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Synthesis and characterization of star-shaped PLLA with sorbitol as core and its microspheres application in controlled drug release

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ABSTRACT: The purpose of this study was to investigate the suitability of a six-arm star-shaped poly(L-lactide)s (s-PLLA) as controlled drug carriers for hydrophobic drug molecules. First, s-PLLA was synthesized by ring-opening polymerization of L-lactide using sorbitol as initiator and stannous octoate as catalyst. The structure and molecular weight (M_w) of s-PLLA was characterized with ^{1}H NMR, ^{13}C NMR, and GPC. Second, rifampicin (RIF) used as a model drug was encapsulated within the microspheres of s-PLLA via oil-in-water emulsion/solvent evaporation technique. The morphology, drug encapsulation efficiency (EE), and *in vitro* release behavior of the prepared microspheres were studied in details. Results indicated that the average diameters of s-PLLA microspheres can be controlled between 8 and 20 μm by varying the copolymer's concentration or M_w. The EE of RIF was mainly determined by the concentration of s-PLLA. The *in vitro* study showed that the burst release behavior can be depressed by increasing the M_w of the s-PLLA. Present work suggests that the synthesized s-PLLA could be used as a new material for drug delivery. © 2015 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2015**, *132*, 42213.

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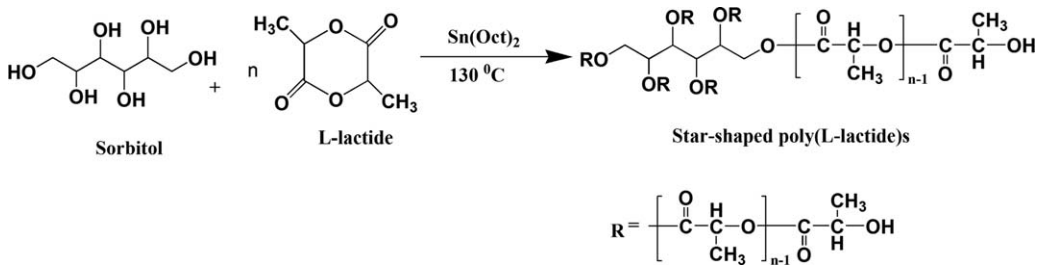
INTRODUCTION

Poly(L-lactide) (PLLA) is one of the commonly used drug-carrier matrices due to its safety and excellent physicochemical properties. As it is nontoxic, biocompatible and biodegradable, PLLA is an eco-friendly aliphatic polyester with better features for use in human body.[1–4] However, linear structure PLLA also has many obvious drawbacks when it confronted with the requirements for controlled drug delivery systems. On the one hand, its degradation through hydrolysis of the ester bonds is too slow, and this process sometimes takes several years,[5–7] which limits its biomedical application. One the other hand, its hydrophobicity coupled with the high crystallinity may elicit inflammatory reactions in the body.[8–10] To overcome these disadvantages, special attention has been paid to the modification of linear PLLA to match the requirements in drug delivery systems. The most common method involved was to copolymerize lactide monomer with functional monomers containing different molecular architectures and functionality (end or pendant group, such as carboxyl, amino, or thiol),[11,12] or to blend PLLA with other materials, such as poly(ethylene glycol) (PEG), poly(β-hydroxybutyrate) (PHB), chitosan.[6,13]

Star-shaped biodegradable polymers with multiple arms radiating from a single core molecule are the simplest branched materials, which have gained significant attention across multiple fields of chemistry, biochemistry and tissue engineering because they exhibit useful rheological, mechanical and biomedical properties that are inaccessible in linear polymers.[14–16] In the family of star-shaped biodegradable polymers, s-PLLA has played an important role in drug delivery because they exhibit significantly different physicochemical properties as compared to the linear counterparts with the similar molecular weight.[17,18] First, s-PLLA molecules have smaller hydrodynamic volume and radius of gyration in solution compared with the linear structures, which means that they are not easily stranded in blood and can ensure the bioavailability of the drugs encapsulated in them.[19] Second, s-PLLA provide more terminal functional groups that are capable of connecting with target molecules.[20] The physicochemical properties of the s-PLLA can be tuned by varying the chemical structure of core or adjusting the arm length by the mole ratio of core and lactide.[21,22]

