

Thermoreversible Hydrogels. II. Effect of Some Factors on the Swelling Behavior of *N,N*-Dimethylacrylamide and *n*-Butoxymethyl Acrylamide Copolymeric Gels

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ABSTRACT: A series of thermoreversible hydrogels are prepared from the various molar ratios of *N,N*-dimethylacrylamide (DMA), *n*-butoxymethyl acrylamide (nBMA), and *N,N'*-methylenebisacrylamide (NMBA). The influences of the amount of DMA in the copolymeric gels, temperature, and polymerization media on the swelling behaviors in water are investigated. Results indicate that the higher the DMA content in the hydrogel systems the higher the swelling ratio and the gel transition temperature. The effects of the gel thickness on the swelling ratio for DMA/nBMA copolymeric gels indicate that the equilibrium swelling time and diffusion coefficient for the thinner gel (1.5 mm) from the dried state to the completely swollen state are obviously faster than are those for the thicker gels (2.0 and 3.5 mm). The effects of the different polymerization media on the swelling ratio for DMA/nBMA copolymeric gels also show that the larger the solvent molecular size and the poor miscibility of the monomer and solvent the higher the swelling ratio and the diffusion coefficient. The drug release in these copolymeric gel systems are also investigated. © 1997 John Wiley & Sons, Inc. *J Appl Polym Sci* **65**: 909–916, 1997

INTRODUCTION

Hydrogels sometimes undergo a reversible discontinuous large volume change in response to a continuous change in the surrounding conditions, such as temperature,^{1–5} solvent composition,^{6–10} pH,^{11,12} salt concentration,¹⁰ and electric field.¹³ Since the volume phase transition brings about a dramatic change in the physical properties of the gels, which have been investigated to use for molecular separation,¹⁴ sorption–desorption of the solute,¹⁵ control of enzyme activity,¹⁶ and release of the solute.¹⁷ This phenomenon demonstrates the universality of the phase transition of gels and the importance of the chemical composition of the gel network and the 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 to under 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 affected over a narrow range of temperatures near the CGTT of the gel matrix.^{15,18} Since the gel deswell leads to the reduction of the 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 the alkoxyalkyl side chain, gel thickness, gel compositions, and crosslinked densities on the swell-

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ing ratio for a series of *N*-ethoxypropylacrylamide (NEPAAm)/butyl acrylate (BA) or *N*-tetrahydrofurfuryl acrylamide (NTHFAAm)/BA copolymeric gels were investigated in our laboratory.¹⁹ A series of DMA/nBMA copolymeric gels were prepared in an attempt to investigate the influences of the molar ratios of DMA/nBMA and to discuss the relationship between the swelling behavior and hydrogel compositions of these gels. For the controlled-release system, the Crystal Violet (CV) and caffeine chosen as model drugs were loaded into the gel and their release profiles during the gel swelling and deswelling were also studied as a function of the gel compositions.

EXPERIMENTAL

Materials

N,N-Dimethylacrylamide (DMA), *n*-butoxymethyl acrylamide (nBMA), and *N,N'*-methylenebisacrylamide (NMBA) as a crosslinking agent and ammonium persulfate (APS) as an initiator were purchased from Tokyo Kasei Industries, Ltd. *N,N,N',N'*-Tetramethylethylenediamine (TEMED) as an accelerator was obtained from Fluka. Crystal Violet (CV) and caffeine as model drugs were obtained from Fluka. All solvents and other chemicals were of analytical grade.

Preparation of Hydrogel Membranes

Various molar ratios of DMA and nBMA and 3 mol % NMBA (based on total monomers) were, respectively, dissolved in 8 mL 50 vol % of several aqueous solutions such as methanol, ethanol, or

isopropanol. To this solution, 0.2 wt % APS and 1 wt % of TEMED as a redox initiator were added, and the mixture was 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 6 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.

