

# Effect of Hydrophobic Comonomer Content on Assembling of Poly (*N*-isopropylacrylamide) and Thermal Properties

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**ABSTRACT:** Copolymers of *N*-isopropylacrylamide and octadecyl acrylate (PNO), of which the content of octadecyl acrylate (ODA) was 1.3% (PNO 1.5), 1.7% (PNO 2.0), and 3.0% (PNO 4.0), were prepared using a free radical reaction. Various assemblies were obtained depending on the concentration of PNOs and the contents of ODA. Hydrophobic interaction between ODA residues is likely to act as crosslinker. PNO 1.5 formed hydrogel at the concentration of 7%. With PNO 2.0, hydrogels were formed when the concentration was 5 and 7%. With PNO 4.0, the opaque gel was obtained when the concen-

tration was 7%. Upon heating across the lower critical solution temperature, the hydrogels shrank but the opaque gel was broken down into a suspension. At 40°C, the release degrees of fluorescein isothiocyanate-dextran were much smaller than those of release at 23°C. The temperature-sensitive release is due to temperature-sensitive swelling ratio. © 2010 Wiley Periodicals, Inc. *J Appl Polym Sci* 120: 2346–2353, 2011

**Key words:** *N*-isopropylacrylamide; hydrophobic interaction; assemblies; thermal properties

## INTRODUCTION

Assemblies, such as nanoparticles, micelles, micro-particles, and hydrogel, could form by noncovalent interactions, including hydrophobic or electrostatic interaction.<sup>1–4</sup> According to recent review, self-assemblies could also be classified to small molecule assembly, porous crystals, lipid assembly, gels and liquid crystals, structure-transcribed material, and macroscopic assembly.<sup>5</sup> They could create patterns or structures spontaneously with order, and researchers would like to control morphologies, sizes, and molecular arrangements for many applications.<sup>6</sup> For instance, self-assemblies of block copolymers were reported to be used for surface patterning, since they are compatible with lots of patterning techniques.<sup>7</sup> Many factors could influence the formation and properties of the assemblies. For example, the sizes of particles were reported to be various in terms of changing the preparation methods, the

composition of copolymers, or the conditions during preparation (e.g., temperature, stirring rate, types of solvent etc.).<sup>8,9</sup> On the other hand, the properties of hydrogel, like swelling ratio, were also reported to be various by changing the crosslinker density.<sup>10</sup> However, most researches have forced on the formation of each kind of assemblies separately. Up to the present, the researches on the controllable change between particles and hydrogels are still few.

Poly(*N*-isopropylacrylamide) (PNIPAM) is well known to exhibit an unique phase separation behavior in aqueous solution when ambient temperature is above the lower critical solution temperature (LCST, about 32°C).<sup>11</sup> According to previous researches, LCST of PNIPAM could be influenced by conjugating the ionizable groups to PNIPAM chain.<sup>12,13</sup> Although many PNIPAM based hydrogels which showed temperature-dependent drug release have been developed by chemically crosslinking,<sup>14–17</sup> but the physically cross-linked PNIPAM hydrogels are rare. Moreover, the researches on the effects of hydrophobic moiety on the properties of NIPAM have not been well investigated yet.

In this study, copolymer of NIPAM and octadecyl acrylate (ODA), a hydrophobic moiety, was prepared at difference mass ratios. The types of assemblies which could form by taking advantage of hydrophobic interactions between ODA would be

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various. Hence, this research could be useful in the further design of hydrophobically cross-linked drug delivery systems. The effects of the ODA content and the concentration of the copolymers on the formation of assemblies, the thermo properties, and the temperature-dependent releases were extensively investigated in this work. Photography, transmission electron microscopy (TEM), and scanning electron microscopy (SEM) were employed to identify the assemblies. The swelling properties were studied in terms of change temperature. The release experiments were carried out at 23 and 40°C with fluorescein isothiocyanate-dextran (FITC-dextran).

## EXPERIMENTAL

### Materials

ODA (Mol. wt. 324.54) was purchased from Aldrich Chemical (Milwaukee, USA). *N*-isopropylacrylamide (NIPAM, Mol. wt. 113.16) was purchased from Tokyo Chemical Industry (TCL, Tokyo, Japan).  $\alpha$ ,  $\alpha'$ -Azobis(isobutyronitrile) (AIBN, Mol. wt. 164.21) was purchased from Junsei Chemical (Tokyo, Japan). Fluorescein isothiocyanate-dextran (FITC-dextran, average Mol. wt. 40,000) was purchased from Sigma (St. Louis, MO). Water was doubly distilled in a Milli-Q water purification system (Millipore) until the resistivity was 18M $\Omega$ /cm. All other reagents were in analytical grade.

