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Journal of Macromolecular Science, Part A

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597274>

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To cite this Article Chen, Jun and Park, Kinam(1999) 'SUPERPOROUS HYDROGELS: FAST RESPONSIVE HYDROGEL SYSTEMS', Journal of Macromolecular Science, Part A, 36: 7, 917 – 930

To link to this Article: DOI: 10.1080/10601329908951189

URL: <http://dx.doi.org/10.1080/10601329908951189>

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SUPERPOROUS HYDROGELS: FAST RESPONSIVE HYDROGEL SYSTEMS

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Key Words: Hydrogel, Superporous Hydrogel, Thermoreversible, Thermosensitive, Fast Swelling, Capillary Channels

ABSTRACT

Superporous hydrogels, hydrogels with pore sizes in the range of 100 μm and larger, were synthesized using N-isopropylacrylamide (NIPAM) and acrylamide (AM). The superporous hydrogels were synthesized by crosslinking polymerization of monomers in the presence of gas bubbles. The pores of superporous hydrogels were connected to each other to form open capillary channels, which provided fast response to the changes in the environmental temperature. Upon increase in temperature from 10°C to 65°C, the superporous hydrogel made from a monomer solution of NIPAM:AM = 9:1 shrank from the fully swollen state (volume of 36 cm^3) to the fully collapsed state (volume of 6.5 cm^3) in 72 \pm 14 sec. When the temperature was changed back to 10°C, the superporous hydrogel swelled to 36 cm^3 in 78 \pm 15 sec. This deswelling-swelling cycle was repeated many times without changes in the thermo-reversible property of the superporous hydrogel. The response time of the superporous hydrogels was thousand times faster than that of conventional hydrogels. The fast response of the superporous hydrogels is

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due to the rapid uptake or exclusion of water molecules through the extensive capillary channels. Because superporous hydrogels still maintain the open capillary structure even after drying, the dried superporous hydrogels can also swell to the equilibrium swelling state within minutes. These fast responsive hydrogels can find many pharmaceutical and medical applications.

INTRODUCTION

Hydrogels, which can change their volume rather abruptly upon small changes in environmental conditions, are known as “smart” or “intelligent” hydrogels. Smart hydrogels respond to changes in the environmental conditions, such as temperature [1-3, pH [4, 5], solvent [6, 7], electric field [8-10], light [11], or pressure [12]. While these smart hydrogels are highly useful in various applications, the typical response time usually ranges from hours to days [13, 14], and this slow response time sometimes limits the usefulness of the smart hydrogels. Making smart hydrogels with fast response time would be highly beneficial in various applications.

Of the many smart hydrogels, thermo-reversible hydrogels have been studied quite extensively. Several approaches have been used to reduce the thermo-response time. Reducing the gel size has been the most commonly employed technique to achieve fast response time [2, 3, 13-17]. Thin hydrogels in either disc-, film-, or rod-shape usually have very fast response time. Engineering the polymer structure at the molecular level is another approach. Recently, comb-type grafted hydrogels showed faster deswelling in the range of 20 minutes [3, 13]. The swelling of these comb-type hydrogels, however, was still quite slow as other hydrogels, since the enhanced hydrophobic interaction responsible for the fast shrinking (or deswelling) of the swollen hydrogels is not effective for swelling. Another common approach for shortening the response time is to increase porosity by crosslinking of polymers [2, 15, 18] or polymerization of monomers [14, 16, 19] at temperatures above the lower critical solution temperature (LCST). Huang *et al.* [18] have synthesized macroporous poly(vinyl methyl ether) (PVME) hydrogels by γ -irradiation of 30 wt% PVME solution mixed with 15 wt% ferric oxide powder, which was used to enhance the heat transfer. They reported reasonably fast deswelling and reswelling of the macroporous hydrogels. Another study by Kabra *et al.* [15], however, showed that the response times of the hydrogels prepared by the similar approach were much longer with approximately 3 hours of swelling and 1 hour of deswelling even

