pH-Thermoreversible Hydrogels. I. Synthesis and Swelling Behaviors of the (*N*-isopropylacrylamide-*co*-acrylamide-*co*-2-hydroxyethyl methacrylate) Copolymeric Hydrogels

WEN-FU LEE, CHIH-HSUAN SHIEH

Department of Chemical Engineering, Tatung Institute of Technology, Taipei, Taiwan, Republic of China

ABSTRACT: A series of pH-thermoreversible hydrogels that exhibited volume phase transition was synthesized by various molar ratios of *N*-isopropylacrylamide (NIPAAm), acrylamide (AAm), and 2-hydroxyethyl methacrylate (HEMA). The influence of environmental conditions such as temperature and pH value on the swelling behavior of these copolymeric gels was investigated. Results showed that the hydrogels exhibited different equilibrium swelling ratios in different pH solutions. Amide groups could be hydrolyzed to form negatively charged carboxylate ion groups in their hydrophilic polymeric network in response to an external pH variation. The pH sensitivities of these gels also depended on the AAm content in the copolymeric gels; thus the greater the AAm content, the higher the pH sensitivity. These hydrogels, based on a temperature-sensitive hydrogel, demonstrated a significant change of equilibrium swelling in aqueous media between a highly solvated, swollen gel state and a dehydrated network response to small variations of temperature. pH-thermoreversible hydrogels were used for a study of the release of a model drug, caffeine, with changes in temperature. © 1999 John Wiley & Sons, Inc. J Appl Polym Sci 71: 221–231, 1999

Key words: hydrogel; *N*-isopropylacrylamide-*co*-acrylamide-*co*-2-hydroxyethyl methacrylate gel; swelling kinetic; drug release

INTRODUCTION

Hydrogels are crosslinked, three-dimensional hydrophilic polymer 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 variables that change in typical physiological, biological, and chemical systems.[8]

Thermoresponsive hydrogel demonstrates a volume transition and associated phase transition from low temperature (a highly swollen gel), to high temperature, (a collapsed gel near its critical point).[9,10] Poly(*N*-isopropylacrylamide) poly(NIPAAm) is one of the best thermotropic polymers and exhibits a lower critical solution temperature (LCST) behavior, collapsing and shrinking above the LCST at 33°C.[9,10] The temperature-induced collapse transition was observed for hydrogel containing a hydrophobic component in our previous study.[11] Poly-(NIPAAm) and its copolymers were studied in the development of temperature modulate drug release systems. In these systems, increased temperature above the polymer LCST results in increased the transport of entrapped molecules through the membrane.[12] Poly(NIPAAm) hydrogels were recently reported in the field of con-

trolled drug delivery[13,14] and immobilization of enzymes[15] and cells.[16]

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

The hydrolysis of polyacrylamide (PAAm) gels, equilibrated in aqueous solution of high pH or formed from an initial highly basic solution (with pH of 11 or 12), led to extensive swelling of the gels when placed in pure water.[20] Ilavsky reported the presence of charges (due to the hydrolysis of the PAAm chain) in the collapse of PAAm gels.[21]

The purpose of this study is to develop a temperature- and pH-reversible hydrogel. In this respect, a series of copolymeric hydrogels with pH and temperature reversibility were synthesized from copolymerizing *N*-isopropylacrylamide and acrylamide (AAm), in various molar ratios, in the presence of an amount of 2-hydroxyethyl methacrylate (HEMA) and crosslinker. The degree of equilibrium swelling of these gels was determined at various pH values and at different temperatures. The swelling reversibilities and release characteristics of these gels were also investigated at different pH values and temperatures.

