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ORIGINAL PAPER

Synthesis and characterization of star-shaped poly (D,L-lactide)-block-poly(ethylene glycol) copolymers

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Abstract Star-shaped hydroxy-terminated poly(D,L-lactide) (s-PDLLA), with arms of different lengths, were obtained by ring-opening polymerization (ROP) of D,L-lactide (LA) initiated by varied contents of pentaerythritol (PETH) in the presence of stannous octoate ($Sn(Oct)_2$), and were condensed with carboxyl-terminated poly(ethylene glycol) methyl ether (CT-mPEG, $M_n = 850$ and 2,000) to afford four-arm star-shaped poly(D,L-lactide)-block-poly(ethylene glycol) copolymer (s-PDLLA-b-PEG). The polymers, including s-PDLLA, CT-mPEG, and s-PDLLA-b-PEG, were characterized and confirmed by ^{1}H-NMR and ^{13}C-NMR spectroscopy, fourier transform infrared spectroscopy (FT-IR), and gel permeation chromatography (GPC).

Keywords Ring-opening polymerization ·
Star-shaped poly(D,L-lactide)-block-poly(ethylene glycol) copolymers ·
Carboxyl-terminated poly(ethylene glycol) methyl ether

Introduction

Poly(lactide)s (PLA) are popular materials that are used extensively for the controlled delivery of protein and peptide drugs, for the manufacture of medical devices and wound dressings as well as for fabricating scaffolds in tissue

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engineering [1–3]. However, the adsorption of peptides and proteins to the surface of PLA is a phenomenon that is frequently reported and can cause severe problems [2]. One approach is to attach a poly(ethylene glycol) (PEG) chain to the biodegradable PLA chain [4]. The hydrophilic PEG chains allow controlling protein and peptide adsorption and, consequently, allow regulating the behavior of cells on the polymer surface [5–10]. Linear di-block or tri-block polymeric systems of PLA–PEG have gained great attention [2–4] due to the aforementioned characteristics as well as its bio-friendly nature. The combination of PLA and PEG makes this copolymer ideal for the use as a possible drug carrier [10, 11].

In recent years, there 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 [11–14]. Owing to their particular architecture, star-shaped polymers 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 [15–18].

Recently, star-shaped PLA polymers, s-PLA [12, 13], di-block three-arm poly (L-lactide)-PEG copolymers [14–17], four-arm PEG–PLA copolymers [11, 18, 19] have been investigated by several research groups. It was found that the star polymers showed shorter degradation times as compared to linear PLA and PLA–PEG copolymers, suggesting use as a short-term drug release agent [11].

In this article, we report some preliminary results on the synthesis and molecular characterization of four-armed star-shaped PDLLA–PEG di-block copolymers with PEG molecular weights of 850 and 2,000. These amphiphilic copolymers, consisting of hydrophobic inner PDLLA segments and hydrophilic PEG external segments, have good potential for the formulation of delivery carriers for bioactive compounds.

Experimental

Materials

D,L-lactide (LA), was prepared from D,L-lactic acid (Wuhan Sanjiang Space GUDE Biotech Co., Ltd., China, chemical reagent) according to [20] using the method of thermo-cracking in laboratory, the products were recrystallized using ethyl acetate for five times before use. Pentaerythritol (PETH, Aldrich, 99%), methoxy poly(ethylene glycol) (mPEG) (Aldrich, $M_n = 750$ and 1,900), methylene chloride, ethyl acetate and acetone (Guangzhou Chemical Reagent Factory, analytical reagent), tetrahydrofuran (THF, Honeywell, analytical reagent), pyrene (Aldrich, 98%), tin(II) 2-ethylhexanoate (stannous octoate, $Sn(Oct)_2$, Sigma-Aldrich), 1,3-diisopropylcarbodiimide (DCC, Sigma-Aldrich, 99%), *p*-toluenesulfonic acid monohydrate (Sigma-Aldrich, 98.5%), 4-(dimethylamino)pyridine (DMAP, Sigma-Aldrich, 99%), and all other reagents were used as received.

