Thermal and Pulse NMR Analysis of Water in Poly(2-hydroxyethyl Methacrylate)

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Synopsis

Hydrophilic three-dimensional methacrylate polymer networks (hydrogels) were prepared from 2-hydroxyethyl methacrylate (HEMA) monomer and tetraethylene glycol dimethacrylate (TEGDMA) as crosslinker. The nature and states of water in these hydrogels were studied by differential thermal analysis and pulse NMR relaxation spectroscopy. The thermal studies showed no endotherm peak for ice melting in the lower water content (bound water region); there are two endotherms peaks for higher water content hydrogels near 0°C. The amounts of bound water, intermediate water, and bulklike (free) water in the hydrogels were determined from a quantitative analysis of the endotherms of the water melting transitions. The water structure ordering in the hydrogels were discussed in terms of the fusion entropy and enthalpy obtained from the endotherm. Nuclear magnetic relaxation spectroscopy was also used to understand the mobilities of the water protons in the hydrogels and the interaction of water molecules with the gel networks. The measured spin-lattice relaxation time (T_1) values for water protons in the hydrogels are greatly reduced compared to that of liquid water. The measured values of spin–spin relaxation times (T_2) of water protons in the hydrogels are approximately 10 times less than that of T_1 and are almost constant in the region of bound water content. Beyond the bound water content region in the hydrogels, the T_2 values rapidly increase as the water content increases.

INTRODUCTION

Hydrophilic methacrylate polymers are being considered for biomedical applications.[1-5] These polymers swell in water to become soft crosslinked gels, so-called hydrogels. Synthetic hydrogels have been extensively discussed in the literature.[6-8] The transport characteristics of hydrogel membranes have been examined for a broad range of potential applications, including soft contact lenses,[9] reverse osmosis membranes,[10-12] kidney dialysis membranes,[13-15] and drug delivery systems for antibiotics,[16-18] steroids,[19,20] and enzymes.[21,22]

In order to develop useful synthetic biomedical hydrogels, it is of interest to understand the state and properties of water in such hydrogels. Water in hydrogels has been treated in terms of a three-state model.[23] To test the validity of the model, dilatometry, specific conductivity, and dielectric studies of water in hydrogels have been carried out from −15°C to room temperature for poly(2-hydroxyethyl methacrylate) (pHEMA)[24,25] and poly(2,3-dihydroxypropyl methacrylate) (pDHPMA) gels.[26]

Using the three-state model, we have determined the amounts of bound water, intermediate water, and bulklike (free) water in hydrophilic methacrylate gels

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by utilizing differential thermal analysis and nuclear magnetic resonance (NMR) relaxation spectroscopy.

EXPERIMENTAL

Preparation of Materials

Purified 2-hydroxyethyl methacrylate (HEMA) was obtained as a gift from Hydro-Med Sciences, Inc., New Brunswick, N.J., containing about 0.2% methacrylic acid, 0.16% diethylene glycol methacrylate, and 0.01% ethylene glycol dimethacrylate. The polymerization of HEMA monomer was initiated by azobis (methyl isobutyrate), 7.84 mmol initiator/mL of HEMA monomer. This ratio is independent of water content in the hydrogels. The other pHEMA copolymers were polymerized with the crosslinking agent tetraethylene glycol dimethacrylate (TEGDMA). The pHEMA of fixed water content was obtained by polymerizing a solution of HEMA with the proper amount of water. The water used in this experiment was distilled three times and exhibited a conductivity of less than 1.4×10^{-6} $(\Omega\ \text{cm})^{-1}$. After degassing the solution, the polymer was prepared by thermal initiation at 60°C for 24 h.

The samples for thermal analysis were sealed in aluminum pans to prevent the evaporation of water during measurements. The exact water content of the hydrogels was obtained by drying to constant weight. The samples for NMR relaxation spectroscopy were prepared by polymerizing in sealed NMR sample tubes after a nitrogen gas purge and freeze-thaw degassing[27,28] to remove the free oxygen. The samples were allowed to stand at room temperature for 60 days to cure completely.

Measurements and Apparatus

Differential Thermal Analysis (DTA)

Differential thermal analysis (DTA) was performed in a Du Pont 990 thermal analyzer and cell base. The temperature scales were calibrated using the melting point of standard pure indium and triple distilled water. The samples sealed in an aluminum pan were weighed before and after DTA runs.

