Transport of Ionizable Drugs and Proteins in Crosslinked Poly(acrylic acid) and Poly(acrylic acid-*co*-2-hydroxyethyl methacrylate) Hydrogels. I. Polymer Characterization

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SYNOPSIS

The purpose of this investigation was to define the polymer structure and elucidate the swelling behavior of ionizable hydrophilic polymers (hydrogels) in water and buffered media. Poly(acrylic acid) (PAA) and poly(acrylic acid-*co*-2-hydroxyethyl methacrylate) [P(AA-*co*-HEMA)] hydrogels were synthesized with varying degrees of hydrophilicity and crosslinking and were designed as potential bioadhesive controlled-release dosage forms. The thermal initiation procedure employed during polymerization was optimized to eliminate unreacted residuals. Equilibrium and dynamic swelling studies were undertaken to determine the polymer mesh size and molecular weight between crosslinks of the hydrogels in the ionized and nonionized states. The PAA hydrogel mesh sizes ranged from 100 to 400 Å over pH values of 3–7, whereas the P(AA-*co*-HEMA) hydrogel mesh sizes were between 13 and 140 Å. These results demonstrated the significance of the swelling medium pH on the hydrated state of the polymers relative to crosslinking or copolymerization composition. © 1996 John Wiley & Sons, Inc.

INTRODUCTION

Understanding of solute (drug) transport in and release from controlled-release devices requires quantitative analysis of solute transport through the macromolecular mesh of the polymer carrier.[1] In solute transport through hydrogels, this description is rather difficult because of the number of parameters participating in the analysis. The most successful theories that describe solute diffusion through hydrogels are based on free volume. Yasuda et al.[2] were the first to extend free-volume theories to hydrogels and proposed eq. (1):

$$\frac{D}{D_\infty} = \phi_2 \exp\left[-\frac{Bq_2}{V_f}\left(\frac{1}{v_{1,s}} - 1\right)\right] \qquad (1)$$

Here, D and D_∞ are the solute diffusion coefficients in the hydrogel membrane and in pure solvent, respectively, q_2 is the cross-sectional area of the solute; V_f, the free volume in the hydrogel; $v_{1,s}$, the volume fraction of water in the hydrogel; ϕ_2, the screening effect of the polymer; and B, a constant. The screening effect is also referred to as the sieving mechanism, where ϕ_2 approaches a value of 1 as the mesh size of the hydrogel becomes much larger than the solute size.

The major disadvantage of the Yasuda theory is that it requires a number of polymer sieving parameters which are impossible to measure by independent techniques. Peppas and Reinhart[3] proposed a predictive free-volume-based model, which contains physically measurable parameters. The model is summarized by eq. (2).

$$\frac{D}{D_\infty} = k_1\left(\frac{\bar{M}_c - \bar{M}_c^*}{\bar{M}_n - \bar{M}_c^*}\right)\exp\left[-\frac{k_2 r_s^2}{Q-1}\right] \qquad (2)$$

Here, $\bar{M}_c$ is the molecular weight between crosslinks; $\bar{M}_c^*$, the critical molecular weight between crosslinks

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below which the solute cannot pass through the mesh structure; $\bar{M}_n$, the number-average molecular weight; r_s, the equivalent spherical solute radius; Q, the equilibrium volume swelling ratio; and k_1 and k_2, constants indicative of the solute and polymer. In this case, the screening or sieving mechanism is represented by the ratio of the molecular weight difference in the crosslinked polymer, $\bar{M}_c - \bar{M}_c^*$, to that of the uncrosslinked polymer, $\bar{M}_n - \bar{M}_c^*$.

Although these two well-known theories[2,3] contain an exponential dependence of the solute diffusivity on the solute molecular size divided by the free volume of the polymer, the latter has the additional advantage that all the parameters are physically measurable. The terms Q and $\bar{M}_c$ can be evaluated from equilibrium swelling studies,[4] as described by eqs. (3) and (4), where $v_{2,s}$ and $v_{2,r}$ are the equilibrium polymer volume fractions in the swollen and relaxed (after crosslinking but before swelling) states, respectively. Thus, Q can be expressed as

$$Q = \frac{1}{v_{2,s}} \tag{3}$$

and $\bar{M}_c$ can be expressed[4] as

$$\frac{1}{\bar{M}_c} = \frac{2}{\bar{M}_n} - \left(\frac{\frac{\bar{v}}{V_1}\left[\ln(1 - v_{2,s}) + v_{2,s} + \chi v_{2,s}^2\right]\left[1 - \frac{v_{2,s}^{2/3}}{N}\right]^3}{v_{2,r}\left[\left(\frac{v_{2,s}}{v_{2,r}}\right)^{1/3} - \frac{1}{2}\left(\frac{v_{2,s}}{v_{2,r}}\right)\right]\left[1 + \frac{1}{N}\left(\frac{v_{2,s}}{v_{2,r}}\right)^{1/3}\right]^2} \right) \tag{4}$$

Here, $\bar{v}$ is the specific volume of the polymer; V_1, the molar volume of water; χ, the polymer solvent interaction parameter; and N, the number of bond vectors per chain. The number of bond vectors is determined by

$$N = 2\frac{\bar{M}_c}{M_r} \tag{5}$$

where M_r is the molecular weight of the repeating unit. These free-volume theories do not account for the effect of solute/polymer interactions on solute diffusion, a subject that will be discussed in a subsequent publication. In this work, we prepared and carefully characterized a number of ionizable hydrogels to be used for controlled-release applications.

EXPERIMENTAL

Materials

Acrylic acid (AA) and 2-hydroxyethyl methacrylate (HEMA) were purchased from Aldrich Chemical Co. (Milwaukee, WI). Prior to polymerization of the monomers, the inhibitor methyl ether hydroquinone was removed by vacuum distillation from AA at 47°C/7 mmHg and from HEMA at 65°C/4 mmHg. The crosslinking agent ethylene glycol dimethacrylate (EGDMA) and the initiator azobisisobutyronitrile (AIBN) were used as received from Aldrich Chemical Co.