The s-PLLA has showed a tremendous application as a drug carrier and is easily synthesized by the ring-opening polymerization (ROP) of lactide in the presence of multifunctional initiators containing hydroxyl or amine groups.[23] Until now, most of the cores of PLLA reported in literatures were small molecules containing multiple hydroxyl functionalities, such as



Scheme 1. Schematic diagram of the synthesis of s-PLLA.

pentaerythritol,[24] trimethylol propane,[25] epoxidized soybean oil,[26] castor oil,[20] dipentaerythritol,[27] dendritic polyols,[28] and so forth. Ouyang *et al.*[29] have synthesized an four-arm star-shaped poly(lactide-*co*-glycolide) (PLGA) by the ROP of glycolide and D, L-lactide with pentaerythritol as the initiator, and followed BSA-loaded PLGA microspheres were prepared through double emulsion/solvent evaporation method. The release experimental results proved that the prepared microspheres are feasible to control the release of BSA. Baimark *et al.*[21] have studied the influence of molecular architectures (arm number and arm length) of star-shaped poly(D,L-lactide)s (PDLLs) on the behaviors of ibuprofen-loaded and drug release. They found that the drug release behavior can be controlled through both the branch arm number and arm length of the star-shaped PDLLs. However, the polyols utilized such as pentaerythritol, dipentaerythritol and dendritic polyols were nonbiodegradable.[30] The employment of these non-bioabsorbable residual compounds may be toxic after PLLA degradation, especially for the controlled drug release delivery carriers.

In present work, a biodegradable polyols sorbitol was used as the initiator to synthesis s-PLLA. Sorbitol is naturally found in many fruits, such as berries, cherries, plums, pears, and apples. It is noncarcinogenic and noncaloric, and cannot be fermented by the bacteria causing dental caries neither. Therefore, sorbitol has applications in a wide range of food products and pharmaceutical products.[31,32] In this work, s-PLLA is firstly synthesized by ring-opening polymerization of L-lactide in the presence of sorbitol as initiator, and rifampicin (RIF), as a model drug, is encapsulated into the s-PLLA microspheres via emulsion/solvent evaporation technique. Furthermore, RIF encapsulation efficiency and the vitro release behavior are investigated in details.

EXPERIMENTAL

Materials

Sorbitol ($C_6H_{14}O_6$), L-(+)-lactic acid (90%), rifampicin (RIF), and poly(vinyl alcohol) (PVA; average M_w 30,000-70,000; 96–98% hydrolyzed) were purchased from Aladdin Industrial Inc. (Shanghai, China). L-lactide monomer was prepared from L-lactic acid using the method of thermo-cracking.[33] Toluene was purified by distillation method, using metallic sodium and benzophenone as separation agents. All other agents were purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China) and used as received.

Methods

Synthesis of s-PLLA Copolymer. s-PLLA was synthesized by ROP of L-lactide as described in the literature with slightly modified.[34] Sorbitol and stannous octoate [$Sn(Oct)_2$] were utilized as initiator and catalyst, respectively. The reaction scheme for synthesis of s-PLLA was showed in Scheme 1, and the formulations were listed in Table I. In brief, as a typical example, L-lactide (5.011 g, 34.7 mmol), sorbitol (0.0904 g, 0.49 mmol), and $Sn(Oct)_2$ (0.0428 g in distilled toluene, 0.3 mol % of total monomers) were added into a glass tube, which was sealed after three-times exhausting-refilling with argon process. The reaction was engaged by placing the sealed tube into an oil bath of 130°C for 48 h. After cooling to room temperature, the sealed tube was broken, and the reaction product was dissolved in dichloromethane (DCM) and then precipitated in excess cold methanol to remove the unreacted L-lactide. The final product was collected by filtration and dried in vacuum oven at 40°C for 48 h.

