Synthesis and Characterization of the Biomaterial Poly(lactic acid-*co*-N^{ε}-carbobenzoyloxy-L-lysine) via Direct Melt Copolymerization

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ABSTRACT: With D,L-lactic acid and N^{ε}-carbobenzoyloxy-L-lysine [Lys(Z)] as the starting monomer material and tin dichloride as the catalyst, the drug carrier material poly(lactic acid-*co*-N^{ε}-carbobenzoyloxy-L-lysine) was synthesized via direct melt polycondensation. The copolymer was systematically characterized with intrinsic viscosity testing, Fourier transform infrared spectroscopy, ^{1}H-NMR, gel permeation chromatography, differential scanning calorimetry, and X-ray diffraction. The influences of different feed molar ratios were examined. With increasing molar feed content of Lys(Z), the intrinsic viscosity, weight-average molecular weight, and polydispersity index (weight-average molecular weight/number-average molecular weight) gradually decreased. Because of the introduction of Lys(Z) with a big aromatic ring into the copolymer, the glass-transition temperature gradually increased with increasing feed charge of Lys(Z), and all of the copolymers were amorphous. The copolymers, with weight-average molecular weights from 10,500 to 6900 Da, were obtained and could reach the molecular weight level of poly(lactic acid) modified by Lys(Z) via the ring-opening polymerization of the cyclic intermediates, such as lactide and morpholine-2,5-dione. However, a few terminal carboxyl groups might have been deprotected during the polymerization reaction under high temperatures. © 2011 Wiley Periodicals, Inc. J Appl Polym Sci 121: 420–426, 2011

Key words: biodegradable; copolymerization; drug delivery systems; melt; polycondensation

INTRODUCTION

For its excellent biocompatibility, biodegradability, and bioabsorbability, poly(lactic acid) (PLA) has been widely applied in biomedical fields, such as in medical sutures, bone fixation materials, drug-delivery microspheres, and tissue engineering.[1–4] However, it has some disadvantages, such as a high crystallinity and the absence of favorable functional groups; these lead to poor hydrophilicity, slow degradation speed, and poor cell affinity.[5–8] To solve these problems, there have been more and more reports on the chemical modification of PLA through the introduction of amino acid (AA) into its molecular chain and the preparation of biodegradable poly(lactic acid-*co*-amino acid) (PLAA) copolymers with functional or reactive groups, such as amino, hydroxyl, carboxyl, and thiol groups. Because these amphiphilic polymers contain both biodegradable esters and amide groups in the chain, their biodegradation behaviors are different from those of the corresponding homopolymers and some copolyesters, and they exhibit a better hydrophilicity and biocompatibility than unmodified PLA; this makes PLAA very useful for biodegradable biomedical materials, including drug-delivery vehicles.[9–17]

Particularly, because of the physiological and biochemical effects of lysine (Lys) for the human body,[18,19] great importance has been directed toward the application of Lys in medical and material fields recently.[12–17] To avoid unfavorable side reactions before use, the terminal amino group of Lys with multifunctional groups must be protected, and this is usually done by the use of N^{ε}-carbobenzoyloxy-L-lysine [Lys(Z)] as a starting material during the synthesis of polymers based on Lys. Generally, copolymers of lactic acid (LA) and Lys have been prepared via a two-step method. First, with Lys(Z), LA, or their derivatives as a starting material, cyclic intermediates, such as N^{ε}-benzyloxycarbonyl-L-lysyl-morpholine-2,5-dione derivatives [or N^{ε}-carboxy-(N^{ε}-benzyloxycarbonyl)-L-lysine anhydride], and lactide, respectively, have been prepared through difficult multistep reactions. Then, the ring-opening

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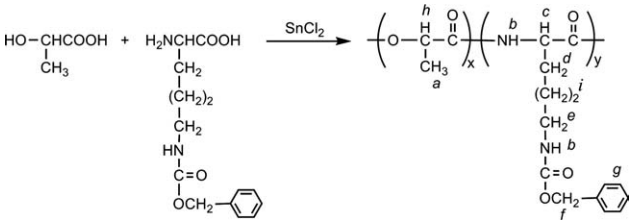

Scheme 1 Synthetic route of P[LA-*co*-Lys(Z)].

polymerization of the cyclic intermediates gave these copolymers.[12–17] Therefore, the protection–deprotection process and the preparation of cyclic intermediates are too complicated to perform economically on an industrial scale, and the two-step method is expensive and time-consuming.[1]

