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Preparation and properties of fast temperature-responsive soy protein/PNIPAAm IPN hydrogels

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Abstract: The interpenetrating polymer network of fast temperature-responsive hydrogels based on soy protein and poly(*N*-isopropylacrylamide) were successfully prepared using sodium bicarbonate ($NaHCO_3$) solutions as the reaction medium. The structure and properties of the hydrogels were characterized by Fourier transform infrared spectroscopy, scanning electron microscopy, differential scanning calorimetry and thermal gravimetric analysis. The swelling and deswelling kinetics were also investigated in detail. The results showed that the proposed hydrogels had a highly porous structure, good miscibility and thermal stability, and a fast temperature response. The presence of $NaHCO_3$ had little effect on the volume phase transition temperature (VPTT) of the hydrogels, and the VPTTs were at about 32 °C. Compared with the traditional hydrogels, the proposed hydrogels had much faster swelling and deswelling rates. The swelling mechanism of the hydrogels was non-Fickian diffusion. These fast temperature-responsive hydrogels may have potential applications in the field of biomedical materials.

Keywords: soy protein; poly(*N*-isopropylacrylamide); hydrogels; fast response.

INTRODUCTION

Stimuli-responsive hydrogels have attracted more and more attention in biomedical and pharmaceutical fields.[1] Increasing interest in a new class of materials based on blends of natural and synthetic polymers has been observed during the last three decades,[2–4] as the blends have the advantages of both natural and synthetic polymers. In recent years, natural polymers due to their renewability, biodegradability and biocompatibility have attracted great interest in blending with stimuli-responsive polymers for biomedical applications.[2,5] An effective

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method to prepare these blends is the interpenetrating polymer network (IPN) technology.[6,7] Recently, poly(*N*-isopropylacrylamide) (PNIPAAm), a typical temperature-responsive polymer with a volume phase transition temperature (VPTT) around 32 °C, has been utilized to blend with some natural polymers using IPN technology to develop new temperature-responsive hydrogels for biomedical utilization.[8–11]

It is noteworthy that natural proteins have also been the subject of significant interest in the design of biomedical materials in recent years. Some animal proteins, such as collagen, gelatin, casein, albumin and whey protein, have been investigated for drug, nutrient, and bioactive peptide delivery.[12] Soy protein, a very important plant protein, was used to blend with other polymers for drug delivery[13,14] and wound dressing materials.[15] However, plant proteins, particularly soy protein, as new devices for drug delivery have not been fully investigated.

It is well known that the response rate of stimuli-responsive hydrogels is one of the most important parameters for evaluating their performance. Hydrogels with a slow response rate may be limited in their applications. Therefore, various strategies have been proposed to improve the response rate. These strategies include the introduction of comb-type grafted chains,[16,17] the fabrication of microgels[18] or nanogels,[19,20] and the formation of macroporous structures in hydrogel matrices using pore-forming agents,[21,22] foaming agents[23,24] and phase separation technologies.[25,26]

In a previous work, the preparation and properties of soy protein/PNIPAAm IPN hydrogels were discussed.[27] In this work, a new strategy was developed to obtain fast responsive soy protein/PNIPAAm IPN hydrogels using phase separation and foaming agent technologies. The structure and properties of the proposed hydrogels were studied by Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA), and their swelling and deswelling kinetics were also investigated in detail.

EXPERIMENTAL

Materials

Soy protein isolate (SPI, protein content > 95 %) was kindly provided by Dupont Yunmeng Protein Ltd., China. *N*-Isopropylacrylamide (NIPAAm) was purchased from Tokyo Chemical Industry Co. Ltd., Japan. Ammonium persulfate (APS) was obtained from Yongda Chemical Reagent Ltd., China. *N*,*N*′-Methylenebisacrylamide (BIS, a crosslinking agent for NIPAAm), glutaraldehyde (GA, a crosslinking agent for SPI) and sodium bicarbonate ($NaHCO_3$) were supplied by Kermel Chemical Reagent Ltd., China. Tetramethylethylenediamine (TEMED) was purchased from Qianjin Chemical Reagent Ltd., China. All reagents were of analytical grade.

