pH/Temperature-Responsive Semi-IPN Hydrogels Composed of Alginate and Poly(*N*-isopropylacrylamide)

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ABSTRACT: Amino semitelechelic poly(*N*-isopropylacrylamide) (PNIPAAm) was prepared by radical polymerization with aminoethanethiol hydrochloride as a chain-transfer agent. Semi-interpenetrating polymer network (semi-IPN) hydrogels, composed of alginate and amine-terminated PNIPAAm, were prepared by crosslinking with calcium chloride. From the swelling behaviors of semi-IPNs at various pH's and Fourier transform infrared spectra at high temperatures, the formation of a polyelectrolyte complex was confirmed from the reaction between carboxyl groups in alginate and amino groups in modified PNIPAAm. Semi-IPN hydrogels reached an equilibrium swelling state within 24 h. The water state in hydrogels, investigated by differential scanning calorimetry, showed that sample CAN55 [alginate/PNIPAAm (w/w) = 50/50] exhibited the lowest equilibrium water content and free water content among the hydrogels tested, which was attributed to its more compact structure compared to other samples and the high content of interchain bonding within the hydrogels. Alginate/PNIPAAm semi-IPN hydrogels exhibited a reasonable sensitivity to the temperature, pH, and ionic strength of swelling medium. © 2002 John Wiley & Sons, Inc. J Appl Polym Sci 83: 1128–1139, 2002

Key words: hydrogels; IPNs; stimuli-sensitive polymers

INTRODUCTION

Hydrogels are three-dimensional networks that swell in an aqueous solution. Considerable research attention has focused on stimuli-responsive hydrogels. Stimuli-responsive hydrogels show phase separation from aqueous solution or an order-of-magnitude large change in the size of the hydrogel according to the surrounding environment. Many investigators have reported on the potential of stimuli-responsive hydrogels for use in several biomedical applications, including drug delivery, biomimetic actuators, bioseparation, and surfaces with switchable hydrophilic–hydrophobic properties.[1] In stimuli-responsive systems, the stimuli may be either chemical signals, such as pH, metabolites, and ionic factors, or physical stimuli, such as temperature or electrical potential.[2,3] Among these stimuli, pH/temperature-responsive systems have been extensively studied because these two factors are important environments inside the human body.[4,5]

Polyelectrolyte complexes are formed by the reaction of a polyelectrolyte with an oppositely charged polyelectrolyte in an aqueous solution. Essentially, this is the result of electrostatic interactions between both polyions. Polyelectrolyte complexes have been applied as membranes, an-

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tistatic coatings, environmental sensors, chemical detectors, and medical prosthetic materials, and so on.[6,7]

Poly(*N*-isopropylacrylamide) (PNIPAAm) exhibits large swelling changes in aqueous media in response to small changes in temperature. This is manifested in aqueous solutions of PNIPAAm at a lower critical solution temperature (LCST) near 32°C. PNIPAAm chains hydrate to form expanded structures in water when the solution temperature is below its LCST but form compact structures by dehydration when heated to temperatures above the LCST. The temperature-responsive properties of PNIPAAm have been utilized in a variety of applications, including controlled drug delivery and solute separation.[8–11]

It is well known that alginate derived from marine algae is a linear copolymer of 1,4-linked β-D-mannuronate (M) and α-guluronate (G) residues. With one carboxyl group in each M or G unit, it is a negatively charged polyelectrolyte at neutral or basic pH. Its gelling properties arise from the cooperative binding of divalent or trivalent cations (usually Ca^{2+}) between the homopolymeric sequence of G residues. Alginate has been much used in medical applications, including wound dressing, scaffolds, and delivery matrices.[12–15]

Our previous studies reported on pH- and temperature-sensitive poly(vinyl alcohol) (PVA)/poly(acrylic acid) (PAAc) interpenetrating polymer network (IPN) hydrogels, their responsive properties and drug release behaviors, and the permeability of various solutes.[16–20] Also, we synthesized chitosan/PAAc complex IPN hydrogels[21] and compared the swelling behaviors of graft copolymers and blends based on chitosan and *N*-isopropylacrylamide (NIPAAm).[22] In this study, we intended to prepare semi-interpenetrating polymer network (semi-IPN) hydrogels composed of alginate and PNIPAAm. Although much research has been done on alginate IPN and PNIPAAm IPN hydrogels, unfortunately the research has focused on the independent polymer rather than on blended IPNs. Recently, Park and Choi prepared IPN hydrogel beads composed of alginate and PNIPAAm and investigated temperature-modulated drug release with indomethacin.[23] However, they only focused on the temperature-sensitive behavior due to the presence of NIPAAm. In their case, alginate was used as a biocompatible and biodegradable polymer. We describe here the synthesis, characterization, and pH/temperature dependence of swelling behavior that results from the reaction between carboxyl groups in alginate and amino groups in modified PNIPAAm.

EXPERIMENTAL

Materials

NIPAAm (Aldrich Chemical Co., Milwaukee, WI) was purified by recrystallization from *n*-hexane/toluene. Sodium alginate and 2-aminoethanethiol hydrochloride (AESH) were purchased from Aldrich. *N*,*N*′-Azobisisobutyronitrile (AIBN; Aldrich) was recrystallized from methanol. *N*,*N*-Dimethylformamide (DMF; Duksan Pure Chemical Co. Ltd., Seoul, Korea) was purified by distillation. Calcium chloride ($CaCl_2$) and ethyl ether (Duksan Pure Chemical) were used as received. Water was first treated with a reverse osmosis system (Sambo Glove Co., Ansan, Korea) and was further purified with a Milli-Q Plus system (Waters, Millipore, MA).

Polymerization of Semitelechelic PNIPAAm

Amino semitelechelic PNIPAAm was synthesized by radical polymerization with AESH as a chain-transfer agent and AIBN as an initiator. NIPAAm (9.7×10^{-2} mol), AESH (4.85×10^{-3} mol), and AIBN (5.5×10^{-5} mol) were dissolved in DMF (110 mL). Dried nitrogen was bubbled into the solution for 20 min prior to polymerization. Polymerization was carried out at 75°C for 8 h. After the reaction, the reactant was precipitated into an excess of diethyl ether and dried in a vacuum oven at room temperature. The dried polymer was purified by precipitation in hot water and dissolved in water. Polymer product was obtained by freeze-drying.

Preparation of Alginate/PNIPAAm Semi-IPN

The aqueous solution of alginate (5 wt %) and PNIPAAm (20 wt %) were mixed in various compositions (80/20, 50/50, and 20/80). Mixed solution was poured into a petri dish and dried to constant weight at room temperature in a vacuum oven.

To prepare semi-IPN hydrogels, the dry film was cut to a size of 1.0×1.0 cm and immersed in 10 mL of $CaCl_2$ aqueous solution (0.5 wt %). After being shaken for 10 min at room temperature, the semi-IPN hydrogel was washed in water and dried to a constant weight at room temperature in a vacuum oven.

