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An investigation of the synthesis and thermal stability of poly(DL-lactide)

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Summary

The synthesis and thermal degradability of poly(DL-lactide) were investigated. Key factors affecting the polymer molecular weight were found to be monomer recrystallization, initiator concentration and the vacuum level during drying/sealing of the polymerization reaction ampoule. It was found that poly(DL-lactide) is thermally unstable above its melting temperature. Monomer recrystallization, polymer precipitation and a low initiator content of the polymer significantly inhibited the rate and extent of thermal degradation.

Introduction

Due to its proven biocompatibility, good mechanical properties and biodegradability, polylactide has been widely used in medicine and surgery for various applications. These include controlled release of drugs (1), biodegradable surgical sutures and implants for fixation of fractures (2-3).

Polylactide (PLA) can be found in two forms: poly(L-lactide) and poly(DL-lactide). These arise from the repeating unit of L-lactide (m.p. 96°C) and a racemic (50% D- and 50% L-lactide) mixture of D- and L-lactide (m.p. 126°C), respectively. Poly(L-lactide) is a crystalline polymer while poly(DL-lactide) is an amorphous polymer. While PLA can be synthesized by a variety of methods, the preferred route for the preparation of high molecular weight PLA is the ring-opening bulk polymerization of lactide (4-7). Various metallic, organometallic, inorganic and organic zinc and tin compounds have been used as initiators. Tetraphenyltin, stannous chloride and stannous octoate are among the most effective (4,6). The preferred initiator is stannous octoate because of its acceptance by the FDA (Food and Drug Administration, Washington DC) as a food additive (4).

The polymerization reaction is very sensitive to the presence of hydroxyl groups. These groups act as initiator and chain transfer agents in the polymerization. This makes it very difficult to control the polymerization, i.e., to control molecular weight (MW), molecular weight distribution (MWD) and to obtain good reproducibility. Therefore the avoidance of hydroxyl impurities in the polymerization procedure is critical and requires great care during the synthesis. The most commonly employed polymerization procedure was developed by R. K. Kulkarni (8). With his technique, a glass flask containing a mixture of monomer (purified by recrystallization) and catalyst, is sealed under vacuum and heated to a desired temperature for a given period of time. After polymerization, the polymer is purified by precipitation. Although many papers have been published on the synthesis of PLA (4-11), only a few have paid attention to the reproducibility of PLA synthesis (4,6). Kohn et al. (6), for example, in order to obtain reproducible batches of polymer, tried unsuccessfully to control the DL-lactide polymerization procedure. Enink (4)

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on the other hand set up a standard polymerization procedure for L-lactide. Good reproducibility was obtained in his case. However, as far as the authors are aware, nothing has been published on the reproducibility of the synthesis of high molecular weight poly(DL-lactide).

Several papers have shown that PLA is a thermally unstable polymer (12-14). The heat molding process for manufacturing fixation devices in surgery may change the polymer molecular weight and its distribution dramatically (15). The biodegradation rate would also be expected to change. Surprisingly the thermal degradation properties of PDLLA under heat molding conditions have been given little attention.

In this paper, we investigated several factors affecting poly(DL-lactide) synthesis such as pretreatment of the reaction ampoule, DL-lactide purification, as well as the polymerization time and the catalyst concentration. Furthermore, the change in the molecular weight of PDLLA under heating was measured. Our long term goal is the development of a biodegradable fixation device for prosthetic shoulder joints.

Experimental

Materials

D,L-lactide, melting point 116°C-119°C, boiling point 42°C/8mmHg, purchased from Aldrich Chemical Company (Wisconsin, U.S.A), was stored in a desiccator at ambient temperature. The monomer was recrystallized from ethyl acetate (60°C) or toluene (70°C) just before use. Stannous octoate (Sigma Chemical Company, St. Louis, U.S.A) was used as catalyst without further purification. Toluene and ethyl acetate were analytical grade quality.

Polymer Synthesis

The polymerization ampoules (1ml) were dried overnight in an oven at 130°C just before use. For comparison, some of the ampoules were cleaned with concentrated hydrochloric acid and nitric acid (3:1, v/v) for several hours at room temperature, dried, then silanized with a trimethylsilyl chloride acetone solution for several hours.

