

Practical Aspects of Polymerization of D,L-Lactide Initiated with Tetraphenyltin

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SYNOPSIS

Melt polymerization conditions for D,L-Lactide initiated with tetraphenyltin were studied with regard to polymer molecular weight. The combined effect of time and temperature on polymer molecular weight and degree of conversion of D,L-Lactide is described. Polymerization at constant initiator concentrations resulted in a narrow scattering of reproducible molecular weight values. The presence of air/moisture and other impurities during the melt polymerization most likely have a detrimental effect on molecular weight. After a short induction period the rather slow polymerization of D,L-Lactide resulted in a maximal molecular weight followed by an almost constant value of molecular weight. © 1995 John Wiley & Sons, Inc.

INTRODUCTION

For more than 2 decades the delivery of bioactive agents from polymeric materials has attracted the scientific community. Although a variety of biodegradable polymers have been used, aliphatic polyesters based on lactic and glycolic acid have received considerable attention because of their biocompatibility and biodegradable nature.¹⁻⁴ Although poly(D,L-Lactide) may be prepared by the direct condensation of L(+) and D(-) lactic acid,⁵⁻⁷ the preferred method for the preparation of high molecular weight poly(D,L-Lactide) used is the ring opening polymerization of the six-membered cyclic dimer, D,L-Lactide, initiated with a suitable initiator, e.g., tin chloride,⁸ Zn,⁹ stannous octoate,¹⁰ or tetraphenyltin. The polymerization can be performed in solution under mild conditions or, for the preparation of high molecular weight polymers, preferably in the melt at higher temperatures.

It has been reported that for the melt polymerization of Lactide the polymer molecular weight can be controlled by varying the amount of initiator. This statement, however, is not in agreement with

other literature data.^{8,10,11} Kohn et al.,¹¹ however, have shown in their studies that an inverse dependency of initiator concentration on polymer molecular weight may not be expected when multiple polymerizations are carried out at different initiator concentrations. Although a number of reports¹⁻¹⁴ are available in the literature, they do not reflect strong correlation among time, temperature, initiator, and molecular weight of polymers. The present study was undertaken to explore the relation between melt polymerization conditions for D,L-Lactide initiated with tetraphenyltin and polymer molecular weight obtained.

EXPERIMENTAL

Materials

D,L-Lactic acid [an 85% w/w aqueous solution containing a racemic mixture of L(+) lactic acid and D(-) lactic acid] was purchased from Sigma. Tetraphenyltin was supplied by Aldrich, and it was recrystallized from dichloromethane before use.

D,L-Lactide was prepared according to the procedures of Kulkarni et al.^{12,13} using antimony trioxide as the depolymerization catalyst. Water, solvent, and part of the condensation water were stripped off in 8–10 h at 120–180°C pot temperature, starting at

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760 mm/Hg and decreasing stepwise to about 25 mm/Hg. The temperature of the bath was then increased to 240°C, and the crude D,L-Lactide was distilled at 0.1 mm/Hg for about 4 h. The crude D,L-Lactide was recrystallized several times in order to remove the meso-lactide. The D,L-Lactide was washed with chloroform to remove yellow color and recrystallized several times from dried ethyl acetate. Purified D,L-Lactide (Yield 20–25%; mp ~ 125°C) was dried in a vacuum oven at room temperature in order to prevent sublimation and stored in a desiccator over phosphorus pentaoxide.

The ring-opening polymerization of D,L-Lactide in the melt was based on the procedures developed by Kulkarni et al.^{12,13} and Kohn et al.¹¹ using tetraphenyltin. A series of polymerization ampules were prepared as follows. Ampules were cleaned and dried 24 h before filling with D,L-Lactide containing 0.02% w/w tetraphenyltin. Each ampule was connected via an adaptor to a purge valve system with an access to vacuum; and subjected to three cycles of heating and cooling in order to remove dissolved air. It was then evacuated and flushed with nitrogen to remove residual vapors of solvent or moisture. Ampules were then sealed under vacuum and subjected to different reaction conditions. For studying the effect of time, ampules were maintained, for example, at $150 \pm 1^\circ\text{C}$ in a stirred oil bath; and representative ampules removed and quenched at different time intervals. For temperature dependence studies, similar experiments were carried out at different temperature settings. The retrieved ampules were stored at -20°C , and the contents dissolved in tetrahydrofuran. Aliquots were used for gel permeation chromatography. Residual monomer gave a late eluting quantifiable peak, which was used to calculate the degree of conversion. The solid contents of ampules were used for physical characterization of the polymers prepared at different sets of experiments using differential scanning calorimeter.

Methods

Gel permeation chromatographic (GPC) measurements were calibrated with polystyrene standards in tetrahydrofuran over the molecular weight range 10^3 to 10^6 .

A TA instruments DSC 10 Differential Scanning calorimeter was used to record the thermal transitions. The samples were crimped in aluminium pans and heated at $2^\circ\text{C}/\text{min}$. Peak temperature and heat of fusion were determined after calibration with an indium standard.

