Thermoreversible Hydrogels. IV. Effect of Some Factors on the Swelling Behavior of *N*-Tetrahydrofurfurylacrylamide

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ABSTRACT: A thermoreversible hydrogel, poly(*N*-tetrahydrofurfurylacrylamide) [poly(NTHFAAm) gel], was prepared from *N*-tetrahydrofurfurylacrylamide, which was synthesized from *N*-tetrahydrofurfurylamine and acryloyl chloride (through acylation), with *N,N′*-methylenebisacrylamide, a crosslinker, in various aqueous solutions. The influences of temperature, gel thickness, and polymerization media on the swelling behaviors in water were investigated. The effect of the gel thickness on the swelling ratio for NTHFAAm gel indicated that the equilibrium swelling time and diffusion coefficient for the thinner gel were faster than those for the thicker gels. The effects of different polymerization media on the gel swelling ratio showed that the larger the solvent molecular size and the poorer the miscibility of the monomer and solvent, the higher the swelling ratio and diffusion coefficient. The drug release profiles in the various gels were also investigated. © 1998 John Wiley & Sons, Inc. J Appl Polym Sci 68: 1597–1603, 1998

Key words: thermoreversible hydrogel; poly(*N*-tetrahydrofurylacrylamide); swelling–deswelling; drug release

INTRODUCTION

Hydrogels sometimes undergo a reversible discontinuous large volume change in response to a continuous change in surrounding conditions, such as temperature,[1–5] solvent composition,[6–10] pH,[11,12] salt concentration,[10] and electric field.[13] The volume-phase transition brings about dramatic changes in physical properties of the gels, which have been investigated for use in molecular separation,[14] sorption–desorption of solute,[15] control of enzyme activity,[16] and release of solute.[17] This phenomenon demonstrates the universality of the phase transition of gels and the importance of chemical composition of the gel network and solvent.

The thermoreversible hydrogel exhibits a sharp volume phase transition near its phase-transition temperature, which is called the critical gel transition temperature (CGTT). As the temperature is increased above the CGTT, the gel deswells extensively with concomitant squeezing out of a large fraction of the water from the inside. When the temperature is decreased below the CGTT, the gel reversibly reswells and absorbs the aqueous solution surrounding it. The deswelling and reswelling of the gel matrix volume could be reversibly effected over a narrow range of temperatures near the CGTT of the gel matrix.[15,18] Since the gel deswell leads to the reduction of gel pore volume, mass transfer of a transporting solute through this thermosensitive gel is a strong function of temperature.

The lower critical solution temperature (LCST) behavior and the effect of various factors such as alkoxyalkyl side chain, gel thickness, gel compositions, and crosslinked density on water content for a series of *N*-ethoxypropylacrylamide (NEPAAm)/butyl acrylate (BA) or *N*-tetrahydrofurfu-

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rylacrylamide (NTHFAAm)/BA copolymeric gels were investigated in the previous paper.[19] In this study, a series of poly(NTHFAAm) gels were prepared in various organic aqueous solutions such as methanol, ethanol, isopropanol, and acetone to investigate the influence of polymerization media on gel swelling behavior. For the controlled release system, crystal violet (CV) and caffeine, chosen as model drugs, were loaded in the gel and their release profiles during the gel swelling and deswelling were also studied as functions of the polymerization condition.

EXPERIMENTAL

Materials

Tetrahydrofurfurylamine, acryloyl chloride, and *N,N,N′,N′*-tetramethyl ethylene diamine (TEMED) as an accelerator were obtained from Fluka. Acrylamide was obtained from Nihon Shiyaku Industries, Ltd. Triethylamine, *N,N′*-methylenebisacrylamide (NMBA) as a crosslinking agent and α,α'-azobisisobutyronitrile or ammonium persulfate (APS) as an initiator were all purchased from Tokyo Kasei Industries, Ltd.

CV and caffeine as model drugs were obtained from Fluka. All solvents and other chemicals were analytical grade.

Synthesis of Monomer

The monomer of NTHFAAm was prepared from the corresponding amines and acryloyl chloride according to previous papers.[19–21] The poly(NTHFAAm) is soluble in water and has an LCST of 28.9°C.[19]

Preparation of Poly(NTHFAAm) Hydrogels

Appropriate amounts of NTHFAAm and 4 wt % NMBA were dissolved in 10 mL aqueous solutions of several organic 50 vol % aqueous solutions such as methanol, ethanol, acetone, or isopropanol. To these solutions, 0.2 wt % APS and 1 wt % TEMED were added as redox initiators, and the mixtures were immediately injected into the space between two glass plates. The gel membrane thickness was controlled by a silicone spacer between the two glass plates. Polymerization was carried out at room temperature for 5 h. After the gelation was completed, the gel membrane was removed and immersed in an excess of deionized water to remove the residual unreacted monomer.

