"On–Off" Thermocontrol of Solute Transport. I. Temperature Dependence of Swelling of *N*-Isopropylacrylamide Networks Modified with Hydrophobic Components in Water

You Han Bae,[1] Teruo Okano,[1] and Sung Wan Kim[1,2]

Received June 27, 1990; accepted October 18, 1990

The swelling in water, as a function of temperature, of two series of *N*-isopropylacrylamide (NIPAAm) polymer networks was studied. In the first series, *n*-butylmethacrylate (BMA) was copolymerized with NIPAAm, and in the second, polytetramethylene ether glycol (PTMEG) was incorporated into NIPAAm network as a chemically independent interpenetrating network. With increasing BMA content in the poly(NIPAAm-co-BMA) network, the gel collapse point was lowered and the gels deswelled in a more gradual manner with increasing temperature. In the interpenetrating polymer networks (IPN) system, the gel collapse point was not significantly changed by the amount of incorporated PTMEG. In DSC thermograms of swollen samples, the shape and onset temperature of the endothermic peak corresponded to the gel deswelling behavior and gel collapse point. The temperature dependence of equilibrium swelling in water was shown to be a function of the gel composition in both network series. The synthesized networks formed a dense surface layer as the temperature increased past the gel collapse point. This dense layer retarded water efflux and thereby resulted in water pockets at the membrane surface.

KEY WORDS: thermosensitivity; hydrogels; *N*-isopropylacrylamide; interpenetrating polymer networks; surface deswelling.

INTRODUCTION

Most polymeric drug delivery systems show release rates ranging from first-order to zero-order kinetics. Recent pharmacokinetic and pharmacodynamic considerations of drug delivery (1), however, reveal that many drugs, especially peptide drugs, require specific input functions, such as zero-order, pulsatile, or mixed wave functions, in order to obtain maximum drug efficacy and to minimize side effects and tolerance development. To achieve a specific input function, one possible methodology could be to use externally modulated drug release with a particular physical stimulus, such as ultrasound (2), temperature (3), or electric current application (4). Toward this end, it might be useful to utilize hydrogels responsive to such external stimuli. By inducing a change in their swelling, which directly correlates to the release rate of the incorporated drugs, one might be able to effect stimuli sensitive drug release. In this regard, temperature-responsive hydrogels are a potential candidate for pulsatile release modulation through the control of the temperature of the device.

[1] Department of Pharmaceutics and Center for Controlled Chemical Delivery, University of Utah, Salt Lake City, Utah 84112.
[2] To whom correspondence should be addressed.

Lower critical solution temperatures (LCST) appear in certain polymer solutions which show phase separation upon heating through this temperature (5–8). The thermodynamic conditions for an LCST include a negative enthalpy of mixing and a negative entropy of mixing (6,7). The LCST phenomenon in an aqueous system is associated with the temperature dependence of molecular interactions, such as hydrogen bonding and hydrophobic interactions. The temperature dependence of viscosities of water soluble polymers relates to the molecular structure of the polymer repeat unit. Polymers such as poly(acrylic acid) and poly(acrylamide), which form intramolecular hydrogen bonds in water, have a decrease in viscosity with increasing temperature, although aqueous solutions of poly(methacrylic acid) and poly(methacrylamide) show the opposite temperature dependence (9). The effect of structural change of the repeat unit in a series of cross-linked poly(*N,N*-alkyl acrylamides) on the temperature dependence of polymer swelling in water was studied and indicated that structural factors of the repeat unit of a water-soluble polymer can be of importance to the temperature dependence of its solubility (10). Additionally, there were several examples where the LCSTs of water soluble polymers were controlled through the hydrophilic/hydrophobic (HPL/HPB) balance of the polymer chain. This HPL/HPB balance can be achieved by several methods, including random copolymerization of HPL and HPB monomers and changing alkyl side groups in monomer units (11,12). Considering this, we hypothesized that the temperature dependence of swelling of a polymer network in water could be affected through a change in the HPL/HPB balance of the polymer chain.

Among polymers showing LCST in aqueous solutions, cross-linked poly(*N*-isopropylacrylamide) [poly(NIPAAm)] and its copolymers have been studied as thermosensitive hydrogels and utilized in molecular separation (13,14), controlled release (3,15,16), and immobilized enzyme activity control (17,18). The collapse of swollen NIPAAm networks with or without ionizable groups at elevated temperature was intensively studied by Tanaka *et al.* (19,20), Matsuo and Tanaka (21), and Hirotsu (22).

Another approach for modifying gel properties would be to synthesize HPL/HPB chain interpenetrating polymer networks (IPN). In IPNs, the second network is independent from the primary thermosensitive network, and the overall hydrophilicity or hydrophobicity of the system can be controlled by varying the proportions of the two networks.

