Rapid Deswelling Response of Poly(*N*-isopropylacrylamide) Hydrogels by the Formation of Water Release Channels Using Poly(ethylene oxide) Graft Chains

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ABSTRACT: Poly(ethylene oxide) (PEO) chains are introduced as graft chains maintaining freely mobile ends in thermo-responsive cross-linked poly(*N*-isopropylacrylamide) (PIPAAm) hydrogels by copolymerization of IPAAm with α-acryloyl-ω-methoxy-PEO. The deswelling response on raising the temperature of this gel above the gel phase transition temperature (T_P) takes place within 10 min, whereas a conventionally cross-linked PIPAAm gel of the same dimensions requires 1 month for deswelling. This difference is due to the formation of water release channels within the skin layer by the hydrophilic PEO graft chains. The rapid deswelling of the grafted gel is compared with the deswelling changes of random copolymer gels composed of IPAAm and hydrophilic acrylic acid (AAc), which also accelerates gel deswelling. Deswelling is fastest in copolymers containing 1.3 wt % AAc and in grafted gels containing 13 wt % PEO. These results were interpreted as reflecting the gel structure.

Introduction

Much attention has been recently focused on stimuli-responsive polymers as advanced biomedical technologies including "on−off" switching materials,[1] drug delivery systems,[2−5] artificial muscles,[6−10] and mass separations.[11,12] We have been studying thermoresponsive poly(*N*-isopropylacrylamide) (PIPAAm) cross-linked gels as drug release regulating devices that respond to temperature changes.[1,2] PIPAAm molecules in aqueous solution exhibit a rapid and reversible hydration−dehydration change in response to small temperature changes around its lower critical solution temperature (LCST; 32 °C).[13,14] Isopropyl groups in the PIPAAm side chain play an important role in temperature dependent hydrophobic aggregation in water, resulting in a phase separation above the LCST. When a cross-linked PIPAAm gel is immersed in water above the LCST, deswelling immediately starts at the gel surface due to the free mobile nature of the surface and the collective diffusion of the cross-linked polymer network in water.[15,16] The gel thus forms a dense polymer skin layer at the surface.[2] This prevents permeability, entrapping water within the gel. We have been investigating thermally induced "on−off" drug release regulation by utilizing the formation of a skin layer impermeable to drug molecules as well as water.[1,2] This skin layer leads to the very slow deswelling of the bulk polymer network.

To promote new applications of hydrogels, such as artificial muscles and rapidly acting actuators, the swelling−deswelling of the bulk gel and its surface has to be accelerated. Many researchers used gels with macropore structures to increase the surface area for rapid swelling−deswelling of PIPAAm,[17−19] poly(vinyl alcohol) gel,[7] and poly(vinyl methyl ether) gels.[8] In addition, hydrophilic moieties such as acrylic acid[20] were incorporated in the PIPAAm network to reduce the hydrophobic aggregation and lead to faster deswelling without skin layer formation.

In contrast to these previous studies, we have introduced a novel deswelling mechanism to enhance the rate of swelling−deswelling of stimuli-responsive hydrogels[21,22] using a PIPAAm cross-linked gel containing PIPAAm graft chains with a freely mobile end. We have already achieved rapid thermosensitivity of bioactive molecules,[23] intelligent surfaces,[24,25] and actuators[26] by utilizing the rapid conformational changes of PIPAAm attached at one end to "on−off" molecular switches. In this graft-type PIPAAm gel, the graft chains undergo rapid dehydration in response to small temperature increase due to the nature of the freely mobile end. As the graft chains become hydrophobic, the backbone network shrinks at the LCST due to hydrophobic sites created within the polymer network[2,27] and water is rapidly released from the gel. These results suggest that this deswelling mechanism of the gel rather than collective diffusion is achieved due to the aggregation forces of graft polymers.[21] Compared with the conventional PIPAAm gel without graft chains, size-independent and rapid gel swelling−deswelling kinetics is obtained.

In this study, we investigate an acceleration of the thermoresponsive gel swelling−deswelling changes through a modification of the molecular structure consisting of hydrophilic graft chains. Hydrophilic poly(ethylene oxide) (PEO) graft chains are introduced into PIPAAm cross-linked network by copolymerization of acryloxy-terminated PEO with IPAAm. The graft chains have freely mobile ends and are designed to form channels for water molecules through the skin layer while maintaining strong hydrophobic attraction between the PIPAAm backbone network during the deswelling. The effect of PEO grafts for the fast deswelling changes are compared with the behavior of

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Table 1. Preparation and Characterization of NG and P(IPAAm-*g*-PEO) Hydrogels

	feed composition						
sample	IPAAm (g)	PEO macromonomer (g)	PEO (wt %)	MBAAm (g)	conversion[a] (%)	PEO[b] (wt %)	T_P (°C)
NG	1.5600	0.0000	0	0.0266	85	0.0	31.0
PEO1.7	1.4820	0.0780	5	0.0266	88	1.7	32.5
PEO4.0	1.4040	0.1560	10	0.0266	87	4.0	33.0
PEO11	1.3260	0.2340	15	0.0266	92	10.9	35.0
PEO13	1.0920	0.4680	30	0.0266	72	13.1	35.5
PEO23	0.7800	0.7800	50	0.0266	83	23.0	48.0

[a] Weight percent of synthesized dry gel to the monomers. [b] PEO content in the gel detemrined by elemental analysis.

gels containing random copolymers of IPAAm and acrylic acid (AAc). Fast and reversible swelling−deswelling changes of the gel in response to oscillating quick temperature changes are also investigated in the PEO-grafted PIPAAm gels.

