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Synthesis and properties of thermo- and pH-sensitive poly(N-isopropylacrylamide)/polyaspartic acid IPN hydrogels

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ABSTRACT

Various interpenetrating polymer network (IPN) hydrogels with sensitivity to temperature and pH were prepared by introducing the pH-sensitive polymer polyaspartic acid (PASP) hydrogel, into the poly(N-isopropylacrylamide) (PNIPAAm) hydrogel system for the purpose of improving its response rate to temperature. The morphologies and thermal behavior of the prepared IPN hydrogels were studied by both scanning electron microscopy (SEM) and differential scanning calorimetry (DSC). The IPN hydrogels showed a large and uneven porous network structure, without showing the common PNIPAAm hydrogel structure. The paper moreover studied their swelling properties, such as temperature dependence of equilibrium swelling ratio, shrinking kinetics, re-swelling kinetics and oscillatory swelling behavior in water. The swelling experiment results revealed that IPN hydrogels exhibited much faster shrinking and re-swelling in function of the composition ratio of the two network components. These fast responsive hydrogels foster potential applications in biomedical and biotechnology fields.

1. Introduction

Hydrogels are three-dimensional hydrophilic polymer networks, which swell but do not dissolve when added to water or biochemical fluid (Mehr, Pourjavadi, Salimi, & Kurdtabar, 2009). Over the past decades, hydrogels, especially environment sensitive hydrogels, have attracted considerable attention: these hydrogels undergo a volume change in response to external stimuli such as pH (Strehin, Nahas, Arora, Nguyen, & Elisseeffv, 2010), temperature (Zhao, Li, Xia, Xi, & Lin, 2008), ionic strength (Rasool, Yasin, Heng, & Akhter, 2010), electric field (Kim, Kim, Park, & Kim, 2004) and magnetic field (Meenach, Hilt, & Anderson, 2010). They are hence extensively applied in biochemical systems. Among these environment sensitive hydrogels, pH and temperature sensitive hydrogels have been most widely investigated because these two factors are important environmental factors in biomedical and other systems (Shim, Kim, Park, Kwon, & Lee, 2006). Thermo-sensitive hydrogels demonstrate a good hydrophilicity in aqueous solutions at low temperatures, and separate from the solution when the temperature is raised above the lower critical solution temperature (LCST). They have been investigated for applications in e.g. controlled drug delivery and solute separation (Guilherme, Silva, Girotto, Rubia, & Muniz, 2003; Lee et al., 2010).

PNIPAAm is a typical thermo-sensitive hydrogel, noted for its relative low LCST of 32–34 °C in aqueous solution. It absorbs water to a swollen state at a temperature below the LCST, and shrinks with a volume decrease when the temperature exceeds the LCST because of the alteration in hydrophilicity and hydrophobicity (Li, Wu, & Liu, 2008). The hydrophilic/hydrophobic balance in PNIPAAm results from the amide group and isopropyl group regions (Han, Wang, Yang, & Nie, 2009). At a temperature below LCST, the hydrophilic moieties (amide group) may interact with water molecules through hydrogen bonds, which lead to enhanced dissolution or swelling of the PNIPAAm hydrogel in water. At a higher temperature, the hydrogen bonding interactions weaken or are destroyed, while hydrophobic interactions among hydrophobic segments (isopropyl group) strengthen, inducing the freeing of the entrapped water molecules from the network and the shrinking of the hydrogel (Zhang et al., 2010).

However, the main limitation of the conventional PNIPAAm hydrogel is the slow rate of response. So far, several strategies have been proposed to improve the response rate of PNIPAAm hydrogel, including tailoring the microstructure to prepare macroporous PNIPAAm (Zhang, Cheng, Huang, & Zhuo, 2003). Introducing mobile grafted hydrophilic chains into the conventional PNIPAAm networks (Wang et al., 2008); and reducing the size of the hydrogel (Ichikawa & Fukumori, 2000). Introducing another polymer into the PNIPAAm hydrogel to form IPN is promising to obtain rapid-response hydrogels. In comparison with other methods, there are some obvious advantages of the IPN technology: the preparation process is simple and feasible (Zhang, Wu, & Chu, 2004), and the

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properties of IPN hydrogels are more versatile (combination of temperature-sensitivity with other properties) (Chen et al., 2007). An IPN is a material comprising two or more networks which are fully or partially interlaced on a molecular scale but not covalently bonded to each other (Lipatov, 2002).

