Thermoreversible Hydrogels. XIX. Synthesis and Swelling Behavior and Drug Release Behavior for the *N*-Isopropylacrylamide/Poly(ethylene glycol) Methylether Acrylate Copolymeric Hydrogels

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ABSTRACT: A series of thermosensitive copolymeric hydrogels were prepared from various molar ratios of *N*-isopropylacrylamide (NIPAAm) and poly(ethylene glycol) methylether acrylate ($PEGMEA_n$), which was synthesized from acryloyl chloride and poly(ethylene glycol) mono methylether with three oxyethylene chain lengths. Investigation of the effect of the chain length of oxyethylene in $PEGMEA_n$, and the amount of the $PEGMEA_n$ in the NIPAAm/$PEGMEA_n$ copolymeric gels, on swelling behavior in deionized water was the main purpose of this study. Results showed that the swelling ratio for the present copolymeric gels increased with increasing chain length of oxyethylene in $PEGMEA_n$ and also increased with increase in the amount of $PEGMEA_n$ in the copolymeric gels. However, the gel strength and effective crosslinking density of these gels decreased with increase in swelling ratio. Some kinetic parameters were also evaluated in this study. Finally, the drug release and drug delivery behavior for these gels were also assessed. © 2003 Wiley Periodicals, Inc. J Appl Polym Sci 90: 1683–1691, 2003

Key words: hydrogels; *N*-isopropylacrylamide/poly(ethylene glycol) methylether acrylate gels; drug delivery

INTRODUCTION

Hydrogels are crosslinked, three-dimensional hydrophilic polymeric networks that swell but do not dissolve when brought into contact with water. There are some hydrogels that sometimes undergo a volume change in response to a change in surrounding conditions such as temperature,[1,2] pH,[3,4] solvent composition,[5–7] and salt concentration.[8]

Poly(*N*-isopropylacrylamide) (NIPAAm) hydrogel exhibits a volume phase transition phenomenon at about 32–33°C.[9,10] This temperature is defined as the critical gel-transition temperature (CGTT). Because NIPAAm gel has this swelling–deswelling behavior, it can be widely used in many fields, such as drug delivery systems,[11,12] extraction,[13] and enzyme activity control.[14]

Abuchowski [10] reported that long poly(oxyethylene) (POE) chains, applied to the blood-contacting materials for the purpose of reducing the adhesion of blood components, would be a promising approach. Interest in applications of poly(ethylene glycol) (PEG)–containing copolymers, for modification of biopolymer and design drug delivery systems, stems mainly from the effective exclusion properties of PEG in aqueous solution (i.e., high protein repulsion and low cell adhesion).[15]

Hydrogels based on PEG have attracted considerable attention in controlled release technology because of their good biocompatibility and excellent physicochemical properties.[9] PEG has unique physicochemical properties, such as a high degree of hydrophilicity and very good solubility in water and in organic solvents, and biological properties.[16–18]

The main interest in studying PEGs and the related POEs and their water mixtures is centered on the structure of their inter- and intramolecular hydrogen bonds.[19] The hydrated long POE chain, which binds three molecules of water per each OE unit, is highly flexible and forms a rapid microstream of water that prevents the stagnation of blood components at the surface of the hydrogels.[20]

Coating or adsorption of PEG-containing amphiphilic block copolymers,[21–23] covalent grafting of PEG,[24] or use of copolymers with PEG at their side chains as a material[25] have realized protein adsorption-resistant, cell adhesion–resistant, or nonfouling characteristics. Applications of amphiphilic PEG copolymers, for modification of biomedical polymer surfaces to reduce protein adsorption and increase their biocompatibility, have been extensively reported.[26]

Kaneko et al.[27] reported on rapid deswelling response hydrogels by copolymerization of NIPAAm

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with α-acryloyl-ω-methoxy–PEO. The hydrophilic PEO graft chain provides a water-release channel during skin layer formation. To date, however, the physical properties and the application in drug delivery of these hydrogels have not been investigated in detail. Hence, the main purpose of this study was to investigate the effect of the OE chain length and the content of the poly(ethylene glycol) methylether acrylate (PEGMEA), derived from poly(ethylene glycol) monomethylether, in the NIPAAm/PEGMEA copolymeric hydrogels on the swelling behavior in deionized water at various temperatures. In addition, a further objective was to assess the suitability of these copolymeric hydrogels for use in drug release and drug delivery.

