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Characterization, dynamic swelling behaviour and solute transport in cationic networks with applications to the development of swelling-controlled release systems

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Poly(diethylaminoethyl methacrylate-*co*-hydroxyethyl methacrylate), poly(diethylaminoethyl acrylate-*co*-hydroxyethyl methacrylate) and poly(methacrylaminopropyl ammonium chloride-*co*-hydroxyethyl methacrylate) were synthesized by free radical polymerization and characterized using differential scanning calorimetry and dynamic mechanical analysis. Transport of citrate–phosphate–borate buffer solutions into the polymer network was investigated at different pH values. The anomalous transport behaviour in these polymers was analysed and the swelling front velocity was determined. The effect on the transport mechanism of polymer structural characteristics, such as the molecular weight between crosslinks and the concentration of ionizable pendent groups, was studied. The transport was found to be anomalous at acidic pH values where the polymer networks were ionized. Transport of oxprenolol HCl, insulin, myoglobin and albumin was investigated and was found to be strongly dependent on the mesh size of the polymer network.

(Keywords: cationic polymers; hydrogels; characterization)

INTRODUCTION

Ionic networks are polymers containing groups that ionize when placed in contact with a polar solvent. Their ability to respond to changes in the external environment is one of the most important properties utilized in many applications. The charged groups in the network ionize under favourable external conditions, and the resulting repulsion between the groups causes the network to expand. Polymer networks undergo discontinuous volume transitions in response to small changes in temperature, solvent composition, pH and ionic strength, or when an electric field is applied. They may be classified according to the nature of the charges present in the network as anionic, cationic and ampholytic networks.

This work examines cationic polymers that are able to swell in acidic environments. When ionized cationic polymers carry positive charges like ammonium (NH_4^+) or amino groups ($-NH_3^+$), owing to their ability to swell in an acidic environment, their diffusional properties are profoundly affected. First-order phase transition in positively ionized acrylamide gels was observed by Hirokawa *et al.*[1]. They also studied non-acrylamide gels like poly(styrene sulfonate) that undergo discontinuous transition. The experiments were carried out with various relative compositions of acrylamide and methacryloyl amidopropyl trimethylammonium chloride with *N*, *N*-methylenebisacrylamide as the crosslinking agent. They proved that the phase transition of ionic networks is universal and not confined to a specific group of polymer networks.

Siegel and co-workers[2–4] studied the copolymers of methyl methacrylate and *N*,*N*′-dimethylaminoethyl methacrylate crosslinked with divinylbenzene. The release of caffeine was studied in citrate-buffered saline solutions at pH values of 3, 5 and ionic strength of 0.1 M, and phosphate-buffered saline at pH 7 and ionic strength of 0.1 M. It was found that the gel adopted a collapsed state at and above the neutral pH, but was highly swollen as the pH was lowered. Studies were also carried out to determine the transition pH between the collapsed and swollen states.

Farahani *et al.*[5] also studied the swelling behaviour of anionic and cationic gels in electrolytic solutions at different pH and salt concentrations. The experiments were carried out using anionic gels made of copolymers of sodium acrylate or cationic gels of 3-methacrylamidopropyl trimethylammonium chloride. Both gels were crosslinked with *N*,*N*-methylene bisacrylamide. In general, the cationic gel imbibed more water than the anionic gel at pH< 6. This was expected because the cationic gel becomes ionized in the acidic range whereas the anionic gel remains largely unionized. Addition of salt to the external solution depressed the degree of swelling. Thus, solutions containing counterions of higher charge were more effective in shrinking of the gels. Farahani *et al.*[5] modelled the equilibrium swelling behaviour by assuming the additivity of osmotic pressure

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of polyelectrolyte–salt solutions and described the ion swelling pressure as a function of the ionic composition of the external solution. Wang and Bloomfield[6] described the osmotic pressure of sodium poly(styrene sulfonate) and poly(styrene sulfonic acid) without added salts using the scaling theory.

Ballestrasse and Beck[7] studied the transport properties and swelling of copolymers of methyl methacrylate with comonomers such as methacrylamidopropyl trimethylammonium chloride, dimethylaminopropyl methacrylamide, and 2-acrylamido-2-methylpropane sulfonic acid. They determined the transference numbers, electrical conductivities, degree of swelling in water and ion exchange capacity of the membranes. They observed that there was very little swelling at low ionic group concentrations in aqueous solutions, thus allowing the polymers to be made without crosslinking.

Prausnitz and collaborators[8,9] studied the swelling of polyacrylamide gels in water, and of copolymers of acrylamide and methacrylamidopropyl trimethylammonium chloride in aqueous NaCl solutions. Gel swelling was investigated as a function of gel structure, degree of gel ionization and solution ionic strength. It was found that since methacrylamidopropyl trimethylammonium chloride dissociates strongly in aqueous solution, the degree of gel swelling was relatively insensitive to pH. Therefore, the variables of interest were the ionic strength or salt concentration. They also studied the swelling equilibria for a copolymer of thermally sensitive *N*-isopropylacrylamide with sodium acrylate and 2-(dimethylamino)ethyl methacrylate in citrate–phosphate buffer solutions, and found that, with increasing ionization, the temperature range over which the gel volume change is greatest becomes larger and shifts to higher temperatures.

The effect of various polymers on insulin release in the nasal cavity was studied. It was determined that sodium hyaluronate and poly(*N*-isopropyl acrylamide) exerted a significant influence on the plasma glucose level[10]. However, crosslinked substituted dextran (substituted with 2-ethylaminoethyl groups) had no effect at all on the plasma glucose level. This was attributed to the binding of insulin to the ionic groups.

In this contribution, we discuss the synthesis and characterization of some novel cationic polymers and examine their applications in the field of controlled drug delivery.

EXPERIMENTAL

Synthesis of polymers

Three sets of copolymers were synthesized: poly(2-diethylaminoethylmethacrylate-*co*-2-hydroxyethylmethacrylate), henceforth designated as P(DEAEM-*co*-HEMA); poly(2-diethylaminoethylacrylate-*co*-2-hydroxyethylmethacrylate), henceforth designated as P(DEAEA-*co*-HEMA); and poly[3-(methacryloylamino)propyl trimethylammonium chloride-*co*-2-hydroxyethyl methacrylate], henceforth designated as P(MAPTAC-*co*-HEMA). The crosslinking agent used for all types of copolymers was ethylene glycol dimethacrylate, henceforth designated as EGDMA. The initiators for the polymerization reaction were 2,2-azobis(2-methylpropionitrile) (AIBN) for the first two copolymers or 4,4-azobis(4-cyanovaleric acid) (ACV) for P(MAPTAC-*co*-HEMA). HEMA [molecular weight (MW) = 130], MAPTAC (MW = 222.5), EGDMA (MW = 198.22), AIBN (MW = 164.21) and ACV (MW = 280.28) were obtained from Aldrich Chemical, Milwaukee, WI, whereas DEAEM (MW = 185) and DEAEA (MW = 171) were obtained from Monomer-Polymer and Dajac Labs, Trevose, PA. The monomers HEMA, DEAEM and DEAEA were purified before polymerization by eliminating the inhibitor (methyl ethyl hydroquinone) using a De-Hibit-500 column (Polysciences Inc., Warrington, PA). The monomer MAPTAC was obtained as a 50 wt% solution in water and was used as received. The initiators AIBN and ACV, and the crosslinking agent EGDMA, were used as received.

Several copolymer samples of P(DEAEM-*co*-HEMA) were prepared containing a feed DEAEM molar fraction of 0.1, 0.3 and 0.6. The crosslinking ratio (X) of these samples varied from 0.001 to 0.005 mol EGDMA/total mol of comonomers. In addition, PHEMA was also prepared with different crosslinking ratios. Similarly copolymers of P(DEAEA-*co*-HEMA) and P(MAPTAC-*co*-HEMA) were prepared containing DEAEA or MAPTAC molar feed fractions of 0.1, 0.3 and 0.6. Again, the crosslinking ratio of these samples varied from 0.001 to 0.005 mol EDGMA/total mol of comonomers.

The polymerization was carried out in polypropylene vials immersed in a water bath at 60°C for 2 h followed by 24 h at 80°C. Upon completion of the reaction, the vials were cut to remove the glassy samples, which were further dried in a vacuum oven for approximately 4 days at 25°C. The cylinders were cut into thin discs (of thickness ~ 1 mm) using a diamond rotary saw (Buehler Ltd, Lake Bluff, IL). The polymer discs were washed in water for approximately 4 days, dried in a vacuum oven at 25°C and stored in a desiccator until further use.