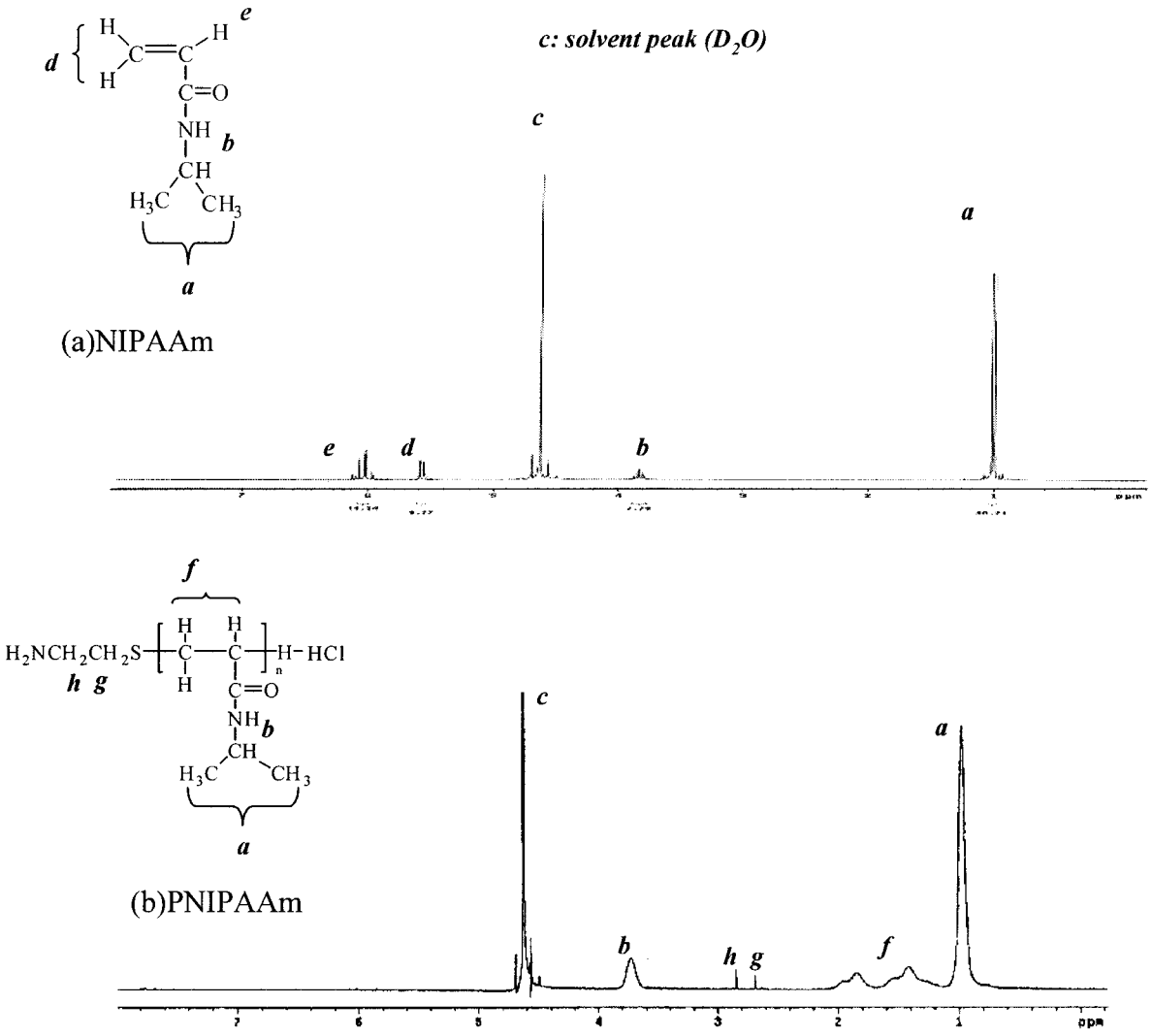

Figure 1 ^{1}H-NMR spectra of (a) NIPAAm and (b) PNIPAAm.

Samples designated as CAN series were crosslinked alginate/PNIPAAm semi-IPNs with a $CaCl_2$ aqueous solution, whereas AN series were alginate/PNIPAAm polyelectrolyte complexes. For example, CAN82 represents the semi-IPN containing 80 wt % alginate and 20 wt % PNIPAAm crosslinked with $CaCl_2$.

Characterization

Fourier transform infrared (FTIR) spectroscopy (Nicolet model Magna IR 550, Madison, WI) was used to confirm the structure of the semi-IPNs. To perform FTIR spectra at high temperatures, a heated cell mount (Spectra Tech., Shelton, CT, diameter = 32 mm) was used. The sample was fixed on the heated cell mount with the KBr pellet technique. FTIR spectra were measured by an increase in the temperature of the heated cell mount. Structural analysis of amino semitelechelic PNIPAAm was performed by 500 MHz ^{1}H-NMR (Bruker AMX-500, Karlsruhe, Germany) with D_2O. The number-average and weight-average molecular weights of PNIPAAm were determined by gel permeation chromatography (GPC; Waters model 510 High Performance Liquid Chromatograph (HPLC) pump, Milford, MA). Three ultrastyragel tetrahydrofuran (THF) columns (each 30 cm $\times$ 7.8 mm internal diameter; HR-0.5, HR-4, HR-5, all Waters, Milford, MA) and a Waters R410 differential refractometric detector were used. The mobile phase was THF with a flow rate of 1 mL/min. The calibration curve was prepared before measurements with five standard polystyrenes with molecular weights of

