Strong Buffering Characteristics and Swelling Behavior of Cationic Copolymers

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SYNOPSIS

The swelling behavior of crosslinked cationic copolymers of 2-hydroxyethyl methacrylate with (3-methacryloylamino propyl) trimethylammonium chloride was investigated in various buffered solutions as a function of ionic strength and pH. The equilibrium degree of swelling increased as the pH decreased or as the cationic group-containing comonomer in the polymer increased. The water transport in such copolymers was controlled by a non-Fickian mechanism. These results can be used in the development of physiologically sensitive controlled drug delivery systems. © 1994 John Wiley & Sons, Inc.

INTRODUCTION

Crosslinked copolymers containing 2-hydroxyethyl methacrylate (HEMA) and other hydrophilic monomers can be prepared and modified for various applications in the field of controlled release.[1] For example, it is possible to develop pH-sensitive hydrogels that deliver peptides and other compounds in response to the physiological environment.[2,3] More specifically, anionic gels could be utilized for controlled release of drugs in alkaline environments whereas cationic gels would release in acidic environments.[3-7] Some of the more important biomedical applications in which hydrogels with pH sensitivity could be used include artificial muscles, components in chemical separation systems, controlled drug delivery devices, site-specific gastrointestinal delivery devices, and buccal or nasal controlled release systems.[1,8]

By varying the monomer composition in the polymer it is possible to control the swelling and diffusion characteristics of these hydrogels. These characteristics may be adjusted to render the hydrogels excellent candidates for controlled drug release studies.[9] The polymer may be primarily anionic or cationic depending on the monomers used for preparation.

In cationic hydrogels prepared from *N,N*-dimethylamino ethyl methacrylate (DMA) it has been shown[6] that as the solution pH is decreased the tertiary amine side chains are protonated. The charge density on the matrix and the mobile counterion content of the network are increased, and, as the counterions become more mobile, the osmotic pressure increases. This directly affects the characteristic equilibrium degree of swelling. Consequently, hydrogels may be designed for specific biomedical applications in which the release of the drug is pH controlled by determining the correct end groups and the overall gel composition. For copolymers of *n*-alkyl methacrylates (*n*-AMA) with DMA it has been shown that the pH at which the transition from the glassy to rubbery state occurs is affected by the pendant chain length. As the molar ratio of *n*-AMA to DMA increases, the pH of the swelling transition shifts to a lower pH and the swelling ratio is decreased. As the side chain length increases from one to six carbons, the water content at the lower pH range (pH = 2–3) decreases from 90 to 50%.

Work by Prausnitz and his collaborators[10,11] has examined the pH-dependent swelling behavior of various cationic hydrogels, including structures containing methacrylamidopropyl trimethylammonium chloride. In general, the swelling equilibrium for a copolymer system at a fixed pH depends on: (i) hydrogen ion concentration, (ii) contribu-

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tions from the ionic strength of the buffer, and (iii) ion valence of the buffer.

Utilization of such systems in pharmaceutical applications has been the subject of much recent work. Basically, the systems developed belong to the category of *swelling-controlled drug delivery* systems.[8] When a drug is loaded into these polymer networks, drug release occurs by polymer swelling. The drug permeability is controlled by the hydrophilicity, crystallinity, and crosslinking density. Hydrogels that are sensitive to pH changes behave similarly to other initially dry polymers except that the effects of the solution may alter the drug release rates from the polymer, depending on the pH of the surrounding fluid.[3] Previously, it was shown that the mechanism of drug release depends on the chain relaxation and drug diffusion, which may exhibit zero-order kinetics under certain conditions.[12-15] Research by Brannon-Peppas and Peppas[3] on anionic polymers has shown that the pH of the solution directly affects the chain relaxations and swelling of the sample.

Siegel et al.[6] prepared copolymers of methyl methacrylate (MMA) and DMA for the controlled release of caffeine. The amount of drug released was studied as a function of pH. None of the caffeine was released at a neutral pH. However, in acidic buffers (pH = 3–5) the drug release occurred with near zero-order kinetics with the rate at pH = 3 greater than the rate at pH = 5. Release in the low pH buffers is controlled primarily by the swelling of the hydrogel. Therefore, the release rate and the amount of drug released were shown to be pH dependent.

