

Synthesis of biodegradable material poly(lactic acid-*co*-glycerol) via direct melt polycondensation and its reaction mechanism

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Abstract To further verify the forming mechanism of multi-core structure during the direct melt copolycondensation of lactic acid (LA) with the compounds containing multifunctional groups, the biodegradable material poly(lactic acid-*co*-glycerol) [P(LA-*co*-GL)] was synthesized as designed using *L*-lactic acid (*L*-LA) and glycerol (GL) as the starting materials. For the molar feed ratio $n(\text{LA})/n(\text{GL})$ of 60/1, the optimal synthetic conditions were discussed. Using 0.3 wt% stannous oxide (SnO) as the catalyst, after the prepolymerization was carried out at 140 °C for 8 h, the melt copolymerization for 8 h at 160 °C gave the polymer with the biggest intrinsic viscosity ($[\eta]$) 0.76 dL·g⁻¹. The copolymers P(LA-*co*-GL)s at different molar feed ratios were characterized by Fourier transform infrared spectroscopy (FT-IR), proton nuclear magnetic resonance (¹H-NMR), gel permeation chromatography (GPC), differential scanning calorimetry (DSC) and X-ray diffraction (XRD). Increasing the molar feed ratio $n(\text{LA})/n(\text{GL})$, the weight-average molecular weight (M_w) didn't increase all the time, but a peak of M_w was formed, which indeed validated the above special phenomenon during the direct melt copolycondensation of LA with the monomers containing multifunctional groups. However, the forming mechanism of multi-core copolymer was different when multihydroxyl alcohol (e.g. GL) was used as the monomer containing multifunctional groups. Because the multi-core structure was linked by the ether bonds with less reversibility in the reaction, the biggest M_w of copolymers was relatively lower. For GL with three terminal hydroxyls as the core, only when $n(\text{LA})/n(\text{GL})$ was

more than 100/1, the star-shaped polylactic acid (SPLA) containing one core could be obtained.

Keywords Biodegradable material · Copolymerization · Drug delivery systems · Melt polycondensation · Polylactic acid · Reaction mechanism · Synthesis

Introduction

As a kind of important biodegradable aliphatic polyester, polylactic acid (PLA) is wholly environment-friendly. Its excellent biocompatibility and biological resorbability afford it extensive applications in bioplastic, biomedical polymer and other fields [1, 2]. In most cases, PLA was synthesized via traditional ring-opening polymerization (ROP) of lactide, and the resulted PLA usually has bigger weight-average molecular weight (M_w) and smaller polydispersity index (PDI). The other method is direct melt polycondensation of lactic acid (LA). It is simpler for shorter synthetic steps, less solvent consumption and lower cost. Unfortunately, the M_w of PLA from the direct method is relatively smaller although some papers reported M_w could reach the same level of ROP method [2–4].

Even so, recently more and more attentions have been attracted to the direct melt copolycondensation of LA with other monomers to improve the properties of PLA, such as the poorer hydrophilicity, the worse cell affinity and unsatisfactory degradation rate [1, 5–37]. Therefore, in these cases, how to get a copolymer with the higher M_w has been becoming an important challenge for the simpler synthetic method. Furthermore, it is strange that during the direct melt copolymerization of LA with the monomers containing multifunctional groups, the M_w didn't increase with the increase of LA feed amount [35–37]. And

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interestingly, the peak phenomena of M_w and multi-core structure of the copolymer were found when increasing the molar feed amount of LA [35, 36].

According to the previous results [35, 36], it could be believed that, in order to get the higher M_w of the copolymer during direct melt copolycondensation of LA with the compounds containing multifunctional groups, only the investigations on the optimal synthetic conditions are not enough, the deeper researches on the reaction mechanism of direct melt copolycondensation should be carried out. Thus, in order to further verify the forming mechanism of multi-core structure during the direct melt copolycondensation of LA with the compounds containing multifunctional groups, the biodegradable material poly(lactic acid-co-glycerol) [P(LA-co-GL)] was synthesized as designed using *L*-lactic acid (*L*-LA) and glycerol (GL) as the starting materials (Scheme 1).

Why using the simple and inexpensive GL with three hydroxyls as the multihydroxyl compound, the reason is due to not only the convenience, but also the extensive applications of PLA modified by GL in biomedical fields. For example, Arvanitoyannis synthesized three-arm star-shaped polylactic acid (SPLA) via ROP using GL as the core, and the product had many special properties, such as good biodegradability, low crystallinity, low melt viscosity and high molecular weight [38]. These advantages made SPLA with GL core and its derivatives used as good drug delivery carriers, tissue engineering scaffolds and medical device materials [39–45]. Therefore, it is well worth to

investigate the direct synthesis of P(LA-co-GL) via melt copolymerization, and the results showed that the formation of SPLA with GL core was related to the feed ratio of reactants (Scheme 1).

