SEMI-IPN HYDROGELS BASED ON N-ISOPROPYLACRYLAMIDE AND 2-HYDROXYETHYL METHACRYLATE

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ABSTRACT

In this research, two series of smart semi-interpenetrating polymer network (semi-IPN) hydrogels based on N-isopropyl acrylamide (NIPAM) and 2-hydroxyethyl methacrylate (HEMA), including linear p(NIPAM-co-HEMA)/pNIPAM (S1-structure) and linear pNIPAM/p(NIPAM-co-HEMA) (S2-structure) were synthesized and investigated. The morphological, chemical, physical properties and swelling behaviors in water of the linear polymer and semi-IPN hydrogels were investigated. Fourier transform infrared (FTIR) spectra confirmed the polymerization/copolymerization ability of monomer/comonomer. Differential scanning calorimetry (DSC) determined the thermal sensitivity of polymer materials with a value of lower critical solution temperature (LCST) in the range of 31.80 ~ 32.80 °C and 33.40 ~ 35.00 °C, respectively for linear polymers and hydrogels. The value of LCST depended only on the composition of feeding material, not on the structure of the material. Scanning electronic microscopy (SEM) images showed that the pore size was in the range of 140.16 ± 19.71 ~ 275.51 ± 62.07 μm. The swelling ratio and swelling rate of semi-IPN hydrogel increased significantly compared to conventional hydrogel. In addition, S1-structure hydrogels showed a faster swelling rate than S2-structure hydrogel.

Keywords: *Swelling behavior; swelling ratio; swelling rate; semi-IPN hydrogel; N-isopropyl acrylamide; 2-hydroxyethyl methacrylate.*

1. INTRODUCTION

Hydrogel is a type of polymer material with a three-dimensional network capable of absorbing water without dissolving. It can be molded into any form, shape, and size for many potential applications. In recent times, smart hydrogel has been studied extensively due to its phase transitions in response to external stimulus. The typical smart hydrogel is thermal-responsive hydrogel, which has phase transitions in response to temperature changes, and poly(N-isopropyl acrylamide) (pNIPAM) is the most widely investigated [1]. pNIPAM exhibits a lower critical solution temperature (LCST), about 32^{o}C in pure water. At temperatures below its LCST, the cross-linked pNIPAM is hydrophilic and absorbs water to a swollen state. On the contrary, it is hydrophobic and water is removed from the network to a shrunken state [2]. However, conventional pNIPAM hydrogels have some disadvantages, such as low swelling ratio, and slow response rate [3]. To overcome these disadvantages, semi-interpenetrating (semi-IPN) hydrogels are usually synthesized by introducing a linear polymer into the pNIPAM network. Semi-IPN hydrogels are usually synthesized by simultaneous polymerization of a monomer system with a cross-linking agent in the presence of linear polymer chains, which will be physically entangled within the polymer network [4]. 2-Hydroxyethyl methacrylate (HEMA) is the organic compound with a vinyl functional group which can participate in the copolymerization with NIPAM. In general, when based-HEMA polymers are subjected to water, it will swell due to the molecule's hydrophilic pendant groups. Depending on the physical and chemical structure of the polymer, it is capable of absorbing from 10 to 600% water relative to the dry weight [5]. In this research,

HEMA was introduced to semi-IPN hydrogel by two methods to synthesize two structures of thermo-responsive semi-IPN hydrogel and investigate their swelling behavior in pure water. First, the S1-structure p(NIPAM-co-HEMA)/pNIPAM semi-IPN hydrogels were prepared by free radical polymerization of NIPAM in the presence of the linear copolymer p(NIPAM-co-HEMA) and the cross-linker. While, S2-structure pNIPAM/p(NIPAM-co-HEMA) semi-IPN hydrogels were synthesized by free radical polymerization of mixture of NIPAM and HEMA in the presence of the linear polymer pNIPAM and the cross-linker. The linear polymers were expected to entangle physically in the polymer network. The chemical structures of hydrogels were investigated by FTIR. The morphology was investigated by SEM. Finally, the LCSTs and swelling behavior in of hydrogels were investigated in various temperatures by DSC and weighing method, respectively.

