

Syntheses of Poly(lactic acid-co-glycolic acid) Serial Biodegradable Polymer Materials via Direct Melt Polycondensation and Their Characterization

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ABSTRACT: The optimal synthetic conditions of poly(lactic acid-co-glycolic acid) (PLGA) via melt copolycondensation directly from L-lactic acid (L-LA) and glycolic acid (GA) with a feed molar ratio of 50/50 are discussed; the important drug-delivery carrier PLGA50/50 is used as a special example. With reaction conditions of 165°C and 70 Pa and with 0.5 wt % SnCl₂ as the catalyst, 10 h of polymerization gave the L-PLGA50/50 with the biggest intrinsic viscosity ($[\eta]$), 0.1993 dL/g. The optimal synthetic conditions were verified by the synthesis of D,L-PLGA50/50 with D,L-lactic acid (D,L-LA) instead of L-LA, but the biggest $[\eta]$ was 0.2382 dL/g. Under the same synthetic conditions with L-LA and D,L-LA as starting materials, serial PLGA with different molar feed ratios, including 100/0, 90/10, 70/30, 50/50, 30/70, 10/90, and 0/100, were synthesized via simple and practical direct melt copolycondensation, and their solubilities were investigated. When the glycolic acid feed molar percentage was equal to or more than 70%, solubilities in tetrahydrofuran and CHCl₃ became worse, and some samples were even wholly insoluble. These biodegradable polymers were also systematically characterized with gel permeation chroma-

tography, Fourier transform infrared spectroscopy, ¹H-NMR spectroscopy, differential scanning calorimetry, and X-ray diffraction. PLGA synthesized from L-LA and D,L-LA had many differences in weight-average molecular weight (M_w), glass-transition temperature, crystallinity, and composition. When the molar feed ratio of LA to GA was 50/50, both the $[\eta]$ and M_w values of D,L-PLGA were higher than those of L-PLGA. With D,L-LA as the starting material, the structure of the PLGA copolymer was relatively simple, and its properties were apt to be controlled by its GA chain segment. When the feed molar percentage of the monomer (LA or GA) was more than or equal to 90%, the copolymer was apt to be crystalline, and the aptness was more obvious for the L-LA monomer. The composition percentage of GA in PLGA was not only higher than the feed molar percentage of GA, but also, the GA percentage in D,L-PLGA was higher than in L-PLGA. © 2005 Wiley Periodicals, Inc. *J Appl Polym Sci* 99: 244–252, 2006

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

INTRODUCTION

Poly(lactic acid-co-glycolic acid) (PLGA), a kind of aliphatic polyester, can completely biodegrade into CO₂ and H₂O and is wholly harmless and nontoxic to the environment. At the same time, PLGA has excellent biological compatibility and biological resorbability, which provides it with extensive applications in many fields, such as medical sutures, bone fixation materials, drug-delivery microspheres, and tissue engineering.^{1–4} However, research and development of PLGA has been limited by the high cost of its synthesis.

PLGA has often been synthesized through a two-step method, the ring-opening polymerization of 3-methylglycolide and the ring-opening copolymerization of lactide and glycolide. These lactone intermediates have usually been prepared from lactic acid (LA), glycolic acid (GA), or the derivatives of LA and GA, which has made the whole synthetic process for PLGA lengthy and troublesome and has made the gross yield lower. At the same time, to synthesize higher molecular weight PLGAs, these intermediates must be recrystallized several times before they are used; this process is tiresome and consumes a lot of organic solvents.^{1,5–8}

Therefore, new methods for synthesizing PLGA are being explored extensively. Recently, in the hope of substituting for the lactone two-step method, Ajioka et al.⁹ reported a kind of one-step method, a direct solution polycondensation from LA and GA. The process is much simpler than the ring-opening polymerization method, but it has brought about another question because the direct solution polymerization was carried out in the

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TABLE I
Effects of the Different Catalysts on $[\eta]$ Values of L-PLGA50/50

Run	Catalyst	Dispersibility	Dissolubility	$[\eta]$ (dL/g)	M_w (Da)	M_n (Da)	M_w/M_n	Yield (%)
1	Sn	Very bad	Agglomerate	0.1574	14,000	10,700	1.31	60.3
2	SnO	Good	Wholly not	0.1769	N	N	N	64.5
3	SnO ₂	Common	Easily sedimented	0.1061	N	N	N	46.9
4	Sn(Oct) ₂	Common	In the end dissolved	0.1549	N	N	N	61.7
5	SnCl ₂	Very good	Good	0.1993	18,000	13,800	1.30	69.6
6	ZnO	Bad	Wholly not	0.1059	N	N	N	41.2
7	ZnCl ₂	Good	Good	0.1480	N	N	N	50.8
8	Zn(LA) ₂	Common	In the end dissolved	0.1020	N	N	N	42.7
9	TSA	Very good	Good	0.0963	N	N	N	34.9

N = not tested. All runs were polymerized with a n_{L-LA}/n_{GA} value of 50/50 an absolute pressure of 70 Pa, a polycondensation temperature of 165°C, a polycondensation time of 10 h, and a catalyst quantity of 0.5 wt %.

azeotropic solvent diphenyl ether, which has a high boiling point and is not easy to purge from the product.