Experimental

Materials

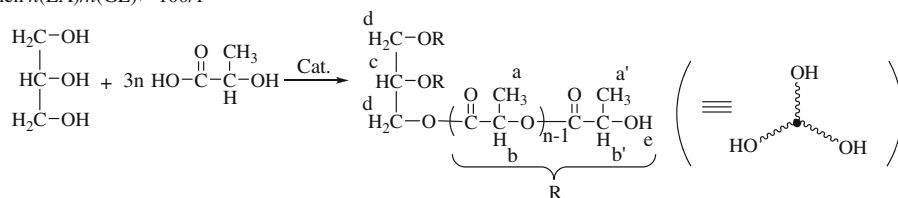
L-Lactic acid (*L*-LA) was purchased from Wako Pure Chemical Industries, Ltd. (Japan), and Glycerol (GL) was purchased from Damao Chemical Reagent Factory (Tianjin, China). All other chemicals, including *p*-toluenesulfonic acid (TSA), stannous oxide (SnO), stannous chloride (SnCl₂), zinc chloride (ZnCl₂) and zinc oxide (ZnO), were commercially available in analytical grade. All these materials were used without further purification.

Instrumental analysis and measurements

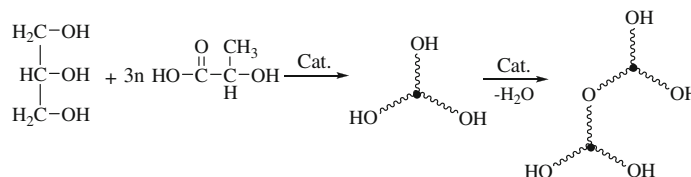
Proton nuclear magnetic resonance (¹H-NMR) spectra were recorded with a DRX-400 NMR spectrometer (Bruker instruments, Billerica, MA) with deuterated chloroform (CDCl₃) as solvent and tetramethylsilane (TMS) as internal standard. Infrared spectra were obtained from a Fourier transform infrared (FT-IR) spectrometer (Bruker Vector 33, Ettlingen, Germany) by the dichloromethane (CH₂Cl₂) liquid film method.

Scheme 1 The synthetic route of P(LA-co-GL)

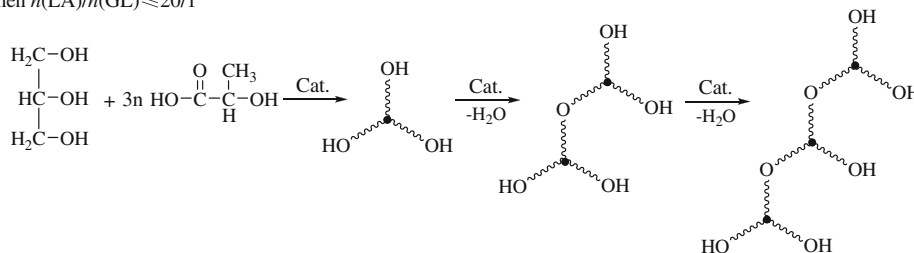
(1) When $n(\text{LA})/n(\text{GL}) > 100/1$



(2) When $20/1 < n(\text{LA})/n(\text{GL}) \leq 100/1$



(3) When $n(\text{LA})/n(\text{GL}) \leq 20/1$



The intrinsic viscosity ($[\eta]$) of PLA modified by GL was determined with Ubbelohde viscometer (Cannon-Ubbelohde, State College, PA) using chloroform (CHCl_3) as solvent at 25 °C. According to literatures [38, 46, 47], the relative molecular weight and molecular weight distribution of the modified PLA were determined by gel permeation chromatography (GPC) (Waters 1,515 pump, Torrance, CA) with tetrahydrofuran (THF) as solvent and with polystyrene (PS) as reference at 40 °C and a flow velocity 1 mL \cdot min $^{-1}$.

Differential scanning calorimetry (DSC) was performed with Perkin-Elmer DSC7 thermal analyzer (Perkin-Elmer, Cetus Instruments, Norwalk, CT) at a heating rate of 10 °C \cdot min $^{-1}$ under a nitrogen atmosphere (flow velocity 20 mL \cdot min $^{-1}$). The crystallinity of PLA modified by GL was investigated by X-ray diffraction (XRD) on a PANalytical X'pert PRO X-ray diffractometer (PANalytical Co., Holland) using $\text{CuK}\alpha$ radiation with a wavelength of 1.5418×10^{-10} m, and scanning range $2\theta = 5\text{--}50^\circ$ at a scanning speed of 0.03 deg \cdot min $^{-1}$.

Prepolymerization

According to the previous works on melt homo-/copolymerization of LA [15, 34–36, 48], LA and GL should be prepolymerized before copolymerization. After LA and GL were uniformly mixed as preplanned molar feed ratio, the mixture was directly dehydrated for 8 h at 140 °C under 4,000 Pa in a flask equipped with mechanical stirring and thermometer.

Melt copolymerization

After prepolymerization, the selected catalyst was added in according to the weight percent (wt%) of dehydrated reactants. The melt copolymerization was carried out at a certain temperature (140–180 °C) and an absolute pressure of 70 Pa for 4–12 h. When the reaction finished, the purification via the dissolution in CHCl_3 and the subsequent precipitation by the mixed solvent of methanol and distilled water ($\text{CH}_3\text{OH}/\text{H}_2\text{O}$) ordinarily produced a white powder after drying *in vacuo*.

Results and discussion

Using *L*-LA and GL as starting materials, the copolymers P(LA-co-GL)s with different molar feed ratios $[n(\text{LA})/n(\text{GL}) = 20/1, 40/1, 60/1, 80/1, 100/1, 120/1, 140/1]$ were directly synthesized via melt copolycondensation after the synthetic conditions were discussed. The structure and properties of these P(LA-co-GL)s were characterized by FT-IR, $^1\text{H-NMR}$, GPC, DSC, XRD and viscosity $[\eta]$ measurements.

