Thermoreversible Hydrogels. XV. Swelling Behaviors and Drug Release for Thermoreversible Hydrogels Containing Silane Monomers

WEN-FU LEE, WEN-YANG YUAN

Department of Chemical Engineering, Tatung University, Taipei 104, Taiwan, Republic of China

Received 28 February 2001; accepted 29 May 2001

ABSTRACT: Three series of thermosensitive copolymeric hydrogels were prepared from [3-(methacryloyloxy)propyl]trimethoxysilane (MPTMOS), [2-(methacryloyloxy)ethoxy]-trimethylsilane (METMS), and (methacryloyloxy)trimethylsilane (MTMS), referred to as the silane monomer, and *N*-isopropylacrylamide (NIPAAm) by solution polymerization. The influence of the structures and amounts of silane monomers on the swelling and drug-released behaviors were studied. The results showed that, because of the hydrophobicity of the silyl group, the more silane monomers in the copolymeric hydrogels the lower was the swelling ratio of the gels. The hydrophobicity of the silyl group affected the swelling mechanism, which resulted from the non-Fickian diffusion for the gels. The copolymeric gels clearly exhibited gel transition temperatures. The copolymeric hydrogels could be applied to a drug-release and drug-delivery system. The delivery amount would approach a steady state after three cycle operations of delivery. The gels also showed an on–off switch behavior on drug release depending on the temperature, and the gels released more CV with the gels in a swollen state. © 2002 Wiley Periodicals, Inc. J Appl Polym Sci 84: 2523–2532, 2002

Key words: thermoreversible hydrogels; *N*-isopropylacrylamide; silane monomer; drug delivery

INTRODUCTION

Hydrogels undergo reversible and discontinuous volume changes in response to changes in the environmental physical and chemical conditions such as solvent composition, temperature, salt concentration, and pH.[1–5] The volume phase transition of gels is known to result from the interactions between the polymer chain and solvent molecules at shrunken and swollen states. Concerning interactions for gels, van der Waals interaction, hydrogen bonding, hydrophobic interaction, and ionic interaction have been considered to explain the phase transition and swelling behavior.[6,7]

It is well known that the poly(*N*-isopropylacrylamide) [poly(NIPAAm)] hydrogel is a thermoreversible hydrogel and exhibits a critical gel transition temperature (CGTT) around 32°C in an aqueous solution, that is, the poly(NIPAAm) hydrogel swells and shrinks below and above the CGTT. The poly(NIPAAm) hydrogel is of interest for its fundamental properties: Many studies have focused on the field of controlled drug delivery,[8,9] regulation of the activity of enzymes and cells,[10,11] and thermocontrolled chromatography.[12]

In recent years, the applications of poly(NIPAAm), modified by functional compounds, has

Correspondence to: W.-F. Lee (wflee@ttu.edu.tw).

Contract grant sponsor: National Science Council of the Republic of China; contract grant number: NSC-89-2216-E-036-003.

Journal of Applied Polymer Science, Vol. 84, 2523–2532 (2002)

attracted much attention. For instance, Kurihara et al. reported on the preparation of a hydrogel membrane by graft copolymerization of NIPAAm onto poly(vinyl alcohol) (PVA-*g*-NIPAAm) and the temperature dependence of permeation through the PVA-*g*-NIPAAm membrane.[12,13] Irie et al. reported on the synthesis of photosensitive gels by incorporating photosensitive triphenylmethane leucocyanide derivatives, which were prepared, using a glass filter 75 and [3-(methacryloyloxy)propyl]trimethoxysilane (MPTMOS), into polyacrylamide gels and poly(NIPAAm) gels.[14,15]

A new class of materials, inorganic–organic hybrid sol–gel, has attracted much attention in material science.[16] The swelling and adsorption behavior of poly(NIPAAm)–SO_2 hybrid gels derived from copolymerization of NIPAAm and MPTMOS was investigated by Kurihara et al.[17] Their results showed that the phase-transition temperature of the hybrid gel decreased with an increasing amount of MPTMOS content. In this article, three silane monomers, MPTMOS, [2-(methacryloyloxy)ethoxy]trimethylsilane (METMS), and (methacryloyloxy)trimethylsilane (MTMS), were copolymerized with NIPAAm and *N,N′*-methylenebisacrylamide (NMBA) as a crosslinking agent to prepare three series of thermosensitive copolymeric hydrogels and to investigate their fundamental properties and swelling behavior at different temperatures. In addition, the potential for the three copolymeric hydrogels to be used for a drug-delivery system and on–off switch behavior was also assessed.

EXPERIMENTAL

Materials

NIPAAm (Fluka Chemical Co., Switzerland) was recrystallized in *n*-hexane before use to remove the inhibitor. MPTMOS (Acros, Belgium), METMS (Aldrich, St. Louis, MO), and MTMS (Aldrich) were used as received. NMBA (Sigma Chemical Co., St. Louis, MO), as a crosslinking agent, and *N,N,N′,N′*-tetramethylethylenediamine (TEMED) (Fluka Chemical Co.), as an accelerator, were used as received. Ammonium peroxodisulfate (APS) and 2,2′-azobisisobutyronitrile (AIBN) (Wako Pure Chemical Co. Ltd., Osaka, Japan), as an initiator, was further purified by recrystallization. Dimethyl sulfoxide (DMSO), as a solvent, was used as received.