with a gel thickness of only 0.8 mm. Polymerizing monomers at temperature above the LCST can cause phase separation of the polymer, which leads to the porous structures of the synthesized hydrogels. Wu *et al.* [14] reported the deswelling time on very thin gel film (2 mm thick) prepared by this method was only a few minutes, but the reswelling time was in the order of hours. Yan *et al.* reported that the macroporous hydrogel film (4 mm thick) made by this method showed a large volume change in only 30 seconds upon temperature changes from 20°C to 50°C. In this study, however, the gel did not reach the equilibrium state during that time period. All the macroporous hydrogels in the previous studies [2, 3, 13-19] had pore sizes less than a few micrometers. The existence of the interconnected channels formed by such pores has been speculated, but never confirmed. In this study, we examined a new approach for accelerating thermo-responsiveness using superporous hydrogels which have large (in the range of hundred micrometers), interconnected pores [20-22].

EXPERIMENTAL

Materials

N-isopropylacrylamide (NIPAM), acrylamide (AM), N,N'-methylenebisacrylamide (Bis), and ammonium persulfate (APS) were obtained from Aldrich Chemical Co., Milwaukee, WI. Tetramethylethylenediamine (TEMED) was purchased from Bio-Rad Laboratories, Richmond, CA. All the chemicals were used as received. Pluronic® F-127 (PF127) was donated by BASF Corporation, Parsippany, NJ. Pluronics® are triblock copolymers of poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO) in the form of PEO-PPO-PEO. Silwet® L7605 (SL7605) was obtained from OSi Specialties, Inc., Sistersville, WV. Both Pluronics® and SL7605 are surfactants.

Synthesis

Three types of poly(NIPAM-co-AM) superporous hydrogels were synthesized. The molar ratios of NIPAM to AM in these superporous hydrogels were 9:1, 8:2, and 7:3, and were labeled for convenience as N90, N80, and N70, respectively. The superporous hydrogels were prepared in a glass test tube with inner diameter of 17 mm. The total monomer concentration was 1.34 M, and the total solution was 1.66 ml. These values, of course, can be varied. The concentration of Bis (a crosslinker) was 1 mol% of the total monomer.

Both PF127 and SL7605 surfactants were used as foam stabilizers. Their function was to stabilize the foam so that the polymerization could be completed at the foam state. Surfactants stabilized the foam by lowering the film-air interfacial tension and by increasing the film viscosity [23]. For the sample N90, both PF127 (10 mg) and SL7605 (3 mg) were used as foam stabilizers. SL7605 was first dissolved in dimethyl sulfoxide to make a 10% solution. When only one surfactant, either PF127 or L7605, was used for the sample N90, the foam did not stay long enough to make a uniform superporous hydrogel. For the samples N80 and N70, however, only 10 mg of PF127 was used as the foam stabilizer. PF127 alone stabilized the foam quite well.

Monomers, crosslinker (3.43 mg of Bis), foam stabilizers, 6 N HCl (50 μ l), and initiators (10 mg each of APS and TEMED) were added sequentially and mixed in a test tube. NaHCO₃ (60 mg) was added last. To prevent premature gelling before addition of NaHCO₃, HCl was added prior to APS and TEMED since the decomposition rate of the initiator (APS in this case) was very low under acidic condition. NaHCO₃ had two functions. First, it reacted with acid to generate CO₂ bubbles, which were essential in making foams. Second, it increased the pH of the solution to accelerate polymerization. We used an excess amount of NaHCO₃ to ensure that the final solution pH was above neutral. The foam volume was controlled by the amount of acid. In making superporous hydrogels, the timing of the foaming and polymerization processes was very important. In our study, the gelling occurred 1-2 minutes after the addition of NaHCO₃ so that the foam could remain stabilized until the polymerization was complete.

The conventional thermoreversible hydrogels were also made for comparison with superporous hydrogels. The molar ratio of NIPAM and AM was 90:10. The amounts of Bis and initiators were the same as those used in the preparation of the superporous hydrogels. No foam stabilizer and foaming agents were added. The hydrogels were prepared in a 10°C water bath to dissipate the polymerization heat so that homogeneous gels could be made. The structure of copolymers of NIPAM and AM is shown in Figure 1.

