Thermoreversible Hydrogels X: Synthesis and Swelling Behavior of the (*N*-Isopropylacrylamide-*co*-Sodium 2-Acrylamido-2-methylpropyl Sulfonate) Copolymeric Hydrogels

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ABSTRACT: A series of thermosensitive hydrogels were prepared from various molar ratios of *N*-isopropylacrylamide (NIPAAm) and sodium-2-acrylamido-2-methylpropyl sulfonate (NaAMPS). Factors such as temperature and initial total monomer concentration and different pH solutions were investigated. Results indicated that the more the NaAMPS content in hydrogel system, the higher the swelling ratio and the gel transition temperature; the higher the initial monomer concentration, the lower the swelling ratio. The result also indicated that the NIPAAm/NaAMPS copolymeric hydrogels had different swelling ratios in various pH environments. The present gels showed a pH-reversible property between pH 3 and pH 10 and thermoreversibility. The swelling ratios of copolymeric gels were lower in a strong alkaline environment because the gels were screened by counterions. Finally, the drug release behavior of these gels was also investigated in this article. © 2000 John Wiley & Sons, Inc. J Appl Polym Sci 77: 1760–1768, 2000

Key words: hydrogels; thermoreversible; drug release; swelling ratio

INTRODUCTION

Hydrogels are three-dimensional hydrophilic polymers that swell but do not dissolve when brought into contact with water, and they sometimes undergo a volume phase change in response to a change in surrounding conditions, such as temperature,[1,2] pH,[3] ionic strength,[4] and electric field.[5,6]

Thermosensitive hydrogel, one of the environmental stimuli response hydrogels, collapses at an elevated temperature through the critical gel transition temperature (CGTT). The volume change occurs within a quite narrow temperature range. Permeability of water through the gel can be changed by an "on–off" switch according to the environmental temperature. Therefore, such materials can be used in many fields such as for a drug delivery system, and enzyme activity control.[7–14]

Poly(NIPAAm) hydrogel demonstrates a nearly continuous volume transition and associated phase transition from low temperature, a highly swollen gel network, to high temperature, a collapsed phase near its critical point between 31–35°C.[15] Hirotsu[16] investigated the phase behavior of the poly(NIPAAm) gel/water/alcohol system, and explained their thermoshrinkage by the destruction of hydrogen bonds between water molecules and amido group of NIPAAm.

A polyelectrolyte gel is formed from crosslinking flexible polymer chains to which ionizable

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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] A series of gels prepared from sodium 2-acrylamido-2-methylpropyl sulfonate (NaAMPS), N-3- dimethylamino propylacrylamide (NDAPA) and betaine were reported by Wada et al.[20] They found that the amphoteric gel containing an equimolar of the NDAPA and NaAMPS (50/50) showed the lowest transition temperature and swelling ratios among the amphoteric gels, which was similar to that of NIPAAm gels.

The swelling behaviors for a series of copolymeric hydrogels copolymerized from NIPAAm and cationic monomers,[21–23] anionic monomers,[24, 25] and sulfobetaine monomers[26–28] were studied in our laboratory. The main purpose of this article was to prepare a series of the copolymeric hydrogels based on NIPAAm and anionic monomer (NaAMPS) and to discuss the swelling behavior in different temperatures. In addition, the pH effect on swelling behavior for the NIPAAm/NaAMPS copolymeric hydrogels was studied. At the same time, the availability of the copolymeric hydrogels used for drug release system was also investigated.

EXPERIMENTAL

Materials

N-Isopropylacrylamide (NIPAAm) (Fluka Chemical Co.) was recrystallized in *n*-hexane before use to remove an inhibitor. 2-Acrylamido-2-methylpropyl sulfonate (AMPS) (Fluka Chemical Co.) was used as received. *N,N′*-Methylene bisacrylamide (NMBA) (Sigma Chemical Co.) as a crosslinking agent, and *N,N,N′,N′*-tetramethylethylene diamine (TEMED) (Fluka chemical Co.) as an accelerator were used as received. Ammonium persulfate (APS) (Wako Pure Chemical Co. Ltd) as an initiator was further purified by recrystallization.

