

# Synthesis and Characterization of Star-Shaped Poly(ethylene glycol)-Block-Poly(L-lactic acid) Copolymers by Melt Polycondensation

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**ABSTRACT:** Compared with linear diblock or triblock poly(ethylene glycol)-block-poly(L-lactic acid) copolymer (PEG-b-PLLA), star-shaped PEG-b-PLLA (sPEG-b-PLLA) copolymers exhibit smaller hydrodynamic radius and lower viscosity and are expected to display peculiar morphologies, thermal properties, and degradation profiles. Compared with the synthesis routine of PEG-b-PLLA from lactide and PEG, the traditional synthesis routine from LA and PEG were suffered by the low reaction efficiency, low purity, lower molecular weight, and wide molecular weight distribution. In this article, multiarm sPEG-b-PLLA copolymer was prepared from multiarm sPEG and L-lactic acid (LLA using an improved method of melt polycondensation, in which two types of sPEG, that is, sPEG<sub>1</sub> (four arm, Mn = 4300) and sPEG<sub>2</sub> (three arm, Mn = 3200) were chosen as the core. It was found the molecular weight of sPEG-b-PLLA could be strongly affected by the purity of

LLA and sPEGs, and the purification technology of vacuum dewater and vacuum distillation could help to remove most of the impurities in commercial available LLA. The polymers, including sPEG and sPEG-b-PLLA with varied core (sPEG<sub>1</sub> and sPEG<sub>2</sub>) and LLA/sPEG feeding ratios, were characterized and confirmed by <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectroscopy, Fourier transform infrared spectroscopy (FT-IR) and gel permeation chromatography, which showed that the terminal hydroxyl group in each arm of sPEGs had reacted with LLA to form sPEG-b-PLLA copolymers with fairly narrow molecular weight distribution. © 2011 Wiley Periodicals, Inc. *J Appl Polym Sci* 124: 4496–4501, 2012

**Key words:** L-lactic acid; multiarm poly(ethylene glycol)-block-poly(L-lactic acid); copolymer; polycondensation; star polymers

## INTRODUCTION

The block copolymers of poly(ethylene glycol) (PEG) and poly(lactide)s or poly(lactic acid) (PLA) are popular materials that are used extensively for the con-

trolled delivery of protein and peptide drugs, for the manufacture of medical devices and wound dressings as well as for fabricating scaffolds in tissue engineering,<sup>1–3</sup> in which the hydrophilic PEG chains could improve the polymer–cell interaction and allow controlling protein and peptide adsorption, and consequently, allow regulating the behavior of cells on the polymer surface.<sup>4–9</sup> Linear diblock or triblock polymeric systems of PLA–PEG have gained great attention<sup>2,3,10</sup> due to the aforementioned characterizations as well as its biofriendly nature. The combination of PLA and PEG makes this copolymer ideal for the use as a possible drug carrier.<sup>9,11</sup>

In recent years, there also has been an increasing interest in star-shaped polymers which are branched polymers distinguished by a structure containing three or more linear arms radiating from a center.<sup>11–14</sup> Owing to their particular architecture, star-shaped polymers might exhibit smaller hydrodynamic radius and lower viscosity compared with linear polymers of the same molecular weight and composition and are expected to display peculiar morphologies, thermal properties, and degradation profiles.<sup>15–18</sup> Recently, star-shaped PLA polymers,<sup>12–13</sup> diblock three-arm poly(L-lactide)-PEG copolymers,<sup>14–17</sup>

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and four-arm PEG-PLA copolymers<sup>11,18–20</sup> have been investigated by several research groups. It was found that the star polymers showed shorter degradation times as compared with linear PLA and PLA-PEG copolymers, suggesting use as a short-term drug release agent.<sup>11</sup>

It was known that poly(lactide) or PLA could be obtained by the ring-opening polymerization of lactide or polycondensation of lactic acid (LA), respectively. The synthesis routine based on lactide was mostly chosen in laboratory and industrial polymerizations for its better reproducibility and higher molecular weight of polymers. It was also noticed that the preparation technology of lactide is also a long-winded and solvent-wasting procedure. PLA based on the melt polycondensation of LA was repaid attention in recent years for its simple and environmental-friendly technology,<sup>19–21</sup> especially in the occasion that low molecular weight of polymers were wanted, such as the carriers for drug delivery, while it was also suffered from the short-comings such as low reaction efficiency, low purity, and wide molecular weight distribution.

