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Body temperature-responsive gels derived from hydroxypropylcellulose bearing lignin

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Abstract

Hydroxypropylcellulose bearing lignin (HPC-L) prepared from softwood by the atmospheric acetic acid pulping followed by derivatization showed the lower critical solution temperature (LCST) of approximate 38 °C in 2% aqueous solution, which were 5° lower than that of pure HPC with a similar molecular mass to HPC-L. Two types, urethane and epoxy, of chemical gels were prepared from HPC-L and HPC using hexamethylene diisocyanate and polyethylene glycol diglycidyl ether as crosslinkers, respectively. The urethane-type gels from both HPC's have undergone shrinking at less than 20 °C. This thermoresponse of the gels did not reflect LCST of the sources. Such low temperature shrinking was brought about by the hydrophobicity of crosslinker. On the other hand, the epoxy-type gels showed a very similar volume transition temperature (VTT) upon shrinking to LCST; the epoxy-type HPC-L gel showed VTT at 38 °C, while the corresponding HPC gel had VTT at 46 °C. This difference in VTT as well as LCST was attributable to hydrophobicity of lignin dangled to HPC. Thus, the body temperature-responsive gel can be prepared from HPC-L with the water-soluble crosslinker.

Keywords: Acetic acid pulp; Body temperature-response; Chemical gel; Hydroxypropylcellulose; Lignin; Lower critical solution temperature

1. Introduction

Thermoresponsive gels, in particular body temperature-responsive gels, have been drawn much attention in drug delivery system (DDS). These intelligent gels are exclusively prepared from vinyl polymers, such as poly(*N*-isopropyl acrylamide) (PNIPAAm) and its copolymer (Eeckman, Moes, & Amighi, 2002; Hsiue, Chang, Wang, & Lee, 2003; Hsiue, Hsu, Yang, Lee, & Yang, 2002; Kaneko, Nakamura, Sasaki, Aoyagi, Kikuchi, Sakurai, & Okano, 1998; Park, 1999; Ramkissoon-Ganorkar, Liu, Baudy, & Kim, 1999; Suzuki, Yumura, Tanaka, & Akashi, 2001). Although biocompatibility of such polymer gels is generally accepted in the medical fields, it seems that medical materials should be essentially produced from natural feedstocks with high biocompatibility. Cellulose and its derivatives are suitable materials to the requirement, and they have already been utilized in wide medical and pharmaceutical fields (Richardson, Lindley, Bartlett, & Will, 2003; Rodriguez, Alvarez-Lorenzo, & Concherio, 2003; Siepmann, Podual, Sriwongjanya, Peppas, & Bodmeier, 1999; Suzuki & Makino, 1999). Among the derivatives, HPC is particularly used in the application fields (Francis, Piredda, & Winnik, 2003; Park & Munday, 2002; Siepmann & Peppas, 2001).

Thermoresponse of gel was closely related to LCST of the original polymer. In the case of PNIPAAm, it showed LCST at 32 °C, resulting in that the VTT of the gel indicates lower temperature than body temperature, where we defined VTT as a temperature at a half volume change based on total volume change rate upon heating in this article. To regulate VTT, copolymerization for the polymer gel was carried out. The VTT was elevated when using hydrophobic monomer together with NIPAAm, while it was dropped with hydrophilic monomer (Feil, Bae, Feijien, & Kim, 1993). Several attempts to prepare thermoresponsive gels based on HPC have also been reported (Marsano, Bianchi, & Sciutto, 2003; Marsano, Bianchi, & Viscardi, 2004; Marsano, Gagliardi, Ghioni, & Bianchi, 2000; Wach, Mitomo, Yoshii, & Kume, 2002). Since, the LCST of HPC is more than 40 °C though its LCST depends on degree of molar substitution (MS) of propylene oxide and molecular mass (Klug, 1971), HPC gel crosslinked by radiation showed remarkable

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shrinking at more than 40 °C (Wach et al.). The body temperature-responsive gel with VTT of 35–40 °C was prepared from HPC methacrylate (Marsano et al.) and interpenetrated polymer network gel of HPC and PNIPAAm (Marsano et al.). However, the gels were composed of vinyl polymer and HPC. When a gel was prepared with more biocompatible polyethylene glycol-based crosslinker, the gel showed a higher VTT at 46 °C than body temperature (Marsano et al.). In this study, we carried out to prepare the body temperature-response gel from hydroxypropylated unbleached pulp (hydroxypropylcellulose bearing lignin (HPC-L)) with an ethylene glycol-based crosslinker.

