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Macroporous Dehydroalanine Polymer Hydrogel with Fast Temperature Response and High Repetition Durability

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ABSTRACT: Thermoresponsive hydrogels based on poly(methyl 2-isobutyramidoacrylate) (PMIBA) were prepared by free-radical crosslinking polymerization of the corresponding monomer using *N*,*N*′-methylenebisacrylamide as a crosslinker. The PMIBA hydrogels showed a reversible temperature-induced volume change with a volume phase transition temperature (VPTT) at 19°C, while they contained more than 60 wt % water even in the equilibrium deswollen state. When the external temperature was raised rapidly above the VPTT, the PMIBA gels shrank smoothly with time at a faster rate than conventional poly(*N*-isopropylacrylamide) hydrogels of the same size. The fast and smooth deswelling response of the PMIBA gel is ascribed to its sponge-like structure with 0.1–1 μm pore sizes formed in the deswollen state. The smooth deswelling response due to the macroporous structure resulted in high durability against repeated changes in the external temperature. The PMIBA gel showed little degradation in the swelling ability when subjected to 50 times of thermal cycling across the VPTT. © 2012 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 000: 000–000, 2012

KEYWORDS: hydrogels; stimuli-sensitive polymers; macroporous polymers; thermoresponsive polymers; dehydroalanine

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INTRODUCTION

Stimuli-responsive hydrogels have attracted a great deal of interest because of their potential applications in biomedical and industrial fields.[1] They exhibit a marked change in swelling volume in response to external stimuli such as temperature, pH, electric field, light, and specific molecules. These unique properties have been utilized to design and construct self-regulated systems of various kinds, such as controlled-release drug delivery systems,[2] integrated sensor and actuators,[3–5] and light modulating devices.[6,7] In most of these "active" devices, slow response of hydrogel elements would limit their performance and restrict their practical applications. Thus, improvement in response rate is one of the key issues in the study of stimuli-responsive hydrogels.

Various methods have been proposed to improve the response rate of stimuli-responsive hydrogels. One approach is the formation of water-releasing channels in the network structure.[8–17] The water-releasing channels allow water molecules to be transferred smoothly from the interior region of a gel to the outward surface, preventing formation of a dense skin layer. Hydrogels equipped with the water-releasing channels have been prepared by several methods, such as introduction of comb-type grafted chains[8–11] and semi-interpenetrating or fully interpenetrating networks with hydrophilic polymers.[11–17] Another approach for improving the response rate of stimuli-responsive hydrogels is the formation of a macroporous structure in hydrogel matrices. The macroporous structure can facilitate the mass transfer of water in the hydrogel matrices by reducing its diffusion path length through the polymer networks. Hydrogels with a macroporous structure have been prepared by various methods, such as the polymerization above the lower critical solution temperature (LCST)[18–20] or below the freezing temperature;[21] incorporation of silica particles,[22] surfactants,[23] pore-forming agent,[24] or liquid templates;[25] freeze-drying followed by rehydration[26,27]; polymerization in aqueous salt,[28] mixed solvents,[29,30] phase separation,[31] or heterogeneous initiation systems.[32]

In this study, we have prepared a thermoresponsive hydrogel which forms a macroporous structure in the deswollen state. It was prepared by simple free-radical crosslinking polymerization of a dehydroalanine derivative, methyl 2-isobutyramidoacrylate (MIBA), using *N*,*N*′-methylenebisacrylamide (MB) as a crosslinker (Scheme 1) without any additives, specific polymerization conditions, or post-treatment procedures as aforementioned. We report here thermoresponsive properties of poly(methyl

2-isobutyramidoacrylate) (PMIBA) gels, whereas those of linear PMIBA in aqueous solutions have already been reported by us and the other group.[33,34] We have evaluated the temperature response of the PMIBA gels by comparing with that of a poly(*N*-isopropylacrylamide) (PIPAAm) hydrogel of the same size. We also evaluated the durability against repeated changes in external temperature. Through these evaluations, we demonstrate that the PMIBA hydrogels have a higher temperature response and higher repetition durability than conventional PIPAAm hydrogels.