### Synthesis of PNIPAM and P(NIPAM-co-ODA)

Homo and copolymers of NIPAM were prepared following a method described elsewhere.<sup>18</sup> NIPAM (10, 9.85, 9.80 mmol or 9.60 mmol), ODA (0, 0.15, 0.20 mmol or 0.25 mmol) and AIBN (0.05 mmol) were dissolved in 20 mmol of freshly distilled dioxane. The contents of ODA in molar ratio were 0, 1.5, 2.0, and 4.0%, and the synthesized homo and copolymers were named as PNIPAM, PNO 1.5, PNO 2, and PNO 4, respectively.

### Determination of ODA contents and LCSTs of copolymers

For the determination of ODA contents in copolymers, <sup>1</sup>H-NMR spectra of PNOs were taken on a Bruker Avance 600 (Karlsruhe, Germany) spectrometer using CDCl<sub>3</sub> as a solvent. The LCST of each copolymer was observed by measuring turbidities of the solutions at 600 nm on a UV spectrophotometer (6505 UV/Vis Spectrophotometer, JENWAY, U.K.) equipped with a temperature controller. The concentration of each copolymer was adjusted to 1% in distilled water at pH 7. The temperature was raised from 20 to 40°C at a rate of 2°C/min.

### Observation of phases of hydrated PNOs

PNIPAM, PNO 1.5, PNO 2, and PNO 4 were added to distilled water in a 20 mL vial so that the concentrations are 1, 3, 5, and 7%. And then each copolymer was hydrated for 48 h to equilibration.

### Characterization of PNO suspensions and PNO hydrogels

The formation properties and phase transition properties of hydrated PNOs were observed by photography at 23 and 40°C. Additionally, the morphology of hydrated PNOs was studied using scanning electron microscope (SEM, Jeol JSM-840A), for the freeze-dried samples, or transmission electron microscope (TEM, LEO-912AB OMEGA, LEO, Germany), for the PNO suspensions. Before observed on SEM, the freeze-dried samples were cross-sectioned using a blade and they were mounted on metal stubs with double-sided tape, sputtered with gold. The sizes of particles in PNO suspensions were measured on a particle size analyzer (Plus 90, Brookhaven, USA) at 23°C.

### Temperature-dependent swelling ratios of PNOs hydrogels

The swelling ratio of PNO hydrogels was investigated with time and temperature. Freeze-dried PNO hydrogels of 0.5 g for each sample were immersed in 25 mL of distilled water, which was preadjusted to pH 7 in a 50-mL beaker. For equilibrated swelling test, each sample in distilled water was kept to either 23°C or 40°C for 16 h in an oven. The PNOs hydrogels under different conditions were quickly taken out and weighed after removing the excess surface water with filter paper. The swelling ratio is defined as follows.

Swelling ratio %

$$= \left( \frac{\text{Wet weight} - \text{Dry weight (mg)}}{\text{Dry weight (mg)}} \right) \times 100 \quad (1)$$

### Temperature-dependent release of FITC-dextran from PNO hydrogels

The FITC-dextran loaded PNO hydrogels were prepared by hydrating PNO copolymers with FITC-dextran-containing solution (3 mg/mL). After equilibration for 48 h, hydrated PNO hydrogels of round flat shape (25 mm in diameter and 10 mm in thickness) was washed by distilled water, and the amount of unloaded FITC-dextran in the washed water was measured on a fluorescence spectrophotometer (Hitachi F2500, Japan) at the emission of 515 nm with excitation of 495 nm. The loading efficiency was defined as follows.

$$\text{Loading efficiency \%} = \left( \frac{\text{FITC - dextran in hydrogel (mg)}}{\text{Total amount of FITC - Dextran before hydrating (mg)}} \right) \times 100 \quad (2)$$

The *in vitro* release experiments were carried out at 23 and 40°C for the investigations on temperature-responsive release properties of PNO hydrogels. Each of FITC-dextran loaded hydrogel was immersed into 25 mL distilled water in a 50 mL beaker, and 0.5 mL of supernatant were sampled at predetermined time intervals (0.25, 0.5, 1, 2, 4, 6, 8, 12, 16 h) with adding 0.5 mL distilled water into the beaker to keep the total volume constant. The amount of FITC-

dextran in the supernatant was determined on fluorescence spectrometer. The released amount could be detected from the sampled solution (0.5 mL per time), while the total amount entrapped FITC-dextran could be calculated from the loading efficiency of each gel. The percentage of release is defined as the percentage of the released amount on the basis of the total amount entrapped in the hydrogel as follow.

$$\text{Release \%} = \left( \frac{\text{FITC - Dextran in sampled supernatant of the releasing medial (mg)}}{\text{Total amount of FITC - Dextran in the releasing hydrogel (mg)}} \right) \times 100 \quad (3)$$