The importance of crosslinking and average molecular weight between crosslinks on the release from such systems was first studied by Walker and Peppas.[16] Copolymers were prepared by bulk free-radical polymerization from ethylene glycol dimethacrylate (EGDMA), diethylene glycol dimethacrylate, and triethylene glycol dimethacrylate with up to 50% HEMA comonomer ar 60°C. Theophylline was incorporated in the polymers for release studies. The rate of theophylline release increased as the percentage of HEMA increased, but the overall release was quasi-Fickian. Shieh and Peppas[17] prepared HEMA and MMA copolymers with tetraethylene glycol dimethacrylate, EGDMA, and dodecaethylene glycol dimethacrylate. Results showed that as the molecular weight of the crosslinking reagent within the copolymer decreased the polymers absorbed more water at equilibrium. The type of solvent used during polymerization had an effect on the swelling characteristics of the copolymers. Copolymers prepared in ethanol showed higher water uptake than copolymers prepared in water.

The primary focus of previous research has been on the preparation and swelling behavior of hydrogels utilizing various comonomers and crosslinking ratios. The purpose of this study was to investigate the dynamic and equilibrium swelling behavior of cationic copolymers exhibiting strong buffering characteristics. Such cationic systems are developed for long-term delivery of peptides and related compounds where control of the external pH is desirable. More specifically, the objectives of this research study were to investigate the influence of pH and mole fraction of HEMA and (3-methacryloylamino) propyl trimethylammonium chloride (MPTAC) comonomers on the relaxational behavior of the ensuing crosslinked hydrogels.

EXPERIMENTAL PART

The copolymers for the cationic, swelling-controlled release devices were prepared by bulk free-radical addition polymerization of HEMA with (3-methacryloylamino propyl) trimethylammonium chloride (MPTAC). All monomers were obtained from Polysciences Inc. Washington, PA, and vacuum distilled before use. Ethylene glycol dimethacrylate (EGDMA) was added as the crosslinking reagent at 0.1 wt %. Ammonium persulfate and sodium metabisulfite were used as the free-radical initiators in amount of 0.25 wt % each. The reaction was carried out in 7 ml polypropylene vials that were securely sealed and placed in a agitated water bath at 40°C for 6 h and 60°C for an additional 12 h.

The ensuing polymer cylinders were cut into disks of diameters ranging from 12 to 14 mm and thickness ranging from 0.8 to 1.4 mm. The disks were swollen in deionized water for 72 h to remove any unreacted monomers. The swollen disks were then air dried for 24 h at 28°C and in a vacuum oven for 48 h at 40°C.

Buffered solutions were used for all swelling studies. Sodium chloride was added to maintain a constant ionic strength of 0.1 M. The species utilized for each pH buffer is a function of the pK_a of the acid or base, which depends on the ionic strength of the medium. Thus, chloroacetic acid buffers were used for pH = 3 and 4, acetic acid for pH = 5 and 6, sodium phosphate for pH = 7 and 8, boric acid for pH = 9 and 10, and triethylamine for pH = 12.

Buffers were also prepared using citrate-phosphate-borate/HCl solutions. A stock solution was prepared with normal citric and phosphoric acid,

boric acid, and sodium hydroxide. Hydrochloric acid was added in precalculated volumes to obtain the desired pH buffer. The ionic strength of the buffer was held constant at 0.06*M* with sodium chloride.

The dry copolymer samples were initially weighed and then placed in separate vials of buffered pH solutions. The dynamic and equilibrium swelling studies were carried out at 37°C. During the swelling, the disks were removed at regular intervals, blotted dry, weighed, and then replaced in the vials. Upon completion of the swelling experimentation the disks were air dried at 28°C for 24 h, and then dried at 40°C for 72 h.

RESULTS AND DISCUSSION

Crosslinked P(HEMA-co-MPTAC) copolymers were prepared with 10, 20, 30, 40, and 50 mol % MPTAC. These copolymer samples were clear and did not exhibit defects or crazing after copolymerization. The equilibrium and dynamic swelling characteristics of these copolymer compositions were analyzed. The weight swelling ratio, q, was plotted as a function of pH for the equilibrium swelling experiments.