Neutralization of AMPS Monomer Solution (NaAMPS)

NaAMPS monomer solution was prepared by adding AMPS into the sodium hydroxide solution. The molar ratio of sodium hydroxide to AMPS was 1 : 1 to approach complete neutralization.

Preparation of Hydrogels

NIPAAm and NaAMPS with various ratios and 3 mol % NMBA based on total monomer content were dissolved in 10 mL of deionized water. To this solution, 0.2 mol % APS and 0.2 mol % TEMED as the redox initiator 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 then immersed in an excess of deionized water for 3 days to remove the residual unreacted monomer. The swollen copolymeric gels were dried at room temperature for 1 day, and then further dried in a 30°C vacuum oven for 2 days.

Measurement of Swelling Ratio

The preweighed dried gels (W_d) were immersed in an excess of deionized water at 25°C until swelling equilibrium was attained. Each gel was then removed from the water bath, tapped with filter paper to remove excess surface water, and weighed as the wet weight (W_w). The swelling ratio (Q) was calculated from the following formula:

$$Q = \frac{W_w - W_d}{W_d} \tag{1}$$

Dynamic Swelling

The dried gels were immersed in an excess of 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 M_∞, The following equation can be used to calculate the diffusion coefficient D for $M_t/M_\infty \geq 0.8$,[29]

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

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

Table I Characterization of the NIPAAm/NaAMPS Copolymeric Hydrogels

Sample No.	NIPAAm (mol %)	NaAMPS (mol %)	Cloud Point Effect[a]	Gel Transition Temperature (°C)	$D \times 10^8$ (cm^2/s)	n	k
N0	100	0	st	30–35	6.1	0.53	0.32
N2	98	2	st	35–40	8.31	0.54	0.5
N3	97	3	w	40–45	10.51	0.62	0.44
N4	96	4	w	50–55	11.12	0.6	0.48
N5	95	5	vw	>60	12.31	0.58	0.45

[a] st = strong, w = weak, vw = very weak.

Measurement of Thermoreversibility for N2 and N5 Copolymeric Gels

Samples N2 and N5 were chosen as model gels to conduct this experiment. The dried gels were equilibrated in 10 mL deionized water at 25°C, and the wet gels weighed. The gels were then moved into 10 mL deionized water at 50°C and weighed at each fixed time interval. When the weights of the gels were approximately constant, the gels were transferred into deionized water at 25°C again and weighed at each fixed time interval. This operation was conducted for several cycles and the swelling ratios calculated.

Measurement of Swelling Ratios in Various pH Solutions and pH Reversibility

The measurement of swelling ratios for the copolymeric gels under various pH solutions was the same as that in deionized water. The pHs of various solutions adjusted by aqueous solution of HCl and NaOH were measured with a pH meter (Radiometer PHM95) calibrated by standard buffer solution. The pH reversible experiments were carried out at pH 3 and pH 10 for 0.01 *M* buffer solution.

Caffeine Release Experiment

The dry gels were equilibrated in 30 mg/10 mL of deionized water at 25°C for 2 days to load caffeine into the gels. The caffeine release 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 fresh water at each fixed time interval. The released caffeine was analyzed at 272 nm by an ultraviolet spectrophotometer (JASCO UV-530).

Indomethacine Release Experiment

The dry gels were equilibrated in 3000 ppm of 10 mL ethanol/water (volume ratio = 8/2) solution at 25°C for 2 days to load indomethacine into the gels. The above drug-incubated gels were dried at ambient temperature for a period, then moved to a 25°C oven for 1 day, and then further dried in a 30°C vacuum oven for 2 days to obtain dried drug-incubated gels. The indomethacine release experiment was carried out by transferring previous dried incubated drug gels into 10 mL of pH 7.4 buffer solution. The gels were repeatedly removed and transferred into 10 mL of fresh pH 7.4 buffer solution at each fixed time interval. The released indomethacine was analyzed at 319.8 nm by an ultraviolet spectrophotometer (JASCO UV-530).