Synthesis of carboxyl-terminated mPEG (CT-mPEG)

A carboxylic acid group was introduced to the chain end of poly(ethylene glycol) methyl ether (mPEG, $M_n = 750$) by reaction of the terminal hydroxyl group of PEG (7.5 g, 10 mmol) with succinic anhydride (1.1 g, 11 mmol) and *p*-toluene sulfonic acid (1.75 mmol). After the reaction was allowed to occur at 80 °C for 3 h under a nitrogen atmosphere, the reaction mixture was dissolved in methylene chloride and filtered to remove un-reacted succinic anhydride. After filtration, the solution was poured into diethyl ether to precipitate the reaction product, and the processing of dissolving and precipitating were repeated three times to purified the products. The precipitate, carboxyl-terminated mPEG (CT-mPEG, 6.8 g, ~80% yields), was obtained after filtering and drying in a vacuum for 24 h.

Synthesis of four-arm star-shaped PLA

D,L-lactide (11.52 g, 80 mmol), PETH (0.1088 g, 0.8 mmol), and $Sn(Oct)_2$ (0.576 g, 0.5 wt% of LA) were placed in a single-neck round-bottom flask equipped with a vacuum pump and a magnetic stirrer. The reaction flask was evacuated and refilled with nitrogen three times and then was allowed to polymerize at 130 °C for 12 h with stirring. After the reaction flask was cooled to room temperature, the resulting product was dissolved in methylene chloride and then poured into excess methanol to precipitate the polymerized product, and the processing of dissolving and precipitating were repeated three times to purified the products. Four-arm star-shaped PLA (9.6 g, about 82% yield) with a hydroxyl group at each chain end was obtained after filtering and drying in a vacuum for 24 h.

Synthesis of four-arm star-shaped PLA-b-PEG copolymer

The four-arm star-shaped PLA-block-PEG copolymer (s-PDLLA-b-PEG) was then synthesized using the reaction between the hydroxyl group of four-arm star-shaped PLA and the carboxylic acid group of mPEG at room temperature. A solution of s-PDLLA (5.5 g, 0.5 mmol) in CH_2Cl_2 (10 mL) and a solution of DCC (1.06 g, 5.15 mmol) in 5 mL of CH_2Cl_2 were added simultaneously at room temperature under a nitrogen flow to a stirred solution of CT-mPEG (2.13 g, 2.5 mmol) and DMAP (0.06 g, 0.5 mmol) in 50 mL of CH_2Cl_2. After 24 h, the precipitated dicyclohexylurea was filtered off. Residual dicyclohexylurea and DCC were precipitated by adding acetone. The filtered solution was evaporated to dryness. The solid was dissolved in CH_3Cl and the solution was extracted with a diluted HCl solution (0.5 wt%), followed by water, and then dried over anhydrous Na_2SO_4. Evaporation of the solvent gave 5.6 g of the s-PDLLA-b-PEG copolymer (about 78% yields).

In summary, the s-PDLLA-b-PEG copolymers were prepared following a two-step synthetic procedure using the "core-first" approach, i.e., a four-armed PLA star-shaped macromer, s-PDLLA, was first obtained using a tetra-functional initiator (PETH), and the functional end groups, i.e., the hydroxyl group, of the PLA chains

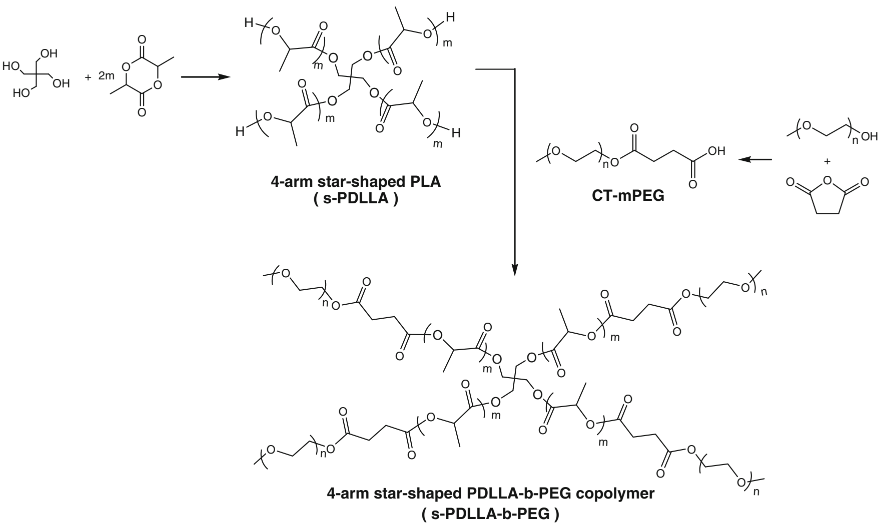

Fig. 1 Synthetic scheme of four-arm star-shaped PLA-b-PEG copolymer (s-PDLLA-b-PEG)

were subsequently reacted with mono-functional PEG macromers (CT-mPEG) in a second step, as shown in Fig. 1.

