Thermoreversible Hydrogels. I. Synthesis and Effect of a Hydrophobic Monomer on Swelling Behaviors of Thermoreversible Gels Prepared by Copolymerizing *N*-Alkoxyalkylacrylamide with Butyl Acrylate

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ABSTRACT: A series of copolymeric gels were prepared from *N*-alkoxyalkylacrylamide and *n*-butyl acrylate (BA) at various feed ratios. The effect of the content of BA in the copolymer on the gel behaviors is discussed. The respective crosslinked copolymer exhibits a gel transition behavior, collapsing and shrinking above gel transition temperature but swelling and reexpanding below gel transition temperature. By utilizing this character, these copolymeric gels could be used for drug release or drug delivery systems. The drug released from the copolymeric gels was plotted as M_t/M_∞ versus t, where M_t/M_∞ is the fraction of drug released at given time t. In this experiment, crystal violet and caffeine were chosen as model drugs. The deswelling-kinetics experiments with caffeine showed that a water pocket was formed within the gel matrix when the gel deswelled rapidly. © 1997 John Wiley & Sons, Inc. J Appl Polym Sci **64:** 1477–1484, 1997

Key words: thermoreversible hydrogel; *N*-ethoxypropylacrylamide-*co*-butyl acrylate copolymeric gel; *N*-tetrahydrofurfurylacrylamide-*co*-butyl acrylate copolymeric gel

INTRODUCTION

Thermoreversible polymers would bring about a soluble–insoluble transition when the temperature of the polymer solution is lower or higher than lower critical solution temperature (LCST). The water-soluble behavior depends on weakly hydrogen-bonding or amide groups that are transferred from a fully soluble polymer to a phase-separated insoluble polymer.

Recently, much work has been carried out on poly(*N*-alkylacrylamide), especially poly(*N*-isopropylacrylamide) [poly(NIPAAm)], which is one of the best thermotropic, water-soluble polymers[1–5] and exhibits an LCST behavior, collapsing and shrinking above the LCST at 32–33°C. Poly(NIPAAm) has been used for drug release and absorption processes.[6–8]

The temperature-induced collapse transition has been observed for the hydrogels containing a hydrophobic group. Recently, many researchers have produced a variety of experimental results demonstrating that hydrophobic interaction plays an important role for the hydrogels in the thermoshrinking type of gel transition.[9–17] For example, Wada and colleagues[17] indicated the importance of hydrophobic interaction in thermoshrinking behavior. The magnitude of hydrophobic interaction of the *N*-substitutent in the repeating unit depended on various factors, and its correlation with the swelling behavior of a gel was presented. Hoffman and associates[18–21] showed that increased water contents were observed at higher temperatures than just above the LCST when wet poly(NIPAAm) gel was initially used to determine the equilibrium water content. Vitamin B-12 release profile experiments exhibited an initially

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rapid release followed by a slow release; this fact indicated that the gel collapse did not occur homogeneously. Hoffman and coworkers postulated that the gel collapse proceeded via a "skin" formation, and also reported that a nonequilibrium and kinetics-limited process had been found during the thermal cycling operation of a packed bed immobilized enzyme reactor.

Monomers of *N*-ethoxypropylacrylamide (NEPAAm) and *N*-tetrahydrofurfurylacrylamide (NTHFAAm) were prepared according to Ito.[22] These two polymers exhibit LCSTs of approximately 26°C and 29°C, respectively, in aqueous solution, but their gel behaviors were not found in the literature. Hence, in this article, we determined the water content of the copolymeric gels poly[NEPAAm-*co*-butyl acrylate (BA)] or poly(NTHFAAm-*co*-BA) with various molar ratios as a function of temperature which is below and above the gel transition temperature, and also investigated the deswelling kinetics. Further, to confirm the existence of the skin formation in these copolymeric gels, caffeine as a model drug was incubated in the gel and the release profile during the gel deswelling studied as a function of the molar ratio of copolymers.

EXPERIMENTAL

Materials

The reagent grade chemicals, 3-ethoxypropylamine, tetrahydrofurfurylamine, BA, and acryloyl chloride were obtained from Fluka (Switzerland). Triethylamine, *N*,*N*′-methylene-bis-acrylamide (NMBA) as a crosslinking agent, and α,α'-azobisisobutyronitrile (AIBN) and ammonium persulfate (APS) as initiators were purchased from Tokyo Kasei Industries Ltd (Japan). *N*,*N*,*N*′,*N*′-tetramethylethylene diamine (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 analytical grade.