For many biomedical applications, it would be preferable if hydrogels could respond to two types of stimuli. It has been reported that a series of semi-IPN hydrogels were synthesized with PNIPAAm and chitosan. These hydrogels exhibited sensitivity to temperature and pH variations, but no obvious improvement in the response rate on temperature was showed (Lee & Chen, 2001). A hydrophilic polymer, PASP hydrogel, was introduced in this paper. Polyaspartic acid (PASP) hydrogel is a biocompatible polymer, which is widely used in medicine (Cao, Zhu, Su, Fang, & Tan, 2008; Zheng et al., 2007) and soil amendments (Yang, Cao, Wang, & Tan, 2007). PASP hydrogel is a type of poly-anionic hydrogel, which exhibits a minimal swelling ratio (SR) in acidic conditions such as in the stomach, but a high swelling ratio at neutral pH such as in colon (Yang et al., 2007). It is therefore an ideal pH sensitive material for localized delivery of drugs.

In view of these aspects, a promising process for preparing novel temperature- and pH-sensitive PNIPAAm/PASP hydrogels has been investigated in this work. The aim of this paper was to accelerate the response rate of PNIPAAm hydrogel on the basis of keeping its thermo-sensitivity. In this study, the influence of the feed ratio on the properties of the IPN hydrogels was investigated. The glass transition temperature (T_g) and interior morphology of the hydrogels were investigated by DSC and SEM. The temperature dependent de-swelling and swelling kinetics of these IPN hydrogels were investigated in detail to determine their thermal response capability. The pH-sensitivity was also studied.

2. Experimental

2.1. Materials

Polysuccinimide (PSI) was prepared by Luoyang Kang'en Chemical Co. Ltd. N-isopropylacrylamide (NIPAAm) and N,N,N′,N′-tetramethyl-ethylenediamine (TEMED) were purchased from J&K Scientific Ltd. N,N′-methylene bisacrylamide (MBA), ammonium persulfate (APS), N,N-dimethylformamide (DMF), 1,6-hexanediamine, ethanol, sodium hydroxide and hydrochloric acid were all purchased of analytical purity from Beijing Chemical Reagent Co. Ltd. (China). Water used in this experiment was de-ionized water and not specifically indicated as such in the succeeding discussion.

2.2. Preparation of PASP hydrogels

PSI powder was completely dissolved in DMF (at a ratio of 28 ml/g). Then, the dispersant water (10 ml water/1 g PSI) and the crosslinker, 1,6-hexamethylene diamine (8% based on PSI) were added. The reaction was performed for 2 h with magnetic stirring at 40 °C. After being precipitated by ethanol, the product was hydrolyzed at 0° C by sodium hydroxide. PASP hydrogel was obtained at pH value of 7. The PASP hydrogel was immersed in distilled water at room temperature for at least 3 days in order to extract unreacted chemicals. The water was refreshed every several hours during this treatment. Finally the PASP hydrogel was dried under a freeze drying condition at −57 °C in a freeze dryer (ALPHA 1-4, Germany Christ's) (Zhao, Su, Fang, & Tan, 2005).

2.3. Preparation of PNIPAAm/PASP IPN hydrogels

Five solutions were prepared by dissolving respectively 1 g, 0.95 g, 0.9 g, 0.85 g, and 0.8 g NIPAAm in water, marked as PNIPAAm, IPN1, IPN2, IPN3, and IPN4. The cross-linker, MBA (2.0 wt% based on NIPAAm) was dissolved in water separately. Predetermined weights of dried PASP hydrogels (0.05 g in IPN1, 0.1 g in IPN2, 0.15 g in IPN3 and 0.2 g in IPN4) were added into this monomer solution until all the monomer solution was absorbed into the hydrogel network. The accelerator TEMED (1.5 wt% based on NIPAAm) and the redox-initiator, APS (2.0 wt% based on NIPAAm), were thereafter added. The reactions were carried out during 24 h at 20 °C with NIPAAm monomer and cross-linker MBA formed a PNIPAAm network within the original PASP network. The resultant IPN hydrogels were immersed into water at room temperature for 3 days to leach unreacted chemicals and monomer. The water was also refreshed every several hours during this treatment.

2.4. Characterization of PNIPAAm and IPN hydrogels

2.4.1. Interior morphology of hydrogels

Hydrogels that swell to equilibrium at room temperature were freeze-dried at −57 °C to completely remove water. After drying, the hydrogel samples were sputter-coated with gold, and the morphologies of the cross-sections of the hydrogels were then observed by SEM (S-4700, Hitachi Corporations).

2.4.2. Thermal analysis of hydrogels

The glass transition temperature of the hydrogels, T_g, was investigated by DSC (204 F1, NETZSCH). First, the samples were heated from ambient temperature to 200 °C at a heating rate of 25 °C/min to eliminate the thermal history. The samples were then immediately cooled to 20 °C at a cooling rate of 10 °C/min. The samples were finally reheated from 10 °C to 250 °C at a heating rate of 20 °C/min. The T_g was measured from the track of this second run according to a literature standard (Zhang et al., 2004).