2. MATERIALS AND METHOD

2.1 Materials

N-isopropyl acrylamide (NIPAM; $C_6H_{11}NO$) obtained from Aldrich Chemical Corp. (Saint Louis, MO, USA) was purified through recrystallization from n-hexane twice. 2-hydroxyl ethyl methacrylate (HEMA, $C_6H_{10}O_3$) also obtained from Aldrich Chemical Corp (Saint Louis, MO, USA). Ammonium persulfate (APS; $(NH_4)_2S_2O_8$) as an initiator was purchased from Aencore Chemical Pty. Ltd. Surrey Hills, Australia). N,N,N',N'-tetramethyl ethylene -diamine (TEMED; $C_6H_{16}N_2$) as a catalyst and N,N' methylene-bisacrylamide (MBA; $C_7H_{10}N_2O_2$) as a cross-linker were purchased from Alfa Aesar Co. (Tewksbury, MA, USA). Except for NIPAM, other reagents were used as received without any further purification.

2.2 Method

The preparation of linear copolymer p(NIPAM-co-HEMA) is shown in Figure 1(a). It was prepared by free radical polymerization, employing APS as an initiator. First, 1.0 g of NIPAM and 70 µL of HEMA were dissolved together in 3.1 mL of pure water by continuous stirring in a degassed condition by a vacuum pump and placed the solution in an ice-water bath. Then, 2.3 mL aqueous solution of APS (0.4792 g APS/25 mL pure water) and 4.6 mL aqueous solution of TEMED (4 mL TEMED/25 mL pure water) were added to initiate the polymerization. After polymerization in the ice-water bath for 2h, the solution was ready for the subsequent processes. The linear polymer pNIPAM was prepared by a similar method as described above for preparation of S2-structure semi-IPN hydrogels.

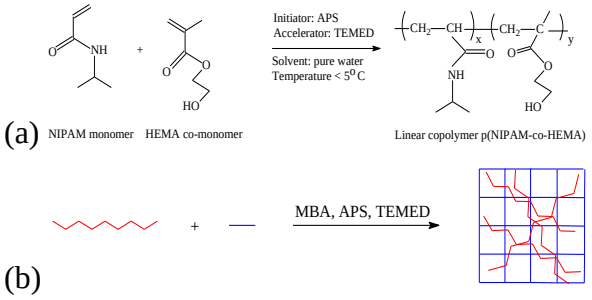

Fig. 1. *Preparation scheme of* (a) *Linear copolymer p(NIPAM-co-HEMA) and* (b) *semi-IPN hydrogels.*

The preparation of semi-IPN hydrogels is shown in Figure 1(b). For S1-structure semi-IPN hydrogels, they were prepared by mixing linear copolymer p(NIPAM-co-HEMA) solutions (≈100 mg/mL) and NIPAM solutions (100 mg/mL, containing 3.0 mole % MBA) in a vial with various designated ratios (0:10, 1:9, 2:8, and 3:7, v/v in an ice-water bath. For S2-structure semi-IPN hydrogels, linear pNIPAM solution (≈100 mg/mL) was mixed with the solution of NIPAM and HEMA (100 mg/mL, containing 3.0 mole % MBA) in a vial with the same ratios as described above and ensured the molar ratio of NIPAM and HEMA in each designated ratio of two semi-IPN structures is the same. The mixture was vacuumed for 30 minute until the solution became homogeneous. After that, TEMED and APS solution were added as a redox initiator pair to initiate the final reaction mixture. The solution was mixed thoroughly and then quickly poured into a

cylindrical glass mold, sealed immediately, and kept at room temperature for 24 h. The obtained hydrogels were carefully removed from the mold and immersed in pure water, which was refreshed every half-day for 1 week to eliminate the unreacted reagents. Finally, they were dried to completely remove water for further investigation. The feed ratios are given in Table 1.

