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# Microwave-Assisted Single-Step Synthesis of Poly(L-lactic acid)-poly(ethylene glycol) Copolymers

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Microwave-assisted synthesis of poly(L-lactic acid)-poly(ethylene glycol) copolymers (PLEG) by single-step polycondensation of L-lactic acid and poly(ethylene glycol) has been studied. The synthetic conditions, including catalysts, reaction time, pressure and feed weight ratios ( $m_{LA}/m_{PEG}$ ) on the molecular weights, yields and appearance of the copolymers have been discussed. PLEG copolymers with a weight-average molecular weight of 11000 g/mol can be obtained when L-lactic acid and PEG800 mixture is irradiated for about 60 min under a reduced pressure of around 40 mmHg using  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  as catalyst. The higher feed weight ratios of  $m_{LA}/m_{PEG}$  lead to copolymers with higher molecular weight. The products are characterized by <sup>1</sup>H-NMR, GPC and DSC. It is found that the resultant polymers have a relatively narrow polydispersity index (PDI), which is lower than 1.3. The higher glass transition and melting temperatures of the copolymers can be obtained when the content of PEG is lower. Microwave irradiation accelerates the copolymerization rate of L-lactic acid and PEG compared with the conventional heating.

**Keywords:** Poly(L-lactic acid), poly(ethylene glycol), microwave, copolymer

## 1 Introduction

Poly(L-lactic acid) (PLLA) is one of the most important biodegradable polymers with good transparency, high mechanical properties, good biocompatibilities and bioabsorbabilities, and is usually used as biomedical materials (1). However, the applications of PLLA are limited due to its semi-crystalline and hydrophobic nature (2). On the other hand, because poly(ethylene glycol) (PEG) has excellent solubility in water and organic solvents, non-toxicity, and absence of antigenicity and immunogenicity (3), it is usually used for the modification of biodegradable polymer, and many copolymers based on PEG such as PPDO-b-PEG and (PCL-b-PEG) have been synthesized (4, 5). Usually, the introduction of PEG segment into PLLA chains would lead to copolymers with controlled hydrophilicity and degradability (6, 7). However, the conventional heating method often takes tens of hours to complete the copolymerization. PLA/PEO/PLA triblock copolymers were synthesized by ring opening polymerization of L-lactide in the presence

of PEG2000. The  $M_n$  of triblock copolymers was about 57000 g/mol after several days polymerization time (8).

Microwave heating has attracted more and more attention because of its non-contacting, environmentally benign, homogeneity and rapidness, and it is a highly specific heating with the material selectivity emerging from the wavelength of microwave irradiation that intrinsically excites dipolar oscillation and induces ionic conduction (9–11). Microwave irradiation has been used for a large number of reactions, both organic and inorganic (9). It is also found that microwave irradiation has great acceleration effect on polymerization. Takeuchi et al. (12) synthesized poly(L-lactic acid) under microwave irradiation within 30 min, and its maximal weight-average molecular weight ( $M_w$ ) was 16000 g/mol. However, for conventional heating method, it usually takes several hours to obtain poly(L-lactic acid) with satisfactory results (13–15). It was reported that poly(L-lactide)-block-poly(ethylene glycol) triblock copolymers with a number-average molecular weight ( $M_n$ ) of 28230 g/mol could be obtained at 100°C for 3 min under microwave irradiation (2). It could be seen clearly that reaction speed undergoes an immense increase under microwave irradiation compared with conventional heating (9).

Much attention has been paid to lactic acid derived from corn because of its renewable nature. Wang et al. (16) synthesized a series of poly(lactic acid)-poly(ethylene glycol)

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copolymers by polycondensation via varying the Mn of PEG in the presence of SnO. The process to remove SnO is intricate, however, the appearance of copolymers was not satisfied because of using SnO as catalyst. Furthermore, it will take more than 10 h to complete the polymerization.