Preparation of hydrogels

A certain amount of $NaHCO_3$ was added into a mixture composed of NIPAAm (2.0 g), SPI (0.4 g) and deionized water (15 mL) and dissolved completely. The mixture was bubbled with nitrogen and then GA (0.2 mL), BIS (0.04 g), APS (0.02 g) and TEMED (20 μL) were added in order. Finally, this mixture was injected immediately into poly(vinyl chloride) tubes (6 mm diameter) to polymerize at 15 °C in a low temperature reactor for 24 h. The hydrogels obtained were cut into pieces of 3 mm in length and put into 0.1 mol L^{-1} HCl solutions until bubble formation ceased. Then, the hydrogels were taken out from HCl solutions and immersed in deionized water for three days. The deionized water was refreshed every 4 h during this period. The swollen hydrogels were dried at room temperature and further dried at 40 °C in a vacuum oven for three days. The sample code, PNS0, PNS1, PNS2 and PNS3 means that the amount of $NaHCO_3$ in the above mixture was 0.0, 0.2, 0.3 and 0.4 g, respectively.

FTIR spectroscopy

The FTIR spectra (Equinox 55, Bruker, Germany) of the vacuum-dried samples were recorded. Each sample was ground with KBr (ratio of sample to KBr 1:100) and compressed into a pellet. The spectra were recorded in the transmission mode as an average of six scans at a resolution of 0.2 cm^{-1}.

Morphology investigation

The hydrogels swollen to equilibrium in deionized water at 25 °C were first frozen at –40 °C for 10 h, and then freeze-dried for 24 h using a SHKY LGJ-18 freeze-dryer (China). Cross-sections of the freeze-dried gels were sputter-coated with gold and the morphologies of the coated gels were examined using an SEM (Quanta 400F, FEI, The Netherlands) operated at an acceleration voltage of 20 kV.

Differential scanning calorimetry investigation

The glass transition temperatures (T_g) of the dried samples were determined by differential scanning calorimetry (DSC 204, Netzsch, Germany). All samples were first heated from room temperature to 120 °C at a rate of 20 °C min^{-1} under a nitrogen atmosphere and then cooled to room temperature. The samples were then reheated to 180 °C at 10 °C min^{-1}. The T_g of the samples was determined from the second cycle. The midpoint of the inflection was taken as the T_g.

Thermal gravimetric measurement

The thermal stability of the hydrogels was examined using a thermal gravimetric analyzer (TG 209, Netzsch, Germany). All vacuum-dried samples were heated from room temperature to 700 °C under a nitrogen atmosphere at a heating rate of 10 °C min^{-1}.

Swelling kinetics measurements

Pre-weighed dried hydrogels were immersed in deionized water to swell. At regular time intervals, the swelling hydrogels were taken out to weigh after removal of the surface water through blotting with filter paper and then put back into the same vials. The swelling ratio (*SR*) was calculated using the following equation:

$$SR = \frac{M_t - M_d}{M_d} \times 100 \quad (0)$$

where M_d is the weight of a dried hydrogel and M_t is the weight of the swollen hydrogel at time *t*.

Measurement of the deswelling kinetics

The swollen hydrogels at equilibrium in deionized water at 25 °C were weighed and then immersed in deionized water at 37 °C to deswell. At regular time intervals, the hydrogels were taken out to weigh and then put back into the same vials. The water retention (*WR*) was defined as the deswelling ratio and was calculated using the following equation:

$$WR = \frac{M_t - M_d}{M_e - M_d} \times 100 \quad (2)$$

where M_d is the weight of a dried hydrogel, M_t is the weight of the swollen hydrogels at the time *t* and M_e is the weight of the swollen hydrogels at the equilibrium state at 25 °C.

RESULTS AND DISCUSSION

Preparation of hydrogels

According to the preparation strategy, fast temperature-responsive soy protein/PNIPAAm IPN hydrogels were obtained through the following two steps. First, the polymerization was performed in $NaHCO_3$ solutions. During the reaction, the presence of $NaHCO_3$ led to phase separation and consequently made the polymer chains curled, intertwisted together and finally agglomerated due to the salt effect,[28] which resulted in the formation of a heterogeneous porous structure.[29] Second, after the polymerization, the $NaHCO_3$ in the hydrogel network was used as a foaming agent. When the hydrogels were removed, cut into pieces and put into HCl solution, carbon dioxide gas was generated due to the reaction between $NaHCO_3$ and HCl, which was released from the hydrogel matrix, resulting in the formation of a highly porous structure. As a result, the proposed hydrogels (PNS1, PNS2 and PNS3) with fast response rates were accordingly achieved.