Measurement of Swelling Ratio

The dried gels were immersed in an excess of deionized water until swelling equilibrium was attained. The weight of wet sample (W_w) was determined after removing the surface water by blotting with filter paper. Dry weight (W_d) was determined after drying the gel in a vacuum oven for 1 day. The swelling ratio (SR) based on W_w and W_d was then calculated.

$$SR = (W_w - W_d)/W_d \tag{1}$$

Dynamic swelling measurements were made primarily by gravimetric means. The swelling ratios of these gels were determined by eq. (1). The penetration velocity (ν) of solvent in each gel was determined by the weight-gain method as described by Peppas and colleagues.[22,23] The penetration velocity was calculated from the slope of the initial portion of the water uptake curve by the following:

$$\nu = \frac{1}{\rho \times A}\frac{dw}{dt} \tag{2}$$

where dw/dt is the slope of the weight gain-versus-time curve, ρ is the density of water, A is the area of the one face of the disc, and factor 2 accounts for the fact that penetration takes place through both sides. The swelling ratio, M_t, of the gel as a function of time t was analyzed according to eq. (3),

$$M_t/M_\infty = Kt^n \tag{3}$$

which could be used to find the Fickian and non-Fickian release behavior. M_∞ is the swelling ratio at equilibrium, K is a constant related to the characteristics of the gel, and n is the exponent describing the Fickian or anomalous swelling mechanism. Using the natural logarithm of eq. (3), eq. (4) is given by

$$\ln(M_t/M_\infty) = \ln K + n \ln t \tag{4}$$

where values of K and n were calculated from the slope and intercept of the plot of $\ln(M_t/M_\infty)$ against $\ln(t)$, respectively. The following equa-

tion can be used to calculate the diffusion coefficient D for $M_t/M_\infty \leqq 0.8$[24]:

$$\frac{M_t}{M_\infty} = \left(\frac{4}{\sqrt{\pi}}\right)\left(\frac{D \times t}{L^2}\right)^{1/2} \quad (5)$$

Measurement of CV Release

In order to load CV into the gels, dry gels were equilibrated in a CV solution (10 mg/100 mL of deionized water) at 20°C for 2 days. The CV release experiments were carried out by transferring previous drug gels into 10 mL of deionized water at 40°C. The gels were repeatedly removed and transferred into 10 mL fresh water at each fixed time interval. The released CV was analyzed at 561 nm by the Jasco ultraviolet (UV)-spectrophotometer (UVDEC-5).

Caffeine Deswelling Kinetics Experiments

The dry gels were equilibrated in 30 mg/10 mL of deionized water at 23°C for 2 days for loading caffeine into the gels. The caffeine deswelling kinetic experiments were carried out by transferring previously incubated-drug gels into 10 mL of deionized water at 40°C. The gels were repeatedly removed and transferred into 10 mL fresh water at each fixed time interval. The released caffeine was analyzed at 272 nm by a UV-spectrophotometer (Hitachi 3200).

RESULTS AND DISCUSSION

The increase or decrease of LCST for thermosensitive polymers, which could transit from a fully hydrated and soluble state to a phase-separated state, is based on the balance of hydrophilic and hydrophobic interactions. Poly(NEPAAm) showed an LCST of 25.5°C, and the LCSTs of a series of NEPAAm/AAm and NTHFAAm/AAm copolymers with molar ratios of 25, 20, and 15, respectively.[25] These results showed that the LCSTs increased with increasing AAm in the copolymeric compositions. The influences of hydrophobic monomer, extent of crosslinker, and gel thickness on the LCST (or CGTT) and water content (or swelling ratio) for the NEPAAm-*co*-BA and NTHFAAm-*co*-BA gels were reported in a previous paper.[19] Hence, the influences of temperature, gel thickness, and polymerization media such as methanol, ethanol, acetone, and isopropanol on the swelling ratio for the NTHFAAm gels were further investigated in this article.

