Phase-Transition Characteristics of Amphiphilic Poly(2-ethyl-2-oxazoline)/Poly(ε-caprolactone) Block Copolymers in Aqueous Solutions

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ABSTRACT: Amphiphilic diblock and triblock copolymers of various block compositions based on hydrophilic poly(2-ethyl-2-oxazoline) (PEtOz) and hydrophobic poly(ε-caprolactone) were synthesized. The micelle formation of these block copolymers in aqueous media was confirmed by a fluorescence technique and dynamic light scattering. The critical micelle concentrations ranged from 35.5 to 4.6 mg/L for diblock copolymers and 4.7 to 9.0 mg/L for triblock copolymers, depending on the block composition. The phase-transition behaviors of the block copolymers in concentrated aqueous solutions were investigated. When the temperature was increased, aqueous solutions of diblock and triblock copolymers exhibited gel–sol transition and precipitation, both of which were thermally reversible. The gel–sol transition- and precipitation temperatures were manipulated by adjustment of the block composition. As the hydrophobic portion of block copolymers became higher, a larger gel region was generated. In the presence of sodium chloride, the phase transitions were shifted to a lower temperature level. Sodium thiocyanate displaced the gel region and precipitation temperatures to a higher temperature level. The low molecular weight saccharides, such as glucose and maltose, contributed to the shift of phase-transition temperatures to a lower temperature level, where glucose was more effective than maltose in lowering the gel–sol transition temperatures. The malonic acid that formed hydrogen bonds with the PEtOz shell of micelles was effective in lowering phase-transition temperatures to 1.0 M, above which concentration the block copolymer solutions formed complex precipitates. © 2000 John Wiley & Sons, Inc. J Polym Sci B: Polym Phys 38: 2400–2408, 2000

Keywords: amphiphilic diblock and triblock copolymers; poly(2-ethyl-2-oxazoline); phase-transition behaviors; gel–sol transition; precipitation

INTRODUCTION

The thermoreversible phase transitions of some classes of micelle-forming amphiphilic block copolymers in an aqueous solution have generated a great deal of interest because of their applicability in the areas of drug delivery and biotechnology.1–9 In particular, phase-transition behaviors of triblock copolymers consisting of poly(ethylene oxide) and poly(propylene oxide) (PEO–PPO–PEO; Pluronics) have been intensively investigated.1–5 They exhibit low-temperature-boundary sol–gel and high-temperature-boundary gel–sol transitions, where gel regions appear at high con-
centrations and intermediate temperature ranges. Besides academic interest, including an understanding of the gel structure and transition mechanism, the gel-forming property is especially attractive in the area of drug delivery, in that it can offer a possibility of gelation of an injected solution containing bioactive agents at body temperature. For PEO–PBO–PEO triblock copolymers, where poly(butylene oxide) (PBO) is introduced as the hydrophobic middle block, replacing the PPO block of Pluronics, a similar phase diagram has been observed in concentrated aqueous solutions. Therefore, it is suggested that the structure of block copolymers demanded for such phase transition is not confined to PEO and PPO or to PEO and PBO if the balance between hydrophilicity and hydrophobicity in block copolymers is moderately adjusted. In recent reports, studies on thermoreversible gel–sol transition have been expanded to structurally varied block copolymer systems including PEO-aliphatic polyesters. In this study, we describe the phase-transition behavior of concentrated aqueous solutions of amphiphilic block copolymers based on hydrophilic poly(2-ethyl-2-oxazoline) (PEtOz) and hydrophobic poly(ε-caprolactone) (PCL). The micelle formation of these block copolymers in aqueous media was confirmed recently by our group. Therefore, it is expected that the concentrated aqueous solutions of block copolymers of PEtOz and PCL will exhibit thermoreversible gel–sol transition, as in the case of PEO-aliphatic polyester block copolymers in an aqueous solution. In water, PEtOz homopolymer exhibits a lower critical solution temperature (LCST), which is similarly shown in the aqueous solution of PEO. Hence, the scope of this study covers precipitation behavior associated with the LCST of PEtOz block as well as gel–sol transitions of block copolymers composed of PEtOz and PCL in an aqueous phase. We also investigated the effect of block composition and copolymer structure (diblock or triblock) on the phase-transition behavior and other unique properties. In addition, this work discusses the effect of third-component additives such as inorganic salts, saccharides, and multifunctional carboxylic acids.