## RESULTS AND DISCUSSION

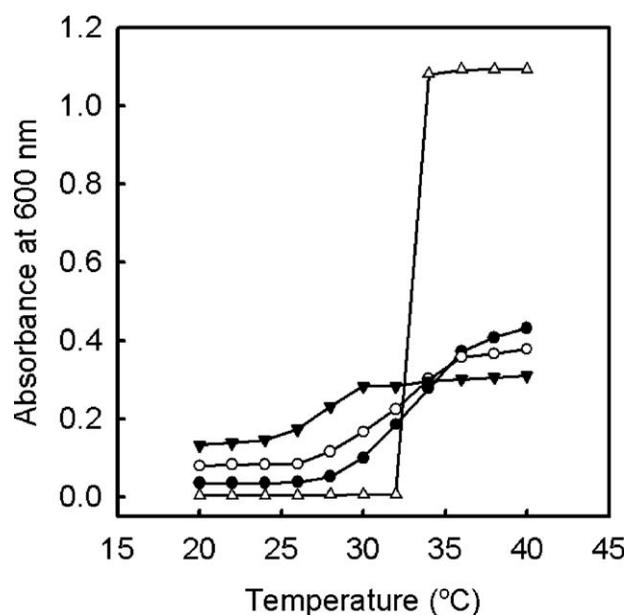
### Characterization of PNOs

According to our previous work, the molecular weight of PNIPAM was around 50,000, which was determined by gel permeation chromatography.<sup>19</sup> The peak around 4.0 ppm is due to the C-H proton of isopropyl groups, the peak around 0.8 ppm is due to the terminal methyl proton of ODA.<sup>20</sup> Therefore, it is believed that PNOs were successfully synthesized. By calculating the area ratio of two peaks, the contents of ODA in PNO 1.5, PNO 2, and PNO 4 were found to be about 1.3, 1.7, and 3.0%, respectively. The contents of ODA in the copolymers were less than those in feed, and this is possibly because the reactivity of ODA is less than that of NIPAM. Figure 1 shows the temperature-dependent turbidities of PNIPAM solution (1%) and PNO solutions (1%) in distilled water. PNIPAM solution started to be turbid around 32°C. The increase in the turbidity is due to the thermal contraction of PNIPAM.<sup>21</sup> Accordingly, the temperature of 32°C is believed to be LCST of PNIPAM, and the temperature is in a good agreement with LCST reported in a literature, which showed the LCST of PNIPAM around 32°C, and it also mentioned that the LCST of PNIPAM was adjustable by copolymerization with other comonomers.<sup>18</sup> PNO 1.5, PNO 2, and PNO 4 started to be turbid around 29, 28, and 25°C, respectively. It was reported that the copolymerization of hydrophobic monomers with NIPAM monomer reduces LCST.<sup>22</sup> Moreover, the decreasing of LCST may not be a simple linear relationship against the copolymer composition.<sup>23</sup> ODA is a hydrophobic monomer and the copolymer having the highest contents of ODA (PNO 4) exhibited the lowest LCST. On the other hand, PNIPAM solution was completely transparent below its LCST but PNO solutions were somewhat turbid even below their

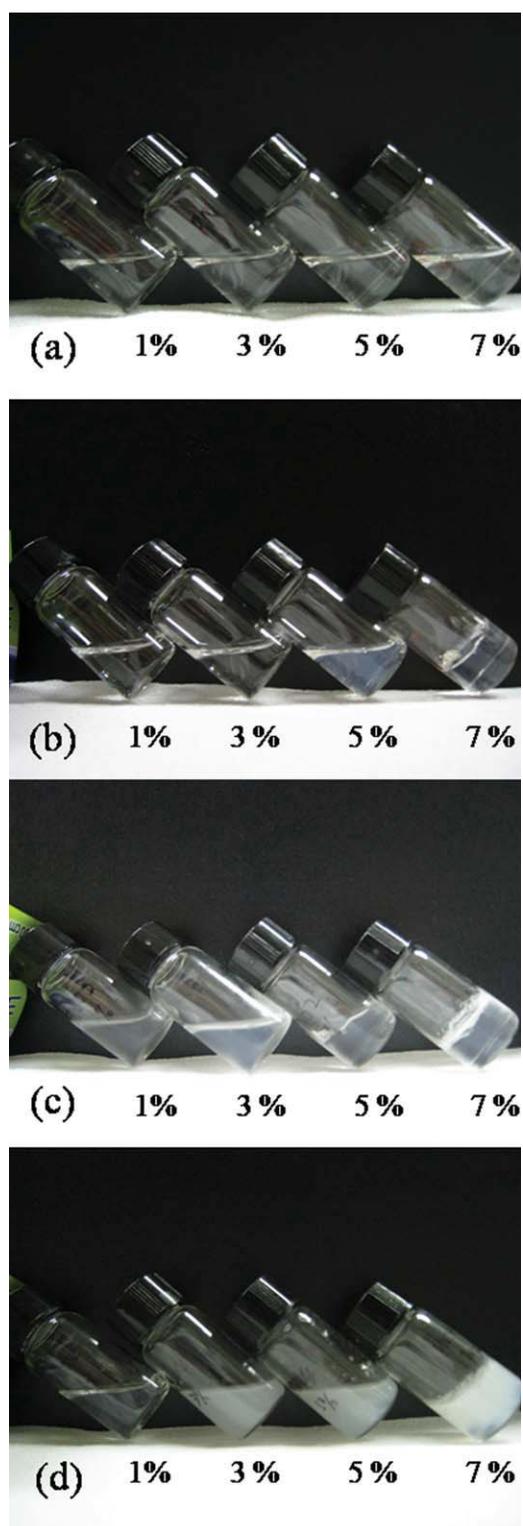
LCSTs. The turbidities of the polymer solutions below LCSTs (e.g., at 20°C) were in the order of PNO 4 > PNO 2 > PNO 1.5 > PNIPAM. PNOs have hydrophobic residues (ODA residues) so they could be agglomerated or assembled into polymeric particles due to the inter/intramolecular hydrophobic interactions, resulting in cloudy solutions.

