

Preparation and Characterization of PEG/PLA Multiblock and Triblock Copolymer

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A series of poly (lactic acid) (PLA) and poly (ethylene glycol) (PEG) tri and multiblock copolymers with relatively high molecular weights were synthesized through the coupling reaction between the bis(acyl chloride) of carboxylated PLA and mono or dihydroxy PEG. The coupling reaction and the copolymer structures were monitored by nuclear magnetic resonance (NMR), Fourier transform infrared spectroscopy (FTIR) and gel permeation chromatography (GPC). The melting temperature (T_m) of PEG blocks decreased with the presence of PLA sequences attaching to PEG blocks. The CMC values were determined to be 10-145 mg/L depending on the length of PLA and PEG blocks and the structure of the block copolymers.

Key Words : Block copolymers, Biodegradable, Biopolymers, Triblock, Multiblock

Introduction

Biodegradable aliphatic polyesters such as poly (ϵ -caprolactone) (PCL), PLA and poly (glycolide) (PGA) and their copolymers have received much attention due to the potential applications in tissue engineering, bone fixation and controlled drug delivery owing to their bioresorbable and biocompatible properties.¹⁻⁵ As a non-biodegradable but biocompatible polymer, PEG has been used for many clinical applications.⁶ PEG presents outstanding properties, such as hydrophilicity, solubility in water and in organic solvents, nontoxicity, and absence of antigenicity and immunogenicity. It has been reported that low molecular weight PEG can be excreted through the kidney, so its biostability is not a problem, whereas the mechanical behavior is confined by its molecular weight.⁷

Copolymerization offers the possibility to combine the characteristics of PEG and biodegradable polyesters. These copolymers consist of biodegradable hard polyester blocks and soft flexible PEG segments and have many interesting properties, such as amphiphilicity, biocompatibility and biodegradability. Among these copolymers, PLA/PEG copolymer has received widespread attention due to the potential applications in microcontainer or micelles. It showed no toxicity, prolonged circulation time *in vivo* due to the shielding effect of PEG chains against the phagocytosis of the mononuclear phagocytic system (MPS),^{3,4} and sustained release of drug molecules due to the controlled degradation of PLA blocks. In the last two decades, various synthetic methods have been developed to prepare a variety of PLA/PEG related copolymers with different structures and compositions. These copolymers can be classified according to their block structure as diblock,⁵ triblock,^{8,9} branched,⁶ star-shaped,⁷ graft and multiblock¹⁰ copolymers. Within the broad range of PLA/PEG related biodegradable block copolymers currently under study, the multiblock

copolymers have received great consideration according to its prolonged degradation period and relatively good mechanical properties due to their high molecular weight compared to di or tri block copolymers. Up to now, many kinds of synthetic methods have been used for preparing PLA/PEG multiblock copolymers since Gross *et al.* first reported the preparation of PLA/PEO multiblock copolymers by the ring-opening polymerization of lactide and ethylene oxide using $Al(Et)_3$ as catalyst.¹¹

In this paper we report on a new synthetic route which containing coupling reaction between the bis(acyl chloride) of carboxylated PLA and PEG to prepare PLG/PEG multiblock copolymers and PEG/PLA/PEG triblock copolymers. Furthermore, the thermal properties of the copolymers and the potentials as biodegradable/biocompatible surfactants are also discussed.

Experimental Section

Chemicals and Methods. L-Lactic acid was purchased from Aldrich and used without further treatment. Di hydroxyl PEG ($M_w = 1000$ g/mol, 2000 g/mol and 4600 g/mol) and monomethyl poly(ethylene glycol) (mPEG) ($M_w = 1000$ g/mol and 2000 g/mol) were provided by Aldrich and dried under reduced pressure for several hours to remove trace of water before use. Methylene chloride was provided by Samchun Chemical, Korea and dried by refluxing over CaH_2 . Thionyl chloride, dimethylformamide (DMF) and pyridine were purchased from Duksan Pure Chemical, Korea and used without further treatment.

Synthesis of Dicarboxylic PLA (PLA-diCOOH) Pre-polymer. 90 wt % aqueous solution of L-lactic acid was introduced into a reactor with a predetermined amount of succinic acid and a magnetic stir bar. The mixture was dehydrated at 180 °C for 48 h under stirring. After the mixture was cooled to room temperature, a high vacuum

was applied, and the temperature was gradually increased to 180 °C within 12 h. Finally the resulting product was dissolved in methylene chloride and precipitated in *n*-hexane followed by drying under vacuum at room temperature overnight.