Structure and morphology analysis

The FTIR spectra of PNS0 (prepared in the absence of $NaHCO_3$) and PNS2 are shown in Fig. 1, and the data of the characteristic absorption bands are listed in Table I. The main characteristic absorption band of PNSO were found at 3434 and 3302 cm^{-1}, due to the stretching vibration of O–H and N–H groups, respectively, and at 1649 and 1543 cm^{-1}, attributed to amide I (C=O group) and amide II (N–H group), respectively. The spectrum of PNS2 was very similar with the respective bands appearing at 3436, 3305, 1652 and 1543 cm^{-1}. This similarity indicates that the $NaHCO_3$ had been completely removed from the PNS2 hydrogel matrix. The presence of soy protein in the hydrogels was hard to evidence because the characteristic absorption bands of soy protein and PNIPAAm are similar.

The morphological images of the cross-sections of the freeze-dried hydrogels are shown in Fig. 2. It was found that the structures of the porous network of

the hydrogels are influenced by the presence of $NaHCO_3$ in the reaction medium. The conventional soy protein/PNIPAAm IPN hydrogel (PNS0) prepared in water had a lower porosity than that of the proposed hydrogels. These porous structures were created during the freeze-drying step, when the ice crystals sublimate and pores are left behind in the hydrogel matrices.[30] Compared with PNS0, the porosity of the proposed hydrogels increased with increasing content of $NaHCO_3$ in the polymerization medium. These results indicate that the presence of $NaHCO_3$ had an effect on the structures of the hydrogel network.

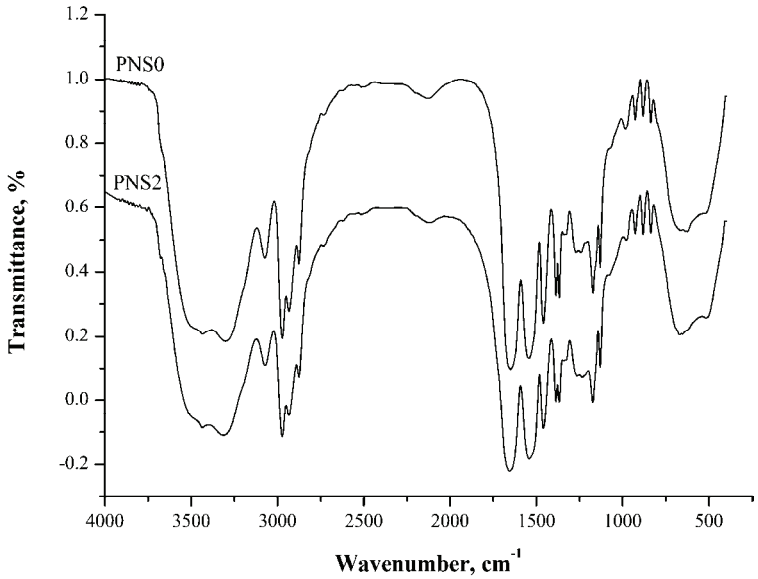

Fig. 1. FTIR spectra of PNS0 and PNS2.

TABLE I. Characteristic absorption bands of the samples

Sample	OH and NH bands, cm^{-1}		Amide I band, cm^{-1}	Amide II band, cm^{-1}
	ν_{O-H}	ν_{N-H}	$\nu_{C=O}$	$\delta_{N-H} + \nu_{C-N}$
PNS0	3434	3302	1649	1543
PNS2	3436	3305	1652	1543

DSC analysis

The glass transition temperature, T_g, is one of the characteristic temperatures for polymer blends. A single T_g means that the blends are miscible. The DSC thermograms of the hydrogels are shown in Fig. 3. All the samples had only a single T_g, which indicates that the samples had good miscibility. The T_g of PNS0, PNS1, PNS2 and PNS3 depicted in Fig. 3 were almost the same, which demonstrates that content of $NaHCO_3$ had almost no effect on the T_g of the proposed hydrogels.

