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Biodegradable Polymers for Orthopedic Applications: Synthesis and Processability of Poly (l-Lactide) and Poly (Lactide-*co*-€-Caprolactone)

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BIODEGRADABLE POLYMERS FOR ORTHOPEDIC APPLICATIONS: SYNTHESIS AND PROCESSABILITY OF POLY(L-LACTIDE) AND POLY(LACTIDE-*co*-ϵ-CAPROLACTONE)

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ABSTRACT

The synthesis of poly(L-lactide) (PLLA), poly(L-lactide-*co*-ϵ-caprolactone), and poly(DL-lactide-*co*-ϵ-caprolactone) by ring-opening bulk polymerization was investigated. Polymerization temperature had a significant effect on the PLLA molecular weight. At 184°C a polymer with

a molecular weight of only 10×10^4 resulted. This was lower by a factor of 2 than that obtained at 103 and 145°C. The stannous octoate (SnOct) concentration, with a monomer/SnOct molar ratio in the range of 1,000 to 10,000, was not found to have a significant effect on the PLLA molecular weight. A heterogeneous structure in polymerized PLLA was observed. The intrinsic viscosity of poly(lactide-*co*-ϵ-caprolactone), obtained at 130°C, monomer/SnOct molar ratio 5,000, and polymerization time of 30 hours, decreased with increasing ϵ-caprolactone content within the first 9 wt% and then leveled off. Die-drawing of PLLA cylinders, for the purpose of increasing the polymer's mechanical strength, was unsuccessful due to the brittleness of the polymer. The drawability of poly(L-lactide), however, was greatly improved by copolymerization with ϵ-caprolactone. With only 3 wt% of ϵ-caprolactone, for example, the tensile strength of die-drawn poly(L-lactide-*co*-ϵ-caprolactone) was increased by a factor of more than 3. Polymer processing temperature was also investigated. The requirement for low processing temperatures in melt manufacture of controlled release matrix devices containing thermal sensitive drugs was accomplished by three methods: through the use of low molecular weight poly(DL-lactide), adding (DL-lactic) acid oligomer to high molecular weight PDLLA, and copolymerizing DLLA with ϵ-caprolactone. The glass transition temperatures of the modified high molecular weight PDLLA decreased significantly. Melt extrusion below 100°C could be performed.

INTRODUCTION

Biodegradable polymers such as poly(L-lactide), poly(DL-lactide), poly(ϵ-caprolactone), and their copolymers have been widely used in medicine and surgery for the controlled release of drugs [1,2], biodegradable surgical sutures, and implants for fixation of fractures [3], primarily due to their high biocompatibility. Polylactide, for example, has been approved by the Food and Drug Administration (FDA), Washington, D.C. [1]. In orthopaedic surgery, biodegradable fixation devices such as screws, plates, and pegs have the advantage of offering temporary fixation for bone prostheses. The device is eventually absorbed by the body after bone tissue growth into the porous structure of the prosthesis becomes effective on fixation of the implant to the bone [4]. In addition, the requirement for local antibiotic administration for prevention and/or treatment of bone infection will be better met by employing biodegradable controlled antibiotic release devices rather than currently used nondegradable poly(methyl methacrylate) antibiotic beads [4, 5].

Semicrystalline poly(L-lactide) (PLLA) has found application mainly in temporary tissue fixations where good mechanical strength is required. A widely used process for increasing polymer mechanical strength is through reinforcement with fibers [6]. PLLA, for example, can be reinforced with biodegradable polymer fibers made from polyglycolide (PGA) and even PLLA itself [7]. It is possible, for example, to increase the flexural strength of PLLA from 50 to 300 MPa by fiber reinforcement [8]. Another technique for increasing the mechanical properties of the

polymer is by solid deformation. In this case the polymer main chain is oriented by extruding or drawing a polymer sample at a temperature between its glass transition temperature (T_g) and its melting point (T_m) [9]. In the case of PLLA, these temperatures are 58 and 184°C, respectively [10].