2.5. Study of the swelling behavior of hydrogels

The classical gravimetric method was used to measure the swelling behavior of hydrogels. Weights of swollen hydrogels were obtained after having removed the excess water on the surfaces with filter paper. The average value of three measurements was taken for each sample.

2.5.1. Swelling kinetics of the hydrogel

To record the swelling kinetics, the dried hydrogels were immersed in water at 20 °C, and the samples were removed from water at regular time intervals. The swelling ratio (SR) at time t was defined as follows:

$$\mathrm{SR} = \frac{W_t - W_d}{W_d} \quad (1)$$

where W_t is the weight of wet hydrogel at regular time intervals, and W_d is the weight of the dried hydrogel.

2.5.2. De-swelling kinetics

The de-swelling kinetics was measured at 50 °C. The hydrogels were first immersed in water at 20 °C until equilibrium. Equilibrated hydrogels were then rapidly heated from 20 °C to 50 °C. The weights of hydrogels with predetermined de-swelling time intervals were recorded. The water retention (WR) was defined as follows:

$$\mathrm{WR} = \frac{W_t - W_d}{W_s - W_d} \times 100 \quad (2)$$

where W_s is the weight of hydrogel in the swollen equilibrium at 20 °C, whilst W_t and W_d are defined by Eq. (1).

2.5.3. Temperature dependence of the equilibrium swelling ratio of the hydrogels

To study the temperature dependence of the equilibrium swelling ratio, the hydrogel samples were swollen in water at a temperature ranging from 20 °C to 50 °C, which covered the expected range of the LCST of the PNIPAAm hydrogel. The hydrogels were immersed in water at a predetermined temperature for 48 h to reach a swollen equilibrium. After the weight measurement at one temperature, the hydrogels were re-equilibrated at another predetermined temperature for subsequent equilibrium swelling ratio measurement. The equilibrium swelling ratio (ESR) was calculated as follows:

$$\mathrm{ESR} = \frac{W_s - W_d}{W_d} \quad (3)$$

where W_s is the weight of the hydrogel sample in the swollen equilibrium and W_d is the weight of the dried hydrogel.

2.5.4. Oscillating swelling/de-swelling kinetics of the hydrogels

The hydrogel samples were first immersed in water at 20 °C till equilibrium, whereafter the oscillatory swelling behavior was observed in water at alternate temperatures of 20 °C and 50 °C. After 30 min of de-swelling at 50 °C, the hydrogel samples were re-immersed in water of 20 °C for another 30 min swelling. This 60 min cycle was repeated several times and the change of the weights of the samples was measured. The SR at time t was calculated according to Eq. (1).

2.5.5. The pH-sensitivity of the hydrogels

The desired pH was adjusted by HCl or NaOH solutions, and pH values were measured by a pH-meter (pH-HJ90B, China). The hydrogel samples were immersed for at least 24 h in the solutions of different pH values (1–9) at 20 °C to reach equilibrium. The ESR at each pH value was calculated according to Eq. (3).

3. Results and discussions

3.1. SEM micrographs of hydrogels

The interior morphology of hydrogels is shown in Fig. 1. It was found that the hydrogel morphologies were dependent on the composition ratio of PNIPAAm and PASP. The morphology of the conventional PNIPAAm hydrogel showed a homogeneous porous texture, while the IPN hydrogels showed an uneven structure with lager pores; the pores of the hydrogel became larger and more uneven with the increasing content of PASP. As shown in Fig. 2, the results were attributed to the highly expanded network formed by electrostatic repulsions among the PASP carboxylate anions (–COO^-) (Zhao, Kang, & Tan, 2006). The incorporation of PASP hydrogel influenced the crosslink density and the hydrophilic/hydrophobic balance of PNIPAAm hydrogel, leading to a change of microstructure of PNIPAAm hydrogels. Due to numerous interconnected pores in the hydrogel network, water molecules can easily spread. Incorporating PAPSP into the PNIPAAm hydrogel network hence affects the rate of the swelling and de-swelling.