### Observation of phases of hydrated PNOs

Figure 2 shows PNIPAM and PNOs in distilled water after hydration at 23°C. PNIPAM was readily



**Figure 1** Temperature-dependent turbidities of PNIPAM solution ( $\Delta$ ), PNO 1.5 solution ( $\bullet$ ), PNO 2.0 solution ( $\circ$ ), and PNO 4.0 solution ( $\blacktriangledown$ ) in distilled water. The concentration of the polymer was 1.0%.



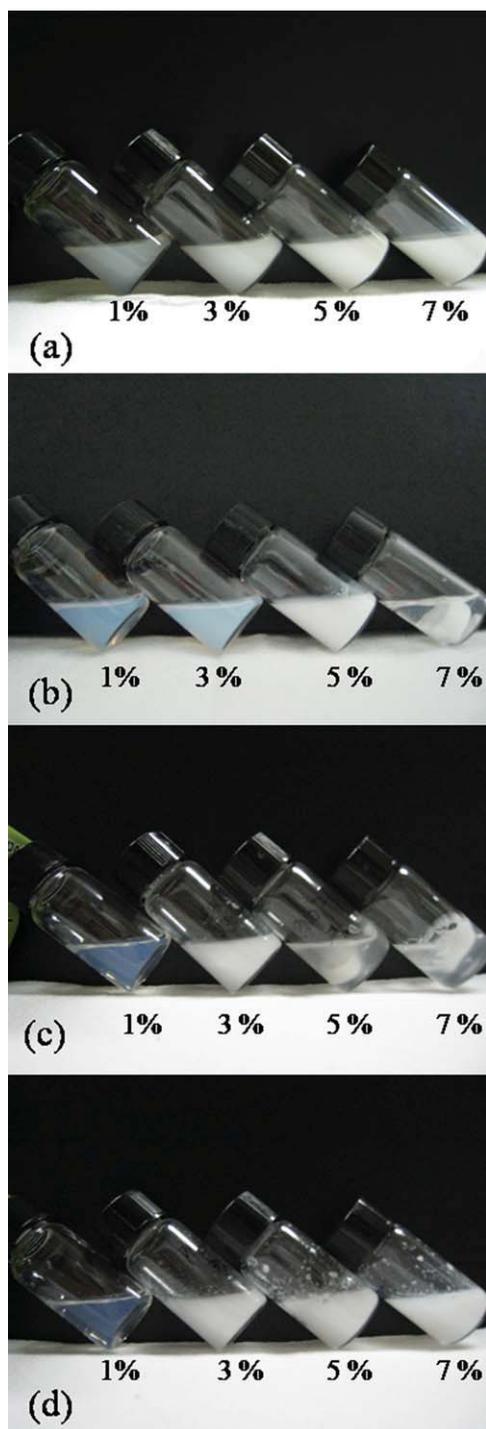
**Figure 2** Photos of PNIPAM (a), PNO 1.5 (b), PNO 2.0 (c), and PNO 4.0 (d) in distilled water after hydration at 23°C. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

soluble in distilled water at all the concentrations tested, and they were fluid. PNIPAM was reported to be water-soluble when the ambient temperature