In this paper, PLA/PEG copolymers was obtained by melt polycondensation of L-lactic acid and poly(ethylene glycol) under microwave irradiation. The effects of reaction conditions including catalyst kinds,  $m_{\text{LA}}/m_{\text{PEG}}$  feed ratios, etc, on the polymerization reaction were investigated.  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  was preferred to be used as a catalyst because of its better catalytic activity and good solubility in reactions mixture. So far as is known, this is the first report on the single-step copolycondensation of L-lactic acid and PEG800, using  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  as catalyst under microwave irradiation. The copolymer was characterized by H-NMR, GPC and DSC.

## 2 Experimental

### 2.1 Materials

L-lactic acid (85% aqueous solution) was purchased from Hubei Chemical Factory (Hubei, China). Stannous chloride and p-toluene sulphonic acid (TSA) were purchased from the Jinshan Chemical Factory (Chengdu, China) and Changzheng Chemical Factory (Chengdu, China), respectively. PEG800 and antimony trioxide were purchased from Sinopharm Chemical Reagent Co., Ltd (Shanghai, China). Tin powder and stannous oxide were both purchased from the Shanghai Chemical Factory (Shanghai, China). All of these materials were used as received. Tin(II)-ethylhexanoate ( $\text{Sn}(\text{Oct})_2$ ) was purchased from Aldrich and dissolved in freshly distilled anhydrous toluene.

### 2.2 Microwave Oven

The MAS I microwave oven was made in Shanghai Sineo Microwave Chemistry Technology Co., Ltd. The temperature of the reaction mixture was monitored by the infrared temperature sensor in the side wall of the cavity. The microwave power could be dynamically adjusted between 0 and 1000 W with 100 W as an interval for temperature control.

### 2.3 Measurements

$^1\text{H-NMR}$  (400 MHz) spectra were obtained by a Varian Germini spectrometer using tetramethylsilane (TMS) as an internal standard and  $\text{CDCl}_3$  as a solvent. Mn, Mw and the polydispersity index (PDI) of copolymers were determined by a Waters (1515-717-2414) high-performance liquid chromatograph. Chloroform was used as an eluent (flow rate  $1.0 \text{ mL} \cdot \text{min}^{-1}$ ) at  $30^\circ\text{C}$  and the molecular weight was calibrated by polystyrene standards.

Differential scanning calorimetry (DSC) analysis was performed on a TA Q20 DSC. All samples were first heated from room temperature to  $150^\circ\text{C}$  and kept isothermal for 5 min to erase any previous thermal history. The samples were then cooled from 150 to  $-20^\circ\text{C}$  at a rate of  $10^\circ\text{C}/\text{min}$ , and subsequently heated from  $-20$  to  $150^\circ\text{C}$  at the same rate.

### 2.4 Synthesis of PLEG under Microwave Irradiation

Microwave-assisted copolymerization was performed in a MAS I microwave oven. 17.65 g of L-lactic acid (85% aqueous solution), varied amounts of PEG800 and catalyst were added to a long-neck flask equipped with a constant pressure funnel which was filled with 3A molecular sieve, and fixed with a condenser connecting to a water pump. The temperature was elevated to  $80^\circ\text{C}$  with the power of 100W and the pressure was reduced to 60 mmHg step by step within 20 min, after that, increasing the reaction temperature to  $160^\circ\text{C}$  with the power of 200W, and the melt copolymerization was carried out for 40 min. After the irradiation was completed, the products were dissolved in chloroform and precipitated with excess methanol. The precipitates were dried under vacuum at  $40^\circ\text{C}$  to a constant weight. The intrinsic viscosity ( $[\eta]$ ) values of PLEG were measured at  $30^\circ\text{C}$  at a concentration of  $0.1 \text{ g}/\text{dL}$  in chloroform using an Ubbelohde viscosimeter.

### 2.5 Synthesis of PLEG Via Conventional Heating

The conventional synthesis of copolymers was carried out in an oil bath. L-lactic acid, PEG800 and  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  were added to a long-neck flask equipped with a constant pressure funnel equipped with a reflux condenser connecting to a water pump. All other procedures were the same as those of microwave-assisted synthesis.

