Syntheses of Poly(lactic acid)-Poly(ethylene glycol) Serial Biodegradable Polymer Materials via Direct Melt Polycondensation and Their Characterization

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ABSTRACT: Directly starting from lactic acid (LA) and poly(ethylene glycol) (PEG), biodegradable material polylactic acid-polyethylene glycol (PLEG) was synthesized via melt copolycondensation. The optimal synthetic conditions, including prepolymerization method, catalyst kinds and quantity, copolymerization temperature and time, LA stereochemical configuration, feed weight ratio m_{LA}/m_{PEG} and M_n of PEG, were all discussed in detail. When D,L-LA and PEG (M_n = 1000 Da) prepolymerized together as feed weight ratio $m_{D,L-LA}/m_{PEG}$ = 90/10, 15 h copolycondensation under 165°C and 70 Pa, and 0.5 wt % SnO as catalyst, gave D,L-PLEG1000 with the highest [η] of 0.40 dL/g, and the corresponding MW was 41,700 Da. Using L-LA instead of D,L-LA, 10 h polymerization under 165°C and 70 Pa, and 0.5 wt % SnO as catalyst, gave L-PLEG1000 with the highest [η] of 0.21 dL/g and MW of 15,600 Da. Serial D,L-PLEG with different feed weight ratio and M_n of PEG were synthesized via the simple and practical direct melt copolycondensation, and characterized with FTIR, ^{1}H NMR, GPC, DSC, XRD, and contact angle testing. D,L-PELG not only had higher MW than PDLLA, PLLA and L-PELG, but also better hydrophilicity than PDLLA. The novel one-step method could be an alternative route to the synthesis of hydrophilic drug delivery carrier PLEG instead of the traditional two-step method using lactide as intermediate. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 102: 577–587, 2006

Key words: biodegradable; copolymerization; drug delivery systems; hydrophilic polymers; melt; polycondensation; synthesis

INTRODUCTION

As a kind of important biodegradable aliphatic polyester, poly(lactic acid) (PLA) is wholly environment-friendly, the excellent biocompatibility and biological resorbability made it have extensive applications in biomedical fields, including suture, bone fixation material, drug delivery microsphere, tissue engineering.[1] However, when PLA is used as hydrophilic drug delivery carrier and tissue engineering material, its hydrophilicity was need to be improved.

Poly(ethylene glycol) (PEG) has good hydrophilicity, and its use in body has been authorized by USA Food and Drug Administration (FDA). Therefore, by introducing PEG into PLA through copolymerization, the synthesis of poly(lactic acid)-poly(ethylene glycol) (PLEG) became an important way to improve the hydrophilicity of PLA. Now, there are many literatures reported on the synthesis of PLEG via the copolymerization of lactide with ethylene oxide (the monomer of PEG),[2–4] or PEG.[5–9]

Usually, lactide was traditionally prepared from lactic acid (LA) through a troublesome and low-yield process, and the purification of lactide by repetitious crystallization consumed a lot of organic solvents. Higher the molecular weight of PLEG hoped, the higher the purity of lactide needed, and the more times of crystallization was necessary.[1] Therefore, the research and development of PLEG were limited to some extent by its high synthesis cost because of the traditional two-step method using lactide as the intermediate.

With the advance of direct syntheses of PLA[10–19] and poly(lactic acid-glycolic acid) (PLGA)[20–25] using LA as starting material, more and more importance has been attached to the direct polycondensation of LA and PEG, the novel one-step method. However, in the past, only few studies have reported on the copolymerization of LA, PEG, and other third monomer.[26,27] And just starting from LA and PEG, the synthesis of PLEG has been investigated seldom.

In this article, based on our previous work on the simple direct melt polycondensation of PLA,[16–19] PLGA,[25] and the application in drug delivery,[18,19] we respectively, used D,L-lactic acid (D,L-LA) and L-lactic acid (L-LA) as starting materials, investigated their

copolycondensation with PEG, and synthesized PLEG serial biodegradable materials with different feed weight ratio m_{LA}/m_{PEG} and number average molecular weight (M_n) of PEG. The structure of the serial PLEG, the relative molecular weight and its distribution, the thermal properties, crystallinity, and hydrophilicity were characterized respectively, with Fourier transform infrared (FTIR) spectroscopy, ^1H NMR spectroscopy, gel permeation chromatography (GPC), differential scanning calorimetry (DSC), X-ray diffraction (XRD), and contact angle testing.

EXPERIMENTAL

Materials

L-LA was purchased from Wako Pure Chemical Industries (Tokyo, Japan), *p*-toluenesulphonic acid (TSA) was purchased from Nacalai Tesque (Kyoto, Japan). Zinc lactate [Zn(LA)$_2$] was self-made from zinc oxide (ZnO) and D,L-LA, and characterized with FTIR at its melting point.

Other chemical reagents, including stannous chloride (analytic reagent), D,L-LA (analytic reagent), and PEG with different M_n (Chemical Purity), were purchased from Guangzhou Chemical Reagent Factory (Guangzhou, China) and Guangzhou Donghong Chemical Factory (Guangzhou, China). All these materials were used without further purification.

Instrumental analysis and measurements

^1H NMR spectra were recorded with a DRX-400 NMR spectrometer (Bruker instruments, Billerica, MA) with CDCl$_3$ as the solvent and internal standard. IR spectra were obtained from an FTIR spectrometer (Bruker Vector 33, Ettlingen, Germany) by the KBr salt slice method.

The intrinsic viscosity ([η]) of PLEG was determined with Ubbelohde viscometer (Cannon-Ubbelohde, State College, PA) with CHCl$_3$ as the solvent at 25°C. The relative molecular weight and its distribution were determined by a Waters 515 high-performance liquid chromatograph (Torrace, CA) with tetrahydrofuran (THF) as the solvent and with polystyrene as the reference at a flow velocity 1 mL/min and at 35°C.

DSC was performed with Perkin–Elmer DSC7 thermal analyzer (Perkin–Elmer, Cetus Instruments, Norwalk, CT) at a heating rate of 10°C/min under an argon atmosphere (flow velocity, 20 mL/min). With a wavelength of 1.5406×10^{-10} m and a scanning scope of $2\theta = 1°-40°$ with Cu·Kα radiation, a Rigaku D/max-1200× X-ray diffractometer (Rigaku, Tokyo) was used to investigate the crystallinity of PLEG.

The hydrophilicity of PLEG was characterized with contact angle testing, which was performed with Dataphysics 15 surface contact angle analyzer (Germany) in the range from 0° to 180°.

