Thermoreversible Hydrogels XIV. Synthesis and Swelling Behavior of the (*N*-isopropylacrylamide-*co*-2-Hydroxyethyl methacrylate) Copolymeric Hydrogels

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ABSTRACT: A series of thermoreversible hydrogels were prepared from various molar ratios of *N*-isopropylacrylamide (NIPAAm), and 2-hydroxyethyl methacrylate (HEMA) with *N,N*-methylene-bis-acrylamide (NMBA) as a crosslinker in various polymerization media. The appearance of the gel membrane formed in various polymerization media, and the influences of various swelling media on the swelling behavior for the copolymeric gels, were investigated in this article. The results indicated that the gel would change from opaque to transparent, and the swelling diffusion mechanism of the gel in water was changed from non-Fickian diffusion to Fickian diffusion when the content of HEMA in the copolymeric compositions increased. The effect of the swelling media on the swelling ratio for poly(NIPAAm-*co*-HEMA) indicated that the more the HEMA content, the lower the swelling ratio of the gel in water and solvent, but the contrary result for the gel was obtained in the 50% solvent aqueous solution. The result for the influence of the polymerization media on the swelling ratio for poly(NIPAAm-*co*-HEMA) indicated that the larger the solvent molecular size of polymerization media, the higher the swelling ratio. On the other hand, the gel transition temperature and the thermoreversibility of the copolymeric gels gradually disappeared as the content of the HEMA in the gel was increased. The larger the solvent molecular sizes of polymerization media, the better the thermoreversiblity of the gel, but the gel transition temperature was not significantly affected. Finally, the drug release and drug diffusion in these copolymeric gels was also investigated. © 2000 John Wiley & Sons, Inc. J Appl Polym Sci 77: 1769–1781, 2000

Key words: thermoreversible; hydrogel; *N*-isopropylacrylamide; 2-hydroxy methacrylate; swelling behavior

INTRODUCTION

Hydrogels are crosslinked, three-dimensional hydrophilic polymeric networks, which swell but do not dissolve when brought into contact with water. There are some hydrogels that sometimes undergo a volume change in response to a change in surrounding conditions, such as temperature,[1,2] pH,[3,4] solvent composition,[5–7] salt concentration,[8] chemical,[9] photoirradiation,[10] and electric field.[11]

Poly(*N*-isopropylacrylamide) poly(NIPAAm) is a kind of temperature-sensitive polymer, and exhibits lower critical solution temperature (LCST) behavior around 32°C. This phenomenon was first reported by M. Heskins and J. E. Guillet,[12] and further demonstrated by Tanaka and coworkers.[13] Bae et al.[14] suggested that the LCST of poly(NIPAAm) can be attributed to the balance

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between the hydrophilic and hydrophobic components in the polymer chains.

For NIPAAm gel, the amide group would form a stronger hydrogen bond with water when the temperature was below the LCST. This occurrence makes the gel swell in water. But when the temperature was above the LCST, the hydrophobic force of the gel increased, the gel would collapse, and the bound water in the gel would be released. This phenomenon lets the gel exhibit a volume phase transition around its LCST. Because NIPAAm gel has this swell–deswell behavior, it can be widely used in many fields, such as drug delivery systems,[14,15] extraction,[16] and enzyme activity control.[17]

In recent studies, the preparation and swelling behaviors for NIPAAm gels, containing anionic comonomer sodium acrylate (SA),[19,20] or cationic comonomer methacrylamidopropyl trimethyl ammonium chloride (MAPTAC),[21] trimethyl acrylamidopropyl ammonium iodide (TMAAI),[22] and diethyl methacryloyloxyethyl ammonium iodide (DEMMAI),[23] or pH-sensitive comonomer acrylic acid (AA)[24–27] and 2-acrylamido-2-methylpropane sulfonic acid (AMPS),[25] or hydrophilic comonomer acrylamide (AAm)[27] and *N*-vinyl pyrrolidone (NVP),[28] or hydrophobic comonomer 2-butyl methacrylate (BMA),[27] were investigated.

Moreover, 2-hydroxyethyl methacrylate (HEMA) has good biocompatibility, and has been used widely in biomedical applications.[29,30] NIPAAm gels containing comonomers AAm and HEMA and the influence of AAm content on the swelling behavior for the copolymeric gels were reported in our previous report.[31] Cicek and Tuncel studied the influence of PEG4000 on the swelling behavior for NIPAAm/HEMA copolymeric gels[32] and the application in enzyme activity.[33] But the HEMA content in this copolymeric gel is merely up to 50%.

With regard to the solvent effect, Tanaka reported that polyacrylamide gel undergoes a continuous volume phase transition from good solvent to poor solvent in various acetone aqueous solutions.[34] A series of acrylamide-derivative gels prepared in various polymerization media were investigated in our previous report, such as *N,N*-dimethyl acrylamide/*n*-butoxymethyl acrylamide, (DMA/nBMA) and *N*-tetrahydrofurfuryl acrylamide (NTHF AAm).[37,38]

Hence, a series of NIPAAm/HEMA copolymeric gels were prepared in acetone aqueous solution and ethanol aqueous solution in an attempt to investigate the swelling behaviors for these copolymeric gels in various aqueous solutions, and the gels were prepared in various polymerization media and applied in drug release.

EXPERIMENT

Materials

N-Isopropylacrylamide (NIPAAm) (Wako Chemical Co.) was recrystallized in *n*-hexane before use to remove an inhibitor. 2-Hydroxyethyl methacrylate (HEMA) (TCI Chemical Co.) was purified by vacuum distillation at 68°C/5 mmHg. *N,N′*-methylene-bisacrylamide (NMBA) (Sigma Chemical Co.), as a crosslinker, was used as received. *N,N,N′,N′*-Tetramethylethylenediamine (TEMED) (Fluka. Chemical Co.), as an accelerator, was used as received. Ammonium peroxodisulfate (APS) (Wako Pure Chemical Co.), as an initiator, was further purified by recrystallization. Caffeine and crystal violet (CV), as model drugs, were obtained from Fluka. All solvents and other chemicals were of analytical grade.

Preparation of Hydrogels

Various molar ratios of NIPAAm and HEMA listed in Table I, and 3 mol % NMBA based on total monomer content were dissolved in 50 vol % solvent aqueous solution to 10 mL. The solvents, with various compositions, were ethanol and acetone. The solvents, as polymerization media, were methanol, ethanol, isopropanol, acetone, and deionized water. To each solution, 1 mol % APS and 1 mol % TEMED as redox initiators were added, and the mixture was immediately injected into the space between two glass plates. The gel membrane thickness was adjusted with a silicone spacer between the two glass plates. Polymerization was carried out at room temperature for 1 day. After the gelation was completed, the gel membrane was cut into disks, 10 mm in diameter, and immersed in an excess of deionized water for 4 days to remove the residual unreacted monomer. Swollen polymer gels were dried at 25°C for 1 day, and these samples were further dried in a vacuum oven at 50°C for 2 days.