## 3 Results and Discussion

$^1\text{H-NMR}$  spectrum of PLEG was shown in Figure 1. For all products, peaks of PLA segment appeared at 1.58 (d,  $-\text{CH}_3$ ), 3.67 (m,  $-\text{CH}_2-\text{CH}_2-\text{O}-$ ), and 5.16 ppm (q,  $-\text{O}-\text{CH}-\text{CH}_3$ ). A weak multiplet resonance at 4.2–4.4 ppm belonged to the terminal methine group of PEG and the methylene group of PLA. The result was in good agreement with the literature (2, 17).

The effects of different catalysts on the intrinsic viscosity of PLEG were shown in Table 1. Among various catalysts, it was found that tin compounds such as  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ , SnO, and  $\text{Sn}(\text{Oct})_2$ , as well as antimony oxide ( $\text{Sb}_2\text{O}_3$ ) gave the copolymer with higher intrinsic viscosity than the other catalysts, but the appearance of crude products was black when using SnO as catalyst. Microwave irradiation gave L-LA-PEG copolymer with the highest intrinsic viscosity of

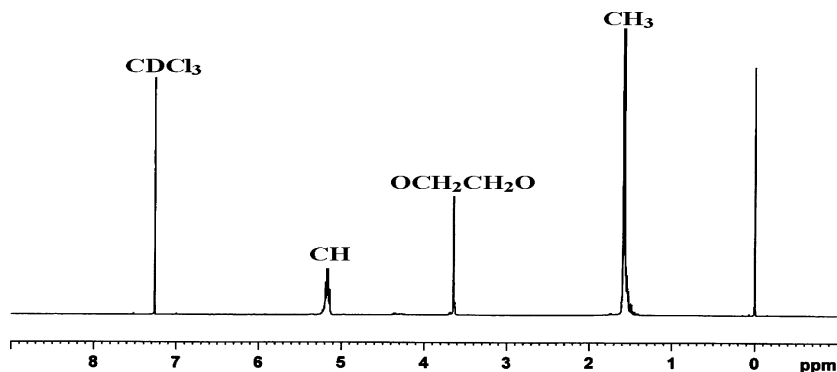


Fig. 1.  $^1\text{H}$ -NMR spectrum of PLEG.

**Table 1.** Microwave-assisted copolymerization of LA and PEG800 with various catalysts

Run	Catalyst	$[\eta]$ (dL/g)	Yields(%) <sup>a</sup>	Appearance
1	$\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$	0.14	39.1	Pale yellow
2	SnO	0.10	/	Black
3	$\text{Sn}(\text{Oct})_2$	0.11	32.0	Transparent
4	Sn	/	trace	Transparent
5	$\text{Sb}_2\text{O}_3$	0.10	22.7	Transparent
6	TSA	0.09	trace	Pale yellow

All trials were preceded as follows: feed weight ratio of  $m_{\text{LA}}/m_{\text{PEG}}$  was 19, the molecular weight of PEG was 800, the absolute pressure was about 60 mmHg, polymerized at 160°C for 40 min, and the catalyst amount based on L-lactic acid was 0.6 wt%.

<sup>a</sup>Yield calculated by the product dissolved and precipitated.

**Table 2.** Influence of reaction time on the microwave-assisted copolycondensation of LA and PEG

Run	$t$ (min)	$[\eta]$ (dL/g)	Appearance
1	40	0.14	Pale yellow
2	50	0.17	Pale yellow
3	60	0.15	Pale yellow

**Table 3.** Effect of pressure on the microwave-assisted copolycondensation of LA and PEG

Run	Pressure (mmHg)	$[\eta]$ (dL/g)	Yields (%) <sup>a</sup>	Appearance
1	20	0.09	30.0	Transparent
2	40	0.13	48.6	Transparent
3	50	0.12	33.6	Transparent
4	60	0.12	38.6	Pale yellow

All runs were catalyzed by  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  for 40 min at 160°C with a feed weight ratios  $m_{\text{LA}}/m_{\text{PEG}}$  of 19.