Temperature Sensitivity and Kinetics of Swelling and Deswelling

Superporous hydrogels were allowed to swell in distilled water. The LCST behavior of the superporous hydrogels was characterized by recording the equilibrium swelling volume when the temperature was increased from 10°C to 75°C at a rate less than 0.2°C/min. The length and diameter of the superporous

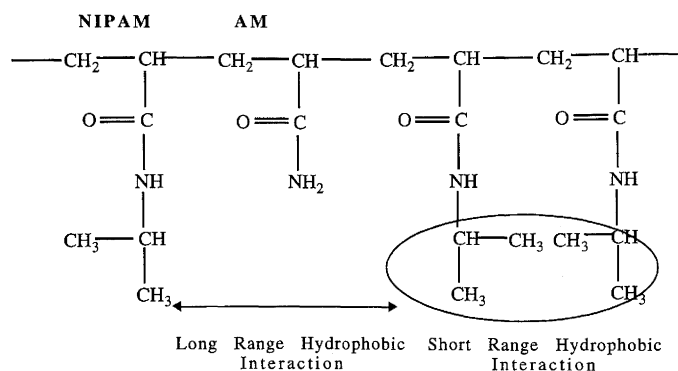


Figure 1. Schematic representation of the random copolymer of NIPAM and AM. Long range hydrophobic interaction requires higher energy to cause aggregation, which leads to higher LCST.

hydrogels were measured to calculate the volume at different temperatures. The normalized swelling volume was calculated from the ratio of the equilibrium swelling volume at a certain temperature to the equilibrium swelling volume at 10°C. To characterize the deswelling kinetics, the superporous hydrogels (N90) that were fully swollen at 10°C were transferred to 65°C. Their volumes were recorded at timed intervals. The swelling kinetics of the superporous hydrogels was characterized by transferring the superporous hydrogels fully collapsed (i.e., no more size changes) at 65°C back to 10°C, and the volumes were also recorded at timed intervals.

SEM Study

After superporous hydrogels (N90) reached the equilibrium state at 10°C or 65°C, they were quickly frozen by dropping them into liquid nitrogen and subsequently freeze-dried. The structures of the freeze-dried superporous hydrogels were examined using a scanning electron microscope (JEOL JSM-840).

RESULTS AND DISCUSSION

Temperature Sensitivity

Superporous hydrogels in a cylindrical shape were allowed to swell in distilled water at 10°C. The diameter of the fully swollen superporous hydrogels

ranged from 2.5 cm to 3.3 cm while the length varied from 3.7 cm to 4.5 cm. The superporous hydrogels made of NIPAM alone were too fragile to handle. Therefore, we added acrylamide to make copolymers to improve the mechanical property of the superporous hydrogels. Figure 2 shows the volume changes of superporous hydrogels as a function of temperature. The volumes of superporous hydrogels at each temperature were measured and compared to those at 10°C to calculate the relative swelling volume. The LCST for N90, N80, and N70 were about 42°C, 53°C, and 68°C, respectively, as estimated from Figure 2, while the NIPAM homopolymer has LCST at about 31°C [24]. The LCST values of the superporous hydrogels in this study match well with the previous study of linear copolymers, where LCST for N90 and N80 were about 42°C and 52°C, respectively [25].

Fast Response Time of the Superporous Hydrogels

The most remarkable property of the superporous hydrogels is their ability to respond fast to the temperature changes. Figure 3 shows the fast deswelling and swelling kinetics of N90 superporous hydrogel at 10°C and 65°C. The dry weight of the superporous hydrogel used in Figure 3 was 245 mg. When the