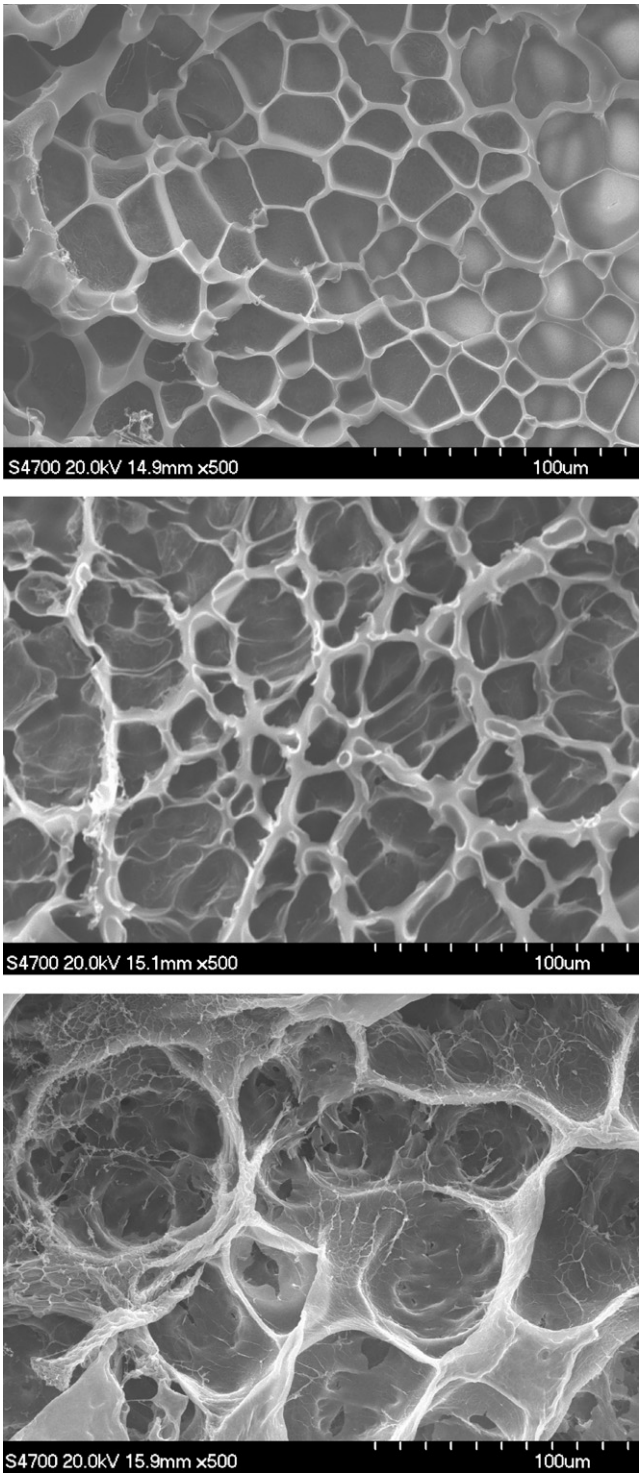

Fig. 1. SEM micrographs of PNIPAAm, IPN2 hydrogel and IPN4 hydrogel.

3.2. DSC thermograms of hydrogels

DSC measurements were used to determine the effect of PASP hydrogel on T_g of PNIPAAm hydrogel and IPN4 hydrogel. The DSC results (Fig. 3) show that the T_g of PNIPAAm and IPN4 are 152 °C and 149 °C, respectively. The T_g of IPN4 showed the typical temperature of an acrylic polymer (Reddy & Takahara, 2009), which demonstrated that the added PASP hydrogel had little effect on the thermal behavior of PNIPAAm. In comparison with PNIPAAm, a small change of T_g was observed for IPN4, and this was due to the intermolecular hydrogen bond in PASP hydrogel.

3.3. Swelling kinetics of the hydrogels

Fig. 4 shows the swelling behavior of PNIPAAm and IPN hydrogels in water at 20 °C. It is clearly seen that IPN hydrogels exhibit a faster swelling rate than the PNIPAAm hydrogel, and as the content of PASP in the IPN hydrogel increased, i.e. from IPN 1 to IPN 4,