In the former studies, it is found that the purity of LA could significantly affect the molecular weight of PLA, and an effective technology was developed based on a two-stage purification procedure. On the basis of the patented purification technologies of LA,<sup>21</sup> we report some preliminary results on the synthesis and molecular characterization of three-armed and four-armed diblock star-shaped PEG-block-poly LLA (sPEG-b-PLLA) copolymers consisting of hydrophilic PEG inner segments and hydrophobic PLLA external segments with varied core of sPEG (sPEG<sub>1</sub>, three arm and sPEG<sub>2</sub>, four arm) and LA/sPEG feeding ratios. These amphiphilic copolymers, consisting of hydrophilic sPEG inner segments and hydrophobic PLLA external segments, have good potential for the formulation of delivery carriers for bioactive compounds.

## EXPERIMENTAL

### Materials

L-Lactic acid (LLA) solution (88 wt %), was supplied by Wuhan Sanjiang Space GUDE Biotech (Wuhan, China). Multiarm sPEGs, that is, sPEG<sub>1</sub> (four arm, Mn = 4300, Mw/Mn = 1.17) and sPEG<sub>2</sub> (three arm, Mn = 3200, Mw/Mn = 1.04), were kindly supplied by LiMing Chemical Research Institute (Luoyang, China). Tetrahydrofuran (THF), Honeywell, analytical reagent, tin(II) 2-ethylhexanoate (stannous octoate, Sn(Oct)<sub>2</sub>, Sigma-Aldrich, 97%), and all other reagents were used as received.

### Characterization

Molecular weights and molecular weight distributions of the copolymers were determined using a

Waters 1515-2414 gel permeation chromatography (GPC) equipped with a three Styragel<sup>®</sup> columns (HR2, HR4, and HR6). The measurements were carried out at 40°C, using THF as eluent (1 mL min<sup>-1</sup>). Monodisperse polystyrene standards were used for calibration.

<sup>1</sup>H-NMR and <sup>13</sup>C-NMR measurements were performed using a 600 MHz spectrometer (Bruker, Avance 600) with CDCl<sub>3</sub> as a solvent and tetramethylsilane as internal reference at room temperature. The molecular weight of the PLA block relative to that of PEG block (sPEG<sub>1</sub> and sPEG<sub>2</sub>) was calculated from the ratio of the integration of the proton peaks ( $\delta = 3.63$  ppm) in the PEG block to that of the protons ( $\delta = 5.16$  ppm) in the PLA block.

FT-IR spectra were recorded on a Nicolet 6700 FT-IR instrument.

### Purification of lactic acid and sPEGs

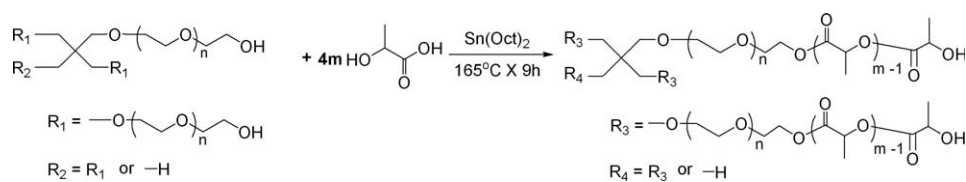
The commercial acquirable LLA solution was purified via a two-step purification procedure<sup>21</sup>: first, it was dewatered at 80°C under vacuum to obtain dewatered LLA; then, the dewatered LLA was vacuum (0.1 kPa) distilled under 170°C to collect the fraction, that is, the purified dehydrated LLA.

The sPEGs were dissolved in dichloromethane and precipitated by cold methanol followed by further drying under vacuum at 40°C for 24 h to obtain purified sPEGs.

### Synthesis of multiarm sPEG-b-PLLA copolymers

Multiarm sPEG-PLLA block copolymers were prepared by the direct polycondensation of LLA and multiarm sPEGs, that is sPEG<sub>1</sub> and sPEG<sub>2</sub>, in the presence of stannous octoate (Sn(Oct)<sub>2</sub>) as a catalyst, as shown in Scheme 1.