Experimental Section

Materials. *N*-Isopropylacrylamide (IPAAm; Kojin Co., Tokyo, Japan) was purified by recrystallization from toluene/*n*-hexane.[14] Triethylamine (Kanto Chemical Co., Tokyo, Japan) was distilled at 90 °C under atmospheric pressure. Acrylic acid (AAc; Kanto Chemical Co.) was distilled and obtained as a fraction boiling at 55 °C/22 mmHg. Poly(ethylene oxide) methyl ether (α-hydroxy-ω-methoxy-PEO) (Aldrich Chemical Co., Milwaukee), acryloyl chloride (Tokyo Kasei Kogyo Co., Tokyo, Japan), *tert*-butyl catechol (Wako Pure Chemical Industry Co., Osaka, Japan), tetrahydrofuran (THF; Kanto Chemical Co.), and diethyl ether (Kanto Chemical Co.) were all used as received. *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TEMED), ammonium persulfate (APS), and *N*,*N*′-methylenebis(acrylamide) (MBAAm) were purchased from Kanto Chemical Co. and used as received. Chloroform (Wako Pure Chemical Industry Co.), chloroform-*d* (Aldrich Chemical Co.), and *N*,*N*-dimethylformamide (Wako Pure Chemical Industry Co.) as a GPC eluent were used as received.

PEO Macromonomer Preparation. α-Hydroxy-ω-methoxy-PEO (0.004 mol) of nominal molecular weight 5000 was dissolved in THF (200 mL). Triethylamine (5.57 mol) as a scavenger for hydrochloric acid and a small amount of *tert*-butyl catechol as a polymerization inhibitor were added to this solution. Acryloyl chloride (0.05 mol) was dropwisely added at 0 °C, and the solution was kept at 40 °C for 1 day with vigorous stirring. After the reaction, the solution was separated from precipitated triethylamine hydrochloride by vacuum filtration using Celite as a filter and was concentrated by evaporating THF. The reactant was poured into diethyl ether to precipitate α-acryloyl-ω-methoxy-PEO. The macromonomer product was then freeze-dried from aqueous solution.

PEO Macromonomer Analysis. The end group of the polymer was analyzed by FT-IR (JASCO VALOR-III, Tokyo, Japan) and ^{1}H NMR measurements. Hydroxy-terminated or acryloyl-terminated methoxy-PEO was cast on NaCl crystal from chloroform solution to obtain FT-IR spectra of polymers. The changes in absorbance at 3630 cm^{-1} for hydroxyl group and 1720 cm^{-1} for carbonyl group were measured to analyze the introduction of the terminal acryloyl group. In the NMR study, polymers were dissolved in chloroform-*d*. Chemical shifts for a ^{1}H attributed to the terminal double bond were measured using 400 MHz NMR equipment (Bruker AM-400FT-NMR, Rheinstetten, Germany). Molecular weight and polydispersity of the prepared PEO macromonomer were determined by gel permeation chromatography (GPC; TOSOH column types; GMPW$_{HR}$ ×2, Tokyo, Japan) using *N*,*N*-dimethyformamide as eluent at a flow rate of 1.0 mL/min at 40 °C and detected on a refractive index (RI) detector (TOSOH RI-8022, Tokyo, Japan). A calibration curve for molecular weight determination was made using known molecular weight PEO standards. Polydispersity was calculated on the ratio of weight- to number-averaged molecular weights.

Synthesis of Cross-Linked Gels. To synthesize the comb-type PEO-grafted gel, IPAAm monomer and PEO macromonomer in various ratios (total weight 1.5600 g), MBAAm as a cross-linker, and TEMED as an accelerator were dissolved in 10 mL of distilled water, and dry nitrogen gas was bubbled into solution for 10 min to remove the dissolved oxygen. After the addition of 8 mg of APS as an initiator, the solution was injected between two Mylar sheets separated by a Teflon gasket (1.0 mm thick) and backed with glass plates. The solution was polymerized at 15 °C for 1 day. The formed graft-type gel (P(IPAAm-*g*-PEO)) membrane was immersed in pure water for 7 days at room temperature with water changed every day to remove unreacted compounds. The swollen gel membrane was cut into disks (15 mm diameter) using a cork borer at 25 °C and dried under ambient conditions for 1 day followed by thorough drying under vacuum for 3 days at room temperature. Compositions of PEO to IPAAm within the P(IPAAm-*g*-PEO) hydrogels were determined by elemental analysis using a Perkin-Elmer 240 elemental analyzer to obtain C/N and C/H ratios. Results of the polymerization are summarized in Table 1. As a control, normal-type PIPAAm gel (NG) without PEO graft chains was also synthesized (IPAAm monomer 100 wt %) and purified by the same method as described above.

