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Poly (D,L-Lactic Acid) Homopolymers: Synthesis and Characterization

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In this study, poly(D,L-lactic acid or D,L-lactide) (PDLLA) homopolymers were synthesized with different molecular weights. Low molecular weight PDLLAs (MW_n: 500-2300) were synthesized by direct polycondensation of DL-lactic acid without using any catalyst, while high molecular weight PDLLAs (MW_n: $8x10^3$-$150x10^3$) were produced by ring-opening polymerization of DL-lactide with stannous chloride as catalyst (initiator). Average molecular weights of PDLLAs were determined by end-group analysis, by viscosimetric measurements and by HPLC. PDLLA homopolymers were characterized by FTIR, NMR and DSC. In the production of PDLLAs by direct polymerization, molecular weights of the PDLLAs increased with the increase in the polymerization time and temperature. However, in the production of PDLLAs by ring-opening polymerization, molecular weights increased with increasing polymerization time and the molar ratio of dimer/initiator, but decreased with increasing temperature. Both low and high molecular weight PDLLAs were amorphous with Tg values around 20°-25°C and 54°-57°C, respectively.

Introduction

Both nondegradable and degradable polymers are used in diverse biomedical applications. Many types of surgically implantable devices and drug delivery systems that only function for a relatively short time in vivo can be made from polymers that are eliminated from the body by hydrolytic degradation and subsequent metabolism after serving their intended purpose[1,3]. The application of degradable polymers can have two major advantages. Firstly, degradable biomaterials do not have to be removed after use by secondary surgery. Secondly, the use of biodegradable polymers may lead to a better recovery of the biological system. Poly(α-hydroxy acids) is the most widely known synthetic polymer family used for the production of biodegradable biomaterials. Especially, poly(lactic acids) (or polylactides) and poly(glycolic acids) (or po lyglycolides), and their copolymers have been investigated intensively as biomaterials[1,7]. Low molecular weight polymers (usually no greater than about 10,000) can be prepared by the direct polyesterification of lactic and/or glycolic acids[6,8]. These polymers have not been found a practical use because of very poor mechanical properties of the materials produced. However, it should be noted that they are used for the synthesis of cyclic dimers (i.e., lactides and/or glycolides) which are the starting materials for production of high molecular weight polymers. The most important method for synthesis of high molecular weight

poly(α-hydroxy acids) is the ring-opening polymerization of the corresponding cyclic mono- or diesters, which has been reviewed[9]. Ring-opening polymerization of cyclic dimers for synthesis of high molecular weight homopolymers of L-lactide, and copolymers of poly(glycolide-L-lactide (or D,L-lactide)) have been extensively investigated by using a broad spectrum of substances (catalysts)[5–7,11–14]. In contrast to homo- and copolymers of L-lactide and glycolide, only non-crystalline (amorphous) materials can be made of poly(D,L-lactide) (PDLLA) homopolymers. Therefore, PDLLAs have been found applications in the design of drug delivery systems, in which the drug diffusion and the degradation rates are the main concerns not the mechanical properties[1,3,6,7,15–21]. Recently, we also attempted to synthesis homopolymers of lactides and glycolides, and their copolymers with polyethyleneglycol, and to process these polymers into particle or fiber forms for diverse biomedical applications[22–29]. Here we present our experience with the synthesis of poly(D,L-lactic acid) (or poly (D,L-lactide) (PDLLA) homopolymers with different molecular weights. PDLLAs with low molecular weights (MW_n: 500-2300) were synthesized by direct polycondensation of D,L-lactic acid. While PDLLAs with higher molecular weights (MW_n: 8000-150000) were produced by ring-opening polymerization of D,L-lactide. This paper reports the details of the methods of synthesis and discusses some properties of these homopolymers.

Materials and Methods

Synthesis

Synthesis of Low Molecular Weight PDLLA

The monomer, i.e., D,L-lactic acid, was purchased from BDH Chemicals Ltd. (UK), as an 88% aqueous solution (density:1.2 g/ml), and was kept in refrigerator until use. All other solvents and reagents were obtained from Merck (Germany), and were used without any further purification. Polymerizations were conducted in ampoule bottles (diameter: 40 mm and volume: 80 ml) under nitrogen atmosphere. D,L-lactic acid (6.0 g) was charged into the bottle which was placed in an oven equipped with temperature controlling system. To synthesis PDLLAs with different molecular weights, polymerizations were conducted at three different temperatures (i.e., 160, 180 or 200° C), and the polymerization time ranged from 4 to 24 h[27–29].