Synthesis of Monomers

The monomers NEPAAm and NTHFAAm were prepared via the following reaction: $CH_2{=}CHCOCl + NH_2R + (C_2H_5)_3N \rightarrow CH_2{=}CHCONH{-}R + (C_2H_5)_3NHCl$, where the reaction solvent was benzene and the reaction temperature was kept at 0 to 10°C. R is 3-ethoxypropyl and tetrahydrofurfuryl group for NEPAAm and NTHFAAm, respectively.

The synthesized monomers NEPAAm and NTHFAAm were purified via vacuum distillation. The boiling points of the two monomers were 122°C/6 mmHg and 146°C/5 mmHg, respectively.

Preparation of Hydrogel Membranes

Various ratios of NEPAAm (or NTHFAAm) and BA and 4 wt % NMBA were dissolved in 10 mL of 50% ethanol aqueous solution. To this solution, 0.2 wt % APS and 1 wt % TEMED were added as redox initiators, 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 5 h. After gelation was completed, the gel membrane was removed and immersed in an excess amount of deionized water to remove the residual unreacted monomer.

Determination of Water Content

The gels were immersed in an excess amount of deionized water until swelling equilibrium was attained. The weight of wet sample (W_w) was determined after surface water was removed by blotting with filter paper. Dry weight (W_d) was determined after drying the gel in a vacuum oven for 1 day. Water content (Q) based on W_w and W_d was then calculated as following relationship: $Q = (W_w - W_d)/W_w \times 100\%$

Measurement of CV Release

In order to load CV into the gels, dry gels were equilibrated in 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 20°C. The gels were periodically removed and transferred into 10 mL of fresh water at each fixed time interval. The released CV was then analyzed at 561 nm with a Jasco ultraviolet (UV)-spectrophotometer (UVDEC-5).

Caffeine Deswelling Kinetics Experiments

The dry gels were equilibrated in 30 mg/10 mL of deionized water at 20°C for 2 days in order to load caffeine into the gels. The caffeine deswelling-kinetics experiments were carried out by transferring previously drug-incubated gels into 10 mL of deion-

Table I Chemical Shifts of Proton NMR for NEPAAm and NTHFAAm Monomer

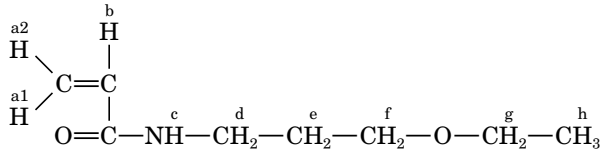
Characteristic Peak	NEPAAm	NTHFAAm
t, 3H, CH_3	0.99–1.09 (H_h)	
m, 2H, CH_2—CH_2—CH_2		1.27–1.37 (H_h)
m, 2H, CH—CH_2—CH_2		1.56–1.81 (H_e)
q, 2H, CH_2—CH_2—CH_2	1.60–1.74 (H_e)	
q, 2H, NH—CH_2	3.22–3.28 (H_d)	2.94–3.07 (H_d)
t, 2H, O—CH_2—CH_2		3.23–3.52 (H_g)
q, 2H, O—CH_2—CH_3	3.30–3.36 (H_g)	
t, 2H, CH_2—CH_2—O	3.37–3.41 (H_f)	
t, 2H, CH_2—CH—O		3.54–3.81 (H_f)
q, 1H, CH_2=CH—CO	5.31–5.49 (H_{a1})	5.31–5.49 (H_{al})
q, 1H, CH_2=CH—CO	5.92–6.05 (H_{a2})	5.92–6.05 (H_{a2})
q, 1H, CH_2=CH—CO	6.10–6.20 (H_b)	6.10–6.20 (H_b)
s, 1H, CO—NH—CH_2	7.23 (H_c)	6.97 (H_c)

ized water at 37°C. The gels were then periodically removed and transferred into 10 mL of fresh water at each fixed time interval. The released caffeine was analyzed at 272 nm by a UV-spectrophotometer. The fractional release, M_t/M_∞, was then reported as a function of the released time t.

