Polymer Vol. 39 No. 24 pp. 6057–6066, 1998
0032-3861/98/$ – see front matter

PII: S0032-3861(98)00087-1

Novel poly(ethylene glycol)-grafted, cationic hydrogels: preparation, characterization and diffusive properties

Lisa M. Schwarte† and Nikolaos A. Peppas*
Polymer Science and Engineering Laboratories, School of Chemical Engineering, Purdue University, West Lafayette, IN 47907-1283, USA
(Received 11 July 1997; revised 20 January 1998)

A new class of poly(ethylene glycol)-grafted, cationic hydrogels was prepared by copolymerization and simultaneous crosslinking of diethylaminoethyl methacrylate (DEAEM) and poly(ethylene glycol) monomethacrylate (PEGMA). The ensuing hydrogels, P(DEAEM-g-PEG), exhibited a strong swelling ratio dependence on pH. At low acidic pH values they expanded to swelling ratios of up to 25, depending on the crosslinking density and feed ratio of the two comonomers. At alkaline pH values they tended to collapse excluding a significant quantity of the incorporated water. This swelling/deswelling process and the associated size can be used for the development of carriers for modulated drug delivery. Proxyphylline, vitamin B_{12}, and various dextrans diffusion studies were used to elucidate the effect of the gel mesh size on the solute diffusion coefficient. © 1998 Elsevier Science Ltd. All rights reserved.

(Keywords: pH-sensitive hydrogels; poly(ethylene glycol); cationic hydrogels)

INTRODUCTION

Hydrogels are often sensitive to environmental conditions and can display swelling transition behaviour due to variations in pH, ionic strength and temperature. This contribution focuses on the preparation and characterization of novel cationic, pH-sensitive hydrogels[1].

Polyelectrolyte gels have been investigated for use as biosensing membranes[2], for the detection of changes in blood glucose concentration, as drug delivery carriers for site specific delivery to the gastrointestinal tract, or for buccal and nasal delivery[3–5], as artificial muscles, and as enteric coatings of tablets[6,7]. Hydrogels may also be used for the delivery of certain pesticides and herbicides[8], as flocculants for treatment of sludge[9], as membranes for monitoring of environmental pollution, and for molecular imprinting[10].

One of the structural parameters often used to characterize the network structure of hydrogels is their mesh size, ξ, which is broadly defined as the distance between two consecutive crosslinks or junctions in the network. In the case of ionic hydrogels where there are variations in swelling with changes in the surrounding environment, a significant change in mesh size can be observed. Therefore, the critical mesh size for a particular hydrogel can also control solute diffusion into or out of the network.

Another parameter commonly used to characterize polymer networks is the molecular weight between crosslinks, $\bar{M}_c$, calculated by the Peppas–Merrill model[11] which is derived from a balance between the force exerted on the macromolecular chains during swelling and the elastic–retractive forces observed, and takes into account that the crosslinks are introduced in the presence of a solvent. For pH-sensitive hydrogels, a better analysis of $\bar{M}_c$ was obtained by the Brannon–Peppas and Peppas model[12].

Several researchers have investigated the swelling behaviour of cationic, polyelectrolyte gels. Siegel and coworkers[6,7,13–15] performed swelling studies on poly(diethylaminoethyl methacrylate-co-methyl methacrylate), P(DEAEM-co-MMA), and observed an abrupt swelling transition from the collapsed to the swollen states of the gel. They also found that the polymer swelling was dependent upon copolymer composition.

Goldraich and Kost[2] investigated the swelling behaviour of cationic hydrogels made from DEAEM, hydroxyethyl methacrylate (HEMA), and ethylene glycol (EG) and they used them as glucose-sensitive delivery systems. As expected, increased swelling ratios were observed in hydrogels with increased cationic group concentration and decreased crosslinking ratio. Hariharan and Peppas[16] investigated the swelling behaviour of cationic hydrogels of poly(diethylaminoethyl methacrylate-co-hydroxyethyl methacrylate), P(DEAEM-co-HEMA), and poly(diethylaminoethyl acrylate-co-hydroxyethyl methacrylate), P(DEAEA-co-HEMA). Dynamic and equilibrium swelling studies were performed on these cationic hydrogels and showed a dramatic decrease in water uptake with increasing pH. Foster and Peppas[17] prepared strong cationic polyelectrolytes based on poly(hydroxyethyl methacrylate-co-methacrylolaminopropyl trimethylammonium chloride) and observed that the weight swelling ratio decreased as the concentration of MPTAC increased.

Although previous studies with cationic gels have shown their dependence on pH, such systems are not optimal candidates as carriers for protein diffusion or delivery studies due to their relatively acidic conditions of performance. Of course, PEG is known to provide improved conditions of protein stability, and stealth characteristics in biological applications. Recently, we have developed a new

* To whom correspondence should be addressed
† Present address: DuPont Electronics. P.O. Box 13999, 14 T. W. Alexander Drive, Research Triangle Park, NC 27709-4425

method of incorporation of poly(ethylene glycol) (PEG) into these cationic gels. Thus, the main goal of this work was to prepare and characterize a class of new crosslinked cationic hydrogels of poly(diethylaminoethyl methacrylate-g-ethylene glycol), henceforth designated as P(DEAEM-g-PEG).

EXPERIMENTAL

Synthesis of P(DEAEM-g-PEG) hydrogels

Hydrogels were prepared with monomer feed ratios of 10:1, 50:1, 75:1, and 99:1 repeating units of DEAEM per graft chain of poly(ethylene glycol) (PEG, mw 1000). In typical polymer preparations, the two monomers, diethylaminoethyl methacrylate (DEAEM, Aldrich Chemical Corporation, Inc., Milwaukee, WI) and poly(ethylene glycol) monomethacrylate (PEGMA, 1000 Da; Polysciences, Inc., Warrington, PA) and the appropriate amounts of the crosslinking agent, tetra(ethylene glycol) dimethacrylate (TEGDMA, Aldrich Chemical Corporation, Inc., Milwaukee, WI) were mixed in deionized water and ethanol which were added to the solution in equal amounts at concentrations of 25 wt% of the monomers. Solutions were purged with nitrogen for 45 min and the u.v. initiator 1-hydroxycyclohexyl phenyl ketane (Irgacure 184; Ciba-Geigy Corporation, Hawthorn, NY) was added at 1 wt% of the monomers. The solution was mixed for an additional 15 min.