RESULTS AND DISCUSSION

With the method of preparation of poly(D,L-Lactide) used here, it is evident that the polymerization time, temperature, and a fixed quantity of catalyst have significant effect on the molecular weight of the polymer. Because it has been suggested in the literature¹⁵ that the impurities have a detrimental effect on the polymerization, much care was taken to exclude impurities during our experiments. The combined effect of time and temperature are best illustrated by three dimensional graphs. Figure 1 shows the degree of conversion of D,L-Lactide. The surface envelope shows that the maximum conversion (above 90%) occurs in the range of 4 to 8 h, and maxima is observed around 7 h. Below 1 h at all temperatures the degree of conversion is less than 60%. Figure 2 shows the dependence of molecular weight of poly(D,L-Lactide) on time and temperature. The surface envelope shows that the maximum molecular weight achieved is around 7–8 h, and the maxima is observed around 165°C . Below 1 h at all temperatures, the molecular weight is below 30,000.

Table I shows the conversion of D,L-Lactide and molecular weight achieved by the polymer in different polymerization conditions. The physical characteristics, like glass transition (T_g) of the polymer and melting transition (T_m) of D,L-Lactide are correlated with GPC data. It is evident from Table I that with the increase in polymerization temperature from 150°C to 180°C (ampule kept in oil bath for 1 h), the conversion of D,L-Lactide to poly(D,L-Lac-

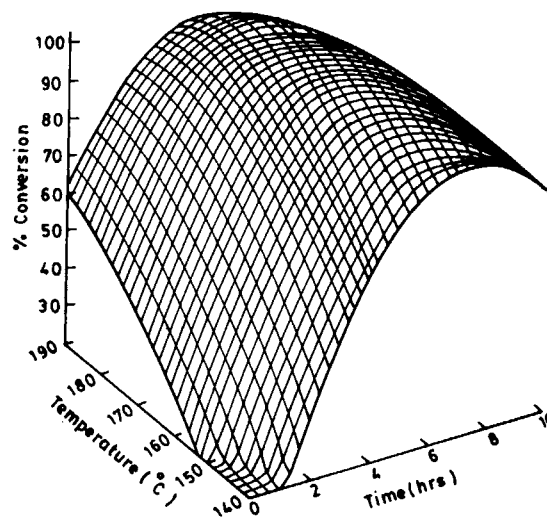


Figure 1 Effect of time and temperature on percent conversion of D,L-Lactide.

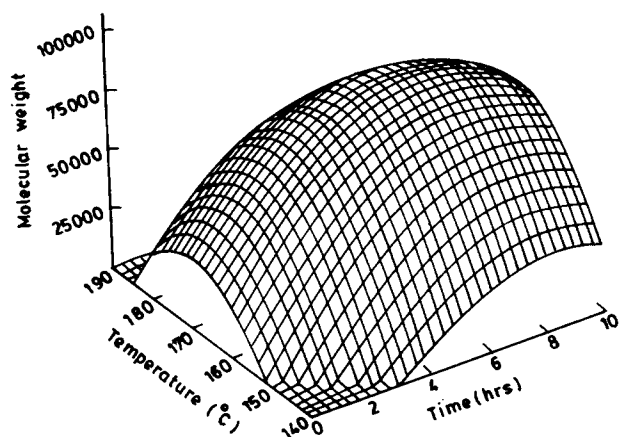


Figure 2 Effect of time and temperature on molecular weight of poly(D,L-Lactide).

tion) increases from 23% to 82%, and the molecular weight of polymer achieved is around 34,000. DSC data shows that the melting peak (T_m) of D,L-Lactide is 122.8°C at 150°C, area under the peak (ΔH_f) is 83.2 J/g, and T_g of polymer is untraceable. At 180°C, the T_m is 101.4°C, ΔH_f is 34 J/g, and T_g is around 29.5°C. The drop in T_m and ΔH_f clearly shows the conversion of D,L-Lactide to polymer. The trend is similar when the reaction time was increased to 2 h. The molecular weight, instead of increasing linearly with the temperature, increases up to 160°C and then decreases. DSC data also supports the observation that above 160°C the T_g of the polymer decreases. Increasing reaction time beyond 2 h and polymerization temperature above 160°C similarly results in the formation of lower molecular weight of polymer.

Table I DSC and GPC Data of Poly(D,L-Lactide)

