Effect of Porosigen on the Swelling Behavior and Drug Release of Porous *N*-Isopropylacrylamide/ Poly(ethylene glycol) Monomethylether Acrylate Copolymeric Hydrogels

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ABSTRACT: A series of porous thermoreversible hydrogels were prepared from *N*-isopropylacrylamide (90 mol %) and poly(ethylene glycol) methylether acrylate (10 mol %), which was derived from poly(ethylene glycol) monomethylether, *N*,*N*′-methylenebisacrylamide, and porosigen, or poly (ethylene glycol) (PEG) with different molecular weights (MWs). The influence of pore volume in the gel on the physical properties, swelling kinetics, and solute permeation from these porous gels was investigated. The results show that the surface areas, pore volumes, and equilibrium swelling ratios for the porous gels increased with increasing MW of PEG, but the shear moduli and effective crosslinking densities decreased with increasing MW of PEG. The results from the dynamic swelling kinetics show that the transport mechanism was non-Fickian. The diffusion coefficients of water penetrating into the gels increased with increasing pore volume of the gels. In addition, we also studied solute permeation through the porous gel controlled by temperature. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 102: 5490–5499, 2006

Key words: hydrogels; macroporous polymers; separation techniques; stimuli-sensitive polymers; swelling

INTRODUCTION

Hydrogels are crosslinked materials absorbing large quantities of water without dissolving. There are some hydrogels that can modulate their swelling ratios (*Q*s) in response to environmental stimuli, such as temperature,[1,2] pH,[3,4] chemicals,[5] photoirradiation,[6] and electric field.[7] Thermoresponsive hydrogels demonstrate a volume transition and associated phase transition from a low-temperature, highly swollen gel to a high-temperature, collapsed gel near their critical temperature.[8–10] Poly(*N*-isopropylacrylamide) and its copolymers have been studied in the development of drug release systems, membrane separation,[11] and controlled drug delivery.[12,13]

Hydrogels based on poly(ethylene glycol) (PEG) have attracted considerable attention in controlled release technology because of their good biocompatibility and excellent physicochemical properties.[14] Porous hydrogels can be prepared by the porosigen method. In the porosigen method, porous hydrogels are prepared in the presence of dispersed water-soluble porosigens, such as sodium chloride and PEG, which can be removed later by washing with water to leave a meshwork.[15,16] The influence of charge effects on drug release behavior for ionic thermosensitive hydrogels prepared from *N*-isopropylacrylamide (NIPAAm) and different charged monomers and pore-forming agents (PEG) was reported in our previous study.[17]

Long PEG side chains, providing water release channels within the skin layer, in thermosensitive hydrogels were presented by Okano et al.[18] The investigation of the effect of the oxyethylene chain length in poly (ethylene glycol) methylether acrylate (PEGMEA) and the PEGMEA content in NIPAAm/PEGMEA copolymeric gels on swelling and drug release behaviors was reported in our previous article.[19] In this study, we fixed the oxyethylene chain length and content of PEGMEA in NIPAAm/PEGMEA copolymeric gels but changed the porosigen content to investigate these hydrogel properties. Hence, a series of porous thermoreversible hydrogels prepared from NIPAAm (90 mol %) and PEGMEA (10 mol %) and PEG with different molecular weights (MWs) were prepared. The influence of the pore effect of these hydrogels on the *Q* behavior, drug delivery behavior, and solute permeation from these gel membranes was studied.

EXPERIMENTAL

Materials

NIPAAm (Wako Pure Chemical Industries, Ltd., Osaka, Japan) was recrystallized in *n*-hexane before use.

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Acryloyl chloride, poly(ethylene glycol) monomethyl ether, and *N,N,N′,N′*-tetramethyl ethylenediamine as an accelerator were obtained from Fluka Chemical Co. (Buchs, Switzerland). PEG as porosigen with different MWs was purchased from Aldrich Chemical Co. (St. Louis, MO). *N,N′*-methylenebisacrylamide as a crosslinking agent and ammonium persulfate as an initiator were purchased from Tokyo Kasei Industries, Ltd. (Tokyo). Caffeine (MW = 194) and crystal violet (CV; MW = 407) as model drugs were obtained from Fluka Chemical Co. The proteins lactalbumin (MW = 14,000), chymotrypsinogen (MW = 25,000), and bovine serum albumin (BSA; MW = 64,000) were obtained from Sigma Chemical Co. (St. Louis, MO). All solvents and other chemicals were analytical grade.

Preparation of PEGMEA

PEGMEA synthesized from poly(ethylene glycol) monomethylether (MW = 350) and acryloyl chloride was reported in our previous study.[19] The boiling point of PEGMEA was 72°C/7 mmHg. IR and NMR techniques identified the monomer of PEGMEA.

Preparation of the porous hydrogels

The monomers, NIPAAm (90 mol %) and PEGMEA (10 mol %), and 5 mol % *N,N′*-methylenebisacrylamide based on total monomer content were dissolved in 10 mL of deionized water. To this solution, 3 g of PEG with various MWs, 1 mol % ammonium persulfate, and 1 mol % *N,N,N′,N′*-tetramethyl ethylenediamine 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 (2 mm) between the two glass plates. Polymerization was carried out at room temperature for 1 day. After gelation was complete, the gel membrane was cut into discs 10 mm in diameter and immersed in an excess amount of deionized water for 4 days to completely remove porosigen, PEG, and residual unreacted monomer until the weight of the gel sample remained constant. Swollen polymer gels were then dried at 25°C for 1 day and dried in a vacuum oven for 2 days.

