Thermal Properties of Copoly(L-lactic acid/glycolic acid) by Direct Melt Polycondensation

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Poly(L-lactic acid-co-glycolic acid) (PLGA) was prepared from hydroxy-acids with melt polymerization. In this way, the copoly(L-LA/GA) (PLGA) was synthesized directly using a binary catalyst (tin chloride dihydrate/p-toluenesulfonic acid). The thermal properties of PLGA were studied by differential scanning calorimetry (DSC) and nuclear magnetic resonance (NMR). The results show that the melting point of PLGA decreases with increasing mole fraction of GA units in the copolymer. In addition, the melting point of polymer also decreases with increasing degree of racemization of the polymer.

Keywords melt polymerization, L-lactic acid, glycolic acid, poly(L-lactic acid-co-glycolic acid) (PLGA), thermal properties, racemization

Introduction

The Ajioka group (1, 2) developed the solution polycondensation of L-LA/GA in 1995, which brought a breakthrough for direct synthesis to get sufficiently high weight-average molecular weight (Mw) polymers. Solution polycondensation can successfully overcome all difficulties in kinetic control, such as efficient removal of water and suppression of depolymerization of the polymers. PLGA with high Mw could be prepared after a relatively long reaction period at 160°C under high vacuum in diphenyl ether solution. However, the solvents lead to complexity of both process control and purification of the end product. Thus the resultant polymers would be very expensive. In 2000, Kimural (3–5) developed a new melt and melt/solid poly-condensation process to overcome these drawbacks, by which high Mw PLLA and PGA could be produced.

Various PLGA were produced in the present work by a process similar to that developed by Kimura. For this paper, copoly(L-lactic acid/glycolic acid)(PLGA) was prepared by direct melt polycondensation instead of a ring-opening process (ROP) which has been used in a great deal of literatures (6–11). The effect of the amount of GA units in the as-polymerized copolymer on the thermal properties was studied. Moreover, the influences of the GA content on the glass transition temperature, solubility and the melting temperature of the as-polymerized copolymer are also discussed.

Experimental

Materials and Reagents

L-LA as a 90 wt% aqueous solution (PH90, pharmaceutical grade) was purchased from Purac Corp. (Netherlands). Aqueous 90 wt% solution of D,L-lactic acid (50/50 molar ratio of L-LA/D-LA), glycolic acid (GA) dihydrate, tin (II) chloride dihydrate, p-tolulene-sulfonic acid monohydrate (TSA), diethyl ether, tin powder, chloroform, and molecular sieve (3 Å) were purchased from Shanghai Chemical Corp (China). Molecular sieve was activated at 300°C for 24 h. All other reagents were analytical grade and used as received.

Preparation of PLGA

The first step was to make the oligomer: a given amount of L-LA aqueous solution 90 wt% and glycolic acid dihydrate were charged into a 100 mL three-necked flask. The flask was equipped with a mechanical stirrer and a reflux condenser packed with molecular sieve (3 Å). The reaction system was connected with a vacuum system through a cold trap. The mixture of aqueous L-LA and GA dihydrate was then dehydrated at a constant temperature of 150°C by stepwise vacuuming the reaction system. First, the reaction system was kept at atmospheric pressure for 2 h, then at a reduced pressure of 13,300 Pa for 2 h, and finally under a pressure of 1300 Pa for more than 4 h. Thus, viscous oligomers of L-LA and GA were formed and the amount of water removed from the system was measured. The water byproduct and solvent was removed to obtain the oligomer. After purification, the samples were subjected to ^{1}H-NMR testing, from which the degree of polymerization of the oligomer was calculated to be about 6.

The second step was to make polymer: tin(II) chloride dihydrate corresponding to 0.4 wt% of the oligomer and TSA with molar ratio of tin(II)/TSA of 1/1, were mixed with oligomers in the flask. Along with the pressure being reduced stepwise to reach 100 Pa, the mixture was gradually heated to appropriate reaction temperatures (typical reaction temperature was 180°C) under mechanical stirring. Then, the reaction system was maintained under these conditions for predetermined hours. With the proceeding of the reaction, gradually the reaction system became viscous, and the resultant L-lactide and glycolide were refluxed through the reflux condenser. At the end of the reaction, the flask was cooled down under vacuum. The obtained product was then dissolved in chloroform and subsequently precipitated into diethyl ether. Finally, the resulting solids were filtered and dried under vacuum at 65°C. PLGA (90/10) was prepared from the mixture of L-LA/GA (90/10) (molar ratio of L-LA/GA 90/10), while PLGA (70/30) from L-LA/GA (70/30). PDLLA and PLLA synthesized by the same process are used as references for microstructure analysis and solubility study of PLGA. D,L-lactic acid (50/50) was utilized to synthesize PDLLA with the same process described above for PLGA.