We have been investigating to create novel functional materials that involve in potential wood functions. Since woods are considered as natural composite material composed of hydrophilic polysaccharides and hydrophobic lignin, it is expected that wood-based derivatives show different functions from the corresponding pure cellulose derivatives. We have previously reported that HPC-L derived from unbleached acetic acid pulp has very unique solution property, self-aggregation (Uraki, Hashida, & Sano, 1997). The phenomenon was caused by the hydrophobic interaction of the residual lignin in the pulp. The self-aggregation resulted in high viscosity and the formation of hydrophobic domains in the assembled molecules. Therefore, HPC-L interacted with hydrophobic compounds and biopolymers in a similar manner to inclusion compounds (Uraki, Hanzaki, Hashida & Sano, 2000). In this study, we further investigated the aqueous solution property of HPC-L in particular, LCST. It was found that the LCST of HPC-L was about 38 °C that was 5° lower than that of commercial HPC with a similar molecular mass in 2% aqueous solution. When HPC-L can be transformed into chemical gel that maintained its LCST using biocompatible crosslinker without introducing artificial hydrophobic functional group, the more biocompatible carrier for DDS would be produced in addition to expanding the utilization of natural feedstock. We prepared two types of chemical gels from HPC and HPC-L, and their thermoresponse was evaluated. It is found that one type gel from HPC-L is a body temperature-responsive gel. In addition, swelling behavior of the gels in aqueous organic solution is investigated to clarify responsive ability to the hydrophobicity of medium.

2. Experimental

2.1. Preparation of HPC-L

HPC-L was prepared from softwood (Todo-fir) unbleached acetic acid pulp with propylene oxide in *i*-propanol as reported previously (Uraki, Hashida, & Sano, 1997). HPC with a similar molecular mass to that HPC-L was kindly supplied by Nippon Soda Co. Ltd (Tokyo, Japan).

The weight average molecular mass (Mw) was estimated by high performance size-exclusion chromatography using a Shodex GF-7MH column (Tokyo, Japan) and polystyrene as molecular mass markers. The eluent was tetrahydrofuran, and refractive index detector was used. The degree of MS of HPC-L was determined by the method reported by Morgan (1946). Lignin content in HPC-L was determined by UV absorption (Uraki, Hashida, & Sano, 1997).

2.2. Lower critical solution temperature (LCST)

LCST was estimated from cloud point. Transmittance of HPC's in 2% aqueous solution at 700 nm was measured on a Hitachi-U3310 spectrophotometer (Tokyo, Japan) equipped with magnetic stirrer in a measurement cell and heating controller. The temperature of solution was directly monitored with a thermocouple. The temperature interval upon heating was 0.5 °C, and the transmittance at every temperature was measured after it reached stable state. LCST was determined as an inflection point of the transmittance profile in Fig. 1.

2.3. Preparation of urethane-type gel

HPC's were dissolved in 1,4-dioxane at concentrations of 2.5–5.0% (w/v). Hexamethylene diisocyanate (HDI) was added to the solution in the range of 5–50% based on the polymers together with a few drops of dibutyltin (IV) dilaurate as a catalyst. The mixture was vigorously stirred for 5 min, then was allowed to stand until gel formation. Cylindrical gels were cut out from the resulting gel mat using cork borer, then they were washed with ethanol and water successively for a week to give test specimens for evaluation of thermoresponse.

