

Comparison Between the Self-Assembling Behaviors of PLLA-PEO-PLLA Triblock Copolymers and PLLA-PEO-PPO-PEO-PLLA Pentablock Copolymers

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ABSTRACT: Poly(L-lactic acids) (PLLAs) were grafted to both ends of poly(ethylene oxide) (PEO) to produce biocompatible amphiphilic PLLA-PEO-PLLA triblock copolymers. The self-assembling behaviors of two PLLA-PEO-PLLA copolymers in aqueous solutions were examined by Dynamic Light Scattering and Transmission Electron Microscopic techniques. PLLA-PEO-PLLA formed spherical micelles, whereas PLLA-PEO-PPO-PEO-PLLA pentablock

copolymers were reported to produce vesicles. It is believed that the PPO segment within the PLLA-PEO-PPO-PEO-PLLA pentablock copolymers has a dominant role in the formation of vesicles. © 2008 Wiley Periodicals, Inc. *J Appl Polym Sci* 111: 2445–2451, 2009

Key words: block copolymers; biocompatibility; self-assembly; vesicles

INTRODUCTION

Amphiphilic block copolymers have been widely studied in the past several decades because of their excellent capacity to self-assemble into nanoparticles containing a hydrophobic core and a hydrophilic shell. Polymeric nanoparticles with good biocompatibility have the potential for various applications, e.g., in drug delivery systems.^{1–5} The morphology of nanoparticles produced from amphiphilic block copolymers can be varied by changing the composition of hydrophobic and hydrophilic blocks on the polymeric chains. Various types of morphologies have been reported, such as sphere, vesicles, rods, lamellas, tubes, large compound micelles, and large compound vesicles.^{6,7} Among these morphologies, vesicles with a hydrophilic core and hydrophobic bilayer are promising drug delivery carriers because they can deliver not only hydrophobic but also hydrophilic drugs.^{8,9}

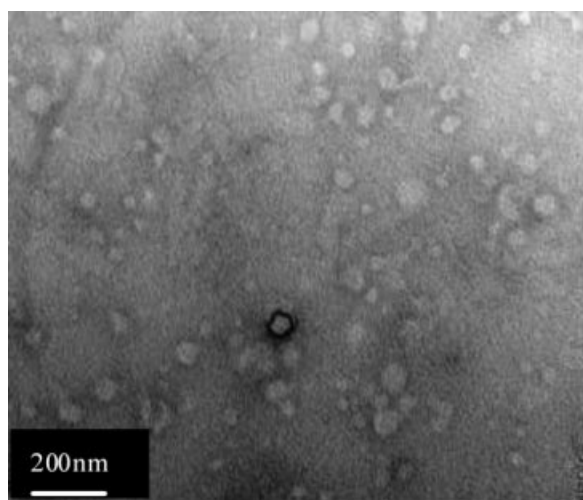
The biocompatible block copolymers comprising of commercial Pluronic F127 (PEO-PPO-PEO, \bar{M}_n 12,600, PEO 70 wt %) and biodegradable poly(L-lactic acid) (PLLA) have been synthesized by our group.¹⁰ The morphology of PLLA-PEO-PPO-PEO-PLLA pentablock copolymers (PLLA-F127-PLLA) in aqueous solutions was found to be vesicles. The PLLA-F127-PLLA vesicles with excellent biocompatibility are expected to be excellent candidates for oral delivery carriers of proteins and peptides. The application of PLLA-F127-PLLA vesicles in oral insulin carriers has recently been reported.¹¹ Sustained and enhanced hypoglycemic effects were observed for oral insulin-loaded PLLA-F127-PLLA vesicles. However, the loading efficiency for insulin in PLLA-F127-PLLA vesicles is only about 12%. It is known that the volume fraction of core to solution is one of the major factors affecting the loading efficiency of drugs. Therefore, the low water solubility of PLLA-F127-PLLA pentablock copolymers results in the low core volume of PLLA-F127-PLLA vesicles, thus leading to the low loading efficiency of insulin in PLLA-F127-PLLA vesicles. To increase the loading efficiency of insulin, one possible method is to improve the water solubility of polymeric vesicles by decreasing the weight fractions of hydrophobic PLLA blocks (W_{PLLA}). However, for PLLA-F127-PLLA pentablock copolymers, normal bilayer vesicles could not be produced when the W_{PLLA} was decreased to 44.7%.¹⁰