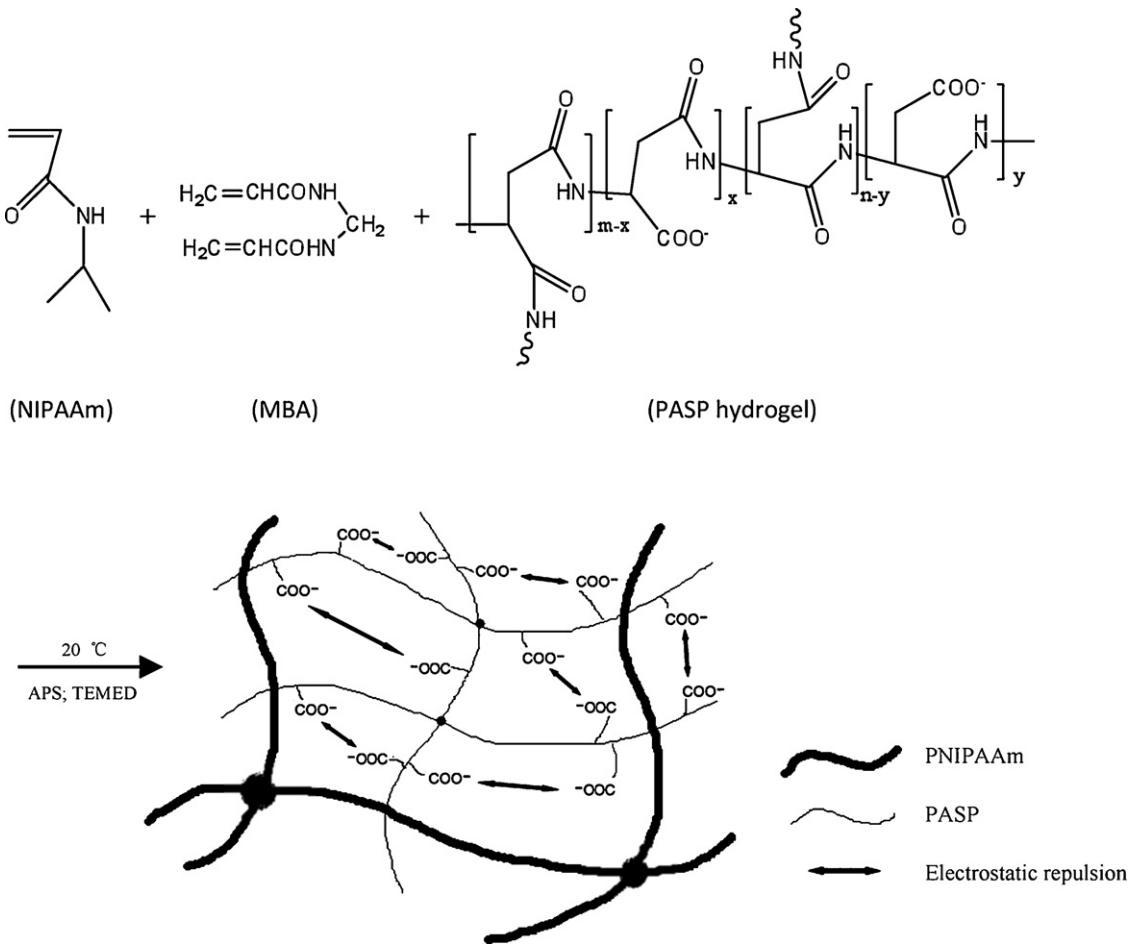

Fig. 2. Synthesis of PNIPAAm/PASP IPN hydrogel and electrostatic repulsion within the polymer.

the swelling rates of the IPN hydrogels were enhanced. The SR of PNIPAAm hydrogel is about 4 g/g within 200 min, while the SR of IPN4 is about 12 g/g within 200 min. This finding is explained by the fact that the presence of PASP hydrogel enhances the hydrophilicity of the networks and facilitates the hydration and expansion of the network. Moreover, PASP acts as water-moving channels and water molecules may easily diffuse into the hydrogel network. In addition, the increased porous structure could also enhance the diffusion of water into the hydrogel network. The swelling rates were hence improved with the increase of PASP content due to excellent hydrophilicity and larger pore structure.

3.4. De-swelling kinetics of the hydrogels

Fig. 5 shows the de-swelling kinetics of the PNIPAAm and IPN hydrogels after transferring equilibrated swollen samples at 20 °C (below their LCST) to hot water of 50 °C (above their LCST). It can be clearly seen that IPN hydrogels display a much faster shrinking

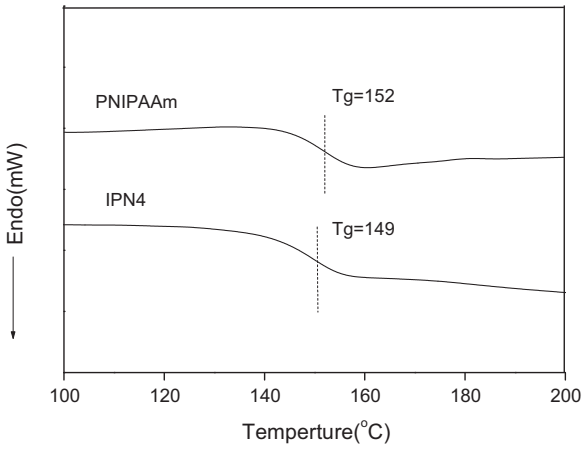

Fig. 3. DSC thermograms of PNIPAAm and IPN4 hydrogel at temperatures between 100 and 200 °C.

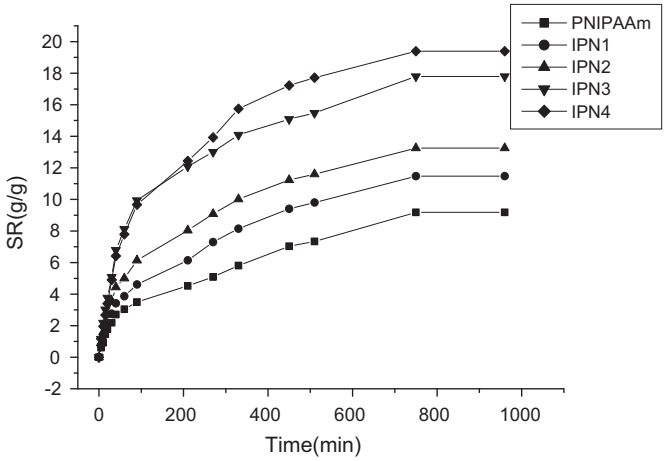

Fig. 4. Swelling kinetics of PNIPAAm and IPN hydrogels in water at 20 °C.