2.4. Preparation of epoxy-type gel

Polyethylene glycol diglycidyl ether (PEGDE) with 1, 9, 13 and 22 of the repeating unit of propylene oxide was

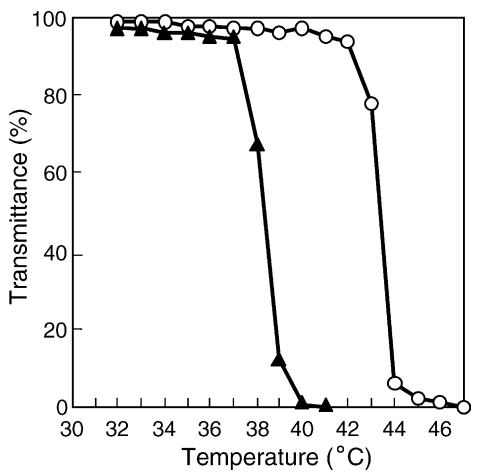

Fig. 1. Transmittance profiles of HPC (○) and HPC-L (▲) in the polymer solution of 2.0% (w/v). The heating interval was 0.5 °C.

added to the dioxane solution of HPC-L and HPC together with several drops of $SnCl_4 \cdot 5H_20$ as a catalyst. The mixture was vigorously stirred, and then allowed to stand in water bath at 60 °C for 3 h. The formed gel was cut out to cylinder. The resulting gel was washed thoroughly with ethanol and water. PEGDE was represented as PEGDE-1, 9, 13 and 22 corresponding to the number of repeating unit, respectively.

2.5. Evaluation of thermoresponse of the gels

All the gels in water were heated from 20 to 55 °C in temperature interval of 2 °C. At each temperature, the gels stand for 12 h, and the dimension of the gels was measured with a caliper. The volume of cylindrical gels was calculated from height and diameter. When the gel shape changed, the volume was estimated from average diameter for more than five measuring points. The volume was represented as a ratio to the volume at 20 °C.

2.6. Thermal reversibility of the gels

The gels were immersed in water at 20 °C for 36 h, and then at 50 °C for 36 h repeatedly. The volume was measured at every 12 h, and the volume change was represented as a ratio to the initial state at 20 °C.

2.7. Gel swelling in aqueous ethanol

Both type of gels were immersed in water, 25, 50, 75%(v/v) aqueous ethanol and ethanol successively at room temperature. Each immersion time was 24 h. The volume was measured, and swelling degree was calculated based on the volume in water.

3. Results and discussion

3.1. LCST

The chemical properties of HPC and HPC-L (HPC's) were summarized in Table 1. HPC-L contained residual lignin. The lignin could not be removed by simple extraction using organic solvents, urea, and salts, although the binding force of lignin to cellulose has been not yet clear. The covalent bonding between lignin and cellulose is being argued (Huttermann et al., 2000). Anyway, the lignin tightly bound to cellulose. LCST of HPL-C in 2% aqueous solution was found to be 5° lower than HPC used in this study. Although LCST of HPC depended on molecular mass and MS (Klug, 1971), it has been reported so far that the lowest LCST of HPC in the dilute solution was approximatly 40 °C. Thus, the LCST of HPC-L was lower than those of general HPC preparations from purified cellulose, and corresponded to human body temperature in conditions of sickness. Such solution property of HPC-L might be attributable to the residual lignin. Since lignin was biosynthesized from cinnamyl alcohol analogues (Freudenberg, 1959), the hydrophobicity of aromatic nuclei would affect the LCST of HPC-L.

In this study, attempts to prepare chemical gels that maintained LCST of the original HPC preparations was investigated, and the results are described in the following sections.

Table 1
Chemical properties of HP-samples

	Lignin content (%)[a]	$\overline{Mw}$[b]	MS[c]	LCST (°C)[d]
HPC	–	3.40×10^5	4.2	43
HPC-L	6.63	7.09×10^5	3.2	38

[a] The lignin content was estimated by UV absorption.
[b] $\overline{Mw}$ is weight average molecular mass determined by high performance size-exclusion chromatography.
[c] Degree of molar substitution.
[d] Lower critical solution temperature.