Hydrogel Synthesis

Poly(acrylic acid) (PAA) hydrogels were produced by free-radical polymerization in water (W) or ethanol (E) solutions containing 10 or 20 mol % AA. For each monomer concentration, the crosslinking agent was added at 0.001, 0.002, 0.003, 0.004, 0.005, 0.01, or 0.02 mol EGDMA/mol AA. The initiator concentration was maintained at 0.1 wt % AIBN. Solution polymerization was carried out in 6 mL cylindrical vials with a 14 mm diameter. Appropriate amounts of initiator, inhibitor-free AA, crosslinking agent, and solvent were transferred into the vials and purged with nitrogen for 10 min before placing them in the temperature bath. The temperature program for the polymerization reactions was 50°C for 1 h, 60°C for 2 h, and 70°C for 24 h.

Copolymers of AA and HEMA were also prepared by solution polymerization of a water or ethanol solution containing 60 mol % of a mixture of AA and HEMA containing 30/70 or 40/60 mol AA/mol HEMA. The crosslinking ratio varied from 0.001, 0.002, 0.003, 0.004, 0.005, 0.01, and 0.02 mol EGDMA/mol total monomer. Bulk polymerization in the absence of solvent was also performed with an initial monomer composition of 55/45 mol AA/mol HEMA. Copolymerizations were performed in the same vials as before and under the same purging conditions. The temperature program used for these reactions was 50°C for 2 h followed by 60°C for 45 h (see also Table I). Upon completion of the polymerization reactions, the hydrogels were washed in deionized/distilled water for 1 week to remove residuals such as unreacted monomer, crosslinking agent, and initiator. The cylindrical glassy polymer samples were subsequently cut into thin discs with a diamond-edge rotary saw (Buehler Ltd., Lake Bluff, IL).

Table I Polymerization Conditions and Composition of Hydrogel Samples

	Reactant Mixture				Polymerization Conditions	
Sample[a]	AA (Mol %)	HEMA (Mol %)	EGDMA (Mol %)	Solvent W or E	Temperature (°C)	Time (h)
A27	10	0	0.1	W	70	48
A28	10	0	0.2	W	70	48
A29	10	0	0.2	W	70	48
A30	10	0	0.3	W	70	48
A31	10	0	0.3	W	70	48
A33	10	0	0.4	W	70	48
A35	10	0	0.5	W	70	48
A36	10	0	1.0	W	70	48
A43	20	0	0.2	W	78	48
A44	20	0	0.3	W	70	48
1A–3A	10	0	1.0	W	50, 60, 70	1, 2, 24
4A–6A	10	0	2.0	W	50, 60, 70	1, 2, 24
7A–9A	20	0	1.0	W	50, 60, 70	1, 2, 24
10A–12A	20	0	2.0	W	50, 60, 70	1, 2, 24
30 : 70W	18	42	0.1	W	50, 60	2, 45
30 : 70W	18	42	1.0	W	50, 60	2, 45
30 : 70E	18	42	0.3	E	50, 60	2, 45
30 : 70E	18	42	0.4	E	50, 60	2, 45
30 : 70E	18	42	0.5	E	50, 60	2, 45
40 : 60W	24	36	0.1	W	50, 60	2, 45
40 : 60W	24	36	0.2	W	50, 60	2, 45
55 : 45	55	45	0.2	—	50, 60	2, 45
55 : 45	55	45	0.3	—	50, 60	2, 45
55 : 45	55	45	0.4	—	50, 60	2, 45
55 : 45	55	45	0.5	—	50, 60	2, 45
55 : 45	55	45	1.0	—	50, 60	2, 45

[a] W = prepared in water; E = prepared in ethanol.

Residual Content in Hydrogels

Hydrogel samples were extracted with deionized water for 24 h. The hydrogel extracting medium was analyzed by gas chromatography (GC Model 1400, Varian, Palo Alto, CA) with a thermal conductivity detector, using a temperature ramp of 20°C/min from 50 to 210°C. According to the boiling points of EGDMA, AA, dimerized AA, and AIBN, the retention times were 4.00, 5.83, 7.25, and 8.63 min, respectively. GC analysis of the residual content was carried out following various polymerization conditions in order to optimize the conversion of the reactions studied.

Determination of Degree of Ionization

The degree of ionization, α, and dissociation constant, K_a, were evaluated by potentiometric titration of the hydrogel over a range of pH values. The studies were carried out over long times to ensure that the hydrogels attained equilibrium.[5] The dry polymer samples were ground in a lab mill (Braun Model KSM-2, Spain), placed in 20 mL deionized/distilled water, and allowed to equilibrate. The pH was measured using a pH meter (Jenco Electronics, Ltd., Model 6071, Taipei, Taiwan), with a resolution of 0.01 pH units. The titration was carried out by adding 50 μL aliquots of 0.1142N NaOH solution (reagent-grade standard, Ricca Chemical Co., Arlington, TX) to the equilibrated hydrogel in solution and stirring at a constant rate. The anionic hydrogels were allowed to completely ionize for each aliquot of base added to the system. This required extensive equilibration times (on the order of hours) to allow the titrant to penetrate the crosslinked hydrogels. The titration data were fit to the generalized Henderson–Hasselbalch eq. (6), where the value of n was assumed[5] to be 2:

$$\text{pH} = \text{p}K_a - n \log\left(\frac{\alpha}{1-\alpha}\right) \tag{6}$$

Equation (6) is commonly used to describe the titration curves of polyacids, since ionization becomes increasingly difficult as the concentration of dissociated neighboring moieties increases.