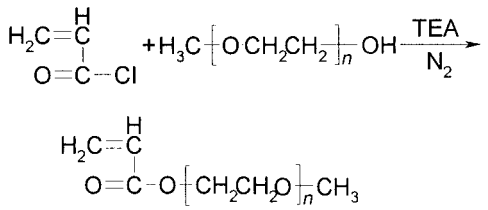
EXPERIMENTAL

Materials

N-Isopropylacrylamide (NIPAAm; Wako Chemical Co., Osaka, Japan) was recrystallized in *n*-hexane before use. Acryloyl chloride, poly(ethylene glycol) monomethyl ether, and *N,N,N′,N′*-tetramethylethylene diamine (TEMED) as an accelerator were obtained from Fluka Chemie (Buchs, Switzerland). *N,N′*-Methylenebisacrylamide (NMBA) as a crosslinking agent and ammonium persulfate (APS) as an initiator were purchased from Tokyo Kasei Industries (Japan). Caffeine and crystal violet (CV) as model drugs were obtained from Fluka. All solvents and other chemicals were of analytical grade.

Preparation of poly(ethylene glycol) methylether acrylate (PEGMEA$_n$)

A solution containing poly(ethylene glycol) monomethylether and triethylamine in 100 mL benzene was added to a 100-mL volume flask equipped with a stirrer, a condenser, and a thermometer. To this, acryloyl chloride was slowly added under nitrogen below 0°C and stirred for 6 h. The mixture was then separated by filtration. The filtrate was then concentrated by rotary evaporation and the products were purified by vacuum distillation. The boiling points for PEGMEA$_7$ and PEGMEA$_{16}$ were 72°C/7 mmHg and 183°C/6 mmHg, respectively. The melting point for PGMEA$_{45}$ was 67°C. The monomers of PEGMEA$_n$ were prepared according to the following equation:



PEGMEA*n*

in which *n* is 7, 16, and 45, respectively.

The structure of the PEGMEA$_n$ obtained was confirmed by NMR and IR spectra. NMR spectra were measured by a JEOL JNM A-500 spectrometer (JEOL, Tokyo, Japan), operating at 400 MHz for ^{1}H-NMR and at 100 MHz for ^{13}C-NMR. All spectra were obtained from a chloroform-*d* solution at room temperature with TMS as the internal standard. IR spectra were measured by a Jasco FTIR 7000, operating at 400–4000 cm^{-1} at room temperature. The typical signals of ^{1}H-NMR spectra for PEGMEA$_n$ were located at 5.5–6.5 ppm for the vinyl group, at 3.3 ppm for the methoxy group (–OCH$_3$), and at 3.6 ppm for the oxyethylene (OE) group (–CH$_2$CH$_2$O–), respectively. The typical signals of ^{13}C-NMR spectra were located at 130 ppm for the vinyl group, at 59 ppm for the methoxy group, and at 72 ppm for the OE group. The characteristic absorption peaks of FTIR spectra at 1610–1640 cm^{-1} for C═C, 1725 cm^{-1} for C═O, and 1100 cm^{-1} for C—O—C were in agreement with their structural characteristics.

Preparation of hydrogels

Various ratios of NIPAAm and PEGMEA$_n$ and 5 mol % NMBA, based on total monomer contents, were dissolved in 10 mL deionized water. To this solution, 1 mol % APS and 1 mol % TEMED as redox initiators were 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 room temperature for 1 day. After the gelation was completed, the gel membrane was cut into disks, 10 mm in diameter, and immersed in an excess amount of deionized water for 4 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 feed compositions of the copolymeric gels are listed in Table I.

Swelling experiments

The dried gels were immersed in an excess amount of deionized water at different temperatures 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 weight (W_d) was determined after drying the gel in a vacuum oven for 2 days. The swelling ratio (Q) was calculated from the following equation:

$$Q = (W_w - W_d)/W_d \quad (1)$$

Dynamic swelling measurements were made primarily by gravimetric means. The penetration velocity (v) of solvent in each gel was determined by the

TABLE I
Feed Compositions and Characterization of Copolymeric Hydrogels

Sample code[a]	NIPAAm	$PEGMEA_7$	$PEGMEA_{16}$	$PEGMEA_{45}$	Q (g/g)	χ	$G \times 10^2$ (MPa)	$\rho \times 10^5$ (mol/cm^3)
$N9P_7$	90	10	—	—	7.02	0.52	9.4	7.28
$N7P_7$	70	30	—	—	7.82	0.51	8.8	7.07
$N5P_7$	50	50	—	—	8.71	0.50	8.2	6.83
$N9P_{16}$	90	—	10	—	9.67	0.49	7.4	6.43
$N9P_{45}$	90	—	—	10	13.22	0.46	5.4	5.17

[a] N_x, NIPAAm with x mol %; P_n, PEGMEA with n repeating units.

weight gain method as described by Peppas et al.[28,29] The penetration velocity was calculated from the slope of the initial portion of the water-uptake curve by the following equation:

$$v = \frac{1}{2\rho_w A}\frac{dw}{dt} \tag{2}$$

where dw/dt is the slope of the weight gain versus time curve, ρ_w is the density of water, A is the area of one face of the disc, and the factor 2 accounts for the fact that penetration takes place through both sides.