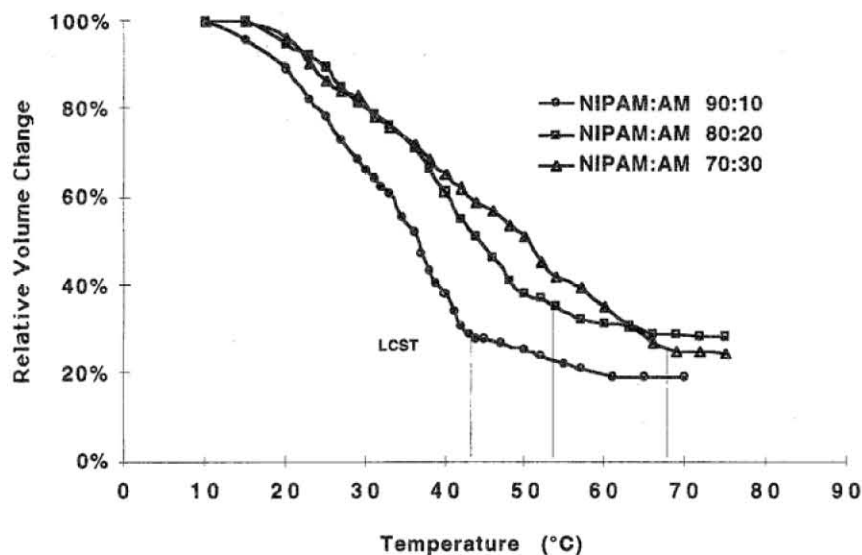


Figure 2. Relative swelling volume change as a function of temperature. The swelling volume changes were measured compared with the fully swollen state at 10°C. The LCST for N90 (○), N80 (□), and N70 (△) were 42°C, 53°C, and 68°C, respectively.

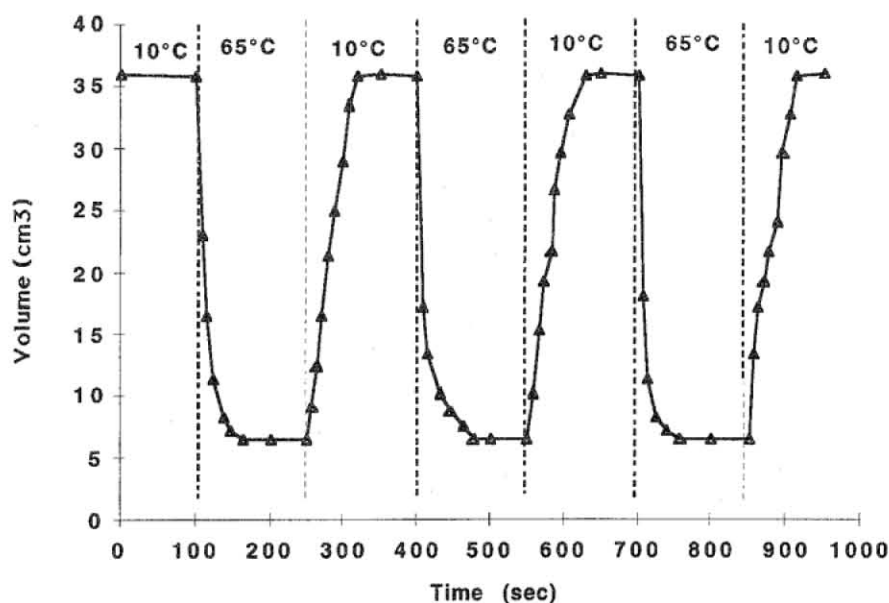


Figure 3. Fast deswelling and swelling kinetics of superporous hydrogels (N90) at 10°C and 65°C. The deswelling completed in 72 ± 14 sec, and the reswelling completed in 78 ± 15 sec. The swelling volume at fully collapsed and fully swollen state were 6.5 cm^3 to 36 cm^3 , respectively.