EXPERIMENTAL

Materials

N-isopropylacrylamide (NIPAAm) (Fluka Chemical Co., Buchs, Switzerland) was recrystallized in *n*-hexane before use to remove the inhibitor, *N,N'*-methylene-bis-acrylamide (NMBA) (SIGMA Chemical Co., St. Louis, MO) as a crosslinker was used as received. Acrylamide (AAm, mp 83–84°C) was recrystallized from reagent-grade benzene and vac-

uum dried at room temperature. HEMA (TCI Co., Tokyo, Japan) was further purified by vacuum distillation at 68°C/5 mmHg. *N,N,N',N'*-tetramethylethylenediamine (TEMED) (Fluka Chemical Co.) was used as received as an accelerator. Ammonium peroxodisulfate (APS) (Wako Pure Chemical Co., Ltd, Osaka, Japan) was further purified by recrystallization and used as an initiator.

Caffeine as a model drug was obtained from Fluka. All solvents and other chemicals were of analytical grade.

Preparation of Hydrogels

Various ratios of NIPAAm and AAm and 0.2 g HEMA with 7.1 mol % (44 mg) NMBA based on total monomer contents were dissolved in 8 mL of deionized water and ethanol (50 vol %). To this solution, 1.7 wt % (6 mg) APS and 1 wt % (10 mg) 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 10-mm-diameter disks and immersed in deionized water for 1 week to remove the residual unreacted monomer. Swollen gels were dried at room temperature for 1 day, and these samples were 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 the surface water was removed by blotting with filter paper. Dry weight (W_d) was determined after the gel was dried in a vacuum oven for 2 days. The swelling ratio (SR) based on W_w and W_d was then calculated; this is defined as

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

Dynamic Swelling

The dried gels were immersed in excess buffer solution at different pH values and different temperatures. The SR 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

Table I   Characterization of the NIPAAm/AAm/HEMA Copolymeric Gels

Sample	NIPAAm (mol %)	AAm (mol %)	HEMA (mol %)	Appearance[a]	Gel Temperature Transition (°C)	Swelling Ratio (g H_2O/g Dry Sample)
X0	0.452 g (72.73%)	—	0.2 g (27.27%)	o	>80	11.32
X1	0.226 g (36.37%)	0.142 g (36.37%)	0.2 g (27.27%)	t	>80	12.61
X3	0.113 g (18.19%)	0.213 g (54.55%)	0.2 g (27.27%)	t	>80	13.14
X5	0.075 g (12%)	0.237 g (60.73%)	0.2 g (27.27%)	t	>80	14.12
X7	0.057 g (9.09%)	0.249 g (63.64%)	0.2 g (27.27%)	t	>80	15.67

[a] o, opaque; t, transparent.

sorption at infinitely long time was designated M_∞. The following equation was used to calculate the diffusion coefficient, D, for $M_t/M_\infty \leq 0.8$:[22]

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

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

Measurement of Swelling Ratios at Various pH Solutions and Temperatures

The measurements of SRs for the copolymeric gel in various pH solutions and temperatures were the same as those in deionized water. Buffer solutions were prepared by aqueous solutions of HCl, KCl, $KHC_8H_4O_4$, NaOH, KH_2PO_4, and H_3BO_3.

Caffeine Deswelling Kinetics Experiments

The dried gels were equilibrated in 30 mg/10 mL of caffeine solution at 25°C for 2 days to load caffeine into the gels. The caffeine deswelling kinetic experiments were carried out by transferring previously incubated-drug gels into 10 mL of deionized water at 50°C. The gels were repeatedly removed and transferred into 10 mL of fresh water at each fixed-time interval. The released caffeine was analyzed at 272 nm with 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, the ionic content, and the

crosslinking agent content. The environmental conditions include pH values and temperature of solution.

The swelling behavior of NIPAAm hydrogels has been studied by many researchers.[4,5,9,10] The series of copolymeric NIPAAm/AAm/HEMA hydrogels (for hydrolysis of acrylamide) has not been investigated in the literature. Therefore, the effect of AAm on the SR of NIPAAm/AAm/HEMA copolymeric gels is studied here.