Preparation of Acyl Halide-Terminated PLA (PLA-diCOCl) Prepolymer. Hereinafter, if not mentioned, all the reactions were carried out in an argon-filled glass reactor which had been flame-dried prior to use. PLA-diCOOH prepolymer was dissolved in anhydrous methylene chloride, and then thionyl chloride and 1 wt % of DMF were added to the solution. The molar ratio of the PLA-diCOOH prepolymer to thionyl chloride was 1:2. The mixture was reacted at 60 °C for 4 h. Finally the methylene chloride and unreacted thionyl chloride were removed under reduced pressure.

Synthesis of PLA/PEG Triblock and Multiblock Copolymers. PLA-diCOCl prepolymer was dissolved in anhydrous methylene chloride and 1 molar ratio of PEG was introduced into the solution. In the case of PEG/PLA/PEG triblock copolymer the molar ratio of the PLA prepolymer to mPEG was 1:2. Anhydrous pyridine was added dropwise while the temperature was maintained at 0 °C. The reaction was carried out at room temperature for 12 h. The product mixture was precipitated into *n*-hexane, washed 3 times with hexane/methylene chloride and dried in vacuum at room temperature for 24 h.

Characterization. NMR spectra were recorded with a Unity-300 NMR spectrometer at room temperature, with CDCl₃ as solvent and tetramethylsilane (TMS) as an internal reference. FTIR spectra were recorded on Bruker FTIR Tensor 27 spectrophotometer. GPC measurement was conducted at 25 °C with a Waters 410 GPC instrument equipped with a series of Waters μStyragel column (HR5, HR4, HR1, HR5E) and a differential refractometer detector. Tetrahydrofuran was used as eluent at a flow rate of 1.0 mL/min, and

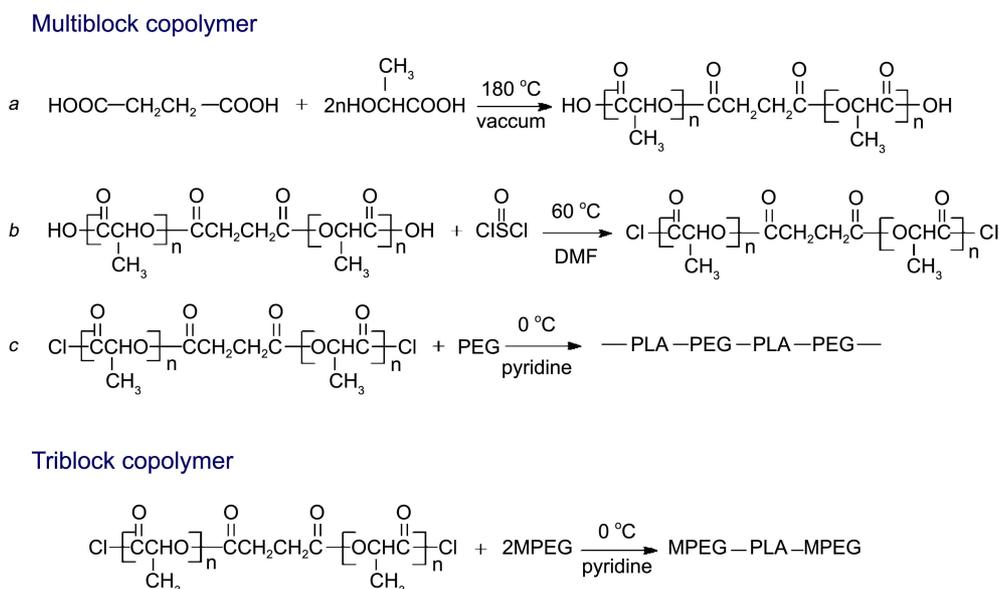
the molecular weights were calibrated with polystyrene standards. DSC was carried out on a Perkin-Elmer DSC-7 instrument with the heating rate of 10 °C/min. The critical micelle concentration (CMC) of the copolymers were determined on a surface tension meter (Fischer Scientific, USA) using the ring method at 25 °C.