Measurement of Swelling Ratio

The preweighed (W_d) dried gels were immersed in an excess of deionized water at different temperatures until swelling equilibrium was attained. The weight of wet sample (W_w) was de-

Table I Characterization of NIPAAm/HEMA Copolymeric Gels

Sample No.	Feed Composition (mol %)		Appearance	Cloud Point Effect	Cloud Point Temperature (°C)	Swelling Ratio (g H_2O/g Dry Gel) (Acetone Series)	Swelling Ratio (g H_2O/g Dry Gel) (Ethanol Series)
	NIPAAm	HEMA					
H0	100	0	o	st	32–34	12.68	—
H1	90	10	o	st	32–34	8.35	13.6
H3	70	30	t	vw	34–36	3.21	3.95
H5	50	50	t	vw	34–36	1.02	1.24
H7	30	70	t	vw	36–38	0.81	0.86
H9	10	90	t	no	> 40	0.67	0.70
H10	0	100	t	no	> 40	0.64	0.66

St = strong; vw = very weak; no = no observed; t = transparent; o = opaque.

termined after removing the surface water by blotting with filter paper. Swelling ratio (SR) was calculated from the following equation:

$$SR = \frac{W_w - W_d}{W_d} \quad (1)$$

Dynamic Swelling

The dried gels were immersed in an excess of various solvent aqueous solutions or deionized water at 25°C. The swelling ratio was obtained by weighing the initial and swollen samples at various time intervals. The amount of water sorbed, M_t, was reported as a function of time, and the equilibrium sorption at infinitely long time was designated M_∞. The following equation can be used to calculate the diffusion coefficient, D, for $M_t/M_\infty \leqq 0.8$.[33]

$$\frac{M_t}{M_\infty} = \frac{4}{\sqrt{\pi}} \times \left(\frac{Dt}{L^2}\right)^{1/2} \quad (2)$$

where t is time, and L is the initial thickness of the dried sample.

Measurement of Swelling Ratio at Various Temperatures

To measure the swelling ratio in various temperatures, the dried gels were immersed in an excess of deionized water at fixed temperature for 2 days. The temperature was then increased, and the gel was kept at each fixed temperature. The swelling ratio was obtained by weighing the initial and swollen samples at various temperatures.

Measurement of Thermoreversibility

The dried gels were immersed in an excess of deionized water at 25°C for 2 days. Then each swollen gel was removed to fresh deionized water at 50°C, and the shrunken gel was weighed at various time intervals. Finally, the gel was removed to deionized water at 25°C, and the swollen sample was weighed at various time intervals. To measure the change of swelling ratio of the gel, this operation was repeated for three cycles.

Measurement of Caffeine Release

To load caffeine into the gel, dry gels were equilibrated in caffeine solution (300 mg/100 mL of deionized water) at 25°C for 2 days. The caffeine release experiments were carried out by transferring incubated drug gels into 10 mL of deionized water at 37°C. The gel was periodically removed and transferred into 10 mL fresh water at each fixed time interval. The released caffeine was analyzed at 272 nm by ultraviolet-spectrophotometer (Jasco V530).

Measurement of Caffeine and CV Diffusion

The dried gels were immersed in an excess of deionized water at 25°C for 2 days. The swollen gel was then clipped between diffusion cells at 25°C. The caffeine diffusion experiments were carried out by filling caffeine or CV solution (10 mg/100 mL of deionized water) in one side cell, and filling deionized water in the other one. The deionized water in the latter cell was periodically taken out and replaced by the same amount of fresh deionized water at each fixed time interval. The diffused caffeine or CV was analyzed at 272

or 561 nm by an ultraviolet spectrophotometer (Jasco V530).

RESULTS AND DISCUSSION

The swelling behavior of the hydrogels depends on the nature of the polymer and the environmental conditions. The polymer's nature involves ionic content and crosslinking density. The environmental conditions include temperature and various solvent solutions. Hence, the effects of the HEMA content, swelling media, and polymerization media on the swelling ratio of these copolymer gels were investigated.

Characterization of NIPAAm/HEMA Copolymeric Gel

Some characteristics of the NIPAAm/HEMA copolymeric gels with various feed compositions are shown in Table I. The results in Table I indicate that the gel is opaque when the HEMA content is below 10 mol %, and then the gels become transparent when the HEMA content is increased. Otherwise, the cloud point effect for the copolymeric gels is weakened with increasing of the HEMA content. From the viewpoint of solubility parameter (δ), the differences in solubility parameter ($\Delta\delta$) for NIPAAm and 50% acetone$_{(aq)}$ or 50% ethanol$_{(aq)}$ is 5.63 and 6.13, respectively. The $\Delta\delta$ for HEMA in 50% acetone$_{(aq)}$ and 50% ethanol$_{(aq)}$ is 4.71 and 5.21, respectively (see Table II). The smaller the $\Delta\delta$, the better the miscibility between monomer and solvent. The more the HEMA content, the better the affinity of polymerization media for the gel. The gel appearance is transferred from opaque (heterogeneous) to transparent (homogeneous), and the gel strength becomes better. In addition, the swelling ratio for the gel H0 prepared in ethanol$_{(aq)}$ cannot be measured because the gel structure is too loose. The equilibrium swelling ratios decrease with increasing HEMA content. These results correspond to the result of Cicek and Tuncel, reported for poly(NIPAAm-*co*-HEMA).[32]

Table II The Solubility Parameter (δ) and the Differences in Solubility Parameter ($\Delta\delta$) of NIPAAm/HEMA Copolymeric Gels and Solvent ($\Delta\delta_{gel} = |\delta_{gel} - \delta_{solvent}|$)

	δ, $\Delta\delta$		
Sample No., Solvent	δ	$\Delta\delta_{H0}$	$\Delta\delta_{H10}$
H0	10.20	—	—
H1	10.29	—	—
H3	10.48	—	—
H5	10.66	—	—
H7	10.84	—	—
H9	11.03	—	—
H10	11.12	—	—
Acetone	7.65	2.55	3.47
50% Acetone	15.83	5.63	4.71
Ethanol	8.65	1.55	2.47
50% Ethanol	16.33	6.13	5.21
Water	24.0	13.80	12.88