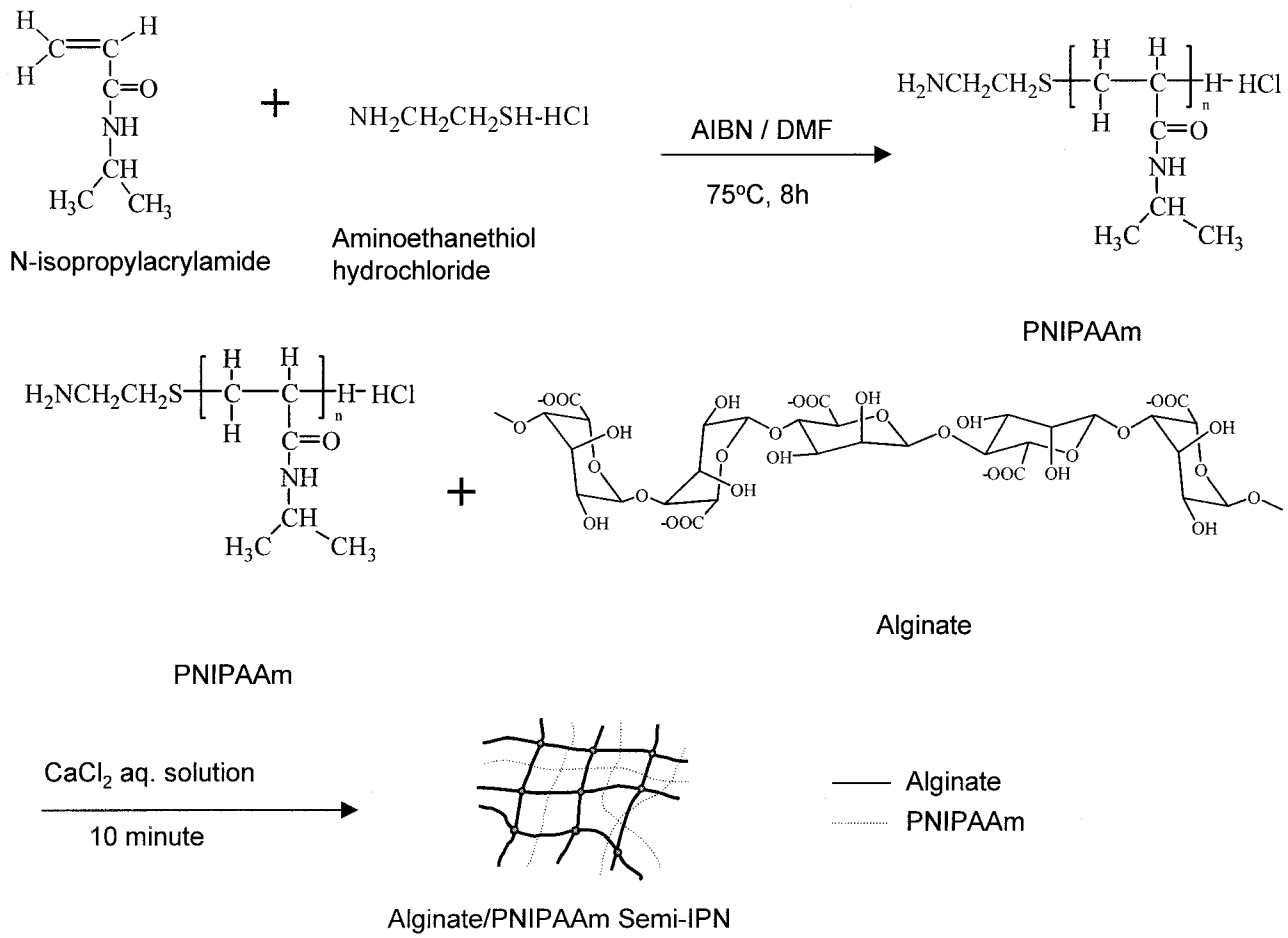

Figure 2 Schematics of the synthesis of alginate /PNIPAAm semi-IPN.

1.285×10^3, 2.965×10^3, 1.135×10^4, 2.285×10^4, and 6.505×10^4, respectively (Shonex standard SM-105, Showa Denko, Japan).

The equilibrium swelling ratio (W_{H2O}/W_d) was defined as the weight of absorbed water (W_{H2O}) per weight of dried gel (W_d). To measure the equilibrium swelling ratio, we immersed preweighed dry samples in water. After the excess surface water was removed with filter paper, the weight of swollen samples was measured at various time intervals.

The state of water in the hydrogels was investigated by differential scanning calorimetry (DSC; TA Instruments, DSC910) in the temperature range of −20 to 20°C with a heating rate of 5°C/min under N_2 flow. The amount of free water and bound water were calculated from the respective melting enthalpies. The following equation assumes that the heat of fusion of free water in the hydrogel (Q_{endo}) is the same as that in ice (Q_f; 79.7 cal/g):

$$W_b(\%) = W_t - (W_f + W_{fb}) = W_t - (Q_{endo}/Q_f) \times 100$$

where W_b is the amount of the bound water (%); W_f and W_{fb} are the amounts of free water and freezing bound water, respectively; and W_t is the equilibrium water content [EWC (%)]. EWC can be expressed by $[(W_s - W_d)/W_s] \times 100$, whereas W_s and W_d are the weights of the semi-IPN at the equilibrium swelling state and dry state, respectively.

RESULTS AND DISCUSSION

Polymerization of Semitelechelic PNIPAAm

To confirm the polymerization of semitelechelic PNIPAAm, FTIR spectroscopy and ^{1}H-NMR spectroscopy measurements were carried out. Figure