RESULTS AND DISCUSSION

Characterization of NIPAAm/NaAMPS Copolymeric Gels

Some characteristics of the NIPAAm/NaAMPS copolymeric gels with various feed compositions are shown in Table I. The results in Table I show that the cloud point effect of the copolymeric gels is weaker as the content of NaAMPS monomer is increased. The gel transition temperatures increase with an increase of the content of NaAMPS in the copolymeric composition; i.e., from 30 to 60°C for N0–N5, respectively. The reason is that addition of NaAMPS monomer into the gel composition makes the gel become more hydrophilic. The equilibrium swelling ratios of the copolymeric gels also increase with an increase of the content of NaAMPS (also see Fig. 1).

Effect of NaAMPS Content on Swelling Ratio

The swelling ratios as a function of time for the NIPAAm/NaAMPS copolymeric gels at 30°C in deionized water are shown in Figure 1. The results in Figure 1 indicate that the swelling ratios increase with NaAMPS content. According to Flo-

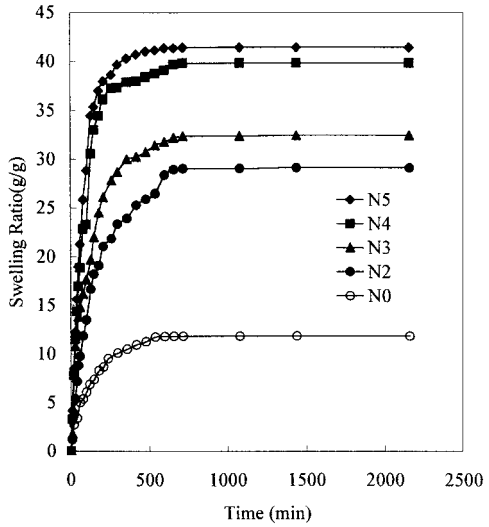


Figure 1 Swelling ratios as a function of time for NIPAAm/NaAMPS copolymeric hydrogels in deionized water at 25°C.

ry's swelling theory,[30] the following equation was given:

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

where i/V_μ is the concentration of fixed charge referred to unswollen network, S is the ionic concentration in external solution, $(1/2 - \chi_1)/v_1$ is the affinity of the hydrogel with solvent, ν_e/V_0 is the crosslinking density of the hydrogel. Hence, the swelling ratio has a relation to ionic concentration, crosslinked density, and the affinity of the hydrogel for water from the above equation. The crosslinking density was fixed in the present copolymeric hydrogels, so the factors that affected the swelling ratio of the hydrogels are the affinity of hydrogel for water and total charges inside the gel. Because the NaAMPS monomer is a hydrophilic anionic monomer, the greater the NaAMPS content, the larger the affinity of the gel for water, and the higher the swelling ratio of the hydrogel. In other words, NaAMPS monomer is ionized in aqueous solution, and the mutual repulsion of their charges causes expansion of the polymeric chain. This occurrence leads to a higher swelling ratio of the hydrogel with more content of NaAMPS.

Effect of Initial Total Monomer Concentration on Swelling Ratio for NIPAAm/NaAMPS Copolymeric Gels

Buchholz[31] reported that the concentration of monomer in the reaction solution affects the properties of the resulting polymer. The swelling ratios for N3 shown in Figure 2 indicate that the swelling ratios of the gels decrease with increasing the initial total monomer concentration. This result conforms to Baker's report[32] for cationic acrylamide-based hydrogels and our previous report for sodium acrylate superabsorbent polymer.[33]

Investigation of Water Diffusion in Xerogels

To obtain a more quantitative understanding of the nature of the sorption kinetic in NIPAAm/NaAMPS series gels, the initial swelling data were fitted to the exponential heuristic equation:[34,35]

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

where k is a characteristic constant of the gel, and n is a characteristic exponent of the mode transport of the penetrate. 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, respectively. For Fickian kinetics in which the rate of penetrate diffusion is rate limiting, $n = 0.5$, whereas values of n between 0.5 and 1 indicate the contribution of non-Fickian processes such as polymer relaxation. The results in Table I indicate that the swelling exponents n for all NIPAAm/NaAMPS copolymeric gels at var-

