pH/Thermoreversible Hydrogels III: Synthesis and Swelling Behaviors of (*N*-isopropylacrylamide-*co*-acrylic acid) Copolymeric Hydrogels

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Abstract: A series of pH-thermoreversible hydrogels exhibiting volume phase transition were synthesized by three degrees of neutralization (DN) of acrylic acid (AA) and *N*-isopropylacrylamide (NIPAAm). The influence of environmental conditions, such as temperature and pH, on the swelling behavior of these copolymeric gels is investigated in this article. Results show that the negatively charged hydrogels exhibit different equilibrium swelling ratios at different pH values depending on the ionic composition. The pH-sensitivities of these gels also strongly depend on the DN of AA in the copolymeric gels. The results show that the higher the DN, the higher the gel pH-sensitivity. These hydrogels based on a temperature-sensitive hydrogel demonstrate a larger change of equilibrium swelling in aqueous media between a highly solvated, swollen gel state and a collapsed dehydrated network in response to a variation of temperature. On the other hand, a significant phenomenon that was found in the gel swelling kinetics was an overshooting under high temperature conditions. The presented hydrogels were used for release of model drugs that occur at the changes of surrounding conditions, such as temperature and pH, in this study. It was also found that the higher the DN of AA, the higher the gel transition temperature and the larger the release in a high temperature environment and, at the same time, the larger the swelling ratios.

Keywords: Hydrogel, pH-thermoreversibility, *N*-isopropylacrylamide-*co*-acrylic acid copolymeric gel, Swelling ratio.

Introduction

Hydrogels are crosslinked, 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 pH [1-3], temperature [4,5], ionic strength [6], and electric field [7]. Temperature and pH are particularly important because they are variables in typical physiological, biological, and chemical systems [8].

Thermoresponsive hydrogels demonstrate a volume transition and associated phase transition from a low temperature highly swollen gel to a high temperature collapsed gel near its critical point [9-11]. Poly(NIPAAm) and its copolymers have been studied in the development of drug release systems, membrane separations [12], controlled drug delivery [13,14], and immobilization of enzymes and cells [15,16].

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 influences the expansion of the gel network [17,18]. Therefore, some controlled drug release devices have been developed based on pH-sensitive swelling characteristics of polyelectrolyte hydrogels [19].

Ionizable, "environmentally sensitive", hydrogels are especially attractive because their permeabilities can be controlled not only by chang-

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J. Polym. Res. is covered in ISI (CD, D, MS, Q, RC, S), CA, EI, and Polymer Contents.

ing 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 cross-linked networks (hydrogels). The incorporation of a hydrophilic comonomer (e.g., acrylic acid, sodium acrylate) into Poly(NIPAAm) hydrogels radically changes gel swelling behavior in aqueous media [20].

In a previous report [21], the swelling behavior of NIPAAm-*co*-acrylic acid copolymeric gels, in which acrylic acid (AA) was neutralized with sodium hydroxide to 50 mol%, exhibited an overshooting phenomenon under higher temperature conditions. Hence, the main purpose of this article is to study the influence of various neutralization degrees on the swelling behaviors for this copolymeric gel. A secondary purpose is to investigate the effect of degree of neutralization (DN) of AA on the swelling kinetics and drug release behaviors for these copolymeric gels at various pH and temperature conditions. Based on this, the gels are prepared by copolymerization of *N*-isopropylacrylamide and acrylic acid (AA), which was neutralized with sodium hydroxide to 30, 50 and 70 mol%, in fixed molar ratios in the presence of a crosslinker.

Experimental

1. Materials

N-isopropylacrylamide (NIPAAm) (Fluka Chemical Co.) was recrystallized in *n*-hexane before use in order to remove an inhibitor. *N*,*N*'-methylene-bisacrylamide (NMBA) (SIGMA Chemical Co.) as a crosslinker was used as received. The materials purchased from Tokyo Kasei Industries Ltd. included acrylic acid (AA) and sodium hydroxide. Sodium hydroxide and NMBA were used directly. *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. Phenolphthalein as a model drug was obtained from Fluka. All solvents and other chemicals were of analytical grade.