**EXPERIMENTAL**

**Materials and Equipment**

2-Ethyl-2-oxazoline (Aldrich) was dried and distilled over calcium hydride. Methyl p-toluenesulfonate (Aldrich) was vacuum-distilled. 1,4-Dibromo-2-butene (Aldrich) was recrystallized twice from n-hexane. ε-Caprolactone (Aldrich) was dried and vacuum-distilled over calcium hydride. Acetonitrile was dried and distilled over calcium hydride. Other solvents such as tetrahydrofuran (THF) and diethyl ether were used without further purification. Stannous octoate (Sigma), pyrene (Aldrich), D(+)-glucose (Sigma), and maltose (Sigma) were used as received. Sodium chloride (NaCl) and sodium thiocyanate (NaSCN) were analytical grade. H NMR spectra were obtained on a Bruker AC 250 spectrometer at 250 MHz. Molecular weights and molecular weight distributions were determined with a gel permeation chromatography (GPC) equipped with a Waters Associates 410 RI detector, 510 HPLC pump, and µ-Styrage columns with pore sizes of 10^2, 500, 10^3, and 10^4 Å. The eluent was THF, and the molecular weights were calibrated with polystyrene standards. Ultraviolet–visible (UV–vis) spectra were obtained with a Hewlett-Packard 8452A spectrophotometer. The pyrene excitation spectra were recorded on a Shimadzu RF-5301 spectrofluorometer. The hydrodynamic diameters of micelles were obtained with an He–Ne laser (Research Electro-Optics 35 mW) and a BI-200SM Brookhaven apparatus.

**Preparation of Amphiphilic Diblock and Triblock Copolymers**

The diblock copolymers of PEtOz and PCL (PEtOz–PCLs) were synthesized according to a procedure reported previously. The synthetic procedure for PEtOz–PCL-0.30, which has a 0.30 molar ratio of ε-caprolactone to 2-ethyl-2-oxazoline, is as follows: A solution of 2-ethyl-2-oxazoline (60.00 g, 605 mmol) and methyl p-toluenesulfonate (1.88 g, 10 mmol) in acetonitrile (300 mL) was refluxed to accept 30 mL of chlorobenzene. After the solution cooled to room temperature, 3.45 g, 30 mmol) of ε-caprolactone was added under nitrogen. After the solution cooled to room temperature, 0.1 N methanolic KOH was added to introduce hydroxyl groups at the end of the PEtOz chain. The polymer was filtered through silica gel. The product, PEtOz—OH, was then isolated by precipitation into diethyl ether and vacuum-dried at 40 °C before use. A solution of PEtOz—OH (10.00 g) in dry chlorobenzene (100 mL) was heated at reflux for 30 h under nitrogen. After the solution cooled to room temperature, 0.1 N methanolic KOH was added to introduce hydroxyl groups at the end of the PEtOz chain. The polymer was filtered through silica gel. The product, PEtOz—OH, was then isolated by precipitation into diethyl ether and vacuum-dried at 40 °C before use. A solution of PEtOz—OH (10.00 g) in dry chlorobenzene (100 mL) was heated at reflux for 30 h under nitrogen. After the solution cooled to room temperature, 0.1 N methanolic KOH was added to introduce hydroxyl groups at the end of the PEtOz chain. The polymer was filtered through silica gel. The product, PEtOz—OH, was then isolated by precipitation into diethyl ether and vacuum-dried at 40 °C before use.
The temperature was raised at reflux, and stannous octoate (4 mg) was added under nitrogen. The reaction was maintained for 30 h. The block copolymer was isolated by precipitation into diethyl ether. Other block copolymers with different PCL block lengths were synthesized in an identical manner, except that different feed molar ratios of ε-caprolactone to the oxazoline unit of PEtOz were employed. Triblock copolymers (PCL–PEtOz–PCLs) with different PCL block lengths were synthesized identically, except that the bifunctional initiator, 1,4-dibromo-2-butene, was employed to prepare PEtOz (HO–PEtOz–OH) with hydroxyl groups at both chain ends.