Polymer Characterization

Both ^{13}C-NMR and ^{1}H-NMR spectra were carried out at a temperature of 300 K on a Bruker DMX-500 NMR spectrometer. All polymer samples were dissolved in deuterated chloroform with tetramethylsilane (TMS) as an internal standard. Chemical shifts in ppm were referenced relatively to TMS, value of chloroform was at 77.00 ppm and 7.26 ppm in ^{13}C-NMR and ^{1}H-NMR spectra respectively. ^{1}H-NMR spectra were acquired from 1%

solutions at 500 MHz. The ^{13}C-NMR measurements were acquired from 10% solutions at 125 MHz, with a pulse angle of $25°$, an acquisition time of 1.6s, and a delay time of 10s. The racemization was analyzed from the ^{13}C-NMR spectra of PLLA, PDLLA and PLGA.

The melting point, the glass transition temperature and the enthalpy of fusion (ΔHf) of polymers were determined by differential scanning calorimetry (DSC) on a Modulated DSC 2910 thermal analyzer (TA Corp. USA.) at a heating rate of $10°C/min$.

X-ray diffraction (XRD) measurements were performed with a Rigaku D-MAX/Rb Diffractometer (Rigaku Corp. Japan) with Cu – Kα radiation at a wavelength of 1.54 Å in the 2θ range of $5-50°$ at 40 kv and 100 mA.

Results and Discussion

A series of copolymerizations of L-LA and GA were prepared. The DSC measurements to check the effect of the amount of GA in the as-polymerized copolymer on the thermal properties was studied. Table 1 shows the effects of copolymerization on the thermal properties. The heat of fusion, melting point, glass transition temperature and crystallinity are strongly affected by compositions of PLGA. The compositions of copolymers were determined by 1H NMR spectra. Molar fraction of GA moiety in PLGA can be calculated from the integrated area of peaks at 5.15 ppm, due to methine protons in LA units, and of peaks at 4.60–4.90 ppm due to methylene protons in GA units of PLGA (7, 10, 13). Assigning IL to the integrated peak area at 5.15 ppm, I_G to the integrated peak area of at 4.6–4.9 ppm, and F_G to the mole fraction of GA, respectively, F_G can be calculated according to the following relationship:

$$F_G = I_G/(2IL + I_G).$$

Figure 1 shows typical DSC scans for the studied system. The PLLA homopolymer shows a sharp melting endotherm peaking at $155.7°C$. Copolymerization of L-LA and GA results in decreasing of the melting temperature, glass transition temperature, degree of crystallinity and heat of fusion in comparison with PLLA. In addition, the

Table 1

Thermal properties of as-polymerized copolymers of L-lactic acid and glycolic acid in the melt at $18°C$

Glycolic acid (%) in copolymer	ΔH(J g^{-1})^a	T_m(°C)^a	T_g(°C)^a	Crystallinity(%)^b
0	53.65	156.4	ND	57.69
4.34	35.47	141.5	59.2	38.14
8.70	30.82	124.9	57.8	33.14
12.12	26.49	116.3	56.9	28.48
16.57	21.55	98.8	55.8	23.17
22.62	18.20	79.5	54.2	19.59
32.20	ND^c	ND^c	52.8	ND^c

^{a}Results from DSC determination.
^{b}Calculated from DSC curve (12).
^{c}Not detected.
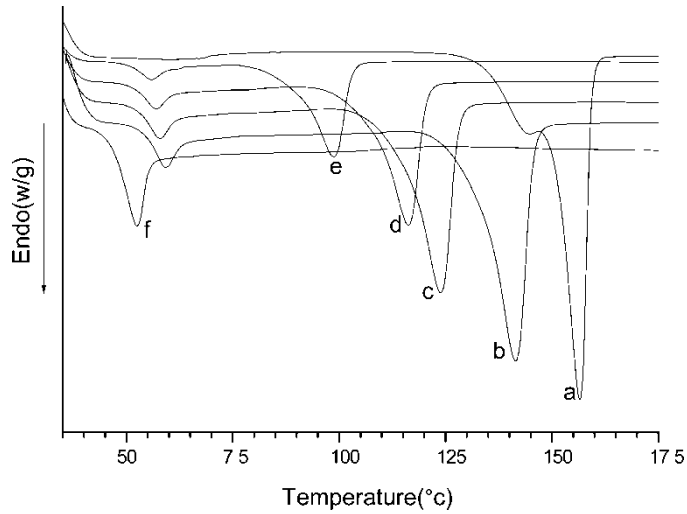
Figure 1. DSC thermograms of PLGA with different molar fraction of GA in samples: (a) 0%, (b) 4.34%, (c) 8.70%, (d) 12.12%, (e) 16.57%, (f) 32.20%.

melting range becomes less sharp as the concentration of monomer L-LA decreases. The copolymer containing 32.2% GA (PLGA (70/30)) shows the characteristics of an amorphous copolymer: the melting peak is absent, and the glass transition temperature has shifted to even lower temperatures.