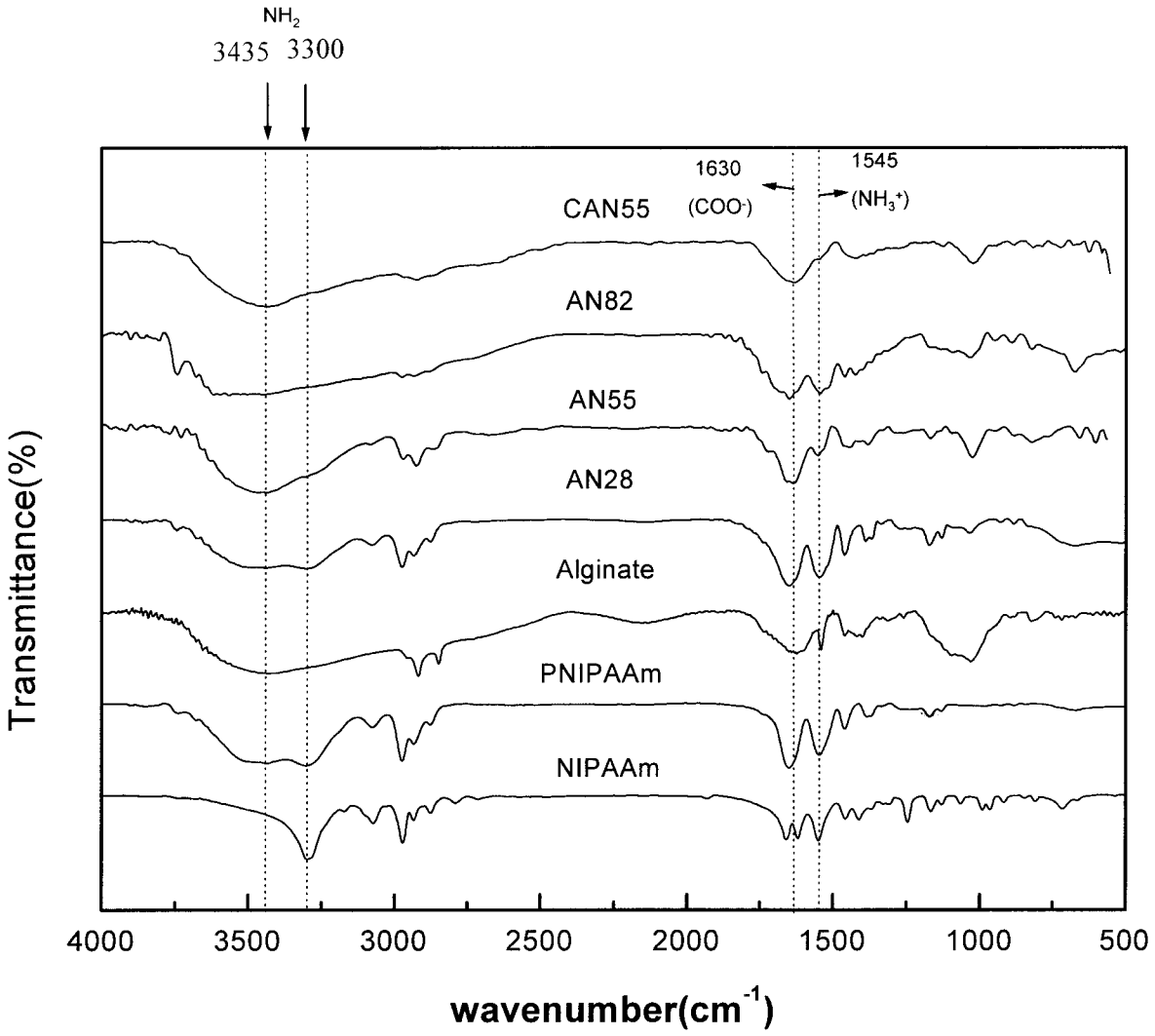

Figure 3 FTIR spectra for NIPAAm, PNIPAAm, alginate, alginate/PNIPAAm polyelectrolyte complexes (AN28, AN55, and AN82), and alginate/PNIPAAm semi-IPN obtained by crosslinking with calcium chloride (CAN55).

1 shows the ^{1}H-NMR spectra of NIPAAm and PNIPAAm in D_2O. The spectrum of PNIPAAm exhibited peaks at 1 ppm due to the presence of methyl groups, 3.85 ppm due to —NH—CH—, and 5.5–6 ppm due to the vinyl proton. In comparison with the spectrum of NIPAAm, the spectra of PNIPAAm showed two broad signals at 1.4 and 1.8 ppm due to the methylene proton instead of the peaks of the vinyl proton at 5.5–6 ppm observed in the spectrum of the monomer. Also, new peaks at 2.7 and 2.8 ppm were observed as the chain-transfer agent (AESH) was introduced into the PNIPAAm. FTIR analysis is discussed later. The number-average and weight-average molecular weights determined by GPC were 11,100 and 15,600, respectively.

Preparation of Alginate/PNIPAAm Semi-IPN

Figure 2 represents the preparation of the semi-IPN composed of alginate and PNIPAAm. Briefly, PNIPAAm was polymerized by radical polymerization with AESH as a chain-transfer agent. Aqueous solutions of alginate and PNIPAAm mixed well because carboxylic acid groups of alginate formed polyelectrolyte complexes with amino groups of PNIPAAm. Then, unreacted carboxylic acid groups in alginate were crosslinked with divalent calcium ions, forming an alginate network.

FTIR Analysis

Figure 3 illustrates the FTIR spectra for NIPAAm, PNIPAAm, alginate, alginate/PNIPAAm polyelec-

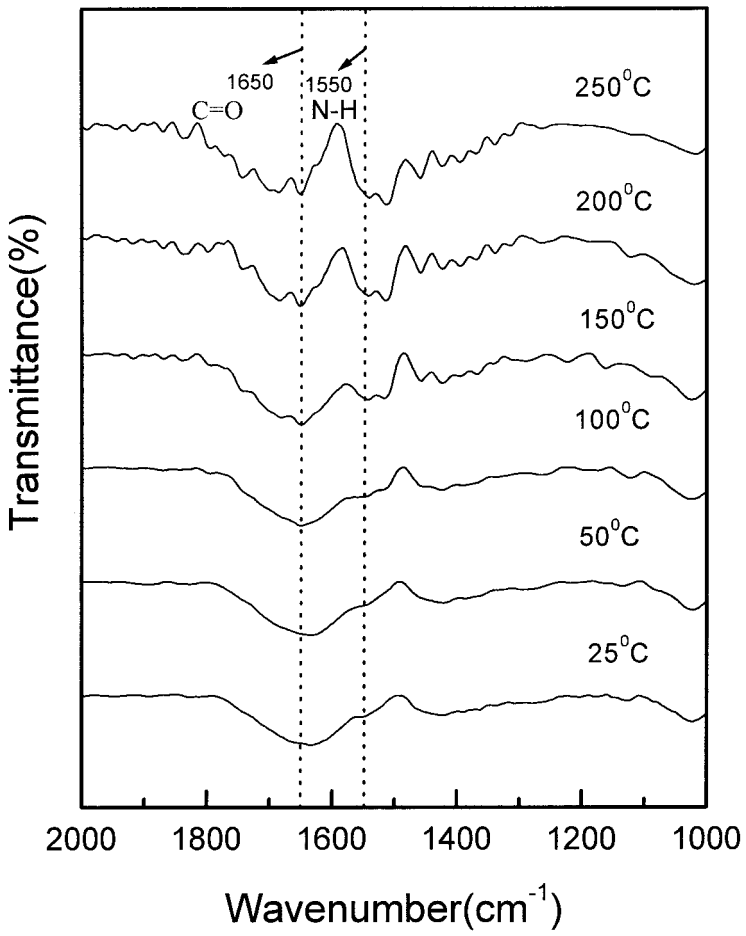

Figure 4 Thermal FTIR spectra of CAN55 in the temperature range between 25 and 250°C.

trolyte complexes (AN28, AN55, and AN82), and alginate/PNIPAAm semi-IPN (CAN55). Characteristic peaks of PNIPAAm were located at 1378 cm^{-1} for the methyl group and at 1655cm^{-1} and 1542cm^{-1} for amide I and amide II, respectively; those of NIPAAm at 1617 cm^{-1} (C═C) and 1409 cm^{-1} (CH_2═) disappeared.[22] Also, two bands at 3436 and 3300 cm^{-1} for the primary amine (NH_2) were observed. These spectra provided evidence of the successful polymerization of amino semitelechelic PNIPAAm. Characteristic absorption peaks of alginate appeared at 3500 cm^{-1} for the hydroxy group and at 1620 and 1410 cm^{-1} for the asymmetric COO^- stretching vibration and symmetric COO^- stretching vibration, respectively. As the ratio of PNIPAAm to alginate increased, the characteristic NH_2 peak in PNIPAAm appeared. The peak shown at 1545 cm^{-1} in Figure 3 was assigned as a symmetric deformation of NH_3^+. The peak that appeared at around 1630 cm^{-1} represented the carboxylate ion. Thus, we could see that the negatively charged COO^- and positively charged NH_3^+ coexisted in the alginate/PNIPAAm polyelectrolyte complex. The COO^- peaks at 1630 and 1420cm^{-1} of CAN55 became broader than those of AN55. Also, the COO^- symmetrical stretching peak at 1413 cm^{-1} of AN55 exhibited a shift to 1420 cm^{-1} of CAN55. A shift in the peak was caused by the change of sodium ions into calcium ions in the alginate blocks, which resulted in the change of the charge density and the radius.[24]

