Synthesis of Biodegradable Material Poly(lactic acid-*co*-aspartic acid) via Direct Melt Polycondensation and Its Characterization

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Received 26 July 2010; accepted 16 January 2011
DOI 10.1002/app.34168
Published online 12 April 2011 in Wiley Online Library (wileyonlinelibrary.com).

ABSTRACT: Directly starting from L-lactic acid (LA) and L-aspartic acid (Asp), biodegradable material poly(lactic acid-*co*-aspartic acid) [P(LA-*co*-Asp)] was synthesized via melt polycondensation. The synthetic conditions, including type and dosage of catalyst, temperature, and time of copolymerization, and influence of molar feed ratio were discussed. The structure and properties of the copolymer were systematically characterized with FTIR, ^{1}H-NMR, GPC, DSC, and XRD. With the increase of Asp in the feed, [η] and M_w decreased, and the crystallinity of the copolymer disappeared gradually. Compared to the homopolymer, poly(L-lactic acid) synthesized via melt polycondensation and the copolymer P(LA-*co*-Asp) had a higher glass-transition temperature (T_g). The copolymer P(LA-*co*-Asp) with M_w of 4400–24300 Da was obtained, which could meet the demand as a drug-delivery carrier material. Compared to the ring-opening polymerization of the cyclic intermediates, including lactide, the novel direct copolycondensation method was a cheap and practical method for the synthesis of copolymer P(LA-*co*-Asp) as biomedical materials. © 2011 Wiley Periodicals, Inc. J Appl Polym Sci 121: 3662–3668, 2011

Key words: biodegradable; copolymerization; melt; polycondensation; synthesis

INTRODUCTION

As an important degradable biomaterial used in clinical application permitted by USA Food and Drug Administration, poly(lactic acid) (PLA) has excellent biocompatibility and bioabsorbability, which provide it extensive applications in biomedical fields, such as sutures, bone fixation, drug delivery, and tissue engineering.[1–4] However, it has some disadvantages, such as high crystallinity and the absence of suitable functional groups, which lead to poor hydrophilicity, slow degradation speed, and poor cell affinity.[5–8]

To solve these problems, the introduction of Asp with multifunctional groups, for example, —COOH and —NH_2 into PLA, is a good method, and more and more attention has been attached to the researches on the synthesis and application of poly (lactic acid-*co*-aspartic acid) [P(LA-*co*-Asp)].[9–16] In many reports, the copolymer P(LA-*co*-Asp) was usually synthesized via the traditional two-step method. First, different cyclic intermediates, such as morpholine-2,5-dione derivatives, aspartic acid-*N*-carboxyanhydride, and lactide, were prepared separately from Asp, lactic acid (LA), or their derivatives through troublesome multistep reactions. Then, the ring-opening polymerization (ROP) of the cyclic intermediates gave the copolymer.[10–13]

Recently, a simplified two-step method was reported for the synthesis of the novel type of amphiphilic biodegradable P(LA-*co*-Asp).[14–16] There is only the copolymerization of lactide with Asp via heating their mixture without additional catalysts or solvents. Even so, lactide was usually prepared from LA (or its derivatives) through a tiresome and low-yield process, and the purification of lactide by the repetitious crystallization consumed a lot of organic solvents, which made the whole process become lengthier and the total yield become lower.[2] Thus, the more extensive application of the copolymer P(LA-*co*-Asp), drug-delivery carrier material, for example, is still restricted for its high cost to a certain extent.

Now, the synthesis of PLA modified by amino acid (AA) via one-step method, the direct melt polycondensation, starting from LA and AA, has been investigated. However, it is a pity that there are only several literatures involving in a fewer AA, for example, glycine,[17] alanine,[18,19] and glutamic acid (glycolic acid as the third monomer also took part in the copolycondensation).[20] In our previous works,