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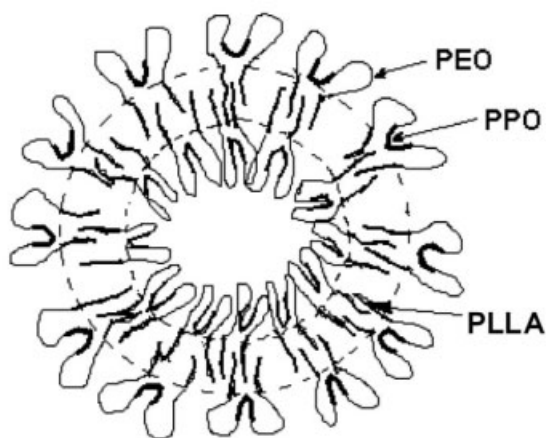
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(A)

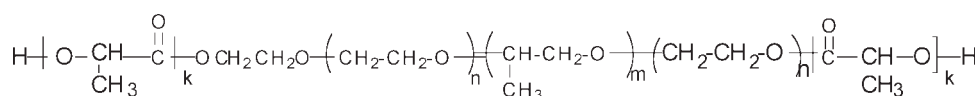


(B)

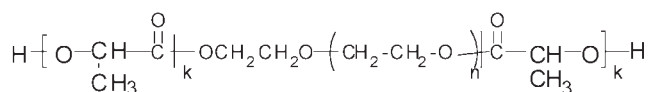
Figure 1 The transmission electron microscope (TEM) micrograph (A) and possible microstructure (B) of PLLAF127-29 vesicles [refer to Ref. 10].

From the possible microstructure of PLLA-F127-PLLA vesicles (see Fig. 1), the presence of PPO block in the middle of PLLA-F127-PLLA pentablock copolymers may hinder the formation of vesicles. Also, it was reported previously that the self-assembling behavior of PLLA₉-F87-PLLA₉ pentablock copolymer (Pluroinc F87, PEO-PPO-PEO, \bar{M}_n 7700, PEO 70 wt %) was more complicated than PLLA₉-PEO₁₈₂-PLLA₉ triblock copolymer of similar W_{PLLA} value.¹² From a thermodynamic perspective, it may be easier for PLLA-PEO-PLLA triblock copolymers (where PPO block is absent) to aggregate compared with PLLA-F127-PLLA pentablock copolymers. Whether PLLA-PEO-PLLA can form vesicles is of interest to us, and a comparison of the two different classes of block copolymer is the subject of the present study. Thus, the aims of this study are to synthesize PLLA-PEO-PLLA triblock copolymers containing different proportion of PLLA and to evaluate the aggregation behaviors of PLLA-PEO-PLLA and PLLA-F127-PLLA pentablock copolymers in aqueous solutions. The chemical structures of PLLA-PEO-PLLA triblock copolymer and PLLA-F127-PLLA pentablock copolymer are shown in Figure 2.

In the past, various chemical architectures of PEO/PLA copolymers have been synthesized, such as diblocks, triblocks, star-blocks, and PLLA/PDLA mixed blocks systems. Their gelation and self-assembling properties in aqueous solutions have been studied.¹³⁻¹⁷ However to our knowledge research on the morphologies of nanoparticles formed from PLA-PEO-PLA triblock copolymers in aqueous solutions is somewhat limited,¹³⁻¹⁵ with only one article focusing on the PLLA-PEO-PLLA nanoparticles.¹⁵ The other two articles report on the formation of nanoparticles from PLLA-PEO-PLLA and PDLA-PEO-PDLA triblock copolymer mixtures.^{13,14}



PLLA-F127-PLLA (PLLA-PEO-PPO-PEO-PLLA)



PLLA-PEO-PLLA

Figure 2 The chemical structures of PLLA-F127-PLLA pentablock copolymers and PLLA-PEO-PLLA triblock copolymers.

EXPERIMENTAL

Materials

Poly(ethylene oxide) (PEO, \overline{M}_n 12,000, $\overline{M}_w/\overline{M}_n$ 1.07) was purchased from Sigma-Aldrich and dried overnight under vacuum before use. L-Lactide was purchased from Sigma-Aldrich and recrystallized twice from ethyl acetate. The purified L-lactide was stored at 4–5°C under argon environment. Stannous octoate [Sn(Oct)₂] and sodium phosphotungstate were purchased from Sigma-Aldrich and used as received. All other chemicals were of reagent grade.