Swelling experiments

The dried gels were immersed in an excess amount of deionized water at different temperatures until the swelling equilibrium was attained. The weight of the wet sample (W_w) was determined after removal of the surface water by blotting with filter paper. Dry weight (W_d) was determined after the gel was dried in a vacuum oven for 2 days. Q was calculated from the following equation:

$$Q = (W_w - W_d)/W_d \tag{1}$$

The penetration velocity (v) of water in each gel was determined by the weight gain method, as described by Peppas and coworkers.[20,21] v was calculated with the following equation:

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

where dw/dt is the slope of the weight gain versus time curve, ρ_w is the density of water, 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 property measurement

The gel strength of these samples was measured by uniaxial compression experiment with universal tester (Lloyd LRX). The following equation was used to calculate the shear gel modulus (G):[22,23]

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

where τ is the compression stress, F is the compression load, A is the cross-sectional area of the swollen gels, and λ is the compression strain (L/L_0). At low strains, a plot of shear stress versus $-(\lambda - \lambda^{-2})$ yield a straight line whose slope is G. The effective crosslinking density (ρ) can be calculated from G and polymer volume fraction (v_2) as follows:

$$\rho = G/v_2^{1/3}RT \tag{4}$$

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

Morphology

Samples were equilibrated in deionized water for 2 days; the swollen gels were frozen at liquid nitrogen and then fractured and freeze-dried. The fractured specimens were examined for morphological details with scanning electron microscopy (SEM; Jeol JXA8600) with an acceleration voltage of 15 kV. The specimens were coated with a gold metal layer to provide proper surface conduction.

Surface area and pore structure

The equipment used for surface area and pore structure characterization was an accelerated surface area and porosimetry system (Micromeritics ASAP2000). It was a fully automatic and computerized system that performed the adsorption of N_2 and processed the data simultaneously. Surface area was calculated with the Brunauer–Emmett–Teller equation, and the pore volume was calculated according to the Barrett–Joyner–Halenda theory.[24]

Drug release experiment

The dry gels were equilibrated in 30 mg of drug/10 mL of deionized water at 25°C for 1 day to load drug into the gels. We carried out the drug release experiments 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 of fresh deionized water at each fixed time interval. The released drug was analyzed at 272 and 561 nm for caffeine and CV, respectively, with a UV spectrophotometer (JASCO V530).

Cycling drug loading and releasing experiment

The dry gels were equilibrated in 30 mg of drug/10 mL of deionized water at 25°C for 1 day to load drug into the gels. We carried out the cycling drug loading and releasing experiments 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 of deionized water at each fixed time interval. When the drug was not released from the gels any more, the gels were reimmersed into the original drug solution for 1 day. Then, the release experiment was repeated. The previous steps were repeated. The released drug was analyzed at 272 nm for caffeine with the UV spectrophotometer (JASCO V530).

Diffusion studies

Side-by-side diffusion cells were used to perform solute diffusion studies. We maintained a constant temperature by circulating constant-temperature fluid through the water jackets. For continuous agitation, each half-cell also contained a magnetic stirrer. The gels were preequilibrated at predetermined temperatures, including 15, 25, and 40°C. A preequilibrated hydrogel membrane was clamped between the half-cells. The drugs used in these studies were caffeine (MW = 194), CV (MW = 407), lactalbumin (MW = 14,000), chymotrypsinogen (MW = 25,000), and BSA (MW = 64,000). In a typical experiment, 25 mL of deionized water was poured into the receptor compartment, and 25 mL of a freshly prepared drug solution with a concentration of 100 ppm was poured into the donor compartment. Drug concentration was detected with the UV spectrophotometer (JASCO V530) at 272 nm for caffeine, 249 nm for CV, 280 nm for lactalbumin, 280 nm for chymotrypsinogen, and 595 nm for BSA.

RESULTS AND DISCUSSION

Some fundamental properties, such as equilibrium *Q*s, pore volume, surface area, and gel strength, for the copolymeric gels were investigated. Also, the drug release and solute permeation through the gels and the relation of crosslinking density and the polymer–solvent interaction parameter (χ) were investigated and are discussed in the following section.

Effect of porosigen (PEG) on the physical properties of the gels

Some characteristics of the porous NIPAAm/PEGMEA copolymeric gels are shown in Table I. The results in Table I indicate that the surface areas and the pore volumes in the gels increased with increasing MW of PEG added during gel preparation. This is because the PEG was washed out in water-washing process; then, the sites occupied by PEG were vacated. The pore in the gel increased with increasing MW and content of PEG during gel formation. That resulted in an increase in the surface area and pore volumes in the gels. Hence, the *Q* increased with increasing pore volume or surface area of the gel when the gel was brought into contact with water (E > D > C > B > A > F). However, the gel strength, that is, *G* obtained from the slope of the plot of shear stress versus $-(\lambda - \lambda^{-2})$, decreased with increasing MW of PEG. This result implies that the gel strength became weaker when PEG with a higher molecular size was introduced during gel formation. This result also shows that the gel structure became looser. This was proven by the morphology of the gels. Similar results were observed in our previous study.[17]