Table 2. Preparation of P(IPAAm-*co*-AAc) Hydrogels

	feed composition					
sample	IPAAm (g)	AAc (μL)	AAc (wt %)	MBAAm (g)	conversion[a] (%)	T_P (°C)
AAc0.32	1.5521	4.7	0.32	0.0266	93	34.0
AAc0.64	1.5443	9.4	0.64	0.0266	94	35.5
AAc1.3	1.5288	18.9	1.3	0.0266	88	37.0
AAc2.6	1.4976	37.8	2.6	0.0266	87	42.0
AAc3.9	1.4644	56.7	3.9	0.0266	86	50.0

[a] Weight percent of synthesized dry gel to the monomers.

To synthesize copolymer gels consisting of IPAAm and AAc, known amounts of AAc and IPAAm were copolymerized and cross-linked by MBAAm in the same method as the graft-type gel. Table 2 summarizes the results of P(IPAAm-*co*-AAc) hydrogel synthesis.

Swelling Equilibria for Hydrogels. The equilibrium swelling ratio (W_{H_2O}/W_p) was defined as the weight of absorbed water (W_{H_2O}) per weight of dried gel (W_p). Equilibrium swelling weights for the gels in water at various temperatures were measured gravimetrically after wiping excess water from the gel surface using filter paper. The gels were first equilibrated at higher temperature for 3 days in Dulbecco's phosphate-buffered saline (PBS; pH7.4) composed of 0.137 M NaCl, 2.68 mM KCl, 8.10 mM Na_2HPO_4, and 1.47 mM KH_2PO_4. After determining the gel mass, the temperature was lowered, and the gels were equilibrated to reach swollen conditions at this temperature for 3 days. This process was repeated until the temperature reached 10 °C. The temperature of the water bath was controlled by a thermostated water bath (LAUDA-RM20, Messgeratewerk, Germany) with a deviation of ±0.1 °C. The experimental plots were averages of three samples.

Swelling−Deswelling Kinetics of Hydrogels. Disk-shaped P(IPAAm-*g*-PEO), P(IPAAm-*co*-AAc), and NG gels were all first equilibrated in PBS at a predetermined temperature. Gels were then quickly transferred into PBS at different temperatures. At specific time intervals these gels were taken out of PBS and weighed after removing excess water from the gel surface. Swelling and deswelling kinetics were defined as

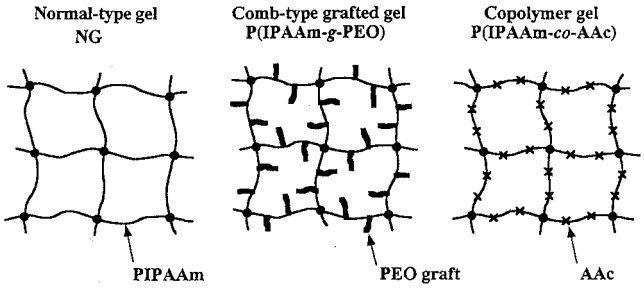

Figure 1. Schematic illustration of structures for normal-type PIPAAm gel (NG), P(IPAAm-*g*-PEO) gel, and P(IPAAm-*co*-AAc) gel.

temporal weight changes for the gels. The average weight of three disk samples was converted to the normalized swelling, which indicated the volume changes of hydrogels between equilibrium swollen (100%) and equilibrium shrunken (0%) states.

To measure the swelling−deswelling reversibility of the gels in response to temperature changes, cylindrical gels were prepared in a Teflon tube (0.5 mm diameter) with the same gel membrane synthesis method. The swollen gels were cut into 3.5 mm length at 20 °C and placed in aluminum pans (6 mm in diameter and 6 mm depth) filled with water equipped with a thermostated water jacket. The water temperature was rapidly changed by circulating water from two thermostated water baths of different temperatures using an HPLC pump with 3-way stopcocks. Size changes of the gels in response to temperature cycles were continuously monitored and recorded using a video camera connected to a microscope. The changes in diameter of cylindrical gels were determined using an image analyzer (LUZEX-FS, NIRECO, Tokyo, Japan).

Results and Discussion

PEO Macromonomer Analysis. FT-IR data for hydroxy-terminated and acryloyl-terminated methoxy-PEO show a decrease in the hydroxy group peak around 3600 cm^{-1} and an increase in the ester carbonyl peak at 1720 cm^{-1} after the substitution reaction of the terminal hydroxy group to an acryloyl group. From NMR measurements, the chemical shift at 5.5−6.5 ppm arising from vinyl protons was observed after the substitution reaction. These results indicate that the end group of the polymer was converted from a hydroxy group to an acryloyl group. GPC analysis of the prepared acryloyl-terminated methoxy-PEO shows the number-averaged molecular weight (M_n) to be 5100 and the weight-averaged molecular weight (M_w) 5300 with a molecular weight distribution of 1.04.

Hydrogel Synthesis. The weight conversions from monomers to synthesized gels are summarized in Tables 1 and 2 for P(IPAAm-*g*-PEO) and P(IPAAm-*co*-AAc) gels, respectively. They were determined to be 72−92% for P(IPAAm-*g*-PEO) and 86−94% for P(IPAAm-*co*-AAc). The conversion for the normal-type gel was determined to be 85%. PEO content of the five P(IPAAm-*g*-PEO) types were determined to be 1.7, 4.0, 10.9, 13.1, and 23.0 wt % by elemental analysis. These PEO-grafted gels were abbreviated as PEO1.7, PEO4.0, PEO11, PEO13, and PEO23, respectively. P(IPAAm-*co*-AAc) gels were abbreviated as AAc*X* where *X* is the weight percent of AAc in the feed. The normal-type PIPAAm gel was designated NG. Structures for three types of gels are schematically illustrated in Figure 1.