was less than its LCST.<sup>24</sup> PNO 1.5 was also readily soluble in distilled water at the concentrations of 1, 3, and 5%. When the concentration was 7%, transparent solid gel was obtained. It is believed that hydrophobic interaction between ODA residues acts as a crosslinker and it is responsible for the formation of the gel. PNO 2 was soluble at the concentrations of 1 and 3% but the solutions were somewhat turbid. As described previously, polymeric particles may be formed due to the hydrophobic interaction among ODA residues, and the turbidity would be ascribed to the polymeric particles. When the concentration increased to 5%, a soft gel was formed. The content of ODA in PNO 2 was 1.7%, and it was higher than that of ODA in PNO 1.5, 1.3%. Accordingly, the number of hydrophobic interactions among PNO 2 chains per volume (defined as the hydrophobic interaction density of PNO 2) would be higher if the concentrations of the copolymers were the same. This would account for why PNO 2 formed the gel at lower concentration than PNO 1.5 did. When the concentration of PNO 2 further increased to 7%, a hard gel was obtained possibly due to an increased hydrophobic interaction density. On the other hand, PNO 4 was soluble in distilled water only when the concentration was 1%. When the concentrations were 3 and 5%, turbid suspensions were obtained. Due to the higher content of ODA, intramolecular hydrophobic interaction will become prominent and the copolymer chains will take a less extended configuration (a contracted configuration). A subsequent intermolecular interaction of the contracted PNO 4 is thought to prefer dispersed particles to continuous gels. When the concentration was 7%, the opaque gel was obtained. The polymeric particles formed by the intra- and intermolecular hydrophobic interaction will be more closely packed at a higher concentration (7%), leading to an opaque gel.

#### Phase transitions of hydrated PNOs

Figure 3 shows hydrated PNIPAM and PNOs at 40°C. Homogeneous milky suspensions were observed with PNIPAM at all concentrations tested. The temperature of 40°C is far above the LCST (about 32°C) of PNIPAM so the polymer chains will be dehydrated and agglomerated into particles, leading to a milky suspension. PNO 1.5 also exhibited homogeneous suspensions at the concentrations of 1, 3, and 5%. When the concentration was 7%, a lump of thermally contracted white gel was observed together with clear water phase. It means that most of the hydrated PNO 1.5 chains were crosslinked one another. That is, the hydrated PNO 1.5 (7%) could be called a hydrogel. PNO 2 exhibited homogeneous suspensions at the concentrations of 1 and 3%. When the concentrations



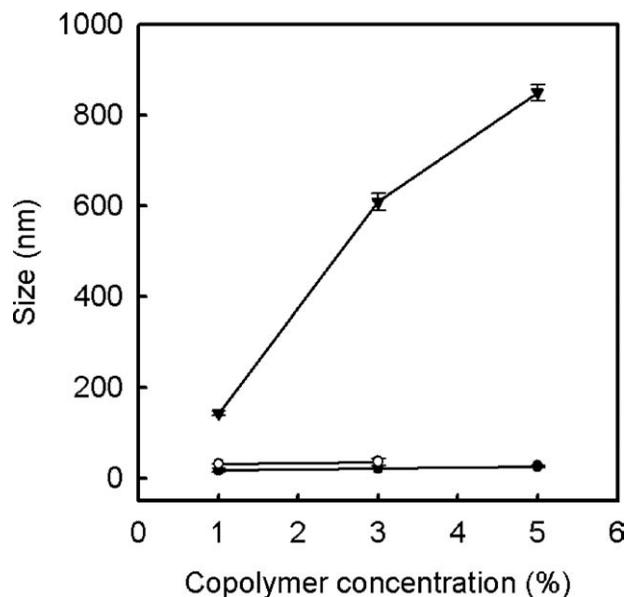
**Figure 3** Photos of hydrated PNIPAM (a), PNO 1.5 (b), PNO 2.0 (c), and PNO 4.0 (d) at 40°C. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

were 5 and 7%, a lump of thermally contracted white gel was observed. Therefore, the hydrated PNO 2s (5 and 7%) were also hydrogels. In case of PNO 4, almost transparent solution was obtained at the concentration of 1%. This is because that the temperature sensitivity of PNO 4 was low at the concentration of 1% (Fig. 1). When the concentrations were 3 and 5%,

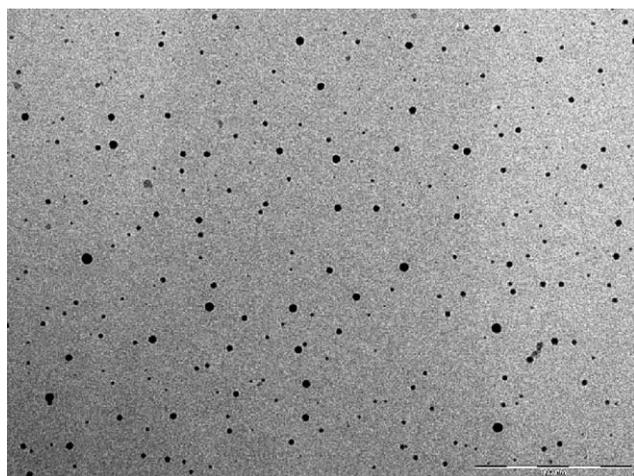
the suspension having visible particles were obtained. The higher content of ODA will give a rise to a stronger intermolecular hydrophobic interaction, possibly leading to the formation of visible particles. On the other hand, the suspension was also obtained even when the concentration was 7%, at which concentration an opaque gel was obtained at room temperature (23°C). As previously described, closely packed polymeric particles are thought to constitute the opaque gels and they will shrink upon raising temperature across the LCST. Recently, the macroscopic phase separation by increasing of temperature was also obtained from the triblock copolymer of PNIPAM which contained two different hydrophobic polymers at two ends of PNIPAM.<sup>25</sup> In spite of increasing temperature, the shrinking rate of PNIPAM based hydrogel was also reported to show a thousand-fold increase with addition of surfactant.<sup>26</sup> In our study, the shrinkage of the polymeric particles would be responsible for the breakdown of the gel.