superporous hydrogel was transferred from 10°C to 65°C, it shrank from the fully swollen state (36 cm^3) to the fully collapsed state (6.5 cm^3) in 72 ± 14 sec. More than 90% of the volume change occurred in less than 30 seconds. When transferred back to 10°C water bath, the fully collapsed superporous hydrogel reswelled to 36 cm^3 in 78 ± 15 seconds. This cycle was repeated many times without change in the thermoreversible properties of the superporous hydrogel. The time for the superporous hydrogels to shrink to the equilibrium state was faster than that for their swelling, although by only several seconds. This may be due to hydrophobic interaction which contributes to shrinking and not to swelling. The response times of conventional thermo-sensitive hydrogels were reported to be several hours to several days, even though the hydrogels had much smaller swollen sizes [13, 14]. The photographs in Figures 4A and 4B show fast deswelling and swelling of N90 superporous hydrogels at 65°C and 10°C, respectively. In contrast, the volume of the conventional hydrogels did not change very much in a time period of 90 seconds (Figures 4C and 4D).

Figure 5 shows SEM pictures of N90 superporous hydrogels at 10°C and 65°C. The diameter of most of the pores at 10°C was several hundred micro-

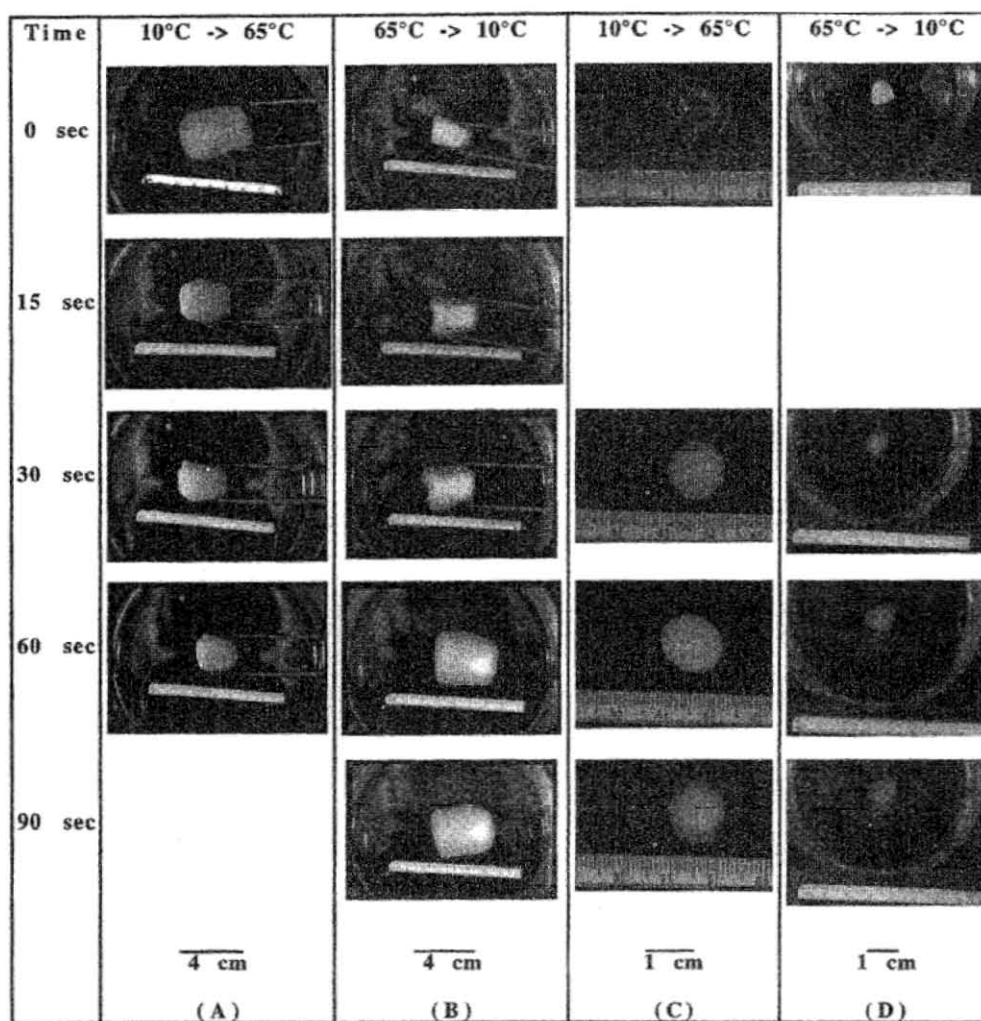


Figure 4. Photograph of (A) deswelling and (B) reswelling of superporous hydrogels (N90), and (C) deswelling and (D) reswelling of conventional hydrogel (N90). Deswelling and reswelling were induced at 65°C and 10°C, respectively.

