Polym. Bull. (2011) 67:793–803
DOI 10.1007/s00289-010-0420-9

ORIGINAL PAPER

Preparation and characterization of the molecular weight controllable poly(lactide-*co*-glycolide)

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Received: 5 July 2010 / Accepted: 5 December 2010 / Published online: 22 December 2010
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Abstract A series of poly(D,L-lactide-*co*-glycolide) (PLGA) polymers with various molecular weight were synthesized by a ring-opening polymerization method using stannous 2-ethyl hexanoate ($Sn(Oct)_2$) as the catalyst. The molecular weight of these polymers was controlled in a novel way, using *t*-butyldimethylsilanol (TBDS) or triphenylsilanol (TPS). The silicon-end group attached to the PLGA copolymer was removed at room temperature using either hydrochloric acid (HCl) or trifluoroacetic acid (TFA). The structures of these polymers before and after end group removal were characterized by ^{1}HNMR spectroscopy, while the molecular weight and polydispersity index (PDI) were determined by viscosity method and gel permeation chromatography (GPC). The residual amounts of stannum in PLGA and the glass transition temperature (T_g) of copolymer before and after end group removal were determined by the atomic absorption spectrum (AAS) and differential scanning calorimetry (DSC), respectively. The results showed that the removal method was effective. This study demonstrated that the molecular weight of PLGA could be easily controlled by altering the monomers/silanol molar ratio and the molecular weight and the purity of PLGA copolymer materials after silicon-end group removal could meet the demand of drug release.

Keywords PLGA · *t*-Butyldimethylsilanol · Triphenylsilanol · Molecular weight controllable · Silicon-end group removal · Drug controlled release

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Introduction

In the research area of controlled release for drug delivery, recent focus has been on the materials used for drug coating [1–10], especially research on the drug delivery carrier prepared from biodegradable polymers. Biodegradable delivery refers to dosages of drug delivery, degradation rates, and release rates of the loaded drugs could be regulated by selecting different coating materials with the different molecular weights and compositions [11, 12].

PLGA [4–7, 13–16] exhibits excellent properties such as biocompatibility, biodegradability, and an adjustable degradation rate and hence has been widely utilized in controlled release drug delivery systems. The selection of PLGA with desired composition and molecular weight becomes critical in the research and formulation of controlled release drug delivery systems because of the important role these properties play in drug delivery applications. The composition of PLGA can be determined by controlling the feed ratio of the monomers; however, control of the molecular weight of PLGA requires extra effort.

Generally, PLGA is prepared by ring-open polymerization of lactide and glycolide using stannous 2-ethyl hexanoate ($Sn(Oct)_2$) as the catalyst. The coordination-insertion mechanism is generally acknowledged [17, 18]: $Sn(Oct)_2$ possesses the catalytic activity because Sn has an empty sp^3d^2 orbit. Trace impurities containing hydroxyl groups as the initiator (such as alcohol or water) coordinate with Sn to form the tin alkoxide. The tin alkoxide then coordinates with lactide/glycolide to push the polarization of the carbonyl group and reacts further with alcohol. Mechanism of PLGA prepared was shown in Fig. 1.

As described above, the hydroxyl-contained compounds play a predominant role in ring-opening polymerization of PLGA. The amount of the hydroxyl-contained compounds within a certain range affects the molecular weight of PLGA. Several types of the hydroxyl-containing compounds, such as 1-dodecanol, glycerol and 1, 4-butanediol, are used for controlling the molecular weight of PLGA [19]; however, these compounds affect not only the molecular weight of the resulting polymers, but also the physical properties. In addition, the introduction of these compounds in

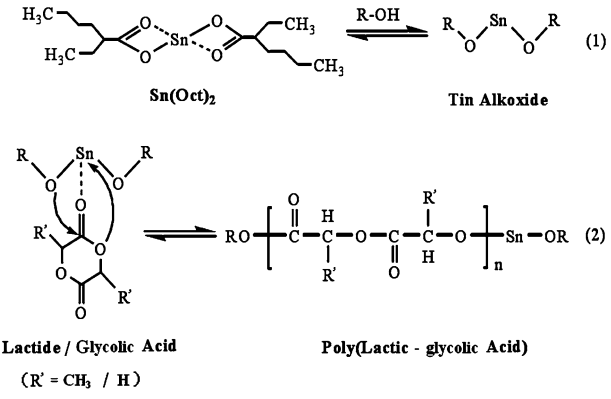

Fig. 1 Mechanism of PLGA prepared by $Sn(Oct)_2$ as catalyst

PLGA means the introduction of the impurities, which influence the safety aspects of the PLGA used as the drug carrier in the controlled release systems could lead to unpredictable effects. Ideally, the hydroxyl-contained compounds could be removed under mild conditions after the polymerization reaction without affecting the molecular weight and the physical properties of the PLGA.