Equilibrium Swelling Measurements. Measurements of equilibrium swelling ratios for the NG and P(IPAAm-*co*-AAc) gels in PBS (pH 7.4) shown in Figure 2 demonstrate that the gels were swollen at lower

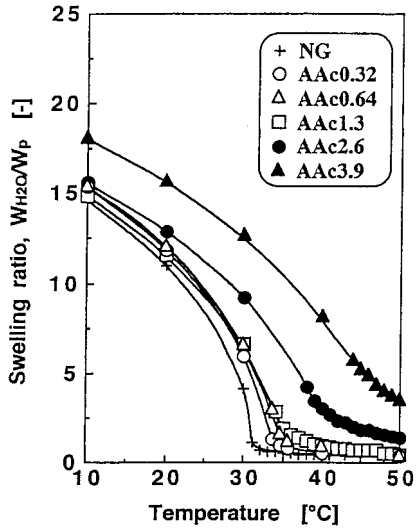

Figure 2. Equilibrium swelling ratio of NG and P(IPAAm-*co*-AAc) (AAc0.32, -0.64, -1.3, -2.6, and -3.9) hydrogels as a function of temperature in PBS (pH 7.4).

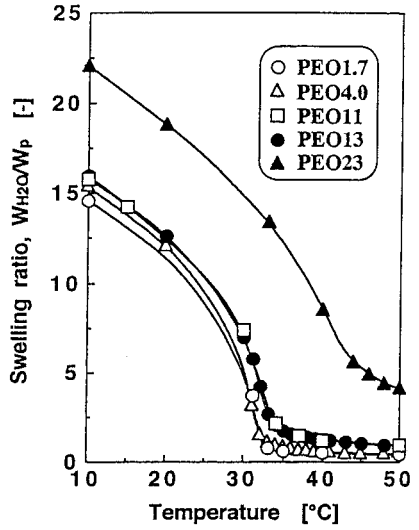

Figure 3. Equilibrium swelling ratio P(IPAAm-*g*-PEO) (PEO1.7, -4.0, -11, -13, and -23) hydrogels as a function of temperature in PBS (pH 7.4).

temperatures and shrunken above the phase transition temperature (T_P). The T_P for NG was observed around 31.0 °C. The T_Ps for AAc0.32, AAc0.64, AAc1.3, AAc2.6, and AAc3.9 were observed around 34.0, 35.5, 37.0, 42.0, and 50.0 °C, respectively. The T_P and equilibrium swelling ratio increase as a function of AAc content. Hydrophilic comonomers, such as acrylamide[28] or acrylic acid[20,29] are known to increase the gel hydration and shift T_P to temperatures higher than that of the PIPAAm homopolymer gel. The acidic groups cause swelling primarily via Donnan ion exclusion,[30] followed by swelling changes by electrostatic repulsion. A repulsive force operating between the carboxylate anions of acrylic acid increases the hydration of the polymer, which restricts the hydrophobic network aggregation.

In the series of P(IPAAm-*g*-PEO) gels, higher T_P and larger swelling ratios were observed when compared to NG, as seen in Figure 3. The T_Ps for PEO1.7, PEO4.0, PEO11, PEO13, and PEO23 were observed around 32.5, 33.0, 35.0, 35.5, and 48.0 °C, respectively. With increasing PEO content, the T_P increased with large equilibrium swelling ratios over wide temperature

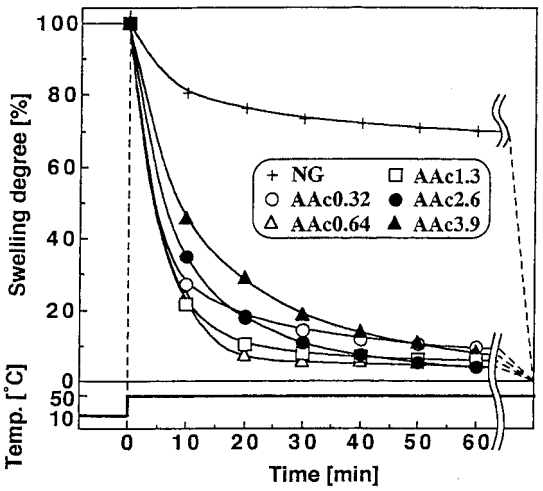

Figure 4. Deswelling kinetics of NG and P(IPAAm-*co*-AAc) (AAc0.32, -0.64, -1.3, -2.6, and -3.9) hydrogels at 50 °C from the equilibrium swelling condition at 10 °C in PBS (pH 7.4) (initial gel dimension: 1.0 mm thick and 15 mm diameter).