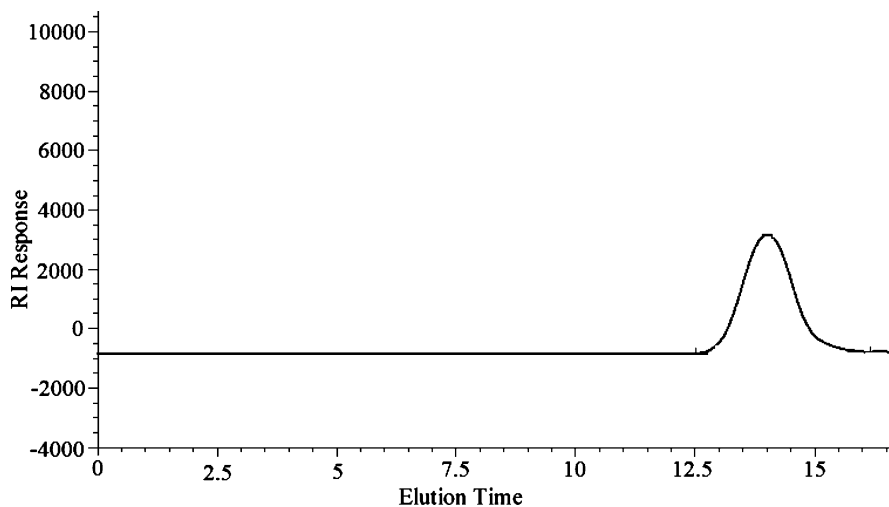
<sup>a</sup>Yield calculated from the product dissolved and precipitated.

0.14 dL/g by using  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  as catalyst. However, no copolymer was obtained after purification using Sn powder as catalyst. According to Table 1, it was found that the catalytic activity of Sn powder was much lower than the other tin compounds. Even if it was used for the homopolycondensation of lactic acid, its catalytic activity was still low (12). The highest yield of PLEG was 39.1% when using  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  as catalyst after purified, but the conventional heating method gave no copolymer under the same reaction conditions. It was proved that microwave irradiation accelerated the rate of copolymerization of LA and PEG.

The influence of microwave irradiation time on the intrinsic viscosity of copolymers was studied and the results were listed in Table 2. The intrinsic viscosity of the resulting products increased first and then decreased with the irradiation time ranging from 40 to 60 min. The copolymer with the highest intrinsic viscosity value of 0.17 dL/g was obtained when the reaction time was 50 min. With the irradiation time was increased to 60 min, the corresponding intrinsic viscosity of the copolymer was 0.15 dL/g. However, the crude product was pale yellow when the polymerization time was 40 min and its appearance was fuscous with the increase of reaction time. Thus, 40 min was adopted in the following copolymerization in order to obtain better results.

The experiments were conducted as follows: feed weight ratio of  $m_{\text{LA}}/m_{\text{PEG}}$  was 9, the molecular weight of PEG was 800, the absolute pressure was about 60 mmHg, polymerized at 160°C, and the catalyst amount based on L-lactic acid was 0.6 wt%.

As the condensation polymerization was concerned, there are many attempts to remove the released water, alcohols or other small molecule in order to carry out the reaction smoothly. One of the methods is to decrease the pressure of the systems. As shown in Table 3, by decreasing the pressure, the intrinsic viscosity and the yields of PLEG first increased and then decreased. When the pressure was lower than 40 mmHg, the intrinsic viscosity of copolymer sharply decreased from 0.13 to 0.09 dL/g, and the yield



**Fig. 2.** GPC chromatogram of PLEG.

also decreased from 48.6 to 30.0%. The intrinsic viscosity and yield under 20 mmHg were lower than those under 40 mmHg, because LA and the other volatile oligomers formed were lost with water (12). The intrinsic viscosity obtained at 50 mmHg was almost the same as that at 60 mmHg, but the appearance of crude product obtained at 60 mmHg was pale yellow. The effect of higher pressures such as 120 and 160 mmHg on the intrinsic viscosity and yields was also investigated, but only a few of pale yellow products could be obtained, indicating that the high pressure will not help the removal of the released water. At the same time, the appearance of the product was pale yellow because of the serious oxidation reaction in the presence of more air.

