

SYNTHESIS, CHARACTERIZATION AND NANOPARTICLE FORMATION OF STAR-SHAPED POLY(L-LACTIDE) WITH SIX ARMS*

Lu Wang, Chen Cai and Chang-Ming Dong**

Department of Polymer Science & Engineering, School of Chemistry and Chemical Technology, Shanghai Jiao Tong University, Shanghai 200240, China

Abstract Well-defined star-shaped poly(L-lactide) with six arms (sPLLA) was synthesized via the ring-opening polymerization of L-lactide using dipentaerythritol as initiator and stannous octoate as catalyst in bulk at 125°C. The effects of molar ratios of both monomer to initiator and monomer to catalyst on the molecular weights of as-synthesized sPLLA polymers were in detail investigated. The molecular weights of sPLLA polymers linearly increased with the molar ratio of monomer to initiator, and the molecular weight distribution was narrow ($M_w/M_n = 1.04\text{--}1.12$). However, the molar ratio of monomer to catalyst had no apparent influence on the polymer molecular weight. Moreover, the maximal melting point, the crystallization temperature, and the degree of crystallinity of sPLLA polymers increased with the increasing molecular weight, meanwhile they exhibited a spherulitic morphology. Furthermore, spherical nanoparticles (less than 100 nm) could be generated by direct injection of sPLLA solutions into distilled water, and the average size of nanoparticles could be adjusted through both the macromolecular architecture and the polymer molecular weight, respectively.

Keywords: Star-shaped poly(L-Lactide); Ring-opening polymerization; Nanoparticles; Drug delivery.

INTRODUCTION

Biodegradable aliphatic polyesters such as polyglycolide, poly(L-lactide) (PLLA), poly(ϵ -caprolactone) (PCL), and their copolymers are increasingly investigated worldwide for pharmacological, biomedical, agricultural, and environmental purposes^[1–3]. The rapidly growing interest in biodegradable polyesters has also increased interest in catalysts or initiators and mechanisms concerning the ring-opening polymerization of lactones and lactides, which provided an effective method for the preparation of the related aliphatic polyesters^[4, 5]. It is well known that PLLA has been widely used in implanted devices, drug delivery systems, and tissue engineering. However, its *in vitro* and/or *in vivo* degradation rate usually can not be controlled because of its high crystallinity and hydrophobicity of the polymer backbone, so it is urgent to design new PLLA-based materials for biomedical research fields^[6, 7].

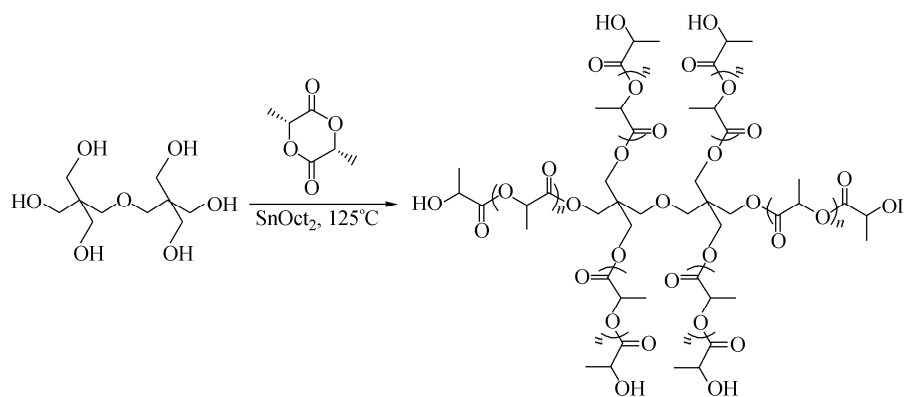
Star-shaped polymers have attracted much attention in the past decades because they exhibit useful rheological and mechanical properties compared to conventional linear polymers, and are expected to display good degradation and controlled drug release properties^[8–10]. Generally, star-shaped polymers can be prepared by two different routes: the “arm-first” strategy based on coupling of linear living polymers with a multifunctional terminator or linking them with a divinyl compound, and the “core-first” approach on the basis of a multifunctional core used as initiator. To this end, biodegradable polyesters with star-shaped architecture have been extensively prepared via the core-first approach. For examples, Hedrick *et al.* reported the synthesis of dendrimer-like star PCL using a hexahydroxy-functional compound as an initiator and stannous octoate

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** Corresponding author: Chang-ming Dong (董常明), E-mail: cmdong@sjtu.edu.cn

