Preparation and Characterization of pH- and Temperature-Responsive Semi–interpenetrating Polymer Network Hydrogels Based on Linear Sodium Alginate and Crosslinked Poly(*N*-isopropylacrylamide)

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ABSTRACT: In this study, pH- and temperature-responsive hydrogels based on linear sodium alginate (SA) and crosslinked poly(*N*-isopropylacrylamide) (PNIPAAm) were prepared by semi-interpenetrating network (semi-IPN) technique. The dually responsive hydrogels were characterized by FTIR, DSC, and SEM, and their temperature- and pH-responsive behaviors were investigated by measuring equilibrium swelling ratios and pulsatile swelling experiments. The results showed that these hydrogels underwent volume phase transition at around 33°C irrespective of the pH value of the medium, but their pH sensitivity was evident only below their volume phase transition temperature. Under basic conditions, the swelling ratios of SA/PNIPAAm semi-IPN hydrogels were greater than that of pure PNIPAAm hydrogel and increased with increasing SA content incorporated into the hydrogels, but the case was inverse under acidic conditions. The pulsatile swelling experiments indicated that the higher the SA content in SA/PNIPAAm semi-IPN hydrogels, the faster the response rate to both pH and temperature change. © 2005 Wiley Periodicals, Inc. J Appl Polym Sci 97: 1931–1940, 2005

Key words: biomaterials; hydrogel; interpenetrating network (IPN)

INTRODUCTION

In recent years, considerable research attention has been focused on intelligent hydrogels that are able to alter their swelling behavior and other properties in response to environmental stimuli, such as temperature,[1] pH,[2] and ionic strength.[3] Because of their drastic swelling and shrinkage in response to environment stimuli, these polymeric hydrogels have been investigated for many biomedical and pharmaceutical applications including controlled drug delivery,[4] molecular separation,[5] tissue culture substrate,[6] and material for improved biocompatibility.[7] Among these intelligent hydrogels, temperature- and pH-sensitive hydrogels are most widely investigated because these two factors are important ones inside the human body.[7–8]

Poly (*N*-isopropylacrylamide) (PNIPAAm) hydrogel is one of the most favorable members of temperature-sensitive hydrogels studied extensively by numerous researchers as an intelligent polymeric matrix, because it undergoes sharp volume phase transition at about 33°C in aqueous solution.[9] Below the volume phase transition temperature (VPTT), the hydrogel is swollen, whereas above the VPTT, the hydrogel dehydrates to collapsed state due to the breakdown of delicate hydrophilic/hydrophobic balance in the network structure. Because of such a particular property, PNIPAAm hydrogel has been extensively used in many fields.[10–16]

It is well known that sodium alginate (SA) is a particularly attractive material to form hydrogels for biomedical applications.[17] It is naturally derived from linear polysaccharide composed of β-D-mannuronic acid (M-block) and α-L-guluronic acid (G-block) units arranged in blocks rich in G units or M units, separated by blocks of alternating G and M units. With one carboxyl group in each M or G unit, it is a negatively charged polyelectrolyte in neutral or basic solution. The advantages of using SA for preparing hydrogels also result from its other properties,[18] as follows: (1) it has a relatively inert aqueous environment within the matrix; (2) it has a high gel porosity that allows for high diffusion rates of macromolecules; and (3) its dissolution and biodegradation under normal physiological conditions enables it to be used as a matrix for the entrapment and delivery of proteins, drugs, and cells.

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TABLE I
Feed Composition for the Preparation of SA/PNIPAAm Semi-IPN Hydrogels

Component	Sample code			
	PNIPAAm	Semi-IPN04	Semi-IPN08	Semi-IPN13
NIPAAm (g)	1.04	1.04	1.04	1.04
SA (wt %)[a]	0	4	8	13
BIS (g)	0.0208	0.0208	0.0208	0.0208
APS (g)	0.0208	0.0208	0.0208	0.0208
TEMD (μl)	40	40	40	40
H_2O (ml)	13	13	13	13

[a] The percentage is based on the mass of monomer NIPAAm.

Recently, a few studies have been performed to combine the temperature-sensitive material, PNIPAAm, and pH-sensitive natural polymer, SA, to prepare dually sensitive hydrogels. For instance, Ju et al. and Kim et al.[7,18] prepared two kinds of hydrogels based on amino semitelechelic PNIPAAm and crosslinked SA with Ca^{2+}. One is comb-type macroporous hydrogels, in which PNIPAAm was grafted on the surface or bulk of SA. Another is semi-interpenetrating polymer network hydrogels, where a polyelectrolyte complex was formed from the reaction between carboxyl groups in SA and amino groups in the modified PNIPAAm. However, the hydrogels based on Ca^{2+} crosslinked SA might be unsuitable for contact with biological fluid because of a loss of mechanical properties with time attributed to the replacement of Ca^{2+} by Na^{+} On the other hand, the reduction of the carboxyl groups in alginate and mobility limitation of SA chain due to Ca^{2+} crosslinking may lead to the decrease in pH sensitivity of the hydrogels. Unfortunately, to date, there have been no reports on the semi-IPN hydrogels based on linear SA and crosslinked PNIPAAm. In addition, we can easily prepare IPN hydrogels by interpenetrating network technique and attain a combination of properties such as temperature-sensitivity and pH-sensitivity from these two polymer networks. Because there is no chemical bonding between the two component networks, each network may retain its own property while the proportion of each network can be varied independently. Moreover, it is reported that interpenetration of the two networks may lead to much higher mechanical strength in comparison to the homopolymer network.[19]

The aim of this study was to prepare the pH- and temperature-responsive hydrogels based on linear SA and crosslinked PNIPAAm by semi-interpenetrating network (semi-IPN) technique. Their surface morphology, molecular interaction, and phase transition were characterized by scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FTIR), and differential scanning calorimeter (DSC), respectively. Their pH- and temperature-responsive behaviors were investigated by measuring equilibrium swelling ratios and pulsatile swelling experiments. This semi-IPN hydrogel, which is responsive to both pH and temperature, would be able to respond to conditions where both phenomena are coupled.