Characterization of NIPAAm/AAm/HEMA Copolymeric Gels

Some characteristics of the NIPAAm/AAm/HEMA copolymeric gels for various feed compositions are shown in Table I. The results in the table show that the appearance of all copolymeric gels is transparent except for sample X0. The gel transition temperatures exceed 80°C. The equilibrium SRs of the copolymeric gels are also increased with decreasing molar ratio of NIPAAm/AAm and are higher than that of NIPAAm/HEMA (X0) gel. This study uses various molar ratios for NIPAAm/AAm—1/1 (X1), 1/3(X3), 1/5(X5), and 1/7(X7)—to compare the different characters of the gels with different amounts of AAm.

Nonionizable HEMA, which exhibits no effect on the temperature characteristics of gels, was added to the hydrogels to increase gel strength. In addition, HEMA will result in less swellable gels with lower equilibrium SRs.

Effect of Different Environments on Swelling Kinetics for NIPAAm/AAm/HEMA Copolymeric Gels

The SRs of gels will be different in various environments of pH and temperature. Figure 1 shows

Figure 1 Swelling ratios as a function of time for X1 (a), X3 (b), X5 (c), and X7 (d) copolymeric gels at different environments (△) 25°C, pH 4; (◇) 25°C pH 10.4; (○) 45°C, pH 4; and (□) 45°C, pH 10.4.

the swelling kinetics of a series of hydrogels in the separated condition. The results shown in this figure indicate that the SRs of gels in the buffer solution with pH 10.4 are larger than those in the buffer solution with pH 4. This evidence shows that the amide groups on the copolymeric gels would be easily hydrolyzed to form carboxylate groups under the basic condition. This phenomenon was confirmed by Park and Hoffman.[25] On the other hand, due to the ionic repulsion of the carboxylate ions (COO^-), the SR at pH 10.4 was larger than that at pH 4. Saito et al.[9] and Tanaka and Hirokawa[10] have reported that polymeric networks polymerized from monomer NIPAAm would result in the phenomenon of network de-

swelling when the temperature exceeds its critical temperature.

Under a basic environment at high temperature (45°C and pH 10.4), the hydrolyzed reaction of an amide group on the gel would be accelerated, and the repulsive effect of the carboxylate ions on the gels would be increased. Both events would increase the SR higher and make the effect of deswelling insignificant. However, under acidic conditions, little repulsive effect of charges would occur by hydrolysis of amide groups, so we can easily observe decreased swelling behavior.

From the foregoing results, the SRs for the gels are related to the external environment. The amide groups of these polymers could become

Table II   ΔSR for NIPAAm/AAm/HEMA Copolymeric Gels Under Different Conditions

Sample	$\Delta SR_{45-25°C}$		$\Delta SR_{pH10.4-4}$	
	pH 10.4	pH 4	25°C	45°C
X1	1.61	2.68	11.63	15.91
X3	6.68	1.55	12.19	20.41
X5	10.32	1.25	12.28	23.85
X7	11.33	0.73	13.24	25.3

more prone to hydrolyze into acid groups under basic and high temperature conditions, increasing the hydrophilicity of gels. This can account for the increased SR.

Effect of Different Environments on Difference in Swelling Ratios (ΔSR) for NIPAAm/AAm/HEMA Copolymeric Gels

The differences of SRs (ΔSR) under the same conditions but in different environments are shown in Table II. The results show that the ΔSR values at 45 and 25°C under pH 10.4 increase with increasing AAm content (X7 > X5 > X3 > X1). This is because the amide groups become more prone to hydrolyze under basic and high temperature conditions, which causes the SRs of copolymeric gels to be higher at 45°C than at 25°C. In addition, this phenomenon is also observed for ΔSR at pH 10.4 and pH 4 at 45°C. The higher the AAm content, the larger the ΔSR under these conditions. Moreover, a similar phenomenon can be found at 25°C for different pHs. Comparing the ΔSR values between 25 and 45°C, all values at 25°C are smaller than those at 45°C. This implies that increasing temperature would promote the amide groups to hydrolyze to form carboxylic acid groups, enhancing hydrophilicity of the copolymeric gels and causing the gels to absorb more water. The greater the hydrophilicity of the gels,

the stronger the affinity of the hydrogel toward water, and the larger the SR. According to these results, ΔSR is controlled mainly by the AAm content in the gels.