In contrast to PLLA, poly(DL-lactide) (PDLLA, T_g = 55°C) is an amorphous polymer. PDLLA is mainly used for controlled drug release applications rather than tissue fixation. A melt procedure should be the preferred technique for manufacturing controlled release systems, primarily because organic solvents are not required. High molecular weight PDLLA normally has to be melt processed above 130°C due to its high glass transition temperature and high melt viscosity. This high temperature is undesirable for thermal sensitive drugs. Therefore, PDLLA with a low T_g is preferred for device manufacturing by the melt process.

Both PLLA and PDLLA are brittle. Poly(ϵ-caprolactone) (PCL), on the other hand, is a semicrystalline elastomer with a T_g of −60°C and a T_m of 60°C [10]. The flexibility and T_g of poly(lactide-*co*-ϵ-caprolactone) [i.e., P(LLA-*co*-CL) and P(DLLA-*co*-CL)] fall in between those of the homopolymers and depend to a great extent on the composition of the copolymer [11–14]. The synthesis of these biodegradable polymers has been investigated in previous studies [15–20]. The best method for obtaining high molecular weight polymers may be ring-opening bulk polymerization in the presence of stannous octoate, which is a food additive approved by the FDA. It is still unclear from the literature whether stannous octoate is an initiator or a catalyst. However, there is evidence that stannous octoate reacts with water and alcohols to form a much more effective initiator [15].

Our interests in PLLA, PDLLA, P(LA-*co*-CL), and P(DLLA-*co*-CL) are the potential applications of such polymers for fixation of prosthetic shoulder joints as well as for the controlled release of antibiotics. Tailoring a biodegradable polymer's properties to meet specific applications, though, requires a thorough understanding of its synthesis. For this paper we investigated the synthesis of poly(L-lactide) and poly(lactide-*co*-ϵ-caprolactone), die-drawing of the polymers to increase mechanical strength, and methods for decreasing the polymer melt process temperature.

EXPERIMENTAL

Materials

The monomers L-lactide and ϵ-caprolactone were purchased from Aldrich Chemical Company (Milwaukee, Wisconsin). L-Lactide was recrystallized from toluene just before use. ϵ-Caprolactone was used as received. Stannous octoate (Sigma Chemical Company, St. Louis, Missouri) was used as an initiator without further purification. DL-Lactic acid was obtained from BDH Chemical Company (Toronto, Ontario).

Polymer Synthesis

High molecular weight poly(L-lactide), poly(L-lactide-*co*-ϵ-caprolactone) and poly(DL-lactide-*co*-ϵ-caprolactone) were synthesized by an established procedure for poly(DL-lactide) [20]. Briefly, a mixture of monomer(s) and stannous octoate was added to a glass ampule. The ampule was sealed under high vacuum and heated

above the monomer's melting point to start the polymerization. After the polymerization was complete, the ampule was broken and the polymer was dissolved in chloroform (for PLLA) or acetone (for the copolymers). The polymer solution was filtered and then the polymer was precipitated from ethanol (for PLLA) or distilled water (for the copolymers). The polymerization yield was obtained from the monomer/polymer ratio.

Low molecular weight poly(DL-lactic acid) and DL-lactic acid oligomer were synthesized by a polycondensation procedure. DL-Lactic acid was added into a flask without any catalyst [21]. The reaction occurred under the protection of nitrogen at 180–200°C. The water generated in the reaction was removed by interval nitrogen purge and vacuum.

Polymer Characterization

The intrinsic viscosity of a polymer/chloroform solution was measured at 25°C with a Cannon-Fenske viscometer. The viscosity average molecular weight of PLLA was calculated using Schindler's [22] Mark-Houwink equation ($K = 5.45 \times 10^{-4}$ dL/g, $a = 0.73$). The glass transition temperature of polymer was measured by DSC (Mettler DSC 30, Mettler TC 10A, TA data processor).