#### Size and TEM photo of hydrated PNO particles

Figure 4 shows the size of hydrated PNO 1.5, PNO 2, and PNO 4 at 23°C. The size of PNO 1.5 particles increased from 17.6 to 25.9 nm as the concentration increased from 1 to 5%. The particles are believed to be polymeric micelles in terms of their size. Aggregation number of micelles increases with increasing the concentration of an amphiphilic molecule, resulting in an increase in the size of micelles.<sup>27</sup> The size of PNO 2 particles increased from 31 to 46 nm when the concentration increased from 1 to 3%. PNO 2 particles were slightly larger than the PNO 1.5



**Figure 4** Particles size of hydrated PNO 1.5 (●), PNO 2.0 (○), and PNO 4 (▼) with various concentrations at 23°C.



**Figure 5** TEM photo of hydrated PNO 1.5 when the concentration was 3%. Bar represents 500 nm.

particles. The higher the content of hydrophobic residue (ODA residue) in PNOs is, the larger the hydrophobic cores are.<sup>27</sup> On the other hand, PNO 4 particles were much larger than PNO 1.5 and PNO 2, and the size increased dramatically with the concentration. For example, the size increased from 143 to 849 nm when the concentration increased from 1 to 5%. With the higher content of ODA in PNO 4, intra- and inter-molecular hydrophobic interaction will be stronger, giving rise to larger particles. In addition, the concentration effect of PNO 4 on the size would be more prominent than those of PNO 1.5 and PNO 2.0, since the concentration of ODA increases with increasing the concentration of PNO 4 more greatly than it does with PNO 1.5 and PNO 2.0. Figure 5 shows the TEM photo of PNO 1.5 particles when the concentration was 3%. Small particles less than 50 nm were found. The order of size was in a good agreement with the result (21.8 nm) obtained using a particle size analyzer. The small particles are believed to polymeric micelles.

#### SEM photos of PNO hydrogels

Figure 6 shows SEM photos of the hydrated PNOs after freeze-drying. Continuous structure was hardly found with hydrated PNO 1.5 (5%) (a). Continuous network-like structure, a typical structure of hydrogel, was found with hydrated PNO 1.5 (7%) (b). In fact, the sol was obtained when the concentration was 5% and hydrogel was obtained at the concentration of 7% [Fig. 2(b)]. PNO 2 exhibited networks-like structures at the concentrations of both 5 and 7%. Following the result of Figure 2(c,d), hydrogels were obtained at those concentrations. On the other hand, loose and discontinuous irregular structures were found with PNO 4 at the concentration of 5% [Fig. 2(e)]. When the concentration was 7%, compact