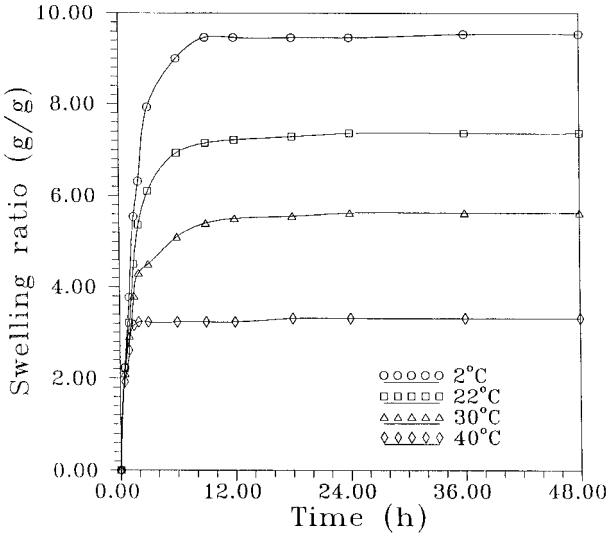

Figure 1 Swelling ratio as a function of time for NTHFAAm gels in deionized water at different temperatures.

Effect of Temperature on Swelling Ratio for Poly(NTHFAAm) Hydrogel

The effect of temperature on the swelling ratio for poly(NTHFAAm) hydrogel is shown in Figure 1. The results shown in Figure 1 indicate that the swelling ratio decreases with increasing the temperature from 2 to 40°C. To elucidate the transport mechanism, the initial swelling ratios are fitted to the exponential heuristic equation [eq. (3)].

A value of $n = 0.5$ indicates Fickian diffusion and a value of $n = 1$ implies Case II transport; values of n between these limits define anomalous transport. The diffusion coefficient D can be calculated from the slope $(4\sqrt{D}/\sqrt{\pi})$ and intercept of the plot of $\log(M_t/M_\infty)$ against $\log(t/L^2)^{1/2}$ at various temperatures, respectively. In addition, eq. (2) was used to calculate the initial penetration velocity (ν) at various temperatures. Table I shows the equilibrium swelling ratio; the swelling exponent, n; the constant, k; the penetration velocity, ν; and the diffusion coefficient, D. The results indicate that the swelling exponents n for the said gels are between 0.72 and 0.45 from low temperature 2°C to high temperature 40°C. This result shows that the swelling transport mechanism changes from a non-Fickian transport to Fickian transport in the temperature range from 2 to 40°C. The data

Table I Effect of Temperature on Swelling Behavior for the NTHFAAm Gel in Deionized Water over a Period of 3 h

Temperature (°C)	Swelling Ratio (g/g)	n	k	ν (cm/h)	$D \times 10^6$ (cm^2/s)
2	9.54	0.72	0.40	2.63	0.13
22	7.36	0.59	0.46	2.02	0.16
30	5.62	0.53	0.53	1.61	0.21
40	3.31	0.45	0.79	1.46	0.33

for the diffusion coefficient shown in Table I indicate that the diffusion coefficient D increases with increasing temperature, but the ν for this gel decreases with increasing temperature. These behaviors correspond to those of the thermoreversible hydrogels reported in our previous article.[26] Compared with the previous report,[26] we can conclude that the transport mechanism is strongly related to the swelling ratio, i.e., the larger the swelling ratio for a hydrogel, the more the transport mechanism tends toward non-Fickian behavior.

Effect of Polymerization Media on Swelling Ratio for Poly(NTHFAAm) Hydrogels

To investigate the effect of the polymerization media on the swelling ratio of the said hydrogel, methanol, ethanol, isopropanol, and acetone were chosen as polymerization media for the gel. The values of the radius of gyration for water, methanol, ethanol, isopropanol, and acetone are 0.6150, 1.5360, 2.2495, 2.7359, and 2.7404 Å, respectively.[27] The swelling behavior for this gel, which was prepared in the above aqueous solutions, is shown in Figure 2. The results for alcohol homologues show that the larger the molecular size of the polymerization media, the higher the swelling ratio. This is due to the larger molecular size of the polymerization media, which makes a hydrogel with a larger pore size and a looser structure. The water, therefore, easily infiltrates the gel network and expands the molecular chain. Hence, the larger the molecular size of the polymerization media, the higher the swelling ratio of the hydrogel. In addition, from the viewpoint of the solubility parameter (δ), the differences in solubility parameter ($\Delta\delta$) for monomer and solvent are 0.31, 0.89, 1.61, and 1.89 for methanol, ethanol, isopropanol, and acetone, respectively. (See Table II.) It obviously indicates that the miscibility of the polymer/monomer and the solvent is in the order of methanol, ethanol, isopropanol, and acetone. This result also implies that the gel prepared in the isopropanol aqueous solution exhibits a poor miscibility (in their homologues) and results in a looser structure and a higher swelling ratio. However, it is notable that the swelling behaviors of the gel prepared in acetone solution do not follow the above-mentioned rule. This may be due to the solubility of acetone in water being better than that of isopropanol in water. In our previous report, the dimethylacrylamide/n-butoxymethacrylamide copolymeric hydrogel have also shown that the swelling behavior of a gel is reflected by the parameters of the polymerization media such as molecular size and miscibility (solubility) of monomer and solvent.[26] Table II shows the effect of polymerization media on swelling behavior for the NTHFAAm hydrogel in deionized water over a period of 3 h at 20°C. The results shown in Table II indicate that the constant (k), the penetration velocity (ν), and the diffusion co-