Synthesis of PLLA-PEO-PLLA triblock copolymers

PLLA segments were attached to both ends of PEO to obtain amphiphilic PLLA-PEO-PLLA block copolymers. A round-bottom flask with a stopcock was heated under reduced pressure to remove the moisture. After cooling to room temperature, argon was introduced into the flask. Following this, appropriate amounts of L-lactide and PEO were added and the mixture was heated with continuous stirring to produce a well-mixed molten phase. The mixture was then cooled, and Sn(Oct)₂ (0.1 wt % of L-lactide) was added to the flask under argon environment. The mixture was degassed by several vacuum-purge cycles, and then heated to 160°C. After stirring for 15 h, the content was cooled to room temperature. The product was dissolved in methylene chloride, and precipitated twice in methanol and once in diethyl ether. The polymers were filtered and dried overnight under vacuum. ¹H NMR (400 MHz, CDCl₃, TMS), δ (ppm); 1.54–1.63 (m, –O–CH(CH₃)–CO– and HO–CH(CH₃)–CO–), 3.35–3.75 (m, –OCH₂–CH₂–), 4.25–4.35 (m, HO–CH(CH₃)–CO– and –CO–OCH₂–CH₂–O–), 5.15–5.19 (m, –O–CH(CH₃)–CO–) (Fig. 3).

Preparation of PLLA-PEO-PLLA nanoparticles

The aggregates of PLLA₉₉-PEO-PLLA₉₉ in aqueous solutions were prepared as follows: PLLA₉₉-PEO-PLLA₉₉ triblock copolymer (15 mg) was dissolved in THF, and then the polymer solution was added drop-wise to ultra pure water (15 g) under gentle stirring. The polymer aggregates solution was dialyzed against ultra pure water for 5 h using a cellulose membrane tubing (molecular weight cut-off 12,000–14,000 Da) to remove THF from the solution. The water was exchanged at intervals of 1 h, and the final concentration of PLLA₉₉-PEO-PLLA₉₉ aggregates is about 0.1 wt %.

Characterization

Nuclear Magnetic Resonance (NMR) spectra were recorded at room temperature using a Bruker AV400

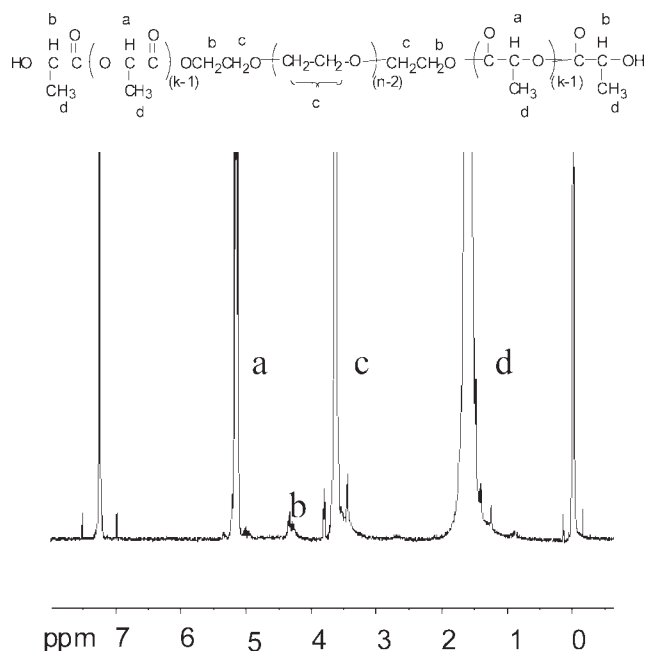


Figure 3 ¹H NMR spectrum of PLLA₉₉-PEO-PLLA₉₉ triblock copolymer (CDCl₃).

(400 MHz) Fourier Transform Spectrometer. Chemical shifts (δ) were given in ppm using tetramethylsilane as an internal reference. Molecular weight and molecular weight distribution of polymers were measured with a gel permeation chromatography (GPC) system equipped with a Waters 2414 refractive index detector, a Waters 1525 binary HPLC pump, and three Waters Styragel Columns (HT2, HT3, and HT4) with THF as an eluent at a flow rate of 1 mL/min at 35°C. Mean diameters and size distributions of PLLA-PEO-PLLA nanoparticles were determined by the dynamic light scattering (DLS) method using a PSS NICOMP 380 ZLS Particle Sizing Systems (Santa Barbara, CA, USA). The analysis lasted 310 s at 23°C with a detection angle of 90°.

