Thermoreversible Hydrogel. XVII. Investigation of the Drug Release Behavior for [*N*-Isopropylacrylamide-*co*-trimethyl acrylamidopropyl ammonium iodide-*co*-3-dimethyl (methacryloyloxyethyl) ammonium propane sulfonate] Copolymeric Hydrogels

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ABSTRACT: A series of copolymeric hydrogels were prepared from various molar ratios of *N*-isopropylacrylamide (NIPAAm), trimethyl acrylamidopropyl ammonium iodide (TMAAI), and 3-dimethyl (methacryloyloxyethyl) ammonium propane sulfonate (DMAPS). Results showed that the swelling ratios of these copolymeric hydrogels increased with an increase of TMAAI content. The drug release behavior of the ionic thermosensitive hydrogels related to their ionicity and drug types. Results indicated that the release ratio of caffeine in the hydrogels was not affected by the ionicity of hydrogels, but increased with increasing of the swelling ratio. The anionic solute (phenol red) strongly interacted with cationic hydrogel (very large K_d), so the phenol red release ratio in cationic gels was very low. On the other hand, CV was adsorbed only on the skin layer of the cationic hydrogel because of the charge repulsion, and released rapidly. Therefore the release ratio was highest for cationic hydrogel to cationic drug. In addition, the partition coefficients (K_d) and the drug delivery behavior of the present gels were also investigated. © 2002 Wiley Periodicals, Inc. J Appl Polym Sci 86: 1592–1598, 2002

Key words: thermoreversible hydrogels; zwitterionic sulfobetaine; cationic polyelectrolyte gels; drug release; drug delivery

INTRODUCTION

Hydrogels are three-dimensional hydrophilic polymer networks that are capable of imbibing large amounts of water. Because of the presence of physical or chemical crosslinks, entanglements, or crystalline regions, hydrogels are insoluble in water. Poly(NIPAAm) hydrogel in aqueous solution exhibits a rapid and reversible hydration–dehydration change, in response to small temperature changes around its lower critical solution temperature (LCST)[1] because isopropyl groups in the poly(NIPAAm) side chain form a hydrophobic aggregation in water, resulting in a phase separation above the LCST. When a swelling poly(NIPAAm) hydrogel is immersed in water above the LCST, deswelling immediately starts at the gel surface. On the contrary, poly(NIPAAm) gel becomes hydrophilic when immersed in water below the LCST.

Polyelectrolyte gels change their structure and physical properties in response to conditions of their surrounding environment, including pH, temperature, solvent composition, buffer composition, ionic strength, pressure, electromagnetic radiation, and photoelectric stimulus. Based on these characteristics, they can be widely applied in biomaterials such as for controlled drug release and delivery systems,[2–6] artificial muscles,[7] biosensing membranes, separations, and adsorptive materials.[8–10]

Hydrogel drug delivery systems have attracted significant attention recently. In addition to their inertness and good biocompatibility, the ability of hydrogels to release entrapped drugs in an aqueous medium, and the ease of regulating such drug release by controlling water swelling and crosslinking density, make hydrogels particularly suitable as drug carriers in the controlled release of pharmaceuticals.[11] The permeability and release rate of drugs are influenced by the type of releasing agent and the water content in the hydrogels.[12] Despite the high water content of the hydrogels, the systems may also be used for the release of drugs that are poorly soluble in water. Solute transport through a polymer membrane is through either the pore or the partition mechanism. In the pore mechanism, the solute diffuses through the water-filled pores and in the partition mechanism, the solute transport is presumed to occur by a process involving

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the dissolution of the solute within the polymer followed by the diffusion through the membrane.[13]

A series of NIPAAm, TMAAI, and DMAPS copolymeric hydrogels were prepared and their swelling kinetics were investigated in our previous study.[14] The results showed that the swelling ratios of NIPAAm/TMAAI/DMAPS copolymeric gels increased with an increase of TMAAI content: the higher the TMAAI content, the greater the affinity of the hydrogels toward water, and the higher the gel-transition temperature of the copolymeric gels. In saline solution, results showed that the swelling ratio of pure NIPAAm gel did not significantly change with an increase of the salt concentration until the salt concentration was greater than 0.5*M*. In addition, the copolymer gels exhibited polyelectrolytic behavior under lower salt concentration (10^{-5}–10^{-1} *M*), exhibited a nonionic gel (like NIPAAm) behavior at the salt concentration from 0.1 to 0.5*M*, and showed antipolyelectrolytic behavior (polyzwitterionic effect) at salt concentrations over 0.5*M*.