Recently, the syntheses of PLA modified by AA via a one-step direct melt polycondensation starting from LA and AA, such as alanine,[20] glycine (Gly),[21] 4-hydroxyproline,[22,23] and glutamic acid,[24] have been investigated in a few reported studies. However, for the AA with multifunctional groups, such as 4-hydroxyproline and glutamic acid, the protection process has still been necessary, or a third starting material with a higher reactivity (e.g., glycolic acid) or certain molecular weight [e.g., poly(ethylene glycol)] has still been used.[22–24] Compared with the simpler AA, for example, alanine[20] and Gly,[21] Lys(Z) is also a kind of AA with multifunctional groups. However, there are no reports on the direct melt polycondensation of Lys(Z) or LA, and the influences of multifunctional groups in Lys(Z) on the copolymerization is not clear. Therefore, to lower the synthesis cost of copolymers based on LA and Lys, it is important to investigate the direct copolymerization of LA and Lys(Z) by the similar simpler method without another monomer.

In this article, in continuation of our previous study on the direct melt copolycondensation of LA with Gly,[21] we report on the simple synthetic method for preparing the copolymer poly(lactic acid-*co*-N^{ε}-carbobenzoyloxy-L-lysine) {P[LA-*co*-Lys(Z)]} directly from LA and Lys(Z) (Scheme 1). The structure and properties of the copolymer were systematically characterized with intrinsic viscosity ([η]) testing, Fourier transform infrared (FTIR) spectroscopy, ^{1}H-NMR, gel permeation chromatography (GPC), differential scanning calorimetry (DSC), and X-ray diffraction (XRD), and the influences of different molar feed ratios were also examined. Because D,L-lactic acid (D,L-LA) is inexpensive and the one-step method is simple, the novel synthetic method is very economical for the synthesis of P[LA-*co*-Lys(Z)]. It is also important that compared with the poly(lactic acid-*co*-glycine) synthesized previously,[21] poly(lactic acid-*co*-lysine) [P(LA-*co*-Lys)] can be prepared by the deprotection of P[LA-*co*-Lys(Z)], and the pendent ε-amine groups of Lys in the side chain of P(LA-*co*-Lys) was expected to be further modified with residual bioactive molecules.[12,13,15,16]

EXPERIMENTAL

Materials

D,L-LA was purchased from Guangzhou Chemical Reagent Factory (Guangzhou, China), Lys(Z) was provided by U.S. Acros Co. (New Jersey, USA), and tin dichloride ($SnCl_2$) was purchased from Guangdong Guanghua Chemical Factory Co., Ltd (Guangzhou, China). All other chemicals were commercially available in analytical grades and were used without further purification.

Preparation of P[LA-*co*-Lys(Z)]

A procedure from our previous study on the melt copolymerization of LA and Gly[21] was adopted. LA and Lys(Z) were uniformly mixed at a preplanned molar feed ratio until a uniform mixture was formed. The mixture was then directly dehydrated for 10 h at 140°C and 4000 Pa in a three-ncked flask equipped with a mechanical stirring device and a thermometer. After LA and Lys(Z) were prepolymerized, the catalyst, $SnCl_2$, was then added at 0.5 wt % of the dehydrated reactants (0.5 wt %).

After prepolymerization, the melt copolymerization was carried out for 8 h at 160°C under an absolute pressure of 70 Pa. When the reaction was completed, the crude product was cooled to room temperature, dissolved in $CHCl_3$ (the insoluble fractions were removed via filtration after the dissolution process), and precipitated in CH_3OH to give a yellowish or white polymer powder. After purification by dissolution and precipitation, the obtained polymer was then dried *in vacuo* to a constant weight. The yield was within the range 36–74%, and in most cases, it was above 50%.