Optimal synthetic conditions for P(LA-co-GL)

The optimal synthetic conditions for P(LA-co-GL), including the influences of catalyst kinds and dosage, melt copolycondensation time and temperature on the synthesis of P(LA-co-GL), were first investigated. Catalyst played an important role in the direct melt polycondensation of LA, and usually tin catalysts gave the best effect for their good dispersibility in the reaction system [49–51]. The influences of different catalysts on reaction are shown as Table 1. Among the catalysts, including SnO, SnCl_2 , ZnCl_2 , TSA and ZnO, although the reaction catalyzed by TSA gave the biggest yield (52%, run 4), the $[\eta]$ was smaller than that using SnO as the catalyst (run 5). Thus, SnO was selected as the catalyst for the following experiments because it was most likely to generate the bigger molecular weight.

The influences of different SnO catalyst quantities are shown as Table 2. Usually, the metallic catalysts, including SnO, have double-side effects. They could accelerate the polymerization, but also make the thermal decomposition of the product catalyzed [15, 19]. With the increase of catalyst quantity, the effect of much dosage was exhibited from the color change of product appearance (run 4 and run 5). Therefore, neither too much nor too little is suitable for the catalyst concentration. And for this reaction, the best quantity of SnO was 0.3 wt% (run 2).

The influences of different melt copolymerization temperatures on reaction are shown as Table 3. When the temperature was 140 °C, the lower temperature was disadvantageous for polycondensation to remove the produced water from the reaction system, and the reaction gave a white product with the smallest $[\eta]$ (0.55 dL \cdot g $^{-1}$, run 1). Increasing the temperature to 160 °C yielded the biggest $[\eta]$ (0.76 dL \cdot g $^{-1}$, run 3). But at the higher temperature, the $[\eta]$ decreased, even the color of the product began to become yellow due to the side-reactions, such as the thermal decomposition and oxidation (run 4 and run 5). Thus, the suitable temperature should be 160 °C.

Table 1 The influences of catalyst kinds on the reaction

Run	Catalyst	Appearance of product	$[\eta]/(\text{dL}\cdot\text{g}^{-1})$	Yield/%
1	ZnO	White powder	0.66	30
2	ZnCl_2	White powder	0.69	31
3	SnCl_2	White powder	0.69	32
4	TSA	White powder	0.26	52
5	SnO	White powder	0.71	37

All runs were polymerized with a molar feed ratio $n(\text{LA})/n(\text{GL})$ of 60/1, a prepolymerization temperature of 140 °C, a prepolymerization time of 8 h, a polycondensation temperature of 160 °C, a polycondensation time of 8 h, and a catalyst quantity of 0.5 wt%

Table 2 The influences of catalyst quantity on the reaction

Run	Catalyst dosage/wt%	Appearance of product	$[\eta]/(\text{dL}\cdot\text{g}^{-1})$	Yield/%
1	0.1	White powder	0.66	27
2	0.3	White powder	0.76	41
3	0.5	White powder	0.71	37
4	0.7	Off-white powder	0.65	39
5	0.9	Yellowish powder	0.64	39

All runs were polymerized with a molar feed ratio $n(\text{LA})/n(\text{GL})$ of 60/1, a prepolymerization temperature of 140 °C, a prepolymerization time of 8 h, a polycondensation temperature of 160 °C, a polycondensation time of 8 h, and using SnO as the catalyst

The influences of melt copolymerization time on reaction are shown as Table 4. Obviously, the suitable time should be 8 h. The reason is similar to the above discussion, but mainly due to the influence of the balance between polycondensation and thermal decomposition. Therefore, when the molar feed ratio of $n(\text{LA})/n(\text{GL})$ was the same as 60/1, the optimal synthetic conditions were as follows: catalyst 0.3 wt% SnO, melt copolymerization temperature at 160 °C, and polycondensation time 8 h. Under these conditions, the biggest $[\eta]$ was 0.76 $\text{dL}\cdot\text{g}^{-1}$, and GPC determination showed that the corresponding M_w was 6,400 Da.

Under the above optimal synthetic conditions, serial P(LA-co-GL)s at different molar feed ratios were synthesized with the yield of 23%~44% (Table 5).

Structure characterization of P(LA-co-GL)

The structural characterization of P(LA-co-GL) synthesized with a molar feed ratio $n(\text{LA})/n(\text{GL})$ of 60/1 under the above optimal synthetic conditions was compared with poly(L-lactic acid) (PLLA), the product of the direct melt homopolymerization of LA [15]. It was elucidated that these compounds show similar absorptions in their FT-IR spectra, especially the strong absorption of ester carbonyl near 1,755 cm^{-1} (Fig. 1). The absorption at 2,945 cm^{-1} from the $-\text{CH}_2-$ group [52, 53], appeared in the FT-IR spectrum of P(LA-co-GL) while it became stronger and broader than that observed in the PLLA spectrum, indicating that GL segment has been introduced into the

copolymer. Similarly, the HO stretch vibration absorption near 3,530 cm^{-1} in copolymer also became stronger and broader than that in homopolymer. From another side, this also indicated that the core GL was existed in the copolymer.