After cooling with liquid nitrogen and allowing to stand at −100°C for 20 min to stabilize, the temperature was raised at a programed rate of 5°C/min under nitrogen gas and the results recorded. The effect of programmed rate at 1, 5, 10, and 20°C/min was tested by detection of the melting transitions of pure water. There was some variation in melting temperature at temperature rates greater than or equal to 10°C/min. The transitions detected at 5°C/min were the same as those measured at slower rates. The heat of fusion of water in the hydrogel was measured from the melting peak area as a function of water content in the samples. The area of the melting peaks were within ±3% on repeated runs.

Nuclear Magnetic Resonance (NMR) Relaxation Spectroscopy

The longitudinal (spin-lattice) and transverse (spin–spin) proton relaxation times were measured by utilizing a pulsed 100-MHz NMR spectrometer (Varian XLFT-100). The spin-lattice relaxation time (T_1) measurements were made

using a π—τ—$\pi/2$ pulse sequence[29,30]; T_1 was determined from the slope of semilogarithmic plots. Spin–spin relaxation times (T_2) were obtained from the full width at half maximum absorption following the pulse sequence.[30,31] The temperature was controlled at 34 ± 1°C during the measurements.

RESULTS AND DISCUSSION

Differential Thermal Analysis

The integral heats of fusion of the water melting transition in hydrogels were measured from the total peak area of the endotherms. Typical melting transition endotherms of water, indium, and water-swollen methacrylate gels are shown in Figure 1. The lower water content (10% H_2O) pHEMA sample does not show any sharp transition near 0°C (Fig. 1, middle). Double peaks in hydrogel systems are found for the higher water content (40% H_2O) pHEMA sample, as shown in Figure 1 (top). The shape of the endotherm was somewhat dependent upon the freezing conditions, though the total area of the endotherm was approximately constant. We define the total water transition to consist of both peaks in the vicinity of 0°C. Figure 2 presents the detailed endotherms for the pHEMA—H_2O samples and Figure 3 for the TEGDMA crosslinked pHEMA—H_2O samples. The integral heats of fusion of the total water transition for each system were determined from eq. (1) on the basis of the standard indium endotherm. The heat of fusion of sample, ΔH_s, is expressed as[32,33]:

$$\Delta H_s = \Delta H_{\text{In}} \cdot \frac{W_{\text{In}} A_s R_s S_{\text{In}}}{W_s A_{\text{In}} R_{\text{In}} S_s} \tag{1}$$

where the subscript s refers to sample and In refers to indium. ΔH, W, A, R, and S are the heat of transition, weight, peak area, range, and chart speed, respectively.

Figures 4 and 5 show the integral heat of fusion of the water melting transition as a function of water content for pHEMA and pHEMA—TEGDMA hydrogels, respectively. In the figures, W_{nf} represents the nonfreezable water. By similar measurements of the total area under the endothermic curves,[34–36] we have determined the integral heat of fusion of the water melting transition. Extrapolation to $\Delta H = 0$ intercepts the water content axis at a point which is the total bound water content of the sample, given in Table I.

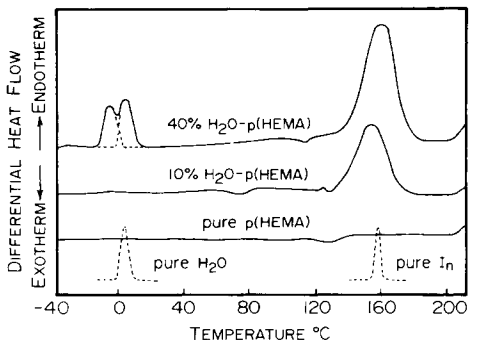

Fig. 1. Endotherms for water, indium, poly(2-hydroxyethyl methacrylate) hydrogels. The program rate is 5°C/min.; flow rate of N_2 gas is 50 mL/min.

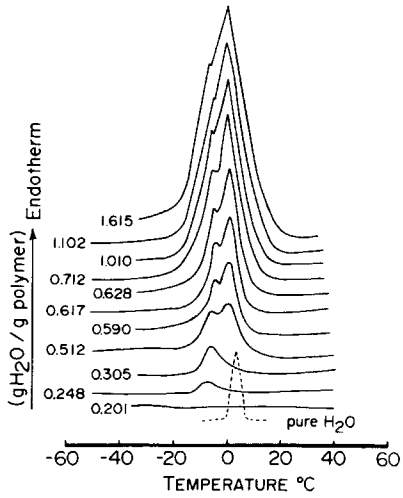

Fig. 2. The endotherms of pHEMA—H_2O samples. The program rate is 5°C/min.; flow rate of N_2 gas is 50 mL/min.