Synthesis of High Molecular Weight PDLLA

The dimer, i.e., DL-lactide, and the catalyst, i.e., stannous chloride ($SnCl_2 \cdot 2H_2O$) were purchased from Polyscience (USA) and BDH (UK), respectively, and all other solvents and reagents were obtained from Merck (Germany) and were used without further purification. The ring-opening polymerization of D,L-lactide in bulk was carried out by a procedure similar to that described in literature[27–31]. Polymerizations were conducted in pretreated ampoule bottles (diameter: 25 mm, volume: 25 ml). For pretreatment, the bottles were filled with aqueous solutions of potassium dichromate/sulfuric acid and left for 24 h at room temperature. They were first washed thoroughly with distilled water several times. Note that it is not possible to reach high molecular weights in the existance of water[9,27–31], therefore, the bottles were washed with acetone, and finally dried overnight at 120° C. For polymerization, the pretreated bottle was cooled down to room temperature with a stream of dry nitrogen. D,L-lactide (3.6 g) was transferred to the bottle under dry nitrogen atmosphere, and 0.5 ml of a freshly prepared stannous chloride solution in ethyl ether, which was containing different amounts of initiator (2.5×10^{-4}-5.6×10^{-4} g in 0.5 ml ethyl ether) depending

on the dimer/initiator ratio used in the recipe was added. The bottle was connected via an adaptor to a purge valve system with access to vacuum or dry nitrogen. It was evacuated for about 5 min to remove the solvent, and was then heat-sealed under vacuum (60 mm Hg), and placed in an oven with a temperature, controlling system. The dimer was melted by preheating up to the desired temperature, and polymerization was started. After the desired polymerization period, the ampoule bottle was transferred to a refrigerator to terminate the reaction. For purification and removing the unreacted dimer and low molecular weight polymer residuals, the product was dissolved in chloroform to make concentration about 10% (w/v). Then, PDLLA was precipitated by adding this solution into a solution of acetone/ heptane (1/2, v/v), with vigorous stirring. The precipitated polymer was filtered, and dried under vacuum at 30°C for 48 h. In order to synthesize PDLLAs with different molecular weights, the polymerization time and temperature,and the molar ratio of the dimer to the initiator (D/I) were changed in the range of 40-360 min, 160°-200°C, and 1000-25000, respectively[27–29].

Characterization

Average Molecular Weights and Molecular Weight Distributions

By End-Group Analysis: End-group analysis was applied to obtain the number average molecular weights of the PDLLAs with low molecular weights. In a typical procedure, 0.2 g of PDLLA was dissolved in 25 ml benzyl alcohol, and 1 ml of the indicator solution (i.e., phenolphthalein in benzyl alcohol) was then added to this solution. Note that this indicator works in the pH range of 8-10. The indicator solution was prepared by dissolving 45 mg of phenolphthalein (BDH, UK) in 15 ml benzyl alcohol. The polymer solution containing the indicator was then titrated with 0.03N potassium hydroxide (KOH) (in benzyl alcohol), until a pink colour appeared and did not disappear for two minutes. Benzyl alcohol (containing no polymer) was used as the blank solution. The number average molecular weights (MW_n) of PDLLAs were calculated from the following equation[27–29,32].

$$MW_n = \frac{1000w}{0.03f(V - V_0)} \tag{1}$$

Where "w" is the weight of the polymer (g), "f" is the titre of KOH solution, "V" and "V_0" are the volumes (ml) of the KOH solutions consumed, for the polymer and the blank solutions, respectively.

