J Mater Sci (2006) 41:7333–7340
DOI 10.1007/s10853-006-0882-1

Swelling behavior and drug release of NIPAAm/PEGMEA copolymeric hydrogels with different crosslinkers

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Received: 19 September 2005 / Accepted: 17 November 2005 / Published online: 17 October 2006

Abstract Poly(ethylene glycol) methylether acrylate (PEGMEA) and tetraethylene glycol diacrylate (TEGDA) were first synthesized. The thermosensitive hydrogels were then prepared from *N*-isopropylacrylamide (NIPAAm), PEGMEA, and three crosslinkers with different structures such as *N*, *N*′-methylene-bis-acrylamide (NMBA), TEGDA, and poly(ethylene glycol) dimethacrylate (EGDMA). The influence of polymerization factors such as the kind and amount of crosslinker and initial total monomer concentration on the swelling behavior, gel strength, effective crosslinking densities, and number-average molecular weight between crosslink points ($\overline{M}_c$) for the present copolymeric hydrogels was investigated. The results indicate that the swelling ratios for the present copolymeric gels decrease with increase in temperature. In addition, the results also showed that the higher swelling ratios for the present gels prepared from TEGDA were obtained due to the larger space between the gel networks. The crosslinking density depends on the swelling ratio and the kind and extent of crosslinker. In addition, the drug release behavior for the present copolymeric gels was investigated.

Introduction

Hydrogels are three-dimensional hydrophilic polymeric networks, which swell but do not dissolve when brought into contact with water. Hydrogels sometimes undergo a volume change in response to a change in surrounding conditions, such as temperature [1, 2], pH [3, 4], chemicals [5], photoirradiation [6], and electric field [7] etc. Thermoresponsive hydrogels demonstrate a volume transition and associated phase transition from low temperature, a highly swollen gel, to high temperature, a collapsed gel near its critical point. It is well known that poly(*N*-isopropylacrylamide) gel [poly(NIPAAm)] exhibits a critical gel transition temperature (CGTT) around 33 °C in aqueous solution, that is, the hydrogel exhibits swelling or deswelling in the temperature below or above CGTT [8–10]. Poly(NIPAAm) hydrogels have recently been reported in the field of controlled drug delivery [11, 12], immobilization of enzymes [13], and cells [14].

Abuchowski reported that the long poly(oxyethylene) chain applied to the blood-contacting materials for the purpose of reducing the adhesion of blood components will be a promising approach [15]. Interest in applications of 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 [16, 17]. Hydrogels based on PEG have attracted considerable attention in controlled release technology because of their good biocompatibility and excellent physicochemical properties [18]. PEG possesses unique physicochemical properties, such as a high degree of hydrophilicity and very good solubility in water and in organic solvents, and biological properties [19–21].

A series of thermosensitive copolymeric hydrogels were prepared from various molar ratios of *n*-isopropylacrylamide (NIPAAm) and poly(ethylene glycol)

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methylether acrylate (PEGMEAn) which was synthesized from acryloyl chloride and poly(ethylene glycol) monomethyl ether with three oxyethylene chain lengths and the effect of porogen on the swelling behavior and drug release for the porous NIPAAm / PEGMEAn copolymeric hydrogels were reported in our previous studies [22, 23]. The results showed that the mesh size of gel structure become larger when larger molecular PEG was added during gel preparation. The surface areas and pore volumes increased with increase in the content of porogen, PEG. The gels with larger pores had higher swelling ratio, but the gels with larger pores become weaker after swelling. To overcome this problem, a series of thermoreversible hydrogels were prepared from NIPAAm and poly(ethylene glycol) methylether acrylate (PEGMEA) with different crosslinking agents. The investigation of the effect of the different crosslinkers and the amount of crosslinker in the NIPAAm/PEGMEA copolymeric hydrogels on the swelling behavior and physical properties is the main purpose. The degree of crosslink, which strongly determines the swelling ratio of hydrogels, can be controlled easily by varying the dose of crosslinker. In addition, the other objective in this article is to access the availability of these copolymeric hydrogels to use for drug release behavior.