In this paper, the thermosensitive swelling in water of NIPAAm networks modified with HPB components is reported as a function of gel composition. In particular, gel deswelling caused by an elevation of temperature has been characterized by using differential scanning calorimetry (DSC) and the observation of swollen samples with reflection optical microscopy.

EXPERIMENTAL

Materials

N-Isopropylacrylamide (NIPAAm), butylmethacrylate (BMA), ethylene glycol dimethacrylate (EGDMA), and bu-

0724-8741/91/0400-0531$06.50/0

tylperoxyoctanoate (BPO) were obtained from Polysciences, Inc. (Warrington, PA). BMA was purified by distillation under nitrogen, and the fraction at 57°C/17 mm Hg was collected. *N,N'*-Methylene-bis-acrylamide (MBAAm) and ammonium persulfate (AP) were obtained from Sigma Chemical Co. (St. Louis, MO). *N,N,N',N'*-Tetramethylethylene diamine (TEMED) was purchased from Aldrich Chemical Co., Inc. (Milwaukee, WI). Polytetramethylene ether glycol (PTMEG) (MW 2000) was obtained from Polysciences, Inc., and vacuum dried at 80°C for 8 hr before use. A triisocyanate compound (1,1,1-tris[*N*-(4'-methyl-3'-isocyanato-phenyl) carbamoyl-oxymethyl]-propane) (Colonate L, Japan Polyurethane Co. Ltd.), used for the cross-linking of PTMEG, was obtained in an ethyl acetate solution having 75 wt% solid content and 13.2 wt% NCO content.

Synthesis

A cross-linked homo-poly(NIPAAm), denoted NIPAAm network I, was formed by using a standard redox system. TEMED and AP were used as redox initiators. MBAAm was used as a cross-linking agent, and distilled-deionized water was used as diluent. The redox initiators (1.75×10^{-5} mol AP and 2.93×10^{-4} mol TEMED) were added to the monomer solution (1.76×10^{-2} mol NIPAAm, 1.76×10^{-4} mol MBAAm, and water to make a total of 10 ml), which was bubbled with dried nitrogen for 15 min. The mixture was then vigorously shaken for 15 sec prior to injection into a glass mold (12.7 × 12.7 cm) separated by a rubber gasket (1-mm diameter). Polymerization was performed in a temperature-controlled water bath at 4°C for 12 hr. The polymer gels were separated from the mold and soaked in distilled-deionized water to extract unreacted compounds. The water was replaced daily for 1 week.

The cross-linked poly(NIPAAm-co-BMA) series, including another homopolymer network denoted by R(100/0), was synthesized using EGDMA as a cross-linker and BPO as an initiator. In the sample code, R indicates random copolymers of NIPAAm and BMA, and the two numbers separated by a slash in parentheses indicate mole percentages of NIPAAm and BMA in the feed composition, respectively. NIPAAm was dissolved in freshly distilled 1,4-dioxane, followed by the addition of BMA, BPO, and EGDMA in the specific feed compositions listed in Table I. The solutions were bubbled with dried nitrogen for 20 min and injected between two Mylar sheets separated by a rubber gasket (1-mm diameter) and backed by glass plates. Mylar sheet was used here because there was no swelling in the polymerization mixtures at elevated temperature and separation was easy after polymerization. Polymerizations were performed at 80°C in a constant-temperature oven for 40 hr. After cooling to room temperature, the membrane was separated from the Mylar sheets. The resultant polymer membranes showed smooth surfaces and had uniform thickness. These were cut into disks with a cork borer (12-mm diameter) and then immersed in 100% methanol to remove water-insoluble components such as BMA. The methanol solution was changed every day over a period of 2 weeks. The membrane was then soaked in an excess amount of 75/25 (v/v%) and 50/50 (v/v%) methanol/distilled water mixtures for 1 day each and, finally, in pure water for 1 day.

Poly(NIPAAm)/PTMEG IPNs with various compositions were synthesized as shown in Table II. The reaction mixtures in DMSO were warmed with hot water to get clear solutions and injected between siliconized glass plates separated by a rubber gasket (1-mm diameter). In this case, a Mylar sheet was not used because it swells in DMSO at high temperatures and polymer membranes formed between Mylar sheets were difficult to separate and had nonuniform thickness. In the sample code in Table II, IPN stands for interpenetrating polymer networks, and the numbers indicate the weight ratio of NIPAAm to PTMEG in the feed composition. The polymerization and cross-linking reactions for both networks of the IPNs were conducted simultaneously at 80°C for 3 days. Here, the NIPAAm network was formed by radical polymerization and the PTMEG network was formed by stepwise cross-linking with the triisocyanate compound. The polymer membranes were separated from the molds and cut into disks using a cork borer (12-mm diameter). DMSO and unreacted compounds were extracted by soaking in a water/ethanol mixture (50/50, v/v%) for 1 week.