Freshly recrystallized D,L-lactide, as well as a stannous octoate toluene solution were added to the ampoules, dried under 100mmHg vacuum until most of the solvent had vaporized and then further dried under 0.05mmHg vacuum for 0.5 hour. The monomer to initiator molar ratio was varied from 150 to 10,000 in these experiments. The ampoules were sealed under high vacuum and submerged in a paraffin oil bath (126±5°C). After the polymerization, each ampoule was broken and the polymer was dissolved in acetone, precipitated in water and dried under vacuum to a constant weight. The yield was obtained from the PDLLA/DLLA weight ratio.

Physicochemical Characterization

The intrinsic viscosity of a PDLLA/benzene solution (0.12-0.25g/dl) was measured at 30°C with a Cannon-Fenske viscometer. The viscosity average molecular weight (Mv) was calculated using the Mark-Houwink equation:

$$[\eta]=2.27\times10^{-4}\overline{M}_v^{0.75}$$

For the thermal degradability tests, polymer was put into a test tube, with one end open to air, for various times (5 to 30 minutes) at different temperatures ranging from 126°C to 200°C. The polymer's molecular weight was then measured.

Results and Discussion

Synthesis of Poly(DL-lactide)

Our experimental results showed that silanization of the ampoules does not have a significant effect on the polymer molecular weight (Table 1). For example, the molecular weight of PDLLA, prepared at a constant monomer to initiator mole ratio of 5,000, with recrystallized monomer but with or without silanization, was found to be about $41.1*10^4$ and $46.0*10^4$ respectively. Enink (4) also found that acid washing and silanization of the glass wall of the reaction vessel did not increase the molecular weight of poly(L-lactide) in his polymerization procedure. In contrast, according to Schindler et al. (16), masking of the hydroxyl groups on the glass wall of the reaction vessel by silanization is necessary to obtain high molecular weight poly(L-lactide), e.g., $Mw=58.9*10^4$.

Recrystallization of the monomer was found to be an effective method for increasing the molecular weight of PDLLA. For example, the Mv increased from $28.6*10^4$ to $35.7*10^4$ after recrystallization of DL-lactide with toluene ([M]/[I]=10,000, reaction time 40 hours) (Table 1). Furthermore, recrystallization of the monomer just before use appears to make the polymerization procedure more controllable. The molecular weight of PDLLA prepared from unrecrystallized monomer ([M]/[I]=5,000), for example, varied by a factor of 9 from $4.20*10^4$ to $36.2*10^4$. The molecular weight of PDLLA obtained from toluene recrystallized monomer on the other hand varied by a factor of less than 2, from $38.4*10^4$ to $54.6*10^4$ (Table 1). In addition our polymerization procedure appears to be fairly reproducible. For example, a Mv of $45.3*10^4$, standard deviation of $7.1*10^4$, was calculated from the first five results in table 1 (toluene recrystallized, [M]/[I]=5,000). The confidence interval was $(45.3\pm8.2)*10^4$ with a 95% confidence level.

The level of vacuum during drying/sealing was found to have the greatest effect on the molecular weight of the polymer. Employing 100 mmHg vacuum for drying/sealing of the ampoule containing the monomer and initiator resulted in a Mv of around $4*10^4$ (Table 2). This was lower by a factor of ten than the Mv obtained by employing high vacuum drying/sealing at 0.05 mmHg. Under high vacuum any remaining toluene, trace amounts of water and even lactic acid would be more effectively removed.

The D,L-lactide polymerization procedure is very sensitive to the presence of hydroxyl groups which act as chain transfer agents. In order to get high molecular weight polymer and to be able to control the polymerization procedure, it is necessary to use a highly purified monomer and to keep moisture out of the reaction vessel during the polymerization. Also the polymerization temperature should be as low as possible (just above the melting point of the lactide) so as to decrease the problem of undesirable side reactions (i.e., back-bitting, intermolecular transesterfication and intramolecular transesterfication) from occurring along with the desired polymerization reaction. The most likely hydroxyl impurities in DL-lactide are lactoyl lactic acid, lactic acid and adsorbed moisture. The lactoyl lactic acid and lactic acid are hydrolysis products of lactide which attracts moisture during storage. The use of freshly recrystallized monomer and application of high vacuum drying/sealing procedure can significantly reduce hydroxyl impurities and guarantee an absence of moisture in the polymerization.