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(SnOct_2) as a catalyst^[11–13]. Sanda *et al.* and Kricheldorf *et al.* synthesized three- and four-arm star-shaped PCL with a multifunctional initiator such as trimethylolpropane or pentaerythritol, and with protonic acid or $\text{Bi}(\text{OAc})_3$ as the catalyst, respectively^[14, 15]. Xi *et al.* reported the synthesis and thermal properties of star-shaped and dendrimer-like PLLA hybrids using dendritic hydroxyl-terminated poly(amidoamine) and poly(aryl ether) as macroinitiators, respectively^[16–19]. Wang *et al.* studied the synthesis and controlled drug release properties of poly(amidoamine)-*g*-PLLA using an amine-terminated poly(amidoamine) macroinitiator^[6]. Qiu and Dong *et al.* reported the synthesis, crystallization kinetic, and spherulitic morphology of star-shaped PCL and related PCL-*b*-PLLA block copolymers respectively^[20–22]. However, it looks to us that the studies on the preparation, characterization of star-shaped PLLA with more than four arms, and the fabrication of biodegradable nanoparticles (less than 100 nm) are still rare. Significantly, this will possibly establish a useful starting point not only to improve the physical properties of the linear PLLA analogues, but also to generate biodegradable nanoparticles with adjustable sizes for targeted drug release^[23, 24]. In this article, the as-synthesized star-shaped sPLLA polymers (Scheme 1) and their nanoparticles were in detail characterized by nuclear magnetic resonance (NMR), gel permeation chromatography (GPC), differential scanning calorimetry (DSC), and polarized optical microscopy (POM), dynamic light scattering (DLS), and transmission electron microscopy (TEM), respectively.



Scheme 1 Synthesis of star-shaped poly(L-lactide) with six arms (sPLLA) using dipentaerythritol as an initiator and SnOct_2 as a catalyst in bulk at 125°C

EXPERIMENTAL

Materials

SnOct_2 (Aldrich) was used as received. L-lactide (L-LA, Aldrich) was recrystallized from dry toluene and dried *in vacuo* overnight. Dipentaerythritol (Aldrich) was dried *in vacuo* overnight. Toluene and benzyl alcohol were distilled from CaH_2 , respectively. The other reagents and solvents were local commercial products.

Methods

^1H -NMR and ^{13}C -NMR spectroscopy was performed on a Varian Mercury-400 spectrometer. Tetramethylsilane was used as an internal standard. Molecular weights and molecular weight distributions of the polymers were determined on a Waters 717 plus autosampler gel permeation chromatograph equipped with Waters RH columns, a refractive index detector, and the DAWN EOS (Wyatt Technology) multiangle laser light-scattering detector at 30°C, THF as the eluent (1.0 mL/min). The differential scanning calorimetry (DSC) analysis was carried out using a Perkin-Elmer Pyris 1 instrument under nitrogen flow (10 mL/min). All samples were first heated from -25°C to *ca.* 200°C at 10 K/min and hold for 5 min to erase the thermal history, then cooled to -25°C at 10 K/min, and finally heated to *ca.* 200°C at 10 K/min. The crystallization morphology of polymer was observed using a Leica DMLP polarized optical microscope (Leica Microsystems GmbH, Germany). All samples were heated from 20°C to 180°C at 50 K/min and hold for 5 min to erase the thermal history, and then quenched to the designed crystallization temperature. The mean size of nanoparticles was determined by dynamic light

scattering using a Malvern Nano_S instrument (Malvern, UK). The solution of nanoparticles was performed at a scattering angle of 90°C and at 25°C. All the measurements were repeated three times, and the average values reported are the mean diameter $\pm$ standard deviation. Transmission electron microscopy (TEM) was performed using a JEM-2010/INCA OXFORD TEM (JEOL/OXFORD) at a 200 kV accelerating voltage. Samples were deposited onto the surface of 200 mesh Formvar-carbon film-coated copper grids. Excess solution was quickly wicked away with a filter paper. The image contrast was enhanced by negative staining with phosphotungstic acid.

Synthesis of Star-Shaped Poly(L-lactide) with Six Arms

The polymerization tubes were dried at 110°C for 24 h. L-LA, dipentaerythritol, and a dry stirring bar were put into the warm tube quickly. The tube was then connected to a Schlenk line, where an exhausting–refilling process was repeated three times. The tube was put into an oil bath at 125°C with vigorous stirring for about 5 min. A certain amount of SnOct₂ in dry toluene was added to the melt mixture, and the exhausting–refilling process was carried out again for removal of the toluene. The tube was cooled after the desired reaction time. The resulting product was dissolved in CH₂Cl₂ and poured dropwise into an excess of cold methanol under vigorous stirring. The purified polymer was dried in a vacuum until a constant weight was obtained. Then the polymer yield was determined gravimetrically. A typical example follows: 1.2 mg (3 μ mol) of the SnOct₂ catalyst was added to the melt mixture of the dipentaerythritol initiator (3.1 mg; 0.012 mmol) and L-LA monomer (0.432 g, 3 mmol). The polymerization was carried out in bulk at 125°C for 24 h. Then, the resulting product was dissolved in 4 mL of CH₂Cl₂ and poured dropwise into 40 mL of cold methanol under vigorous stirring at room temperature. The precipitate was filtered and dried in vacuum at 40°C to give 0.380 g of the sPLLA4 sample (87.9% yield).

Fabrication of PLLA Nanoparticles

A direct solution injection method was used to fabricate nanoparticles from the PLLA polymers^[24]. Briefly, 2 mL of the PLLA polymer solution (10 mg/mL) in acetone was added dropwise to 10 mL of distilled water under vigorous stirring. Acetone was completely evaporated under reduced pressure, and then the nanoparticles solution was filtered through a 0.45 μ m microfilter membrane to remove possible aggregates. The yield of nanoparticles varied within 50–60 wt%.