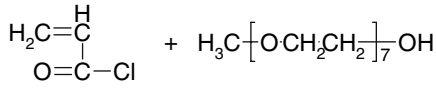
Experimental

Materials

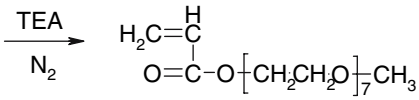
N-Isopropylacrylamide (NIPAAm) (Wako Chemical Co.) was recrystallized in *n*-hexane before use. Acryloyl chloride, poly(ethylene glycol) monomethyl ether, and *N*, *N*, *N*′, *N*′-tetramethylethylenediamine (TEMED) as an accelerator were obtained from Fluka Chemical Co. Poly(ethylene glycol) (PEG) was obtained from Acros Chemical Co. *N*, *N*′-methylene-bisacrylamide (NMBA) and ethylene glycol dimethacrylate (EGDMA) as crosslinkers and ammonium persulfate (APS) as an initiator were purchased from Tokyo Kasei Industries, Ltd. Caffeine as model drug was obtained from Fluka Chemical Co. All solvents and other chemicals were of analytical grade.

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

The monomer, PEGMEA, was prepared from Eq. (1): where the reaction solvent was benzene and the reaction temperature was kept at 0–10 °C. The synthesized PEGMEA was purified via vacuum distillation. The



(1)

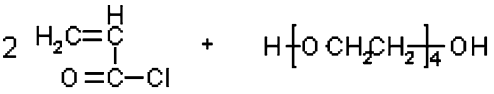


PEGMEA

boiling point of the PEGMEA was 72 °C/7 mm Hg. The product was identified by IR and NMR spectra in previous report [22].

Preparation of tetraethylene glycol diacrylate (TEGDA)

The crosslinker, TEGDA, was prepared as Eq. (2):



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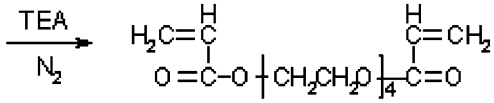

TEGDA

where the reaction solvent was benzene and the reaction temperature was kept at 0–10 °C. The synthesized TEGDA was purified via vacuum distillation. The boiling point of the TEGDA was 112 °C/6 mm Hg.

Preparation of hydrogels

NIPAAm, PEGMEA, and crosslinker were dissolved in 10 mL deionized water (Table 1). To this solution, 1 mol% APS and 1 mol% TEMED as redox initiators were added, and then the mixture was immediately injected into the space between two glass plates. The gel membrane thickness was adjusted with a silicone rubber spacer between two glass plates. Polymerization was carried out at room temperature for 1 day. After 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, then further dried in a vacuum oven for 2 days. The yields for all gel samples are over 90% and all samples exhibit transparent. The feed compositions and polymerization conditions and sample codes are shown in Table 1.

Table 1 Feed compositions and polymerization conditions of NIPAAm/PEGMEA copolymeric hydrogels

Sample code	NIPAAm	PEGMEA	Initial monomer concentration (M)	Crosslinker	
				type	mol %
N9M5	90	10	1	EGDMA[a]	5
N9N5	90	10	1	NMBA[b]	5
N9E5	90	10	1	TEGDA[c]	5
N7E5	70	30	1	TEGDA	5
N5E5	50	50	1	TEGDA	5
N9E10A	90	10	0.6	TEGDA	10
N9E10	90	10	1	TEGDA	10
N9E10B	90	10	1.5	TEGDA	10
N9E15	90	10	1	TEGDA	15

[a] Ethylene glycol dimethacrylate $[CH_2=C(CH_3)COOCH_2]_2$

[b] *N*, *N*-methylene bisacrylamide $(CH_2=CHCONH)_2CH_2$

[c] Tetraethylene glycol diacrylate $[CH_2=CHCO(OCH_2CH_2)_2]_2$

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 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. Swelling ratio (Q) was calculated from Eq. (3):

$$Q = (W_w - W_d)/W_d \tag{3}$$

Dynamic swelling experiments were made primarily by gravimetric means. The penetration velocity (v) of solvent in each gel was determined by the weight gain method as described by Pappas et al. [24, 25]. The penetration velocity was calculated from the slope of the initial portion of the water uptake curve by Eq. (4):

$$v = \frac{1}{2\rho_w A} \cdot \frac{dw}{dt} \tag{4}$$

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

Physical properties measurement

The gel strength of these samples was measured by uniaxial compression experiment with universal tester (LLOYD LRX). Equation (5) was used to calculate the shear modulus (G) [26, 27]:

$$\tau = F/A = G(\lambda - \lambda^{-2}) \tag{5}$$

where τ is compression stress, F is the compression load, A is the cross-sectional area of swollen gels, and λ is 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 G. The effective crosslink density (ρ) can then be calculated from the shear modulus and polymer volume fraction (v_2) as follows:

$$\rho = G/v_2^{1/3}RT \tag{6}$$

where R is the gas constant and T is the absolute temperature. The number of average molecular weight between crosslink points ($\overline{M}_c$) can be calculated from Eq. (7) [26]:

$$\overline{M}_c = 1/(\rho v) \tag{7}$$

where v is the polymer specific volume.

Caffeine release experiment

The dry gels were equilibrated in 30 mg caffeine / 10 mL of deionized water at 25 °C for 1 day to load caffeine into the gels. The caffeine release experiments were carried out by transferring previously incubated-drug gels into 10 mL deionized water at 60 °C. The gels were repeatedly removed and transferred into 10mL fresh deionized water at each fixed time interval. The released caffeine was analyzed at 272 nm by ultraviolet spectrophotometer (JASCO V530).

Results and discussion

The fundamental properties, such as equilibrium swelling ratio, gel strength, crosslinking density, and average molecular weight between crosslink points ($\overline{M}_c$), for the present copolymeric gels with different crosslinkers were investigated.

Effect of different crosslinkers on swelling ratio

The results in Table 2 indicate that the swelling ratio for N9E5 is larger than those for N9N5 and N9M5. From the viewpoint of chemical structure of these crosslinkers, the TEGDA bears 4 oxyethylene repeating units, which allow more water molecules hydrogen-bonding on its chains. In addition, the distance between two main chains for N9E5 is longer than those for N9N5 and N9M5. So the gel crosslinked with TEGDA, N9E5, exhibits the largest swelling ratio. On the other hand, the swelling ratio for N9N5 is slightly

Table 2 Characteristic properties of NIPAAm/PEGMEA copolymeric gels

Sample code	Q(g/g)	$G \times 10^2$ (MPa)	$\rho \times 10^6$ (mol/cm^3)	$\overline{M}_c$
N9M5	6.42	9.8	75.3	15900
N9N5	7.02	9.4	72.83	16500
N9E5	23.55	0.6	6.45	195000
N7E5	27.04	0.5	5.79	207000
N5E5	30.42	0.3	4.87	246000
N9E10A	20.37	0.6	6.14	185000
N9E10	16.89	0.8	8.75	137000
N9E10B	12.69	1.0	9.43	127000
N9E15	11.34	3.5	14.55	82000

larger than that for N9M5. This is because the amido group in NMBA (N9N5) has larger affinity for water than the ester group in EGDMA.

The effect of the crosslinker content on the swelling ratio for the copolymeric gels, coded by N9E5, N9E10, and N9E15, in Table 2 indicates that the swelling ratios for these gels increase in the order of N9E5 > N9-E10 > N9E15. This result implies that the structure of the gels would become denser and more tightened as the amount of crosslinker increased. This occurrence would decrease the space between gel networks and resulted in the decrease of swelling ratio. This result can also be confirmed by crosslinking density (ρ). In addition, the influence of initial monomer concentration on the swelling ratio of the gels prepared from three initial monomer concentrations i.e. 0.6M, 1.0M, and 1.5M, were coded by N9E10A, N9E10, and N9E10B. The result showed that swelling ratios for these gels increased with decrease in the initial monomer concentration. This result conforms to our previous results [28]. The effect of gel compositions, coded by N9E5, N7E5, and N5E5, on the swelling ratio shown in Table 2 indicates that the swelling ratio increases in the order of N5E5 > N7E5 > N9E5. That is, the higher the extent of PEGMEA in the gel the higher the swelling ratio. This result also shows that the hydrophilicity of PEGMEA is stronger than that of NIPAAm.