Polymer membranes were also prepared by casting the comonomer solution between glass plates using a Teflon sheet as a spacer. The glass plates (10 cm × 10 cm) were coated with a thin layer of silicone oil to prevent adhesion of the polymer to the plate. The temperature scheme used for the polymerization was the same as before. After polymerization, the glass plates were immersed in deionized water for a period of 1 week after which the polymer membrane was separated from the plates and stored in deionized water until use.

Elemental analysis was carried out to determine the nitrogen concentration in the polymer samples. Small amounts of polymer (~ 10 g in the form of cylindrical discs) were analysed for nitrogen concentration by Kjeldahl analysis in the Chemistry Department at Purdue University. The polymers analysed were P(DEAEA-*co*-HEMA) with 30 mol% DEAEA in feed and crosslinking ratios X = 0.001 and 0.005, P(DEAEA-*co*-HEMA) with 60 mol% DEAEA in feed and crosslinking ratio of 0.001, and P(DEAEM-*co*-HEMA) with 30 mol% DEAEM in feed and crosslinking ratio X = 0.001. From the last polymer, specimens were taken from the top and bottom of the cylinder and analysed. In addition, P(DEAEM-*co*-HEMA) with 60 mol% DEAEM in the feed and crosslinking ratio X = 0.001 was also analysed.

Dynamic and equilibrium swelling studies

The dynamic and equilibrium swelling studies were carried out in a simulated physiological buffer solution

by dissolving 7 g citric acid monohydrate (Mallinckrodt, Paris, KY), 3.83 g phosphoric acid (85 wt% solution, Fisher Scientific, Fairlawn, NJ) and 3.54 g boric acid (J. T. Baker Inc., Phillsburgh, NJ) in 343 ml of 1 M sodium hydroxide solution (Mallinckrodt, Paris, KY). This solution was mixed with deionized water to make a 1 l stock solution. A dilute solution of HCl (Mallinckrodt, Paris, KY) was prepared by adding 10 M HCl to deionized water. The amount of HCl added was such that the resulting HCl solution had a molarity of 0.1 M. Buffer solutions with pH values of 2, 4, 6, 8, 10 and 12 were prepared. Sodium chloride (Fisher Scientific, Fairlawn, NJ) was added to adjust their ionic strength to 0.1 M.

The dynamic swelling behaviour of the polymer samples P(DEAEM-*co*-HEMA), P(DEAEA-*co*-HEMA) and P(MAPTAC-*co*-HEMA) was studied using dry cylindrical polymer discs ($\sim$ 1 cm diameter $\times$ 1 mm thickness) immersed in 100 ml of a buffer solution at 37 ± 2°C. The equilibrium swelling value was determined by leaving the discs in the buffer solution at 37°C for 24 h. Sample weights were taken periodically to ensure that equilibrium was attained.

The effect of ionic strength was studied on P(MAPTAC-*co*-HEMA) by immersing the polymer samples in buffer solutions (pH 6) at ionic strengths of 0.1, 0.3, 0.5 and 1.0 M. The high ionic strengths were obtained by adding appropriate amounts of sodium chloride to the buffer solution.

The position of the glassy-rubbery front during the swelling was determined using a separate experimental set-up. Polymer specimens in the form of thin sheets ($\sim$ 3 cm $\times$ 0.7 cm $\times$ 0.1 cm) were cut from the membranes (stored in water) and dried in a convective oven at 70°C sandwiched between two glass slides for 24 h. The experimental set-up consisted of an optical bench where the dry glassy thin polymer strip was placed in a transparent glass cuvette and visible light was passed through one side. The glass cuvette was filled with the buffer solution and the glassy–rubbery front was observed using an objective lens at periodic intervals.

Thermal and dynamic mechanical analysis

The glass transition temperatures of the various polymers prepared were determined using a differential scanning calorimeter (model 2910, TA Instruments, Wilmington, DE). Dynamic mechanical analysis was performed on polymer samples in the form of thin sheets (4 cm $\times$ 1 cm $\times$ 0.1 cm) that were cut from each membrane (stored in water) and dried in a convective oven at 70°C while sandwiched between two glass slides for 24 h. The polymer sample was then clamped between two parallel arms of the dynamic mechanical analyser (model 983, TA Instruments, Wilmington, DE) and deformed under an oscillating stress using a sinusoidal driver signal. The dry polymer samples were subjected to an 0.1 Hz sinusoidal wave with an amplitude of 0.2 mm and the temperature of the polymer was raised at a programmed rate of 10°C min^{-1}. In some cases the amplitude was increased to 0.7 mm or decreased to 0.1 mm due to unusually tough or very soft material. The behaviour of a polymer sample under this deformation was monitored by a linear variable displacement transducer. The displacement and lag between the driver signal and the transducer were measured and related to the storage modulus, G', and loss modulus, G'', of the sample.

The polymers studied using a dynamic mechanical analyser were P(DEAEM-*co*-HEMA) samples with 10 mol% DEAEM in feed and crosslinking ratio of 0.001, and with 30 ml% DEAEM in feed and crosslinking ratios of 0.001 and 0.005. Copolymers of P(DEAEA-*co*-HEMA) with 10 mol% DEAEA and crosslinking ratios of 0.001 and 0.005, and 30 mol% DEAEA in feed and crosslinking ratio of $X = 0.001$ were also tested.

Tensile experiments

A polymer sample in the form of a thin sheet (4 cm $\times$ 1 cm $\times$ 0.1 cm) was cut from the membrane (stored in water) and swollen in buffer solutions of different pH values at 37°C. The swollen polymer strips were mounted on a tensile tester (model 4301, Instron Corp, Canton, MA) and stretched at a rate of 2 mm min^{-1}. Each sample was stretched to a maximum of 20% of its original length and the stress–strain data were recorded.

Solute loading and release studies

Solutes used for release studies included oxprenolol HCl, bovine pancreatic insulin, bovine albumin and myoglobin, obtained from Sigma Chemical Co., St. Louis, MO. Drug solutions in water were prepared at concentrations of 10 and 20 g l^{-1}. Ethanol was added to the drug solution (1 wt%). Dry polymer discs were immersed in this solution for 1 week at 4°C. The polymer discs were later dried at room temperature for 2 days and then stored in a desiccator until further use.

The release studies were carried out in a dissolution apparatus (Hanson Research, Northridge, CA). Release studies of insulin were carried out at 25°C whereas the release studies of all the other solutes were carried out at 37°C. Release studies were carried out in 300 ml of a buffer solution for small molecular weight drugs like oxprenolol HCl, and in 100 ml of a buffer solution for large molecular weight proteins like albumin, insulin and myoglobin. The solution was continuously stirred at 60 rev min^{-1} to eliminate any drug concentration gradient developing in the solution. Buffer solution was added periodically to the release vessel to compensate for the solution lost due to evaporation. Aliquots were taken periodically and stored in a glass vial for analysis. The solution samples were analysed using an ultraviolet spectrophotometer (model 559, Perkin–Elmer, Norwalk, CT) at a wavelength at which the drug solution showed a maximum absorbance.

ANALYSIS OF EXPERIMENTAL RESULTS

Polymer preparation characteristics

Upon synthesis of the various ionic polymers, it was necessary to determine the nature of the copolymers formed during the polymerization reaction. This was done by an elemental analysis of the nitrogen content (from the amine group) in the polymer sample. For example, elemental analysis of P(DEAEA-*co*-HEMA) samples with 30 mol% DEAEA in the feed and crosslinking ratio of 0.001 yielded a nitrogen concentration of 2.45 wt%. Thus, the weight fraction of DEAEA in the

Table 1 Results of elemental analysis of P(DEAEA-*co*-HEMA) and P(DEAEM-*co*-HEMA) samples

Polymer	Crosslinking ratio in the feed, X (mol/mol)	Feed mol fraction, f_1^a	Product mol fraction, F_1^a
P(DEAEA-*co*-HEMA)	0.001	0.30	0.29 ± 0.013
	0.005	0.30	0.27 ± 0.014
	0.001	0.60	0.50 ± 0.005
P(DEAEM-*co*-HEMA)	0.001	0.30	0.27 ± 0.010^b
			0.25 ± 0.012^c
	0.001	0.60	0.54 ± 0.010

[a] Molar fraction of ionic compound DEAEA or DEAEM
[b] Samples from bottom of vial
[c] Samples from top of vial