Figure 1 illustrates the pH dependence of the weight swelling ratio for the cationic network P(HEMA-co-MPTAC) with 10 mol % MPTAC. The weight swelling ratio decreased sharply as the pH of the buffered solution increased and leveled off at about pH = 10. The same figure shows the pH dependence on the weight swelling ratio for P(HEMA-co-MPTAC) with 30 mol % MPTAC. Again, a sharp decrease in swelling was observed in

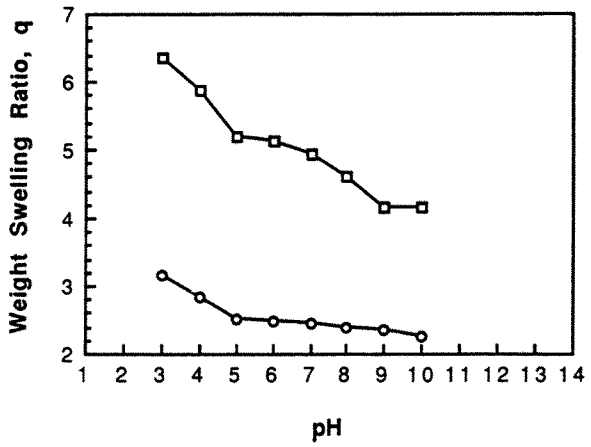

Figure 1 Equilibrium weight swelling ratio, q, as a function of pH for crosslinked P(HEMA-co-MPTAC) samples with 10 mol % MPTAC (○) and 30 mol % MPTAC (□) at 37°C.

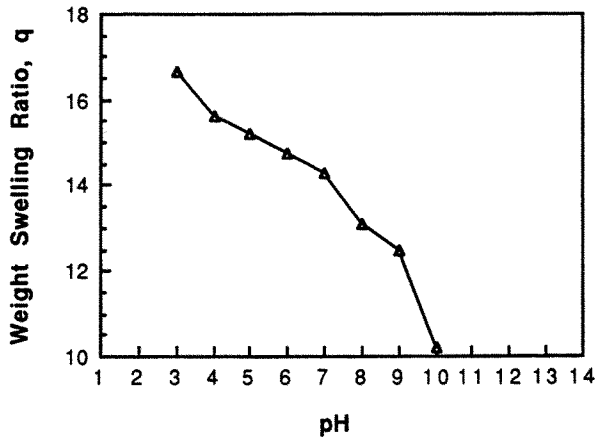

Figure 2 Equilibrium weight swelling ratio, q, as a function of pH for crosslinked P(HEMA-co-MPTAC) with 50 mol % MPTAC (△) at 37°C.

the pH range between pH = 3 and pH = 5. In the pH region of 5–9, the swelling ratio continued to decrease, but the dependence of the weight swelling ratio on pH was not as distinct. The weight swelling ratio leveled off at a pH = 9.

Experimental results of the pH dependence on the weight swelling ratio for P(HEMA-co-MPTAC) with 50 mol % MPTAC are shown in Figure 2. The abrupt decrease in swelling was observed in the acidic pH region and continued through pH = 10. A very steep decrease in pH dependence was exhibited between pH = 9 and pH = 10. In general, the swelling ratio was greater for the polymers containing increasing amounts of MPTAC. The weight swelling ratio was a function of the amount of MPTAC in the hydrogel.

We also utilized a phosphoric–citric acid buffer with an ionic strength of 0.06*M* and studied the equilibrium swelling behavior of the previous copolymers over the pH range of 3–11. The ionic strength was held constant by the addition of sodium chloride. The equilibrium swelling characteristics of the copolymer compositions were analyzed and compared to the results obtained from the swelling experiments with different buffers for each pH. Figure 3 shows the weight swelling ratios of P(HEMA-co-MPTAC) gels with 20, 30, and 40 mol % MPTAC as a function of pH. The swelling ratio decreased in the pH range of 3–7 and then began to level off. The copolymers swelled the most in the acidic pH buffers. In the lower pH buffers, the pendant groups became protonated and therefore the charge density on the gel increased. This caused an increase in mobile counterions within the gel that increased the osmotic pressure relative to the solution.

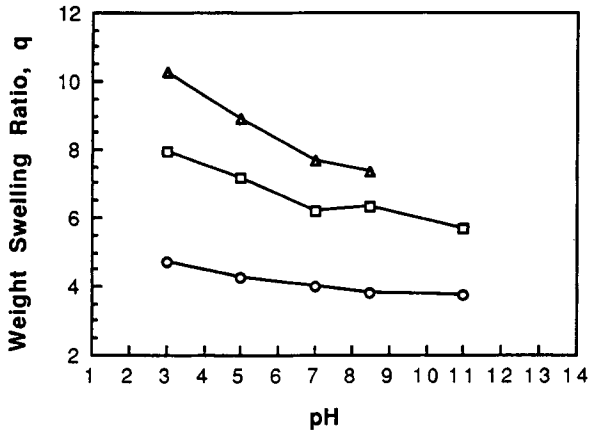

Figure 3 Equilibrium weight swelling ratio, q, as a function of pH for crosslinked P(HEMA-co-MPTAC) with 20 mol % MPTAC (△), 30 mol % MPTAC (□), and 40 mol % MPTAC (○) in phosphoric/citric buffer at 37°C.