Effect of different crosslinkers on gel strength

The gel strength of the present copolymeric gels was evaluated from the gel modulus obtained from Eq. (5). The influence of different crosslinkers on the gel modulus for N9E5, N9N5, and N9M5 gels in Table 2 indicates that the gel modulus for N9M5 is higher than that for N9N5 and N9E5 gels. In other words, the gel strengths for the gels crosslinked with EGDMA and NMBA are higher than that for the gel crosslinked with TEGDA. This is because the crosslinker TEGDA bears long chain spacer between two vinyl groups (four oxyethylene repeating units). In the same manner, this result can be reflected by crosslinking density (ρ) and number-average molecular weight ($\overline{M}_c$). The results shown in Table 2 indicate that the values of ρ and $\overline{M}_c$ respectively obtained from Eqs. (6) and (7) for N9M5 gel are larger than those for N9N5 and N9E5. From above results, it is explicitly indicated that the crosslinking density (ρ) of a gel is reciprocal to $\overline{M}_c$, but proportional to shear modulus and the higher the crosslinking density is, the lower the swelling ratios is. Peppas reported that if all reagents used forms elastically effective crosslinkers, then the theoretical crosslinking density, ρ_t, is given as:

$$\rho_t = Cf/2 \tag{8}$$

where C is crosslinker concentration of the bulk polymer and f is crosslinker functionality [26, 29]. From Eq. (8), the crosslinking density is proportional to the crosslinker concentration. Based on this concept, the influence of the amount of crosslinker on the crosslinking density for the gels, N9E5, N9E10, and N9E15, crosslinked with 5 mol%, 10mol%, and 15mol% TEGDA, respectively, shows an increase in the order of N9E15 > N9E10 > N9E5. But, the $\overline{M}_c$ values for these gels show a contrary order. On the other hand, the crosslinking density depends on the swelling ratio for the gels with same crosslinker concentration such as N × E5 and N9E10 series gels. These results show that the ρ values decrease with increase in swelling ratios for these gels. Hence, the crosslinking density for these gels is related to the swelling ratio, crosslinker content, and initial monomer concentration, and the structure of crosslinker. Hence, the gel strength can be improved by the crosslinking density and crosslinker of the gels.

Effect on the swelling kinetics

The swelling ratios as a function of time for the present copolymeric gels in deionized water at 25 °C are shown in Figs. 1, 2, 3, and 4. According to Flory's swelling theory for nonionic gels, the following equation was given [30]:

$$Q^{5/3} = [\frac{(1/2 - \chi_1)}{V_1}]/(v_e/V_0) \tag{9}$$

where $(1/2\text{-}\chi_1)/V_1$ is the affinity of the hydrogel for water and v_e/V_0 is the crosslinking density of the hydrogel. Hence, the equilibrium-swelling ratio has a relation to the crosslinking density and the affinity of

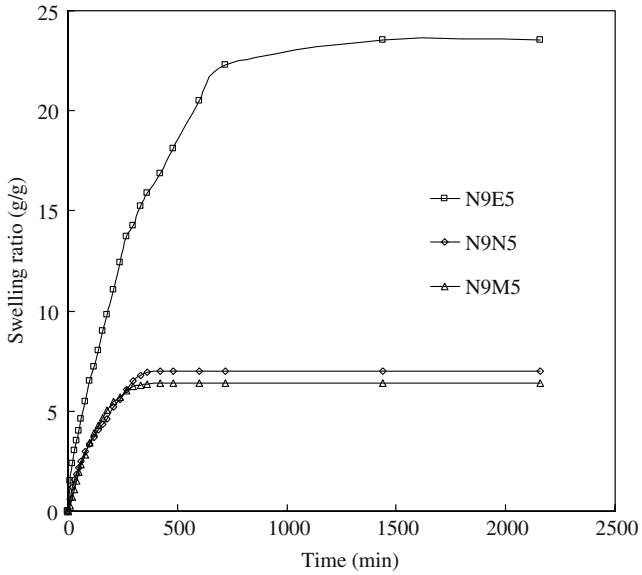

Fig. 1 Swelling ratio as a function of time for the copolymeric gels with different crosslinkers at 25 °C in deionized water