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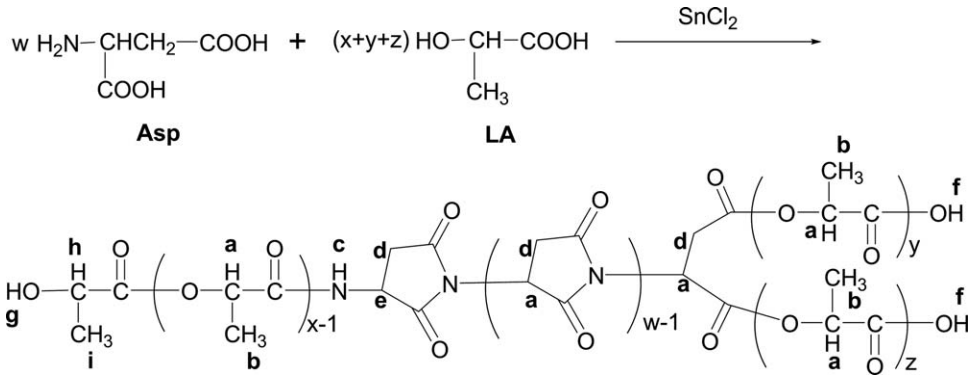
Contract grant sponsor: Guangdong Provincial Natural Science Foundation of China; contract grant number: 5300082.

Contract grant sponsor: National Natural Science Foundation of China; contract grant number: 20772035.



Scheme 1 The synthetic route of P(LA-*co*-Asp).

the direct melt homopolycondensation of LA[21] and direct melt copolycondensation of LA, respectively, with glycolic acid,[22] cholic acid,[23] and glycine, the simplest AA[17] has been investigated. As the continuation of the direct method, using Asp with multifunctional groups as AA instead of glycine, the copolymer P(LA-*co*-Asp) was synthesized by direct melt copolycondensation only LA with Asp (Scheme 1). This method is simple and has never been reported. The structure and properties of P(LA-*co*-Asp) were systematically characterized with intrinsic viscosity [η], FTIR, ^{1}H-NMR, GPC, DSC, and XRD, and the influences of different molar feed ratios were also discussed.

EXPERIMENTAL

Materials

LA was purchased from Wako Pure Chemical Industries (Tokyo, Japan), and L-aspartic acid (Asp) was purchased from Shanghai Huixing Biochemical Reagent Co. (Shanghai, China). All other chemicals, including *p*-toluenesulfonic acid (TSA), $SnCl_2$, and ZnO, were commercially available as analytical grades from Guangzhou Chemical Reagent Factory (Guangzhou, China) and used without further purification.

Instrumental analysis and measurements

The intrinsic viscosity ([η]) of the copolymer P(LA-*co*-Asp) was determined with Ubbelohde viscometer (Cannon-Ubbelohde, State College, PA) using $CHCl_3$ as solvent at 25°C. The relative molecular weight and molecular weight distribution of the polymer were determined by gel permeation chromatography (Waters 1515 pump, Torrance, CA) with tetrahydrofuran as solvent at 35°C and a flow velocity 1 mL min^{-1}. Three Styragel HR columns from Japan covering a molecular weight range of 1×10^3–10^6 Da were used and calibrated using five polystyrene narrow standards from BF Goodrich (Richfield, OH). Molecular weight distributions for the samples were calculated using the Millennium 2010 software from Waters and reported as polystyrene equivalent values.

IR spectra were obtained from an FTIR spectrometer (Bruker Vector 33, Ettlingen, Germany) by the KBr salt slice method. ^{1}H-NMR spectra were recorded with a Varian NMR system 400 MHz (USA) with DMSO-d_6 as the solvent and TMS as internal standard. The thermal properties of the polymer were measured with Perkin–Elmer DSC7 thermal analyzer (Perkin–Elmer, Cetus Instruments, Norwalk, CT) at a heating rate of 10°C min^{-1} under nitrogen atmosphere (flow velocity, 20 mL min^{-1}), and the transition temperature was calculated from the second run. With a wavelength of 1.5406×10^{-10} m and a scanning scope of 2θ from 5° to 50° with Cu Kα radiation, a Rigaku D/max-2000X X-ray diffractometer (Dandong, China) was used to investigate the crystallinity of the polymer.

Prepolymerization

According to the previous works on melt homo-/copolymerization of LA,[17,21–23] LA and Asp should be prepolymerized before copolymerization. After LA and Asp were uniformly mixed as preplanned molar feed ratio (LA/Asp = 40 : 1, 32 : 1, 24 : 1, 20 : 1, 10 : 1, and 8 : 1), the mixture was directly dehydrated for 10 h at 140°C under 4000 Pa in a three-necked flask equipped with mechanical stirring and thermometer.