A plot of the integral heat of fusion versus water content of gels shows approximately a straight line in the measured range.[36] The slope at high water contents is approximately equal to the heat of fusion of bulk water (ΔH_f = 79.7 cal/g).[37] From the slope of the straight line, the specific heats of water transition in the samples were evaluated as listed in Table I. The values of ΔH_f of polymeric systems, such as pHEMA—H_2O and pHEMA—EGDMA—H_2O, are less than that of ΔH_f of bulk water. The lower ΔH_f values may be due to volume shrinkage and structuring of water in the gel network, which can be directly observed by dilatometry.[24] The values of ΔH_f obtained for the hydrogel systems based on pHEMA are reasonable and are similar to related systems.[38,39] One can also compare with the reported values of 77.6 cal/g for purified elastin[40] and 77.5 cal/g for native elastin.[40]

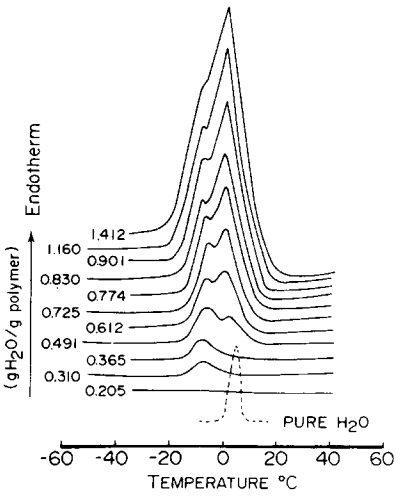

Fig. 3. The endotherms of pHEMA—TEGDMA—H_2O samples. The program rate is 5°C/min.; flow rate of N_2 gas is 50 mL/min.

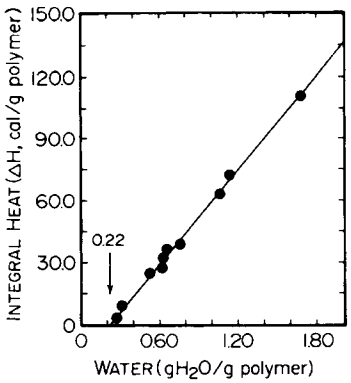

Fig. 4. The integral heat of fusion of the water transition as a function of water content for the pHEMA—H_2O system. W_{nf} is 0.22 g H_2O/g polymer (18.0 wt % H_2O).

The specific entropies of fusion of the water transition as the melting point were evaluated from the relationship $\Delta S_f = \Delta H_f/T_m$, using the ΔH_f data listed in Table I. The observed entropy deficit can be interpreted as the ordering of the bulklike water in the hydrogels and is somewhat greater than the ordering of ordinary water and ice, whose specific entropy of fusion is 0.292 eu.[27] It is interesting to compare the specific entropy of fusion of the water transition in

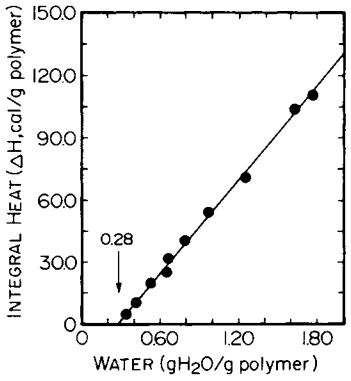

Fig. 5. The integral heat of fusion of the water transition as a function of water content for the pHEMA—TEGDMA—H_2O system. W_{nf} is 0.28 g H_2O/g polymer (21.9 wt % H_2O).

TABLE I
Total Bound Water Content and Specific Thermal Parameters of Water Transition in Some Methacrylate Systems

Systems	Bound water content (wt %)	Mole ratio of bound H_2O/ monomer unit	Specific enthapy of fusion, ΔH_f (cal/g)[a]	Specific entropy of fusion, ΔS_f (eu)[a]
Ice	100.0	—	79.7[b]	0.292[b]
pHEMA—H_2O	18.0	1.59	76.3 ± 0.7	0.279 ± 0.003
pHEMA—(1 mol % TEGDMA)—H_2O	21.9	2.05	75.2 ± 0.7	0.275 ± 0.003

[a] For freezing (intermediate and bulklike) water in the hydrogels.
[b] Data taken from Ref. 37.

pHEMA hydrogels with the values found for various tissues, which range from 0.259 eu to 0.279 eu.[41] Water molecules bound to polymer networks are distinguishable from other water molecules by a higher binding energy, an appreciably lower rational freedom, and an extended lifetime.