The structural studies on P(LA-co-GL) copolymers with different molar feed ratios by FT-IR (Fig. 2) showed similar features. However, there were some differences in the strength of HO stretch vibration absorption between different molar feed ratios. Obviously, the less LA content in the feed ratio, the more the relative amount of terminal HO in the copolymer, which indicated that not only three terminal HO groups per a polymer molecule were existed in the copolymer for all $n(\text{LA})/n(\text{GL})$ molar feed ratios, and the number of the terminal HO group per a copolymer molecule may be more than 3 in some cases, especially for the lower $n(\text{LA})/n(\text{GL})$ molar feed ratios.

$^1\text{H-NMR}$ data of P(LA-co-GL) with a molar feed ratio $n(\text{LA})/n(\text{GL})$ of 60/1, δ , ppm (CDCl_3 as solvent and TMS as internal standard, Fig. 3): 1.502 (Ha', CH_3 in terminal PLA segment), 1.592 (Ha, CH_3 in PLA chain), 2.710 (He, terminal OH), 4.260 (Hb', CH in terminal PLA segment), 4.351 (Hd, CH_2 in GL segment), 5.136 (Hc, CH in GL segment), 5.171 (Hb, CH in PLA chain). Compared with the PLAs modified by GL via ROP (CH_3 in PLA: 1.56 [40], or 1.55 [54], or 1.55–1.58 [55]; He: 2.8 [38] or 2.85 [40]; Hb': 4.20 [54]; Hd: 4.35 [40, 54]; Hb and Hc: 5.16 [40, 54]), the structure of the copolymer P(LA-co-GL) was basically demonstrated by $^1\text{H-NMR}$ as anticipated.

Table 3 The influences of polymerization temperature on reaction

Run	Temperature/°C	Appearance of product	$[\eta]/(\text{dL}\cdot\text{g}^{-1})$	Yield/%
1	140	White powder	0.55	46
2	150	White powder	0.69	31
3	160	White powder	0.76	41
4	170	Yellowish powder	0.71	20
5	180	Yellow powder	0.65	34

All runs were polymerized with a molar feed ratio $n(\text{LA})/n(\text{GL})$ of 60/1, a prepolymerization temperature of 140 °C, a prepolymerization time of 8 h, a polycondensation time of 8 h, and using 0.3 wt% SnO as the catalyst

Table 4 The influences of melt copolycondensation time on the reaction

Run	Time/h	Appearance of product	$[\eta]/(\text{dL}\cdot\text{g}^{-1})$	Yield/%
1	4	White powder	0.62	34
2	6	White powder	0.75	31
3	8	White powder	0.76	41
4	10	White powder	0.65	41
5	12	Yellow viscous solid	0.61	28

All runs were polymerized with a molar feed ratio $n(\text{LA})/n(\text{GL})$ of 60/1, a prepolymerization temperature of 140 °C, a prepolymerization time of 8 h, a polycondensation temperature of 160 °C, and using 0.3 wt% SnO as the catalyst

Therefore, the examination of FT-IR and $^1\text{H-NMR}$ indicated that the obtained products were copolymers and lactate moieties were incorporated into the polyester backbones. However, the analysis of FT-IR for different molar feed ratios and the following more serial analyses, especially $^1\text{H-NMR}$ calculation results of P(LA-co-GL)s at different molar feed ratios, showed that in some cases the structure of P(LA-co-GL) was not a simple star-shaped polymer only embedding a GL core as Scheme 1-(1).

Influences of different molar feed ratios on $[\eta]$ and M_w

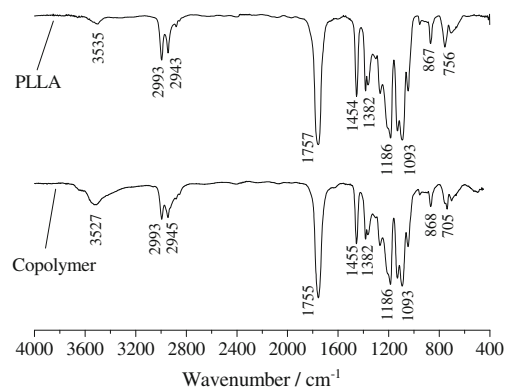
The influences of different molar feed ratios on $[\eta]$ and GPC results are shown in Table 5. Obviously, with the increase of the molar feed ratio of LA, M_w didn't increase all the time, and a peak of M_w was found as reported before [35, 36] (herein, the biggest M_w was 8,800 Da, run 5). Therefore, this indeed validated the special peak phenomena of M_w during the direct melt copolycondensation of LA with the monomers containing multifunctional groups. Of course, for $n(\text{LA})/n(\text{GL})$ 100/1, the PDI (M_w/M_n) was 1.87, the biggest of all, but it was still less than 2. Combined with the single peak shapes in all GPC curves, these PDI data showed that the product of direct melt copolycondensation from two

Table 5 The influences of different molar feed ratios on P(LA-co-GL)

Run	$n(\text{LA})/n(\text{GL})$	Product appearance	$[\eta]/(\text{dL}\cdot\text{g}^{-1})$	Yield/%	M_n/Da	M_w/Da	M_w/M_n^a
1	20/1	Yellow viscous solid	0.60	23	2,600	3,100	1.19
2	40/1	Yellow viscous solid	0.69	31	3,100	4,300	1.39
3	60/1	White powder	0.76	41	4,000	6,400	1.60
4	80/1	White powder	0.79	42	3,300	4,900	1.48
5	100/1	White powder	1.20	35	4,700	8,800	1.87
6	120/1	White powder	0.84	38	3,200	4,900	1.53
7	140/1	White powder	0.94	44	3,200	5,100	1.59

All runs were polymerized with a prepolymerization temperature of 140 °C, a prepolymerization time of 8 h, a polycondensation temperature of 160 °C, a polycondensation time of 8 h, and using 0.3 wt% SnO as the catalyst

^a The peak shapes in all GPC curves are similar, and only a single peak

**Fig. 1** FT-IR spectrum of P(LA-co-GL) synthesized at $n(\text{LA})/n(\text{GL})$ 60/1

monomers was indeed a copolymer P(LA-co-GL) and not a mixture containing any homopolymer PLLA.

