Investigation of hydrogel water in polyelectrolyte gels using differential scanning calorimetry

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Characterization of the water structure in hydrogels is of the utmost importance in understanding their dynamic and equilibrium swelling behaviour as well as in analysing solute transport and other diffusive properties of such systems. Polymer–water interactions coupled with the physical property changes of the water associated with the hydrogel structure can determine the permeability characteristics of solutes through these hydrogels. The water structures inside ionic copolymeric networks of poly(2-hydroxyethyl methacrylate-*co*-methacrylic acid) and poly(2-hydroxyethyl methacrylate-*co*-acrylic acid) were investigated as a function of the pH and ionic strength of the swelling medium and the type of counterion in the swelling medium using differential scanning calorimetry. The free water content increased with an increase in pH and a decrease in ionic strength. The bound water content was found to be independent of the pH of the external swelling medium. The Donnan ionization equilibrium concept was used to explain the observed trends. This study is useful in correlating the hydrogel water structure with solute diffusion through these hydrogels.

(Keywords: hydrogels; free water; polyelectrolytes)

INTRODUCTION

In recent years, ionic hydrogels have been investigated for a variety of pharmaceutical and biomedical applications because of their swelling properties which are dependent upon physical parameters such as pH, ionic strength and temperature[1]. Abrupt changes in equilibrium swelling occur at the pK_a of the gel. This behaviour can be used in the development of site-specific drug delivery systems, biosensors, artificial muscles and osmotic pumps[2–4].

Numerous investigators have studied the influence of the volume swelling ratio on solute transport in equilibrium and dynamically swelling hydrogels[5]. We have previously reported that solute transport is affected by this parameter in an exponential way and have shown that two to three order of magnitude changes may be observed both in solute diffusivities as well as in the associated transport rates as a result of large changes in the swelling ratio[6,7]. We are now directing our attention to the fact that not all the water accounted for in the swelling ratio contributes to an increase of the diffusion coefficient. Thus, the solute mobility depends strongly not only on the total swelling ratio but also on the nature of the water inside the hydrogel[8]. The physical properties of water such as viscosity or melting point change when the water molecules are present in a constrained geometry[9]. Similarly, inside a hydrogel, owing to the constrained geometry and the polymer–water interactions, the viscosity of water which is present in the vicinity of polymer chains increases; this in turn affects the solute mobility through hydrogels.

The water physical properties may be affected by ionization of ionizable groups attached to the main polymer backbone through the interaction between polymer and water in hydrogen bonding and dipole–dipole interactions. The water structure may be altered by the affinity of ionizable groups for counterions which in turn solvate to form an aqueous shell around fixed charges. Owing to these changes in the hydrogel water structure, the solute diffusivity and permeability do not depend on the swelling ratio, but only on the fraction of water which is 'available' for solute diffusion.

The nature of water in hydrogels may be important in controlling the solute diffusional mechanism in swelling-controlled release systems, as reported by Kim *et al.*[8], and through hydrogel membranes, as reported by Tighe and his associates[10]. The physical properties of water inside hydrogels change because of the extensive hydrogen bonding and polar interactions with the polymer[9,11]. This change controls the solute diffusion and partition coefficients. One of the structural models of water proposed by Jhon and Andrade[12] indicates the presence of three different classes of water in any hydrogel. Bound water is strongly associated with the macromolecular chains by hydrogen bonding or by polar interactions. Interfacial water is characterized by ice-like configurations around the hydrophobic groups. This form of water is not as strongly held by the polymer chains as bound water. Free, or bulk, water has the same physical properties as normal water, and is not attached

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to the polymer chains. Thus, the polymer chains do not influence the interactions between the adjacent water molecules.

Recent nuclear magnetic resonance measurements of the relaxation times of water molecules in poly(2-hydroxyethyl methacrylate) hydrogels indicate that there are two distinct sets of relaxation times corresponding to bulk free water and bound water[13]. Bound water is tightly held by the polymer and has a lower mobility. Therefore, the diffusion coefficient of a hydrophilic solute through the bound water fraction would be lower than that through the free water. However, some investigators suggest that the so-called bound water is still mobile and question the clear distinction between free and bound water[14].