Characterization of copolymers

The molecular weight and molecular weight distribution of the block copolymers were measured by ^{1}H-NMR and gel permeation chromatography (GPC), respectively. ^{1}H-NMR and ^{13}C-NMR measurements were performed using a 600 MHz spectrometer (Bruker, Avance 600 MHz) with $CDCl_3$ as a solvent and tetramethylsilane (TMS) as internal reference at room temperature. The molecular weight of the PLA block relative to that of PEG block (M_n: 750 and 1,900) was calculated from the ratio of the integration of the proton peaks in the PEG block to that of the protons in the PLA block. GPC measurements were performed with a Waters 1515-2414 system equipped with three Styragel® columns (HR2, HR4, and HR6). Tetrahydrofuran (THF) was used as an eluent (flow rate: 1 mL/min, at 40 °C), and monodisperse polystyrene standards were used for calibration. FT-IR spectra were recorded on a Nicolet 6700 FT-IR instrument.

Results and discussion

Characterization of CT-mPEG

CT-mPEG with varied molecules (labeled as CT-mPEG$_1$ and CT-mPEG$_2$, with $M_n = 850$ and 2,000, respectively) were obtained by replacing the hydroxyl end groups of mPEG with carboxyl groups using succinic anhydride, as shown in Fig. 1.

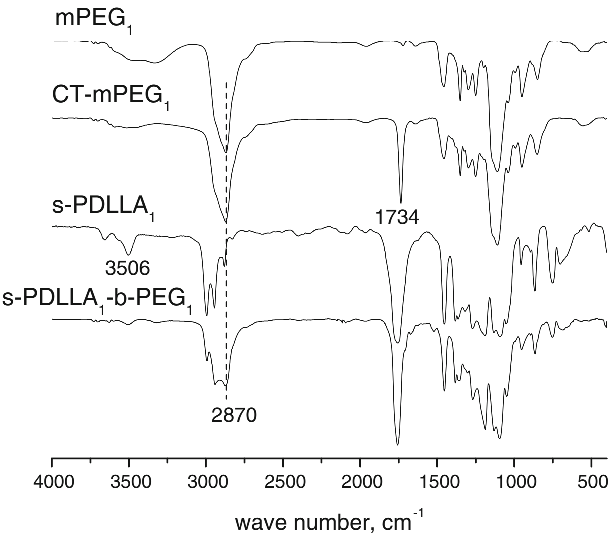

Fig. 2 The FT-IR spectrum of $mPEG_1$, $CT\text{-}mPEG_1$, $s\text{-}PDLLA_1$, and $s\text{-}PDLLA_1\text{-}b\text{-}PEG_1$

After purification, the CT-mPEG macromer were obtained in satisfied yield (78–81%). Figure 2 showed the FT-IR spectrum of mPEG ($M_n = 750$) and CT-mPEG ($M_n = 850$). The absorption peak at 1,734 cm^{-1} was assigned to C=O stretch vibration and the peaks at 1,170 cm^{-1} was assigned to C–O stretch vibration [16, 17], which indicating the formation of ester group.

Peaks (b') at 4.25 ppm and (d) at 2.65 ppm in Fig. 2, peak (10) at 28.7 ppm in Fig. 5 for $–CH_2–CH_2–$, peaks (9′) at 173.6 ppm and (9) at 172.1 ppm in Fig. 5 for –(C=O)–OH and –(C=O)– in CT-mPEG demonstrate the reaction of succinic anhydride, and the peaks (c) at 2.56 ppm for end $–CH_2–OH$ of mPEG disappeared by conversion to the peaks (e) at 5.25 ppm for end (C=O)–OH [15–17], as shown in Fig. 3. Both the FT-IR spectrum and the ^1H-NMR spectroscopy indicated that succinic anhydride had reacted hydroxyl end groups of mPEG to form CT-mPEG.