Results and Discussion

The synthetic routes for PLA-diCOOH and PLA-diCOCl prepolymer and the coupling reaction for the PEG/PLA alternating multiblock and triblock copolymers are illustrated in Scheme 1. A series of tri and multiblock copolymers with PEG and PLA segments of different lengths were synthesized. The molecular characteristics of the copolymers and corresponding macromonomers are listed in Table 1.

Two kinds of PLA-diCOOH prepolymers with average molecular weights of 1000 (PLA1000) and 2000 (PLA2000) were prepared by changing the molar ratios of lactic acid/succinic acid. Figure 1(a) shows the ¹H NMR spectrum of the PLA1000 prepolymer. The peaks at 5.2 and 1.5 ppm are assigned to the methyne (a) and methyl (d) protons of the PLA repeating unit respectively. The peaks at 4.4 and 2.7 ppm are attributed to the methyne proton of PLA repeating unit adjacent to the COOH end group (b) and methylene (c) protons from succinic acid. The molecular weights of the prepolymer could be calculated from the integration area ratios of the NMR peaks. The equation is molecular weight = [(a+b)/(c/4)]*72, in which the letters represent the areas of the corresponding NMR peaks.

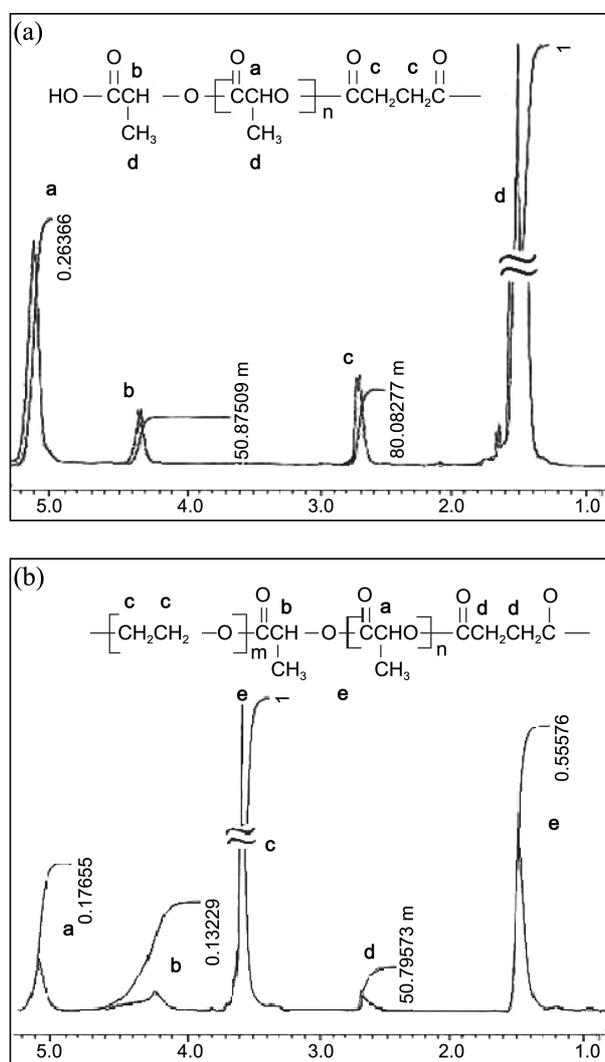
PLA-diCOOH was reacted with thionyl chloride to convert the COOH group to more active COCl group. The ¹H NMR spectrum of the PLA-diCOCl is not shown here for their high sensitivity to humidity. The coupling reaction between PLA-diCOCl prepolymer and mPEG or dihydroxy PEG was carried out in anhydrous methylene chloride with



