pH–Thermoreversible Hydrogels. II. Synthesis and Swelling Behaviors of N-Isopropylacrylamide-*co*-acrylic acid-*co*-sodium acrylate Hydrogels

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ABSTRACT: A series of pH–thermoreversible hydrogels are prepared from the three molar ratios of *N*-isopropylacrylamide (NIPAAm) and acrylic acid neutralized 50 mol % by sodium hydroxide (SA50) and *N,N′*-methylene bisacrylamide (NMBA). The influence of the environmental conditions, such as temperature and pH values, on the swelling behavior of these copolymeric gels is also investigated in this article. Results show that the hydrogels bearing negative charges exhibit different equilibrium swelling ratios under various pH media. The pH sensitivities of these gels also strongly depend on the molar ratio of SA50 in the copolymeric gels; thus, the more the SA50 content, the higher the gel pH sensitivity. These hydrogels exhibited thermosensitivity demonstrating a larger change of the equilibrium swelling ratio in aqueous media under temperature changes. An overshooting phenomenon is observed from the gel swelling kinetics under high-temperature conditions. The said hydrogels are also used to investigate the release of model drugs in this study. © 1999 John Wiley & Sons, Inc. J Appl Polym Sci 73: 1955–1967, 1999

Key words: reversibility; pH-thermoreversible hydrogel; N-isopropylacrylamide-*co*-acrylic acid copolymeric gel; overshooting; drug release

INTRODUCTION

Hydrogels are three-dimensional hydrophilic polymeric networks that 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 pH,[1–3] temperature,[4,5] ionic strength,[6] and electric field,[7] especially temperature and pH, because those factors are variable changes in typical physiological, biological, and chemical systems.[8]

Thermoresponsive hydrogels demonstrate a volume transition and associated phase transition from at low-temperature, highly swollen gel, to, at high-temperature, collapsed gel near its critical point.[9,10] Poly(*N*-isopropylacrylamide) poly(NIPAAm) is one of the best thermotropic polymers and exhibits lower critical solution temperature (LCST) behavior, collapsing and shrinking above the LCST at 33°C. The temperature-induced collapse transition for hydrogels containing a hydrophobic group has been observed in our previous study.[11] Poly(NIPAAm) and its copolymers have been studied in the development of temperature-modulated drug release systems. In these systems, an increase in temperature above the polymer LCST resulted in an increase in the transport of entrapped molecules through the membrane.[12] Applications of poly(NIPAAm) hydrogels have recently been reported for use in the fields of controlled drug delivery,[13,14] immobilization of enzymes,[15] and cells.[16]

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A polyelectrolyte gel is formed from crosslinking flexible polymer chains to which ionizable groups are attached. These ionizable groups will completely dissociate in solution to form strong electrolyte groups, or partially dissociate to form weak electrolyte groups along its chains. These charged groups produce an electrostatic repulsion force among themselves, which will enhance the expansion of the gel network.[17] For example, in the case of anionic polymeric networks containing carboxylic or sulphonic acid groups, ionization takes place as the pH of the external swelling medium rises above the pka of the ionizable moiety. The polymeric network becomes more hydrophilic as the degree of ionization increases.[18] Therefore, some controlled drug release devices, based on pH-sensitive swelling characters of polyelectrolyte hydrogels, have been developed.[19]

Ionizable, environmentally sensitive hydrogels are especially attractive because their permeabilities can be controlled not only by changing their molecular structures but also by adjusting external conditions. Poly(NIPAAm) has been well characterized in terms of its lower critical temperature in solution, as well as its dramatic, reversible aqueous swelling/deswelling behavior in crosslinked networks (hydrogel). Incorporation of a hydrophilic comonomer (e.g., acrylic acid and sodium acrylate) into poly(NIPAAm) hydrogels radically changes gel swelling behavior in aqueous media.[20–22]

The purpose of this study is to develop a temperature and pH-sensitive hydrogel with swelling behavior and drug release. In this respect, a series of copolymeric hydrogels with pH and temperature sensitivity behavior were prepared through copolymerizing *N*-isopropylacrylamide and acrylic acid (AA), which was neutralized with sodium hydroxide to 50 mol %, with various molar ratios in the presence of an amount of crosslinker. The equilibrium swelling ratios were determined at various pH values and different temperatures. The swelling reversibilities and release characteristics of these gels were also investigated under different conditions.

EXPERIMENTAL

Materials

N-isopropylacrylamide (NIPAAm) (Fluka Chemical Co.) was recrystallized in *n*-hexane before use in order to remove the inhibitor. *N,N′*-methylenebisacrylamide (NMBA) (SIGMA Chemical Co.) as a crosslinker was used as received. The materials were purchased from Tokyo Kasei Industries Ltd., including AA and sodium hydroxide. Sodium hydroxide and NMBA were directly used. *N,N,N′,N′*-tetramethylethylenediamine (TEMED) (Fluka Chemical Co.), as an accelerator was used as received. Ammonium peroxodisulfate (APS) (Wako Pure Chemical Co. Ltd.), as an initiator, was further purified by recrystallization.

Crystal violet (CV) and phenolphthalein, as model drugs, were obtained from Fluka. All solvents and other chemicals were of analytical grade.

Preparation of SA50

Acrylic acid was carefully added to a predetermined amount of aqueous caustic solution in order to obtain sodium acrylate (SA) with complete theoretical neutralization (sodium hydroxide and AA in equal 0.05 mol). Then the degree of neutralization of 50 mol % AA was prepared by adding 0.05 mol AA to the SA solution. This solution was thereafter designated as SA50.

Preparation of Hydrogels

Various molar ratios of NIPAAm and SA50 with 4 mol % NMBA were dissolved in deionized water to 10 mL. To this solution, 1.5 m*M* APS and 1 m*M* of 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 into an excess amount of deionized water for 7 days to remove the residual unreacted monomer. The resulting gels were dried at room temperature for 1 day and then further dried in a vacuum oven for 2 days at 60°C.

Measurement of Swelling Ratio

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. A

swelling ratio (SR) based on W_w and W_d was then calculated.

The swelling ratio is defined as follows:

$$\mathrm{SR} = (W_w - W_d)/W_d \quad (1)$$

Dynamic Swelling

The dried gels were immersed in an excess amount of buffer solution at different pH solutions and 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 infinitely long time was designated to M_∞. The following equation can be used to calculate the diffusion coefficient D for $M_t/M_\infty = 0.8$[23]:

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

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

Measurement of Swelling Ratio at Various pH Solutions and Temperatures

The method was the same as for the swelling ratio in deionized water. Buffer solutions were prepared by aqueous solution of HCl, KCl, $KHC_8H_4O_4$, NaOH, KH_2PO_4, and H_3BO_3, respectively.