Now, more and more importance has been attached to another one-step method, the direct melt polycondensation of LA and GA without any azeotropic solvents. After Wang et al.¹⁰ directly synthesized PLGA with molecular weights ranging from 900 to 1400 Da in 1997, Gao and coworkers^{11,12} reported the syntheses, microstructure, and thermal properties of part-serial L-PLGA with feed molar ratios of L-lactic acid to glycolic acid (n_{L-LA}/n_{GA}) of 100/0, 90/10, and 70/30. To improve the molecular weight of PLGA90/10 ($n_{L-LA}/n_{GA} = 90/10$, the means of the following ratios were similar), further solid polycondensation after direct melt polycondensation was investigated in Japan.¹³

Recently, Zhou et al.¹⁴ reported the direct syntheses of D,L-PLGA with feed molar ratios of D,L-lactic acid to glycolic acid ($n_{D,L-LA}/n_{GA}$) of 100/0, 85/15, 75/25, 65/35, 50/50 and its application in protein-delivery systems. However, their melt copolycondensation was carried out under a N₂ atmosphere, as Fukuzaki et al.¹⁵ described 14 years ago. This one-step method, accompanied with N₂ bubbling, is also troublesome, and the molecular weight of PLGA needs to be further increased.

At the same time, although these one-step methods have been established, the optimal synthetic conditions for PLGA, especially PLGA50/50, which has often been used as a drug-delivery carrier or tissue engineering material,^{4,8} have seldom been mentioned in the literature of the direct melt copolycondensation of LA and GA.¹⁰⁻¹⁵ Furthermore, a whole and systematic study on PLGA as directly synthesized via melt copolycondensation, including the effects of different n_{L-LA}/n_{GA} values (ranging from 100/0 to 0/100) and different LA conformations in stereochemistry on the properties of PLGA, has not been reported.

Therefore, we investigated the optimal synthetic conditions of PLGA50/50 through the new one-step method at an absolute pressure of 70 Pa, including

catalyst kinds and quantities, polymerization temperature, and reaction time. Then, with D,L-lactic acid (D,L-LA) and L-lactic acid (L-LA) as starting materials, we synthesized whole serial PLGA via direct melt copolycondensation with GA, and these products were systematically characterized with gel permeation chromatography (GPC), Fourier transform infrared (FTIR) spectroscopy, ¹H-NMR spectroscopy, differential scanning calorimetry (DSC), and X-ray diffraction (XRD).

EXPERIMENTAL

Materials

L-LA and stannous octoate [Sn(Oct)₂] were purchased from Wako Pure Chemical Industries, Ltd. (Tokyo), and *p*-toluenesulfonic acid (TSA) was purchased from Nacalai Tesque Co. (Kyoto, Japan). Zinc lactate [Zn(LA)₂] was self-made from zinc oxide (ZnO) and D,L-LA, and was characterized by FTIR and its melting point.

Other chemical reagents, including stannous chloride (analytical reagent), D,L-LA (analytical reagent), and GA (chemical purity), were purchased from Guangzhou Chemical Reagent Factory (Guangzhou, China) and Guangzhou Donghong Chemical Factory (Guangzhou, China). All these materials were used without further purification.

Instrumental analysis and measurements

¹H-NMR spectra were recorded with a DRX-400 NMR spectrometer (Bruker Instruments, Billerica, MA) with CDCl₃ as the solvent and internal standard. IR spectra were obtained from an FTIR spectrometer (Bruker Vector 33, Ettlingen, Germany) by the KBr salt slice method.

The intrinsic viscosity ($[\eta]$) of PLGA was determined with Ubbelohde viscometer (Cannon-Ubbelohde, State College, PA) with CHCl₃ as the solvent at

TABLE II
Effects of the SnCl₂ Catalyst Quantity on the $[\eta]$ Value of L-PLGA50/50

Run	Catalyst quantity (wt %) ^a	Dispersibility	Dissolubility	$[\eta]$ (dL/g)	Yield (%)
1	0.1	Very good	Good	0.1469	50.2
2	0.3	Very good	Good	0.1812	64.0
3	0.5	Very good	Good	0.1993	69.6
4	0.7	Very good	Good	0.1628	57.5
5	0.9	Very good	Good	0.1415	49.6

All runs were polymerized with a n_{L-LA}/n_{GA} value of 50/50, an absolute pressure of 70 Pa, a polycondensation temperature of 165°C, a polycondensation time of 10 h, and SnCl₂ as the catalyst.

^a Weight percentage of dehydrated reactants.

25°C. The relative molecular weight and its distribution were determined by a Waters 515 high-performance liquid chromatograph (Torrance, CA) with tetrahydrofuran (THF) as the solvent and with polystyrene as the reference at a flow velocity of 1 mL/min and at 35°C.