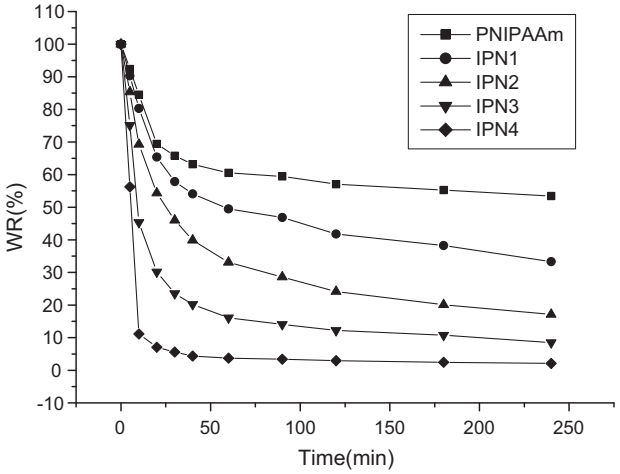

Fig. 5. De-swelling kinetics of PNIPAAm and IPN hydrogels in water at 50 °C.

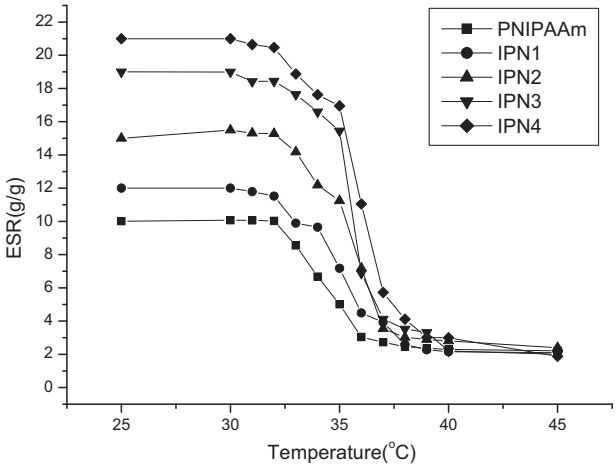

Fig. 6. ESR of the PNIPAAm and IPN hydrogels over the temperature range from 25 to 45 °C.

and loose much more water within the same time as compared to the conventional PNIPAAm hydrogel. After 10 min in 50 °C water, the IPN4 shrinks and looses almost 90% water. In contrast, about 70% water is freed from PNIPAAm within the same time frame.

It is well known that at temperatures above the LCST of PNIPAAm hydrogel, the hydrophilic/hydrophobic balance is destroyed and the hydrogels begin to shrink. For the conventional PNIPAAm hydrogel, the outermost surface would be affected firstly forming a thick and dense layer, which entrapped the inner water, greatly slowing down the flow rate of water and leading to a slow shrinking rate. During this shrinking process, the internal pressure of the hydrogel starts to build up, leading to the appearance of water-containing bubbles on the surface. The water in the hydrogel must permeate through the bubbles to reduce pressure before the hydrogel can reach a stable shrunk state. However, the introduction of the hydrophilic component can inhibit the formation of the dense skin layer, and the hydrophilic component can act as releasing channels for water molecules (Chen et al., 2010; Cheng, Zhang, & Zhuo, 2003). In this study, PASP hydrogel was interpenetrated into the PNIPAAm networks to form IPN, acting as water-releasing channels and disrupting the dense layer on the surfaces of the IPN. As a result, the water molecules were easily removed from the gel matrix, and the shrinking rates were enhanced. These results could also be observed in the experiments since no small water bubbles appeared on the surfaces of IPN2–IPN4 hydrogels during the de-swelling process.

In addition, the higher the concentration of PASP in the hydrogel network, the more water-releasing channels were formed, so the water molecules can be squeezed out easily, and the existence of the large and interconnected pore structures would lead to a faster response rate. During the de-swelling process, pores enhance the rapid heat transfer from the hot water to the inner hydrogel, which results in a rapid phase separation throughout the network (Zhang et al., 2003). A highly uneven porous network like IPN4 may furthermore discourage the formation of a continuous dense skin layer during the initial de-swelling process, resulting in enhanced water diffusion. As observed by SEM, the pore size of the hydrogel networks increased with the increase of PASP content, which is translated in a higher de-swelling rate with the increase of the PASP content in IPN.