Thin films were cast between microscope slides (70 × 50 × 1 mm) using spacers to control the thickness. These films were polymerized under an u.v. light source (Ultracure 100; Engineered Fiber Optic Systems, Buffalo, NY) with an intensity of 5 mW/cm^2. Polymerization times were 13 min for the 10:1 gels, 16 min for the 50:1 gels, 18 min for the 75:1 gels, and 22 min for the 99:1 gels. After polymerization, the films were removed from the slides and stored in deionized water.

The same monomer feed ratios and crosslinking ratios were used for polymer preparation using oxidation–reduction polymerizations. The solvents, deionized water and ethanol, were used in equal amounts and were 40 wt% of the monomers. The initiators used were ammonium persulfate, crystal (J.T. Baker, Inc., Phillipsburg, NJ) and sodium metabisulfite (Fischer Scientific Company, Fairlawn, NJ) and were each 2 wt% of the monomers and solvents. Nitrogen was bubbled directly through into solution for 25 min, then the initiator solutions were added to the monomer solutions and mixed for three min before the solutions were poured between microscope slides with 0.9–1 mm spacers between them and sealed. The solutions were reacted for 24 h at 37°C, and the ensuing polymers were removed from the petri dishes, rinsed in ethanol for a day and stored in deionized water.

Equilibrium swelling of P(DEAEM-g-PEG) gels

Glutaric acid buffer solutions with pH values of 3.0, 3.9, 4.6, 5.8, and 6.8 were prepared from 0.1 M 3,3-dimethylglutaric acid (DMGA buffer, Sigma Chemical Company, St. Louis, MO). The pH values of the buffers were adjusted using 1.0 N NaOH (Sigma Chemical Company), whereas the ionic strength was adjusted to 0.1 M using NaCl (Mallinckrodt Baker, Inc., Paris, KY). Sodium borate/NaOH buffer solutions with pH values of 9.4 and 10.1 were prepared from 0.2 M boric acid (Mallinckrodt Baker) and 1.0 N NaOH. The pH of the buffers was adjusted by additional quantities of NaOH, and the ionic strength was adjusted to 0.1 M with NaCl.

Disks were cut from the gels to a diameter of 1.60 cm, placed in 50 ml of separate buffer solutions and allowed to equilibrate for at least a week at 37°C. Buffer solutions were changed every other day, and the disks were weighed daily to monitor changes in water uptake. Equilibrated disks were also weighed in air and in heptane (a non-solvent). The disks were then dried in air for 5 days and their dry weights determined in air and heptane. The equilibrium swelling ratios and the polymer volume fractions, in the swollen state, were determined from these weights.

Oscillatory swelling of P(DEAEM-g-PEG) gels

Gels made by redox polymerization of varying molar ratios were cut into disks of diameter 1.60 cm and were pre-equilibrated in pH 10.1 sodium borate buffer solution at 37°C. At time zero, the polymers were transferred to a 3,3-dimethylglutaric acid buffer with a pH of 4.8 at 37°C. The disks were allowed to swell for 30 min at this pH, were blotted to remove excess surface buffer, and weighed every 5 min to monitor changes in water uptake. After 30 min, the disks were transferred to a pH 9.4 Na borate buffer solution at 37°C where they remained for 30 min. Again, the disks were blotted and weighed every 5 min to monitor the deswelling/collapse. The swelling/collapse cycle was repeated three more times with each swelling and collapse period being 30 min. At the completion of these four cycles, the disks were dried in air for 5 days and the dry weights determined.

DIFFUSION STUDIES

Side-by-side diffusion cells (Crown Glass Company, Inc., Somerville, NJ) were used to perform solute diffusion studies at 37°C. Each half cell had a volume of 3 ml and a circular opening of diameter 9 mm. For continuous agitation, each half cell also contained a magnetic stirrer. A pre-equilibrated hydrogel membrane was placed between the half cells before they were secured into place. To prevent evaporation of buffer from the membrane, a barrier was placed around the joint between the two half cells.

The drugs used in these studies were 7-(β-hydroxypropyl) theophylline (proxyphylline), vitamin B_{12}, fluorescein isothiocyanate-dextran with mw 4400 (FITC-dextran 4400), and fluorescein isothiocyanate-dextran with mw 9400 (FITC-dextran 9400), all purchased from Sigma Chemical Company. The molecular characteristics of each solute are given in *Table 1*.

Table 1 Characterization of solutes used in the diffusion studies[a]

Solute	Molecular weight	pK_a	Experimental diffusion coefficient (10^7 cm^2/s)	Effective radius, r_e (Å)	Function
Proxyphylline	238.2	Neutral	74.9[21]	3.53[23]	Bronchodialator
Vitamin B_{12}	1355	Neutral	44.3[21]	8.51[24]	Aids in blood formation
FITC-dextran (4400)	4400	Neutral	11.4[22]	16.5[25]	Model solute
FITC-dextran (9400)	9400	Neutral			

[a]Experimental diffusion coefficients were determined in water or saline at 37°C

In a typical experiment, a 3 ml aliquot of dilute drug solution in buffer was added to the donor cell. Similarly, a 3 ml sample of buffer without drug, was placed in the receptor cell. The entire contents of the receptor cell were removed at regular time intervals (e.g. 30, 45, or 60 min) and replaced with fresh buffer solution. Drug concentration was detected using a u.v.-vis spectrophotometer at 275 nm for proxyphylline, 359 nm for vitamin B_{12}, 281 nm for FITC-dextran 4400, and 457 nm for FITC-dextran 9400.

RESULTS AND DISCUSSION

Determination of the molecular weight between crosslinks

Upon preparation of the new hydrogels, the theoretical molecular weight between crosslinks, $\bar{M}_{c,\text{theor}}$, was determined as:

$$\bar{M}_{c,\text{theor}} = \frac{M_r}{2X} \tag{1}$$

where M_r is the molecular weight of a polymer repeating unit, and X is the nominal crosslinking ratio. The calculated $\bar{M}_{c,\text{theor}}$ values for each sample are shown in *Table 2*. In general, $\bar{M}_{c,\text{theor}}$ increased with increasing number of repeating units of DEAEM.