Table 1. *Composition of raw materials used for the preparation of semi–IPN hydrogels*

Sample	Linear p(NIPAM-co-HEMA) [a] Solution, (mL)	Linear pNIPAM [a] Solution, (mL)	NIPAM (g)	Pure water (Ml)	MBA (mg)	APS [b] Solution (mL)	TEMED [c] Solution (mL)	Total Volume (mL)
SN1-0	-	-	1.0	3.1	40.0	2.3	4.6	10.0
SN1-1	1	-	0.9	3.0	36.0	2.0	4.0	10.0
SN1-2	2	-	0.8	2.9	32.0	1.7	3.4	10.0
SN1-3	3	-	0.7	2.5	28.0	1.5	3.0	10.0
SN2-1	-	1	0.9	3.0	36.0	2.0	4.0	10.0
SN2-2	-	2	0.8	2.9	32.0	1.7	3.4	10.0
SN2-3	-	3	0.7	2.5	28.0	1.5	3.0	10.0

[a] Solution of 1 mg/10 mg DI water; [b] solution of 0.4792 g APS/25 mL DI water; [c] solution of 4 mL TEMED/25 mL DI water.

2.3 Characterization

Fourier transform infrared (FTIR) spectra were measured by a Perkin Elmer Spectrum RXI FTIR 10.5.2 instrument (Waltham, MA, USA) within 4000-400 cm^{-1}.

The lower critical solution temperature (LCST) of the linear polymers and hydrogels was measured using a differential scanning calorimeter (DSC 214, Netzsch, Selb, Germany). The samples were tested at the heating rate of 1^oC/min in the temperature range of 20-45^oC. The LCSTs of the samples were determined at the maximum endothermic point.

The SEM images of freeze-dried hydrogels were taken by a Hitachi S-4700 scanning electron microscope (SEM) (Hitachi, Tokyo, Japan) to investigate the interior morphology. All samples were sputter-coated with gold for 10 min to enhance the conductivity and SEM images were acquired at an accelerating voltage of 15.0 kV. The pore sizes and standard deviations were analyzed by ImageJ.

The swelling kinetics of the hydrogels were studied using the gravimetric method. Dried hydrogels were immersed in pure water at 20^oC. At predetermined time points, swelling hydrogels were eliminated the excess water on the surface by filter paper and weighed by an electronic balance. The swelling ratio (SR) was calculated according to the following equation:

$$SR = \frac{W_s - W_d}{W_d} \qquad (1)$$

where Ws is the weight of the swelling hydrogel and Wd is the weight of the freeze-dried hydrogel.

The thermo-sensitive property of the hydrogels was investigated by calculation the equilibrium swelling ratio as a function of temperature. Dried hydrogels were immersed in pure water at different temperature points in the range of 20-50 ^oC until equilibrium. The swelling hydrogels were eliminated the excess water on the surface by a filter paper and weighed by an electronic balance, and SR was calculated using the above equation.

3. RESULTS AND DISCUSSION

3.1 FTIR Measurement

The FTIR spectra of NIPAM monomer, conventional pNIPAM, and semi-IPN hydrogels (SN2-3) are shown in Figure 2. In the spectrum of NIPAM monomer, the amide C=O stretching peak is shown at about 1650 cm^{-1}, the amine N–H bending peak is shown at about 1550 cm^{-1}, the amine N–H stretching peak is shown at 3500~3250 cm^{-1}, and the mono substituted C=C peak is shown at 960 cm^{-1} [6].

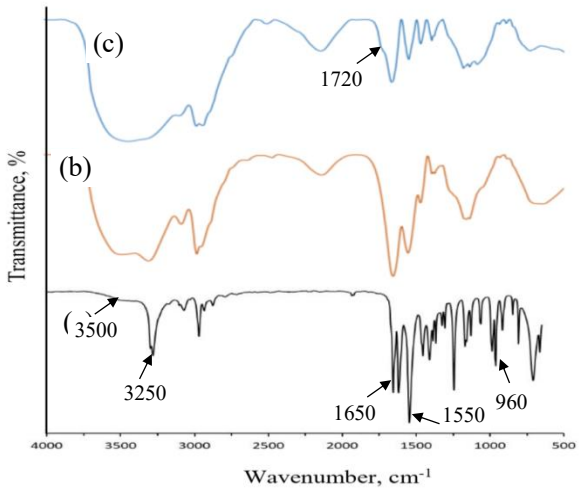

Fig.2. *FTIR spectra of, (a) NIPAM monomers, (b) conventional pNIPAM (SN1-0 sample), and (c) semi-IPN hydrogels (SN2-3 sample).*