TABLE I
Characterization of the Copolymeric Hydrogels with 90 mol % NIPAAm and 10 mol % PEGMEA and Various PEG Amounts

Sample	PEG M_w	PEG (g)	Surface area (m^2/g)	Pore volume $\times 10^3$ (cc/g)	*G* (MPa)	$\rho \times 10^6$ (mol/cm^3)	χ	*Q* (g/g)
A	200	3	0.811	1.810	0.069	58.27	0.505	8.94
B	2,000	3	1.245	2.655	0.047	43.71	0.502	12.32
C	8,000	3	2.096	2.865	0.025	25.32	0.489	14.34
D	20,000	1	2.188	3.655	0.009	9.15	0.481	17.21
E	20,000	3	3.459	5.471	0.007	7.31	0.462	20.08
F			0.150	0.853	0.094	72.83	0.524	7.02

M_w, weight-average molecular weight.

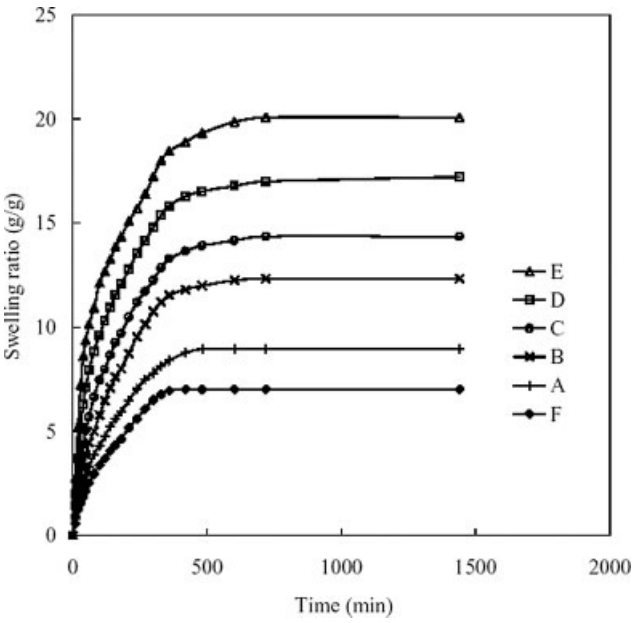

Figure 1 Q as a function of time for the copolymeric gels in deionized water at 25°C.

ρ for these gels, obtained from eq. (4) and shown in Table I, indicated that the ρ values decreased with increasing PEG content. As shown by eq. (4), ρ depended on G and Q. Because Q for the gels did not have much variation, the ρ values were mainly related to G. Hence, the ρ values decreased with decreasing G for these gels.

On the other hand, the total copolymer–water interaction parameter (χ) could be calculated from eq. (5):

$$\ln(1-\nu_2)+\nu_2+\chi\nu_2^2+\rho V_1\left(\nu_2^{1/3}-0.5\nu_2\right)=0 \quad (5)$$

which was derived from the Flory–Rehner equation,[25–27] where V_1 (cm^3/mol) is the molar volume and ν_2 is the volume fraction of copolymer in hydrogel. χ accounts for the free energy change caused by the mixing process. The χ values shown in Table I indicated that χ values decreased with decreasing crosslinking density and with increasing Q for these gels. That is, on the basis of increasing pore volume, the gel matrix became more flexible when a PEG of higher MW was added during gel preparation.

Effect of porosigen on the swelling kinetics

The Q values as a function of time for the copolymeric gels in deionized water are shown in Figure 1. The influence of PEG on the swelling kinetic parameters, including the kinetic exponent (n), characteristic constant (k), initial diffusion coefficient of water (D), and v of water penetrated through copolymeric gels at 25°C was investigated and is discussed in this section.

To investigate the diffusion model of the gel, the initial swelling data were fitted to the exponential heuristic equation for $M_t/M_\infty \leq 0.6$:[28,29]

$$\frac{M_t}{M_\infty}=kt^n \quad (6)$$

where M_t is the amount of water sorbed at a given time, M_∞ is the equilibrium sorption at infinitely long time, and n is a 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_∞ versus log t, respectively. The results in Table II indicate that the n values were between 0.71 and 0.75. This result implies that the transport mechanism was non-Fickian, according to the classification of diffusion mechanisms proposed by Alfrey et al.[30] The results also indicate that the n values increased with increasing size (MW) of PEG.

The diffusion of a gel depends on the diffusion rate of absorbing solvent into a gel and the relaxation rate of a gel network. D can be used to investigate the diffusion process of a gel during the initial swelling stage. Equation (7) was used to calculate D for $M_t/M_\infty \leq 0.8$:[31]

$$\frac{M_t}{M_\infty}=\frac{4}{\sqrt{\pi}}\times\left(\frac{Dt}{L^2}\right)^{1/2} \quad (7)$$

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

In addition, eq. (2) was used to calculate the initial v at 25°C. The data shown in Table II indicated that the D values increased two times with increasing pore volume inside the gels, that is, E > D > C > B > A > F, and v for these gels also increased with increasing pore volume of the gels. These results explicitly show that the gels with larger pore volumes had higher v values; that is, water easily penetrated into the gels during the initial swelling process.