Preparation of Copolymeric Hydrogels

NIPAAm and silane monomers, such as MPTMOS, METMS, and MTMS, with various molar ratios (NIPAAm/silane monomer = 97/3, 93/7, and 90/10) and 3 mol % NMBA, based on the total monomer concentration, were dissolved in 10 mL DMSO. To this solution, 0.2 mol % AIBN as an initiator was added, and the mixture was immediately injected into the space between two glass plates. The gel membrane thickness was adjusted with a silicone spacer between the two glass plates. Polymerization was carried out at 75°C with shaking (75 rpm) in a water bath for 4 days. After the gelation was completed, the gel membrane was cut into disks, 10 mm in diameter, and then immersed in 200 mL 1.0*N* $HCl_{(aq)}$ as a catalyst for 6 days only for NIPAAm/MPTMOS copolymeric hydrogels [change of the $HCl_{(aq)}$ once every 2 days]. All gels were then transferred into excess acetone to remove the unreacted monomers and DMSO. After the above treatment, the swollen gels were dried at room temperature for 1 day and then further dried in a vacuum oven for 1 day.

Measurement of Swelling Ratio

The preweighed dried gels (W_d) were immersed in an excess of deionized water at 25°C until swelling equilibrium was attained. Each gel was then removed from the water bath, tapped with filter paper to remove excess surface water, and weighed as the wet weight (W_w). The swelling ratio (Q) was calculated from the following equation:

$$Q = \frac{W_w - W_d}{W_d} \tag{1}$$

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 as M_∞. The following equation can be used to calculate the diffusion coefficient D for $M_t/M_\infty \leq 0.8$ (ref. 18):

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

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

Physical Properties Measurement

The gel strength of these samples was measured by a uniaxial compression experiment with a universal tester (Lloyd LRX). Equation (3) can be used to calculate the shear modulus (G)[19–21]:

$$\tau = F/A = G(\lambda - \lambda^{-2}) \quad (3)$$

where τ is the compression stress; F, the compression load; A, the cross-sectional area of swollen gels; and λ, the compression strain (L/L_0). At low strains, a plot of shear stress versus $-(\lambda - \lambda^{-2})$ would yield a straight line whose slope is the shear modulus (G). The effective crosslink density (ρ) can then be evaluated from the shear modulus and polymer volume fraction (ν_2) as follows:

$$\rho = \frac{G}{(\nu_2^{1/3} RT)} \quad (4)$$

where R is the gas constant, and T, the absolute temperature. The value of ν_2 was calculated from the ratio of the volume of the dry gel sample to that of the swollen gels.

Caffeine-delivery Experiment

The dry gels were equilibrated in 30 mg caffeine/10 mL of deionized water at 25°C for 2 days to load caffeine into the gels. The caffeine-delivery experiments were carried out by transferring previously incubated drug gels into 10 mL of deionized water at 37°C. The gels were repeatedly removed and transferred into 10 mL fresh water at each fixed time interval. When the caffeine was not released from the gels any more (about 2 h), the gels were reimmersed into the original caffeine solution for 2 days. Then, the release experiment was repeated. The above steps were repeated to perform the drug-delivery tests. The released caffeine was analyzed at 272 nm by an ultraviolet spectrophotometer (JASCO UV-530).

On–Off Switch Behavior

To load crystal violet (CV) into the gels, dry gels were equilibrated in the CV solution (10 mg/100 mL deionized water) at 25°C for 2 days. The CV-release experiments were carried out by transferring previous drug gels into the fresh deionized water. The CV-loaded gels were moved to the deionized water at 37 or 45°C (off-stage) for 2 h and then moved to the deionized water at 20°C (on-stage). The above step was repeated every 2 h. The released CV was analyzed at 561 nm by an ultraviolet spectrophotometer (JASCO UV-530).

RESULTS AND DISCUSSION

Poly(NIPAAm) gels swell (in the hydrophilic state) at low temperature and deswell (in the hydrophobic state) around 32°C. The hydrogels which were copolymerized by NIPAAm and some hydrophilic monomers increased the gel transition temperature above 32°C. On the contrary, the gel transition temperature decreases as the NIPAAm was copolymerized with the hydrophobic monomers. In this article, we introduced three hydrophobic monomers containing the silyl group into NIPAAm and investigated the thermosensitive behavior of these copolymeric hydrogels.

Characterization of NIPAAm/Silane Monomer Copolymeric Gels

Some characteristics of NIPAAm/silane monomer copolymeric gels with various feed compositions are shown in Table I. In this article, MPTMOS was chosen as a model monomer containing the trimethoxysilane group on the side chain. The trimethoxysilane group was hydrolyzed and condensed into the siloxane structure by hydrochloric acid. This process can make a gel more stable when the copolymeric gels swell in deionized water. Furthermore, the effect of the spacer between the carboxyl and silicon atoms in the silane monomers on the swelling behavior was investigated. The results in Table I indicate that the yields for all the gels are over 90%. The prepared gels are transparent because the NIPAAm and silane monomers are dissolvable in DMSO; the gelation is homogeneous in this polymerization system, so the gels had a transparent appearance.