The investigation of the drug release behavior and drug delivery behaviors as well as the partition coefficients of various drugs on these copolymeric hydrogels constitute the main purpose of this study.

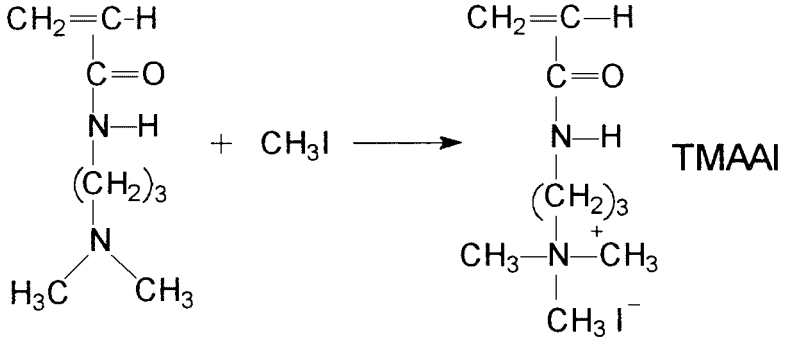
EXPERIMENTAL

Materials

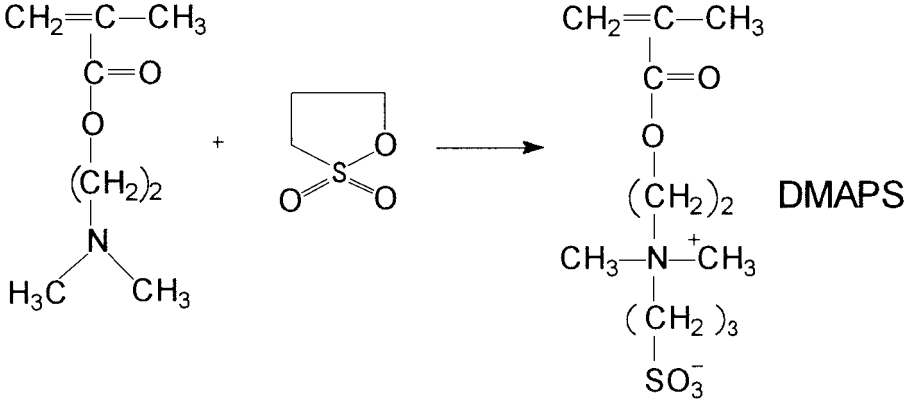
N-Isopropylacrylamide (NIPAAm) (Wako Pure Chemical, Tokyo, Japan) was recrystallized in *n*-hexane before use. *N,N*-(3-Dimethylaminopropyl) acrylamide (DMAA), dimethyl amino ethyl methacrylate (DMAEMA), and propane sultone (PS) were purchased from Tokyo Kasei Chemical Industry (Japan). Methyl iodide and the accelerator *N,N,N′,N″*-tetramethylethylenediamine (TEMED) were obtained from Fluka Chemie (Buchs, Switzerland). The crosslinking agent *N,N′*-methylenebisacrylamide (NMBA) was obtained from Sigma Chemical (St. Louis, MO). The initiator ammonium persulfate (APS) was purchased from Wako Pure Chemical. All solvents and other chemicals were of analytical grade.

Synthesis of monomers

Synthesis of the cationic monomer trimethyl (acrylamidopropyl) ammonium iodide (TMAAI), from DMAA, methyl iodide, and butanone as a solvent in a 0°C ice bath for 7 h, was reported in our previous study. Yield: 96.6%.[15]



Synthesis of the zwitterionic monomer 3-dimethyl (methacryloyloxyethyl) ammonium propane sulfonate (DMAPS), from DMAEMA, PS, and acetone as a solvent in a 0°C ice bath for 4 h, was also reported in our previous study. Yield: 98.7%.[16]



Preparation of hydrogels

The hydrogels used were prepared by free-radical polymerization in deionized water (18.3 MΩ cm^{-1}). The hydrogels were synthesized from NIPAAm (88 mol %), TMAAI, and DMAPS with various molar ratios: 5 mol % NMBA, 1 mol % APS, and 1 mol % TEMED, based on total monomers, were used as a crosslinker, an initiator, and a coinitiator, respectively. The reaction was processed in the space provided by a silicon spacer between two glass plates. Polymerization was carried out for 1 day. After the gelation was completed, the gel membrane was cut into disks (8 mm in diameter) and immersed in an excess amount of deionized water for 3 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 for 2 days. The sample codes, compositions, and fundamental properties of the gels are listed in Table I.