Characterization of star-shaped PDLLA with varied LA/PETH ratios

Star-shaped poly(D,L-lactide), s-PDLLA, were obtained by the ring-opening polymerization (ROP) of LA in bulk, catalyzed by $Sn(Oct)_2$ and initiated by PETH. The crude products were purified by precipitating their chloroform solutions into an excess of methanol. The s-PDLLAs with varied LA/PETH ratios were characterized by ^1H-NMR spectroscopy and GPC.

The M_n of the s-PDLLAs were set according to the LA/PETH molar ratio, assuming an almost quantitative conversion of the monomer, and the synthesis results are summarized in Table 1. The formation of star-shaped four-armed PDLLA could be confirmed by the $–CH_2–$ group (a, $\delta = 4.17$ ppm) in ^1H-NMR (Fig. 3), (2, $\delta = 75.0$ ppm) in ^{13}C-NMR [15–18] (Fig. 5), and the stretch vibration peak at 2,870 cm^{-1} in Fig. 2. They exhibited a rather narrow molecular weight

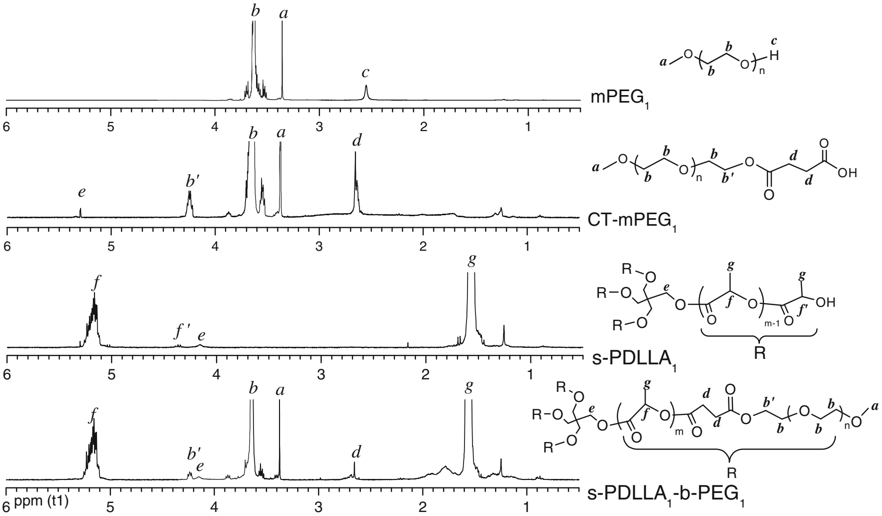

Fig. 3 Chemical structures and ^{1}H-NMR spectra of polymers: mPEG$_1$, CT-mPEG$_1$, s-PDLLA$_1$, and s-PDLLA$_1$-b-PEG$_1$ copolymer

Table 1 Characterizations of s-PDLLA obtained by bulk ROP of LA at 130 °C

s-PDLLA code	LA/PETH (mol/mol)	M_n^a		PDI^b
		Theory	Experiment	
s-PDLLA$_1$	50/1	0.73×10^4	1.08×10^4	1.16
s-PDLLA$_2$	75/1	1.09×10^4	1.60×10^4	1.19
s-PDLLA$_3$	100/1	1.45×10^4	2.10×10^4	1.21
s-PDLLA$_4$	200/1	2.89×10^4	3.97×10^4	1.29

[a] Calculated from the LA/PETH molar ratio (Theory) and determined by GPC (Experiment)

[b] Polydispersity index (M_w/M_n) determined by GPC

distribution (PDI = 1.16–1.29) as shown by GPC. The molecular weight distribution of s-PDLLAs with varied LA/PETH molar ratio was reported in Fig. 4. The M_n values determined by GPC using polystyrene standards were higher than those calculated from the feed or by ^{1}H-NMR, as observed by other authors for PLA and other polyesters [12–19].