Microwave-assisted polycondensation of LA and PEG, with different feed weight ratios of L-LA and PEG800 were shown in Table 4.  $M_w$ ,  $M_n$ , and PDI of PLEG were obtained from GPC. The mLA/mPEG weight ratios found in the product were calculated from  $^1\text{H-NMR}$  spectra. The copolymers with  $M_w$  of 11000, 8960, 8850

and 7550 g/mol were obtained when the feed weight ratios of LA to PEG800 were 37.7, 19.0, 9.0 and 6.6, respectively. With the increase of feed content of PEG800, both  $M_w$  and  $[\eta]$  values of PLEG decreased. The PDI was very narrow, lower than 1.3, which was smaller than that of the triblock copolymers of L-lactide and PEG. (2). It could be seen from Table 4 that the mLA/mPEG ratios found in product were lower than the feed ratios. L-lactic acid perhaps lost during the polymerization refluxing with water. However, the decreasing trend of feed weight ratios of mLA/mPEG was in accordance with the calculated.

GPC chromatogram of the product was shown in Figure 2. The results indicated that the copolymerization of L-lactic acid and PEG800 indeed only gave the copolymer PLEG after purified, and no peaks of the homopolymer were found. The GPC results also showed that the products had  $M_n$  values ranging from 6120 to 8540 g/mol and PDI ranging from 1.23 to 1.29.

Thermal properties of the PLEG copolymers with different  $m_{\text{LA}}/m_{\text{PEG}}$  feed ratios were shown in Table 5. The melting temperatures ( $T_m$ ) were 131.1, 128.7, 122.9 and 118.42°C for different  $m_{\text{LA}}/m_{\text{PEG}}$  feed weight ratios, and the glass transition temperatures ( $T_g$ ) were 42.4, 30.5, 23.6

**Table 4.** PLEG copolymers obtained from L-lactic acid in the presence of PEG800 at different feed weight ratio under microwave irradiation

Run	LA/PEG (in feed)	LA/PEG (in product)	$[\eta]$ (dL/g)	$M_w$ (g/mol)	$M_n$ (GPC) (g/mol)	PDI
1	37.7	35.3	0.18	11000	8540	1.29
2	19.0	15.0	0.15	8960	6920	1.29
3	9.0	8.6	0.14	8850	6840	1.29
4	6.6	7.0	0.13	7550	6120	1.23

All runs were polymerized with an absolute pressure of 40 mmHg, a polycondensation temperature of 160°C, a reaction time of 40 min and 0.67 wt%  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  as the catalyst.

**Table 5.** Thermal transition temperature of PLEG determined by DSC

Run	LA/EG (in product)	$M_w$ (g/mol)	$T_m$ (°C)	$T_g$ (°C)
1	35.3	11000	131.1	42.4
2	15.0	8960	128.7	30.5
3	8.6	8850	122.9	23.6
4	7.0	7550	118.42	21.3

and 21.3°C, respectively. From Table 5, we can see that the  $T_g$  and  $T_m$  of PLEG decreased as the PEG content increased.

#### 4 Conclusions

The copolymers (PLEG) of poly(ethylene glycol) and L-lactic acid could be synthesized successfully under microwave irradiation. The reaction time is shortened considerably by the microwave irradiation compared with the conventional heating method.  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  had more catalytic activity than the other Sn compounds during the synthesis of PLEG. The optimal reaction conditions were as follows: feed weight ratio of mLA/mPEG was 38; the absolute pressure was about 40 mmHg, polymerized at 160°C for 40 min. The resultant products are colorless and have enough strength to make capsule, which could be used for sustained release drug delivery systems.

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