

Synthesis and Structure Control of L-Lactic Acid-Glycolic Acid Copolymer by Homo-Copolymerization

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ABSTRACT: A two-step direct melt copolymerization process of L-lactic acid (L-LA)/glycolic acid (GA) was developed: poly(L-lactic acid) (PLLA) and poly(glycolic acid) (PGA) with different molecular weight was first synthesized respectively by binary catalyst (tin chloride/*p*-toluenesulfonic or tin chloride); and then poly(L-lactic-*co*-glycolic acid) (b-PLGA) was produced by melt polymerization of the as-prepared PLLA and PGA, wherein the composition and chain structure of b-PLGA copolymers could be controlled by the molecular weight of PLLA. The chain structure and thermal properties of copolymers were studied by Wide-angle X-ray diffraction, nuclear magnetic resonance, differential scanning calorimetry, and thermogravimetric analysis. In comparison with the random PLGA (r-PLGA) synthesized by one-step direct melt polymerization, the average L-lactic blocks length (L_{LA}) in b-PLGA was longer while the average glycolic blocks length (L_{GA}) in b-PLGA was shorter which further resulted in the improved crystallinity and thermostability.
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INTRODUCTION

Poly(L-lactic-*co*-glycolic acid) (PLGA), approved by US Food and Drug Administration for medical use, for example, implants for interior bone fixation, artificial skin, tissue scaffolds, and drug delivery,¹ is the most widely employed biodegradable and bioassimilable polymers both experimentally and clinically.^{2–4} The control to its structure and composition is a permanent topic for meeting various needs, especially sequence and/or stereo-control, which is a powerful tool for creating PLGAs with the precisely tuned behavior and became an exciting new frontier recently.

Ring opening polymerization (ROP)^{5,6} and direct polycondensation^{7,8} are commonly used to synthesize poly(D,L-lactic acid) (PDLLA), poly(L-lactic acid) (PLLA), poly(glycolic acid) (PGA), and PLGA homopolymer and copolymer. PLGA with high molecular weight and narrow molecular weight distributions usually can be obtained by ROP of lactide and glycolide with stannous octoate as a catalyst. However, the synthetic route is long and complex process, and the cost is expensive. Direct polycondensation from monomers, i.e. lactic acid (LA) and glycolic acid (GA), is usually relatively simple and ecologically attractive. However, in the direct polycondensation, the produced segments of GA units were longer since the reactivity ratio of GA to LA is much high,^{9–11} which further resulted in low crystallization of

PLGA. If using the previously prepared homopolymers, i.e. PLLA and PGA, as reactants, it is possible to control the length of segments by the molecular weight of respective homopolymers so that polymer chains structure could be controlled, which provides an opportunity to adjust polymer properties, e.g. crystallization. Normally, ROP could control the structure of the products very strictly, however, since the synthesis of multiple rings is difficult, it is difficult to synthesize PLGA with longer LA chain segment. And directly melt polycondensation is unable to control the polymer structure, the product is usually random polymer. The crystallinity of polymer effects the mechanical performance, for example, as orthopedic fixation material, crystalline polymer is more suitable than the amorphous one with the same molecular weight; crystallization of polymer generally results in the higher melting point so that they can be used at higher temperature.

Tan and coworkers^{12–14} had synthesized poly(1,4-butylene terephthalate-*co*-DL-lactide) (BLA) copolymers with high molecular weight by melt reaction between DL-oligo(lactic acid) (OLA) and poly(1,4-butylene terephthalate) (PBT) without any catalysts. They also synthesized poly(ethylene terephthalate-*co*-ethylene oxide-*co*-DL-lactide) by the same method.

We hereby report the preliminary results of homo-copolymerization, where the molecular structure of b-PLGA,

such as LA unit length, GA unit length, was influenced seriously by the molecular weight of homopolymer PLLA. A series of copolymers of L-lactic and GA, with long -LL- chain length and short -GG- chain length, were synthesized by melt copolymerization of PLLA and PGA homopolymers. Their structures could be controlled by the molecular weight of PLLA and PGA.