Since the endotherms show two different peaks in higher water content gels,[24,36] an enthalphic heat of fusion can be obtained from each peak. Each peak was manually resolved and the individual peak areas were determined.[36] The water which melts near 0°C is called "bulklike" water; the water which has a lower melting temperature is called "intermediate" water; and the water which does not show any melting transition above −100°C is called "bound" water.[24,36]

Figures 6 and 7 show the partial enthalpic heats of the freezable water as a function of water content in the system pHEMA—H_2O and pHEMA—TEGDMA—H_2O, respecitvely. In Figures 6 and 7, $W_f(I)$ is the "intermediate" (lower melting) water; $W_{f(F)}$ is the "free" or "bulklike" (0° melting) water in the hydrogels. The slope of bulklike (free) water in the hydrogels is very close to the heat of fusion of bulk water. The amounts of bound water, intermediate water, and bulklike water in each hydrogel system were determined from the data of Figures 4–7 and are presented in Table II for pHEMA hydrogels of different total water contents; Table III gives the data for 1 mol % TEGDMA—pHEMA—H_2O systems. As seen in Tables II and III, bulklike (free) water in the hydrogels increases only after the bound water and intermediate water are saturated.

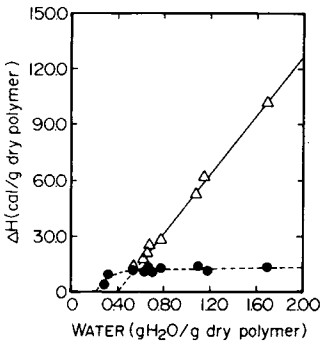

Fig. 6. The heat of fusion of the $W_{f(I)}$ and $W_{f(F)}$ transitions as a function of water content for the pHEMA—H_2O hydrogels; (●) $W_{f(I)}$; (△) $W_{f(F)}$.

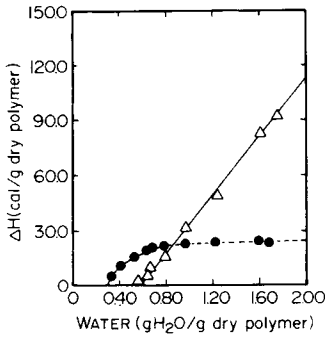

Fig. 7. The heat of fusion of the $W_{f(I)}$ and $W_{f(F)}$ transitions as a function of water content for the pHEMA—TEGDMA—H_2O hydrogels; (●) $W_{f(I)}$; (△) $W_{f(F)}$.

TABLE II
Determination of Bound Water, Intermediate Water, and Bulklike Water in pHEMA Hydrogels (Uncrosslinked) of Different Total Water Content

wt % of total water in hydrogels	18.0	20.0	25.0	30.0	35.0	40.0	45.0	50.0
Total water/polymer (g/g)	0.22	0.25	0.33	0.43	0.54	0.67	0.82	1.00
Bound water/polymer (g/g)	0.22	0.22	0.22	0.22	0.22	0.22	0.22	0.22
Intermediate water/polymer (g/g)	0	0.03	0.11	0.16	0.16	0.16	0.16	0.16
Bulklike water/polymer (g/g)	0	0	0	0.05	0.16	0.29	0.44	0.62

The process of water imbibition in the hydrogels may be interpreted in terms of three steps: (1) An amount of water is first bound to the hydrophilic sites; (2) additional water is preferentially oriented around the bound water and the polymer network structure as a secondary or tertiary hydration shell; and (3) any other water is present as free or bulklike water.

Nuclear Magnetic Relaxation Spectroscopy

Table IV presents the spin-lattice relaxation times (T_1) as a function of water content for the pHEMA and pHEMA—TEGDMA systems at 100 MHz and 34°C. Comparing with the T_1 of pure water (4.50 s at 34°C), the average T_1 values for the hydrogel systems are reduced, suggesting that there are considerable interactions between the water molecules and the polymer networks. The short T_1 of water protons in the hydrogel suggests that the water is less mobile than in pure water. This can be interpreted in terms of the structure ordering of water molecules in gel networks. The most probable binding positions of water molecules are the polar sites, such as the hydroxyl and ester groups. The effect of a crosslinking agent, such as TEGDMA, produces rather slight changes in T_1,

TABLE III
Determination of Bound Water, Intermediate Water, and Bulklike Water in 1 mol % TEGDMA—pHEMA Hydrogels of Different Total Water Content

wt % of total water in hydrogels	21.9	25.0	30.0	35.0	40.0	45.0	50.0
Total water/polymer (g/g)	0.28	0.33	0.43	0.54	0.67	0.82	1.00
Bound water/polymer (g/g)	0.28	0.28	0.28	0.28	0.28	0.28	0.28
Intermediate water/polymer (g/g)	0	0.05	0.15	0.25	0.29	0.29	0.29
Bulklike water/polymer (g/g)	0	0	0	0.01	0.10	0.25	0.43