Determination of equilibrium swelling ratio

To understand the equilibrium swelling ratio of the different ionic thermosensitive hydrogels, the dried gels were immersed in an excess amount of deionized water at different temperatures (25–65°C) until swelling equilibrium was attained. The weight of the wet sample (W_t) was determined after removing the surface water by blotting with filter paper. The dry weight (W_0) was determined after drying the gel in a vacuum oven for 2 days. The swelling ratio (SR) was calculated from the following equation:

$$\mathrm{SR} = \left[\frac{W_t - W_0}{W_0}\right] \tag{1}$$

Partition coefficient determination

Partition coefficients were determined by the solution depletion technique using a UV-spectrophotometer to measure the solution concentration. The hydrogels that had been preswollen in deionized water were allowed to achieve equilibrium in a drug solution at 25–45°C. The partition coefficient K_d was calculated from a decrease in the solute concentration of the external solution, represented by the following equation[2]:

$$K_d = \frac{(C_0 - C_s)V_s}{C_s V_m} \tag{2}$$

where C_0 and C_s are the initial and final solute concentrations in solution, V_s is the solution volume, and V_m is the hydrogel volume.

TABLE I
Equilibrium Swelling Ratio at Different Temperatures and Compositions of the Hydrogels

Sample code	NIPAAm (mol %)	TMAAI (mol %)	DMAPS (mol %)	Yield (%)	Equilibrium swelling ratio (g/g)									
					Deionized water					0.9 wt % NaCl solution				
					15°C	25°C	35°C	45°C	55°C	65°C	15°C	25°C	35°C	45°C	55°C	65°C
Poly (NIPAAm)	100	0	0	95.54	9.81	8.12	0.66	0.22	0.17	0.17	7.32	5.99	0.40	0.21	0.13	0.12
T0	88	0	12	96.10	11.00	9.24	5.28	2.25	1.17	0.83	7.68	6.61	4.13	2.62	1.41	0.86
T2.4	88	2.4	9.6	97.39	17.06	15.21	11.70	8.51	5.11	3.14	7.98	6.90	4.83	3.11	1.99	1.25
T6.0	88	6.0	6.0	96.63	23.77	22.25	19.38	17.10	13.78	9.98	9.17	8.00	6.02	4.17	2.84	1.88
T9.6	88	9.6	2.4	95.40	31.77	30.48	28.29	25.57	22.71	20.62	9.77	8.66	7.06	5.75	4.14	3.32
T12	88	12	0	96.81	36.52	35.45	33.81	32.52	30.98	28.59	11.02	10.27	8.43	6.81	5.53	4.27

Drug release and delivery experiments

The solutes used in drug release and drug delivery experiments were caffeine (MW = 194), vitamin B12 (MW = 1355), crystal violet (MW = 408), and phenol red (MW = 354). The dry gels were equilibrated in drug solution at 25°C for 1 day to load drug into the gels. The drug release experiments were carried out by transferring previously incubated drug gels into 10 mL deionized water at 35°C. The gels were repeatedly removed and transferred into 10 mL fresh deionized water at fixed time intervals.

For the drug delivery experiments, the dry gels were equilibrated in drug solution at 25°C for 1 day to load drug into the gels. The drug delivery experiments were carried out by transferring previously incubated drug gels into 10 mL deionized water at 35°C. The gels were repeatedly removed and transferred into 10 mL deionized water at fixed time intervals over a period of 100 min. The gels were then reimmersed into the original drug solution for 1 day and the release experiment was repeated. The above steps were repeated to perform the drug delivery tests. The released drugs were analyzed by ultraviolet spectrophotometer (Jasco V530; Jasco, Tokyo, Japan).