Effect of temperature on Q

The effect of temperature on the equilibrium Qs for the copolymeric hydrogels is shown in Figure 2. The

TABLE II
Initial D, v, n, and k Values of Water Penetrated Through the Copolymeric Gels at Various Temperatures

Sample	Q (g/g)	v (cm/min)	n	k	$D \times 10^7$ (cm^2/s)
A	8.94	0.06	0.71	0.51	2.65
B	12.32	0.07	0.72	0.52	2.69
C	14.34	0.11	0.72	0.51	2.75
D	17.21	0.14	0.73	0.48	2.81
E	20.08	0.18	0.75	0.50	2.94
F	7.02	0.04	0.71	0.61	1.35

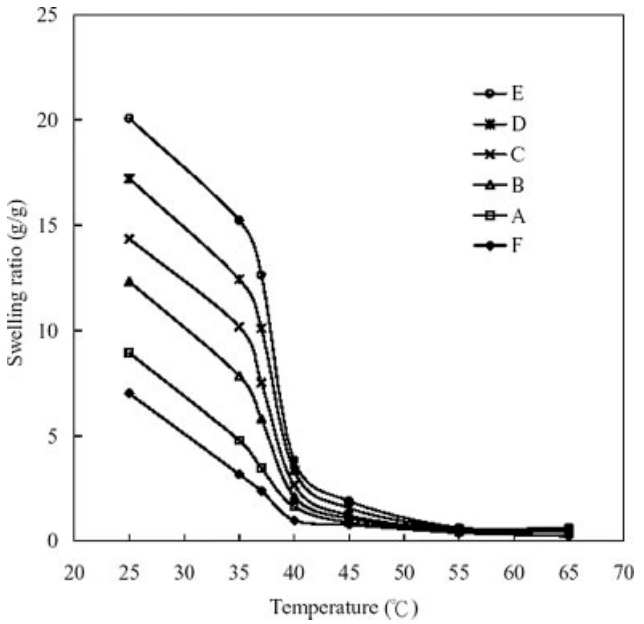

Figure 2 Effect of temperature on equilibrium Q for the copolymeric gels in deionized water.

results shown in Figure 2 indicate that Q decreased with increasing temperature, the gel transition temperatures were not affected by the addition of PEG into the gel composition, and Q decreased rapidly for the larger pore gel (gel E).

Drug release in the gels

Figure 3 shows the drug release fraction at 37°C for these gels. The result show that the fractional release for the gels increased in the order A < B < C < D < E. This result explicitly indicates that the drug release was improved by the increase of pore volume inside the gel and that the water pocket effect was reduced at higher temperature (37°C). When Figure 3(a) is compared with Figure 3(b), one can see that the release amount of CV was lower than caffeine. This was because the larger molecular size of CV entrapped into the gel could not easily penetrate through the denser skin layer. Hence, more CV could not release in the releasing process.[32–34]

The cycling drug loading and releasing of the copolymeric gels was performed by the immersion of the dried gels into drug solution to load the drug at 25°C and release the drug at 37°C. According to the previous discussions, the gels showed thermosensitive properties in different temperatures and responded to the volume change of the gels. We applied the thermosensitive behavior of the gels to the cycling drug release test for these copolymeric gels. Figure 4 shows the result of caffeine release in the long term between 25 and 37°C in the gels. The release amount of drug at the first cycle release increased in the order E > D > C > B > A > F. This result is the same order as the Q values of these gels. As the gel released at the second cycle, the drug-released amounts for gel F were lower than the first cycle and approached constant release after three cycle operations. However, the released amount for other porous gels reached a constant value at the second cycle release. Hence, the porous gels could shorten the cycling drug release behavior.

Pore effect on solute permeation through the hydrogels

The pore size of the gel membrane changed with the operation temperature of the gel and the amount of PEG during gel preparation. Hence, the swelling vol-