EXPERIMENTAL

Materials

The monomer MIBA was synthesized as described previously.[33] The crosslinker MB and monomer IPAAm (Tokyo Chemical Industry Co., Japan) were recrystallized twice from ethanol. Ammonium peroxodisulfate (Kanto Chemical Co. Inc., Japan) was recrystallized from methanol. Dimethyl sulfoxide (DMSO) (Wako Pure Chemical Industries Ltd., Japan) was purified by vacuum distillation before use. Deionized water was supplied from an ultra-pure water system, CPW-102 (Advantec Toyo Kaisha Ltd., Japan).

Preparation of Hydrogels

Free radical crosslinking polymerization of MIBA was carried out at various feed-concentrations (C_X) of the crosslinker relative to that of the monomer. A PMIBA gel with $C_X = 3.3$ mol % was prepared in the following procedure: A DMSO solution (1.0 mL) of MIBA (1.0 mol/dm^3), MB (3.3×10^{-2} mol/dm^3), and ammonium peroxodisulfate (5.0×10^{-3} mol/dm^3) was degassed by a freeze-thaw method and sealed under vacuum. It was allowed to stand at 30°C for 60 h. The polymerization mixture was pushed out from the ampoules and poured into deionized water. It was allowed to stand at 5°C for 7 days with the surrounding water replaced every 12 h to remove unreacted monomer, crosslinker, and linear polymers. A PIPAAm gel with $C_X = 3.3$ mol % was prepared in the same procedure as that of the PMIBA gel ($C_X = 3.3$ mol %). The resulting hydrogels were cut into desired shapes using a razor blade.

Determination of Equilibrium Swelling Ratio

Since the swelling ratio of a hydrogel is defined as the weight of water uptake per unit weight of the dry gel, the equilibrium swelling ratio (SR_e) is given by $SR_e = (w_s - w_d)/w_d$, where w_s is the weight of a hydrogel swollen to the equilibrium at a given temperature and w_d is that of the dry gel. The w_ss were obtained by weighing a hydrogel, which had been allowed to stand in deionized water at each temperature for 48 h. The w_d was determined by thermogravimetry (TG) using a TG analyzer, TG/DTA220 (Seiko Instruments., Japan) in which the hydrogel was heated to 120°C at 10°C/min and kept at this temperature until the weight became constant.

Measurement of Deswelling and Reswelling Kinetics

A PMIBA gel ($C_X = 3.3$ mol %) was cut into a cylindrical shape 6.0 mm in diameter and 2.5 mm in height and then divided into four equal quadrants (cylindrical sectors). The cylindrical sector-shaped PMIBA gel was placed in a rectangular polystyrene cuvette (4 mm wide and 10 mm long) filled with deionized water. The temperature in the cuvette was monitored with a linear thermistor, model 44201 (Nikkiso-Therm. Co., Ltd. Japan), and controlled with two Peltier plates (11.5 × 11.5 mm^2) attached to both sides of the cuvette. First, the temperature in the vessel was kept at 9°C. Then, the temperature was raised to 29°C (or 50°C) at 30°C/min and kept at this temperature until the PMIBA gel reached the equilibrium deswollen state. Finally, the temperature in the cuvette was dropped to 9°C at 20°C/min and kept at this temperature until the PMIBA gel reached the equilibrium swollen state. During the temperature-jump and temperature-drop experiments, variation in the size and shape of the PMIBA gel was recorded with a digital camera, Caplio RR30 (Ricoh Co., Japan) at given intervals. The experiments for the PIPAAm gel were carried out in the same manner as those for the PMIBA gels except that the temperature was switched between 22 and 42°C.

Thermal Cycling

A cylindrical PMIBA gel 6.0 mm in diameter and 2.5 mm in height was placed in the polystyrene cuvette and subjected to temperature cycles between 5°C for 6 h and 50°C for 2 h. After a given number of temperature cycles, the PMIBA gel was weighed to obtain a swelling ratio at the equilibrium deswollen state. Then, the PMIBA gel was allowed to stand in deionized water at 5°C for 48 h, followed by weighing to obtain a swelling ratio at the equilibrium swollen state.

