co*-MEG) and P(MAA-*g*-EG) hydrogels, the swelling mechanism exhibited little dependence on the copolymer compositions of each hydrogel at the same pH.

The prediction of water uptake profiles from mathematical models also showed that an increase in pH rendered the mechanism of penetrant transport more case II.

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