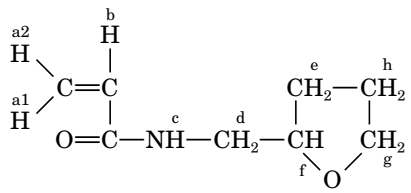
RESULTS AND DISCUSSION

Characterization of NMR Spectra of *N*-Alkoxyalkylacrylamide

^{1}H-NMR spectra were measured with a spectrophotometer (Bucker FT-NMR) operating at 200 MHz for ^{1}H at 30°C. NEPAAm and NTHFAAm were dissolved in $CDCl_3$ to measure ^{1}H-NMR. The chemical shifts of the respective groups identified from spectra of NEPAAm and NTHFAAm monomers are shown in Table I. The chemical structures of NEPAAm and NTHFAAm are as follows:



NEPAAm



NTHFAAm

Characterization of IR Spectra of *N*-Alkoxyalkylacrylamide

N-alkoxyalkylacrylamide monomers were injected into a potassium bromide window to measure infrared (IR) spectra with a spectrophotometer (Jasco FT/IR-7000). The result is shown in Figure 1.

For NEPAAm and NTHFAAm, with the C=C stretch at 1660–1620 cm^{-1}, the weak conjugation often moves the C=C stretch to the right and increases the intensity. The amide groups have C=O absorption in the range from 1670 to 1620 cm^{-1}. An N—H stretching band appears at about 3330 cm^{-1} and N—H bending around 1600 to 1500 cm^{-1}. For NTHFAAm, the five-membered ring containing oxygen usually gives a medium intensity stretching vibration at about 1250 cm^{-1}; for NEPAAm, the C—O—C stretching vibration leads to a strong absorption signal appearing at about 1200 cm^{-1}.[23]

Effect of Alkoxyalkyl Side Chain on Water Content

It is well known that the polymers of the alkoxyalkylacrylamides derived from acrylamides exhibit thermoreversible and LCST behavior in aqueous solution. The polymeric gels prepared by the crosslinking of the said alkoxyalkylacrylamides and NMBA should show a phase transition under heating in the same manner as their polymers in the aqueous solution. The relationship between the polymeric gels crosslinked from the said alkoxyalkylacrylamide with hydrophobic monomer (BA) and the water contents of these polymeric gels is investigated in the following sections. In

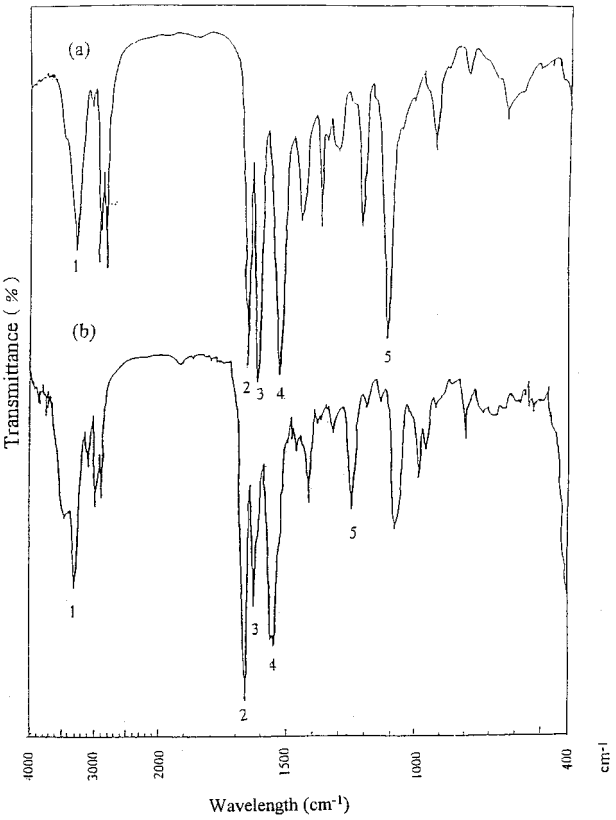


Figure 1 IR spectra for (a) NEPAAm; (b) NTHFAAm.

addition, these polymeric gels are also assessed as applications for drug release or drug delivery systems.