Figure 2. X-ray diffractograms of PLLA-1, PDLLA (50/50), and PLGA (90/10).

X-ray diffractograms are shown in Figure 2. The crystalline PLLA-1 shows a large number of diffraction peaks. The sharpest and most intense one is at 16.84 degree 2θ, due to the 020 reflection. Other peaks can be observed at 14.90, 19.21, and 22.45 degree $2\th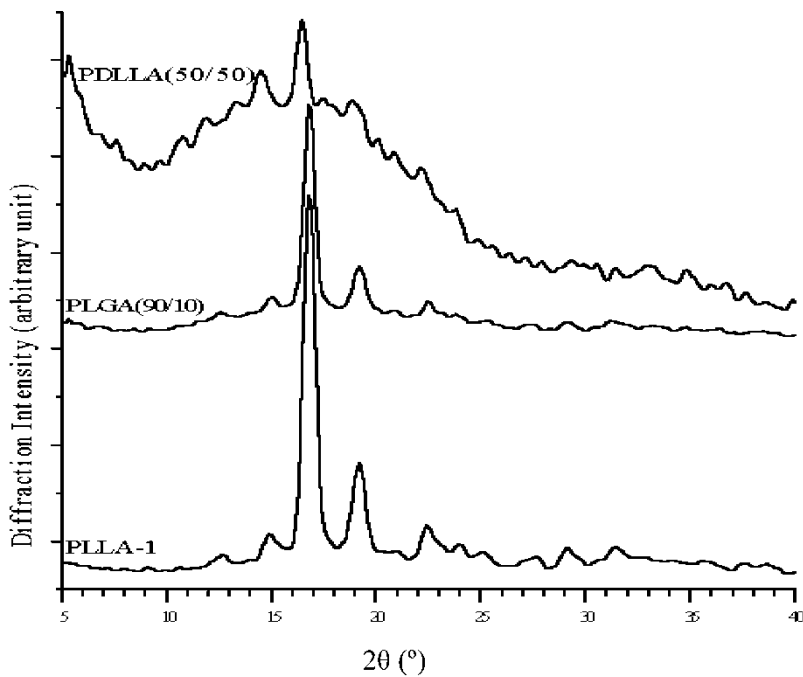eta$ due to 101, 023, and 121 reflections, respectively (13–16). These values coincide with the observed values of the α structure of PLLA. As for PGA, with $\overline{Mn}$ of 2900 prepared by direct synthesis, reflections were seem at $2\theta = 22.2°$ and $28.9°$ (13). The diffraction spectrum of PLGA (90/10) consists of a relatively intense reflection at 16.84 degree 2θ and two smaller peaks at 14.90 and 19.21 degree 2θ, but the crystallization of GA sequences can not be detected.

The crystallization of copolyester yields smaller and less perfect crystallites, because the crystal lattice of L-LA units tends to exclude GA units. This incorporation causes lattice defects and results in a decrease in overall crystallinity, heat of fusion and melting temperature. Copolymerization lowers the melting point except in rare instances where the different types of monomeric units are capable of replacing one another in their crystal lattices. The mole fraction of GA units in PLGA also has effects on glass transition temperature and degree of crystallinity. As shown in Figure 3 both the glass transition temperature and the degree of crystallinities of as-polymerized PLGA decrease with increasing mole fraction of GA units in PLGA. This result was consistent with messurements based on samples prepared with the ROP method preparing of PLGA (8).