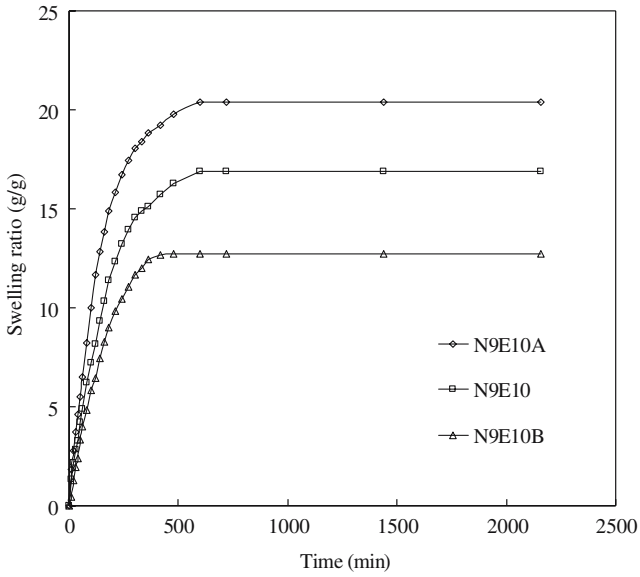

Fig. 3 Swelling ratio as a function of time for the copolymeric gels prepared by different initial monomer concentrations at 25 °C in deionized water

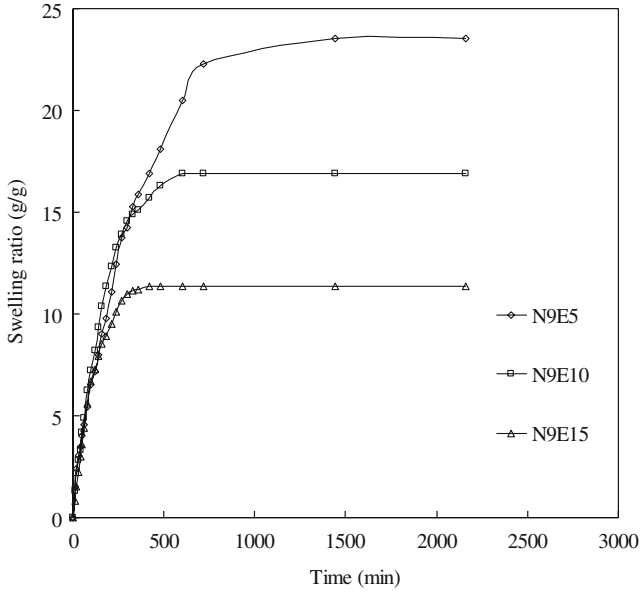

Fig. 2 Swelling ratio as a function of time for the copolymeric gels with different extents of TEGDA at 25 °C in deionized water

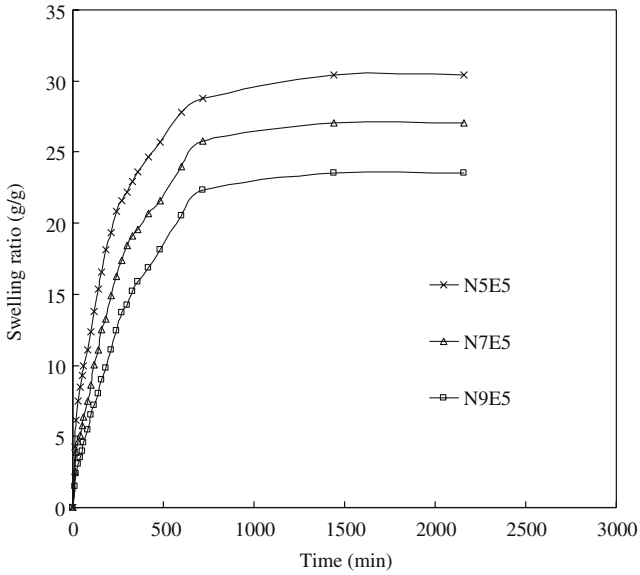

Fig. 4 Swelling ratio as a function of time for various copolymeric gels with different compositions at 25 °C in deionized water

the gel for water from above equation. This qualitative result conforms to our previous discussions.

Investigation of water diffusion in xerogels

The influence of the copolymeric gels on the swelling kinetic parameters such as kinetic exponent n, characteristic constant k, penetration velocity v, and initial diffusion coefficient D of water penetrated through copolymeric gels at various temperatures was investigated in this section.