Measurement of CV Release

In order to load CV into the gels, dry gels were equilibrated in CV solution (10 mg/100 mL of deionized water) at 25°C for 2 days. The CV release experiments were carried out by transferring previous drug gels into 10 mL of deionized water at 50°C. The gels were periodically removed and transferred into 10 mL fresh water at each fixed time interval. The released CV was analyzed at 561 nm by an ultraviolet (UV) spectrophotometer (Milton Roy Spectronic Genesys 5).

Phenolphthalein Deswelling Kinetics Experiments

The dry gels were equilibrated in 10 mL of 40 ppm phenolphthalein buffer solution at 25°C for 2 days for loading phenolphthalein into the gels. The phenolphthalein deswelling kinetic experiments were carried out by transferring previously incubated drug gels into 10 mL of buffer solution without phenolphthalein at 50°C or another pH. The gels were removed and transferred into a 10-mL fresh buffer solution at each fixed time interval. The released phenolphthalein was analyzed at 299 nm by a Milton Roy UV-spectrophotometer (SPECTRONIC GENESYS 5).

RESULTS AND DISCUSSION

The swelling behavior of the hydrogels depends on the nature of the polymer and the environmental conditions. The polymer's nature involves the nature of the charge, ionic content, and crosslinking agent content. The environmental conditions include pH and temperature.

The swelling behavior of NIPAAm hydrogels has widely studied by many researchers.[4,5,9,10] A series of copolymeric NIPAAm/SA50 hydrogels are investigated since SA50 will improve the pH reversibility NIPAAm gel. The effect of the amount of SA50 on the swelling ratio of NIPAAm/SA50 copolymeric gels are studied here.

Characterization of NIPAAm–SA50 Copolymeric Gels

Some characteristics of the NIPAAm–SA50 copolymeric gels for various feed compositions are shown in Table I. The results in Table I show that the cloud point effect of the copolymeric gels is gradually weaker with an increase of the content of SA50. The gel transition temperatures are increased with an increase of the content of SA50 in the copolymeric compositions, that is, from 35–40°C for M2 gel to 45–55°C for M10 gel, respectively. The equilibrium swelling ratios of the copolymeric gels in deionized water are also increased with increasing of the content of SA50.

Effect of pH on Swelling Kinetics for NIPAAm–SA50 Copolymeric Gels

The swelling ratios, as a function of time for NIPAAm–SA50 copolymeric hydrogels in several pH buffer solutions, are shown in Figure 1. The results shown in this figure indicate that the swelling ratios increased with increasing SA content. Because SA50 is a hydrophilic monomer, the more the SA50, the larger the affinity of gels with water, and the higher the swelling ratio of the hydrogel. The results also show that under acidic conditions, anionic carboxylate groups are proton-

Table I Characterization of the NIPAAm–SA50 Copolymeric Gels

Sample No.	NIPAAm (Molar Ratio)	SA (Molar Ratio)	Cloud Point Effect[a]	Gel Temperature Transition (°C)	Equilibrium Swelling Ratio (g H2O/g Dry Sample)
M2	1	0.0196	vs	35–40	25.11
M5	1	0.049	st	40–45	33.15
M10	1	0.098	w	45–55	45.6
M20	1	0.196	vw	>80	68.62

[a] Abbreviations are as follows: vs, very strong; st, strong; w, weak; vw, very weak.

ated, and the copolymeric network deswelled. As the pH of aqueous media is increased from low pH, the concentration of anionic carboxylate groups in polymer network increases. This occurrence makes the swelling ratio of the gels drastically increase with an increase of SA50 content in the copolymeric gels. The maximum swelling ratio occurred at pH 10.64. This may reflect the complete neutralization of carboxylic acid groups.

The difference of swelling ratio for M20 and M5 and for M10 and M5, respectively expressed by ΔSR2 and ΔSR1, are shown in Table II. The results show that the ΔSR increases with increasing pH, except at pH 4.13, especially under high pHs (e.g., pH 9.02 and pH 10.64). The reason is the enhancement of the ionization degree and electrostatic repulsion between anionic carboxylate groups. The results also show that ΔSR2 are larger than ΔSR1 at all pHs, and the differences between ΔSR2 and ΔSR1 are larger at high pHs than those at low pHs. The results indicate that the hydrophilicity of gels is obviously influenced by the amount of SA50 and the degree of ionization of the carboxylate groups.

Effect of pH on Swelling Ratio for NIPAAm–SA50 Copolymeric Gels

Poly(NIPAAm) gels are well known for their thermosensitive properties, exhibiting dramatic swelling–deswelling changes at a lower critical solution temperature (LCST, 33°C). By incorporating SA50 into poly(NIPAAm) as a comonomer, the LCST variation depends on the external pH.[21] For higher pH solutions, the LCST shifts to a higher temperature, owing to ionization and electrostatic repulsion between anionic carboxylate groups. For lower pH solutions, however, the LCST shifts to a lower temperature, owing to polymer interactions enhanced by hydrogen bonding between protonated carboxylic acid groups. As a result, at a certain constant temperature, the gels undergo substantial swelling–deswelling changes in response to external pH changes. Figure 2 shows the pH dependence of the gel equilibrium swelling ratio for the said copolymeric gels at 25°C. The gel transition for the samples M20 and M10 occurs near pH 4 and pH 8, leading both swelling ratios to increase with an increase of the external pH, but it is not obviously apparent for sample M5. This is because the ionization of polymeric networks containing carboxylic acid groups takes place as the pH of the external medium increases.[18] Basic conditions, however, will accelerate the reaction of carboxylic acid groups and increase the repulsive effect of the charges of (COO^-) on the gels, and both factors would make the swelling ratio higher and make the effect of deswelling insignificant. Therefore, the gel containing the most carboxylate ions (COO^-) will cause the largest ionic repulsion inside the gels and can affect the pH-sensitive character of gels (M20 > M10 > M5).