Characterization

[η] was determined in an Ubbelohde viscometer (Cannon-Ubbelohde, State College, PA, capillary inner diameter = 0.46 mm). All samples for [η] testing had an accurate weight of 5 mg and were dissolved in a 25-mL volumetric flask with $CHCl_3$ as the solvent at 25°C. The number-average molecular weights (M_n), the weight-average molecular weights (M_w), and the polydispersity index (PDI; M_w/M_n) were determined from GPC. GPC analysis was performed on a Waters 1515 isocratic high-performance liquid chromatography pump with a Waters Instruments 2414 refraction index detector (Torrance, CA). Three Waters Styragel HR columns (300 × 7.8 mm^2) were used in series with tetrahydrofuran as the solvent and polystyrene for

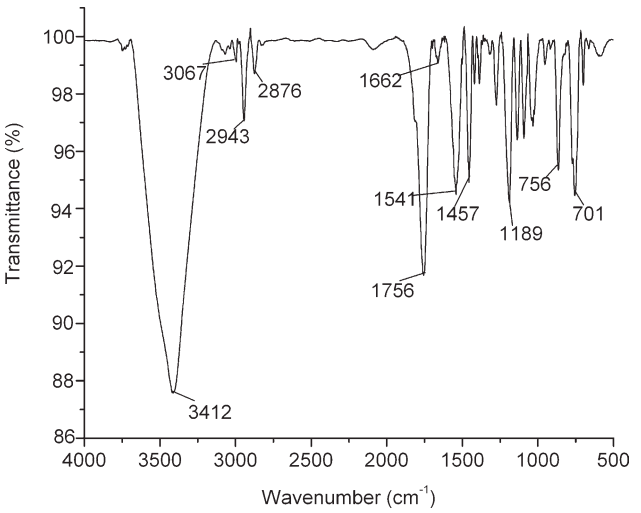

Figure 1 FTIR spectrum of P[LA-*co*-Lys(Z)] synthesized with an LA/Lys(Z) molar feed ratio of 90/10.

calibration, with a flow velocity 1 mL/min at 40°C, and a sample concentration of 4.0 mg/mL was applied. In the polymer characterization tests, the insoluble fractions were removed via filtration after the dissolution process for all of the samples.

FTIR spectra were recorded on a Bruker Vector 33 FTIR spectrometer (Ettlingen, Germany). In a typical procedure, an accurate 0.2 mg of sample was crushed to make potassium bromide pellets under a hydraulic pressure of 500 kg/cm^2. The spectra were taken in the wavelength region between 400 and 4000 cm^{-1}. ^{1}H-NMR spectra were measured on a Varian 400-MHz NMR system (Bruker Instruments, Billerica, MA) in $CDCl_3$ and with tetramethylsilane as internal reference at 25°C. Typical acquisition parameters for ^{1}H-NMR spectra included a 6.7-μs observe pulse, a 6.4-kHz sweep width, a 32-s acquisition time, a 2-s recycle delay, and eight scans.

The thermal properties of the polymer were measured by DSC (DSC7, PerkinElmer, Cetus Instruments, Norwalk, CT) in the temperature range between −50 and 200°C. The samples for DSC measurements (average weight = 4 mg) were scanned at a heating rate of 10°C/min under a nitrogen atmosphere (flow velocity = 20 mL/min), and then, they were cooled to −50°C for 5 min and heated again to 200°C. The crystallinity of the polymer was carried out on a Y-2000 XRD apparatus (made by China Dandong XRD Apparatus Co., Ltd., Dandong, China) with Cu Kα radiation with a wavelength of 1.5406 × 10^{-10} m and a 2θ scanning range of 5–50° at a scanning speed of 0.3°/min.

RESULTS AND DISCUSSION

Using D,L-LA and Lys(Z) as starting materials, we directly synthesized the random copolymers P[LA-*co*-Lys(Z)] with different molar feed ratios [LA/Lys(Z) = 98/2, 95/5, 90/10, 80/20, 70/30, 60/40, and 50/50] via melt copolycondensation. The structure and properties of these P[LA-*co*-Lys(Z)] were characterized by FTIR spectroscopy, ^{1}H-NMR, GPC, DSC, and XRD techniques and [η] measurements.

Structural characterization of P[LA-*co*-Lys(Z)]

The structural characterization of P[LA-*co*-Lys(Z)] synthesized with an LA/Lys(Z) molar feed ratio of 90/10 was compared with poly(D,L-lactic acid) (PDLLA), the product of the direct melt homopolymerization of LA.[2,25] We elucidated that these compounds showed similar absorptions in their FTIR spectra, especially the strong absorption of ester carbonyl near 1756 cm^{-1}. The absorptions at 3412, 1662, and 1541 cm^{-1} belonged to amide; those at 3067, 1457, 756, and 701 cm^{-1}, from the benzene ring of Lys(Z), appeared in the FTIR spectrum of P[LA-*co*-Lys(Z)] (Fig. 1) but were not observed in that of PDLLA. This was a strong indication that Lys(Z) chain segments were introduced into the copolymer.