Table 2 Density of polymers in the dry and swollen states

	Composition		Density ($g\,cm^{-3}$)		
Polymer	In the feed (mol%)	Crosslinking ratio in the feed, X (mol/mol)	Dry	Swollen	Volume fraction in swollen polymer, v_2
PHEMA	100	0.001	1.28	1.04	0.49
	100	0.005	1.28	1.16	0.56
P(DEAEM-*co*-HEMA)	10	0.001	1.22	1.16	0.47
	10	0.005	1.26	1.15	0.63
	30	0.001	1.18	1.12	0.23
	30	0.005	1.14	1.05	0.58
	60	0.001	1.15	1.14	0.25
	60	0.005	1.15	1.14	0.35
P(DEAEA-*co*-HEMA)	10	0.001	1.24	1.11	0.71
	10	0.005	1.26	1.22	0.58
	30	0.001	1.24	1.10	0.42
	30	0.005	1.22	1.17	0.42
	60	0.001	1.18	1.07	0.33
	60	0.005	1.18	1.13	0.43
P(MAPTAC-*co*-HEMA)	10	0.001	1.26	1.19	0.03
	10	0.005	1.25	1.05	0.16
	30	0.001	1.24	NA	NA
	30	0.005	1.22	0.99	0.02

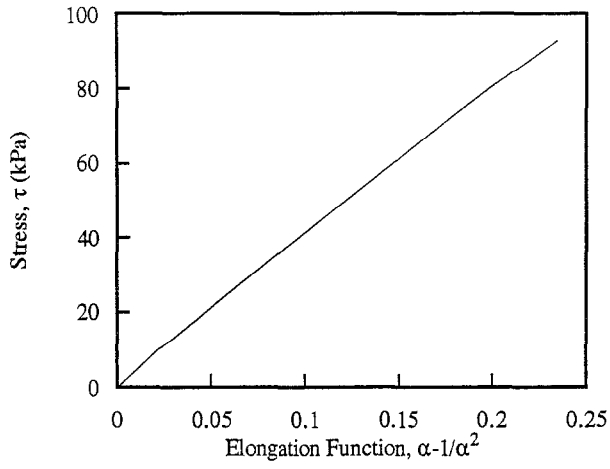

Figure 1 Stress–elongation curve of swollen P(DEAEA-*co*-HEMA) samples containing 30 mol% DEAEM in the feed with a crosslinking ratio of 0.001 mol EGDMA/mol monomers

P(DEAEA-*co*-HEMA) sample, w_1, was calculated as 29.92%. The mole fraction of DEAEA in P(DEAEA-*co*-HEMA), F_1, was calculated as 24.50%.

The results of the analysis are shown in *Table 1*. In the case of both P(DEAEA-*co*-HEMA) and P(DEAEM-*co*-HEMA) samples, the product composition follows the feed composition within the experimental range of error (± 0.3 wt%). An error of ± 0.3 wt% in the nitrogen concentration in P(DEAEA-*co*-HEMA) sample containing 30 mol% DEAEA in the feed and crosslinking ratio of 0.001 mol EGDMA/mol monomers translates to ± 1.3 mol% in the polymer. The homogeneity of the polymer samples was studied by taking samples from the top and bottom of the cylindrical polymer rod and analysing them for nitrogen content. The elemental analysis was carried out for P(DEAEM-*co*-HEMA) samples with 30 mol% DEAEM in the feed and a crosslinking ratio of 0.001. The difference in these two values is within the range of experimental error and, thus, it was concluded that the polymer samples were homogeneous.

Determination of molecular weight between crosslinks, $\bar{M}_c$

The effective molecular weight between crosslinks, $\bar{M}_c$, was determined from the stress–strain behaviour of swollen polymer samples. The stress–strain data were converted to stress–elongation function ($\alpha - 1/\alpha^2$) data and were then analysed using regression; excellent correlation coefficients (> 0.99) were obtained using the classical[11] equation. A typical stress–elongation function curve is shown in *Figure 1*.

$$\tau = RT\left(\frac{\rho_{sp}}{\bar{M}_c}\right)\left(1 - \frac{2\bar{M}_c}{\bar{M}_n}\right)\left(\alpha - \frac{1}{\alpha^2}\right) \qquad (1)$$

Table 3 Analysis of the crosslinked structure of the networks

Polymer	Composition: In the feed (mol%)	Composition: Crosslinking ratio in the feed, X (mol/mol)	$\bar{M}_c$	$\bar{N}_c$	$\bar{M}_{c,theor}$
P(DEAEM-*co*-HEMA)	10	0.001	8540	61	77915
	10	0.005	10745	77	15580
	30	0.001	10110	64	79025
	30	0.005	6835	43	15805
P(DEAEA-*co*-HEMA)	10	0.001	9765	73	67270
	10	0.005	9290	70	13455
	30	0.001	9555	67	71765
	30	0.005	7610	53	14355

Table 4 Polymer–solvent interaction parameters, χ

Polymer	In the feed (mol%)	Crosslinking ratio in the feed, X (mol/mol)	Interaction parameter, χ
P(DEAEM-*co*-HEMA)	10	0.001	0.71
	10	0.005	1.17
	30	0.001	0.28
	30	0.005	1.00
P(DEAEA-*co*-HEMA)	10	0.001	1.50
	10	0.005	1.01
	30	0.001	0.59
	30	0.005	0.59
P(MAPTAC-*co*-HEMA)	10	0.001	0.03
	10	0.005	0.17
	30	0.001	–
	30	0.005	0.02

Here, τ is the stress, α is the elongation ($= \epsilon + 1$, where ϵ is the strain), R is the universal gas constant, T is the absolute temperature, ρ_{sp} is the density of the swollen polymer network, and $\bar{M}_n$ is the number-average molecular weight of the uncrosslinked chains (taken[12] as $\bar{M}_n = 75000$). The density of the swollen polymer samples was measured using the buoyancy technique[12]. *Table 2* lists the densities and volume fractions of the dry and swollen polymer samples. In general[3], as the crosslinking ratio was increased, the density of the polymer increased. When developing the above equation, an assumption was made that the ratio of the mean square length of the chains in the unstrained state to the mean square length of the freely rotating chain, otherwise known as the front factor, was equal to one.

The $\bar{M}_c$ for polymers prepared are listed in *Table 3*. The average of two readings is shown for each polymer sample. An increase in the crosslinking ratio led to a decrease of the molecular weight crosslinks in all cases, except in P(DEAEM-*co*-HEMA) samples containing 10 mol% DEAEM in the feed. This can only be explained by the fact that the crosslinking agent added during the polymerization reaction was not fully incorporated into the polymer network even though the reactivity ratios of the comonomers in the polymer indicated otherwise. For comparison purposes, the theoretical molecular weight between crosslinks is also shown in *Table 3*. Due to partial incorporation of EGDMA in the low HEMA content terpolymers, typical theoretical values of the number-average molecular weight between crosslinks could be calculated. For example, the theoretical molecular weight between crosslinks in a P(DEAEM-*co*-HEMA) sample containing 10 mol% DEAEM in the feed and a crosslinking ratio of 0.001 was calculated as follows:

$$\bar{M}_{c,theor} = \frac{M_r}{2X} = \frac{0.21 \times M_{DEAEM} + 0.78 \times M_{HEMA}}{2 \times 0.0009} = 77915 \quad (2)$$

where M_r is the molecular weight of the repeating unit, and the coefficients 0.21 and 0.78 indicate the molar fractions of the two comonomers in the final copolymer as determined by elemental analysis. The average number of repeating units between two crosslink junctions, $\bar{N}_c$, was calculated from the following equation

$$\bar{N}_c = \frac{\bar{M}_c}{M_r} \quad (3)$$

where the experimentally determined value of the molecular weight between crosslinks was used. The number of repeating units decreased from 64 to 43 when the crosslinking ratio was increased in P(DEAEM-*co*-HEMA) samples containing up 30 mol% DEAEM in the feed. The value of $\bar{M}_c$ calculated from experiments is always lower than the theoretical $\bar{M}_c$ due to entanglements and other network defects[13].

Determination of the polymer–solvent interaction parameter, χ

The polymer–solvent interaction parameter, χ, was determined using the Flory–Rehner equation. The conventional interaction parameter χ as described by Flory does not take into account ionic interactions in the polymer network. Hence, for cationic polymers, we have

Table 5 Glass transition temperature and theshold concentration of ionic polymers

Polymer	Composition		T_g^0 (°C)	$c^* \times 10^2$ (g/g)
	In the feed (mol%)	Crosslinking ratio in the feed, X (mol/mol)		
PHEMA	100	0.001	112.3	0.12
	100	0.005	113.1	0.12
P(DEAEM-*co*-HEMA)	10	0.001	58.1	3.38
	10	0.005	70.3	5.33
	30	0.001	64.4	4.38
	30	0.005	75.7	6.20
	60	0.001	73.8	5.88
	60	0.005	68.4	5.02
P(DEAEA-*co*-HEMA)	10	0.001	60.1	3.69
	10	0.005	82.1	7.21
	30	0.001	65.7	4.60
	30	0.005	85.3	7.73
	60	0.001	60.4	3.74
	60	0.005	74.7	6.03
P(MAPTAC-*co*-HEMA)	10	0.001	61.7	3.95
	10	0.005	61.7	3.94
	30	0.001	68.1	4.97
	30	0.005	81.5	7.13

determined an interaction parameter which takes into account the various interactions in a polymer network. We have evaluated an interaction parameter from the Flory–Rehner expression which describes the total interaction (mixing and ionic) of the gel with water. At equilibrium, the chemical potentials of water inside and outside the polymer network[13] are equal:

$$\ln(1-v_2)+v_2+\chi v_2^2+\frac{v_1}{\bar{v}\bar{M}_c}\left(1-\frac{2\bar{M}_c}{\bar{M}_n}\right)\left(v_2^{1/3}-\frac{v_2}{2}\right)=0 \quad (4)$$

The interaction parameter χ was obtained by substituting the corresponding values of the polymer volume fraction, v_2, density, v^{-1}, and molecular weight between crosslinks, $\bar{M}_c$, in equation (4). The calculated polymer–solvent interaction parameters, χ, for the polymer samples are listed in *Table 4*. An increase in the ionizable comonomer content decreases the interaction parameter, thus increasing the compatibility between the polymer and water.

