Thermoresponsive Hydrogels Based on Biodegradable Poly(amino acid)s

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Thermoresponsive hydrogels based on biodegradable poly(amino acid)s have been developed by crosslinking of poly(*N*-(ω-hydroxyalkyl) α/β-asparagine)s with diisocyanate. The poly(amino acid) hydrogels showed a thermoresponsive release of a model drug.

There has been significant interest in thermoresponsive polymers and hydrogels for various applications such as drug delivery, biomimetic actuators, chromatographic separations, gene-transfection agents, and immobilized biocatalysts.[1] Poly(*N*-isopropylacrylamide) (PNIPAAm) is one of the most typical thermoresponsive polymers.[2] A rapid and reversible hydration-dehydration change is observed in response to small temperature cycles around its lower critical solution temperature (LCST). PNIPAAm hydrogel, prepared by copolymerization of NIPAAm with a small amount of divinyl crosslinking agent, exhibited a volume phase transition at LCST and its volume significantly decreased above LCST with release of water. Recently, rapid deswelling of PNIPAAm hydrogel was achieved by incorporation of silica particles.[3] However, PNIPAAm is non-biodegradable, resulting in limitation of its use in medical fields.

Amino acid-based polymers including polypeptides have been remarkably developed owing to their wide potential applications for biocompatible materials as well as useful chemical materials.[4] Some of these polymers have unique properties and functions derived from amino acid moiety. Poly(aspartate), a poly(amino acid) with carboxylate side chain, which is synthesized by thermal polymerization of aspartic acid followed by alkaline hydrolysis, has received much attention as a new useful class of biodegradable, water-soluble polymeric materials.[5] In the preparation of biodegradable poly(aspartate), poly(succinimide) (PSI) is obtained as an intermediate product, which is readily subjected to reaction with various nucleophiles. It was reported that alkaline hydrolysis of PSI produced poly(aspartate) with a mixed structure of α and β units. Very recently, we have synthesized new thermoresponsive polymers based on biodegradable poly(amino acid)s; reaction of PSI with an appropriate combination of amino alcohols produced poly(*N*-(ω-hydroxyalkyl) α/β-asparagine)s (**1**) showing a clear LCST in water.[6]

We report herein synthesis and properties of new biodegradable thermoresponsive poly(amino acid) hydrogels, which were synthesized by crosslinking of **1** with hexamethylene diisocyanate (5 mol% for hydroxy group of **1**) in *N*,*N*-dimethylformamide at 60 °C for 24 h (Eq 1). In this study, 4-aminobutanol (**2a**) and 5-aminopentanol (**2b**) were used for synthesis of **1**[6] and three hydrogel samples were prepared: sample A prepared from **2a**, sample B from an equimolar mixture of **2a** and **2b**, and sample C from **2b**.

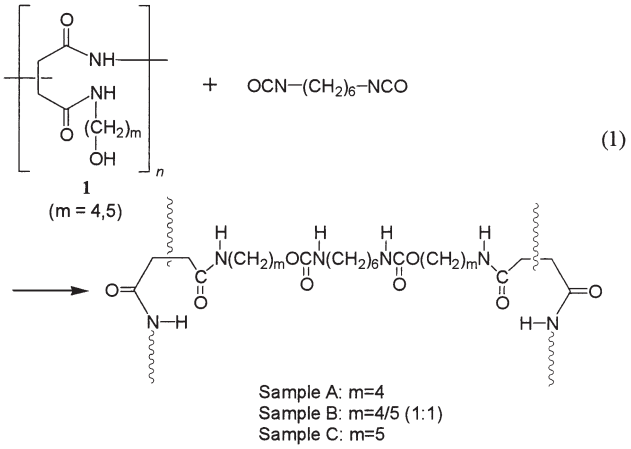

Figure 1 shows photographs of samples A–C swollen in water at 30 and 60 °C. Sample A swelled at both temperatures and the volume change was relatively small. On the other hand, sample B significantly shrank at 60 °C. Interestingly, sample C rapidly became opaque at 60 °C with small volume change, suggesting large potential of sample C as thermosensor materials.