The de-swelling kinetic data demonstrate that the response rate of IPN hydrogels can be controlled via the composition ratio of the two network structures. This fast response property could be used to design fast drug delivery systems for some biomacromolecules, such as proteins or enzymes.

3.5. Temperature dependence of the hydrogels

The ESR of the PNIPAAm and IPN hydrogels as a function of temperature over the range from 25 °C to 45 °C is shown in Fig. 6. The ESR of all samples was higher at low temperature (<32 °C) due to the fact that PNIPAAm hydrogel was hydrophilic and swellable at temperatures below the LCST. Moreover, at the same temperature below the LCST, the ESR of the hydrogels increased with the increase of the PASP content in the corresponding hydrogel, and IPN4 had the largest ESR in the respective classes. Compared to IPN hydrogels, the ESR of the conventional PNIPAAm hydrogel was the lowest. This phenomenon can be explained as follows: it is well known that PASP hydrogel is a highly hydrophilic polymer (Zhao et al., 2005). When incorporated into IPN, PASP hydrogel presents an expanded configuration. The SEM data (Fig. 1) also support this point of view. Besides, due to the larger pore size of the IPN hydrogel observed in SEM figure, the IPN hydrogels exhibited a greater water uptake. There exists a hydrophilic/hydrophobic balance in the PNIPAAm hydrogel network. At a temperature below its LCST, the hydrophilic groups of the PNIPAAm hydrogel are bonded to water molecules through hydrogen bonds, and these hydrogen bonds behave cooperatively to form a stable shell around the hydrophobic groups (Han et al., 2009), according to a water uptake by the PNIPAAm hydrogel. The hydrophilic property of the polymer network has a significant impact on the swelling behavior (Chen et al., 2010). As a result, the hydrophilicity of the IPN hydrogels would increase relatively, and the swelling ratios would improve, when PASP hydrogel was incorporated into the IPN network.

At a temperature between 32 °C and 40 °C, the swelling ratios of all the hydrogels decreased with increasing temperatures, indicating all hydrogels were thermo-sensitive. The thermo-sensitivity of the PNIPAAm hydrogel was attributed to the hydrophilic/hydrophobic of the network. When the temperature increased, the water molecules would gain enthalpy (Kim, Park, & Kim, 2003), and the hydrophilic group in the PNIPAAm would be turned into an intramolecular hydrogen bond under this condition. At the same time, the hydrophobic force of the isopropyl group of PNIPAAm increased. As a result, the water molecules entrapped in the network were released. This phenomenon made the swelling ratios of the hydrogels decrease significantly at the gel transition temperature.

LCST was generally defined as the temperature at which the swelling ratio decreased to the largest extent of its value at the corresponding temperature (Zhang, Bhat, & Jandt, 2009). According to this definition, LCSTs of IPN, obtained from the data,

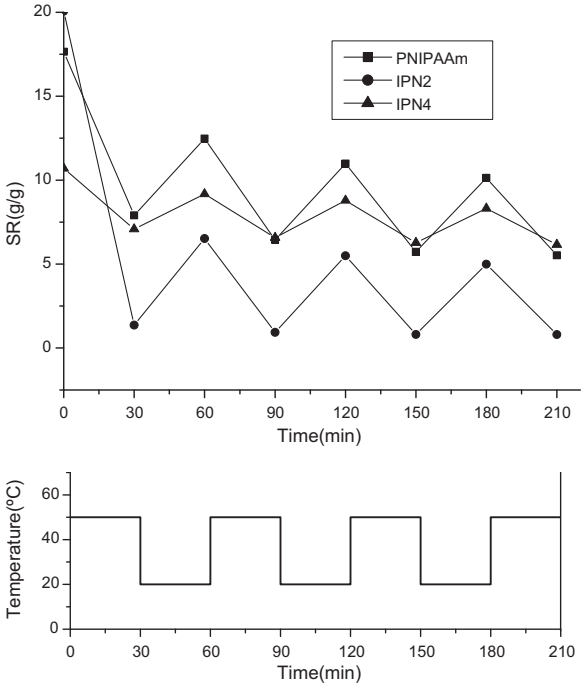

Fig. 7. Oscillatory swelling/de-swelling kinetics of hydrogels between 20 and 50 °C.

increased with the increasing PASP content. The intermolecular hydrogen bond between hydrophilic groups of PASP, PNIPAAm and water molecules obstructs the hydrophobic interactions which make the PNIPAAm shrink. The higher the PASP content, the stronger the interactions and inhibitions were, leading to the higher LCST.

The data also showed that the IPN composition had no effect on the swelling ratio of hydrogels at temperatures above their LCST (>40 °C), suggesting that all IPN hydrogels would collapse into similar network structures at a temperature above their LCST (Zhang et al., 2004).