By Viscosity Measurements: Viscosity measurements were used to obtain average molecular weights of the PDLLAs with high molecular weights. Viscosities of the PDLLA solutions with different concentrations (0.1-2.0 g/100 ml) were measured with a capillary viscosimeter (i.e., Ubbelhode viscosimeter) in a constant temperature water bath at 25.0°±0.1°C. Ethyl acetate was used as the solvent. The "flow times" for the solvent (t_0) and the polymer solutions (t) were measured. The relative viscosities (η_r) were then found from the t_0/t values. Specific viscosities (η_{sp}), which is equal to $\ln \eta_r/c$,were plotted against polymer concentration (c). From the intercept at Y-axis after extrapolation, the intrinsic viscosity, i.e., $[\eta]$, was obtained. The following Mark-Houwink equations given below were used to calculate the number (MW_n) and weight (MW_w) average molecular weights[27–30,33,34]:

$$[\eta] = 1.58e^{-4} \cdot MW_n^{0.78}$$
$$\eta = 1.63e^{-4} \cdot MW_w^{0.73}$$

By HPLC Measurements: The molecular weights and molecular weight distributions of the PDLLAs

were determined by a HPLC system (Waters, USA). The GPC unit, consisting of Waters model 510 HPLC pump and a Waters U6K injector, was equipped with two Ultrastyragel columns (Waters, 104 $\AA$ and 500 $\AA$) in series and a Waters 486 Tunable Absorbance Detector. Tetrahydrofuran (THF) was used both as the solvent and the eluent. Elution was performed at a temperature of 30 ° C and at a flow rate of 1 ml/min, using a Waters 510 HPLC pump. The columns were calibrated with polystyrene standards (Shodex Standarts, SL-105, Showa Denko, Japan)). The number (MW_n) and weight (MW_w) average molecular weights and the heterogenity indices (H.I.: MW_w/MW_n) were evaluated as given in the related literature[35,36].

Structural Analysis

FTIR Studies: The PDLLA sample was dissolved in chloroform (concentration: 5 % w/v). Potassium bromide (KBr) tablets were coated with this solution to form very thin films. Then the FTIR spectra of the samples were recorded by a FTIR spectrophotometer (DR-8001, Shimadzu, Japan) at room temperature.

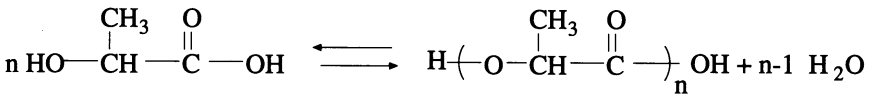
NMR Studies: The PDLLA sample was dissolved in CDCl3. The H^1-NMR spectra of the sample was then recorded by a NMR spectrophotometer (Brucker AC 250, USA) at room temperature, with tetramethylsilane as the internal standard.

DSC Studies: The PDLLA (5.0 mg) sample was pressed in a sample capsule. The thermogram was then recorded with a Differential Scanning Calorimeter (DSC, Thermal Analysis 2000, Version 4.1, Dupont USA), at a heating rate of 10 ° C/min and in a temperature range from -80 ° C to 250 ° C.

Results and Discussion

Characterization of Low Molecular Weight PDLLAs

In this study, PDLLA homopolymers with low molecular weights (i.e., poly(D, L-lactic acids)) were produced by direct polycondensation of the respective monomer, i.e., D,L-lactic acid[8,27,28], as given in the following reaction. Some important properties of these homopolymers are discussed in the separate sections given below.



Lactic Acid — Low Molecular Weight Polylactic acids

Average Molecular Weights and Molecular Weight Distributions

Figure 1 gives the data obtained by the end-group analysis described in the previous section. The number average molecular weights (MW_n) of the PDLLAs synthesized at different polymerization temperatures and with different polymerization times are given in this figure. The number average molecular weight of the PDLLA increased significantly with the polymerization time, almost linearly up to about 20 h, a little or no benefit was gained by further extention of the polymerization time. This is a general behaviour in all condensation polymerizations[37]. Theoretically, polycondensation reactions are equilibrium reactions. These reactions usually take place by the elimination of a low molecular weight component, which is water in our case. An equilibrium is achieved depending on the degree of dehydration. Higher molecular weights require higher degrees of dehydration. It is difficult to remove water in the bulk (melt) polymerization,