3.2. Preparation of urethane-type gel and its thermoresponse

First, we tried to prepare HPC's-based chemical gel by using HDI with relatively high reactivity to hydroxyl group as a crosslinker. The gel was easily formed by addition of more than 5% HDI based on the polymers in dioxane at ambient temperature. The resulting urethane-type HPC's-based gels were turbid, and the HPC-L-based gel was pale brown that corresponded to that of original HPC-L.

The volume change profiles of the urethane-type gels in water upon heating are shown in Fig. 2. Obviously, all the gels have already undergone shrinking at 20 °C. Accordingly, no clear volume transition was observed in the measurement temperature range. Comparing temperature (T_H) at a half volume, T_H of HPC-L-based gels was lower than that of HPC-based gels. This difference was attributed to LCST of the original polymers. In addition, T_H was shifted to lower temperatures as increasing crosslinker charge. In the case of HPC-L gels, it was also shifted by the increase of polymer concentration in the crosslinking reaction. Thus, the volume transition of chemical gels was influenced by not only the nature of original polymer but also crosslinking conditions. The volume transition of the urethane-type gels at the lower temperatures than LCST might be brought about by the hydrophobicity of crosslinker due to the hexamethylene moiety. In conclusion, the urethane-type gels did not have body temperature-response.

3.3. Preparation of epoxy-type gel and its thermoresponse

From the above results, a suitable crosslinker must be selected in order to prepare thermoresponse gel reflecting LCST. A requisite for crosslinker is that its polarity is similar to that of original polymer. Therefore, PEGDE having ethylene oxide as repeating unit, which was a similar