^{1}H-NMR {P[LA-*co*-Lys(Z)] with a LA/Lys(Z) molar feed ratio of 90/10, with hexadeuterated dimethyl sulfoxide as the solvent and tetramethylsilane as the internal reference, δ, ppm (Fig. 2): 1.17–1.29 [H_i, CH_2—CH_2 in the Lys(Z) branch chain], 1.42 (H_a, CH_3 in the PLA chain), 1.59 [H_d, CH_2 in the Lys(Z) branch chain], 2.94 [H_e, CH_2—NH in the Lys(Z) branch chain], 4.21 [H_c, CH in the Lys(Z) main chain], 4.97 [H_f, CH_2 in N^{ε}-carbobenzoyloxy groups from the Lys(Z) branch chain], 5.13 (H_h, CH in the PLA chain), 7.19–7.33 [H_g, Ar—H in Lys(Z)], 8.29–8.42 (H_b, H_c, NH from —CONH—).[21,26]

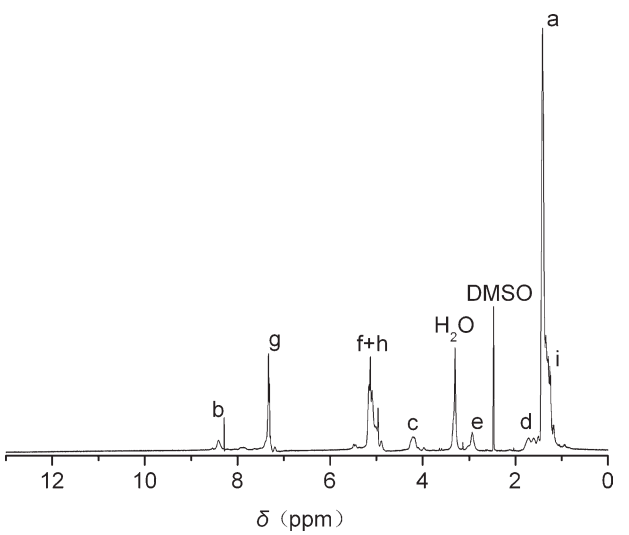

Figure 2 ^{1}H-NMR spectrum of P[LA-*co*-Lys(Z)] synthesized with an LA/Lys(Z) molar feed ratio of 90/10 (DMSO = dimethyl sulfoxide).

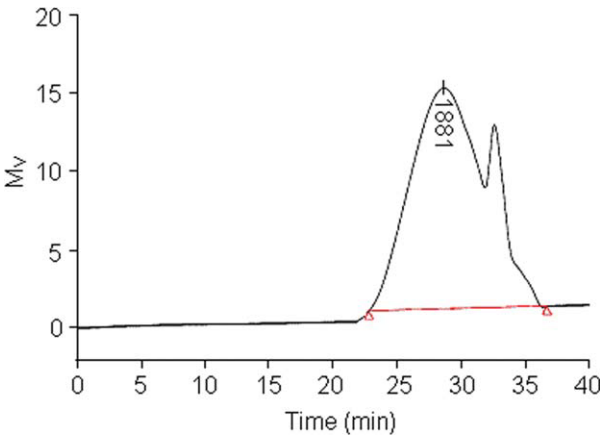

Figure 3 GPC curve of P[LA-*co*-Lys(Z)] synthesized with an LA/Lys(Z) molar feed ratio of 90/10 (M_n = number-average molecular weight). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

The ratio of H atom number H_g/H_e was calculated from the ratio of the H peak integral at 7.19–7.33 to the integral at 2.94, and the result was about 4/2. This value was smaller than the theoretical H atom number ratio 5/2 for a few terminal carboxyl groups that might have been deprotected during the polymerization reaction under high temperatures.[27] The data from FTIR and ^{1}H-NMR spectroscopy were similar to those in the reported literature.[13,26] Therefore, the structure of the copolymer P[LA-*co*-Lys(Z)] was demonstrated by FTIR and ^{1}H-NMR spectroscopy, as expected (Scheme 1).