Characterization of s-PLLA Copolymer. Nuclear magnetic resonance (NMR) spectrometry (Bruker AV 400) was used to characterize the structure of synthesized s-PLLA with $CDCl_3$ as solvent. The molecular weight and molecular weight distribution was determined by gel permeation chromatography (GPC, Waters 410 system, USA). The data were calibrated against polystyrene standard with tetrahydrofuran as eluent at a flow rate of 1 mL min^{-1}.

Preparation of RIF-Loaded Microspheres. Oil-in-water (O/W) single emulsion/solvent evaporation method was used to prepare the RIF-loaded s-PLLA microspheres.[35] In brief, a pre-weighed amount RIF powders and 1 g s-PLLA were dissolved into 10 mL DCM. Then the DCM solution was dropwise added into 200 mL aqueous solution (including 2.5% PVA w/v) under stirring to form O/W emulsion. To evaporate DCM and solidify the microspheres, the resulting emulsion was stirred uncovered overnight at room temperature. The obtained microspheres were collected by centrifugation at 4000 rpm for 10 min and washed with deionized water to remove the PVA and

Table I. Recipes and Characterization Data of s-PLLA Samples

Run[a]	LLA/SB[b]	LLA/SB[c]	M_n(g/mol)[d]	M_w(g/mol)[d]	PDI[d]
s-PLLA70	70/1	80/1	16,908	22,458	1.33
s-PLLA100	100/1	110/1	23,432	32,769	1.40
s-PLLA200	200/1	203/1	37,075	53,704	1.45

[a] $Sn(Oct)_2$ 0.3 mol % to total monomers and dissolved in 350 μL toluene.
[b] Feed mole ratio of monomers
[c] Polymer mole ratio determined by ^1H NMR
[d] Determined with GPC using the following calibration standard: polystyrene for s-PLLA (solvent: THF).

Table II. Characteristics of RIF-loaded s-PLLA Microspheres ($n = 3$)

Run	Sample	Polymer conc. in DCM (%, w/v)	Average diameter (μm)	Actual RIF loading (%)	Encapsulation efficiency (%)
F1	s-PLLA70	5	8.8 ± 5	2.2 ± 0.01	13.2 ± 0.24
F2	s-PLLA70	10	14.8 ± 8	6.7 ± 0.13	40.1 ± 4.56
F3	s-PLLA70	15	20.2 ± 6	8.6 ± 0.06	51.5 ± 2.16
F4	s-PLLA100	10	15.3 ± 2	7.5 ± 0.04	44.7 ± 1.52
F5	s-PLLA200	10	19.4 ± 4	6.7 ± 0.13	37.6 ± 3.56

unencapsulated RIF. Finally, the obtained microspheres were dried in vacuum oven at 30°C for 48 h. The drug-free microspheres were prepared in the same manner.

Characterization. The morphology of the prepared RIF-loaded microspheres was investigated by scanning electron microscopy (SEM, S-4800, Hitachi, Japan). X-ray diffraction (XRD) patterns of s-PLLA powder and RIF-loaded microspheres were recorded on an X-ray diffractometer (XD-3, Beijing purkinje general instrument Co., Ltd.). The average diameter and size distribution of RIF-loaded microspheres were measured by static light scattering particle size analyzer (Microtrac Instrument, S3500, USA).