Fluorescence and Light Scattering Measurements

The samples for fluorescence and light scattering measurements were prepared according to a reference method. For the measurement of pyrene excitation spectra, emission and excitation slit widths were set at 3.0 and 1.5 nm, respectively. For excitation spectra, λexc was 393 nm. Dynamic light scattering measurements were performed according to a literature procedure.

Gel–Sol Transition and Precipitation Temperature

Aqueous copolymer solutions of various concentrations were prepared by the dissolution of copolymers in water in a tightly capped tube (internal diameter = ca. 10 mm) until homogeneous solutions were obtained. Samples were equilibrated at 5 °C for 12 h. After immersion in a water bath at desired temperatures for 15 min, the phase behavior was evaluated. The gel–sol transition was detected by a tube-rotating method from a vertical position to a horizontal position in the water bath. When the sample was immobile for 1 min, it was regarded as a gel. The transition was observed with an accuracy of ±1 °C. The precipitation temperature was detected visually in an oil bath with an accuracy of ±1 °C.

RESULTS AND DISCUSSION

Synthesis and Characterization of Block Copolymers

The synthesis of amphiphilic PEtOz–PCL diblock and PCL–PEtOz–PCL triblock copolymers is illustrated in Scheme 1. The polymerization of 2-ethyl-2-oxazoline for the preparation of PEtOz–OH was carried out with methyl tosylate as the initiator to produce PEtOz with oxazolinium living end groups, which were then terminated by methanolic KOH to introduce hydroxyl groups at the chain end. For the HO–PEtOz–OH, which had hydroxyl groups at both chain ends, the bifunctional initiator 1,4-
dibromo-2-butene was utilized in the polymerization of 2-ethyl-2-oxazoline.18 The hydroxyl groups of PEtOz–O–OH ($M_n = 6400$) and HO–PEtOz–O–OH ($M_n = 3000$) were used as the initiation sites for the ring-opening polymerization of $\varepsilon$-caprolactone in the presence of a catalyst, stannous octoate, to produce the block copolymers, PEtOz–PCL and PCL–PEtOz–PCL, respectively. The block copolymers were prepared by the length of the hydrophobic PCL block being varied, whereas the length of the hydrophilic PEtOz block was fixed. The molecular weights and block compositions of the block copolymers were determined by the analysis of $^1$H NMR spectra. The $^1$H NMR spectrum of PEtOz–PCL-0.30 in Figure 1, as a representative example, shows the characteristic resonance peaks of PEtOz–PCL block copolymers. The molar ratios of repeating units in PEtOz and PCL blocks were determined by the peak integration ratios of methyl protons (1.10 ppm) in PEtOz and CH$_2$OCO (4.02 ppm) in the PCL block. The PCL–PEtOz–PCL block copolymers were characterized in an identical manner. All the diblock copolymers have identical PEtOz blocks with $M_n = 6400$ and $M_w/M_n = 1.05$. The gel permeation chromatograms of the diblock copolymers were narrow and did not show a trace of PEtOz homopolymer. All the triblock copolymers are based on an identical PEtOz with $M_n = 3000$ and $M_w/M_n = 1.11$ and also show narrow distribution. The block compositions and molecular weights of PEtOz–PCL and PCL–PEtOz–PCL block copolymers are summarized in Table I.

Micelles of Block Copolymers

The micelle formation of PEtOz–PCLs and PCL–PEtOz–PCLs in an aqueous media was confirmed with fluorescence techniques and dynamic light scattering. The critical micelle concentrations (cmc) were determined with pyrene excitation spectra.15,19–21 Upon micellization, pyrene molecules are preferably partitioned into the hydrophobic microdomain of micelles, resulting in the red shift of the (0,0) band of excitation spectra from 335 to 338 nm. Figure 2 shows the intensity ratios ($I_{338}/I_{335}$) of pyrene excitation spectra versus the logarithms of block copolymer concentration. The cmc value was determined by the interception of two straight lines at a low concentration range. The cmc values of PEtOz–PCLs and PCL–PEtOz–PCLs, depending on the block composition, were in the range of 4.6–35.5 and 4.7–9.0 mg/L, respectively (Table II). As the length of