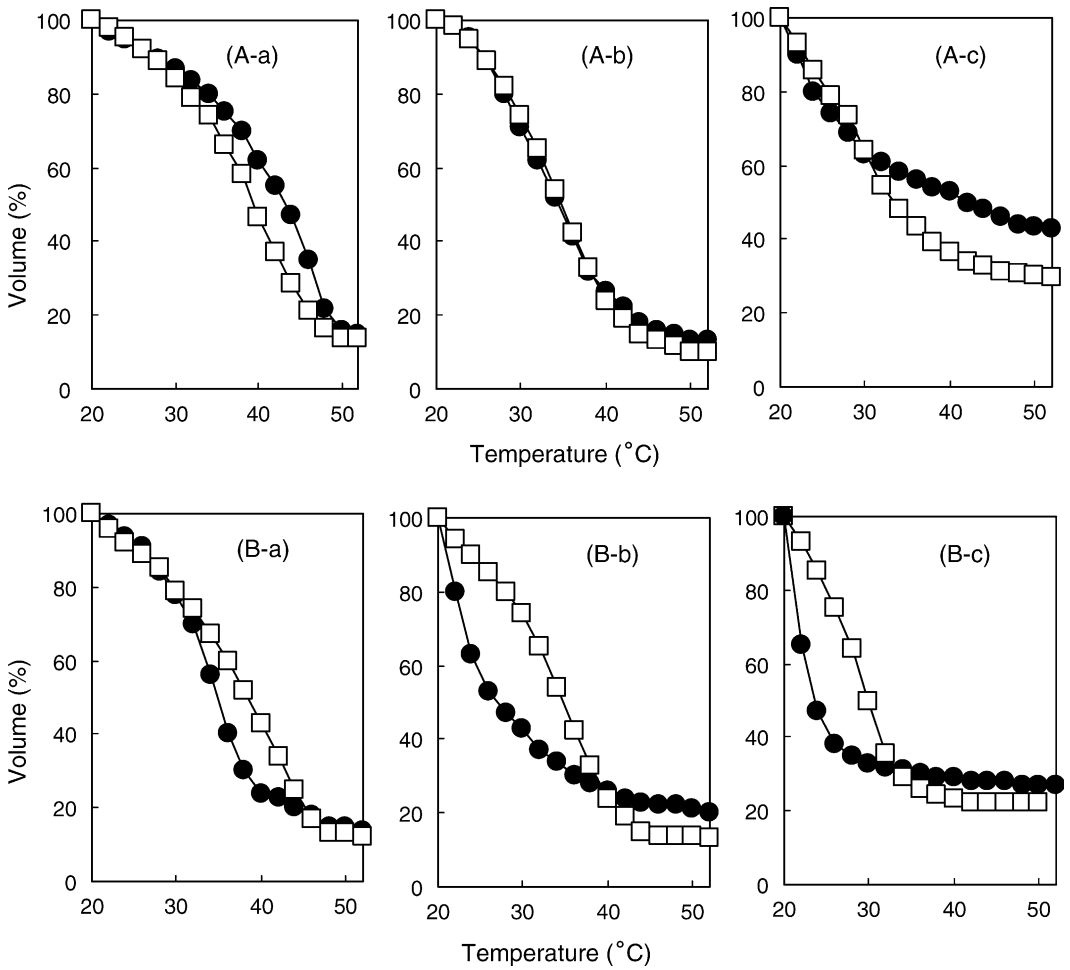

Fig. 2. Thermoresponse of urethane-type HPC (A) and HPC-L (B) gels. Gel preparation conditions: crosslinker charges based on polymer charge were 20% (a), 50% (b), and 80% (c); polymer concentrations were 2.5% (□) and 3.3% (●).

structure to the repeating unit of propylene oxide in HPC, was selected as a candidate for crosslinker.

PEGDE can act as crosslinker in water with alkali metal hydroxide as catalysts (Uraki, Nishida, & Sano, 2003). Thus, gel preparation with the crosslinker was initially carried out in aqueous solution, but no gel formation was observed even by varying reaction conditions. Furthermore, other catalysts, $Zn(BF_4)_2$ and $SnCl_4$, did not contribute to gel formation in aqueous solution. Evidently, it is difficult to prepare HPC gel in water. Finally, epoxy-type gels with the crosslinker were prepared from dioxane solution using $SnCl_4$ as catalyst. The HPC in 2.5%(w/v) solution was transformed into gel by more than 5% charge of PEGDE with a repeating unit (PEGDE-1) based on HPC, while 50% charge was required for the gel formation of HPC-L. The crosslinker charge required for gel formation decreased as increasing polymer concentration. In 5.0% polymer solution, the gel could be obtained by 20% addition of crosslinker. As PEGDE-1 is the most reactive among the used PEGDE crosslinkers, HPC-L has a very low reactivity toward PEGDE.

The volume change of HPC-based epoxy-type gel was measured as a function of temperature to elucidate influence

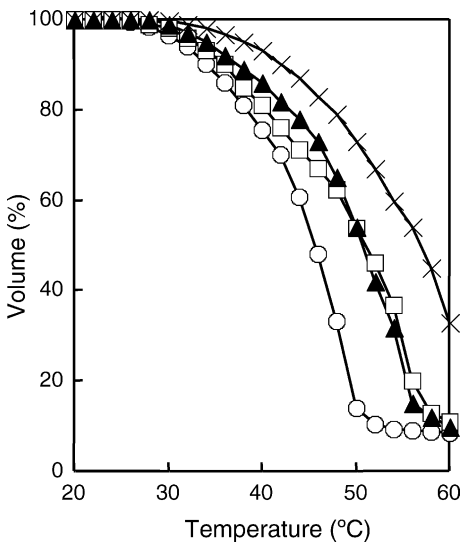

Fig. 3. Effect of chain length of crosslinkers, PEGDE-1 (○), PEGDE-9 (□), PEGDE-13 (▲) and PEGDE-22 (x), on the thermoresponse of epoxy-type HPC gels. Polymer concentration and crosslinker charge in the gel preparation were 3.3% (w/v) and 50%, respectively. The heating interval was 2.0 °C, and each temperature was kept for12 h.