When $n(\text{LA})/n(\text{GL})$ was 80/1, run 4 had the same M_w as run 6 (4,900 Da), though its corresponding $[\eta]$ was lower than that of run 6. These indicated that the multi-core structure of the copolymer may be existed in this case, but for run 6 it may be not existed. The explanation is similar to the reported before [35, 36], and could be further confirmed by the following investigations. The M_w peak phenomena and the multi-core structure in the copolymer also should be related to the copolymerization mechanism as reported before [35, 36].

At the same time, it could be seen that, when $n(\text{LA})/n(\text{GL})$ was 20/1, the smallest M_w was 3,100 Da (Table 5, run 1). In the literature [40], when $n(\text{lactide})/n(\text{GL})$ was 9/1, the copolymer P(LA-co-GL) synthesized via ROP was waxy, and its molecular weight by GPC was 1,513 Da; when $n(\text{lactide})/n(\text{GL})$ was 15/1, the GPC molecular weight of the solid copolymer synthesized via ROP was 2,674 Da; for $n(\text{lactide})/n(\text{GL})$ 27/1, the molecular weight was 4,860 Da. Thus, when the feed molar ratio is close, it is possible for the direct method to give the M_w that reached or surpassed the level of ROP method.

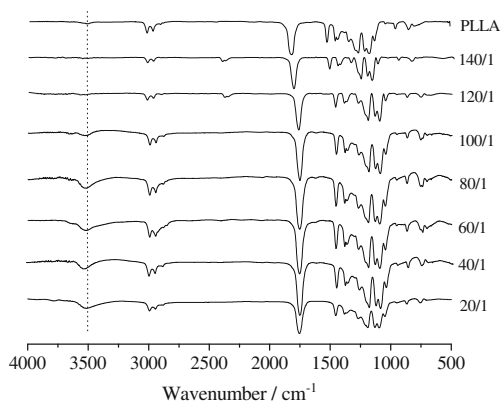


Fig. 2 FT-IR spectra of P(LA-*co*-GL)s with different $n(\text{LA})/n(\text{GL})$ molar feed ratios

Usually, when the PLA biodegradable polymers were used as drug-delivery materials, the M_w was no more than 30,000 Da [7, 48, 56]. As reported in the literature, the PLA material with a molecular weight of 1,800 Da could be applied in drug delivery, even PLA copolymers with M_w of only 900 Da could be used as drug-delivery device [57, 58]. The M_w of P(LA-*co*-GL) synthesized in these experiments was overwhelmingly higher than 900 Da (Table 5). Therefore, the M_w could meet the requirement for drug delivery application at the least.

Influences of different molar feed ratios on thermal properties

The thermal properties of P(LA-*co*-GL) copolymers were characterized by DSC, and the data were shown in Table 6. Obviously, increasing LA content in the feed, the glass transition temperature (T_g) increased gradually (runs 1–7). On the one hand, compared with the linear PLLA synthesized via the direct melt copolycondensation [15] (run 8), the T_g and the melting temperature (T_m) of the copolymers were lower in all cases. This indicated that the introduction of the core GL made the structure changed and T_g decreased indeed as the literature reported that SPLA usually had a lower T_g than the linear PLA [59].

What's more, compared with the star-shaped P(LA-*co*-GL) synthesized via ROP [38] (in Table 6, the data of T_g and T_m were cited in the parentheses), T_g and T_m were also lower in all corresponding cases. These further indicated that the introduction of GL made the structure the copolymers changed, and the regularity of the copolymers was also decreased. The latter should be related to the fact that the copolymer P(LA-*co*-GL) maybe have more PLA arms, rather than the normal three arms. In other words, these phenomena indicated that the multi-core structure may be formed during the direct melt copolymerization of LA with GL.

The data of T_g and T_m in Table 6 also showed that, the bigger LA content in the feed, the smaller difference between two PLA modified by GL using different methods. This revealed that increasing $n(\text{LA})/n(\text{GL})$ could reduce the core number in the multi-core copolymer, which was further demonstrated in the following analyses of XRD characterization and $^1\text{H-NMR}$ calculation.

Influences of different molar feed ratios on crystallinity

The crystallinity of polymers has an important effect on their physical and biological properties, especially their degradability which is crucial for biomaterials. However, no data of XRD characterization was reported before when the star-shaped P(LA-*co*-GL) synthesized via ROP. Even so, compared with the homopolymer PLLA (its XRD absorption peaks appeared at the 2θ of 16.7° and 19.1°) [15], the position of the XRD absorption peaks of all powder solid P(LA-*co*-GL)s was basically similar (Fig. 4).

Further compared with PLLA synthesized via the direct melt copolycondensation [15] (Table 6, run 8), the XRD data of the copolymers showed that the crystallinity (X_c ,%) was obviously lowered due to the introduction of the core GL. Especially, the more GL content in the feed, the smaller X_c datum. Even when $n(\text{LA})/n(\text{GL})$ was no more than 40/1, the multi-core structure of the copolymers was more complicated, which made the copolymer a yellow viscous solid, and no XRD data could be obtained.