Melt copolymerization

After prepolymerization, the selected catalyst (including $SnCl_2$, SnO, $ZnCl_2$, TSA, and ZnO) was added as predetermined weight percentage of dehydrated reactants (such as 0.1, 0.3, 0.5, 0.7, and 0.9 wt %). 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 was

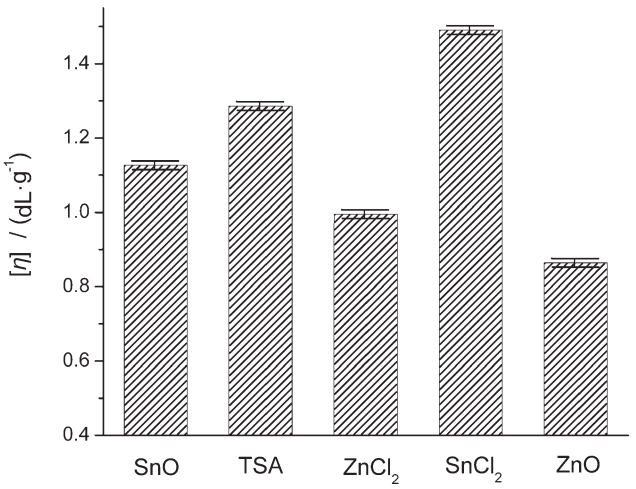


Figure 1 Influences of different catalysts on the viscosity of P(LA-*co*-Asp) (conditions: 160°C, 8 h, and catalyst dosage 0.7 wt %).

finished, the simple purification via the dissolution in $CHCl_3$ and the subsequent precipitation by CH_3OH ordinarily produced a white (or yellowish) powder after drying *in vacuo* to constant weight. The yield was within the range of 44–76%, and, in most cases, it was above 55%.

RESULTS AND DISCUSSION

Recently, increasing importance has been attached to the direct melt homo-/co- polycondensation of LA for its simple process, high efficiency, and low cost on the whole although sometimes the yield was not very high.[3,17–32] Thus, in this article, using LA and Asp as starting materials, P(LA-*co*-Asp) with different molar feed ratios (LA/Asp = 40 : 1, 32 : 1, 24 : 1, 20 : 1, 10 : 1, and 8 : 1) were directly synthesized via melt copolycondensation after the synthetic conditions were discussed. The structure and properties of the copolymer P(LA-*co*-Asp) were characterized by FTIR, ^{1}H-NMR, GPC, DSC, and XRD techniques and viscosity [η] measurements.

Appropriate synthetic conditions

In melt copolycondensation, the catalyst was of great significance to increase the relative molecular weight of polymer.[24,25] When the direct melt copolycondensation was carried out for 8 h at 160°C, absolute pressure 70 Pa, with the catalyst quantity of 0.7 wt % and LA/Asp feed molar ratio of 10 : 1, the influences of catalyst types on the [η] of P(LA-*co*-Asp) were shown in Figure 1. It can be observed that the reaction catalyzed by $SnCl_2$ gave higher [η] than other familiar catalysts, such as SnO, $ZnCl_2$, TSA, and ZnO used in the direct melt homo-/co- polymerization of LA.[17–25] Therefore, $SnCl_2$ was selected as the catalyst in the following experiments.

When the direct melt copolycondensation was carried out at 160°C and absolute pressure 70 Pa for 8 h with the feed molar ratio LA/Asp of 10 : 1, the influences of catalyst $SnCl_2$ quantity on the [η] of P(LA-*co*-Asp) were shown in Figure 2. Obviously, the [η] reached a maximum value when the weight percent of catalyst $SnCl_2$ quantity was 0.7 wt % of the prepolymer. Once the quantity was too small, the reaction was so insufficient after a certain time that the [η] was not high. When the quantity of $SnCl_2$ was excessive, short-chain molecule was apt to be formed through the degradation of polymer, which was also catalyzed by the metal catalyst.[22,26] Therefore, the suitable dosage of catalyst $SnCl_2$ was 0.7 wt %.