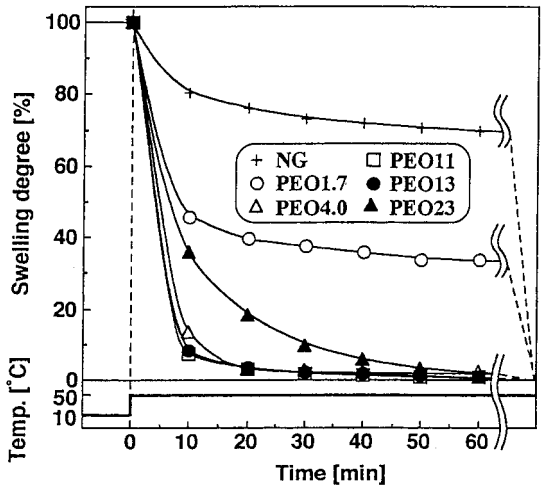

Figure 5. Deswelling kinetics of NG and P(IPAAm-*g*-PEO) (PEO1.7, -4.0, -11, -13 and -23) hydrogels at 50 °C from the equilibrium swelling condition at 10 °C in PBS (pH 7.4) (initial gel dimension: 1.0 mm thick and 15 mm diameter).

ranges. Compared with the swelling ratios of P(IPAAm-*co*-AAc) as seen in Figure 2, the magnitude of the T_P shift and equilibrium swelling ratios of P(IPAAm-*g*-PEO) was small although a larger amount of hydrophilic moiety was introduced into the network. This is because AAc unlike PEO chains divides PIPAAm sequences into multiple short segments. The mole percentages of the hydrophilic moiety compared with IPAAm calculated from the molecular weight of the graft polymer over that of IPAAm were 0.038, 0.092, 0.27, 0.33, and 0.66 mol % with respect to PEO1.7, PEO4.0, PEO11, PEO13, and PEO23. Hydrophilic comonomer AAc contents determined from AAc0.32, AAc0.64, AAc1.3, AAc2.6, and AAc3.9 were 0.50, 1.0, 2.0, 4.0, and 6.0 mol %, respectively. By contrast with P(IPAAm-*co*-AAc) gels, P(IPAAm-*g*-PEO) with PEO freely mobile chains could maintain the longer sequences of PIPAAm together with the larger amount of hydrophilic moiety in the PIPAAm network. Therefore, without interfering with PIPAAm aggregation, the graft structure kept a high thermosensitivity, as shown in the abrupt volume phase transitions.

The role of polymer sequence on the LCST phenomena of PIPAAm has also been studied for a copolymer of PIPAAm and PEO by Yoshioka and co-workers.[31,32] The endothermic peak due to the phase transition of a copolymer was compared with the random copolymer of PIPAAm and acrylamide. Although no endothermal peak was observed in the random copolymer, the copolymer of PIPAAm and PEO showed an endothermal peak on heating due to the existence of long PIPAAm sequences. These results are consistent with the LCST phenomena of our gels with PEO graft structures.

Deswelling Kinetics of Hydrogels. Figures 4 and 5 show the deswelling kinetics of NG, P(IPAAm-*co*-AAc) (in Figure 4), and P(IPAAm-*g*-PEO) (in Figure 5) after a jump from equilibrium at 10 °C to above the T_P at 50 °C. The deswelling of the NG gel proceeded more slowly as the gel approached a new equilibrium. The transparent NG at 10 °C became opaque as the temperature increased to 50 °C, indicating formation of a heterogeneous structure of an aggregated polymer network. The slow deswelling change of NG was attributed to the skin layer formation. In the previous paper, we have systematically investigated the effect of skin layer formation on the deswelling kinetics of PIPAAm by controlling the temperature and gel chemical compositions.[33] Below the gel T_P, the gel deswelling kinetics is dominated by the collective diffusion mechanism. Thus, the gels decreased their swelling ratios exponentially without the formation of a skin layer. By contrast, at temperatures above T_P, the surface of the gel immediately dehydrates to form the skin layer,[1,33,34] which blocks the water flow out of the gel. The hydrodynamic internal pressure then gradually increases and water accumulates near the surface of the gel due to the increasing internal pressure.[15,33] When the internal pressure becomes too large, the water is convectionally transported from the gel.[33,35] By incorporating the hydrophilic acrylamide, a weak skin layer was formed on the surface of the IPAAm copolymer gel,[33] while a dense and strong skin layer was formed with the butyl methacrylate comonomer. This resulted in the accumulation of large internal pressure due to strong hydrophobic aggregation. The strong hydrostatic internal pressure induced water outflow from the gel, forming a bubble-like structure at the skin leading to fast gel contraction after the skin layer formation.

Another method of acceleration can be observed by avoiding skin formation and relying on increased diffusion and the hydrophobic polymer backbone. In Figure 4, we can observe the exponential deswelling curves of P(IPAAm-*co*-AAc) with various AAc contents above their T_Ps, suggesting the deswelling changes without skin layer formation and internal pressure accumulation. AAc copolymer gels at 10 °C kept their transparencies in the course of deswelling at 50 °C except AAc0.32 and AAc0.64. These two gels became slightly opaque during the deswelling changes. This result suggests that the rapid phase transition does not occur during the deswelling changes of AAc copolymerized gels. An optimum concentration of AAc for the fastest deswelling change was observed around 1.3 wt %.