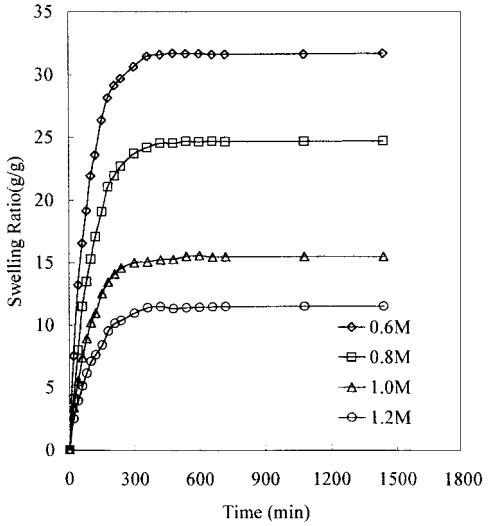


Figure 2 Swelling ratios as a function of time for various initial monomer concentrations for N3 copolymeric hydrogels in deionized water at 25°C.

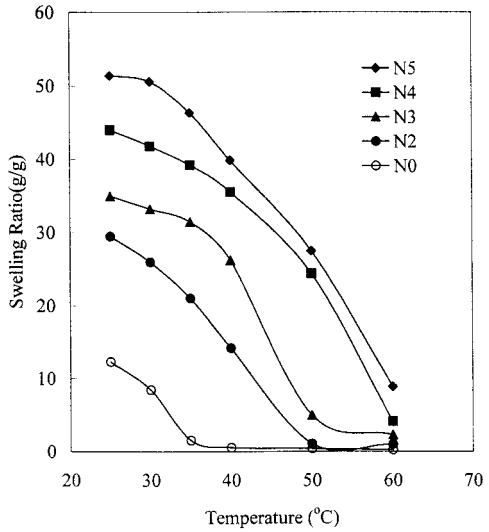


Figure 3 Swelling ratios as a function of temperature for NIPAAm/NaAMPS copolymeric hydrogels in deionized water.

ious temperatures are in the range from 0.53 to 0.62. These results indicate that the swelling transport mechanism belongs to non-Fickian transport. In other words, their swelling mechanisms are not changed in deionized water. But the diffusion coefficients D increase with an increase in the NaAMPS content in the present hydrogels. This is due to the hydrophilicity for these copolymeric hydrogels in the order of N5 > N4 > N3 > N2, and the more hydrophilic groups in the gel, the easier the diffusion for water molecules. So N5 has a higher D value.

Temperature on Swelling Ratio of the Copolymeric Gels

The effect of temperature on the equilibrium swelling ratio for a series of NIPAAm/NaAMPS copolymeric gels is shown in Figure 3. The results shown in Figure 3 indicate that the higher the temperature, the lower the swelling ratio; and the more the NaAMPS content, the higher the gel transition temperature. For the NIPAAm gel, the hydrophilic group (amido μNHCOμ) in the polymer structure would form an intermolecular hydrogen bond with the surrounding water at low temperature (below the gel transition temperature). Hence, water penetrated into the NIPAAm gels is in a bound state at low temperature. The water molecule would gain an enthalpy during the temperature increase, and the hydrophilic groups (amido) in the NIPAAm gels would be turned into intramolecular hydrogen bonds in this condition. At the same time, the hydrophobic forces of isopropyl group of NIPAAm gel increases. These two results make the water molecules inside the gel change from a bound state to a free state and release out of the gel network. This phenomenon makes the swelling ratio of the gel rapidly decrease at the gel transition temperature. The results shown in Figure 3 also indicate that the greater the NaAMPS content, the higher the hydrophilicity of the gel, and the stronger the affinity of the hydrogel for water. Therefore, the gel transition temperature becomes higher as the NaAMPS content in these copolymeric gel increases. These results conform to our previous studies for NEPAAm/AAm or NTHFAAm/AAm hydrogels.[36]