DSC was performed with PerkinElmer DSC7 thermal analyzer (PerkinElmer, Cetus Instruments, Norwalk, CT) at a heating rate of 10°C/min under an argon atmosphere (flow velocity = 20 mL/min). With a wavelength of 1.5406×10^{-10} m and a scanning scope of $2\theta = 1-40^\circ$ with Cu K α radiation, a Rigaku D/max-1200X X-ray diffractometer (Rigaku Co., Tokyo) was used to investigate the crystallinity of PLGA.

Melt copolymerization

According to our previous research on the melt homopolymerization of LA,¹⁶⁻¹⁸ after LA and GA were uniformly mixed at a preplanned feed molar ratio, the mixture was directly dehydrated for 6 h at 140°C and 4000 Pa in a three-necked flask equipped with a mechanical stirring device and a thermometer; we then selected the catalyst as a weight percentage of dehydrated reactants was added. At a certain temperature (150–190°C) and an absolute pressure of 70 Pa, the melt copolymerization was carried out for 5–20 h.

When the reaction finished, purification gave a white powder product after the sample was dried *in vacuo*.

RESULTS AND DISCUSSION

Optimal synthetic conditions for L-PLGA50/50

For PLGA50/50, which is often used as a drug-delivery carrier or tissue engineering material,^{4,8} we selected a value of n_{L-LA}/n_{GA} of 50/50 to examine the appropriate synthetic conditions for PLGA. In the reported literature on the melt polymerization of LA, L-LA has been used more extensively⁹⁻²⁶ and has easily given higher molecular weight polymers, especially in homopolymerization, than did D,L-LA.^{16,18} Therefore, we first selected L-LA and then confirmed the optimal synthetic conditions for PLGA50/50 with D,L-LA.

The effects of different catalysts on $[\eta]$ of L-PLGA50/50 are shown in Table I. The effect of the catalysts was determined not only by the metal type but also their dispersability and dissolubility in the polymerization system. The stannum series catalysts (runs 1–5) were relatively better than the zinc series catalysts (runs 6–8) and TSA (run 9). SnCl₂ had very good dispersability and good dissolubility when it was used as the catalyst; also, when SnCl₂ was used, $[\eta]$ reached a maximum (run 5). However, TSA (run 9) also dispersed and dissolved well, and its corresponding $[\eta]$ was the lowest of all.

The influences of SnCl₂ quantity on $[\eta]$ of L-PLGA50/50 are shown in Table II. When the quantity of SnCl₂ was 0.5 wt %, $[\eta]$ reached a maximum (run 3); too much or too little was not appropriate. When the quantity was too small, the reaction was so insufficient after a certain time that $[\eta]$ was not high. When the quantity of SnCl₂ was excessive, although it did not affect the dispersability and dissolubility of the catalyst in the polymerization system, short-chain molecules were apt to form through the degradation of the polymer, which was also catalyzed by SnCl₂, so $[\eta]$ was not high.

The effects of melt copolymerization time on $[\eta]$ of L-PLGA50/50 are shown in Table III. It was obvious

TABLE III
Influences of the Melt Copolymerization Time on the $[\eta]$ Value of L-PLGA50/50

Run	Time (h)	Crude product	Color after purification	$[\eta]$ (dL/g)	Yield (%)
1	5	Yellowish and transparent	White	0.1736	52.2
2	8	Yellow and transparent	White	0.1783	62.3
3	10	Light brown and semitransparent	White	0.1993	69.6
4	12	Light brown and semitransparent	White	0.1882	66.1
5	15	Light brown and opaque	Yellowish	0.1801	62.7
6	20	Brown and obviously opaque	Yellow	0.1715	60.5

All runs were polymerized with a n_{L-LA}/n_{GA} value of 50/50, an absolute pressure of 70 Pa, a polycondensation temperature of 165°C, and 0.5 wt % SnCl₂ as the catalyst.

TABLE IV
Effects of the Melt Polycondensation Temperature on the $[\eta]$ Value of L-PLGA50/50

Run	Temperature (°C)	Crude product	Color after purification	$[\eta]$ (dL/g)	Yield (%)
1	150	Yellowish and transparent	White	0.1385	49.6
2	158	Yellow and transparent	White	0.1545	51.7
3	165	Light brown and semitransparent	White	0.1993	69.6
4	173	Brown and opaque	Yellow	0.1634	55.7
5	180	Dark brown	Brown ^a	0.1266	20.4

All runs were polymerized with a n_{L-LA}/n_{GA} value of 50/50, an absolute pressure of 70 Pa, a polycondensation time of 10 h, and 0.5 wt % SnCl_2 as the catalyst.

^a The yield often ranged from 50 to 70% when SnCl_2 was used as the catalyst; the run 5 yield was only 20.4%.

that $[\eta]$ reached a maximum after the reaction lasted for 10 h (run 3). When the reaction time was too much shorter, further dehydration and polymerization were insufficient. However, when the reaction time was longer than 10 h, the oxidation and thermal degradation of the polymer became serious, so $[\eta]$ dropped, and even when the reaction lasted for 20 h, the product became yellow (run 6). Thus, the appropriate time was 10 h.