2. Preparation of neutralized of acrylic acid [22]

Sodium acrylate (SA) solution was prepared by adding AA to a predetermined amount of aqueous caustic solution in order to obtain a theoretically complete neutralization (sodium hydroxide and AA in equal mole of 0.003, 0.005 and 0.007). Then the 30, 50, and 70 mol% neutralized acrylic acid was obtained from adding 0.007, 0.005 and 0.003 mole of AA to the SA solution. These solutions are hereafter referred to as DN30, DN50, and DN70.

3. Preparation of hydrogels

A fixed ratio of NIPAAm (83.35 mol%) and neutralized AA (16.65 mol%) and 4 mol% NMBA were dissolved in deionized water to a total volume of 10 mL. To this solution, 1.5 mM APS and 1 mM 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 one day. After the gelation was completed, the gel membrane was cut into disks, 10mm in diameter, and immersed in an excess amount of deionized water for 7 days to remove the residual unreacted monomer. Swollen polymer gels were dried at room temperature for one day, and these samples were further dried in a vacuum oven for two days at 60 °C.

4. 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 two days. Swelling Ratio (SR) based on W_w and W_d was then calculated.

Swelling Ratio is defined as :

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

5. Dynamic swelling

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

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

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

Table I. Characterization of the NIPAAm-*co*-AA copolymeric gels.

Sample No.	NIPAAm (mol%)	AA (mol%)	AA (DN mol%)	Appearance	Gel transition temperature (°C)	Equilibrium swelling ratio (g H_2O/g Dry Sample)
S0	100	0	0	o	30 - 35	14.2
S3	83.35	16.65	30	t	50 - 60	40.5
S5	83.35	16.65	50	t	55 - 65	42.4
S7	83.35	16.65	70	t	> 80	45.2

DN = degree of neutralization of AA
t = transparent
o = opaque

6. Measurement of swelling ratio in solutions of various pHs and temperatures

The method was the same as the swelling ratio in deionized water. The pHs of various solutions were adjusted by aqueous solution of HCl or NaOH.

7. Phenolphthalein deswelling kinetics experiments

The dry gels were equilibrated in 10 mL of 40 ppm phenolphthalein deionized water 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 deionized water without phenolphthalein at 50 °C. The gels were removed and transferred into 10 mL fresh water 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 pH-thermoreversible 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 the content of the crosslinking agent. The environmental conditions include pH and temperature.

The swelling behavior of NIPAAm hydrogels has been widely studied by many researchers [4,5,9,10]. A series of copolymeric hydrogels of NIPAAm/SA50 were investigated in a previous study [21]. A significant overshooting pheno menon was observed in the gel swelling process under high temperature conditions. In order to investigate the difference in the gel swelling behaviors with changing the DN of AA, the effect of the DN on the swelling ratio for the presented copolymeric gels is studied.

1. Characterization of NIPAAm/AA/SA copolymeric gels

Some characteristics of the copolymeric gels for the same feed composition but with different DN's of AA are shown in Table I. At the cloud point, pure NIPAAm gel (S0) is opaque, but that effect is gradually weakened for other copolymeric gels with increase of the DN of AA. The gel transition temperature increases with an increasing DN of AA in the copolymeric compositions; i.e., 30-35 °C for S0, 50-60 °C for S3 gel, and 55-65 °C for S5 gel, respectively (also see Figure 5). The equilibrium swelling ratios of the copolymeric gels in deionized water are also increased with the DN of AA (S7>S5>S3>S0).

2. Effect of pH on swelling ratio for NIPAAm/AA copolymeric gels

Poly(NIPAAm) gel is well known for its thermosensitive property, which exhibits dramatic swelling-deswelling changes at lower critical solution temperature (LCST, 33 °C). By incorporating AA/SA into Poly(NIPAAm) as a comonomer, the LCST depends on the external pH [20]. At higher pH, the LCST shifts to higher temperature owing to ionization and electrostatic repulsion between anionic carboxylate groups. At lower pH, however, the LCST shifts to lower temperature owing to polymer interactions enhanced by hydrogen bonding between protonated carboxylic acid groups. As a result, at a certain temperature the gels undergo substantial swelling-deswelling changes in response to external pH changes. Figure 1 shows the pH dependence of the gel equilibrium swelling ratio for the copolymeric gels at 25 °C. The gel transitions of the samples S5 and S7 occur near pH=2, leading both swelling ratios to increase with an increase of the external pH. Such a phenomenon appears at pH=3 for sample S3 and is due to the anionic polymeric networks containing carboxylic acid groups, where ionization takes place as the pH of the external swelling medium increases [18]. As the pH of the external medium increases, it acceler-