The crosslinked hydrogels poly(NEPAAm) and poly(NTHFAAm) exhibit a swelling–deswelling reversible process in response to temperature. The water contents of these two polymeric gels under heating and cooling cycles are shown in Figure 2. The results shown in Figure 2 indicate that the temperatures of phase transition are 24.5°C and 30°C for poly(NEPAAm) and poly(NTHFAAm) gels, respectively. The mobility of the alkoxyalkyl side chain in the thermosensitive hydrogels plays an important role in gel swelling, and this can be clearly demonstrated by the behaviors of poly(NEPAAm) and poly(NTHFAAm). There are considerable differences in the swelling behavior of these two hydrogels, even though there are five carbon atoms and one oxygen atom in each side chain. From the viewpoint of the gel structure, the rotational freedom of side-chain carbons in the NTHFAAm network is restricted due to the configurational structure of the five-membered ring which is associated with the rigid amide bond.[23] This occurrence makes the NTHFAAm networks less hydrophobic, and shows an higher transition temperature.

The heating temperature is elevated stepwise from 20°C to 40°C during the experimental process. The swelling–deswelling process of these two thermoresponsive hydrogels similar to poly(NIPAAm) exhibits a reversible phenomenon. Apparently, the deswelling process (in the heating-up stage) can be divided into two steps (see Fig. 2). Hoffman and associates also observed this phenomenon in some gels.[18–21]

Effect of Gel Thickness on Gel Swelling Kinetics

In order to understand the swelling kinetics of a dried gel in water and the effect of gel thickness on the water content, poly(NEPAAm) gels with three different thicknesses were prepared.

The effect of the gel thickness on the water content for poly(NEPAAm) is shown in Figure 3. The results show that the equilibrium absorption 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 mm, 3.5 mm). (See Table II). This is due to the fact that the water molecule can more easily permeate the thinner gel and fill the gel networks.[23]

The influence of gel thickness on the swelling kinetic of poly(NEPAAm) gel was also investigated. The swelling kinetic of the dried gel in the water was analyzed according to the equation

$$M_t/M_\infty = kt^n \qquad (1)$$

where M_t is the water content of the dried gel at

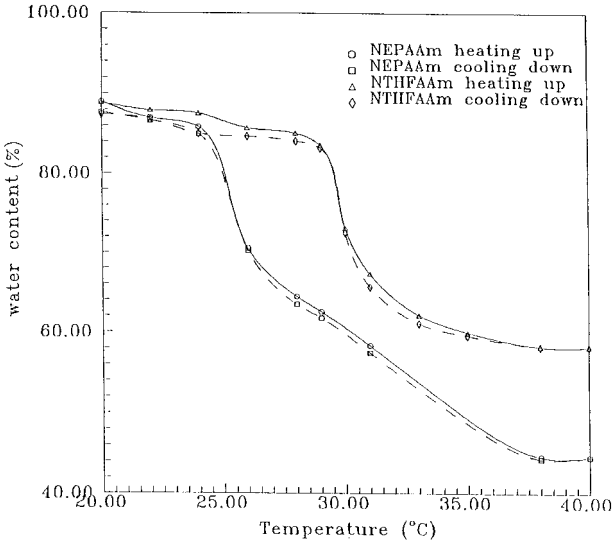


Figure 2 Effect of temperature on water content of polymer gels.

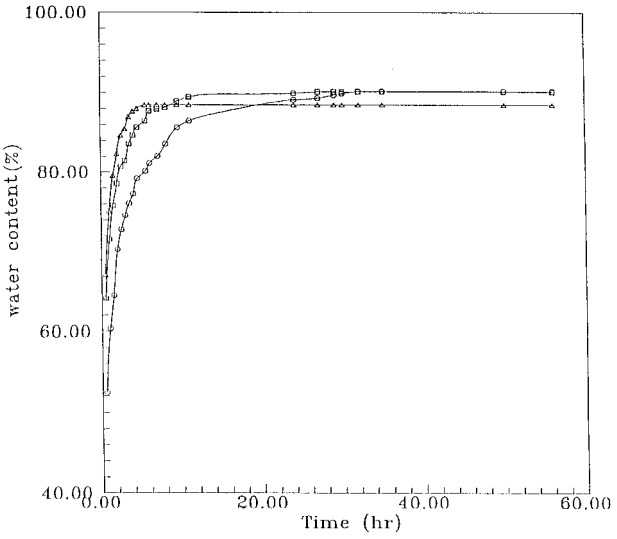


Figure 3 Water content of NEPAAm gels, having different thicknesses, as a function of time at 20°C: (○) 3.5 mm; (□) 2.0 mm; (△) 1.5 mm.