which results lower molecular weights, as also observed in our case. The condensation equilibrium constant usually increases with temperature, therefore, one might expects to achieve higher molecular weights at higher temperatures, as observed on Figure 1. MW_n of the PDLLA increased also with temperature. PDLLAs with different molecular weights in the range of 500-2300, were synthesized by changing the polymerization temperature. Note that in this direct polycondensation procedure it was not possible to utilize temperatures higher than 200°C because a severe oxidation occured, which was observed by the formation of the dark brown colour. The number and weight average molecular weights and the heterogenity indices of some selected PDLLAs obtained by HPLC are given in Table 1. This table shows that both the number and weight average molecular weights increased with the polymerization time, as mentioned above. The heterogenity indices were around 2, which is a typical value usually observed in simple condensation polymerizations[27,28,37]. Note that a larger heterogenity index means a wider molecular weight distribution, which also increased with polymerization time as seen in Table 1. For comparison of the two methods, namely end-group analysis and HPLC, the MW_n values obtained by end-group analysis are also shown in Table 1. The values obtained by these two techniques were quite close to each other. Because of its simplicity, end-group analysis may be used to obtain MW_n values. However, for the molecular weight distribution, HPLC is needed.

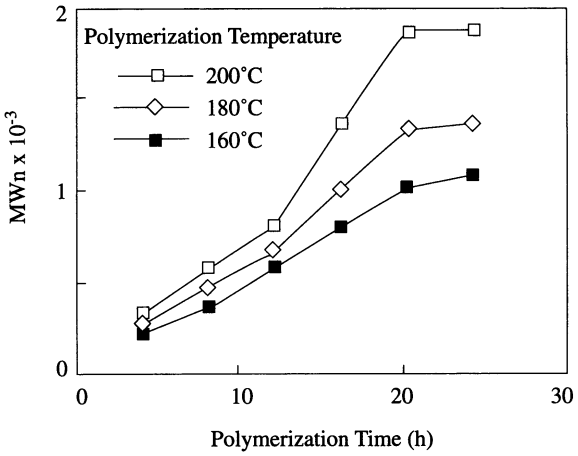


Figure 1. Effects of polymerization time and temperature on MW_n of PDLLAs (obtained by end-group analysis)

Table 1. Average Molecular Weights of Low Molecular Weight PDLLAs Obtained by HPLC

Sample No	t (h)*	T (°C)*	MW_n**	MW_w	H.I.
1	12	200	691 (812)	1477	2.14
2	16	200	1001 (1373)	2157	2.16
3	20	200	1668 (1878)	4032	2.42
4	24	200	2282 (1886)	6059	2.65

*t: polymerization time; and T: polymerization temperature

** The values in the paranthesis show the MW_n values obtained by end-group analysis

It should be noted that the yields of homopolymers, which was defined as "(the amount of monomer/the amount of polymer)x100", obtained by direct polymerization of D,L-lactic acid were around 96-98% in all cases described above.

Structural Analysis

Figure 2 shows FTIR spectrum of the PDLLA with a number average molecular weight of 1886 (obtained by end-group analysis) which was prepared by direct polycondensation of DL-lactic acid at a temperature of 200 °C and with a polymerization time of 24 h. The intense bands at 3000 cm^{-1} and 2945 cm^{-1} due to C-H stretching of the methyl and methyne groups, together with the band at 1756 cm^{-1} due to the ester carbonyl group[11]. Other significant bands are in the region 1300-1050 cm^{-1} typical of the ester sequence -CO-O-. The strong hydroxyl peak observed around 3500 cm^{-1} shows the terminal -OH groups, and may be used as an indication of the low molecular weights of the polymers. Figure 3 shows H^1-NMR spectrum of the PDLLA with a number average molecular weight of 1886. The peaks at 1.56, 4.36, and 5.20 ppm correspond to CH_3, CH next to terminal group, and CH, respectively[38]. The broader and rather weak peak observed around 6.30 ppm corresponds the terminal -COOH groups, which may be used as an indication of the low molecular weights of the polymers produced by direct polycondensation. One might expect stonger peak for D,L-lactic acid.