Table I. Molecular Weights and Compositions of the Block Copolymers

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<tr>
<th>Block Copolymers$^a$</th>
<th>[CL]/[EtOz] Feed Ratio$^b$</th>
<th>$M_n^{c}$</th>
<th>Composition Ratio$^d$</th>
<th>PCL (wt %)$^e$</th>
<th>$M_w/M_n^{f}$</th>
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<tr>
<td>PEtOz–PCL-0.09</td>
<td>0.10</td>
<td>7100</td>
<td>0.09</td>
<td>9.9</td>
<td>1.09</td>
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<tr>
<td>PEtOz–PCL-0.19</td>
<td>0.20</td>
<td>7800</td>
<td>0.19</td>
<td>17.9</td>
<td>1.09</td>
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<tr>
<td>PEtOz–PCL-0.30</td>
<td>0.30</td>
<td>8600</td>
<td>0.30</td>
<td>25.6</td>
<td>1.11</td>
</tr>
<tr>
<td>PCL–PEtOz–PCL-0.26</td>
<td>0.30</td>
<td>3900</td>
<td>0.26</td>
<td>23.1</td>
<td>1.23</td>
</tr>
<tr>
<td>PCL–PEtOz–PCL-0.31</td>
<td>0.35</td>
<td>4100</td>
<td>0.31</td>
<td>26.8</td>
<td>1.26</td>
</tr>
<tr>
<td>PCL–PEtOz–PCL-0.34</td>
<td>0.40</td>
<td>4200</td>
<td>0.34</td>
<td>28.6</td>
<td>1.35</td>
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$^a$ PEtOz–PCLs and PCL–PEtOz–PCLs were prepared via PEtOz–OH with an $M_n$ of 6400 and HO–PEtOz–OH with an $M_n$ of 3000, respectively.

$^b$ Molar feed ratio of $\varepsilon$-caprolactone to the repeating unit of PEtOz–OH or HO–PEtOz–OH.

$^c$ Estimated by $^1$H NMR.

$^d$ Molar composition ratio of the repeating units of PCL to that of PEtOz by $^1$H NMR analysis.

$^e$ Weight percentage of hydrophobic PCL block in the block copolymers.

$^f$ Estimated by GPC.
hydrophobic PCL block increases, the cmc value decreases. The hydrodynamic diameters of micelles from dynamic light scattering were in the range of 25–52 nm for PEtOz–PCLs and 19–22 nm for PCL–PEtOz–PCLs, with a narrow distribution, as listed in Table II. The polydispersity factors ($\mu_2/G^2$) of the micelles, estimated by the cumulant method, were fairly low (0.05–0.29), reflecting the narrow size distribution.

**Phase-Transition Behavior of Concentrated Aqueous Solutions**

The phase diagrams of aqueous PEtOz–PCL diblock copolymer solutions are shown in Figure 3. The aqueous solution of PEtOz–PCL-0.09 did not exhibit any gel phase up to the concentration of 45 wt %, probably because of the small portion of hydrophobic PCL block. Gel regions appeared at a high concentration (>25 wt %) and an intermediate temperature range (from room temperature to 70 °C) for PEtOz–PCL-0.19 and PEtOz–PCL-0.30 solutions. These block copolymer solutions exhibited a transition from gel to sol (gel–sol transition) when the temperature was increased, which is similar to the behavior observed in aqueous solutions of PEO-aliphatic polyesters.14 In contrast to the solutions of PEO–PPO–PEO, PEO–PBO–PEO, or PEO–PBO block copolymers, PEtOz–PCL solutions did not show low-temperature-boundary sol–gel transitions. In this system, it may be inferred that at a high concentration level, the micelles are closely packed to dominantly occupy the system, thus resulting in the formation of immobile gels. As shown in the phase diagram, the gel–sol-transition temperature was controlled by adjustment of the hydrophobic PCL block length. As the hydrophobic PCL portion of the block copolymers increased, the gel–sol transitions were observed at higher temperatures.14 A transition from sol to precipitation (precipitation temperature) was observed over a wide concentration range for aqueous solutions of all the diblock copolymers of PEtOz–PCL. The precipitation, depending on the block composition and the concentration, occurred between 65 and 78 °C. This precipitation behavior of the diblock copolymers in aqueous solutions may be induced by the shrinkage of PEtOz blocks at elevated temperatures, which might be associated with the LCST of the PEtOz homopolymer in water.16 For the PEtOz homopolymer ($M_n = 6400$) used for the PEtOz–PCLs in this study, the LCSTs in an aqueous phase ranged from 87 to 101 °C, depending on