EXPERIMENTAL

Materials

NIPAAm (TCI Co., Japan) was purified by recrystallization from *n*-hexane/toluene (60/40, v/v) before use to remove inhibitor. Ammonium persulfate (APS; Shanghai Chemical Reagent Co., China) as an initiator, *N*,*N*′-methylenebisacrylamide (BIS; Fluka Chemical Co., Buchs, Switzerland) as a crosslinker, and *N*,*N*,*N*′,*N*′-tetramethylethylene diamine (TEMED; Sigma Co., St. Louis, MO) as an accelerator were used as received. SA (Chemical Reagent Factory of Shanghai, China) has an M/G ratio of 1.56; its molecular weight, determined by viscosity method in our laboratory, is 2.9×10^5 g mol^{-1} Disodium hydrogen phosphate and sodium dihydrogen phosphate were purchased from Shanghai Chemical Reagent Co. All other reagents used were of analytical grade and used without further purification.

Preparation of SA/PNIPAAm semi-IPN hydrogels

Various ratios of NIPAAm to SA and 2 wt % BIS based on the total monomers were dissolved in 13 mL of deionized water. To this solution, 1 wt % APS and 1 wt % TEMED as redox initiators were added. Polymerization was carried out in an ice-water bath for 24 h. After the gelation was completed, the gel was cut into disks 10 mm in diameter and 1–3 mm in thicknesses and then immersed into an excess amount of deionized water for 7 days to remove the residual unreacted monomer. Swollen polymeric gels were dried at room temperature for 24 h and then further dried in a vacuum oven for 2 days at 40°C prior to characterization. The composition for SA/PNIPAAm semi-IPN hydrogels is shown in Table I.

FTIR analyses

Prior to the measurement, SA/PNIPAAm semi-IPN hydrogels were immersed in pH 1.2 and pH 7.4 buffer

solution for at least 24 h, respectively, and picked up and then dried for 48 h at 50°Cin a vacuum oven. The samples were directly analyzed by using a FTIR spectrograph (Nicolet NEXUS-670) in a KBr tablet.

Volume phase transition temperature (VPTT) measurement

The VPTTs of SA/PNIPAAm semi-IPN hydrogels were determined by using a DSC (TA-Modulated DSC 2910). All hydrogels were immersed into deionized water at room temperature and allowed to swell for at least 24 h to reach the equilibrium state. The thermal analyses were performed from 25 to 45°C at a heating rate of 3°C/min on the swollen hydrogels under a nitrogen atmosphere with a flow rate of 40 mL/min. Deionized water was used as the reference in the DSC measurement.

Scanning electron microscopy

The semi-IPN hydrogels equilibrium swollen in deionized water at room temperature were quickly frozen in liquid nitrogen and then freeze-dried (−48°C, 3.8×10^{-4} mbar) for at least 24 h until all the solvent was sublimed. The freeze-dried hydrogel was fractured carefully and the interior morphology of the hydrogels was observed by use of a SEM (JSM-5600LV, JEOL, Japan).

Measurement of the swelling ratios for SA/PNIPAAm semi-IPN hydrogels

The swelling ratios of hydrogel samples were measured in the temperature range from 25 to 45°C or in the pH range from 1.2 to 9.0 using a gravimetric method. Under each particular condition, hydrogel samples were incubated in the medium for at least 24 h and removed, wiped with moistened filter paper to remove water from the sample surfaces, and weighed. Here, the swelling ratio is defined as the weight of water absorbed in the swollen gel (W_s) divided by the dried weight of the gel (W_d).

Pulsatile swelling experiments

Pulsatile swelling studies were conducted on these hydrogel samples as functions of temperature and pH value of the medium to examine their responsive rate to pH and temperature change at the same period of time. In the pulsatile swelling experiments, the semi-IPN hydrogels were swollen in deionized water for the same period of time before they were transformed into another solution with higher pH value or higher temperature. The temperature was changed alternatively between 20 and 45°C; pH value between 1.2 and 7.4 was also alternated every 5 min and their swelling ratios were determined gravimetrically.

RESULTS AND DISCUSSION

Preparation of SA/PNIPAAm semi-IPN hydrogels

SA/PNIPAAm semi-IPN hydrogels were prepared by solution polymerization in aqueous medium with the existence of SA, NIPAAm as monomer, BIS as crosslinker, and redox initiators, as shown in Figure 1. In our work, we employed neutral water as the polymerization solvent, and the pH value of the polymerization system measured by pH meter was in the range from 6.8 to 7.0. Because the pH value is remarkably higher than pKa of β-D-mannuronic acid (M) and α-L-guluronic acid (G) unit (4.0 and 3.2, respectively), SA was a negatively charged polyelectrolyte in the polymerization system. The strong electrostatic repulsions among SA carboxylate anions (—COO^-) could have resulted in expanded network of the hydrogel, which might have had an extremely high water uptake. Because the hydrogel network is reported to retain memory of its formation history and molecular conformation,[20–22] an expanded network structure with a special conformation would remain even after the hydrogel had been transferred to acidic medium after the synthesis and after —COO^- had changed to —COOH. The expanded structure was confirmed by the porous structure observed by SEM after the swollen hydrogel samples were freeze-dried and fractured, as illustrated below.