RESULTS AND DISCUSSION

Synthesis of Star-Shaped Poly(L-lactide) with Six Arms (sPLLA)

The ring-opening polymerization of L-LA was carried out with a commercial dipentaerythritol as an initiator and SnOct₂ as a catalyst in bulk at 125°C. The results of the polymerization using various amounts of initiator are compiled in Table 1 (samples sPLLA1–5). From Fig. 1, it is demonstrated that the number-average molecular weight of the resulting sPLLA determined by GPC ($M_{n, \text{GPC}}$) linearly increases with the molar ratio of monomer to initiator ($[M]/[I]$), and the molecular weight distribution (M_w/M_n) is rather narrow in every case (from 1.06 to 1.12). Figure 2 shows the typical GPC curves of the resulting sPLLA polymers, revealing a symmetrical elution peak with narrow molecular weight distribution. However, the molecular weight distribution of control PLLA sample synthesized without dipentaerythritol initiator added is very broad ($M_w/M_n = 1.68$), which suggests that the ring-opening polymerization of L-LA can not be controlled under SnOct₂ catalyst used only. Furthermore, the polymer molecular weight determined by ¹H-NMR ($M_{n, \text{NMR}}$) is consistent with the theoretical molecular weight of polymer ($M_{n, \text{th}}$), where $M_{n, \text{th}} = [M]/[I] \times M_{\text{L-LA}} \times \text{Yield}$. These indicate that the molecular weights of the sPLLA polymers can be accurately predicted by the molar ratio of monomer to initiator. As a note, $M_{n, \text{GPC}}$ is slightly less than the $M_{n, \text{th}}$, which is attributed to the smaller hydrodynamic volume of star-shaped polymers than their linear analogues.

Table 1. Synthesis of star-shaped poly(L-lactide) with six arms (sPLLA) and linear poly(L-lactide) (LPLLA) using both dipentaerythritol and benzyl alcohol as initiators and SnOct₂ as catalyst in bulk at 125°C^a

Entry	[M]/[I] ^b	[M]/[SnOct ₂]	$M_{n, GPC}$	$M_{n, th}$ ^c	$M_{n, NMR}$ ^d	M_w/M_n ^e	Yield (%)
sPLLA1	60/1	1000/1	5530	6370	7770	1.07	73.7
sPLLA2	117/1	1000/1	12700	14990	15000	1.10	89.0
sPLLA3	184/1	1000/1	14990	20800	21600	1.12	78.5
sPLLA4	248/1	1000/1	23360	31390	—	1.06	87.9
sPLLA5	294/1	1000/1	29060	35140	—	1.04	83.0
sPLLA6	119/1	250	13940	14430	—	1.06	84.2
sPLLA7	118/1	500	11370	13890	—	1.11	80.4
sPLLA8	119/1	2000	12510	12920	—	1.03	75.4
LPLLA1	60/1	1000/1	5330	6910	—	1.11	80.0
LPLLA2	120/1	1000/1	15460	15550	—	1.44	90.0
Control ^f	—	1000/1	16700	—	—	1.68	80.5

^a All the polymerization time was 24 h except that 36 h was used for sPLLA8; ^b $M = L-LA$, $I =$ dipentaerythritol or benzyl alcohol; ^c $M_{n, th} = [M]/[I] \times M_{L-LA} \times \text{Yield}$, $M_{n, th}$ denotes the theoretical number-average molecular weight of sPLLA polymer; ^d $M_{n, NMR}$ was determined from the integral ratio of the signals on the main chain of polymer ($-\text{CH}(\text{CH}_3)$, $\delta(\text{H}^c) = 5.00\text{--}5.30$) and the signals on lactyl end group ($\text{HOCH}(\text{CH}_3)\text{CO}$, $\delta(\text{H}^b) = 4.36$): $M_{n, NMR} = M_{\text{initiator residue}} + \delta(\text{H}^c)/\delta(\text{H}^b) \times 72 \times \text{arm number}$; ^e Weight-average molecular weight (M_w) and number-average molecular weight (M_n) are determined by GPC; ^f The control PLLA polymer was synthesized using SnOct₂ catalyst without dipentaerythritol initiator added in bulk at 125°C.

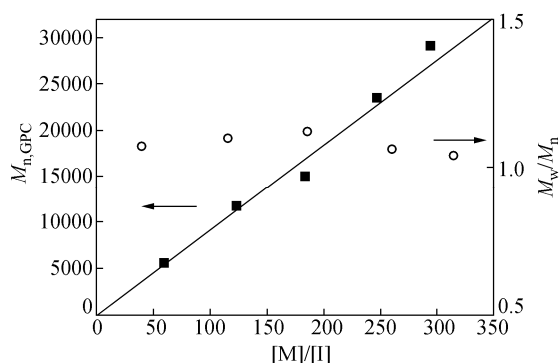


Fig. 1 Dependence of $M_{n, GPC}$ on the molar ratio of $[M]/[I]$ with dipentaerythritol initiator and SnOct₂ catalyst in bulk at 125°C