EXPERIMENTAL

Materials

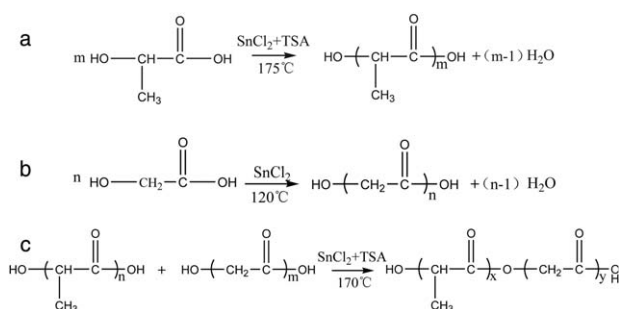
L-Lactic acid (L-LA) as a 90 wt % aqueous solution purchased from Musashino Chemical (China) Co. was dehydrated by vacuum distillation at 100°C before use. GA (AR grade) purchased from Guangfu Chemical reagent factory (China) was purified by recrystallization with ethyl acetate. Stannous chloride (SnCl₂) (GR grade) was purchased from Acros. *p*-Toluenesulfonic acid (TSA) (AR grade) was purchased from Tianjin Fucheng Chemical Reagent Factory (Tianjin, China). Acetone, chloroform, and ethanol (AR grade) were purchased from Beijing Chemical Corp (Beijing, China).

Preparation of Lactic Acid and Glycolic Homopolymers

PLLA and PGA homopolymers were firstly synthesized from L-LA and GA by direct melt polycondensation. PLLA with different average molecular weight were obtained at 175°C by controlling the reaction time and pressure of the reaction system, where L-LA, stannous chloride (SnCl₂) (0.4 wt % of L-LA), and TSA (TSA : SnCl₂ = 1 : 1, molar ratio) were charged into a 250 mL three-necked flask equipped with a mechanical stirrer and a vacuum system. The produced PLLA was dissolved in chloroform and then precipitated into ethyl alcohol for purification. The same process was utilized to prepare PGA at 120°C with stannous chloride (SnCl₂) (0.5 wt % of GA) as catalyst. Then, the obtained PLLA and PGA (PLLA : PGA = 80 : 20, molar ratio, $[\eta_{PGA}] = 0.18$ dL/g) were melted and reacted at different temperatures with SnCl₂ (0.3 wt % of the total mass of PLLA and PGA) and TSA (TSA : SnCl₂ = 1 : 1, molar ratio); 4 h later, crude copolymer product was obtained. The crude product was dissolved in acetone and separated after centrifugation, and then the soluble part was precipitated with ethyl alcohol for getting clean b-PLGA. The purified b-PLGA was stored in desiccator after dried in vacuum oven at 40°C for 6 h. For comparison, random PLGA (r-PLGA) was synthesized at 175°C by L-LA and glycolic monomer with SnCl₂ and TSA as catalysts in direct melt polycondensation.

Characterizations and Measurements

The molecular weight (M_w) and dispersity index (PDI) of PLLA and b-PLGA samples were determined by gel permeation chromatography (GPC) (Waters GPC515-2410 System, US) using polystyrene (PS) as standard and tetrahydrofuran (THF) as an eluent with a flow rate of 1 mL/min at 30°C. Viscosity of PGA at a concentration of 1 g/L was measured using 1,1,1,3,3,3-hexafluoroisopropanol as solvent with a Ubbelodhe viscosimeter at 25°C. Intrinsic viscosity ($[\eta]$) was calculated by the "One Point Method" and expressed in dL/g: $[\eta] = [2(\eta_{sp} - \ln\eta_r)]^{1/2}/c$ where $\eta_r = \eta/\eta_0$ and $\eta_{sp} = \eta_r - 1$, η and η_0 being the viscosity of the polymer solution and that of the solvent, respectively. The samples were dissolved in THF at a concentration of 1–2 mg/mL. The melting temperature of the b-PLGA was determined by a differential scanning calorimeter (DSC) (DSC6200, Seiko Instruments, Japan).



Scheme 1. Synthesis routes of LA/GA copolymers (b-PLGA).