Thermal Analysis

Thermal characterization of ground polymer samples (5–7 mg) in a differential scanning calorimeter (DSC, DuPont Model 910, connected to a TA 2000 thermal analyzer, TA Instruments, Wilmington, DE) was used to determine the glass transition temperature, T_g, and the concentration of residuals. The system was purged with nitrogen at a rate of 140 mL/min.

A preliminary thermogram was obtained to detect any residuals present in the sample, by scanning from ambient conditions to 140°C under nitrogen atmosphere at a scan rate of 10°C/min. The sample was then cooled to ambient conditions using the nitrogen purge and a second thermogram was obtained at a scanning rate of 5°C/min. The value of T_g was determined from the intersection of the tangential lines drawn on either side of the secondary transition region. Replication of the scanning process for each sample eliminated any variation in thermal history between samples, for proper comparison.

The general empirical relationship[6] between the glass transition temperature and the number-average molecular weight between crosslinks in crosslinked polymers was used to determine $\bar{M}_c$, according to eq. (7):

$$\bar{M}_c = \frac{3.9 \times 10^4}{(T_g - T_{g0})} \tag{7}$$

Here, T_g is the glass transition temperature of the crosslinked polymer, and T_{g0}, the glass transition temperature of the uncrosslinked polymer with the same chemical composition. Uncrosslinked PAA exhibited[7] a glass transition temperature T_{g0} of 105.8°C, whereas Krause et al.[8] determined a T_{g0} value for PHEMA of 55°C.

For a random copolymer, the glass transition temperature was taken[9] as the weighted average of the two homopolymer T_g values:

$$\frac{1}{T_g} = \frac{w_1}{T_{g1}} + \frac{w_2}{T_{g2}} \tag{8}$$

Here, T_{g1} and T_{g2} are the two homopolymer glass transition temperatures, and w_1 and w_2, the corresponding weight fractions.

Polymer Swelling Characterization

The polymer discs were dried to a constant weight after exposure to 37°C. The polymer volume fraction, $v_{2,s}$, equilibrium volume swelling ratio, Q, and specific volume of polymer, $\bar{v}$, were experimentally determined by equilibrium swelling measurements according to a method developed for gels prepared by crosslinking in the presence of a solvent.[4] The polymer discs were weighed in air and heptane (a nonsolvent): (i) after crosslinking but before swelling; (ii) after equilibrium was attained in the swelling medium; and (iii) after complete redrying. These studies were carried out at 37°C in 100 mL of buffered solution with $I = 0.1N$ for 3 days. The ionic strength was adjusted by addition of NaCl.

The equilibrium volume swelling ratio, Q, is expressed as an inverse of the equilibrium polymer volume fraction, $v_{2,s}$ as shown in eq. (3). This swelling ratio is the ratio of the swollen hydrogel volume to the dry polymer volume.

Dynamic swelling studies were undertaken to elucidate the mechanism of water diffusion into the polymer samples as determined by the dynamic portion of the gravimetric curve. The water uptake, M_t, was monitored as a function of time until equilibrium was attained, M_∞, in order to provide the data for dynamic and equilibrium time frames. The polymer discs were placed in 100 mL of buffered solution, which was maintained at 37°C. The polymer samples were periodically removed from the solution, patted dry, and weighed.

The dynamic portion of the swelling behavior was monitored to determine the water diffusion coefficient, D. The short-term approximation of the Fickian equation for swelling agent diffusion in a slab with constant boundary conditions is given by eq. (9):

$$\frac{M_t}{M_\infty} = 4\left[\frac{Dt}{\pi\delta^2}\right]^{1/2} \tag{9}$$

Here, δ is the half-thickness of the thin film tested.

The mesh size, ξ, is a term that describes the available space for solute transport within the polymer network. This parameter was determined from the polymer volume fraction in the swollen state, $v_{2,s}$, and the end-to-end distance of the polymer chains between two consecutive crosslinks in their unperturbed state, $(\bar{r}_0^2)^{1/2}$, according to eqs. (10) and

(11), which are described in more detail by Canal and Peppas[10]:

$$\xi = \upsilon_{2,s}^{-1/3}(\bar{r}_0^2)^{1/2} \quad (10)$$

$$(\bar{r}_0^2)^{1/2} = \left(2\frac{\bar{M}}{M_r}\right)^{1/2} C_n^{1/2} l \quad (11)$$

Here, M_r is the molecular weight of the repeating unit; l, the C—C bond length of 1.54 Å; and C_n, the characteristic ratio. The characteristic ratio was determined as 6.9 for PHEMA by Dušek and Sedláček[11] and as 8.4 for poly(methacrylic acid)[7]; the latter was used for PAA in this investigation. The effect of polymer structural parameters on the dynamic swelling behavior was investigated by varying the pH, ionic strength, polymer sample aspect ratio, and mesh size, ξ.

RESULTS AND DISCUSSION

Gas Chromatography Studies

The extract solutions from the polymers of AA were analyzed by varying the initial monomer concentration relative to the solvent, varying the molar content of crosslinking agent (EGDMA), and varying the temperature profile during the initiation by AIBN, as seen from the results of Table II. The initial monomer concentration of AA in the reactant mixture was 10 mol % for samples A33, 2A, and 5A, vs. 20 mol % for samples 8A and 11A. Extracted monomer levels for the 10 mol % AA hydrogels appeared to decrease with increased amounts of the crosslinking agent. The improved conversion was a result of the optimization of the polymerization conditions during thermal initiation from a constant to a gradient temperature profile.

The unreacted crosslinking agent and extracted monomer quantities from sample A33 which was polymerized at 70°C for 48 h were attributed to rapid free-radical formation. However, the extracts of the remaining polymer samples prepared by reaction under a temperature program of 1 h at 50°C, 2 h at 60°C, and 24 h at 70°C, contained less than 0.08 vol % unreacted monomer. The polymer samples prepared from 20 mol % AA in the reactant mixture (8A and 11A) had undetectable levels of residuals. These results demonstrated that the incremental temperature program during polymerization provided the highest conversion for AIBN-initiated reactions of AA.