Property characterization of P[LA-*co*-Lys(Z)]

The molecular weight and molecular weight distribution of P[LA-*co*-Lys(Z)] synthesized at a LA/Lys(Z) molar feed ratio of 90/10 were characterized by GPC. The results show that the GPC flow curves not only had a main peak, but a smaller peak was also found to its right (Fig. 3). At the same time, M_w was 7700 Da, M_n was 3800 Da, and PDI was 2.03. Both the double peak and bigger PDI indicated that the direct melt copolycondensation from two monomers not only mainly gave P[LA-*co*-Lys(Z)] as the target copolymer (Scheme 1) but also produced a few other copolymers with lower molecular weights; this may have resulted from the deprotection of a few terminal carboxyl groups during the polymerization reaction under high temperatures.[27] These GPC results were in line with the previously discussed ^{1}H-NMR results.

Usually, when PLA biodegradable polymers are used as drug-delivery materials, their molecular weights are no greater than 30,000 Da.[2,28] As reported in the literature, PLA materials with a molecular weight of 1800 Da can be applied in drug delivery; even PLA polymers with a molecular weight of only 900 Da can be used as drug-delivery devices.[21,29,30] The molecular weight of P[LA-*co*-Lys(Z)] synthesized here via direct melt copolycondensation was overwhelmingly bigger than 900 Da. Therefore, its molecular weight meets the requirement for drug-delivery applications.

On the DSC curve, the glass-transition temperature (T_g) was observed for P[LA-*co*-Lys(Z)] synthesized at an LA/Lys(Z) molar feed ratio of 90/10, and the corresponding datum of T_g was 36.5°C (Fig. 4). It was obvious that T_g of P[LA-*co*-Lys(Z)] was smaller than that of the homopolymer PDLLA [T_g = 54.6°C, melting temperature (T_m) = 120.0°C].[31,32] The reason may have been the introduction of Lys(Z), with a relatively long side chain, into the copolymer, and the chain segments of the resulting copolymer molecules were very apt to move, which was similar to the literature.[33] At the same time, no peak of T_m was detected on the DSC curve (Fig. 4); this indicated that the copolymer may have been amorphous. No diffraction peaks could be found in the XRD spectrum of P[LA-*co*-Lys(Z)] synthesized at an LA/Lys(Z) molar feed ratio of 90/10; this coincided well with the corresponding DSC results.

Influences of different molar feed ratios on the IR and ^{1}H-NMR results

Collecting the absorbance of PLAA at respective characteristic peaks, we conveniently determined the content of the copolymer by IR spectroscopy.[34] The structural studies of the P[LA-*co*-Lys(Z)] copolymers with different molar feed ratios by FTIR spectroscopy showed similar features (Fig. 5). However, with increasing Lys(Z) content and more —CONH— linkages being formed, the amide first- and second-belt absorptions became obviously

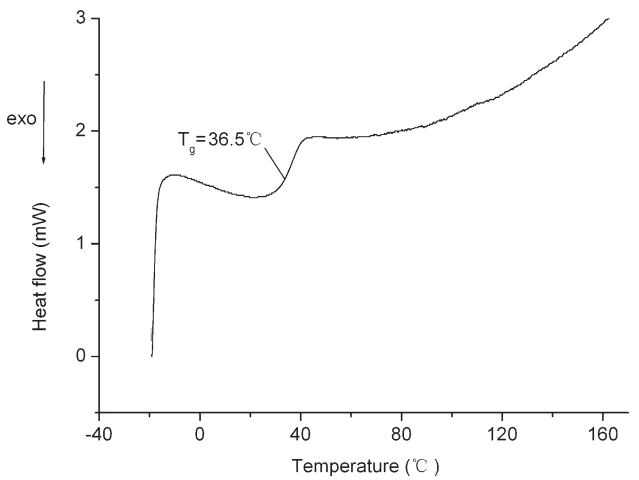

Figure 4 DSC curve of P[LA-*co*-Lys(Z)] synthesized with an LA/Lys(Z) molar feed ratio of 90/10.