A low boiling point hydroxyl-containing compound could not be used in the ring-opening polymerization of PLGA because the reaction is carried out under high vacuum condition. We therefore chose some high boiling point hydroxyl-containing compounds to use as the initiators and to regulate the molecular weight of PLGA. In this paper, PLGA has been prepared via the ring-opening melting polymerization of D,L-lactide and glycolide, using *t*-butyldimethylsilanol (TBDS) or triphenylsilanol (TPS) as the molecular weight regulator and $Sn(Oct)_2$ as a catalyst. The molecular weight of PLGA could be controlled by the silanol selection. The silicon-end group attached on the PLGA copolymer was removed at room temperature using dilute hydrochloric acid (HCl) or trifluoroacetic acid (TFA).

Experimental

Materials

Glycolide (mp 83.5–84.5 °C) and D,L-lactide (mp 126.5–127.5 °C) were purchased from Beijing Yuan-Sheng Rong Technology Co., LTD (China). *t*-Butyldimethylsilanol (TBDS) (bp 139.0–139.5 °C) was prepared by hydrolysis of *t*-butyldimethylchlorosilane (Henan Yu-Chen Fine Chemical Co., LTD, China) in our laboratory [20]. Triphenylsilanol (TPS) (mp 150–153 °C) and trimethylchlorosilane were purchased from the J&K. Trifluoroacetic acid (TFA) and pyridine were purchased from the Tianjin Chemical Reagents Sixth Factory (China). HCl was purchased from the Beijing Organic Chemical Plant (China). $Sn(Oct)_2$ (Sigma 95%) was diluted to desired concentration (1 g/mL) with CH_2Cl_2. CH_2Cl_2 and CH_3OH were distilled after treatment with anhydrous $MgSO_4$. All chemicals were analytical grade.

Instruments

The measurements of the ^{1}HNMR spectra were performed on a VARIAN UNITY plus 400 MHz NMR spectrometer (Varian, USA) with $CDCl_3$ as the solvent. The intrinsic viscosity ($[\eta]$) of PLGA was determined at 25 °C with an Ubbelohde viscometer ($\Phi = 0.45$ μm) with THF as the solvent. The corresponding viscosity-average molecular weight (M_η) was calculated according to the formula [21] ($[\eta] = 1.07 \times 10^{-4} M_\eta^{0.761}$). The weight-average molecular weight (M_w) and PDI of the copolymers were determined with a Waters 510 gel permeation chromatography with HPLC grade THF as the solvent and polystyrene as the standard. Specimen concentrations were 2.5–5 mg/mL, and the flow rate was 1 mL/min at 30 °C. Differential scanning calorimetry (DSC) was performed on the NETZSCH differential scanning calorimetry with 2–3 mg sample. DSC scans were carried out over the temperature range from 0 to +80 °C at a heating rate of 5 °C/min, kept

down the data. The measurements of the Atomic Absorption Spectrum (AAS) were performed on a 180-80 Polarized Zeeman Atomic Absorption Spectrophotometer (HITACHI, Japan).

Preparation of PLGA copolymer

D,L-Lactide, glycolide, the molecular weight regulator (TBDS or TPS) and $Sn(Oct)_2$ in CH_2Cl_2 were mixed and kept in a silanized polymerization glass tube with a solution of trimethylchlorosilane/pyridine (15%, V/V), which was connected to a vacuum system. An exhausting–refilling process with high purity nitrogen was repeated three times and the mixture kept vacuum (20–30 Pa) about 30 min. The tube was sealed and reacted at 160 °C for 10 h. The resulting product was dissolved in CH_2Cl_2 and precipitated with CH_3OH. The purified copolymer was dried in a vacuum oven at 40 °C for 48 h. The ratio of materials used is listed in Table 1.

Removal of silicon-end group from PLGA

A 0.50–1.00 g amount of PLGA sample, 8 mL CH_2Cl_2 and 8 mL HCl (or TFA) were mixed in 100 mL flask, reacted at room temperature with intense electromagnetic stirring (Table 1). The specific removal conditions used are listed in Table 3. After reaction, the product in the oil phase was separated and precipitated with CH_3OH. The product was vacuum-dried at 40 °C for 48 h. Scheme of removal of the end group attached on the PLGA by acid was shown in Fig. 2.