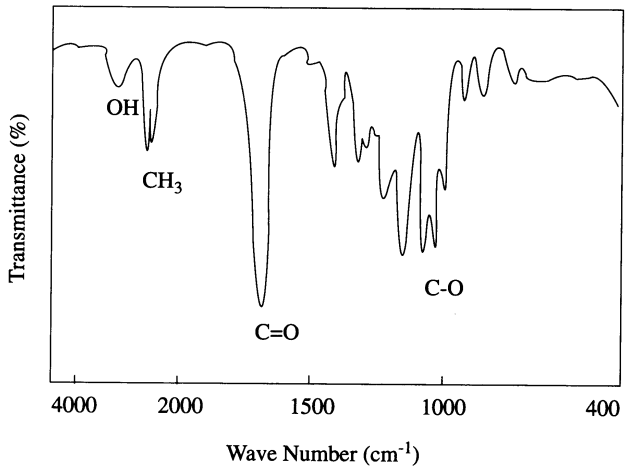


Figure 2. FTIR spectrum of PDLLA (MW_n: 1886)

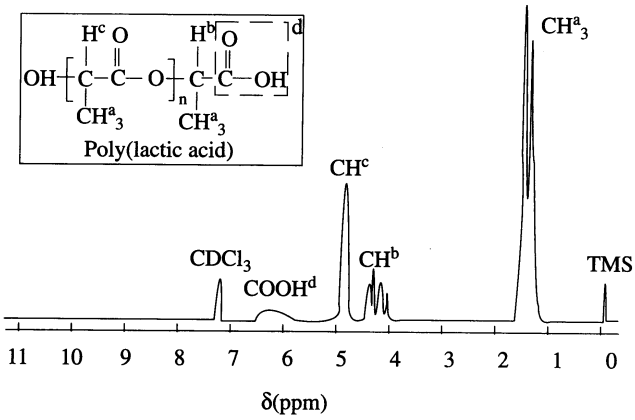


Figure 3. H^1-NMR spectrum of PDLLA (MW_n: 1886)

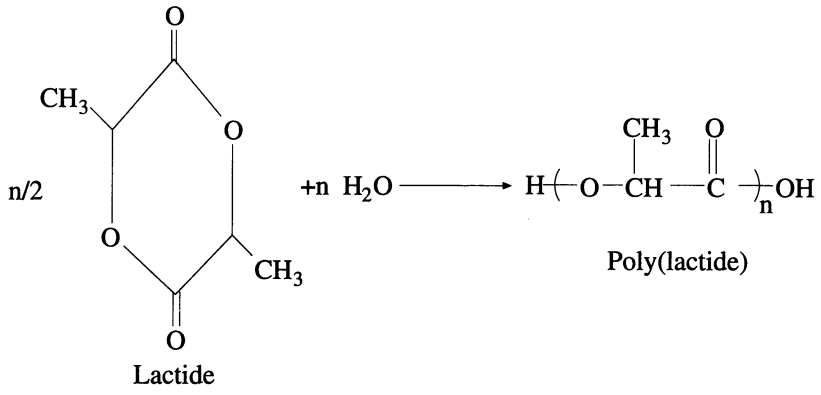
Figure 4 shows a thermogram of the PDLLA with a number average molecular weight of 1886. This thermogram was recorded by a differential scanning calorimeter at a heating rate of 10 °C/min, and in the temperature range from -80 °C to 250 °C. As seen in Figure 4, there is only one thermal transition at around 20 °-25 °C, i.e., the glass transition temperature (Tg). Note that this value is lower than those reported in literature, which may be due to lower molecular weights of the PDLLAs synthesized in our case[39].

Characterization of High Molecular Weight PDLLAs

In this study, PDLLA homopolymers with high molecular weights (i.e., poly(D, L-lactides) were produced by ring-opening polymerization of the respective dimer, i.e. DL-lactide, with stannous chloride, as the initiator[6,27,28,11–13,40,41], as given in the following reaction. Some important properties of these homopolymers are discussed in the separate sections given below.

Dimer and Oligomer Residuals

The dimer and oligomer residuals are not desirable, especially in biomedical applications of these polymers. Therefore, we investigated the residual dimer and oligomer left within the PDLLA matrices, after purification steps.