After polymerization, the spectra of conventional pNIPAM and semi-IPN hydrogels showed an absence of the peak at about 960 cm^{-1}, indicating that C=C is formed into C–C in the three-dimensional hydrogels. The semi-IPN hydrogel has a distinct characteristic shoulder at 1720 cm^{-1} with a relatively low absorbance which corresponds to carbonyl group in HEMA section indicating the successful introduction of HEMA to the semi-IPN hydrogels [3].

3.2 Morphology

(a) (b) (c)

Fig. 3. *Optical images of (a) conventional pNIPAM, (b) S1-structure (S1-2 sample) and (c) S2-structure (S2-2 sample) semi-IPN hydrogels.*

Figure 3(a–c) shows photographs of conventional pNIPAM, S1-structure and S2-tructure semi-IPN hydrogels, respectively. The transmittance of three samples is different, indicating that the linear polymer had altered the structural state of the obtained semi-IPN hydrogels. This may be related to the hydrophobicity of HEMA and HEMA in three-dimensional structure is more strongly influenced in linear copolymer. Similar observations have been previously reported for salecan/pNIPAM semi-IPN hydrogels [4].

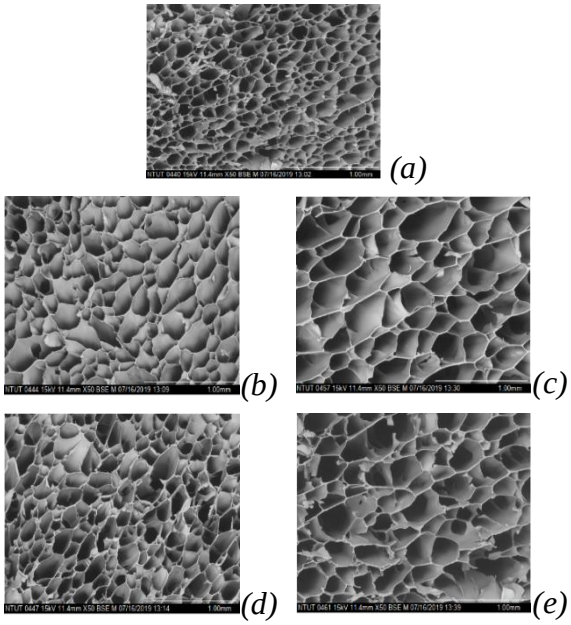

Fig. 4. *SEM images of conventional pNIPAM and semi-IPN hydrogels: SN1-0 (a), SN1-1 (b), SN1-3 (c), SN2-1(d) and SN2-3 (e).*

SEM images of the hydrogels in Figure 4(a-e) shows a porous structure with uniform pore size. It was observed that the average pore size was significantly affected by the linear polymer content introduced into the semi-IPN hydrogels. They are listed on the Table 2.

Table 2. *Pore sizes of conventional pNIPAM and semi-IPN hydrogels.*

Sample	Pore size (μm)
SN1-0	140.16 ± 19.71
SN1-1	177.87 ± 36.54
SN1-3	275.51 ± 62.07
SN2-1	177.74 ± 41.31
SN2-3	261.55 ± 31.34

The conventional pNIPAM hydrogel had the smallest pore size is 140.16 ± 19.71 μm. The linear polymer content increased leading to an increase in the pore size of semi-IPN hydrogel from 177.87 ± 36.54 to 275.51 ± 62.07 μm, and from 177.74 ± 41.31 to 261.55 ± 31.34 μm, for S1-structure and S2-structure, respectively. This result shows that the morphology of the two structures are quite similar and only depends on the content of linear polymer and hydrophilic pedant groups introducing from HEMA section. This result is also consistent with reports of Rwei et. al [7] and Wei et. al [4].