The effects of polymerization time and the initiator concentration on polymer yield and polymer molecular weight were also assessed. The yields levelled off after 15 hours of polymerization for [M]/[I]=1,000, after 26 hours for [M]/[I]=5,000 and after 40 hours for [M]/[I]=10,000 (Figure 1). The discrepancy between the maximum experimental yields and theoretical yield of 100% might due to monomer loss during vacuumization and oligomer loss during precipitation. It is interesting to note that the polymer molecular weight passes through a maximum as a function of reaction time and monomer/initiator ratio (Figures 2 & 3). The drop in polymer molecular weight at longer reaction times can be explained by a back bitting reaction which produces cyclic oligomer and is catalysed by stannous octoate, intra- and intermolecular transesterfications (Figure 4). The fact that the Mv of PDLLA passes through a maximum is in accordance with Enink's (4) results for poly(L-lactide). Our results for poly(DL-lactide) suggest that the optimum [M]/[I] ratio is about 6,000 and the ideal reaction time approximately 30 hours, for the synthesis of high molecular weight (Mv=50*10^4) PDLLA.

Table 1. Effect of acid washing, silanization of ampoule and monomer recrystallization on the polymerization reaction.

Ampoule acid wash	Ampoule silanization	Solvent for recrystallization	Initiator concentration [M]/[I]	polymerization time, hr	Polymer yield %	Polymer M.W. Mv*10^{-4}
yes	yes	toluene	5,000	36	--	40.6
yes	yes	toluene	5,000	36	--	41.7
no	no	toluene	5,000	36	75.2	54.6
no	no	toluene	5,000	26	83.1	38.4
no	no	toluene	5,000	26	82.5	51.2
no	no	ethyl acetate	5,000	24	76.9	40.0
no	no	ethyl acetate	5,000	40	--	34.0
no	no	none	5,000	48	--	4.20
no	no	none	5,000	26	85.2	12.1
no	no	none	5,000	26	87.6	24.4
no	no	none	5,000	36	88.5	36.2
no	no	none	10,000	40	78.6	28.6
no	no	toluene	10,000	40	83.3	35.7

*polymerization temperature, 126±5°C.
*vacuum 0.05 mmHg.

Table 2. Effect of vacuum level on molecular weight of poly(DL-lactide).

Vacuum level (mmHg)	Polymerization time (hour)	Polymer yield (%)	Polymer molecular weight Mv*10^{-4}
100	36	79.6	4.20
100	120	79.3	4.01
0.05	36	--	40.6
0.05	36	--	41.7

* ampoules acid washed and silanized.
* monomer recrystallized.
* polymerization temperature 126±5°C.
* [M]/[I]=5,000

Thermal stability of PDDLA

Poly(DL-lactide) (PDLLA) is a thermally unstable polymer. The molecular weight of PDLLA, with initial Mv=38.5*10^4, while relatively stable at a temperature below 178°C, decreased significantly at 183°C over 30 minutes, to less than 25% of its original value (Figure 5). The sudden molecular weight change in the polymer corresponds to an observed PDLLA phase change, from a solid state to a liquid state, at 178°C to 183°C. Poly(DL-lactide) does not have a sharp melting point because it is an amorphous polymer. Such polymers change from a solid to a liquid over a temperature range. The melting temperature range for PDLLA depends on the polymer's molecular weight. The higher the molecular weight, the higher the melting temperature.

The thermal degradability of PDLLA was affected by the recrystallization of monomer and precipitation of polymer, as well as by the initiator content (Figure 6). Precipitated poly(DL-lactide) made from recrystallized monomer with a low initiator content, for example, lost 25% of its molecular weight during 10 minute heating at 200°C; While precipitated PDLLA prepared from