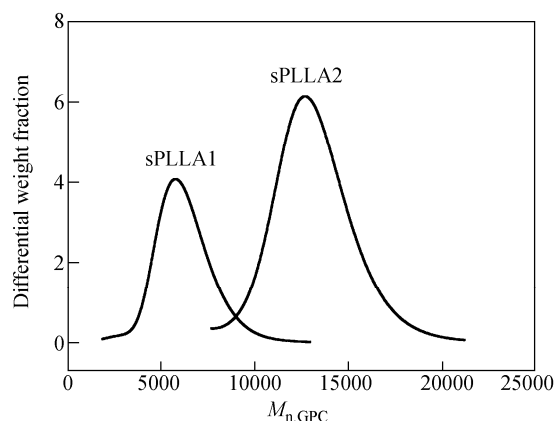


Fig. 2 GPC traces of the sPLLA1 and sPLLA2 samples

The results of the polymerization of L-LA using various amounts of SnOct₂ catalyst are also compiled in Table 1 (samples sPLLA2, and sPLLA6–8). It is demonstrated that the amount of SnOct₂ catalyst has no apparent influence on the $M_{n, GPC}$ of the sPLLA polymers when the molar ratio of monomer to initiator is a constant ($[M]/[I] = ca. 120$), and that the molecular weight distribution is also very low (from 1.03 to 1.11). This indicates that the dipentaerythritol compound is a real initiator, which can stoichiometrically control the molecular weights of the sPLLA polymers. Moreover, the molecular weight distribution is much lower when the amount of SnOct₂ catalyst used is much less (such as $[M]/[\text{SnOct}_2] = 2000$, $M_w/M_n = 1.03$) although the polymerization time was increased from 24 h to 36 h. This indicates that the star-shaped architecture of as-synthesized sPLLA polymers can be effectively controlled under the reaction condition used, while the prolonged polymerization time did not cause the intra- and/or inter-transesterification reactions, which would probably broaden the molecular weight distribution^[5].

The ¹H-NMR spectrum of the sPLLA polymer clearly shows that besides the typical proton signals of its main chain at $\delta(\text{H}^d) = 1.40\text{--}1.70$ and $\delta(\text{H}^c) = 5.00\text{--}5.30$, there are additional proton signals of its end groups, i.e. the signals assigned to the proton on lactyl end group ($\text{HOCH}(\text{CH}_3)\text{CO}$, $\delta(\text{H}^b) = 4.36$), and the protons on the

methyleneoxy groups assigned to the dipentaerythritol initiator residue (CH_2OCO , $\delta(\text{H}^e) = 4.04\text{--}4.20$; CH_2OCH_2 , $\delta(\text{H}^f) = 3.32$). No carboxylic acid proton could be detected (Fig. 3). On the assumption that each PLLA chain is selectively capped by a secondary hydroxyl group at one end and a methyleneoxy group at the other end, $M_{n,\text{NMR}}$ calculated from the ^1H -NMR spectra is in good agreement with $M_{n,\text{th}}$ (Table 1). Moreover, the integral ratio of both the proton signal on one methyleneoxy group (H^e) to the lactyl end group (H^b) and H^e to the other methyleneoxy group (H^f) is 1.9 and 3.2, respectively, which are very close to the theoretical values ($S_{\text{H}^e}/S_{\text{H}^b} = 2$, and $S_{\text{H}^e}/S_{\text{H}^f} = 3$). This observation convincingly confirms that star-shaped PLLA polymers had six arms, and that L-LA monomers have been inserted into the “ $\text{CH}_2\text{O}-\text{H}$ ” bonds of the dipentaerythritol initiator through the selective acyl-oxygen cleavage of the monomer, as shown in Scheme 1. This also suggests that the dipentaerythritol initiated ring-opening polymerization of L-LA monomer conforms to the known “coordination-insertion” mechanism^[4, 5]. Similarly, the ^{13}C -NMR spectrum of the sPLLA polymer also indicates that the dipentaerythritol compound played its role as an initiator in the polymerization process of L-LA monomer (Fig. 4). In all, the above shows that the sPLLA polymers with six arms were successfully synthesized from the ring-opening polymerization of L-LA monomer with a commercial dipentaerythritol initiator and SnOct_2 catalyst in bulk at 125°C .