Melt copolymerizations were carried out at 150, 158, 165, 173, and 180°C, and the results are shown in Table IV. Obviously, the optimal temperature was 165°C (run 3). The appropriate reaction temperature was advantageous to dehydration and copolycondensation, so $[\eta]$ of L-PLGA50/50 quickly increased with increasing temperature up to 165°C. When the temperature was too high, side reactions, such as oxidation and thermal degradation markedly took place, so $[\eta]$ dropped, and the color of the purified product changed from white to yellow and then brown. Even when temperature was 180°C, the yield was obviously smaller than at other temperatures (run 5).

Therefore, the optimal synthetic conditions for L-PLGA50/50 were as follows: catalyst = SnCl_2 , catalyst quantity = 0.5 wt %, temperature = 165°C, abso-

lute pressure = 70 Pa, and reaction time = 10 h. Using these results as a reference to synthesize other PLGAs may be suitable because, under these conditions, D,L-PLGA 50/50 with the biggest $[\eta]$ was prepared as follows.

Optimal synthetic conditions for D,L-PLGA50/50

The effects of temperature on $[\eta]$ of D,L-PLGA50/50 when we started with D,L-LA and GA are shown in Table V. Obviously, the appropriate temperature was 165°C, which was same as when we started with L-LA. The reason was similar that in the synthesis of L-PLGA50/50. It was noticeable that although the optimal temperature was same, the biggest $[\eta]$ of the D,L-type copolymer (0.2382 dL/g, run 2), was much bigger than that of L-PLGA50/50 (0.1993 dL/g).

The effects of reaction time on $[\eta]$ of D,L-PLGA50/50 are shown in Table VI. For the same reason as in the synthesis of the L-type copolymer, the results were similar. It was obvious that the appropriate time was 10 h (run 2). This time was same as that starting from L-LA.

Therefore, even if we used D,L-LA and GA as starting materials, although the biggest $[\eta]$ was different, the appropriate synthetic conditions for PLGA50/50

TABLE V
Effects of the Polycondensation Temperature on the $[\eta]$ Value of D,L-PLGA50/50

Run	Temperature (°C)	$[\eta]$ (dL/g)	Yield (%)
1	150	0.1423	50.3
2	165	0.2382	65.5
3	173	0.2060 ^a	34.2
4	180	N ^b	N
5	190	N	N

All runs were polymerized with a $n_{D,L-LA}/n_{GA}$ value of 50/50, an absolute pressure of 70 Pa, a reaction time of 10 h, and 0.5 wt % SnCl_2 as the catalyst.

^a The color of the purified product was yellow, and the yield was only 34.2%, which was obviously lower than that of the others.

^b The crude product was dark, and further purification did not polymer.

TABLE VI
Effects of the Polycondensation Time on the $[\eta]$ Value of D,L-PLGA50/50

Run	Time (h)	$[\eta]$ (dL/g)	Yield (%)
1	8	0.2361	60.6
2	10	0.2382	65.5
3	12	0.2070	54.7
4	15	0.1936	49.8
5	20	N ^a	N

N = not tested. All runs were polymerized as with a $n_{D,L-LA}/n_{GA}$ value of 50/50, an absolute pressure of 70 Pa, a reaction temperature of 165°C, and 0.5 wt % SnCl_2 as the catalyst.

^a The crude product was dark, and further purification did not yield polymer.

TABLE VII
GPC Test Results of PLGA from D,L-LA and L-LA

Run	PLGA	[η] (dL/g)		Retention time (min)		M_w (Da)		M_w/M_n	
		D,L-LA	L-LA	D,L-LA	L-LA	D,L-LA	L-LA	D,L-LA	L-LA
1	100/0	0.2302	0.3462	25.2	25.9	17,800	25,400	1.25	1.28
2	90/10	0.1799	0.3905	26.4	26.3	13,900	16,100	1.51	1.32
3	70/30	0.1843	0.1835	26.3	26.2	15,400	15,700	1.69	1.51
4	50/50	0.2382	0.1993	25.4	25.9	24,300	18,000	1.40	1.30

All runs were polymerized with an absolute pressure of 70 Pa, a reaction temperature of 165°C, a reaction time of 10 h, and 0.5 wt % SnCl₂ as the catalyst.

were not different. Thus, under the same synthetic conditions, including the use of single SnCl₂ as the catalyst, a catalyst quantity of 0.5 wt %, a temperature of 165°C, an absolute pressure of 70 Pa, and a reaction time 10 h, when we altered the feed molar ratio of lactic acid to glycolic acid (n_{LA}/n_{GA}), including 100/0, 90/10, 70/30, 50/50, 30/70, 10/90, and 0/100, and started from L-LA or D,L-LA, serial biodegradable PLGA materials were synthesized via direct melt polycondensation.

Solubilities in organic solvents, [η] values, and relative molecular weights of serial PLGA

Although the starting material, LA, had different stereochemical configurations, the serial PLGA materials with different n_{LA}/n_{GA} values had similar solubilities in organic solvents. When the glycolic acid feed molar percentage (n_{GA}) was more than or equal to 70%, the solubilities in CHCl₃ and THF became worse, and some samples were even wholly insoluble. Thus, only PLGA with n_{GA} values ranging from 0 to 50% had test results of [η] measurements with CHCl₃ as the solvent (25°C) and GPC measurements with THF as the solvent (Table VII).