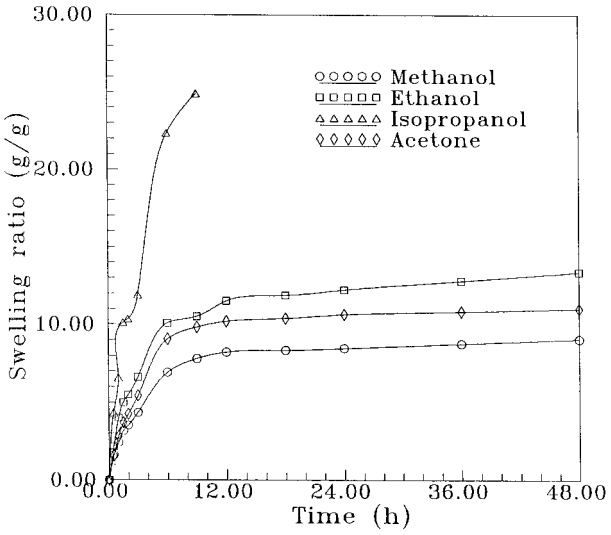

Figure 2 Effect of polymerization media on swelling ratio as a function of time for NTHFAAm gels.

Table II Effect of Polymerization Media on Swelling Behavior for the NTHFAAm Gel with the Solubility Parameter (δ) of the Sample Being 9.54

Solvent	δ[a]	Swelling Ratio (g H_2O/g sample)	n	K	ν (cm/h)	$D \times 10^6$ (cm^2/s)
H_2O	24.0	7.53	0.59	0.46	2.02	0.20
CH_3OH	9.23	9.06	0.58	2.40	4.54	0.20
C_2H_5OH	8.65	13.36	0.59	3.61	6.93	0.22
Iso-C_3H_7OH	7.93	24.89[a]	0.63	6.78	12.41	0.31
Acetone	7.65	11.00	0.69	2.66	5.67	0.21

Solubility parameters were calculated by Hoy's method.

efficient (D) increase with increases in the molecular size of the polymerization media. The swelling exponents n are between 0.58 and 0.63. Hence, the transport mechanisms are non-Fickian.

Figure 3 shows the swelling–deswelling reversibility for the NTHFAAm gel prepared in various media between 22 and 40°C. The procedure was repeated three times and the swelling ratio was measured as a function of time. The swelling–deswelling behavior (in Fig. 3) shows that the NTHFAAm gel has a good reversibility.

The dependence of the temperature and swelling ratio for NTHFAAm gel prepared in various solvents is shown in Figure 4. The results show a gradient deswelling with an increase in temperature, indicating that the higher the temperature, the lower the swelling ratio. The gel transition temperature (about 29°C) observed in Figure 4 is not significantly affected by the polymerization media in these swelling ratios. In addition, the swelling ratios for the gel prepared in deionized water and in various solvents show a difference in lower temperature and higher temperature. Especially at higher temperature (40°C), the gel swelling ratio decreased to zero except in the gel prepared in deionized water. This is due to the gel pore size being very small for gel prepared in deionized water. Hence, the small water molecule cannot be rapidly forced out of the gel when the gel deswells in temperatures over the gel transition temperature.