To determine the amount of RIF encapsulated within the s-PLLA microspheres, ~2.5 mg of RIF-loaded microspheres was weighted and dissolved into 10 mL of N, N-dimethyl formamide (DMF) in a screw-top test tube with a Teflon-coated Cap. Then RIF loading contents (LC) were determined at 340 nm using a UV-spectrophotometer (UV-1800, Shimadzu, Japan) assay with a RIF calibration curve (4–32 μg mL^{-1} concentration range in DMF). The linear calibration curve ($y = 0.03561x + 0.00192$; $R^2 = 0.9999$). The encapsulation efficiency (EE %) of RIF was calculated as the percent ratio of the determined loading to the theoretical loading that should be obtained in case of a 100% encapsulation efficiency. The LC and EE of the RIF-loaded microspheres were calculated by the following equations, each batch was performed in triplicate and the results of LC and EE are expressed as a mean ± standard deviation.[36]

$$\mathrm{LC}(\%) = \frac{\text{Weight of RIF in the microspheres}}{\text{Weight of the microspheres}} \times 100\% \quad (1)$$

$$\mathrm{EE}(\%) = \frac{\text{Weight of RIF in the microspheres}}{\text{Weight of the feeding RIF}} \times 100\% \quad (2)$$

***In Vitro* Drug Release.** An amount of RIF-loaded microspheres corresponding to 2 mg RIF was dispersed in 5 mL of a release medium consisting of phosphate buffer saline (PBS, pH = 7.4) in screw-top test tubes with a Teflon-coated Cap. Then the RIF-loaded microspheres dispersion was immersed in a shaker bath with a constant temperature of 37°C and was shaken horizontally with a rate of 100 rpm. At predetermined time intervals, release tubes were removed and was centrifuged at 4000 rpm for 10 min to sediment the microspheres, and 5 mL of the supernatant was withdrawn for UV analysis and the amount of RIF released was calculated from the result of UV absorption measurement of the sample at 335 nm using a calibration curve prepared in PBS ($y = -0.00377 + 0.02636x$; $R^2 = 0.9995$; standard solution 0.36–40 μg mL^{-1}). The remaining media was removed and replaced with fresh PBS to maintain sink conditions.[37] All release experiments were performed as triplicates. The solubility of RIF is 4.13×10^{-2} g L^{-1}, and no point did the concentration of either RIF reach these limits during this measurement of the RIF release from the s-PLLA microspheres.

RESULTS AND DISCUSSION

Synthesis and Characterization of s-PLLA Copolymer

Ring-opening polymerization (ROP) is the most commonly route to prepare PLLA with high molecular weight. Initiators containing multiple hydroxyls can be used to control the architectures of copolymer, such as dendrimer, hyperbranched polymer, and star-shaped structure.[14] In this study, s-PLLA was synthesized via ROP of L-lactide and the multifunctional initiator sorbitol with $Sn(Oct)_2$ as the catalyst in bulk at 130°C (Scheme 1).

Figure 1 shows the ^{1}H NMR and ^{13}C NMR spectra of the synthesized s-PLLA. For sorbitol functionalized s-PLLA, typical signals from the L-lactide repeating units can be observed. The a ($\sigma = 1.59$ ppm L-lactide repeating unit: –CHC**H**3), b ($\sigma = 5.16$ ppm L-lactide repeating unit: –C**H**CH_3), d and e ($\sigma = 4.28$-4.44 ppm, –C**H**$_2$C**H** in the sorbitol), f ($\sigma = 2.7$ ppm) could be an –O**H** group, due to its relative mobility (2.7- 3.5 ppm). Similar results were reported in the open literatures.[17,34] In the ^{13}C NMR spectrum, the chemical shifts a ($\sigma = 16.4$ and 16.8 ppm) were assigned to –**C**H_3, b ($\sigma = 68.8$ and 69.2 ppm) were assigned to the –**C**H–, and c ($\sigma = 169.4$ and 169.8 ppm) were assigned to the –**C**O– Peaks d ($\sigma = 66.6$ ppm) and e ($\sigma = 20.6$ ppm) were assigned to the –**C**H– and –**C**H_2 in the sorbitol and f belongs to the solvent $CDCl_3$, which was similar with literature report.[17] The result confirmed that the s-PLLA was preliminary prepared by the multifunctional initiator sorbitol and L-lactide. The composition calculated from ^{1}H NMR fits well with the monomer actual feed mole ratio (Table I). Table I shows that, as anticipated, the molecular weight of the s-PLLA increased with the increasing of the feed mole ratio of L-lactide to sorbitol. Combining the GPC results and the NMR spectrum of the polymer, it could be inferred that the six-armed s-PLLA has been successfully synthesized.