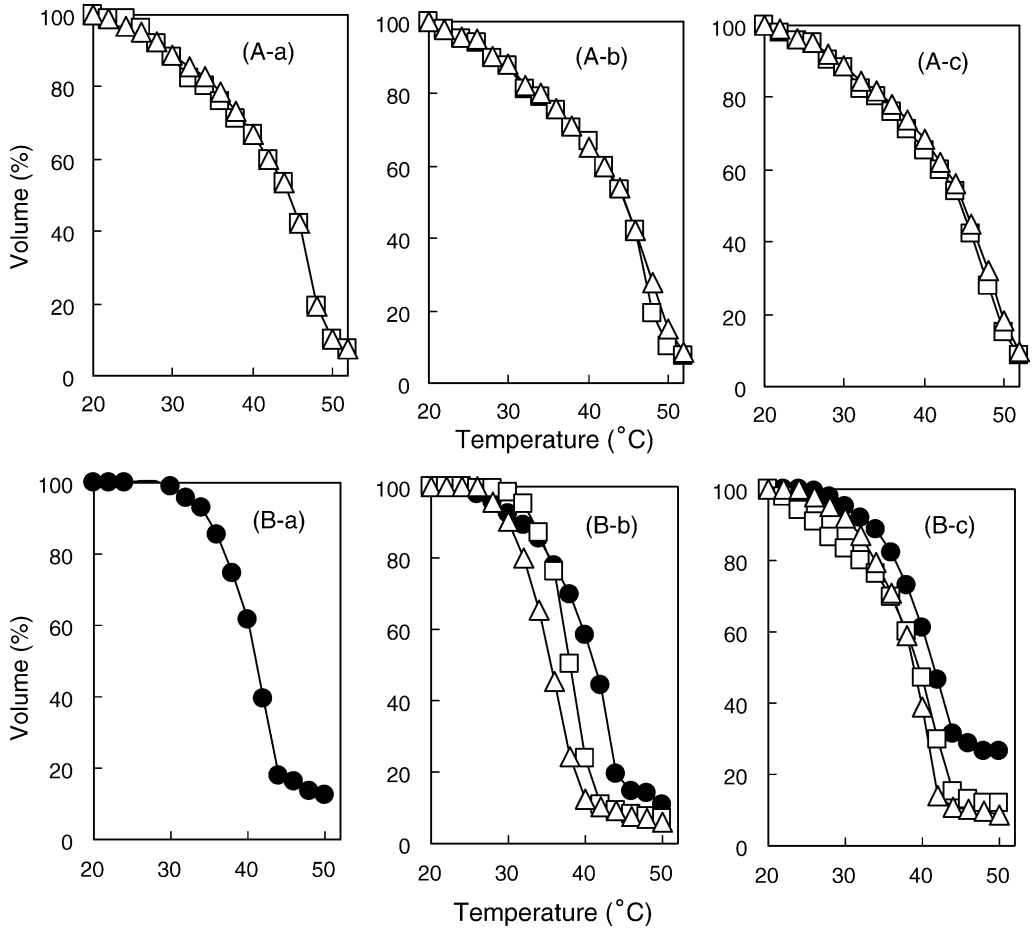

Fig. 4. Thermoresponse of epoxy-type HPC (A) and HPC-L (B) gels. Gel preparation conditions: crosslinker charges based on polymer charge were 20% (a), 50% (b), and 80% (c); polymer concentrations were 2.5% (△), 3.3% (□) and 5.0% (●).

of chain length of PEGDE on thermoresponse property of the resulting gels (Fig. 3). Although the volume change profiles of the gel with PE-9 and PE-13 were almost identical, the VTT decreased as shortening the chain length of PEGDE. The gel prepared with PEGDE-1 showed the lowest VTT. This result indicates that the chemical gel prepared by using PEGDE-1 as crosslinker almost preserve LCST of the original material.