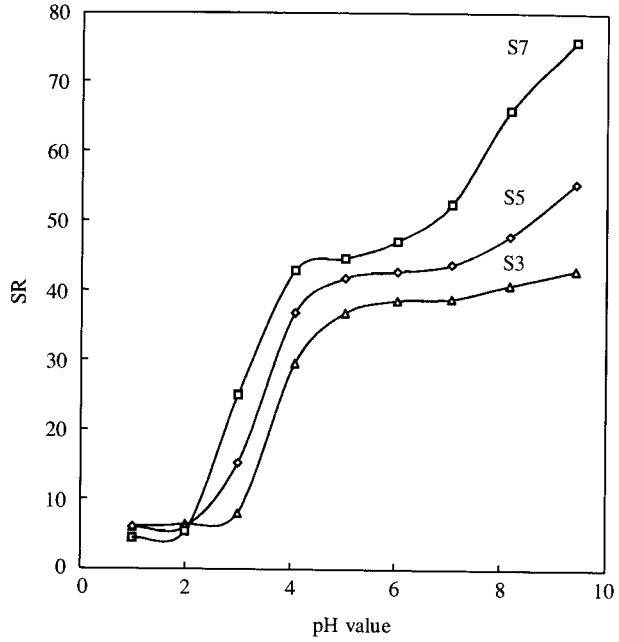

Figure 1. Swelling ratios as a function of pH for NIPAAm/AA copolymeric gels with different DNs.

ates the interaction of carboxylic acid groups and promotes the repulsive effect of the charges of carboxylate ions (COO^-) on the gels. This action raises the swelling ratio and makes the effect of deswelling insignificant. Therefore, the gels containing the higher DN of AA cause the larger ionic repulsion inside the copolymer networks and can afford the pH-sensitive character of gels (S7>S5>S3).

3. Effect of various DNs of AA on swelling ratio for NIPAAm/AA copolymeric gels

The swelling ratios as a function of time for NIPAAm/AA copolymeric gels in deionized water at various temperatures (15-50 °C) are shown in Figures 2. The results indicate that the swelling ratios increase with increasing DN of the AA content, i.e., S7>S5>S3. According to Flory's swelling theory [24], the swelling ratio is related to the ionic osmotic pressure, crosslinking density, and affinity of the hydrogel with water. The crosslinking density is fixed in the presented hydrogels, so the control factors for the swelling ratio are the fixed charge and the affinity of gel with water. Because AA is a hydrophilic monomer with easily ionized groups, the higher the DN of AA, the larger the affinity of the gels with water and the greater the number of charges of carboxylate ions (S7), so a higher swelling ratio of the hydrogel is induced.

An interesting phenomenon was also observed from Figure 2, that is, an overshooting behavior. The maximum swelling ratio over the equilibrium values appeared for the S7 gel when the temperature was raised to over 25 °C (see Figures 2(b), 2(c) and 2(d)). To further check whether this behavior appears for other gels (S5 and S3) at higher temperatures, the temperature was raised in this experimental process. The swelling ratios for the hydrogels as a function of time at higher temperatures (65 and 75 °C) are shown in Figures 3 and 4. The dynamic swelling ratios of S3, S5, and S7 exhibit more significant water "overshoot". These phenomena were not observed for poly(acrylic acid) gel, but similar results for hydroxyethyl methacrylate gel were reported by Shieh and Peppas [25] and our previous studies [26]. This behavior can be attributed to molecular chain relaxation, where water diffuses into the network before the chains have enough time to relax (diffusion is faster than relaxation), so that the swelling ratio curve reaches a maximum, the overshoot value. When the chains finally relax, water is forced out of the networks, and the swelling ratios eventually reaches its equilibrium value even to the gel transitions. This phenomenon is more apparent when the higher DN of AA (see Figure 2(d), S7) was contained in the gels. In HEMA gel, the overshooting behavior gradually disappears as the temperature of environment increases. On the other hand, the overshooting behavior gradually appears in the present gel systems, especially for S3 and S5. This result implies that as the temperature is increased, the rate of diffusion for water into gel is faster than that of chain relaxation. This phenomenon is more significant in the copolymeric gel with high DN of AA.