On the other hand, the effect of NIPAAm content on the ΔSR at different temperatures under pH 4 for the NIPAAm/AAm/HEMA gels is shown in Table II. The ΔSR values under pH 4 at 25 and 45°C decrease with decreasing NIPAAm content (X7 < X5 < X3 < X1). The samples prepared with more NIPAAm (X1) exhibited a greater change in SR than those prepared with less NIPAAm (X7). This suggests that the temperature-sensitive character of this copolymeric gel series is influenced mainly by the amount of NIPAAm in the networks.

Effect of Different Environments on Initial Swelling Rate for NIPAAm/AAm/HEMA Copolymeric Gels

The effect of different environments on the initial swelling rate for the copolymeric gels listed in Table III indicates that the initial swelling rates increase with increasing AAm content in all of the environments except deionized water. This is because the amide groups would attract ions in the buffer solutions to increase the charges in the copolymeric networks. This action promotes water molecule penetration into the polymeric networks through the difference of ion osmotic pressure during the initial swelling periods. This is why the initial swelling rates of the X7 gel are the largest. But when the gels are immersed in the deionized water, the initial swelling rates are larger than those in the buffer solutions and decrease with increasing AAm content. This result implies that the elastic recovery force of the gels is greater than the swelling force and increases with increasing AAm content in this condition.

For samples at the same temperature and in different pH environments, such as at 25 or 45°C under pH 4 and pH 10.4, the results shown in

Table III   Initial Rate (g/min) for NIPAAm/AAm/HEMA Copolymeric Gels in Different Environments

Sample	25°C in Deionized Water	25°C, pH 4	25°C, pH 10.4	45°C, pH 4	45°C, pH 10.4
X0	8.3×10^{-2}				
X1	8.0×10^{-2}	2.9×10^{-2}	3.3×10^{-2}	2.1×10^{-2}	5.1×10^{-2}
X3	7.5×10^{-2}	3.1×10^{-2}	3.6×10^{-2}	2.6×10^{-2}	5.2×10^{-2}
X5	7.1×10^{-2}	3.5×10^{-2}	4.0×10^{-2}	3.3×10^{-2}	5.6×10^{-2}
X7	6.6×10^{-2}	3.8×10^{-2}	4.2×10^{-2}	3.6×10^{-2}	7.3×10^{-2}

Figure 2 Swelling ratios as a function of pH for various NIPAAm/AAm/HEMA copolymeric gels at 25°C.

Table III indicate that the initial swelling rates are greater at high pH. It suggests that an increase in the effect of hydrolysis would increase the swelling driving force during the initial period. A similar phenomenon can be found by comparing the initial rate values of 25°C, pH 10.4 and 45°C, pH 4. The results also show little difference in initial swelling rates between 25 and 45°C under pH 4. These results imply that the initial swelling rate for these gels will be not be significantly affected by temperature in a low-pH environment.

Effect of pH on Swelling Ratio for NIPAAm/AAm/HEMA Copolymeric Gels in Buffer Solutions

Figure 2 shows the pH dependence on the gel equilibrium SR for our synthesized poly-(NIPAAm/AAm/HEMA) gels at 25°C. The AAm groups will hydrolyze into carboxylic acid groups, which will promote an increase in SR (see Fig. 2). The higher the AAm content, the more the amide groups are hydrolyzed, so it would be proportional to SR. The anionic polymeric networks containing carboxylic acid groups will be imidized as the pH of the external swelling medium increases,[18] and meanwhile hydrophilicity will be increased to enhance the SRs.

From these results, we can determine the sensitivities of gels to pH, and find that the greater the acrylamide content, the higher the SR for the gels under the basic condition. Thus, the SRs of

gels would have a negative correlation to the ratio of NIPAAm and AAm under the higher pH condition.