Prepolymerization method

According to previous work on melt homopolymerization or copolymerization of LA,[16–19,25] LA and PEG should be prepolymerized before melt copolymerization. In this study, two prepolymerization methods were investigated and compared.

In the first prepolymerization method, after LA and PEG were uniformly mixed as preplanned feed weight ratio, the mixture was directly dehydrated for 6 h at 140°C and 4000 Pa in a three-necked flask equipped with mechanical stirring and thermometer.

In the second prepolymerization method, LA was first prepolymerized singly for 6 h at 140°C and 4000 Pa in a three-necked flask equipped with mechanical stirring and thermometer, and then it was mixed with PEG together as preplanned feed weight ratio. In the end, the mixture was dehydrated for 6 h at 140°C and 4000 Pa again in three-necked flask.

Melt copolymerization

After LA and PEG have been prepolymerized, the selected catalyst was added in according to the weight percent (wt %) of dehydrated reactants. At a certain temperature (145–185°C) and absolute pressure (70 Pa), the melt copolymerization was carried out for 5–24 h. When the reaction finished, the purification via solution in CHCl$_3$ and succedent precipitation by CH$_3$OH ordinarily gave white powder product after the sample was dried *in vacuo*.

As a comparison reference in the test of GPC and FTIR, homopolymers, including poly(D,L-lactic acid) (PDLLA) and poly(L-lactic acid) (PLLA), were also synthesized under similar conditions as the previously reported melt polymerization respectively, starting from D,L-LA and L-LA.[16–19,25]

RESULTS AND DISCUSSION

Optimal synthetic conditions for D,L-PLEG

As D,L-LA was more cheaper than L-LA, we first investigated the optimal synthetic conditions for poly(D,L-lactic acid)-polyethylene glycol (D,L-PLEG), including the effects of different prepolymerization methods, catalyst kinds and quantity, copolymerization time, reaction temperature, monomer feed weight ratio $m_{D,L}$-LA/m_{PEG} on [η] of D,L-PLEG.

According to the report of Moon et al.,[11] during the melt polymerization of LA, the prepolymerization was very important to the dehydration. So, we thought, if LA was first singly prepolymerized, then the oligomer PLA was mixed and prepolymerized again with PEG together, the continuous twice dehy-
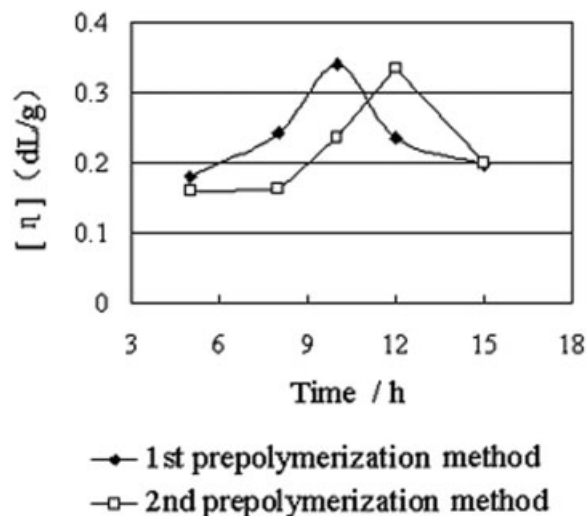
Figure 1 Effects of different prepolymerization methods on [η] of D,L-PLEG under the same reaction time (165°C, 70 Pa, catalyzed by 0.5 wt % SnCl$_2$).

TABLE II
Effects of Different Catalysts on the [η] Value of D,L-PLEG

Run	Catalyst	[η] (dL/g)	M_w (Da)	M_n (Da)	M_w/M_n
1	Sn	0.33	N	N	N
2	SnO	0.34	35,300	24,200	1.46
3	SnCl$_2$	0.34	32,300	21,300	1.52
4	SnCl$_4$	0.32	N	N	N
5	SnO$_2$	0.15	N	N	N
6	ZnO	0.22	N	N	N
7	ZnCl$_2$	0.20	N	N	N
8	Zn(LA)$_2$	0.16	N	N	N
9	TSA	0.18	N	N	N

N, Not tested. All runs were polymerized with a feed weight ratio $m_{\text{D,L-LA}}/m_{\text{PEG}}$ value of 90/10, an M_n of PEG of 1000 Da, an absolute pressure of 70 Pa, a polycondensation temperature of 165°C, a polycondensation time of 10 h, and a catalyst quantity of 0.5 wt %.

dration (in this research, which was named as the second prepolymerization method) might be more effective and advantageous to give higher [η] PLEG than the first prepolymerization method, in which LA and PEG was directly mixed and prepolymerized only once.

However, the result was not as anticipated. In Figure 1, it was obvious that, the time of D,L-PLEG [η] reaching maximum at 0.34 dL/g in the first prepolymerization method was shorter than that of [η] reaching maximum at 0.33 dL/g in the second method. If the whole time in the synthetic process, including prepolymerization and polycondensation, was all reckoned in, the time via the first prepolymerization method was markedly shorter and more favorable than that via the second prepolymerization method. Furthermore, maybe for the prepolymerization time was too long, the second prepolymerization was apt to give the imperfect product in color and appearance (Table I). Thus, to save time and synthesize better product, only the first prepolymerization method was adopted in the following polycondensation.

The effects of different catalysts on [η] of D,L-PLEG are shown in Table II. The effect of catalysts had in touch with metal kinds. Stannum series catalysts except SnO$_2$ (Runs 1–5) were obviously better than zinc series catalysts (Runs 6–8) and TSA (Run 9). As the maximum [η] was almost same (Runs 2 and 3), further testing was determined with GPC, and the result showed that SnO was better than SnCl$_2$ (Run 2).

The effects of melt copolymerization time on [η] of D,L-PLEG are shown in Table III. It was obvious that [η] reached a maximum after the reaction lasted for 15 h (Run 5). When the time was too shorter, polymerization was insufficient. However, once the reaction time was longer than 15 h, the oxidation and thermal degradation of polymer became serious. So, [η] dropped, the color of the purified product became yellow or brown. The yield also decreased from normal 50 ('7e70) to 27% (Run 7). Even when the reaction lasted for 24 h, no product could be obtained (Run 8). Thus, appropriate time should be 15 h.