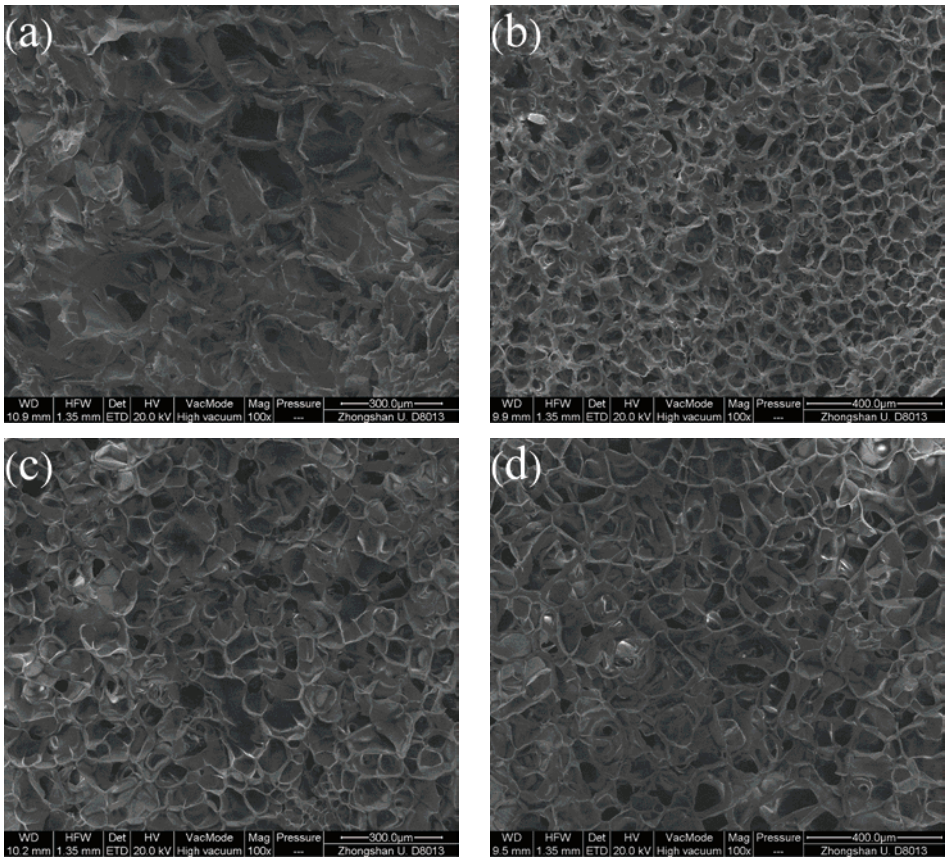

Fig. 2. SEM micrographs of: a) PNS0, b) PNS1, c) PNS2 and d) PNS3.

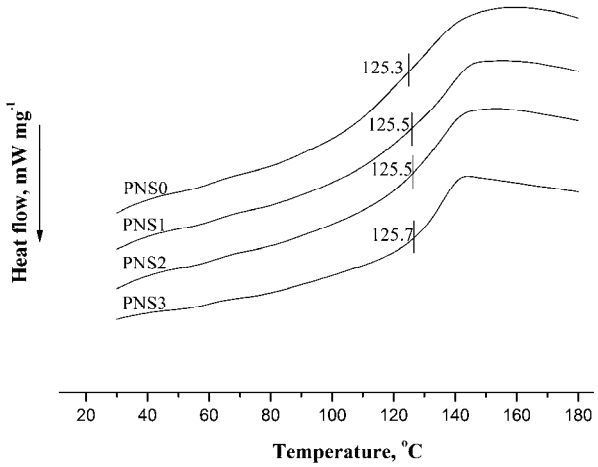

Fig. 3. DSC thermograms of dried hydrogels.

Thermogravimetric analysis

Thermal gravimetric analysis (TGA) is a useful technique to study the thermal stability of composite polymeric materials. The rate of weight loss of the samples as a function of temperature is depicted in Fig. 4. It could be observed that all samples underwent two decomposition stages. The first stage of weight loss for the samples was observed at *ca.* 210 °C (4.65 % weight loss) due to the decomposition of small molecules. In the second stage, the maximum weight loss of the samples was observed. The maximum decomposition temperature of PNS0, PNS1, PNS2 and PNS3 were 419.5 (95.63 % weight loss), 409.4 (88.93 % weight loss), 410.1 (91.01 % weight loss) and 411.6 °C (91.06 % weight loss), respectively. These results show that the hydrogels had good thermal stability for biomaterial applications.