Measurement of thermoreversibility for copolymeric gels

The dried gels were equilibrated in 10 mL deionized water at 25°C, and the wet gels were weighed. The gels were then transferred into 10 mL deionized water at 37°C and weighed at each fixed time interval. When the weight of gels was constant, the gels were transferred into deionized water at 25°C again and weighed at each fixed time interval. This operation was conducted for several cycles after which the swelling ratios were calculated.

Measurement of physical properties

The gel strength of these samples was measured by a uniaxial compression experiment with a universal tester (Lloyd LRX). The following equation was used to calculate the shear modulus[30,31]:

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

where τ is the compression stress, F is the compression load, A is the cross-sectional area of swollen gels, and λ is 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 calculated from the shear modulus and polymer volume fraction (ν_2) as follows:

$$\rho = G/\nu_2^{1/3}RT \tag{4}$$

where R is the gas constant and T is the absolute temperature.

Drug release experiment

The dry gels were equilibrated in 30 mg drug/10 mL of deionized water 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 37°C. The gels were repeatedly removed and transferred into 10 mL fresh deionized water at each fixed time interval. The released drug was analyzed at 272 and 561 nm for caffeine and CV, respectively, by an ultraviolet spectrophotometer (Jasco V530, Tokyo, Japan).

Drug delivery experiment

The dry gels were equilibrated in 30 mg drug/10 mL of deionized water 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 37°C. The gels were repeatedly removed and transferred into 10 mL deionized water at each fixed time interval. When the drug was no longer released from the gels, the gels were reimmersed in the original drug solution for 1 day, after which the release experiment was repeated. The preceding steps were repeated to perform the drug delivery tests.

On-off release experiment

To load CV into the gels, dry gels were equilibrated in CV solution (30 mg/10 mL deionized water) at 25°C for 1 day. The incubated-drug gels were transferred into fresh deionized water to carry out the CV release experiments. The CV-loaded gels were transferred to deionized water at 70°C for 2 h and then to deionized water at 25°C. The above step was repeated every 2 h. The released CV was analyzed at 561 nm by an ultraviolet spectrophotometer (Jasco V530).

RESULTS AND DISCUSSION

The fundamental properties such as equilibrium swelling ratio, gel strength, crosslinking density, and polymer–water interaction parameter χ for the present copolymeric gels, prepared from NIPAAm and PEGMEA$_n$, were investigated.

Effect of PEGMEA$_n$ on swelling ratio

Some characteristics of the NIPAAm/PEGMEA$_n$ copolymeric gels with various feed compositions are shown in Table I. The results shown in Table I indicate that the longer the OE chain length in PEGMEA, the higher the swelling ratio (i.e., N9P$_{45}$ > N9P$_{16}$ > N9P$_7$). This result explicitly shows that the longer OE chain unit in PEGMEA possesses stronger affinity toward water for the gel. The results in Table I also indicate that the greater the PEGMEA content in the gels, the higher the swelling ratio of the gels (i.e., N5P$_7$ > N7P$_7$ > N9P$_7$). This result also implicitly indicates that the hydrophilicity of PEGMEA$_n$ is higher than that of NIPAAm.

Effect of PEGMEA$_n$ on gel strength

Gel strength was assessed by the shear modulus (G) measured from the uniaxial compression experiment. The results in Table I show that G values decrease with increase in OE chain length in PEGMEA$_n$ for the N9Pn series (i.e., N9P$_7$ > N9P$_{16}$ > N9P$_{45}$). That is to say, for the same compositional gel system, the gel becomes softer when the OE chain length in PEGMEA$_n$ increases. This is because hydrogen bonding occurs between oxyethylene and water when the gel is immersed in water. As a result the swelling ratio of the gel increases and the gel strength decreases. On the other hand, the G values also decrease with the increase of PEGMEA$_7$ in the present copolymeric gels based on the NxP$_7$ series (i.e., N9P$_7$ > N7P$_7$ > N5P$_7$); that is, the gel becomes softer while the content of PEGMEA$_7$ increases in the gel system. This is because the PEGMEA is a hydrophilic monomer; thus the swelling ratios for this gel series increase with increasing content of PEGMEA$_7$.