meters, while it was reduced to about 100 μm at 65°C. Figure 5A also shows that the pores are well connected to each other so that water can easily be excluded or reabsorbed through open channels. In the conventional hydrogels, however, there are no similar structures, and the swelling is governed by diffusion of water through glass polymers, which is a very slow process [3].

Superporous hydrogels are made by crosslinking polymerization of monomers in the presence of gas bubbles. This process is similar to those used

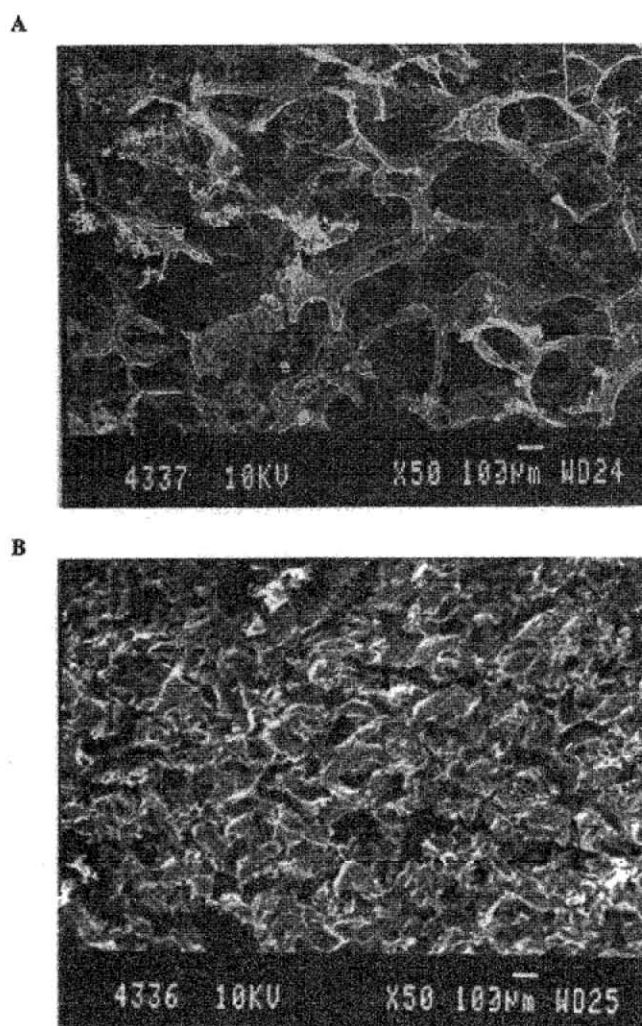


Figure 5. SEM pictures of freeze-dried N90 superporous hydrogels at (A) 10°C and (B) 65°C. The pore sizes were several hundred μm and about one hundred μm at 10°C and at 65°C, respectively.

in the plastic foam industry. Superporous hydrogels are also similar in structure to the plastic foams. Because of their hydrophilicity, however, superporous hydrogels have very different properties than the plastic foams. In aqueous solution, the plastic foams (e.g., polystyrene foams) have little swelling if at all, while superporous hydrogels can swell hundreds times their original sizes in a very short time. The superporous hydrogels that we have prepared are different from other porous hydrogels commonly called “hydrogel sponges” (e.g., poly(2-