3.3 Differential Scanning Calorimetry

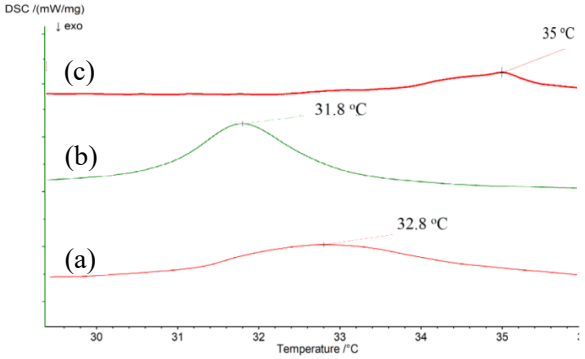

Fig. 5. *DSC curves of (a) linear pNIPAM, (b) linear copolymer p(NIPAM-co-HEMA) and (c) conventional pNIPAM hydrogel.*

DSC analysis was used to confirm the LCST of the linear polymers and hydrogels. Figure 5 shows the DSC curves of linear polymer solutions (10%) and swelling conventional pNIPAM hydrogel. The LCST of linear copolymer decreased (from 32.8 ^{o}C to 31.8 ^{o}C) as the HEMA monomer was added. This results can be explained by the hydrophobicity of HEMA section in copolymer structure. In addition, the LCST of pNIPAM hydrogel increased to 35.0^{o}C. This explained because the three dimensional structure of hydrogel, which causes a delay in heat gain for phase transition compared to linear pNIPAM [8].

Figure 6(a) shows the DSC curves of S1-structure semi-IPN hydrogel, which the HEMA comonomer was added into the linear polymer. While the DSC curves of S2-structure semi-IPN hydrogels, which contained HEMA comonomer in three-dimensional section, were showed in Figure 6(b). The results show that the LCST of semi-IPN hydrogels is lower than that of conventional pNIPAM hydrogel. In the case of semi-IPN hydrogels, LCST decreased as more HEMA comonomer was added into the network. This is due to the hydrophilicity of HEMA as discussed above. Moreover, LCST of two semi-IPN structures with the same content of HEMA is quite similar. This phenomenon indicated that the location of HEMA did not affect the final semi-IPN hydrogels. The LCST was only affected by the ratio of hydrophilic and hydrophobic groups in the obtained semi-IPN hydrogels.

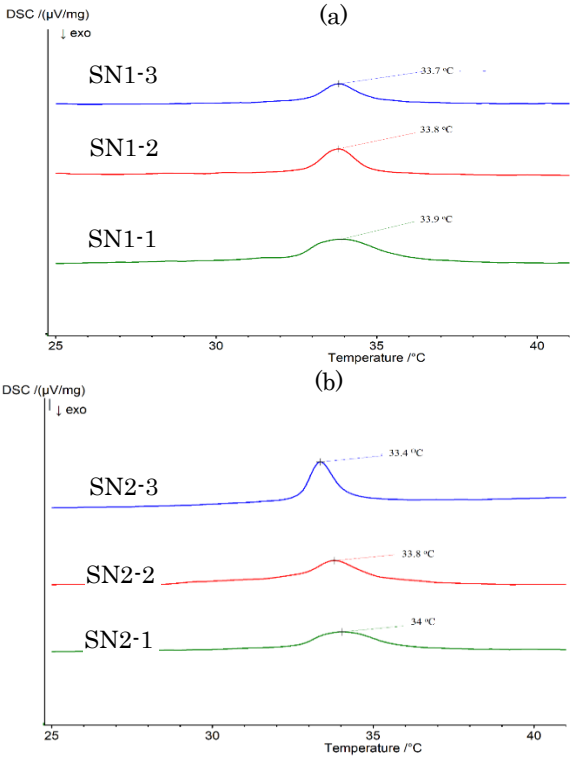

Fig. 6. *DSC curves of (a) S1-structure and (b) S2-structure semi-IPN hydrogels.*