Die-Drawing of Polymer Cylinders

Solid deformation was performed on a tensile testing machine (Instron, Model 1122, VACS LTD, Toronto) by drawing a polymer cylinder (diameter, 5.7 mm), obtained from directly polymerized samples, through a die with an outlet diameter of 4 mm [23]. The drawing temperature was controlled by a thermal couple. The polymer cylinders were prepared for die-drawing as follows. After polymerization was finished, one end of the glass reaction ampule was cut off. The ampule was then connected to a 100–200 mmHg vacuum, heated above the melting point of the polymer to remove voids, and then cooled to room temperature. The glass was removed from the polymer cylinder by putting the ampule into liquid nitrogen and then carefully hammering the glass away. One end of the cylinder was then machined (for PLLA) or hand drawn at a temperature of 110°C (for P(LLA-*co*-CL)) so that it would fit into the die. The die-drawing speeds were 1000 mm/min at 93 to 116°C and 200 mm/min at 82°C.

Melt Extrusion

Polymers were placed in a plastic syringe and heated in an oven to 100°C. The syringe had an extruder of 14 mm in diameter and an exit of 2 mm in diameter, 10 mm in length. The polymer was extruded through this syringe by hand.

A mixture of high molecular weight PDLLA and DLLA oligomer for the extrusion was made by dissolving the materials in acetone followed by drying.

RESULTS AND DISCUSSION

Synthesis of PLLA, P(LLA-co-CL), and P(DLLA-co-CL)

A high polymerization temperature led to a high reaction rate (Fig. 1). For a monomer to stannous octoate molar ratio, [M]/[SnOct], of 5000, PLLA yields increased rapidly during the first 55 and 25 hours at temperatures of 103 and 145°C,

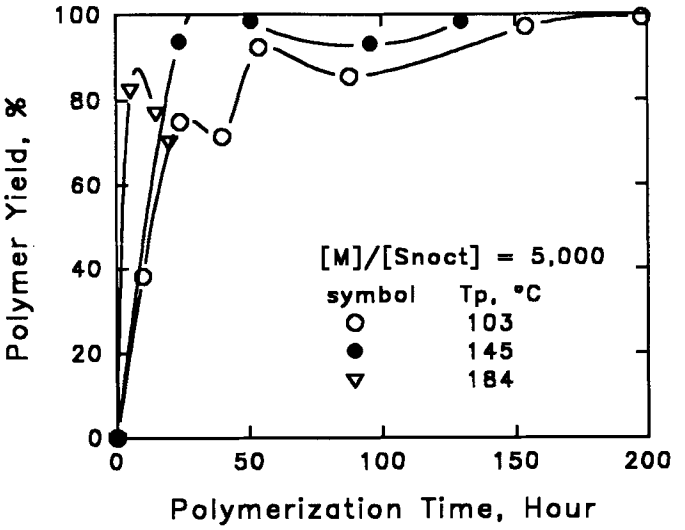


FIG. 1. The relationship between PLLA yield, polymerization time at [M]/[SnOct] = 5000, and reaction temperature.

respectively. After this, the yields slowly leveled off. At 184°C the yield increased sharply in the first few hours but then decreased with time. The decrease in yield is presumably due to the side reactions (transesterfication, back-biting, and depolymerization) which are more significant at high temperatures [24, 25]. A high stannous octoate concentration also resulted in a high reaction rate (Fig. 2). For [M]/