As shown in Figure 5, rapid deswelling of PEO4.0, PEO11, and PEO13 gels was observed. The rapid deswelling of PEO-grafted PIPAAm gels is demonstrated, and the deswelling is much faster than AAc1.3. The PEO1.7 and PEO4.0 gels changed their appearances from transparent (10 °C) to opaque (50 °C). In contrast to these opaque gels, PEO11 became translu-

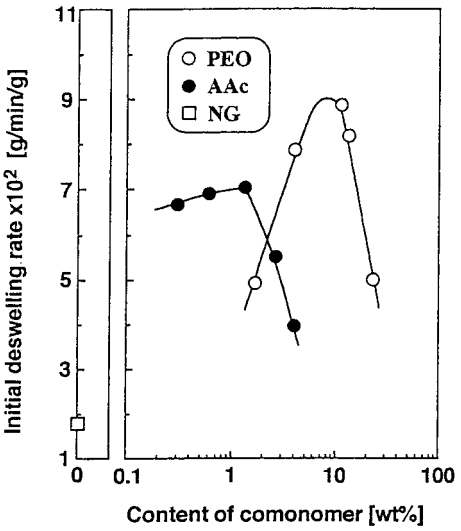

Figure 6. Changes in initial deswelling rate of hydrogels as a function of content of hydrophilic comonomers.

cent and PEO13 and PEO23 kept their transparency during the deswelling changes. The optimum concentration for the fastest deswelling of P(IPAAm-*g*-PEO) was observed around 11 wt % PEO. This concentration was around 8.5 times larger than the corresponding AAc concentration in the optimum AAc copolymerized gel.

Mechanism of Deswelling Kinetics. Figure 6 shows the initial deswelling rates of hydrogels calculated from weight decreases for the first 10 min as a function of hydrophilic comonomer content. P(IPAAm-*co*-AAc) gels showed a peak at low AAc concentration. The skin layer formed on the surface of NG was disrupted by incorporation of AAc. The deswelling rate gradually increased with increasing AAc content up to 1.3 wt %. As noted in a former section, the PIPAAm sequences in P(IPAAm-*co*-AAc) were divided by hydrophilic AAc units, which restricted the strong hydrophobic aggregation within the PIPAAm backbone. P(IPAAm-*co*-AAc) gels with AAc content of more than 1.3 wt % did not show marked hydrophobic aggregation to form the skin structure as observed by the continued gel transparency. With an increasing amount of AAc, the gel deswelling became slower. The hydrophobic aggregation force was weakened due to the division of the PIPAAm network into multiple short segments, thus the gel deswelling rate showed an abrupt decreasing trend.

By contrast, P(IPAAm-*g*-PEO) gels kept a large deswelling rate over a wide range of hydrophilic PEO content (PEO4.0−13.1 wt %). This is because the graft structure, which maintains hydrophobic aggregation of the PIPAAm backbone together with the formation of a large number of water releasing channels. At low PEO concentration, the gel formed a skin layer at the surface. With increasing PEO concentration, the deswelling rate showed an increasing trend, demonstrating a larger deswelling rate than P(IPAAm-*co*-AAc) gels. The hydrophilic PEO chains form hydrophilic domains in the deswelling hydrophobic PIPAAm network due to their hydrated nature as well as the higher mobility of the freely mobile end.[21,22] For PEO4.0−11, the hydrophilic PEO graft chains act as releasing channels for water molecules within the skin layer. The graft structure is independent of the PIPAAm backbone network in mobility and thus does not interfere with the hydrophobic aggregation of the PIPAAm backbone network. Therefore, the water inside the gel is rapidly released through the skin layer. The hydrophobic aggregation force, however, was weakened in the case of PEO23 due to the large bulk concentration of the hydrophilic moiety, resulting in a slower deswelling rate.

Although PEO4.0 and PEO13 show almost the same deswelling rate, there was a large difference in transmittance changes. PEO4.0 became opaque at the deswelling just after the temperature increase. This was because the size of hydrophobic aggregates became larger than the wavelength of visible light in the case of PEO4.0. In contrast, PEO13 kept its transparency during the deswelling. The larger amount of hydrophilic moieties formed larger hydrophilic domains, and thus the size of hydrophobic aggregates, remained smaller than the wavelength of visible light; therefore the gel kept its transparency. The PEO13 gel shrank quickly without the formation of a skin layer.

Thus, hydrophilic graft chains lead to a fast deswelling of PIPAAm gels due to the following:

(1) The hydrophilic graft chains act as releasing channels for water molecules within the skin layer, preventing a reduction of the deswelling rate, especially for the gels with a low PEO content.

(2) The graft structure maintains a strong hydrophobic attraction of PIPAAm due to the existence of longer PIPAAm sequences.

The balance of forces attributing to the hydrophobicity and hydrophilicity should be an important factor to determine the gel deswelling kinetics. The longer sequences of hydrophilic and hydrophobic polymers in the graft structure allow control of the gel swelling−deswelling kinetics because of maintenance of a balance between hydrophilic and hydrophobic forces. The PEO11 gel shows the fastest deswelling change due to the best balance of hydrophobicity and hydrophilicity of the network. The content of graft chains was controlled to regulate the rate of deswelling changes attributed to this hydrophilic/hydrophobic balance. This balance could also be changed by the length of graft chains.