Preparation and Characterization of RIF-Loaded Microspheres

An oil-in-water (O/W) single emulsion/solvent evaporation method, using DCM as a suitable solvent, was used to fabricate

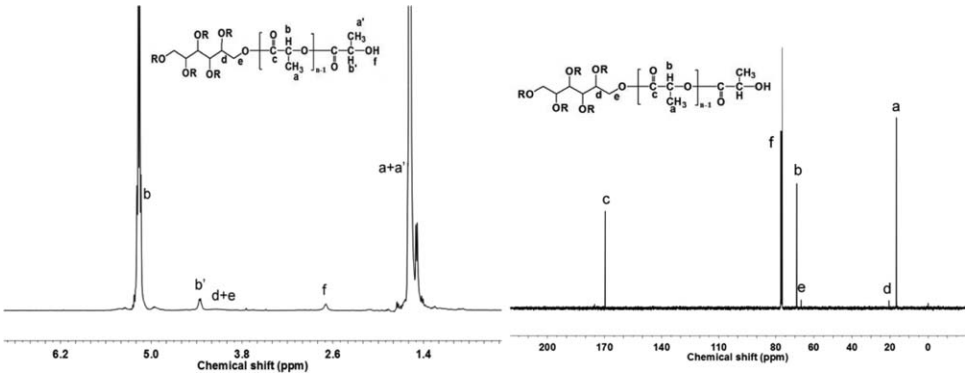


Figure 1. ^{1}H NMR and ^{13}C NMR spectrum of s-PLLA70 (L-lactide/sorbitol =70/1 mole ratio).

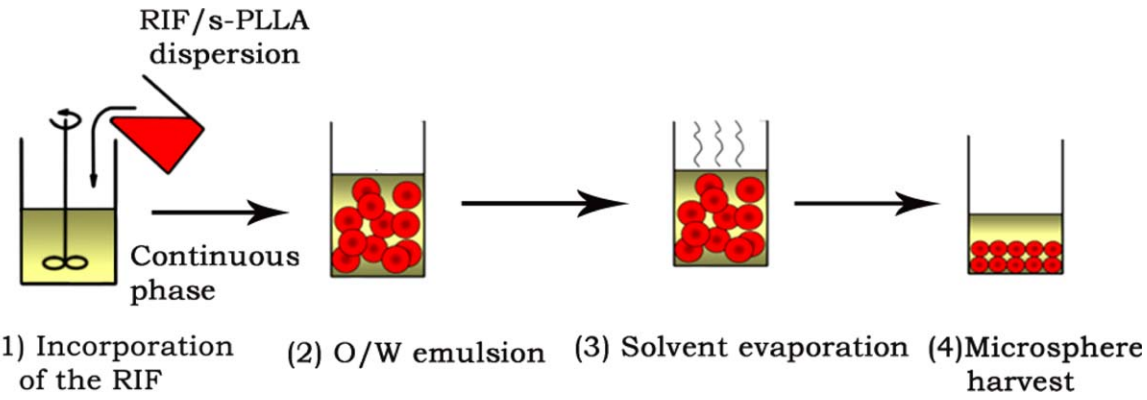
RIF-loaded microspheres, which was a mild, facile and energy-saving pathway for hydrophobic drug encapsulation.[38] The schematic illustration of the fabrication process of RIF-loaded microspheres is shown in Scheme 2. The characteristics of the obtained RIF-loaded microspheres were summarized in Table.