Effect of SA50 Content on Swelling Ratio

The swelling ratios, as a function of time for NIPAAm–SA50 copolymeric gels in deionized water at various temperatures (20–40°C), are shown in Figure 3. The results shown in Figure 3 indicate that the swelling ratios increase with increasing SA50 content. According to P. J. Flory's swelling theory,[24] it is known that the swelling ratio has a relation to ionic osmotic pressure, crosslinked density, and the affinity of the hydrogel with water. The crosslinked density was fixed in a series of different compositions for the present hydrogels, so the factors affected the swelling ratio for the said hydrogel are the charge concentration and the affinity of gel with water. Because SA50 is a hydrophilic monomer with a high degree of ionization, the more the SA50, the

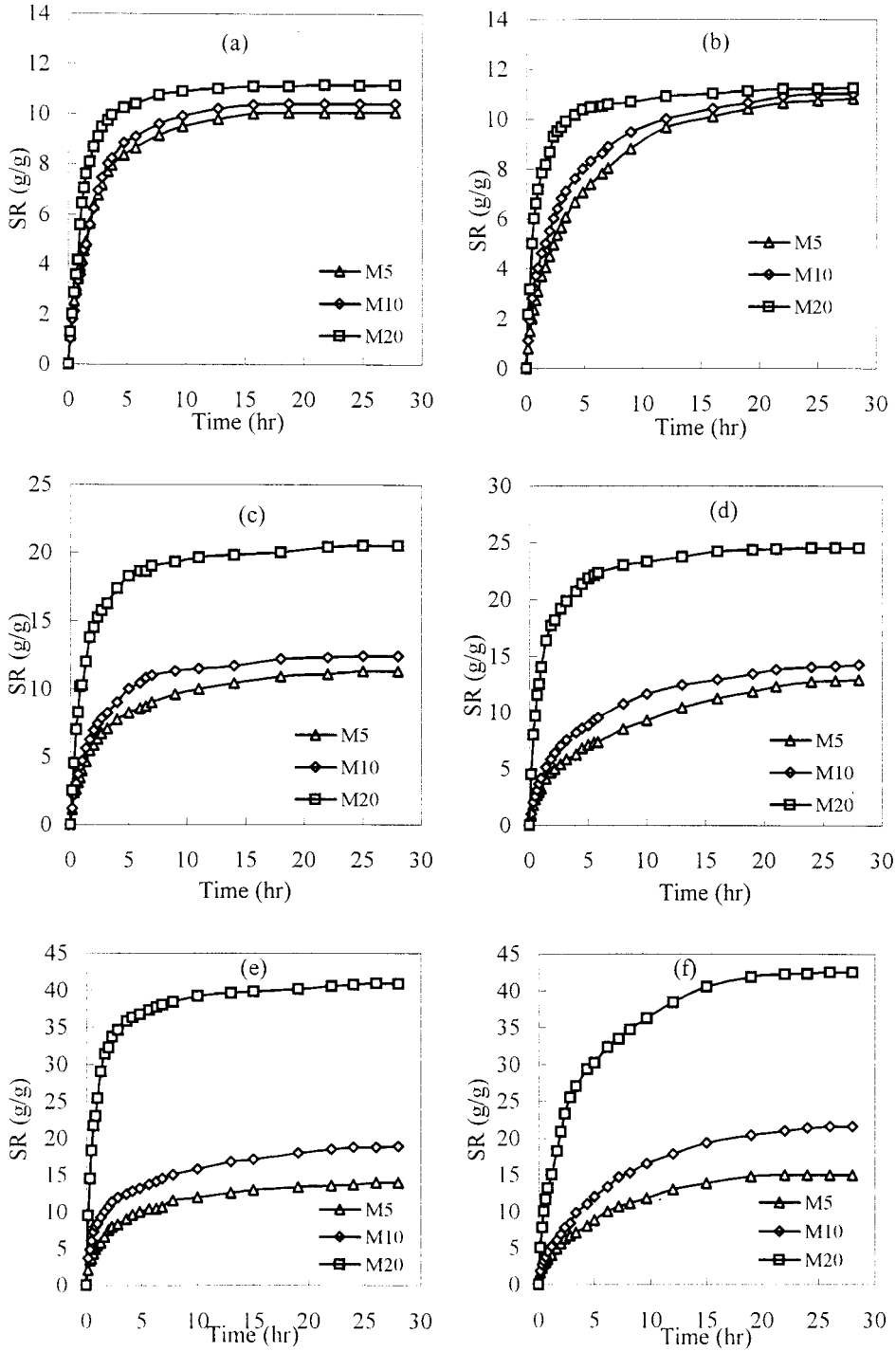

Figure 1 Swelling ratios as a function of time for the series of NIPAAm-*co*-SA50 gels at 25°C under pH (a) 2.244, (b) 4.13, (c) 6.05, (d) 7.96, (e) 9.02, and (f) 10.64.

larger the affinity of the gels with water and the higher the swelling ratio of the hydrogel.

In addition, an interesting phenomenon was observed from Figure 3. That is, an overshooting behavior, defined as the maximum swelling ratio over the equilibrium values, appeared for M20 gel while the temperature was raised to over 35°C [see Fig. 3(d) and (e)]. Hence, to check whether this behavior appeared or not under higher temperature for other gels (M10 and M5), the tem-

Table II ΔSR for NIPAAm–SA50 Copolymeric Gels at Different pHs

Sample No.[a]	pH Value					
	2.24	4.13	6.05	7.96	9.02	10.64
ΔSR1	0.34	0.17	1.11	1.30	4.96	6.66
ΔSR2	1.08	0.42	9.20	11.61	26.89	27.57

[a] SR is the swelling ratio; ΔSR1 = SR(M10)–SR(M5); ΔSR2 = SR(M20)–SR(M5).

perature was further raised to higher temperatures in this experimental process.

The swelling ratios for the said hydrogels as a function of time at higher temperatures (45°C–65°C) are shown in Figure 4. The results obtained from Figures 3 and 4 indicate that the overshoot behavior for the present copolymeric hydrogels gradually appeared with an increase of temperature [see Fig. 4(d) and (e)]. This specific behavior has not been disclosed in the literature for these gels; but a similar behavior for poly(hydroxyethyl methacrylate) gel systems, which showed a gradual decrease with increasing temperature, was reported by Shieh and Pappas[25] and in our previous studies.[26,27] This contrary result for these two systems explicitly shows that the overshooting behavior strongly depends upon the gel structure, the balance of osmotic and retractive force of polymeric chains, and the surrounding temperature. This interesting phenomenon will be investigated in future.