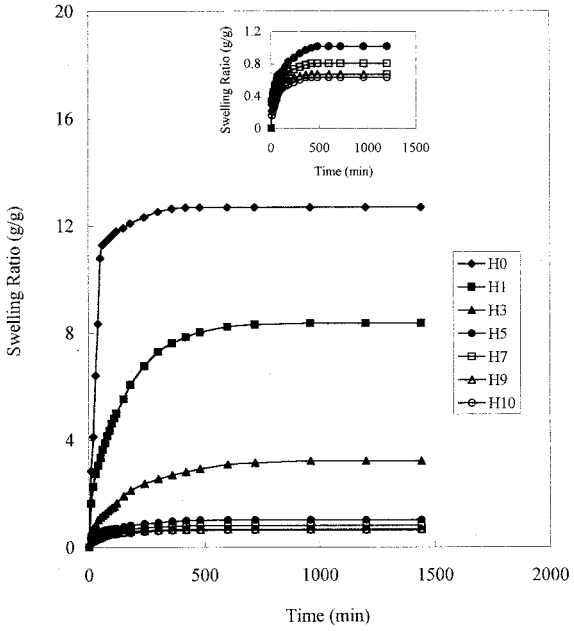

Figure 1 Swelling ratios as a function of time for NIPAAm/HEMA copolymeric hydrogel in deionized water at 25°C (acetone series).

Effect of Swelling Media on Swelling Ratio for NIPAAm/HEMA Copolymeric Gels

Swelling Ratio in Deionized Water

The swelling ratios as a function of time for NIPAAm/HEMA copolymeric gels in deionized water are shown in Figures 1 and 2. The results in these figures indicate that, the more the HEMA content, the lower the swelling ratio. According to rubber elasticity theory,[40] the following equation is given:

$$Q^{5/3} = (1/2 - \chi_1)/v_1/(\nu_e/V_0) \quad (3)$$

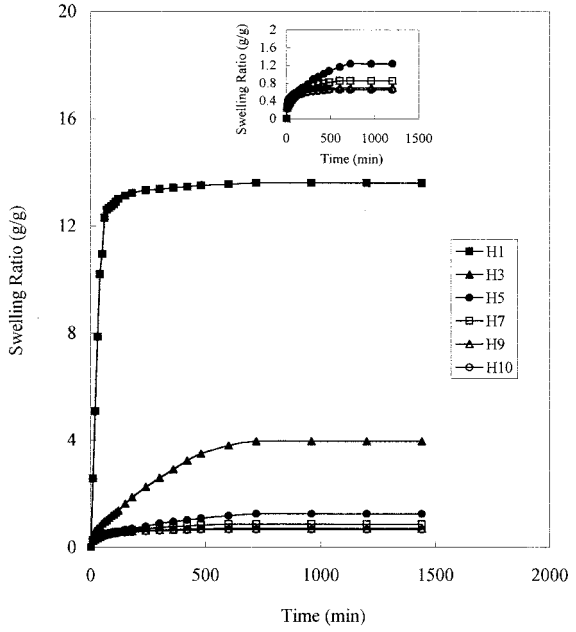

Figure 2 Swelling ratios as a function of time for NIPAAm/HEMA copolymeric hydrogel in deionized water at 25°C (ethanol series).

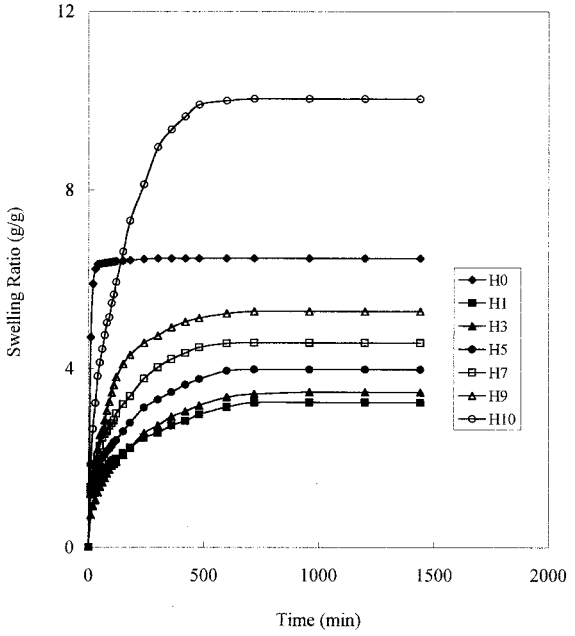

Figure 3 Swelling ratios as a function of time for NIPAAm/HEMA copolymeric hydrogel in 50 vol % acetone aqueous solution at 25°C (acetone series).

where Q is the swelling ratio, $(1/2 - \chi_1)/v_1$ is the affinity of the hydrogel for deionized water or solvent, and ν_e/V_0 is the crosslinking density of the hydrogel.

Thus, the swelling ratios for the nonionic gel depend on the crosslinking density, and the affinity of the hydrogel for deionized water or solvent. Because the amount of crosslinking agent was kept constant, the crosslinking density for the present copolymeric gels was assumed to be fixed. Hence, the swelling ratios of the gel were only dependent on the affinity of the gel for deionized water or solvent. Therefore, the more the HEMA content, the poorer the affinity of the copolymeric gels for deionized water and the less the swelling ratio.

Swelling Ratio in 50% Acetone or Ethanol Aqueous Solution

The swelling ratio, as a function of time for the evaluated copolymeric gels in 50% acetone and 50% ethanol aqueous solutions, are shown in Figures 3 and 4, respectively. The results indicate that, the more the HEMA content, the higher the swelling ratio. This result is contrary to that in deionized water. From the viewpoint of the solubility parameter, the $\Delta\delta$ for H0 in 50% acetone$_{(aq)}$ and 50% ethanol$_{(aq)}$ is 5.63 and 6.13, respectively. The $\Delta\delta$ for H10 in 50% acetone$_{(aq)}$ and 50% ethanol$_{(aq)}$ is 4.71 and 5.21, respectively (see Table II). The smaller the $\Delta\delta$, the stronger the attrac-

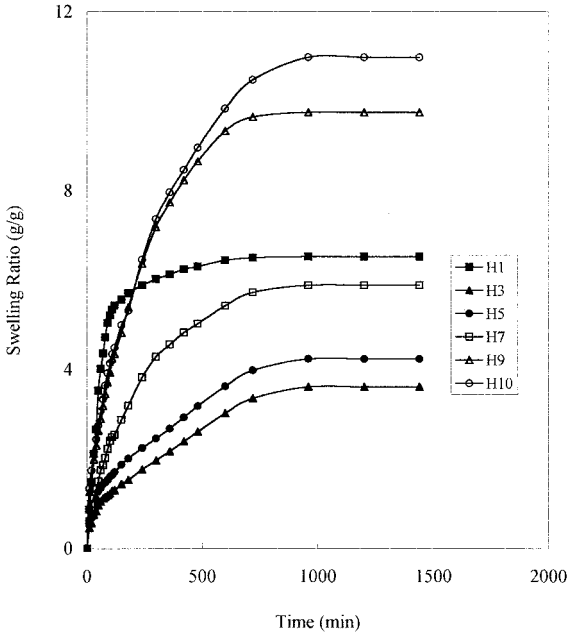

Figure 4 Swelling ratios as a function of time for NIPAAm/HEMA copolymeric hydrogel in 50 vol % ethanol aqueous solution at 25°C (ethanol series).