About 6.0 mg of b-PLGA sample was analyzed in the temperature range from 20 to 200°C with a heating rate of 10°C/min in nitrogen gas at a flow rate of 50 mL/min. Wide-angle X-ray diffraction (WAXD) measurements were carried out at room temperature with a Rigaku Model D/max-RB diffractometer system using Cu-K α radiation (40 kV, 200 mA). ¹H-NMR and ¹³C-NMR were performed with Bruker avance II 500 NMR spectrometer using tetramethylsilane as internal reference and CDCl₃ as solvent. ¹H-NMR spectra were acquired on 1 wt % solutions at 500 MHz, while ¹³C-NMR spectra were acquired on 5 wt % solutions at 125 MHz, with a pulse angle of 25°, acquisition time of 1.6 s, and a delay time of 10 s. Thermal stability of these samples were measured with thermogravimetric analysis (TGA) utilizing Seiko 6300 Seiko Instrument with a heating rate of 10°C/min in nitrogen gas at a flow rate of 50 mL/min.

RESULTS AND DISCUSSION

As shown in Scheme 1, homopolymer PLLA and PGA was respectively synthesized first, then copolymerization was carried out on the basis of the as-prepared homopolymers, where the molecular structure of copolymer, especially segmental length, is closely related with the molecular weight of the homopolymers.

Influence of the Molecular Weight of PLLA on the Composition and Chain Structure of b-PLGA

A series of b-PLGA were synthesized with different molecular weight of PLLA and the same PGA with $[\eta_{PGA}] = 0.18$ dL/g by melt copolymerization at 170°C, where the ratio of PLLA to PGA is always kept at 80 : 20. The compositions of the copolymers were determined by ¹H-NMR spectra shown in Figure 1(a). The molar component ratio of GA segment in PLGA (p_{GA}) can be calculated from the integrated area of the multiplets at 4.6–4.9 ppm and 5.2 ppm which were assigned to the methylene (—CH₂) protons in GA units and methane (—CH) protons in LA units, respectively. The mole fraction of GA units of the PLGA (p_{GA}) was calculated according to eq. (1) and listed in Table I, wherein I_G represents the integrated area of the peaks at 4.6–4.9 ppm, I_L represents the integrated area of the peak at 5.2 ppm respectively.^{15,16}

$$p_{GA} = I_G / (2I_L + I_G) \quad (1)$$

It is known that carbonyl ¹³C-NMR resonances are sensitive to sequential changes and thus can provide macromolecular fine structures and important sequential information.¹⁷ Experimental average lengths of GA (L_{GA}) and L-LA (L_{LA}) blocks can be calculated from the relative intensity of the signals corresponding

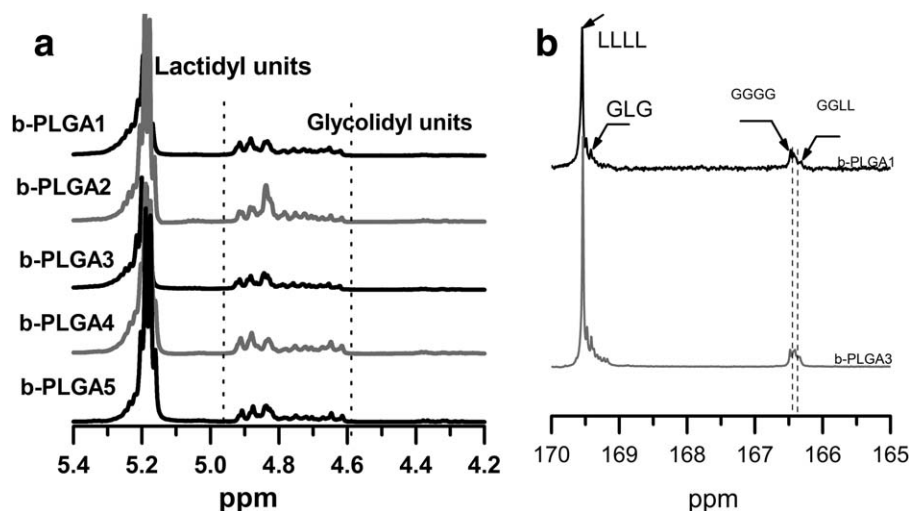


Figure 1. ^1H -NMR and ^{13}C -NMR spectra of b-PLGA.