Figure 4 shows the FTIR spectra of CAN55 at temperatures ranging from 25 to 250°C. A broad peak at around 1630 cm^{-1} (COO^-) was observed at temperatures up to 100°C. At above 150°C, the peak intensities of the amide bond (—NH—CO—) at 1650 and 1550cm^{-1} increased. It seems reasonable to suppose that the COO^- or COOH groups of alginate reacted with the opposite NH_3^+ or NH_2 groups of PNIPAAm to form amide bonds (—NH—CO—) at elevated temperatures.[21,25]

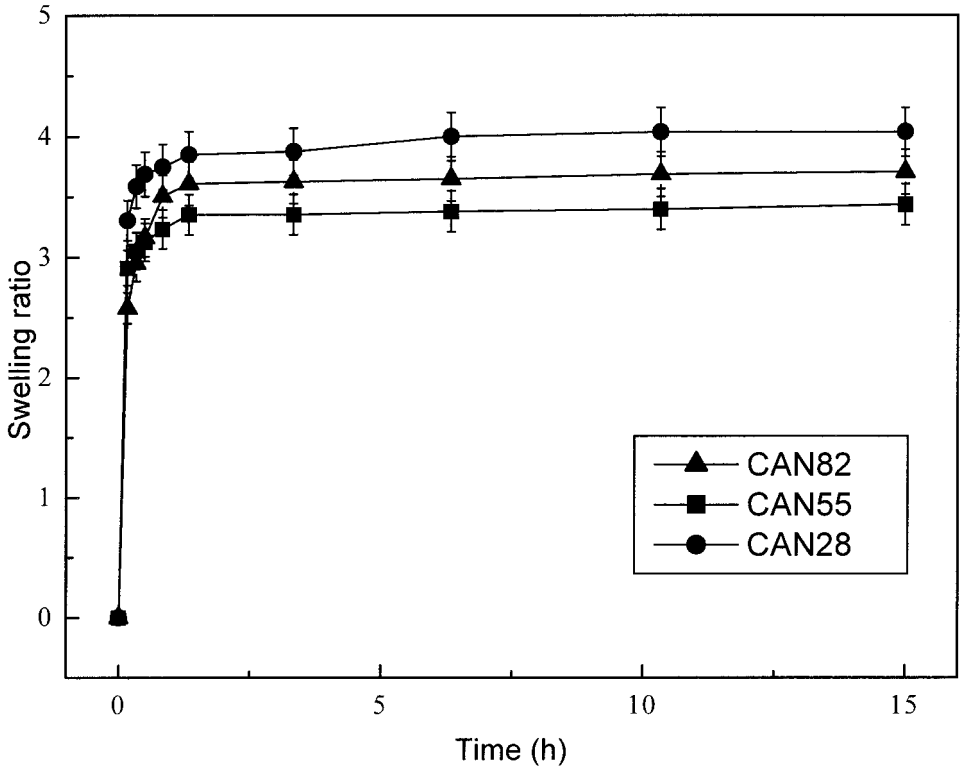

Figure 5 Swelling kinetics of alginate/PNIPAAm semi-IPNs (CAN28, CAN55, and CAN82) in water (pH = 5.4) at 25°C.

Swelling Characteristics

The swelling kinetics of the hydrogels in water (pH = 5.4) at 25°C are shown in Figure 5. The equilibrium swelling ratios of all hydrogels were in the range of 3.7–4. As the ratio of alginate to PNIPAAm increased, the degree of crosslinking of the hydrogel increased. Therefore, CAN28, with smaller amounts of alginate, had the highest swelling ratio at 4.04. However, the swelling ratio of CAN55 was lower than that of CAN82 because of the degree of complexation. Semi-IPNs formed polyelectrolyte complexes composed of carboxylic acid groups in alginate and amino groups in PNIPAAm. The polyelectrolyte complex captured the hydrophilic group and produced a tight and ionic bonded structure. Thus, we could expect that CAN55 had a more compact complex structure than other semi-IPNs.

To further elucidate the swelling behavior of alginate/PNIPAAm semi-IPNs, the water state in the hydrogel was investigated by DSC. The free water had no interaction with polymer chains, whereas the bound water was involved in the hydrogen bonding with polymer. The endothermic peak appeared at around 0 to 10°C and was attributed to the presence of free water in the hydrogels. The fraction of free water in total water was approximately calculated as the ratio of the endothermic peak area for the water-swollen hydrogel to the melting endothermic heat of fusion (79.9 cal/g) for pure water. Bound water was expressed as the difference between total water and free water. EWC values, free water contents, and bound water contents, respectively, were calculated and are listed in Table I. CAN55 had the lowest EWC and free water content. This result confirmed that CAN55 had a more compact structure than CAN82 or CAN28.

Table I Water States of Alginate/PNIPPAm Semi-IPN Hydrogels Estimated with DSC Analysis

Number	Sample[a]	EWC (%)	Free Water (%)	Bound Water (%)
1	CAN28	80.16	64.73	15.43
2	CAN55	77.27	10.45	66.82
3	CAN82	78.77	34.05	44.72

[a] All samples were fully swollen in deionized distilled water for 24 h at 25°C.

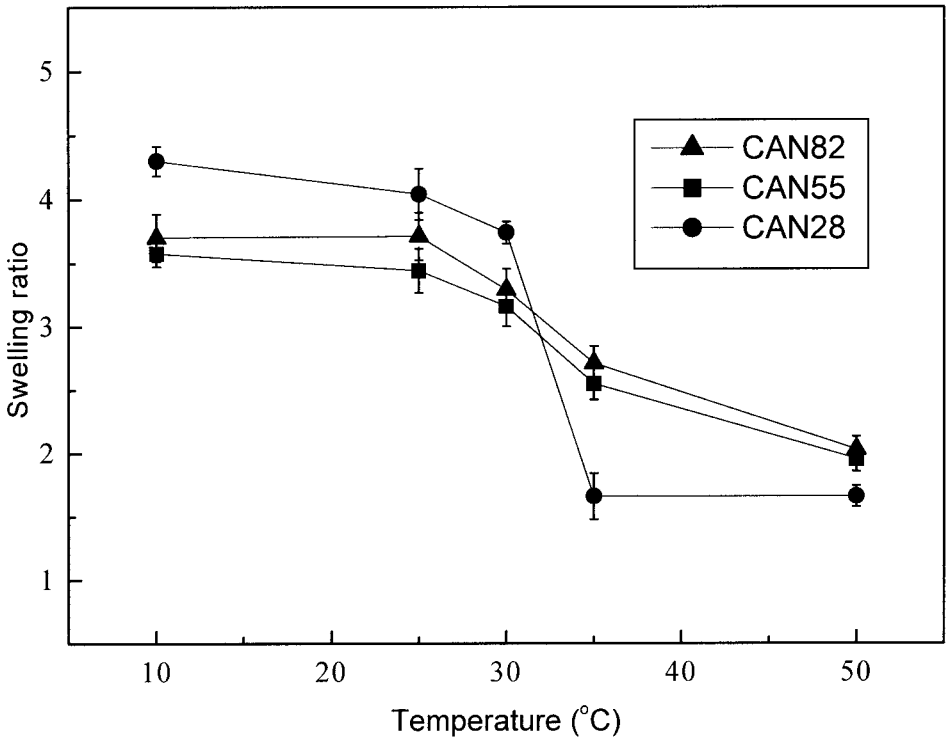

Figure 6 Swelling ratio of alginate/PNIPAAm semi-IPNs (CAN28, CAN55, and CAN82) as a function of temperature in water.