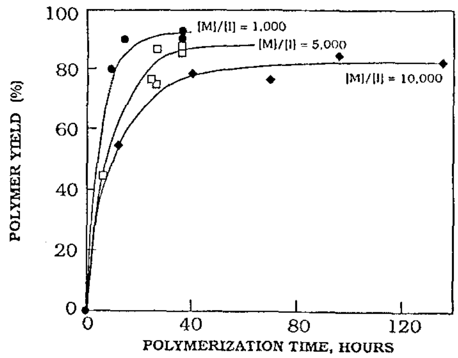

Figure 1

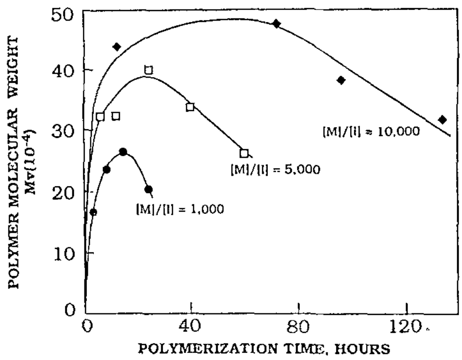

Figure 2

Figure 1. The relationship between polymer yield and polymerization time at various monomer to initiator ratios. The monomer was recrystallized from ethyl acetate, the polymerization temperature was 126±5°C.

Figure 2. The relationship between polymer viscosity average molecular weight and polymerization time at various monomer to initiator ratios. The monomer was recrystallized from ethyl acetate, the polymerization temperature was 126±5°C.

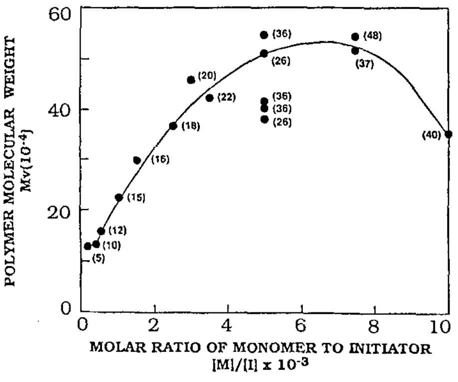

Figure 3. The relationship between polymer viscosity average molecular weight and monomer/initiator mole ratio. The monomer was recrystallized from toluene, the polymerization temperature was 126±5°C, the polymerization time shown in brackets is in hours.

recrystallized monomer but with high initiator content lost 65% of its molecular weight during the same period of time. Unprecipitated PDLLA obtained from unrecrystallized monomer with a low initiator content, on the other hand, showed the greatest molecular weight loss, 85% in 10 minutes.

The content of such impurities as monomer, oligomer and hydroxy groups in PDLLA will depend on whether or not the monomer was recrystallized and/or the polymer was precipitated. A precipitated polymer made from recrystallized monomer should have a lower hydroxyl content than that of unprecipitated polymer prepared from unrecrystallized monomer. It was assumed that the remaining initiator content of the polymer was equal to the initial initiator concentration employed in the polymerization. It has previously been shown that the precipitation procedure does not remove stannous octoate from the polymer (4).

The main reason for thermal degradation of PDLLA might be zip-like depolymerization (back-bitting) catalysed by remaining stannous octoate, and