Ionization of PAA Hydrogels

A typical titration curve of PAA containing 0.01 mol EGDMA/mol AA with 50 μL aliquots of 0.1142N aqueous NaOH solution is shown in Figure 1. The titration data were fit to the generalized relationship of eq. (6) and the pK_a of the PAA sample was de-

Table II Gas Chromatography Analysis of Extracts from PAA Samples Using Two Different Thermal Initiation Sequences for Polymerization

	PAA Sample				
Reactant Conditions	A33[a]	2A	5A	8A	11A
AA (mol %)	10	10	10	20	20
Crosslinking ratio X	0.004	0.010	0.020	0.020	0.020
Extracted component (vol %)					
Water	93.57	99.92	99.94	100	100
EGDMA	2.80	n.d.	n.d.	n.d.	n.d.
AA	2.83	0.08	0.06	n.d.	n.d.
Dimerized AA	0.65	n.d.	n.d.	n.d.	n.d.
AIBN	0.15	n.d.	n.d.	n.d.	n.d.
Extracted component (mol %)					
AA (mol)	0.0209	0.0006	0.0005	0	0
EGDMA (mol)	0.0103	0	0	0	0
Total (mol)	2.628	2.6904	2.937	0	0
AA (%)	0.79	0.02	0.02	0	0
EGDMA (%)	0.39	0	0	0	0

Polymerization conducted for 1 h at 50°C, 2 h at 60°C, and 24 h at 70°C.
[a] Polymerization of hydrogel sample A33 was carried out at 70°C for 48 h.

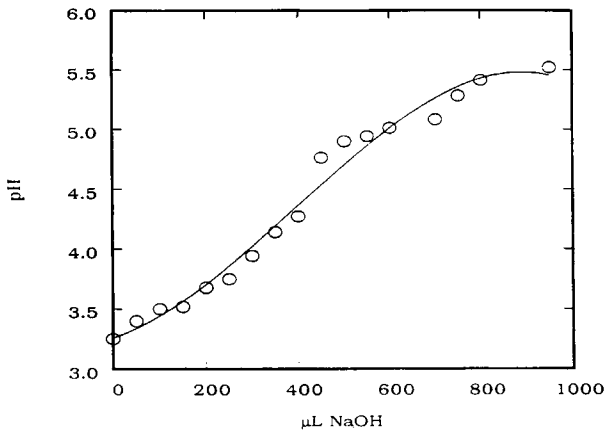

Figure 1 Potentiometric titration of PAA containing 0.01 mol EGDMA/mol AA with 50 μL aliquots of 0.1142*N* NaOH.

termined to be 4.25. Uncrosslinked PAA was previously reported[5] to have a pK_a value of 6.1. These results are consistent with the findings of Thomson[12] that showed reduction in the pK_a value of PAA to 4.2 with incorporation of crosslinking agents into the PAA network.

Molecular Weight Between Crosslinks Determined by DSC

The glass transition temperatures for the dehydrated polymers are summarized in Table III. For lightly crosslinked PAA samples (with nominal crosslinking ratios less than 0.01 mol EGDMA/mol AA), there was no discernible correlation between T_g and the crosslinking ratio, X. In fact, for the lowest crosslinking levels of 0.001 mol EGDMA/mol AA, the thermograms from three separate polymer samples produced widely varying results of T_g from 106.1 to 113.1°C. Although the sample standard deviation in the glass transition temperature was only ±3.5°C, the resulting standard deviation in the value of $\bar{M}_c$ is ±70,000 g/mol. Further analysis revealed that the lower T_g value resulted from the incomplete incorporation of EGDMA into the hydrophilic network, consistent with the extraction analysis (sample A33).

Thermal analysis of highly crosslinked PAA (with $X \geq 0.01$ mol EGDMA/mol AA) provided the expected trend of increased T_g at increased crosslinking concentrations from 0.01 to 0.02 mol EGDMA/mol AA. The standard sample deviation of the molecular weight between crosslinks, $\bar{M}_c$, decreased from 70,000 to 1500 and 140 as the crosslinking ratio, X, increased from 0.001 to 0.01 and 0.02 mol EGDMA/mol AA.

Results from differential thermal analysis of copolymers prepared in either 40 mol % water or ethanol are also included in Table III. Samples in the form of discs cut from the top and middle of a cylindrical polymer sample (30 : 70 AA:HEMA in 40 mol % water) were evaluated for homogeneity. The average $\bar{M}_c$ values determined from triplicate samples at each position were equivalent (1700 g/mol). The copolymer containing 30 mol % AA and 70 mol % HEMA polymerized in water and having $X = 0.001$ mol EGDMA/mol AA led a similar mesh size to that of PAA with $X = 0.02$ and initial AA content of 10 mol %, as indicated by the $\bar{M}_c$ values of 1700 and 1760, respectively. To achieve similar mesh sizes, a higher degree of crosslinking was required for PAA in order to reduce the hydrophilicity and the swellability of the network. The effect of increased crosslinking ratio on the glass transition temperature was a dramatic increase in T_g, which further resulted in a reduction in the value of $\bar{M}_c$.

A 10-fold increase in the crosslinking ratio (from 0.001 to 0.010) in P(AA-*co*-HEMA) hydrogels containing 30 mol % AA and 70 mol % HEMA produced the significant increase of $\bar{M}_c$. The molecular weights between crosslinks obtained from analysis of the DSC results were consistently lower than the theoretical values calculated from the molecular weights of the repeating unit, M_r, and X, as shown in eq. (12):

$$\bar{M}_{c,\text{th}} = \frac{M_r}{2X} \tag{12}$$

It is known that association of proximate carboxyl groups in the backbone polymer chains leads to a lower effective $\bar{M}_c$. The presence of additional crosslinks decreased the chain mobility, which resulted in higher T_g values. The deviation between the calculated and theoretical $\bar{M}_c$ values decreased with increased EGDMA content for PAA.