The swelling behavior of semi-IPN hydrogels was investigated as a function of temperature. As shown in Figure 6, all hydrogels had significant changes in swelling ratios over the temperature range between 30 and 35°C. When the amounts of PNIPAAm in the hydrogels were increased, the swelling behavior of hydrogels at around 30–35°C displayed a sharp decrease. PNIPAAm in water exhibited a reversible phase transition in response to small temperature changes at around 32°C.[26] It could be expected that the temperature sensitivity of PNIPAAm was due to the dissociation of ordered water molecules surrounding hydrophobic *N*-isopropyl groups in PNIPAAm. As a result, semi-IPN hydrogels composed of alginate and PNIPAAm underwent a volume phase transition in water at around the LCST of PNIPAAm (32°C).

Figure 7 shows the equilibrium swelling ratio with increases in the ionic strength of the external solution. The ionic strength of the medium was altered by changes in the amount of NaCl in solution. In general, the equilibrium swelling ratio of polyelectrolyte gels is determined by three major forces: mixing of the polymer network with a swelling medium, the elastic–retractive force exerted on the network, and the ionic osmotic pressure generated from mobile counterions to charged ions in the network.[27] For hydrogels crosslinked with calcium ions, unlike chemically crosslinked hydrogels, the increase of ionic strength in solution increases the number of the charged groups in the gel. This results from the increase of ion exchange between Ca^{2+} ions and Na^{+} ions as the ionic strength of the medium increases. The large number of the charged groups decrease the crosslink density and increase the hydrophilicity of the network.[28] As shown in Figure 7, the swelling ratio of the semi-IPN hydrogels composed of alginate and PNIPAAm increased up to about 0.05*N* NaCl but decreased at higher NaCl concentrations. The decrease of the swelling ratio at high ionic strengths was caused by the decrease of the crosslink density or destruction of the alginate network. Particularly, CAN28, with smaller amounts of alginate, dissolved in NaCl solution (>0.1*N*), so that we were unable to measure the swelling ratio.

pH-dependent swelling behaviors were observed at 25°C with changes in pH (NaCl concentration = 0.01*N*), as shown in Figure 8. The swelling ratio of alginate hydrogels increased continu-

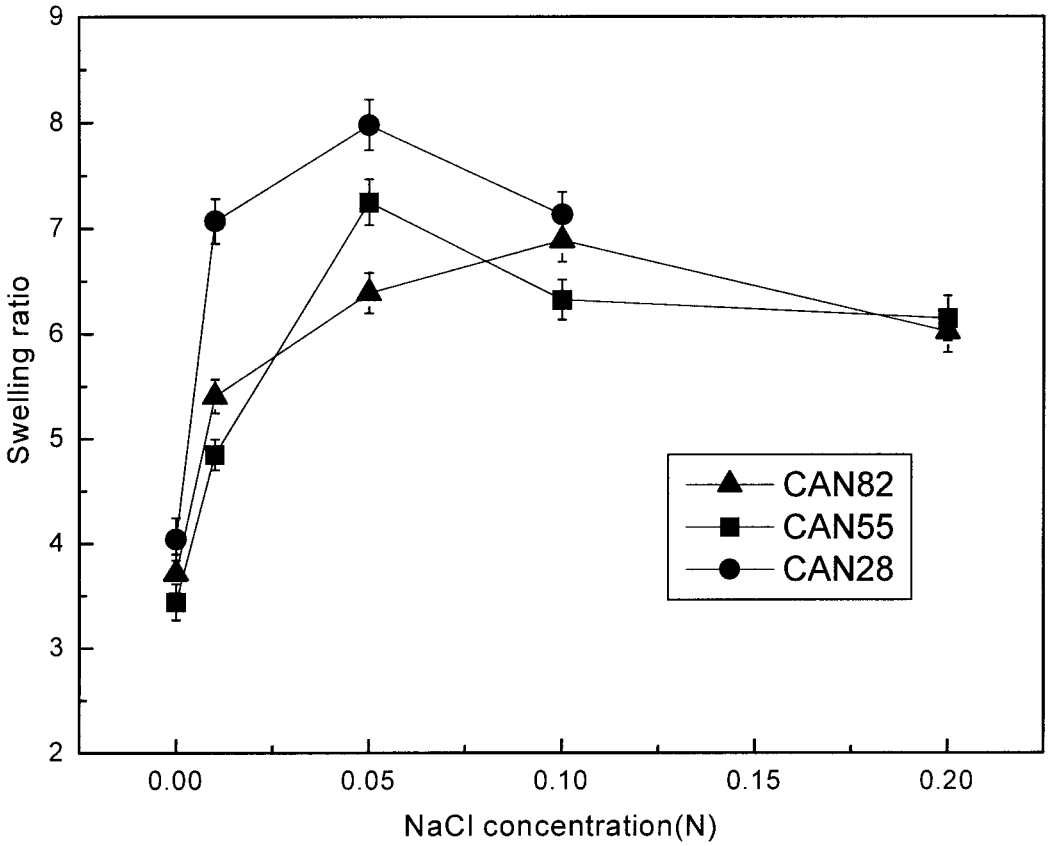

Figure 7 Effect of ionic strength on the swelling behaviors of alginate/PNIPAAm semi-IPNs (CAN28, CAN55, and CAN82) at 25°C in water.

ously with increasing pH values. The pK_a of alginate was about 3.2 and 4 for guluronic and mannuronic acids, respectively. At a low pH region, most carboxylic acid groups in alginate are in the form of COOH. As the pH of the medium increases, the carboxylic acid groups become ionized, and the resulting electrostatic repulsion in the network causes the hydrogels to swell. However, in the case of the semi-IPN hydrogels composed of alginate and PNIPAAm, carboxylic acid in alginate and ammonium ions in PNIPAAm coexisted at pH 2 and 3. In this pH range, the swelling ratio increased because of the dissolution of ammonium salt. Above pH 3, the swelling ratio of semi-IPNs tended to depend on the composition of PNIPAAm to alginate. For example, the swelling ratio of CAN28 increased up to pH 4, but at higher pH, the swelling ratio of CAN28 decreased due to the formation of polyelectrolyte complexes. Although the carboxylic acid of guluronic acid in alginate became the carboxylate ion (COO^-) at pH >3.2, the number of ammonium ions exceeded that of carboxylate ions, resulting in an increase of the swelling ratio up to pH 4.