Apart from the effect of composition of PLGA on melting point, the effect of racemization on melting point was also investigated. The racemization was analyzed from ^{13}C-NMR spectra of PLLA, PDLLA, and PLGA. Figure 4 shows the carbonyl regions at 169–170 ppm of these NMR spectra. The PLLA and PDLLA were prepared by a similar process to PLGA. In the spectra of PLGA, a new peak at 169.44 ppm appears
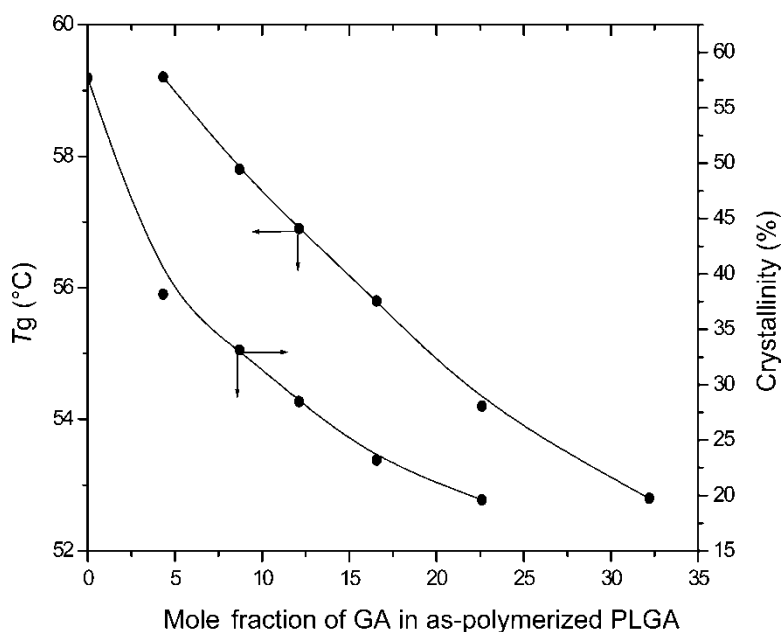
Figure 3. Dependence of the glass transition temperature and the degree of crystallinity of as-polymerized PLGA on the copolymer composition.

Figure 4. Carbonyl regions of ^{13}C-NMR spectra of PLLA, PDLLA, and PLGA: (i) isotactic, (s) syndiotactic.

and increases with GA fraction; it which could result from LG (L-LA linked with GA) units. The assignments of signals due to the isotactic (i) and syndiotactic (s) sequences of the lactate units were shown in Figure 4 according to literature reports for PLLA, PDLLA, and poly(L-lactide-co-glycolide) (3, 7, 9, 10, 15, 17). The degrees of

Figure 5. ^{13}C-NMR spectra of PLLA, PDLLA, and PLGA (methine region) obtained in CDCl$_3$ solutions.

Table 2
The relation between racemization and melting point of polymer[a]

Samples[b]	Racemization (%)	T_m (°C)	Mole %GA in PLGA
PLLA-1	0.0	156.4	—
PLLA-2	6.76	155.7	—
PLLA-3	19.4	149.6	—
PLLA-4	4.00	ND	—
PLGA-1 (90/10)	12.5	119.4	11.90
PLGA-2 (90/10)	17.5	118.2	11.76
PLGA-3 (90/10)	29.3	116.3	12.12
PLGA-4 (90/10)	34.5	112.6	11.24

[a]Racemization (%) is calculated from carbonyl signals in ^{13}C-NMR; mol% GA in PLGA is calculated from ^{1}H-NMR.
[b]Samples were prepared under different reaction time and temperature.

racemization of the LA component of the polymer were calculated from the integral ratio of isotactic and syndiotactic sequence signals. It is known from literatures (3, 7, 9, 10, 15, 17) that all signals in the spectra of PLLA, PDLLA, and poly(L-lactide-co-glycolide) from 169.0 ppm to 169.4 ppm are due to racemization. Comparing the spectra of PLGA (90/10) and PLGA (70/30) at 169.0–169.4 ppm in Figure 4, the intensities of carbon signals of PLGA (70/30) due to the racemic units increase with GA fractions, which indicates the addition of GA increases the racemization of LA units.

The methine signals at 68.5–69.5 ppm (Figure 5) are also designated for comparison of poly(D,L-lactide) and poly(L-lactide) (18, 19). The spectrum of PLLA-2, possessing more intense signals due to tetrads such as iss, sss, isi, and ssi than PLLA-1, confirms the effect of reaction time on the PLLA racemization. The intensities of peaks due to iss, sss, isi, and ssi increase greatly with increasing GA, which supplies further evidence of the promotion of racemization of LA blocks in the presence of GA. A new peak at 68.84 ppm can be caused by GA blocks, because it appears and increases with increasing GA fractions in PLGA.

The results of the relation between degrees of racemization and melting temperature of polymer are shown in Table 2; the melting temperature decreases with increasing degree of racemization. In comparison with the effect of different composition of PLGA on the melting point of polymer, as shown in Table 1, the effect of the degree of racemization of polymer is much more limited.

Conclusions

A series of copolymerizations of L-LA and GA were prepared by direct melt polycondensation. In this case, the heat of fusion, melting temperature, glass transition temperature and crystallinity are strongly affected by the compositions of PLGA. The melting temperature of PLGA decreases with increasing the mole fraction of GA units in copolymer. When the molar fraction of GA in the feed is more than 30%, amorphous copolyester is formed because the crystal lattice of L-LA units tends to exclude GA units. On the other hand, racemization promoted by the addition of GA

monomer could also play an important role in the decrease of T_m and crystallinity of PLGA (9). The mole fraction of GA units in PLGA has similar effects on glass transition temperature and the heat of fusion.

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