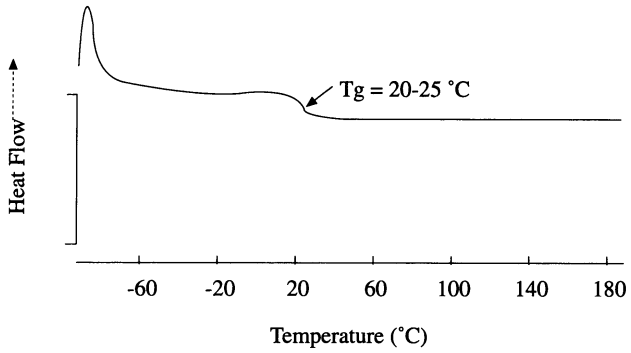


Figure 4. DSC thermogram of PDLLA (MW_n : 1886)

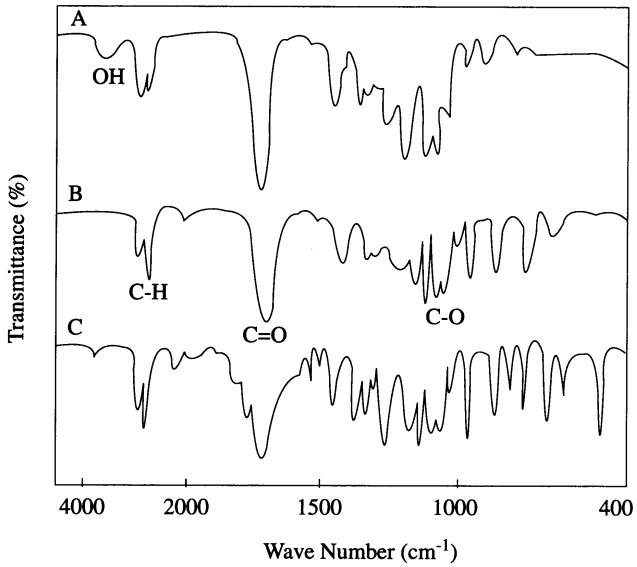


Figure 5. FTIR spectra: (A) PDLLA with low molecular weight (MW_n: 1886); (B)PDLLA with high molecular weight (MW_n: 25400) ; (C) D,L-lactide

FTIR Studies: FTIR spectra of DL-lactide and PDLLAs with both low (MW_n: 1886) and high molecular weights (MW_n: 25400) are given in Figure 5. Notice that the main difference in the spectra of the PDLLAs with high and low molecular weights is the peak at 3300-3500 cm^{-1}, which reflects the OH end-groups on the polymer chains. Since the number of OH groups in the PDLLA samples with high molecular weights is relatively low, this peak is absent in the spectrum. This peak may also be used as an indication of the oligomer residuals in the PDLLA with high molecular weights. Since there was no such a peak in the FTIR spectum of our PDLLAs (with high molecular weight), we may conclude that we removed the residual dimer and oligomers succesfully at the purification step. FTIR spectra of the PDLLA with high molecular weight and DL-lactide are significantly different. As seen in Figure 5, there are a series of peaks around 400-600 cm^{-1} in the spectrum of DL-lactide, which disappeared in the PDLLA spectrum. From these observations

we may conclude that our PDLLAs do not contain the dimer, or we removed it succesfully at the purification step.

DSC Studies: Figure 6 shows the thermograms of D,L-lactide and PDLLA produced by ring- opening polymerization of D,L-lactide (MW_n: 25400). The thermograms were recorded by a differential scanning calorimeter, at a heating rate of 10°C/min, and in the temperature range from -80°C to 250°C. As seen in Figure 6, at the temperature range of -80° to 200°C, there is almost only one thermal transition for PDLLA, which is the glass transition temperature (Tg) at 54°-57°C, which shows that it is amorphous [6,40]. Note that this is because the random distribution of D- or L- chiral carbon in the polymer chain backbones disrupts the regular configuration of the chains and causes the chains unable to fold regularly into crystalline lattice. In contrast, D,L- lactide exhibit a thermal transition around 124°-126°C, which is its melting point. Comparing the thermograms of PDLLA and D,L-lactide, we may say that there were no dimer residuals left in our PDLLA after purification step.