A 250-mL three-neck reaction flask, which was equipped with a mechanical stirrer, a vacuum meter, and a high-vacuum stopcock, was connected to a vacuum line. Purified four-arm sPEG (sPEG<sub>1</sub>, 10 g) and LLA (LLA, 30 g) and Sn(Oct)<sub>2</sub> (0.3 g, 1 wt % according to the LLA amount) were added into the reaction flask under room temperature. The reaction was carried out with a three-stage procedure: the first stage was carried out under low vacuum and low temperature to prevent the excess volatilization of LLA, the typical condition is 120°C and 10 kPa for 1 h; in the second stage, the vacuum and temperature increased step-by-step at the same time, with a typical rate of 5°C h<sup>-1</sup> and 1 kPa h<sup>-1</sup> till the reaction temperature and vacuum reached 165°C and 0.5 kPa; in the third stage, the polycondensation reaction was maintained under 165°C and 0.5 kPa for 9 h. Then, the reaction mixture was cooled to room temperature, dissolved in chloroform (about 100 mL)



**Scheme 1** Synthetic scheme of multiarm sPEG-b-PLLA copolymer from sPEG and LLA.

and precipitated into cold methanol to give a white product; the products were filtered and washed with cold methanol, then dried at room temperature for 24 h in vacuum. The polymer was characterized by FT-IR spectroscopy, NMR spectroscopy, and GPC analysis.

$^1\text{H-NMR}$  (600 MHz,  $\text{CDCl}_3$ ,  $25^\circ\text{C}$ ):  $\delta = 1.54$  (m,  $-\text{CHCH}_3-$ ), 3.64 (m,  $-\text{CH}_2-$ ), 5.15 (m,  $-\text{CHCH}_3-$ ), 3.41 (s,  $-\text{C}-\text{CH}_2-$ ), 4.27 [m,  $-\text{C}(\text{O})\text{OCH}_2\text{CH}_2-$ ].  $^{13}\text{C-NMR}$  (600 MHz,  $\text{CDCl}_3$ ,  $25^\circ\text{C}$ ):  $\delta = 16.8$  [ $-\text{C}(\text{O})\text{OCHCH}_3-$ ], 69.2 [ $-\text{C}(\text{O})\text{OCHCH}_3-$ ], 70.2 ( $-\text{CH}_2-$ ), 169.8 ( $-\text{COO}-$ ), 44.3 [ $\text{C}(\text{CH}_2)_4-$ ], 72.2 [ $\text{C}(\text{CH}_2)_4-$ ]. IR (KBr):  $\nu = 2999$  ( $\nu_{\text{sr}}$ ,  $-\text{CH}_3$ ), 2947 ( $\nu_{\text{sr}}$ ,  $-\text{CH}-$ ), 2887 ( $\nu_{\text{sr}}$ ,  $-\text{CH}_2-$ ), 1754 ( $\nu_{\text{sr}}$ ,  $-\text{C}(\text{O})\text{O}-$ ), 1170  $\text{cm}^{-1}$  ( $\nu_{\text{sr}}$ ,  $-\text{C}-\text{O}-$ ).

The same procedure was analogously performed for all the copolymers listed in Table II.

## RESULTS AND DISCUSSION

### Influence of reactants purity on the molecular weight of copolymers

As most of commercial supplied LLA containing about 10–15 wt % moisture and other impurities, such as polyoses and multihydroxyl chemicals, which could be good chain-end terminating agent during the polymerization,<sup>21</sup> it is necessary to purify the reactants before using. Table I shows the influence of purification procedure on the molecular weight of sPEG<sub>1</sub>-b-PLLA<sub>2</sub> copolymers. The results showed that purity of reactants especially the purity of LLA significantly affected the molecular weight of the final copolymer. In the following stated reac-

tions, all the reactants were purified according to the procedure listed in “Characterization” section.