tion of the polymer toward solvent, the easier the expansion of polymer chains, and the higher the swelling ratio. However, the gel H0 prepared in 50% acetone$_{(aq)}$, and the gel H0 prepared in 50% alcohol$_{(aq)}$, do not obey the above rule. Because these gels are heterogeneous, the structures of the gel are loose. This occurrence makes the water easily penetrate into the gel and the swelling ratio increases. Therefore, the more the HEMA content, the higher the swelling ratio.

Swelling Ratio in Acetone or Ethanol

The swelling ratios, as a function of time for the said copolymeric gels in acetone and ethanol, are shown in Figures 5 and 6, respectively. The results indicate that, the more the HEMA content, the lower the swelling ratio, and the initial rates (at initial 0.5 h) in acetone and ethanol are faster than that in deionized water. From the viewpoint of the solubility parameter (δ), the $\Delta\delta$s for H0 and H10 in acetone and ethanol are 2.55 and 1.55; 3.47 and 2.47, respectively (also see Table II). The smaller the $\Delta\delta$, the stronger the attraction of the polymer toward solvent and the easier the expansion of polymer chains. Based on this reason, the higher the HEMA content, the lower the swelling ratio. Moreover, the initial rates for the gel in acetone or ethanol are faster than that in deionized water, because the $\Delta\delta$ for acetone and ethanol are smaller than water, and the affinity of the polymer gel toward acetone or ethanol is better than that toward water. Therefore, the diffusion of the acetone or ethanol molecule into the gel is easier than for the water molecule. It is interesting that the gel swollen in ethanol shows that the higher the HEMA content, the higher the equilibrium swelling ratios after 10 h (Fig. 6). Because of the stiff structure of the HEMA, it is difficult for ethanol to diffuse into the gel initially. However, the higher the HEMA content, the stronger the affinity of the gel toward ethanol. In other words, the equilibrium swelling ratio increases with an increase of the content of HEMA.

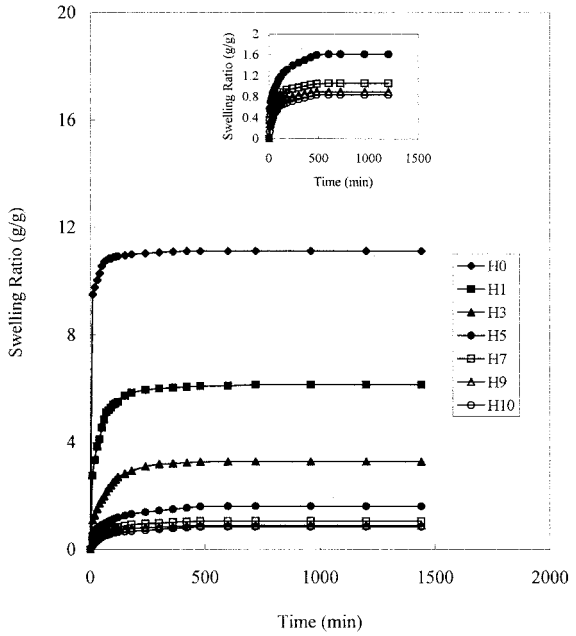

Figure 5 Swelling ratios as a function of time for NIPAAm/HEMA copolymeric hydrogel in acetone at 25°C (acetone series).

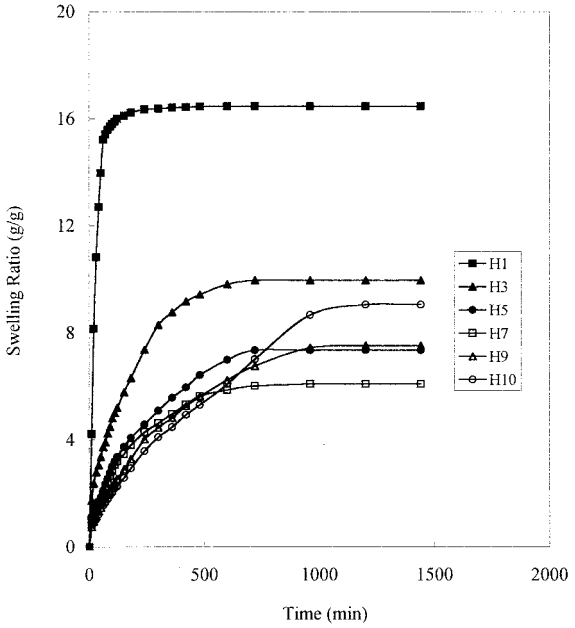

Figure 6 Swelling ratios as a function of time for NIPAAm/HEMA copolymeric hydrogel in ethanol at 25°C (ethanol series).

Effect of Polymerization Media on Swelling Ratio for NIPAAm/HEMA Copolymeric Gels

To investigate the effect of polymerization media for the copolymeric gels, 50 vol % aqueous solutions of methanol, ethanol, isopropanol, acetone, and pure deionized water were chosen as polymerization media for the H1 gel. The swelling ratio as a function of time for the H1 gel prepared in the above aqueous solution is shown in Figure 7.

The results in Figure 7 indicate that, the larger the solvent molecule size of the polymerization

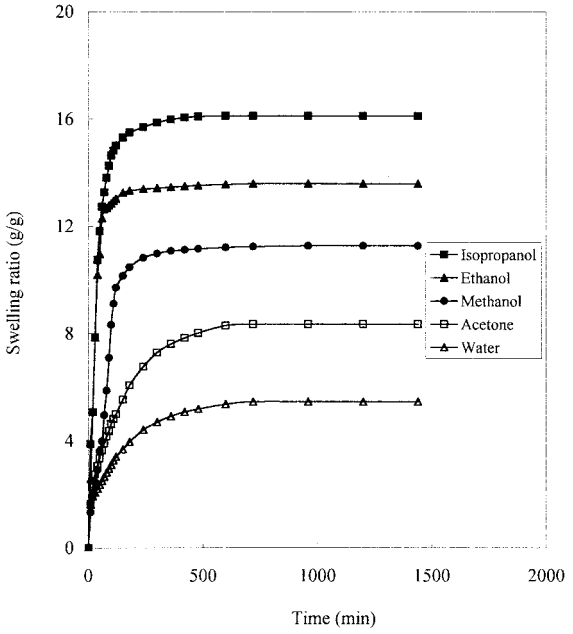

Figure 7 Effect of polymerization media on swelling ratios for H1 hydrogel in deionized water at 25°C.