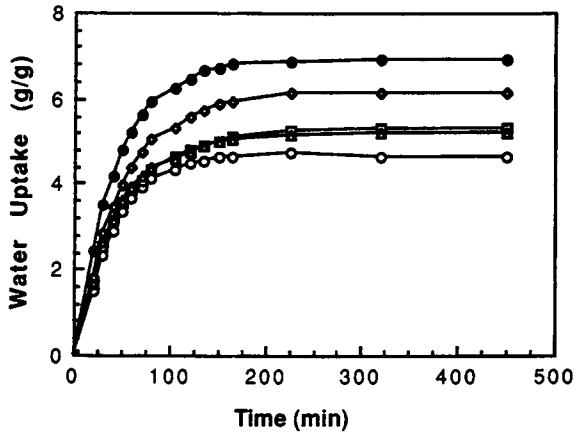

Figure 5 Dynamic swelling water uptake (g water/g dry polymer) as a function of time for crosslinked P(HEMA-co-MPTAC) with 30 mol % MPTAC. The swelling curves are for pH = 11 (○), pH = 8.5 (□), pH = 7 (△), pH = 5 (◇), and pH = 3 (●).

Investigation of the applicability of these gels in controlled release was done by studying their dynamic swelling behavior. Dynamic swelling experiments were conducted with P(HEMA-co-MPTAC) with 20, 30, and 40 mol % MPTAC in buffered solutions of pH = 11, pH = 8.5, pH = 7, pH = 5, pH = 3 at 37°C. Figures 4 through 6 illustrate the water uptake, in grams water per gram dry copolymer, as a function of time for each composition and pH buffer studied.

All of the copolymers swelled more in the acid pH than in the alkaline buffer solutions. Initially, the rate of water uptake increased steadily and then began to level off. The initial swelling rates were calculated and are shown in Table I. The equilibrium degree of swelling was reached after 100–125 min for each copolymer composition and pH. The equilibrium values are summarized in Table II.

The dynamic swelling experiments were analyzed by plotting the ratio of the mass of penetrant uptake at any time, M_t, to the mass of dry polymer, M_p, as a function of time according to

$$\frac{M_t}{M_p} = kt^n \tag{1}$$

The diffusional exponent, n, and the rate constant, k, were determined from logarithmic plots of water

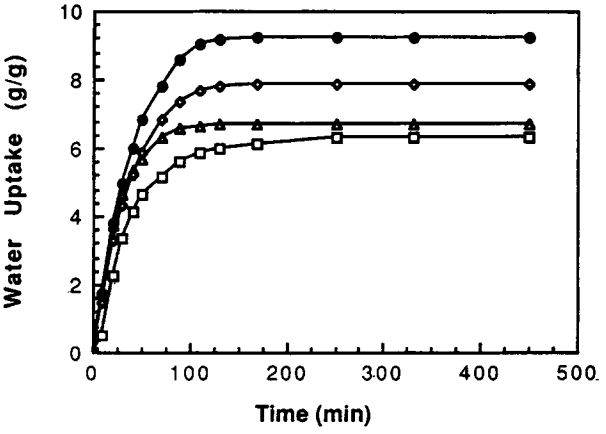

Figure 4 Dynamic water uptake (g water/g dry polymer) as a function of time for crosslinked P(HEMA-co-MPTAC) with 20 mol % MPTAC. The swelling curves are for pH = 8.5 (□), pH = 7 (△), pH = 5 (◇) and pH = 3 (●).

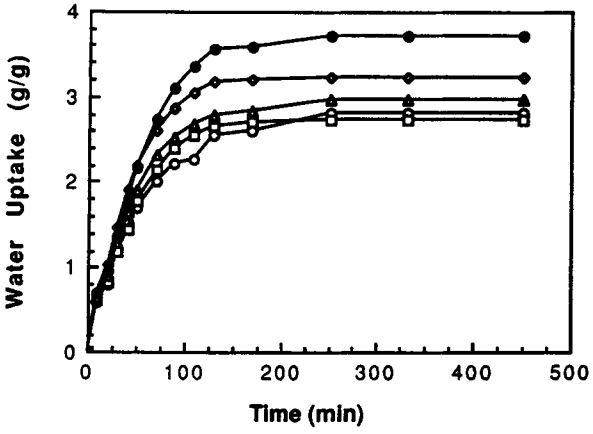

Figure 6 Dynamic swelling water uptake (g water/g dry polymer) as a function of time for crosslinked P(HEMA-co-MPTAC) with 40 mol % MPTAC. The swelling curves are for pH = 11 (○), pH = 8.5 (□), pH = 7 (△), pH = 5 (◇), and pH = 3 (●).