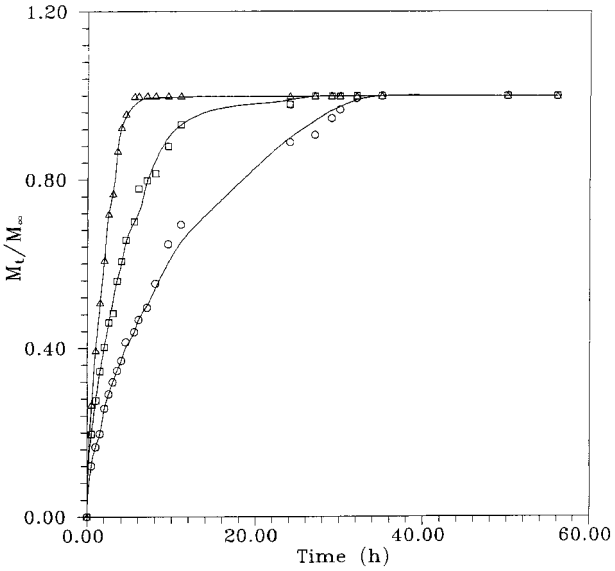


Figure 4 Plots of fractional water content versus time of poly(NEPAAm) gels, with three thicknesses, at 20°C: (○) 3.5 mm; (□) 2.0 mm; (△) 1.5 mm.

a given time, t; M_∞ is the water content of the dried gel at equilibrium; k is a characteristic constant of the gel; and n is the exponent describing the Fickian or non-Fickian diffusion processes. Figure 4 shows the relationship of M_t/M_∞ versus t for different gel thicknesses. The results obtained from Figure 4 are shown in Table II. The data shown in Table II indicate an increase in weight gain rate (dw/dt) and k with a decrease in gel thickness at initial swelling stage. This result rationally implies that the penetration velocity of water into the gel increases with a decrease of gel thickness. The swelling exponent n shows a depature from Fickian-type diffusion.

Effect of Hydrogel Composition on Water Content

Figures 5 and 6 show the effects of various molar ratios of poly(NEPAAm-*co*-BA) and poly(NTHFAAm-*co*-BA) gels on the water content as a function of temperature. During the deswelling process from 20°C to 40°C, the water content shows a remarkable difference among the four different composition gels. These results suggest that the formation process of the surface-shrinking type is dependent on the content of BA in the polymeric chain. The thickness of the skin formed at the molar ratio of 16.83 is thicker than that of the skin formed at molar ratios of 22.31 and 24.75, and on pure poly(NEPAAm), whereas the pure poly(NEPAAm) with the least

Table II Swelling Analysis of Poly(NEPAAm) Gels with Different Thicknesses

Thickness (mm)	n	K	dw/dt[a] (g H_2O/s) × 10^4	t_{eq} (h)
3.5	0.57	0.17	2.97	32
2.0	0.54	0.28	4.67	27
1.5	0.61	0.40	6.11	7

[a] Initial water uptake rate.

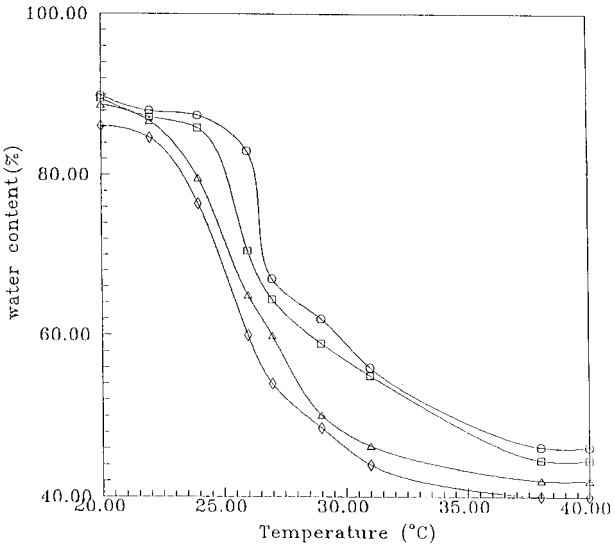


Figure 5 Water content as a function of temperature for various molar ratios of NEPAAm/BA copolymeric gels: (○) pure NEPAAm; (□) 24.75; (△) 22.31; (◇) 16.83.