Effect of Temperature on Swelling Ratio for NIPAAm/AAm/HEMA Copolymeric Gels

The effect of temperature on the SRs of a series of NIPAAm/AAm/HEMA copolymeric gels in buffer solution (pH 7.4) and deionized water are shown in Figures 3 and 4. The results show that the polymeric networks exhibit a deswelling behavior at higher temperatures. This is because the amido group of NIPAAm in the polymer forms an intermolecular hydrogen bond with surrounding water at low temperature, which would turn into an intramolecular hydrogen bond over its gel transition temperature (32°C). This phenomenon causes makes the gel's hydration capability to decrease. At the same time, the hydrophobicity of isopropyl groups of the NIPAAm gel increase. These two results make the state of water molecule in the gel change from bound water to free water and make the SR of the gel decrease over its gel transition temperature (32°C). But the results shown in Figures 3 and 4 show a gradual collapse with increasing temperature. The SR decreases significantly with increasing NIPAAm content (X1). These results conform to those of our previous studies of *N*-ethoxypropylacrylamide/acrylamide (NEPAAm/

Figure 3 Swelling ratios as a function of temperature for various NIPAAm/AAm/HEMA copolymeric gels in pH 7.4.

Figure 4 Swelling ratios as a function of temperature for various NIPAAm/AAm/HEMA copolymeric gels in deionized water.

AAm) and *N*-tetrahydro-furfurylacrylamide (NTH-FAAm)/AAm hydrogels.[11]

Generally, the gels containing hydrophilic groups will affect deswelling. The results shown in Figures 3 and 4 also indicate that the greater the AAm content, the higher the SR for the NIPAAm/AAm/HEMA copolymeric gels. From the results, we could find that hydrophilic groups had more influence when more AAm was incorporated into the gels at the same temperature. This influence makes the more hydrophilic characteristic of the gels and the profiles of SR increase (X7 > X5 > X3 > X1). Therefore, we could find that the gels with different AAm content have different characteristics, and the gels with more AAm content are more hydrophilic. This result does not cause the gel to shrink sharply as the temperature increases.

Figure 4 shows that the swelling ratios of X3, X5, and X7 increase at the temperature of 65°C. The swelling behaviors of the gels exhibit the specific characteristic behavior of HEMA gel when the composition of NIPAAm is less than HEMA in the copolymeric gels (X3, X5, X7); that is, the SR of HEMA gel has a minimum value at 55°C, then increases with increasing temperature above 55°C.[23] This behavior was observed in our previous reports.[24] This specific phenomenon was not observed in the X1 gel, because the NIPAAm content is greater than the HEMA content in the gel. This may be because the hydrophobic effect is greater than the hydrophilic effect contribution from the HEMA under higher temperature.

Effect of Reversibilities on Swelling Ratio for NIPAAm/AAm/HEMA Copolymeric Gels

Thermoreversible polymers would bring about a soluble–insoluble transition. The water-soluble behavior depends on weak hydrogen-bonding or amide groups that are transferred from a fully soluble polymer to a phase-separated insoluble polymer. Figure 5 shows the change in SRs for this series of gels when they were immersed in deionized water at 25 and 50°C. The gels can swell and deswell when temperature is recycled periodically between higher temperature (50°C) and lower temperature (25°C). As seen from these curves, the SR is lower at 50°C, but higher at 25°C. Moreover, the SRs of samples X1, X3, X5, and X7 can be deswelled from 8.5 to 4, 14 to 11, 16 to 14, and 19 to 18 when gels are immersed at 50°C. Then these copolymeric gels can reswell to 8.5, 14, 16, and 19 when reimmersed at 25°C. Therefore, these gels exhibited a reversible change in SR between 25 and 50°C. From the foregoing results, the more NIPAAm in the gel, the more obvious the thermosensitive effect, and the greater the range of reversibilities.

Figure 6 presents the effect of cycling pH on the swelling behavior for these gels. The pH of the

Figure 5 Swelling ratios of various NIPAAm/AAm/HEMA copolymeric gels as a function of time repeated abrupt change of temperature between 25 and 50°C. (□) X1; (△) X3; (○) X5; (◇) X7.