media, the higher the swelling ratio. The radii of gyration of isopropanol, ethanol, methanol, acetone, and water are 2.7359, 2.2495, 1.5360, 2.7404, and 0.6150 Å, respectively.[36] According to these data, the larger molecular size of the polymerization media will produce a larger pore size and a looser structure of the gel. Consequently, the larger the solvent molecule size of the polymerization media, the higher the swelling ratio. On the other hand, from the viewpoint of the solubility parameter, the $\Delta\delta$s for the gel H1 in isopropanol, ethanol, methanol, and acetone are 2.36, 1.64, 1.06, and 2.64, respectively. The larger the $\Delta\delta$, the poorer the miscibility of the polymer and solvent. This makes the structure of the gel become looser, and the swelling ratio increases. However, the gels prepared in acetone$_{(aq)}$ do not follow the above rules.

In fact, the appearance of the gel prepared in methanol$_{(aq)}$ is more opaque than that prepared in acetone$_{(aq)}$. Hence, the structure of the gel prepared in methanol$_{(aq)}$ is looser than that prepared in acetone$_{(aq)}$, and makes the swelling ratio of the gel increase. Thus, the influence of the structure of the gel is more significant than the solvent molecular size. These results correspond to our previous studies for DMA/nBMA[37] and NTHFAAm[38] hydrogels.

Effect of Swelling Media on Swelling Behavior for NIPAAm/HEMA Copolymeric Gels

To investigate the diffusion model of the gel, the initial swelling data are fitted to the exponential heuristic equation[27,28]:

$$\frac{M_t}{M_\infty} = kt^n \quad \left(\frac{M_t}{M_\infty} \leq 0.6\right) \tag{4}$$

where k is a characteristic constant of the gel, and n is a characteristic exponent of the mode transport of the penetrate. Values of n and k were calculated from the slopes and intercepts of the plot of $\log M_t/M_\infty$ against $\log t$, respectively. From eq. (2), the diffusion coefficient D can be calculated from the slope of the plot of M_t/M_∞ against $(t/L^2)^{1/2}$. The diffusion of the gel depends on the diffusion rate of absorbing solvent into the gel and the relaxation rate of the polymer network. The value of n is 0.5, the diffusion mechanism is called Case I transport or Fickian diffusion, i.e., the rate of diffusion is much less than the rate of relaxation. The value of $n = 1.0$ is called Case II transport, i.e., the rate of relaxation is much less than the rate of diffusion. When values of n are between 0.5 and 1.0, that n is called non-Fickian diffusion, i.e., the rate of diffusion is comparable to the rate of relaxation.[37] The results observed from Tables III and IV indicate that the values of n for the gel are below 0.5, except for the gel H0 prepared in acetone$_{(aq)}$ and the gel H1 prepared in ethanol$_{(aq)}$ which are between 0.5 and 1.0. The gels prepared in acetone$_{(aq)}$ swell in water or acetone, and the gels prepared in ethanol$_{(aq)}$ swell in water. The value of n decreases with increasing the HEMA content, but the diffusion coefficient D increases when the content of the HEMA increases. Otherwise, the gels prepared in acetone$_{(aq)}$ swell in 50% acetone$_{(aq)}$ or ethanol and the gels prepared in ethanol$_{(aq)}$ swell in 50% ethanol$_{(aq)}$. The value of n decreases for the gel H0–H3 when the content of the HEMA increases. The values of n, D, and the equilibrium swelling ratio for the gel H5–H10 increase as the content of the HEMA increases.

The results observed from Table V indicate that the values of n for the gel H1 prepared in alcohol$_{(aq)}$ and nonalcohol$_{(aq)}$ are 0.5–0.85 and 0.18–0.31, respectively.

To sum up, the higher the HEMA content of the gel, when the gel swells in water the transport mechanism is transferred from non-Fickian to Fickian diffusion. The gel H1, prepared in alco-

Table III Initial Diffusion Coefficient, *D*, and Kinetic Exponent, *n*, and Characteristic Constant, *k*, of Solvent Penetrated Through NIPAAm/HEMA Copolymeric Gels at Various Solvents and 25°C (Acetone System)

Sample No.	Solvent	*n*	*k*	$D \times 10^8$ (cm^2/s)	$S.R._{eq}$ (g/g)	Initial Rate (g Solvent/h)
H0	Water	0.58	0.04	81.2	12.68	0.316
	50% Acetone	0.41	0.11	280	6.48	0.296
	Acetone	—	—	—	11.12	0.478
H1	Water	0.32	0.13	13.6	8.35	0.110
	50% Acetone	0.31	0.14	4.50	3.25	0.057
	Acetone	0.23	0.13	24.4	6.14	0.154
H3	Water	0.20	0.23	5.88	3.21	0.038
	50% Acetone	0.19	0.24	4.94	3.47	0.050
	Acetone	0.20	0.23	13.9	3.27	0.071
H5	Water	0.10	0.53	5.29	1.02	0.023
	50% Acetone	0.10	0.53	5.38	3.98	0.079
	Acetone	0.10	0.53	5.35	1.61	0.044
H7	Water	0.08	0.61	3.79	0.81	0.017
	50% Acetone	0.20	0.26	5.47	4.58	0.078
	Acetone	0.08	0.61	4.29	1.03	0.024
H9	Water	0.08	0.62	2.06	0.67	0.013
	50% Acetone	0.24	0.21	7.18	5.28	0.100
	Acetone	0.08	0.62	4.13	0.9	0.022
H10	Water	0.07	0.64	1.93	0.64	0.010
	50% Acetone	0.35	0.12	7.92	10.05	0.022
	Acetone	0.07	0.64	3.84	0.84	0.011

Table IV Initial Diffusion Coefficient, *D*, and Kinetic Exponent, *n*, and Characteristic Constant, *k*, of Solvent Penetrated Through NIPAAm/HEMA Copolymeric Gels at Various Solvents and 25°C (Ethanol System)