Results and discussion

The ^{1}HNMR results of PLGA before and after removal

The ^{1}HNMR of 1-PLGA-50/1 with TBDS-end group before and after removal are shown in Fig. 3a, b, respectively. As can be seen from these figures, the chemical shift at $\delta = 1.56$, 4.82, and 5.21 ppm were assigned to the protons of Hc (–CH_3),

Table 1 The materials proportion of preparing PLGA

Copolymer	Lactide/glycolide (mol/mol)	Monomers/silanol (mol/mol)	Monomers/catalyst (mol/mol)
1-PLGA-50/1	3:1	50:1	10,000:1
1-PLGA-100/1	3:1	100:1	10,000:1
1-PLGA-200/1	3:1	200:1	10,000:1
2-PLGA-50/1	3:1	50:1	10,000:1
2-PLGA-100/1	3:1	100:1	10,000:1
2-PLGA-200/1	3:1	200:1	10,000:1
2-PLGA-400/1	3:1	400:1	10,000:1
2-PLGA-800/1	3:1	800:1	10,000:1

1-PLGA TBDS as initiator, *2-PLGA* TPS as initiator

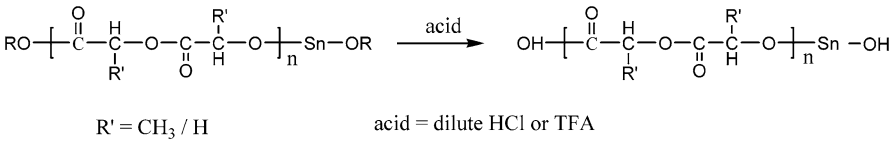

Fig. 2 Scheme of removal of the end group attached on the PLGA by acid

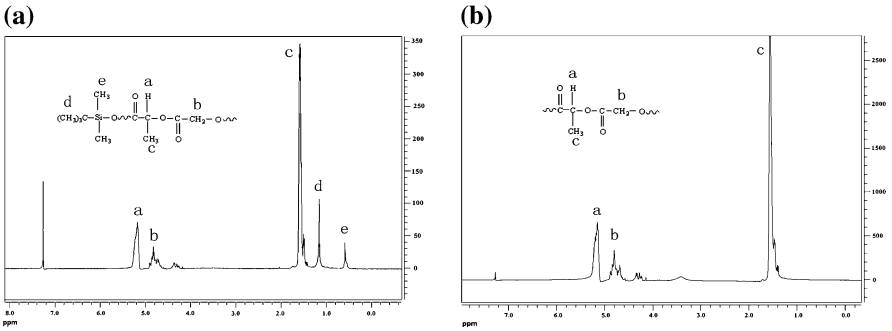

Fig. 3 The ^{1}HNMR of 1-PLGA-50/1: **a** containing the TBDS-end group and **b** the TBDS-end group was removed by HCl

Hb ($-CH_2$), Ha (–CH) in the PLGA, respectively [22]. Figure 3a, b presented that the chemical shift at about $\delta = 0.54$, 1.15 ppm corresponding to the protons of He and Hd in the TBDS completely disappeared after removal reaction, which confirmed synthesis of 1-PLGA-50/1 and the TBDS-end group was successfully cleaved from the copolymer by acid.

The ^{1}HNMR of 2-PLGA-50/1 with TPS-end group before and after removal are shown in Fig. 4a, b, respectively. The chemical shift about at $\delta = 7.37$–7.46, $\delta = 7.61$–7.66 ppm corresponds to the protons of TPS. Similar results were obtained as in Fig. 3a, b, which also confirmed synthesis of 2-PLGA-50/1 and that the TPS-end group was successfully removed from copolymer.

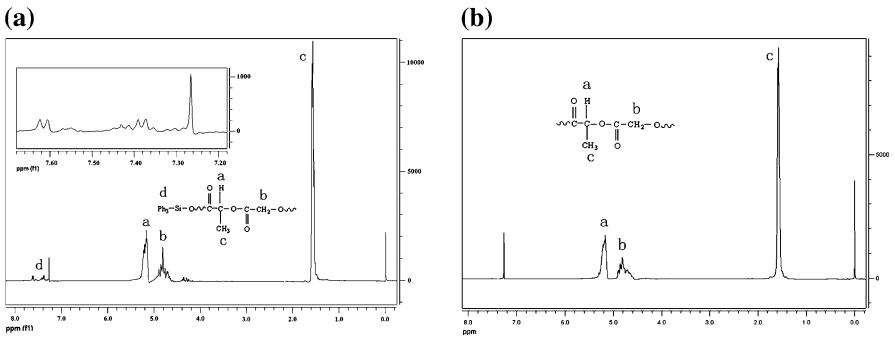

Fig. 4 The ^{1}HNMR of 2-PLGA-50/1: **a** containing the TPS-end group and **b** the TPS-end group was removed by HCl