to the different diad sequences assigned in ^{13}C -NMR spectra [Figure 1(b)], by using the eqs. (2) and (3): where I_{LL} is the integral of carbonyl signals of LA units linked with LA(-LLLL-sequence), and I_{LG} is the integral of carbonyl signals of LA units linked with GA(-GLG-sequence); I_{GG} is the integral of carbonyl signals of GA units linked with GA(-GGGG-sequence), and I_{GL} is the integral of carbonyl signals of GA units linked with LA(-GLL-sequence).^{18–22} The compositional and chain structural parameters obtained from the GPC and NMR results are listed in Table I.

$$L_{\text{GA}} = \frac{I_{\text{GG}} + I_{\text{GL}}}{I_{\text{GL}}} \quad (2)$$

$$L_{\text{LA}} = \frac{I_{\text{LL}} + I_{\text{LG}}}{I_{\text{LG}}} \quad (3)$$

As shown in Table I, the molecular weight of copolymer decreased with that of PLLA. When PLLA had a low molecular weight of 8.6 kDa, the molecular weight of b-PLGA reached a maximum value of 46.5 kDa. And conversely, when the PLLA had a larger molecular weight of 46.5 kDa, the molecular weight of the b-PLGA decreased to 21.8 kDa, which was smaller than

that of the feeded homopolymer PLLA. The reason is related with the balance during polymerization between the growth of polymer chains and the breaking of PLLA. With the increase of the molecular weight of PLLA, the number of end groups decreased, which led to reduction of the macromolecular activity. When the molecular weight of PLLA was up to 37.6 kDa, the motion of polymer chains became slow very much while the hydrolysis and alcoholysis became the main reactions in the system, which led to the breaking of PLLA chains. When the chain growth during polycondensation of PLLA and PGA was not enough to make up the decrease of molecular weight of PLLA, the chains cleavage was shown so that the molecular weight of b-PLGA4 and that of b-PLGA5 were lower than those of the original PLLA. This result evidently implied that the copolymerization was in accordance with the second mode of transesterification proposed by Dobrzynski and coworkers,^{15,23–26} i.e. the molecular chains of homopolymer PLLA and PGA could break first and combine together between different fragments again.

Furthermore, the average segment length of LA and GA (defined as L_{LA} and L_{GA}) in copolymer b-PLGA increased with

Table I. Influence of the Molecular Weight of PLLA on the Composition and Sequence Structure of b-PLGA

Sample	$M_{\text{w(PLLA)}}$ (kDa)	$M_{\text{w(b-PLGA)}}$ (kDa)	b-PLGA content in product (wt %)	Molar fraction of GA in PLGA (mol %)		Average seg- ment lengths	
				Feed ratios	^1H -NMR	L_{LA}	L_{GA}
m-PLGA ^a	LA	27.8	100	20	25.4	4.5	3.3
b-PLGA1 ^b	8.6	46.5	95.9	20	18.7	6.5	2.5
b-PLGA2 ^b	10.3	37.2	95.1	20	16.9	7.0	2.8
b-PLGA3 ^b	19.9	32.5	92.6	20	15.0	8.1	2.8
b-PLGA4 ^b	37.6	21.8	26.6	20	13.9	9.0	3.4
b-PLGA5 ^b	73.7	25.6	7.6	20	11.3	9.5	1.9
r-PLGA	LA, GA	22.4	100	20	22.3	3.1	3.3

^am-PLGA was synthesized by homo-copolymerization with LA monomer and PGA.

^bb-PLGA1–b-PLGA5 were synthesized by homo-copolymerization with different PLLA.