Sample No.	Solvent	*n*	*k*	$D \times 10^8$ (cm^2/s)	$S.R._{eq}$ (g/g)	Initial Rate (g Solvent/h)
H1	Water	0.82	0.04	84.6	13.6	0.280
	50% Ethanol	0.53	0.07	60.3	6.52	0.073
	Ethanol	0.37	0.22	132	16.47	0.375
H3	Water	0.23	0.16	5.92	3.95	0.034
	50% Ethanol	0.20	0.19	5.45	3.61	0.031
	Ethanol	0.33	0.47	20.7	9.96	0.107
H5	Water	0.11	0.42	5.03	1.24	0.019
	50% Ethanol	0.25	0.16	5.78	4.24	0.034
	Ethanol	0.31	0.49	6.27	7.34	0.069
H7	Water	0.09	0.55	4.62	0.86	0.015
	50% Ethanol	0.33	0.10	6.12	5.88	0.041
	Ethanol	0.31	0.49	6.14	6.08	0.069
H9	Water	0.09	0.58	4.29	0.7	0.015
	50% Ethanol	0.38	0.08	6.54	9.75	0.041
	Ethanol	0.34	0.46	6.30	7.52	0.062
H10	Water	0.08	0.65	3.71	0.66	0.013
	50% Ethanol	0.40	0.07	7.09	10.93	0.082
	Ethanol	0.35	0.44	6.50	9.06	0.41

Table V Effect of Polymerization Media on Swelling Behavior for H1 Hydrogels in Deionized Water with the Solubility Parameter (δ) of the Gel Being 10.29

Solvent	δ	Swelling Ratio (g H_2O/g Dry Gel)	n	k	$D \times 10^7$ (cm^2/s)
Isopropanol	7.93	16.12	0.85	0.03	8.76
Ethanol	8.65	13.60	0.82	0.04	8.46
Methanol	9.23	11.28	0.50	0.06	2.07
Acetic acid	10.60	8.87	0.33	0.13	1.49
Acetone	7.65	8.35	0.32	0.13	1.36
Water	24.0	5.45	0.18	0.27	1.12

The solubility parameters were calculated by Hoy's method.

$hol_{(aq)}$ and $nonalcohol_{(aq)}$, swells in water and the transport mechanism is also transferred from non-Fickian to Fickian diffusion.

Effect of Temperature on Swelling Ratio for NIPAAm/HEMA Copolymeric Gels

The effect of temperature on the swelling ratio for NIPAAm/HEMA copolymeric gels prepared in $acetone_{(aq)}$, $ethanol_{(aq)}$, and various polymerization media in deionized water are shown in Figures 8–10. The results shown in these figures indicate that the higher the temperature, the lower the swelling ratio.

For NIPAAm gel (H0), because of the hydrophilic group (amide group) in the polymer, its structure would transfer from an intermolecular hydrogen bond with surrounding water below the gel transition temperature to an intramolecular hydrogen bond above the gel transition temperature. This occurrence makes the swelling ratio of the gel rapidly decrease around the gel transition temperature (see Fig. 8, H0).

Moreover, the higher the HEMA content, the lower the swelling ratio for the copolymeric gels, and the gel transition temperature gradually disappears (see Figs. 8 and 9). This is because the affinity of the HEMA for water is weakened when

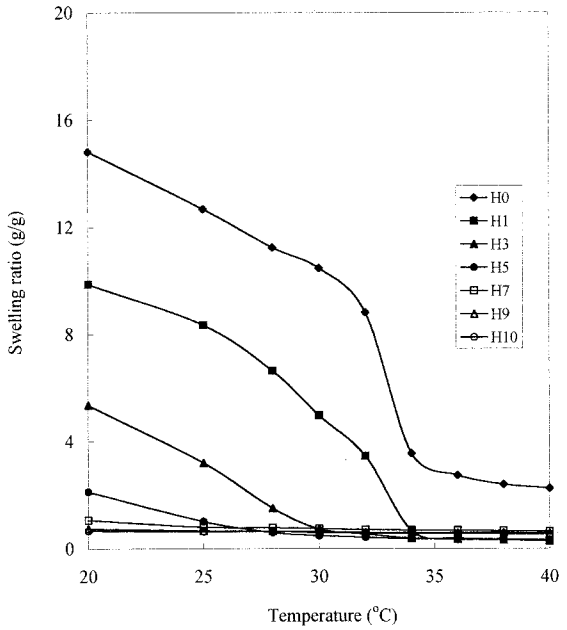

Figure 8 Swelling ratios for NIPAAm/HEMA copolymeric hydrogel in deionized water at different temperatures (acetone series).

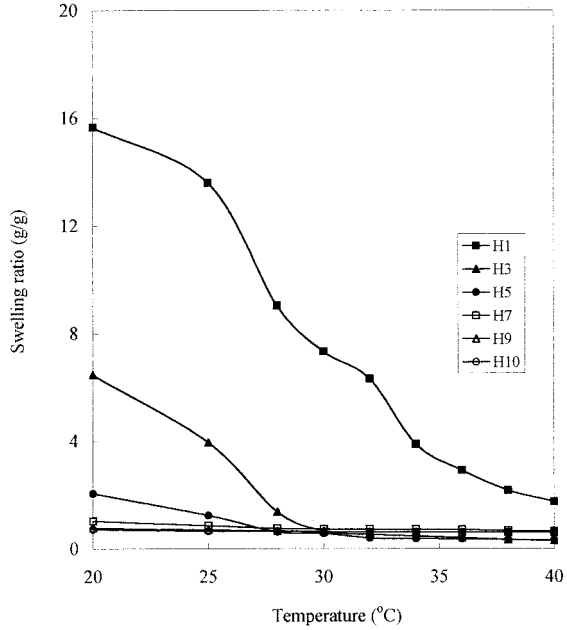

Figure 9 Swelling ratios for NIPAAm/HEMA copolymeric hydrogel in deionized water at different temperatures (ethanol series).

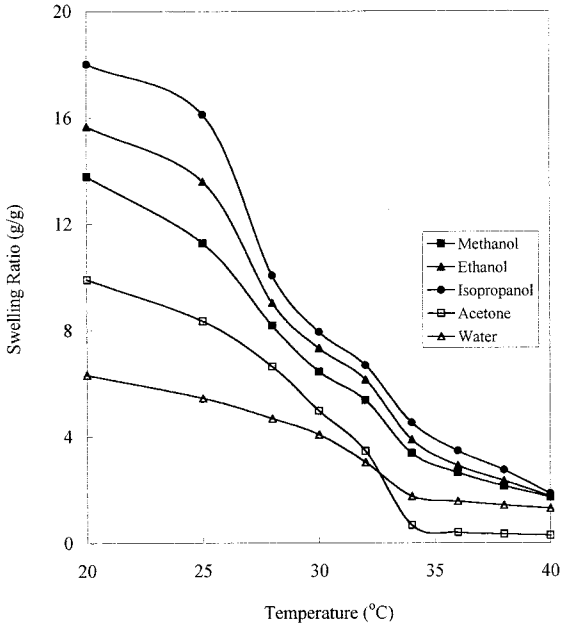

Figure 10 Effect of polymerization media on swelling ratios for H1 hydrogel in deionized water at 25°C.