Table I. Feed Compositions for Cross-Linked Poly(NIPAAm-co-BMA)

	Sample code				
Component	R(100/0)	R(97.5/2.5)	R(95/5)	R(92.5/7.5)	R(90/10)
NIPAAm					
g	4.00	4.00	4.00	4.00	4.00
mol	3.53×10^{-2}	3.53×10^{-2}	3.53×10^{-2}	3.53×10^{-2}	3.53×10^{-2}
BMA					
g	0.00	0.142	0.266	0.408	0.559
mol	0.00	1.00×10^{-3}	1.87×10^{-3}	2.87×10^{-3}	3.93×10^{-3}
EGDMA					
ml	0.070	0.072	0.074	0.076	0.078
mol	3.71×10^{-4}	3.82×10^{-4}	3.92×10^{-4}	4.03×10^{-4}	4.14×10^{-4}
BPO					
ml	0.012	0.012	0.012	0.012	0.012
mol	4.97×10^{-5}	4.97×10^{-5}	4.97×10^{-5}	4.97×10^{-5}	4.97×10^{-5}
1,4-Dioxane (ml)	4.00	4.13	4.27	4.41	4.56

Table II. Feed Compositions for Poly(NIPAAm)/PTMEG IPNs

Component	Sample code				
	IPN(100/0)	IPN(95/5)	IPN(90/10)	IPN(75/25)	IPN(50/50)
NIPAAm					
g	5.00	4.75	4.50	3.75	2.50
mol	4.42×10^{-2}	4.20×10^{-2}	3.98×10^{-2}	3.31×10^{-2}	2.21×10^{-2}
EGDMA					
ml	0.083	0.079	0.075	0.063	0.042
mol	4.40×10^{-4}	4.19×10^{-4}	3.98×10^{-4}	3.34×10^{-4}	2.23×10^{-4}
BPO					
ml	0.015	0.015	0.015	0.015	0.015
mol	6.21×10^{-5}	6.21×10^{-5}	6.21×10^{-5}	6.21×10^{-5}	6.21×10^{-5}
PTMEG					
g	0.00	0.25	0.50	1.25	2.50
mol	0.00	1.25×10^{-4}	2.5×10^{-4}	6.25×10^{-4}	12.5×10^{-4}
Tri-NCO					
g	0.00	0.054	0.108	0.269	0.539
mol	0.00	8.40×10^{-5}	1.68×10^{-4}	4.19×10^{-4}	8.39×10^{-4}
DMSO (ml)	5.00	5.00	5.00	5.00	5.00

Swelling Measurement

In order to obtain dried polymer weights before swelling measurements, three samples of each polymer were dried at room temperature for 1 day and then dried under vacuum (20–30 μm Hg) at 50°C for 3 days. These dried samples were then kept in a thermostated water bath (range, 60 to 3°C). The polymer samples were removed from water and blotted with filter paper to remove excess water on the sample surface. The polymer samples were weighed at given time intervals at a fixed temperature (±0.1°C) until the weight change detected was less than 1%. After equilibration at one temperature, samples were reequilibrated at another temperature. The weight swelling ratio was defined as $(W_s + W_p)/W_p$, where W_s is the weight of absorbed water and W_p is the polymer weight in the dried state. Changes in the gel surface with time were observed by reflection optical microscopy (Nikon SMZ-10) upon raising the temperature past the gel collapse point of the polymer sample.

Differential Scanning Calorimetry

Thermal characterization of the gels equilibrated in distilled-deionized water at room temperature was conducted with scanning rates of 10°C/min with a differential scanning calorimeter (DSC) (Perkin Elmer DSC-4). The sample weight was ca. 5 mg. Helium was used as a sweep gas (24 ml/min).

RESULTS AND DISCUSSION

The temperature dependences of swelling in water of two homo-NIPAAm networks [NIPAAm network I and R(100/0)], formed by different synthesis procedures, are compared in Fig. 1. R(100/0) showed a higher swelling level before gel collapse, a lower gel collapse point (temperature for complete deswelling), and a lower swelling level after gel collapse than NIPAAm network I. These results suggest an increased thermosensitivity in swelling in water in comparison with NIPAAm network I.