The GPC results showed that when n_{LA}/n_{GA} was the same, although the stereochemical configuration of LA was different, all the retention times were similar. At the same time, all of the GPC flow curves had only single symmetrical peaks (e.g., for run 4, Fig. 1), and all polydispersity index values [weight-average molecular weight (M_w)/number-average molecular weight (M_n)] were less than 2. These indicated that no matter what configuration LA had, the melt copolycondensation of LA and GA indeed only gave the copolymer PLGA and did not produce any poly(lactic acid) or poly(glycolic acid) homopolymer.

As also shown in Table VII, with increasing n_{GA} , ranging from 0 to 50%, first, [η] of D,L-PLGA was lower than that of L-PLGA (runs 1 and 2); also, two data became close (run 3). In the end, the former was higher than the latter (run 4), so did the M_w change also. Notably, D,L-PLGA50/50 had bigger [η] and M_w values than L-PLGA50/50. It has often been found and believed in the reported literature on the melt polymerization of LA that L-LA could easily give higher molecular weight polymers than D,L-LA.⁹⁻²⁶ Therefore, the previously discussed different phenomena

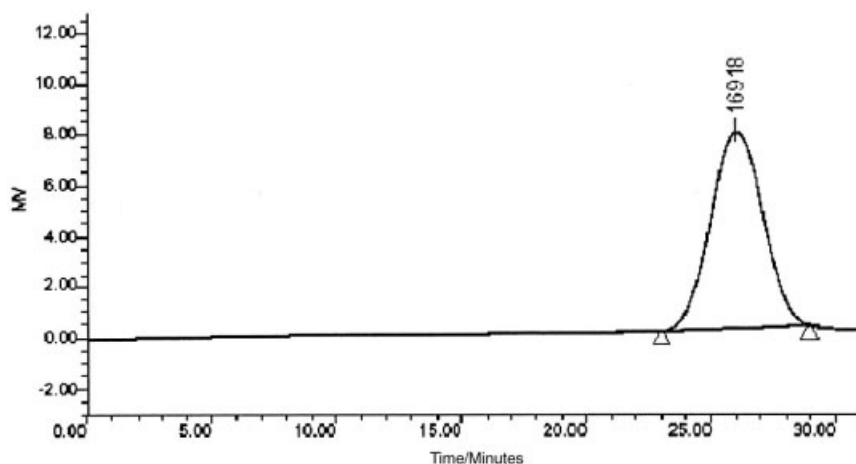


Figure 1 GPC flow curve of L-PLGA50/50.

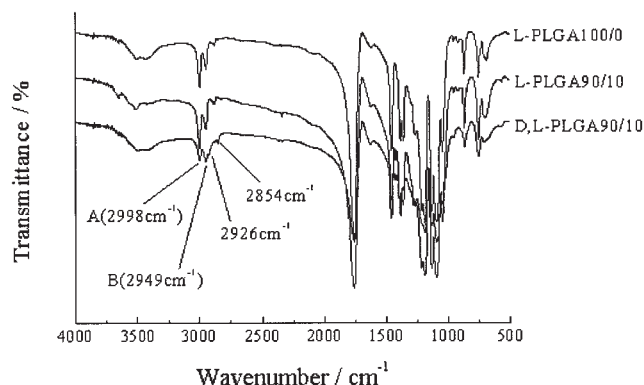


Figure 2 IR spectra of PLGA90/10, respectively from L-LA and D,L-LA.

may be related to the melt copolycondensation mechanism of LA and GA; further research is still in progress.

FTIR characterization of serial PLGA

The structure of PLGA was characterized with FTIR and $^1\text{H-NMR}$ spectroscopy. When the LA starting material stereochemical configuration and $n_{\text{LA}}/n_{\text{GA}}$ were different, the IR data of the serial PLGA had many similarities, including the following.

IR (KBr, cm^{-1}): 1750 (ester carbonyl $\text{C}=\text{O}$ in copolyester, strong); 1160–1187, 1093 ($\text{C}-\text{O}-\text{C}$ in ester group, strong); 2850–3010, 1360–1460 (saturated $\text{C}-\text{H}$ in copolyester, including CH_3 , CH_2 , and CH); 3510 (terminal OH in copolyester, weak).

However, some differences existed when the starting material LA had different stereochemical configurations.

The two absorptions at 2993–3010 cm^{-1} (indexed as A) and 2947–2962 cm^{-1} (indexed as B) not only included the contribution of CH_3 in the LA segment but also the contribution of CH_2 in the GA segment. When $n_{\text{LA}}/n_{\text{GA}}$ changed from 90/10 (Fig. 2, the IR spectra of PLGA90/10) to 70/30 (Fig. 3, the IR spectra of PLGA70/30), for D,L-PLGA, the A absorption decreased, and the B absorption increased. However, for

the L-type copolymer, the A absorptions were relatively stronger than those of B. Furthermore, the D,L-type copolymer obviously had absorptions at 2926 and 2854 cm^{-1} contributed by CH_2 in the GA segment. Therefore, when we started from D,L-LA, the GA component in the copolymer may have been higher than that in the L-type copolymer.