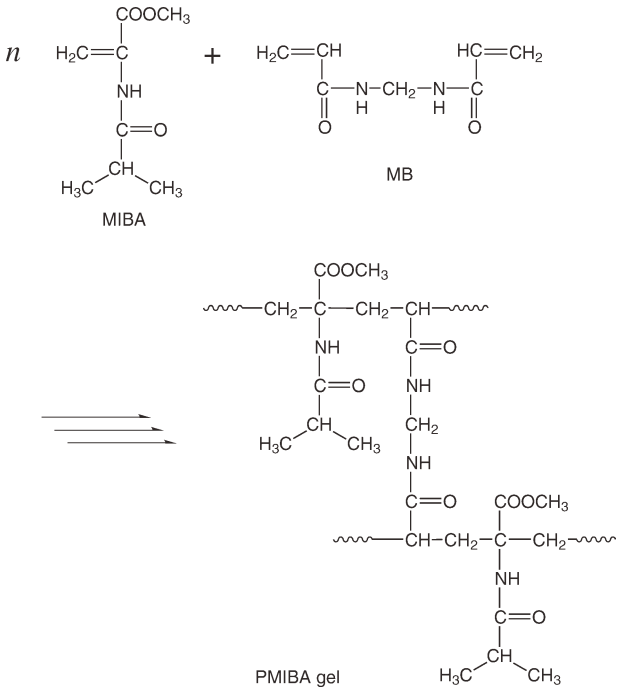
Scanning Electron Microscopy (SEM) Observations

Hydrogel samples were dried by two different methods: (1) freeze-drying at −10°C under vacuum (1×10^2 Pa) after being frozen in liquid nitrogen; (2) heat-drying by isothermal heating at 120°C on the TG analyzer. They were observed with a scanning electron microscope, JSM-6390HV (Jeol Ltd., Japan), after being sputter-coated with Pt/Pd using an ion sputter, E-1020 (Hitachi Science System Ltd., Japan).

RESULTS AND DISCUSSION

Temperature Dependence of Equilibrium Swelling Ratio

The polymerization mixtures prepared at C_Xs of 3.3 and 6.7 mol % showed gelation in DMSO and turned into hydrogels in deionized water, whereas those prepared at C_Xs lower than 1.7 mol % remained a sol even after 60 h heating. The nongelation at the low crosslinker concentrations is probably due to the difference in reactivity between the monomer MIBA and the crosslinker MB. The PMIBA hydrogels ($C_X = 3.3$ and 6.7 mol %) had a mechanical strength sufficient to be handled in air. Figure 1 shows temperature-dependence of SR_e for the PMIBA gels. Since SR_e changed most greatly in a temperature range between 17 and 20°C for both C_Xs, the volume phase transition temperature (VPTT) is determined to be 19°C from the inflection point of the SR_e vs. temperature curves. This VPTT is consistent with the LCST of linear PMIBA in deionized water.[33,34] It should be noted that the PMIBA gels contain a certain amount of water (1.5–2.0 times the weight of the dry gel) even in the equilibrium deswollen state. The SR_e values of 1.5–2.0 correspond to water contents of 60–67 wt % as determined by the TG analysis.



Scheme 1. Crosslinking polymerization of MIBA with MB.

Kinetics of Deswelling and Reswelling Processes

For evaluating the response rate of the PMIBA gels, we used a PIPAAm gel as a reference because it is the most studied thermoresponsive hydrogel. Since the swelling and deswelling rates of a hydrogel are highly dependent on the degree of crosslinking and the size, the PMIBA and PIPAAm hydrogels were prepared at the same C_X of 3.3 mol % and cut into the same size. In addition, the external temperature was switched between their each VPTT±10°C in the temperature-jump and temperature-drop experiments to equalize the effect of temperature shift from the VPTT.

Figure 2 shows variations of the relative volume (V/V_0) with time for PMIBA and PIPAAm gels after a temperature jump,

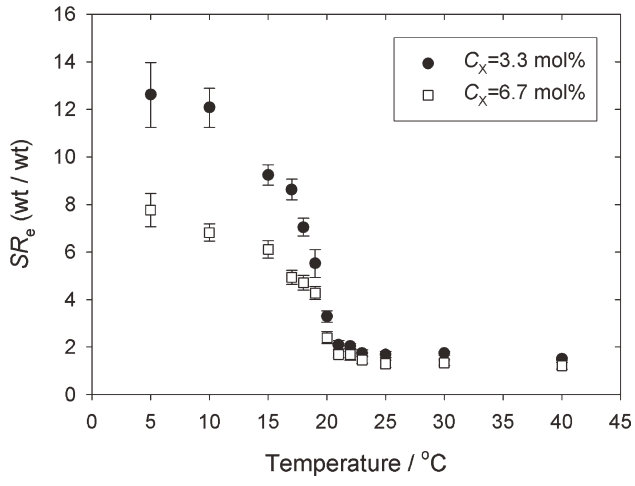


Figure 1. Temperature-dependence of the equilibrium swelling ratio for PMIBA gels prepared at crosslinker concentrations of 3.3 and 6.7 mol %.