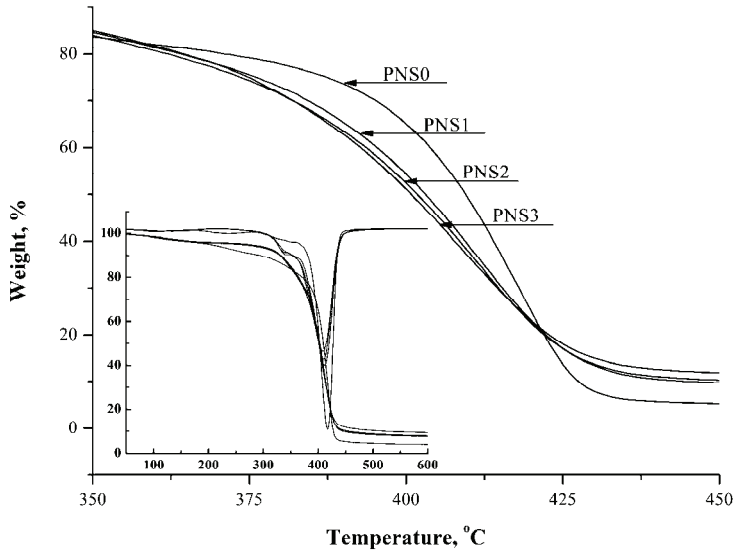

Fig. 4. TGA thermograms of dried hydrogels.

Temperature responsivity

The temperature response of the samples was evaluated by measuring their equilibrium swelling ratios, and the results are shown in Fig. 5. It could be seen that the samples had similar equilibrium swelling ratios and almost the same VPTT (around 32 °C). The equilibrium swelling ratios decreased with increasing temperature. Hydrophobic groups ($–CH(CH_3)_2$) and hydrophilic groups (–CONHR) existed in the hydrogels, which correspond to the hydrophobic and hydrophilic regions, respectively. When the temperature was below the VPTT, hydrogen-bonding interactions between the hydrophilic groups and water molecules were dominant, resulting in high equilibrium swelling ratios, while when

the temperature was above the VPTT, the hydrophobic interactions in the hydrogels become dominant and weakened the hydrophilic interactions, eventually leading to hydrogel shrinkage and the equilibrium swelling ratio decrease markedly. It is noteworthy that the presence of $NaHCO_3$ in the polymerization medium had little effect on the VPTT of the hydrogels.

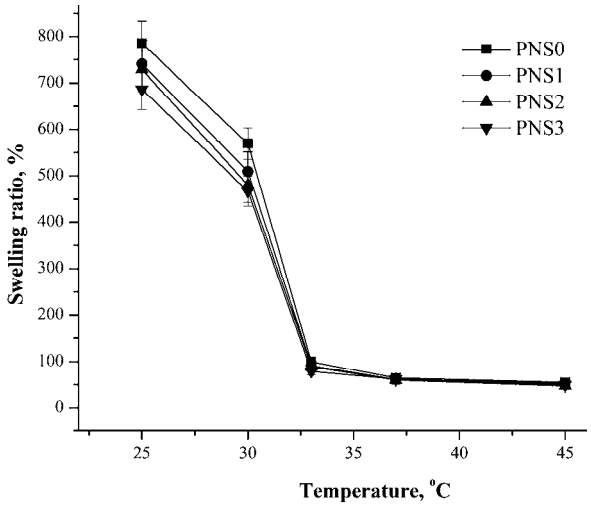

Fig. 5. Equilibrium swelling ratios as a function of temperature.