FTIR analysis

The FTIR spectra of the SA/PNIPAAm semi-IPN hydrogels treated with pH 1.2 and pH 7.4 buffer solution was shown in Figure 2(a, b), respectively. It can be seen from Figure 2(b) that there is a broad band at ~ 3343 cm^{-1}, which is attributed to N—H stretching vibration of PNIPAAm component in the semi-IPN hydrogel and a typical amide I band (~ 1648 cm^{-1}) assigned to C═O stretching of PNIPAAm and amide II band (~ 1545 cm^{-1}), which belongs to N—H vibration. As shown in Figure 2(a), one can observe that N—H stretching vibration is shifted to 3318 cm^{-1} and a carboxyl stretching peak occurs at 1737 cm^{-1}. It is due to the fact that most of —COO^- groups of SA component in the semi-IPN hydrogels are protonated under acidic conditions (pH 1.2), thus forming a hydrogen bond between —COOH and —CONH— groups. As a result, it can be concluded that interaction between SA component and PNIPAAm networks in the semi-IPN hydrogels is associated with pH value of the medium.

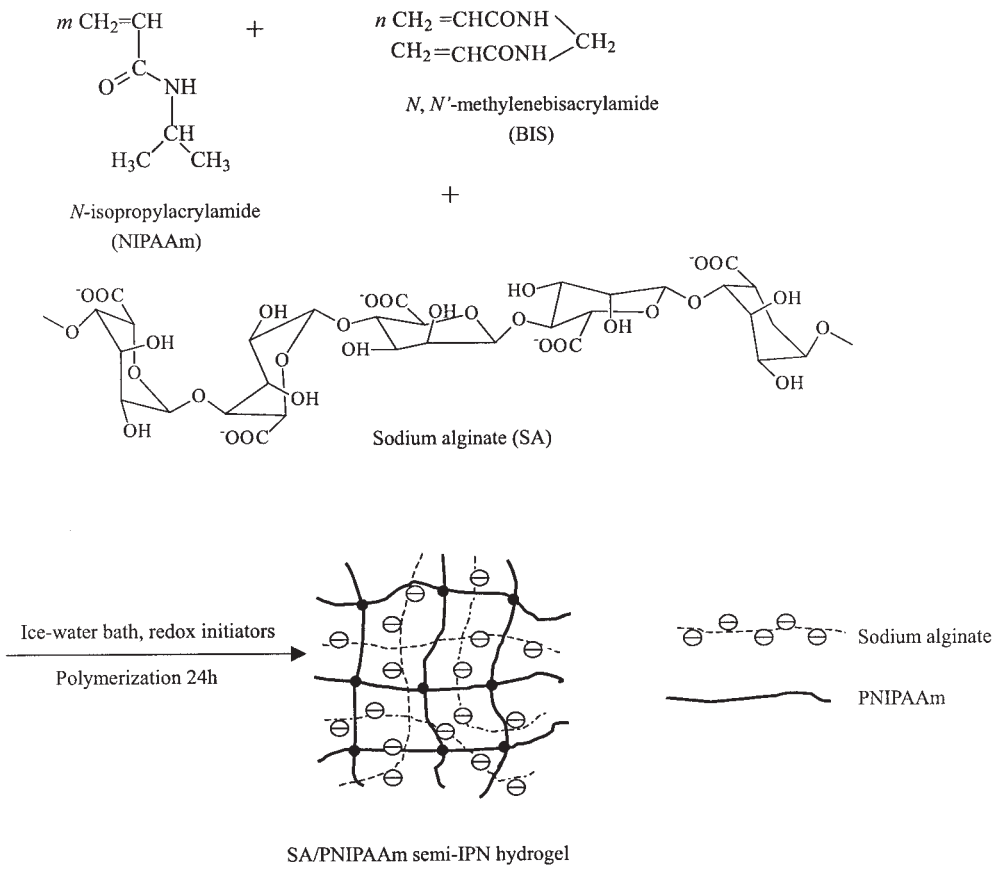

Figure 1 Synthesis scheme of SA/PNIPAAm semi-IPN hydrogel.

DSC behaviors of SA/PNIPAAm semi-IPN hydrogels

The DSC thermograms of conventional PNIPAM and SA/PNIPAAm semi-IPN hydrogels are shown in Figure 3. The temperature at the onset point of the DSC endotherm is referred to the VPTT of hydrogel as reported in the previous studies.[23–25] At the temperature of VPTT, water in the hydrogels separated from the system and led to a smaller heat capacity. It can be noted from Figure 3 that all SA/PNIPAAm semi-IPN hydrogel samples exhibit a similar VPTT around 33°C, and there is no significant deviation from the VPTT of conventional PNIPAAm hydrogel, indicating that, in the semi-IPN systems, the PNIPAAm network retains its own property because of no chemical bond formed between SA and PNIPAAm network.

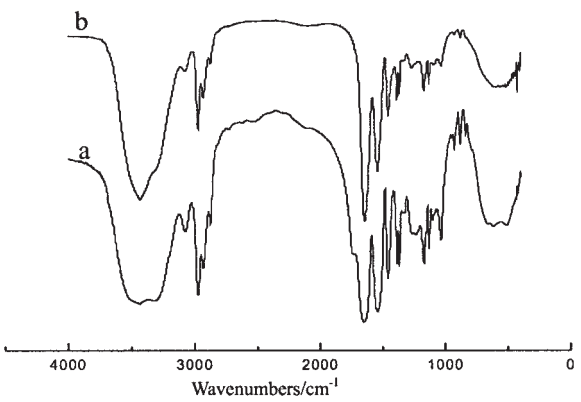

Figure 2 FTIR spectra of SA/PNIPAAm semi-IPN hydrogel with different buffer solutions: (a) pH 1.2; (b) pH 7.4.