Effect of Aspect Ratio on Dynamic and Equilibrium Swelling

We have shown in the past[13] that the aspect ratio, i.e., the ratio of sample disc diameter to its thickness, a, is an important parameter that can influence the dynamic/equilibrium swelling behavior. In this investigation, the aspect ratio affected the equilibrium volume swelling ratio, Q, of lightly crosslinked PAA ($X < 0.01$ mol EGDMA/mol HEMA) placed in deionized/distilled water as seen in Table IV. The equilibrium volume swelling ratio increased significantly as the aspect ratio was reduced. The increase

Table III Glass Transition Temperature and Molecular Weight Between Crosslinks as Determined by DSC Analysis of the Polymer Samples

AA to HEMA in Reactant Mixture (Mol AA/Mol HEMA)	X (Mol EGDMA/Mol Monomer)	T_g (°C)	$\bar{M}_c$ (g/mol)	$\bar{M}_{c,th}$ (g/mol)
PAA				
100 : 0	0.001	106.1	130,000	36,000
	0.001	108.9	12,580	36,000
	0.001	113.1	5340	36,000
	0.002	113.4	5130	18,000
	0.002	112.7	5650	18,000
	0.003	104.2	—	12,000
	0.004	110.1	9070	9000
	0.004	113.5	5060	9000
	0.010	115.1	4200	3600
	0.010	124.7	2060	3600
	0.020	128.2	1740	1800
	0.020	127.7	1780	1800
	0.020	132.0	1490	1800
	0.020	131.0	1550	800
P(AA-*co*-HEMA)				$T_{g,0}$ (°C)
30 : 70W[a]	0.001	84.0	1700	61
	0.001	84.0	1700	61
	0.010	103.8	910	61
	0.010	102.5	940	61
	0.010	100.5	990	61
30 : 70E	0.003	103.5	920	61
	0.004	101.1	970	61
	0.005	101.4	970	61
40 : 60W[a]	0.001	104.2	950	63
	0.002	102.5	990	63

[a] Solution polymerized in 40% water, W, or ethanol, E, with the total monomer content of 60 mol %. AA : HEMA represents the molar percentages of each monomer relative to the total monomer content.

in Q correlated well with increased disc thickness for values of the aspect ratio lower than 20. The relative importance of the aspect ratio on the equilibrium volume degree of swelling did not affect the mesh size or $\bar{M}_c$, as each remained essentially constant at 650 Å and 37,300 g/mol. The significance of the aspect ratio in altering the equilibrium swelling was more dramatic for the highly swellable polymers, such as lightly crosslinked PAA in pH 5 or greater media.

The dynamic swelling thickness, δ, of a PAA disc with a crosslinking ratio of 0.01 mol EGDMA/mol AA in a pH 7 solution with ionic strength 0.1N was reported as a function of time as shown in Figure 2. As water diffused into the glassy polymer sample, the thickness quickly attained a maximum within 2–4 min. The movement of the glassy/gel fronts on either side of the disc proceeded until the two fronts met at the center. The observed maximum dimensions resulted from the presence of a glassy core within the polymer sample. After the gel fronts met, the maximum diameter and thickness attained new equilibrium values which were found to be higher than the initial maximum value.

Typical water transport curves as a function of time are shown in Figure 3. The effect of the aspect ratio on the rate of water transport into the polymer samples was examined by calculating the water diffusion coefficient determined from the early time swelling data according to eq. (9). The results of water transport in PAA are summarized in Table V. The reduction in sample aspect ratios from 44 to 27 (for samples 5A and 6A) in a medium with pH 3 resulted in a fourfold increase of the water diffusion coefficient.

Table IV Parameters Determined from Equilibrium Swelling Studies for PAA Sample Discs

Sample ID	X (Mol EGDMA/Mol Monomer)	pH	Aspect Ratio a	Equilibrium Volume Swelling Ratio Q	Mesh Size ξ (Å)	$\bar{M}_c$ (g/mol)
A27	0.001	Water	10.7	102.1	672	37,370
A28	0.002	Water	20.9	83.0	626	37,300
A29	0.002	Water	11.9	87.8	639	37,340
A30	0.003	Water	5.2	106.2	681	37,380
A31	0.003	Water	9.7	95.0	655	37,240
A33	0.004	Water	7.5	92.4	650	37,350
A35	0.005	Water	12.4	85.3	633	37,390
1A	0.01	3	32.8	7.6	172	13,870
3A	0.01	3	21.6	9.0	191	15,220
7A	0.01	3	24.5	6.6	124	7,810
8A	0.01	3	33.3	5.9	107	6,290
1A	0.01	5	41.0	20.8	390	36,360
3A	0.01	5	24.4	21.2	387	35,390
7A	0.01	5	25.4	16.3	335	31,720
8A	0.01	5	32.7	10.8	282	29,430
1A	0.01	7	27.3	16.4	354	35,100
2A	0.01	7	21.7	46.8	335	35,320
3A	0.01	7	21.2	41.2	390	35,150
7A	0.01	7	33.7	26.3	307	31,570
8A	0.01	7	33.7	22.7	396	35,350
9A	0.01	7	29.7	15.7	335	32,280
5A	0.02	3	44.0	7.1	137	9,260
6A	0.02	3	27.0	8.3	164	12,030
5A	0.02	5	21.2	19.4	368	33,900
6A	0.02	5	22.6	18.8	366	34,280
5A	0.02	7	28.7	14.4	377	35,650
6A	0.02	7	27.1	18.7	367	34,380

Effect of Crosslinking Ratio on Swelling Behavior

No correlation could be established between the initial crosslinking ratio and the equilibrium volume swelling ratio for lightly crosslinked ($X < 0.01$ mol EGDMA/mol AA) PAA samples. For samples with aspect ratios greater than 20, the effect of crosslinking ratio on equilibrium swelling for constant pH values is summarized in Table IV.