TABLE IV
Proton NMR Spin-Lattice Relaxation Times for Hydrogels Based on pHEMA of Different Total Water Contents at 100 MHz and 34°C (Unit:s)

wt % of total water content in the hydrogel	pHEMA—H_2O		pHEMA—1 mol % TEDGMA—H_2O	
	T_1	T_{11}	T_1	T_{11}
25	0.189	0.272	0.182	0.217
30	0.214	0.298	0.190	0.232
35	0.260	0.311	0.207	0.279
40	0.300	0.337	0.238	0.304
45	0.340	0.336	0.268	0.302

T_{1F} = 4.50 s at 34°C.
T_{1B} = 0.169 s for 18% H_2O—pHEMA; 0.178 s for 21.9% H_2O—pHEMA—TEGDMA.

though the hydrophilic tendency can be seen. The results are in good agreement with the bound water quantities obtained from the differential thermal analysis data.

The measured values of the proton spin-lattice relaxation times, T_1, can be considered as an average of three states of water in the hydrogels: bound water, intermediate water, and bulklike (free) water,[25]

$$\frac{1}{T_1} = \frac{f_B}{T_{1B}} + \frac{f_I}{T_{1I}} + \frac{f_F}{T_{1F}} \tag{2}$$

where f_B, f_I, and f_F are the fraction of bound, intermediate, and bulklike water in the hydrogels, and T_{1B}, T_{1I}, and T_{1F} are the spin-lattice relaxation times for bound, intermediate, and bulklike water in the hydrogels, respectively. T_{1F} is taken to be that of pure water; f_B, f_I, and f_F are obtained from the differential thermal analysis data. T_{1B} corresponds to the measured T_1 for the known content of W_{nf} in Figures 4 and 5. Hence, one can estimate T_{1I} for intermediate water in the hydrogels. Table IV gives T_{1I} determined for pHEMA—H_2O and 1 mol % crosslinked (TEGDMA)—pHEMA—H_2O systems.

The T_1 values are inversely proportional to the magnitude of the interactions between water protons and lattice environments, i.e., the lower value of T_{1I} means a stronger interaction between water molecule and polymer network.

According to the data in Table IV, the spin-lattice relaxation times (T_{1B}) of bound water in the hydrogels are about 30 times less than that of water protons in pure liquid water. The values of T_{1I} of intermediate water in the hydrogels are approximately twice that of T_{1B} of bound water. The proton spin-lattice relaxation times directly give the mobility of water molecules in the hydrogels. Comparing the data with the T_{1F} of bulklike (free) water, the mobility of water protons of bound water or intermediate water is less than that of water protons in pure liquid water. This indicates that some water molecules around the polar sites in the gels may be structured and preferentially ordered, probably due to hydrogen bonding or strong polar interactions. That is in line with the specific entropy data obtained from the thermal analysis listed in Table I.

Figure 8 shows the spin–spin relaxation times (T_2) of water protons as a function of water content in pHEMA and pHEMA—TEGDMA hydrogel systems. The values of T_2 are approximately 10 times less than those of T_1, in general agreement with the principles of spin relaxations.[30,31] In the region of

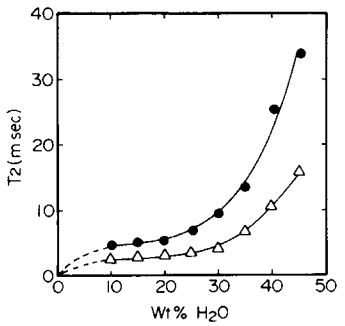

Fig. 8. The spin–spin relaxation times (T_2) of water protons as a function of water content in polyhydroxyethyl methacrylate polymers at 34°C and 100 MHz; (●) pHEMA—H_2O; (△) pHEMA—TEGDMA—H_2O.

less than 25% water content, the values of T_2 are almost constant. However, beyond this region the T_2 values rapidly increase as the water content gradually increases, indicating the presence of increasing amounts of free and intermediate water. These results are in good agreement with the spin-lattice relaxation results.

CONCLUSIONS

It is proposed that the interaction of water with hydrophilic methacrylate polymers occurs in three ways: (1) Water molecules are strongly bound to specific sites such as the hydroxyl or ester groups within the polymer network; dynamically and thermodynamically they behave as part of the chains. (2) Water molecules are weakly bound to the hydrophilic sites and/or preferentially structured around the polymer network. (3) Water molecules behave dynamically and thermodynamically as "bulklike" or free water.

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