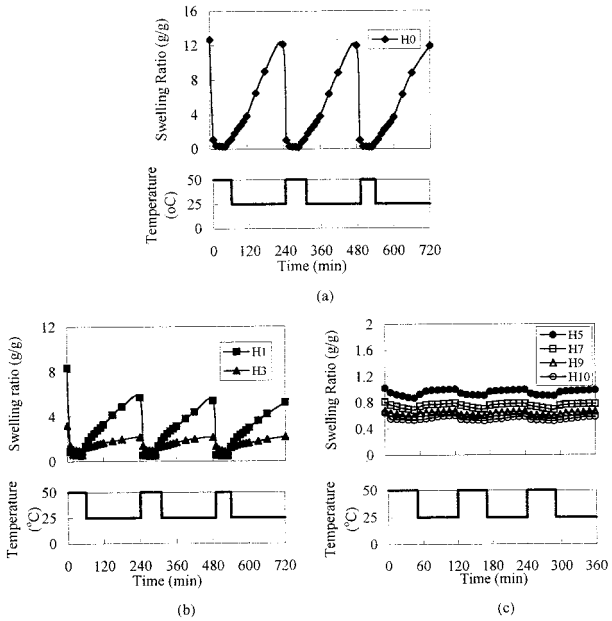

Figure 11 Swelling ratios for NIPAAm/HEMA copolymeric hydrogels as a function of time with repeated abrupt changes of temperature between 25 and 50°C (acetone series).

the content of the HEMA increases. Therefore, the curves of swelling ratio vs. temperature become flatter with increasing the HEMA content. The results, shown in Figure 10, show that the polymerization media do not significantly affect the gel transition temperatures of the copolymeric gels. Hence, the polymerization media do not affect the affinity of the gel for water, but do affect the swelling ratio of the copolymeric gel.

Thermoreversibility of the NIPAAm/HEMA Copolymeric Gels

The amido groups in NIPAAm gel are in a hydrated state, or a dehydrated state, when the temperature is below and above its gel transition temperature, respectively. This phenomenon leads to the gel networks swelling and shrinking, and the swelling ratio of the gel undergoes repeated abrupt change. The swelling and deswelling behaviors for the copolymeric gels prepared in acetone$_{(aq)}$, ethanol$_{(aq)}$, and various polymerization media and swollen in deionized water at 25 and 50°C are shown in Figures 11–13. The results shown in these figures indicate that all NIPAAm/HEMA copolymeric gels have thermoreversibilities.

The thermoreversibility is dependent on the differences of swelling ratio (ΔSR) for the gel at 25 and 50°C. The results shown in Figures 11 and

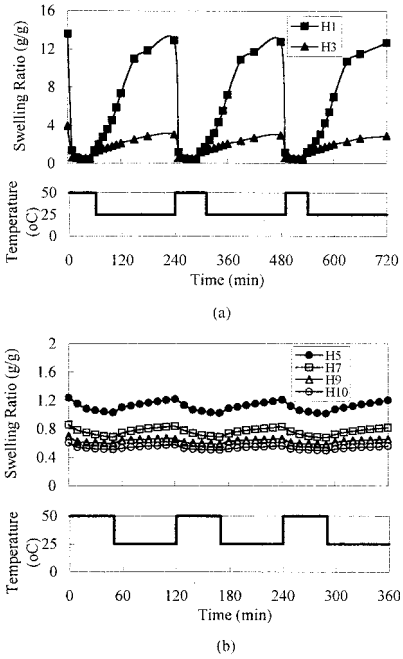

Figure 12 Swelling ratios for NIPAAm/HEMA copolymeric hydrogels as a function of time with repeated abrupt changes of temperature between 25 and 50°C (ethanol series).

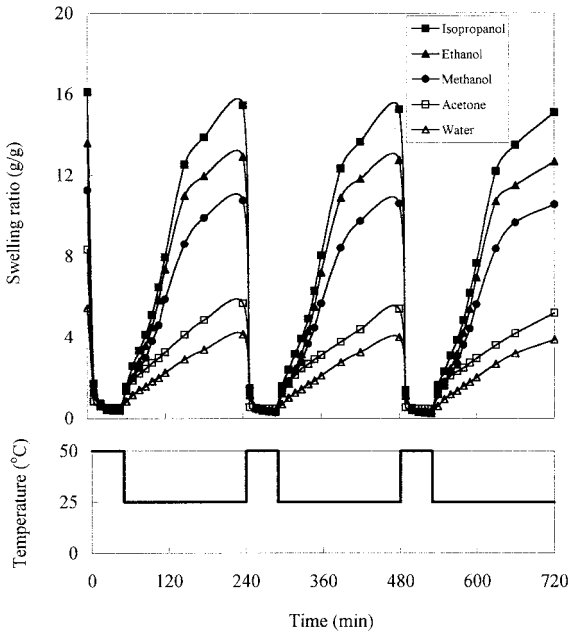

Figure 13 Swelling ratios for H1 hydrogels as a function of time with repeated abrupt changes of temperature between 25 and 50°C.

12 indicate that the ΔSRs for the gel H0, H1, H3, H5, H7, H9, and H10 prepared in acetone$_{(aq)}$ are 12.36, 7.82, 2.27, 0.15, 0.12, 0.11, and 0.1, respectively. The ΔSR for the gel H1, H3, H5, H7, H9, and H10 gel prepared in ethanol$_{(aq)}$ are 13.19, 3.40, 0.21, 0.17, 0.11, and 0.1. From these data, it can be concluded that, the more the HEMA content, the weaker the thermoreversiblity of the gel. This may be attributed to the higher the HEMA content, the fewer the amido groups in the gel, and the weaker the thermoreversibility of the gel. The results shown in Figure 13 indicate that ΔSRs for the gel prepared in 50 vol % isopropanol$_{(aq)}$, ethanol$_{(aq)}$, methanol$_{(aq)}$, acetone$_{(aq)}$, and pure deionized water are 15.74, 13.19, 10.82, 7.82, and 4.93, respectively. In other words, the larger the solvent molecular sizes of the polymerization media, the better the thermoreversiblity of the gel. This may be attributed to the larger solvent molecular size of polymerization media causing a looser gel structure. Therefore, the water molecules diffuse into and release out of the gel easily.

Effect of HEMA Content on Fractional Release of Caffeine

The gel was transferred from an "on" status to an "off" status when the temperature was changed from below the gel transition temperature to above the gel transition temperature. This makes the gel shrink, and caffeine is released from the gel.