$^1\text{H-NMR}$ characterization of serial PLGA

For the reason of solubilities in chloroform, only part-serial PLGAs were characterized with $^1\text{H-NMR}$ (with the solvent CDCl_3 and with a chemical shift of 7.26 ppm as an internal standard), and the results are shown in Table VIII. It was obvious that although the starting material LA stereochemical configuration and $n_{\text{LA}}/n_{\text{GA}}$ were different, the chemical shifts of CH , CH_2 , and CH_3 were similar.

However, the peak split of CH_3 (last two columns, Table VIII) were different. For D,L-PLGA, all peaks were double. For L-PLGA, some were double, and some were triple (run 2 and 3); the latter was caused by the overlap of the double peak. These results indicate that when we started with LA with different stereochemical configurations, the mechanism of the melt copolycondensation between LA and GA might have been different, which made the segment array of PLGA different, and the array in D,L-PLGA was relatively simpler than in L-PLGA.

According to Gilding and Reed,¹ with the integral data of the CH peak near $\delta = 5.19$ ppm and the data of the CH_2 peak near $\delta = 4.85$ ppm, the molar component ratio of the LA segment in PLGA and the molar component ratio of the glycolic acid segment in poly(lactic acid-co-glycolic acid) (F_{G}) were calculated and are listed as Table IX. Obviously, all the F_{G} data were higher than the n_{GA} data. These results were consistent with the literature on the two-step method,¹ but the reason was different.

In the two-step method, via the ring-opening polymerization of lactone, it has often been believed that the reason was the difference between the velocity of the ring-opening polymerization of glycolide and that

TABLE VIII
 $^1\text{H-NMR}$ Spectral Data of PLGA from D,L-LA and L-LA

Run	PLGA	CH chemical shift (ppm)		CH ₂ chemical shift (ppm)		CH ₃ chemical shift (ppm)	
		D,L-LA	L-LA	D,L-LA	L-LA	D,L-LA	L-LA
1	100/0	5.18 (q)	5.18 (q)	N		1.59 (d)	1.59 (d)
2	90/10	5.16–5.26 (m)	5.17–5.20 (m)	4.62–4.92 (m)	4.60–4.95 (m)	1.61 (d)	1.59 (t)
3	70/30	5.18–5.28 (m)	5.18–5.26 (m)	4.69–4.92 (m)	4.67–4.92 (m)	1.60 (d)	1.60 (t)
4	50/50	5.13–5.26 (m)	5.13–5.23 (m)	4.61–4.89 (m)	4.63–4.88 (m)	1.57 (d)	1.57 (d)

N = none existed. All runs were polymerized with an absolute pressure of 70 Pa, a reaction temperature of 165°C, a reaction time of 10 h, and 0.5 wt % SnCl_2 as the catalyst. Peak splits are listed in parentheses.

TABLE IX
GA Composition Calculated from $^1\text{H-NMR}$ of PLGA
from D,L-LA and L-LA

Run	PLGA	n_{LA}	n_{GA}	F_G (%)	
				D,L-LA	L-LA
1	90/10	90	10	19.4	11.9
2	70/30	70	30	45.6	38.8
3	50/50	50	50	64.8	58.4

All runs were polymerized with an absolute pressure of 70 Pa, a reaction temperature of 165°C, a reaction time of 10 h, and 0.5 wt % SnCl_2 as the catalyst.

of lactide and that glycolide has a higher velocity than lactide.^{1,5-8} In the one-step method, via the direct copolycondensation of LA and GA, the hydroxyl group (OH) of GA was primary, and the OH of LA was secondary, which led to a different velocity of polycondensation and to GA being more easily reacted than LA, even L-LA.

When we compared the F_G value of D,L-PLGA with that of the L-type copolymer (Table IX, last two columns), the former was obviously higher. This phenomenon coincided with the fact that the B absorption (2947–2962 cm^{-1}) in the IR spectra of PLGA90/10 and PLGA70/30 of D,L-PLGA was stronger than that of the L-type copolymer (Figs. 2 and 3). If we combined this question with the direct melt homopolycondensation of LA,^{16,18} we might conclude that this was related to the experimental fact that LA with different stereochemical configurations had different velocities.

Usually, because of its higher purity, L-LA reacted more easily in the melt polymerization under the same synthetic conditions and gave higher molecular weight poly(lactic acid) than D,L-LA.^{16,18} Similarly, L-LA had a higher velocity than D,L-LA during the direct copolycondensation. Therefore, the velocity difference between D,L-LA and GA was bigger than that between L-LA and GA, which made F_G of D,L-PLGA bigger than that of L-PLGA and n_{GA} .