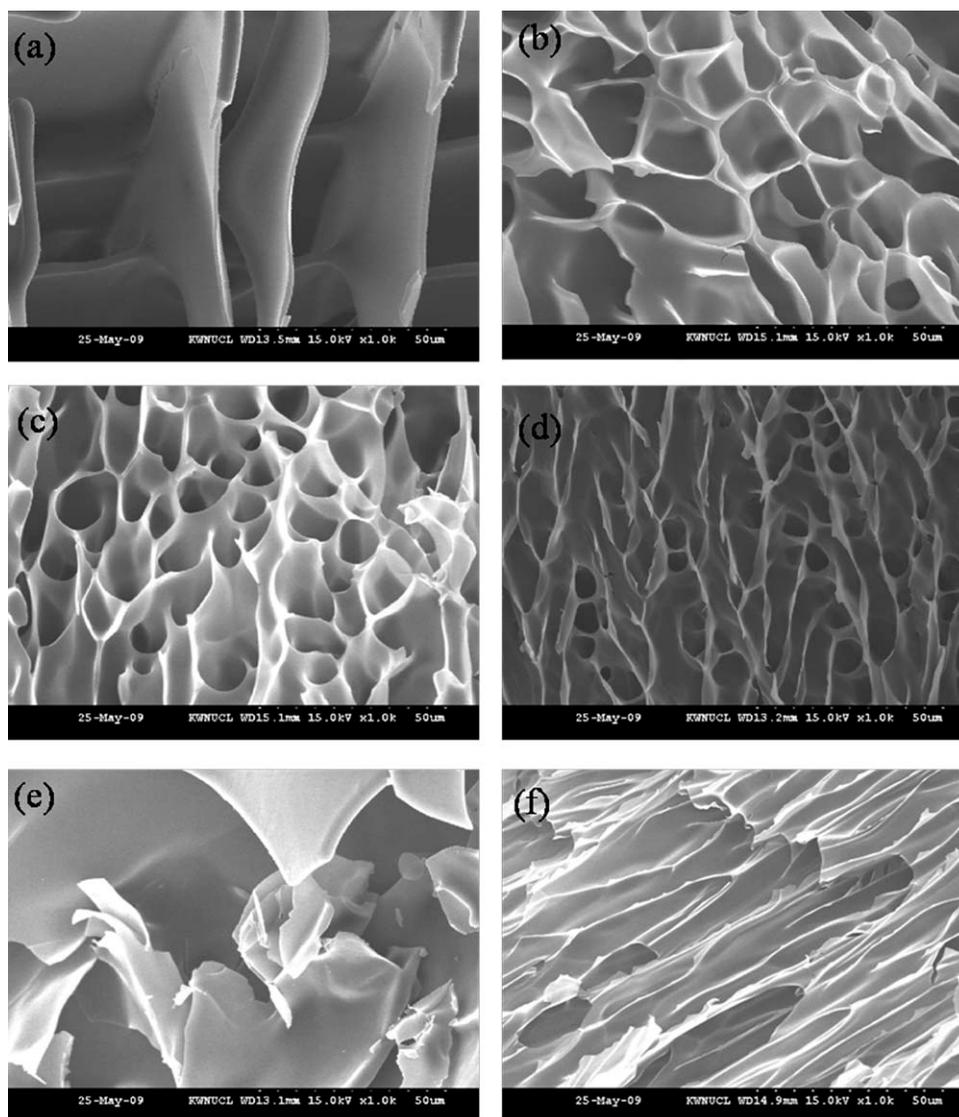
and wave-like discontinuous structures were obtained but networks-like structures were hardly found [Fig. 2(f)]. The opaque gels shown in Figure 2(d) would be ascribed to the compact structures. And the breakdown of the gel at 40°C [Fig. 3(d)] is possibly due to the discontinuous structure of the gel.

#### Temperature-dependent swelling ratio of PNO hydrogels

Figure 7 shows the swelling ratios of PNO 1.5 and PNO 2 hydrogels at 23 and 40°C. The swelling ratios increased with time in a saturation manner and the swellings were almost completed in 4 h except for the swelling ratio of PNO 2 (7%) at 23°C. PNO 2 (7%) swelled over 12 h. The slower swelling of PNO 2 (7%) hydrogel is possibly due to the higher hydrophobic interaction density. At 23°C, the swelling ratio of PNO 1.5 (5%) hydrogel in 16 h was about 350% and the value was greater than the swelling ratio of PNO 2 (5%), about 270%. The crosslinking density (hydrophobic interaction density) of PNO 1.5 (5%) hydrogel will be less than that of PNO 2 (5%), since the contents of hydrophobic residue (ODA) of PNO 1.5 is less. It was reported that the swelling ratio increases with decreasing crosslinking density.<sup>28</sup> On the other hand, the swelling ratio of PNO 2 (7%) hydrogel in 16 h was about 230% and the value was less than the swelling ratio of PNO 2 (5%). Due to the higher concentration, PNO 2 (7%) hydrogels will have higher crosslinking density (hydrophobic interaction density) than PNO 2 (5%) hydrogels. This would account for the reason why the swelling ratio of PNO 2 (7%) hydrogel was less than the swelling ratio of PNO 2 (5%) hydrogel. No big difference in swelling ratio of PNO hydrogels was found at 40°C and the swelling ratios were much less than those at 23°C. The temperature of 40°C is far above the LCST of PNO 1.5 and PNO 2. Accordingly, the copolymers will be hydrophobic, and they could hardly absorb water as much as they could at 23°C. The degree of swelling is likely to strongly depend on the content of hydrophobic residue (ODA residue) and the hydrophobic interaction density.

#### Temperature-dependent release from PNO hydrogels

According to the calculated results, the FITC-dextran loading efficiency was about 80.20, 75.95, and 65.23% for PNO 1.5 (7%), PNO 2 (5%), and PNO 2 (7%), respectively. Figure 8 shows FITC-dextran releases from PNO hydrogels at 23°C and 40°C for 16 h. The release increased in a saturation manner and they were almost completed in 4 h except for the release from PNO 2 (7%) at 23°C. In 16 h, the