Table II. Molecular Characteristics of b-PLGA at Different Reaction Temperature

Sample	$M_w(\text{b-PLGA})$ (kDa)	Contents of b-PLGA (wt %)	Molar fraction of GA in PLGA		Average sequence length	
			Feed ratio (mol %)	$^1\text{H-NMR}$ (mol %)	L_{LA}	L_{GA}
b-PLGA140 ^a	8.9	61.6	20	8.6	9.58	1.42
b-PLGA150	11.9	69.3	20	11.1	8.26	1.80
b-PLGA160	18.3	92.2	20	16.6	8.57	2.49
b-PLGA170	36.1	95.6	20	23.3	7.34	2.10
r-PLGA	22.4	100	20	22.3	3.14	6.10

^a The number represents the reaction temperature

PLLA molecular weight, which indicates that the molecular structure of b-PLGA could be controlled and adjusted by the as-prepared PLLA although it could be broken during polymerization. As a comparison, r-PLGA was synthesized by monomers (LA and GA), whose results are also shown in Table I. The r-PLGA has a low molecular weight and very short L_{LA} segments; apparently, L_{LA} in b-PLGA is longer than that of r-PLGA,¹⁰ which is very important to their crystallization. In the direct melt condensation of r-PLGA, as the reaction ratio of LA was lower than that of GA, GA tended to link with GA monomer and form the longer chain segments. With GA consumption, LA began to participate in the copolymerization, which results in copolymer growth finally. Except the above polymer growth, alcoholysis and hydrolysis reaction of PLLA and PGA took place in the homo-copolymerization, which to some extent reduced the molecular chain length. Since the polylactic acid has a certain molecular weight which could retain a higher chain length. Transesterification occurred between the broken segments of PLLA and PGA for generating PLGA with long LA segment and short GA segment. The result in turn exhibits the advantage of the homo-copolymerization, especially on controlling segments and molecular weight.

Influence of Reaction Temperature on the Product Composition and Chain Structure

Without any doubt, reaction temperature will influence the sequence structure of copolymer b-PLGA according to the breaking/growing mechanism. A series of samples were prepared with PLLA ($M_w = 6.8$ kDa) and PGA by direct melt polymerization at different reaction temperature. The compositional and chain structural parameters obtained from the GPC and NMR results are listed in Table II.

Both of the composition and the molecular weight increased with the reaction temperature. Specifically, for the sample with the reaction temperature of 140°C, the content of b-PLGA is 61.6%, and the molecular weight is 8.9 kDa; but for the sample prepared at 170°C, they were 95.6% and 36.1 kDa, respectively. Higher reaction temperature resulted in the higher molecular weight and higher yield, which resulted from kinetic factor. The copolymerization of PLGA was a condensation and exothermic reaction. In the view of reaction equilibrium, the low temperature was beneficial to generate polymer. But by the dynamics of polyester, raising the temperature can improve the reaction rate

and lower the viscosity of the system. This will be in favor of the elimination of water and the generation of polymer, thereby increasing the molecular weight of the polymer. The more important is that the molecular chains of homopolymer PLA could be broken more easily when the reaction temperature rises according to the breaking/growing mechanism so that L_{LA} decreased with temperature, whose results are also shown in Table II.

Crystallization and Thermal Properties of PLGA

WAXD of b-PLGA is shown in Figure 2, which indicated that all b-PLGA samples were crystal polymer and DSC curve in Figure 3 also proved this conclusion. The diffraction peaks of PLGA observed at $2\theta = 16.7^\circ$ (200 reflection) and 19.1° (203