Thermoreversibilities of the NIPAAm/NaAMPS Copolymeric Gels

Thermoreversible gel exhibits a swell–deswell transition. This behavior depends on the weak hydrogen bonding of amide groups that are transferred from a swelling state to a deswelling state under a certain temperature range. Figure 4 shows the change of the swelling ratio for gels N2 and N5 when they were immersed in deionized water at 25 and 50°C. Both gels can swell and deswell in a period of time when the temperature is cycled through their gel transition temperatures. As seen from Figure 4, the swelling ratio is lower at 50°C but higher at 25°C. Furthermore, the equilibrium time of deswelling is faster than

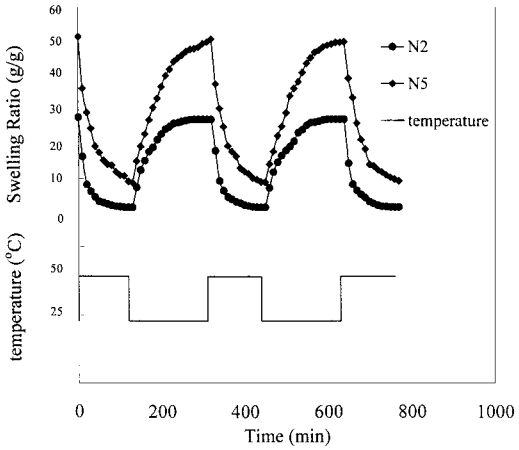


Figure 4 NIPAAm/NaAMPS hydrogels (samples N2 and N5) swell and deswell between 25 and 50°C in deionized water.

that of swelling between 50 and 25°C. The water inside the gels is squeezed out quickly by elastic retractive force of the networks with a violent volume phase change at higher temperature (50°C). This driving force is larger than water infiltrating into the gels during swelling process of the gel from high temperature to low temperature (25°C). In addition, the equilibrium time for N2 is faster than N5 in the swelling and deswelling process. Because the temperature (50°C) is over the gel transition temperature of N2, N2 deswells more quickly at this temperature. However, the gel transition temperature of N5 is over 60°C, so the deswelling behavior is different from N2. In addition, because the volume phase change is not very significant when the gel deswells or swells below its transition temperature, it must take a lot of time to swell or deswell. As a result, a shorter equilibrium time to deswell is observed in N2 and N5.

Effect of pH on Equilibrium Swelling Ratios for NIPAAm/NaAMPS Copolymeric Gels

The equilibrium swelling ratios for the present copolymeric hydrogels in the different pH solutions shown in Figure 5 indicate that the swelling ratios increase with an increase in pH value until pH 10, then sharply decrease. This result can be explained by Scheme 1. In low pH (pH = 2), the sodium ions on NaAMPS dissociated from the sulfonate groups and diffused out of the gels, are replaced by the hydrogen ions in the external solution. Hence, the charges on polymeric side chains in this condition are less than that in the deionized water, so the swelling ratios are smallest in this low pH solution. With increasing the pH in the external solution, the degree of replacement of sodium ion decreases, and the charges on the polymeric chains increase. This results in the expansion of the gel, so the swelling ratio of the gel gradually increases. Finally, in a high alkaline environment (pH > 10), the sodium ions will not be dissociated from the sulfonate groups due to the higher sodium ion concentrations in the external solution. (This is also called the salt-screen effect.) Hence, the swelling ratio of the gel decreases rapidly in this condition.

pH Reversibilities for NIPAAm/NaAMPS Copolymeric Gels

Because the present copolymeric gels show different swelling behaviors in various pH solutions, we investigated the pH reversibility of these gels in 0.01 *M* buffer solutions at pH 3 and pH 10. The results shown in Figure 6 for N2 and N5 gels indicate that the difference of the swelling ratios (ΔSR) at pH 3 and pH 10 are 4.4 and 6.9 for the gels N2 and N5, respectively. This result implies that the more NaAMPS in the hydrogels, the better the pH reversibility. The same result, shown in Figure 7, is obtained in the hydrogels in which 50% of the AMPS component was neutralized.