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 kinetic in the present copolymeric gels, the initial swelling data were fitted to exponential heuristic Eq. (10) $M_t/M_\infty \leqq 0.6$ [31, 32]:

$$\frac{M_t}{M_\infty} = kt^n \tag{10}$$

where M_t is the amount of water sorbed at a given time, M_∞ is the equilibrium sorption at infinitely long time, k is a characteristic constant of the gel, and n is an characteristic exponent of the mode transport of the penetrate. The values of n and k were calculated from the slopes and intercepts of the plot of log M_t/M_∞ against log t, respectively. Alfrey et al. [33] proposed a useful classification according to the relative rates of diffusion and polymer relaxation. Three classes are distinguished: (1) Case I or Fickian diffusion ($n = 0.5$), in which the rate of diffusion is much smaller than that of relaxation. In this case the system is controlled by a diffusion process. (2) Case II ($n = 1.0$) is the other extreme, in which the diffusion process is very fast compared to the relaxation process. The controlling step is the velocity of an advancing front, which forms the boundary between a swollen gel and a glassy core. (3) Case III, Non-Fickian diffusion ($n = 0.5$~1.0) describes those cases where the diffusion and relaxation rates are comparable.

The Eq. (11) was used to calculate the diffusion coefficient D of water for $M_t/M_\infty \leqq 0.8$ [34].

$$\frac{M_t}{M_\infty} = \frac{4}{\sqrt{\pi}} \times \left(\frac{Dt}{L^2}\right)^{1/2} \tag{11}$$

where t is time, and L is the initial thickness of the dried sample. The penetration velocity v can be calculated from Eq. (4).

The values of n for N9 × 5 gel series (with different crosslinkers) shown in Table 3 are ranged from 0.57 to 0.98. This evidence shows that the swelling transport mechanisms for this series gels belong to non-Fickian transport. The n values for N9E × gel series (with different extents of crosslinkers) also increase from 0.65 to 0.93; i.e. N9E15 > N9E10 > N9E5, that is, their swelling transport mechanisms also belong to non-Fickian transport. But, for N × E5 gel series, the n values decrease from 0.65 to 0.47. This evidence shows that their swelling transport mechanism transforms from non-Fickian transport to Fickian transport as the PEGMEA in copolymeric composition increases. Hence, from above discussions, it is found that the transport mechanism of water diffused into the copolymeric gels is mainly related to their gel compositions, but not significantly related to the kind and the extent of different crosslinkers. In addition, based on the swelling ratios for these gels, the n values decrease with increase in swelling ratio; i.e. the transport mechanism is more approached to Fickian transport when the swelling ratios for these gels are higher.

Table 3 Initial diffusion coefficient of water D, penetration velocity v and kinetic exponent n, characteristic constant k of water penetrated through NIPAAm/PEGMEA copolymeric gels

Sample code	n	k	$D \times 10^7$ (cm^2/sec)	v(cm/min)
N9M5	0.98	0.47	1.35	0.041
N9N5	0.71	0.61	1.35	0.043
N9E5	0.65	0.57	1.61	0.115
N7E5	0.57	0.67	1.74	0.139
N5E5	0.47	0.92	1.91	0.157
N9E10A	0.74	0.58	1.59	0.111
N9E10	0.75	0.57	1.53	0.107
N9E10B	0.89	0.50	1.41	0.097
N9E15	0.93	0.51	1.38	0.076

The D values for the present copolymeric gels increase in the order of N9E5 > N9N5 = N9M5, N9E5 > N9E10 > N9E15, and N9E10A > N9E10 > N9E10B. These tendencies indicate that the diffusion coefficients for these gels increase with increase in their swelling ratios. At the same time, the penetration velocities (v) calculated from Eq. (4) for the present copolymeric gels also increase as the same tendency as their diffusion coefficients. These results imply that the higher the hydrophilicity of the gel; the more the water diffused into the gels; and the higher the velocity of water penetrated through the gels.

Effect of temperature on swelling ratio

The effect of temperature on the swelling ratios for the present copolymeric gels in deionized water is shown in Fig. 5. The results in Fig. 5 show that the swelling ratios decrease with increase in temperature. The deswelling behavior is more significant when the gels possess higher swelling ratio, that is, the tendency of deswelling is in the order N5E5 > N7E5 > N9E5 > N9E10 > N9N5 > N9M5. The results shown in Fig. 5 also indicate that the gel transition temperatures for these gels are shifted to higher temperature and the deswelling curves are steeper from the gel N9M5 to N5E5. This is due to the higher swelling ratio or more hydrophilicity for N5E5 gel.