Figure 6 Swelling ratio of various NIPAAm/AAm/ HEMA copolymeric gels as a function of time repeated abrupt change of pH between pH 6.05 and pH 9.69 at 25°C in buffer solution. (□) X1; (△) X3; (○) X5; (◇) X7.

buffer solution was changed from 9.69 to 6.05, and the same cycle was repeated several times. The first swelling time at pH 9.69 was a period of swelling equilibrium followed by 8 h at pH 6.05 and then 8 h at pH 9.69. During the first swelling time, some amide groups of gels hydrolyzed into carboxylate ions (COO^-), enhancing the SRs. When the gels were transferred to low pH (6.05), the carboxylate ions protonated to carboxylic acid groups (COOH), which led to a decrease in the electrostatic repulsive force between the changes on networks and promoted decreased SRs. The higher the AAm content in the gels, the larger the ΔSR. Therefore, the SRs and ΔSRs of gels were larger for samples X7 and X5 than for samples X3 and X1. Moreover, the gels did not lose their elasticity in these systems.

Effect of Temperature on Swelling Kinetics for NIPAAm/AAm/HEMA Copolymeric Gels in Deionized Water

The SRs as a function of time for NIPAAm/AAm/ HEMA (a)–(d) and NIPAAm/HEMA (e) copolymeric hydrogels in deionized water are shown in Figure 7. The results indicate that the SRs increase with increasing AAm content. According to Flory's swelling theory,[26] the following equation is given:

$$Q^{5/3} = [(i/2V_\mu S^{1/2})^{1/2} + (1/2 - \chi_1)/v_1]/(\nu_e/V_0) \quad (3)$$

where i/V_μ is the concentration of fixed charge referred to an unswollen network; S is the ionic concentration in the external solution, $(1/2 - \chi_1)/v_1$ is the affinity of the hydrogel toward water; and ν_e/V_0 is the crosslinked density of the hydrogel. It is known that the SR is related to ionic osmotic pressure, crosslinked density, and the hydrogel's affinity toward water from the above equation. The total fixed charge was zero, and the crosslinked density was fixed in a series of NIPAAm/AAm/HEMA hydrogels, so the influence of the SR of the hydrogel is only the affinity with water. Because AAm is a hydrophilic monomer, the higher the AAm content, the greater the affinity of the gels toward water and the higher the SR of the hydrogel.

The effects of temperature on SR for the copolymeric gels in deionized water are shown in Figure 7. The SRs decrease with increasing temperature. On the other hand, the SRs of (Xo) are all lower than those of the gels containing AAm (X1–X7), because of the hydrophilicities of the gels.

Investigation of Water Diffusion in Xerogels

Swelling kinetics can be generally described in two terms: the diffusion rate of imbibing solvent into the gels and the relaxation rate of the polymeric networks. As the charge density of gel matrix rises, the driving force for swelling also increases.[26]

To elucidate the transport mechanism of the nature of the sorption kinetic in the copolymeric gels, the initial swelling data were fitted to the exponential heuristic equation[27,28]

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

where K is a characteristic constant of the gel and n is a characteristic exponent of the mode transport of the penetrant. Values of n and K were calculated from the slopes and intercepts of the plot of $\log(M_t/M_\infty)$ against $\log(t)$ at various temperatures. In addition, eq. (2) was used to calculate the diffusion coefficient D from the slope in the plot of (M_t/M_∞) at different temperatures. Table IV shows the diffusion coefficient D, the index n, and the constant K for a series of NIPAAm/AAm/HEMA copolymeric gels at various temperatures. The results indicate that the n

Figure 7 Swelling ratios as a function of time for various NIPAAm/AAm/HEMA copolymeric gels: X1 (a), X3 (b), X5 (c), and X7 (d), and NIPAAm/HEMA copolymeric gel (e) in deionized water at 20°C (□), 25°C (◇), 35°C (△), 45°C (×), and 55°C (+).