Temp.	Parameters	Time (h)			
		1	2	4	8
150°C	\bar{M}_w	18144	26622	33456	42338
	%	I-23	I-69	I-83	I-92.7
	Conversion	II-77	II-31	II-17	II-7.3
	T_g/T_m	$T_m = 122.8$	$T_m = 105.5$	$T_m = \text{ND}$	$T_m = \text{ND}$
	(°C)	$\Delta H_f = 83.2$	$\Delta H_f = 33$	$T_g = 37$	$T_g = 42$
	ΔH_f (J/g)	$T_g = \text{ND}$	$T_g = 29.8$		
160°C	\bar{M}_w	23739	45679	72374	85075
	%	I-51	I-85.3	I-92.5	I-94.8
	Conversion	II-49	II-14.7	II-7.5	II-5.2
	T_g/T_m	$T_m = 116$	$T_m = \text{ND}$	$T_m = \text{ND}$	$T_m = \text{ND}$
	(°C)	$\Delta H_f = 48.5$	$T_g = 40.2$	$T_g = 42.2$	$T_g = 43$
	ΔH_f (J/g)	$T_g = 29.5$			
170°C	\bar{M}_w	26599	31909	57495	57289
	%	I-53.3	I-88	I-95	I-91.7
	Conversion	II-46.7	II-12	II-5	II-8.3
	T_g/T_m	$T_m = 101.4$	$T_m = \text{ND}$	$T_m = \text{ND}$	$T_m = \text{ND}$
	(°C)	$\Delta H_f = 34$	$T_g = 36$	$T_g = 40.4$	$T_g = 40.8$
	ΔH_f (J/g)	$T_g = 29.8$			
180°C	\bar{M}_w	34634	35474	38738	39056
	%	I-82	I-86.5	I-87	I-92
	Conversion	II-18	II-13.5	II-13	II-8
	T_g/T_m	$T_g = 39.8$	$T_g = 39.2$	$T_g = 39.8$	$T_g = 39.6$
	(°C)				

\bar{M}_w = Weight average molecular weight of polymer.

I = Peak 1 corresponds to polymer.

II = Peak 2 corresponds to D,L-Lactide.

T_m = Melting transition of D,L-Lactide.

T_g = Glass transition of polymer.

ΔH_f = Heat of fusion of D,L-Lactide.

ND = Not detectable.

Table I shows that when the reaction temperature is maintained at 150°C, and the time of polymerization increased from 1 h to 8 h, the conversion of D,L-Lactide to polymer increases from 23 to 92.7%. The molecular weight also increases from 18,000 to 42,000. DSC data also supports the observation that the reaction has, indeed, progressed. The ΔH_f decreases from 83.2 J/g (1 h) to 33 J/g (2 h), and T_g of the polymer also increases with the increase in time. The maximum increment in molecular weight of polymer is achieved at 160°C and 8 h. At 180°C the molecular weight of the polymer remains almost unchanged, even after raising the time of polymerization.

Keeping in view the outcome of surface analysis of Figures 1 and 2, a set of polymerizations was performed at 165°C, at a fixed concentration of catalyst, and the time varied from 6 h to 16 h. GPC data shows that the molecular weight increases linearly with time. Around 10–12 h, the maximum molecular weight is observed. Further increase in reaction time does not lead to any change in molecular weight; instead, there is a little drop in molecular weight.

Surface analysis of Figures 1 and 2 and other experiments suggest that after an induction period (<1 h) there is a rapid rise in molecular weight during the first 8 h. In this period, above 90% of the D,L-Lactide is converted to polymer. This conversion is rather slow during the first 2 h. The maximum molecular weight achieved is in the time range of 10–12 h. At this stage the conversion of D,L-Lactide is around 95%. In the next few hours a fairly constant molecular weight is achieved. Kohn et al.¹¹ have reported that high molecular weight poly(D,L-Lactide) could not be prepared reproducibly by melt polymerizing D,L-Lactide initiated with tetraphenyltin. We, too, have observed in our studies variation in molecular weight of the product. However, the fluctuation is around ± 5000 .

The polymerization reaction is very sensitive to hydroxyl groups, which act as chain transfer agents during the polymerization reaction.¹⁵ The high sensitivity to hydroxy impurities, such as moisture and lactic acid, makes it very difficult to control the polymerization. In order to see the effect of impurities, a set of polymerizations was carried out. During melt polymerization a small amount of water, ethyl acetate mother liquor, and lactic acid was added in separate ampules along with D,L-Lactide plus initiator. The polymerization was carried out in the usual manner as discussed in the Experimental section. GPC results show that the poly(D,L-Lactide) prepared in the presence of ethyl acetate mother

liquor had a significant lower weight average molecular weight ($M_w \sim 17,277$) in comparison to the polymer ($M_w \sim 47,827$) prepared without impurity. Polymer prepared with lactic acid impurity showed a drop in $M_w \sim 22,515$, whereas it was only 39,574 in the case of water impurity. This indicates that possible contaminants such as moisture, monomers, or the recrystallization solvent should be effectively removed prior to polymerization. The avoidance of these impurities in the polymerization is critical and requires great care during the synthesis.¹⁶ To achieve higher molecular weight of D,L-Lactide with minimum batch to batch variation, three steps were considered essential: (1) freshly recrystallized D,L-Lactide from dried ethyl acetate, (2) three cycles of heating and cooling in ampules to remove dissolved air/moisture in vacuum and, (3) high vacuum (>0.01 mm/Hg) sealing of an ampules.

CONCLUSIONS

1. The results of melt polymerization of D,L-Lactide indicate the polymer molecular weight can be predicted with variation ± 5000 , provided the great precautions (as described above) are taken during synthesis.
2. The melt polymerization of D,L-Lactide at 165°C initiated with tetraphenyltin is a slow process, reaching the maximum polymer molecular weight around 10–12 h, followed by a fairly constant value of molecular weight.

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