Effect of Silane Monomer on the NIPAAm/Silane Monomer Copolymeric Hydrogels

The swelling ratios as a function of time for the NP, NE, and NT copolymeric gels at 25°C in deionized water are shown in Figures 1–3. According to Flory's swelling theory,[21] the following equation is given:

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

Table I Characterization of (NIPAAm/Silane Monomers) Copolymeric Hydrogels

Sample Code	Silane Monomer	Feed Composition		Yield (%)	Equilibrium Swelling Ratio at 25°C (g/g)	Polymer Volume Fraction ν_2	Crosslinking Density ($\times 10^{-5}$ cm^3/mol)	Shear Modulus G (g/cm^2)	χ
		NIPAAm	Si						
NP3	MPTMOS	97	3	92.6	1.79	0.388	1.749	322.45	0.683
NP7		93	7	93.5	1.17	0.426	2.183	415.18	0.711
NP10		90	10	91.2	0.99	0.493	2.406	480.35	0.765
NE3	METMS	97	3	94.3	8.59	0.112	1.615	197.35	0.531
NE7		93	7	94.0	7.44	0.127	2.027	257.58	0.537
NE10		90	10	92.1	6.52	0.135	2.335	302.75	0.540
NT3	MTMS	97	3	92.6	14.74	0.099	0.892	104.39	0.529
NT7		93	7	92.1	11.79	0.125	1.485	187.45	0.538
NT10		90	10	90.3	9.21	0.138	2.044	266.92	0.543

where $i/V\mu$ is the concentration of the fixed charge referred to the unswollen network; S, the ionic concentration in an external solution; $(½ - \chi_1)/V_1$, the affinity of the hydrogel with the solvent; and ν_e/V_0, the crosslinking density of the hydrogel. From the above equation, it is well known that the swelling ratio has a relation to the ionic osmotic pressure, the crosslinked density, and the affinity of the hydrogel for water. These copolymeric hydrogels were synthesized by the nonionic monomer, NIPAAm, and silane monomers, so the value of the $i/V\mu$ term is zero. Equation (5) can be rewritten as

$$Q^{5/3} = \left[\frac{(½ - \chi_1)}{V_1}\right]/(\nu_e/V_0) \qquad (6)$$

Hence, the factors that affect the swelling ratio of the copolymeric hydrogels are the affinity of the hydrogel for water and the crosslinking density. The affinity of the copolymeric gel for water is poor, because these three silane monomers are hydrophobic, which resulted in lower swelling ratios as more silane monomers were introduced into the copolymeric gels. In addition, the methoxysilane group is condensed to the siloxane structure by treatment with $HCl_{(aq)}$ for NIPAAm/MPTMOS (NP). This treatment makes the gel have more crosslinked structures and causes the molecular chains to be denser, so the swelling ratios for the gels containing more of the methoxysilane group are the lowest (NP3 > NP7 > NP10). The alkyl length of the ester group in

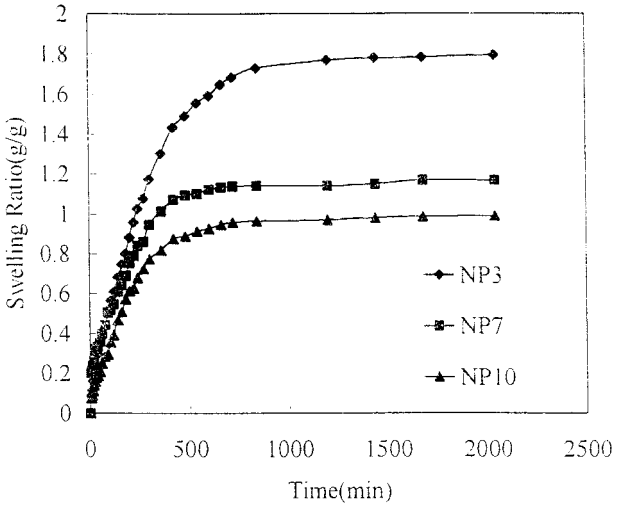

Figure 1 Swelling ratio as a function of time for NIPAAm/MPTMOS copolymeric hydrogels.

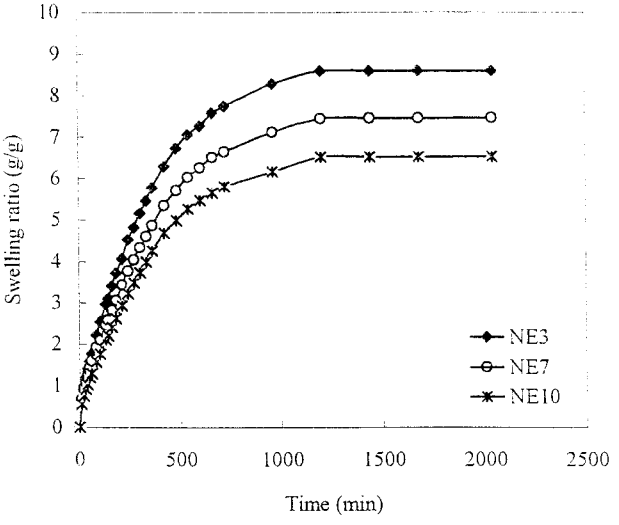

Figure 2 Swelling ratio as a function of time for NIPAAm/METMS copolymeric hydrogels.

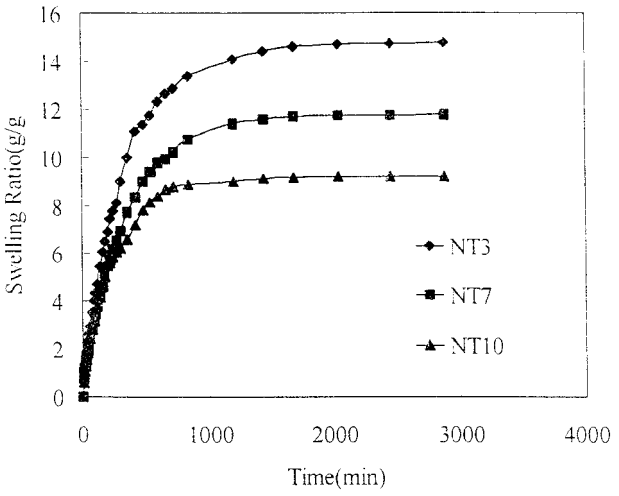

Figure 3 Swelling ratio as a function of time for NIPAAm/MTMS copolymeric hydrogels.

the silane monomers also affects the swelling ratios of the gels. The propyl group in MPTMOS shows more hydrophobicity than does the ethoxy group in METMS and without an alkyl group in MTMS. Hence, the swelling ratios for these three series of copolymeric hydrogels prepared were in the order NT > NE > NP (also see Table I).