### Characterization of sPEG-b-PLLA

sPEG-b-PLLA was obtained by the polycondensation of LLA with in bulk, catalyzed by  $\text{Sn}(\text{Oct})_2$ , and initiated by varied core of sPEG, that is, sPEG<sub>1</sub> (three arm,  $M_n = 4300$ ) and sPEG<sub>2</sub> (four arm,  $M_n = 3200$ ). The crude products were purified by precipitating their chloroform solutions into an excess of methanol. The sPEG-b-PLLA copolymers with varied sPEGs and LLA/sPEG feeding ratios according to Scheme 1, as shown in Table II, were characterized by FT-IR,  $^1\text{H-NMR}$ ,  $^{13}\text{C-NMR}$ , and GPC.

Figure 1 shows the typical FT-IR spectra of sPEG<sub>1</sub>, linearly PLLA and sPEG<sub>1</sub>-b-PLLA<sub>1</sub>. The absorption peak at  $1754 \text{ cm}^{-1}$  was assigned to  $\text{C}=\text{O}$  stretch vibration, and the peak at  $1170 \text{ cm}^{-1}$  was assigned to  $\text{C}-\text{O}$  stretch vibration, and the absorption peaks at  $2999 \text{ cm}^{-1}$ ,  $2947 \text{ cm}^{-1}$ , and  $2887 \text{ cm}^{-1}$  were assigned to  $-\text{CH}-$ ,  $-\text{CH}_3$ , and  $-\text{CH}_2-$  stretch vibration, which indicated the incorporation of PLLA segments and PEG segments in the products.

The coupling of sPEGs and LLA could be confirmed by the following evidence, as shown in Figures 2 and 3. First, the disappearance of peak (*b'*,  $-\text{CH}_2-$ ) at 3.72 ppm in  $^1\text{H-NMR}$  spectrum and the peak (*3''*,  $-\text{CH}_2-$ ) at 60.8 ppm in  $^{13}\text{C-NMR}$  spectrum, which was assigned to the methylene ( $-\text{CH}_2-$ ) next to the terminal hydroxyl group ( $-\text{OH}$ ) of sPEGs. Second, the disappearance of peak (*4'*) at 178.6 ppm in  $^{13}\text{C-NMR}$  spectrum, which was assigned to the terminal carboxyl group ( $-\text{COOH}$ )

**TABLE I**  
The Influence of Purity of Reactants on the Molecular Weight of sPEG<sub>1</sub>-b-PLLA<sub>2</sub> Copolymer

No.	Treatment of sPEG <sub>1</sub>	Treatment of L-lactic acid	LA/sPEG <sub>1</sub> (wt/wt)	$M_{n\text{GPC}}^a$ ( $\times 10^4$ )	Appearance of products
Ref. 1#	Without purification	Dewatered only <sup>b</sup>	7/1	0.62	Oily
Ref. 2#	Without purification	Dewatered and vacuum distilled <sup>c</sup>		0.93	White waxy
Ref. 3#	Purified <sup>d</sup>	Dewatered only <sup>b</sup>		0.78	Oily
Control 1#	Purified <sup>d</sup>	Dewatered and vacuum distilled <sup>c</sup>		1.43	White powder

<sup>a</sup>  $M_{n\text{GPC}}$  was the molecular weight measured by GPC.

<sup>b</sup> L-Lactic acid was dewatered according to the method detailed in “Characterization” section, without further vacuum distillation.

<sup>c</sup> L-Lactic acid was dewatered and vacuum distillation according to the method detailed in “Characterization” section.

<sup>d</sup> sPEG<sub>1</sub> was purified according to the method detailed in “Characterization” section.

TABLE II  
The Molecular Weight and Appearance of sPEG-b-PLLA Copolymers

sPEG-b-PLLA code	LA/sPEG (wt/wt; mol/mol)	Mn <sup>Theory</sup> <sup>a</sup> (×10 <sup>4</sup> )	Mn <sup>H-NMR</sup> <sup>b</sup> (×10 <sup>4</sup> )	Mn <sup>GPC</sup> <sup>c</sup> (×10 <sup>4</sup> )	PDI <sup>d</sup>	Appearance of products
sPEG <sub>1</sub>	–	–	0.43	0.42	1.05	–
sPEG <sub>2</sub>	–	–	0.32	0.34	1.05	–
sPEG <sub>1</sub> -b-PLLA <sub>1</sub>	3/1 (143.3/1)	1.38	1.21	1.07	1.26	White waxy
sPEG <sub>1</sub> -b-PLLA <sub>2</sub>	7/1 (334.4/1)	2.75	1.59	1.43	1.29	White powder
sPEG <sub>1</sub> -b-PLLA <sub>3</sub>	10/1 (477.7/1)	3.78	2.11	1.87	1.60	White powder
sPEG <sub>2</sub> -b-PLLA <sub>1</sub>	3/1 (106.7/1)	1.02	0.85	0.75	1.22	White powder
sPEG <sub>2</sub> -b-PLLA <sub>2</sub>	7/1 (248.9/1)	2.04	1.13	1.02	1.46	White powder
sPEG <sub>2</sub> -b-PLLA <sub>3</sub>	10/1 (355.6/1)	2.81	1.33	1.21	1.53	White powder