<table>
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<th>Table II. Properties of PEtOz–PCL and PCL–PEtOz–PCL Block Copolymer Micelles</th>
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<td>Block Copolymers</td>
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<tr>
<td>PEtOz–PCL-0.09</td>
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<td>PEtOz–PCL-0.19</td>
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<td>PCL–PEtOz–PCL-0.26</td>
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<td>PCL–PEtOz–PCL-0.31</td>
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<td>PCL–PEtOz–PCL-0.34</td>
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</table>

$^a$ Measured at 25 °C.
$^b$ Mean diameters by dynamic light scattering at 25 °C.
$^c$ Polydispersity factor.
the concentration (15–45 wt %), as shown in Figure 4. The precipitation temperatures of the copolymer solutions were much lower than those of the PEtOz homopolymer solutions. This result suggests that the hydrophobic PCL core of micelles may facilitate the collapse of the PEtOz shell, leading to the decrease in the precipitation temperature. In addition, as the portion of the hydrophobic PCL in block copolymers increased, lower precipitation temperatures were detected.

Figure 5 shows the phase diagrams of aqueous solutions of PCL–PETOz–PCL triblock copolymers. Similarly to the solutions of PEtOz–PCL-0.19 and PEtOz–PCL-0.30, they exhibited gel–sol transitions and precipitation with increasing temperature. These transitions were thermally reversible. The gel–sol-transition temperatures could be controlled by adjustment of the block compositions. The solution of the triblock copolymers with a higher PCL portion exhibited gel–sol transition at a higher temperature range. As the portion of hydrophobic PCL in the triblock copolymers increased, the precipitation temperatures of solutions decreased. In contrast to the aqueous solutions of PEtOz homopolymer (Mn = 6400), for the PEtOz homopolymer (Mn = 3000) utilized in the synthesis of the triblock copolymers, the LCSTs of aqueous solutions were not observed in the concentration range of 15–55 wt %, probably because of its low molecular weight. With respect to this result, it is interesting to note that the precipitation temperatures of triblock copolymer solutions were much lower than those of diblock copolymer solutions, especially in the low concentration range.

The presence of inorganic salts as a third component in copolymer solutions can influence the phase-transition behavior because they cause conformational changes of polymer chains.\textsuperscript{1,22–25} Figure 6 shows that NaCl, a salting-out solute, and NaSCN, a salting-in solute, affect the phase behavior of aqueous PEtOz–PCL-0.30 solutions. The gel–sol transitions and the precipitation were displaced to lower temperatures in the presence of NaCl, which resulted in a decrease in the solubility of the polymer.\textsuperscript{1} Furthermore, the transition temperatures decreased in a linear fashion with the increasing concentration of NaCl, as shown in Figure 7. For PEtOz–PCL-0.19 solu-

Figure 4. LCSTs of PEtOz homopolymer (M_n = 6400) in aqueous solutions.

Figure 5. Phase behavior of aqueous PCL–PETOz–PCL solutions. □ and ◐ = PCL–PETOz–PCL-0.26; • and ▲ = PCL–PETOz–PCL-0.31; ○ and △ = PCL–PETOz–PCL-0.34.