Effect of Silane Monomer on Gel Strength

The gel strength can be accessed by the shear modulus (G) measured from the uniaxial compression experiment. The results shown in Table I indicate that the G values increase with an increasing amount of the silane monomer, that is, for the same composition gel system, the gel would become stronger when the amount of the silane monomer increases. This is because the silane monomer is a hydrophobic monomer. Hence, the swelling ratios for these gels decrease with increase of the added content of the silane monomer. This leads to a decrease of the swelling ratio of the gel and the increase of the gel strength. According to eq. (4), the effective crosslinking density (ρ) depends on the swelling ratio and shear modulus at a constant temperature. For the NP, NE, and NT gel series, the ρ values increase with increase of the silane monomer, such as NP10 > NP7 > NP3, and also increase in the order NP > NE > NT. From the above discussion, the gel properties such as Q, G, and ρ are dependent mainly upon the structure and content of the silane monomer in the system.

Effect of Silane on Copolymer–Water Interaction Parameter χ

The total copolymer–water interaction parameter χ can be calculated according to the Flory–Rehner equation[21–24]:

$$\pi = \pi_{mix} + \pi_{elas} + \pi_{ion} + \pi_{elec} \quad (7)$$

The osmotic pressure π of a hydrogel during swelling is given as the sum of the pressures due to polymer–solvent mixing (π_{mix}) and due to deformation of network chains to a more elongated state (π_{elas}). For the gels with ionizable groups, the terms π_{ion} and (π_{elec} are included; π_{ion} represents osmotic pressure arising from a concentration difference of ions between the gel and solution, while π_{elec} accounts for the electrostatic interactions of charges on the polymer chains. In the present gel systems, the terms π_{ion} and π_{elec} can be ignored due to the gels containing no ionizable groups. Hence, eq. (7) can be given by

$$\pi = \pi_{mix} + \pi_{elas} \quad (8)$$

According to the Flory–Huggins theory, π_{mix} is given by

$$\pi_{mix} = RT/V_1[\ln(1 - \nu_2) + \nu_2 + \chi\nu_2^2] \quad (9)$$

where R is the gas constant; T, the absolute temperature; V_1 (cm^3/mol), the molar volume of water $V_1 = 18.05 + 3.6 \times 10^{-3}$ (T-298); and ν_2, the volume fraction of the copolymer in the hydrogel. To describe the elastic contribution π_{elas} to the swelling pressure, the simplest affine network model used to describe the behavior of our gels. π_{elas} can be given by eq. (10):

$$\pi_{elas} = RT\rho(\nu_2^{1/3} - 0.5\nu_2) \quad (10)$$

Hence, if a gel swells in the thermodynamic equilibrium state, eq. (8) can be given by eq. (11):

$$\ln(1 - \nu_2) + \nu_2 + \chi\nu_2^2 + \rho V_1(\nu_2^{1/3} - 0.5\nu_2) = 0 \quad (11)$$

The polymer–solvent interaction parameters accounts for free-energy changes caused by the mixing process. Values of χ are usually between 0 and 1, with an increasing of χ indicating poorer solvents for the polymer and thus reduced degrees of polymer swelling. It is impor-

Table II Initial Diffusion Coefficient of Water, *D*, and Kinetic Exponent, *n*, and Characteristic Constant, *K*, of Water Penetrated Through (NIPAAm/Silane Monomers) Copolymeric Gels at 25°C

Sample Code	Kinetic Exponent n	Characteristic Constant K	Diffusion Coefficient $D \times 10^7$ (cm^2/s)	Equilibrium Swelling Time (min)
NP3	0.47	0.06	0.63	840
NP7	0.45	0.05	0.44	660
NP10	0.42	0.04	0.18	660
NE3	0.38	0.15	0.48	1440
NE7	0.35	0.18	0.42	1440
NE10	0.33	0.19	0.47	1200
NT3	0.51	0.18	1.79	1680
NT7	0.45	0.16	1.41	1440
NT10	0.44	0.15	1.06	1440
N0	0.57	0.18	2.04	2040

tant to recognize that χ is not a constant for a given system but is a function of temperature and concentration.

The results shown in Table I indicate that the χ values increase with an increase of the silane monomer content in the NP, NE, and NT gels. This result explicitly indicates that the more silane content in the gel system the more water becomes a poorer solvent for the present copolymeric gels. The results also show that the χ values for NP gels are higher than are those for the NE and NT gels. This result also indicates that the NP gels possess stronger hydrophobicity and lower swelling ratios.