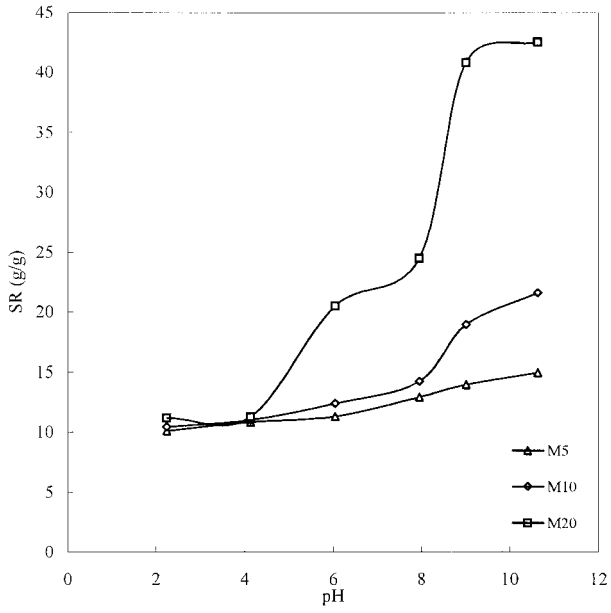

Figure 2 Swelling ratio as a function of pH value for the series of NIPAAm-*co*-SA50 gels at 25°C.

Effect of Temperature on Swelling Ratio for NIPAAm–SA50 Copolymer Gels

The effect of temperature on swelling ratio for the said copolymeric gels in deionized water is shown in Figure 5. The results in Figure 5 indicate that the higher the temperature, the lower the swelling ratio, and the more the SA50, the higher the gel transition temperature. For NIPAAm gel, the hydrophilic group (amide) in the polymer structure would form an intermolecular hydrogen bond with surrounding water at low temperature (below gel transition temperature). The water penetrated into the gels is in a bound state at a low-temperature condition. But, the water molecule in the hydrogel would gain an enthalpy when the temperature is increased. The hydrophilic group (amide) in the NIPAAm component would be turned into an intramolecular hydrogen bond. This occurrence leads to the ability of the hydration force in the gel to decrease. At the same time, the hydrophobicity of the isopropyl group in the NIPAAm increases. These two results cause the state of the water molecule in the gel to change from bound water to free water released from the gel network. This phenomenon makes the swelling ratio of the gel rapidly decrease at the gel transition temperature; but the results shown in Figure 5 also indicate that the more the SA50 content, the higher the LCST for the NIPAAm–SA50 copolymeric gel. These results are because the SA50 is a hydrophilic component. The larger the hydrophilicity of the gel, the stronger the affinity of the hydrogel with water. Therefore, the curves of swelling ratio vs. temperature become more flatten when the SA50 content is increased (M20). This result means the gel does not readily shrink as the temperature increases.

The results shown in Figures 1 and 3, under various pH solutions at 25°C and deionized water

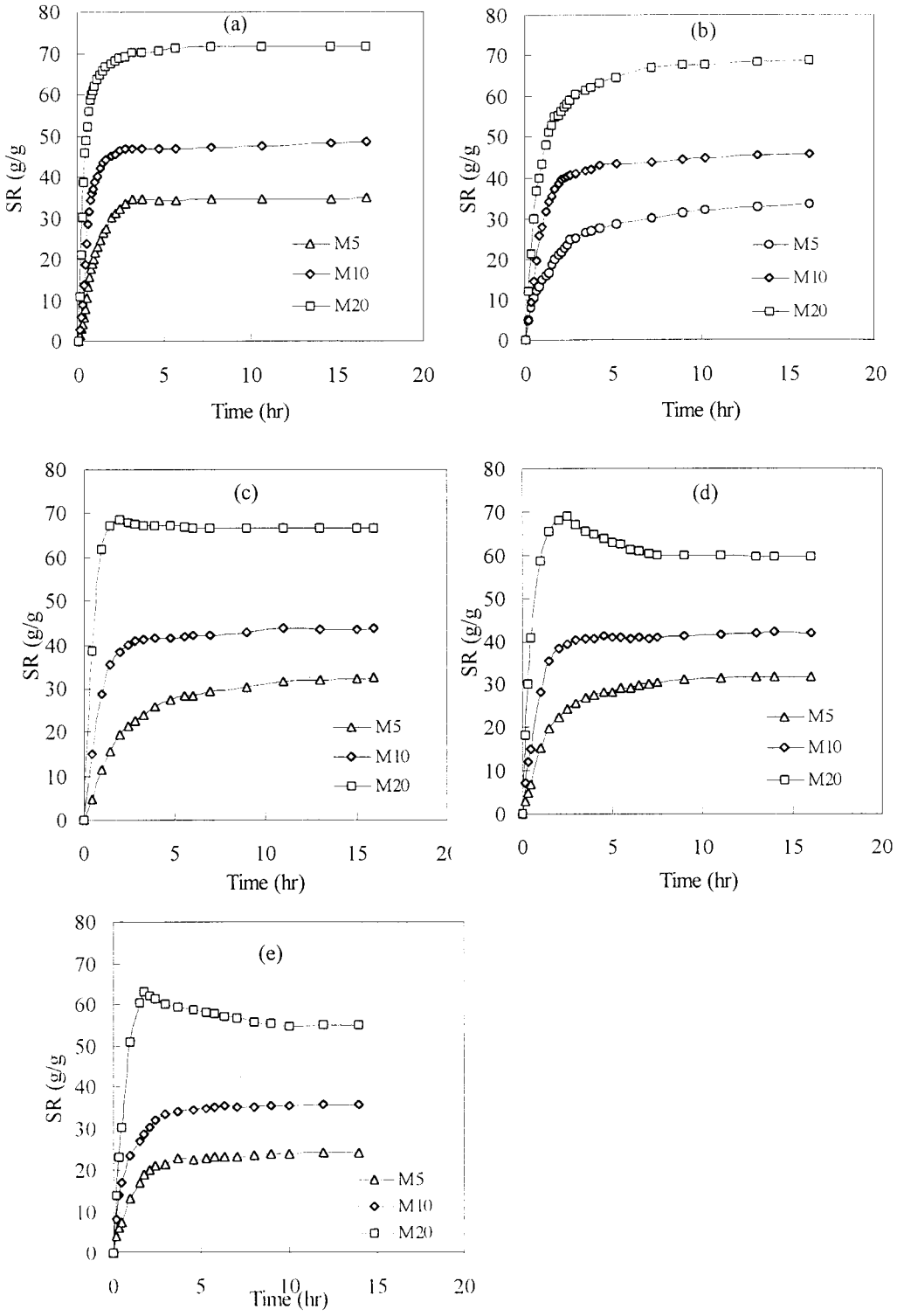

Figure 3 Swelling ratios as a function of time for the series of NIPAAm-*co*-SA50 gels in deionized water under (a) 20, (b) 25, (c) 30, (d) 35, and (e) 40°C.