3.4 Swelling behavior

3.4.1 Swelling Kinetics and Equilibrium Swelling Ratio

Figure 7(a,b) shows the swelling kinetic curves of S1- and S2-structure semi-IPN hydrogels in pure water at 25 ^{o}C. It can be found that the swelling rate and equilibrium swelling ratio of the hydrogel increased from SN1-1 to SN1-3 and SN2-1 to SN2-3 for S1-1 and S2-structure, respectively. These results can be explained by the molecule's hydrophilicity pedant groups of HEMA were introduced into semi-IPN hydrogels such as carbonyl and hydroxyl groups. When the HEMA content increased, the semi-IPN hydrogels possessed more hydrophilicity groups and absorbed more water, leading to a higher equilibrium swelling ratio. Besides, the linear polymers have supported the water molecules to move more easily from outside into the hydrogel network, leading to an increased swelling rate [9]. Equilibrium swelling ratio of two semi-IPN structures with

the same content of HEMA is quite similar, indicating that it only depended on the content of the hydrophilic group within hydrogels as discussed above.

Figure 7(c) shows that the swelling rate of SN1-3 was higher than SN2-3 sample. This result can be explained by the higher hydrophilicity of the linear copolymer p(NIPAM-co-HEMA) than the linear polymer pNIPAM. The higher hydrophilicity of linear copolymer in the S1-structure semi-IPN hydrogel helped water molecules travel faster, leading to an increased swelling rate.

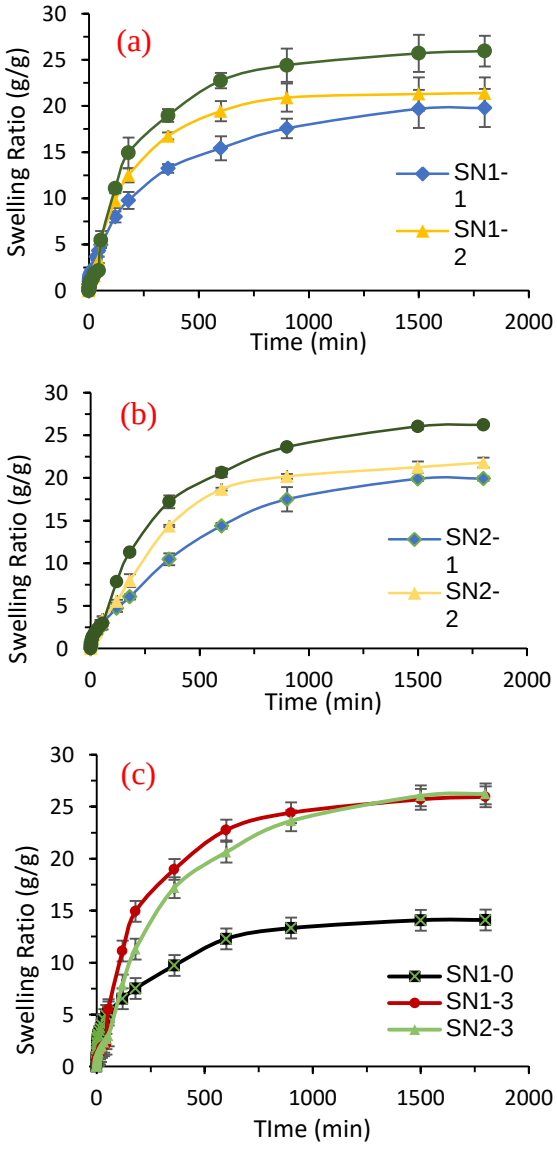

Fig. 7. *Swelling kinetic curves in pure water at 25 °C of (a) S1-structure; (b) S2-structure and (c) in a comparison between S1- and S2-structure semi-IPN hydrogels.*