Measurement of the bound water content of a gel can be done by differential scanning calorimetry (d.s.c.), nuclear magnetic resonance spectroscopy, or Fourier transform infra-red spectroscopy[13]. D.s.c. monitors the gross phase changes of water in polymers. When a hydrogel sample is cooled well below 0°C, the free and interfacial water freeze but the bound water remains in the non-frozen state, since it is strongly associated with the polymer chains. D.s.c. measures the freezable water, and the remaining water in the concentrated polymer phase is unfrozen. This unfrozen water fraction is herein termed the bound water fraction. The peak at lowest temperature in the d.s.c. thermogram of a hydrogel is at a temperature slightly or significantly lower than 0°C, which is associated with the freezing of interfacial water. The second fusion peak which appears at 0°C is owing to the free water portion of the hydrogel water[13].

Previous work[10,15,16] has analysed to a great extent the water structure in certain types of neutral hydrogels, e.g. poly(2-hydroxyethyl methacrylate) (PHEMA) and poly(*N*-vinyl-2-pyrrolidone/methyl methacrylate) gels. It has been found that the relative amounts of bound and free water depend on the copolymer composition, degree of crosslinking and the nature of the ions from the swelling medium. The diffusion coefficients have been determined for ions through PHEMA gels[10], and for water-soluble solutes as well as hydrophobic solutes in PHEMA films[8], and for temperature-sensitive copolymer gels of *N*-isopropylacrylamide and acrylic acid[17]. As expected, the diffusivities of solutes through these hydrogels were found to depend upon free water content.

However, until now, little has been done to analyse the water structure in ionic hydrogels. In this research, ionic hydrogels of poly(2-hydroxyethyl methacrylate-*co*-methacrylic acid), henceforth designated as P(HEMA-*co*-MAA), and poly(2-hydroxyethyl methacrylate-*co*-acrylic acid), henceforth designated as P(HEMA-*co*-AA), were synthesized and the hydrogel water structures were characterized as a function of pH, ionic strength of the swelling medium and nature of the counterion in the swelling medium.

EXPERIMENTAL

Hydrophilic copolymeric networks of P(HEMA-*co*-MAA) and P(HEMA-*co*-AA) were synthesized using solution polymerization. HEMA was added to appropriate quantities of MAA or AA to give 5 g of mixture. Quantities of 0.5 wt% ammonium persulfate and sodium bisulfite were added as redox initiators and 0.45 mol ethylene glycol dimethacrylate (EGDMA) was used as a crosslinking agent per 100 mol of total comonomers used. The solution polymerization was carried out in polyethylene vials using distilled, deionized water as solvent at a level of 50 wt% of the total mixture in a constant temperature water bath at 37°C for 24 h, followed by gradual cooling to room temperature. The vials were cut away from the polymer gels and the latter were dried at 25 ± 2°C; discs were cut from the dried glassy polymer cylinders using a lathe. These samples were dried in a vacuum oven at 40°C for a week. The ensuing glassy, crosslinked samples in disc form (12–15 mm diameter, 1 mm thickness) were swollen in a pH 7.4 phosphate buffer solution with an ionic strength of 0.1 M; or in 3,3′-dimethylglutaric acid (Sigma Chemicals, St Louis, MO) buffer solutions of pH 4 to 7 and with an ionic strength of 0.1 M; or in 3,3′-dimethylglutaric acid buffer solutions of pH 7 with ionic strengths of 0.01 M or 0.1 M; or in aqueous solutions of NaCl and $CaCl_2$ with an ionic strength of 0.1 M; or in distilled, deionized water at pH 7. All the swelling studies were carried out at 25 ± 2°C. The samples were allowed to swell for two to three weeks or until equilibrium swelling had been attained. The total water content was obtained gravimetrically.

The free water content of the swollen gel was determined using a differential scanning calorimeter (model 910, TA Instruments, Wilmington, DE). Hydrogel specimens (10–15 mg) were cut from the pre-equilibrated gels, placed in the appropriate aluminium pan, sealed, cooled to -50°C at a rate of $5°C\,min^{-1}$, and then reheated at the same rate up to 30°C. The melting peak of frozen free water was observed around 0°C, and was used to compute the amount of free water based on its enthalpy of fusion of $320\,J\,g^{-1}$. The total water content was computed from the gravimetric swelling studies. All the equilibrium swelling and d.s.c. measurements were done in duplicate. All the water uptake values were reported as grams of water absorbed per gram of dry polymer.