On the other hand, the swelling ratio of CAN82 slightly increased with pH. Despite the formation of polyelectrolyte complexes between COO^- in alginate and NH^{3+} in PNIPAAm, the swelling ratio was not reduced, even with the relatively larger amounts of carboxylate ions. The swelling ratio of CAN55 decreased at pH's ranging between 3 and 6. This was due to the high amount of interchain bonding between carboxylate ions and ammonium ions. At pH's between 4 and 6, CAN55 showed the lowest swelling ratio among the hydrogels. As mentioned before, this means CAN55 formed the most compact complex structure. It was reported that the calcium alginate (crosslinked sodium alginate) disintegrated into sodium alginate in ethylenediaminetetraacetic acid or in alkaline solution because of the exchange reaction between Ca^{2+} and Na^+.[29] The semi-IPN hydrogels were dissolved in solution at pH 7, which was attributed to the ion exchange between Na^+ ions and complexed Ca^{2+} ions.

Stepwise swelling behaviors were observed in water with temperature alternating between 20 and 40°C, as shown in Figure 9. The swelling

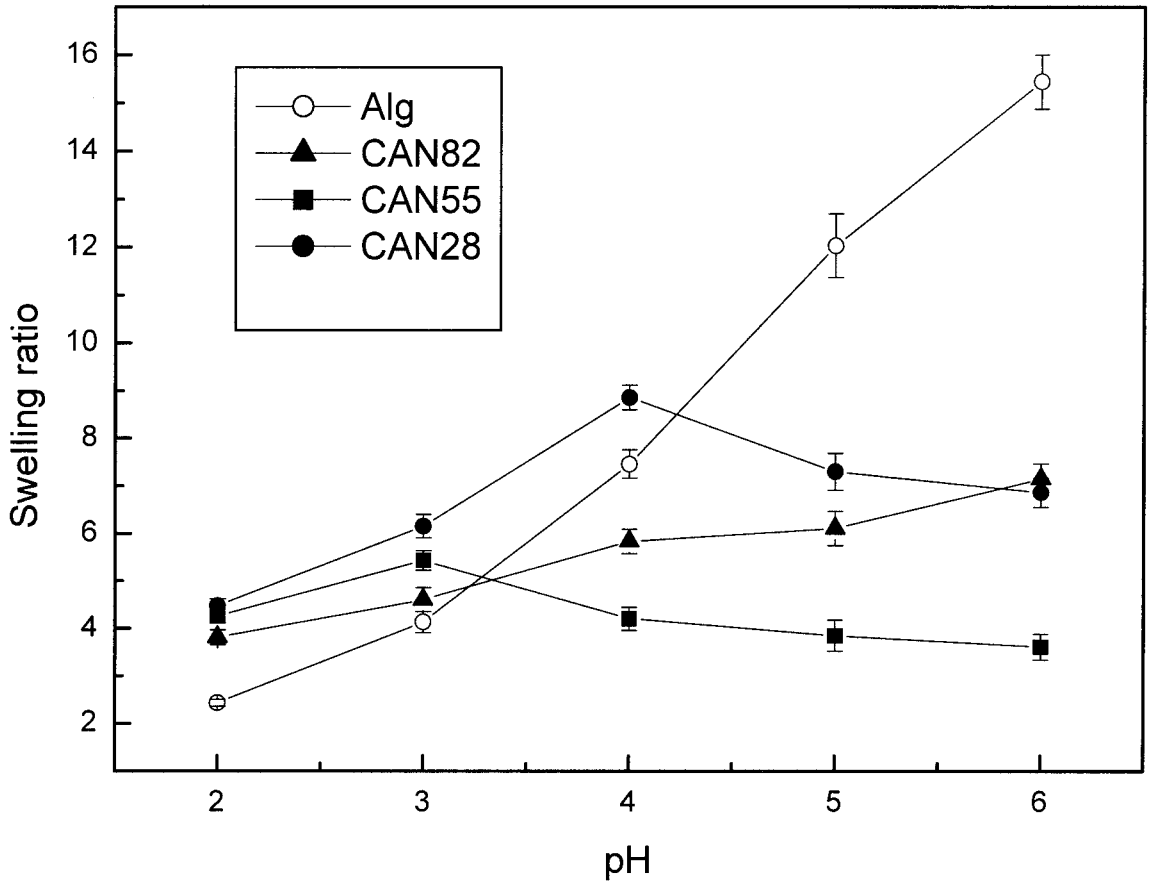

Figure 8 pH-dependent swelling behaviors of alginate/PNIPAAm semi-IPNs (CAN28, CAN55, and CAN82) and alginate at 25°C (NaCl concentration = 0.01*N*).

ratio was measured every 30 min, and the temperature was switched every 2 h. The swelling processes were proven to be repeatable with temperature changes. Among three semi-IPNs, CAN28 showed the most drastic changes in swelling ratio because of its large amounts of PNIPAAm.

CONCLUSIONS

We prepared semi-IPN hydrogels composed of alginate and amine-terminated PNIPAAm with various compositions by crosslinking with calcium ions. From the swelling behaviors at various pH's and FTIR spectra at high temperatures, the formation of polyelectrolyte complexes due to the reaction between carboxyl groups in alginate and amino groups in modified PNIPAAm was confirmed. FTIR showed that the peak intensity of the amide bond (—NH—CO—) at 1650 and 1550 cm^{-1} increased with temperature. Among semi-IPN hydrogels, CAN55 exhibited the lowest swelling ratio in the pH range of 4–6. Alginate/PNIPAAm semi-IPN hydrogels reached an equilibrium swelling state within 24 h and exhibited a relatively high swelling ratio of 3.7–4 in water at pH 5.4. CAN55 semi-IPN showed the lowest swelling ratio among the three semi-IPNs due to low free water content and relatively high bound water content, as shown by DSC analysis. This means that CAN55 formed the most compact structure due to the reaction between carboxyl groups in alginate and amino groups in PNIPAAm. All the hydrogels exhibited a change in swelling ratio at around 32°C because of PNIPAAm's LCST behaviors. Particularly, CAN28 showed a sharp volume phase transition due to large amounts of PNIPAAm. Temperature-sensitive swelling patterns were displayed in a reversible way. Also, the swelling ratio of semi-IPN hydrogels was affected by ionic strength in solution. When the ionic strength in the solution increased, the crosslink density decreased, result-