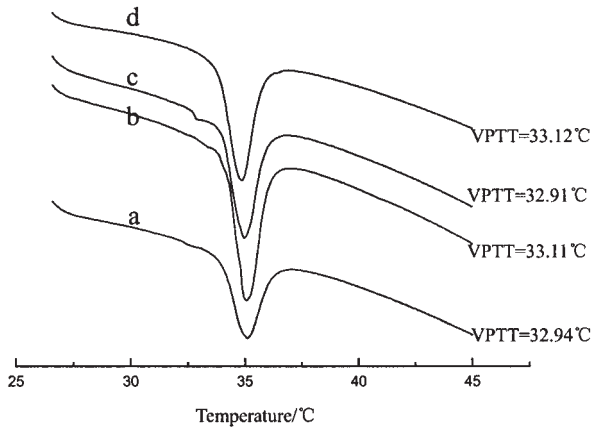

Figure 3 DSC thermograms of the conventional PNIPAAm and semi-IPN hydrogels at a heating rate of 3°C/min from 25 to 45°C:. (a): PNIPAAM; (b): semi-IPN04; (c): semi-IPN08; (d): semi-IPN13.

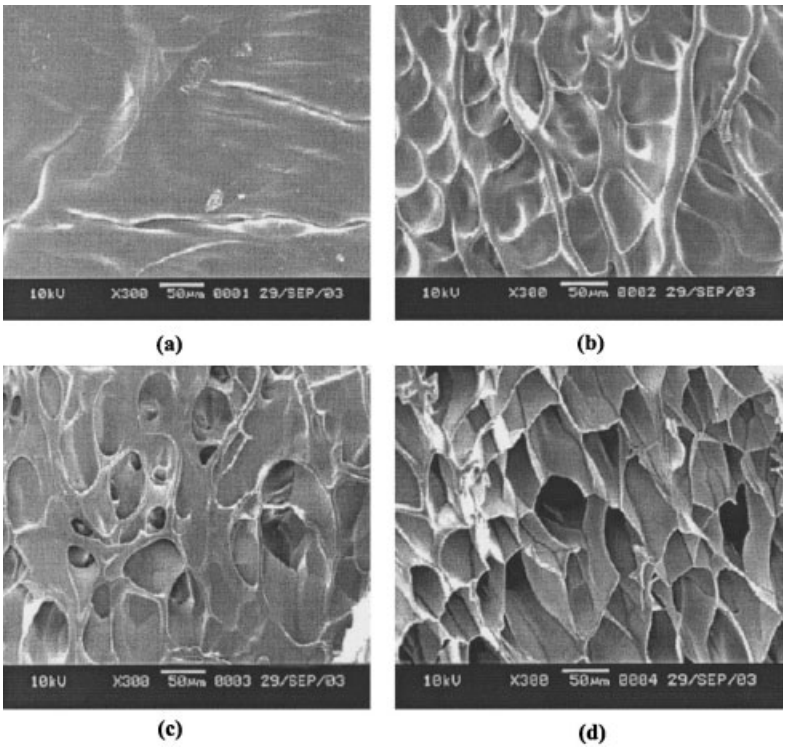

Figure 4 SEM micrographs of the conventional PNIPAAm and semi-IPN hydrogels: (a): PNIPAAM; (b): semi-IPN04; (c): semi-IPN08; (d): semi-IPN13.

SEM observation of the internal structure of SA/PNIPAAm semi-IPN hydrogels

Figure 4 show the SEM micrographs of the internal structure of SA/PNIPAAm semi-IPN hydrogels, from which we can see that conventional PNIPAM hydrogel has a relatively dense structure, whereas the semi-IPN hydrogels show a porous network structure in character. Their pore sizes increase with the increase in SA content in the semi-IPNs. These results support our above analysis that a highly expanded network can be generated by electrostatic repulsions among SA carboxylate anions (—COO^-) during the polymerization process. With increasing SA content, the expansion of the gel matrices enhanced, resulting in the increase in the pore size. When the temperature is above the hydrogel's VPTT, the shrinking or deswelling and thus the water molecules are easy to diffuse out as a result of numerous small pores in the hydrogel network. Therefore, the response rate could greatly be enhanced by the incorporation SA into the PNIPAAm hydrogel network during the deswelling process.

Temperature dependence for SA/PNIPAAm semi-IPN hydrogels

The swelling ratios of SA/PNIPAAm semi-IPN hydrogels were investigated as a function of temperature in buffer solutions (pH 1.2 and 7.4), respectively, as shown in Figure 5. At pH 1.2 and temperature below the VPTT, the swelling ratios of SA/PNIPAAm semi-IPN hydrogels are lower than those of pure PNIPAAm hydrogel in the temperature range [see Fig. 5(a)]. Among SA/PNIPAAm semi-IPN hydrogels, the semi-IPN13 holds the lowest swelling ratio, whereas the semi-IPN04 has the highest swelling ratio. This is due to the fact that most of —COO^- groups in the semi-IPN hydrogels are protonated under acidic conditions, thus forming a hydrogen bond between —COOH and —CONH- groups; the higher the SA content in the semi-IPN hydrogels, the stronger the hydrogen bond between intermolecules. As a result, the swelling ratios of pure PNIPAAm hydrogel are higher than those of the semi-IPN hydrogels in acidic conditions. However, at pH 7.4, the results that the swelling ratios of pure PNIPAAm hydrogel are lower than those of the semi-IPN hydrogels at the same temperature range and the semi-IPN13 has the maximum swelling ratio among the semi-IPN hydrogels are adverse to those in acidic conditions [see Fig. 5(b)]. This phenomenon may be due to the fact that under basic conditions the hydrogen bonding interaction is weakened and destroyed, which is confirmed by FTIR analysis mentioned above, and that electrostatic repulsion occurs rendering the hydrogels more hydrophilic. The high SA content in the polymer networks leads to higher swelling ratios. As a result, the swelling ratios of the semi-IPN hydrogels increase with increasing SA