4. Effect of temperature on swelling ratio for NIPAAm/AA copolymeric gels

The effect of temperature on the swelling ratio of a series of NIPAAm/AA copolymeric gels in deionized water is shown in Figure 5. It indicates that the higher the temperature the lower the swelling ratio, but the gel transition temperature is not obviously affected by the DN of AA. The gel transitions for these copolymeric gels are governed solely by the NIPAAm component because the hydrophilic group (amide) in the polymer structure forms intermolecular hydrogen bonds with surrounding water at low temperatures (below gel transition temperature). The water penetrating into the gels is in a bound state at low temperature. But the water molecules in the hydrogel gain an enthalpy as the temperature is increased. The hydrophilic group (amide) in the NIPAAm component is turned into an intramolecular hydrogen bonds. This leads to the decreasing ability of the hydration force in the gel. At the same time, the hydrophobic force of the isopropyl group in the NIPAAm increases. These

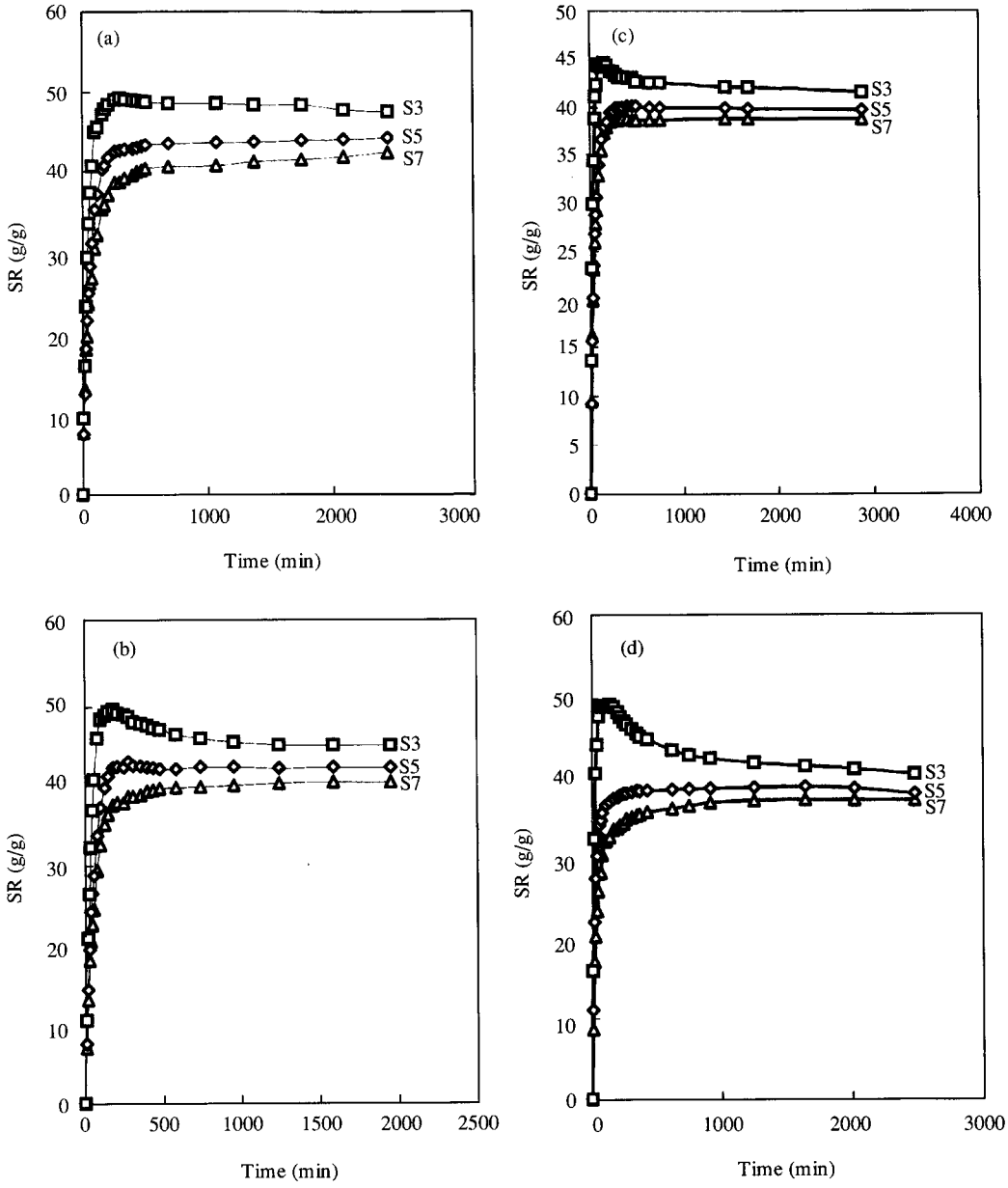

Figure 2. Swelling ratios as a function of time for NIPAAm/AA copolymeric gels with different DNs in deionized water at (a)15 °C, (b) 25 °C, (c)35 °C and (d)50 °C.