<sup>a</sup> Calculated from the feeding ratio of sPEGs and LLA, assuming the rate of conversion is 100%.

<sup>b</sup> Calculated from the <sup>1</sup>H-NMR spectra.

<sup>c</sup> Measured by GPC.

<sup>d</sup> Polydispersity index (PDI = Mw/Mn) determined by GPC.

of PLLA. Thus, it could be concluded that all the hydroxyl groups in sPEG had reacted with the carboxyl group of LLA, and the PLLA segment was also obtained by the polycondensation of LLA.

The molecular weight of each copolymer was evaluated by the relative intensity of signals at  $\delta = 5.15$  (–CH– of PLLA block, signal b in Fig. 2,  $A_{CH}$ ) and 3.64 (–CH<sub>2</sub>– of sPEG block, signal a in Fig. 2,  $A_{CH_2}$ ), based on the known molecular weight of the sPEGs core (sPEG<sub>1</sub>, Mn<sub>sPEG1</sub> = 4300; sPEG<sub>2</sub>, Mn<sub>sPEG2</sub> = 3200), the Mn<sub>H-NMR</sub> of the copolymers could be evaluated according to the following equation:

$$Mn_{H-NMR} = Mn_{sPEG} + (MW_{LLA} - 20) \times \frac{Mn_{sPEG}}{MW_{ethylene\ oxide}} \frac{2A_{CH}}{A_{CH_2}} \quad (1)$$

The theoretical molecular weights (Mn<sup>Theory</sup>) of copolymers were also calculated from the equation, assuming the conversion rate of LLA is 100%:

$$Mn_{Theory} = Mn_{sPEG} + (MW_{LLA} - 20) \frac{M_{LLA}}{MW_{LLA}} \frac{Mn_{sPEG}}{M_{sPEG}} \quad (2)$$

where  $M_{LLA}$  and  $M_{sPEG}$  are the feeding weight of LLA and sPEG,  $MW_{LLA}$  and  $MW_{ethylene\ oxide}$  are the molecular weight of LLA and ethylene oxide chain element of sPEG, respectively.

The formation of block copolymers could also be shown by the increase of Mn of sPEG-b-PLLAs with respect to those macromers of sPEGs by GPC, which showed unimodal molecular-weight-distribution curves at molecular weights higher than those of the corresponding sPEGs macromers and fairly narrow polydispersity Index (PDI) (1.26–1.60) values, as shown in Table II and Figure 4. The molecular weights of sPEG-b-PLLA copolymers measured by GPC (Mn<sub>GPC</sub>) were lower than the molecular weight estimated according to the LLA/sPEG feeding ratios (Mn<sup>Theory</sup>) calculated according to eq. (2) but were similar as the molecular weight (Mn<sub>H-NMR</sub>) calculated from the <sup>1</sup>H-NMR spectrum according to eq. (1).

It was noticed that the higher LLA/sPEG feeding ratio, the more difference between Mn<sub>GPC</sub> and Mn<sup>Theory</sup> and also the higher PDI, which was mainly caused by the volatilization of LLA and the generation of L-lactide by the pyrolysis of PLLA oligomers. Also, as reported previously for star-shaped poly(D,L-lactide), the molecular weight of sPEG-b-PLLAs were overestimated because of their different hydrodynamic behavior from polystyrene standards.