RESULTS AND DISCUSSION

The copolymers P(HEMA-*co*-AA) and P(HEMA-*co*-MAA) are ionizable because of the presence of charged carboxylic acid groups; their pK_a values were calculated as 5.5 and 5.9, respectively, using equilibrium swelling data with the assumption that the equilibrium degree of swelling is directly proportional to the degree of ionization of a polymer hydrogel[18]. Therefore, the gels are completely ionized at pH 7. AA and MAA are very hydrophilic in nature, although HEMA is moderately hydrophilic. Thus, the incorporation of HEMA gives a moderate hydrophilic character to these copolymer networks and provides desirable swelling characteristics. In this study, the free water content was measured for two copolymers containing 20 mol% AA or MAA. The ionizable content in both copolymers was kept constant. Both P(HEMA-*co*-AA) and P(HEMA-*co*-MAA) copolymers were synthesized using a similar experimental protocol. However, there is the possibility that these polymers have different tacticities. The free water content in each of these polymers was measured as a function of pH, ionic strength and nature of the counterion.

Figures 1 and *2* show the total water and free water contents, respectively, of the two copolymers studied in

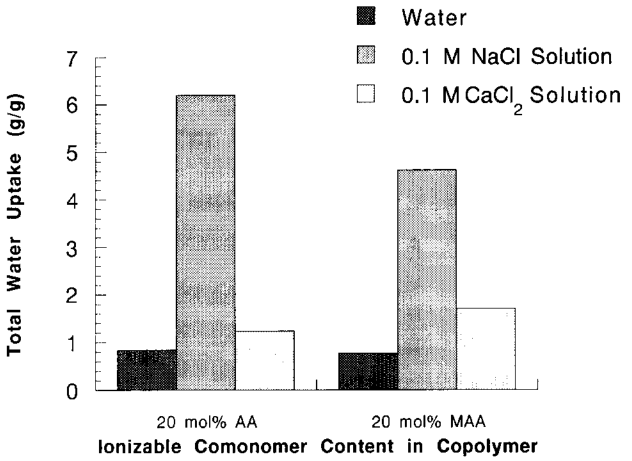

Figure 1 Total water uptake of crosslinked P(HEMA-*co*-MAA) and P(HEMA-*co*-AA) samples containing 20 mol% MAA or AA at equilibrium with a 0.1 M aqueous NaCl solution, a 0.1 M aqueous $CaCl_2$ solution and in deionized water at 25°C

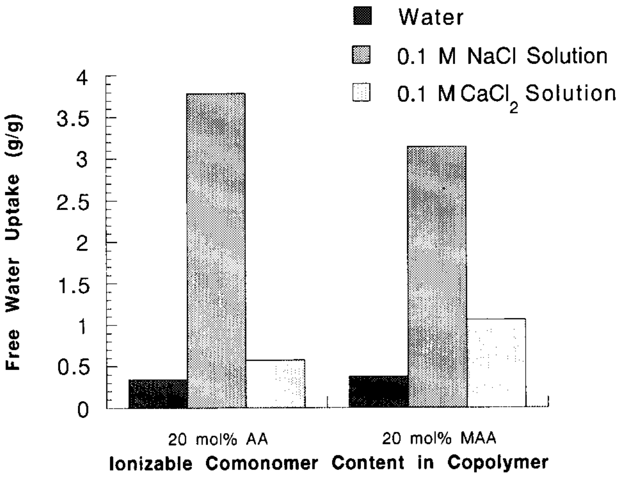

Figure 2 Free water uptake of crosslinked P(HEMA-*co*-MAA) and P(HEMA-*co*-AA) samples containing 20 mol% MAA or AA at equilibrium with a 0.1 M aqueous NaCl solution, a 0.1 M aqueous $CaCl_2$ solution and in deionized water at 25°C

various salt solutions having the same ionic strength. The overall trend from these studies is that the free water and total water contents were highest in NaCl solutions followed by $CaCl_2$ solutions, whereas the lowest amounts of free water and total water were observed in distilled, deionized water. This is owing to the limited ionization of the carboxylic acid groups in the salt solutions. The decrease in free water and total water contents observed from NaCl to $CaCl_2$ solutions is owing to a increase in counterion valency. Calcium ions bind to two COO^- groups from the polymer, thereby possibly reducing the end-to-end distance of the polymer chain. In water, the carboxylic acid groups are mostly in the unionized form that leads to the lowest free water and bound water contents. The free water and bound water contents absorbed from NaCl solutions were higher in AA-containing copolymers than in MAA-containing copolymers. Surprisingly enough, the exactly opposite behaviour was observed in MAA-containing copolymers in water and aqueous $CaCl_2$ solutions. Since MAA-containing copolymers are more hydrophobic than AA-containing copolymers owing to the presence of the α-methyl group in methacrylic acid, this increase in water content may be owing to the different polymer morphology and polymer–counterion interactions.