The molecular weight between crosslinks could not be determined for crosslinked P(MAPTAC-*co*-HEMA) samples because they were so highly swollen in water that they crumbled upon mounting them on the tensile tester. Hence, the theoretical $\bar{M}_c$ values of 12 000 and 9000 were used for P(MAPTAC-*co*-HEMA) polymer samples with crosslinking ratios of 0.001 and 0.005, respectively. Very low values of the interaction parameter were obtained through this analysis for P(MAPTAC-*co*-HEMA) samples. This may be explained by the fact that these samples swelled to a very high degree in water.

Thermal analysis for determination of glass transition temperature

The glass transition temperatures of various polymers tested are listed in *Table 5*. As the ionic comonomer composition of the polymer increased, the glass transition temperature of the polymer increased. As the crosslinking of the polymer increased, the glass transition temperature also increased due to a decrease in the mobility of the polymer chains. The glass transition temperature could be used to determine the threshold water concentration of ionic polymers, c^*, which is defined as the minimum concentration of the penetrant required to convert a polymer from a glassy state to a rubbery state at the experimentation temperature. This is expressed by the following equation derived from the free volume theory:

$$c^* = \frac{T_g^0 - T_g}{(\beta/\alpha_2)} \quad (5)$$

where T_g^0 is the glass transition temperature of the glassy polymer and T_g is the experimentation temperature (= 37°C). Williams *et al.*[14] have suggested a universal value for the thermal expansion α_2 of 4.8×10^{-4} K^{-1}. Values of the diluent expansion coefficient β depend on the size of the penetrant molecules and the specific interaction (either physical or chemical) with the polymer chain element. By comparison with similar systems of poly(methyl acrylate) with water as a diluent[15], we have chosen $\beta = 0.30$ for our calculation.

The threshold concentrations of the polymer samples are listed in *Table 5*. The trends are very similar to the ones obtained for the glass transition temperature due to the linear relationship between the glass transition temperature and the threshold concentration. The threshold concentrations for most of the polymer samples were small, thereby allowing the polymer to attain a completely rubbery state at an early stage of the water uptake process.

Equilibrium swelling studies

The effect of pH and ionic strength on the equilibrium water uptake was studied for a wide range of ionic polymers. *Figure 2* shows the equilibrium water uptake in P(DEAEA-*co*-HEMA) samples with a crosslinking ratio of 0.005 mol EGDMA mol monomers in a citrate–phosphate–borate buffer solution. The water uptake is shown as g water per g dry polymer. An increase in the pH of the buffer solution decreased the water uptake dramatically. This is due to the fact that as the alkalinity

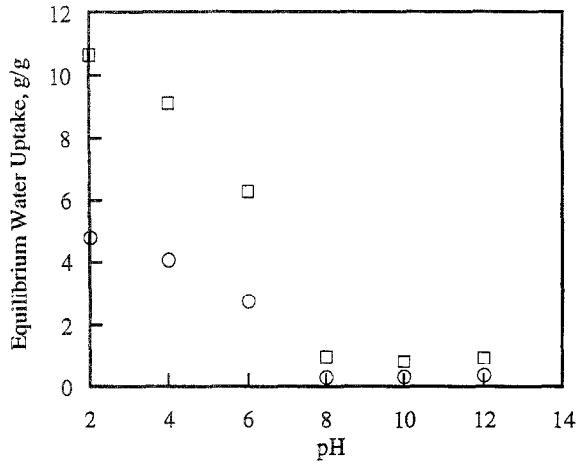

Figure 2 Equilibrium water uptake of P(DEAEA-*co*-HEMA) samples with a crosslinking ratio of 0.005 model EGDMA/mol monomers in a citrate–phosphate–borate buffer solution as a function of pH. Samples with 30 mol% DEAEA in the feed (○) and with 60 mol% DEAEA in feed (□)

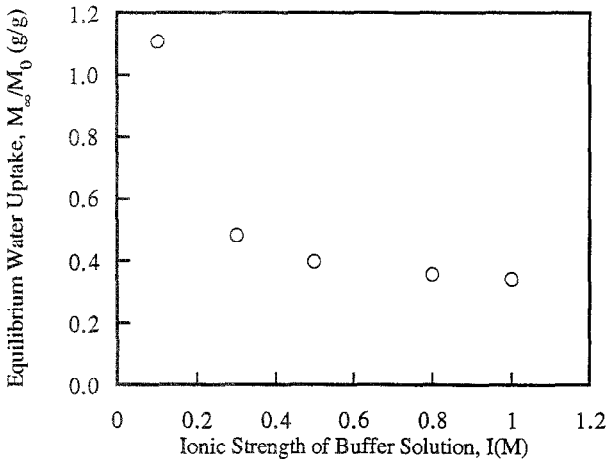

Figure 3 Equilibrium water uptake of P(MAPTAC-*co*-HEMA) samples containing 10% mol% MAPTAC in feed with a crosslinking ratio of 0.001 mol EGDMA/mol monomers in a citrate–phosphate–borate buffer solution as a function of ionic strength

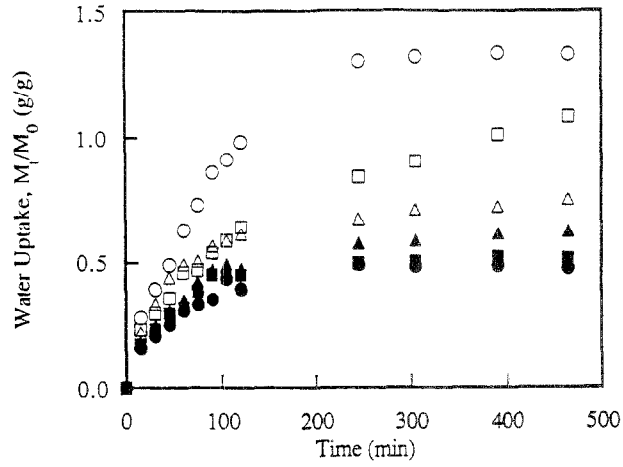

Figure 4 Dynamic water uptake of P(DEAEM-*co*-HEMA) samples containing 10 mol% DEAEM in feed with a crosslinking ratio of 0.001 mol EGDMA/mol monomers in a citrate–phosphate–borate buffer solution: (○) pH 2, (□) pH 4, (△) pH 6, (●) pH 8, (■) pH 10

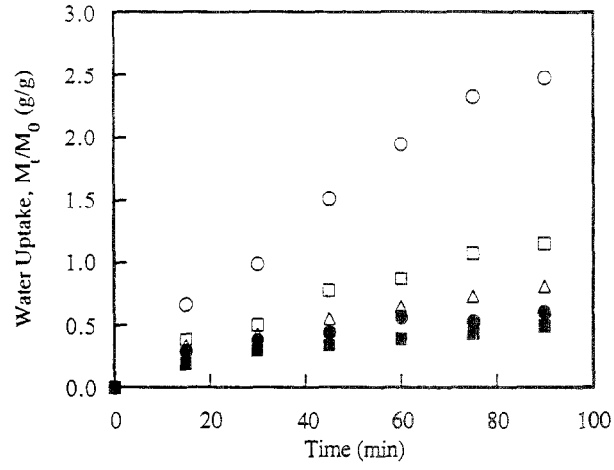

Figure 5 Dynamic water uptake of P(DEAEM-*co*-HEMA) samples containing 30 mol% DEAEM in the feed with a crosslinking ratio of 0.001 mol EGDMA/mol monomers in a citrate–phosphate–borate buffer solution: (○) pH 2, (□) pH 4, (△) pH 6, (●) pH 8, (■) pH 10

of the buffer solution increases, the concentration of ionized groups in the polymer decreased drastically. Hence the resultant electrostatic repulsion decreases, thereby reducing the swelling and the water uptake.