Characterization of s-PDLLA-b-PEG copolymer

In the last step of the synthetic procedure, the –OH terminated s-PDLLAs were reacted at room temperature with a slight excess of CT-mPEG having $M_n = 850$ and 2,000. DCC and DMAP were used in the coupling process as a carboxyl group activating agent and as a catalyst, respectively.

The coupling of s-PDLLA and CT-mPEG could be confirmed by the disappearance of end hydroxyl group –OH of s-PDLLA (3,506 cm^{-1} in FT-IR,

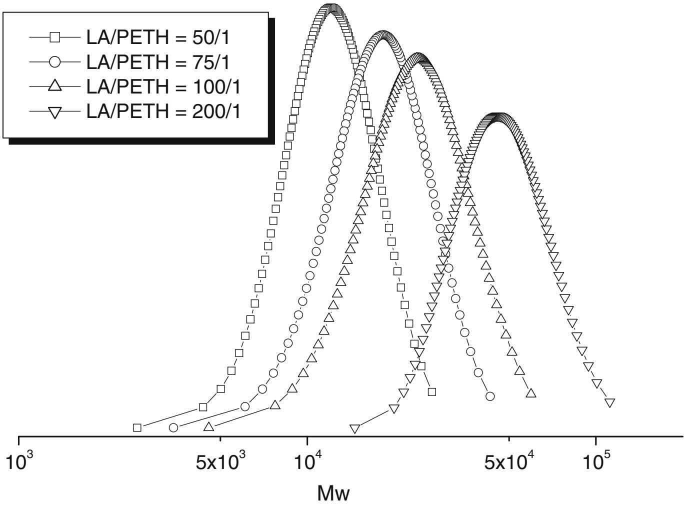

Fig. 4 The molecular weight distribution of s-PDLLA with varied LA/PETH mol ratios

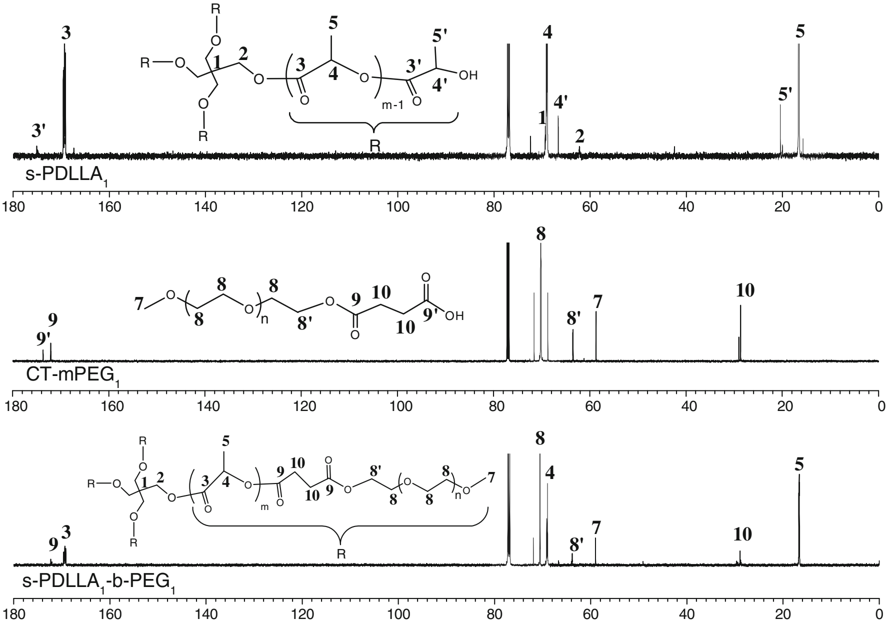

Fig. 5 Chemical structures and ^{13}C-NMR spectra of polymers: s-PDLLA$_1$, CT-mPEG$_1$, and s-PDLLA$_1$-b-PEG$_1$ copolymer

Fig. 2) and $\delta = 2.18$ ppm in ^{1}H-NMR (Fig. 4), the strengthen of –CH$_2$– stretch vibration (2,870 cm^{-1}) of s-PDLLA-b-PEG (Fig. 2), the disappearance of end methyne group –CH– of s-PDLLA ($\delta = 4.35$, b') in ^{1}H-NMR (Fig. 3) and the