Determination of Swelling Ratio

The dried gels were immersed in an excess of deionized water until swelling equilibrium was attained. The weight of the wet sample (W_w) was determined after removing the surface water by blotting with filter paper. Dry weights (W_d) were 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:

$$\text{Swelling ratio is defined as } SR = (W_w - W_d)/W_d$$

Dynamic Swelling

The dried gels were immersed in an excess of deionized water at different temperatures. 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 an infinitely long time was designated M_∞ . The following equation can be used to calculate the diffusion coefficient D for $M_t/M_\infty \leq 0.8$ (Ref. 20):

Table I Characterization of the DMA/nBMA Copolymeric Gels

Copolymer	Feed Composition (Wt %)		Molar Ratio DMA/nBMA	Cloud Point Effect ^a	Cloud Point Temperature (°C)	Swelling Ratio (g H ₂ O/g Sample)
	DMA	nBMA				
X1	56.0	44.0	2.0	st	< 0	4.31
X2	58.0	41.7	2.2	st	30–40	4.85
X3	61.3	38.7	2.5	st	35–45	5.95
X4	64.0	36.0	2.8	st	45–60	7.32
X5	65.4	34.6	3.0	w	60–70	7.70
X6	71.7	28.3	4.0	vw	> 80	8.48

^a w = weak, vw = very weak, st = strong.

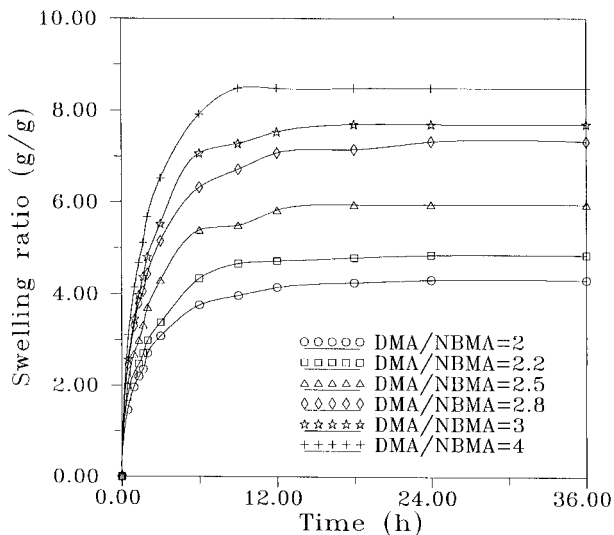


Figure 1 Swelling ratio as a function of time for DMA/nBMA copolymeric hydrogels at 25°C.

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

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

Measurement of CV Release

To load CV into the gels, dry gels were equilibrated in a CV solution (10 mg/100 mL of deionized water) at 4°C for 2 days. The CV release experiments were carried out by transferring previ-

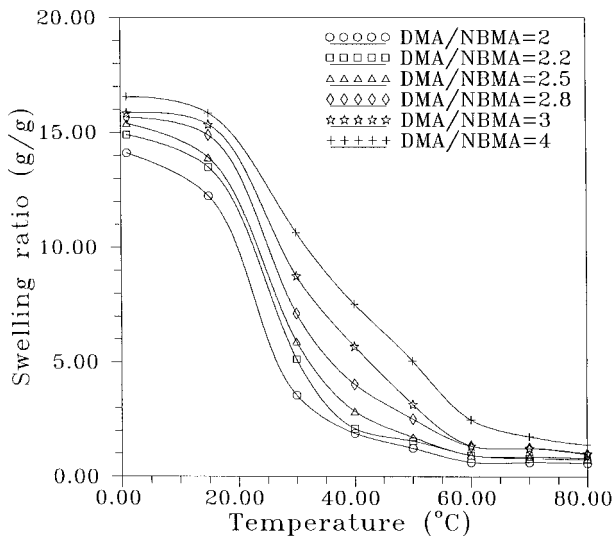


Figure 2 Swelling ratio as a function of temperature for DMA/nBMA copolymeric hydrogels.