An increase in the concentration of ionizable groups in the polymer also increased the water uptake due to increased repulsion between the groups in their ionized state.

The effect of ionic strength on P(MAPTAC-*co*-HEMA) samples is shown in *Figure 3*. A dependence on pH was not observed since this polymer remains ionized in all aqueous solutions. However, a strong dependence of the water uptake on the ionic strength of the buffer solution was observed. This was due to screening of the charges in the network and the Donnan effect which resulted in a decrease in the difference in the mobile ionic species concentration inside and outside the polymer.

Dynamic swelling studies

The effect of pH, ionic strength and ionizable group concentration on the dynamic water uptake was studied for a wide range of ionic polymers. The effect of pH on the dynamic water uptake in P(DEAEM-*co*-HEMA) samples with crosslinking ratio of 0.001 mol EGDMA mol monomers and 10 and 30 mol% DEAEM in the feed are shown in *Figures 4* and *5*, respectively. The water uptake was represented as g water per g dry polymer (M_t/M_0). It can be seen in each of these figures that an increase in pH of the swelling medium led to a dramatic decrease of water uptake. The water uptake in polymer samples was analysed using equation (6), proposed by Ritger and Peppas[16] to analyse water uptake in and solute diffusion from hydrogels:

$$\frac{M_t}{M_0} = kt^n \tag{6}$$

where M_t is the water uptake at time t, M_0 is the weight of the dry polymer, and k and n are constants. The parameter n describes the mechanism of water uptake or release. A value of n equal to 0.5 indicates the water uptake to follow the classical Fickian behaviour, whereas a value of 1.0 indicates that relaxation processes control

Table 6 Exponent n of equation (6) for P(DEAEM-*co*-HEMA) samples crosslinked with 0.001 mol EGDMA/mol monomers in the feed

pH of buffer solution	Exponent n from equation (6)	
	DEAEM feed 10% mol	DEAEM feed 30 mol%
2	0.53 ± 0.08	0.78 ± 0.16
4	0.47 ± 0.04	0.67 ± 0.15
6	0.33 ± 0.10	0.52 ± 0.07
8	0.40 ± 0.15	0.41 ± 0.16
10	0.35 ± 0.12	0.51 ± 0.08
12	0.38 ± 0.10	0.45 ± 0.12

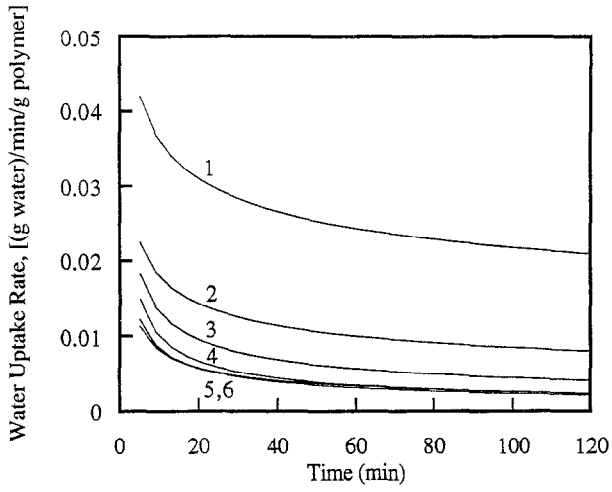

Figure 6 Water uptake rate in P(DEAEM-*co*-HEMA) samples containing 30 mol% DEAEM in the feed with a crosslinking ratio of 0.001 mol EGDMA/mol monomers in a citrate–phosphate–borate buffer solution. Curve 1: pH 2, curve 2: pH 4, curve 3: pH 6, curve 4: pH 8, curve 5: pH 10 and curve 6: pH 12

the water uptake or release. Any value between 0.5 and 1.0 indicates that the water uptake or release is controlled by relaxation and diffusion. The first 60% of the water uptake data were used to evaluate the exponent n. Since about eight data points were available in the first 60% of the water uptake, narrow confidence intervals were obtained when using equation (6). An analysis with intercept not equal to zero gave a very large confidence interval due to insufficient number of data points available for analysis. The n values for water uptake in P(DEAEM-*co*-HEMA) polymer samples containing 10 and 30 mol% DEAEM in the feed and a crosslinking ratio of 0.001 mol EGDMA mol monomers are listed in *Table 6*.

The n values indicate that the water uptake in polymer samples containing 10 mol% DEAEM followed Fickian transport, whereas for samples containing 30 mol% DEAEM the n values at pH 2 indicate that ionization of the network and the resultant swelling of the polymer caused the relaxation process to dominate over diffusion. However, at high pH the diffusion process was mostly Fickian.

The water uptake rates in P(DEAEM-*co*-HEMA) samples are shown in *Figure 6*. Since relaxation of the polymer was higher at acidic pH, the water uptake rates were also higher at acidic pH resulting from the ionization of the pendent groups.

The crosslinking ratio of the polymer also affected the dynamic water uptake to a significant extent (*Figure 7*).

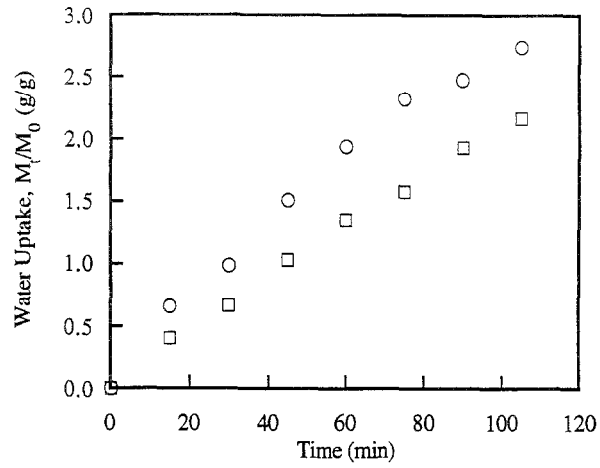

Figure 7 Dynamic water uptake of P(DEAEM-*co*-HEMA) samples containing 30 mol% DEAEM in the feed in a citrate–phosphate–borate buffer solution. Crosslinking ratio $X = 0.001$ mol EGDMA/mol monomers (○) and $X = 0.005$ mol EGDMA/mol monomers (□)

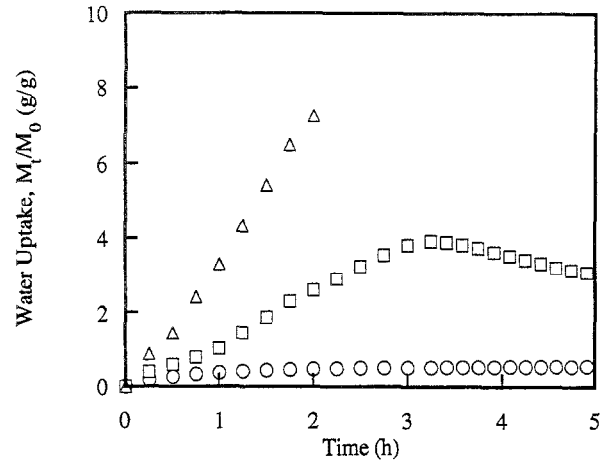

Figure 8 Dynamic water uptake of P(DEAEA-*co*-HEMA) samples with crosslinking ratio of 0.005 mol EGDMA/mol monomers in citrate–phosphate–borate buffer solution. The polymers are placed in a pH 2 buffer solution for 3 h and then placed in a pH 6 buffer solution: PHEMA (○) and P(DEAEA-*co*-HEMA) with 30 mol% DEAEA in the feed (□) and 60 mol% DEAEA in the feed (△)

An increase in the crosslinking ratio (followed by a decrease in $\bar{M}_c$ from 10 110 to 6835 as shown in *Table 3*) decreased the water uptake to a considerable extent due to the decrease in free volume available for diffusion of water.

The effect of a change in pH on the time taken to respond to the pH change in ionic polymers was also determined. *Figure 8* shows the effect of change in pH on the water uptake when the polymer samples were placed in a buffer solution of pH 2 and subsequently transferred to a buffer solution at pH 6. P(DEAEA-*co*-HEMA) samples responded within a short period of time to an increase in the pH of the surrounding environment. P(DEAEA-*co*-HEMA) samples containing 60 mol% DEAEA in the feed and a crosslinking ratio of 0.001 EGDMA/mol monomers broke into pieces after about 2 h due to excessive stress build-up in the sample caused by the repulsion between the ionized groups. Change in buffer solution had no effect on the water uptake of the PHEMA sample because PHEMA is a non-ionic polymer.