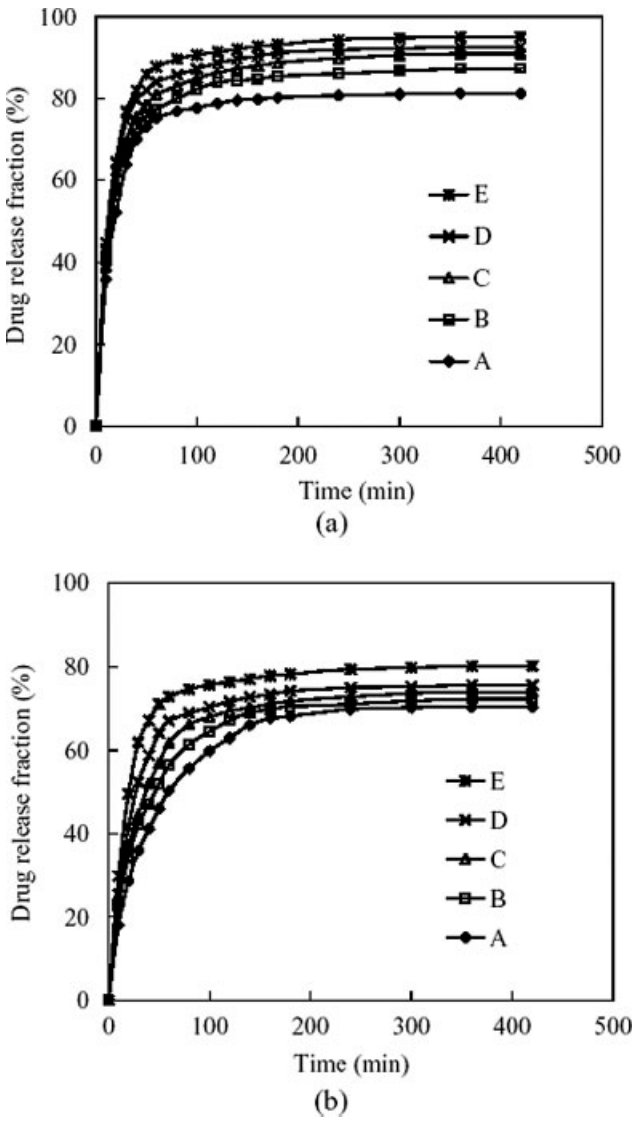

Figure 3 Drug release profiles during loading at 25°C and releasing at 37°C: (a) caffeine and (b) CV.

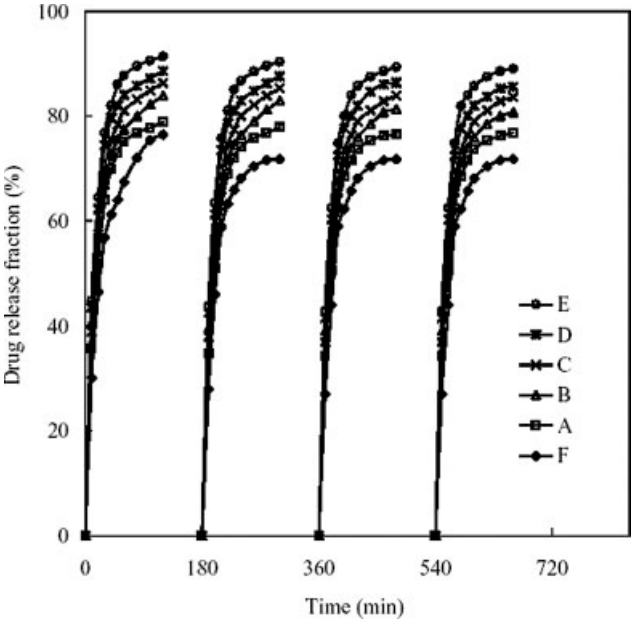

Figure 4 Caffeine cycling releasing profile during loading at 25°C and releasing at 37°C.

ume of the gel decreased under higher temperature operations. In this condition, the gel membrane tensed, and the pore size of the gel membrane was smaller, which resulted in difficult penetration of the bigger solute at higher temperature. To confirm this concept, Figures 5, 6, and 7 show the diffusion experiment for some solutes, including caffeine, CV, lactalbumin, chymotrypsinogen, and BSA, permeated through the porous gel membranes porosigened with different MWs of PEG at 15, 25, and 40°C, respectively. The results in these figures show that when larger molecules of PEG were added to the gels or the gels at low temperature, larger solutes easily permeated through the gel membrane. For example, as shown in Figure 5, under 15°C, the higher MW solutes, chymotrypsinogen (MW = 25,000) and BSA (MW = 64,000), could not penetrate through the small-pore-size membrane (sample A) but could penetrate through the larger pore size membrane (sample E). However, when the temperature was modulated to 25°C (Fig. 6), lactalbumin (14,000) could not penetrate through the sample A membrane, and chymotrypsinogen (MW = 25,000) could not penetrate through the sample B membrane. When the temperature was modulated to 45°C (Fig. 7), solute with a MW smaller than 14,000 nearly could not penetrate through the membranes of samples A, B, and C until 200 h of penetration. Because the pore size of the gels became smaller when the temperature was elevated, the bigger solute could not easily pass through gel membrane. Hence, the excellent behavior of this porous gel could be used to separate solutes with different MWs.

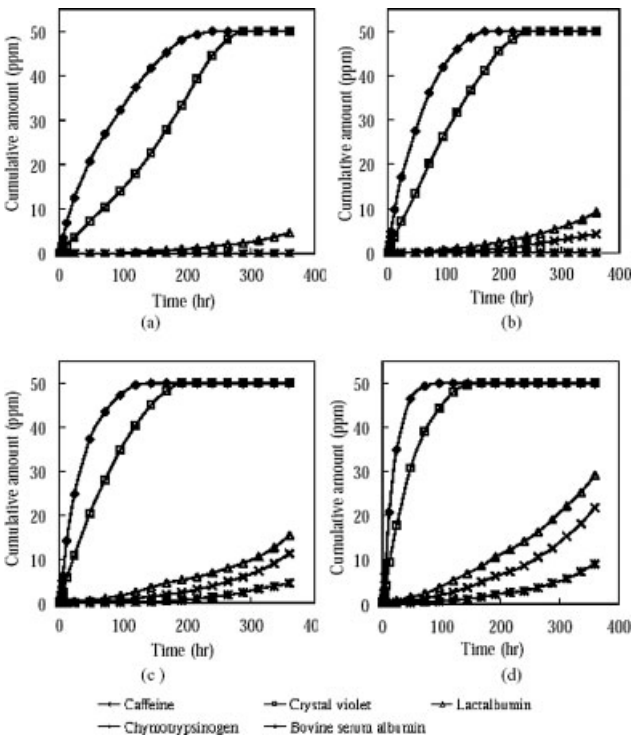

Figure 5 Cumulative amount of solute permeated through the membrane as a function of time at 15°C: samples (a) A, (b) B, (c) C, and (d) E.