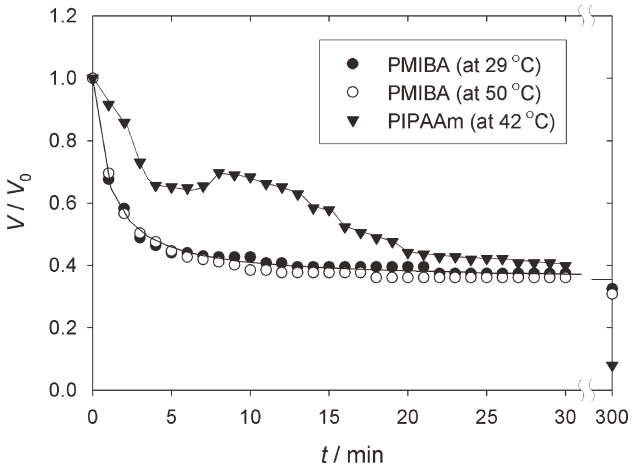


Figure 2. Variations of the relative volume with time after the external temperature was jumped from 9 to 29 and 50°C for a PMIBA gel (C_X = 3.3 mol %) and from 22 to 42°C for a PIPAAm gel (C_X = 3.3 mol %).

where V is the volume of a gel at time t and V_0 is that before the temperature jump. The relative volume of the PMIBA gel decreased at a faster rate than the PIPAAm gel, regardless of temperature between 29 and 50°C, and reached a semi-steady state value within 15 min. The PMIBA gel retained the initial cylindrical-sector shape throughout the deswelling process, as shown in Figure 3, in contrast to the PIPAAm gel which

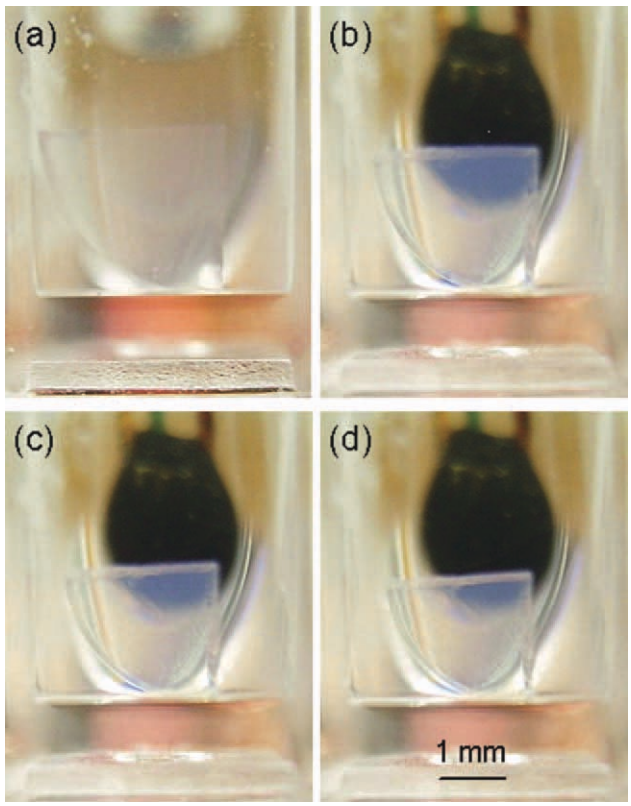


Figure 3. Photographs of a PMIBA gel (C_X = 3.3 mol %) before (a) and after (b, c, d) the temperature jump from 9 to 29°C: (b) t = 2, (c) t = 5, (d) t = 20 min. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