The effect of adding molecular weight regulator on the molecular weights of PLGA

Molecular weights of PLGA, as determined by viscosity methods and GPC, are shown in Table 2. Table 2 indicated that the both results were changed regularly almost at the same proportion. For 1-PLGA-50/1, the M_n and M_η were 7,342 and 8,537, respectively, and the PDI was 1.24. While, the M_n and M_η of the 1-PLGA-100/1 which prepared by less silanol were accelerated at the same time and they were 12,054 and 13,794, respectively, and the PDI was 1.23. Besides, the change trend in the percent yield of copolymer was as same as the change of PLGA M_n. It shows that when the proportion of monomer/catalyst was fixed at certain reaction condition, greater silanol addition led to lower M_n 1-PLGA and yield. Similar results are shown in Table 2 when the molar ratio of monomers/TPS was 50/1–400/1. When the molar ratio of monomers/TPS exceeded 400/1, the 2-PLGA M_n and yield were also relatively low; because the ring-opening polymerization is a chain-polymerization process, when the ratio of monomers/silanol was too high, the active hydroxyl groups were too many preventing a high PLGA M_n. When the ratio of monomers/TPS was too low, the active sites were few, making it difficult for full monomer polymerization to occur, resulting again in a low PLGA M_n. The M_n of PLGA prepared was 7,000–33,000 Da and PDI were rather narrow varying from 1.20 to 1.25, which could meet the requirements as a drug release materials [23].

The residual amounts of stannum in PLGA before and after end group removal

The residual amounts of stannum in PLGA before and after end group removal are shown in Table 3. It was found that the residual amounts of stannum in PLGA (1-PLGA or 2-PLGA) after end group removal were remarkably decreased compared to the amounts before removal. For the copolymer 1-PLGA-100/1, the residual amounts of stannum in PLGA before end group removal was 0.00347%, however, when the silicon-end group attached to the copolymer was removed by 2 M HCl for 24 h, the residual amounts of stannum in PLGA was decreased significantly to as low as 0.000116%; it was further observed that its value was

Table 2 The results of the molecular weight of PLGA

Copolymer	M_η (viscosity method)	M_n (GPC)	M_W/M_n (GPC)	Yield (%)
1-PLGA-50/1	8,537	7,342	1.24	70.71
1-PLGA-100/1	13,794	12,054	1.23	72.16
1-PLGA-200/1	20,364	18,629	1.25	77.00
2-PLGA-50/1	8,729	7,387	1.22	72.28
2-PLGA-100/1	13,063	12,843	1.22	76.02
2-PLGA-200/1	21,885	20,175	1.24	77.56
2-PLGA-400/1	34,957	32,947	1.25	78.96
2-PLGA-800/1	27,428	25,643	1.20	78.40

Table 3 The residual amounts of stannum in PLGA before and after end group removal

Copolymer	The residual amounts of stannum before removal (%)	The removal condition Reagent/reaction time	The residual amounts of stannum after removal (%)
1-PLGA-100/1	0.00347	2 M HCl	0.000116
		24 h	
		2 M HCl	0.000094
		27 h	
2-PLGA-100/1	0.00234	3 M HCl	0.000079
		18 h	
2-PLGA-800/1	0.00326	3 M HCl	0.000039
		33 h	

decreased to 0.000094% when the reaction time was 27 h. It indicated that similar results were obtained from the other copolymers in Table 3. These results demonstrated that the removal methods which were in favor of the use of PLGA as carrier for drug delivery were very effective.

DSC analysis

The glass transition temperature (T_g) of 3-PLGA, 1-PLGA-50/1, and 2-PLGA-50/1 before and after end group removal were shown in Table 4. From Table 4, it was seen that, the T_g of 1-PLGA-50/1 after end group removal was 35.3 °C (M_n: 6,973), which was close to the T_g of 3-PLGA (35.4 °C, M_n: 7,238) that added no initiator. While the T_g of the 1-PLGA-50/1 before end group removal was 35.6 °C (M_n: 7,342). The similar results about the 2-PLGA-50/1 were also shown in the Table 4. These results indicated to some extent that the removal after the polymerization reaction did not affect the physical properties of the PLGA.