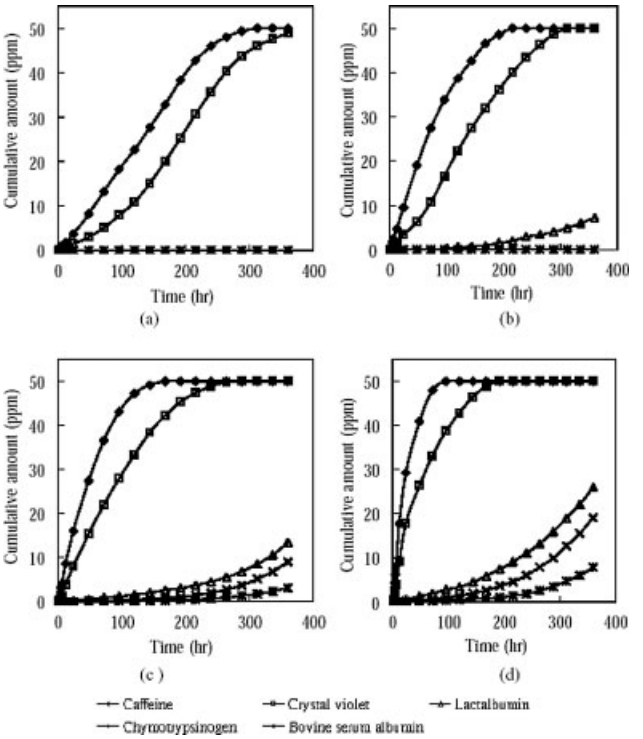

Figure 6 Cumulative amount of solute permeated through the membrane as a function of time at 25°C: samples (a) A, (b) B, (c) C, and (d) E.

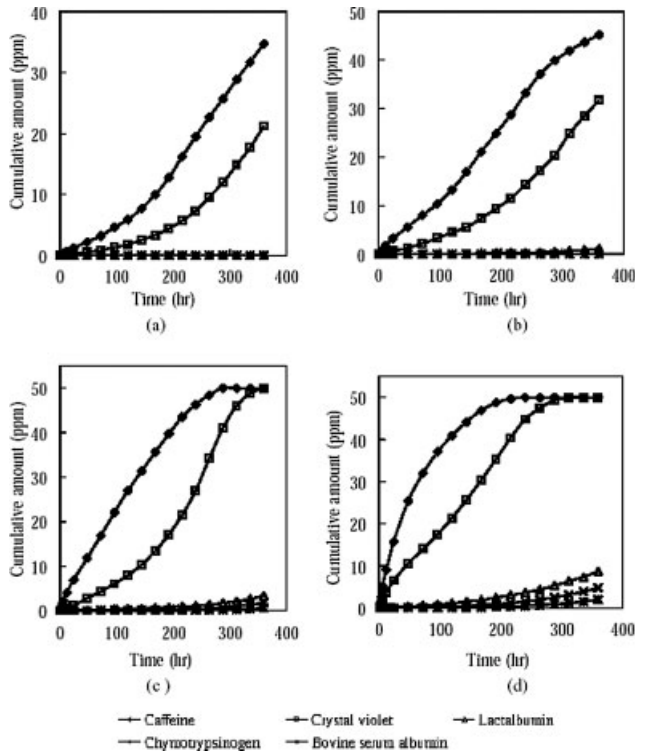

Figure 7 Cumulative amount of solute permeated through the membrane as a function of time at 40°C: samples (a) A, (b) B, (c) C, and (d) E.

Determination of *D* of permeation

The solute permeability coefficients (P) were determined with eq. (8):[35–38]

$$\ln\left(\frac{2C_t}{C_0} - 1\right) = \frac{2A}{V}Pt \tag{8}$$

where C_t is the solute concentration in the receptor cell at time t, C_0 is the initial solute concentration in the donor cell, V is the solution volume of each of the half-cells, A is the effective area for permeation, and P is the permeability coefficient. To determine the permeability coefficient, a plot of $-\ln(1–2C_t/C_0)$ versus time yielded a straight line with slope of $2AP/V$.

The partition coefficient (K_d) was calculated from experimental data with eq. (9):[39,40]

$$K_d = C_m/C_s = V_s(C_i - C_0)/V_mC_0 \tag{9}$$

where C_m and C_s are the concentrations of the solute in the membrane and in the surrounding solution at equilibrium, respectively; C_i is the initial concentration of solute in solution; C_0 is the concentration of solute in the solution at equilibrium; and V_s and V_m are the volumes of the solution and membrane, respectively.

The solute diffusion coefficient (D_p) was calculated from the permeability coefficients (Table III) and K_d (Table IV) along with the characteristic thickness of each hydrogel membrane, according to eq. (10):

$$D_p = PL/K_d \tag{10}$$

where L is the thickness of the hydrogel membrane. In general, some factors that affect the solute permeation velocity can be summarized as the size of solutes, polymer network, and interactive force between the solute and polymer. We discuss these factors next.