In general, the temperature dependence of the ESR experiments suggests that due to the high hydrophilicity of the PASP hydrogel, the capability of the thermo-sensitivity of IPN hydrogels was enhanced when the content of PASP in the hydrogels increased. The controllable change of the ESR was very useful for meeting the various future applications.

3.6. Oscillatory swelling/de-swelling kinetics of the hydrogels

Fig. 7 shows the reversible process of the temperature response between 20 °C and 50 °C. After the hydrogel reached its ESR at 20, it began to shrink readily when immersed into a 50 °C environment. From Fig. 7, it can be observed that with the increasing of PASP content, the magnitude of the oscillating swelling/de-swelling of IPN hydrogel is increased, and the most rapid and largest magnitude of the oscillating swelling/de-swelling is IPN4 hydrogel. With the presence of the PASP hydrogel, the hydrophilicity of the IPN hydrogel was enhanced and the pores of IPN hydrogel were enlarged. The greater the difference of SR between de-swelling and swelling, the better the thermo-sensitivity was. The above results also show that during the swelling/de-swelling process, the SR of hydrogels decreased slightly with increasing number of cycles due to their relatively slow swelling rate comparing with their shrinking rate. IPN hydrogels are very stable (Li et al., 2009). Thus, the oscillating swelling/de-swelling kinetics demonstrated that IPN hydrogels can be expected as reversible thermo-responsive materials in many fields of biomedical bioengineering and biotechnology.

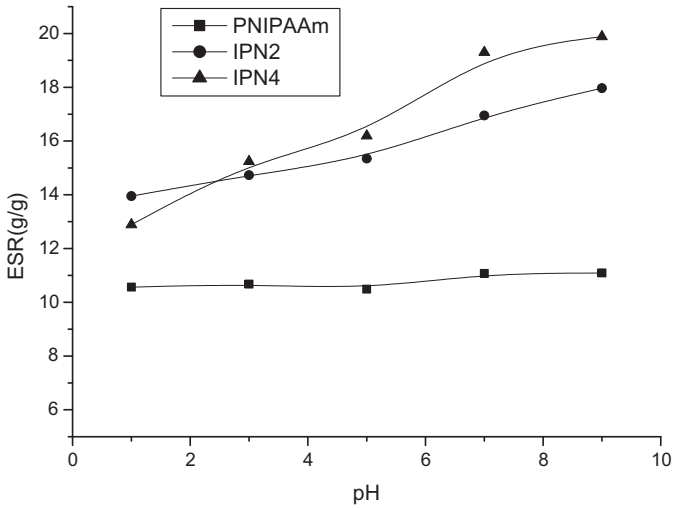

Fig. 8. pH dependence of the ESR of the hydrogels.

3.7. pH dependence of the hydrogels

To investigate the influence of pH value on the swelling ratios, the hydrogels were immersed into a buffer solution with pH range from 1 to 9. As shown in Fig. 8, the ESR of IPN hydrogels increases gradually as the pH value increases. However, the ESR of PNIPAAm hydrogel do not exhibit obvious differences with the variation of pH value. This phenomenon can be attributed to the ionization behavior of –COOH groups existing in PASP hydrogel. At very lower pH (pH < 3), anionic carboxylate groups were protonated, so the network of PASP hydrogel collapsed and the hydrogels shrank. It is known that the pK_a of the amino acid monomer is about 2.09–3.86 (Liu, Chen, & Chen, 2010) and its ionization occurs above this value. So at around pH 3, the water absorption of PASP hydrogel may increase. With a further increase in pH value, ionization of carboxylic acid groups occurs and the electrostatic repulsive force between the –COO– groups leads to high swelling (Zhao et al., 2005). With the increasing content of PASP hydrogel in IPN hydrogels, there are more –COO– groups. The results clearly indicate that the prepared hydrogels exhibit pH-sensitive characteristics, which will increase their uses for the controlled drug delivery system, with specific-colonic drug release behaviors.

4. Conclusions

A series of thermo- and pH-sensitive IPN hydrogels, composed of PNIPAAm and PASP hydrogel, were synthesized via redox radical polymerization in the presence of crosslinkers. Through introducing PASP hydrogel, the porous structure of IPN hydrogels was widened and the hydrophilicity was increased. Compared with pure PNIPAAm hydrogel, IPN hydrogels exhibited enhanced thermal sensitivity and faster de-swelling and swelling rates, in function of the content of PASP hydrogel. Due to the existence of –COOH groups in the PASP hydrogel, the IPN hydrogels also possessed a pH-sensitivity. The integration of PASP components with IPN technology improves the thermo- and pH-sensitive behavior of the PNIPAAm hydrogel, and these novel IPN hydrogels are expected to find widespread application in biomedical and biotechnology fields.

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