hydroxyethyl methacrylate) (PHEMA) sponges [26]) or “macroporous hydrogels” [27]. The hydrogel sponges or macroporous hydrogels are typically synthesized by phase separation. PHEMA hydrogel sponges were prepared in aqueous solution where water was a solvent to the monomer but a non-solvent to the polymer. Phase separation occurred between the polymer and water and resulted in porous structure [26]. Thermo-sensitive macroporous poly(NIPAM) hydrogels were also synthesized by phase separation. At a temperature above the LCST, water became a non-solvent to the polymer. The phase separation occurred during the synthesis and caused the macroporous structures [14, 16, 19]. However, the size of pores in the hydrogel sponges or macroporous hydrogels were only a few micrometers or less. The pore size of the superporous hydrogels is a magnitude larger than the pore size in hydrogel sponges or macroporous hydrogels. This difference leads to significantly different properties of superporous hydrogels. Our superporous hydrogels swelled and deswelled much faster than the macroporous hydrogels, even though the latter were made into very thin discs, films, or rods. The capillary channels (Figure 5) in the superporous hydrogels are big, while the macroporous hydrogels are not likely to have similar open structures. In addition, unlike macroporous hydrogels prepared by the phase separation method or others, superporous hydrogels are easy to control the foam volume and pore size by using a different amount of foaming agent and surfactant.

As shown in Figure 2, when the content of a hydrophilic component (acrylamide) increased, the temperature sensitivity decreased. Among the three copolymers, N70 showed the least thermosensitivity. This is not surprising since thermosensitive polymers are expected to lose their sensitivity when the content of hydrophilic components reaches a certain level [28]. The mechanism of thermoshinking is believed to be the increase in hydrophobic interaction as well as weakening of the water-amide hydrogen bonding at elevated temperatures. These changes cause the aggregation of the NIPAM side chains [24] and the deswelling of the superporous hydrogels. Acrylamide, however, conveys hydrophilicity to offset the aggregation of the hydrophobic components. When the temperature rises, the NIPAM side chains tend to aggregate. However, the hydrophilic AM side chains interfere with the aggregation. In order to overcome this interference, higher energy is required for the NIPAM side chains to reach each other and aggregate. Thus, LCST has to shift to a higher temperature (Figure 2).

Superporous hydrogels are expected to find many applications in different fields. In this study, we have synthesized superporous hydrogels that can respond rapidly to the temperature change regardless of their size. Using the

same technique, we can also make other fast responsive hydrogels that can quickly respond to changes in pH, solvent, light, or electric field. Fast swelling along with superabsorbent properties of superporous hydrogels make them good candidates for improved baby diapers, sanitary napkins, or surgical pads. Fast swelling hydrogels are also useful in designing gastric retention devices [29]. For gastric retention, hydrogels have to swell before the next strong gastric contraction, known as the housekeeper wave, which sweeps the stomach to empty its contents. Superporous hydrogels swell in a matter of minutes and reach the fully swollen state much before the next housekeeper wave. Macromolecules such as proteins can also be easily absorbed into the superporous hydrogels due to the large size of pores. In biotechnology, many enzymes or cells have been immobilized in hydrogels in order to protect them from environmental stresses [30, 31]. Some of these immobilized enzymes or cells are used as bioreactors. However, one of the major problems of such systems is the mass transfer resistance of the nonporous hydrogels [32]. By providing much larger surface area and fast mass transport, superporous hydrogels are expected to provide higher reaction rate and faster product recovery. Compared with those in the conventional hydrogels, cells or tissues immobilized in superporous hydrogels can be more viable because nutrients and wastes can be easily transported via the open channels. Superporous hydrogels can also be used in restorative surgery where the superporous hydrogels fill the cavity and allow new tissue growth in the porous structure [33].

Currently, superporous hydrogels become rather weak upon swelling. Considering more than 99% of the total weight is water, it is not surprising that the fully swollen superporous hydrogels do not maintain high mechanical strength. Superporous hydrogels maintaining high mechanical strength would be more useful. For this reason, we improved the mechanical strength of superporous hydrogels by making composites. Hydrophilic particulate materials can be included to form composite materials. We noticed that the mechanical strength of the fully swollen hydrogels increased dramatically without sacrificing the swelling kinetics. Thus, it is possible to prepare superporous hydrogel composites which respond fast to environmental changes.

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