3.4.2 Temperature Dependence

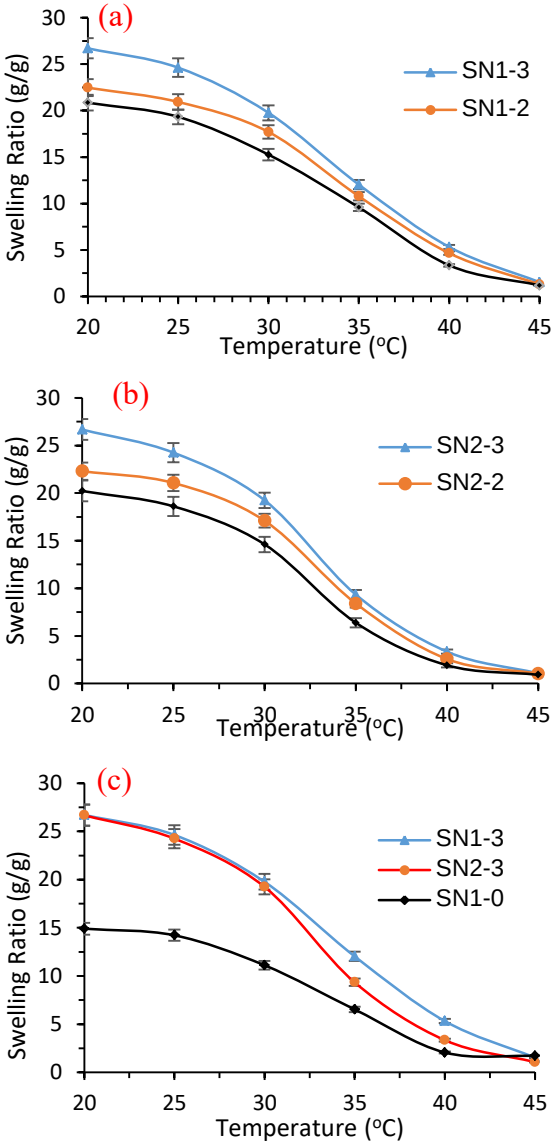

Fig. 8. *Swelling ratio values in water as a function of temperature from 20-45 °C of (a) S1-structure; (b) S2-structure and (c) in a comparison between S1- and S2-structure semi-IPN hydrogels.*

Figures 8(a-b) indicated the thermo-sensitive property of the semi-IPN hydrogels. High swelling ratios were found in the temperature of 20-30 °C. While there is a significant decreasing in swelling ratios was found in the range of 30-40°C. These results showed the strong influence of temperature on the phase transition of semi-IPN hydrogels which shrunk above the LCST and swelled below the LCST. Moreover, in the range of 40-45°C (above their LCST) shows no

significant difference in the swelling ratios may be due to all hydrogel samples retracted to form the same tight structure. The phase transition of semi-IPN hydrogels as a function of temperature in this work proving that it can be used as a drug delivery system or an absorbing material. Finally, around the LCST (the range of 35-40^{o}C), SN1-3 (represent S1-structure) shows higher swelling ratios than SN2-3 sample (represent S2-structure). These results may be related to the higher hydrophilicity of linear copolymer p(NIPAM-co-HEMA) than linear polymer pNIPAM as discussed above.

4. CONCLUSION

In this work, two series of semi-IPN hydrogels based on NIPAM and HEMA were synthesized by free radical polymerization. The S1-structure hydrogelp(NIPAM-co-HEMA)/pNIPAM was prepared by introducing comonomer HEMA into linear polymer. While the S2-structure pNIPAM/ p(NIPAM-co-HEMA) hydrogel was received by introducing HEMA into three-dimensional network. The chemical structure was confirmed by FTIR spectra. A uniform porous structure of the semi-IPN hydrogels with the pore size in the range from 177.87 ± 36.54 to 275.51 ± 62.07 μm. LCST and swelling behaviors of the hydrogels in water were confirmed. The LCST of the semi-IPN hydrogels in water decreased slightly from 34 to 33.4^{o}C with increased HEMA content. Moreover, the LCST of S1-structure and S2-structure semi-IPN hydrogels were not significant difference indicating that LCST values did not depend on the position of HEMA comonomer. The equilibrium swelling ratios were influenced by the content of HEMA introducing into hydrogel network: increased the HEMA content leading to an increased the swelling ratio. With the same HEMA content introducing into network, S1-structure hydrogels exhibited higher swelling ratios and swelling rate than S2-structure hydrogels. The phase transition and swelling behavior of the semi-IPN hydrogels in this study can be changed by a change of temperature and position of HEMA comonomer, showing that they can be used for a drug system or as an absorbing material.

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