According to eq. (4), the effective crosslinking density ρ depends on the swelling ratio and shear modulus at constant temperature. For the N9 gel series, the ρ values decrease with an increase of OE chain length in PEGMEA (i.e., N9P$_7$ > N9P$_{16}$ > N9P$_{45}$). Similarly, for the NxP$_7$ gel series, the ρ values decrease with increase in PEGMEA$_7$ content.

From the above discussion, gel properties such as Q, G, and ρ are mainly dependent on the PEGMEA$_n$ content and the OE chain length in the system, especially for the chain length of the oxyethylene unit in PEGMEA$_n$.

Effect of PEGMEA$_n$ on copolymer–water interaction parameter χ

The total copolymer–water interaction parameter χ was calculated from the Flory–Rehner equation[32–34]:

$$\pi = \pi_{mix} + \pi_{elas} + \pi_{ion} + \pi_{elec} \quad (5)$$

The osmotic pressure π of a hydrogel during swelling is given as the sum of the pressures attributed to polymer–solvent mixing (π_{mix}) and 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, whereas 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 neglected because the gels do not contain any ionizable groups. Thus eq. (5) can be simplified to

$$\pi = \pi_{mix} + \pi_{elas} \quad (6)$$

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

$$\pi_{mix} = RT/V_1[\ln(1 - \nu_2) + \nu_2 + \chi\nu_2^2] \quad (7)$$

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

$$\pi_{elas} = RT\rho(\nu_2^{1/3} - 0.5\nu_2) \quad (8)$$

Thus if a gel swells in the thermodynamic equilibrium state, eq. (6) can be expressed as

$$\ln(1 - \nu_2) + \nu_2 + \chi\nu_2^2 + \rho V_1(\nu_2^{1/3} - 0.5\nu_2) = 0 \quad (9)$$

The polymer–solvent interaction parameters account for free-energy changes caused by the mixing process. Values of χ are usually between 0 and 1, with increasing of χ indicating poorer solvents for the polymer, and thus reduced degrees of polymer swelling. It is important to recognize that χ is not a constant for a given system but, rather, is a function of temperature and concentration.

The results shown in Table I indicate that χ values decrease with increase in OE chain length and PEGMEA$_7$ content for the N9 series and the NxP$_7$ series, respectively. This result explicitly indicates that the longer OE chain length and the greater PEGMEA content in the gel system cause water to become a better solvent for this gel series.

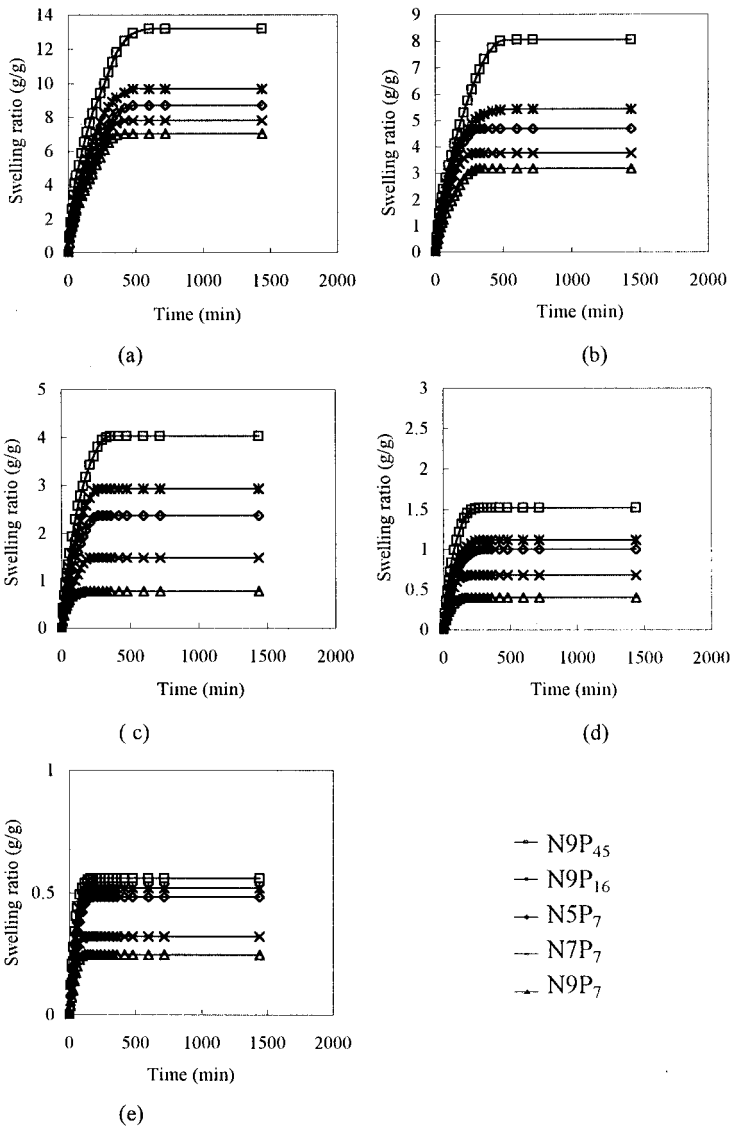


Figure 1 Swelling ratio as a function of time for copolymeric gels at various temperatures in deionized water: (a) 25°C, (b) 35°C, (c) 45°C, (d) 55°C, and (e) 65°C.