Average Molecular Weights and Molecular Weight Distributions: Here, the data obtained by viscosity measurements described in the previous section are discussed. Figure 7, 8 and 9 shows the number and weight average molecular weights of the PDLLAs synthesized with different polymerization times, at different temperatures, and by changing the initial molar ratio of the dimer (i.e., D,L-lactide) and the initiator (i.e., stannous chloride), respectively. The average molecular weights of PDLLAs synthesized with different polymerization times (40-360 min) are given in Figure 7, in which the polymerization temperature and the dimer/initiator ratio are 160°C and 1000, respectively. The average molecular weights increased with the increase in the polymerization time almost linearly up to certain values. Then, plateau values were reached in 120 min. Note that the yields of homopolymers produced with different polymerization times, namely 40, 80, 120 and 360 min, were 45, 78, 94 and 96%, respectively. Here the yield was defined as "(the amount of polymer/the amount of dimer after purification) x100". This may be considered as an indication that polymerization reactions were completed around two hours. Note also that the heterogenity indices (the ratio of MW_w to MW_n) increased with time (which means molecular weight distribution became wider). These effects may be due to transesterification between the homopolymer molecules which may occur for longer polymerization times[41–43].

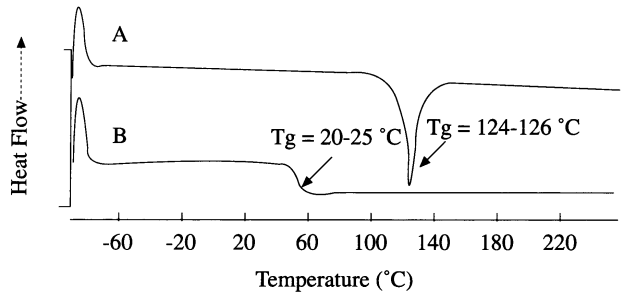


Figure 6. DSC thermograms of (A) D,L-lactide; (B) PDLLA (MW_n: 25400)

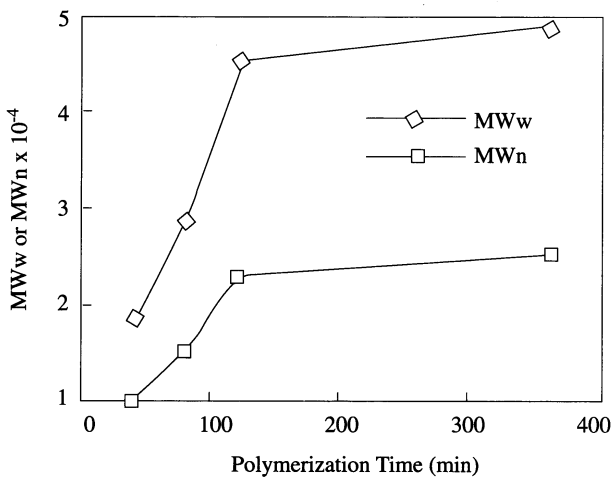


Figure 7. Effects of polymerization time on average molecular weights of PDLLAs (polymerization temperature and D/I ratio, 160°C and 1000, respectively)

The average molecular weights of PDLLAs synthesized with different polymerization temperatures (160°-180° C) are given in Figure 8, in which the polymerization time and the dimer/initiator ratio are 360 min and 1000, respectively. Note that the yields of homopolymers produced by ring-opening reactions in the temperature range studied here were above 95%. The average molecular weights decreased very significantly with temperature. Higher heterogenity indices (which means wider molecular weight distributions) were obtained at low temperatures. This effect is different than that we have observed in the direct polymerization of D,L- lactic acid. Here, polymerization is a catalytic reaction. Therefore, as expected, at the high temperatures more initiator molecules can be activated, which means that the polymerization reactions are initiated from more points, which in turn leads polymers chains with lower molecular weights.