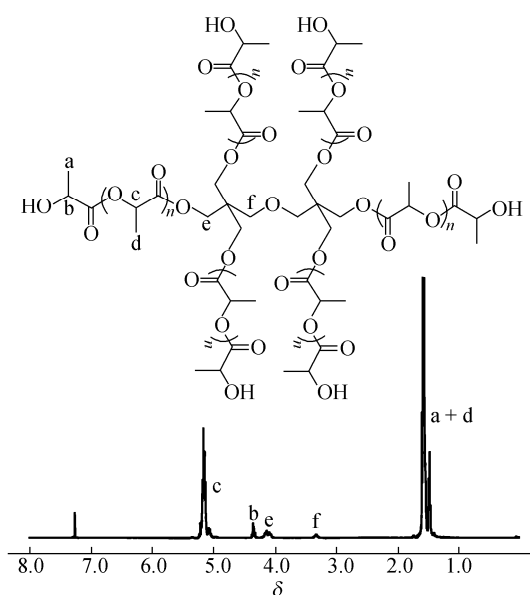


Fig. 3 ^1H -NMR spectrum of a sPLLA1 polymer

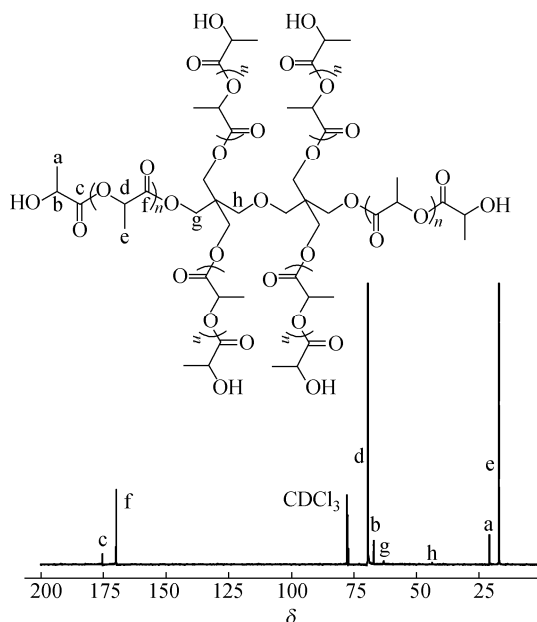


Fig. 4 ^{13}C -NMR spectrum of a sPLLA1 polymer

Differential Scanning Calorimetry (DSC) Analysis

The melting and crystallization behaviors of the sPLLA and the linear PLLA polymers are investigated by DSC, as shown in Fig. 5. For example, the linear PLLA polymer (LPLLA1 sample, $M_{n,\text{GPC}} = 5330$) has a monomodal melting point at $T_m = 161.7^\circ\text{C}$ in the first heating run (Fig. 5A), a crystallization point at $T_c = 107.6^\circ\text{C}$ in the cooling run (Fig. 5B), and a monomodal endotherm peak at $T_m = 159.5^\circ\text{C}$ in the second heating run (Fig. 5C), respectively. However, the sPLLA polymer with similar molecular weight (sPLLA1 sample, $M_{n,\text{GPC}} = 5530$) gives a broad melting peak at about 120.5°C in the first heating run, while both the crystallization peak in the cooling run and the melting peak in the second heating run can not be observed, respectively. This can be attributed to the relatively slow crystallization rate induced by both the short arm length and the strong interactions among the relatively more hydroxyl end groups of sPLLA1 polymer. Moreover, the other sPLLA polymers (from sPLLA2 to sPLLA5) all have a monomodal exotherm crystallization peak at $100.5\text{--}109.4^\circ\text{C}$ and bimodal melting peaks with a maximal melting point at $147.7\text{--}161.0^\circ\text{C}$ in the first heating run, respectively. This indicates that there possibly existed the crystallinities of different size and imperfect crystallization, which continued to rearrange and crystallize in the first heating run compared with the linear PLLA analogues^[16, 17].

Notably, the exotherm crystallization peak did not appear for the sPLLA polymers in the cooling run except sPLLA4 sample, while they all showed an apparent exotherm crystallization peak at 100.1–105.7°C and the bimodal melting peaks with a maximal melting point at 145.4–159.8°C in the second heating run, respectively. This also suggests that the sPLLA polymers had a relatively slow crystallization rate, and the crystallinities of different size and imperfect crystallization were concomitantly produced in the second heating run because of the intermolecular interactions (such as van der Waals, dipole-dipole, and hydrogen-bond interactions) among the star-shaped polymers with hydroxyl end groups. Furthermore, both the maximal melting point and the crystallization temperature of sPLLA polymers increased with the increasing polymer molecular weight, and they were lower than those of the linear analogues, as shown in Table 2.