This higher swelling in a low-temperature region may result from the lower cross-linking density of R(100/0) (about 1/13 that of the NIPAAm network I), which is estimated by compression modulus measurements of swollen samples, as described elsewhere (10,23). The small amounts of components such as cross-linker probably affect gel deswelling behavior. Hoffman *et al.* (15) reported the swelling behavior of NIPAAm networks synthesized by redox initiation with different diluents, monomer, and cross-linker concentration. These polymers showed different swelling ratios before and after gel collapse and gradual swelling changes around 40°C, although the thermosensitivity (the slope in the swelling–temperature curve) did not change in the temperature range of 30 to 40°C. The weight swelling ratios $[(W_s + W_p)/W_p]$ above 40°C were 4 to 6, regardless of the synthetic conditions, while those for the networks we synthesized were less than 2. The gel collapse point was not affected by different

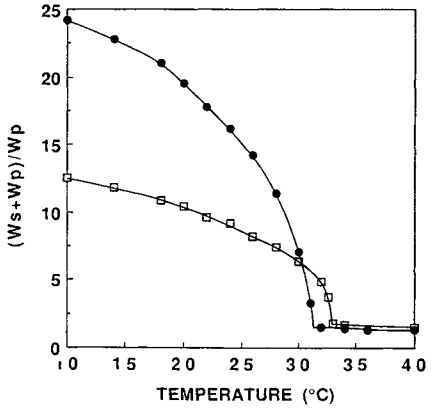

Fig. 1. Comparison of aqueous swelling as a function of temperature for two homo-NIPAAm networks synthesized under different synthetic conditions (n = 3, ±5%). Open squares, NIPAAm network I; filled circles, R(100/0). Refer to the text for synthetic conditions.

synthetic conditions (different diluents and monomer concentrations). Cussler *et al.* (13) used similar synthetic conditions and reported a relatively sharp deswelling around 33°C. This sharp deswelling was consistent with our results but contrasted with the results reported by Hoffman *et al.* (15). This different gel deswelling behavior could possibly be caused by impurities in monomers and solvents, such as ionizable components or other monomers.

The effects of the introduction of a hydrophobic component into the NIPAAm network, demonstrated by copolymerization of NIPAAm with hydrophobic BMA, on the network swelling in water are shown in Fig. 2. As the BMA content in the feed composition increased, the gel collapse point occurs at a lower temperature. A characteristic feature of the copolymers is that more gradual deswelling is observed and this tendency was enhanced with increasing BMA content in feed composition. This result indicates that the small amount of HPB components, such as BMA, incorporated into NIPAAm polymer chain may substantially affect the thermosensitivity of the NIPAAm network and gel deswelling pattern. Among *N,N*-alkyl derivatives of acrylamide, only cross-linked poly(NIPAAm) showed a sharp deswelling around 33°C. This unique behavior could be attributed to the HPL/HPB balance of the repeat unit of the polymer (10). With increasing temperature, hydrogen bond interaction decreases while hydrophobic interaction is enhanced. These two interactions may be responsible for the thermosensitivity in swelling of tested gel networks. Thus, incorporated hydrophobic BMA may disturb the HPL/HPB balance affecting deswelling behavior. This effect was enhanced by increasing the BMA content. The comonomer in the NIPAAm copolymer networks appears to affect the temperature dependency of swelling in the same manner as changing monomeric structure, which is similar to the effects on LCST (11).

Calorimetric studies of swollen gels were performed with a differential scanning calorimeter. Figure 3 shows an example of the thermogram of a swollen NIPAAm network I. The gel samples used in the DSC study were equilibrated in distilled-deionized water at room temperature. The melting water isotherm shows multiple peaks located between

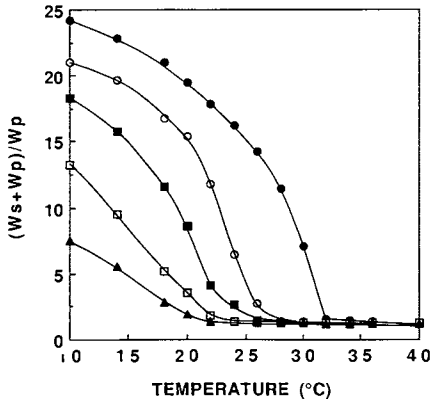

Fig. 2. Equilibrium swelling of cross-linked poly(NIPAAm-co-BMA) in water as a function of temperature (n = 3, ±5%). Filled circles, R(100/0); open circles, R(97.5/2.5); filled squares, R(95/5); open squares, R(92.5/7.5); filled triangles, R(90/10).

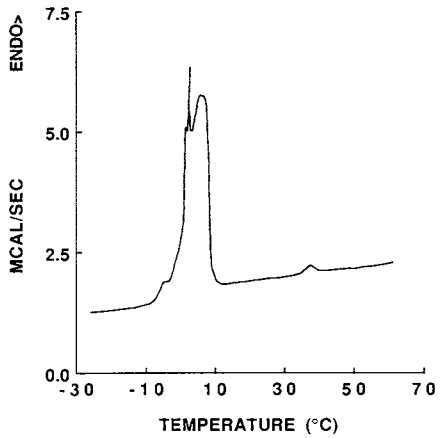

Fig. 3. DSC thermogram for the swollen matrix NIPAAm network I in water at room temperature. The scan rate used was 5°C/min.