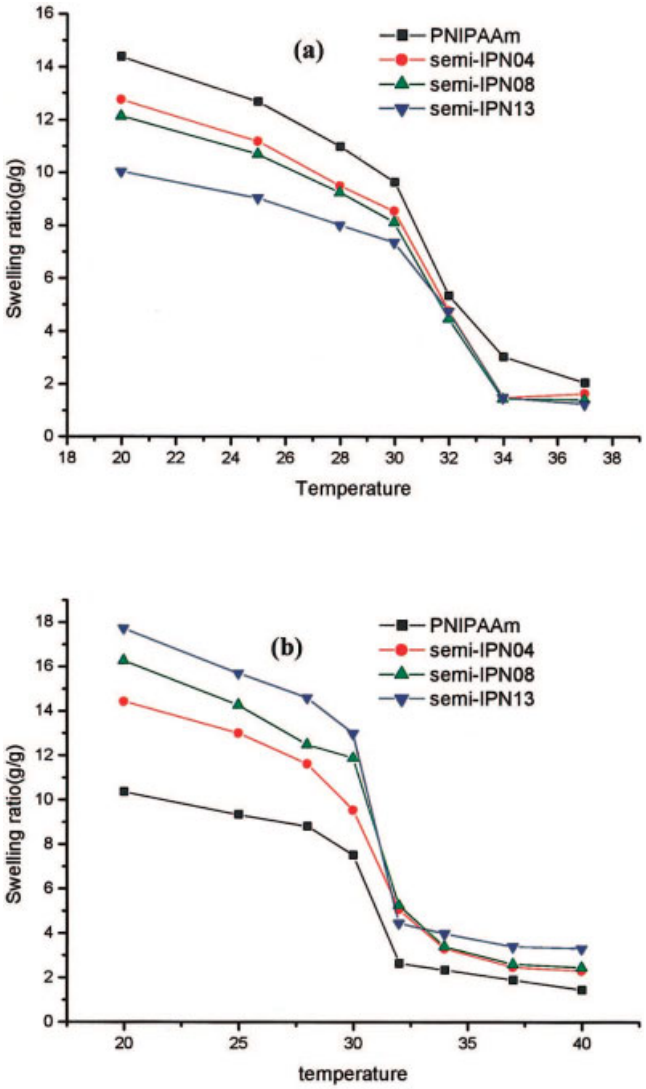

Figure 5 Swelling ratios as a function of temperature at pH 1.2 (a) and pH 7.4 (b) for SA/PNIPAAm semi-IPN hydrogels.

content. Based on the above analysis, the schematic structure of SA/PNIPAAm semi-IPN hydrogel and pure PNIPAAm hydrogel under acidic and basic conditions are brought forward, as shown in Figure 6, from which the above conclusions are easily understood. However, as the temperature increases, the swelling ratios of all the gels decrease. Both the semi-IPN hydrogels and pure PNIPAAm hydrogel exhibited phase transition at around 33°C regardless of pH value of the medium, indicating that the PNIPAAm network retains its own temperature sensitivity in the semi-IPN systems.

pH-dependence for SA/PNIPAAm semi-IPN hydrogels

SA is a kind of natural polyelectrolyte, which has many carboxylic groups in its molecular chain. The dissociation degree of carboxyl group is closely related to the pH value of the medium. To investigate the influence of pH value of the medium on the swelling ratios for the semi-IPN hydrogels, thus, the pH range is selected from 1.2 to 9.0 in this study. The pH dependence of the swelling ratios for SA/PNIPAAm semi-IPN hydrogels was investigated at 25°C (below the VPTT of PNIPAAm) and 37°C (above the VPTT of PNIPAAm), respectively. As shown in Figure 7(a), the swelling ratios of SA/PNIPAAm semi-IPN hydrogels with various SA contents are lower than those of pure PNIPAAm hydrogel in the pH value range from 1 to 2 at 25°C. It is due to the formation of hydrogen bond between —COOH in the SA and —CONH— in the PNIPAAm and, thus, leading to polymer–polymer interactions predominating over the polymer–water interactions, as a result, the swelling ratios of SA/PNIPAAm semi-IPN hydrogels decrease. Furthermore, such behaviors depend strongly on the SA content in the semi-IPN hydrogels; that is, under strong acidic conditions, the higher the SA content in the semi-IPN hydrogels, and the lower the swelling ratios of the semi-IPN hydrogels. In the pH range from 1 to 4.5, the swelling ratios of the semi-IPN hydrogels continuously increase with increas-