Effect of size of the solute

The diffusion of a solute through a gel membrane is affected by the size of solute.[41] The results from our experiment shown in Figures 5–7 indicate that the diffusion rate of macromolecular protein was lower. After the calculations, the solute permeability coefficients (P)

TABLE III
Permeability Coefficients of Various Solutes Permeated Through NIPAAm/PEGMEA Gels of Different Sizes

		$P \times 10^6$ (cm/s)			
Temperature (°C)	Model solute	A	B	C	E
15	Caffeine	27.19	39.06	63.00	95.82
	CV	8.87	22.07	28.87	46.63
	Lactalbumin	0.46	1.02	1.88	4.46
	Chymotrypsinogen	—	0.23	1.17	2.73
	BSA	—	—	0.44	0.91
25	Caffeine	15.56	26.83	41.51	62.53
	CV	10.19	14.48	24.17	35.65
	Lactalbumin	—	0.77	1.38	3.51
	Chymotrypsinogen	—	—	0.74	2.06
	BSA	—	—	0.25	0.67
40	Caffeine	6.42	13.84	17.93	33.54
	CV	2.49	4.91	7.75	13.48
	Lactalbumin	—	—	0.32	1.02
	Chymotrypsinogen	—	—	0.14	0.47
	BSA	—	—	0.05	0.16

TABLE IV
K_d Values of Various Solutes in NIPAAm/PEGMEA Gels of Different Sizes

		K_d			
Temperature (°C)	Model solute	A	B	C	E
15	Caffeine	0.10	0.09	0.10	0.07
	CV	0.10	0.12	0.10	0.09
	Lactalbumin	0.14	0.14	0.13	0.14
	Chymotrypsinogen	—	0.52	0.11	0.13
	BSA	—	—	0.10	0.10
25	Caffeine	0.16	0.14	0.14	0.10
	CV	0.17	0.15	0.13	0.12
	Lactalbumin	—	0.18	0.11	0.14
	Chymotrypsinogen	—	—	0.14	0.14
	BSA	—	—	0.08	0.09
40	Caffeine	0.11	0.09	0.08	0.07
	CV	0.13	0.11	0.08	0.08
	Lactalbumin	—	0.24	0.13	0.09
	Chymotrypsinogen	—	—	0.15	0.06
	BSA	—	—	0.24	0.36

at the same temperature decreased with increasing MW of solutes and in the order caffeine > CV > lactalbumin > chymotrypsinogen > BSA. In addition, the P values increased with increasing pore volume of the gel membrane (Table III).

Effect of the pore volume of the polymer network

Crosslinking agent, temperature, pH value, ionic concentration and pore forming agent added affect the pore volume of a polymer network. The results shown in Table V indicate that the gels had larger D values at 15°C. That is, when gels were at 15°C, the polymer network of the gels became larger, and then, more solutes could pass through the gel membrane. The gel prepared with PEG20000 had the largest pore, so larger solute-like proteins could pass through. All solutes in this experiment could pass through the gel membrane with PEG20000 [see Fig. 5(d)]. The permeation rates and D values decreased with increasing temperature because of the decreasing pore size in the gel membranes.

Effect of the interactive force between the solute and the polymer

One of the changing factors of the solute diffusion behaviors in gels is the interactive force. Papini et al.[42] obtained K_d values above 1 by a penetration experiment, and therefore, they judged that an interactive force existed between the solutes and gels. Kim et al.[43] found that there was a stronger interactive force between drugs and gels when K_d values were above 1 with a hydrophilic carbohydrate solute and hydro-

TABLE V
***D*s of Various Solutes Permeated Through NIPAAm/PEGMEA Gels of Different Sizes**

		$D_p \times 10^6$ (cm^2/s)			
Temperature (°C)	Model solute	A	B	C	E
15	Caffeine	52.26	88.57	132.59	264.01
	CV	17.15	38.31	58.07	98.76
	Lactalbumin	0.63	1.47	2.95	6.52
	Chymotrypsinogen	—	0.09	2.14	4.25
	BSA	—	—	0.89	1.84
25	Caffeine	18.91	37.71	59.56	129.41
	CV	11.88	19.56	36.99	57.58
	Lactalbumin	—	0.88	2.52	4.99
	Chymotrypsinogen	—	—	1.06	2.86
	BSA	—	—	0.59	1.43
40	Caffeine	11.21	29.72	47.38	95.36
	CV	3.94	8.78	19.68	35.75
	Lactalbumin	—	0.08	0.51	2.35
	Chymotrypsinogen	—	—	0.19	1.46
	BSA	—	—	0.04	0.09