Swelling kinetics

Pre-weighed dried hydrogels were immersed in deionized water at 25 °C to swell, and the swelling ratios were measured to evaluate their swelling properties. The results are shown in Fig. 6. In the initial swelling stage, the hydrogels had a similar swelling profile. However, as the swelling continued, the swelling rates of PNS1, PNS2 and PNS3 were faster than that of the conventional hydrogel (PNS0). Moreover, the swelling rate increased with increasing amount of $NaHCO_3$. PNS3 hydrogel reached equilibrium swelling first. Initially, the much smaller distance between the polymer chains in the dry hydrogels produced strong interaction forces that prevented the water molecules from diffusing into the hydrogel matrices, which resulted in low swelling rates and similar swelling profiles. As the swelling continued, the polymer chains become stretchable and the porous structures become the dominant factors, which enabled the water molecules to permeate easily into matrices of the hydrogels and resulted in a fast swelling rate. As a result, the higher the content of $NaHCO_3$ in the polymerization mixture, the higher was the achieved swelling rate. It was also found that PNS0 had a higher swelling ratio in the late stages of swelling than those of the proposed hydrogels. As mentioned above, the proposed hydrogels obtained in $NaHCO_3$ solutions had more physical entanglements among the polymer chains

due to the salt effect and consequently had a relatively low swelling ratio in the late stages of swelling.

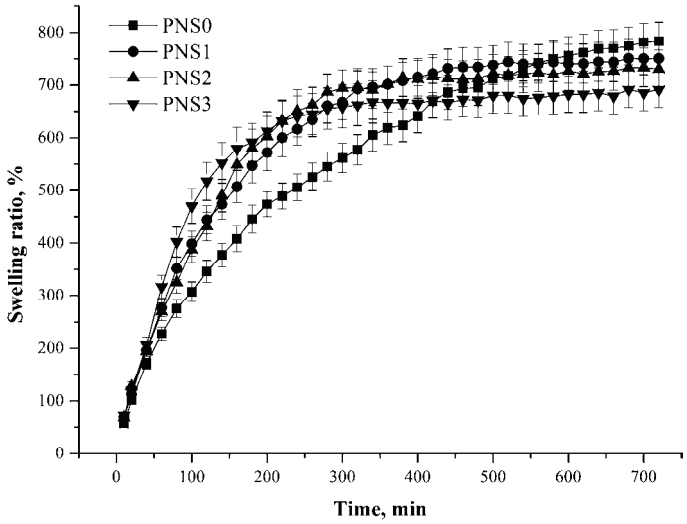

Fig. 6. Swelling kinetics of hydrogels in deionized water at 25 °C.

In order to investigate the swelling mechanism of the hydrogels, a simple and effective method was employed to analyze the swelling data for $M_t/M_\infty < 0.6$, that is:[31–34]

$$M_t / M_\infty = kt^n \quad (3)$$

where M_t and M_∞ are the amount of water absorbed at time t and at equilibrium, respectively; k is a characteristic constant and n is the characteristic exponent of the mode. The exponent n was obtained from the slope of a plot of ln (M_t/M_∞) *versus* ln t (Fig. 7), and the results are given in Table II. The values of n in Table II indicate that the swelling mechanism of the hydrogels was non-Fickian diffusion and the value of n increased with increasing amount of $NaHCO_3$ in the polymerization mixture. Thus, the content of $NaHCO_3$ influenced the swelling kinetics of the hydrogels.

Deswelling kinetics

The hydrogels swollen to equilibrium in deionized water at 25 °C were immersed in deionized water at 37 °C to deswell. The water retention was measured to evaluate their deswelling properties, and the results are shown in Fig. 8. It could be seen that the deswelling rates of the proposed hydrogels were much faster than that of the conventional hydrogel (PNS0). The water retention of PNS1, PNS2 and PNS3 after 30 min were 37.56, 27.70 and 25.72 %, respectively, whereas it was 47.35 % after 300 min for PNS0. When a to equilibrium