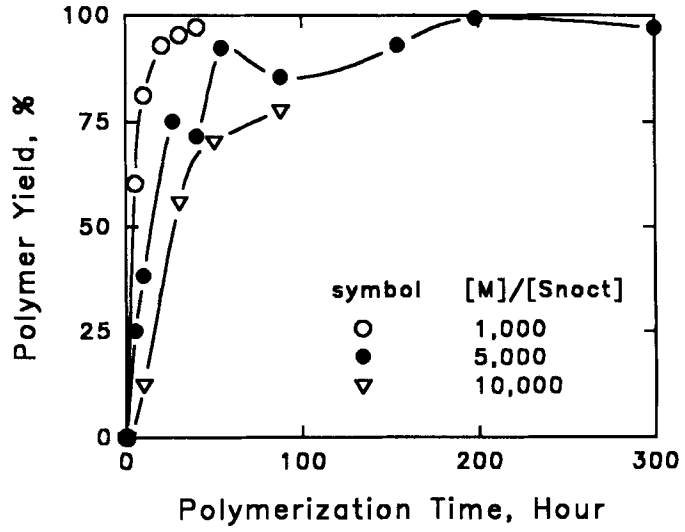


FIG. 2. The relationship between PLLA yield and polymerization time at various [M]/[SnOct] ratios and 103°C.

[SnOct] = 1000 and 5000, at 103°C, the reaction times required for reaching 100% yield were 40 and 200 hours, respectively.

The molecular weight of precipitated PLLA passed through a maximum with increasing polymerization time (Fig. 3). The optimum polymerization time for high molecular weight PLLA was in the 55 to 155 hours range at 103°C, 25 to 90 hours at 145°C, and less than 5 hours at 184°C. The highest PLLA molecular weights obtained were 22 × 10^4 at 103°C, 22 × 10^4 at 145°C, and only 8.7 × 10^4 at 184°C. The drop in polymer molecular weight at longer reaction times, as well as

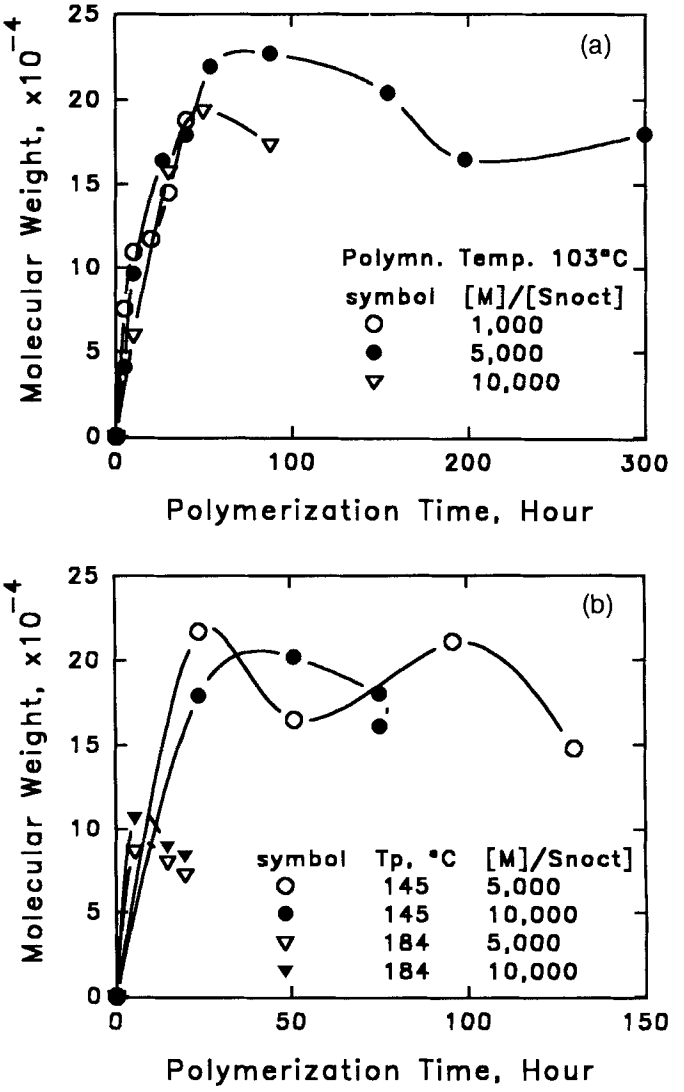


FIG. 3. The relationship between PLLA molecular weight and polymerization time. (a) At T_p of 103°C and [M]/[SnOct] of 1,000, 5,000, 10,000. (b) At T_p of 145 and 184°C and [M]/[SnOct] of 5,000 and 10,000.