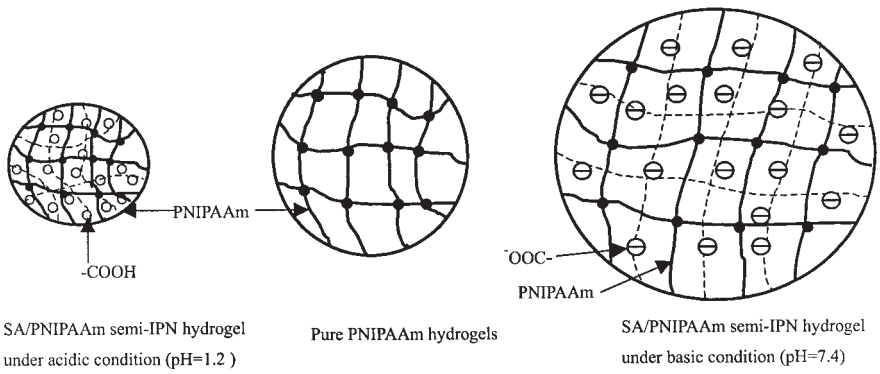

Figure 6 Schematic illustration of the pure PNIPAAm hydrogel and SA/PNIPAAm semi-IPN hydrogel under pH 1.2 and 7.4 conditions.

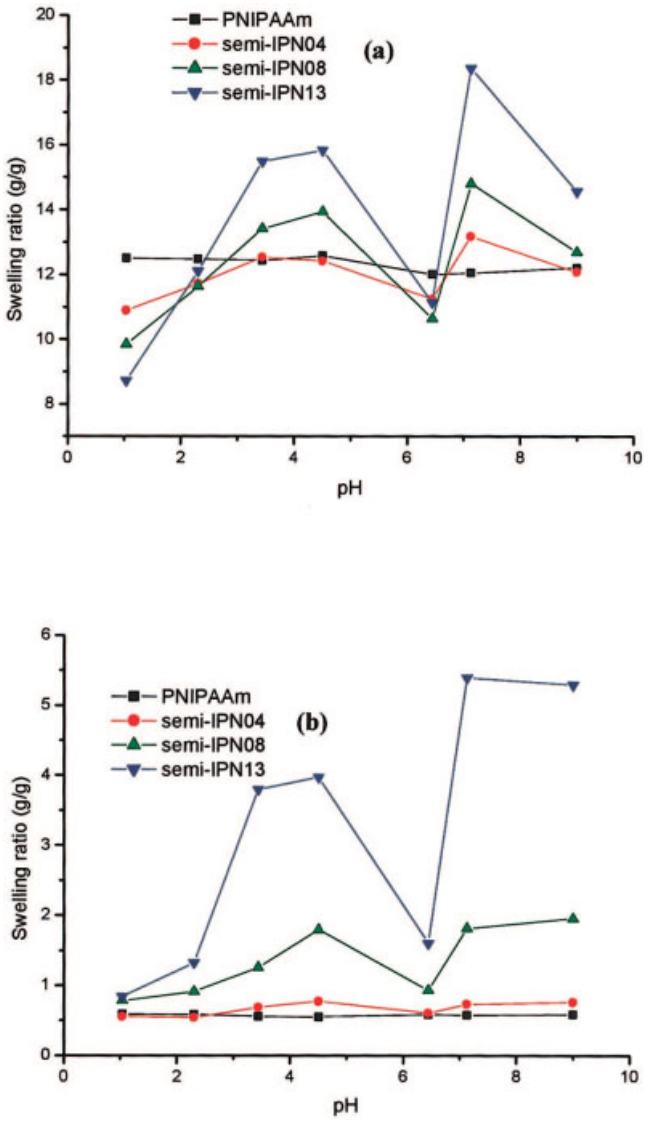

Figure 7 Swelling ratios of SA/PNIPAAm semi-IPN hydrogels as a function of pH value of the medium at 25°C (a) and 37°C (b).

ing pH values. This is mainly attributed to the carboxyl group of SA in the semi-IPN hydrogel, in which the pK_a of SA is about 3.2 and 4 for guluronic and mannuronic acids, respectively. As the pH value of the medium increases, the carboxylic acid groups become ionized, and a small quantity of H^+ acts as the bridge between SA molecules. As a result, the swelling ratio of the semi-IPN hydrogels increases. When pH value increases to 6.4, the amount of H^+ drops off and the bridge of H^+ was weakened, and thus, results in a decrease in the swelling ratios of the semi-IPN hydrogels. At pH 4.5, there is the first maximum swelling ratio for the semi-IPN hydrogels. This can be understood according to Flory's swelling theory.[26] The swelling ratios of the semi-IPN hydrogels increase as pH value continues to increase, which can result from a stronger solvation effect of SA component in the semi-IPN hydrogel. However, with a further increase in the pH value, the swelling ratios of the semi-IPN hydrogels attain the second maximum at pH 7.4. Beyond this value, the swelling ratios of the semi-IPN hydrogels start to decrease, which is due to the shielding effect of Na^+ at higher pH. The above results are consistent with the relation between pH and viscosity of SA solution studied by Chen et al.[27] The similar phenomenon was also observed at 37°C in the same conditions. However, the pH response of the semi-IPN hydrogel at 37°C is less sensitive than that of semi-IPN hydrogel at 25°C, as shown in Figure 7(b). This is because the PNIPAAm hydrogel network is in the collapsed state above the VPTT. As a contrast, for the pure PNIPAAm gel, the swelling ratios keep constant when pH changes in the range studied above. In addition, by using the semi-IPN13 as a typical example, we compared the influence of environmental pH on the morphology of semi-IPN hydrogels by SEM. Figure 8(a–e) was obtained from semi-IPN13 samples under different environmental pH values. From Figure 8(a–e), the pH values are 1.0, 3.0, 4.5, 6.4, and 7.4, respectively. The temperature was kept at room temperature of 25°C. We noticed that, at pH range from 1.0 to 4.0, the pore sizes of the semi-IPN13 samples increased drastically. However, the pore sizes at pH 6.4 were smaller than those of at pH 3.0 and 4.0 and at pH 7.4 the pore sizes increased instead. As a result, we found that the influence of environmental pH on the morphology of semi-IPN hydrogels was identical with the influence of pH value of the medium on the swelling ratios of the semi-IPN hydrogels.