Effect of PEGMEA$_n$ on the swelling kinetics

Swelling ratios as a function of time for the present copolymeric gels at various temperatures in deionized water are shown in Figure 1. Results in Figure 1 indicate that the swelling ratios increase in the order of $N9P_{45} > N9P_{16} > N5P_7 > N7P_7 > N9P_7$ and decrease with increase in temperature. According to Flory's swelling theory for nonionic gels, the following equation is given[32]:

$$Q^{5/3} = \left[\frac{(1/2 - \chi_1)}{V_1}\right]/(\nu_e/V_0) \qquad (10)$$

where $(1/2 - \chi_1)/V_1$ is the affinity of the hydrogel for water and ν_e/V_0 is the crosslinking density of the hydrogel. The swelling ratio therefore has a relation to the crosslinking density and the affinity of the gel for water, as expressed in the preceding equation. The differences of the crosslinked densities for the present copolymeric gels are very small, so the influence of swelling ratio of the hydrogels is the affinity of hydrogel for water. In these gel systems, the affinity of the gel for water is dependent on the chain length of the OE repeating unit in PEGMEA$_n$ and the content of PEGMEA in the copolymeric gels. This result conforms to our previous discussion.

Effect of temperature on swelling ratio

The effect of temperature on equilibrium swelling ratio for the present copolymeric gels is shown in Figure 2. The results in Figure 2 indicate that the higher the temperature, the lower the swelling ratio; and the longer the OE chain and the greater the PEGMEA

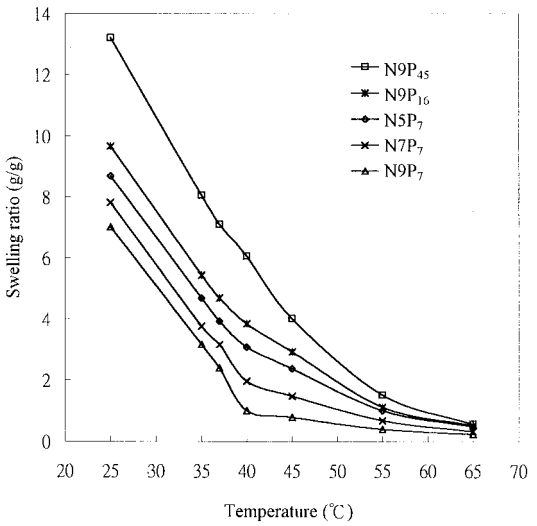


Figure 2 Equilibrium swelling ratio for various copolymeric gels in deionized water.

contents, the higher the gel-transition temperature. The OE unit would hydrogen-bond with water (hydration at low temperature). This hydrogen-bonding force gradually decreases with increase in temperature and shows a dehydration state. This hydration-dehydration ability depends on the extent and hydrophilicity of the hydrophilic group in the copolymeric gel. Therefore, the curves of swelling ratio versus temperature become smoother as the chain length of the OE unit and the content of PEGMEA in these copolymeric gels increase. This result means that the gel-transition temperature for the gels gradually disappears as the OE chain length in $PEGMEA_n$ or the content of PEGMEA in the copolymeric gels increases.

Investigation of water diffusion in xerogels

This section focuses on the investigation of the influence of chain length of the OE unit in $PEGMEA_n$ and the content of $PEGMEA_7$ in the copolymeric gels on the swelling kinetic parameters, such as kinetic exponent n, characteristic constant k, penetration velocity v, initial diffusion coefficient of water D, and activation energy E_a of water that penetrates through copolymeric gels at various temperatures.

Swelling kinetics can be generally described in two terms, the diffusion rate of imbibing solvent into the gel and the relaxation rate of the polymer network. To obtain a quantitative understanding of the nature of the sorption kinetics in the NP series gels, the initial swelling data were fitted to an exponential heuristic equation for $M_t/M_\infty \leqq 0.6$.[35,36]

$$\frac{M_t}{M_\infty} = kt^n \tag{11}$$

where M_t is the amount of water sorbed at a given time, M_∞ is the equilibrium sorption at an infinitely long time, k is a characteristic constant of the gel, and n is a characteristic exponent of the mode 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 $\log t$, respectively.