The Brannon-Peppas model[18] was used to calculate the molecular weight between crosslinks for crosslinked ionic hydrogel networks, polymerized in the presence of a solvent and containing non-Gaussian chain length distributions.

$$\frac{V_1}{4IM_r}\left(\frac{v_{2,s}}{\bar{v}}\right)^2\left(\frac{K_b}{10^{(\text{pH}-14)}}+K_b\right)^2 = \left[\ln(1-v_{2,s})+v_{2,s}+\chi_1 v_{2,s}^2\right] + \frac{\left(\frac{V_1}{\bar{v}\bar{M}_c}\right)\left(1-\frac{2\bar{M}_c}{\bar{M}_n}\right)v_{2,r}\left[\left(\frac{v_{2,s}}{v_{2,r}}\right)^{1/3}-\frac{1}{2}\left(\frac{v_{2,s}}{v_{2,r}}\right)\right]\left[1+\frac{1}{N}\left(\frac{v_{2,s}}{v_{2,r}}\right)^{1/3}\right]^2}{\left(1-\frac{1}{N}v_{2,s}^{2/3}\right)^3} \tag{2}$$

Here, V_1 is the molar volume of water (18 mol/cm^3), $\bar{v}$ is the specific volume of the dry polymer, I is the ionic strength of the buffer solution, χ_1 is the Flory interaction parameter, equal to 0.20 as estimated by Hariharan and Peppas[16], N is the number of structural units between consecutive crosslinks, $\bar{M}_n$ is the molecular weight of the polymer before crosslinking (taken[16] as 75 000), K_b is the base dissociation constant, and $v_{2,s}$ is the polymer volume fraction of the swollen polymer. The value of N was calculated as

$$N = \frac{2\bar{M}_c}{M_r} \tag{3}$$

where M_r is the molecular weight of a repeating unit.

The experimental values of the molecular weight between crosslinks are summarized also in *Table 2*. The values for the experimental determination of this parameter were smaller than the theoretical values and varied with content of ionic material as did the equilibrium swelling of these networks.

Table 2 Theoretical and experimental molecular weight between crosslinks

Monomer ratio (repeats: grafts)	$\bar{M}_{c,\text{theor}}$	$\bar{M}_{c,\text{exp}}$
10:1	5900	4825
50:1	7800	6700
75:1	7700	6900
99:1	7600	7200

Equilibrium swelling studies

Equilibrium swelling studies were performed on gels equilibrated in buffers with pH values ranging from 3.0 to 10.1. At each of the pH values, the equilibrium weight ratio, q, was determined according to equation (4).

$$q = \frac{W_s}{W_d} \tag{4}$$

Here, W_s and W_d are the swollen and dry weights of the polymers, respectively.

The equilibrium weight ratios were plotted as a function of pH as shown in *Figure 1*. In these networks, the swelling behaviour was a result of electrostatic repulsion between charged amino groups on the DEAEM units. Electrostatic repulsion eventually overcame the hydrophobic tendencies of the gel to exclude water, and the gel swelled. The figure shows that at high pH values all of the gels were collapsed and had equilibrium weight swelling ratios between about 2 and 3. As the pH decreased, the gels began to swell. The final equilibrium weight swelling ratios at pH 3.0 ranged from 15 to about 25. There was a general trend toward increasing equilibrium weight swelling ratio with increasing content of the pH-sensitive material, DEAEM, until the 99:1 molar ratio polymer. This polymer had a final equilibrium weight ratio of 18 and decreased in between the 10:1 and 50:1 molar ratio polymer. This was because there was so much of the pH-sensitive material included in the network, that it could not fully overcome the hydrophobic interactions and did not swell to as great an extent as would be

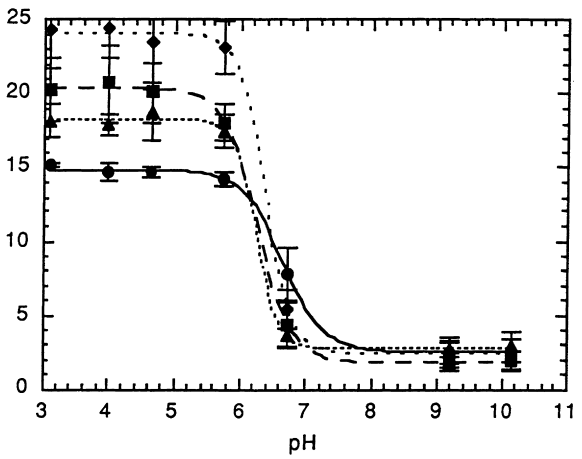

Figure 1 Equilibrium swelling behaviour of 10:1 (l), 50:1 (n), 75:1 (u), and 99:1 (s) P(DEAEM-g-PEG) gels as a function of pH at 37°C.

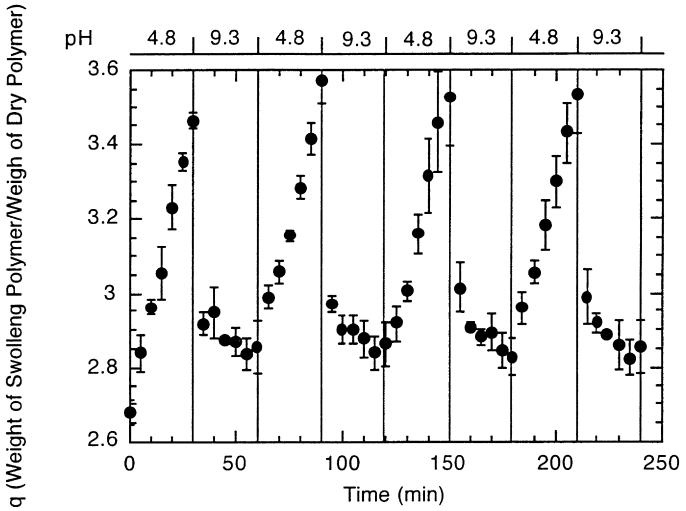

Figure 2 Oscillatory response of the 10:1 molar ratio P(DEAEM-g-PEG) gel to changes in pH at 37°C