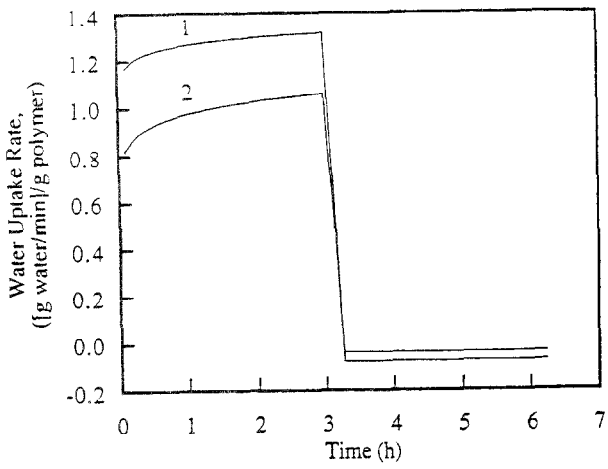

Figure 9 Water uptake rate in P(DEAEMA-*co*-HEMA) samples containing 30 mol% DEAEA in the feed in a citrate–phosphate–borate buffer solution. The polymers are placed in a pH 2 buffer solution for 3 h and then placed in a pH 6 buffer solution. Crosslinking ratio $X = 0.001$ mol EGDMA/mol monomers (curve 1) and $X = 0.005$ mol EGDMA/mol monomers (curve 2)

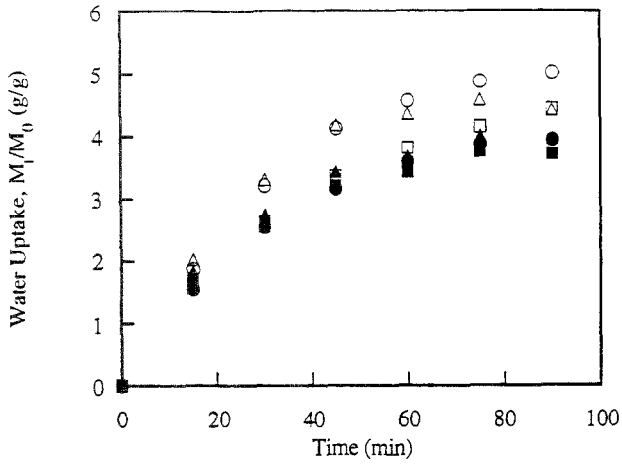

Figure 10 Dynamic water uptake of P(MAPTAC-*co*-HEMA) samples containing 20 mol% MAPTAC in the feed with a crosslinking ratio of 0.005 mol EGDMA/mol monomers in a citrate–phosphate–borate buffer solution: (○) pH 2, (□) pH 4, (△) pH6, (●) pH 8, (■) pH 10, (▲) pH 12

The rate of water uptake was calculated by differentiating equation (6) during the period in which the water uptake increases and equation (7) during the period in which the water uptake decreases, as shown in *Figure 9*. Equation (7) was obtained by analogy with equations developed by Brannon-Peppas and Peppas [17] using a Boltzman superposition equation to relate the strain to the ionic strength or pH:

$$\frac{M_t}{M_0} = ae^{-bt} \tag{7}$$

As can be observed from *Figure 9*, the water uptake decreased at a very high rate when the environment of the polymer was changed after 3 h. This was due to the ionized groups in the polymer sample being converted to unionized form, thereby reducing the electrostatic repulsions between the charged groups.

Figure 10 illustrates the effect of pH on water uptake in P(MAPTAC-*co*-HEMA) sample with a crosslinking ratio of 0.005 mol EGDMA/mol monomers. As the concentration of MAPTAC increased in the polymer, the water uptake also increased considerably, although the effect of pH on the water uptake was very minimal. This was due to the presence of quaternary ammonium groups in the polymer which remained ionized in any aqueous solution. Hence, this polymer showed very little dependence to pH of the surrounding medium as can be seen from the figures.

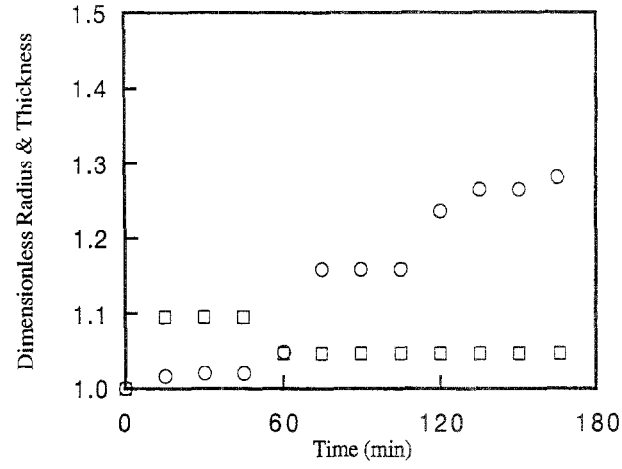

Figure 11 Dimensionless radius and thickness of P(DEAEA-*co*-HEMA) samples containing 30 mol% DEAEM in the feed with a crosslinking ratio of 0.005 mol EGDMM/mol monomers in a citrate–phosphate–borate buffer solution at pH 4: dimensionless radius (○) and dimensionless thickness (□)

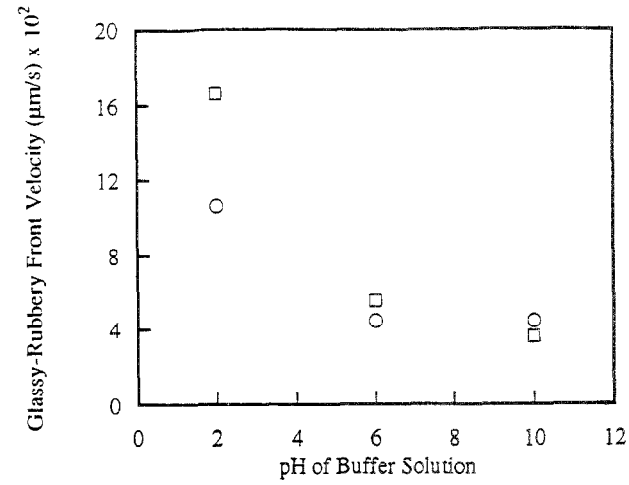

Figure 12 Glassy–rubbery front velocity in P(DEAEM-*co*-HEMA) containing 30 mol% DEAEM in the feed as a function of pH of citrate–phosphate–borate buffer solution. Crosslinking ratio $X = 0.001$ mol EGDMA/mol monomers (○) and 0.005 mol EGDMA/mol monomers (□)

Dimensional changes during dynamic water uptake

Typical results of the change in sample thickness and diameter during water uptake are shown in *Figure 11* for P(DEAEM-*co*-HEMA) samples. The sample thickness in a thin slab increases initially and then decreases once the glassy–rubbery front reaches the centre of the polymer sample because the sample undergoes a readjustment of its shape. The threshold concentrations calculated from the glass transition temperatures for the polymer samples under consideration were very small and, hence, the readjustment in sample thickness occurred in the initial stages of swelling. This rearrangement occurred at

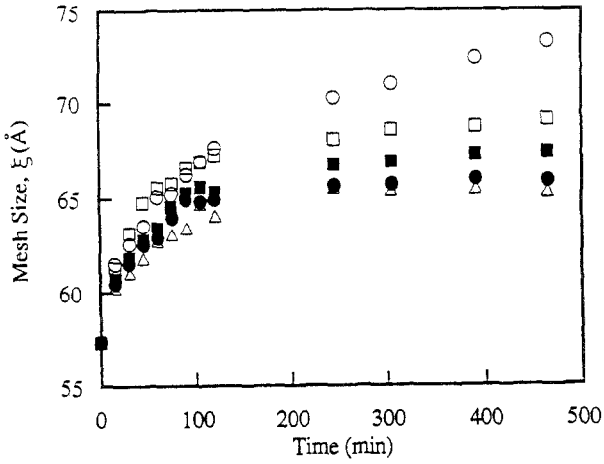

Figure 13 Mesh size of P(DEAEM-*co*-HEMA) samples containing 10 mol% DEAEM in the feed with a crosslinking ratio of 0.001 mol EGDMA/mol monomers in a citrate–phosphate–borate buffer solution: (○) pH 2, (□) pH 4, (△) pH 6, (●) pH 8, (■) pH 10

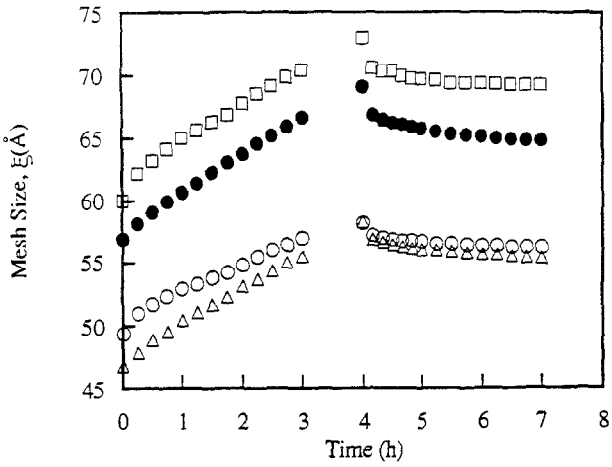

Figure 14 Mesh size of P(DEAEM-*co*-HEMA) samples in a citrate–phosphate–borate buffer solution: (○) 30 mol% DEAEM in the feed and $X = 0.001$ mol EGDMA/mol monomers, (□) 30 mol% DEAEM in the feed and $X = 0.005$ mol EGDMA/mol monomers, (△) 10 mol% DEAEM in the feed and $X = 0.001$ and EGDMA/mol monomers, (●) 10 mol% DEAEM in the feed and $X = 0.005$ mol EGDMA/monomers

approximately 60 min as shown by the constant diameter until that time and the increase in diameter thereafter. The time taken to attain complete equilibrium was approximately 50 h.