two effects make the state of the water molecules in the gel change from bound water to free water and release from the gel network. This phenomenon consequently leads to the rapid drop of swelling ratio at the gel transition temperature. The results in Figure 5 also indicate that the higher the DN of AA (S7), the higher the swelling ratio for the NIPAAm/AA copolymeric gel. These results are due to the fact that the SA 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 flatter with increasing DN of AA (S7). This brings about a gel that does not easily shrink as the temperature increases.

From the above discussion, we can see that the swelling ratios for these copolymeric gels are increased with increasing pH values of external solution and decreased with an increase of temperature.

5. Investigation of water diffusion in xerogels

The swelling kinetics can generally be described in two terms, namely, the diffusion rate of imbibing solvent into the gel and the relaxation rate of the polymer network. To elucidate the transport mecha-

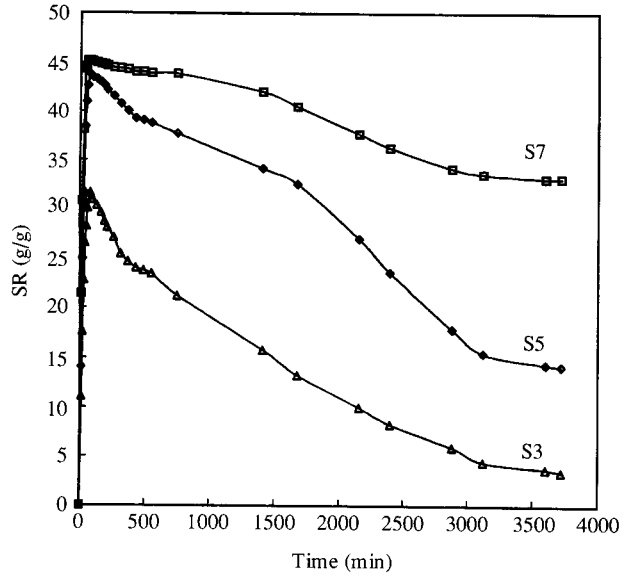

Figure 3. Swelling ratios as a function of time for NIPAAm/AA copolymeric gels with different DNs at 65 °C in deionized water.

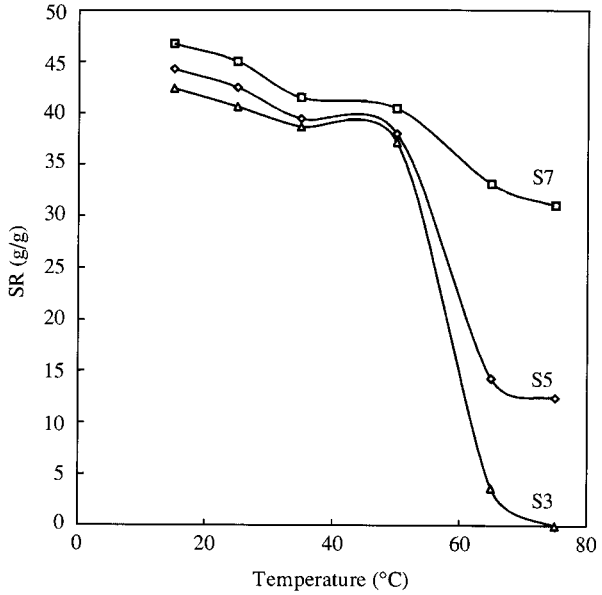

Figure 5. Swelling ratios as a function of temperature for NIPAAm/AA copolymeric gels with different DNs in deionized water.