Though all X_c data were lower than that of PLLA, to some degree, increasing $n(\text{LA})/n(\text{GL})$ could increase the crystallinity, and this may be related to the reduction of the core number in the multi-core copolymer. At the same time, though the whole regularity of the copolymers was decreased due to the introduction of GL as the core, the crystallite dimension contrarily became bigger than that of PLLA also for the same reason. In a word, the XRD characterization also showed that the multi-core structure

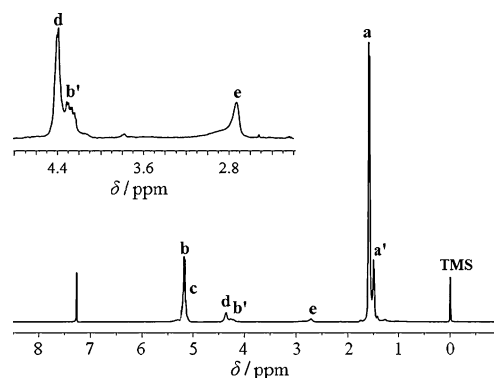


Fig. 3 $^1\text{H-NMR}$ spectrum of P(LA-*co*-GL) synthesized at $n(\text{LA})/n(\text{GL})$ 60/1

Table 6 The DSC and XRD results of P(LA-co-GL)s at different molar feed ratios

Run	$n(\text{LA})/n(\text{GL})$	$T_g/^\circ\text{C}^a$	$T_m/^\circ\text{C}^a$	$2\theta/^\circ$		X/%	Crystallite Dimension/ 10^{-10} m	
				Face 110	Face 020		L_{110}	L_{020}
1	20/1	6 (18)	ND ^b	No Test				
2	40/1	25 (44)	ND (127)	No Test				
3	60/1	35	100	16.5	18.8	15.3	286.2	143.1
4	80/1	37 (45)	98 (140)	16.5	18.9	16.6	357.7	178.9
5	100/1	41	119	16.5	18.8	17.7	357.7	204.4
6	120/1	40	115	16.5	18.9	18.5	484.6	242.5
7	140/1	41 (47)	123 (152)	16.5	18.9	20.8	238.5	178.9
8 ^[15]	PLLA	50.0	134.1	16.7	19.1	45.1	143.4	69.5

All runs were polymerized with a prepolymerization temperature of 140 °C, a prepolymerization time of 8 h, a polycondensation temperature of 160 °C, a polycondensation time of 8 h, and using 0.3 wt% SnO as the catalyst

^aThe data in the parentheses were cited from literature [38]

^bNot detected

was formed when PLA was modified by GL via the direct melt copolymerization.

¹H-NMR calculation results of P(LA-co-GL)s

According to the principle that the integral of proton peak area ratio reflects the amount of substance containing hydrogen group ratio, we calculated the composition of the copolymer molar ratio of each unit using $S_{\text{Ha}+\text{Ha}'}/S_{\text{Hb}'+\text{Hd}}$ as the standard (here, S is the integration area). Supposed that only one GL core was contained in the copolymer, and x is the degree of polymerization (DP) for LA repeating unit, its calculation method could be shown as Formula 1-A.

$$S_{\text{Ha}+\text{Ha}'}/S_{\text{Hb}'+\text{Hd}} = 3x/7 \quad (1 - A)$$

Furthermore, according to the integral of the proton peak area ratio, the number-average molecular weight (M_n) of the copolymer also could be roughly estimated. And the calculation method is shown as Formula 2-A (where 92 is the molecular weight of GL, 72 is the molecular weight of LA repeating unit, x is the DP of LA repeating unit).

$$M_n = 72x + 92 \quad (2 - A)$$

According to the above two formulae, when the copolymers were synthesized at the different molar feed ratios, the results of ¹H-NMR calculation were shown as Table 7 (All M_n values are based on 100 Da as the unit). It could be seen that, M_n of the copolymers tested by ¹H-NMR is usually smaller than the corresponding theoretic value for the escape of LA out of the reaction systems as lactide during the direct melt copolycondensation.

On the other hand, when the $n(\text{LA})/n(\text{GL})$ molar feed ratio is no more than 100/1, the M_n tested by ¹H-NMR is

also correspondingly smaller than that tested by GPC (Table 7, runs 1–5). This suggested that the copolymers with multi-cores should be formed via the ether bond between the terminal hydroxyl of the copolymer. In our previous work, the forming of ether bond has been found during the copolymerization of LA with diethanolamine [60].

According to the similar approach [35], the numbers of GL core in the copolymers could be estimated from the ratio of the M_n tested by GPC to the corresponding M_n tested by ¹H-NMR. It could be found that, when the $n(\text{LA})/n(\text{GL})$ molar feed ratio was less than or equal to 100/1, all ratios were bigger than 1.00, even above 2.00 (Table 7, runs 1–5). These further indicated that two-core or three-core copolymers may be formed during the melt copolycondensation. But when $n(\text{LA})/n(\text{GL})$ was more than 100/1, the corresponding M_n tested by ¹H-NMR was gradually bigger than that tested by GPC (runs 6 and 7). These indicated that P(LA-co-GL) mainly was the copolymer with one GL core in these cases, which was shown as Scheme 1-(1).