Various HPC's-based epoxy-type gels were prepared with PEGDE-1. All the resulting gels were transparent, but the HPC-L-based gels were colored in yellow reflecting the original color of HPC-L. The epoxy-type gels became turbid upon heating. Their profiles of volume change upon heating are shown in Fig. 4. The HPC-based epoxy gels showed gradual shrinking from 20 °C, and after 40 °C, the volume dramatically decreased, indicating that the HPC gel had no clear volume transition. The VTT of HPC epoxy gels were approximatly 45 °C independent of gel preparation conditions, although in the case of HPC, T_H was a precise term rather than VTT. This high VTT was consistent with that of hydrogel from HPC using PEGDE (Marsano, Bianchi, & Sciutto, 2003). This result suggests that any gel with body

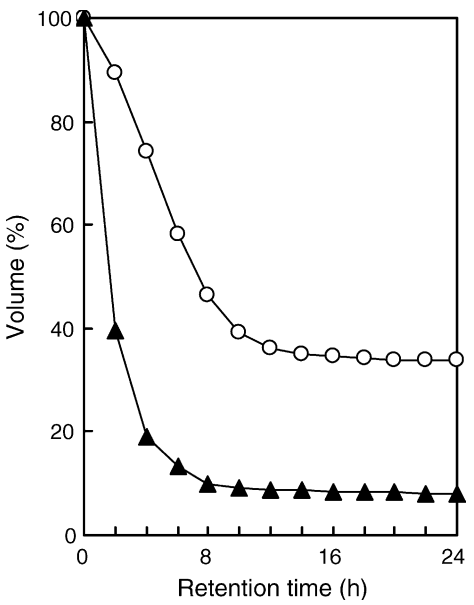

Fig. 5. Volume change rate of epoxy-type HPC (○) and HPC-L (▲) gels. Polymer concentration and crosslinker charge in the gel preparation were 3.3% (w/v) and 50%, respectively. The water temperature was 50 °C.

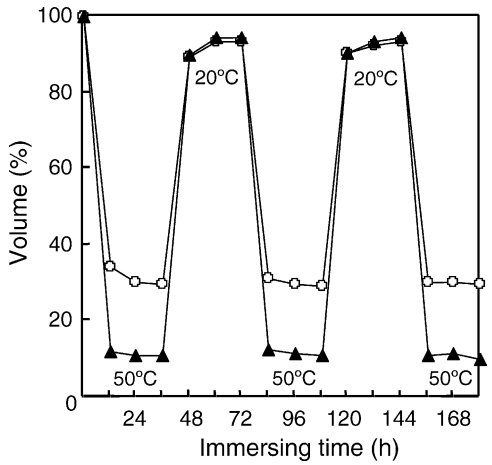

Fig. 6. Thermal reversiblility of epoxy-type HPC (○) and HPC-L (▲) gels. Polymer concentration and crosslinker charge in the gel preparation were 3.3% (w/v) and 50%, respectively.

temperature-response cannot be prepared from HPC and PEGDE. On the other hand, HPC-L-based epoxy gels revealed distinct volume transition; no volume change was observed until shrinking began. The VTT of HPC-L epoxy gel was likely not to be influenced by crosslinker charge. Polymer concentration significantly affected VTT. Among the epoxy gels, the HPC-L gel prepared by 50% PEGDE-1 charge in 3.3% polymer concentration showed the VTT at 38 °C corresponding to body temperature in a morbid state. The gel shrinking almost completed at 40 °C. This is a body temperature-responsive gel, which is our target material in this study. These results evidently suggest that the residual lignin affects gel shrinking behavior as well as LCST, which might result from hydrophobicity of lignin.

3.4. Response rate and thermal reversibility of volume change of epoxy-type

Fig. 5 shows the volume change rate of HPC's epoxy gels when the gels stored in water at 20 °C was immersed in water at 50 °C, at which HPC gel shrinking was almost completed. The HPC-L gel reached equilibrium state within 8 h, while the HPC gel took 12 h. This result suggests that the volume transition of the HPC-L gel occurred at a lower temperature. It seems that the response rate is not so fast, but it would be overcome by shape transformation to small particles or porous gels (Chen & Park, 2000; Lynch & Dawson, 2003; Sayil & Okay, 2001; Zhang, Yang, Chung, & Ma, 2001).