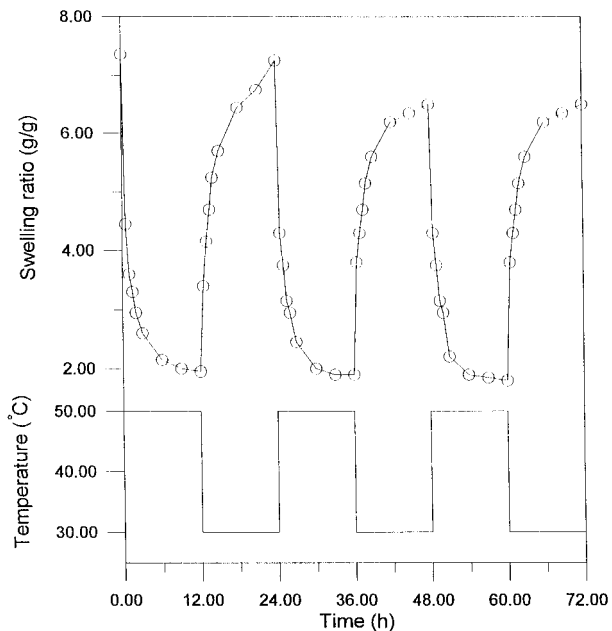


Figure 3 Swelling ratio of hydrogel (DMA/nBMA = 2.8) as a function of time with repeated abrupt changes of temperature between 30 and 50°C.

ous drug gels into 10 mL of deionized water at 50°C. The gels were periodically removed and transferred into 10 mL fresh water at each fixed time interval. The released CV was analyzed at 561 nm by the Jasco UV spectrophotometer (UVI-DEC-5).

Caffeine Deswelling Kinetics Experiments

The dry gels were equilibrated in 30 mg/10 mL of deionized water at 0°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 50°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 U3200).

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. The influence of the hydrophobic monomer and extent of the crosslinker

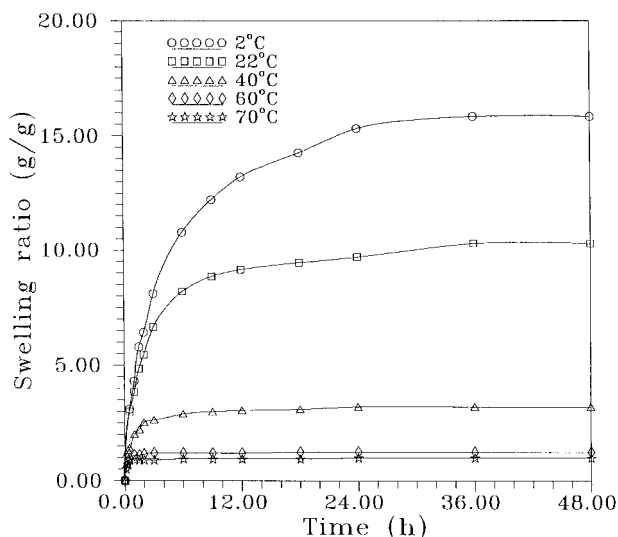


Figure 4 Swelling ratio as a function of time for sample DMA/nBMA = 2.8 at different temperatures.

on the LCST or CGTT and the swelling ratio for the poly(DMA-*co*-alkyl acrylate) copolymeric gels was reported by Muller in a previous article.²¹ DMA is a weakly hydrogen-bonding amide compound and nBMA is a hydrophobic alkoxyalkylacrylamide compound. Hence, the influence of the hydrophobic monomer (nBMA), gel thickness, and polymerization media such as methanol, ethanol, and isopropanol on the swelling ratio for the DMA/nBMA copolymeric gels is investigated in the following sections.

Characterization of DMA/nBMA Copolymeric Gels

Some characteristics of the DMA/nBMA copolymeric gels for various feed compositions are shown in Table I. The results observed from Table I show that the cloud point effect of the copolymeric gels is weaker with increase of the content of the DMA monomer. The gel transition temperatures are increased with increase of the content

of DMA in the copolymeric composition, i.e., from 0 to 80°C for samples X1–X6, respectively (also see Fig. 2). The equilibrium swelling ratios of the copolymeric gels are also increased with increase of the content of DMA (also see Fig. 1).

Effect of DMA on the Swelling Ratio of Copolymeric Gels

To investigate the effect of the DMA amount in the thermoreversible gels on the swelling behavior, the crosslinked copolymeric gels were prepared from the copolymerization of nBMA and DMA and with NMBA as a crosslinker. The swelling ratios as a function of time for DMA/nBMA copolymeric hydrogels in deionized water are shown in Figure 1. The results shown in Figure 1 indicate that the swelling ratio increases with increasing of DMA content. According to Flory's swelling theory,²² the copolymeric gels are non-ionic copolymeric gels and the crosslinked density was fixed in a series of different compositions of DMA/nBMA hydrogels, so the swelling ratio of the hydrogel is affected only by the affinity of the hydrogels for water. DMA is a weakly hydrogen-bonding amide and a hydrophilic monomer, so the more the DMA content, the larger the affinity of the gels for water and the higher the swelling ratio of the hydrogel. In addition, the equilibrium swelling time observed in Figure 1 is significantly affected by the addition of DMA content into the gels for these copolymeric gels. The results indicate that the equilibrium swelling time decreases with increasing DMA content.