## CONCLUSIONS

Multiarm sPEG-b-PLLA with varied sPEG cores and LLA/sPEG feeding ratios were synthesized by melt polycondensation of sPEG and LLA following a three-stage procedure. It was found that the molecular weight of sPEG-b-PLLA could be strongly affected by the purity of reactant especially the

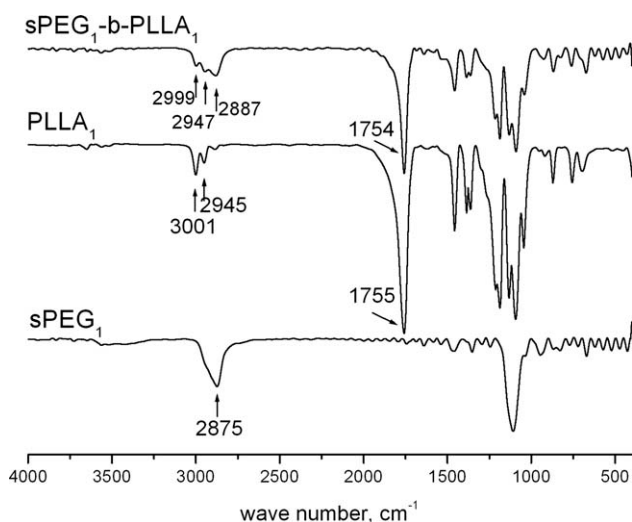
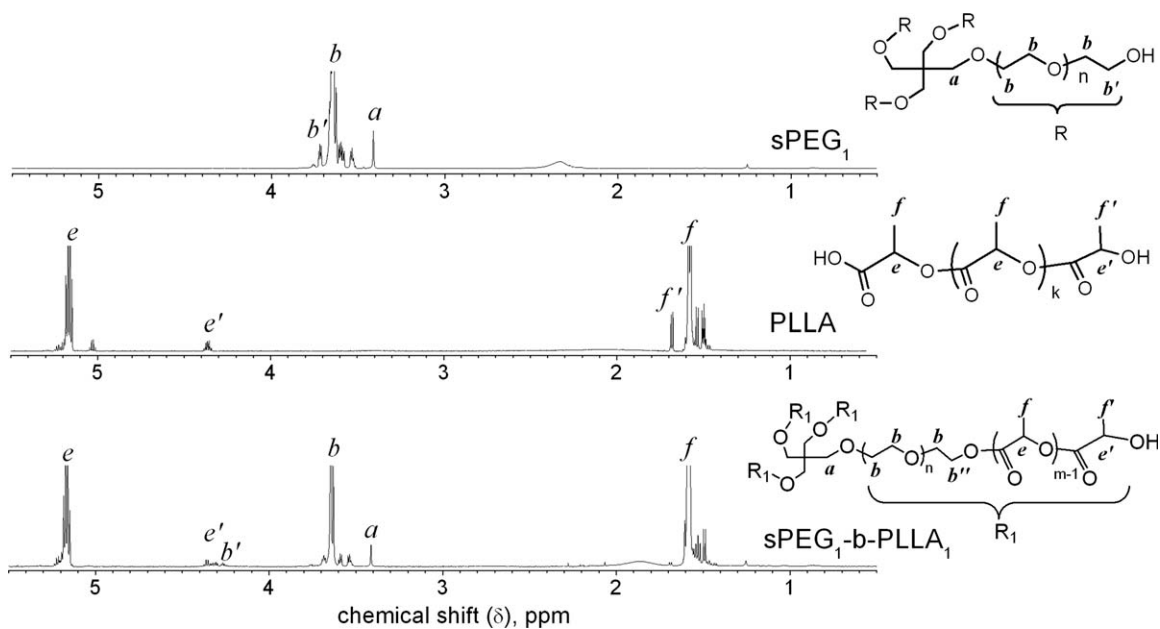
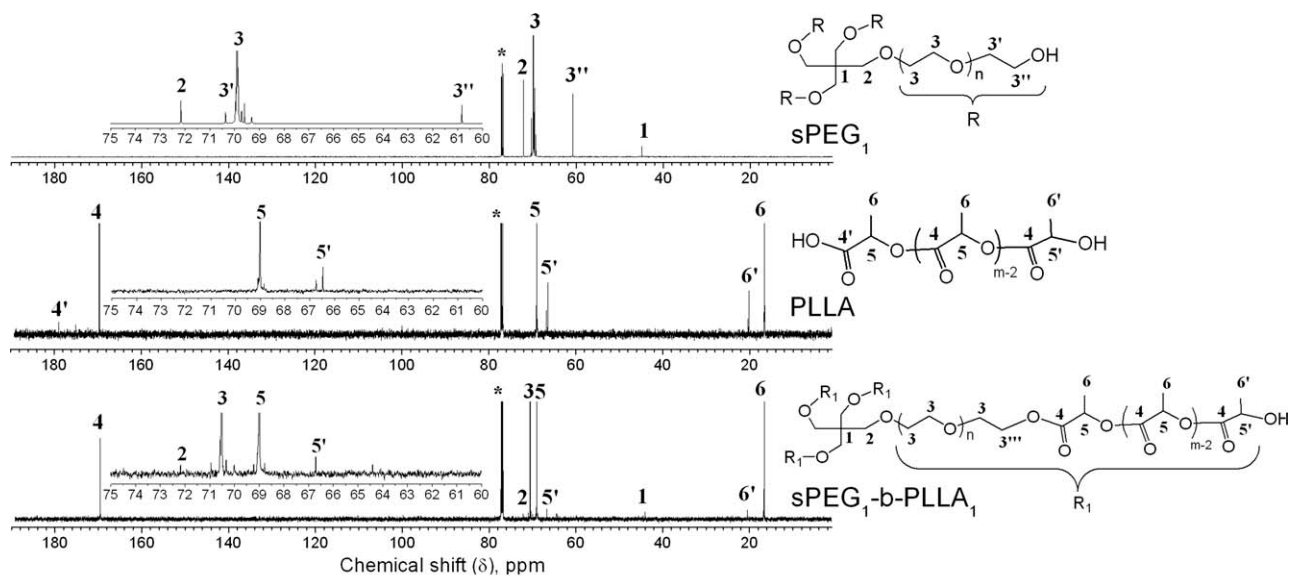