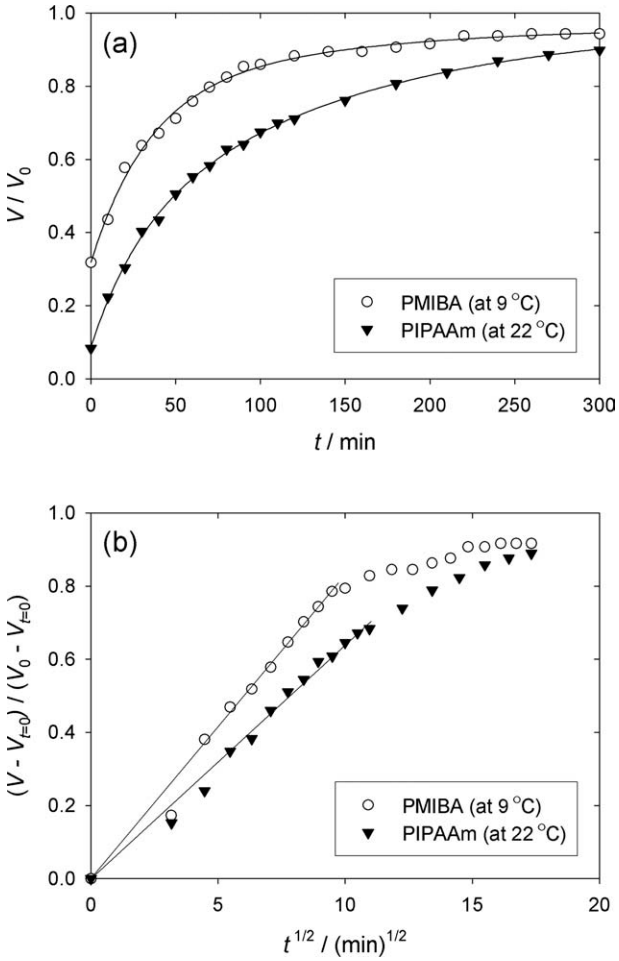


Figure 4. (a) Variations of the relative volume with time after the external temperature was dropped from 29 to 9°C for a PMIBA gel (C_X = 3.3 mol %) and from 42 to 22°C for a PIPAAm gel (C_X = 3.3 mol %). (b) Analysis of the reswelling process based on the Fickian diffusion model.

exhibited large deformation as reported previously.[9,20,35–38] Since the deformation of the PIPAAm gel is caused by an increase in internal osmotic pressure through the formation of a skin layer,[35] the fast and smooth shrinking of the PMIBA gel indicates that it undergoes thermoresponsive deswelling without forming a dense skin layer. Although the PMIBA gel shrank at a faster rate than the PIPAAm gel, it showed a much lower degree of volume change than the PIPAAm gel over the entire deswelling process, as indicated by their relative volumes at t = 300 min. This is because the PMIBA gel holds more than 60 wt % water even in the equilibrium deswollen state as described previously in this article.

The kinetic of the reswelling process was measured in the same manner as that of the deswelling. Figure 4a shows time-variations of the relative volume of the PMIBA and PIPAAm gels after a temperature drop. These curves appear to have a parabolic relation with time, characteristic to diffusion-limited processes. Thus, we analyzed them using the following equation based on the Fickian diffusion model: $(V - V_{t=0})/(V_0 - V_{t=0}) = D_{app}t^{1/2}$, where $V_{t=0}$ is the volume of a gel at $t = 0$ and D_{app} the apparent diffusion constant (Figure 4b). These plots fall on each straight line with different slopes for the initial 100 min, indicating that their reswelling processes are controlled by diffusion of water in the hydrogel matrices and that the PMIBA gel has a higher D_{app} than the PIPAAm gel.