Melt copolymerization were respectively, carried out at 145, 155, 165, 175, 185°C, and the results are shown in Table IV. It was obvious that the optimal temperature was 165°C (Run 3). The appropriate reaction temperature was advantageous to copolycondense. When the temperature was too high, the side reactions such as oxidation and thermal degradation markedly took place. So, [η] and yield decreased, and the color of the purified product changed from white

TABLE I
Effects of Reaction Time Using the Second Prepolymerization Method on the [η] Value of D,L-PLEG

Run	Time (h)	Crude product	Purified product	[η] (dL/g)
1	5	Yellowish and transparent	White powder	0.15
2	8	Yellow and semitransparent	White powder	0.16
3	10	Brown and semitransparent	Yellow powder	0.24
4	12	Brown and semitransparent	Brown and viscous solid	0.33
5	15	Brown and opaque	Brown and viscous solid	0.20

All runs were polymerized with a feed weight ratio $m_{\text{D,L-LA}}/m_{\text{PEG}}$ value of 90/10, an M_n of PEG of 1000 Da, an absolute pressure of 70 Pa, a polycondensation temperature of 165°C, and 0.5 wt % SnCl$_2$ as the catalyst.

TABLE III
Effects of Melt Copolymerization Time on the $[\eta]$ Value of D,L-PLEG

Run	Time (h)	Crude product	Purified product	$[\eta]$ (dL/g)
1	5	Yellowish and semitransparent	White powder	0.20
2	8	Yellow and semitransparent	White powder	0.30
3	10	Yellow and semitransparent	White powder	0.34
4	12	Light brown and semitransparent	White powder	0.37
5	15	Brown and semitransparent	Yellowish powder	0.40
6	18	Brown and opaque	Yellow powder	0.37
7	21	Dark brown and opaque[a]	Brown and viscous solid[a]	0.34
8	24	Dark brown and opaque[b]	N[b]	N[b]

All runs were polymerized with a feed weight ratio $m_{D,L-LA}/m_{PEG}$ value of 90/10, an M_n of PEG of 1000 Da, an absolute pressure of 70 Pa, a polycondensation temperature of 165°C, and 0.5 wt % SnO as the catalyst.
[a] The crude product was relatively less than the normal case, the yield often ranged from 50% to 70%, and in run 7, was only 27%.
[b] The crude product was so obviously less than the normal case that no product could be given by the precipitation with CH$_3$OH after the crude product was dissolved in CHCl$_3$.

to brown. Even when temperature was 185°C, no purified product could be obtained (Run 5).

The effects of catalyst SnO quantity on $[\eta]$ of D,L-PLEG are shown in Table V. When the quantity of SnO was 0.5 wt %, $[\eta]$ reached a maximum (Run 3), too much or less was not appropriate. When the quantity was too small, the reaction was so insufficient after a certain time that $[\eta]$ was not high. When the quantity of SnO was excessive, short-chain molecule was apt to be formed through the degradation of polymer, which also was catalyzed by SnO, so $[\eta]$ was not high too.

Therefore, the optimal synthetic conditions for D,L-PLEG were as follows: catalyst = SnO, catalyst quantity = 0.5 wt %, temperature = 165°C, absolute pressure = 70 Pa, and reaction time = 15 h. Under these conditions, the highest $[\eta]$ of D,L-PLEG was 0.40 dL/g, and GPC determination showed that the corresponding MW was 41,700 Da.

Optimal synthetic conditions for L-PLEG

Changing the stereochemical configuration of reactant LA, starting from L-LA and PEG (M_n = 1000 Da), the optimal synthetic conditions for L-PLEG was also investigated, and the result was different from that of D,L-PLEG.

The effects of different catalysts on $[\eta]$ of L-PLEG are shown in Table VI. When catalyzed by different catalysts, the dissolubility and dispersibility of catalysts were similar to that used in the synthesis of D,L-PLEG. The color and appearance of crude product was also similar, and almost all were brown and semitransparent. However, under same purification, only the crude product catalyzed by SnO gave enough purified product for the $[\eta]$ testing (Run 2). This indicated that SnO was the best catalyst for the synthesis of L-PLEG. It was noticeable that the highest $[\eta]$ 0.21 dL/g was markedly lower than that of D,L-PLEG (0.34 dL/g, Table II, Run 2) under the same synthetic conditions.

The effects of reaction time on $[\eta]$ of L-PLEG are shown in Table VII. For the same reason as the synthesis of D,L-PLEG, the appropriate time was 10 h (Run 3). This result was different from that starting from D,L-LA (15 h, Table III, Run 5). Even both during the same time (10 h), D,L-PLEG also had higher $[\eta]$ (0.34 dL/g, Table III, Run 3) than L-PLEG (0.21 dL/g, Table VII, Run 3). Therefore, D,L-LA might be more apt to produce higher molecular weight PLEG than L-LA in the direct copolycondensation of LA and PEG.

Thus, using L-LA and PEG as starting materials, the appropriate synthetic conditions for L-PLEG were as

TABLE IV
Effects of Melt Polycondensation Temperature on the $[\eta]$ Value of D,L-PLEG

Run	Temperature (°C)	Crude product	Purified product	$[\eta]$ (dL/g)
1	145	Yellowish and transparent	White powder	0.19
2	155	Yellow and transparent	White powder	0.17
3	165	Brown and semitransparent	Yellowish powder	0.40
4	175	Brown and opaque[a]	Brown and viscous solid[a]	0.34
5	185	Dark brown and opaque[b]	N[b]	N[b]

All runs were polymerized with a feed weight ratio $m_{D,L-LA}/m_{PEG}$ value of 90/10, an M_n of PEG of 1000 Da, an absolute pressure of 70 Pa, a polycondensation time of 15 h, and 0.5 wt % SnO as the catalyst.
[a] The yield often ranged from 50% to 70%, but the yield in run 4 was only 31%.
[b] The crude product was too less to be purified.

TABLE V
Effects of SnO Catalyst Quantity on the [η] Value of D,L-PLEG

Run	Catalyst quantity (wt %)[a]	[η] (dL/g)
1	0.1	0.23
2	0.3	0.26
3	0.5	0.40
4	0.7	0.37
5	0.9	0.35

All runs were polymerized with a feed weight ratio $m_{D,L-LA}/m_{PEG}$ value of 90/10, an M_n of PEG of 1000 Da, an absolute pressure of 70 Pa, a polycondensation temperature of 165°C, a polycondensation time of 15 h, and SnO as the catalyst.
[a] Weight percent of dehydrated reactants.

follows: catalyst = SnO, catalyst quantity = 0.5 wt %, temperature = 165°C, absolute pressure = 70 Pa, and reaction time = 10 h. The conclusion was different from that for D,L-PLEG, and the highest [η] was also outstandingly lower. These differences may be related to the reaction mechanism of the direct melt copolycondensation between LA and PEG.