Pulsatile stimuli-responsive behaviors

To investigate whether the responses to the environmental pH and temperature change were reversible and to examine how fast the semi-IPN hydrogels could respond to the external stimuli, the pulsatile stimuli-responsive swelling studies were performed, as shown in Figure 9. A stepwise swelling behavior was observed in deionized water with alternating temperature between 25 and 45°C in Figure 9(a). The swelling process could be repeatable with temperature changes. The semi-IPN hydrogels rapidly responded to temperature change in comparison with PNIPAAm hydrogel. The higher the SA contents in the semi-IPN hydrogels, the faster the sensitivity of the semi-IPN hydrogel. The remarkable difference in response to temperature change is detected for the semi-IPN hydrogels, which is due to the incorporation SA into the PNIPAAm network. It is well known that PNIPAAm hydrogel forms the dense and thick layer

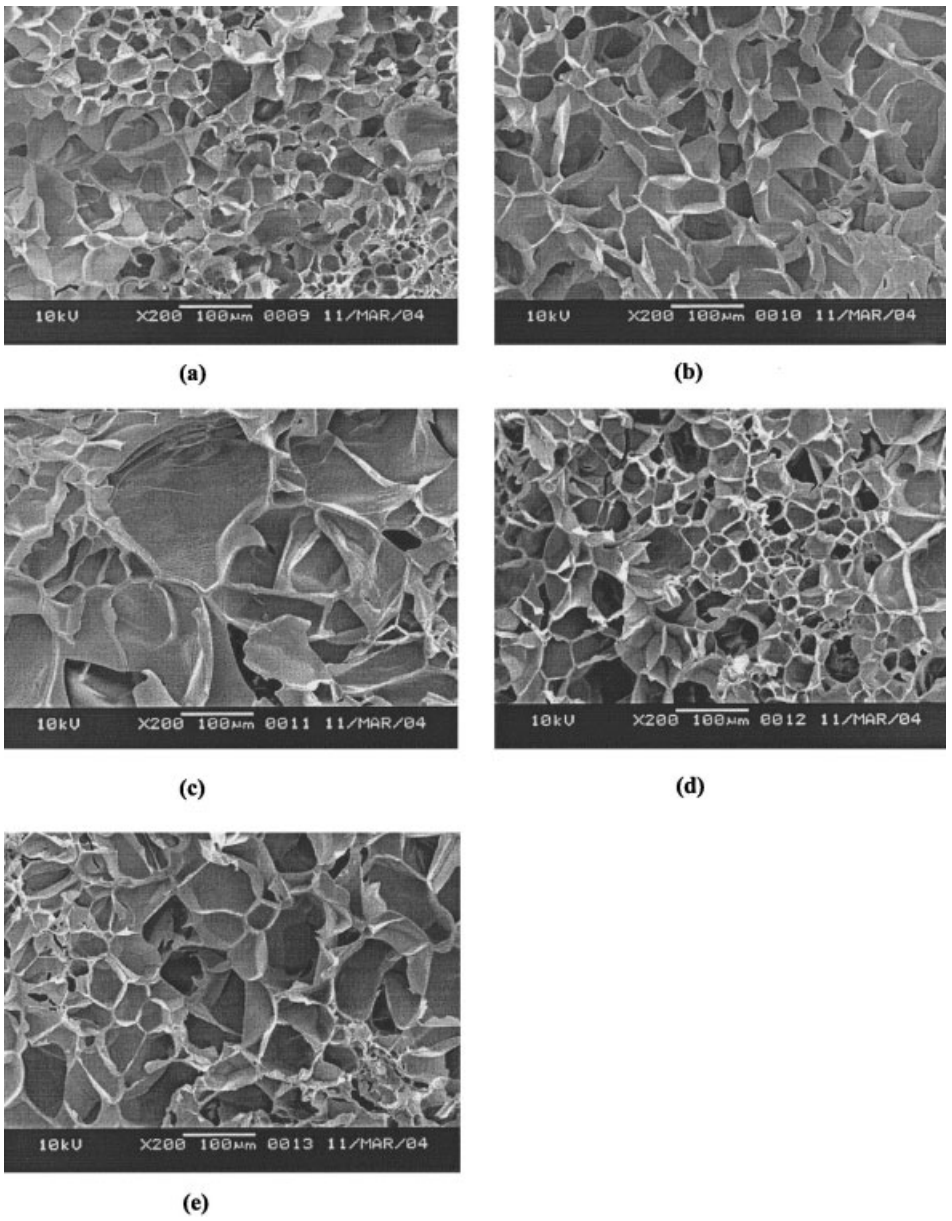

Figure 8 SEM micrographs of semi-IPN13 hydrogels under different pH values: (a) 1.0; (b) 3.0; (c) 4.5; (d) 6.4; (e) 7.4.