Effect of Temperature on Swelling Ratio for DMA/nBMA Copolymeric Gels

The dependence of temperature and swelling ratio for various copolymeric gels of poly(DMA-*co*-nBMA) is shown in Figure 2. The results show a

Table II Effect of Temperature on Swelling Behavior for the Sample DMA/nBMA = 2.8 in Deionized Water

Temperature (°C)	Swelling Ratio (g H ₂ O/g Sample)	<i>n</i>	<i>K</i>	<i>D</i> × 10 ⁷ (cm ² /s)
2	15.84	0.51	3.54	0.33
22	10.3	0.45	2.57	0.59
40	3.21	0.45	1.51	1.17
60	1.25	0.42	1.28	4.45
70	1	0.42	1.27	5.59

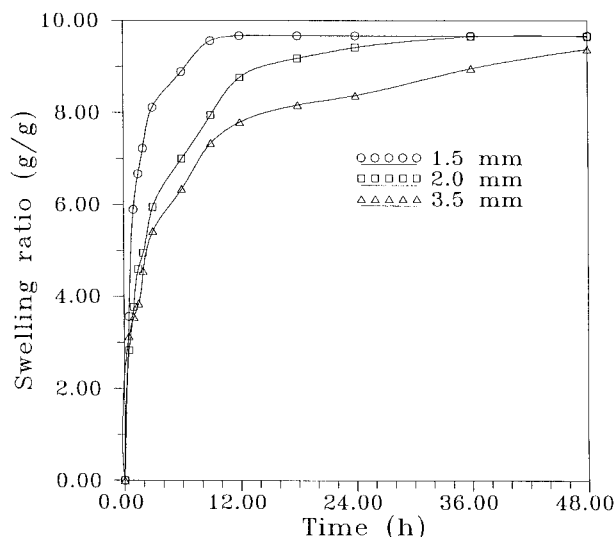


Figure 5 Swelling ratio of sample DMA/nBMA = 2.8 gels, having different thicknesses, as a function of time at 25°C.

gradually deswell with increasing of temperature, indicating that the higher the temperature the lower the swelling ratio, and the more the DMA content the higher the gel transition temperature. Bae et al.²³ presented that the gel deswelling is driven by a negative entropy change gain in water molecules, which go from the bound state to the free state and thereby are released from the gel. These results conform to our previous studies for NEPAAm/BA or NTHFAAm/BA hydrogels.¹⁹

Figure 3 shows the swelling kinetics and reversibility for the sample X4 between 30 and 50°C. The procedure was repeated three times and the swelling ratio was measured as a function of time. The swelling–deswelling behavior shown in Figure 3 exhibits that the DMA/nBMA gel is a thermoreversible gel.

The effect of temperature on the swelling ratio for sample X4 is shown in Figure 4. The results observed from Figure 4 indicate that the swelling ratio decreases with increasing of the temperature. To elucidate the transport mechanism, the

initial swelling data are fitted to the exponential heuristic equation^{24,25}:

$$\frac{M_t}{M_\infty} = Kt^n \quad (2)$$

where K is a characteristic constant of the gel and n is a characteristic exponent of the mode transport of the penetrant. 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. “ n ” and “ K ” were calculated from the slope and intercept of the plot of $\log(M_t/M_\infty)$ against $\log(t)$ at various temperatures, respectively. In addition, eq. (1) was used to calculate the diffusion coefficient D from the slope $4\sqrt{D}/\sqrt{\pi}$ and intercept of the plot of (M_t/M_∞) against $(t/L^2)^{1/2}$ at different temperatures, respectively. Table II shows the diffusion coefficient, D , the index, n , and the constant, K , for a series of DMA/nBMA copolymeric gels at various temperatures. The results indicate that the swelling exponent “ n ” for all DMA/nBMA copolymeric gels at various temperatures are between 0.5 and 0.4. This result shows that the swelling transport mechanism is a Fickian transport from 2 to 70°C. In addition, the data for the diffusion coefficient shown in Table II indicate that the diffusion coefficients D for the DMA/nBMA = 2.8 copolymeric gel is increased with increase of the temperature. The results shown in Figure 4 also indicate that the equilibrium swelling time is shortened with increasing of the temperature for this gel.