Equation (12) was used to calculate the diffusion coefficient D for $M_t/M_\infty \leqq 0.8$.[37]

$$\frac{M_t}{M_\infty} = \frac{4}{\sqrt{\pi}}\left(\frac{Dt}{L^2}\right)^{1/2} \tag{12}$$

where t is time and L is the initial thickness of the dried sample. The penetration velocity v was calculated from eq. (2).

Table II shows values of n, k, v, and D for all the present copolymeric gels at various temperatures. The results shown in Table II indicate that the swelling exponents n for the copolymeric gels decrease with increase in temperature. The values of n for all gels range from 0.74 to 0.45. This evidence indicates that the swelling transport mechanism for all copolymeric gels will be transformed from non-Fickian transport to Fickian diffusion transport as temperature increases from low temperature to high temperature. That is, the swelling transport mechanism is not significantly related to the chain length of OE in PEGMEA and the content of PEGMEA in the copolymeric gels.

In addition, D values for all copolymeric gels increase with increase in temperature; the diffusion rate is faster at higher temperature. For the N9 gel series, D values increase with increase in chain length of the OE unit in PEGMEA ($N9P_{45} > N9P_{16} > N9P_7$) and also increase with the content of $PEGMEA_7$ in the copolymeric gels ($N5P_7 > N7P_7 > N9P_7$).

According to the Arrhenius equation:

$$D = D_0\exp(-E_a/RT) \tag{13}$$

The activation energies (E_a) of water, which diffuses into glassy polymer, are calculated from the plot of the logarithm of the diffusion coefficient D against the reciprocal of temperature. The activation energies, shown in Table II, indicate that the E_a values for the N9 copolymeric gels are in the order of $N9P_{45} > N9P_{16} > N9P_7$. That is, the longer the OE chain length in PEGMEA, the smaller the E_a of diffusion of water into the dry gel (i.e., the water diffuses more easily into the hydrogels). Table II also indicates that the E_a values for the P_7 series copolymeric gels decrease in the order of $N5P_7 < N7P_7 < N9P_7$. That is, the greater the PEGMEA content, the smaller the activation energy of water diffused into the dry gel. In addition, the results in Table II also show that the penetration velocity (v) decreases with increase in temperature. This is because the hydrophilic-

TABLE II
Initial Diffusion Coefficient of Water D, Penetration Velocity v, Kinetic Exponent n, Characteristic Constant k, and Activation Energy E_a of Water Penetrated Through Copolymeric Gels at Various Temperatures

Sample	T (°C)	Q (g/g)	n	k	$v \times 10^2$ (cm/min)	$D \times 10^7$ (cm^2/s)	E_a (kJ/mol)
$N9P_7$	25	7.02	0.71	0.61	4.0	1.35	7.22
	35	3.17	0.68	0.63	2.9	1.42	
	45	0.78	0.64	0.87	2.3	1.47	
	55	0.40	0.59	1.37	2.1	1.52	
	65	0.25	0.45	1.52	1.7	1.64	
$N7P_7$	25	7.82	0.72	0.63	4.2	1.37	5.72
	35	3.77	0.66	0.75	3.0	1.45	
	45	1.48	0.64	1.13	3.0	1.56	
	55	0.68	0.61	1.45	2.8	1.59	
	65	0.32	0.46	1.53	2.1	1.68	
$N5P_7$	25	8.71	0.73	1.11	4.5	1.42	5.69
	35	4.69	0.65	1.24	3.3	1.49	
	45	2.37	0.62	1.35	3.0	1.62	
	55	1.02	0.61	1.43	2.9	1.66	
	65	0.48	0.51	1.57	2.2	1.73	
$N9P_{16}$	25	9.67	0.74	1.19	4.9	1.46	5.29
	35	5.44	0.69	1.26	3.4	1.53	
	45	2.93	0.65	1.32	3.8	1.69	
	55	1.12	0.62	1.41	3.2	1.74	
	65	0.52	0.53	1.56	2.4	1.86	
$N9P_{45}$	25	13.24	0.74	1.21	5.2	1.52	4.12
	35	8.06	0.71	1.35	3.9	1.63	
	45	4.02	0.65	1.42	3.8	1.71	
	55	1.52	0.63	1.58	3.6	1.76	
	65	0.56	0.53	1.61	3.2	1.87	

ity decreases with an increase of temperature. The v values also increase with increase of the chain length of OE in PEGMEA ($N9P_{45} > N9P_{16} > N9P_7$) and increase with increase of the content of $PEGMEA_7$ in the copolymeric gels ($N5P_7 > N7P_7 > N9P_7$). That is, the value of v is mainly dependent on the content of hydrophilic groups in the copolymeric gel compositions.