at various temperatures, respectively, also indicate that the swelling ratios are increased with increasing pH values of external solution and decreased with an increase of the temperature. The swelling kinetics can be generally described in the following two terms: the diffusion rate of imbibing

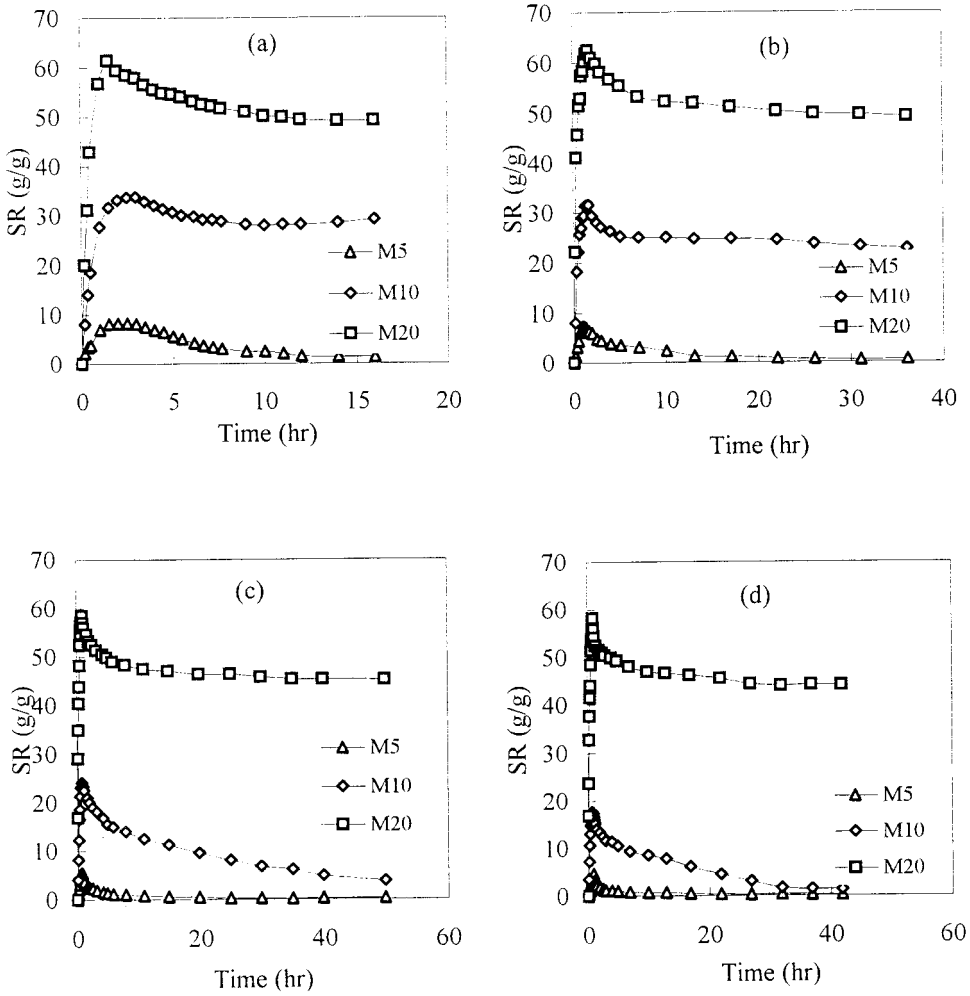

Figure 4 Swelling ratios as a function of time for the series of NIPAAm-*co*-SA50 gels in deionized water under (a) 45, (b) 50, (c) 55, and (d) 60°C.

solvent into the gel and the relaxation rate of the polymer network.

Investigation of Water Diffusion in Xerogels

To elucidate the transport mechanism of the nature of the sorption kinetics in said copolymeric gels, the initial swelling data were fitted to the following exponential heuristic equation[28,29]:

$$\frac{M_t}{M_\infty} = \mathrm{K}t^n \tag{3}$$

where K is a characteristic constant of the gel, and n is a characteristic exponent of the mode transport of the penetrant. n and K were calculated from the slopes and intercepts of the plot of $\log(M_t/M_\infty)$ against $\log(t)$ at various pHs and temperatures, respectively. In addition, eq. (2) was used to calculate the diffusion coefficient D from the slope in the plot of (M_t/M_∞) against $\sqrt{t}$ at different pHs and temperatures, respectively. Tables III and IV show the diffusion coefficient D, the index n, and the constant K for a series of NIPAAm–SA50 copolymeric gels at various temperatures and pHs.

The results shown in Table III indicate that the swelling exponents n for M5 and M10 at various pH media range from are 0.58 to 0.43 and from 0.61 to 0.47, respectively. These evidences show that the swelling transport mechanism will be transferred from non-Fickian to Fickian transport; but for M20, the n values are between 0.63 and 0.51. This evidence shows that the swelling transport mechanism is a non-Fickian transport. The data for diffusion coefficient shown in Table

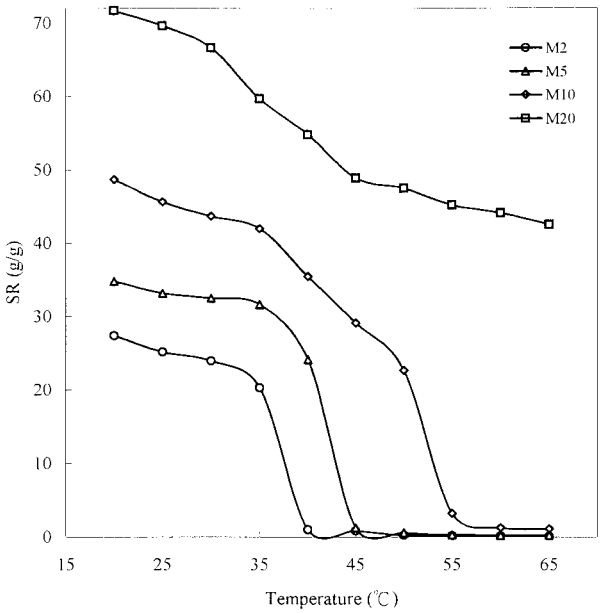

Figure 5 Swelling ratios as a function of temperature for various NIPAAm-*co*-SA50 gels in deionized water.