Effect of Gel Thickness on Gel Swelling Kinetics

To understand the swelling kinetics of a dried gel in water and the effect of gel thickness on the swelling ratio, the DMA/nBMA copolymeric gels with three different thicknesses were prepared. The effect of the gel thickness on the swelling ratio for the DMA/nBMA = 2.8 copolymeric gel is

Table III Effect of Thickness on Swelling Behavior for the Sample DMA/nBMA = 2.8 in Deionized Water

Thickness (mm)	Swelling Ratio (g H ₂ O/g Sample)	n	k	$D \times 10^7$ (cm ² /s)
1.5	9.67	0.59	2.68	0.78
2.0	9.65	0.47	2.55	0.61
3.0	9.38	0.41	2.56	0.53

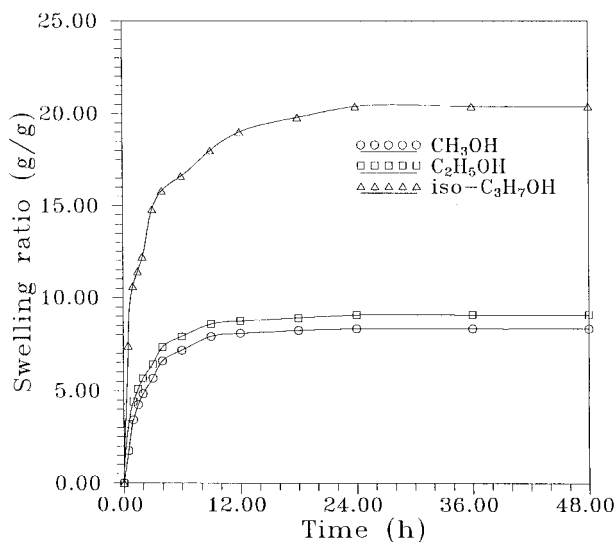


Figure 6 Effect of polymerization medium on swelling ratio as a function of time for DMA/nBMA copolymeric hydrogels.

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 the thicker gels (2.0 and 3.5 mm). This is because the water molecule can easily permeate to the thinner gel and fill the gel networks.²³ In addition, the data shown in Table III also indicate that the swelling exponent “ n ” and diffusion coefficient D are decreased as the thickness increased.

Effect of Polymerization Media on Swelling Ratio for DMA/nBMA Copolymeric Gels

To investigate the effect of the polymerization media on the swelling ratio of the copolymeric gel, methanol, ethanol, and isopropanol were chosen as polymerization media for the sample X4 copolymeric gel. The values of the radius of gyration for water, methanol, ethanol, and isopropanol are

0.6150, 1.5360, 2.2495, and 2.7359 Å, respectively.²⁶ The swelling behavior for this copolymeric gel X4 which was prepared in the above said solution is shown in Figure 6. The results 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 the copolymeric gel have a larger pore size and a looser structure. The water, therefore, easily infiltrates into the hydrogel network and expands the molecular chain. Hence, the larger the molecular size of the polymerization media, the higher the swelling ratio of the hydrogel. On the other hand, from the viewpoint of the solubility parameter (δ), the differences of the solubility parameter ($\Delta\delta$) for monomer and solvent are 0.55, 0.03, and 0.75 for methanol, ethanol, and isopropanol, respectively (see Table IV). It obviously indicates that the miscibility of the polymer/monomer and the solvent is in the order of ethanol, methanol, and isopropanol. This result also implies that the gel prepared in the isopropanol solution exhibits poor miscibility and results in a looser structure and a higher swelling ratio. Hence, from above discussion, it is known that the swelling behavior of a gel is also reflected by the parameters of the polymerization media such as molecular size and miscibility of the monomer and solvent. Table IV shows the effect of the polymerization media on the swelling behavior of the sample DMA/nBMA = 2.8 in deionized water. The result also indicates that the swelling exponent “ n ” and diffusion coefficient D increase as the molecular size of the polymerization media increased.