As shown in Table IV, the values of $\bar{M}_c$ were constant at 37,350 ± 50 for all the lightly crosslinked polymers. This value of the molecular weight between crosslinks was subsequently used to calculate the experimental crosslinking ratio of 0.001 mol EGDMA/mol AA from eq. (11). The equilibrium swelling data for the lightly crosslinked PAA samples indicate that a large portion of the crosslinking agent, EGDMA, was not incorporated into the polymer network. These results are consistent with the residual analysis observations from GC.

Replicate samples of PAA containing 10 mol % AA in solution and crosslinked with 0.01 and 0.02 mol EGDMA/mol AA (samples 1A and 3A, 5A and 6A) were polymerized according to the optimized thermal initiation schedule. These polymer samples produced networks with $\bar{M}_c$ values that decreased from 14,550 to 10,650 as the crosslinking ratios increased from 0.01 to 0.02 mol EGDMA/mol AA. The theoretical values of the molecular weight between crosslinks, $\bar{M}_{c,\text{th}}$, were found to be much lower than the experimentally determined values, although the experimental data followed the expected trend. This deviation was determined to be due to the effects of pH and polymer ioniza-

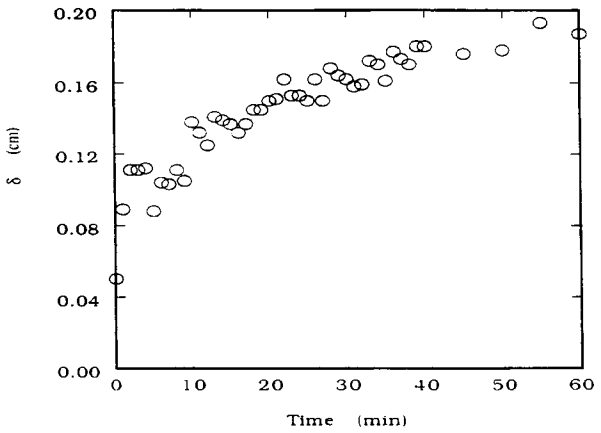

Figure 2 Thickness of a PAA sample containing 0.01 mol EGDMA/mol AA in a pH 7 medium as a function of time (initial dry sample thickness of 0.05 cm).

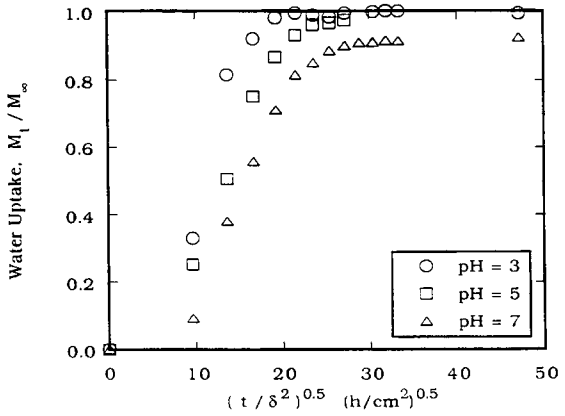

Figure 3 Effect of pH on the water uptake of PAA samples prepared from solutions of 10 mol % AA with 0.01 mol EGDMA/mol AA, as a function of normalized time at 37°C.

tion, which produced an increase in the ability to imbibe additional counterions to neutralize the fixed charges.

Effect of AA/HEMA Copolymerization on Swelling Properties

Copolymerization of AA with nonionizable HEMA resulted in less swellable polymers with lower equilibrium swelling ratio, Q. Results for some of the most swellable copolymers prepared are shown in Table VI. The equilibrium swelling ratio decreased from 7.3 for nonionized PAA (average of samples 1A, 3A, 7A, 9A) to 2.0 for P(AA-*co*-HEMA) with 55 mol % AA to 45 mol % HEMA.

More notably, the nonionizable copolymers attained the same equilibrium ratio regardless of degree of crosslinking, as reflected by the values of Q of 1.93, 2.00, 2.02, to 1.98 as the crosslinking ratio increased from 0.002, 0.003, 0.004, to 0.010 mol EGDMA/mol monomer. The effect of crosslinking on the dynamic swelling behavior for constant pH values was a reduction in the rate of water absorption, as indicated by the water diffusion coefficients of Table V.

This trend was even more evident when examining the water diffusion coefficient of the less hydrophilic copolymers of Table VII. Once again, the effect of an increased crosslinking ratio on the diffusion coefficient was investigated at a pH value of 3. It was found that the diffusion coefficient decreased from 1.42, 0.67, 0.27, to 0.05 $\times$ 10^{-7} cm^2/s as the crosslinking ratio increased from 0.002, 0.003, 0.004 to 0.010 mol EGDMA/mol AA.

Effect of pH on Dynamic Swelling Studies

The pH of the swelling medium had a significant effect on the swelling behavior of ionizable hydrophilic polymers. For PAA with a crosslinking ratio of 0.01 mol EGDMA/mol AA, the average value of

Table V Water Diffusion Coefficient in PAA as Determined from Equilibrium Swelling Studies

Sample ID	X (Mol EGDMA/Mol Monomer)	pH	Aspect Ratio a	Diffusion Coefficient, $D \times 10^7$ (cm^2/s)
1A	0.01	3	32.8	0.16
2A	0.01	3	33.4	4.85
3A	0.01	3	21.6	1.56
7A	0.01	3	33.3	0.40
1A	0.01	5	33.3	0.20
3A	0.01	5	24.4	2.43
7A	0.01	5	32.7	0.94
1A	0.01	7	27.3	1.10
2A	0.01	7	21.8	1.54
3A	0.01	7	21.2	1.43
3A	0.01	7	26.3	2.66
7A	0.01	7	33.7	0.54
8A	0.01	7	33.7	1.60
9A	0.01	7	24.0	1.82
5A	0.02	3	44.0	0.23
6A	0.02	3	27.0	0.92
5A	0.02	5	28.2	0.42
6A	0.02	5	22.6	2.19
5A	0.02	7	28.7	1.02
6A	0.02	7	27.1	2.56