We have already observed the rapid deswelling response of PIPAAm-grafted PIPAAm gel in response to temperature increase.[21,22,26] In this case, the rapid dehydration of graft chains induced the strong hydrophobic aggregation of the entire gel, thus the water inside the gel was released, resulting in rapid deswelling of the gels. The deswelling rate of PIPAAm-grafted PIPAAm gel is almost 10 times larger than that of P(IPAAm-*g*-PEO) gels with an identical dimension of cylindrical gel (2.0 mm diameter) by the temperature changes from 10 to 40 °C for PEO13- and PIPAAm-grafted PIPAAm gel.

Reversibility of Rapid Swelling−Deswelling Kinetics of P(IPAAm-*g*-PEO). Many researchers have varied the gel molecular structure to develop an actuator function of gels.[6−10] The typical methods to create the gel actuators are forming the macropore structure for artificial muscle,[7,8,17−19] applying an oscillating current to the electric-responsive polymer gels,[6] and coupling by the Belousov−Zhabotinsky (BZ) reaction to obtain self-swelling−deswelling oscillation of gels[9] and bigel structure composed of thermosensitive IPNs gels.[10] To establish actuators for drug release regulation or artificial muscle, it is important to achieve rapid reversible swelling−deswelling of the gels. This has been investigated for PEO graft structures.

Figure 7 shows the swelling−deswelling kinetics of cylindrical gels with 2-min temperature cycles between

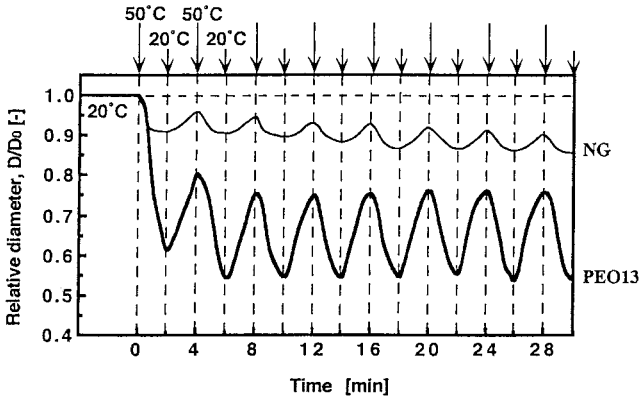

Figure 7. Swelling−deswelling kinetics of NG and graft-type PEO13 in response to temperature changes for 2-min cycles between 20 and 50 °C in water (initial gel dimension: 0.7 mm diameter and 3.5 mm length).

20 and 50 °C in water. A small swelling−deswelling of the NG gel was observed as slight and gradual changes in diameter in repeated temperature cycles. In contrast, rapid and large swelling−deswelling was observed for the PEO13 gel. During the first two cycles, rapid swelling−deswelling are accompanied by a slight decrease of swelling levels (D/D_0). The gel swelling repeatedly and reproducibly oscillated between 0.55 and 0.75 from the third cycle onward. A fast and reversible swelling−deswelling temperature response with an accompanying large volume change of the gel was achieved by the graft-type structure. These results indicate that the graft-type gel is suitable for use in artificial muscles or actuators.

Conclusions

We have enhanced gel deswelling rates in response to temperature change by incorporation of PEO graft chains into the PIPAAm network. The conventional PIPAAm gel (NG) shrinks slowly due to the formation of a surface skin layer restricting water permeation from the gel. Hydrophilic PEO graft chains form channels for water molecules within the skin layer. Due to the strong hydrophobic aggregation of the PIPAAm backbone network, the water was rapidly released from the gel. The effect of hydrophilicity on a fast deswelling was clarified by comparing graft gels with random copolymer gels of PIPAAm and AAc. The 1.3 wt % AAc-containing gel shrinks more rapidly than the NG gel, but the gel deswelling rate decreases with increasing AAc content. This is because a small content of AAc decreased the hydrophobic aggregation forces of PIPAAm chains due to the division of PIPAAm into short segments. A graft structure maintained long PIPAAm sequences, thus a strong hydrophobic backbone aggregation operated within the PIPAAm network although a large amount of a hydrophilic moiety was introduced into the network. Graft-type gels exhibited the fastest deswelling when containing 11 wt % PEO. This PEO11 gel showed approximately 1.3 times faster deswelling than the gel with 1.3 wt % AAc. The rapid deswelling of the graft-type gel might find applications as a gel actuator or for regulation of mass transfer, such as in artificial muscles or drug delivery systems.

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Abbreviations

AAc: acrylic acid
AAc*X*: *X* wt % AAc copolymerized gel
APS: ammonium persulfate
IPAAm: *N*-isopropylacrylamide
LCST: lower critical solution temperature
MBAAm: *N*,*N*′-methylenebis(acrylamide)
NG: normal-type gel
PBS: phosphate-buffered saline
PEO: poly(ethylene oxide)
PEO*X*: *X* wt % PEO-grafted PIPAAm gel
PIPAAm: poly(*N*-isopropylacrylamide)
TEMED: *N*,*N*,*N*′,*N*′-tetramethylethylenediamine
T_p: phase transition temperature
THF: tetrahydrofuran