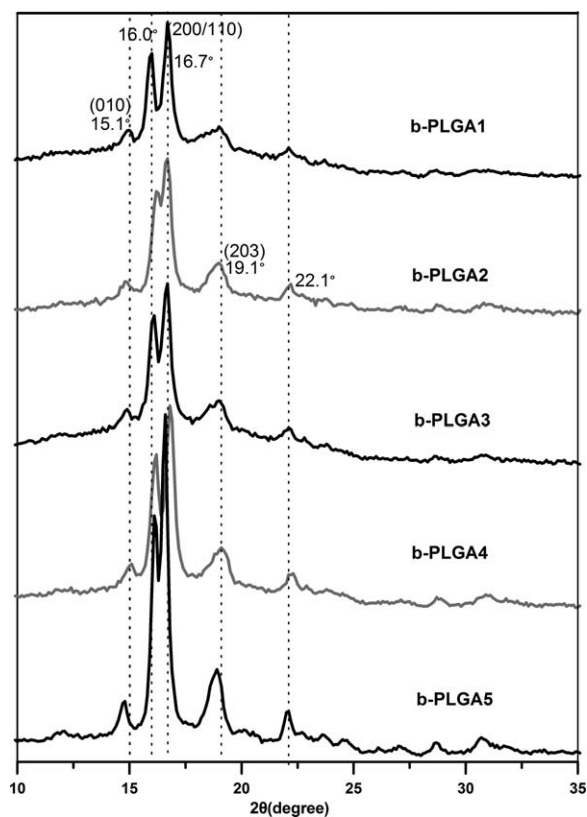


Figure 2. WAXD spectrogram of b-PLGA.

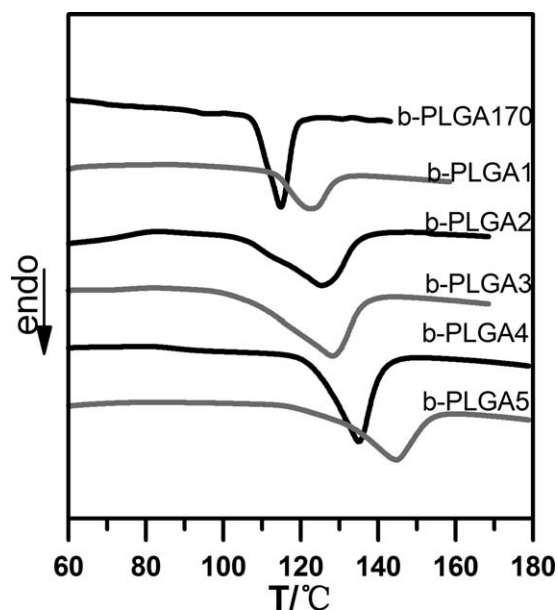


Figure 3. DSC curves of b-PLGA synthesized with different PLLA.

reflection) can be assigned to α' form, and $2\theta = 16^\circ\text{--}16.2^\circ$ can be assigned to α'' form.^{27–29} The crystal of b-PLGA was a blending form of α'' and α type since PLLA crystalline was destroyed by GA segment. Compared with the α form, α'' type had the larger interplanar spacing, the poor regularity chain accumulation, and the lower crystal density. With the increase of LA segment length (shown in Table I), the crystallization became better and better. There are two main theories of copolymer crystallization, one is the comonomer inclusion model and another is the comonomer exclusion model. Gao et al.⁷ suggested that when the molar fraction of GA in feed was less than 20%, the crystallization of PLGA resulted from the crystallization of long L-LA sequences, which tended to exclude GA units. So, L-LA sequences, derived from PLLA, directly influenced the crystallization of b-PLGA, i.e. the crystallization properties of copolymer could be controlled by the molecular weight of PLLA.

Figure 3 shows the typical DSC thermograms of b-PLGA synthesized with different molecular weight of PLLA and the same PGA by homo-copolymerization. With the increasing molecular weight of PLLA, the decreased molar fraction of GA in PLGA

Table III. Influence of b-PLGA Chain Structure to T_m and χ_c

Sample	F_{GA}^a (%)	T_m (°C)	χ_c^b (%)
b-PLGA170	23.3	119.6	44.3
b-PLGA1	18.7	122.5	45.0
b-PLGA2	16.9	125.5	46.4
b-PLGA3	15.0	128.2	47.4
b-PLGA4	13.9	135.0	57.8
b-PLGA5	11.3	144.6	62.7
m-PLGA	25.4	ND	ND
r-PLGA	22.3	ND	ND

^a Calculated from ¹H-NMR spectrum.

^b Calculated from WAXD diffract graph.