Effect of gel composition on fractional release of caffeine

The release profiles of caffeine in N9M5, N9N5, and N9E5 copolymeric gels during deswelling at 60°C are shown in Fig. 6. The results shown in Fig. 6 indicate that the gel N9E5 has a higher and faster release profile of caffeine. This can be attributed that the gel crosslinked with TEGDA has a higher swelling ratio than that

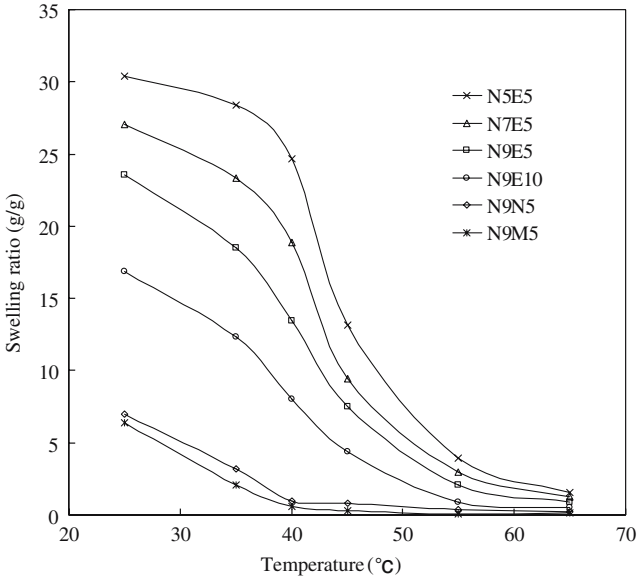

Fig. 5 Equilibrium swelling ratio for various copolymeric gels in deionized water at different temperatures

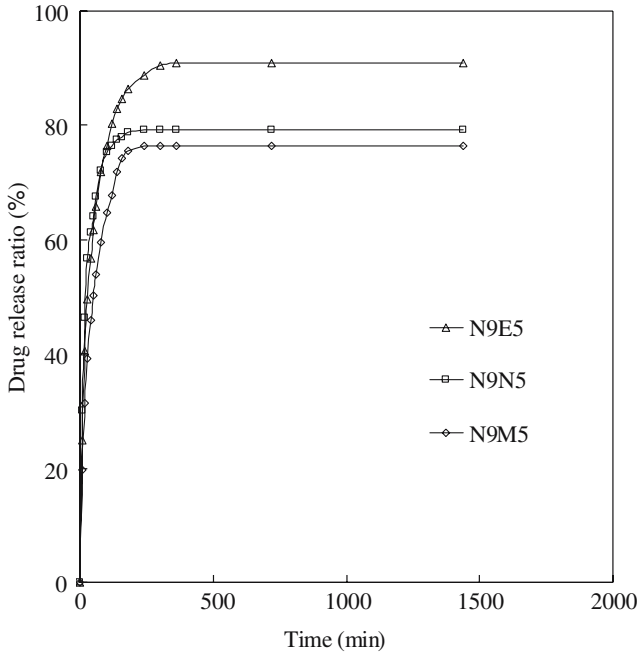

Fig. 6 Caffeine release profile on deswelling at 60 °C for the gels with different crosslinkers

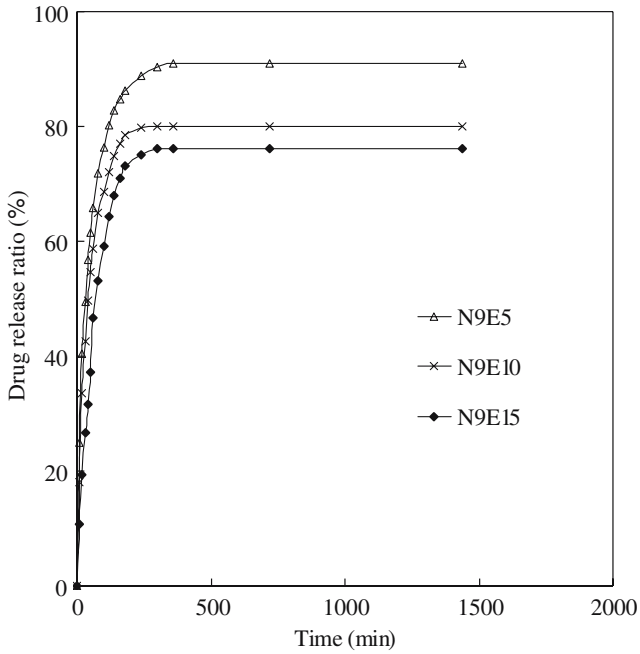

Fig. 7 Caffeine release profile on deswelling at 60 °C for the gels with different extents of TEGDA