References and Notes

(1) Okano, T.; Yui, N.; Yokoyama, M.; Yoshida, R. In *Japanese Technology Reviews, Section E*; Ikoma, T., Ed.; Gordon & Breach Science Publishers: New York, 1994; p 67.
(2) Okano, T.; Bae, Y. H.; Jacobs, H.; Kim, S. W. *J. Controlled Release* **1990**, *11*, 255.
(3) Hoffman, A. S. *J. Controlled Release* **1987**, *6*, 297.
(4) Brønsdsted, H.; Kopecek, J. *Biomaterials* **1991**, *12*, 584.
(5) Yeh, P.; Kopečková, P.; Kopeček, J. *J. Polym. Sci., Polym. Chem.* **1994**, *32*, 1627.
(6) Osada, Y.; Okuzaki, H.; Hori. H. *Nature* **1992**, *355*, 242.
(7) Suzuki, M. In *Polymer Gels*; DeRossi, D., et al., Eds.; Prenum Press: New York, 1991; p 221.
(8) Hirasa, O.; Ito, S.; Yamauchi, A.; Fujishige, S.; Ichijo, H. In *Polymer Gels*; DeRossi, D., et al., Eds.; Plenum Press: New York; 1991; p 247.
(9) Yoshida, R.; Takahashi, T.; Yamaguchi, T.; Ichijo, H. *J. Am. Chem. Soc.* **1996**, *118*, 5134.
(10) Li, Y.; Hu, Z.; Chen, Y. *J. Appl. Polym. Sci.* **1997**, *63*, 1173.
(11) Gehrke, S. H.; Andrews, G. P.; Cussler, E. L. *Chem. Eng. Sci.* **1986**, *41*, 2153.
(12) Feil, H.; Bae, Y. H.; Feijen, J.; Kim, S. W. *J. Membr. Sci.* **1991**, *64*, 283.
(13) Heskins, M.; Guillet, J. E. *J. Macromol. Chem.* **1968**, *A2*, 1441.
(14) Schild, H. G. *Prog. Polym. Sci.* **1992**, *17*, 163.
(15) Sato Matsuo, E.; Tanaka, T. *J. Chem. Phys.* **1988**, *89*, 1695.
(16) Li, Y.; Tanaka, T. *J. Chem. Phys.* **1990**, *92*, 1365.
(17) Kabra, B. G.; Gehrke, S. H. *Polym. Commun.* **1991**, *32*, 322.
(18) Wu, A. S.; Hoffman, A. S.; Yager, P. *J. Polym. Sci., Polym. Chem.* **1992**, *30*, 2121.
(19) Kishi, R.; Hirasa, O.; Ichijo, H. *Polym. Gels Networks* **1997**, *5*, 145.
(20) Gutowska, A.; Bae, Y. H.; Kim, S. W. *J. Controlled Release* **1992**, *22*, 95.
(21) Yoshida, R.; Uchida, K.; Kaneko, Y.; Sakai, K.; Kikuchi, A.; Sakurai, Y.; Okano, T. *Nature* **1995**, *374*, 240.
(22) Kaneko, Y.; Sakai, K.; Kikuchi, A.; Yoshida, R.; Sakurai, Y.; Okano, T. *Macromolecules* **1995**, *28*, 7717.
(23) Matsukata, M.; Aoki, T.; Sanui, K.; Ogata, N.; Kikuchi, A.; Sakurai, Y.; Okano, T. *Bioconjugate Chem.* **1996**, *7*, 96.
(24) Okano, T.; Kikuchi, A.; Sakurai, Y.; Takei, Y.; Ogata, N. *J. Controlled Release* **1995**, *36*, 125.
(25) Kanazawa, H.; Kashiwase, Y.; Yamamoto, K.; Matsushima, Y.; Kikuchi, A.; Sakurai, Y.; Okano, T. *Anal. Chem.* **1997**, *69*, 823.
(26) Kaneko, Y.; Sakai, K.; Kikuchi, A.; Sakurai, Y.; Okano, T. *Macromol. Symp.* **1996**, *109*, 41.

(27) Bae, Y. H.; Okano, T.; Kim, S. W. *J. Polym. Sci., Polym. Phys.* **1990**, *28*, 923.
(28) Yoshida, R.; Kaneko, Y.; Sakai, K.; Okano, T.; Bae, Y. H.; Kim, S. W. *J. Controlled Release* **1994**, *32*, 97.
(29) Shibayama, M.; Mizutani, S.; Nomura, S. *Macromolecules* **1996**, *29*, 2019.
(30) Hirokawa, Y.; Katayama, S.; Tanaka, T. In *Microbial Adhesion and Aggregation*; Marshall, K. C.; Ed.; Springer-Verlag: Heidelberg and Berlin, 1984.
(31) Yoshioka, H.; Mikami, M.; Mori, Y.; Tsuchida, E. *J. Macormol. Sci., Pure Appl. Chem*. **1994**, *A31*, 109.
(32) Yoshioka, H.; Mikami, M.; Mori, Y.; Tsuchida, E. *J. Macormol. Sci., Pure Appl. Chem*. **1994**, *A31*, 113.
(33) Kaneko, Y.; Yoshida, R.; Sakai, K.; Sakurai, Y.; Okano, T. *J. Membr. Sci*. **1995**, *101*, 13.
(34) Yoshida, R.; Sakai, K.; Okano, T.; Sakurai, Y. *J. Biomater. Sci. Polym. Ed*. **1992**, *3*, 243.
(35) Yoshida, R.; Sakai, K.; Okano, T.; Sakurai, Y. *Ind. Eng. Chem. Res*. **1992**, *31*, 2339.

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