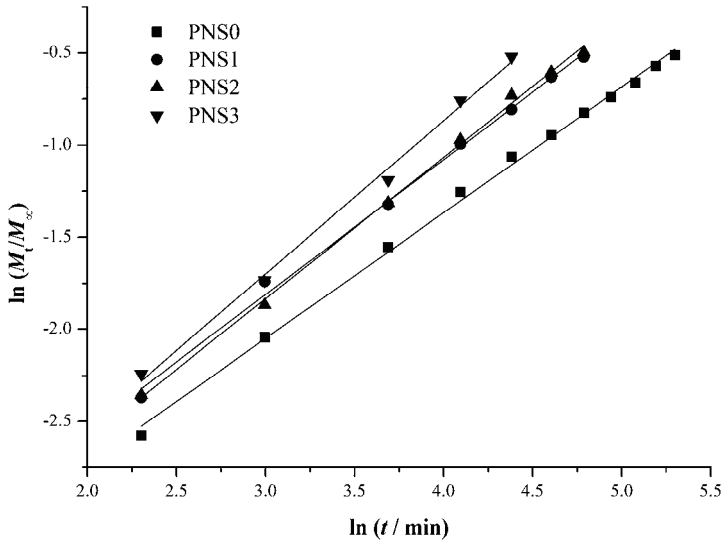

Fig. 7. Fitting of swelling kinetics for hydrogels in deionized water at 25 °C.

TABLE II. Diffusional exponents and deswelling constants for swelling and deswelling kinetics

Sample	Equation (3)		Equation (4)	
	n	R^2	k / min^{-1}	R^2
PNS0	0.68	0.99749	0.00274	0.97955
PNS1	0.73	0.99599	0.03164	0.98486
PNS2	0.76	0.99799	0.04196	0.96967
PNS3	0.83	0.99446	0.04527	0.97621

swollen hydrogel is transferred into higher temperature deionized water, the temperature rises first on the hydrogel surface; hence, if the initial temperature was below and the final temperature above the VPTT, the surface PNIPAAm molecules shrink first in the surface, which results in the formation of a dense skin layer on the hydrogel surface. This skin layer can hinder the outward permeation of water molecules from the hydrogel interior.[35] As the shrink continues, the water molecules inside the hydrogels continue to be extruded. As a result, PNS0 deswells slowly and some bubbles on its surface were observed during the deswelling. In an earlier study,[27] hydrogels containing soy protein were shown to have a higher deswelling rate than that of a PNIPAAm hydrogel, which indicates that soy protein on the hydrogel surface could reduce the density of the skin layer, resulting in relatively high deswelling rates. In the present case, the proposed hydrogels have highly porous structures on the surface and in the interior of the hydrogels. The porous effect is greater than the soy protein effect on the skin layer, and consequently the dense skin layer has little effect on PNS1, PNS2 and PNS3. Therefore, PNS1, PNS2 and PNS3 had faster deswelling rates.

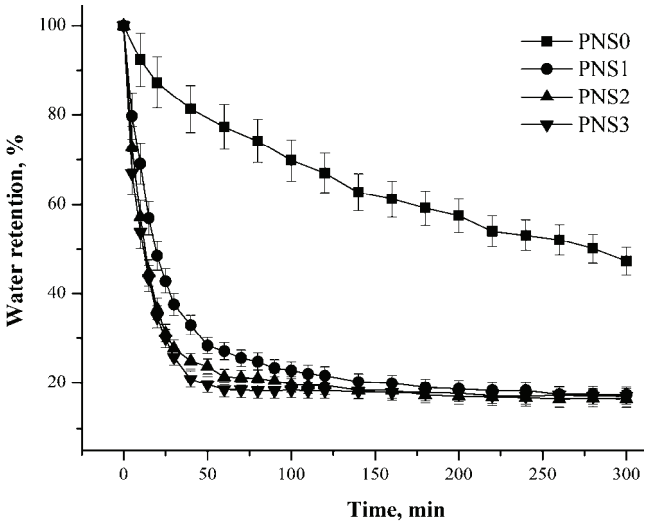

Fig. 8. Deswelling kinetics of hydrogels in deionized water at 37 °C.

To investigate the deswelling kinetics quantitatively, a semi-logarithmic plot of a first-order rate analysis was used to fit the time dependence of the deswelling given by Eq. (4):[36]

$$\ln \frac{M_t - M_d}{M_e - M_d} = -kt \tag{4}$$

where k is the deswelling constant and t is time. A larger k means a faster deswelling process. The value of k obtained from the slope of the plot of ln $((M_t - M_d)/(M_e - M_d))$ *versus* t (Fig. 9) are given in Table II. As shown in Table II, the value of k for PNS3 is 16 times greater than that for PNS0. Moreover, the value