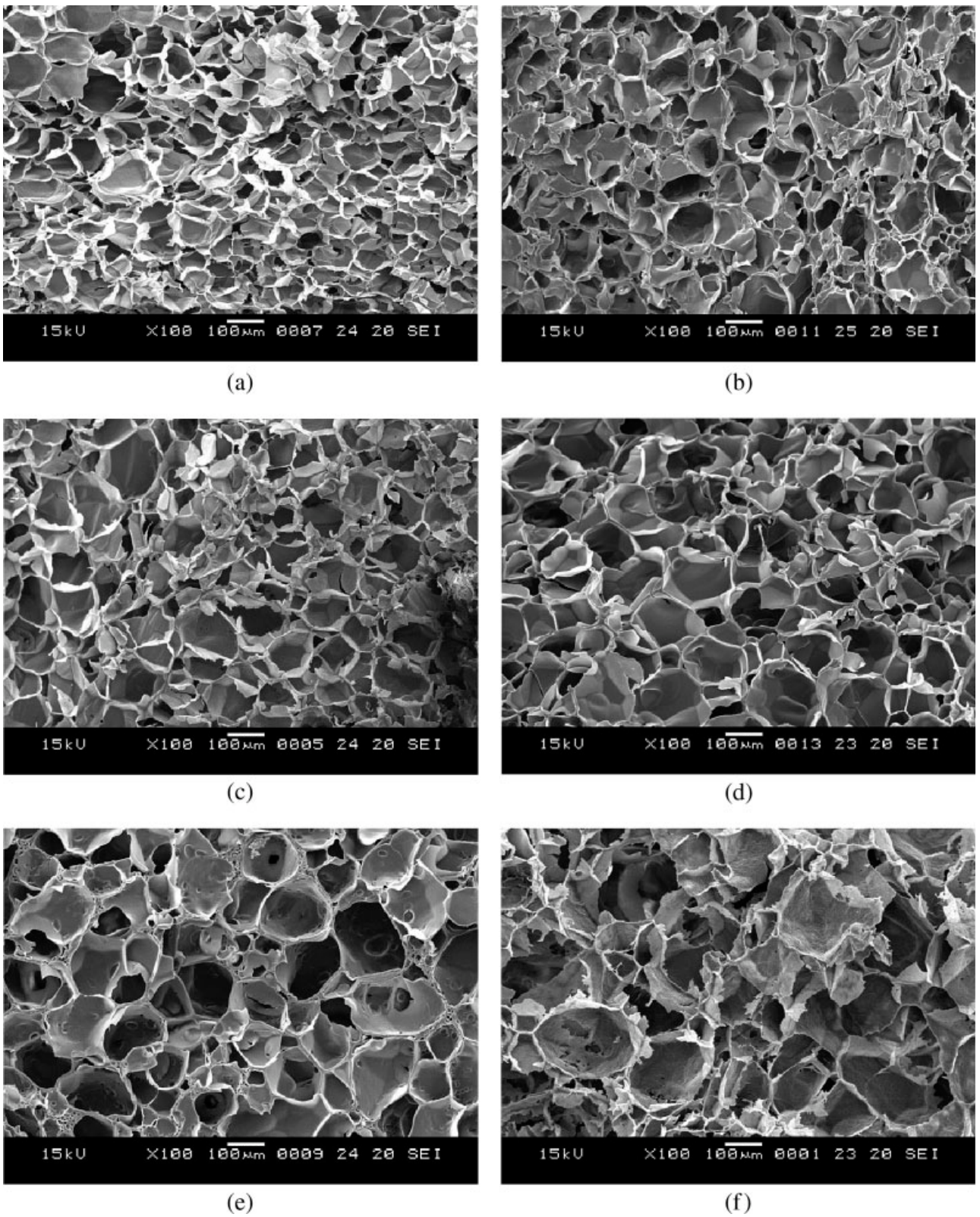

Figure 8 Cross-sectional scanning electron micrographs of the gels (×100): samples (a) F, (b) A, (c) B, (d) C, (e) D, and (f) E.

phobic steroid solute experiment. For chemical potential energy, solutes tend to stay in the solution phase because the K_d values are below 1. In this manner, the interactive force can be ignored, and the diffusion behavior can only be described by the size of solute. In our gel systems, the K_d values (Table IV) decreased

with increasing pore volume of the gel membrane. All K_d values were below 1. Hence, the diffusion behavior of the solute in the gels was obviously affected by the size of solute.

Finally, as discussed previously, these porous thermosensitive hydrogels could be used to separate solute mixtures with different molecular sizes by the changing of the temperature to control the pore size of the gel.

SEM

Finally, to prove the fact that the gels prepared with higher MWs of PEG had larger pore sizes, the morphologies of the swollen and freeze-dried gels were examined by SEM. The results in Figure 8 show that the pore size increased with increasing MW of PEG added during gel preparation (F < A < B < C < D < E).

CONCLUSIONS

A series of porous thermosensitive copolymeric hydrogels were prepared from NIPAAm and PEGMEA and a pore-forming agent. The SEM images showed that the pore size of gel structure became larger when PEG with a larger MW was added during gel preparation. The surface areas and pore volumes increased with increasing content of PEG. On swelling behavior, the gels with larger pores had higher Q value, but the gels with larger pores become weaker after swelling. Ds and v for these gels increased with increasing pore volume inside the gels. The pore size of these gels could be easily controlled by the modulation of the temperature, and temperature could used to separate the solutes with different MWs. On drug release, the gels with higher Q values had better drug release behavior. The results in the solute diffusion experiment indicate that gels with larger pores could make macromolecular proteins pass through gel membrane. These porous thermosensitive gels at high temperature possessed lower D_p values.

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