Figure 3 shows the total water and bound water contents in the samples tested as a function of the pH of the glutarate buffer solutions. The bound water content remained constant even though the pH of the buffer solution was increased past the pK_a of the gel. Thus, the bound water content remains constant independent of the pH of the buffer, i.e. the degree of ionization of the polymer. Thus, the bound water is strongly associated with the polymer chains by hydrogen bonding and polar interactions leading to a shielding of the carboxylic acid groups and an insensitivity to polymer polarity. An increase in the pH of the buffer led to an increase in the total water content in both polymer gels. This means that the free water content also increases with an increase in pH, since this is given by the difference between the total water and the bound water. This increase is also owing to an increase in the degree of ionization in both polymeric samples. The total water content in both polymers was found to be similar and no clear trend was observed.

Figures 4 and *5* give the total water and free water

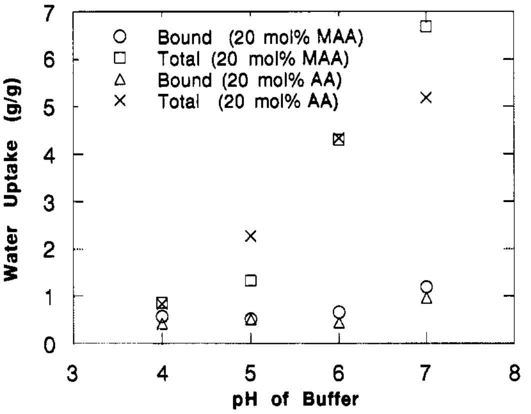

Figure 3 Total water and bound water uptake of crosslinked P(HEMA-*co*-MAA) and P(HEMA-*co*-AA) samples containing 20 mol% MAA or AA at equilibrium with 0.1 M glutarate buffers as functions of pH at 25°C

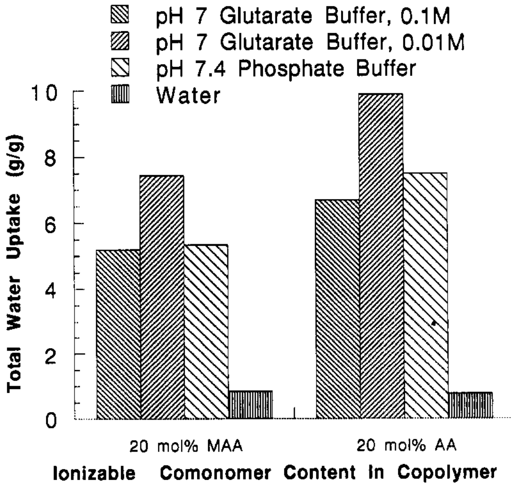

Figure 4 Total water uptake of crosslinked P(HEMA-*co*-MAA) and P(HEMA-*co*-AA) samples containing 20 mol% MAA or AA at equilibrium with a 0.1 M pH 7 glutarate buffer solution, a 0.01 M pH 7 glutarate buffer solution, a 0.1 M pH 7.4 phosphate buffer solution, and in deionized water at 25°C

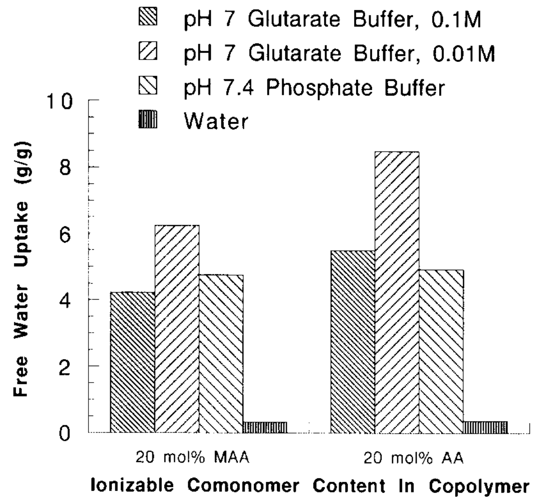

Figure 5 Free water uptake of crosslinked P(HEMA-*co*-MAA) and P(HEMA-*co*-AA) samples containing 20 mol% MAA or AA at equilibrium with a 0.1 M pH 7 glutarate buffer solution, a 0.01 M pH 7 glutarate buffer solution, a 0.1 M pH 7.4 phosphate butter solution, and in deionized water at 25°C