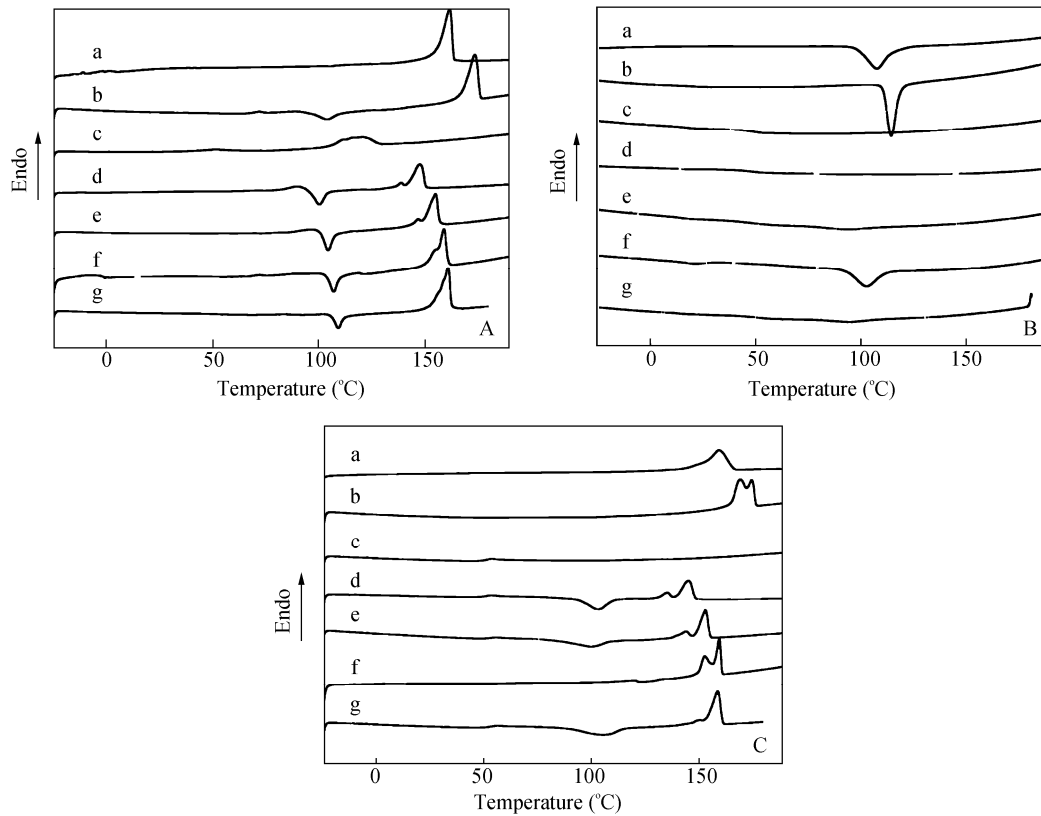


Fig. 5 DSC curves of the linear LPLLA and star-shaped sPLLA polymers in the first heating run (A), in the cooling run (B), and in the second heating run (C)

a) LPLLA1; b) LPLLA2; c) sPLLA1; d) sPLLA2; e) sPLLA3; f) sPLLA4; g) sPLLA5

Table 2. The melting and crystallization behaviors of sPLLA and LPLLA polymers

Entry	T_{m1}^a (°C)	T_{m2}^a (°C)	T_g^b (°C)	T_{c1}^c (°C)	ΔH_{m1}^d (J/g)	X_{c1}^e (%)	T_{c2}^c (°C)	ΔH_{m2}^d (J/g)	X_{c2}^e (%)
sPLLA1	120.5	—	44.6	—	32.9	35.1	—	0	0
sPLLA2	147.7	145.4	49.3	100.5	38.4	41.0	103.5	29.6	31.6
sPLLA3	155.2	153.3	53.7	104.7	42.8	45.7	100.1	33.5	35.8
sPLLA4	159.1	159.8	—	107.2	48.4	51.7	102.9	44.0	47.0
sPLLA5	161.0	158.9	53.4	109.4	54.9	58.7	105.7	47.1	50.3
LPLLA1	161.7	159.5	41.6	—	64.8	69.2	107.6	54.4	58.1
LPLLA2	173.7	169.3	52.6	—	59.0	63.0	114.3	61.9	66.1

^a T_{m1} and T_{m2} denote the maximal melting temperature of polymer in the first and second heating run, respectively; ^b The glass transition temperature of polymer; ^c T_{c1} and T_{c2} denote the crystallization temperature of polymer in the first heating and the cooling or the second heating run, respectively; ^d ΔH_{m1} and ΔH_{m2} denote the fusion enthalpy of polymer in the first and second heating run, respectively; ^e $X_{c1} = \Delta H_{m1}/\Delta H_m^0$, $X_{c2} = \Delta H_{m2}/\Delta H_m^0$, $\Delta H_m^0 = 93.6$ J/g

Degree of crystallinity (X_c) of sPLLA was determined from DSC analysis with the aid of the enthalpy of fusion of 93.6 J/g for the perfectly crystalline PLLA. The X_c increases with the increasing polymer molecular weight, and it is less than that of the linear analogue (Table 2). As a note, the X_c value determined in the first heating run was a little higher than that determined in the second heating run. This indicates that the thermal history also had some effect on the X_c of sPLLA polymers, which was usually observed in the semicrystalline PLLA^[17].

Polarized Optical Microscopy (POM) Analysis

A polarized optical microscope was used to observe the crystalline morphologies of the sPLLA and the linear PLLA polymers, as presented in Fig. 6. The crystallization temperature was chosen between T_m and T_c . For example, the linear PLLA polymer (LPLLA2 sample, $M_{n,GPC} = 15460$) gave a spherulitic morphology with apparent Maltese-cross patterns at a crystallization temperature of 125°C when it crystallized for 5 min (Fig. 6a). Similarly, the sPLLA polymer (sPLLA2 sample, $M_{n,GPC} = 11680$) also presented a spherulitic morphology, while its average diameter of spherulites was less than that of LPLLA2 sample under the same crystallization temperature and time (Fig. 6b). With the increasing molecular weight of polymer, sPLLA4 ($M_{n,GPC} = 23360$) gave spherulites with a better morphology than sPLLA2, and the average diameter of spherulites was a slightly more than that of sPLLA2 (Fig. 6c). These preliminary results suggest that the crystallization behavior and the spherulitic morphology of PLLA can be adjusted through both macromolecular architecture and the polymer molecular weight, which is in agreement with the analysis of DSC. Furthermore, a plenty of small spherulites formed in the isothermal crystallization of sPLLA4 sample when the crystallization temperature was decreased to a lower point at 115°C (Fig. 6d), which is attributed to both the relatively fast nucleation rate and the slow growing rate of spherulites^[25]. Meanwhile, the average diameter of spherulites increased over the crystallization time (Figs. 6e and 6f).