−10 and 10°C. Similar water melting isotherms have been observed between −15 and 20°C in swollen poly(HEMA) and reported in the literature (24,26). The size and shape of these melting endotherms were explained in terms of either bound water, intermediate water, and free water existing in the swollen gel (24,25) or the development of a metastable nonequilibrium situation upon cooling the gel (26). There appears to be a small, but clear, endothermic peak between 30 and 40°C. This peak appeared at the same position with various scan rates (3, 5, and 10°C/min) and even after repeated scannings with the same gel sample. For comparison, the magnified thermograms in the temperature range of 25 and 50°C for swollen NIPAAm network I and random copolymer networks in distilled-deionized water at room temperature are shown in Fig. 4. It is interesting to note that the peak shape for NIPAAm gels, NIPAAm network I, and R(100/0) is relatively symmetric and sharp, whereas copolymer gels show broad peaks. The onset points of the peaks, determined by the intersecting point of two tangent lines for baseline and upslope of peak determined manually as shown in Fig. 4, are closely related to the temperature defined by

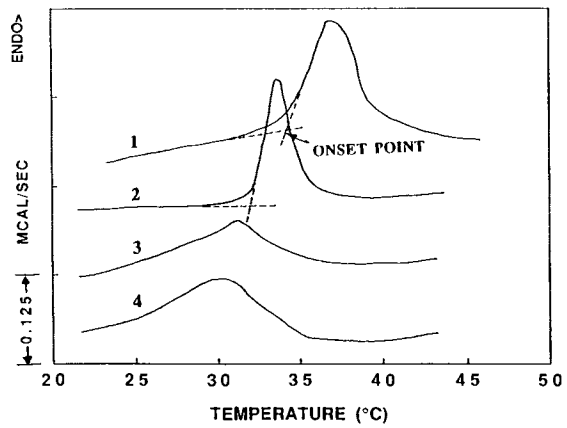

Fig. 4. Magnified DSC thermogram for swollen NIPAAm network I and cross-linked poly(NIPAAm-co-BMA) equilibrated in distilled-deionized water in room temperature. Scanning was done from 25 to 70°C at a scan rate of 10°C/min. The swollen sample weight was ca. 5 mg: 1, NIPAAm network I; 2, R(100/0); 3, R(97.5/2.5); 4, R(95/5).

the intersecting point of a tangent line for downslope and the line of completely shrunken state in the equilibrium swelling as a function of temperature (Fig. 2). These intersecting points determined manually were reproducible within ±1°. These facts indicate that gel deswelling involves a weak endothermic process and that there may be unknown additional interactions. It is likely that there are hydrophobic interactions between polymer segments in the hydrated state when the gel collapses.

The types of gel collapse can be distinguished by the endothermic peak shape located between 30 and 40°C. The sharp deswelling of NIPAAm homopolymers is reflected by a relatively narrow endothermic peak in the corresponding DSC thermogram, and this peak becomes broader with increased BMA content [e.g., R(97.5/2.5) and R(95/5)], corresponding to the gradual deswelling.

The equilibrium swelling of poly(NIPAAm)/PTMEG IPNs in water as a function of temperature is presented in Fig. 5. The apparent transparency of dried IPNs was reduced with an increasing PTMEG content. IPN(95/5) was yellowish and slightly translucent and IPN(50/50) was opaque. In a highly swollen state, at low temperatures, all of the IPNs were opaque. These changes in transparency can indicate phase separation or incompatibility between two networks in the swollen state (27).

As seen in Fig. 5, IPN(95/5) showed comparable swelling behavior to IPN(100/0) at all temperatures. The gel collapse temperature was not significantly changed by the amount of incorporated PTMEG, while thermosensitivities below 32°C decreased as PTMEG content increased. This behavior was confirmed by the shape and onset point of endothermic peaks at the swelling transition temperature of poly(NIPAAm)/PTMEG IPNs (Fig. 6). This indicates that the PTMEG network in the gels is independent from NIPAAm network and exists as a separate phase in the swollen state. With more than 5 wt% of PTMEG, this separate phase may play a role in restricting the swelling of the NIPAAm network. The swelling and thermosensitivities decreased due to the physical restriction of the NIPAAm network and as a result of the hydrophobicity of the PTMEG network.