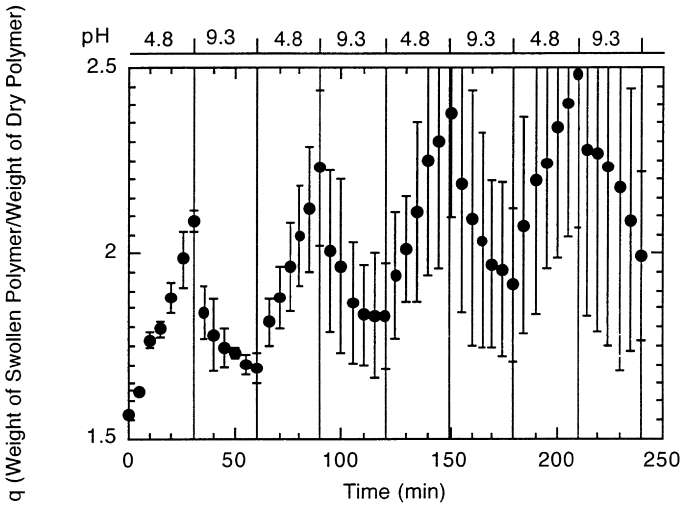

Figure 3 Oscillatory response of the 50:1 molar ratio P(DEAEM-g-PEG) gel to changes in pH at 37°C

Table 3 Mesh size of P(DEAEM-g-PEG) gels

Swelling pH	Mesh size, ξ (Å) Polymer composition (DEAEM repeating units: PEG chain grafts)			
	10:1	50:1	75:1	99:1
2.95	102	101	145	133
3.90	103	136	148	133
4.60	102	134	144	130
5.80	100	131	143	129
6.80	74	85	84	61
9.20	51	56	62	63
10.10	54	57	61	65

expected. From the equilibrium swelling curves, we were able to determine the pH at which the gels experienced a transition from their collapsed to their swollen states as 6.6 (for the 10:1 gels), 6.3 (for the 50:1 and 75:1 gels) and 6.2 (for the 99:1 gels).

Determination of the network mesh size

The mesh size, ξ, was calculated from the theoretical value of $\bar{M}_c$ for each network studied. The mesh size defines the linear distance between consecutive crosslinks and may control the diffusion of certain molecules through the network. The mesh size, ξ, was expressed as

$$\xi = \alpha\left(\bar{r}_0^2\right)^{1/2} \tag{5}$$

where α is the extension factor of a macromolecular chain and $\bar{r}_0$ is the end-to-end distance of the polymer chains in the unperturbed state. In cases where the extension was isotropic, then α was assumed to be equal to $v_{2,s}^{-1/3}$, where $v_{2,s}$ is the polymer volume fraction in the swollen state. The end-to-end distance, $\bar{r}_0$, was further calculated as

$$\bar{r}_0^2 = C_n N l^2 \tag{6}$$

where C_n is the Flory characteristic ratio ($C_n = 11$ for this hydrogel), N is the number of links between consecutive crosslinks or junctions (see equation (3)), and l is the carbon–carbon bond length (1.54 Å). By combining equations (3), (5) and (6) we obtain

$$\xi = v_{2,s}^{-1/3}\left[C_n \frac{2\bar{M}_c}{M_r}\right]^{1/2} l \tag{7}$$

The mesh size of the various gels prepared here is shown in *Table 3*. A general trend was observed toward increasing mesh size with increasing content of the pH-sensitive

material to the 99:1 molar ratios. The mesh sizes of the 99:1 molar ratio gels fell between those of the 10:1 and 50:1 molar ratio gels, the same trend as that seen in the equilibrium swelling curves. There was also a trend towards decreasing mesh size as pH was increased. A significant shift in values was noted between pH values of 5 and 6, the pH where the transition between the swollen and collapsed states was observed.

Oscillatory swelling studies

Oscillatory swelling studies were performed to determine the ability of the gel to swell and collapse in cyclic operation. The pH values chosen for the experiments were selected because they fell on either side of the gel's transition pH. *Figure 2* shows the dynamic swelling behaviour of the 10:1 molar ratio polymer. The initial weight ratio was about 2.7, and the polymer swelled to a weight ratio of about 3.5 after 30 min. When the polymer was transferred to a pH 9.3 buffer, it began to collapse, and after 30 min had reached a weight ratio of about 2.9. The 10:1 molar ratio gel was able to return to its original equilibrium value after each of its swelling/collapse cycles.

Different behaviour was noted for the remaining gels. *Figure 3* gives the results of the oscillatory swelling of the 50:1 molar ratio gel. Gels that were allowed to remain in the high pH buffer solution for an extended period of time, returned to their original equilibrium values.

Figure 4 shows the dynamic swelling response of the 75:1 molar ratio gel. This gel swelled from an initial equilibrium weight swelling ratio of about 2 to a weight swelling ratio of 2.5. The gel was able to return to a weight swelling ratio of about 2.1 after 30 min of collapse, which is again very near the initial weight ratio. The behaviour of the oscillatory swelling of the 99:1 molar ratio gels (*Figure 5*) was very similar to that of the 75:1 molar ratio gel. The equilibrium weight ratio was about 2.1, and when the gel was placed in low pH buffer solution, the weight ratio reached a value of 2.9 after 30 min. Subsequent oscillations showed the gel moving continually farther from its equilibrium.

Analysis of the swelling behaviour of P(DEAEM-g-PEG) gels

It was important to determine if the swelling and collapse behaviour of these pH-sensitive gels was a function of the diffusion of ions into or out of the network. Thus, an analysis was performed of the oscillatory behaviour of the gels to relate the slope of the swelling curves to the rates or water and ion transport. Because water transport in swollen

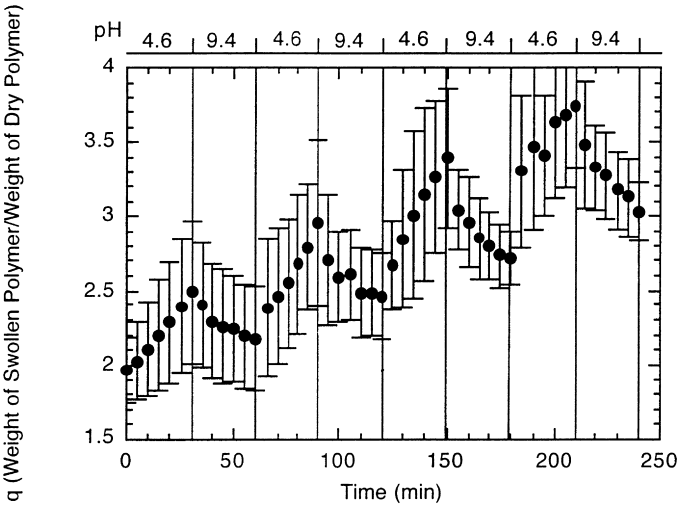

Figure 4 Oscillatory response of the 75:1 molar ratio P(DEAEM-g-PEG) gel to changes in pH at 37°C

