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Communications

Biodegradable Thermo- and pH-Responsive Hydrogels Based on Amphiphilic Polyaspartamide Derivatives Containing *N,N*-Diisopropylamine Pendants

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Introduction

Hydrogels are hydrophilic polymer networks that can absorb large amounts of water, but are insoluble due to the presence of physical or chemical crosslinks, entanglements, or crystalline regions. Hydrogels can have various biomedical applications such as drug delivery systems, biosensors, contact lenses, catheters, and wound dressings.

Recently, stimuli-responsive polymers and hydrogel materials have attracted considerable attention in the field of novel drug delivery and tissue engineering due to their promising potential. Among them, polymer and hydrogel systems that undergo a phase transition and volume-phase transition in response to environmental stimuli, such as temperature and pH, have been widely investigated for use in gene or tumor targeting delivery, oral drug delivery, and other medical devices.[1] Cationic hydrogels have been employed for localized delivery of antibiotics in the stomach. Chitosan hydrogel based on polyionic complex or IPN type networks has been used in many studies because of its suitable good biocompatibility, sustained drug release properties and pH-responsive swelling properties.[2] Poly(*N*-isopropyl acrylamide), PNIPAAm, is a typical thermo-sensitive polymer that undergoes a rapid and reversible hydration-dehydration change through the lower critical solution temperature (LCST). Most commonly, the polymers used to prepare thermo- and pH-responsive hydrogels include PNIPAAm copolymers containing poly(acrylic acid) (PAA), or poly(dimethylaminoethyl-methacrylate) (PDMAEMA). These hydrogels are widely used in controlled drug delivery systems as well as in various bio-related applications.[3] However, most are non-biodegradable, which has limited their use in the biomedical field.

Polypeptides and their related synthetic poly(amino acid)s have become important on account of their biocompatibility and biodegradability, which are useful in various bio-related applications.[4] Poly(*N*-2-hydroxyethyl-DL-aspartamide), PHEA, is one of these synthetic polymers, which is water-soluble, biocompatible and non-toxic. The attachment and chemical modification of the pendent groups either through an aminolysis reaction to polysuccinimide (PSI) or via a secondary reaction with the hydroxyl groups on PHEA can provide a variety of biodegradable functional polymers with specific properties. These polymers have been reported to have physicochemical characteristics suitable for the development of biomaterials for drug carriers, such as macromolecular prodrugs, hydrogels and nano- or microparticles.[5] Until now, however, studies of PHEA derivations were focused only on the pH-responsive hydrogel.

Results and Discussion

This paper reports the synthesis and characterization of a novel biodegradable double-responsive polymer and crosslinked gel based on new amphiphilic polyaspartamides containing *N,N*-diisopropylaminoethyl pendent groups. The synthesis of PSI, the precursor polymer, has been well described in the literature.[6] The molecular weight of PSI was determined to be 120,000 Da by viscosity measurement. Polyaspartamide (PolyAspAm) copolymers were synthesized through the successive aminolysis of PSI with quantitative 2-diisopropylaminoethylamine (DIPAEA) and an excess of ethanolamine (EA). The crosslinked gels were prepared from copolymer D using hexamethylene diisocyanate (HMDI, 40 mol% of hydroxyl moiety of copolymer D) (Scheme I).

Table I summarizes their hydrophobic/hydrophilic component ratio and the LCST values in an aqueous solution. Copolymers A-E (DIPAEA content of ca. 90-32%) showed relatively sharp phase separation at temperatures ranging from 12 to 45 °C due to the presence of LCST in this particular system.