Investigation of Water Diffusion in Xerogels

To obtain a more quantitative understanding of the nature of the sorption kinetic for the present series gels, the initial swelling data were fitted to the following exponential heuristic equation[25,26]:

$$\frac{M_t}{M\infty} = kt^n \tag{12}$$

where k is a characteristic constant of the gel and the value of n is a characteristic exponent of the mode of transport of the penetrate. Values of n and k were calculated from the slopes and intercepts of the plot of $\log(M_t/M_\infty)$ against $\log(t)$ at 25°C, respectively. For Fickian kinetics in which the rate of penetrate diffusion is rate-limiting, $n = 0.5$, whereas values of n between 0.5 and 1 indicate the contribution of non-Fickian processes such as polymer relaxation. The results shown in Table II indicate that the characteristic exponents n for NP (0.42–0.47), and NE (0.33–0.38) copolymeric hydrogels are below 0.5. These results demonstrate that the swelling transport mechanism is a Fickian transport. These results are quite different from the n values of the hydrophilic hydrogels based on NIPAAm,[27–30] even for the poly(NIPAAm) gels (N0 = 0.57). The gels containing a hydrophilic group always showed higher n values over 0.5, which is considered the non-Fickian diffusion for water entering into the gels. The hydrophobicity for MPTMOS and METMS is stronger and leads to the lower swelling ratio for copolymeric gels. When the external water entered inside the gels, the swelling mechanism is dependent only on the hydrophilicity of the amido group of NIPAAm and the hydrophobicity of the alkyl chain and silyl structure. The diffusion coefficient (D) was also affected by the hydrophobic component. The ranges of D for the NP and NE gels were $(0.18–0.63) \times 10^{-7}$ cm^2/s. The values of D for the gels containing MPTMOS and METMS were lower than those of the hydrophilic copolymeric hydrogels reported in our previous report.[26] In addition, for the NT series copolymeric gels, the swelling mechanism for the NT3 gel approached Fickian diffusion; even the NT3 gel has weaker hydrophobicity. But the copolymeric gels with a higher content of the MTMS monomer still showed Fickian diffusion (NT7 and NT10). As a result, the gel's structure or composition, such as silane or alkyl groups, would affect the swelling mechanisms. On the other hand, the equilibrium swelling time decreases with an increase in the silane monomer content in the copolymeric gels (Table II).

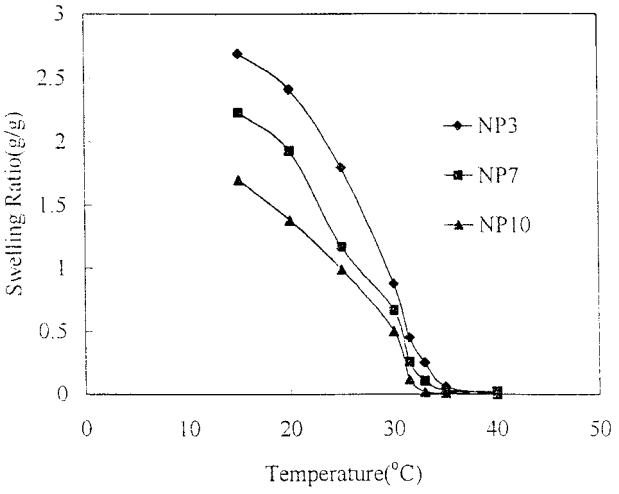

Figure 4 Equilibrium swelling ratio as a function of temperature for NIPAAm/MPTMOS copolymeric hydrogels.

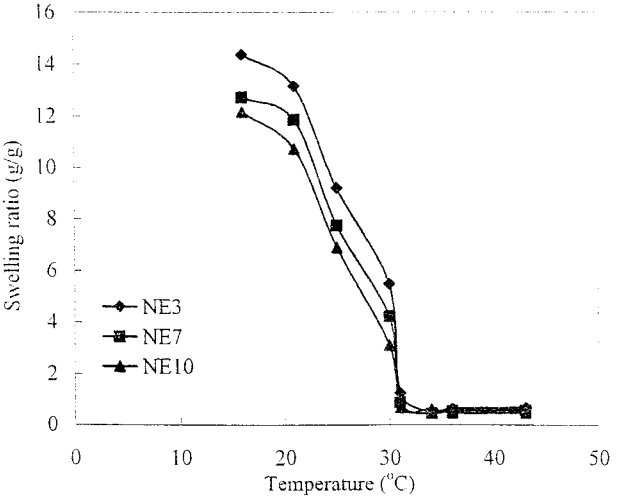

Figure 5 Equilibrium swelling ratio as a function of temperature for NIPAAm/METMS copolymeric hydrogels.

Effect of Temperature on Swelling Ratio for NIPAAm/Silane Monomer Copolymeric Gels

The CGTT is around 32°C for the NIPAAm gels. For the NIPAAm gel, the hydrophilic group (amido —NHCO—) in the polymer structure would form an intermolecular hydrogen bond with surrounding water at low temperature (below the gel transition temperature). Hence, water penetrated into the NIPAAm gels is in a bound state at low temperature. The water molecule would gain an enthalpy as the temperature increases, and the hydrophilic groups (amido) in the NIPAAm gels would turn into intramolecular hydrogen bonds in this condition. At the same time, the hydrophobic forces of the isopropyl group of the NIPAAm gels increased. These two results made the water molecules inside the gel change from a bound state to a free state and release out of the gel network. This phenomenon makes the swelling ratio of the gel rapidly decrease at the gel transition temperature. Figures 4–6 show the equilibrium swelling ratios for these three series of copolymeric gels at different temperatures. From Figures 4 and 5, the swelling ratios decreased drastically at 30 and 35°C for the NP and NE series gels, and the changes in CGTT for the NP gels were obviously observed, as shown in Figure 4. For the NP gels, the more the MPTMOS content in the copolymeric gels, the lower is the CGTT of the gels. The strong hydrophobic monomers copolymerized with NIPAAm, like MPTMOS, decrease the hydrophilicity of the copolymeric hydrogels, which results in the CGTT being less than 32°C, that is, the more hydrophobic groups in the gels, the lower is the CGTT, that is, NP10 < NP7 < NP3. This result was opposite to that of the copolymeric gels, which contain the hydrophilic group monomer. The behavior of a decreasing CGTT is not obviously shown for the NE and NT series of gels because of the weaker hydrophobicity in METMS and MTMS.