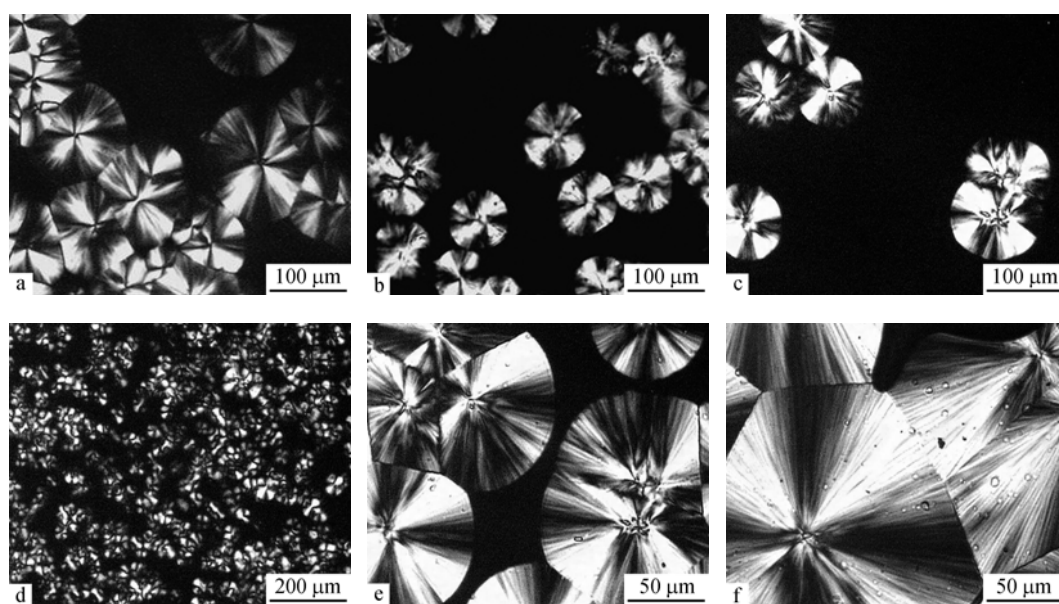


Fig. 6 POM photomicrographs of the LPLLA and the sPLLA samples at different crystallization temperature and time

a) LPLLA2, 125°C, the crystallization time = 5 m; b) sPLLA2, 125°C, the crystallization time = 5 m; c) sPLLA4, 125°C, the crystallization time = 5 m; d) sPLLA4, 115°C, the crystallization time = 5 m; e) sPLLA4, 125°C, the crystallization time = 10 m; f) sPLLA4, 125°C, the crystallization time = 20 m

PLLA Nanoparticles

Using a direct solution injection method, the PLLA polymers were conveniently fabricated into nanoparticles, and the dynamic light scattering (DLS) analysis was summarized in Table 3 and Fig. 7. It can be seen that nanoparticles of sPLLA polymers were bigger than those of linear analogues, and the average diameter of nanoparticles varied from 63 nm to 86 nm. Meanwhile, the average diameter of sPLLA nanoparticles slightly decreased over the polymer molecular weight, and it was in the order of sPLLA4 < sPLLA3 < sPLLA2. These results preliminarily indicate that the size of nanoparticles can be adjusted from both macromolecular architecture (star-shaped versus linear) and polymer molecular weight. The morphology of nanoparticles was further observed by TEM using negative staining, as shown in Fig. 8. For example, sPLLA2 sample showed nearly spherical nanoparticles, whose diameter was basically consistent with that determined from DLS analysis. As a note, the nanoparticles were stable in aqueous solution at least within one month at 4°C, which suggests they are suitable for drug delivery. In all, these results indicate that biodegradable nanoparticles with adjustable sizes can be easily fabricated from these PLLA polymers, and they completely meet the size prerequisite for targeted drug delivery^[23, 24].

Table 3. PLLA nanoparticles fabricated by a direct solution injection method

Entry	Diameter (nm)
LPLLA1	75.2 ± 3.0
LPLLA2	63.0 ± 6.2
sPLLA2	85.7 ± 1.1
sPLLA3	80.9 ± 4.6
sPLLA4	77.9 ± 3.8

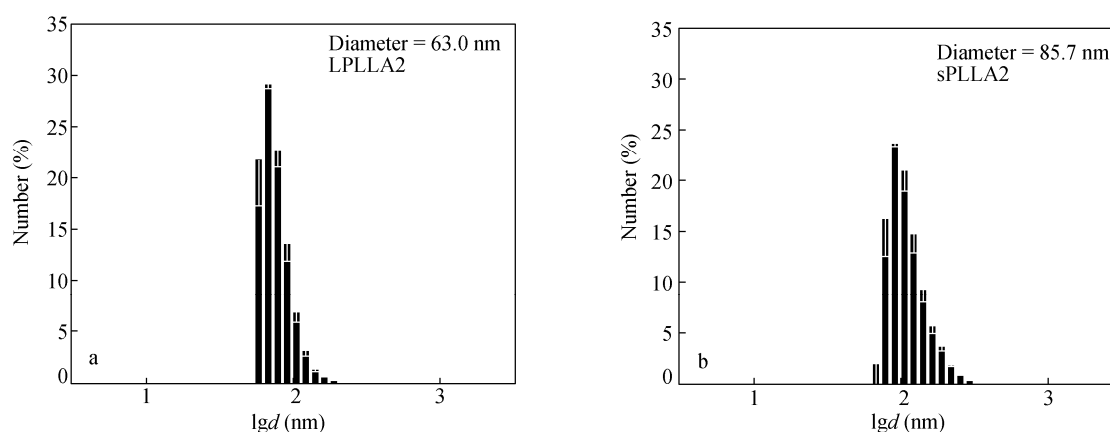


Fig. 7 Nanoparticle size distribution of LPLLA2 (a) and sPLLA2 (b) in aqueous solution
d: mean diameter