contents, respectively, in both polymer samples as a function of ionic strength in pH 7 glutarate buffer solutions and in a pH 7.4 phosphate buffer solution. The total water and free water contents decreased as the ionic strength increased from 0.01 to 0.1 M in pH 7 glutarate buffer solutions. At pH 7 both the polymer samples are completely ionized with a degree of ionization of approximately unity. Owing to the electroneutrality condition inside the hydrogel, the counterion concentration inside the gel is constant and any increase in the counterion concentration in the external swelling medium reduces the concentration differential across the gel and the swelling medium. According to the Donnan equilibrium, this leads to a decrease in the Donnan potential. This, in turn, leads to a decrease in the ion-osmotic swelling pressure with an increase in the ionic strength. The free water and total water contents decrease in the pH 7.4 phosphate buffer solution. This may be owing to the nature of the buffering agent, i.e. phosphoric acid. The free water and total water contents were found to be lowest in water, since the degree of ionization of the polymer network is very low in water and water is an unbuffered system. Finally, the free water and total water contents are higher in the AA-containing copolymers than in the MAA-containing copolymers having the same ionizable content, owing to the factors discussed earlier.

CONCLUSIONS

In summary, it has been shown that the free water content in pH-sensitive polymers as measured by d.s.c. depends upon the pH, ionic strength and the nature of the counterion present in the external swelling medium. The bound water content was found to be independent of the pH of the external swelling medium. The Donnan ionization equilibrium concept was useful in explaining the observed trends.

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REFERENCES

1 Tanaka, T. in 'Polyelectrolyte Gels' (Eds R. S. Harland and R. K. Prud'homme), ACS Symposium Series 480, American Chemical Society, Washington, DC, 1992, p. 1
2 Brannon-Peppas, L. and Peppas, N. A. *J. Controlled Release* 1989, **8**, 267
3 Kuo, J. H., Amidon, G. L. and Lee, P. I. *Pharm. Res.* 1988, **5**, 592
4 Siegel, R. A. and Firestone, B. A. *Macromolecules* 1988, **21**, 3254
5 Peppas, N. A. and Lustig, S. R. in 'Hydrogels in Medicine and Pharmacy' (Ed. N. A. Peppas), CRC Press, Boca Raton, FL, 1987, p. 57
6 Reinhart, C. T. and Peppas, N. A. *J. Membr. Sci.* 1984, **18**, 227
7 Peppas, N. A. and Moynihan, H. J. *J. Appl. Polym. Sci.* 1985, **30**, 2589
8 Kim, S. W., Cardinal, J. R., Wisniewski, S. and Zentner, G. M. in 'Water in Polymers' (Ed. S. P. Rowland), ACS Symposium Series 127, American Chemical Society, Washington, DC, 1980, p. 347
9 Stillinger, F. H. in 'Water in Polymers' (Ed. S. P. Rowland), ACS Symposium Series 127, American Chemical Society, Washington, DC, 1980, p. 11
10 Hamilton, C. J., Murphy, S. M., Atherton, N. D. and Tighe, B. J. *Polymer* 1988, **29**, 1879
11 Quinn, F. X., Kampff, E., Smyth, G. and McBrierty, V. J. *Macromolecules* 1988, **21**, 3191
12 Jhon, M. S. and Andrade, J. D. *J. Biomed. Mater. Res.* 1973, **7**, 509
13 Quinn, F. X., McBrierty, V. J., Wilson, A. C. and Friends, G. D. *Macromolecules* 1990, **23**, 4576
14 Franks, F. in 'Water Relationships in Foods: Advances in the 1980s and Trends for the 1990s' (Eds H. Levine and L. Slade), Plenum Press, New York, 1991, p. 1
15 Smyth, G., Quinn, F. X. and McBrierty, V. J. *Macromolecules* 1988, **21**, 3198
16 Roorda, W. E., Bouwstra, J. A., de Vries, M. A. and Junginger, H. E. *Biomaterials* 1988, **9**, 494
17 Dong, L. C. and Hoffman, A. S. *J. Controlled Release* 1991, **15**, 141
18 Khare, A. R. and Peppas, N. A. *Macromolecules* in press