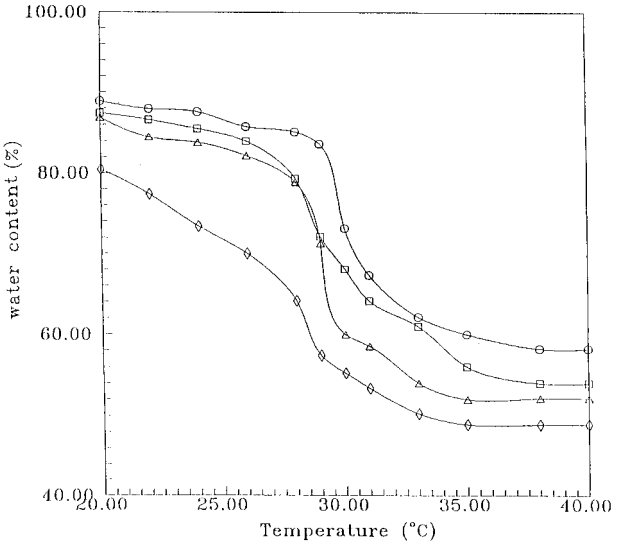


Figure 6 Water content as a function of temperature for various molar ratios of NTHFAAm/BA copolymer hydrogels: (○) pure NTHFAAm; (□) 24.75; (△) 22.31; (◇) 16.83.

hydrophobic side chain forms the thinnest surface layer and keeps the highest water content inside the polymeric gel.

Effect of Crosslinking Agent Content on Water Content

According to Flory's swelling theory,[24] swelling behavior is affected by three factors: rubber elasticity, affinity to the solution, and crosslinked density. Figures 7 and 8, present the equilibrium swelling of different contents of crosslinking agents on NEPAAm and NTHFAAm gels, respectively, as a function of temperature. These results show that the water contents are obviously decreased with increased temperature and that the water contents are lowered with an increase in the amount of the crosslinker. This is due to the fact that the excess crosslinking agents restrict the relaxation of polymeric chains in the aqueous solution, thus leading to the reduction of water contents.

Effect of Hydrogel Composition on Fractional Release of CV

Figure 9 shows the fractional release of CV from different hydrogel compositions in the feed at the temperature of 20°C. The results show that the fractional release of CV for NTHFAAm gel systems is greater than that for NEPAAm gel systems. This occurrence shows that the higher the gel transition temperature, the higher the fractional release. In addition, the fractional release of CV observed from experimental data for NTHFAAm/BA or NEPAAm/BA copolymeric gel systems (not shown) shows a decrease with increasing the added BA contents in the copolymeric compositions. This phenomenon also confirms that the more the hydrophilic group of the gel is contained, the faster the CV is diffused. These results, described above, suggest that the hydrophilicity of the side chain in these two polymers is an important parameter which contributed to

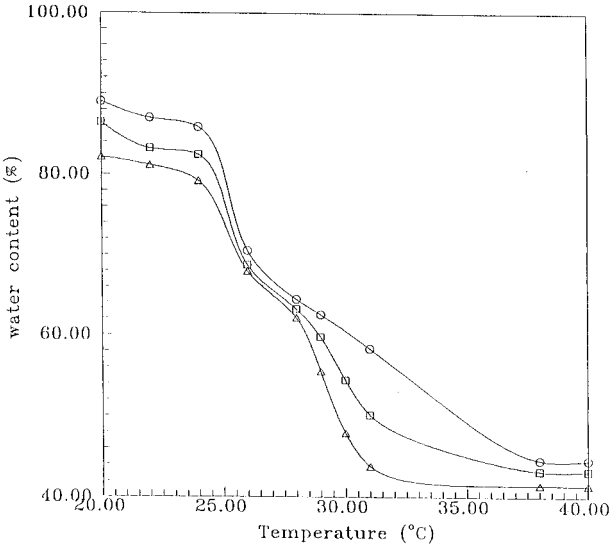


Figure 7 Water content of NEPAAm gels having different amounts of crosslinking agent, as a function of temperature: (○) 4%; (□) 6%; (△) 8%.