Figure 1 shows the temperature dependence of light transmittance of a 1 wt% aqueous solution at 500 nm. The pH dependence of the phase transition was investigated using the copolymer C sample. At pH 10, the LCST was observed at approximately 22 °C. The LCST shifted toward a higher temperature with decreasing pH, e.g. 38, 51 and 80 °C at pH 9, 8 and 7, respectively. On the other hand, no LCST behav-

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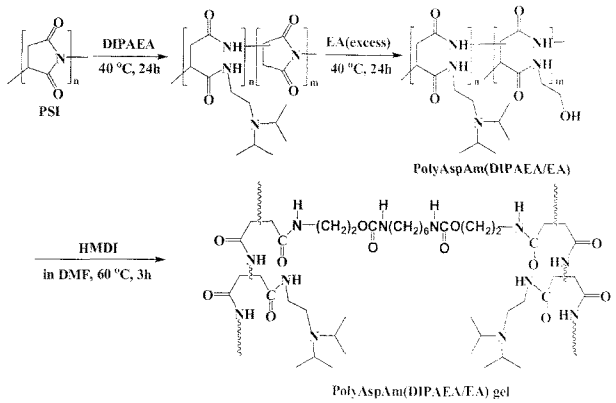

Scheme I. Preparation of biodegradable thermo- and pH-responsive hydrogels.

Table I. Composition and LCSTs of Polyaspartamide Copolymers

PolyAspAm (DIPAEA/EA)	Content of DIPAEA[a]/mol%	LCST[b]/°C
Copolymer A	90	13
Copolymer B	75	18
Copolymer C	66	22
Copolymer D	51	33
Copolymer E	42	41
Copolymer F	32	-

[a]The compostion of each group in the copolymers was determined by ^{1}H-NMR.[7] [b]Temperature at 90% light transmittance of the copolymer solution was defined as LCST.

ior was observed in the polymer solution at pH 6 at temperatures up to 85 °C. At < pH 7, protonation of the tertiary amine group leads to electrostatic repulsion causing the polymer to be more soluble in water. In addition, the polymer-water interaction should increase due to ionization of the tertiary amine.

Figure 2 and Figure 3 show the reversible swelling-deswelling behavior of the PolyAspAm(DIPAEA/EA) gel measured at different pH and temperature. The swelling ratio(SR) was defined as W_s/W_d, where W_d and W_s are the weights of the dry gel and swollen gel at equilibrium, respectively. Figure 2 shows the change in the equilibrium swelling ratio of hydrogel (from copolymer D) measured at 10 and 50 °C in a cyclic function. This reversible change in swelling suggests the presence of a thermal transition within the temperature range in this specific copolymer system with amphiphilic molecular characteristics.

Figure 3 shows the equilibrium swelling ratio of hydrogel (from copolymer D) at room temperature between pH 2 and 10. At pH 2, the swelling ratio was high but the SR decreased at basic pH 10. The increased swelling ratio at pH 2 will be attributed to ionization of the tertiary amine pendants of the

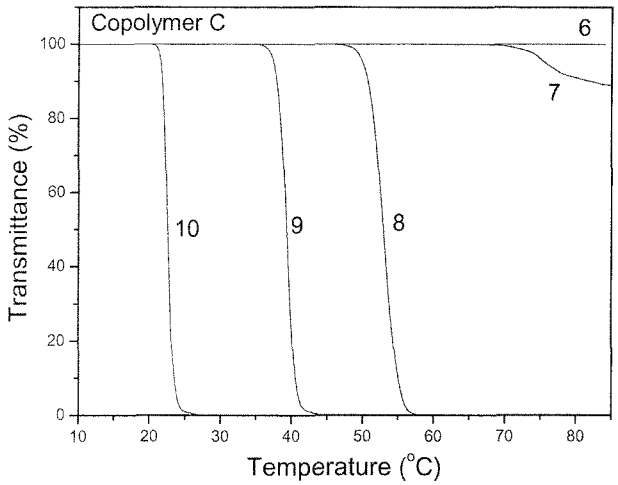

Figure 1. LCST curves of PolyAspAm(DIPAEA/EA) aqueous solutions with different pHs.