Results of silicon-end group removal from PLGA

The silicon-end group removal from PLGA is shown in Table 5. It can be seen that the silicon-end group attached to 1-PLGA-50/1 was not completely removed using 1 M HCl for 12 h; when the reaction time was prolonged to 15 h, the end group was

Table 4 The glass transition temperature (T_g) of PLGA before and after end group removal

Copolymer	M_n of before removal	The T_g before removal (°C)	The removal condition	M_n of after removal	The T_g after removal (°C)
3-PLGA[a]	7,238	35.4	–	–	–
1-PLGA-50/1	7,342	35.6	2 M HCl	6,973	35.3
			9 h		
2-PLGA-50/1	7,387	35.7	3 M HCl	6,825	35.3
			12 h		

[a] No silanol initiator added and the materials proportion of preparing PLGA was like 1-PLGA in Table 1

Table 5 The removal results of the silicon-end group attaching on the PLGA at room temperature

PLGA	The removal condition Reagent/reaction time	Result of removal	M_n of before removal	M_n of after removal
1-PLGA-50/1	1 M HCl	×		/
	12 h			
	1 M HCl	✔		6,887
	15 h			
	2 M HCl	✔	7,342	6,973
	9 h			
	TFA:H_2O = 1:4	×		/
	6 h			
	TFA:H_2O = 1:4	✔		6,834
	12 h			
1-PLGA-100/1	1 M HCl	×	12,054	/
	15 h			
	2 M HCl	✔		11,207
	24 h			
1-PLGA-200/1	2 M HCl	×	18,629	/
	24 h			
	3 M HCl	✔		17,304
	18 h			
2-PLGA-50/1	2 M HCl	×	7,387	/
	24 h			
	3 M HCl	✔		6,825
	12 h			
	TFA:H_2O = 1:1	×		/
	15 h			
	TFA:H_2O = 1:1	✔		6,702
	18 h			
2-PLGA-100/1	3 M HCl	×	12,843	/
	12 h			
	3 M HCl	✔		11,938
	24 h			
2-PLGA-200/1	3 M HCl	×	20,175	/
	24 h			
	3 M HCl	✔		18,693
	30 h			
2-PLGA-400/1	3 M HCl	×	32,947	/
	30 h			
	3 M HCl	✔		30,885
	36 h			

Table 5 continued

PLGA	The removal conditionReagent/ reaction time	Result of removal	M_n of before removal	M_n of after removal
2-PLGA-800/1	3 M HCl 30 h	×	25,643	/
	3 M HCl 33 h	✔		24,146

"✔" means removal success, "×" means still there were some residue of the silicon end groups left on the PLGA, "/" means the experiment was not carried out

removed, definitively. When 2 M HCl was used, reaction time was cut to 9 h, demonstrating that the reaction could be accelerated by increasing acid concentration. This concentration and reaction time relationship was also observed with other products from Table 5. This indicated that the silicon-end group removal conditions could be mild when the PLGA M_n was low, whether the polymer was 1-PLGA or 2-PLGA. Contrasted the removal result of 1-PLGA-50/1, the silicon-end group attached to 2-PLGA-50/1 was not completely removed using 1 or 2 M HCl. Only when 3 M HCl was used for 12 h, it could be removed entirely. The other copolymer also showed similar results. It could illustrate that the 1-PLGA attached by the TBDS-end group was easier removed than 2-PLGA that prepared with TPS in same conditions. There was no significant difference in the PLGA M_n before and after end group removal. The molecular weight of PLGA after cleavage could meet the demands for drug-releasing materials.

Conclusions

PLGA has been prepared via the ring-opening melting polymerization of D,L-lactide and glycolide, using the molecular weight regulators TBDS and TPS and catalyst $Sn(Oct)_2$. The molecular weight of PLGA was easily controlled by altering the monomers/silanol molar ratio. The results indicated that the molecular weight of PLGA approached to the theoretical values under all experimental conditions. The silicon-end group attached to PLGA was removed at room temperature using either HCl or TFA. ^{1}HNMR analysis demonstrated the silicon-end group was completely cleaved from PLGA using acid of a certain concentration. The molecular weight of PLGA after cleavage was determined by GPC. Removal conditions were mild and the extent of silicon group removal could be improved by increasing the concentration of the acid and prolonging the reaction time. Besides, the residual amounts of stannum in PLGA after end group removal were much less than the amounts before removal and the T_g of 1-PLGA (or 2-PLGA) after end group removal were close to the PLGA that added no initiator and had similar molecular weight. Under the same reaction conditions, the TBDS-end group attached to 1-PLGA was easier to remove than was the TPS group from 2-PLGA. The molecular weight and the purity of PLGA showed no significant difference before

and after the silicon-end group was removed. The molecular weight of PLGA after cleavage could meet the requirements of drug-releasing materials.

Acknowledgments The authors thank the financial support of Tianjin Science and Technology Key grants (05YFGPGX26200) and the NSFC of China grants (50873114).

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