Figure 2 shows swelling ratio of hydrogels as a function of temperature. The gel was swollen in water at each temperature for 12 h. The swelling ratio is defined as $(W–W_0)/W_0$, in which W and W_0 are weights of swollen and dry gels, respectively. Sample B exhibited a relatively clear phase transition around 35 °C, which may be suitable for biomedical applications. On the other hand, the volume change of sample C was small at the measured temperatures and sample A swelled even at high temperatures. These results indicate that swelling behaviors of the hydrogels

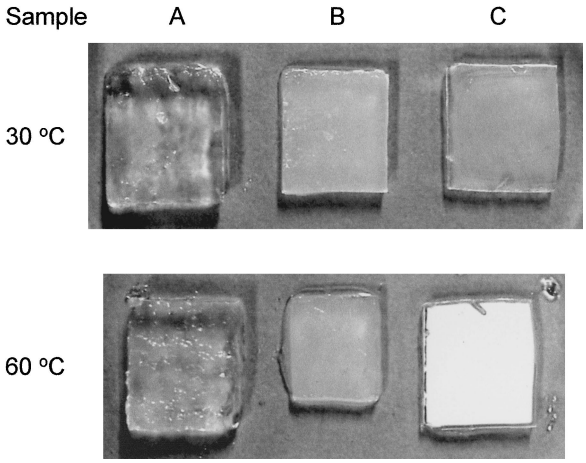

Figure 1. Photographs of poly(amino acid) hydrogels swollen at 30 and 60 °C.

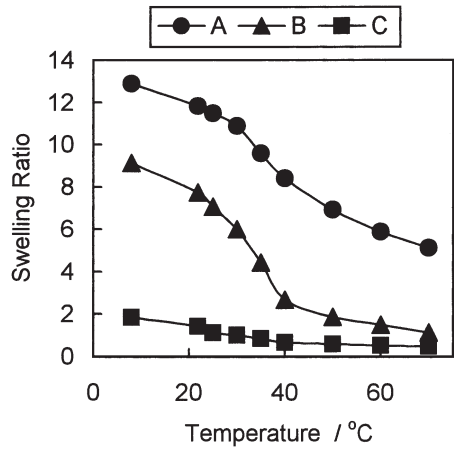

Figure 2. Swelling ratio of samples A-C in water as a function of temperature.

from **1** greatly depend on the structure (hydrophilicity) of the side chain in **1** and thermoresponsive hydrogels are prepared by selecting an appropriate combination of amino alcohols in the synthesis of precursor poly(α/β-asparagine)s (**1**).

As a possible application of the present hydrogels for drug delivery system, release behaviors of brilliant blue FCF (BB), a model drug, encapsulated into the hydrogel were examined. The hydrogel was immersed in an aqueous solution of BB for 1 week, and used for the release test.[7] The release amount was determined by UV-vis spectrometer with absorption of 630 nm. In the case of sample B, BB was released faster at 50 °C than 30 °C (Figure 3). On the other hand, no significant change in release behaviors was observed in samples A and C (data not shown). These data

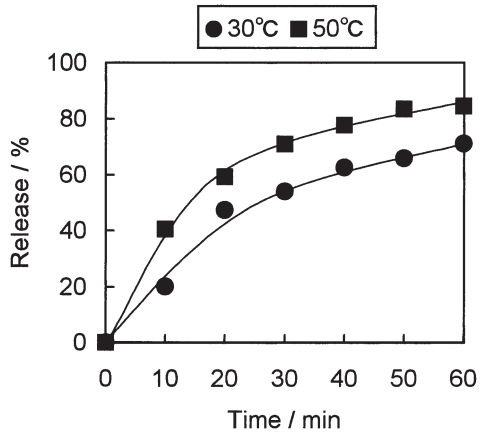

Figure 3. Release behaviors of BB from sample B at 30 and 50 °C.

indicate good thermoresponsive release of BB of sample B.

In conclusion, new thermoresponsive hydrogels based on biodegradable poly(amino acid)s have been developed. Relatively sharp thermoresponsive property was found in the hydrogel prepared by selection of an appropriate combination of amino alcohols for synthesis of poly(α/β-asparagine) precursors. Furthermore, this hydrogel showed a thermoresponsive release of the model drug. Further studies on new thermoresponsive polymeric materials based on biodegradable poly(amino acid)s are under way in our laboratory.

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