Figure 1 The FT-IR spectrum of sPEG<sub>1</sub>, PLLA and sPEG<sub>1</sub>-b-PLLA<sub>1</sub>.

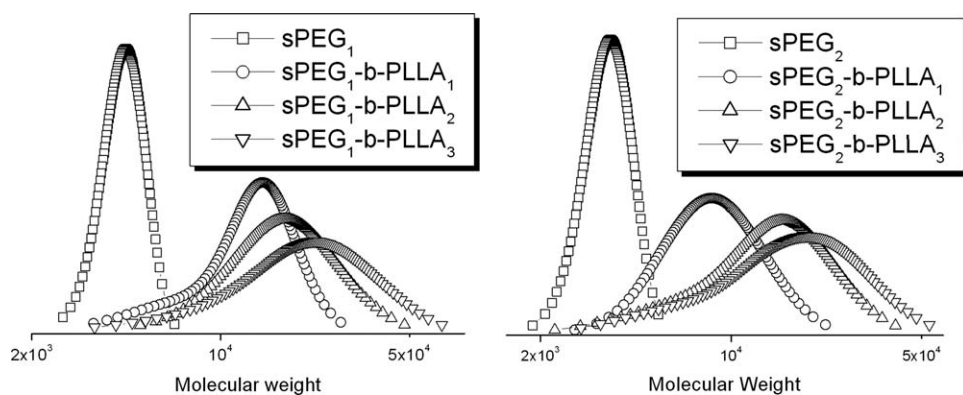




**Figure 2** Chemical structures and  $^1\text{H-NMR}$  spectra of  $\text{sPEG}_1$ , PLLA and  $\text{sPEG}_1\text{-b-PLLA}_1$ .



**Figure 3** Chemical structures and  $^{13}\text{C-NMR}$  spectra of  $\text{sPEG}_1$ , PLLA and  $\text{sPEG}_1\text{-b-PLLA}_1$ .



**Figure 4** The molecular weight distribution curves of sPEGs and sPEG-b-PLLA copolymers determined by GPC.

purity of LLA, and the technology of vacuum dewater and followed by vacuum distillation could effectively help to remove most of the impurities in commercial available LLA. The copolymers were characterized and confirmed by  $^1\text{H}$  and  $^{13}\text{C}$ -NMR, FT-IR, and GPC.

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