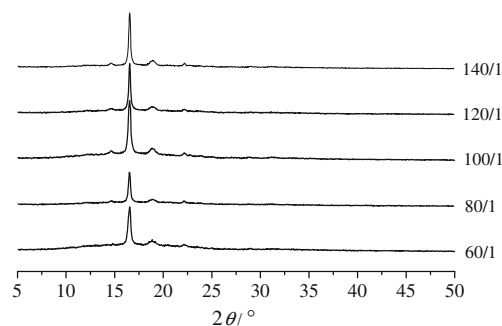


Fig. 4 The XRD spectra of P(LA-co-GL)s at different molar feed ratios [$n(\text{LA})/n(\text{GL})$]

Table 7 The $^1\text{H-NMR}$ calculation results of P(LA-*co*-GL)s according to one GL core

Run	$n(\text{LA})/n(\text{GL})$		$S_{\text{Ha}+\text{Ha}'}/S_{\text{Hb}'+\text{Hd}}$		Theory M_n/Da	Test M_n by $^1\text{H-NMR}/\text{Da}$	Test M_n by GPC/Da	M_n^a/M_n^b
	Feed	Test	Theory	Test				
1	20/1	13/1	60/7	40/7	1,600	1,100	2,600	2.36
2	40/1	21/1	120/7	63/7	3,000	1,600	3,100	1.94
3	60/3	27/1	180/7	81/7	4,500	2,100	4,000	1.90
4	80/1	36/1	240/7	109/7	5,900	2,700	3,300	1.23
5	100/1	49/1	300/7	147/7	7,300	3,600	4,700	1.31
6	120/1	53/1	360/7	160/7	8,800	4,000	3,200	0.80
7	140/1	60/1	420/7	171/7	10,200	4,200	3,200	0.76

^a Tested by GPC^b Tested by $^1\text{H-NMR}$

If P(LA-*co*-GL) mainly was the copolymer with two GL cores, the calculation formulae should be changed from Formula 1-A and Formula 2-A to the following Formula 1-B and Formula 2-B. And the corresponding calculation results of $^1\text{H-NMR}$ data were listed as Table 8.

$$S_{\text{Ha}+\text{Ha}'}/S_{\text{Hb}'+\text{Hd}} = 3x/12 \quad (1 - B)$$

$$M_n = 72x + 92 \times 2 - 18 \quad (2 - B)$$

From Table 8, it could be seen that, for runs 2 and 3, the M_n data of tested by $^1\text{H-NMR}$ were close to those tested by GPC, and the corresponding ratios were very close to 1.00. Namely, when the molar feed ratio $n(\text{LA})/n(\text{GL})$ was 40/1 or 60/1, the resulted P(LA-*co*-GL) was more tended to be the two-core copolymer, which was shown as Scheme 1-(2).

For $n(\text{LA})/n(\text{GL})$ 80/1, the M_n tested by GPC (3,300 Da) was between the M_n tested by $^1\text{H-NMR}$ according two cores (4,700 Da, Table 8, run 4) and that according to one GL core (2,700 Da, Table 7, run 4), which implied that the

copolymers' structure was more complex for the products simultaneously contained one-core and two-core copolymers. For $n(\text{LA})/n(\text{GL})$ 100/1, the similar conclusion could be drawn from the corresponding data (Table 8, run 5; Table 7, run 5).

When the molar feed ratio $n(\text{LA})/n(\text{GL})$ was 20/1 (Table 8, run 1-B), it could be seen that, the M_n data of tested by $^1\text{H-NMR}$ (1,900 Da) was still smaller than that tested by GPC (2,600 Da). Therefore, we supposed that P(LA-*co*-GL) mainly was the copolymer with three GL cores, and the calculation formulae were shown as Formula 1-C and Formula 2-C.

$$S_{\text{Ha}+\text{Ha}'}/S_{\text{Hb}'+\text{Hd}} = 3x/17 \quad (1 - C)$$

$$M_n = 72x + 92 \times 3 - 18 \times 2 \quad (2 - C)$$

The corresponding calculation results in Table 8 (run 1-C) showed that the M_n tested by $^1\text{H-NMR}$ was very consistent with that tested by GPC. Namely, in this case, the resulted P

Table 8 The $^1\text{H-NMR}$ calculation results of P(LA-*co*-GL)s according to multi-core structure

Run	$n(\text{LA})/n(\text{GL})$		$S_{\text{Ha}+\text{Ha}'}/S_{\text{Hb}'+\text{Hd}}$		Test M_n by $^1\text{H-NMR}/\text{Da}$	Test M_n by GPC/Da	M_n^a/M_n^b	
	Feed	Test	Theory	Test				
1	1-B ^c	40/2	46/2	60/12	69/12	1,900	2,600	1.37
	1-C ^d	60/3	99/3	60/17	98/17	2,600		1.00
2 ^c		80/2	72/2	120/12	108/12	2,800	3,100	1.10
3 ^c		120/2	93/2	180/12	139/12	3,500	4,000	1.14
4 ^c		160/2	125/2	240/12	187/12	4,700	3,300	0.70
5 ^c		200/2	167/2	300/12	250/12	6,200	4,700	0.76

^a Tested by GPC^b Tested by $^1\text{H-NMR}$ ^c According to two cores^d According to three cores

(LA-co-GL) was very tended to be three-core copolymer, which was shown as Scheme 1-(3). Thus, when the molar feed ratio $n(\text{LA})/n(\text{GL})$ was different, the copolymer with different main structure was formed, which was related to the reaction mechanism of the direct melt copolymerization.