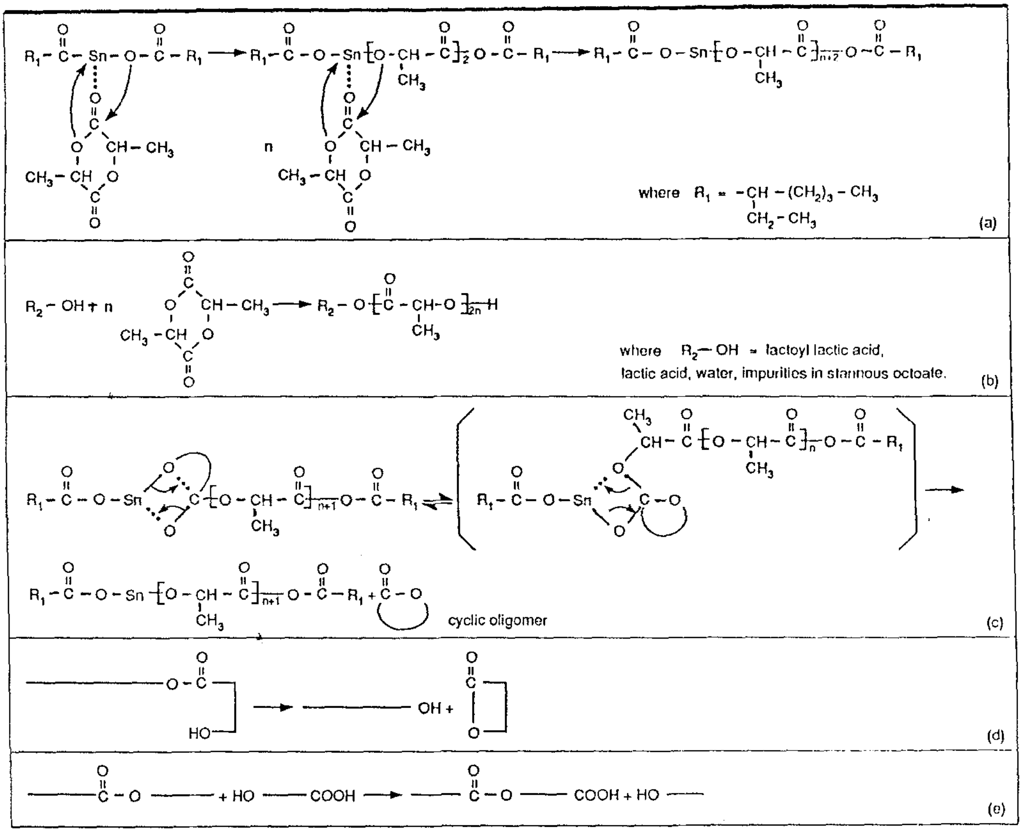

Figure 4. The reactions in the polymerization and thermal degradation. (a). Polymerization initiated by stannous octoate (4). (b). Polymerization initiated by hydroxy groups. (c). Back-biting catalyzed by stannous octoate. (d). Intramolecular transesterfication (14). (e). Intermolecular transesterfication (14).

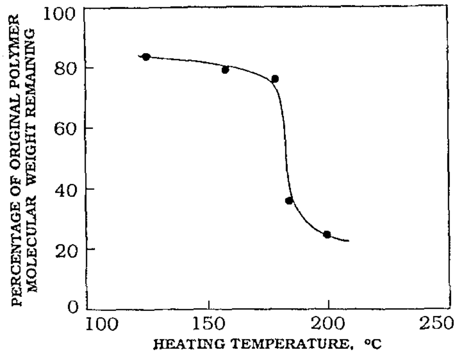

Figure 5

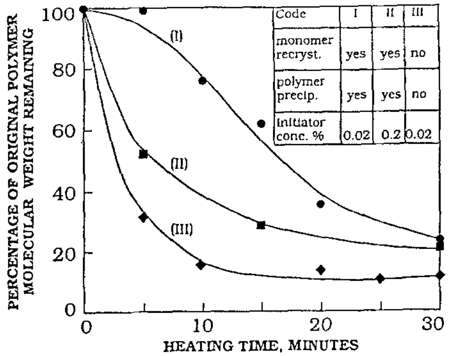

Figure 6

Figure 5. The reduction in polymer molecular weight as a function of heating temperature. Initial Mv=38.5*10^4, [M]/[I]=5,000, recrystallized monomer and precipitated polymer. The polymer was heated for 30 minutes in each test.

Figure 6. Effect of heating time on polymer molecular weight at various initiator concentrations, and with or without monomer and polymer purification. Heating temperature = 200°C.

intra- and intermolecular transesterfications which would be accelerated by the existence of monomer, oligomer and hydroxy groups (Figure 4) (14). Obviously, the higher the initiator and hydroxyl impurity contents in the polymer, the more rapid the degradation. Although it is hard to assess these side reactions quantitatively, our results qualitatively support their existence.

Conclusions

Key factors which were found to affect the molecular weight of poly(DL-lactide) were the concentration of initiator employed in the polymerization, recrystallization of the monomer and the level of vacuum used in the drying/sealing procedure. Our results for poly(DL-lactide) suggest that the optimum [M]/[I] ratio is about 6,000 and the ideal reaction time approximately 30 hours, for the synthesis of high molecular weight ($Mv=50*10^4$) PDLLA. Poly(DL-lactide) is thermally unstable above its melting temperature. A low initiator concentration, monomer recrystallization and polymer precipitation, appear to inhibit the rate and extent of the polymer thermal degradation.

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