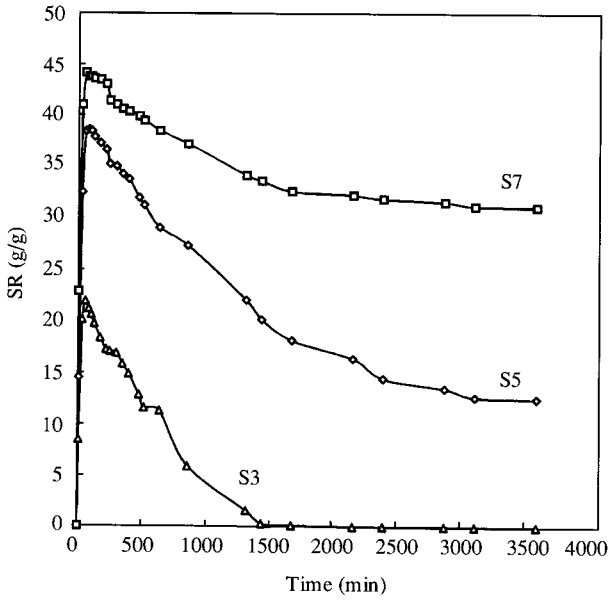

Figure 4. Swelling ratios as a function of time for NIPAAm/AA copolymeric gels with different DNs at 75 °C in deionized water.

nism and the nature of the sorption kinetics in the copolymeric gels, the initial swelling data were fitted to the exponential heuristic equation [27,28]:

$$\frac{M_t}{M_\infty} = Kt^n \qquad (4)$$

where K is a characteristic constant of the gel, and n is a characteristic exponent relating to the mode of transport of the penetrate. "n" and "K" were calculated from the slope and intercept of the plot of $\log(M_t/M_\infty)$ against $\log(t)$ respectively at various pHs and temperatures. In addition, Eq.(2) was used to calculate the diffusion coefficient D from the slope, $4\sqrt{D}/\sqrt{\pi}L$, of the plot of (M_t/M_∞) against $\sqrt{t}$ at different pHs and temperatures. Table II lists the diffusion coefficient D, the index n, and the constant K for NIPAAm/AA copolymeric gels at various temperatures and pHs.

The results in Table II indicate that the n values for these copolymer gels at various temperatures are between 0.5 and 1.0. This indicates that the swelling transport mechanism is non-Fickian. The diffusion coefficients for various copolymeric gels increase with increasing temperature. Moreover, the diffusion coefficient also increases with the DN of AA at a given temperature. The same result is also observed for the initial swelling rate. Therefore, the data in Table II show that the swelling transport mechanisms for S3, S5, and S7 are all non-Fickian transports.

The overshoot values were calculated for temperatures ranging from 35 to 75 °C. The values of S3 range from 1.03 % at 50 °C to 1620.90 % at 75 °C (because the equilibrium swelling ratio converges to zero), from 2.02 % at 50 °C to 210.27 % at 75 °C for S5, and from 6.95 % at 35 °C to 41.68 % at 75 °C for S7. The overshoot values thus increase with temperature, and the lower the DN of AA, the higher the overshoot value, especially for S3 at high temperatures.

Table II. Initial diffusion coefficient of water, D, kinetic exponent, n, and characteristic constant, K, for water penetrating through NIPAAm/AA copolymeric gels at various temperatures.

Sample No.	T (°C)	n	K	$D \times 10^7$ (cm^2/sec)	Initial swelling rate (g/min)
S3	15	0.70	0.66	1.62	0.31
	25	0.89	0.68	1.77	0.32
	35	0.64	0.1	2.46	0.36
	50	–	–	2.62	0.38
S5	15	0.76	0.66	1.75	0.35
	25	0.85	0.82	2.16	0.37
	35	0.68	0.8	2.56	0.37
S7	50	–	–	4.39	0.42
	15	0.82	0.86	2.75	0.45
	25	0.86	1.01	3.96	0.48
	35	0.91	0.98	5.49	0.49
	50	–	–	8.08	0.51