Transmission electron microscope

Transmission electron microscope (TEM) was performed on a JEOL JEM-100CXII electron microscope at an acceleration voltage of 80–100 kV. The copper grid (300 meshes) with a carbon film was used. The copper grid was immersed in a drop of the aqueous polymer solution for 2 min, and then removed and dried. A drop of sodium phosphotungstate aqueous solution (2 wt %) was placed on the copper grid for 2 min. The copper grid was then dried overnight at room temperature before measurement.

RESULTS AND DISCUSSION

Synthesis and characterization of PLLA-PEO-PLLA triblock copolymers

PLLA-PEO-PLLA triblock copolymers were synthesized by ring opening polymerization of the

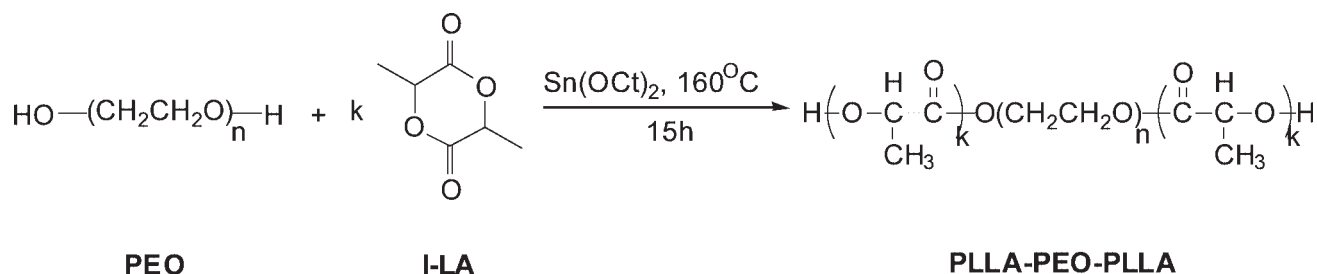


Figure 4 The synthesis scheme of PLLA-PEO-PLLA triblock copolymers.

monomer L-lactide using PEO as the initiator and $\text{Sn}(\text{Oct})_2$ as the catalyst (Fig. 4). The mechanism of the reaction is that of coordination polymerization similar to that of PLLA-F127-PLLA pentablock copolymers.¹⁰ The polymer composition, structure, and molecular weight were characterized by NMR and GPC techniques. Figure 3 shows the ^1H NMR spectrum of a typical PLLA-PEO-PLLA in CDCl_3 . The small peak at δ of 4.30 ppm belongs to methylene protons of $\text{PLLA}-\text{CO}-\text{OCH}_2-\text{CH}_2-\text{O}-\text{PEO}-$ segment, indicating the successful synthesis of PLLA-PEO-PLLA block copolymer. The absence of a peak at δ of 4.9–5.0 ppm, which could have been contributed by the methine proton of the $\text{PLLA}-\text{O}-\text{CH}(\text{CH}_3)-\text{COOH}$ group, suggest that there was negligible or no PLLA homopolymer in the PLLA-PEO-PLLA block copolymer.

The degree of polymerization (k) of PLLA in $\text{PLLA}_k\text{-PEO-PLLA}_k$ copolymers was calculated from the peak intensity ratio of methyl protons of PLLA ($\text{O}-\text{CH}(\text{CH}_3)-\text{CO}-$; $\delta = 1.58$ ppm) and methylene protons of PEO ($-\text{OCH}_2-\text{CH}_2-$; $\delta = 3.35\text{--}3.75$ ppm). The number-average molecular weight (\overline{M}_n) of the $\text{PLLA}_k\text{-PEO-PLLA}_k$ copolymer was obtained by using the following expression:

$$\overline{M}_n = \overline{M}_n(\text{PEO}) + 144k$$

Two different compositions of PLLA-PEO-PLLA triblock copolymers were synthesized. The molecular

weights and PLLA weight fractions of PLLA-PEO-PLLA copolymers were calculated and summarized in Table I.

Figure 5 shows the GPC trace of PLLA-PEO-PLLA triblock copolymer. The molecular weight distributions ($\overline{M}_w/\overline{M}_n$) of PLLA-PEO-PLLA triblock copolymers were determined by GPC measurements (Table I).