Based on the investigation of synthetic conditions, under the same conditions, including the use of SnO as the catalyst, a catalyst quantity of 0.5 wt %, a temperature of 165°C, an absolute pressure of 70 Pa, and a reaction time of 15 h, when we altered the feed weight ratio m_{LA}/m_{PEG}, and the M_n of PEG, serial biodegradable PLEG materials were directly synthesized via the simple and practicable melt copolycondensation, and characterized with GPC, FTIR, ^{1}H NMR, DSC, XRD, and contact angle testing.

Intrinsic viscosity [η] of serial PLEG

The effects of different prepolymerization method, catalyst kinds and quantity, reaction temperature and time, the stereochemical configuration of reactant LA on [η] of PLEG has been respectively, discussed as

TABLE VI
Effects of Different Catalysts on the [η] Value of L-PLEG

Run	Catalyst	[η] (dL/g)
1	Sn	N[a]
2	SnO	0.21
3	SnO$_2$	N
4	SnCl$_2$	N
5	TSA	N

All runs were polymerized with a feed weight ratio m_{L-LA}/m_{PEG} value of 90/10, an M_n of PEG of 1000 Da, an absolute pressure of 70 Pa, a polycondensation temperature of 165°C, a polycondensation time of 10 h, and a catalyst quantity of 0.5 wt %.
[a] The purified product was too less to be tested.

TABLE VII
Effects of Polycondensation Time on the [η] Value of L-PLEG

Run	Time (h)	[η] (dL/g)
1	5	0.18
2	8	0.19
3	10	0.21
4	12	0.20
5	15	0.18

All runs were polymerized with a feed weight ratio m_{L-LA}/m_{PEG} value of 90/10, an M_n of PEG of 1000 Da, an absolute pressure of 70 Pa, a polycondensation temperature of 165°C, and 0.5 wt % SnO as the catalyst.

above. The effects of the feed weight ratio m_{LA}/m_{PEG} on [η] of PLEG are shown in Table VIII.

It could be found that the appropriate feed weight ratio (m_{LA}/m_{PEG}) should be 90/10. Once the weight percent of PEG was more than 30%, even altering the solvent and precipitator according to literatures,[3,5,6,28,29] the different purification method could not give satisfied results too (Table IX). This indicated that the main reason was that only low molecular weight PLEG was produced.

The effects of different M_n of PEG on [η] of PLEG are shown in Table X. With the increase of M_n, [η] of PLEG first increased and then decreased. When M_n of PEG was 1000 Da, [η] was maximal. Therefore, the appropriate M_n of PEG should be 1000 Da.

Thus, under the conditions including the use of SnO as the catalyst, a catalyst quantity of 0.5 wt %, a reaction temperature of 165°C, an absolute pressure of 70 Pa, and a reaction time of 15 h, when the feed weight ratio m_{LA}/m_{PEG} was 90/10, and M_n of PEG was 1000 Da, [η] of PLEG synthesized from D,L-LA and PEG was maximum (0.40 dL/g). Its corresponding MW was 41,700 Da, and M_n was 27,100 Da, the polydispersity index (PDI) MW/M_n was 1.46 (Table XI).

TABLE VIII
The [η] Value Comparison of PLEG from D,L-LA and PEG (M_n = 1000 Da) at Different Feed Weight Ratio

Run	$m_{D,L-LA}/m_{PEG}$	[η] (dL/g)
1	95/5	0.24
2	92/8	0.33
3	90/10	0.40
4	88/12	0.30
5	85/15	0.20
6	70/30	N[a]
7	50/50	N
8	30/70	N

All runs were polymerized with an absolute pressure of 70 Pa, a polycondensation temperature of 165°C, a reaction time of 15 h, and 0.5 wt % SnO as the catalyst.
[a] No product was given by the precipitation with CH_3OH after the crude product was dissolved in $CHCl_3$.

Run	Solvent	Precipitator	Result
1	CHCl$_3$	MeOH	N[a]
2	CHCl$_3$	Et$_2$O	N
3	Me$_2$CO	H$_2$O	N
4	EtOAc	n-C$_7$H$_{16}$	Less viscous solid[b]

All runs were polymerized with a feed weight ratio $m_{D,L-LA}/m_{PEG}$ value of 70/30, an M_n of PEG of 1000 Da, an absolute pressure of 70 Pa, a polycondensation temperature of 165°C, a reaction time of 15 h, and 0.5 wt % SnO as the catalyst.

[a] No product was given by the precipitation.
[b] The product was too less to be tested.

Relative molecular weight of serial PLEG

The GPC results (Table XI) showed that, though the stereochemical configuration of reactant LA, and the prepolymerization method were different, all retention time was similar. At the same time, all GPC flow curve only had single symmetrical peak (e.g., for Run 4, its corresponding curve was shown in Fig. 2), and all PDI (MW/M_n) was less than two. These indicated that the melt copolycondensation of LA and PEG indeed only gave copolymer PLEG, and no homopolymer was produced.

In Table XI, it could also be found that [η] and MW of PLEG synthesized from L-LA was lower than that of D,L-PLEG, but PDI was narrower (Run 6). It was often found and believed in the reported literatures on the melt polymerization of LA that L-LA could easily give higher molecular weight polymer than D,L-LA, and used more extensively in the syntheses of PLAs biodegradable materials.[10–24,29–32] Therefore, the above different phenomena may also be related to the direct melt copolycondensation mechanism of LA and PEG.

Run	M_n (Da)	[η] (dL/g)
1	200	N[a]
2	600	0.23
3	1000	0.40
4	2000	0.37
5	4000	0.35

All runs were polymerized with a feed weight ratio m_{LA}/m_{PEG} value of 90/10, an absolute pressure of 70 Pa, a reaction temperature of 165°C, a polycondensation time of 15 h, and 0.5 wt % SnO as the catalyst.

[a] No product was given by the precipitation with CH$_3$OH after the crude product was dissolved in CHCl$_3$.

Under same synthetic conditions, including an absolute pressure of 70 Pa, a reaction temperature of 165°C, and 0.5 wt % SnCl$_2$ as the catalyst, though all copolymer PLEG (both D,L-PELG and L-PELG) had broader molecular weight distribution (higher PDI) than homopolymer PLA, including PDLLA and PLLA (Runs 7 and 8, Table XI), D,L-PELG had higher MW. Therefore, copolycondensation did not always produce the polymer with lower MW than homopolycondensation. In our study, this phenomenon might have in touch with the certain molecular weight of the reactant PEG itself and the guidance polymerization of PEG terminal hydroxyl group (OH).