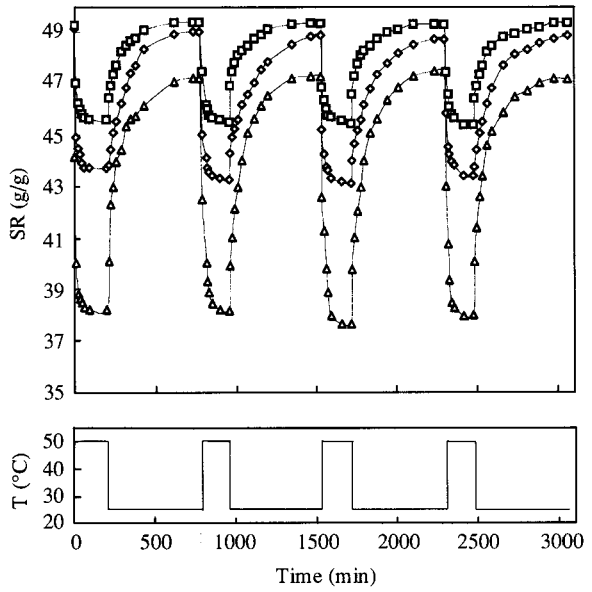

Figure 6. Swelling ratios of NIPAAm/AA copolymeric gels with different DNs as a function of time repeated abrupt change of temperature between 25 °C and 50 °C in deionized water. (Δ: S3, ◊: S5, ❑: S7)

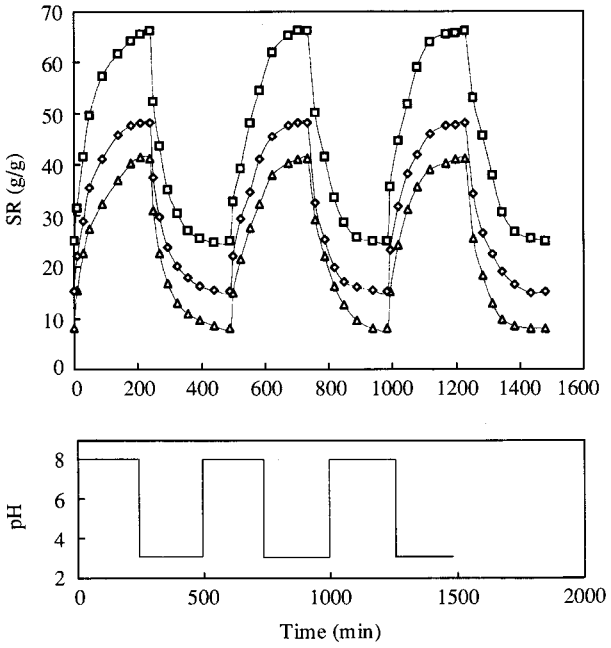

Figure 7. Swelling ratios of NIPAAm/AA copolymeric gels with different DNs as a function of time repeated abrupt change of pH between pH 3.08 and pH 8.02 in deionized water. (Δ: S3, ◊: S5, ❑: S7)

6. Effect of reversibilities on swelling ratio for NIPAAm/AA copolymeric gels

Thermoreversible gels exhibit a swell-deswell transition. This behavior depends on the weak hydrogen-bonding of amide groups which are transferred from a swelling state to a deswelling state over a certain temperature range. Figure 6 shows the change of swelling ratio for this series of gels when they were immersed in deionized water at 25 and 50 °C. All gels can swell and deswell in a period of time when the temperature is cycled through their gel transition temperature. As seen from the curves, the swelling ratio is lower at 50 °C but higher at 25 °C. Moreover, the swelling ratios of S3, S5 and S7 were changed from about 47.2 to 38.2, 49.0 to 43.7, and 49.4 to 45.6, respectively, when gels were immersed at 50 °C first and then at 25 °C. These gels subsequently reswelled to 47.2, 49.0, and 49.4, respectively, when reimmersed at 25 °C. Therefore, these copolymeric gels exhibited a reversible behavior between 25 and 50 °C, especially for the S3 gel, which showed an apparent and rapid change in swelling ratio when the temperature was above the gel transition temperatures. Concerning

this series of gels, the amount of SA on copolymeric gel significantly affects the thermoreversibility of the gels.

Figure 7 presents the effect of cycling of pH on the swelling behaviors of these ionic networks. The pH was changed from 8.02 to 3.04 and the same cycle was repeated several times. The first swelling time in pH 8.02 was a period of swelling equilibrium followed by 4 hrs. in pH 3.04 and then 4 hrs. in a pH 8.02 buffer. At the first swelling time, the carboxylate ions (COO^-) enhances the swelling ratios, but when the gels are transferred to low pH (3.02), the carboxylate ions are protonated to carboxylic acid groups (COOH), decreasing the electrostatic repulsive forces between the charge sites on the network and making the swelling ratios decrease. Figure 7 also shows that the higher the DN of AA, the larger the swelling ratios. Hence, the changes of the swelling ratios for the gels follow the order of S7>S5>S3.