RESULTS AND DISCUSSION

Effect of comonomer on the swelling ratio

The equilibrium/swelling ratios for the present copolymeric hydrogels are shown in Table I. According to Flory's swelling theory for ionic gels, the following equation was given[17]:

$$Q^{5/3} = \left[\frac{(i/2V_\mu S^{0.5})^2 + (1/2 - \chi_1)}{V_1}\right] \Big/ (\nu_e/V_0) \quad (3)$$

where Q is the equilibrium swelling ratio, i/V_μ is the fixed charge density in the hydrogel, S is the ionic strength of external solution, $(\frac{1}{2} - \chi_1)/V_1$ is the affinity of the hydrogel, and ν_e/V_0 is the crosslinking density of the hydrogel. Thus, from eq. (3), it is clear that the swelling ratio has a relation to the charge density of the hydrogel, the crosslinking density, and the affinity of the gel for water. The crosslinking density and ionic strength of external solution in these hydrogel systems were fixed; thus, the swelling ratio is affected only by the charge density and the affinity of the hydrogels.

The results shown in Table I indicate that the swelling ratios for the present copolymeric gels in deionized water were in the order of T12 > T9.6 > T6.0 > T2.4 > T0. In other words, the greater the TMAAI contents, the higher the swelling ratios for the present copolymeric gels, given that the molecular chains of TMAAI with quaternary ammonium group would bear positive charges. This results in chain expansion in deionized water because of charge repulsion; that is, the hydrogel could absorb a lot of water. However, DMAPS is a hydrophilic zwitterionic monomer with an inner salt structure from interaction of the sulfonate group (SO_3^-) with the quaternary ammonium group (R_4N^+). This inner salt structure would not bear net charges in deionized water, such that the i/V_μ term is zero. The swelling ratio for the copolymeric hydrogel that contains DMAPS monomer depends only on the hydrophilic group (T0). As a result, the improvement of swelling ratios for these hydrogels is mainly attributed to the amount of TMAAI in the gels.

The results shown in Table I also indicate that the swelling ratios for the present copolymeric gels were lower in 0.9 wt % NaCl solution than in deionized water. For poly(NIPAAm) gel, because of the Donnon effect, the swelling of the gel is slightly lower in 0.9 wt % NaCl solution. For ionic hydrogels, this is attributed to the fact that the positive charges on polymeric side chains could be neutralized by the anion (Cl^-). Thus the electrostatic repulsion in the ionic hydrogel decreases and the swelling ratio also decreases.

Effect of the interactive force between solute and gel on the partition coefficient of solute in ionic gels

One of the changing factors of the solute diffusion behaviors in gels is interactive force. Kim[18] found that there is a stronger interactive force between drugs and gels when partition coefficients K_d are above 1 by hydrophilic carbohydrate solute and hydrophobic steroid solute experiments. For chemical potential energy, solutes tend to stay in the solution phase because the partition coefficients are below 1. The results of the effect of the interactive force between solute and gel on the K_d of solute in the gels are shown in Table II. For caffeine and vitamin B12 (MW = 1355) solution, the K_d values in the present gels are in the order of T12 > T9.6 > T6.0 > T2.4 > T0. This indicates that the interactive force between hydrogels and nonionic drugs, such as caffeine and vitamin B12, increases with an increase of swelling ratio. This is because the larger the swelling ratio, the more solutes could be contained in the gel. For a cationic drug solute such as CV, the interactive force between the drug solute and cationic hydrogel is affected by electrostatic repulsion. The CV solute does not easily load into cationic gels, so the K_d of the solutes in the gel is very small and the K_d value decreases with an increase in TMAAI content. However, the K_d value between CV and T0 gel is greater than that for cationic gels. Because the inner ionic crosslinked network of DMAPS in the T0 gel can be opened by counterions in the ionic drug, more solute can combine with T0 gel. For example, the K_d of CV in T12 gels is 0.07, but in T0 gels is 4.14 for 25°C, respectively. For anionic solute (phenol red), because

TABLE II
Partition Coefficient (K_d) of Various Solutes in the Ionic Hydrogel at Different Temperatures

Temperature	Sample code	Partition coefficient (K_d)			
		Caffeine	Crystal violet	Phenol red	Vitamin B12
25°C	T0	0.33	4.14	2.52	0.76
	T2.4	0.70	0.45	11.08	0.79
	T6.0	0.93	0.22	15.53	0.89
	T9.6	1.20	0.14	19.33	1.11
	T12	1.26	0.07	22.67	1.21
35°C	T0	0.31	5.59	5.96	0.73
	T2.4	0.60	1.26	16.18	0.75
	T6.0	0.85	0.52	19.06	0.85
	T9.6	1.08	0.41	23.87	1.12
	T12	1.19	0.10	25.92	1.16
45°C	T0	0.24	6.39	10.31	0.66
	T2.4	0.41	1.28	23.26	0.70
	T6.0	0.53	0.68	24.38	0.79
	T9.6	0.62	0.59	28.31	0.99
	T12	0.90	0.46	29.66	1.03

the drug and the hydrogel have different charges, the interactive force between the drug solute and the hydrogel with the different charge is strongly affected by electrostatic attraction. Thus the K_d of phenol red in cationic gels is very large and increases with increasing TMAAI content. Thus, the ionicity of solutes profoundly affects the release behavior of solute in the gels.