In many literatures of two-step method, the MW of PLEG was not mentioned. Some are higher than ours.[3,28,33] On the other hand, some are lower than MW of 41,700 Da.[2,6,34,35] However, under the similar synthetic conditions,[5,36,37] the MW of two-step method, even using L-lactide, were lower than the above one-step method result (Table XII, Runs 4–6). Therefore, with respect to the molecular weight of PLEG, the one-step method can be an alternative route to the synthesis of PLEG.

TABLE XI
GPC Test Results of PLEG Respectively from D,L-LA and L-LA

Run	Material	Catalyst	Reaction time (h)	[η] (dL/g)	Retention time (min)	M_w (Da)	M_n (Da)	M_w/M_n
1[a]	D,L-LA/PEG	SnCl$_2$	12	0.33	25.1	31,300	22,700	1.38
2	D,L-LA/PEG	SnCl$_2$	10	0.34	25.0	32,300	21,300	1.52
3	D,L-LA/PEG	SnO	10	0.34	24.8	35,300	24,200	1.46
4	D,L-LA/PEG	SnO	15	0.40	24.6	41,700	27,100	1.54
5	D,L-LA/PEG	SnO	18	0.37	24.7	35,500	24,300	1.46
6	L-LA/PEG	SnO	10	0.21	26.4	15,600	12,000	1.30
7[b]	D,L-LA	SnCl$_2$	10	0.23	25.2	17,800	14,200	1.25
8[b]	L-LA	SnCl$_2$	10	0.35	25.9	25,400	19,800	1.28

All runs except runs 7 and 8 were polymerized via melt copolycondensation with a feed weight ratio m_{LA}/m_{PEG} value of 90/10, an M_n of PEG of 1000 Da, an absolute pressure of 70 Pa, a reaction temperature of 165°C, and a catalyst quantity of 0.5 wt %.

[a] Only run 1 used the second method to dehydrate in prepolymerization, but other runs were dehydrated by the first prepolymerization method.
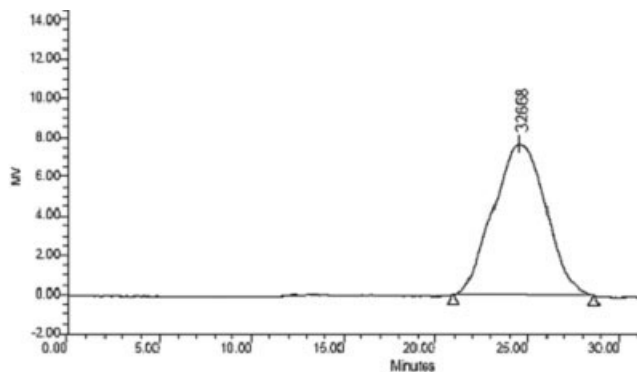[b] PLA was synthesized via melt homopolycondensation by the similar way[25] and used for comparison.

Figure 2 GPC flow curve of D,L-PLEG synthesized as feed weight ratio $m_{LA}/m_{PEG} = 90/10$ (M_n of PEG 1000 Da) under 165°C, 70 Pa, 15 h, and SnO catalyst quantity of 0.5 wt %.

Structure characterization of serial PLEG

The structure of PLEG was characterized with FTIR and ^{1}H NMR spectroscopy. Even the stereochemical configuration of starting material LA, M_n of PEG, and the feed weight ratio m_{LA} / m_{PEG} were different, the IR data of the serial PLEG were almost same (e.g., for M_n of PEG 1000 and 4000 Da, respectively, indexed as D,L-PLEG1000 and D,L-PLEG4000 in Fig. 3).

The data of D,L-PLEG synthesized as feed weight ratio $m_{LA}/m_{PEG} = 90/10$ (M_n of PEG 1000 Da) under 165°C, 70 Pa, 10 h, and catalyst SnCl$_2$ of quantity 0.5 wt % were obtained as follows (Fig. 4). IR (KBr, cm^{-1}): 1759 (ester carbonyl C=O in copolymer, strong); 1214, 1188, 1134, and 1091 (C—O—C in ester or ether group, strong); 2998, 2947, 2923, and 1459, 1388, 1363 (the saturated C—H in copolymer including CH$_3$, CH$_2$, and CH); 3505 (terminal OH in copolymer, weak).

Compared with PLA (e.g., PDLLA, Fig. 4), the absorption in 2923 cm^{-1} was not only obvious, but also had relatively broad peak, which indicated the marked strengthening of CH$_2$ in copolymer PLEG because of the introduction of PEG segment. At the same time, as the hydrophilicity of PLEG increased, the absorption in 3505 cm^{-1} of OH relative to the absorption in 2998 cm^{-1} of saturated C—H became stronger than PDLLA.

The structure of PLEG was also characterized with ^{1}H NMR (with the solvent CDCl$_3$ and with a chemical shift of 7.28 ppm as an internal standard). Though the stereochemical configuration of the starting material LA, M_n of PEG and the feed weight ratio m_{LA}/m_{PEG} were different, the chemical shift of CH, CH$_2$, and CH$_3$ were similar.

Using D,L-PLEG (synthesized as feed weight ratio $m_{LA}/m_{PEG} = 90/10$, M_n of PEG 1000 Da, under 165°C, 70 Pa, 10 h, and SnCl$_2$ catalyst quantity of 0.5 wt %) as an example, the data of ^{1}H NMR were obtained as follows (Fig. 5). ^{1}H NMR (δ, ppm): 1.60 (d, CH$_3$ in LA chain segment); 5.18 (q, CH in LA chain segment); 3.66 (s, CH$_2$ in PEG segment). Therefore, the structure of PLEG was demonstrated by FTIR and ^{1}H NMR as expected.

DSC characterization of serial PLEG

On the DSC curve, the glass-transition temperature (T_g) was not observed for all samples synthesized under different conditions, and the corresponding data of T_g were listed in Table XIII. It was obvious that, no matter what different conditions were, T_g of all PLEGs was lower than that of PLA for the introduction of flexible PEG segment.

Compared with homopolymer PLA,[25] some peaks of melting temperature (T_m) were confirmed, and their corresponding data of T_m were also shown in Table XIII. It could be found that, when prepolymerized via the second method, no peak of T_m was detected (Run 2), but the T_m peak could be observed on the DSC curves of the first prepolymerization method. Combined with the detection of T_g, it could be believed that the second prepolymerization method was more apt to give amorphous and random PLEG.