Swelling and deswelling kinetics of NP copolymeric gels and thermoreversibility

The swelling–deswelling kinetics for the present copolymeric gels with temperature modulation between 37 and 25°C are shown in Figure 3. From Figure 3, the gels were swelled and deswelled in deionized water at 25 and 37°C, respectively, and weighed for several cycles: in this way, the thermoreversibility of the gels can be tested. The results shown in Figure 3 for all gels indicate that the differences of the swelling ratios (ΔSR) at 25 and 37°C are 4.62, 4.65, 4.77, 4.98, and 6.10 for the gels $N9P_7$, $N7P_7$, $N5P_7$, $N9P_{16}$, $N9P_{45}$, respectively. These results indicate that the thermosensitive gels have good reversibility.

Effect of hydrogel composition on fractional release of caffeine and CV

The release profiles of caffeine and CV in the NxPn series copolymeric gels at 37°C are shown in Figures 4 and 5, respectively. The results shown in these figures indicate that the longer the OE chain length in the PEGMEA the greater the amount of caffeine and CV released (i.e., $N9P_{45} > N9P_{16} > N9P_7$); the greater the content of $PEGMEA_7$ in the gels, the greater the amount of drugs released (i.e., $N5P_7 > N7P_7 > N9P_7$), which is attributed to the faster gel deswelling; that is, the fewer hydrophilic groups contained in the present

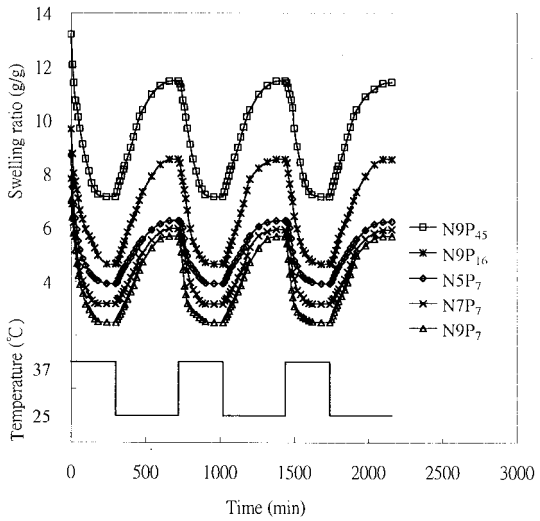


Figure 3 Swelling–deswelling kinetics for the present copolymeric gels by temperature modulation from 25 to 37°C.

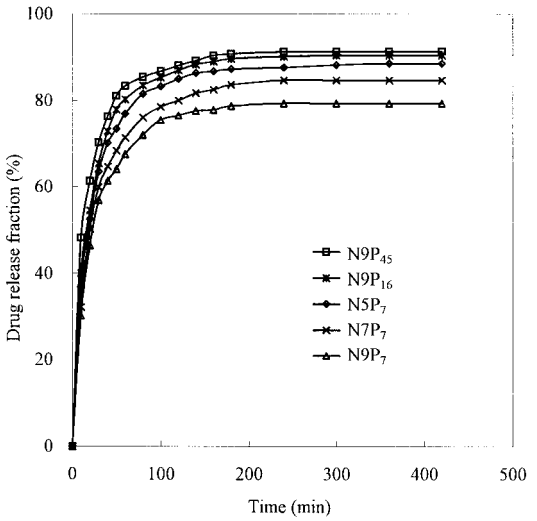


Figure 4 Caffeine release profile during swelling at 25°C and deswelling at 37°C.

copolymeric gels, the faster the gel deswelled. The results also show that the fractional release of the drugs does not reach 100% (i.e., the drugs were not completely released and some portions were entrapped within the gel). This effect supports the idea of a water-pocket formation in the deswelled gel. This phenomenon was also observed in some previous studies.[12,38,39]

In addition, it was found that the release profiles of caffeine in various copolymeric gels are faster than those of CV in the 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.