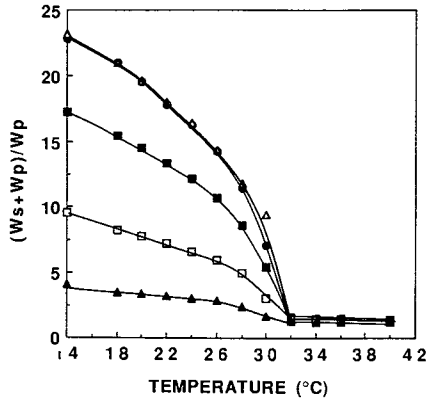

Fig. 5. Equilibrium swelling of the NIPAAm/PTMEG IPNs in water as a function of temperature (n = 3, ±5%). Filled circles, IPN(100/0); open triangles, IPN(95/5); filled squares, IPN(90/10); open squares, IPN(75/25); filled triangles, IPN(50/50).

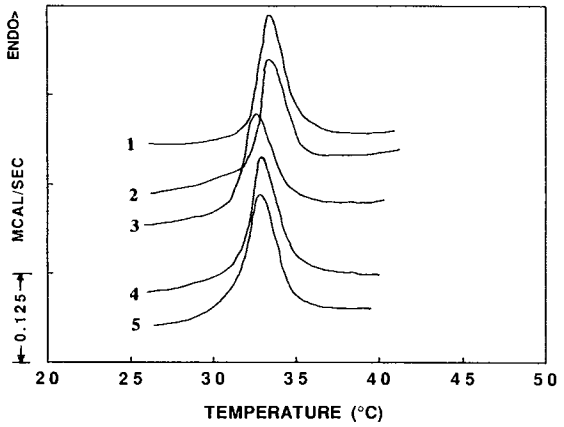

Fig. 6. DSC thermograms for swollen poly(NIPAAm)/PTMEG IPNs equilibrated in distilled-deionized water in room temperature. The scanning was from 25 to 70°C with a scan rate of 10°C/min. The swollen sample weight was ca. 5 mg: 1, IPN(100/0); 2, IPN(95/5); 3, IPN(90/10); 4, IPN(75/25); 5, IPN(50/50).

In the IPN system, PTMEG affects the overall HPL/HPB balance of the system, but not the basic NIPAAm network properties. As a result, the gel collapse point and thermosensitivity can be independently controlled if we use IPNs and random copolymerization simultaneously. This can be a useful tool for the design of thermosensitive gels for different applications.

When the temperature was increased through the gel collapse point, the slow formation of a dense surface layer was found for all the polymers during gel deswelling. The rate of the dense surface formation is slower than the case of a submicron bead composed of *N*-isopropylacrylamide and ionizable comonomer (21), whose swelling and deswelling equilibria were reached within a minute. A possible explanation for this skin formation is that, when the gel was exposed to a temperature above its gel collapse point, the outermost layer of the gel interacts with its environment and deswells quickly, forming a dense surface (21). When the deswollen exterior layer was dense enough to retard water efflux, water pockets formed at the surface and the size of these pockets increased with time. A typical example of skin formation for matrix R(97.5/2.5) is illustrated in Fig. 7. When the temperature increased from 20°C (equilibrium state) to 30°C, a white layer formed on the swollen disk surface after 20 min and clear water pockets were present after 55 min (Fig. 7A). Equilibrium swelling at 30°C without water pockets took longer than 1 month. The dense surface layer was dissipated by decreasing the temperature from 30°C (the sample was kept for 130 min at this temperature) to 20°C, as shown in Fig. 7B. The clear interface between the water pockets and the bulk water was dissipated immediately, and the gel completely recovered its initial shape at 20°C after 100 min. Even though several researchers have reported gel swelling kinetics (28,29) and gel collapse (19–22), the surface phenomenon including water pocket formations is another topic to be considered and needs further detailed study. This phenomenon can be applied as a solute release barrier and will be reported in paper II (30).