When the stereochemical configuration of reactant LA was different, it could be found that, L-PLEG1000 (Table XIII, Run 6) had higher T_g and T_m than D,L-PLEG1000. At the same time, L-PLEG1000 obviously had a peak of crystallization on the DSC curve, and the crystallization temperature (T_c) was 101.0°C, but the crystallization peak did not exist on any D,L-

TABLE XII
The Comparison of Molecular Weight of PLEG Synthesized by Different Methods

Run	Polymerization material and time	PEG%[a]	n_{LA}/n_{EG}[b]	M_w (Da)	M_n (Da)	M_w/M_n
1	D,L-LA/PEG (M_n = 1000 Da), 10 h	10	4.4	35,300	24,200	1.46
2	D,L-LA/PEG (M_n = 1000 Da), 15 h	10	4.4	41,700	27,100	1.54
3	D,L-LA/PEG (M_n = 1000 Da), 18 h	10	4.4	35,500	24,300	1.46
4[5]	D,L-Lactide/PEG (M_n = 1100 Da), 10 h	10	N[c]	24,100	8,900	2.70
5[36]	D,L-Lactide/PEG (M_w = 1500 Da)[d]	10	N	7,400	5,300	1.39
6[37]	L-Lactide/PEG (M_n = 2000 Da), 30–40 h	N	4.0	33,400	21,200	1.58

[a] Weight percent in feedstock of PEG.
[b] Repeat unit molar ratio in feedstock, can be converted from PEG% in feedstock each other.
[c] Not converted.
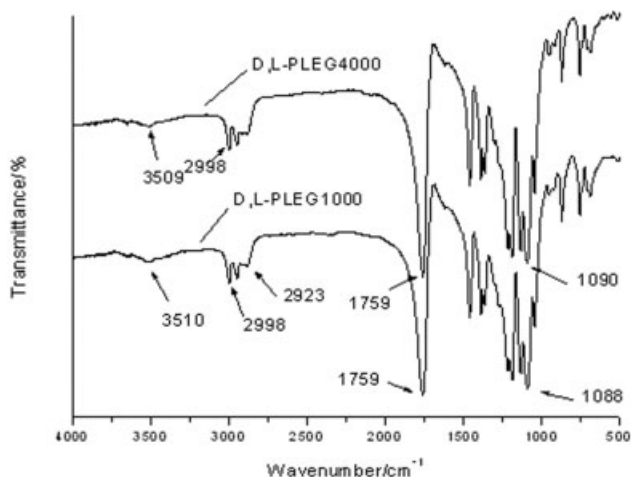[d] Polymerization time was not reported in Ref. 36.

Figure 3 IR spectra of D,L-PLEG synthesized as feed weight ratio $m_{LA}/m_{PEG} = 90/10$ under 165°C, 70 Pa, 15 h, and SnO catalyst quantity of 0.5 wt % respectively, from M_n of PEG 1000 and 4000 Da.

PLEG1000 scanning DSC curves of quenching after heating. Therefore, L-PLEG1000 should marked have higher crystallinity than D,L-PLEG1000. This conclusion was further confirmed by the following XRD characterization.

Similarly, when M_n of PEG was different, D,L-PLEG1000 with higher [η] (Table XIII, Run 4) than D,L-PLEG4000 might also have higher crystallinity. Because the aptness of PEG segment in PLEG to be crystalline made the former have 6°C higher T_g than the latter, and also higher T_m. Of course, these phenomena were also consistent with the results in the following XRD characterization.

PLEG as a copolymer of PLA and PEG, a peak at 92.7°C was also investigated accidentally on the DSC curve (Fig. 6). It may possibly be attributed to the
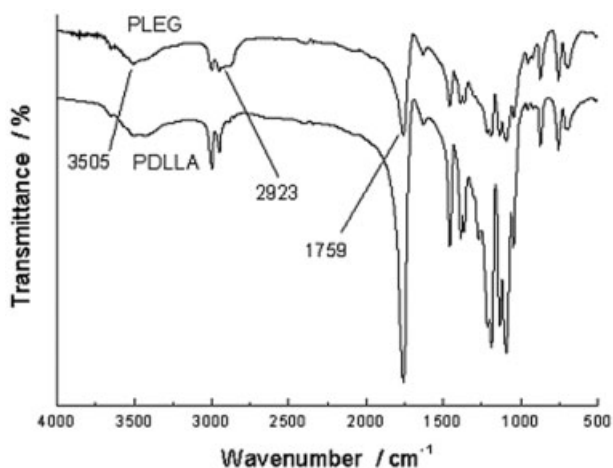
specific interaction between PEG and PLA chains because of their specific miscibility.

XRD characterization of serial PLEG

DSC characterization showed that the serial PLEGs had a difference in the crystallinity, but more evidence should be relied on XRD determination, and the experimental data are shown in Table XIV. It could be found that, for PEG segment was apt to be crystalline, no matter what differences in synthetic conditions were, such as different stereochemical configurations of LA and M_n of PEG, the diffraction peak position of PLEG basically existed at $2\theta = 16.6°$, $19.0°$, and $22.3°$ (Fig. 7).

According to literatures on the XRD determination of PEG copolymer[38–40] and homopolymer PLA directly synthesized from LA (Table XIV, Runs 4 and 5),[19,25] the diffraction peak that existed at $2\theta = 16.6°$ resulted from LA chain segment in PLEG, and it was the same as the face (110) of PLA. Similarly, the diffraction peak at $2\theta = 22.3°$ resulted from PEG segment in PLEG, and it was the same as the face (200) of PEG. The diffraction peak that existed at $2\theta = 19.0°$ resulted from the face (020) of PLA and the face (110) of PEG together.

As LA chain segment was the main component in PLEG synthesized as feed weight ratio $m_{LA}/m_{PEG} = 90/10$, and the diffraction peak of PLA face (110) was higher than that of PLA face (020) in the XRD spectra of PLA homopolymer,[19,25] the intensity of the diffraction peak that existed at $2\theta = 16.6°$ was the strongest of three (Fig. 7). Similarly, the diffraction peak at $2\theta = 19.0°$ was higher than that of the peak at $2\theta = 22.3°$, as the latter was only attributed to PEG face (200).

Compared with L-PLEG1000, the crystallinity of D,L-PLEG1000 was obviously lower (Table XIV, Runs 1 and 2). This indicated that L-LA chain segment in PLEG also contributed to the aptness of PLEG to be
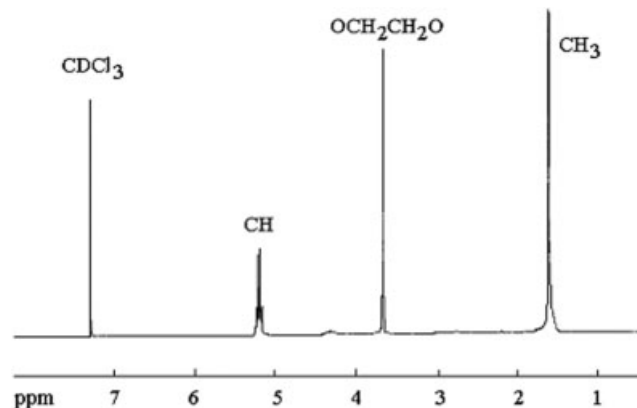

Figure 4 IR spectrum of D,L-PLEG synthesized as feed weight ratio $m_{LA}/m_{PEG} = 90/10$ (M_n of PEG 1000 Da) under 165°C, 70 Pa, 10 h, and SnCl₂ catalyst quantity of 0.5 wt %.