Investigation of Drug Release and Drug Delivery for Copolymeric Hydrogels: Effect of Different Silane Monomers on Caffeine Delivery and Release

The method of caffeine delivery of copolymeric gels is performed by immersing the dried gels or

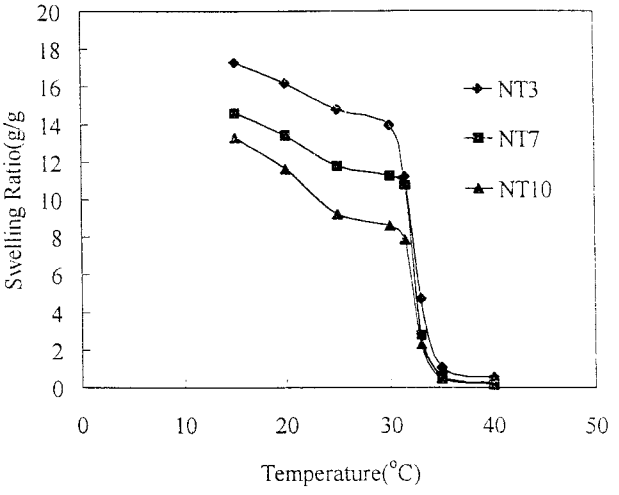

Figure 6 Equilibrium swelling ratio as a function of temperature for NIPAAm/MTMS copolymeric hydrogels.

deswollen gels to load a drug in the caffeine solution at 25°C and to release caffeine at 37°C. From above discussion, the gels show thermosensitive properties at different temperatures and respond to the volume change of the gels. We applied the thermosensitivity of the gels to determine the drug-delivery behaviors for these copolymeric gels. Figure 7 shows the result of caffeine delivery at a long time between 25 and 37°C for NP3, NE3, and NT3. The release amount of caffeine at the first time release is in the order NT3 > NE3 > NP3. This result shows the same tendency as that of the swelling ratios of these three gels. As the gel is released at the second cycle, the release caffeine amounts were lower than were those at the first cycle. But the release amount reached a constant value for the third-cycle release. As the gels deswelled at 37°C (above the CGTT), the NIPAAm collapsed and formed a hydrophobic layer in the gels.[31] This layer could hinder the delivery of the drug in the gel, that is, the gels could reach a stable delivery after the third-cycle delivery.

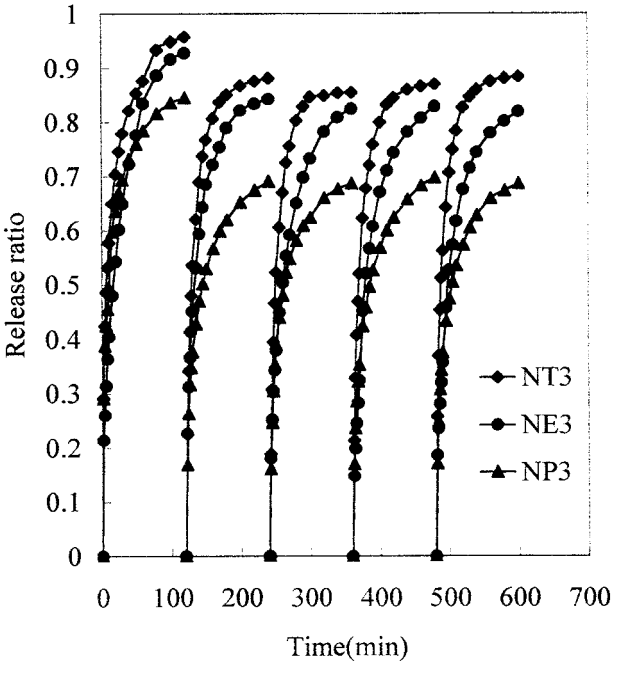

Figure 7 Effect of silane monomer on caffeine-delivery profile during deswelling at 37°C.

Investigation of On–Off Switch Behavior of CV for the NE Gels

Corresponding to the lower CGTT for these series of copolymeric hydrogels, the on–off switch behavior on the drug release for the gels dependent on the temperature was investigated. CV was chosen as the model drug because of the larger molecular size than that of caffeine for a long-time trace. The CV amounts released for NE gels at different temperatures are shown in Figure 8. The release mechanism at low temperature (20°C) and high temperatures (37 and 45°C) were quite different. The drugs are diffused out of the gels with a swollen force by the hydrophilicity on NIPAAm at 20°C (below the CGTT). The drugs are then squeezed out of the gels with the pressure caused by the drastic volume decrease at 37 or 45°C (above the CGTT). During the off-stage, the hydrophobic layers are rapidly formed because the gel volume decreased sharply and results in the drugs hardly diffused out of the gel network. When the gels transfer to a lower temperature from higher temperature, according to the thermoreversible of the gels, the gels were in the swollen state repeatedly (on-stage). The networks of the gels expanded again, and the CV molecules, which were entrapped by the hydrophobic layers in the inner networks at a higher temperature, were diffused out of the gels again.