Characterization of PLLA-PEO-PLLA nanoparticles

The morphologies of PLLA-PEO-PLLA nanoparticles were examined by TEM. The nanoparticles were negatively stained by sodium phosphotungstate. PLLA-PEO-PLLA nanoparticles produced for the two block copolymers were found to be spherical micelles comprising of hydrophobic PLLA core and hydrophilic PEO shell (Fig. 6). The mean diameters of $\text{PLLA}_{99}\text{-PEO-PLLA}_{99}$ and $\text{PLLA}_{141}\text{-PEO-PLLA}_{141}$ nanoparticles were about 110 and 100 nm, respectively.

The particle sizes and size distributions of PLLA-PEO-PLLA nanoparticles were also measured by the DLS using PSS Particle Sizing Systems. The unimodal size distributions were observed for both PLLA-PEO-PLLA nanoparticles (data not shown). From the results shown in Table I, the mean diameters of $\text{PLLA}_{99}\text{-PEO-PLLA}_{99}$ and $\text{PLLA}_{141}\text{-PEO-PLLA}_{141}$ nanoparticles were 140 and 147 nm, respectively, which were larger than that obtained from TEM. This is not unexpected because the hydrated PEO

TABLE I
Characterizations of PLLA-PEO-PLLA Triblock Copolymers and Nanoparticles

| Sample | W_{PLLA}^a (%) | \overline{M}_n (NMR) | $\overline{M}_w/\overline{M}_n$ (GPC) | Nanoparticles | |
|---|----------------------------|---------------------------|--|---------------------|-------------------------------------|
| | | | | Morphology (TEM) | Diameter (nm) (DLS) ^b |
| $\text{PLLA}_{99}\text{-PEO-PLLA}_{99}$ | 54.3 | 26,200 | 1.29 | Spheres | 140 ± 64 |
| $\text{PLLA}_{141}\text{-PEO-PLLA}_{141}$ | 62.9 | 32,300 | 1.35 | Spheres | 147 ± 64 |

^a W_{PLLA} stands for the weight fraction of PLLA blocks in PLLA-PEO-PLLA triblock copolymers.

^b The diameters of PLLA-PEO-PLLA nanoparticles are expressed as mean ± standard deviation.

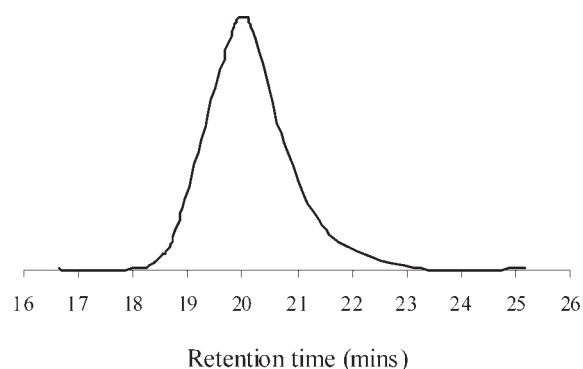


Figure 5 The gel permeation chromatography (GPC) trace of PLLA₉₉-PEO-PLLA₉₉ triblock copolymer.