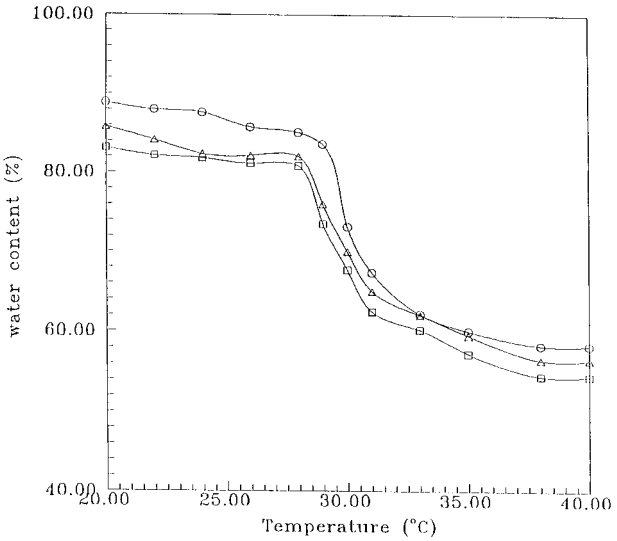


Figure 8 Water content of NTHFAAm gels having different amounts of crosslinking agent for sample: (○) 4%; (□) 6%; (△) 8%.

a greater concentration gradient of drug dispersed in the swollen gel state and then resulted in faster diffusion in the aqueous solution.

Effect of Temperature on Drug Release

Investigation was performed on how temperature influences drug release for the polymeric gel based on the NEPAAm/BA (molar ratio of 24.75) copolymeric gel loading CV. The release profile of CV from the poly(NEPAAm-*co*-BA) gel against 20°C, 23°C, and 25°C is shown in Figure 10. These data indicate that higher temperature can provide great thermal stimulation and energy for water molecules in the gel matrix, thereby leading to an increase in drug diffusion. On the other hand, higher temperature will contribute to the contraction of the polymeric gel; that is, higher temperature will lead to faster decrease of the gel network volume. This action would squeeze out excess water molecules and drug (CV). However, skin formation is not observed in the gel matrix at 20°C, 23°C, or 25°C because these are all below the gel transition temperatures.

Evidence of Water Pocket Existence

In order to confirm the existence of the water pocket, caffeine was loaded in the gel, and its release profile during the gel deswelling process was studied as a function of different hydrogel compositions in response to a rapidly changing temperature from 20°C to 37°C. The results, shown in Figure 11, demonstrate that the more BA the gel contains, the less caffeine is released. This result is due to the fact that the more rapid and thicker skin is formed by the gel containing more BA at the temperature of 37°C. It can also be observed that the fractional release M_t/M_∞, from 78% for pure NEPAAm to 53% for NEPAAm/BA = 16.83,

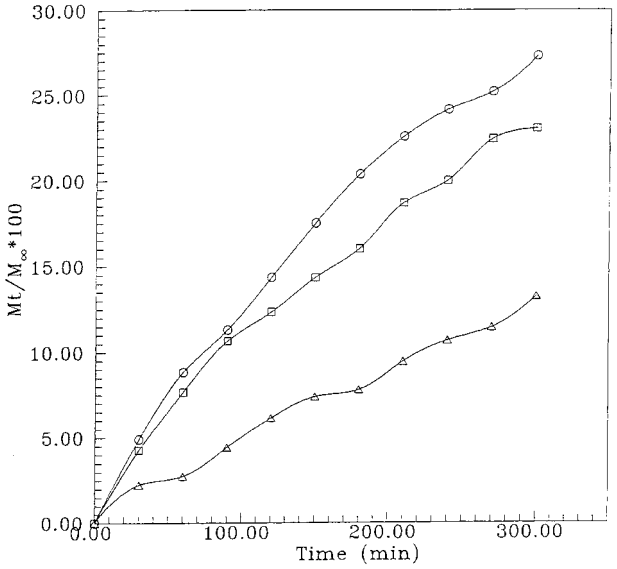


Figure 10 Release profile of CV from poly(NEPAAm-*co*-BA) gels (NEPAAm/BA = 24.75) in response to temperature: (○) 20°C; (□) 23°C; (△) 25°C.