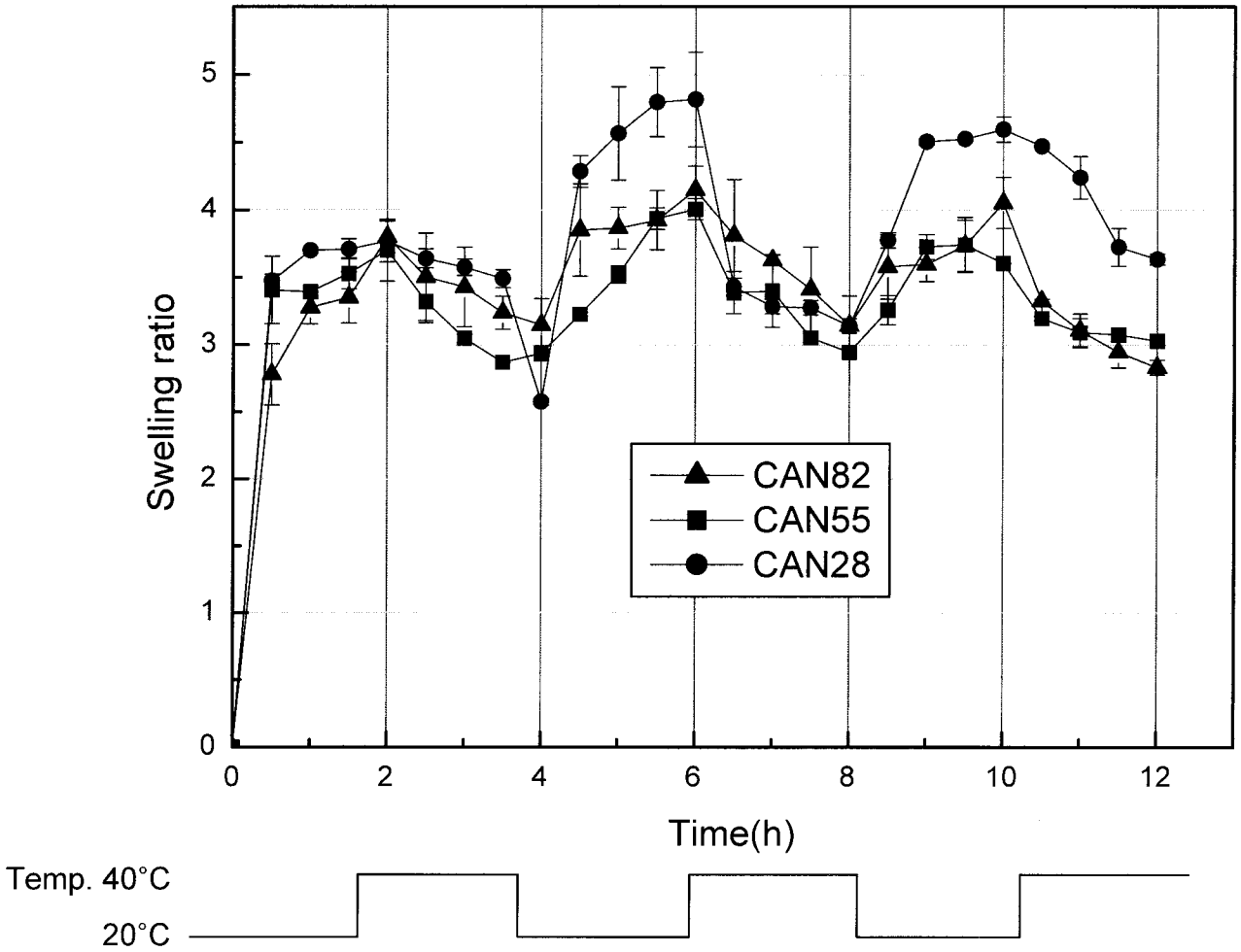

Figure 9 Pulsatile temperature-dependent swelling behaviors of alginate/PNIPAAm semi-IPNs (CAN28, CAN55, and CAN82) in water.

ing in the increase of the swelling ratio. It is expected that alginate/PNIPAAm semi-IPN hydrogels could be useful in biomedical fields for stimuli-responsive drug delivery systems.

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REFERENCES

1. Galaev, I. Y.; Mattiasson, B. TIBTECH 1999, 17, 335.
2. Park, K. Controlled Drug Delivery; ACS Professional Reference Book; American Chemical Society: Washington, DC, 1997; Chapter 8.
3. Okano, T. Biorelated Polymers and Gels; Academic: San Diego, CA, 1998; Chapter 1.
4. Yao, K. D.; Peng, T.; Goosen, F. A.; Min, J. M.; He, Y. Y. J Appl Polym Sci 1993, 48, 343.
5. Tanaka, Y.; Kagami, Y.; Matsuda, A.; Osada, Y. Macromolecules 1995, 28, 2574.
6. Kuen, Y. L.; Won, H. P.; Wan, S. H. J Appl Polym Sci 1997, 63, 425.
7. Kang, D. Y.; Haili, T.; Fa, C.; Jing, W. Z.; Jing, L. Angew Makromol Chem 1997, 245, 63.
8. Hoffman, A. S.; Afrassiabi, A.; Dong, L. C. J Controlled Release 1986, 4, 213.
9. Feil, H.; Bae, Y. H.; Feijen, J.; Kim, S. W. J Membr Sci 1991, 64, 283.
10. Okahata, Y.; Noguchi, H.; Seki, T. Macromolecules 1986, 19, 493.
11. Yoshida, R.; Kaneko, Y.; Sakai, K.; Okano, T.; Sakurai, Y.; Bae, Y. H.; Kim, S. W. J Controlled Release 1994, 32, 97.
12. Huguet, M. L.; Dellacherie, E. Process Biochem 1996, 8, 745.

13. Kikuchi, A.; Kawabuchi, M.; Watanabe, A.; Sugihara, M.; Sakuri, Y.; Okano, T. J Controlled Release 1999, 58, 21.
14. Draget, K. I.; Skjak-Bræk, G.; SmidsrØd, O. Int J Biol Macromol 1997, 21, 47.
15. Choi, Y. S.; Hong, S. R.; Lee, Y. M.; Song, K. W.; Park, M. H.; Nam, Y. S. Biomaterials 1999, 20, 409.
16. Lee, Y. M.; Kim, S. H.; Cho, C. S. J Appl Polym Sci 1996, 62, 301.
17. Shin, H. S.; Kim, S. Y.; Lee, Y. M. J Appl Polym Sci 1997, 65, 685.
18. Shin, H. S.; Kim, S. Y.; Lee, Y. M.; Lee, K. H.; Kim, S. J.; Rogers, C. J Appl Polym Sci 1998, 69, 479.
19. Kim, S. Y.; Shin, H. S.; Lee, Y. M.; Jeong, C. N. J Appl Polym Sci 1999, 73, 1675.
20. Kim, S. Y.; Lee, Y. M. J Appl Polym Sci 1999, 74, 1752.
21. Lee, J. W.; Kim, S. Y.; Kim, S. S.; Lee, Y. M.; Lee, K. H.; Kim, S. J. J Appl Polym Sci 1999, 73, 113.
22. Kim, S. Y.; Cho, S. M.; Lee, Y. M. J Appl Polym Sci 2000, 78, 1381.
23. Park, T. G.; Choi, H. K. Macromol Rapid Commun 1998, 19, 167.
24. Sartori, C.; Finch, D. S.; Ralph, B. Polymer 1997, 38, 43.
25. Nam, S. Y.; Lee, Y. M. J Membr Sci 1997, 135, 161.
26. Schild, H. G. Prog Polym Sci 1992, 17, 163.
27. Park, T. G.; Hoffman, A. S. J Appl Polym Sci 1992, 46, 659.
28. Wang, X.; Spencer, H. G. Polymer 1998, 39, 2759.
29. Yuk, S. H.; Cho, S. H.; Lee, H. B. J Controlled Release 1995, 37, 69.