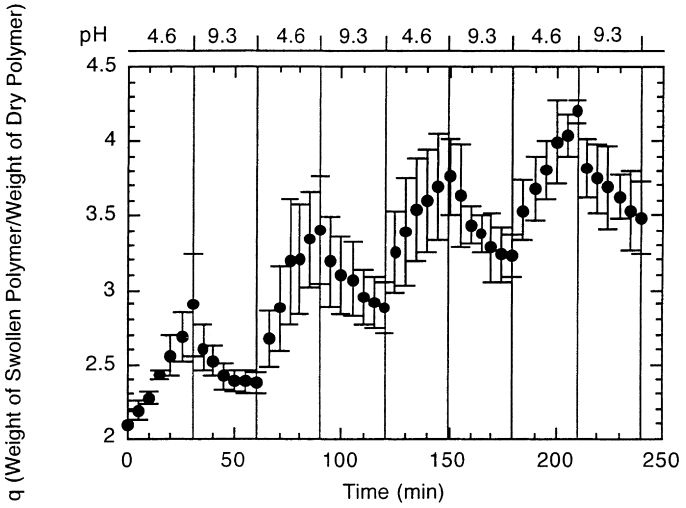

Figure 5 Oscillatory response of the 99:1 molar ratio P(DEAEM-g-PEG) gel to changes in pH at 37°C

Table 4 Diffusional analysis of water and ion transport in P(DEAEM-g-PEG) gels with 10:1 and 50:1 molar ratio

Swelling/collapse interval (min)	Swelling medium pH	Gels with 10:1 molar ratio		Gels with 50:1 molar ratio	
		Initial rate (min^{-1})	Rate at midpoint (min^{-1})	Initial rate (min^{-1})	Rate at midpoint (min^{-1})
0–30	4.8	0.0167	0.0200	0.0133	0.0100
30–60	9.3	0.0400	0.0067	0.0200	0.0067
60–90	4.8	0.0133	0.0167	0.0133	0.0100
90–120	9.3	0.0467	0.0033	0.0167	0.0067
120–150	4.8	0.0200	0.0200	0.0133	0.0133
150–180	9.3	0.0400	0.0033	0.0200	0.0100
180–210	4.8	0.0133	0.0133	0.0200	0.0100
210–140	9.3	0.0400	0.0033	0.0133	0.0067

Table 5 Diffusional analysis for water and ion transport in P(DEAEM-g-PEG) gels with 75:1 and 99:1 molar ratio

Swelling/collapse interval (min)	Swelling medium pH	Gels with 75:1 molar ratio		Gels with 99:1 molar ratio	
		Initial rate (min^{-1})	Rate at midpoint (min^{-1})	Initial rate (min^{-1})	Rate at midpoint (min^{-1})
0–30	4.6	0.1667	0.0200	0.0100	0.0133
30–60	9.4	0.0233	0.0100	0.0133	0.0033
60–90	4.6	0.0333	0.0300	0.0200	0.0133
90–120	9.4	0.0200	0.0100	0.0233	0.0067
120–150	4.6	0.0333	0.0133	0.0267	0.0200
150–180	9.4	0.0200	0.0133	0.0267	0.0100
180–210	4.6	0.0300	0.0200	0.0467	0.0167
210–240	9.4	0.0300	0.0067	0.0267	0.0100

gels is a Fickian diffusional process, the starting point of this analysis was the one-dimensional Fickian diffusion equation:

$$J = -D\frac{dc}{dx} \tag{8}$$

Here, J is the flux, D is the diffusion coefficient, c is the concentration, and x is the position within the polymer. Equation (8) was integrated, and the flux, J, was expressed as the rate per area, to give

$$J = \frac{1}{A}\frac{dM_w}{dt} = D\frac{\Delta c}{\delta} \tag{9}$$

In this case, A is the area available for transport, d is the thickness of the polymer sample tested, and dM_w/dt is the rate of transport. Equation (9) was rearranged to give

$$\frac{dM_w}{dt} = A\frac{D}{\delta}\Delta c \tag{10}$$

It is clear, then, that the rate of water uptake (or the slope of the swelling curve) is proportional to the local water concentration change, Δc, which is directly related to the local swelling ratio change, ΔQ. This analysis was applied to the oscillatory data, and the results are summarized in *Table 4*, *Table 5*. The swelling periods are shown in regular print, whereas the collapse (or syneresis) periods are shown in italics. The initial rates and midpoint rates were calculated for each of the monomer ratios.

To assure that it was a diffusional process that controlled the swelling and collapse of these gels, the Peppas–Reinhart theory[19] was used to describe the transport of hydrogen ions into collapsed gels or sodium ions into expanded gels.

$$\frac{D_{1,m}}{D_{i,w}} = k_1\left(\frac{\bar{M}_c - \bar{M}_c^*}{\bar{M}_n - \bar{M}_c^*}\right)\exp\left(-\frac{k_2 r_s^2}{Q_m - 1}\right) \tag{11}$$

In this expression, $D_{i,m}$ and $D_{i,w}$ are the ion diffusion coefficients in the hydrogel and in pure water, respectively, k_1 and k_2 are the structural parameters of the polymer/water system, Q is the volume swelling ratio, r_s is the radius of the diffusing ion, $\bar{M}_c$ is the number average molecular weight between crosslinks, and $\bar{M}_n$ is the number average molecular weight of the polymer before crosslinking. In this analysis the pre-exponential term was the same for both the expansion and collapse of the gel, and $k_2 = 1$ since the same polymer was used throughout the study. Thus, the collapsed gels were compared to the swollen gels and the following expression was obtained by writing equation (12) for the hydrogen ion in the collapsed state and the sodium ion in the expanded state and dividing.

$$\frac{D_{H^+,coll}}{D_{Na^+,exp}} = \frac{D_{H^+,w}}{D_{Na^+,w}}\exp\left(-\frac{r_{H^+}^2}{Q_{coll}-1} + \frac{r_{Na^+}^2}{Q_{exp}-1}\right) \tag{12}$$

The values for the radii of the sodium and hydrogen ions were calculated by using the Stokes–Einstein theory as 1.73 and 0.2 Å, respectively. The diffusion coefficients of the sodium and hydrogen ions (in pure water at 25°C) were 1.33×10^{-5} and 9.31×10^{-5} cm^2/s, respectively. Average values of Q_{coll} and Q_{exp} were determined at pH values commonly used in the oscillatory swelling studies.