When the melt copolymerization was carried out, respectively, at different temperatures for 8 h under the conditions of the molar feed ratio of LA/Asp 10 : 1, absolute pressure 70 Pa, and catalyst $SnCl_2$ quantity 0.7 wt %, the [η] of the resulting polymer was shown in Figure 3. It was obvious that the appropriate higher temperature was advantageous to increase molecular chain of the copolymer. However, when the temperature was too high, the side reactions, such as thermal degradation and oxidation, markedly took place. Even when the temperature was 180°C, the color of the purified product became dusky, and the lowest [η] was obtained (Fig. 3). Thus, the appropriate temperature should be 160°C.

When the molar feed ratio of LA/Asp was 10 : 1, the catalyst $SnCl_2$ quantity was 0.7 wt %, and the melt copolycondensation was carried out at 160°C and absolute pressure 70 Pa, the influences of the melt polymerization time on the [η] of P(LA-*co*-Asp)

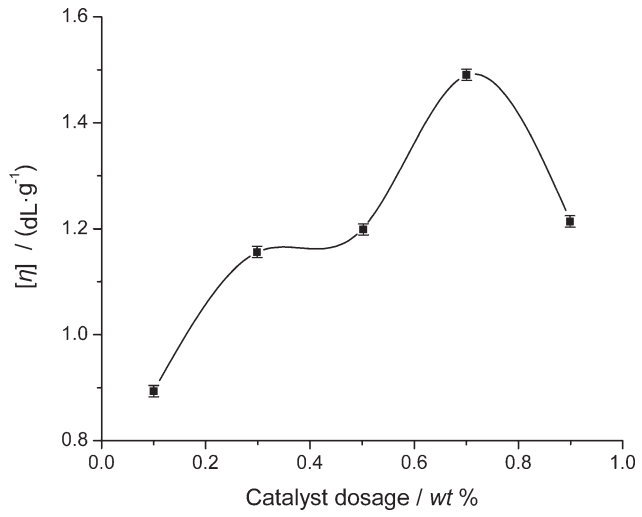


Figure 2 Influences of catalyst dosage on the viscosity of P(LA-*co*-Asp) (conditions: 160°C, 8 h, and catalyst $SnCl_2$).

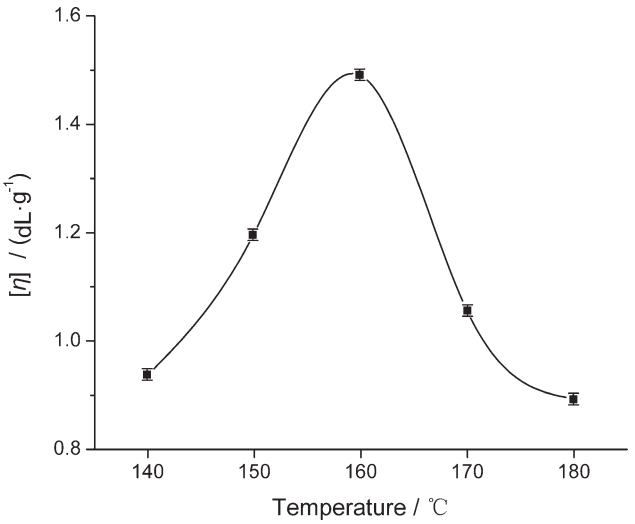


Figure 3 Influences of melt polymerization temperature on the viscosity of P(LA-*co*-Asp) (conditions: 8 h, and catalyst $SnCl_2$ dosage 0.7 wt %).

were shown in Figure 4. It was obvious that the [η] reached a maximum value after the reaction lasted for 10 h. When the time was too short, the polymerization was insufficient. However, once the reaction time was longer than 10 h, the oxidation and thermal degradation of polymer became serious. So, the [η] dropped, and the color of the purified product became deeper. Thus, the appropriate time may be 10 h.

To remove the by-product water during melt copolycondensation, the lower absolute pressure of the reaction system is usually beneficial to improve the [η] of the polymer.[3,17–32] Therefore, the lowest absolute pressure 70 Pa was selected in the above experiments. Thus, when the molar feed ratio of LA/Asp was 10 : 1, the appropriate conditions for the synthesis of the copolymer P(LA-*co*-Asp) via direct melt copolycondensation were as follows: catalyst $SnCl_2$ quantity 0.7 wt %, reaction temperature 160°C, absolute pressure 70 Pa, and reaction time 10 h. In this case, the maximum [η] was 1.53 dL g^{-1}, and the corresponding weight–average molecular weight (M_w) was 8400 Da.