The results in Table II also show the partition coefficients at different temperatures. For nonionic solute, caffeine, and vitamin B12, the partition coefficients decrease with increase in temperature, which is attributed to the fact that caffeine and hydrogel combine with hydrogen bonding. With increasing temperature, the hydrogen bonding between them is easily weakened, and thus the interactive force between solute and gel decreases. For ionic solutes, such as CV and phenol red, however, the partition coefficients increase with increase in temperature. Prausnitz and coworkers[19] reported that the effect of rising temperature is to increase the partition coefficient between polyelectrolyte hydrogel and ionic solute.

Drug release

The solutes used in drug release and delivery experiments were nonionic caffeine and vitamin B12, cationic CV, and anionic phenol red. The concentration of all drug solutions was 300 ppm. The dry gels were equilibrated in drug solution at 25°C for 1 day to load drug into the gels.

Figure 1 shows that the release ratio of caffeine in the hydrogels is proportional to the swelling ratio of the gels. The release ratios for the presented copolymeric gels in deionized water at 35°C are in the order T12 > T9.6 > T6.0 > T2.4 > T0. Because of the chain

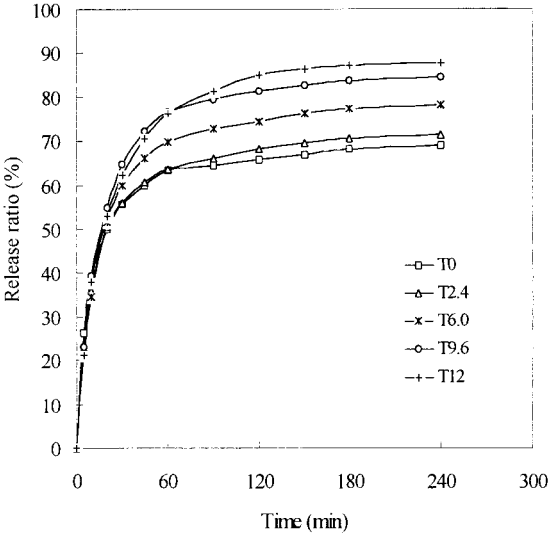


Figure 1 Caffeine release profile during swelling at 25°C and deswelling at 35°C for the presented gels in deionized water.

expansion of cationic hydrogels in deionized water, the hydrogels can absorb a larger amount of unbound water, thus allowing greater solute transport. Therefore the drug release ratio of T12 gel is the highest. Figure 2 shows the caffeine release behavior of the presented copolymeric gels in 0.9 wt % NaCl solution at 35°C. Because the positive charges on polymeric side chains are neutralized by the anions (Cl^-), the volume of the gel decreases and the pores on the surface will shrink. Hence, the caffeine release ratios are lower in 0.9 wt % NaCl solution than those in deionized water. Figure 3 shows the vitamin B12 release of the gels. By comparing Figures 1 and 3, one

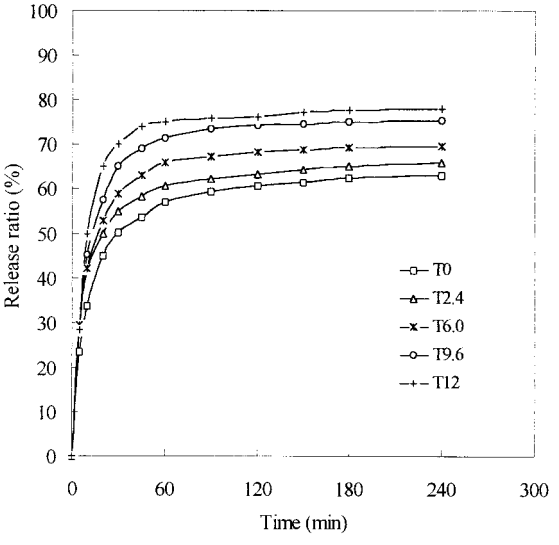


Figure 2 Caffeine release profile during swelling at 25°C and deswelling at 35°C for the presented gels in 0.9 wt % NaCl solution.