Assessment of Drugs Release for NIPAAm/NaAMPS Copolymeric Hydrogels

The Influence of NaAMPS Content on the Release of Caffeine

The influence of NaAMPS content on the release of caffeine is investigated at 37 and 50°C for the present gels. The results shown in Figure 8 indicate that the more NaAMPS content in the copolymeric gels, the higher the fractional release of caffeine. That is, the order of release fraction for the gel is N5 > N4 > N3 > N2. The above results indicate that the more NaAMPS in the gel, the higher the swelling ratio. Hence, more drug was diffused into the gel when the dried gel was incubated in the drug solution at 25°C and more drug was diffused out of the gel when the temperature was raised to 37°C. A more significant release behavior was observed at higher temperature (50°C) in these gels.

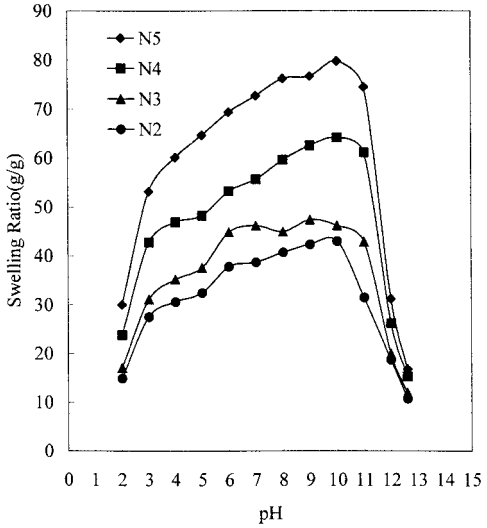
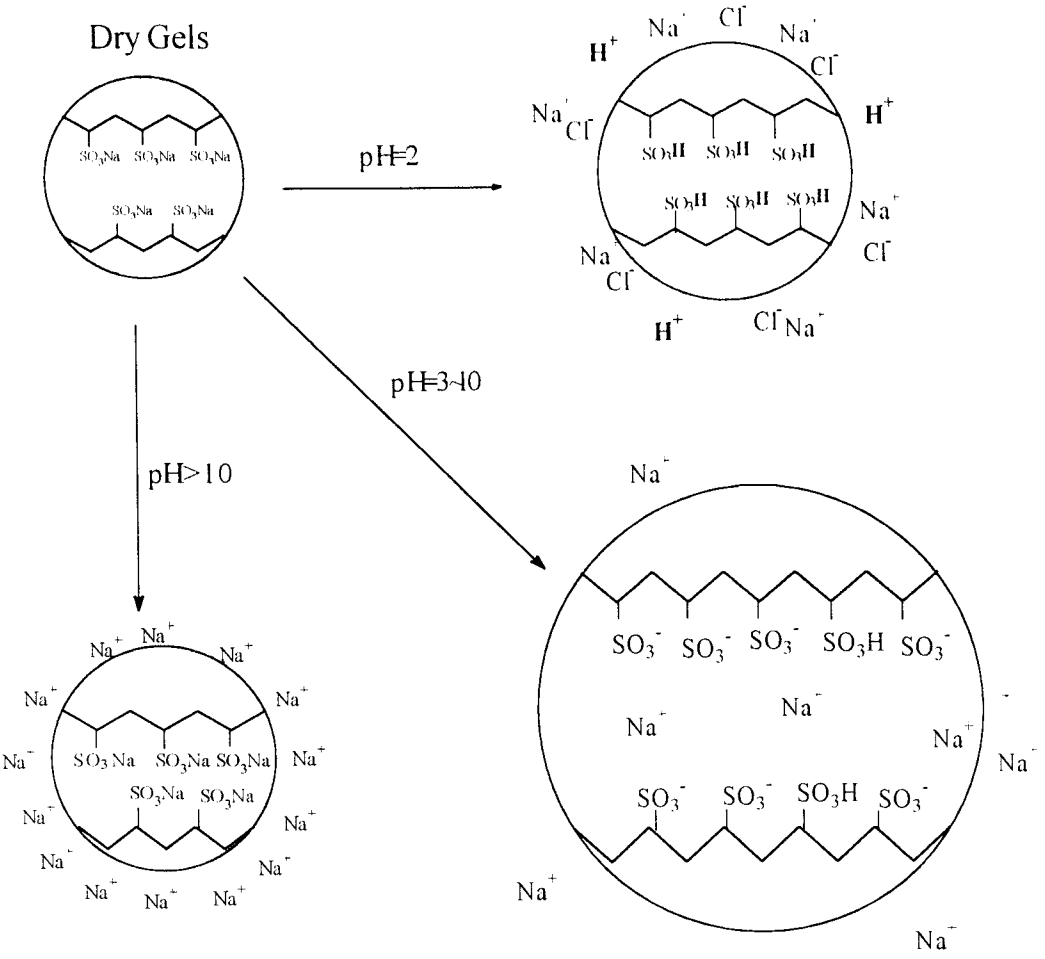