Table IV Initial Diffusion Coefficients of Water *(D)* and Kinetic Exponents *(n)* and Characteristic Constants *(K)* of Water Penetrated Through NIPAAm/AAm/HEMA Copolymeric Gels at Various Temperatures

Sample	T (°C)	n	$K \times 10$	$D \times 10^8$ (cm²/s)
X0	25	0.68	2.71	0.97
	35	0.62	2.43	2.51
	45	0.51	1.85	3.53
	55	0.52	3.72	4.20
X1	25	0.65	1.93	2.24
	35	0.52	3.10	5.52
	45	0.51	2.33	6.12
	55	0.47	2.14	6.68
X3	25	0.74	4.37	1.89
	35	0.59	2.26	3.41
	45	0.61	1.29	5.37
	55	0.54	2.67	6.81
X5	25	0.67	1.78	3.25
	35	0.66	2.82	4.38
	45	0.53	2.89	4.59
	55	0.47	1.41	7.27
X7	25	0.58	1.95	2.79
	35	0.61	4.64	5.16
	45	0.54	3.11	5.51
	55	0.47	2.36	6.49

values for X1, X5, and X7 at various temperatures decrease from 0.65 to 0.47, 0.67 to 0.47, and 0.61 to 0.47, respectively. This evidence indicates that the swelling transport mechanisms will be transformed from non-Fickian ($1.0 < n < 0.5$) to Fickian transport ($n = 0.5$) with increasing temperature; but for X0 and X3, they show a non-Fickian to a near-Fickian transport.[29] The data for the diffusion coefficients in Table IV also indicate that the diffusion coefficients for various NIPAAm/AAm/HEMA copolymeric gels increase with increasing temperature.

Effect of Hydrogel Composition on Fraction Release of Caffeine

A common application of poly(AAm) hydrogels is in drug-release systems.[12] The drug-release system of these copolymeric gels occurs through variation in the SR. In this experiment, we observe the relationships between the release of caffeine and time. The release profiles of caffeine in NIPAAm/AAm/HEMA copolymeric gels at 50°C are shown in Figure 8. The release amount of caffeine increases with release time. Moreover,

the amount of NIPAAm in the gels also controls the ΔSR between 25°C and 50°C and then affects the amounts of caffeine in the release.

The results in Figure 8 indicate that the lower the NIPAAm content in the hydrogel system, the lower the caffeine release, which is due mainly to the lower ΔSR as the gels deswell. The results also show that the fractional release (M_t/M_∞) of caffeine does not reach 1.0. This implies that the caffeine is not completely released and some portions are entrapped within the gel. This effect supports the idea of water pocket formation in the collapse gel. Caffeine dissolves only in the free water. Thus, caffeine molecules located in the porous region of the gel may be squeezed out quickly or trapped in water pockets as the gel collapses.[30] This phenomenon was also observed and explained in our previous report for NEPAAm/butyl acrylate (BA) and NTHFAAm/BA copolymeric gels,[11] and in some other papers.[31–33] Therefore, the greater the ΔSR of gels between low and high temperature, the more caffeine molecules are squeezed out in the release system.

CONCLUSIONS

A significant result obtained in this article is the hydrolysis of acrylamide at high pH and high temperature that causes the hydrophilicity of gels to increase. The SRs of NIPAAm/AAm/HEMA co-

Figure 8 Effects of various NIPAAm/AAm/HEMA copolymeric gels on caffeine release profile during deswelling (50°C).

polymeric gels increase with increasing AAm content. In addition, the higher the AAm content in the copolymeric gels, the greater the affinity of the gel toward water. The pH-sensitive character also increases with increasing AAm content. In diffusion, the results indicate that the diffusion coefficients for all NIPAAm/AAm/HEMA copolymeric gels increase with increasing temperatures.