The average diameters of the RIF-loaded microspheres increased from 8.8 to 20.2 μm with increasing the s-PLLA70 concentration in DCM from 5 to 15 wt % (compare F1, F2, and F3). Meanwhile, with the increasing of s-PLLA M_w (s-PLLA70< s-PLLA100< s-PLLA200), the mean diameters of the RIF-loaded microspheres increased from 14.8, 15.3, to 19.4 μm, respectively. The morphology of RIF-loaded microspheres prepared with different formulations was characterized by SEM and showed in Figure 2(A). All of the microspheres were spherical in shape with a smooth surface. Figure 2(B) shows the size distribution of drug-loaded microspheres obtained from the static light scattering particle size analyzer. With the increasing of s-PLLA concentration (F2 and F3) or M_w (F4 and F5), the peak broaden slightly. A higher viscosity of the oil phase (due to higher polymer concentration or M_w) results in a reduction of the stirring efficiency in the same input power of stirring, and multiple-dispersed droplets and consequent microspheres are obtained, which is consistent with the literatures.[38–40]

With the increase of s-PLLA70 concentration from 5, 10, to 15 wt %, the drug encapsulation efficiency (EE) was enhanced from 13.2, 40.1, to 51.5 wt %, respectively. The enhanced EE was attributed to the higher viscosity of oil droplets with increase of s-PLLA70 content, which provided an effective barrier against RIF into aqueous phase.[41–43] However, the EE of formulations with varied molecular weight s-PLLA (F2, F4, and F5 formulations) was similar and was about 40 wt %, which indicated that there was not significant relationship between the EE and the polymer molecular weight.

X-ray Powder Diffraction

The X-ray powder diffraction diagram is shown in Figure 3. The s-PLLA powder exhibited two diffraction peaks [Figure 3(A)]. One at $2\theta = 16.7°$ was corresponding to the (200) and (110) reflection and another at $2\theta = 19.3°$ was corresponding to the 023 reflection, which was coincided with the literature.[44] The XRD patterns of the raw material RIF exhibited sharp peaks and indicated its crystalline state [Figure 3(B)]. In contrast, the absence of peaks in the XRD patterns of the blank microspheres and RIF-loaded microspheres indicated that the crystallinity of s-PLLA and RIF [Figure 3(C,D) had been changed from crystal form to amorphous form during the encapsulation process. The transformation might be due to the impediment effect each other during the s-PLLA and RIF



Scheme 2. Schematic illustration of the fabrication process of RIF-loaded microspheres. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