III indicate that the diffusion coefficients for various NIPAAm–SA50 copolymeric gels are increased with an increase of pH.

Table III Initial Diffusion Coefficients of Water *D* Kinetic Exponents *n*, and Characteristic Constants K of Water Penetrated Through NIPAAm–SA50 Copolymeric Gels at Various pHs and 25°C

Sample No.	pH	n	K × 10	$D \times 10^7$ (cm^2/s)
M5	2.24	0.58	0.83	0.27
M5	4.13	0.58	0.92	0.35
M5	6.05	0.52	0.8	0.34
M5	7.96	0.44	1.15	0.48
M5	9.02	0.49	1.15	0.52
M5	10.64	0.43	1.31	0.67
M10	2.24	0.61	0.08	0.31
M10	4.13	0.59	0.88	0.35
M10	6.05	0.55	0.62	0.59
M10	7.96	0.48	0.89	0.53
M10	9.02	0.47	1.41	0.67
M10	10.64	0.52	1.31	0.81
M20	2.24	0.59	0.4	1.27
M20	4.13	0.52	0.33	1.19
M20	6.05	0.63	0.42	1.48
M20	7.96	0.55	0.68	1.76
M20	9.02	0.57	0.74	1.87
M20	10.64	0.51	0.96	1.89

Table IV Initial Diffusion Coefficients of Water *D* Kinetic Exponents *n*, and Characteristic Constants K of Water Penetrated Through NIPAAm–SA50 Copolymeric Gels at Various Temperatures

Sample No.	T (°C)	n	K × 10	$D \times 10^7$ (cm^2/s)
M5	20	0.67	0.16	0.65
M5	25	0.60	0.38	0.91
M5	30	0.51	0.36	1.23
M5	35	0.49	0.49	1.30
M5	40	0.49	0.59	2.24
M10	20	0.72	0.10	0.72
M10	25	0.58	0.30	1.52
M10	30	0.47	1.14	1.78
M10	35	0.4	1.35	1.79
M10	40	0.53	0.56	2.35
M20	20	0.73	0.2	1.77
M20	25	0.69	0.21	2.67
M20	30	0.51	0.79	3.01
M20	35	0.58	0.57	3.98
M20	40	0.61	0.36	4.19

On the other hand, the results in Table IV indicate that the n values for M5 at various temperatures are decreased from 0.67 to 0.49. This evidence indicates that the swelling transport mechanism will be transformed from non-Fickian to Fickian transport with increasing temperature. But the n values for M10 and M20 decrease with increasing of temperature from 20 to 35°C and from 20 to 30°C, respectively, then increase. This occurrence can be accounted for by the overshooting phenomenon. In our previous studies, we also found similar results.[27] Hence, the data in Table IV show that the swelling transport mechanism for M10 will be transformed from non-Fickian to Fickian; but for M20, it will be only non-Fickian transport. The data for diffusion coefficient, shown in Table IV, indicate that the diffusion coefficients for various NIPAAm–SA50 copolymeric gels are increased with an increase of temperature.

Effect of Reversibilities on Swelling Ratio for NIPAAm–SA50 Copolymeric Gels

Thermoreversible gels would bring about a swell–deswell transition. This behavior depends on weak hydrogen-bonding of amide groups, which are transferred from a swelled state to a deswelled state under certain temperature ranges.

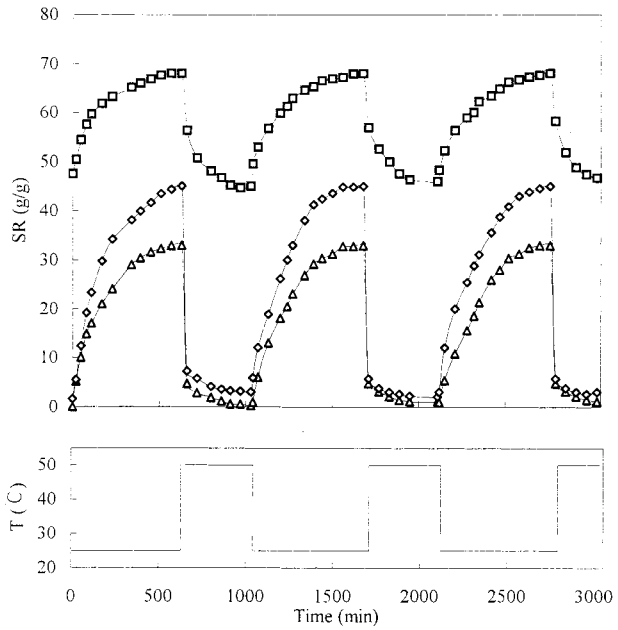

Figure 6 Swelling ratios of NIPAAm-*co*-SA50 gels as a function of time repeated abrupt change of temperature between 25 and 55°C in deionized water: (△) M5; (◇) M10; (□) M20.

Figure 6 shows the change of swelling ratio for this series of gels when those were immersed in deionized water between 25 and 55°C. The gels M5, M10, and M20 can swell and deswell over a period of time when temperature is cycled through their gel transition temperatures. The results of deswelling behavior are also shown in Figure 5. As seen from the curves, the swelling ratio is lower at 55°C but is higher at 25°C. Moreover, the swelling ratios of sample M5, M10, and M20 can be changed from 33.1 to 0.2, 45.0 to 3.1, and 67.0 to 45.1, respectively, when gels are immersed at 55°C. Then these gels can reswell to 33, 45, and 67 when those reimmersed at 25°C. Therefore, these copolymeric gels exhibit reversible behavior between 25 and 55°C, especially for M5 and M10 gels, which show an apparent and rapid change in swelling ratio when the temperature goes above their gel transition temperatures. As a result, the SA content in the copolymeric gel will significantly affect thermoreversibility of the gels.