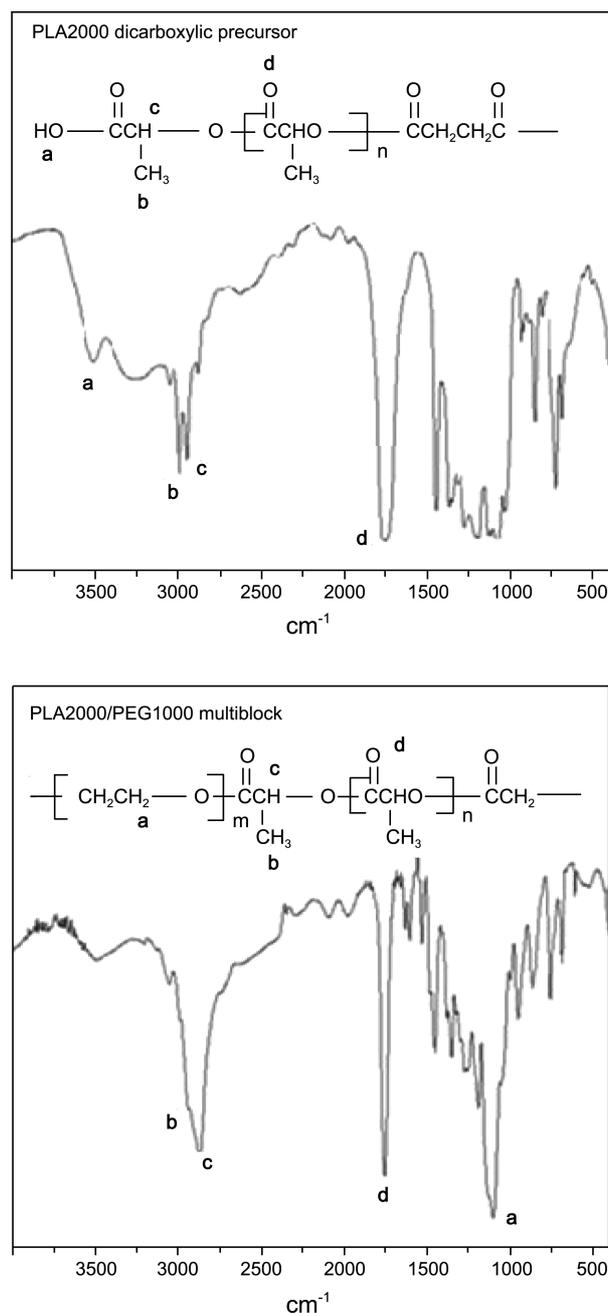
Scheme 1. Synthetic route for PEG/PLA multiblock copolymer.

Table 1. Molecular weights and compositions of PEG/PLA multi and tri-block copolymers

No.	PEG (g/mol)	PLA ^a (g/mol)	PEG/PLA	Mw ^b (g/mol)	PDI ^b	PEG/PLA
1	1000	1000	1.0:1.0	13900	1.67	0.82
2	2000	1000	2.0:1.0	37400	1.35	1.21
3	4600	1000	4.6:1.0	36700	1.55	1.12
4	m2000 ^c	1000	4.0:1.0	8130	1.18	2.08
5	1000	2000	1.0:2.0	16700	1.38	1.18
6	2000	2000	1.0:1.0	15900	1.59	1.18
7	4600	2000	2.3:1.0	34300	1.31	1.14
8	m2000 ^c	2000	2.0:1.0	10300	1.20	2.20

^aCalculated according to the integrated area ratio of the NMR peaks.^bDetermined by the GPC analysis. ^cmPEG 2000**Figure 1.** ¹H NMR spectrum of PLA1000 dicarboxylic precursor (1a) and PLA1000/PEG1000 multiblock copolymer (1b).

pyridine as a catalyst. Figure 1(b) shows the ¹H NMR spectrum of PLA1000/PEG1000 multiblock copolymer. The peak at 3.7 ppm (c) is assigned to the methylene protons of the PEG repeating unit. The ratios of PEG and PLA blocks in the synthesized copolymers could be calculated from the

**Figure 2.** IR spectra of PLA2000 dicarboxylic precursor and PLA2000/PEG1000 multiblock copolymer.

integration area ratios of the corresponding PLA and PEG peaks in NMR. It is shown that the ratios of PLA/PEG for multiblock copolymers are close to 1:1, whereas the ratios are close to 1:2 for triblock copolymers.

The coupling reaction was also characterized with FTIR analysis. Figure 2 shows the IR spectra of the PLA2000 prepolymer and PLA2000/PEG1000 multiblock copolymer. For PLA2000 prepolymer, the band at 3500 cm⁻¹ is corresponded to the O-H stretching vibration of -COOH end groups and the bands at 2996 and 2945 cm⁻¹ are due to the C-H stretching vibration of -CH₃ and -CH- groups. The sharp peak at 1752 cm⁻¹ is assigned to the stretching vibration