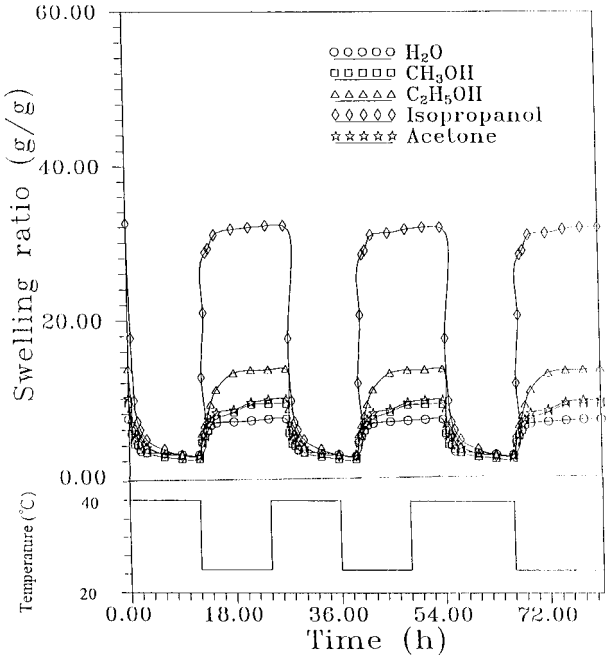

Figure 3 Swelling ratio of NTHFAAm hydrogels as a function of time with repeated abrupt changes of temperature between 22 and 40°C.

Effect of Gel Thickness on Gel Swelling Kinetics

To understand the swelling kinetics of a gel in water and the effect of gel thickness on the swell-

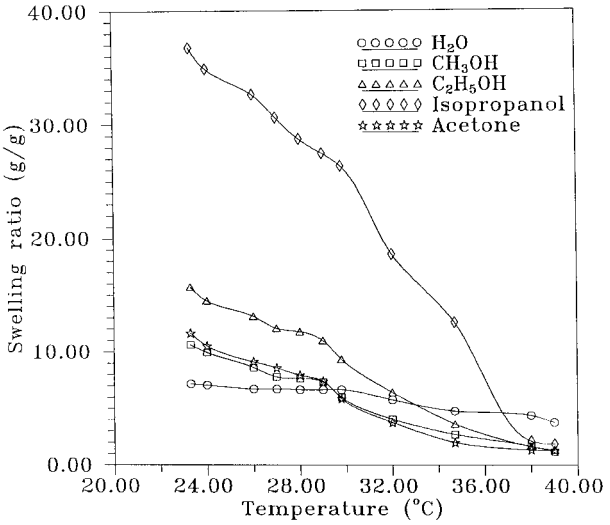

Figure 4 Effect of polymerization media on swelling ratio of NTHFAAm gels at different temperatures.

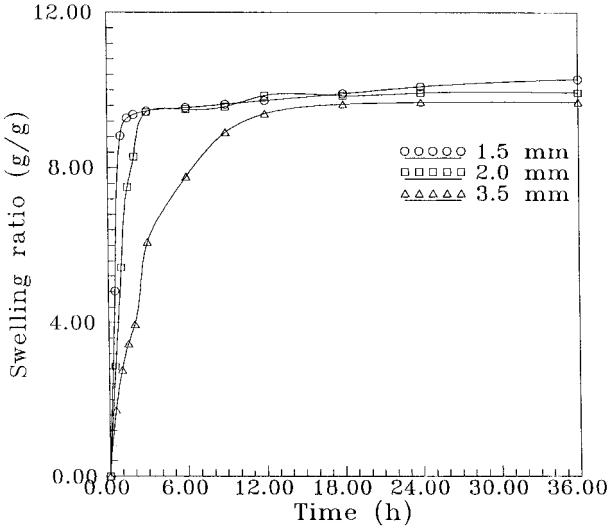

Figure 5 Swelling ratio of NTHFAAm gels having different thickness as a function of time at 25°C.

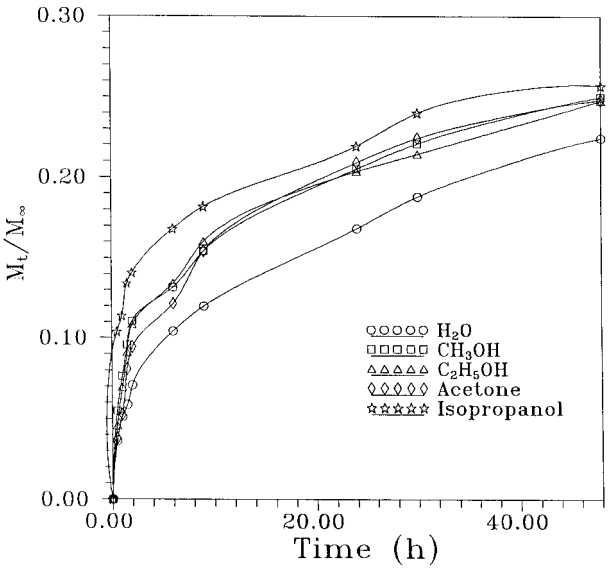

Figure 6 Effect of NTHFAAm gels on CV release profile during deswelling (40°C).