Table I Initial Swelling Rate (g water/g polymer · min) of P(HEMA-co-MPTAC) Samples During Dynamic Swelling at 37°C

pH of Buffer Solution	Molar Ratios of HEMA/MPTAC in Copolymers		
	80 : 20	70 : 30	60 : 40
11.0	—	0.048	0.036
8.5	0.100	0.087	0.037
7.0	0.089	0.088	0.038
5.0	0.100	0.099	0.043
3.0	0.110	0.10	0.042

uptake as a function of time and are shown in Table III. The diffusional exponents range from 0.56 to 0.86. Exponents approaching 1.0 indicate highly relaxation-controlled water transport in the polymer, which in turn is a condition for zero-order release of incorporated drugs.[15,18,19] A slight increase in the exponent n was observed as the pH decreased, indicating that in hydrogels that expand significantly at equilibrium, the relaxational mechanism becomes more prominent.

The initial penetration velocity of the advancing water front could be calculated from

$$u = \frac{dw}{dt}\frac{1}{\rho_w 2A} \qquad (2)$$

Here, dw/dt is the weight of water absorbed by the copolymer per unit time, ρ_w is the water density at 37°C and A is the area of one face of the disk (with d = 1.2 cm). Table IV summarizes the penetration front velocity for all the samples tested. These values are about two orders of magnitude higher than those

Table III Diffusional Exponents of Dynamic Swelling of P(HEMA-co-MPTAC) as Analyzed According to Eq. (1)[a]

pH of Buffer Solution	Molar Ratios of HEMA/MPTAC in Copolymers		
	70 : 20	70 : 30	60 : 40
11.0	—	0.61	0.73
		(0.98)	(0.97)
8.5	0.68	0.57	0.77
	(0.89)	(0.98)	(0.99)
7.0	0.65	0.55	0.75
	(0.92)	(0.99)	(0.99)
5.0	0.76	0.61	0.75
	(0.96)	(0.99)	(0.98)
3.0	0.76	0.56	0.86
	(0.96)	(0.99)	(0.99)

[a] The values in parentheses are the correlation coefficients of the linear logarithmic regression.

calculated by Davidson and Peppas[15,18] for water transport in noncharged P(HEMA-co-MMA) copolymers, indicating that the cationically charged groups have a significant influence on the water transport process.

CONCLUSIONS

In conclusion, crosslinked cationic P(HEMA-co-MPTAC) hydrogels swell more in acidic pH solutions than alkaline solutions due to the cationic pendant chains. The weight swelling ratio and rate of water uptake increase as the amount of MPTAC is decreased. The copolymers exhibit highly relaxation-controlled water transport within the matrix,

Table II Weight Equilibrium Degree of Swelling of P(HEMA-co-MPTAC) Samples After Dynamic Swelling in Phosphoric/Citric Buffers at 37°C

pH of Buffer Solution	Molar Ratios of HEMA/MPTAC in Copolymers		
	80 : 20	70 : 30	60 : 40
11.0	—	5.65	3.82
8.5	7.35	6.32	8.74
7.0	8.70	6.20	3.77
5.0	8.90	7.16	3.23
3.0	10.24	7.91	3.75

Table VI Water Penetration Front Velocity, u (in cm/s), in P(HEMA-co-MPTAC) Samples During Swelling at 37°C

pH of Buffer Solution	Molar Ratios of HEMA/MPTAC in Copolymers		
	80 : 20	70 : 30	60 : 40
11.0	—	5.46×10^{-4}	4.45×10^{-4}
8.5	3.68×10^{-4}	6.12×10^{-4}	4.52×10^{-4}
7.0	12.88×10^{-4}	6.37×10^{-4}	4.80×10^{-4}
5.0	11.17×10^{-4}	6.72×10^{-4}	5.19×10^{-4}
3.0	12.96×10^{-4}	8.86×10^{-4}	5.11×10^{-4}

which in turn is a condition for zero-order release of incorporated drugs.

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