Velocity of the glassy–rubbery front

When a glassy polymer sample was placed in a buffer solution, a visible glassy–rubbery front developed as the solution penetrated the sample. The velocity of this glassy–rubbery front was measured as a function of the pH of the surrounding medium. As can be seen in *Figure 12*, an increase in pH reduced the velocity of this front. This was attributed to a decrease in the ionization of the network because ionization increases the hydrophilicity of the network and promotes diffusion of the penetrant. However, this effect was more pronounced at pH 2 and 6 than at pH 10 when only a fraction of the groups were ionized. It can also be seen that the velocity increased with an increase in the crosslinking ratio due to the fact that at high crosslinking ratios, the polymer did not swell to a large degree and hence the diffusion length was smaller.

Determination of mesh size

The mesh size is a very important parameter in understanding of transport of macromolecules through the polymer network. A critical mesh size controls the diffusion of the macromolecule through the network. The mesh size, ξ, can broadly be defined as:

$$\xi = \alpha(\bar{r}_0^2)^{1/2} \tag{8}$$

where α is the extension of a macromolecular chain and $\bar{r}_0^2$ is the end-to-end distance of polymer chains in the unperturbed state. If the extension is isotopic, then α can be expressed as $v_{2,s}^{-1/3}$ where $v_{2,s}$ is the volume fraction of the polymer in the swollen state. The end-to-end distance of polymer chains in the unperturbed state is calculated through the Flory characteristic ratio, also defined as the rigidity factor C_n

$$\bar{r}_0^2 = C_n N l^2 \tag{9}$$

where N is the number of links between two crosslinks (or junctions) and l is the length of a carbon–carbon bond (= 1.54 Å). The number of links, N, is defined as:

$$N = \frac{2\bar{M}_c}{M_r} \tag{10}$$

where $\bar{M}_c$ is the molecular weight between crosslinks and M_r is the molecular weight of the repeating unit.

After substituting the expressions for the various parameters, the mesh size ξ is given by:

$$\xi = v_{2,s}^{-1/3}\left(C_n \frac{2\bar{M}_c}{M_r}\right)^{1/2} l \tag{11}$$

The characteristic ratio $C_n = 11$ by comparison with similar systems[12] of poly(acrylic acid). The molecular weight of the repeating unit was obtained by adding the molecular weight of the two comonomers multiplied by their mole fraction.

It can be seen from *Figure 13* that at large times, the mesh size decreases from ~ 74 to ~ 65 Å when the sample was kept at pH 10 instead of pH 2. This becomes very critical for solutes whose effective diameter is in the range of 60 to 80 Å. The changes in the mesh size of the polymer as a result of the changes in the environment are shown in *Figure 14*, where the changes in the mesh size as a result of placing the polymers at pH 6 for 4 h and then placing them in a solution of pH 10 are shown.

Dynamic mechanical analysis

Analysis of storage and loss modulus was carried out on a number of polymer samples. No significant difference was observed in the behaviour of P(DEAEM-*co*-HEMA) and P(DEAEA-*co*-HEMA) samples. As seen in *Figure 15*, the storage modulus decreased with an increase in temperature due to increased mobility of the chains. Also the tan δ increased beyond the glass transition temperature (= 58.1°C) due to increased dissipation of energy. The samples failed in the instrument at temperatures above 90°C. An increase in the crosslinking ratio increased the storage modulus in both cases, as shown in the figure. Beyond the glass transition temperature, the

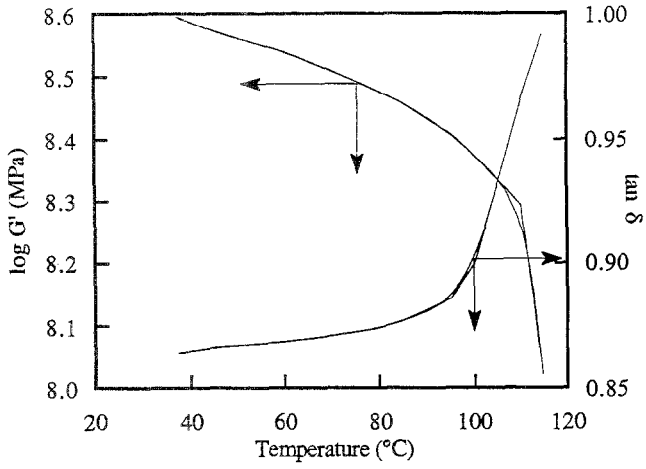

Figure 15 Dynamic modulus G' and tan δ of P(DEAEM-*co*-HEMA) samples containing 10 mol% DEAEM in the feed with a crosslinking ratio of 0.001 mol EGDMA/mol monomers as a function of temperature.

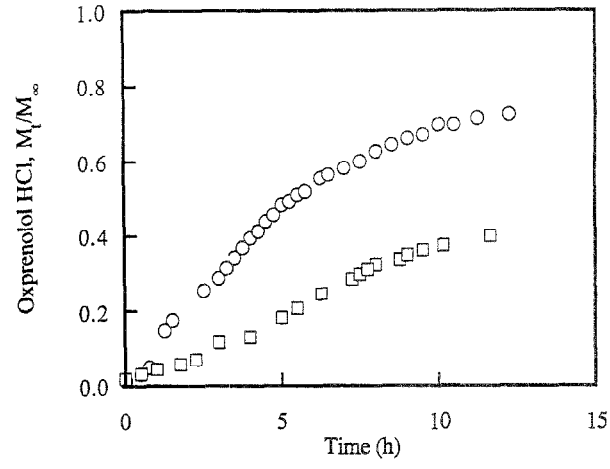

Figure 17 Oxprenolol HCl release from P(DEAEM-*co*-HEMA) samples containing 30 mol% DEAEA in the feed in a citrate–phosphate–borate buffer solution. Crosslinking ratio $X = 0.001$ mol EGDMA/mol monomers (○) and $X = 0.005$ mol EGDMA/mol monomers (□)

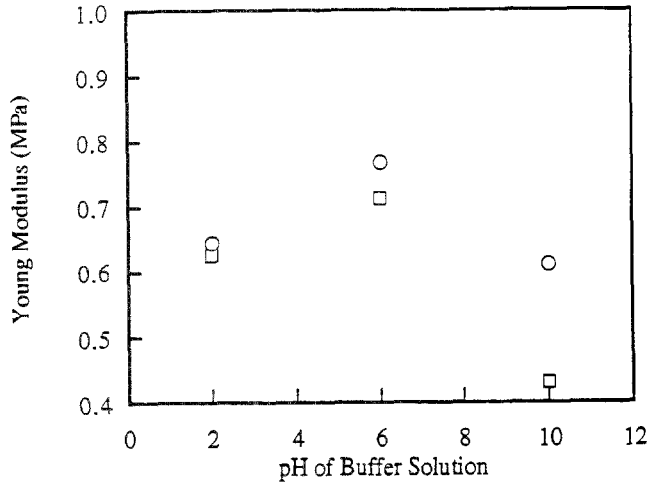

Figure 16 Young modulus of P(DEAEA-*co*-HEMA) samples containing 10 mol% DEAEA in the feed as a function of pH of citrate–phosphate–borate buffer solution. Crosslinking ratio $X = 0.001$ mol EGDMA/mol monomers (○) and $X = 0.005$ mol EGDMA/mol monomers (□)

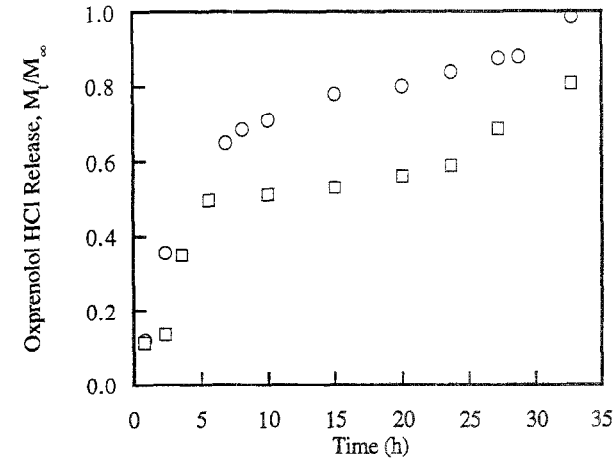

Figure 18 Oxprenolol HCl release from P(DEAEM-*co*-HEMA) samples containing 60 mol% DEAEA in the feed in a citrate–phosphate–borate buffer solution. Crosslinking ratio $X = 0.001$ mol EGDMA/mol monomers (○) and $X = 0.005$ mol EGDMA/mol monomers (□)

modulus changes by many orders of magnitude. At certain frequencies and amplitudes, the temperature at which the damping factor tan δ exhibits a maximum is equal to the glass transition temperature. However, at other frequencies the maximum can differ from the glass transition determined from differential scanning calorimetry by as much as 5°C. However, this analysis still provided us with means of getting an approximate value of the glass transition temperature.