the more significant drop at 184°C, can also be explained by side reactions. While the relationship between PLLA molecular weight and reaction time at 103 and 145°C was almost the same, at 184°C it was significantly different (Figs. 3a and 3b). The stannous octoate concentration was found to have an effect, though not significant, on PLLA molecular weight (Fig. 3a). A low stannous octoate concentration, for example, led to a low reaction rate and therefore slow polymer chain growth. These results are in contrast to the case of DL-lactide polymerization at 126°C, where the PDLLA molecular weights and optimum polymerization times for [M]/[SnOct] of 1,000, 5,000, and 10,000 were 16×10^4, 50×10^4, and 33×10^4, respectively [20].

An interesting phenomenon was observed in our experiments. Direct polymerized PLLA billets (or cylinders) had a heterogeneous structure when the polymerization temperatures were 103 and 145°C, while the billet had a homogeneous structure at 184°C (Fig. 4, Table 1). This phenomena was also mentioned by Leenslag et al. [15]. The reason may be due to the fact that PLLA chains tend to crystallize instead of adopting a very extended coil conformation in the polymer/monomer mixture at the lower temperatures. The appearance of these heterogeneous structures started at polymer yields of 60 to 81% for [M]/[SnOct] = 1,000 at T_p = 103°C (Figs. 4a and 4b), and somewhere between polymer yields of 56 to 70% for [M]/[SnOct] = 10,000 at T_p = 103°C (Figs. 4d and 4e). The degree of heterogeneity increased with polymer yields (Figs. 4a-c, 4d-f). Our experiments showed that the heterogeneous structure was greatly affected by stannous octoate concentration. A low stannous octoate concentration gave a larger sphere size (comparing Figs. 4f, 4h, and 4c). Low polymerization temperatures also gave a more heterogeneous structure (comparing Fig. 4f to 4i, Fig. 4h to 4g). The largest sphere size was obtained at the lowest stannous octoate concentration [M]/[SnOct] = 10,000 and the lowest polymerization temperature T_p = 103°C (Fig. 4f).