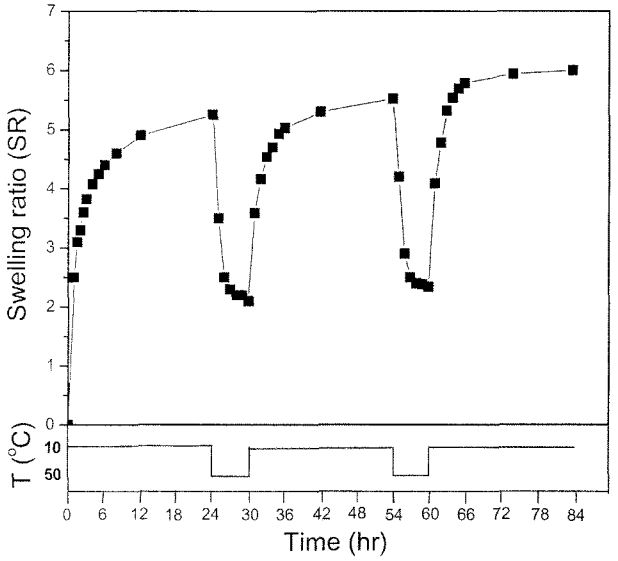

Figure 2. Reversible swelling curves of hydrogel as a function of temperature.

gel matrix. The swelling-deswelling behavior of the volume-phase transition from this hydrogel was demonstrated by changing the temperature or pH of the medium as the typical photographs are shown in Figure 4.

A detailed study on the dynamics of gel swelling and the hydrolytic degradation of these gels is currently underway.

In conclusion, novel copolymers based on amphiphilic polyaspartamides with diisopropylamine and hydroxy ethyl pendants, and the crosslinked gels were prepared and characterized. The phase transition of the LCST of the copolymers was controllable with a balance between the hydrophobic-hydrophilic composition and different pH. In addition, the swelling-deswelling behavior of the volume-phase transition from the hydrogel was demonstrated by changing the

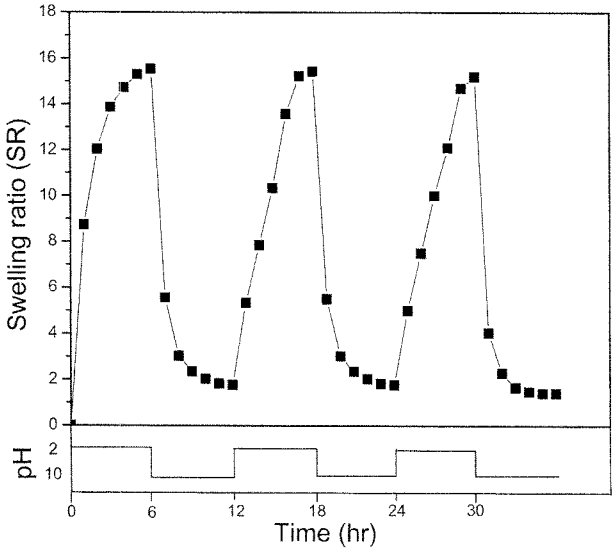

Figure 3. Reversible swelling curves of hydrogel as a function of pH of buffer solution.

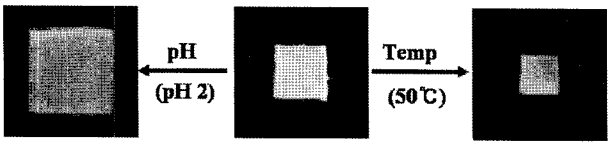

Figure 4. Photographs of hydrogel showing thermo- and pH-responsive volume changes.

temperature or pH of the medium. These novel stimuli-responsive hydrogels have potential biomedical applications for controlled and targeted drug delivery system.

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(7) The composition of each group in the polyaspartamide copolymers was determined from the integration ratio between methyl proton of isopropyl amine δ=0.91-1.14 (DIAPEA, 12H) and methylene proton adjacent to OH δ=3.48-3.6 (EA, 2H) in the ^{1}H-NMR.