The results shown in Figure 7 indicate that the pH reversibility for S3 gel is less significant. Hence, the pH-reversibility for the copolymeric gels is dependent on the DN value of AA in the gel.

7. Effect of hydrogel composition on fractional release

A new class of hydrogels whose water swelling ratios are sensitive to small changes in environmental conditions has attracted great interest recently. Many different biomolecules, such as drugs, enzymes and antibodies, may be incorporated into these gels [3,12,19,29,30]. This study has also incubated drugs in these pH and temperature-sensitive gels. These incubated species may be physically entrapped within the gel structure. When a drug is incubated in such gels, it may be turned "off and on" by deswelling and reswelling the pores 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 phenolphthalein in NIPAAm/AA copolymeric gels at 55 °C are shown in Figure 8. The lower DN of AA (S3) in the hydrogel system exhibits a slower release, which is due to the faster gel deswelling; that is to say, the fewer the carboxylate groups on the copolymeric gels, the faster the gel deswelling. Therefore, the amount of drug released from sample S3 was smaller than that released from S5 and S7 at temperatures above the gel transition temperature.

The results also show that the fractional release (M_t/M_∞) of phenolphthalein does not reach 1.0. This implies that some phenolphthaleins were entrapped within the gel. This effect supports the concept of a water pocket formation in the collapsed gel. Phenolphthalein only dissolves in free water. The phenolphthalein molecules located in the porous region of the gel may either be squeezed out quickly or trapped in water pockets as the gel collapses [31]. These findings mean that, in the case of deswelling, the dehydration of the copolymeric gels occurred from the gel 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 some other systems [29,32,33].

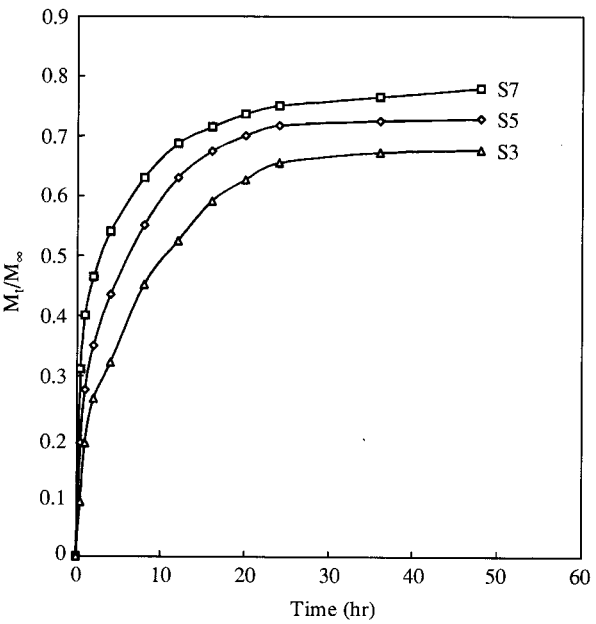

Figure 8. Phenolphthalein release profile for NIPAAm/AA gels with different DNs during deswelling at 55 °C.

Conclusion

The swelling ratios of NIPAAm/AA copolymeric gels are increased with increasing DN of AA. In addition, the higher the DN of AA, the larger the affinity of the gel with water. Moreover, the gel transition temperatures are affected by the DN of AA. The diffusion studies indicate that the diffusion coefficient "D" of all NIPAAm/AA copolymeric gels increased with increasing temperatures and DN of AA. A significant and interesting result was found in this study, that is, the dynamic swelling ratios of the hydrogels exhibited an overshoot phenomenon under higher temperature condition. For the thermosensitive gels, the DN of AA in the copolymeric gels obviously affected their thermosensitivities, and the changes of swelling ratios for thermoreversibilities were larger when the temperatures were

above gel transition temperatures. Regarding the pH-reversible characteristics, the higher the DN of AA, the better the reversibilities with respect to pH for the gels. Finally, the hydrogel with a lower DN value exhibited a slower phenolphthalein release, which was due to the faster gel deswelling and skin formation at high temperatures.

Acknowledgements

The author wishes to thank the National Science Council of the Republic of China for financial support by grant NSC 88-2216-E-036-024.

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