Possible mechanism of direct melt copolycondensation of LA with GL

Based on the above analyses and our previous works [35, 36, 60], the possible mechanism of direct melt copolycondensation of LA with GL was proposed as Scheme 2. It could be believed that, in the first stage of the direct melt copolycondensation, the main reaction was the forming of SPLA using GL as the core shown as Scheme 2-(1), and the increment of M_w was dependent on the length of PLA arms.

In the late stage of the copolycondensation, especially increasing the molar feed of GL, the terminal hydroxyl of PLA arms was likely to form ether bond by dehydration, and the two-core or three-core copolymer was produced, which was the reaction shown as Scheme 2-(2). Hence, the product was not the simple three-arm PLA. And the structure of the copolymers was dependent on the molar feed ratio $n(\text{LA})/n(\text{GL})$ during direct melt copolycondensation.

When the molar feed ratio $n(\text{LA})/n(\text{GL})$ was less than or equal to 100/1, the SPLA with smaller M_w was combined with ether bond, and the copolymer with multi-core structure was obtained. The less the molar feed of LA was, the easier the forming of multi-core structure was. Only when the molar feed ratio $n(\text{LA})/n(\text{GL})$ was more than 100/1, the SPLA with bigger M_w could be synthesized as anticipated, which was shown as Scheme 2-(3).

During the forming of multi-core copolymers, the M_w of copolymers also could be increased. Hence, two factors had influence on the value of M_w . One was the length of PLA arm, and the other was the number of GL core. Increasing

the molar feed of LA was advantageous to make the PLA arm longer. Contrarily, it was disadvantageous to make the forming of multi-core structure harder because the forming of ester bond was easier than that of ether bond. Thus, only the simultaneous existence of both suitable arm length and core number could make the copolymer with the biggest M_w , namely make the M_w peak value formed.

These phenomena of multi-core structure and M_w peak value also explained why M_w was not increased constantly with the increase of LA molar feed when LA and pentaerythritol (also a multihydroxyl core) were directly copolymerized [61]. These conclusions were indeed similar to the reported before [35, 36]. However, for different multi-core structure, the connection bond was different. During the direct melt copolycondensation of LA with cholic acid (CA), multi-core structure was combined with ester bond [35]. For the copolymerization of LA with trimesic acid (TMA), the connection bond was anhydride bond [36]. In this study, it was ether bond.

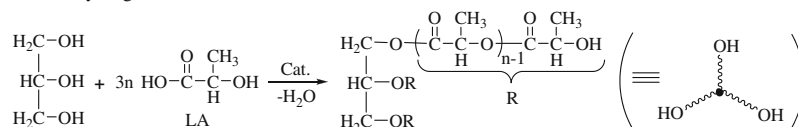
The forming reversibility of ester bond or anhydride bond, and the further transesterification [35] or esterification [36] could make M_w increased. However, once the ether bond in the reaction system was formed, it was difficult to convert the ether bond into alcohol hydroxyl. Therefore, the biggest M_w (8,800 Da) in this reaction system was relatively smaller than that in other cases (for the copolymerization of LA and CA, the biggest M_w was 12,800 Da [35]; for the copolymerization of LA and TMA, the biggest M_w was 23,100 Da [36]).

Conclusions

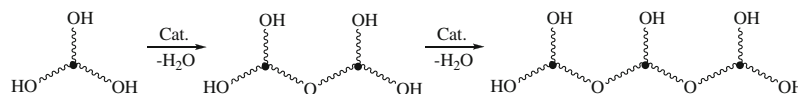
To further verify the forming mechanism of multi-core structure during the direct melt copolycondensation of LA with the compounds containing multifunctional groups, the

Scheme 2 The possible mechanism of direct melt copolycondensation of LA with GL

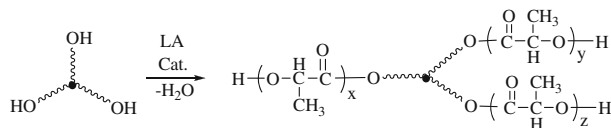
(1) At the early stage of the reaction



(2) At the late stage of the reaction when $n(\text{LA})/n(\text{GL}) \leq 100/1$



(3) At the late stage of the reaction when $n(\text{LA})/n(\text{GL}) > 100/1$



biodegradable material P(LA-co-GL) was synthesized as designed using L-LA and GL as the starting materials. For the molar feed ratio $n(\text{LA})/n(\text{GL})$ of 60/1, after the prepolymerization was carried out at 140 °C for 8 h, the melt copolymerization catalyzed by 0.3 wt% SnO for 8 h at 160 °C gave the polymer with the biggest $[\eta]$ 0.76 dL·g⁻¹.

The systematical characterization of the copolymers P(LA-co-GL)s at different molar feed ratios by FT-IR, ¹H-NMR, GPC, DSC and XRD showed that, the forming of the multi-core structure and the M_w peak phenomenon was found indeed as expected. And only when $n(\text{LA})/n(\text{GL})$ was more than 100/1, SPLA containing one GL core could be obtained. The further confirmed mechanism of the direct melt copolycondensation of LA and other monomers is favorable for the modification of PLA by more monomers containing multifunctional groups via direct melt copolycondensation.

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