The dependence of the temperature and swelling ratio for various DMA/nBMA copolymeric gels is shown in Figure 7. The results show a gradual deswell with increase of the temperature, indicating that the higher the temperature the lower the swelling ratio. The gel transition temperature observed in Figure 7 is not significantly affected by the polymerization media in these swelling ratios.

Table IV Effect of Polymerization Medium on Swelling Behavior for the Sample DMA/nBMA = 2.8 in Deionized Water with the Solubility Parameter (δ^*) of the Sample being 8.68

Solvent	δ^*	Swelling Ratio (g H ₂ O/g Sample)	n	K	$D \times 10^7$ (cm ² /s)
CH ₃ OH	9.23	8.33	0.46	2.51	0.59
C ₂ H ₅ OH	8.65	9.08	0.47	2.55	0.61
iso-C ₃ H ₇ OH	7.93	20.4	0.56	2.32	0.79

^a The solubility parameters were calculated by Hoy's method.

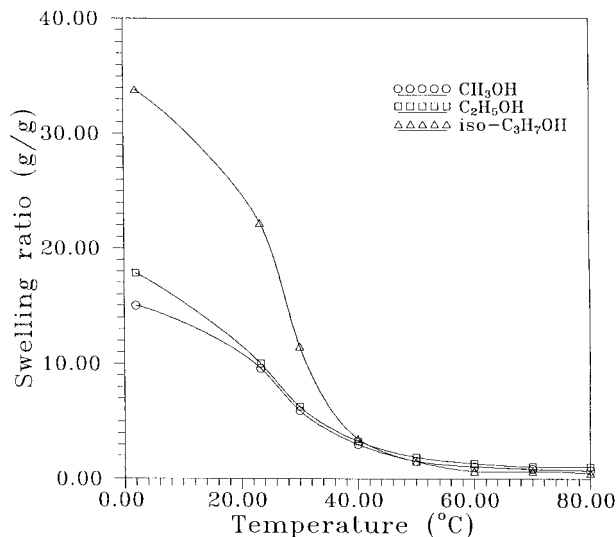


Figure 7 Effect of polymerization medium on swelling ratio of sample DMA/nBMA = 2.8 at different temperatures.

Effect of Hydrogel Composition on Fractional Release of CV and Caffeine

The release profiles of CV and caffeine in DMA/nBMA copolymeric gels at 50°C are shown in Figures 8 and 9, respectively. The results shown in these figures indicate that the less DMA content in the hydrogel system the slower the CV and caffeine release exhibited, which is due to the

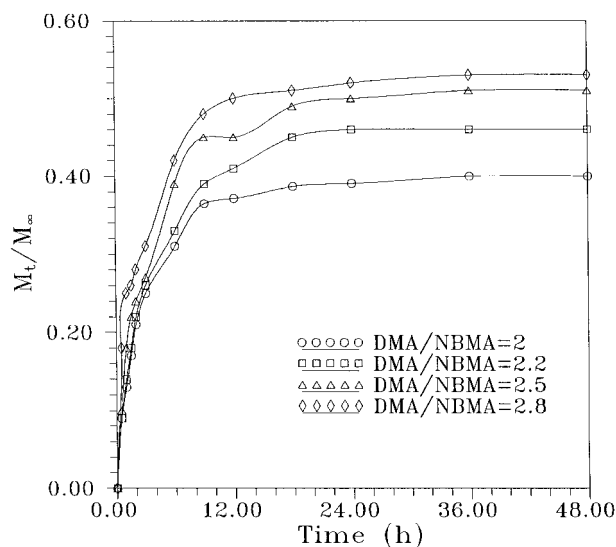


Figure 8 Effect of nBMA content on CV release profile during deswelling (50°C).