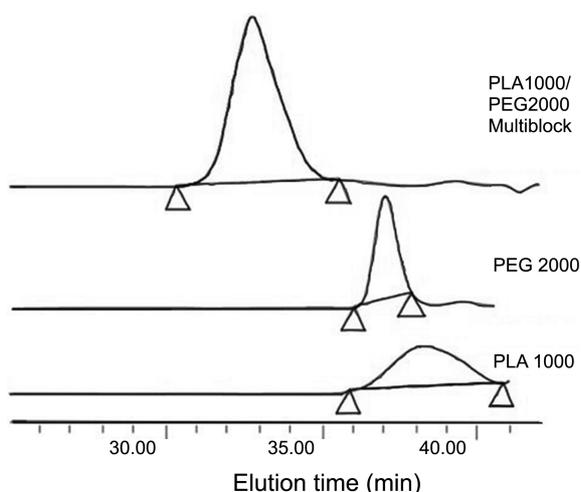


Figure 3. GPC curves of PLA1000, PEG2000 and PLA1000/PEG2000 multiblock copolymer.

of ester carbonyl group. In the spectrum of the PLA2000/PEG1000 multiblock copolymer, all of these typical absorbing bands of PLA2000 prepolymer are detected. Furthermore, the characteristic -C-O-C- stretching vibration at 1109 cm^{-1} from PEG block is also detected, suggesting the presence of the two component blocks in the copolymer. Moreover, the bands of -OH end groups were much smaller than those of the two macromonomers, indicating most of the end groups were participated in the condensation reaction and produced much higher molar mass of multiblock copolymer.

The molecular weights of the PLA prepolymers and PLA/PEG tri and multiblock copolymers were also determined by GPC and calibrated against polystyrene standards (Table 1). Figure 3 shows the typical GPC traces of PEG2000, PLA1000 prepolymer and the corresponding PEG2000/PLA1000 multiblock copolymer. The narrow molecular weight distribution and the symmetric GPC profile of the copolymer confirms the absence of unreacted low molecular weight precursor homopolymers, like PEG or PLA-diCOCl. The retention time for the PEG2000/PLA1000 multiblock

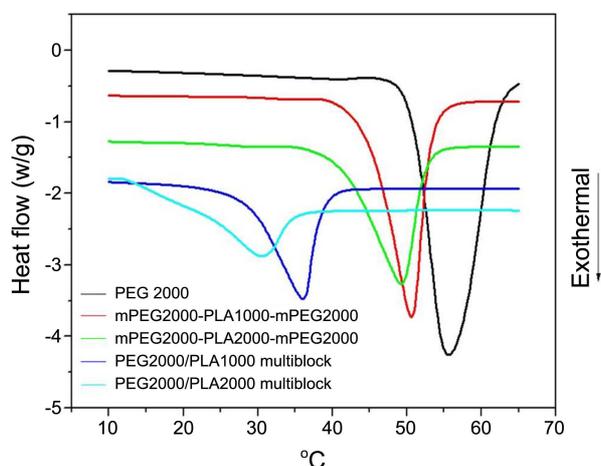


Figure 4. DSC heating curves of PEG 2000 and Sample 2, 4, 6 and 8 (in Table 1).

Table 2. Tm and Tc of PEG block

PEG	Tc (°C)		Tm (°C)	
	PLA1000	PLA2000	PLA1000	PLA2000
2000	-	-	35.7	30.3
4600	23.9	22.0	50.1	47.6
m2000	18.6	15.1	49.9	48.1

copolymer is shorter than those of PLA1000 and PEG prepolymers, indicating that the multiblock copolymer was successfully synthesized.

The thermal properties of the copolymers and their macromonomers were investigated by DSC. Figure 4 shows the DSC curves of PEG2000, PEG2000/PLA1000, PEG2000/PLA2000 multiblock copolymers and mPEG2000/PLA1000, mPEG2000/PLA2000 triblock copolymers, which have the same molecular weight of PEG block and different chain lengths of PLA blocks. Only the melting peaks from the PEG blocks were observed. It can be attributed to the short PLA blocks and the confined chain mobility, which greatly influence the crystallization ability of the PLA blocks. The Tm and Tc of PEG blocks for the tri and multiblock copolymers are listed in Table 2. It is shown that the Tm and Tc of the PEG blocks for triblock polymers are much higher than those of multiblock copolymers with similar molecular weight of PEG blocks, and decrease slightly with increasing the chain length of the PLA blocks. The values are close to the Tm and Tc of the homopolymer of PEG, which means that the PLA blocks have a minor effect to the crystallization of PEG blocks for triblock copolymers. For the multiblock copolymers, the Tm and Tc also increase with increasing the molecular weight of PEG and slightly decrease with increasing the chain length of the PLA blocks. However the values are lower than the Tm and Tc of the PEG homopolymer suggesting that the hindrance to the PEG crystallization of the PLA block is bigger than those of triblock copolymers.