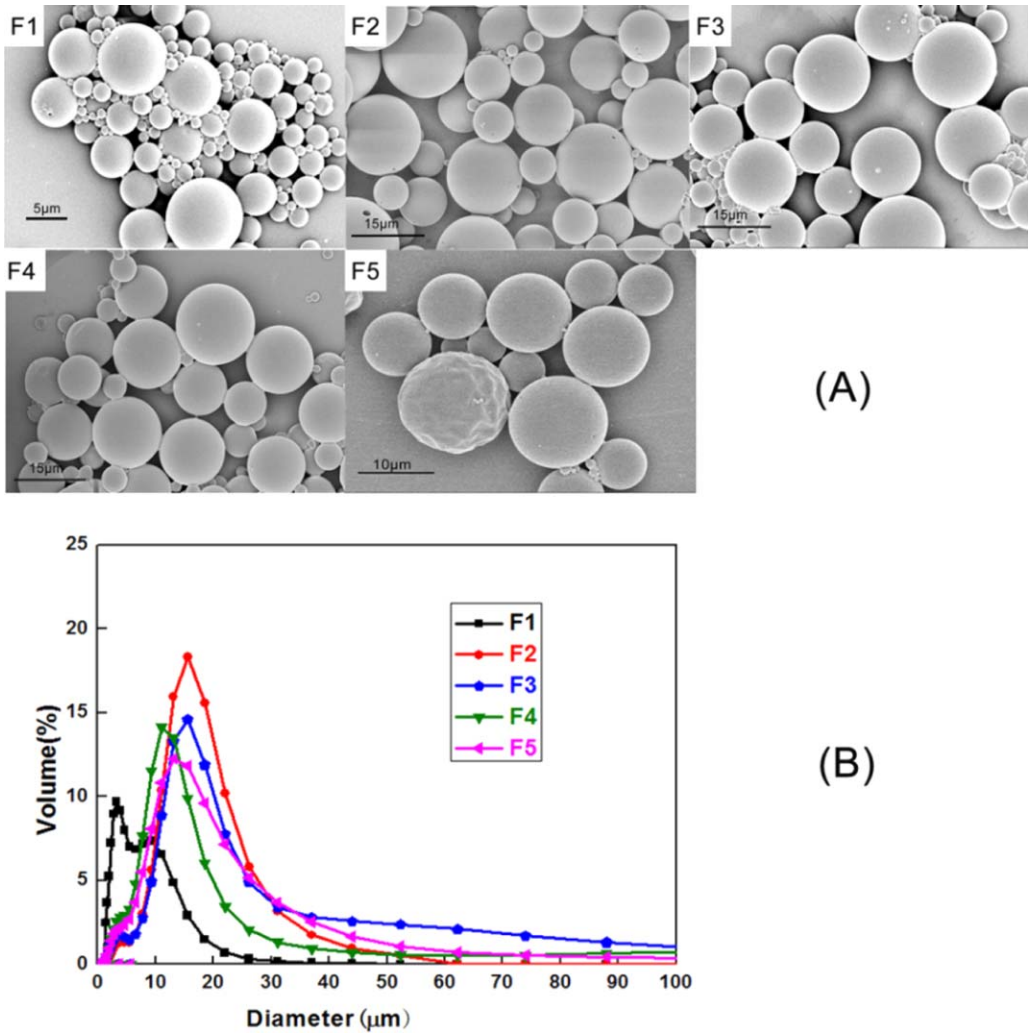


Figure 2. SEM morphology (A) and size distribution of (B) of run F1, F2, F3, F4, and F5 RIF-loaded microspheres. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

crystallization process. The similar phenomena could also be found in the study of clonidin-loaded PLGA microspheres[39] and azithromycin-loaded PLGA or PLLA microspheres.[45]

In Vitro Drug Release

A variety of reports can be found in the open literature dealing with RIF-loaded PLGA microspheres, which described in detail the experimental variables associated with the influence of them on the performance of the microspheres as drug carriers. In spite of this, to the best of our knowledge, the release time of entrapped RIF from PLGA (M_w=5000–20,000 g mol^{-1}) could sustain over 20 to 60 days, and the burst release were difficult to tailor.[46–48] So for drug delivery systems it is necessary to carefully adjust the drug release rate and burst release. Figure 4 shows the *in vitro* release profiles of RIF-loaded s-PLLA microspheres obtained from the different formulations. The overall trend of the release behavior is similar and shows a biphasic release, (i) a burst release in the initial 12 h, and (ii) followed a slow linear release over 10 days. The burst effect is normally attributed to the included drug near the surface, which is preferred to diffuse into water.[43] Microspheres made with 15 wt %