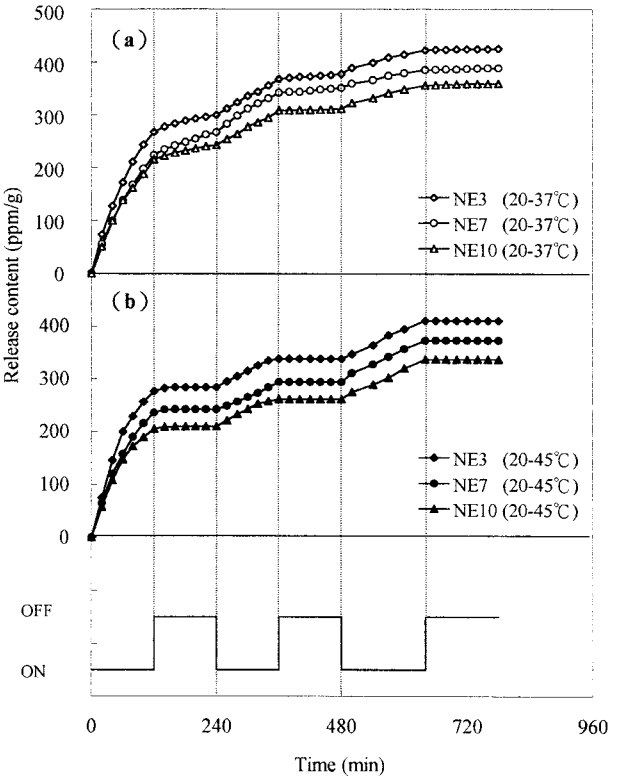

Figure 8 On–off switch behavior on drug release for NE hydrogels.

Table III On–Off Switch Behavior During On-stage and Off-stage

	Release Rate (ppm/g^{-1} h^{-1})					
Sample Code	0–2 h (On)	2–4 h (Off)	4–6 h (On)	6–8 h (Off)	8–10.7 h (On)	10.7–13 h (Off)
NE3 (20–37°C)	133.15	13.61	33.11	2.38	15.07	1.85
NE7 (20–37°C)	118.22	13.03	35.46	1.61	15.05	1.30
NE10 (20–37°C)	107.93	12.44	30.91	1.10	15.51	1.10
NE3 (20–45°C)	138.65	0.69	29.74	0	28.62	0
NE7 (20–45°C)	118.29	0.31	27.00	0	27.31	0
NE10 (20–45°C)	102.88	0.30	27.09	0	26.54	0

As a result, the release amount of CV inside the gels was higher at lower temperature than at higher temperature.

The same results are shown in Table III and the release rates for the NE series of gels are in the order NE3 > NE7 > NE10. The result in Figure 8 also indicates an obvious on–off switch behavior on CV release for NE hydrogels between 20 and 45°C and 20 and 37°C. From Figure 8 and Table III, the drugs are completely locked inside the gels at 45°C (off-stage), but are not completely locked inside the gel at 37°C. The results in Table III also showed that the release rate of CV for NE gels during on–off switching between 25 and 45°C showed a stable state after a one-cycle operation. This behavior was dependent on the shrinking behavior of the NE gels. To investigate this phenomenon, the gels carried out deswelling behavior of the NE gels at 37 and 45°C. The results are shown in Figure 9 and Table IV. From Table IV, the shrinking ratios for NE gels ranged from 52.3 to 70.7% and 35.9 to 67.4% at 45 and 37°C, respectively. In comparison with Figure 8 and Table III, this result indicated that the surface layers of the NE gels were completely hydrophobicized and hindered the drug released out of gels at 45°C, but those of the NE gels were not completely locked during off switching at 37°C.

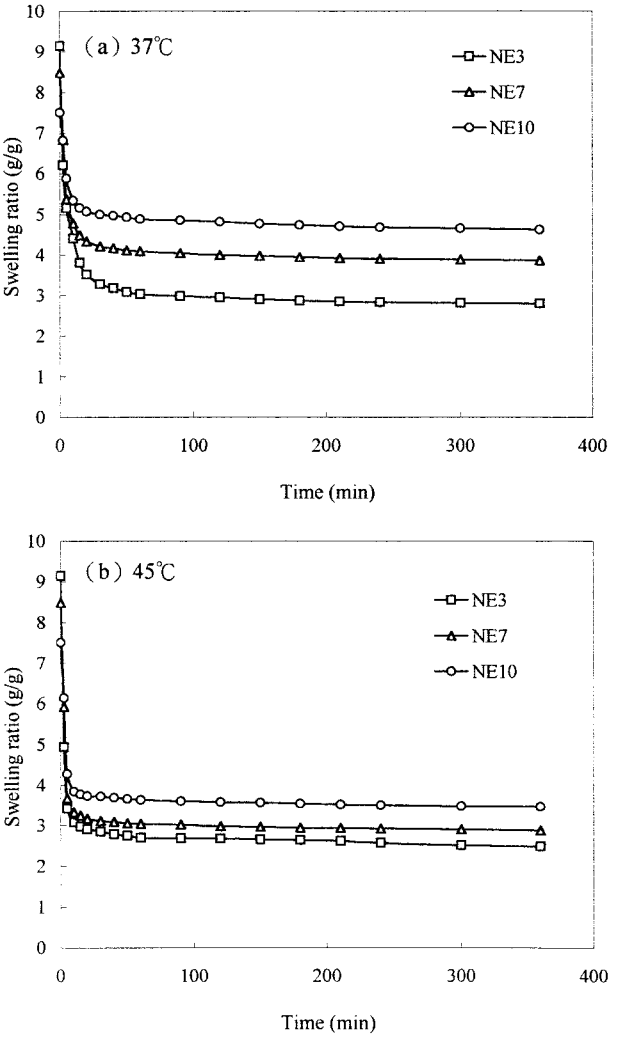

Figure 9 Shrinking behaviors for the NE gels at (a) 37°C and (b) 45°C.