Figure 7 presents the effect of cycling of pH on the swelling behavior of these ionic networks. The pH was changed from 9.02 to 2.24, and the same cycle was repeated several times. The first swelling time in pH 9.02 was a period of swelling equilibrium, followed by 4 h in pH 2.24, and then 4 h in pH 9.02 buffer. At the first swelling stage, the carboxylate groups (COO^-) enhance the swelling ratios, but when the gels transferred to low pH (2.24), the carboxylate groups will be protonated to carboxylic acid groups (COOH), which decreases the electrostatic repulsive force between the charge sites on network, and make the swelling ratios decrease. This figure also shows that the more the SA50, the larger the swelling ratios. Hence, the changes of the swelling ratio for the gels are M20 > M10 > M5.

The results shown in Figure 7 explicitly indicate that the pH reversibility for M5 gel is not significantly evident. Hence, the pH reversibility for the said copolymeric gels is dependent on the SA50 content in the gel compositions.

Effect of Temperature on Fractional Release of CV for NIPAAm–SA50 Copolymeric Gels

A new class of hydrogels, for which swelling ratios are sensitive to small changes in environmental conditions has been of great interest recently. Hydrogels can incorporate many different biomolecules, such as drugs, enzymes, and antibodies.[3,12,19,30,31] Hence, CV was incubated into the present gels to investigate its release profile. The

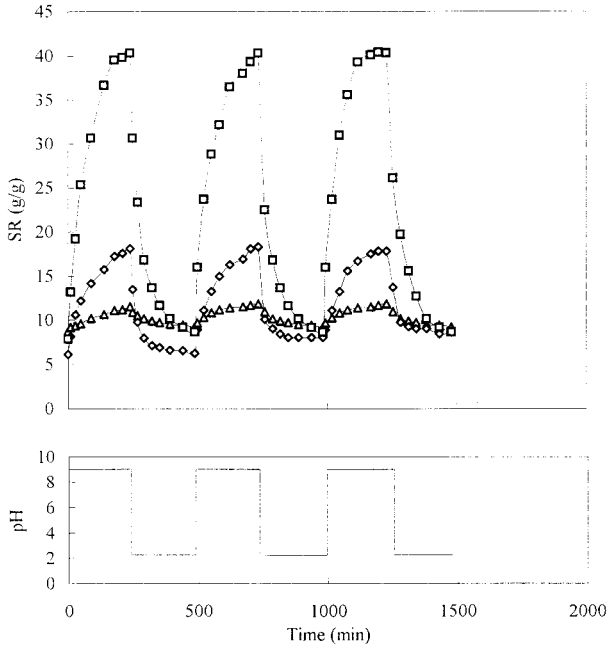

Figure 7 Swellings ratios of NIPAAm-*co*-SA50 gels as a function of time repeated abrupt change of pH between pH 2.24 and 9.02 in buffer solution at 25°C: (△) M5; (◇) M10; (□) M20.

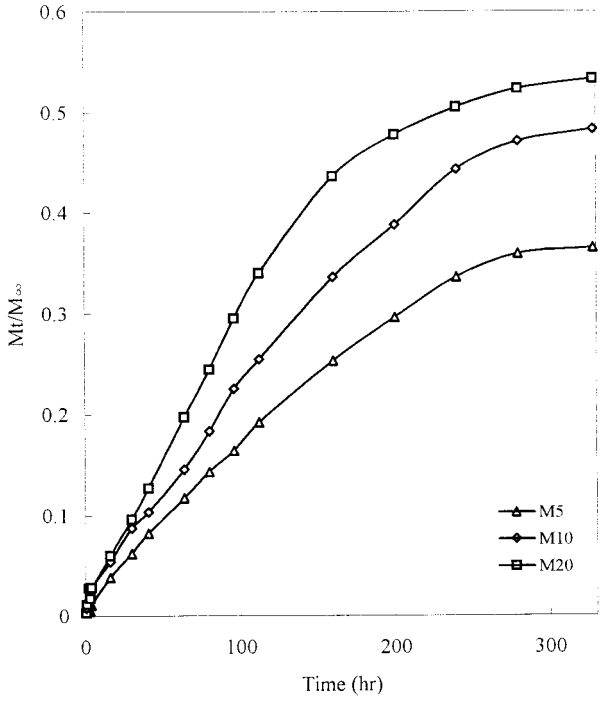

Figure 8 CV release profile for NIPAAm-*co*-SA50 gels during deswelling at 50°C.

incubated species may be physically entrapped within the gel structure. The gel may be switched off and on by deswelling and reswelling its pores to release drug as the temperature is raised and then lowered around the gel transition temperature. This is due to the closing and opening of the pathways for molecular diffusion.

The release profiles of CV in NIPAAm–SA50 copolymeric gels at 50°C, shown in Figure 8, indicate that the gel containing less content of SA50 (M5) exhibits a slower CV release, which is due to the faster gel deswelling; that is to say, the less the hydrophilic group content of the copolymeric gels, the faster the gel deswelled. Therefore, the CV released from M5 was smaller than that released from M10 and M20 at temperatures above the gel transition temperature.

The results also show that the fractional release of CV does not reach 1.0. This occurrence implies that CV was not completely released, and some portions were entrapped within the gel. This effect supports the idea of a water pocket formation in the collapse gel. CV only dissolves in the free water. The CV molecules located in the porous region of the gel may be squeezed out quickly or trapped in a water pocket as the gel collapses.[32] These findings mean that in the case of deswelling, dehydration of the copolymeric gels studied occurred, accompanying the initial rapid shrinkage. This phenomenon was also observed and explained in our previous report for NEPAAm–BA and NTHFAAm–BA copolymeric gels[11] and in some other articles.[30,33,34]

Effect of pH on Fractional Release of Phenolphthalein for NIPAAm–SA50 Copolymeric Gels

A polymer gel undergoing rapid dehydration during the deswelling process may have potential