Table VI Parameters Determined from Equilibrium Swelling Studies of P(AA-*co*-HEMA) Sample Discs Prepared by Bulk Polymerization of 55 : 45 AA : HEMA

X (Mol/ EGDMA/Mol Monomer)	pH	Aspect Ratio a	Equilibrium Volume Swelling Ratio Q	Mesh Size ξ (Å)	$\bar{M}_c$ (g/mol)
0.002	3.09	22.4	1.9	13.7	240
	3.21	21.2	1.9	13.3	230
	5.04	39.0	5.5	75.7	3640
	7.37	41.9	7.7	142	10,120
	Ethanol	15.1	3.4	36.3	1,150
0.003	3.32	36.0	2.0	14.6	260
	5.03	27.4	4.5	69.5	3,240
	7.31	26.6	7.0	125.8	8,500
	Ethanol	29.6	3.3	34.3	1,030
0.04	3.12	26.4	2.0	14.6	260
	5.11	33.3	6.5	98.5	5,480
	7.38	40.4	7.7	141.5	10,050
	7.38	38.3	7.4	129.3	8,650
	Ethanol	37.7	3.1	33.2	1,010
0.01	3.32	28.4	2.0	14.1	250
	5.06	20.3	4.3	49.5	1,840
	7.31	22.9	6.1	101.1	6,020
	Ethanol	25.9	3.0	27.2	700

Table VII Water Diffusion Coefficient in P(AA-*co*-HEMA) Prepared by Bulk Polymerization of 55 : 45 AA : HEMA as Determined from Equilibrium Swelling Studies

X (Mol EGDMA/Mol Monomer)	pH	Ionic Strength, I	Aspect Ratio a	Diffusion Coefficient, $D \times 10^7$ (cm^2/s)
0.002	3.09	0.01	22.4	1.42
	3.21	0.10	44.5	2.33
	3.21	0.10	21.2	3.57
	5.04	0.30	39.0	0.64
	7.37	0.05	41.9	2.77
0.003	3.32	0.01	36.0	0.67
	5.03	0.03	27.4	0.35
	7.31	0.04	26.6	5.23
0.004	3.12	0.01	26.4	0.27
	5.11	0.03	33.3	1.24
	7.38	0.05	40.4	2.00
	7.38	0.05	38.3	1.70
0.01	3.32	0.01	28.4	0.05
	5.06	0.03	20.3	0.61
	7.31	0.04	22.9	2.43

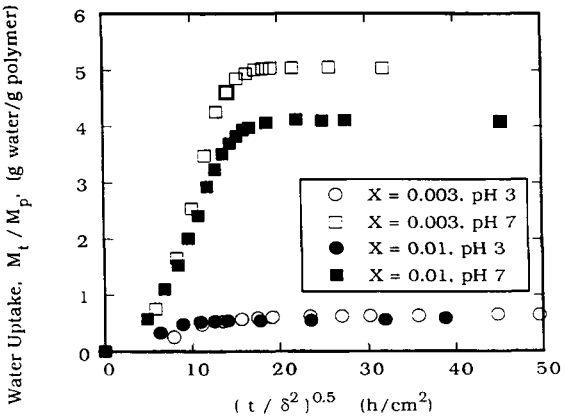

Figure 4 Comparison between the effects of pH and crosslinking ratio on the penetrant uptake of P(AA-*co*-HEMA) samples containing 55 mol % AA and 45 mol % HEMA, at 37°C in buffered media.

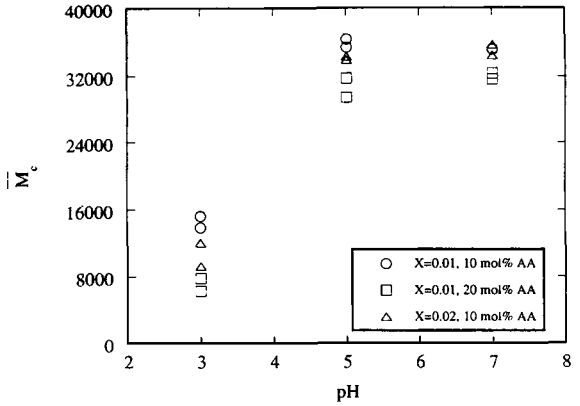

Figure 5 Effects of pH and crosslinking ratio on the molecular weight between crosslinks, $\bar{M}_c$, of PAA hydrogels swollen at 37°C with initial reactant mixture concentration of 10 or 20 mol % AA.

the equilibrium volume swelling ratio increased from 7.3 to 17.3 and 27.3 as the pH increased from 3 to 5 and 7, respectively (Table IV). Analysis of the dynamic sorption data (Fig. 3) revealed the transition in diffusional mechanism from Fickian to non-Fickian with increased ionization of the polymer. P(AA-*co*-HEMA) containing 55 mol % AA and 45 mol % HEMA with the same crosslinking ratio of 0.01 showed a similar trend of increased equilibrium volume swelling ratio from 2.0 to 4.2 and 6.1 as the pH increased from 3.1 to 5.1 and 7.3, respectively (Table VI).

The relative effects of the degree of crosslinking and swelling pH are summarized in Figure 4 for P(AA-*co*-HEMA) swelling at 37°C. The mass of water imbibed into the polymer per mass of polymer, M_t/M_p, was plotted vs. the thickness-normalized square root of time. The most remarkable effect on the equilibrium mass uptake of water per unit mass of polymer was observed as the pH increased from 3 to 7. The mass uptake of water into the nonionized polymer was not significantly affected by the crosslinking ratio. The effect of crosslinking on swelling became more evident at the higher pH value, since the polymer network swelled to its maximum value. These studies also established the effect of increased concentrations of water in the polymer samples on the mesh size as shown in Table VI.