It is well known that amphiphilic block copolymers consisting of a hydrophilic PEG block and a hydrophobic PCL or PLA block can form micelles.^{1,13,14} In an aqueous system, the hydrophobic blocks aggregate to form the core and the hydrophilic blocks constitute the outer shell to minimize the free energy.¹⁵ The concentration of surfactants in the bulk at which micelles start forming is defined as CMC, which is considered as an important characteristic of a surfactant. One can determine CMC by monitoring the changes of the electrical conductivity, surface tension or optical properties of a surfactant solution. In this study, we determined the CMC values of the PLA/PEG tri and multiblock copolymers by measuring the surface tension of the polymer water solution with the simple ring method.

Figure 5 shows the development of the surface tension of PEG1000/PLA1000 multiblock copolymer in water solution against negative logarithmic concentration. Below a certain concentration, the surface tension is essentially constant. And above the concentration, the surface tension decreases dramatically with increasing the polymer concentration,

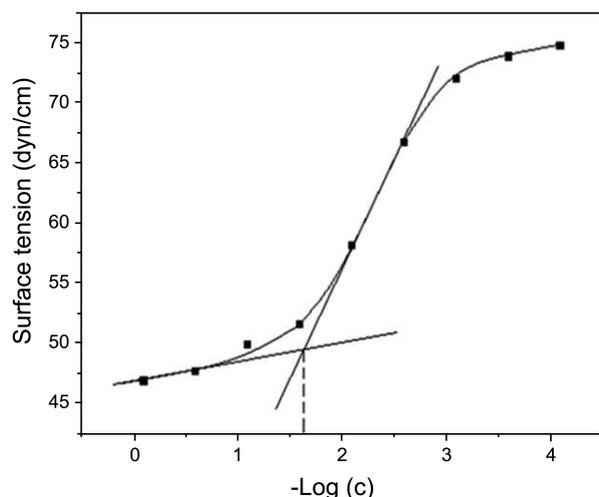


Figure 5. Surface tension vs $[-\log(c)]$ PLA1000/PEG1000 multi-block.

Table 3. CMC values of the block copolymers

PEG	CMC (g/L)	
	PLA1000	PLA2000
1000	0.0269	0.0106
2000	0.0596	0.0216
4600	0.0811	0.0396
m2000	0.145	0.0823

indicating the formation of micelles. The CMC was taken as the intersection of the tangents of curve in these two parts. All the CMC values are listed in Table 3. For triblock copolymer, the longer PLA lengths are the lower CMC values are. It is because the longer hydrophobic blocks in the micellar core would rearrange to find their lower energy formation.¹⁶ It is of interest to note that all the multiblock copolymers have a lower CMC values than those of the triblock copolymers. It could be attributed to the covalent bond of the multiblock copolymer forms a local high concentration of hydrophobic region by changing the chain conformation rather than the aggregation of the triblock copolymer. Furthermore, the CMC values of the multiblock copolymers are dependent on the relative length of the hydrophilic PEG and hydrophobic PLA; the CMC values decrease with increasing the PLA block length and increase with increasing the PEG blocks.

Conclusion

In this paper a series of PEG-PLA multiblock copolymers and triblock copolymers were synthesized using coupling reaction between the bis(acyl chloride) of carboxylated PLA and PEG. The block structure was confirmed by ¹H NMR, IR and GPC analysis. The composition of the block co-

polymers can be controlled by changing the macromonomer molecular weights and the feed ratios. Furthermore, the crystallization behaviors of the block copolymers were investigated by DSC analysis. The T_m and T_c of the PEG domain were influenced by the relative length of the PLA and PEG blocks. The CMC values were determined to be 10-145 mg/L by surface tension measurements, depending on the length of PLA and PEG blocks and the structure of the block copolymers. The mechanical and degradation comparison between triblock and multiblock copolymers and the applications of the multiblock copolymers to biocompatible and biodegradable surfactant are under investigation.

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