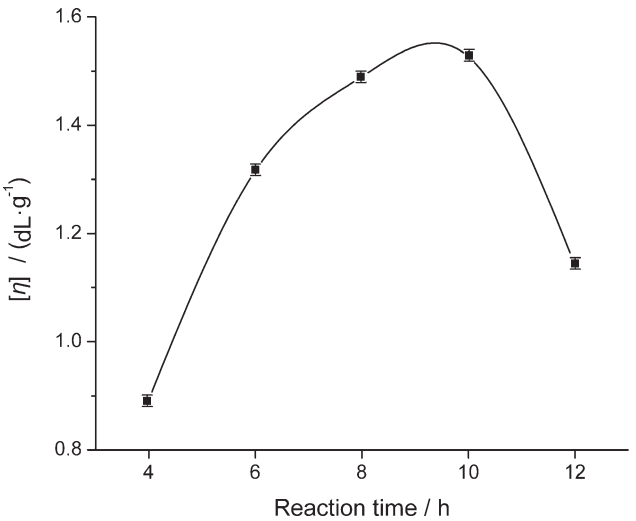


Figure 4 Influences of melt polymerization time on viscosity of P(LA-*co*-Asp) (conditions: 160°C, and catalyst $SnCl_2$ dosage 0.7 wt %).

Structure characterization of P(LA-*co*-Asp)

The structure of poly(lactic acid-*co*-aspartic acid) [P(LA-*co*-Asp)] synthesized as the molar feed ratio LA/Asp 10 : 1 under the above appropriate synthetic condition was characterized with FTIR and ^{1}H-NMR spectroscopy.

Compared to the homopolymer poly(L-lactic acid) (PLLA) synthesized via direct melt polycondensation,[22] it was elucidated that these compounds showed similar absorptions in their FTIR spectra, especially the strong absorption of ester carbonyl near 1757 cm^{-1} (Fig. 5). The absorptions at 3398 cm^{-1} from —NH— group and —OH group at 1539 cm^{-1} from the second amide band of —CONH— group appeared in the FTIR spectrum of P(LA-*co*-Asp) as expected. However, the absorption at 1670 cm^{-1} from the first amide band of —CONH— group was not obvious, and this phenomenon was similar to the reported literature.[14] Even so, these data in the FTIR spectrum of P(LA-*co*-Asp) were a strong indication that Asp chain segments had been introduced into the copolymer.

The structural studies on copolymers with different molar feed ratios by FTIR showed similar features (Fig. 6). Moreover, in case of increasing Asp content, more —CONH— linkage was formed, and the second amide band absorption at 1539 cm^{-1} became stronger obviously. However, the absorption

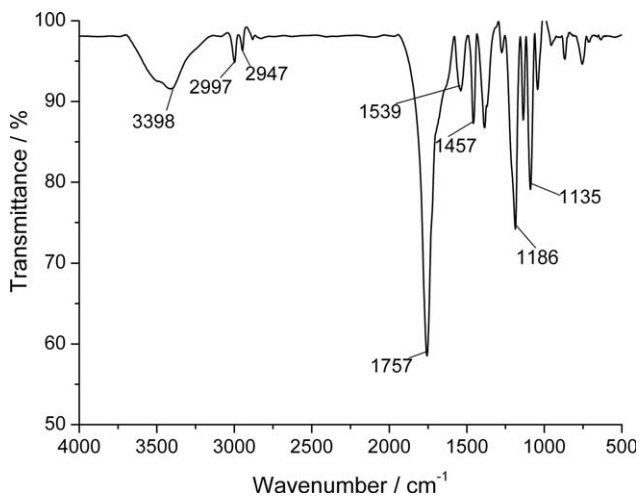


Figure 5 FTIR spectrum of P(LA-*co*-Asp) synthesized as the molar feed ratio 10/1 (LA/Asp).