To calculate the ratio of the rates of ion transport, first the short-term solution to ion diffusion into a thin slab[20] was used as

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\pi\delta^2}\right)^{1/2} \tag{13}$$

where M_t is the quantity of ion diffused at time, t, M_∞ is the ion diffused at infinite times, and d is the thickness of the sample.

This equation indicates that the quantity of ions diffusing into the gel, M_t, was proportional to $D^{1/2}$ and $1/\delta$. Thus, the rate of ions diffusing into the gels was also proportional to these parameters as

$$\frac{(dM_w/dt)_{H^+,coll}}{(dM_w/dt)_{Na^+,exp}} \approx \frac{\delta_{exp}}{\delta_{coll}}\left(\frac{D_{H^+,coll}}{D_{Na^+,exp}}\right)^{1/2} \tag{14}$$

Equation (12) was substituted into equation (14) along with

values for δ_{coll} and δ_{exp}, determined experimentally, to give the ratio of the hydrogen ion diffusion rate into the collapsed gels to the sodium ion diffusion rate into the expanded gels. The results of this analysis are shown in *Table 6* and indicate that the ratio of ion transport rates is close to that observed in the experimental studies. Thus, the expansion and collapse of these networks are controlled purely by ion diffusion.

Solute permeation through P(DEAEM-g-PEG) hydrogels

Solute permeation studies were performed to investigate the ability of solutes with varying sizes and molecular weights to diffuse through these ionic hydrogels. The gels were pre-equilibrated to a pH of 4.6. Vitamin B_{12} and proxyphylline were allowed to permeate through the various gels for at least 8 h, while both the FITC-dextran (mw 4400) and FITC-dextran (mw 9400) only required about 6–7 h for permeation. *Figures 6–8* show typical results of the permeation studies expressed as mass of solute permeated through the P(DEAEM-g-PEG) gels as a function of normalized time. The normalized time was expressed by dividing the time by the square of the membrane thickness.

Table 6 Peppas-Reinhart[19] analysis of the ion diffusion rates of swelling and deswelling for P(DEAEM-g-PEG) gels

Molar ratio of P(DEAEM-g-PEG) gel	Ratio of ion diffusion rates	Ratio of experimental rates from *Tables 4* and *5*
10:1	4.95	5.06
50:1	5.00	1.49
75:1	5.78	3.00
99:1	6.47	4.03

Figure 6 shows the mass of proxyphylline permeated in a 75:1 gel as a function of the normalized time and is characteristic of the results for the permeation of proxyphylline. Proxyphylline permeates linearly with time.

Figure 7 shows typical results for the permeation of vitamin B_{12} through a 99:1 molar ratio gel. All plots showed an initial induction period where there was almost no permeation of the solute through the hydrogel membrane before the solute finally began to permeate linearly. This was due to binding of the solute with the membrane.

The masses of both the proxyphylline and the vitamin B_{12} permeated proved to be much smaller than expected for these gels. Since the mesh sizes were so much larger than the effective radii, the permeability coefficients should be much closer to the diffusion coefficients in water and saline. Typical results of the permeation studies performed with FITC-dextran (mw 4400) are shown in *Figure 8*. A slight induction time was noted in all diffusion studies. After several hours, though, the mass permeated became more linear with time. This induction period was the result of binding.

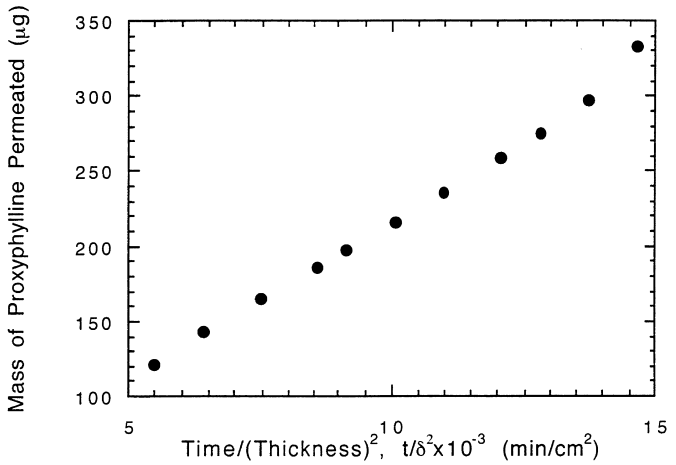

Figure 6 Diffusion of proxyphylline through a 75:1 molar ratio P(DEAEM-g-PEG) gel at pH 4.6 and 37°C

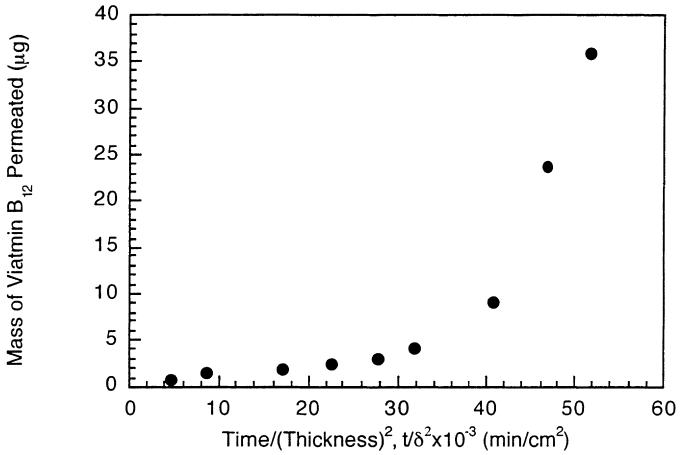

Figure 7 Diffusion of vitamin B_{12} through a 99:1 molar ratio P(DEAEM-g-PEG) gel at pH 4.6 and 37°C