Table 2 Characterizations of s-PDLLA-b-PEG copolymers

s-PDLLA-b-PEG code	M_n^a		PDI[b]
	^{1}H-NMR	GPC	
s-PDLLA$_1$-b-PEG$_1^c$	1.06×10^4	1.36×10^4	1.16
s-PDLLA$_1$-b-PEG$_2$	1.48×10^4	2.18×10^4	1.17
s-PDLLA$_2$-b-PEG$_1$	1.22×10^4	1.55×10^4	1.19
s-PDLLA$_2$-b-PEG$_2$	1.75×10^4	2.46×10^4	1.20
s-PDLLA$_3$-b-PEG$_1$	1.57×10^4	1.90×10^4	1.22
s-PDLLA$_3$-b-PEG$_2$	2.15×10^4	2.92×10^4	1.22
s-PDLLA$_4$-b-PEG$_1$	2.35×10^4	2.77×10^4	1.31
s-PDLLA$_4$-b-PEG$_2$	3.54×10^4	4.25×10^4	1.32

[a] Calculated from the ^{1}H-NMR spectra (theory) and determined by GPC (Experiment)

[b] Polydispersity index (M_w/M_n) determined by GPC

[c] M_n of PEG$_1$ block and PEG$_2$ block are 850 and 2,000, respectively

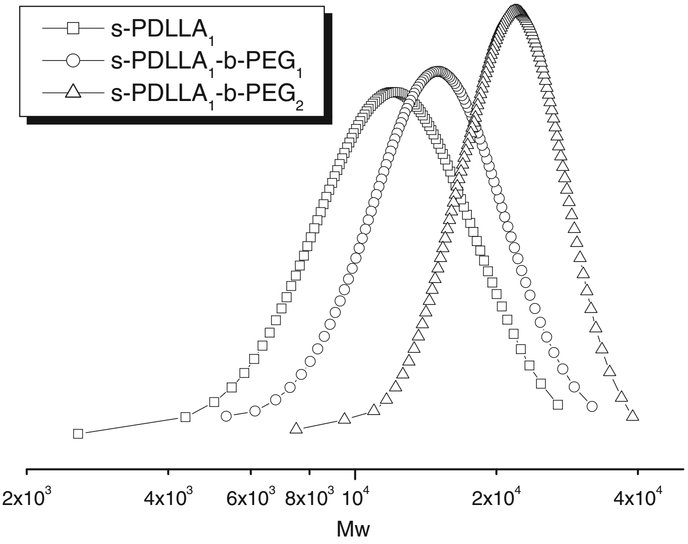

Fig. 6 The molecular weight distribution of: (*a*) s-PDLLA$_1$, (*b*) s-PDLLA$_1$-b-PEG$_1$ copolymer, and (*c*) s-PDLLA$_1$-b-PEG$_2$ copolymer

disappearance of the 3′ ($\delta = 175$ ppm), 4′ ($\delta = 66.7$ ppm), 5′ ($\delta = 20.4$ ppm), and 9′ ($\delta = 173.6$ ppm) peaks in ^{13}C-NMR (Fig. 5). It was concluded that all of the hydroxy group in s-PDLLA were reacted with the carboxyl group of CT-mPEG.

The formation of block copolymers was shown by the increase of M_n of s-PDLLA-b-PEGs with respect to those of the parent macromers by GPC, which showed unimodal molecular weight distribution curves at molecular weights higher than those of the corresponding s-PDLLA macromers, and fairly narrow PDI

(1.16–1.32) values, as shown in Table 2 and Fig. 6. As reported previously for s-PDLLAs, the molecular weight of s-PDLLA-b-PEGs was overestimated because of their different hydrodynamic behavior from polystyrene standards.

Conclusion

Four-arm star-shaped poly(D,L-lactide)-block-poly(ethylene glycol) copolymer (s-PDLLA-b-PEG) with varied length of PLA block and PEG block were synthesized using a two-step method. In the first step, star-shaped poly(D,L-lactide) with varied LA/PETH ratios were got by ROP, and in the second step, s-PDLLA were condensed with carboxyl-terminated poly(ethylene glycol) methyl ether to obtain s-PDLLA-b-PEG copolymers. The polymers were characterized and confirmed by ^{1}H-NMR and ^{13}C-NMR, FT-IR, and GPC.

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