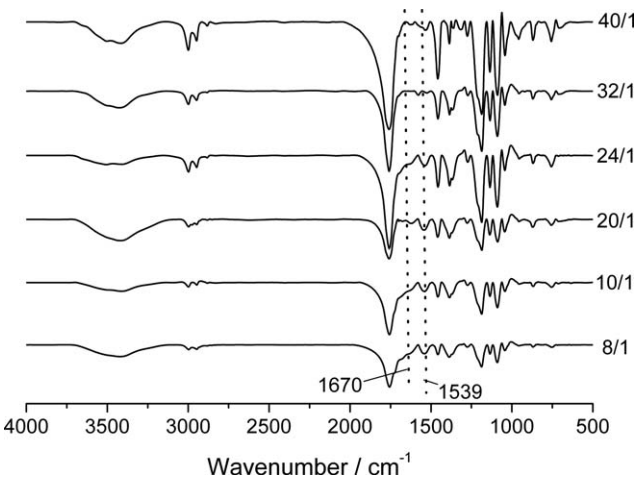


Figure 6 Infrared spectra of P(LA-*co*-Asp) with different molar feed ratios (LA/Asp).

at 1670 cm^{-1} from the first amide band of —CONH— group of the copolymers with different molar feed ratios was not obvious yet. In fact, it was covered by the increasing absorption of ester carbonyl for more ester bonds were formed with the increase of Asp in the feed (Fig. 6).

The data of ^{1}H-NMR spectrum of P(LA-*co*-Asp) synthesized as the molar feed ratio LA/Asp 10 : 1 (Fig. 7) were obtained as follows. ^{1}H-NMR (DMSO-d_6 as solvent and TMS as internal reference), δ, ppm: 1.34 (*d*, H_i, and CH_3 in the end of PLA segment), 1.46 (*d*, H_b, and CH_3 in PLA segment), 2.82–3.17 (*m*, H_d, and CH_2 in Asp and succinimide segments), 4.17–4.23 (*m*, H_h, and CH in the end of PLA segment), 4.60–4.76 (*m*, H_e, and CH in succinimide segment), 4.98–5.22 (*m*, H_a, and CH in PLA, Asp, and succinimide segments), 5.48 (*s*, H_g, and OH in the end of PLA segment), 8.31–8.80 (*m*, H_c, and NH in amide bonds), and 13.14 (*s*, H_f, and COOH in the end of PLA segment). All data were similar to the reported literature.[14] Therefore, the data from FTIR and ^{1}H-NMR indicated that the direct melt copolycondensation of LA and Asp indeed gave the multiblock P(LA-*co*-Asp) copolymers[14,15] (Scheme 1).

Molecular weight of P(LA-*co*-Asp)

The influences of different molar feed ratios on yield, [η], and GPC results are shown in Table I. Obviously, with the increase of the molar feed ratio of Asp, not only [η] decreased gradually, but also M_n, M_w, and PDI (M_w/M_n) had the trend of gradual decrease. Because Asp with multireaction point was directly used as starting material, the resulting copolymers had cyclic and branched chain. Therefore, for LA/Asp $\geq$ 20 : 1, PDI of the copolymers was above 2, which is similar to the results in literature.[15] Nevertheless, to get higher M_w for the synthesis of P(LA-*co*-Asp) via the direct melt polymerization, lower Asp content in the feed is recommended (Table I).

At the same time, the minimum M_w of serial P(LA-*co*-Asp) was 4400 Da in this study (Table I, Run 6). Generally, when the PLA biodegradable polymers were used as drug-delivery materials, their molecular weights were no more than 30,000 Da.[21,33] As reported in the literatures,[17,34,35] the PLAs material with molecular weight of 1800 Da could be applied in drug delivery, even the PLAs polymer with molecular weight of only 900 Da could be used as drug-delivery device. The molecular weight of P(LA-*co*-Asp) synthesized here via direct melt copolycondensation was overwhelmingly higher than 900 Da. Therefore, its molecular weight meets the requirement for drug-delivery applications.

More importantly, the maximum M_w of serial P(LA-*co*-Asp) was 24,300 Da even with a higher PDI (Table I, Run 1). When P(LA-*co*-Asp) was synthesized by simply heating a mixture of Asp and L-lactide without additional catalysts or solvents, the maximum M_w was 25,800 Da.[14,16] Even when M_w was only 10,000 Da, the corresponding PDI was above 2.[15] Therefore, the M_w of P(LA-*co*-Asp) obtained via the direct melt polymerization can reach the molecular weight level of that synthesized by the simplified ROP of the cyclic intermediate L-lactide. Not only that, but the novel direct copolycondensation is a cheaper and more practical method for the synthesis of P(LA-*co*-Asp) than that has been reported before, especially when the copolymer is used as drug-delivery carrier material.