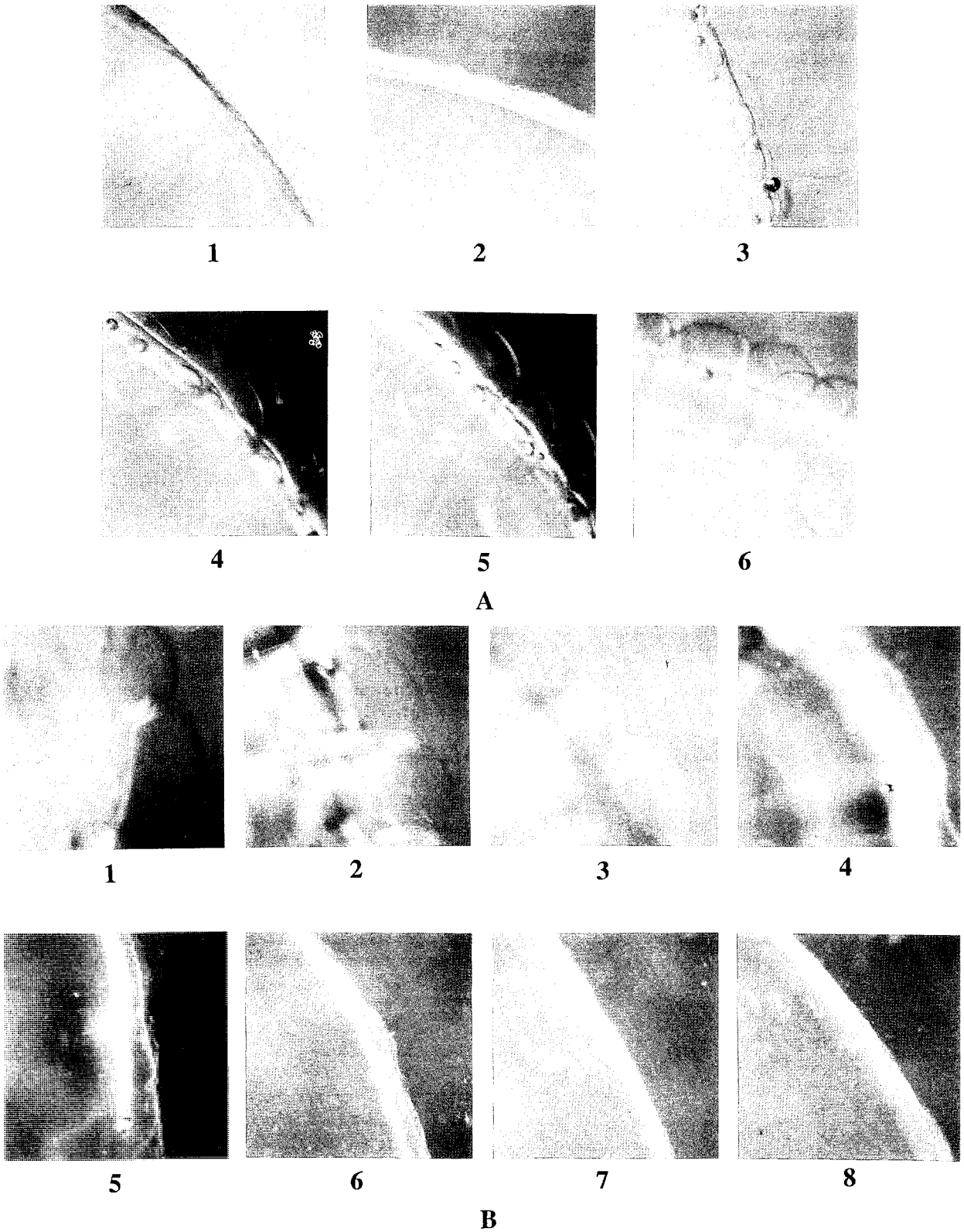

Fig. 7. Photographs of skin formation and diminishing of unloaded n atrix by temperature changes between 20 and 30°C. The pictures were obtained by using the matrix of R(97.5/2.5). (A) Skin formation by an increasing temperature from 20°C (equilibrium state) to 30°C: 1, 0 min; 2, 20 min; 3, 55 min; 4, 65 min; 5, 80 min; 6, 90 min. (B) Skin diminishing by a decreasing temperature from 30°C (the sample was kept at this temperature for 130 min) to 20°C: 1, 0 min; 2, 10 min; 3, 30 min; 4, 35 min; 5, 50 min; 6, 80 min; 7, 100 min; 8, 250 min.