Figure 5 Swelling ratios as a function of pH for NIPAAm/NaAMPS copolymeric hydrogels at 25°C in different pH solutions.



Scheme 1 NIPAAm/NaAMPS copolymeric hydrogels swelling at different pH aqueous solutions.

The Influence of Temperature on the Release of Indomethacine

Figure 9 shows the release of indomethacine for the present copolymeric gels in pH = 7.4 buffer solution at 25°C. The release content for dry gels is related to the NaAMPS content in the gels, i.e., N5 > N4 > N3 > N2. At higher swelling ratios for the gels, the loaded drugs would be easily diffused out of the gels in the swelled state. So the greater the NaAMPS content in the copolymeric gels, the higher the release amount for the gels. Unfortunately, indomethacine would decompose in strong alkaline and acid solution, so we cannot conduct experiments on the pH effect for the copolymeric hydrogels. Figure 10 is the result of the released indomethacine in the same pH = 7.4 environment at 37°C. In comparison with Figure 9, the released amount is lower than 25°C, but the equilibrium time for releasing is shorter. This result is

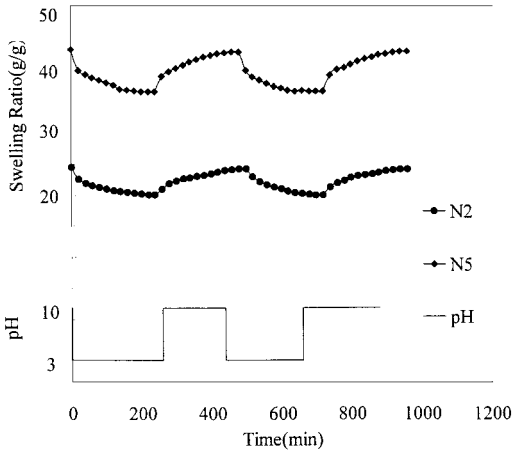


Figure 6 The behavior of swelling (pH = 10) and deswelling (pH = 3) for NIPAAm/NaAMPS copolymeric hydrogels.

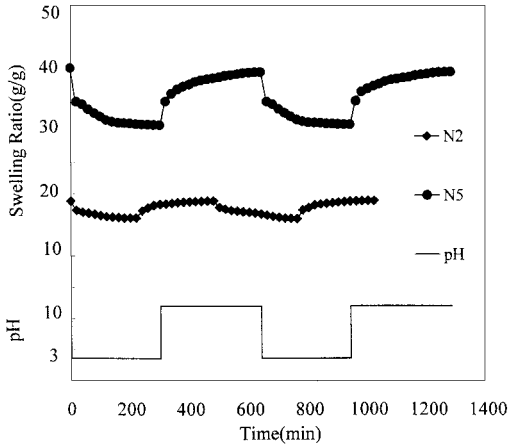


Figure 7 The behavior of swelling (pH = 10) and deswelling (pH = 3) for NIPAAm/NaAMPS (50% neutralized) copolymeric hydrogels.

the same as for caffeine release with gels in the deswelled state. The swelling ratios for copolymeric gels were smaller due to the collapsed structure of NIPAAm, and this led indomethacine molecules to reside in the inner network of the gels at 37°C. Hence, the released amount of indomethacine at 37°C was lower than at 25°C. The order of the released drug was the same as that released at 37°C, i.e., N5 > N4 > N3 > N2.