The average molecular weights of PDLLAs synthesized with different dimer/ initiator molar ratios (100-22500) are given in Figure 9, in which the polymerization time and temperature are 360 min and 160C, respectively. Note that the yields of homopolymers produced by ring-opening reactions in the temperature range studied here were above 95%. Effects of the D/I ratio on the average molecular weights up to about a value of 15000 were insignificant. However, above this value there were steep increases in the average molecular weights, and also in the heterogenity indices. It seems that the change in the concentration of the initiator did not affect the polymerization kinetics at constant temperature, at higher initiator concentrations (i.e., lower D/I ratios). However, as proposed in the related literature, at low initiator concentarations (D/I > 15000), some unknown reactions may occur[44,45]. These side-reactions may terminate some of the growing polymer chains. This gives chance for the other chains to become longer. This means that the average molecular weights may increase and, at the same time, molecular weight distribution become wider.

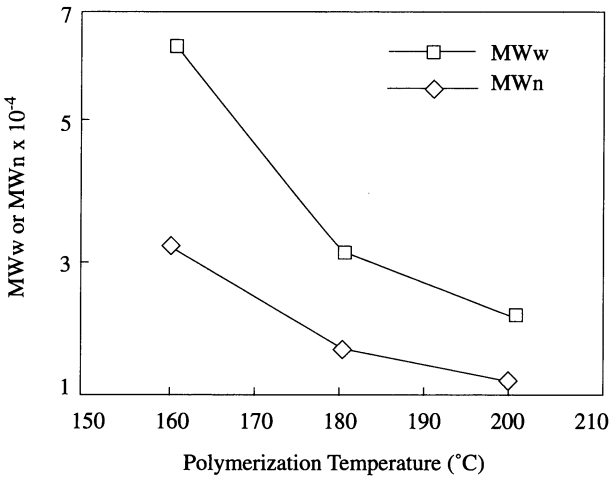


Figure 8. Effect of polymerization temperature on average molecular weights of PDLLA (polymerization time and D/I ratio, 360 min and 10000, respectively)

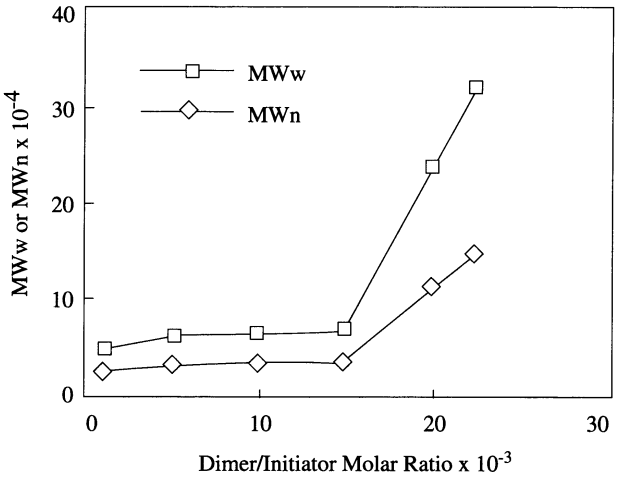


Figure 9. Effect of D/I molar ratio on average molecular weights of PDLLAs (polymerization time and temperature, 360 min and 160° C, respectively)

Table 2. Average Molecular Weights of High Molecular Weight PDLLAs Obtained by HPLC

Sample No	t (min)*	T (°C)*	MW_{n}**	MW_{w}**	H.I.**
1	40	160	8010 (10200)	16580 (18500)	2.07 (1.81)
2	80	160	12490(15100)	26890 (28500)	2.15 (1.89)
3	120	160	22020(23000)	49210 (45200)	2.23 (1.97)
4	360	160	23500(25400)	54300 (49500)	2.31 (1.95)

* t: polymerization time; and T: polymerization temperature

** The values in the paranthesis show the values obtained by viscosity measurements

The number and weight average molecular weights and the heterogenity indices of some selected PDLLAs obtained by HPLC are given in Table 2. This table shows also that both the number and weight average molecular weights increased with the polymerization time, as mention above. The heterogenity indices were around 2. For comparison of the two methods, namely viscosity measurements and HPLC, the values obtained by viscosity measurements are also given in Table 2 (in paranthesis). As seen here the values obtained by these two techniques are similar. Because of its simplicity, viscosity measurements may be used to obtain molecular weight data.

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