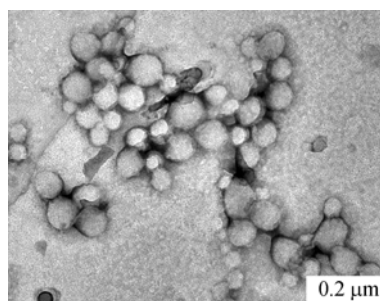


Fig. 8 TEM photographs of sPLLA2 nanoparticles

CONCLUSIONS

Star-shaped poly(L-lactide) with six arms (sPLLA) was successfully synthesized *via* the ring-opening polymerization of L-lactide using a commercial dipentaerythritol as an initiator and SnOct₂ as a catalyst in bulk at 125°C. The polymer molecular weight can be accurately predicted by the molar ratio of monomer to initiator, and the molecular weight distribution is very low; while the molar ratio of monomer to catalyst has no apparent influence on the polymer molecular weight. The maximal melting point, the crystallization temperature, and the degree of crystallinity of sPLLA polymers increase with the increasing molecular weight, and they are lower than those of the linear analogue. Moreover, the sPLLA polymers presented a spherulitic morphology with Maltese-cross patterns, and the average diameter of spherulites increases with the increasing crystallization temperature and time, respectively. Furthermore, spherical nanoparticles (less than 100 nm) could be easily generated by direct injection of sPLLA solutions into distilled water. Significantly, this will possibly establish a useful starting point to improve the physical properties of the linear PLLA analogues, but also to generate biodegradable nanoparticles with adjustable sizes for targeted drug release.

REFERENCES

- 1 McKee, M.G., Wilkes, G.L. and Long, T.E., *Prog. Polym. Sci.*, 2005, 30: 507
- 2 Södergard, A. and Stolt, M., *Prog. Polym. Sci.*, 2002, 27:1123
- 3 Sudesh, K., Abe, H. and Doi, Y., *Prog. Polym. Sci.*, 2000, 25: 1503
- 4 Dechy-Cabaret, O., Martin-Vaca, B. and Bourissou, D., *Chem. Rev.*, 2004, 104: 6147
- 5 Mecerreyes, D., Jerome, R. and Dubois, Ph., *Adv. Polym. Sci.*, 1999, 147: 1
- 6 Cai, Q., Zhao, Y.L., Bei, J. and Wang, S., *Biomacromolecules*, 2003, 4: 828
- 7 Kissel, T., Li, Y.X. and Unger, F., *Adv. Drug. Deliv. Rev.*, 2002, 54: 99
- 8 Tomalia, D.A., *Prog. Polym. Sci.*, 2005, 30: 294
- 9 Lee, C.C., Grayson, S.M. and Fréchet, J.M.J., *J. Polym. Sci. Polym. Chem.*, 2004, 42: 3563
- 10 Astruc, D. and Chardac, F., *Chem. Rev.*, 2001, 101: 2991
- 11 Trollsas, M. and Hedrick, J.L., *J. Am. Chem. Soc.*, 1998, 120: 4644
- 12 Atthoff, B., Trollsas, M., Claesson, H. and Hedrick, J.L., *Macromol. Chem. Phys.*, 1999, 200: 1333
- 13 Trollsas, M., Atthoff, B., Claesson, H. and Hedrick, J.L., *J. Polym. Sci. Polym. Chem.*, 2004, 42: 1174
- 14 Sanda, F., Sanada, H., Shibasaki, Y. and Endo, T., *Macromolecules*, 2002, 35: 680
- 15 Kricheldorf, H.R., Hachmann-Thiessen, H. and Schwarz, G., *Macromolecules*, 2004, 37: 6340
- 16 Zhao, Y.L., Cai, Q., Jiang, J., Shuai, X.T., Bei, J.Z., Chen, C.F. and Xi, F., *Polymer*, 2002, 43: 5818
- 17 Zhao, Y.L., Shuai, X.T., Chen, C.F. and Xi, F., *Chem. Mater.*, 2003, 15: 2836
- 18 Zhao, Y.L., Shuai, X.T., Chen, C.F. and Xi, F., *Chem. Comm.*, 2004, (14): 1608
- 19 Zhao, Y.L., Shuai, X.T., Chen, C.F. and Xi, F., *Macromolecules*, 2004, 37: 8854
- 20 Dong, C.M., Qiu, K.Y., Gu, Z.W. and Feng, X.D., *Macromolecules*, 2001, 34: 4691
- 21 Wang, J.L. and Dong, C.M., *Polymer*, 2006, 47: 3218
- 22 Wang, J.L. and Dong, C.M., *Macromol. Chem. Phys.*, 2006, 207: 554
- 23 Haag, R., *Angew. Chem. Int. Ed.*, 2004, 43: 278
- 24 Feng, H. and Dong, C.M., *Biomacromolecules*, 2006, 7: 3069
- 25 Teng, C.Q., Yang, K., Ji, P. and Yu, M.H., *J. Polym. Sci. Polym. Chem.*, 2004, 42: 5045