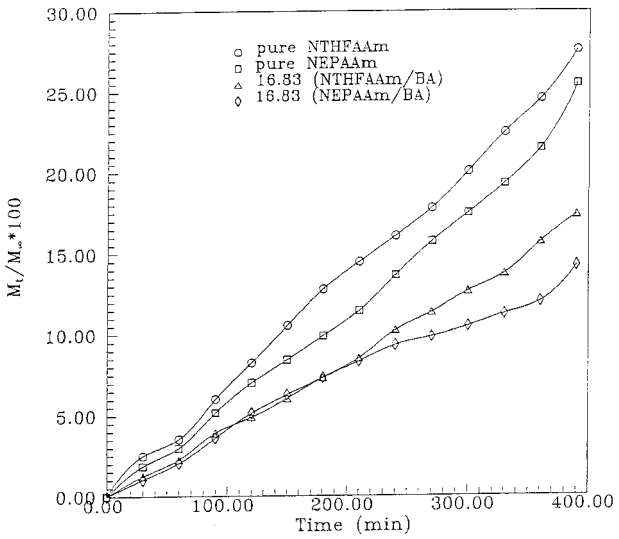


Figure 9 Drug-release versus time curve for CV-loaded gels at 20°C: (○) pure NTHFAAm; (□) pure NEPAAm; (△) NTHFAAm/BA = 16.83; (◇) NEPAAm/BA = 16.83.

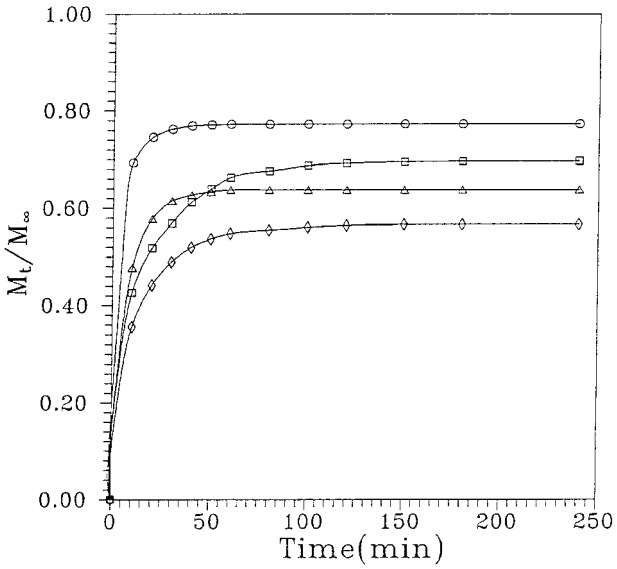


Figure 11 Effect of BA content on caffeine released during deswelling (37°C): (○) pure NEPAAm; (□) NEPAAm/BA = 24.75; (△) NEPAAm/BA = 22.31; (◇) NEPAAm/BA = 16.83.

does not reach 100%. This implies that the caffeine is not completely released; instead, a portion is entrapped within the gel. This occurrence supports the notion that a water pocket is formed in the collapsed gel. No significant amount of caffeine is released after 60 min, while the gel continuously deswells over a period of 240 min. This might be due to the two-step deswelling kinetic, as described above. Park and Hoffman reported that caffeine molecules located in the porous region of the gel may be squeezed out quickly or trapped in water pockets as the gel collapses.[21] However, water molecules will still be released through the micropores, which form during the densification of the gel.

CONCLUSIONS

Hydrogen bonding interactions between amide groups in the side chains and water molecules play an important role in the exertion of the major hydration force of the tested networks at lower temperatures. The side groups of the gel networks at undergo intermolecularly or intramolecularly hydrophobic interactions at higher temperatures.

The water content of poly(NEPAAm-*co*-BA) and poly(NTHFAAm-*co*-BA) gels during the deswelling process is affected by (1) gel thickness, (2) hydrogel compositions, and (3) amount of crosslinking agent. A thicker gel has a higher possibility of trapping water in the collapsed gel matrix. The more BA the copolymeric gel contains, the thicker the skin that forms. This result leads to reduction of the water content. As more crosslinking agents are contained in the gel, the higher crosslinking degree will restrict the relaxation of polymeric chains in the aqueous solution and lower the water content.

The experiment of CV release from different hydrogel compositions indicates that the more hydrophobic group the gel contains, the faster the rate of CV diffusion. The hydrophilicity of the side chain also contributes a great concentration gradient of drug dispersed in the swollen gel state and then leads to fast diffusion in the aqueous solution.

During the gel deswelling process, it can be seen that the fractional release does not reach 1.0. This behavior supports the idea that a water pocket is formed in the collapsed gel.

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