Figure 5 ¹H NMR spectrum of D,L-PLEG synthesized as feed weight ratio $m_{LA}/m_{PEG} = 90/10$ (M_n of PEG 1000 Da) under 165°C, 70 Pa, 10 h, and SnCl₂ catalyst quantity of 0.5 wt %.

TABLE XIII
DSC Results Comparison of PLEG Synthesized under Different Conditions

Run	M_n of PEG (Da)	Catalyst	Time (h)	$[\eta]$ (dL/g)	M_w (Da)	T_g (°C)	T_m (°C)
1	1000	SnCl$_2$	10	0.34	32,300	N	110.5
2[a]	1000	SnCl$_2$	12	0.33	31,300	N	N
3	1000	SnO	10	0.34	35,300	20.7	111.9
4	1000	SnO	18	0.37	35,500	33.1	130.4
5	4000	SnO	15	0.35	N	27.0	129.0
6[b]	1000	SnO	10	0.21	15,600	33.6	135.4
7[c]	(PLLA)	SnCl$_2$	10	0.35	25,400	50.0	134.0
8[c]	(PDLLA)	SnCl$_2$	10	0.23	17,800	54.6	120.0

N, Not detected (for T_g and T_m), or not tested (for M_w). All runs were usually polymerized with a feed weight ratio $m_{\text{D,L-LA}}/m_{\text{PEG}}$ value of 90/10, an absolute pressure of 70 Pa, a reaction temperature of 165°C, a catalyst quantity of 0.5 wt %, and after treated via the first prepolymerization method.
[a] Pretreated via the second prepolymerization method.
[b] L-LA as starting material.
[c] As a comparison reference, homopolymers (PLLA and PDLLA) were synthesized under similar conditions, and tested.[25]

crystalline, and the aptness was higher than D,L-LA chain segment. This conclusion was very coincident with the above DSC characterization.

When M_n of starting material PEG was different, the crystallinity of D,L-PLEG1000 was slightly higher than that of D,L-PLEG4000 (Table XIV, Runs 2 and 3). The result was also coincident with the above DSC conclusion.

Contact angle testing of serial PLEG

The contact angle testing was one of the ways to characterize the hydrophilicity of biodegradable polymer material PLEG,[37,41] and usually, the better is the hydrophilicity, the less is the contact angle.

When the feed weight ratio $m_{\text{LA}}/m_{\text{PEG}}$ was different, the contact angle decreased with the increase of PEG feed weight, and the hydrophilicity of D,L-PLEG was improved as expected (Table XV). Compared with PDLLA (Run 1), the hydrophilicity of all copolymer material modified by PEG was obviously bet-

tered for the introduction of hydrophilic PEG segment.

When M_n of PEG was different, compared with PDLLA (Table XVI, Run 5), the hydrophilicity of all copolymer material D,L-PLEG was also bettered, and the contact angle decreased with the increase of M_n (Runs 1–3).

Even using L-LA instead of D,L-LA as starting material, the hydrophilicity of L-PLEG1000 was also improved (Table XVI, Run 4). This indicated that the difference of LA stereochemical configuration did not alter the increasing trend of hydrophilicity.

Therefore, the hydrophilic modification of PLA by the introduction of PEG via the melt copolymerization of LA and PEG was successful. And the obtained effect of direct synthesis PLEG in improving hydrophilicity was also similar to that of the two-step method using lactide as intermediate.[5–9,37]
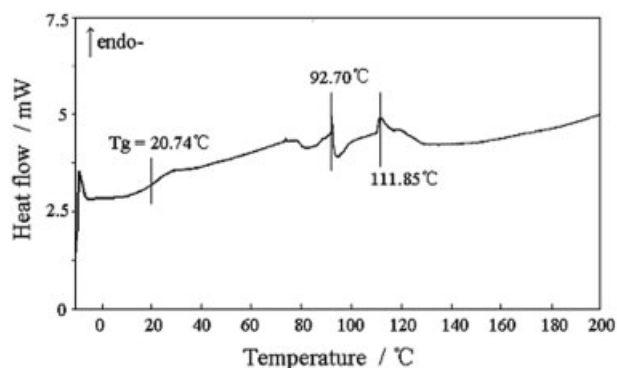

Figure 6 Magnified DSC curve of PLEG synthesized via the first prepolymerization method as feed weight ratio $m_{\text{D,L-LA}}/m_{\text{PEG}} = 90/10$ (M_n of PEG 1000 Da) under absolute pressure 70 Pa, reaction time 10 h, temperature 165°C, and SnO catalyst quantity 0.5 wt %.
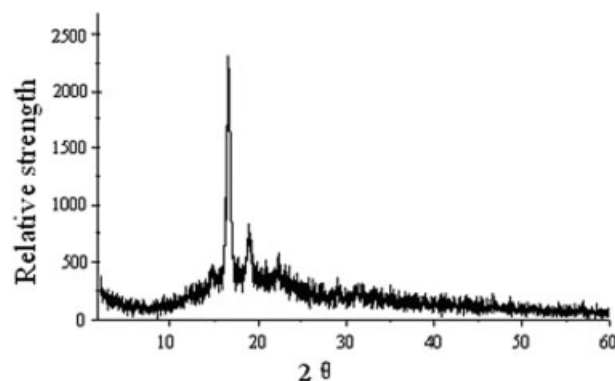

Figure 7 XRD spectrum of L-PLEG1000 synthesized as feed weight ratio $m_{\text{LA}}/m_{\text{PEG}} = 90/10$ (M_n of PEG 1000 Da) and under absolute pressure of 70 Pa, temperature of 165°C for 10 h, and SnO catalyst quantity of 0.5 wt % via the first prepolymerization method.