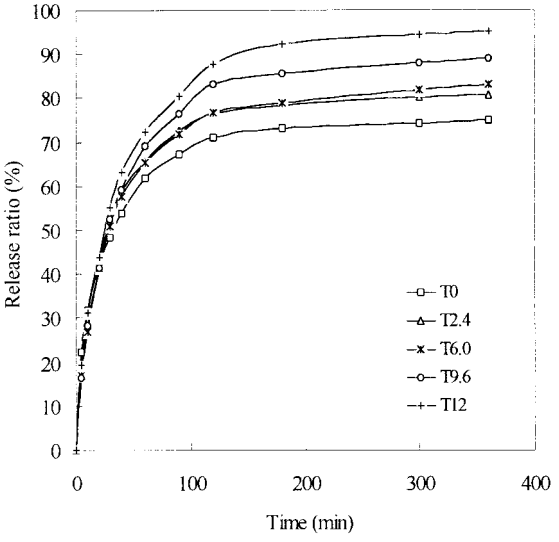


Figure 3 Vitamin B12 release profile during swelling at 25°C and deswelling at 35°C for the presented gels.

finds that the molecular weight of caffeine (MW = 194) is smaller than that of vitamin B12 (MW = 1355), but the release ratio of the gels for vitamin B12 is greater than that of caffeine. The reason for this phenomenon can be explained, given that vitamin B12 has a larger molecular size and vitamin B12 molecules could not enter the smaller pores. Thus vitamin B12 can easily release out of the gel.

The results of anionic phenol red solutes releasing from the gels in water and ethanol are shown in Figures 4 and 5, respectively. When the charges of the drug solute and the hydrogel are opposite, electrostatic attraction exists between them. Therefore, the phenol red solutes strongly bind in the cationic gels (T2.4, T6.0, T9.6, and T12) and are difficult to release

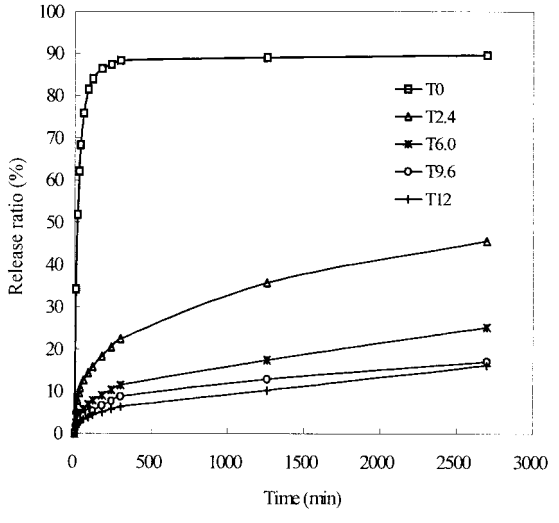


Figure 4 Phenol red release profile during swelling at 25°C and deswelling at 35°C for the presented gels in deionized water.

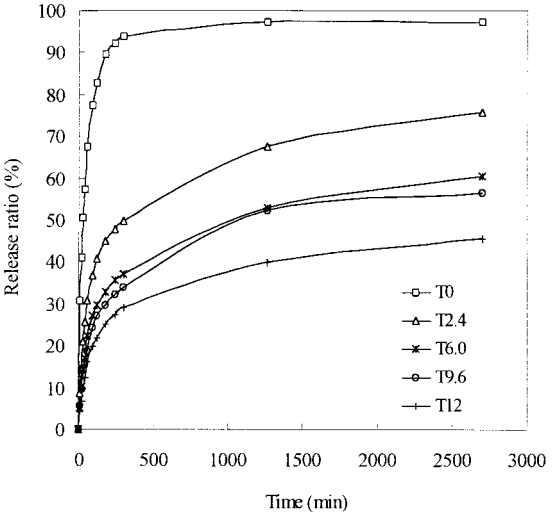


Figure 5 Phenol red release profile during swelling at 25°C and deswelling at 35°C for the presented gels in ethanol.