As mentioned previously, at low pH values, $\bar{M}_c$ was a strong function of the crosslinking ratio, with the lowest concentration of EGDMA allowing the most water to penetrate the polymer sample. As the pH was increased to 5 and 7, this effect was not significant (see Fig. 5 and Table VII). This unusual result provided insight into the most important variable that controlled the water content and swelling of PAA, which was the pH.

Effect of Ionic Strength in Swelling

The mass uptake of water into the P(AA-*co*-HEMA) samples containing 40 mol % AA and 60 mol % HEMA was investigated as a function of time and ionic strength (see Fig. 6). At higher concentrations of salt, i.e., at increased ionic strength of the external solution, the mass uptake was lower. Since the hydrogel contained fixed charges of carboxylate anions, the concentration of cations within the gel was higher than the external solution. This led to a greater osmotic pressure inside the gel compared to the solution, which caused the polymer to swell.

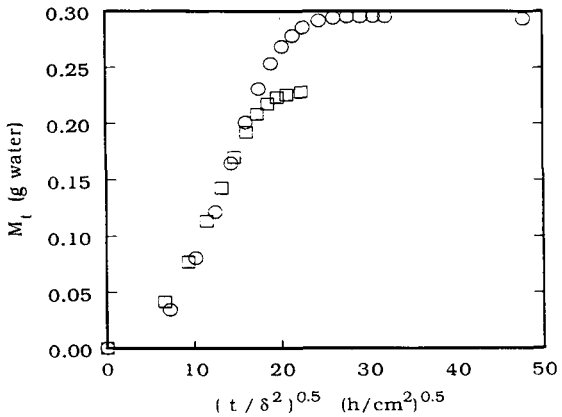

Figure 6 Effect of ionic strength on the water uptake of P(AA-*co*-HEMA) hydrogels containing 40 mol % AA and 60 mol % HEMA and crosslinked with 0.001 mol EGDMA/mol monomer, in pH 7 buffer media at 37°C: (○) $I = 0.038N$; (□) $I = 0.10N$.

When the ionic strength of the swelling media was increased from 0.038 to 0.1N, the osmotic pressure decreased. The final result of increased ionic strength of the external solution was a lower equilibrium volume swelling ratio, Q, and a lower amount of water imbibed into the polymer at equilibrium, M_∞.

Polymer Mesh Size

Previously, Canal and Peppas[10] determined that in most hydrogels a linear relationship exists between the mesh size, ξ, and the inverse of the polymer volume fraction in the swollen state, $v_{2,s}^{-1}$. The mesh size of P(AA-*co*-HEMA) samples was also found to be inversely related to the polymer volume fraction in the swollen state, as shown in Figure 7. The observed increase in the mesh size was a direct result of the increased amount of water present in the hydrogel. PAA was more hydrophilic than were the P(AA-*co*-HEMA) copolymers. Hence, the larger amount of water in the polymer led to an increased mesh size. These studies established the effect of increased swelling ratio on the diffusional space for anionic polymers based on AA.

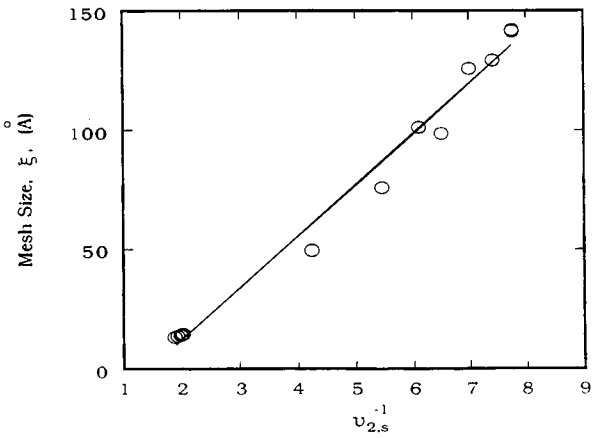

Figure 7 Mesh size, ξ, of P(AA-*co*-MAA) hydrogels as a function of polymer volume fraction in the swollen state, $v_{2,s}$ for copolymers containing 55 mol % AA and 45 mol % HEMA.

CONCLUSIONS

This investigation was conducted to optimize the polymerization reaction procedure and to establish the swelling behavior of ionizable hydrogels in the absence of solutes, so that the diffusion and solute/polymer interaction studies could be interpreted more accurately. GC analysis of the polymer extract solution verified the presence of unreacted residuals. The titration of PAA hydrogels containing 0.010 mol EGDMA/mol AA with 50 μL aliquots of 0.1142 N NaOH established a pK_a of 4.25, which corresponded well with literature values. The experimentally determined values of molecular weight between crosslinks, $\bar{M}_c$, predicted from DSC were consistently lower than the theoretical values. This was attributed to the association between carboxyl groups along the polymer backbone chain.

The equilibrium swelling studies demonstrated that the mesh sizes of the hydrogels, ξ, were controlled by the monomer concentration in the reactant polymerization mixture, the swelling solution pH, and the ionic strength. The experimental values of the molecular weight between crosslinks determined from the swelling experiments were greater than the theoretical values, due to the absorption of counterions from the external solution into the hydrogel to neutralize the fixed charges present in the ionized polymer. It was also noted that $\bar{M}_c$ attained a limiting value as the solution pH was increased above the pK_a of PAA. This state was described as being limited by the chemical crosslinks, since self-associations and physical entanglements were eliminated. The mesh sizes of P(AA-*co*-HEMA) hydrogels increased linearly with the inverse of the swollen polymer volume fraction in the pH range from 3 to 7, regardless of the crosslinking ratio.

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