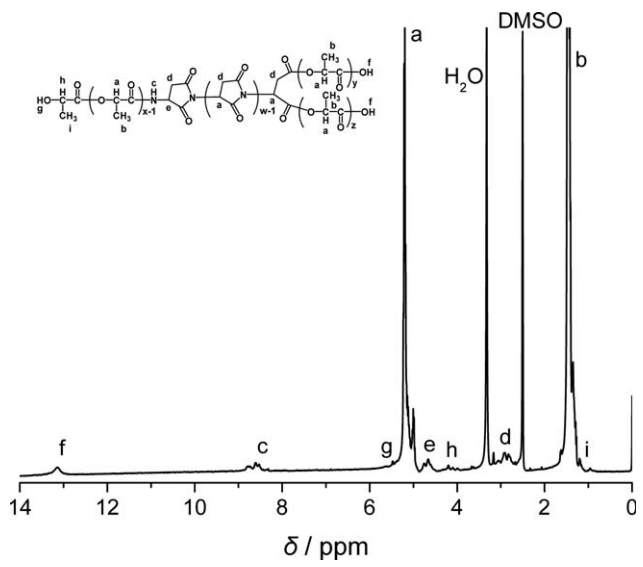


Figure 7 ^{1}H-NMR spectrum of P(LA-*co*-Asp) synthesized as the molar feed ratio 10 : 1 (LA/Asp).

TABLE I
The Influences of Feed Molar Ratios on Yield [η] and M_n of the Copolymers[a]

Run	LA/Asp	Yield (%)	[η] (dL g^{-1})	M_n (Da)	M_w (Da)	M_w/M_n[b]
1	40 : 1	44.4	1.62	6100	24300	3.98
2	32 : 1	58.6	1.55	5500	15500	2.82
3	24 : 1	75.8	1.53	5500	13500	2.45
4	20 : 1	55.3	1.59	5700	19500	3.42
5	10 : 1	56.9	1.53	4300	8400	1.95
6	8 : 1	57.6	1.40	3000	4400	1.47

[a] All runs were polymerized with a polycondensation temperature of 160°C, a polycondensation time of 10 h, and catalyst $SnCl_2$ quantity of 0.7 wt %.
[b] All the GPC flow curves only showed a single peak.

Thermal properties of P(LA-*co*-Asp)

The influences of different molar feed ratios on T_g and T_m of the copolymer poly(lactic acid-*co*-aspartic acid) [P(LA-*co*-Asp)] were presented in Table II. The —CONH— linkage is conducive to the formation of interchain hydrogen bonds. Thus, T_g of copolymers was higher than that of homopolymer PLLA, which is similar to the reported results.[14] With the increase in Asp content of the feed, more —CONH— linkages are introduced to the copolymers, suggesting that T_g values for P(LA-*co*-Asp) become bigger gradually.

At the same time, T_m decreased as the number of —CONH— linkages in the copolymers increased. For the molar feed ratio LA/Asp $\leq$ 20 : 1, it is obvious that both T_m and the heat of fusion (ΔH) of the complex product are not observed. These all indicated that the introduction of the cyclic succinimide and branched Asp fragments into PLA chain affected the regularity. In other words, the obtained P(LA-*co*-Asp) seems to begin to become a random copolymer, which is further demonstrated by the XRD results (Table II). In addition, both the results of DSC and XRD show that for the direct melt copolycondensation, the suitable molar feed ratio LA/Asp should be more than 20 : 1.

Crystallinity of P(LA-*co*-Asp)

There seems no any reports on the XRD results of biomaterial poly(lactic acid-*co*-aspartic acid) [P(LA-*co*-Asp)] before. However, the crystallinity of PLAs material is crucial for their physical and biological properties, especially degradability. The XRD results (Table II) showed that P(LA-*co*-Asp) is not totally amorphous.