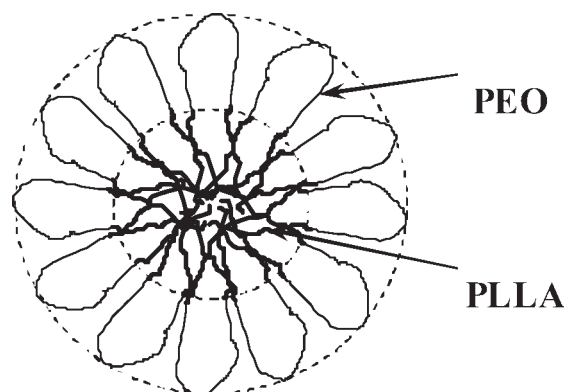
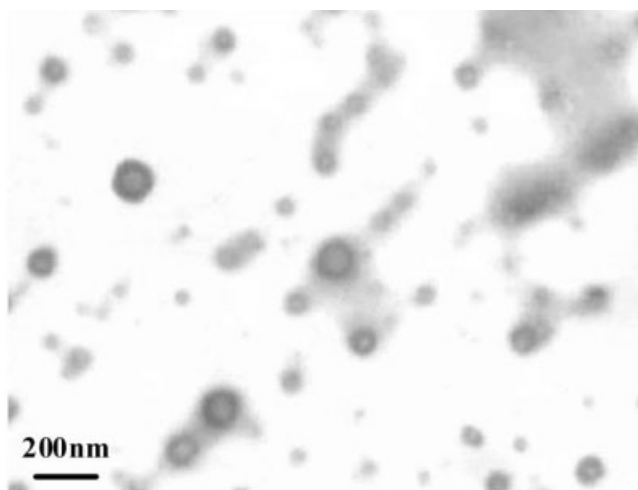
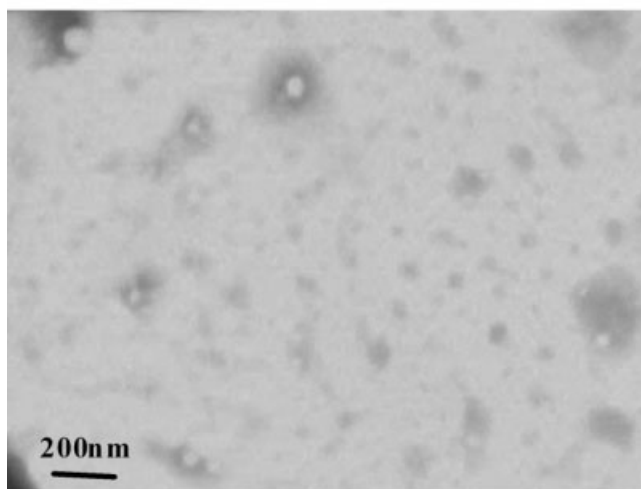


Figure 7 The possible microstructure of PLLA-PEO-PLLA spherical micelles in aqueous solution.



(A)



(B)

Figure 6 TEM micrographs of nanoparticles formed from PLLA₉₉-PEO-PLLA₉₉ (A) and PLLA₁₄₁-PEO-PLLA₁₄₁ (B) triblock copolymers in water.

shells of PLLA-PEO-PLLA nanoparticles were swollen due to the existence of water when the micelles are solvated. On the basis of these results, we proposed the possible microstructure of PLLA-PEO-PLLA nanoparticles, which is schematically illustrated in Figure 7.

Comparison on the aggregation behaviors between PLLA-PEO-PLLA triblock copolymers and PLLA-F127-PLLA pentablock copolymers

As described earlier, the main goal of this study is to examine the possibility of producing vesicles from PLLA-PEO-PLLA triblock copolymers with a shorter PLLA block length compared with PLLA-F127-PLLA pentablock copolymers.

Three PLLA-F127-PLLA pentablock copolymers with different PLLA block lengths have been synthesized previously.¹⁰ Table II summarizes the characterizations of PLLA-F127-PLLA copolymers and nanoparticles in aqueous solutions. PLLA-F127-PLLA pentablock copolymers with weight fractions of PLLA blocks (W_{PLLA}) of 73.8% and 57.2% could form vesicles, whereas PLLA-F127-PLLA with the lower W_{PLLA} value (44.7%) forms more complicated vesicles, namely, onion-like vesicles with internal hydrophobic cores. As delivery carriers of hydrophilic drugs, it was demonstrated that lower amounts of hydrophilic drugs was loaded into PLLAF127-23 onion-like vesicles compared with PLLAF127-29 vesicles.¹⁸ This suggests that PLLA-F127-PLLA with W_{PLLA} of 44.7% is not a suitable carrier for hydrophilic drugs, although its water solubility is higher compared with PLLAF127-29 and PLLAF127-48. The above data also indicated that PLLA-F127-PLLA pentablock copolymers with higher W_{PLLA} can readily form normal bilayer vesicles, which is consistent with the results obtained for poly(1,2-butadiene-ethylene oxide) (PB-

TABLE II
Characterizations of PLLA-F127-PLLA Pentablock Copolymers and Nanoparticles
[refer to Ref. 10]

| Sample | W_{PLLA}^a (%) | \overline{M}_n (NMR) | $\overline{M}_w/\overline{M}_n$ (GPC) | Nanoparticles | |
|-------------|----------------------------|---------------------------|--|---------------------|------------------------|
| | | | | Morphology (TEM) | Diameter (nm) (DLS) |
| PLLAF127-23 | 44.7 | 22,800 | 1.34 | Onion-like vesicles | 100 |
| PLLAF127-29 | 57.2 | 29,000 | 1.54 | Vesicles | 112 |
| PLLAF127-48 | 73.8 | 48,000 | 1.41 | Vesicles | 112 |

^a W_{PLLA} stands for the weight fraction of PLLA blocks in PLLA-F127-PLLA pentablock copolymers.