DSC characterization of serial PLGA

The DSC results of serial PLGA are shown in Table X. From the data on melting temperature (T_m) and melting heat (ΔH), we found that compared with L-PLGA, D,L-PLGA was basically amorphous, except for PLGA10/90 (run 6), which indicated that the L-type copolymers were relatively advantageous for the formation of crystalline structure. Only for L-PLGA when $n_{\text{LA}}/n_{\text{GA}}$ ranged from 100/0 to 70/30 was the change in the glass-transition temperature (T_g) and ΔH similar to the literature values from the direct method.¹²

In the T_g column (Table X), with the advance of n_{GA} , the T_g of L-PLGA gradually decreased, which was similar to the literature results on the direct melt co-

polycondensation of GA and L-LA with $n_{\text{LA}}/n_{\text{GA}}$ ranging from 100/0 to 70/30.^{11,12} However, for D,L-PLGA, only the partly crystalline PLGA10/90 had a higher T_g (run 6) value; the T_g values of the others were markedly lower, and the data were close to each other.

The differences resulting from the LA starting material stereochemical configuration indicated that the L-LA chain segment in PLGA could weaken the reduction of T_g aroused by the flexible GA chain segment in PLGA to a certain extent, but the D,L-LA chain segment in PLGA hardly caused this counteraction. Therefore, the T_g values of the D,L-type copolymers were basically controlled by the GA chain segment. Thus, when n_{GA} was 90%, the contribution to crystallinity of the GA chain segment surpassed its contribution to flexibility, and the T_g of PLGA increased markedly again (Table X, run 6).

With increasing n_{GA} , the decomposition temperature (T_d) of L-PLGA gradually increased (Table X). However, for D,L-type copolymers, T_d first gradually decreased and then markedly increased, which indicated that the interaction between the LA chain segment and the GA chain segment in PLGA was affected by the different LA stereochemical configurations.

XRD characterization of serial PLGA

The crystallinity of serial PLGA was characterized with XRD (Figs. 4 and 5), and the corresponding data are shown in Table XI. Compared with L-PLGA, only D,L-PLGA 10/90 was partly crystalline (run 6), and the other feed molar ratio D,L-PLGAs were amorphous (Fig. 4). This result was coincided well with the previous DSC conclusions.

For D,L-PLGA10/90, the diffraction peak position of face 110 and face 020 were, respectively, at $2\theta = 22.2$ and 28.8° (Table XI, run 6); both were very close to that of poly(glycolic acid) (PLGA0/100, run 7). At the same time, the crystallinity and crystal dimension of D,L-PLGA10/90 were obviously bigger than that of

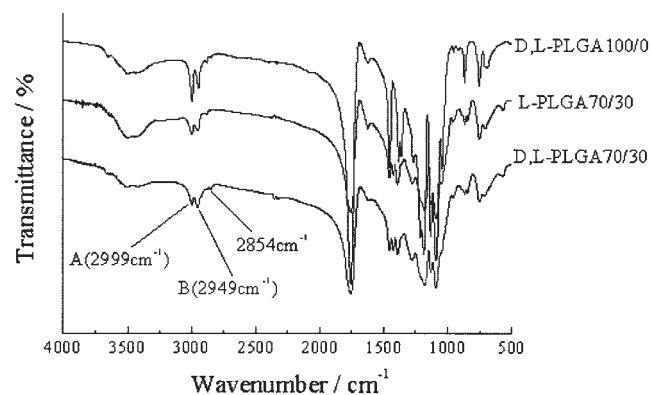


Figure 3 IR spectra of PLGA70/30 from L-LA and D,L-LA.

TABLE X
DSC Results of PLGA from D,L-LA and L-LA

Run	PLGA	T_g (°C)		T_m (°C)		T_d (°C)		ΔH (J/g)	
		D,L-LA	L-LA	D,L-LA	L-LA	D,L-LA	L-LA	D,L-LA	L-LA
1	100/0	54.6	50.0	120.0	134.1	283.6	265.2	17.1	46.7
2	90/10	28.6	44.8	N	121.2	274.7	272.4	N	40.4
3	70/30	31.3	35.2	N	N	272.6	279.1	N	N
4	50/50	31.0	33.5	N	N	270.0	298.2	N	N
5	30/70	24.4	20.7	N	109.5	303.3	309.0	N	4.1
6	10/90	58.1	18.3	177.1	165.0	N	N	54.5	60.8
7	0/100	N		199.51		N		137.0	

N = not detected. All runs were polymerized with an absolute pressure of 70 Pa, a reaction temperature of 165°C, a reaction time of 10 h, and 0.5 wt % SnCl₂ as the catalyst.

L-PLGA10/90 (run 6). These all indicated that PLGA10/90 was deeply affected by the GA chain segment in PLGA and the effects on D,L-PLGA10/90 were more marked than on the L-type.

Only for L-PLGA when n_{LA}/n_{GA} ranged from 100/0 to 70/30 was the crystallinity change similar to that in the literature from the direct method, but the results in the literature were calculated from DSC curves, and no crystal dimensions were reported.¹²

CONCLUSIONS

1. We have discussed the optimal synthetic conditions of PLGA via melt copolycondensation directly from L-LA and GA with $n_{L-LA}/n_{GA} = 50/50$. When the reaction took place at 165°C and 70 Pa and with 0.5 wt % SnCl₂ as the catalyst, 10 h of polymerization gave L-PLGA50/50 with the biggest $[\eta]$, 0.1993 dL/g. With D,L-LA instead of L-LA, these optimal synthetic conditions were verified by the synthesis of D,L-PLGA50/50, an

important drug-delivery carrier, and its biggest $[\eta]$ was 0.2382 dL/g.