CONCLUSIONS

Three series of thermosensitive copolymeric hydrogels were prepared from MPTMOS, METMS, MTMS, and NIPAAm by the solution method. The swelling ratios of the gels were influenced by the structures and the extent of the silane monomers in the copolymeric gels. The more silane monomers in the copolymeric hydrogels, the lower were

Table IV Shrinking Ratios of NE Series Hydrogels

Sample Code	Temperature (°C)	Shrinking Ratio (%) 0–10 (min)	10–60 (min)	60–120 (min)	0–120 (min)
NE3	37°C	51.79	15.00	0.94	67.74
NE7		43.65	8.23	1.07	52.95
NE10		28.81	6.20	0.91	35.92
NE3	45°C	66.28	4.15	0.29	70.71
NE7		60.70	3.40	0.77	64.86
NE10		48.81	2.74	0.72	52.27

the swelling ratios of the gels due to the hydrophobicity of the silane group. The gel strength and the polymer–water interaction were related to the structure of the silane monomer in the copolymeric gels. The hydrophobicity of the silane group affected the swelling mechanism and resulted in n values in the range of Fickian diffusion. The CGTTs of the gels were not significantly affected by the extent of the silane monomer in the copolymeric gels. The copolymeric hydrogels could be applied for drug release and delivery. The delivery amount would approach a steady state after three cycles of delivery. The gels also showed an excellent on–off switch behavior on drug release; depending on the temperature, the gels released more CV than did the gels in the swollen state.

The authors wish to thank the National Science Council of the Republic of China for financial support under Grant No. NSC-89-2216-E-036-003.

REFERENCES

1. Tanaka, T. Phys Rev Lett 1978, 40, 820.
2. Tanaka, T.; Fillmore, D. J.; Sun, S. T.; Nishio, Swislow, I. G; Shah, A. Phys Rev Lett 1980, 45, 1636.
3. Ilavsky, M. Macromolecules 1982, 15, 182.
4. Ohmine, I.; Tanaka, T. J Chem Phys 1982, 77, 5725.
5. Katayama, S.; Hirokawa, Y.; Tanaka, T. Macromolecules 1984, 17, 2641.
6. Ilmain, F.; Tanaka, T.; Kokufuta, E. Nature 1991, 34, 400.
7. Otake, K.; Inomata, H.; Konno, M.; Saito, S. J Chem Phys 1989, 91, 13455.
8. Dong, L. C.; Hoffman, A. S. J Control Rel 1990, 13, 21.
9. Okano, T.; Bae, Y. H.; Kim, S. W. J Control Rel 1989, 9, 271.
10. Park, T. G.; Hoffman, A. S. H. J Biomed Res 1990, 24, 21.
11. Gewehr, M.; Nakamura, K.; Ise, N.; Kitano, H. Makromol Chem 1992, 193, 249.
12. Nonaka, T.; Ogata, T.; Kurihara, S. J Appl Polym Sci 1994, 52, 951.
13. Ogata, T.; Nonaka, T.; Kurihara, S. J Membr Sci 1995, 103, 159.
14. Irie, M.; Kunwatchakun, D. Macromolecules 1986, 19, 2476.
15. Mamada, A.; Tanaka, T.; Kunwatchhun, D.; Irie, M. Macromolecules 1990, 23, 1517.
16. Schmid, H. J Non-Crystal Solid 1985, 73, 681
17. Kurihara, S.; Minagoshi, A.; Nonaka, T. J Appl Polym Sci 1996, 62, 153.
18. Kabra, B. G.; Gehrke, S. H.; Hwang, S. T. J Appl Polym Sci 1991, 42, 2409.
19. Peppas, N. A.; Barr-Howell, B. D. Hydrogels in Medicine and Pharmacy; CRC: Boca Raton, FL, 1986; Vol. 1, p 27.
20. Treloar, L. R. G. The Physics of Rubber Elasticity; Clarendon: Oxford, 1975.
21. Flory, P. J. Principles of Polymer Chemistry; Cornell University: Ithaca, NY, 1953.
22. Flory, P.J.; Rehner, J., Jr. J Chem Phys 1943, 11, 521.
23. Frenkel, J. Rubb Chem Technol 1940, 13, 264.
24. Van Krevelen, D. W.; Holtyzer P. J. Properties of Polymers: Their Estimation and Correlation with Chemical Structure; Elsevier: Amsterdam, 1976.
25. Korsmeyer, R. W.; Merrwall, E. W.; Peppas, N. A. J Polym Sci Polym Phys Ed 1986, 24, 409.
26. Franson N. M.; Peppas, N. A. J Appl Polym Sci 1983, 28,1299
27. Lee W. F.; Hsu, C. H. Polymer 1998, 39, 5393.
28. Lee W. F.; Hsu, C. H. J Appl Polym Sci 1998, 69, 229.
29. Lee W. F.; Hsu, C. H. J Appl Polym Sci 1998, 69, 1793.
30. Lee W. F.; Yeh, P. L. J Appl Polym Sci 1999, 74, 2170.
31. Park T. G.; Hoffman, A. S. J Appl Polym Sci 1994, 52, 89.