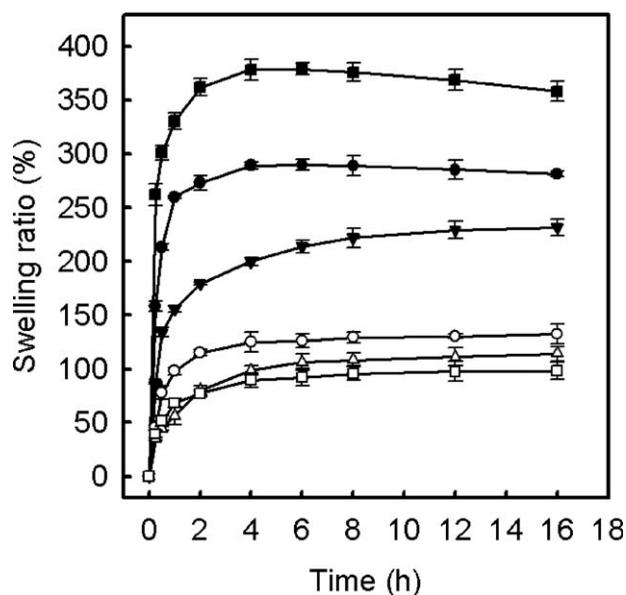
**Figure 6** SEM photos of hydrated PNO 1.5 [5% (a), 7% (b)], PNO 2.0 [5% (c), 7% (d)], and PNO 4.0 [5% (e), 7% (f)] after freeze-drying.

degrees of release at 23°C from PNO 1.5 (7%), PNO 2 (5%), and PNO 2 (7%) were about 95, 85, and 81%, respectively. The profiles of release resembled those of swelling ratios shown in Figure 7. A higher swelling ratio gave a rise to a higher degree of release. A higher swelling ratio means that the amount of water imbibed by hydrogels is larger and the proximity of polymer chains, which constitute the hydrogels, is lower. Therefore, when the swelling ratio is higher, FITC-dextran trapped in the hydrogels could diffuse out more freely, resulting in a higher degree of release. The releases from PNO 1.5 (7%) and PNO 2 (5%) were almost completed in 4 h, but the release from PNO 2 (7%) was completed in 12 h. Following the profiles of swelling ratios, the PNO 2 (7%) swelled over 12 h. The slower swelling could be responsible for the slower release. At 40°C, the degrees of release were much smaller than those of release at

23°C. In parallel, the swelling ratios at 40°C were also much smaller than those at 23°C. A lower swelling ratio means that polymer chains, which constitute the hydrogels, are closer to one another. Accordingly, when the swelling ratio is lower, FITC-dextran trapped in the hydrogels could diffuse out less freely, resulting in a lower degree of release.

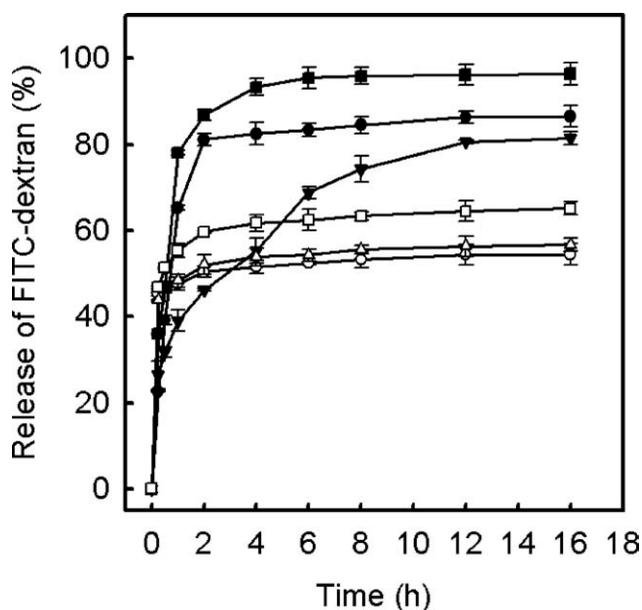
## CONCLUSION

Hydrogels were obtained with PNO 1.5 or PNO 2.0 when the concentration was 7% for PNO 1.5, and 5 and 7% for PNO 2.0. The swelling ratio at 23°C was higher with PNO 1.5 (7%) hydrogel possibly due to the lower hydrophobic interaction density which could influence the thermo-sensitivity. The degrees of FITC release at 23°C from PNO hydrogels were much higher than those of release at 40°C. The temperature



**Figure 7** Swelling ratios of PNO 1.5 (7%) (■,□), PNO 2.0 (5%) (●,○), and PNO 2.0 (7%) (▼,△) hydrogels at 23°C (■,●,▼) and 40°C (□,○,△).

sensitive releases were due to the temperature-sensitive swelling ratios. The formation types of the hydrophobically modified NIPAM assemblies were highly influenced by the contents of hydrophobic side group (ODA) and the concentration of the copolymer. The



**Figure 8** FITC-dextran releases from PNO 1.5 (7%) (■,□), PNO 2.0 (5%) (●,○), and PNO 2.0 (7%) (▼,△) hydrogels at 23°C (■,●,▼) and 40°C (□,○,△).

formation of micelles was changed to the formation of transparent hydrogel by increasing the contents of ODA or the concentration of copolymer. And by further increasing ODA contents, opaque hydrogel was obtained with the formation of large particles. It is very useful to know the phenomena in further design and optimization of amphiphilic copolymer based drug delivery vehicles.

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