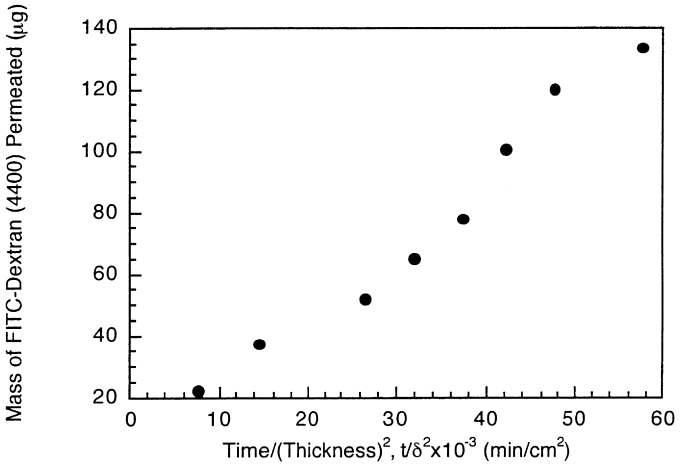

Figure 8 Diffusion of FITC-dextran (4400) through a 75:1 molar ratio P(DEAEM-g-PEG) gel at pH 4.6 and 37°C

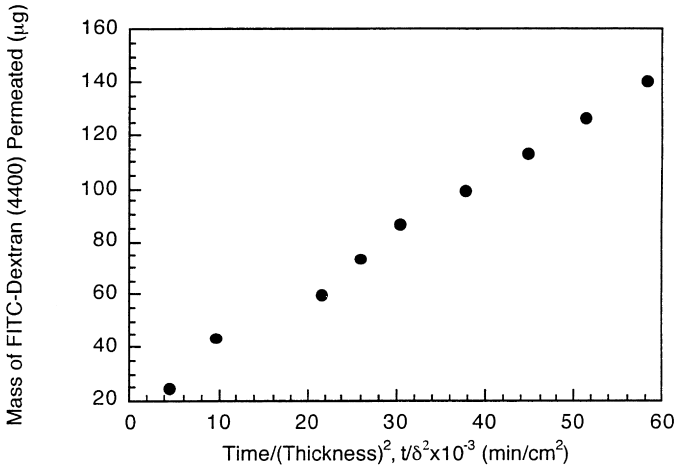

Figure 9 Diffusion of FITC-dextran (4400) through a pre-equilibrated 99:1 molar ratio P(DEAEM-g-PEG) gel at pH 4.6 and 37°C

Despite the fact that both FITC-dextran (mw 4400) and FITC-dextran (mw 9400) are larger than either the proxyphylline and vitamin B_{12}, the dextrans showed a larger mass of solute permeated than either of the previous solutes. This was a result of the interaction of dextran with the PEG grafts of the hydrogel. Because PEG and dextran are immiscible, the PEG chains tend to coil in the presence of the dextran which then increases the area available for diffusion[22]. Thus, the real mesh sizes would be much smaller than those calculated (*Table 3*) due to the presence of grafted PEG groups in the hydrogels.

To examine what effect the grafted chains might have on the mesh size, the end-to-end distance of the PEG (mw 1000) graft was calculated using the following equation

$$\left(\bar{r}_0^2\right)^{1/2} = \alpha\sqrt{3C_nNl} \tag{15}$$

Here, C_n is the characteristic ratio (taken to be 4), l is the carbon–carbon bond length (1.54 Å), and α is the extension ratio (or expansion factor). The extension factor depended on the degree of swelling and was calculated as:

$$\alpha^5 - \alpha^3 = 2C_M\Psi M_{\mathrm{PEG}}^{1/2}\left(1 - \frac{\Theta}{T}\right) \tag{16}$$

where C_M is 0.105, Ψ is −0.5, M_{PEG} was 1000, and Θ is the theta temperature (368 K). Finally, N (in equation (15)) was the degree of polymerization and was determined from equation (17)

$$N = \frac{M_{\mathrm{PEG}}}{M_r} \tag{17}$$

where M_r is the molecular weight of a repeating unit. These calculations indicated that the length of a PEG (mw 1000) grafted chain was about 28 Å. Thus, if the PEG chains were extended in the mesh, they would decrease the mesh size by about 56 Å.

As a test to determine whether the induction periods observed in some of the previous diffusion data were the result of solute binding to the network, permeation studies were performed using a 99:1 molar ratio gel that had been pre-equilibrated in a solution of FITC-dextran (mw 4400) (see *Figure 9*). The relation between the mass of FITC-dextran (mw 4400) permeated and time is linear and does not show the induction period of the data using a non pre-equilibrated gel (*Figure 8*).

Determination of the permeability, partition, and diffusion coefficients

The solute permeability coefficients were determined from the concentration data obtained from the permeation

Table 7 Permeability coefficients for FITC-dextran (4400) and FITC-dextran (9400) through P(DEAEM-g-PEG) gels with varying molar ratios at pH 4.6 and 37°C

Molar ratio (DEAEM repeats: PEG grafts)	Permeability coefficient, $P \times 10^4$ (cm/s)	
	FTIC-dextran (4400)	FTIC-dextran (9400)
50:1	9.62	6.24
75:1	6.61	2.80
99:1 (not pre-equilibrated)	7.04	3.49
99:1 (pre-equilibrated)	—	8.07

Table 8 Partition coefficients for FITC-dextran (4400) and FITC-dextran (9400) in P(DEAEM-g-PEG) gels with varying molar ratios at pH 4.6 and 37°C

Molar ratio (DEAEM repeats: PEG grafts)	Solute	Partition coefficient, K_d
50:1	FITC-dextran (4400)	58.00
	FITC-dextran (9400)	73.07
75:1	FITC-dextran (4400)	103.07
	FITC-dextran (9400)	110.68
99:1	FITC-dextran (4400)	11.21
	FITC-dextran (9400)	58.64

Table 9 Diffusion coefficients for FITC-dextran (4400) and FITC-dextran (9400) in P(DEAEM-g-PEG) gels with varying molar ratios at pH 4.6 and 37°C

Molar ratio (DEAEM repeats: PEG grafts)	Mesh size (Å)	Diffusion coefficient, $D \times 10^7$ (cm^2/s)	
		FTIC-dextran (4400)	FTIC-dextran (9400)
50:1	129	8.83	0.72
75:1	143	12.23	9.47
99:1 (not pre-equilibrated)	131	26.12	11.56
99:1 (pre-equilibrated)	131	59.0	—

studies, using the following equation:

$$\ln\left(\frac{2c_t}{c_0} - 1\right) = \frac{2A}{V}Pt \tag{18}$$

Here, c_t is the solute concentration in the receptor cell at time t, c_0 is the initial solute concentration in the donor cell, V is the volume of each of the half cells (the volume in each half cell is 3 ml), A is the effective area for permeation ($A = 0.636\ cm^2$), and P is the permeability coefficient. To determine the permeability coefficient, a plot was made of $-\{(V/2A)\ln[1-2(c_t/c_0)]\}$ *versus* time. These results are shown in *Table 7*.