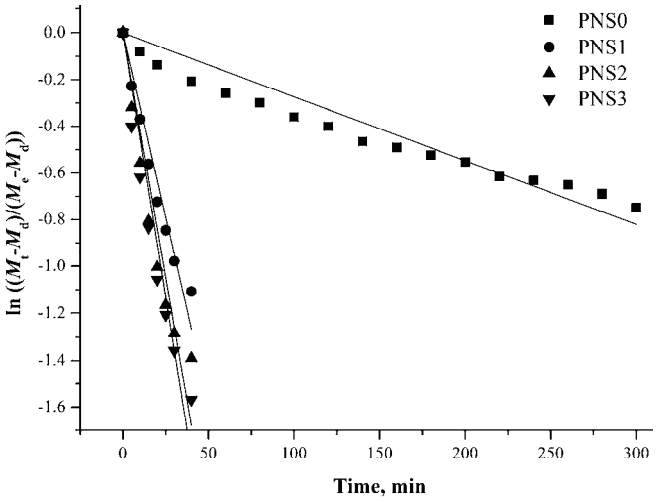

Fig. 9. Deswelling rate analysis of hydrogels in deionized water at 37 °C.

of k increases with increasing mass of $NaHCO_3$ in the polymerization medium (Fig. 10), which further confirms the analyses above.

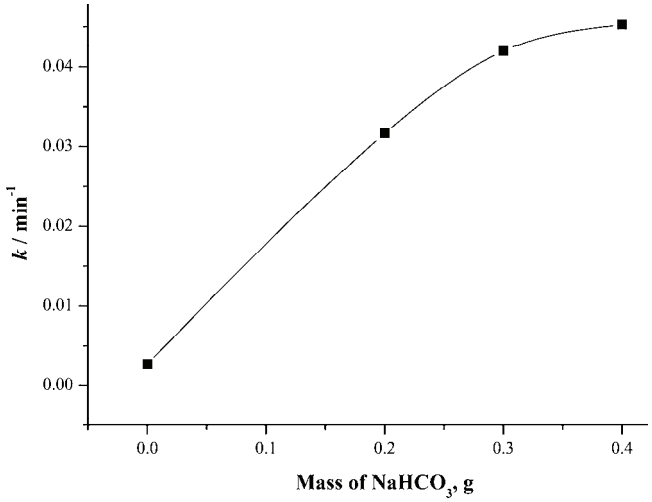

Fig. 10. Dependence of slope k on mass of $NaHCO_3$ in the feed.

CONCLUSIONS

Fast temperature-responsive soy protein/PNIPAAm IPN hydrogels were successfully prepared using the phase separation and foaming agent technologies. All the proposed hydrogels showed good miscibility and thermo-response, and thermal stability. The hydrogels prepared in $NaHCO_3$ solutions had a highly porous structure and showed fast swelling and deswelling rates.

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И З В О Д

ДОБИЈАЊЕ И СВОЈСТВА ТЕМПЕРАТУРНО-ОСЕТЉИВИХ ХИДРОГЕЛОВА НА БАЗИ ПРОТЕИНА СОЈЕ/PNIPAAm IPN СА БРЗИМ ОДГОВОРОМ

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Интерпенетрирајуће полимерне мреже, IPN, температурно осетљивих хидрогелова на бази протеина соје и поли(*N*-изопропилакриламида) успешно су синтетисане у раствору натријум-хидрогенкарбоната ($NaHCO_3$). Структура и својства синтетисаних IPN хидрогелова су окарактерисани инфрацрвеном спектроскопијом, скенирајућом електронском спектроскопијом, диференцијалном скенирајућом калориметријом и термогравиметријском анализом. Кинетика процеса бубрења и дехидратације хидрогелова, праћена преко промене степена бубрења, детаљно је приказана. У раду је показано да синтетисани хидрогелови поседују порозну структуру, добру мешљивост компоненти

полимерне смеше, термичку стабилност, као и брз температурни одговор. Присуство порогена, $NaHCO_3$, у реакционој смеши незнатно је утицало на температуру запреминског псеудо-фазног прелаза (VPTT) (око 32 °C). У поређењу са конвенционалним хидрогеловима, синтетисани IPN хидрогелови са порознијом структуром показују веће брзине бубрења и дехидратације. Процес бубрења хидрогелова се може описати не-фиковским законом дифузије. Синтетисани хидрогелови са брзим температурним одговором могу наћи потенцијалну примену у области биомедицинских материјала.

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