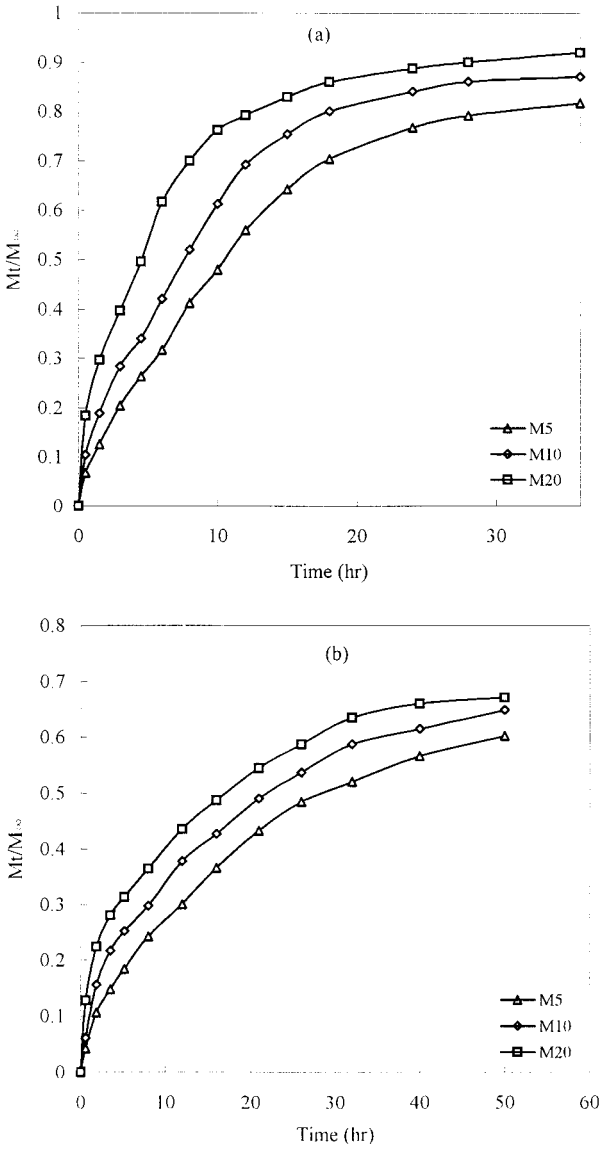

Figure 9 Phenolphthalein release profile for NIPAAm-*co*-SA50 gels (a) during swelling at pH 5 and deswelling at pH 11 (37°C) and (b) during swelling at pH 9.02 and deswelling at pH 2.24 (37°C).

utility in on–off regulation of solute permeation due to the formation of a barrier (skin) layer at the surface of the gel matrix. In this context, the NIPAAm–SA50 gels may be applicable as a drug release system responding to pH.

Drug release systems with transport across the NIPAAm–SA50 gels responding to a pH jump in external milieu were demonstrated using phenolphthalein as a model drug and are shown in Figure 9. The result shown in Figure 9(a) shows rapid release as a function of time for phenolphthalein from the gels in alkali milieu (pH 11), and it can be seen that the release rate of phenolphthalein from the gels increases considerably with time. The theory of drug release, via controlling the surrounding pH, is similar to the temperature as described above. The incorporation of SA50 into the polymer network with high molar ratio will lead to an increase in electrostatic repulsive force between charge sites on carboxylate ions and enhance a more extended configuration. The extended structure with more SA50 content might cause a higher amount of the drug incubated into the gel to be released.

Comparing Figures 9(a) and 9(b), the release from pH 9.02 to 2.24 is smaller than that from pH 5.01 to pH 11. This is because the carboxylate groups of SA50 were protonated, and the polymer networks deswelled at acidic conditions. Hence, phenolphthalein was effectively shut off by transferring the gels from alkali to acidic milieu, suggesting the formation of a surface barrier layer.[3] Therefore, the drug released from the gels at pH 2.24 is due to less diffusion of drug through the deswelled polymer networks. At pH 11, the overall release rate increased because the swelling of polymer network increased due to the ionization of carboxylic groups at high pH.

Effects of NIPAAm–SA50 gels on phenolphthalein release profile during deswelling at 50°C at pH 11 are shown in Figure 10. The phenomenon is similar to CV release in deionized water during deswelling at 50°C. In addition, it is found that the release profiles of phenolphthalein in the said copolymeric gels are faster than those of CV in these copolymeric gels. This is because the molecular size of CV is larger than that of phenolphthalein. Therefore, the release profiles of phenolphthalein in these copolymeric gels are faster. All of these results also show that the fractional release (M_t/M_∞) of phenolphthalein does not reach 1.0. This occurrence also implies that phenolphthalein was not completely released, and some portions were entrapped within the gel.

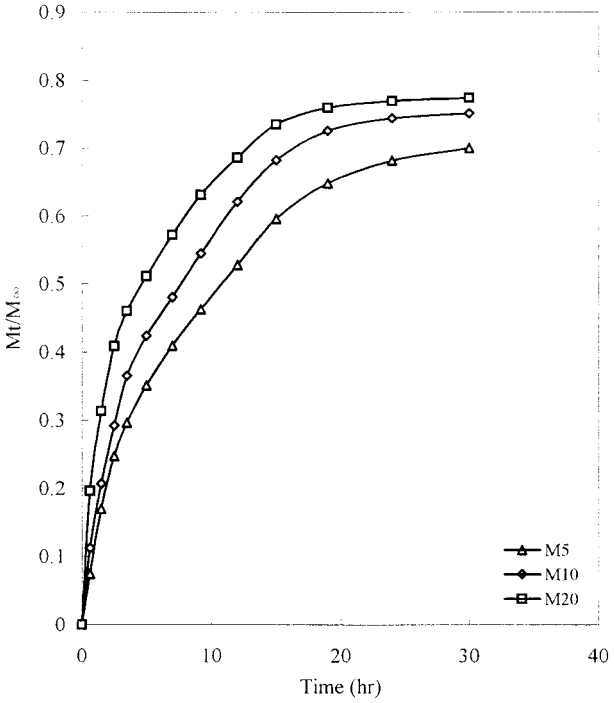

Figure 10 Phenolphthalein release profile for NIPAAm-*co*-SA50 gels during swelling at 25°C and deswelling at 50°C under pH 11 buffer solution.

CONCLUSIONS

The swelling ratios of NIPAAm–SA50 copolymeric gels are increased with an increase of SA50 content. In addition, the higher the content of SA50, the larger the affinity with water, and the higher the gel transition temperatures; the same is true for pH-sensitive characteristics. In diffusion, the results indicate that the diffusion coefficients D for all NIPAAm–SA50 copolymeric gels are increased with an increase in temperature and pH.

A critical overshooting phenomenon was observed in the dynamic swelling kinetics. For these gels, the amount of SA50 would obviously affect their thermosensitivities, and the change of the swelling ratio for thermoreversibilities would be larger. Concerning pH-reversible characters for these gels, they also show that the more the SA50, the better the reversibilities on pH.

Finally, gels containing less SA50 exhibit slower CV and phenolphthalein release. The release profiles of phenolphthalein in the said copolymeric gels are faster than these of CV in these copolymeric gels.

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