out of the gel accompanied with unbound water. Thus the release ratios are lower and decrease with an increase of TMAAI content. For the T0 gel, the interactive forces between phenol red and T0 gel are smaller than those for cationic gels, so the release ratio is the highest. By comparing Figures 4 and 5, one can observe that the release ratio for the presented copolymeric gels are in the order T0 > T2.4 > T6.0 > T9.6 > T12, although the release ratios in ethanol are higher in deionized water. Because the solubility of phenol red is better in ethanol, the phenol red can easily release from the gels in ethanol. The results of cationic CV solutes releasing from cationic gels are shown in Figure 6. When the charges of the drug solute and hydrogel are the same, the drug release ratio of gels is higher, given the charge repulsion that

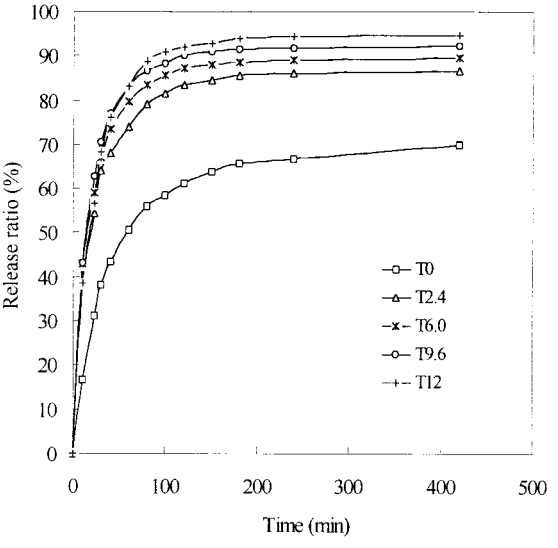


Figure 6 CV release profile during swelling at 25°C and deswelling at 35°C for the presented gels.

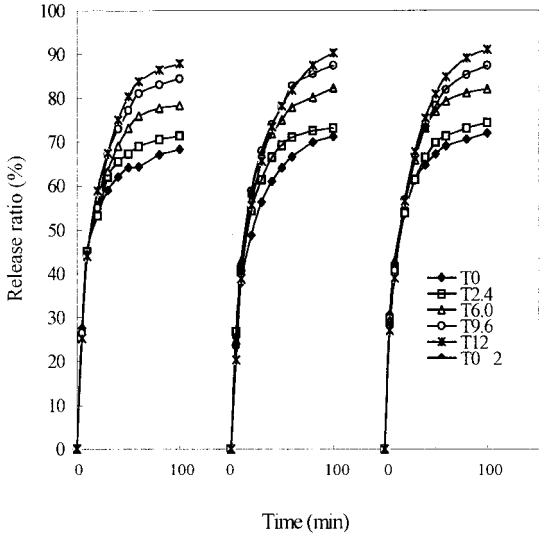


Figure 7 Caffeine delivery profile during swelling at 25°C and deswelling at 35°C.

exists between the drug solutes and gels; thus, the solute is not easily loaded into the hydrogel and is easily released from the gels.

Drug delivery

The drug delivery tests of the copolymeric gels were performed by immersing the dried gels or deswollen gels into drug solution at 25°C, to load drug, and at 35°C, to release drug. From the preceding discussion, it is clear that the gels behave with thermosensitive properties in different temperatures and respond to the volume change of the gels. We applied the thermosensitivity of the gels to follow the drug delivery test for these copolymeric gels. Figure 7 shows the results of caffeine delivery over a long period of time between 25 and 35°C for the present gels. The amount of drug released at the first-time release is in the order T12 > T9.6 > T6.0 > T2.4 > T0. This result is in the same order as that for the swelling ratios of these gels. As the gel released at the second time, the released-drug amounts were higher than those at the first time. The released amount reached a constant value at the third-time release; that is, the gels could reach a steady delivery behavior after three delivery cycles.

CONCLUSIONS

The drug release behavior of the ionic thermosensitive hydrogels is related to their ionicity and drug types. Results show that the release ratio of caffeine in the hydrogels is not affected by the ionicity of hydrogels, but increases with increasing of the swelling ratio. The anionic solute (phenol red) strongly interacts with cationic hydrogel (very large K_d), so the phenol red release ratio in cationic gels is very low. On the other hand, CV is adsorbed only on the skin layer of the cationic hydrogel (low K_d) because of the charge repulsion, and releases rapidly. Therefore the release ratio is highest for cationic hydrogel to cationic drug. In addition, the gels could reach a steady delivery behavior after three delivery cycles.

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