When the molar feed ratio LA/Asp $\geq$ 24 : 1, the XRD pattern gives two diffraction peaks at the positions close to 16.4° and 18.9° (Fig. 8, and Table II), almost the same positions as those of PLLA.[22] Meanwhile, the crystallinity was obviously lower than that of PLLA and decreased with the increase of Asp in the feed. Especially, once LA/Asp $\leq$ 20 : 1, the copolymers became amorphous. These indicate that increasing the number of —CONH— linkages, cyclic succinimide segments and branched Asp segments create a less-ordered structure, and the crystallization becomes more difficult. This is consistent with the DSC results. Generally, the lower crystallinity is desirable to obtain a better degradation of poly(lactic acid-amino acid) (PLAA). In fact, the research on the hydrolytic degradation of the copolymer derived from LA and alanine by direct

TABLE II
The Influences of Molar Feed Ratio on the Results of DSC and XRD[a]

Run	LA/Asp	T_g (°C)	T_m (°C)	ΔH (J g^{-1})	Crystallinity (%)	Crystallite size (10^{-10} m)	
						L_{110}	L_{020}
	100 : 0[22]	50.0	134.1	46.7	45.1	143.4	69.5
1	40 : 1	60.0	112.5	7.8	20.1	113.5	125.6
2	32 : 1	57.7	109.4	21.8	9.9	114.2	136.5
3	24 : 1	62.5	94.8	5.8	8.9	116.1	263.5
4	20 : 1	69.9	ND[b]	ND[b]	Amorphous		
5	10 : 1	67.8	ND[b]	ND[b]	Amorphous		
6	8 : 1	79.7	ND[b]	ND[b]	Amorphous		

[a] All runs were polymerized with a polycondensation temperature of 160°C, a polycondensation time of 10 h, and catalyst $SnCl_2$ quantity of 0.7 wt %.
[b] Not detected.

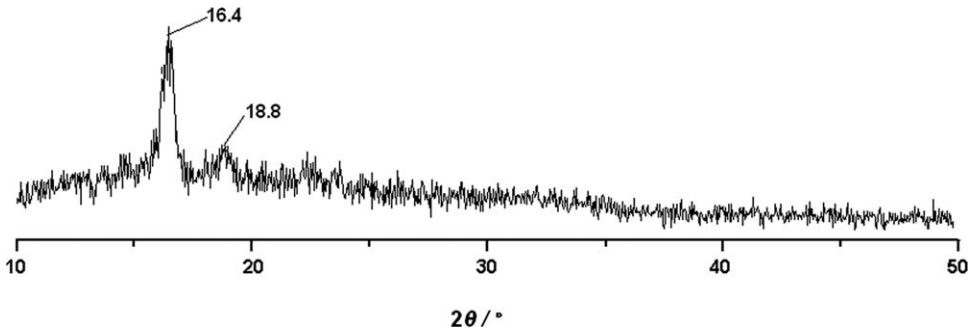


Figure 8 XRD pattern of P(LA-*co*-Asp) synthesized as the molar feed ratio 40 : 1 (LA/Asp).

melting copolymerization showed that increasing of the content of AA in feed enhanced the PLAA's degradation rate.[19]

At the same time, for the molar feed ratio LA/Asp $\geq$ 24 : 1, the crystallite size increased with the increase of Asp in the feed for the introduction of —CONH— linkages. Especially, the crystallite size for L_{020} was bigger than that of homopolymer PLLA (Table II). Therefore, the results of many respects suggested that the introduction of Asp into the polymer had a greater influence on the crystalline properties of P(LA-*co*-Asp). These investigations showed that it would be essential to control the feed ration of Asp content to obtain a copolymer with suitable component of chain units and thus introduce good biological properties to the copolymers.

CONCLUSIONS

An important biodegradable biomaterial P(LA-*co*-Asp) can be directly synthesized via melt copolycondensation of LA and Asp. The relative molecular weight, thermal properties, and crystallinity of the copolymer could be controlled by the content of Asp in the feed. The novel method is cheaper and more practical than the traditional two-step method via the ROP of lactide, and the M_w of the directly obtained P(LA-*co*-Asp) could meet the demand of drug-delivery carrier material.

We also thank Dr Li-Ming FANG from South China University of Technology for helpful discussion.

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