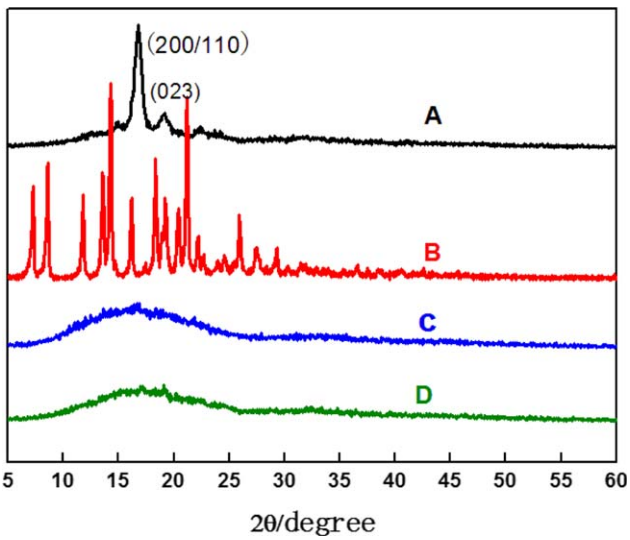


Figure 3. X-ray powder diffraction patterns of (A) s-PLLA70 powder, (B) raw RIF, (C) s-PLLA70 microsphere, and (D) RIF-loaded microspheres (F2). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

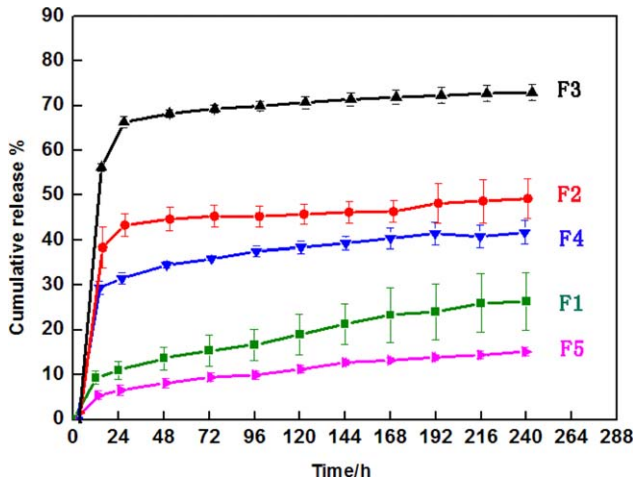


Figure 4. *In vitro* RIF release profiles from the different formulations studied ($n = 3$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

polymer solution in DCM (F3), showed a highest burst release (> 50 wt %) and the final released RIF can reach 70 wt % over the next 10 days. Decreasing the polymer concentration from 10 wt % (F2) to 5 wt % (F1), the initial burst amount of RIF decreased from 38 to 9 wt %. The burst release amount was dependent on the total loaded RIF amount, and the drug was inclined to accumulate on the surface or near the surface of the microspheres at a high drug loading level.[41] In comparison with F2, F4, and F5, the results indicated that the release of RIF from s-PLLA microspheres was also affected by the polymer molecular weight. With increasing the molecular weight from s-PLLA70 (M_w 22,458 g mol^{-1}), s-PLLA100 (M_w 32,769 g mol^{-1}), to s-PLLA200 (M_w 53,704 g mol^{-1}), the burst release can decrease from 56, 28, to 5 wt %, respectively. This might at least partially be attributed to an increased polymer-polymer entanglement degree at high M_w, and denser networks could be formed during the encapsulation process and reduced drug mobility.[39]

CONCLUSIONS

Star-shaped aliphatic polyester, s-PLLA has been successfully prepared via ROP reaction by L-lactide and sorbitol with $Sn(Oct)_2$ as the catalyst in bulk. The molecular weight is well and easily controlled by varying the mole ratio of L-lactide and sorbitol. Micrometer-sized RIF-loaded s-PLLA microspheres were obtained by using O/W emulsion/solvent evaporation technique. With the increasing of s-PLLA concentration or molecular weight, the average diameters can be controlled between 8 and 20 μm. The drug encapsulation efficiency was mainly determined by the polymer's concentration. And the in vitro release behavior indicated that the burst release can be depressed with higher s-PLLA molecular weight. The present study shows that the synthesized s-PLLA has potential use for sustained hydrophobic drug release system. Further studies to check the stability, toxicity, and the correlation of the *in vitro-in vivo* release profiles of RIF-loaded microspheres are going on.

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