The solute partition coefficients were determined (see *Table 8*) for the various polymers in both the FITC-dextran (mw 4400) and the FITC-dextran (mw 9400). The partition coefficient was calculated from experimental data using the following equation:

$$K_d = \frac{c_m}{c_s} = \frac{V_s(c_o - c_e)}{V_m c_o} \tag{19}$$

where c_m and c_s are the concentrations of the solute in the membrane and in the surrounding solution at equilibrium, respectively, V_s and V_m are the respective volumes of the solute and membrane. c_o is the initial concentration of solute in the solution, c_e is and the equilibrium solute concentration in solution. The partition coefficients determined for both FITC-dextran (mw 4400) and FITC-dextran (mw 9400) were rather large, indicating that there was some binding between the solute and the polymer. For both FITC-dextran (mw 4400) and FITC-dextran (mw 9400), the partition coefficient increased with increasing mesh size.

The solute diffusion coefficients were calculated from the permeability coefficients (*Table 7*) and the partition coefficient (*Table 8*), along with the characteristic thickness of each hydrogel membrane, according to equation (20):

$$D_m = \frac{Pl}{K_d} \tag{20}$$

The results from these calculations are shown in *Table 9*.

Clearly, dextran diffusion through these gels showed a size exclusion effect characteristic of the mesh size. In general, solute transport was easier in the more swollen gels as expected.

These results indicate that PEG-grafted cationic hydrogels could be used for transport of small or large biological agents and that a change of pH could lead to their diffusion or exclusion.

CONCLUSIONS

Cationic hydrogels of P(DEAEM-g-PEG) were prepared by varying the comonomer ratios. All gels were characterized through both dynamic and equilibrium swelling studies, and the structural parameters, mesh size and molecular weight between crosslinks, were determined. The swelling studies showed a definite pH-dependence. To determine the ability of the gels to swell and collapse repeatedly, oscillatory swelling studies were also performed.

ACKNOWLEDGEMENTS

This work was supported in part by a National Institutes of Health grant (GM 43337) and by the Showalter Foundation.

REFERENCES

1. Peppas, N. A., *J. Bioact. Compat. Polym.*, 1991, **6**, 241–246.
2. Goldraich, M. and Kost, J., *Clinical Materials*, 1993, **14**, 135–142.
3. Siegel, R. A., Firestone, B. A., Johannes, I. and Cornejo, J., *Polym. Prep.*, 1993, **31**(1), 231–232.
4. Kim, C.-J. and Lee, P. I., *Pharm. Res.*, 1992, **9**, 195–199.
5. Khare, A. R. and Peppas, N. A., *Biomaterials*, 1995, **16**, 559–567.
6. Siegel, R. A. and Firestone, B. A., *Macromolecules*, 1988, **21**, 3254–3259.
7. Siegel, R. A., Falamarzian, M., Firestone, B. A. and Moxley, B. C., *J. Contr. Rel.*, 1988, **8**, 179–182.
8. Langer, R. S. and Peppas, N. A., *J. Macromol. Sci., Rev. Macromol. Chem. Phys.*, 1983, **C23**, 61–126.
9. Liaw, D.-J., Shiau, S.-J. and Lee, K.-R., *J. Appl. Polym. Sci.*, 1992, **45**, 61–70.
10. Piletsky, S. A., Parhometz, Y. P., Lavryk, N. V., Panasyuk, T. L. and El'skaya, A. V., *Sensors and Actuators B*, 1994, **18–19**, 629–631.
11. Peppas, N. A. and Merrill, E. W., *J. Polym. Sci. Polym. Chem.*, 1976, **14**, 441–459.
12. Brannon-Peppas, L. and Peppas, N. A., *J. Contr. Rel.*, 1991, **16**, 319–330.
13. Cornejo-Bravo, J. M., Arias-Sanchez, V., Alvarez-Anguiano, A. and Siegel, R. A., *J. Contr. Rel.*, 1995, **33**, 223–229.
14. Siegel, R. S. and Firestone, B. A., *Proceed. Intern. Symp. Control. Rel. Bioact. Mater.*, 1988, **15**, 24–25.
15. Firestone, B. A. and Siegel, R. A., *J. Biomater. Sci. Polymer Edn*, 1994, **5**, 433–450.
16. Hariharan, D. and Peppas, N. A., *Polymer*, 1996, **37**, 149–161.
17. Peppas, N. A. and Foster, L. K., *J. Appl. Polym. Sci.*, 1994, **52**, 763–768.
18. Brannon-Peppas, L. and Peppas, N. A., in *Absorbent Polymer Technology*, ed. L. Brannon-Peppas and R. S. Harland. Elsevier, Amsterdam, 1990, pp. 67–102.

19. Reinhart, C. T. and Peppas, N. A., *J. Membr. Sci.*, 1983, **15**, 275–287.
20. Crank, J., *The Mathematics of Diffusion*. Clarendon Press, London, 1968.
21. Lustig, S. R. and Peppas, N. A., *J. Appl. Polym. Sci.*, 1988, **36**, 735–747.
22. Feil, H., Bae, Y. H., Fiejen, J. and Kim, S. W., *J. Membr. Sci.*, 1991, **64**, 283–294.
23. Bondi, A., *J. Phys. Chem.*, 1964, **68**, 441–451.
24. Colton, C. K., Permeability and transport studies in batch and flow dialyzers with applications to hemodialysis. Ph.D. thesis, School of Chemical Engineering, Massachusetts Institute of Technology, 1969.
25. Dong, L. C., Yan, Q. and Hoffman, A. S., *J. Contr. Rel.*, 1992, **19**, 171–177.