crosslinked with NMBA or EGDMA, the more caffeine could be loaded into the gel at lower temperature (25 °C) and the more caffeine would be released out of the gel at higher temperature. The results also indicate that the caffeine loaded in the gels is not completely released and some portions are entrapped into the gels. This is due to the water pocket formed in the collapsed gel at high deswelling temperature.

The release profiles of caffeine in N9E5, N9E10, and N9E15 copolymeric gels, crosslinked with different extents of EGDA, during deswelling at 60 °C are shown in Fig. 7. The results in Fig. 7 also show that the fractional release of caffeine for the gel N9E5 is higher and faster than those for the gels N9E10 and N9E15. This is due to the lower crosslinking density and higher swelling ratio of N9E5.

The similar results for N9E10A, N9E10, and N9E10B copolymeric gels prepared from different initial monomer concentrations are obtained in Fig. 8. From above results, it can be found that the caffeine release behavior only depends on the swelling ratio for the present copolymeric gel, i.e. the higher the swelling ratio of the gel, the more the caffeine—incubated in the gel and the higher the caffeine released out of the gel.

Conclusions

The swelling behavior of thermoreversible NIPAAm/PEGMEA copolymeric hydrogels is related to the hydrophilicity of crosslinker used and crosslinking density of gels. The swelling ratios for the present copolymeric gels increase with the hydrophilicity of crosslinker (TEGDA > NMBA > EGDMA) and decrease with an increase of the contents of crosslinker (N9E5 > N9E10 > N9E15). The gel strength increases in the order EGDMA > NMBA > TEGDA for the

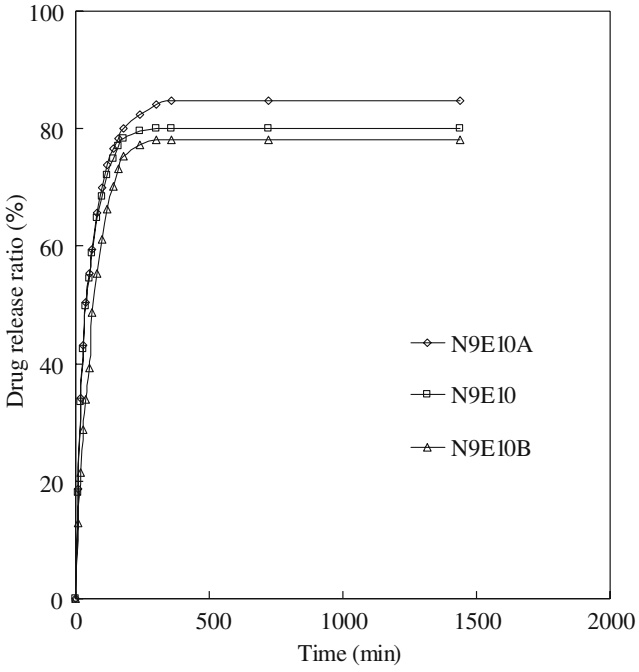

Fig. 8 Caffeine release profile on deswelling at 60 °C for the gels prepared by different initial monomer concentrations

present copolymeric gels. In diffusion transport mechanism, the results indicate that the swelling transport mechanisms for the present gels in water belong to non-Fickian transport except for N5E5 gel. The diffusion coefficients (D) of water for various gels increase with an increase of swelling ratio and penetration velocities (v). The release profiles of caffeine in the gels with higher swelling ratio are higher and faster than those of caffeine in the gels with lower swelling ratio.

Acknowledgements The authors wish to thank the National Science Council of the Republic of China for financial support under Grant No. NSC 89–2218-E-036–013.

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