Fig. 6 shows thermal reversibility of volume change of the epoxy-type gels, where the gels were alternately immersed in water at 20 and 50 °C. All the gels almost swelled to initial state even after shrinking. Fig. 6 shows unambiguous thermal reversibility for both gels in three-times repeating experiment. We confirmed that the reversible transition occurred until 5-times repeating experiment. Thus, these HPC's-based epoxy-type gels had high thermal reversibility.

3.5. Response to hydrophobic environment

As one of the studies on the response of the resulting gels to other external stimuli, the gel behavior in ethanol aqueous solutions in the range of 0–100% was investigated. The urethane-type gels obviously swelled in ethanol aqueous solution of more than 50% (Fig. 7). These results suggest that urethane-type gels have high affinity to organic medium probably due to the interaction of hydrophobic crosslinker. Furthermore, the gel derived from HPC-L showed much larger swelling than did the corresponding HPC gel. This result might support that the residual lignin affects the sensitivity of the gels to hydrophobic environment. On the other hand, no volume change of epoxy-type gels was observed. We have reported that PEGDE-13 gel, which was prepared from the PEGDE alone by self-crosslinking, did not significantly undergo volume change in aqueous ethanol (Uraki, Nishida, & Sano, 2003). Deducing from the result, PEGDE-1 did not also respond to aqueous ethanol. The epoxy gels contained large amount of PEGDE-1. The PEGDE-1 moiety in the gel resisted gel swelling in organic medium even if the residual lignin in

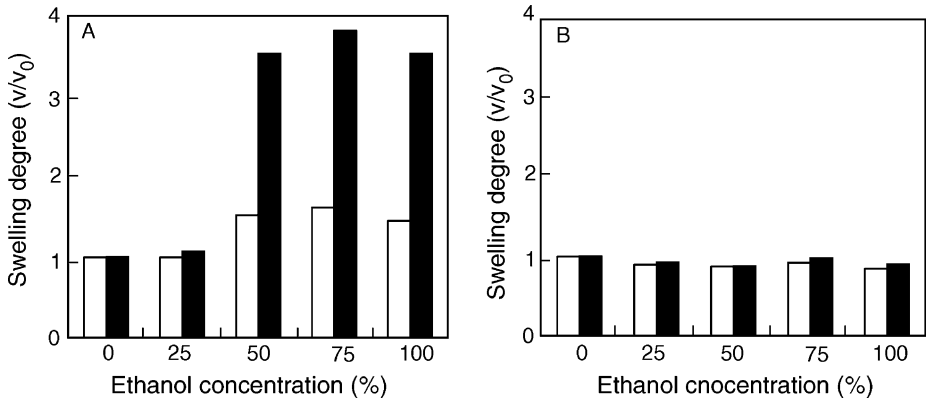

Fig. 7. Swelling properties of urethane-type (A) and epoxy-type gels (B) prepared from HPC (□) and HPC-L (■). Polymer concentration and crosslinker charge in the gel preparation were 3.3% (w/v) and 50%, respectively.

the gel was hydrophobic. Therefore, crosslinkers influenced stimuli-response of HPC gel.

4. Conclusions

Two types of HPC-based chemical gels were prepared in this study. The urethane-type gels shrank from low temperature of 20 °C, while the epoxy-type gels showed distinct volume transition at 35–50 °C. HPC-based epoxy-type gel showed volume transition at more than 45 °C. The HPC-L-based gel prepared in 3.3% polymer solution with 50% PEGDE-1 based on the polymer as crosslinker, however, indicated the transition at human body temperature without introducing hydrophobic functional group to HPC. Evidently, lowering VTT was brought about by the residual lignin in HPC-L. In general, chemical pulps for papermaking and feedstock of cellulose are produced from wood by complete delignification, digestion and bleaching (Gellerstedt, 2001). In this viewpoint, lignin is an undesired wood component. However, this study exemplified that highly functional materials are readily produced by using potential function of lignin. Thus, novel functional biomaterials can be inspired and created by the extraction of native function of biomass components as feedstock.

To establish viable application of the thermoresponsive gels in the medical field, we are investigating on the other stimuli-response, such as pH and ionic strength, and interactions of biopolymers of the gels.

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