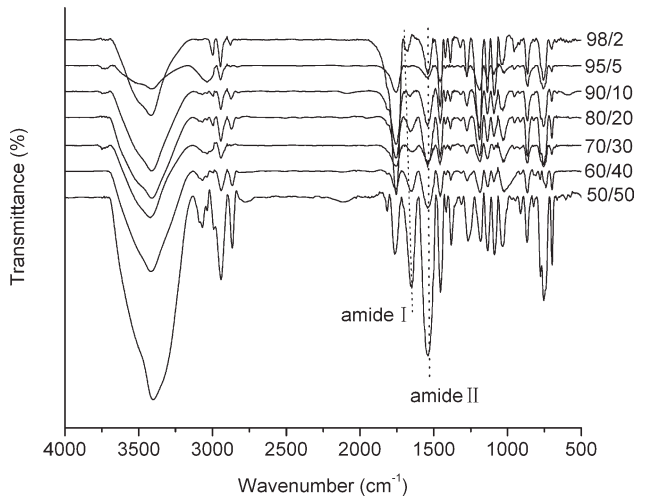

Figure 5 IR spectra of P[LA-*co*-Lys(Z)] samples synthesized with different LA/Lys(Z) molar feed ratios.

stronger. Particularly, for LA/Lys(Z) molar ratios of 60/40 and 50/50, the intensity of the absorption from the carbonyl group in —CONH— was stronger than that of the carbonyl group in esters (Fig. 5).

On the basis of the integrals of H_a and H_e, the molar composition ratios of different units in the copolymer were calculated, and the results are shown in Table I. When the LA/Lys(Z) molar ratio was 80/20 or greater, the LA/Lys(Z) molar ratio of the theoretical feed was bigger than that tested by ^{1}H-NMR for the escape of LA out of the reaction systems as lactide during the melt copolycondensation. However, when the LA/Lys(Z) molar feed ratio was 70/30 or lower, the LA/Lys(Z) molar ratio tested by ^{1}H-NMR was contrarily bigger than the theoretical value; this showed that not all of the Lys(Z) monomer took part in the reaction. Combined with the previous FTIR analysis, these indicated that an Lys(Z) content that was too big in the feed was not advantageous for the direct melt copolycondensation.

Influences of different molar feed ratios on the molecular weight of P[LA-*co*-Lys(Z)]

The influences of different molar feed ratios on [η] and the GPC results are also shown in Table I. Obviously, with increasing molar feed content of Lys(Z), not only did [η] gradually decrease but M_n and M_w also both gradually decreased. Even so, the minimum M_w of serial P[LA-*co*-Lys(Z)] was 6900 Da (Table I, run 7). Therefore, all molecular weights met the requirement for drug-delivery applications.[2,21,28–30]

At the same time, the maximum M_w of serial P[LA-*co*-Lys(Z)] was 10,500 Da in this study (Table I, run 1). When P[LA-*co*-Lys(Z)] has been synthesized by the ring-opening polymerization of the cyclic intermediates, including lactide, there have been some reports on P[LA-*co*-Lys(Z)] showing a maximum M_w only 9200 Da.[13] Thus, the M_w of P[LA-*co*-Lys(Z)] obtained via the direct melt polymerization reached the molecular weight level of PLA modified by Lys(Z) via the ring-opening polymerization of the cyclic intermediates. More importantly, the novel direct copolycondensation is a cheaper and more practical method for the synthesis of P[LA-*co*-Lys(Z)], especially when it is used as drug-delivery carrier material.

The GPC results also showed that the GPC flow curves not only had a main single peak, but also one (or two) smaller peak(s) could be found to its right; in most cases, the PDI was even above 2 (Table I). These further confirmed that a few terminal carboxyl groups might have been deprotected during the polymerization reaction under high temperature,[27] but the majority of P[LA-*co*-Lys(Z)] was still normal.

TABLE I
Influence of Different Molar Feed Ratios on the Properties of P[LA-*co*-Lys(Z)]

Run	LA/Lys(Z) molar ratio		[η]	Yield	M_n	M_w		T_g
	Feed	Tested by NMR	(dL/g)	(%)	(Da)	(Da)	M_w/M_n[a]	(°C)
1	98/2	36/2	1.25	73.8	4300	10,500	2.44	40.7
2	95/5	45/5	1.16	64.5	3800	8100	2.13	30.0
3	90/10	60/10	0.91	70.1	3800	7700	2.03	36.5
4	80/20	73/20	0.74	68.3	3500	7300	2.09	30.2
5	70/30	70/18	0.96	37.7	3800	7900	2.08	36.2
6	60/40	60/28	0.53	42.1	3600	7100	1.97	37.7
7	50/50	50/34	0.40	36.1	3500	6900	1.97	45.2

All of the samples were polymerized with a polycondensation temperature of 160°C, a polycondensation time of 8 h, a catalyst concentration of 0.5 wt %, and $SnCl_2$ as the catalyst.