Microstructure of PMIBA Gels

To explain the fast deswelling and reswelling kinetics of the PMIBA gels and their water holding property in the deswollen state, we analyzed their microstructure by SEM. Figure 5 shows SEM images of PMIBA gel specimens prepared in three different manners: (a) freeze-drying from the equilibrium swollen state, (b) freeze-drying from the equilibrium deswollen state, (c) heat-drying from the equilibrium deswollen state. The PMIBA gel freeze-dried from the equilibrium swollen state (a) shows a complicated structure with curled ribbons and flakes, the surface of which appears dense and smooth. These ribbons and flakes must have been formed by sublimation of water from an expanded network of hydrophilic PMIBA chains because similar structures have been observed in PIPAAm gels freeze-dried from the swollen state.[17,30–32] In contrast, the PMIBA gel freeze-dried from the equilibrium deswollen state (b) shows a sponge-like structure with pore sizes ranging from 0.1 to 1 μm in diameter. This sponge-like structure must have been formed by sublimation of water from a collapsed network of hydrophobic PMIBA chains. However, when the same PMIBA gel was dried by isothermal heating (c), it gave a dense and flat surface. This result indicates that when water is removed by vaporization, the hydrophobic PMIBA chains undergo further aggregation to form a compact aggregate with a dense surface. In other words, such compact aggregation does not occur when water is present around the hydrophobic PMIBA chains. Instead, the hydrophobic PMIBA chains loosely aggregate to form a sponge-like macroporous structure, as shown in the images b-1 and b-2. These results suggest that the aggregation of hydrophobic PMIBA chains is limited to such an extent that they form only small (submicron-sized) aggregates. The limited aggregation of hydrophobic PMIBA chains can also explain thermoresponsive behavior of aqueous solutions of linear PMIBA which form a colloidal dispersion of submicron-sized particles when heated above the LCST.[33] Although the precise mechanism for the limited aggregation of hydrophobic PMIBA chains is not clear at present, it must be related to the characteristic molecular structure of PMIBA bearing two kinds of polar groups (—COOR and —NHCOR′) at every monomer unit. It is possible that these polar groups form a specific hydration structure which limits the aggregation of hydrophobic PMIBA chains and also serves to hold water in the deswollen PMIBA gels. The fast deswelling and reswelling kinetics of the PMIBA gels can also be explained by the formation of sponge-like macroporous structure in the deswollen state. The submicron-sized pores interconnected throughout the hydrogel matrices would act as macroscopic water-releasing channels and thus retard the formation of a dense skin layer.

Durability Against Thermal Cycling

Repeated swelling and deswelling cycles cause degradation of thermoresponsive hydrogels. The degradation has been observed as a marked decrease in mechanical strength and swelling ability