Figure 6. Phase behavior of aqueous PEtOz–PCL-0.30 solutions. ○ = gel–sol transition in water; • = gel–sol transition in the presence of 1.0M NaCl; ◐ = gel–sol transition in the presence of 1.0M NaSCN; △ = precipitation in water; ▲ = precipitation in the presence of 1.0M NaCl.
tions, a similar effect of NaCl on phase-transition behavior was observed. For Pluronic F127 solutions, similar behaviors were reported in the presence of NaCl. In contrast to the effect of NaCl, NaSCN shifted gel regions to a higher temperature level because thiocyanate anion shows a tendency to accumulate at an interface and thus also close to the polymer, resulting in an increase in the solubility of the polymer. The gel–sol-transition temperatures were slightly increased with the increasing NaSCN concentration, as shown in Figure 7. Also, the precipitation temperature increased linearly up to the NaSCN concentration of 0.2 M, whereas precipitation did not occur above 0.2 M, even at the boiling point of water.

The phase-transition behavior could also be controlled by the addition of saccharides to the polymer solutions. In the presence of glucose, as an example, the phase transitions of PEtOz–PCL-0.30 solutions, including the gel–sol transition and the precipitation, occurred at a lower temperature level, as shown in Figure 8(a). The transition temperatures decreased with increasing glucose and maltose concentrations, as shown in Figure 8(b), probably because low molecular weight saccharides, including glucose and maltose, are likely to strongly construct water structures near them via hydrogen bonding and consequently weaken the hydration of the block copolymers. As in the case of the effect of NaCl, the activity of water to hydrate or solubilize the polymers decreased in the presence of saccharides. As clearly shown, glucose is more effective than maltose in lowering the gel–sol-transition temperature. Maltose, a 1,4-linked disaccharide, is reported to show a possibility of forming intramolecular hydrogen bonds in an aqueous phase, and so the capability of maltose to form water structures with itself may become less than that of glucose. Therefore, maltose may provide a more hydrated environment for the polymer chains than glucose does. In the presence of cosolutes with carboxyl groups, PEtOz, a hydrophilic outer shell of micelles, has a capability to form hydrogen bonding with carboxyl H-donor functionality. In a recent report, we demonstrated that the complex precipitates are formed from PEtOz–PCL micelles and
poly(acrylic acid) (PAA) at a pH below 3.5 via hydrogen bonding between shell-forming PEtOz of micelles and PAA. Therefore, the addition of multifunctional carboxyl compounds is expected to influence the phase transitions of the amphiphilic copolymers in water. For a 35 wt % PEtOz–PCL-0.30 solution, the gel–sol-transition and precipitation temperatures decreased from 60 to 32 °C and from 69 to 53 °C, respectively, when the concentration of malonic acid was increased to 1.0 M, above which point the solutions became turbid, even at room temperature, indicating the formation of precipitates. The decrease in transition temperatures could be understood in that the hydrogen bonding between PEtOz chain and malonic acid induced the enhancement of the hydrophobicity of block copolymers by screening the hydration of PEtOz chains. The formation of precipitates above a 1.0 M malonic acid concentration could be ascribed to the reduced solubility of the polymer phase.

CONCLUSIONS

The phase-transition behaviors of the amphiphilic block copolymers based on PEtOz and PCL in an aqueous phase were investigated. Aqueous solutions of diblock or triblock copolymers exhibited thermoreversible gel–sol transitions and precipitations. The gel–sol-transition and precipitation temperatures were highly dependent on the block composition. As the hydrophobic composition of the copolymers increased, a larger gel region was generated. The phase-transition behavior was influenced by the addition of third components such as inorganic salts, saccharides, and low molecular weight diacid, which could induce the conformational change of polymer chains. The NaCl, glucose, maltose, and malonic acid displaced phase transitions to a lower temperature level. However, NaSCN contributed to the shift of the gel region and the precipitation temperatures to a higher temperature level. The phase behavior observed in the aqueous solutions of PCL–PEtOz–PCL triblock copolymers could possibly provide a new type of fabrication method for microparticles containing bioactive agents such as therapeutic proteins at a physiological temperature range. When the aqueous solutions exhibiting precipitation near the physiological temperature range are allowed to drop to a homogenized water around 37 °C, the fabrication of microparticles may be possible without the use of organic solvents, which usually denature the therapeutic proteins during the fabrication in the conventional oil-in-water emulsion method. A detailed study on the fabrication of microparticles via the phase-transition behavior of PCL–PEtOz–PCL triblock copolymers will be published in the near future.

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REFERENCES AND NOTES