CONCLUSION

The swelling ratios of NIPAAm/NaAMPS copolymeric gels increase with an increase of NaAMPS

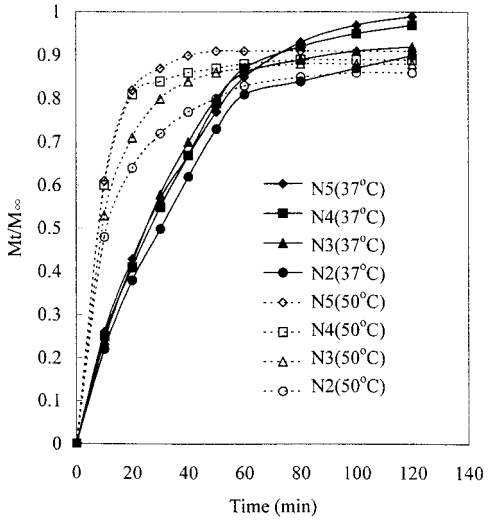


Figure 8 Caffeine release profiles for NIPAAm/NaAMPS copolymeric hydrogels in deionized water at 37 and 50°C.

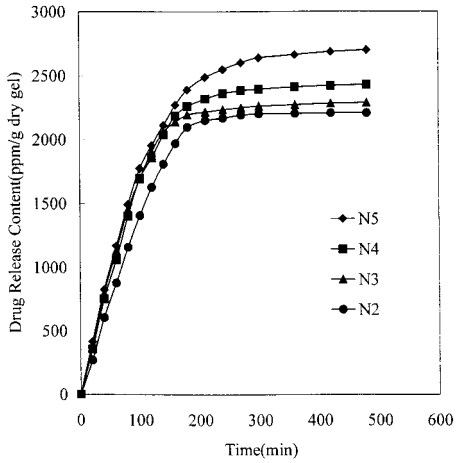


Figure 9 Indomethacine release profiles for NIPAAm/NaAMPS copolymeric hydrogels in pH 7.4 buffer solution at 25°C.

content. In addition, the higher the NaAMPS content, the larger the affinity of the hydrogels for water. The gel transition temperature increases with increasing the NaAMPS content. In the diffusion transport mechanism study, the results indicate that the swelling exponents n for all NIPAAm/NaAMPS copolymeric gels at 25°C are in the range from 0.53 to 0.62. This implies that the swelling transport mechanism is a non-Fickian transport. The diffusion coefficients (D) for the copolymeric gels increase with an increase of NaAMPS content, so the water molecule easily infiltrates into hydrogels for gels containing more NaAMPS. The swelling ratios for NIPAAm/

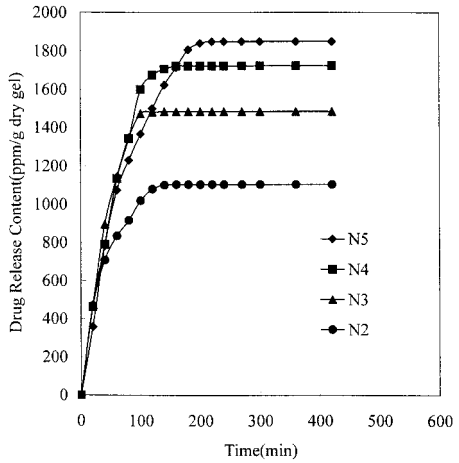


Figure 10 Indomethacine release profiles for NIPAAm/NaAMPS copolymeric hydrogels in pH 7.4 buffer solution at 37°C.

NaAMPS hydrogels are lower in strong acid and alkaline solution. The charge repulsion force in the gels gradually increased from pH 3 to 10. This occurrence resulted in changing of the swelling ratio, and the gels also exhibited pH reversible properties in this range. In caffeine release experiments, the greater the NaAMPS content, the higher the release fraction for gels. Due to water pocket formation at high temperature (50°C), the gels released fewer amounts of caffeine but took a shorter time for release at the lower temperature (37°C). In indomethacine experiments, because the indomethacine loaded in the gel can diffuse to the external solution by the swollen force of the gels, the best release content for N5 with the highest swelling ratio is obtained among the gels. The gels also released more indomethacine at 25 than at 37°C, due to the collapsed structure of NIPAAm at 37°C.

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