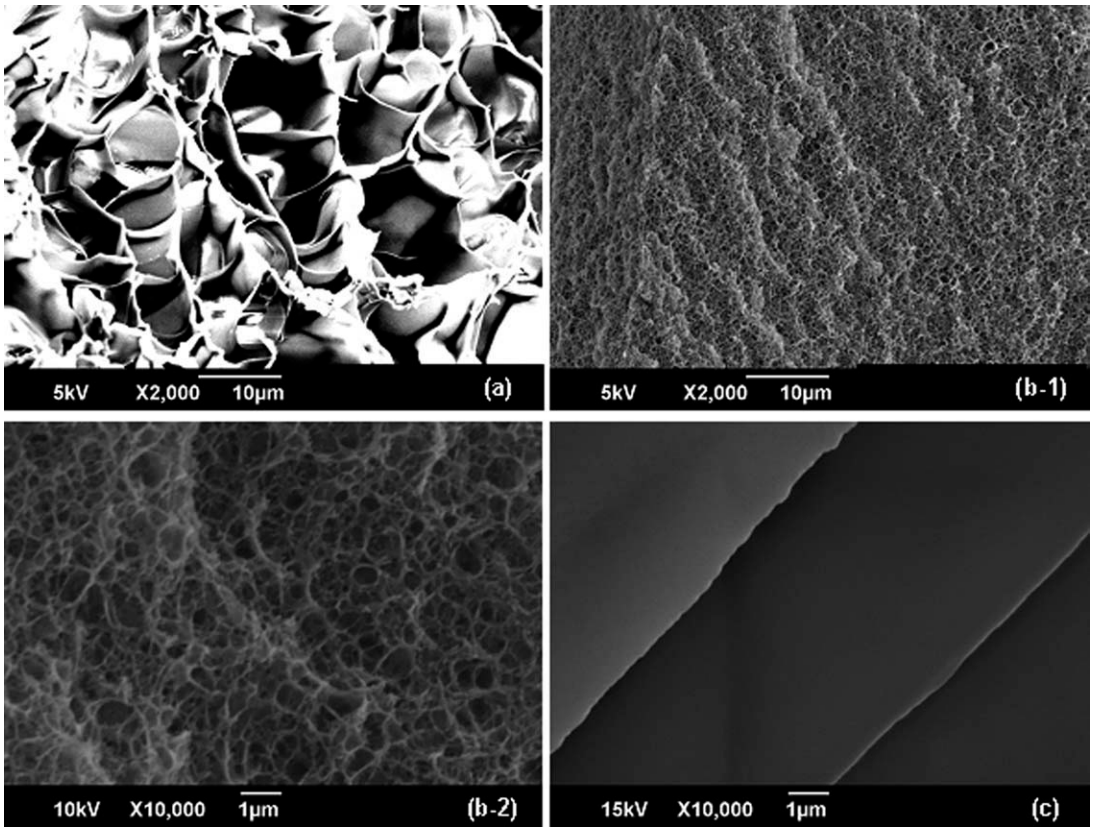


Figure 5. SEM images of PMIBA gels (C_X = 3.3 mol %) (a) freeze-dried from the equilibrium swollen state, (b) freeze-dried from the equilibrium deswollen state, and (c) heat-dried at 120°C from the equilibrium deswollen state.

after several tens of times of thermal cycling.[39,40] The degradation of thermoresponsive hydrogels has also been ascribed to the skin layer formation, which causes cracks on the surface by increasing hydrostatic pressure inside the gel. Thus, the PMIBA gel is expected to have high durability against thermal cycling because it doesn't form a skin layer. Figure 6 shows variation in swelling ability with the number of thermal cycling for PMIBA gels. The swelling ratio at the equilibrium swollen state deceased slightly (ca. 2.5%) at the first cycle and held this value until 50 cycles for both C_Xs, whereas that at the equilibrium deswollen state remained constant over 50 cycles. The decrease in the equilibrium swelling ratio after 50 cycles is much lower than that reported for PIPAAm gels, more than 15% decrease after 15 or 30 cycles.[40] From these results the PMIBA gels have a higher durability against thermal cycling than conventional PIPAAm gels.

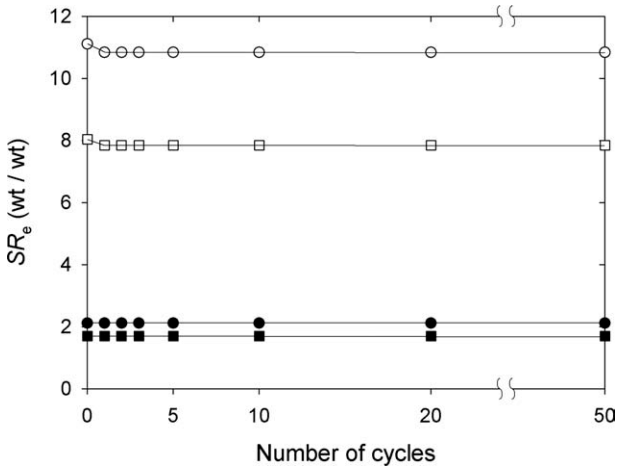


Figure 6. Plots of swelling ratios against the number of thermal cycling between 5 and 50°C for PMIBA gels prepared at C_X = 3.3 mol % (circles) and 6.6 mol % (squares). Open symbols represent swelling ratios at the equilibrium swollen state and closed symbols those at the equilibrium deswollen state.

CONCLUSIONS

Free-radical crosslinking polymerization of a dehydroalanine derivative MIBA yields a thermoresponsive hydrogel with a VPTT at 19°C. The PMIBA gel forms a sponge-like macroporous structure in the deswollen state and holds a certain amount of water even in the equilibrium deswollen state. These properties have been ascribed to limited aggregation of hydrophobic PMIBA chains. Although the precise mechanism remains to be elucidated, the limited aggregation of hydrophobic PMIBA chains must be related to the molecular structure characteristic to dehydroalanine polymers having two kinds of polar groups (—COOR and —NHCOR′) at every monomer unit. Because of the macroporous structure formed in the deswollen state, the PMIBA gel has a fast temperature response, high repetition durability, and relatively small volume change with retaining the initial shape.

These properties make the PMIBA gel suitable for applications as active elements of integrated sensor and actuator systems, such as microvalves, micropumps, and micromanipulators.

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