2. Under the same synthetic conditions, with L-LA and D,L-LA as starting materials, serial PLGAs with different molar feed ratios, including 100/0, 90/10, 70/30, 50/50, 30/70, 10/90, and 0/100, were systematically synthesized via simple and practical direct melt copolycondensation. The solubilities of the serial PLGAs were investigated. When n_{GA} was equal to or more than 70%, the solubilities in THF and CHCl₃ became worse, and some samples were even wholly insoluble.
3. These biodegradable polymers were also systematically characterized with GPC, FTIR spectroscopy, ¹H-NMR spectroscopy, DSC, and XRD. PLGAs synthesized from L-LA and D,L-LA had many differences in M_w , T_g , crystallinity, and composition. When the molar feed ratio of LA to GA was 50/50, both $[\eta]$ and M_w of D,L-PLGA were higher than that of

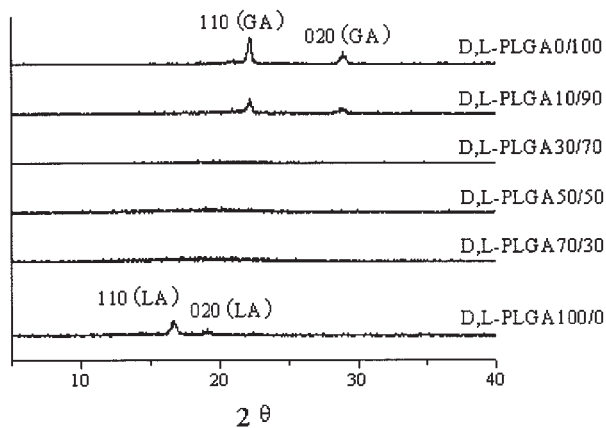


Figure 4 XRD spectra of D,L-PLGA with different feed molar ratios.

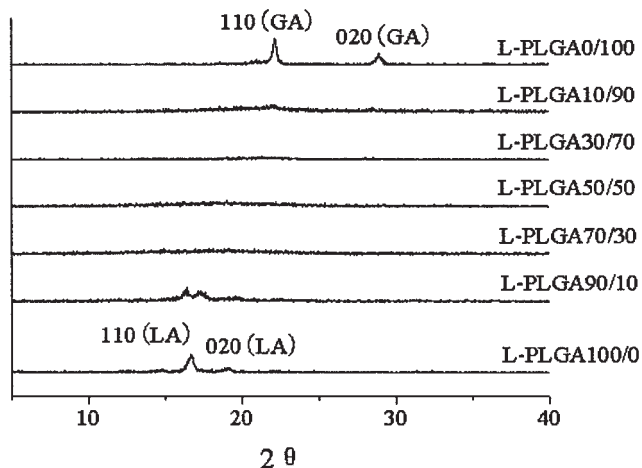


Figure 5 XRD spectra of L-PLGA with different feed molar ratios.

TABLE XI
XRD Results of PLGA Synthesized from D,L-LA and L-LA

Run	PLGA	2 θ (°)				Crystallinity (%)		Crystal dimension (10 ⁻¹⁰ m)			
		Face 110		Face 020		D,L-LA	L-LA	L ₁₁₀		L ₀₂₀	
		D,L-LA	L-LA	D,L-LA	L-LA			D,L-LA	L-LA	D,L-LA	L-LA
1	100/0	16.7	16.7	19.1	19.1	20.8	45.1	154.4	143.4	83.9	69.5
2	90/10	N	17.2 ^a	N	19.6	N	31.1	N	167.5	N	32.0
3	70/30	N	N	N	N	N	N	N	N	N	N
4	50/50	N	N	N	N	N	N	N	N	N	N
5	30/70	N	22.0 ^b	N	N	N	N	N	N	N	N
6	10/90	22.2	22.1	28.8	28.5	27.9	18.7	144.6	19.6	146.5	70.7
7	0/100	22.2		28.9		54.4		224.9		205.1	

N = not detected. All runs were polymerized with an absolute pressure of 70 Pa, a reaction temperature of 165°C, a reaction time of 10 h, and 0.5 wt % SnCl₂ as the catalyst.

^a At 2 θ = 16.3°, a diffraction peak of face 110 with equal intensity existed (Fig. 5), and its corresponding L₁₁₀ was 154.4 × 10⁻¹⁰ m.

^b The diffraction peak of face 110 was too weak to calculate its crystal dimension.

L-PLGA. With D,L-LA as the starting material, the properties of the PLGA copolymer were apt to be controlled by its GA chain segment. When the feed molar percentage of the monomer (LA or GA) was more than or equal to 90%, the copolymer was apt to be crystalline, and the aptness was more obvious for the L-LA monomer. The composition percentage of GA in PLGA was not only higher than the feed molar percentage of GA, but also the GA percentage in D,L-PLGA was higher than that in L-PLGA.

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