on its surface during the volume phase transition, which prevents water molecules from being squeezed out and leads to the slow response rate.[28] For the semi-IPN hydrogels, the skin layer is not easy to be formed. This is because the SA chains are independent of the PNIPAAm backbone network and do not disturb the hydrophobic aggregation of the PNIPAAm hydrogel network when temperature is raised above the VPTT. Thus, the hydrophilic SA chains can act as water-releasing channels when the collapse occurs. It is evident that the more SA incorporated into the semi-IPN hydrogel, the more water-releasing channels were formed, and the more easily the water molecules were squeezed out of the semi-IPN hydrogels when temperature is raised above the VPTT. The dramatic improvement in the response rate could be explained by SEM results. In Figure 9(b), the pulsatile swelling behavior of the semi-IPN hydrogels at 25°C with alternating pH values between 1.2 and 7.4 was investigated. The swelling ratio was also measured in 5-min steps. The pH-dependent pulsatile swelling behavior was also observed and the semi-IPN hydrogels exhibited a similar pulsatile swelling behavior, whereas the swelling ratio of the PNIPAAm hydrogel was not affected by the pH change because there was no pH-sensitive component in the PNIPAAm hydrogel network. Furthermore, a distinctive difference in the reversible swelling behavior among the semi-IPN hydrogels was also observed from Figure

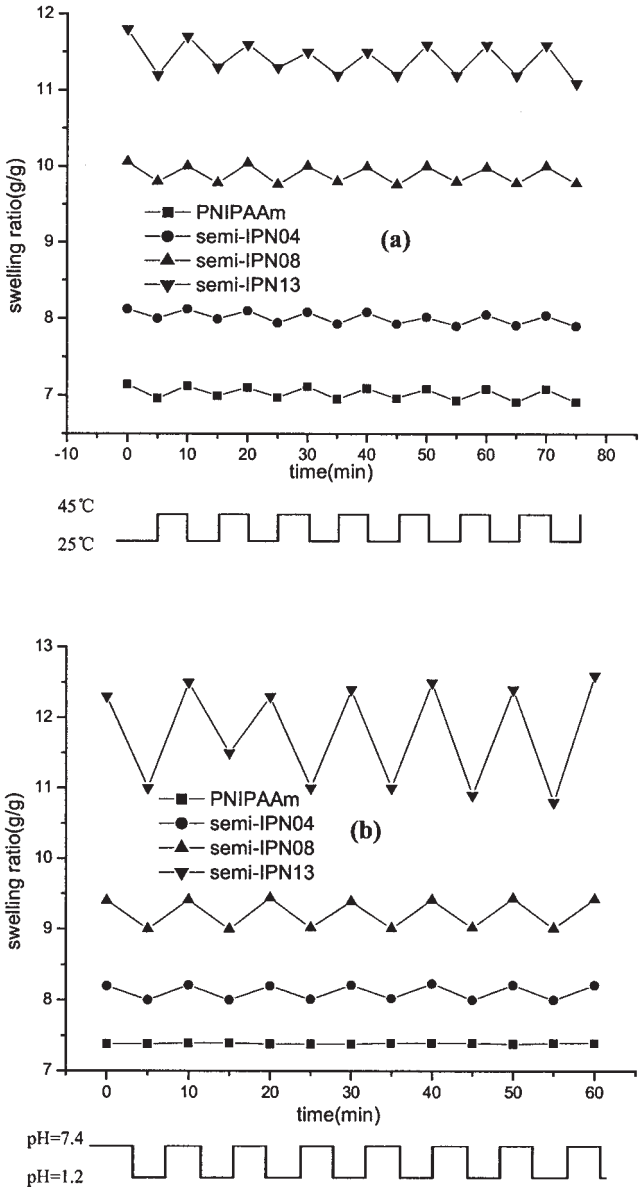

Figure 9 Pulsatiles swelling behaviors of SA/PNIPAAm semi-IPN hydrogels in response to temperature changes between 22°C and 45°C at pH 7 (a) and pH changes between 1.2 and 7.4 at 25°C (b).

9(b); that is, the more SA introduced into the semi-IPN hydrogel, the faster the sensitivity to pH change. On the other hand, all the semi-IPN hydrogels still keep good shape in the course of the alternating pH stimuli. As a result, incorporation SA into PNIPAAm hydrogel network increases the sensitivity of the semi-IPN hydrogels to both pH- and temperature-alternating change.

CONCLUSIONS

In this study, a series of temperature- and pH-sensitive semi-IPN hydrogels composed of crosslinked PNIPAAm and linear SA were prepared from the various mass ratios of NIPAAm to SA by solution polymerization. The swelling behaviors of the semi-IPN hydrogel as a function of temperature and pH value of the medium, respectively, were investigated in detail. Experimental results show that under acidic conditions (pH 1.2) and weak alkaline conditions (pH 7.4), the swelling ratios for the semi-IPN hydrogel decrease with increasing temperature, and the swelling ratios for the semi-IPN hydrogel at pH 1.2 are lower than those of pure PNIPAAm hydrogel, whereas the swelling ratios for the semi-IPN hydrogel at pH 7.4 are higher than those of pure PNIPAAm hydrogel, and the influence of pH on the swelling ratios of the semi-IPN hydrogel displays that pH response of this hydrogel at 25°C is faster than that of at 37°C. Pulsatile stimuli-responsive swelling behaviors of this hydrogel also reveal that the swelling process could be repeatable not only with alternating temperature stimuli but also with pH alternating stimuli. The sensitivity of this hydrogel to alternating changes in pH and temperature is improved because of the incorporation of SA. Also, the semi-IPN hydrogels show suitable mechanical strength during the repeatable shrinkage and swelling period. Thus, it is expected that this type of the semi-IPN hydrogel could be used in biomedical fields for stimuli-responsive drug delivery systems.

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