Tensile experiments of polymers under different pH conditions

Tensile experiments were used to study the stress–strain behaviour of polymer samples. The stress–strain data were analysed to obtain the Young modulus of the polymer sample. The moduli of P(DEAEA-*co*-HEMA) samples of differing crosslinking ratio are shown in *Figure 16*. An increase in pH leads to a decrease in the ionization of the network and reduced swelling of the network, and hence to an increase in the modulus. Also, an increase in the crosslinking ratio decreased the modulus due to decreased flexibility of the polymer chains. It can also be observed that the modulus drops above pH 6. This phenomenon is not clearly understood but we feel that this may be due to the fact that at this pH, the polymer was completely non-ionized and the network chains had less mobility.

Solute release from ionic polymers

The effect of molecular weight of the solute, ionizability of the solute, ionic content of the polymer, crosslinking ratio and pH of the release medium was studied. *Figure 17* shows the effect of crosslinking ratio P(DEAEA-*co*-HEMA) on the release of oxprenolol HCl. It can be clearly seen that as the crosslinking ratio increased, the solute release decreased due to a decrease in the free volume available for diffusion. The mesh size in the polymer decreased from 64 to 42 Å when the polymer had a crosslinking ratio of 0.005 instead of 0.001. This supports our argument that the free volume available for diffusion is reduced. The incomplete

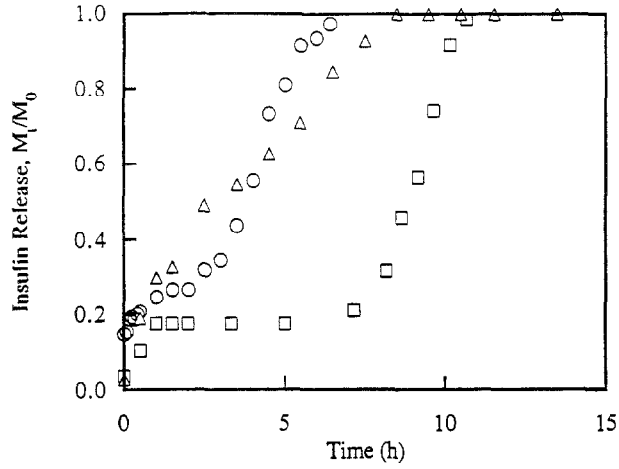

Figure 19 Insulin release from P(DEAEM-*co*-HEMA) containing 30 mol% DEAEM in the feed and 0.001 mol EGDMA/mol monomers in a citrate–phosphate–borate buffer solution: (○) pH 4, (□) pH 6, (△) pH 10

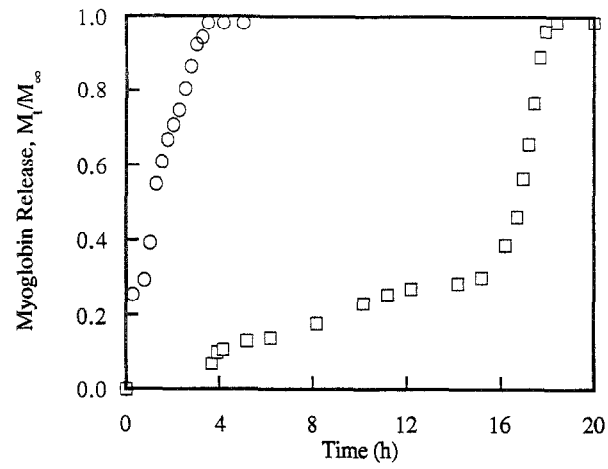

Figure 21 Myoglobin release from PHEMA and P(DEAEA-*co*-HEMA) with crosslinking ratio of 0.005 mol EGDMA/mol monomers in a citrate–phosphate–borate buffer solution. PHEMA (○) and copolymer with 30 mol% DEAEA in the feed (□)

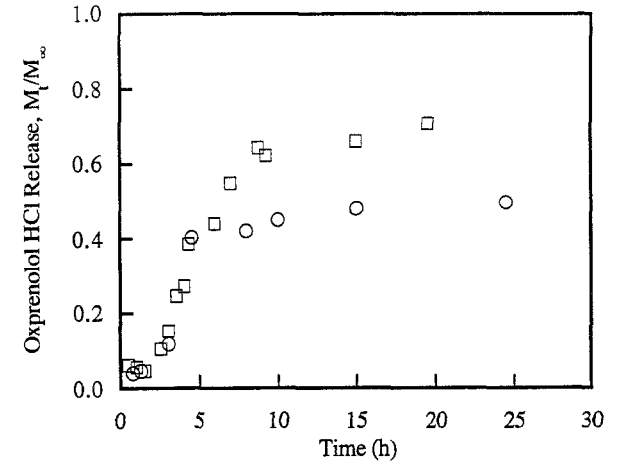

Figure 20 Oxprenolol HCl release from P(DEAEM-*co*-HEMA) with crosslinking ratio of 0.005 mol EGDMA/mol monomers in a citrate–phosphate–borate buffer solution. Samples containing 30 mol% DEAEM in the feed (○) and 60 mol% DEAEM in the feed (□)

release of oxprenolol HCl was suspected due to binding of the drug to the polymer. The release behaviour was analysed using an exponential equation similar to equation (6) and an n value of 0.95 ± 0.09 was obtained. This implies that the release mechanism was controlled primarily by relaxation of the polymer sample, which was also the case during swelling of the polymer sample. However, in PHEMA samples the release was controlled primarily by Fickian diffusion as shown by an n value close to 0.5.

The effect of crosslinking ratio on oxprenolol HCl release from a P(DEAEM-*co*-HEMA) sample shown in *Figure 18*. The results are very similar to the release from P(DEAEA-*co*-HEMA) though complete drug release was observed. The release was analysed using equation (6) and an n value of 0.34 ± 0.10 was obtained.

The effect of pH on the release of insulin from P(DEAEM-*co*-HEMA) samples is shown in *Figure 19*. An increase in pH decreased the degree of ionization of the cationic polymer, thus decreasing the swelling of the polymer. It can also be observed that the release rate was higher at pH 4 than at pH 6 or pH 10. However, the release at pH 10 is higher than at pH 6. This can only be explained by the decrease in the diffusional path at pH 10.

The effect of the concentration of ionizable groups on the release of oxprenolol HCl is shown in *Figure 20*. As the concentration of ionizable groups increased, the repulsion between the charged pendent groups also increased and this caused the network to swell to a greater extent. The increased swelling increased the mobility of the drug in the polymer and thus the release was faster.

The release of myoglobin from PHEMA and P(DEAEA-*co*-HEMA) samples is shown in *Figure 21*. The change in pH of the buffer solution did not have an effect on the release behaviour from the PHEMA samples. However, it did have a profound effect on the release from P(DEAEA-*co*-HEMA) samples. It can also be observed that there was a lag period in the release from the P(DEAEA-*co*-HEMA) samples. As the polymer was transferred to a pH 6 solution, the mesh size increased considerably, leading to an increase of the mobility of myoglobin.

CONCLUSIONS

We have synthesized and characterized cationic polymer networks containing amine and ammonium pendent groups. The effect of polymer structural characteristics such as the concentration of ionizable groups and the molecular weight between crosslinks was studied on various properties of the polymer. The transport of a simulated physiological solution into the polymer and the associated solute release were studied. The importance of the mesh size of the polymer network during the swelling and also the importance of increased swelling caused by the increase in the concentration of ionizable groups were emphasized.

ACKNOWLEDGEMENT

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