REFERENCES

1. N. A. Mazer. Pharmacokinetic and pharmacodynamic aspects of polypeptide delivery. *J. Control. Rel.* 11:343–356 (1990).
2. J. Kost, K. W. Leong, and R. Langer. Ultrasonic controlled polymeric delivery. *Proc. Int. Symp. Control. Rel. Bioact. Mater.* 10:84–85 (1983).
3. Y. H. Bae, T. Okano, and S. W. Kim. Thermo-sensitive polymers as on-off switches for drug release. *Makromol. Chem. Rapid Commun.* 8:481–485 (1987).
4. S. R. Eisenberg and A. J. Grodzinsky. Electrically modulated membrane permeability. *J. Membr. Sci.* 19:173–194 (1984).
5. P. I. Freeman and J. S. Rowlinson. Lower critical points in polymer solutions. *Polymer* 1:20–26 (1960).
6. D. Patterson. Free volume and polymer solubility. A qualitative view. *Macromolecules* 2:672–679 (1969).
7. A. H. Liddell and F. L. Swington. Thermodynamic properties of some polymer solutions at elevated temperatures. *Disc. Faraday Soc.* 49:115–120 (1970).
8. F. W. Billmeyer, Jr. *Textbook of Polymer Science,* 2nd ed., John Wiley & Sons, New York, 1970, pp. 39–41.
9. A. Silberberg, J. Eliassaf, and A. Kachalsky. Temperature-dependence of light scattering and intrinsic viscosity of hydrogen bonding polymers. *J. Polym. Sci.* 23:259–281 (1957).
10. Y. H. Bae, T. Okano, and S. W. Kim. Temperature dependence of swelling of crosslinked poly(N,N′-alkyl substituted acrylamides) in water. *J. Polym. Sci. Part B Polym. Phys.* 28:923–936 (1990).
11. L. D. Taylor and L. D. Cerankowski. Preparation of films exhibiting a balanced temperature dependence to permeation by aqueous solution—A study of lower consolute behavior. *J. Polym. Sci. Polym. Chem. Ed.* 13:2551–2570 (1975).
12. J. H. Priest, S. L. Murry, R. J. Nelson, and A. S. Hoffman. Lower critical solution temperatures of aqueous copolymers of N-isopropylacylamide and other N-substituted acrylamides. *ACS Symp. Ser.* 350:255–264 (1987).
13. Roberto F. S. Freitas and E. L. Cussler. Temperature sensitive gels as extraction solvents. *Chem. Eng. Sci.* 42:97–103 (1987).
14. Roberto F. S. Freitas and E. L. Cussler. Temperature sensitive gels as size selective absorbants. *Separat. Sci. Technol.* 22:911–919 (1987).
15. A. S. Hoffman, A. Afrassiabi, and L. C. Dong. Thermally reversible hydrogels. II. Delivery and selective removal of substances from aqueous solutions. *J. Control. Rel.* 4:213–222 (1986).
16. Y. Okahata, H. Noguchi, and T. Seki. Thermoselective permeation from a polymer-grafted capsule membrane. *Macromol.* 19:493–494 (1986).
17. L. C. Dong and A. S. Hoffman. Thermally reversible hydrogels. III. Immobilization of enzymes for feedback reaction control, *J. Control. Rel.* 4:223–227 (1986).
18. T. G. Park and A. S. Hoffman. Effect of temperature cycling on the activity and productivity of immobilized galactosidase in a thermally reversible hydrogel bead reactor. *Appl. Biochem. Biotech.* 19:1–9 (1988).
19. S. Hirotsu, Y. Hirokawa, and T. Tanaka. Volume-phase transitions of ionized N-isopropylacrylamide gels. *J. Chem. Phys.* 87:1392–1359 (1987).
20. Y. Hirose, T. Amiya, Y. Hirokawa, and T. Tanaka. Phase transition of submicron gel beads. *Macromol.* 20:1342–1344 (1987).
21. E. S. Matsuo and T. Tanaka. Kinetics of discontinuous volume-phase transition of gels. *J. Chem. Phys.* 89:1695–1703 (1988).
22. S. Hirotsu. Critical points of the volume phase transition in N-isopropylacryamide gels. *J. Chem. Phys.* 88:427–431 (1988).
23. E. F. Cluff, E. K. Gladding, and R. Pariser. A new method for measuring the degree of crosslinking in elastomers. *J. Polym. Sci.* XLV:341–345 (1960).
24. Y. K. Sung, D. E. Gregonis, M. S. John, and J. D. Andrade. Thermal and pulse NMR analysis of water in poly(2-hydroxyethyl methacrylate). *J. Appl. Polym. Sci.* 26:3719–3728 (1981).
25. H. B. Lee, M. S. John, and J. D. Andrade. Nature of water in synthetic hydrogels. 1. Dilatometry, specific conductivity, and differential scanning calorimetry of polyhydroxyethyl methacrylate. *J. Colloid Interface Sci.* 51:225–331 (1975).
26. W. E. Roorda, J. A. Bouwstra, M. A. de Vries, and H. E. Junginger. Thermal behavior of poly hydroxy ethyl methacrylate (pHEMA) hydrogels. *Pharm. Res.* 5:722–725 (1988).
27. L. H. Sperling. *Interpenetrating Polymer Networks and Related Materials,* Plenum Press, New York, 1981.
28. A. Peters and S. J. Candau. Kinetics of swelling of polyacrylamide gels. *Macromol.* 19:1952–1955 (1986).
29. Y. Hirokawa, E. Sato, S. Hirotsu, and T. Tanaka. Critical kinetics of isopropylacrylamide gel swelling. *Polym. Mater. Sci. Eng.* 52:520–521 (1985).
30. Y. H. Bae, T. Okano, and S. W. Kim. "On–off" thermocontrol of solute transport. II. Solute release from thermosensitive hydrogels. *Pharm. Res.* 8:624–628 (1991).