[a] With an LA/Lys(Z) molar feed ratio greater than or equal to 70/30, the GPC flow curves showed a main peak and a smaller peak to the right, whereas with an LA/Lys(Z) molar feed ratio of less than or equal to 60/40, the GPC flow curves showed one main peak and two smaller single peaks to the right.

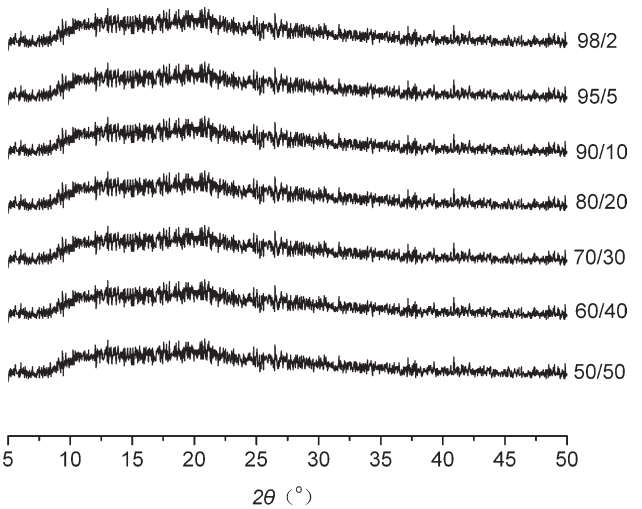

Figure 6 XRD spectra of P[LA-*co*-Lys(Z)] samples synthesized with different LA/Lys(Z) molar feed ratios.

These were in line with the previously discussed ^{1}H-NMR results. Thus, too a high reaction temperature was unfavorable for the synthesis of P[LA-*co*-Lys(Z)] via the direct melt copolymerization of LA and Lys(Z).

Influences of different molar feed ratios on the thermal properties and crystallinity

The thermal properties of P[LA-*co*-Lys(Z)] were characterized by DSC, and the data are shown in Table I. It was obvious that with increasing molar feed content of Lys(Z), more —CONH— linkages were introduced into the copolymer; this suggested that the T_g values for P[LA-*co*-Lys(Z)] gradually became bigger. However, because of the introductions of Lys(Z) with relatively long side chains into the copolymer, the chain segments of the resulting copolymer molecules were apt to move; this suggested that the T_g values of all of the copolymers with different molar feed ratios were smaller than that of the homopolymer PDLLA (T_g 54.6°C).[31,32] This was similar with reported data.[33]

At the same time, the deprotection of Lys(Z) during the melt copolycondensation under high temperatures[27] and the introductions of —CONH— linkages[21,22,35,36] and Lys(Z) with a big aromatic ring into the copolymer made the structure of the resulting polymer more complex,[33] and the alignment of the polymer chains was disturbed. Therefore, T_m of the relatively complex products was not observed, and no T_m data are shown in Table I.

The crystallinity of polymers has an important effect on their physical and biological properties, especially their degradability, which is crucial for biomaterials. Similarly, because of the deprotection of Lys(Z) during the melt copolycondensation under high temperatures,[27] with the introductions of —CONH— linkages[21,22,35,36] and Lys(Z) with a big aromatic ring into the copolymer, no diffraction peak was observed (Fig. 6), and all of the copolymers with different molar feed ratios were amorphous. Thus, no XRD data is shown in Table I. Fortunately, lower or no crystallinity is more beneficial for PLA biodegradable materials to be applied in the biomedical fields, especially for drug-delivery carrier materials because there will be no residual microcrystallinity after degradation *in vivo*.[2,25,28]

CONCLUSIONS

With Lys(Z) with polyfunctional groups as a starting monomer material, an important biodegradable biomaterial, P[LA-*co*-Lys(Z)], was directly synthesized via the melt copolycondensation of inexpensive D,L-LA and Lys(Z). With increasing molar feed content of Lys(Z), [η], M_w, and its PDI decreased gradually. All of the copolymers were amorphous and had lower T_g values than PDLLA. M_w's from 6900 to 10,500 Da were high enough to meet the demand of drug-delivery carrier materials and reached the molecular weight level of PLA modified by Lys(Z) via the two-step method. This novel method is cheaper and more practical.

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