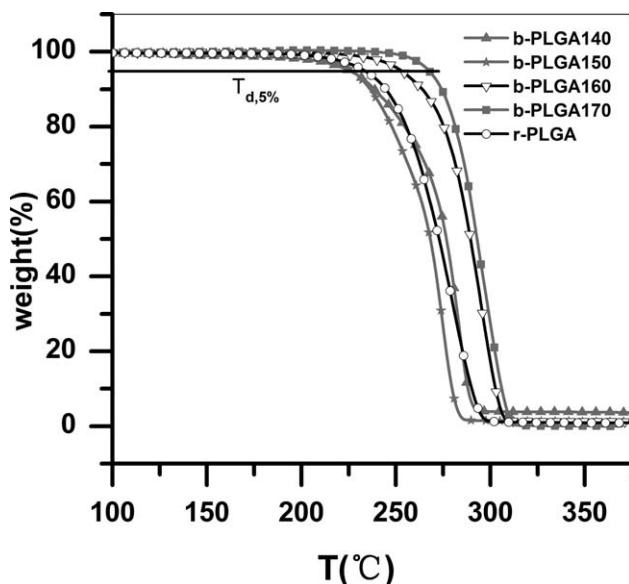


Figure 4. TGA results of PLGA polymers synthesized at different temperatures.

and longer LA segments length (shown in Table I), the melting temperature (T_m) and the crystallinity of b-PLGA increased. F_{GA} (the molar ratio of GA) and χ_c were respectively calculated by ¹H-NMR and WAXD graph and are listed together with T_m in Table III. With the increase of GA content in b-PLGA, melting temperature (T_m) gradually decreased. Furthermore, at the similar molar content of GA, chain segments length play more important role on the crystallization of copolymer, especially for samples with the high content of LA, e.g. the longer -LL- segments and the lower -GG- segments, the higher T_m and the higher χ_c . For example, T_m of b-PLGA5 is 144.6°C which is about 32°C higher than the reported³⁰ T_m of PLGA with the similar composition. Especially, T_m of b-PLGA170 was 119.6°C, but T_m of r-PLGA and m-PLGA were not observed though they had the same GA content of them. This is consistent with WXR results. Moreover, T_m increased with the molecular weight of PLLA (Table III). Therefore, the average chain segments length of each component in b-PLGA could be adjusted in homo-copolymerization method by the different molecular weight of PLLA so that their crystallization and melting temperature could be controlled.

Thermal degradation of PLLA was a back biting reaction, namely chain scission from the hydroxyl-terminated.^{31–33} In general, thermal degradation of PLA can be attributed to hydrolysis by trace amounts of water, random main-chain scission, intermolecular transesterification to monomer and oligomeric esters, or intramolecular transesterification.³⁴ Thermal decomposed behavior of PLGA copolymers prepared at different reaction temperature was investigated by TGA. As shown in Figure 4, all PLGA samples with different chain structures could be completely decomposed before 325°C, whose mass loss was ~100%. For b-PLGA samples, the onset value and the temperature at the maximum mass loss increased with the reaction temperature in copolymerization, which can be ascribed to the increasing molecular weight of PLGA with the reaction

temperature (as shown in Table II). According to the thermal degradation mechanism, when the molecular weight increased, the number of terminal hydroxyl groups decreased, which caused an improved thermal stability. The effect of molecular weight on thermal stability is weak when M_w is over 20,000 g/mol.³⁵ It is worth to pay an attention that $T_{d,5\%}$ of b-PLGA 160 is about 20°C higher than that of r-PLGA though M_w (b-PLGA160) was lower than M_w (r-PLGA) (wherein M_w (b-PLGA160) = 18.3 kDa and M_w (r-PLGA) = 22.4 kDa), which could only be ascribed to the longer LA segment length in b-PLGA than in r-PLGA.

CONCLUSION

On the basis of homo-copolymerization, a series of b-PLGA with the different component ratios and various segment structures were synthesized. Calculated by NMR spectra, the LA unit lengths were longer and GA unit lengths were shorter in polymer chains of b-PLGA than r-PLGA prepared with monomers. Furthermore, the segment length of LA and GA could be controlled by homopolymer PLLA. DSC, WAXD, and TGA data indicated that the structure of b-PLGA was beneficial to their crystallization and thermal stability, which is seriously influenced by the length of LA segment, that is the longer LA segmental length, the better the b-PLGA crystallization and the thermal stability. For b-PLGA with the same GA content, the melting point and the decomposition temperature of PLGA could vary with the different average segment lengths. Such improvement in crystal properties and thermal stability will be very helpful to enhance the properties and processing of PLGA.

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