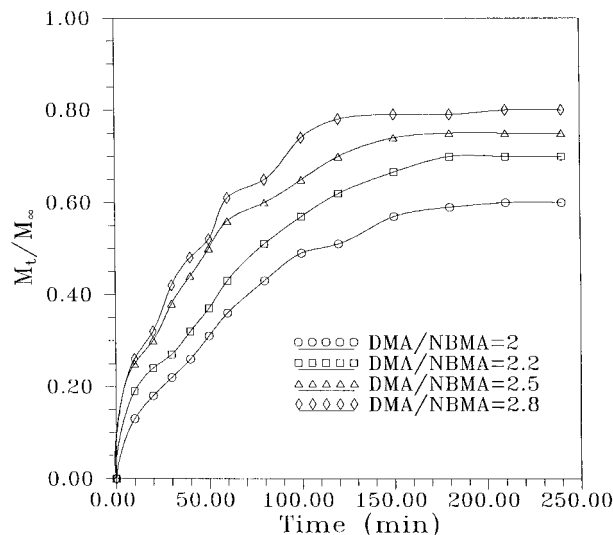


Figure 9 Effect of nBMA content on caffeine release profile during deswelling (50°C).

faster gel deswelling, i.e., the fewer hydrophilic groups of the DMA/nBMA copolymeric gels contained, the faster the gel deswelled. 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 was not completely released and some portion was entrapped within the gel. This effect supports the idea of a water pocket formation in the collapsed gel. CV and caffeine are only dissolved in the free water. CV and caffeine molecules located in the porous region of the gel may be squeezed out quickly or trapped in the water pocket as the gel collapses.²⁷ This phenomenon was also observed and explained in our previous report for NEPAAm/BA and NTHFAAm/BA copolymeric gels¹⁹ and in some other articles.^{15,16,27} In addition, it was found that the release profiles of caffeine in various copolymeric gels are faster than are those of CV in various copolymeric gels. This is because the molecular size of CV is larger than that of caffeine. Therefore, the release profiles of caffeine in various copolymeric gels are faster.

The effects of the polymerization media on the release profiles of CV in the DMA/nBMA copolymeric gel at 50°C are shown in Figure 10. It was found that the larger the molecular size of polymerization media the faster the release profiles of CV in copolymeric gels. This can be attributed to that the copolymeric gel has a loose structure and has a larger pore size in the copolymeric gel. Therefore, the CV molecule is squeezed out easily.

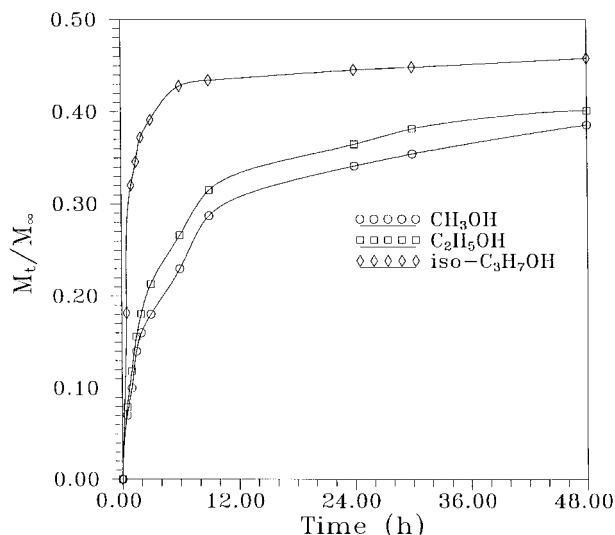


Figure 10 Release profile of CV from sample DMA/nBMA = 2.8 in response to polymerization medium.

CONCLUSIONS

The swelling behavior of these thermoreversible copolymeric gels is related to their structure, their chemical composition, and the surrounding temperature. The swelling ratios of DMA/nBMA copolymeric gels are increased with increase of the DMA content, and the equilibrium swelling time of the hydrogel is shorter. In addition, the higher the DMA contents, the larger the affinity for water. Also, the gel transition temperatures are increased as the DMA content is increased.

The effects of the gel thickness on the swelling ratio for DMA/nBMA copolymeric gels indicate that the equilibrium swelling time and diffusion coefficient for the thinner gel (1.5 mm) from the dried state to the completely swollen state are obviously faster than those of the thicker gels. The effects of the polymerization media on the swelling ratio for DMA/nBMA copolymeric gels also show that the larger the molecular size of the polymerization media and the poorer the miscibility of the polymer and solvent, the higher the swelling ratio and the higher the diffusion coefficient.

Finally, the less DMA content in this hydrogel system exhibits a slower CV and caffeine release, which is due to the faster gel deswelling. The release profiles of caffeine in various copolymeric gels are faster than are those of CV in various copolymeric gels. In addition, the larger the molecular size of the polymerization media, the faster the release profiles of CV in the copolymeric gels.

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