ing ratio, NTHFAAm gels with three different thicknesses were prepared. The effect of the thickness on the swelling ratio for the NTHFAAm gel is shown in Figure 5. The results show that the equilibrium swelling time for the thinner gel (1.5 mm), from the dried state to the completely swollen state, is obviously faster than that of thicker gel. This is because the water molecule can easily permeate the thinner gel and fill the gel networks. This phenomenon was also observed by Bae and associates.[21] In addition, the data shown in Table III also indicate that the swelling exponent n, diffusion coefficient, and penetration velocity decreased as the thickness was increased.

Effect of Polymerization Media on Fractional Release of CV and Caffeine

The release profiles of CV and caffeine in NTHFAAm gels prepared in various solvents at 40°C are shown in Figures 6 and 7, respectively. The results shown in these figures indicate that the larger the molecular size of polymerization media, the faster the release profiles of CV and caffeine in the NTHFAAm gels. This can be attributed to the gel having a looser structure and a larger pore size; therefore, the CV and caffeine molecules are squeezed out easily. The results also show that the fractional release (M_t/M_∞) of CV and caffeine does not reach 1.0. This occurrence implies that the caffeine (see Fig. 7) was not completely released and some portion was entrapped into the gel. This supports the idea of a water pocket formation in the collapsed gel. This phenomenon was also observed in many other gels.[15,16,21] In addition, it was found that the release profiles of caffeine in various gels are faster than those of CV in various gels. This is because the molecular size of CV is larger than that of caffeine.

Table III Effect of Thickness on Swelling Behavior for the NTHFAAm Gel in Deionized Water over a Period of 3 h

Thickness (mm)	Swelling Ratio (g H_2O/g sample)	n	k	ν (cm/h)	$D \times 10^6$ (cm^2/s)
1.5	10.27	0.87	0.86	3.97	0.21
2.0	9.93	0.59	0.46	2.02	0.20
3.0	9.68	0.56	0.25	1.72	0.17

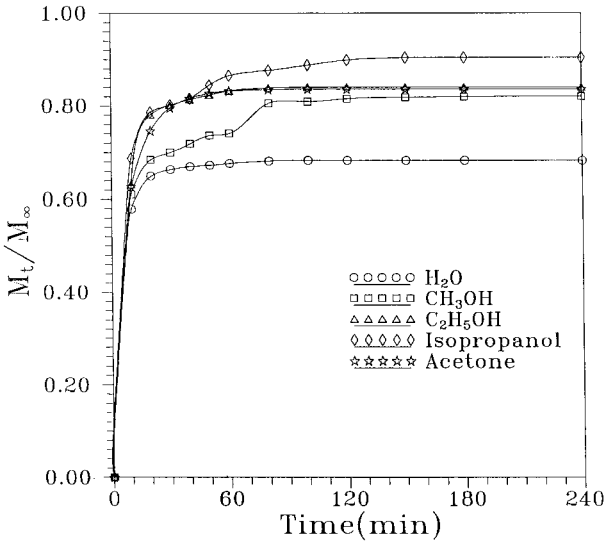

Figure 7 Effect of NTHFAAm gels on caffine release profile during deswelling (40°C).

CONCLUSIONS

The swelling behavior of thermoreversible hydrogels is related to their structure (looser or denser), surrounding temperature, and polymerization media.

The effects of the gel thickness on the swelling ratio for these hydrogels indicate that the equilibrium swelling time and diffusion coefficient for the thinner gel are faster than those of thicker gels. The effects of the polymerization media on the swelling ratio for these gels also show that the larger the molecular size of the polymerization media and the poorer the miscibility of the monomer and solvent, the higher the swelling ratio and the higher the diffusion coefficient. The transport mechanism transformed from a non-Fickian to Fickian behavior for this gel going from low temperature (2°C) to high temperature (40°C). Finally, the release profiles of caffeine in various gels are faster than are those of CV in various gels; and the larger the molecular size of polymerization media, the faster the release of CV and caffeine in the gels.

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