Effect of PEGMEA$_n$ on drug delivery behavior

The drug delivery for the gels was conducted by loading the drug in one condition (25°C), and then releasing it in another condition (37°C). After the drug was released, the gel was reimmersed in the original drug solution to reload the drug. This loading–releasing action was repeated for some cycles to test the delivery stability of drug inside the gel. Figures 6 and 7 show the drug release profiles for the present copolymeric gels on caffeine and CV delivery. The results from these two figures show that the fractional drug release for the present gels decrease in the order of $N9P_{45} > N9P_{16} > N5P_7 > N7P_7 > N9P_7$ in the first cycle, although the release fraction in the second cycle was slightly lower than that in the first cycle. This is because the gels swelled at 25°C to load the drug and deswelled at 37°C to release the drug, but in the releasing stage, some drugs entrapped within the gel cannot be released. Thereafter, the release fraction ap-

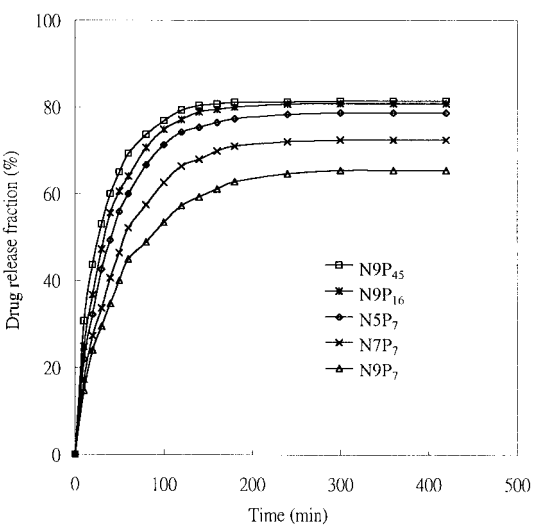


Figure 5 CV release profile during swelling at 25°C and deswelling at 37°C.

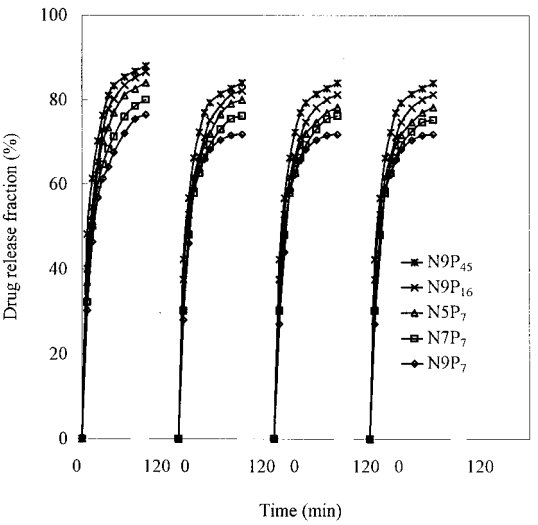


Figure 6 Caffeine delivery profile during swelling at 25°C and deswelling at 37°C.

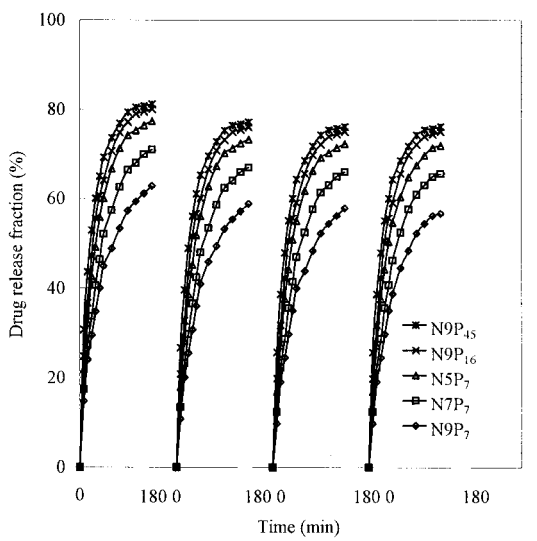


Figure 7 CV delivery profile during swelling at 25°C and deswelling at 37°C.

proached stability after two cycles of gels delivering drug.

CONCLUSIONS

NIPAAm/PEGMEA$_n$ copolymeric gels were successfully synthesized in this study. The fundamental properties of the present copolymeric gels were investigated. Some conclusions can be asserted as follows: the swelling ratios of the gels increase with an increase in the chain length of the OE unit in PEGMEA and the content of the PEGMEA in the gels, although the χ values decrease with an increase in the OE chain length and PEGMEA$_7$ content for N9 series and NxP$_7$ series, respectively. This result explicitly indicates that longer OE chain length and greater PEGMEA content in the gel system cause water to become a better solvent for this gel series. For the N9 gel series, the value of ρ decreases with an increase of OE chain length in PEGMEA (i.e., N9P$_7$ > N9P$_{16}$ > N9P$_{45}$). Similarly, for the NxP$_7$ gel series, ρ decreases with an increase in PEGMEA$_7$ content. In addition, the drug release also increases with the OE chain length in the PEGMEA (i.e., N9P$_{45}$ > N9P$_{16}$ > N9P$_7$) and the amount of PEGMEA$_7$ in the gels (i.e., N5P$_7$ > N7P$_7$ > N9P$_7$).

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