To investigate the effect of HEMA content in the gel on the release fraction of caffeine, H0, H1, and H3 gels prepared in acetone$_{(aq)}$ were chosen. The release of caffeine for these gels at 37°C is shown in Figure 14. The results shown in Figure 14 indicate that, the higher the HEMA content, the slower the release profile of caffeine. The results also indicate that the fractional release does not reach 1.0. This is due to a water pocket being formed in the collapsed gel and caffeine is entrapped in the gel and cannot be released completely.[43]

Effect of Polymerization Media on Fractional Release of Caffeine

The effect of polymerization media on the fractional release of caffeine is shown in Figure 15. The results in Figure 15 indicate the, the larger the solvent molecule size of polymerization media, the faster the release profile of caffeine. This may be attributed to the larger molecular size causing a looser gel structure and the larger pore size of the gel. This occurrence leads to caffeine being squeezed out easily. Moreover, the results

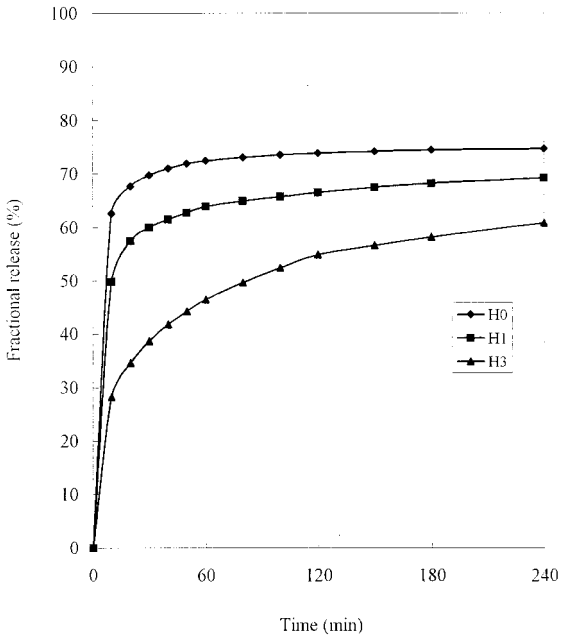

Figure 14 Effect of HEMA content for H0, H1, and H3 hydrogels on caffeine release profile at 37°C (acetone series).

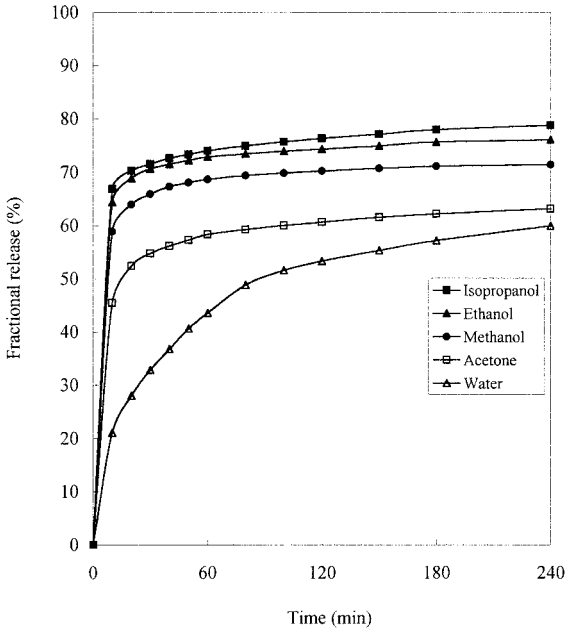

Figure 15 Effect of polymerization media for H1 hydrogels on caffeine release profile at 37°C.

shown in Figure 15 also indicate that the fractional release also does not reach 1.0. These results correspond to the previous discussion in this article.

Effect of Polymerization Media on Diffusion Amount of Caffeine or CV

To confirm the influence of polymerization media on the change of pore size in the gel, caffeine, and CV as the diffused drug were chosen. The drugs can diffuse into and pass through the gel due to the concentration gradient. The effect of polymerization media on the amount of diffusion of caffeine is shown in Figure 16. The results indicate that the larger the solvent molecular sizes of polymerization media, the faster the diffused profiles of caffeine.

The effect of polymerization media on amount of diffusion of CV is also shown in Figure 16. The result shows that CV cannot pass through the gel within 6 h because the CV molecule is too large to pass through the gel. These results prove that the pore size of the gel can be controlled by the polymerization media in the polymerization process.

CONCLUSION

The swelling behavior of the NIPAAm/HEMA copolymeric gels is related to the gel structure, the surrounding temperature, the swelling media, and the polymerization media. The gel transition temperature and the thermoreversibility of the copolymeric gels gradually disappear when the content of the HEMA increases. The larger the solvent molecular sizes of polymerization media, the better the thermoreversiblity of the gel, but the gel transition temperature is not significantly affected.

The effect of the swelling media on the swelling ratio for poly(NIPAAm-*co*-HEMA) indicates that, the higher the HEMA content, the lower the swelling ratio of the gel in water and solvent, but the higher it is in the 50% solvent aqueous solution. The effect of the polymerization media on the swelling ratio for poly(NIPAAm-*co*-HEMA) indicates that the larger the solvent molecular sizes of polymerization media, the looser the gel structure, and the higher the swelling ratio.

Finally, the higher the HEMA content, the slower the release profile of caffeine. The larger the solvent molecular size of the polymerization media, the larger the pore size in the gel, and the faster the release profile and diffused profile of the caffeine.

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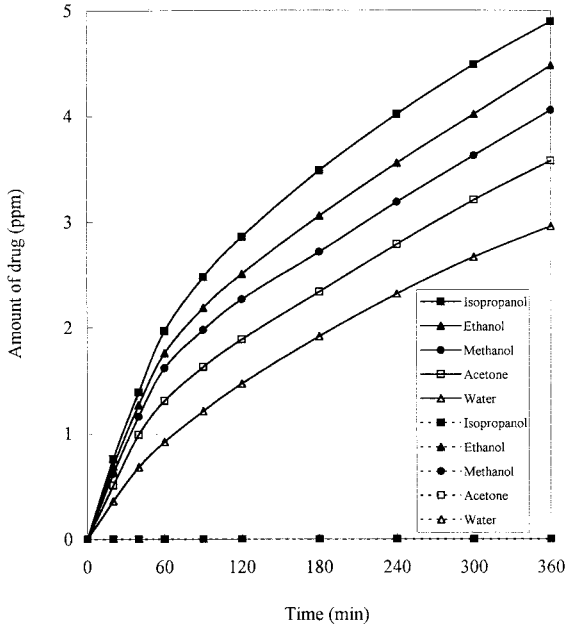

Figure 16 Effect of polymerization media for H1 hydrogels on caffeine (—) or CV (· · ·) diffusion at 25°C.

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