PEO) diblock copolymers.¹⁹ From the morphology diagram of PB-PEO in water, vesicles were produced when the weight fraction of hydrophobic PB block was between 60 and 80%. On the other hand, cylinders and spheres were produced with decreasing weight fraction of PB block. On the basis of these results, we concluded that the possibility for bilayer vesicle formation is higher for copolymers with larger weight fractions of hydrophobic blocks. This is unfavorable for application in the delivery carriers of hydrophilic drugs because hydrophobic polymeric vesicles may limit the loading efficiency of hydrophilic drugs.

Therefore, for comparative purposes, the molecular weight of PEO (\overline{M}_n 12,000) chosen in this study is similar to that of F127 (\overline{M}_n 12,600). The W_{PLLA} in two PLLA-PEO-PLLA triblock copolymers were designed based on those in PLLA-F127-PLLA pentablock copolymers. It is shown in Table I that the W_{PLLA} values of both PLLA₉₉-PEO-PLLA₉₉ and PLLA₁₄₁-PEO-PLLA₁₄₁ copolymers are fairly similar to those of PLLAF127-29 and PLLAF127-48 copolymers, respectively. Unexpectedly, the nanoparticles formed from both PLLA₉₉-PEO-PLLA₉₉ and PLLA₁₄₁-PEO-PLLA₁₄₁ copolymers in aqueous solutions are spherical micelles. The PLLA-PEO-PLLA triblock copolymer (\overline{M}_n of PEO, 4000; W_{PLLA} , 90%) with large W_{PLLA} value synthesized by Yuan et al.¹⁵ were also found to be spherical micelles (93.5 nm). On the basis of the above results, we concluded that the PPO block in the middle of PLLA-F127-PLLA pentablock copolymers plays an important role on their vesicle formation in aqueous solutions.

The relevant question is what is the role of PPO block on the formation of PLLA-F127-PLLA vesicles? An important consideration is to review the theory of micellization of amphiphilic copolymers (mainly diblock copolymers) that was developed recently for such polymeric systems.^{9,20,21} In general, from the thermodynamic analysis, the total Gibbs free energy of the micelle [$G(\text{micelle})$] is expressed as the sum of several contributions, mainly those related to the

core $G(\text{core})$, shell $G(\text{shell})$, and core/shell interface $G(\text{interface})$:

$$G(\text{micelle}) = G(\text{core}) + G(\text{shell}) + G(\text{interface})$$

Among these three factors, $G(\text{interface})$ is believed to be the most important because the monomers at the interface of micelles are in contact with both the core and the shell. From the proposed microstructures of PLLA-F127-PLLA vesicles [Fig. 1(B)] and PLLA-PEO-PLLA micelles (Fig. 7), the difference between their interfacial groups is the existence of PPO groups for the former. The PPO block may prefer to reside at the interface of vesicles because of its weak hydrophobic characteristic. Furthermore, in the conformation of the PPO block, the methyl groups of the PPO block could be close to the hydrophobic PLLA domain, whereas the oxygen molecules of the PPO block could be close to the hydrophilic PEO domain. Such conformations of PPO block will result in the reduction in the interfacial tension of PLLA-F127-PLLA vesicles, thus resulting in the decrease in the $G(\text{interface})$ value and the decrease in the $G(\text{micelle})$ value, correspondingly.

CONCLUSIONS

In the present study, biocompatible PLLA-PEO-PLLA triblock copolymers with two different PLLA block lengths were synthesized. The morphologies of both PLLA-PEO-PLLA nanoparticles in aqueous solutions were spherical micelles. The aggregation behaviors of PLLA-PEO-PLLA triblock copolymers were compared with those of PLLA-PEO-PPO-PEO-PLLA pentablock copolymers. Two PLLA-PEO-PPO-PEO-PLLA (PLLAF127-29 and PLLAF127-48) produced vesicles, whereas the PLLA-PEO-PLLA formed spherical micelles. The PPO block in the middle of PLLA-F127-PLLA pentablock copolymers could favor the formation of PLLA-F127-PLLA vesicle by decreasing the interface Gibbs free energy [$G(\text{interface})$] of vesicles.

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