TABLE XIV
Comparison of XRD Results of PLEG Synthesized under Different Conditions

Run	Samples	PLA face 110 (°)	PLA face 020 and PEG face 110 (°)	PEG face 200 (°)	Crystallinity (%)
1	L-PLEG1000 (M_w = 15,600)[a]	16.6	19.0	22.3	40.2
2	D,L-PLEG1000 (M_w = 35,500)[b]	16.6	19.0	22.3	30.6
3	D,L-PLEG4000 ([η] =0.35 dL/g)[c]	16.7	18.9	22.2	28.0
4	PLLA (M_w = 25,400)[d]	16.7	19.1	N	45.1
5	PDLLA (M_w = 17,800)[d]	16.7	19.1	N	20.8

N, Not existing. All runs were polymerized via the first prepolymerization method with a feed weight ratio m_{LA}/m_{PEG} value of 90/10, an absolute pressure of 70 Pa, a reaction temperature of 165°C, and a catalyst quantity of 0.5 wt %.
[a] Other conditions: SnO, 10 h.
[b] Other conditions: SnO, 18 h.
[c] Other conditions: SnO, 15 h.
[d] As a comparison reference, homopolymers PDLLA and PLLA were synthesized and tested with XRD all under the similar conditions (other conditions: SnCl$_2$, 10 h).[19,25]

CONCLUSIONS

Using LA and PEG as starting material, PLEG, an important biodegradable material used as drug carrier, could be directly synthesized via melt copolymerization. The optimal synthetic conditions for PLEG, including prepolymerization method, catalyst kinds and quantity, reaction temperature, copolycondensation time, the stereochemical configuration of LA, feed weight ratio m_{LA}/m_{PEG} and M_n of PEG, were all investigated in detail. And the properties of serial PLEG directly synthesized were also systematically characterized with GPC, FTIR, ^{1}H NMR, DSC, XRD, and contact angle testing. The conclusion could be summarized as follows:

1. The first prepolymerization method, where LA and PEG were mixed together and dehydrated only once, could save time in whole process, and obtain higher MW PLEG than the second prepolymerization method, where LA is first dehy-

TABLE XV
Contact Angles of D,L-PLEG Synthesized at Different Feed Weight Ratio m_{LA}/m_{PEG} (M_n of PEG 1000 Da)

Run	m_{LA}/m_{PEG}	[η] (dL/g)	M_w (Da)	Contact angles (°)
1	100/0[a]	0.23	17,800	68.7
2	95/5	0.24	N	65.9
3	92/8	0.33	N	65.4
4	90/10	0.40	41,700	63.7
5	88/12	0.30	N	60.9
6	85/15	0.20	N	59.9

N, Not tested. All runs except run 1 were polymerized via the first prepolymerization method with an absolute pressure of 70 Pa, a reaction temperature of 165°C, a reaction time of 15 h, and 0.5 wt % SnO as the catalyst.
[a] As a comparison reference, homopolymer PDLLA was synthesized under the similar conditions, including an absolute pressure of 70 Pa, a temperature of 165°C, a reaction time of 10 h, and 0.5 wt % SnCl$_2$ as the catalyst,[19,25] and tested under the same conditions.

drated singly and then dehydrated again with PEG. And the second prepolymerization method was more apt to give amorphous and random PLEG.

2. Of all selected catalysts, SnO was a good catalyst for the copolymerization of LA and PEG, and its suitable quantity was 0.5 wt % both in the syntheses of D,L-PLEG and L-PLEG. The structure of different PLEG was similar, and confirmed by FTIR and ^{1}H NMR. T_g of all PLEG was markedly lower than homopolymer (PDLLA and PLLA) for the introduction of flexible PEG segment, no matter what prepolymerization method was used, or what M_n of PEG and the stereochemical configuration of LA were.

3. When starting from D,L-LA and PEG (M_n = 1000 Da) as feed weight ratio $m_{D,L-LA}/m_{PEG}$ = 90/10, and pretreated as the first prepolymerization method, 15 h copolycondensation under 165°C and 70 Pa, and 0.5 wt % SnO as catalyst, gave an important drug delivery carrier, D,L-PLEG1000 with the highest [η] of 0.40 dL/g, and the corresponding MW was 41,700 Da. D,L-PLEG1000 with higher [η] than D,L-PLEG4000 also had higher T_g, T_m, and crystallinity.

4. Using L-LA instead of D,L-LA, the optimal synthetic conditions for L-PLEG1000 were different, 10 h polymerization under 165°C and 70 Pa, and 0.5 wt % SnO as catalyst, gave L-PLEG1000 with the highest [η] of 0.21 dL/g and MW of 15,600 Da. Though the MW was lower, L-PLEG1000 had higher T_g, T_m, and crystallinity than D,L-PLEG1000 for the aptness of L-LA chain segment to be crystalline.

5. No matter what LA stereochemical configuration was, the contact angle testing showed that all copolymer modified by PEG had better hydrophilicity than PDLLA, and the contact angle decreased with the increase of PEG feed weight or M_n. The hydrophilic modification of PLA by the

TABLE XVI
Contact Angles of PLEG Synthesized Starting from Different Materials

Run	M_n of PEG (Da)	LA stereochemical configuration	Time (h)	$[\eta]$ (dL/g)	M_w (Da)	Contact angles (°)
1	600	D,L-LA	15	0.23	N	67.3
2	1000	D,L-LA	15	0.40	41,700	63.7
3	2000	D,L-LA	15	0.37	N	61.9
4	1000	L-LA	10	0.21	15,600	64.1
5	(PDLLA)[a]	D,L-LA	10	0.23	17,800	68.7

N, Not tested. All runs except run 5 were polymerized via the first prepolymerization method with a feed weight ratio m_{LA}/m_{PEG} value of 90/10, an absolute pressure of 70 Pa, a reaction temperature of 165°C, and 0.5 wt % SnO as the catalyst.

[a] As a comparison reference, homopolymer PDLLA was synthesized under the similar conditions, including an absolute pressure of 70 Pa, a reaction temperature of 165°C, and 0.5 wt % SnCl$_2$ as the catalyst,[19,25] and tested under the same conditions.

simple and practical direct melt copolymerization of LA and PEG could obtain the same purpose in making PLEG have enough high MW and better hydrophilicity than PLA as the traditional two-step method using lactide as intermediate.

Under the same synthetic conditions, D,L-PELG not only had higher MW than L-PELG, but it also had higher MW than PDLLA and PLLA. Now, PDLLA directly produced have been successfully applied in the field of drug delivery, such as antibacterial (including erythromycin and ciprofloxacin)[18] and Chinese traditional medicine compound prescription "Osteitis No. 1"[19] PDLLA microspheres. Therefore, the novel one-step method can be an alternative route to the synthesis of PLEG, an important drug delivery carrier, instead of the traditional two-step method using tiresome lactide as intermediate.

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