According to the results of this study, the monomer NIPAAm in the gels obviously affected their thermal sensitivities and the SR change of thermoreversibilities. In pH-reversible characters, the greater the AAm content, the greater the SR change with pH change. Finally, the higher NIPAAm content in this hydrogel system exhibits a greater caffeine release, which is due to the greater gel volume change at high temperature.

REFERENCES

1. Grignon, J.; Scallan, A. M. J Appl Polym Sci 1980, 25, 2829.
2. Vazquez, B.; Gurruchaga, M.; Goni, I.; Narvarte, E.; Roman, J. S. Polymer 1995, 17, 3327.
3. Kataoka, K.; Koyo, H.; Tsuruta, T. Macromolecules 1995, 28, 3336.
4. Bae, Y. H.; Okano, T.; Kim, S. W. J Polym Sci Polym Phys 1990, 28, 923.
5. Yu, H.; Grainger, D. W. Macromolecules, 1994, 27, 4554.
6. Ricka, J.; Tanaka, T. Macromolecules 1984, 17, 2916.
7. Eisenberg, S. R.; Grodzinski, A. J. J Membr Sci 1984, 19, 173.
8. Ramaraj, B.; Radhakrishnan, G. J Appl Polym Sci 1994, 52, 837.
9. Otaka, K.; Inomata, H.; Konno, M.; Saito, S. Macromolecules 1992, 23, 283.
10. Hirokawa, Y.; Tanaka, T. J Chem Phys 1984, 81, 6379.
11. Hung, G. C. M.S. thesis, Tatung Institute of Technology, Taipei, Taiwan, 1995.
12. Dinarvand, R.; D'Emanuele, A. J Control Rel 1995, 36, 221.
13. Yan, Q.; Hoffman, A. S. Polymer 1995, 36, 887.
14. Bae, Y. H.; Okano, T.; Kim, S. W. J Control Rel 1989, 9, 271.
15. Park, T. G.; Hoffman, A. S. J Biomed Res 1990, 24, 21.
16. Park, T. G.; Hoffman, A. S. Biotech Bioeng 1990, 35, 152.
17. Chu, Y.; Varanasi, P. P.; Mcglade, M. J.; Varanasi, S. J Appl Polym Sci 1995, 58, 2161.
18. Khare, A. R.; Peppas, N. A. Biomaterials 1995, 16, 559.
19. Dressman, J. B.; Derbin, G. M.; Ismailos, G.; Jarvis, C.; Ozturk, A.; Palsson, B. O.; Wheatley, T. A. J Control Rel 1995, 36, 251.
20. Mallo, P.; Candau, S.; Cohen, C. Polym Commun 1985, 26, 232.
21. Ilavsky, M. Macromolecules 1982, 15, 782.
22. Kabra, B. G.; Gehrke, S. H.; Hwang, S. T. J Appl Polym Sci 1991, 42, 2409.
23. Warren, T. C.; Prins, W. Macromolecules 1972, 5, 506.
24. Lee, W. F.; Chen, C. F. J Polym Research, to appear.
25. Flory, P. J. Principles of Polymer Chemistry; Cornell University Press: Ithaca, NY, 1953.
26. Park, T. G.; Hoffman, A. S. J Appl Polym Sci 1992, 46, 659.
27. Franson, N. M.; Peppas, N. A. J Appl Polym Sci 1983, 28, 1299.
28. Korsmeyer, R. W.; Merrwall, E. W.; Peppas, N. A. J Polym Sci Polym Phys Ed 1986, 24, 409.
29. Alfrey, T.; Gurnee, E. F.; Lloyd, W. G. J Appl Polym Sci 1966, C12, 249.
30. Park, T. G.; Hoffman, A. S. J Appl Polym Sci 1994, 52, 85.
31. Yoshida, M.; Asano, M.; Kumakura, M. Eur Polym J 1989, 25, 1197.
32. Dong, L. C.; Hoffman, A. S. J Control Rel 1986, 4, 223.
33. Hoffman, A. S.; Afrassiabi, A.; Dong, L. C. J Control Rel 1986, 4, 213.