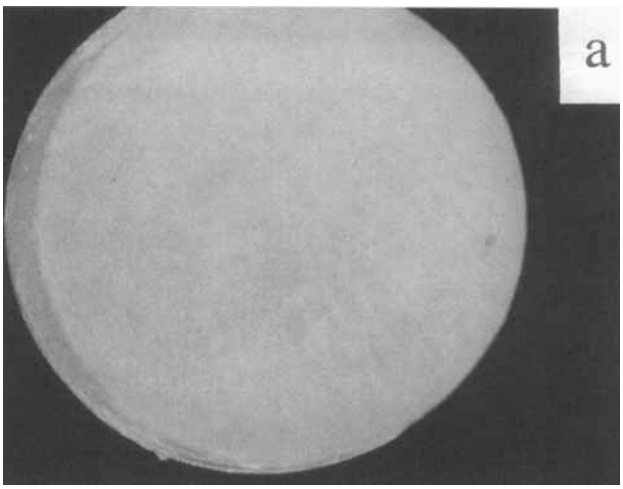
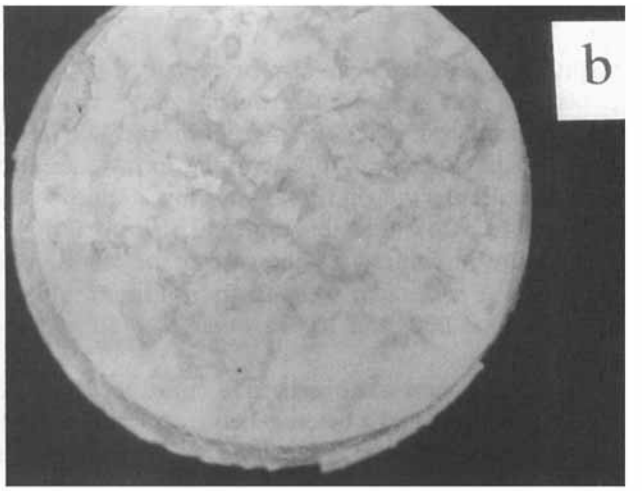
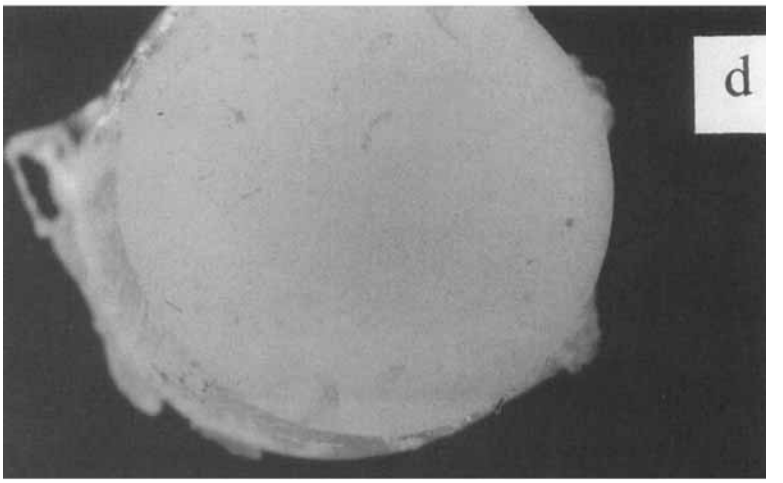
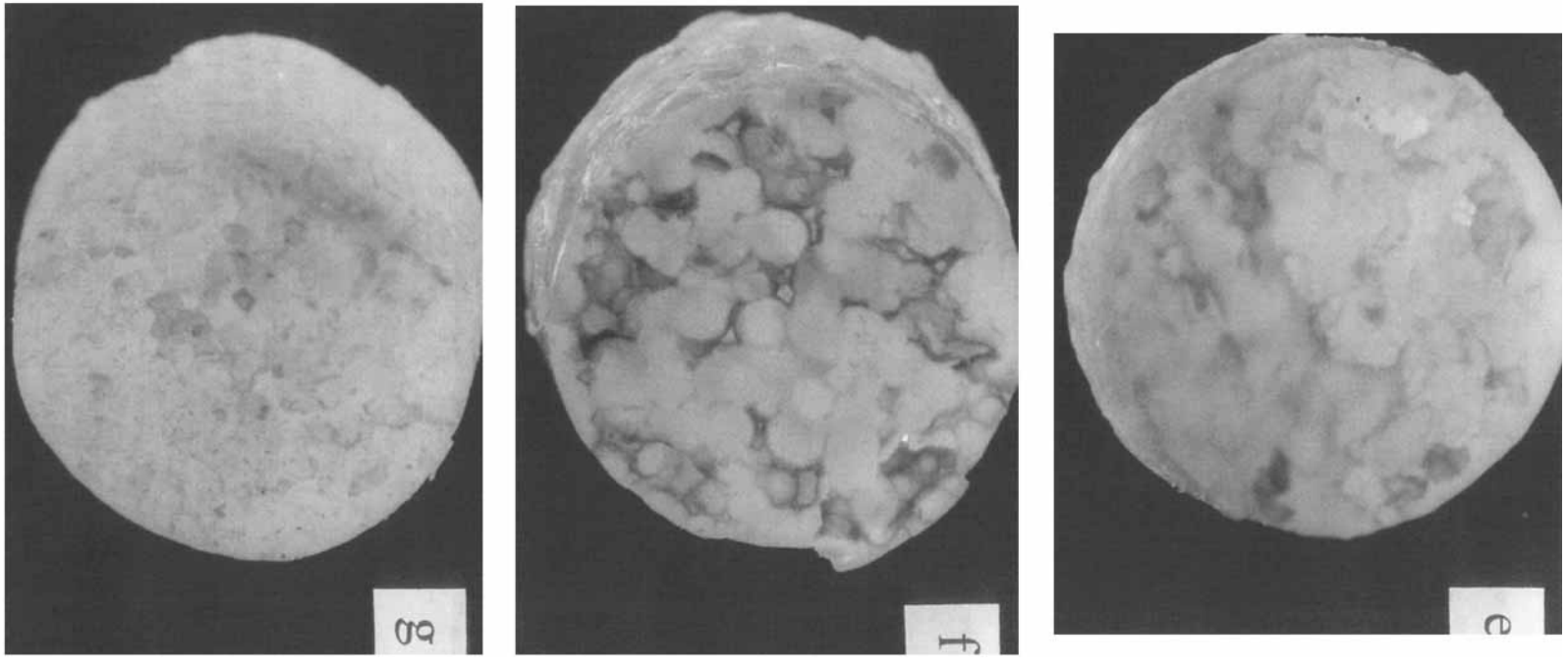
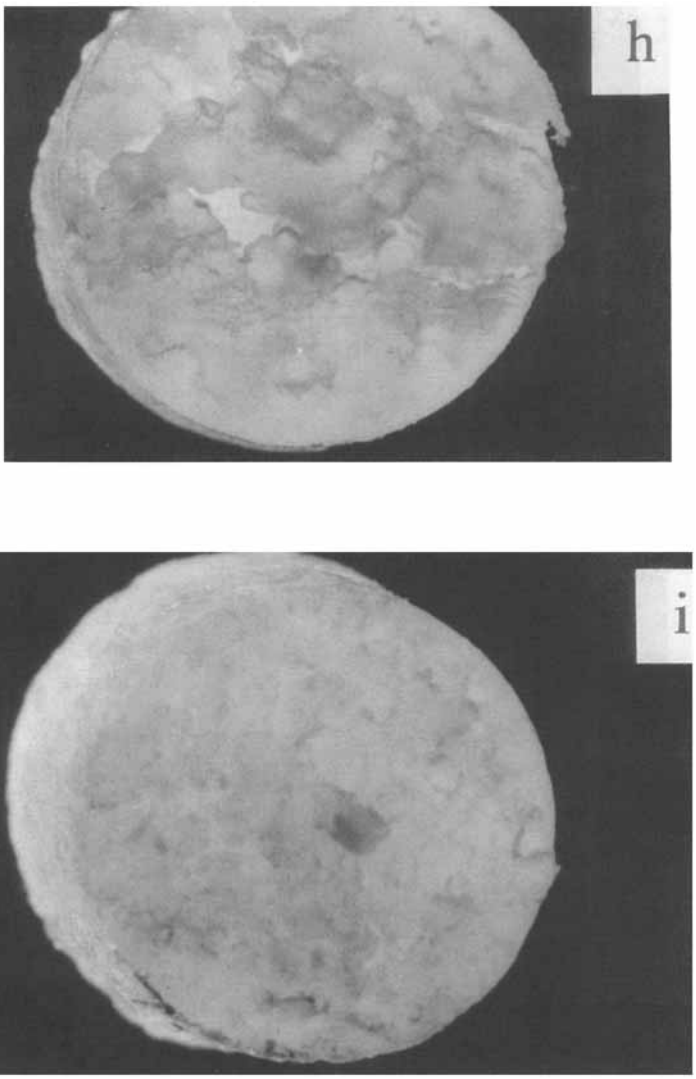


FIG. 4. The heterogeneous structures of PLLA were developed during polymerization. This figure is continued on the following 3 pages. See Table 1 for explanations.









The copolymers P(LLA-*co*-CL) and P(DLLA-*co*-CL) with caprolactone, CL, contents of 3 to 16 wt% and 0 to 55 wt%, respectively, were synthesized at T_p = 130°C, [M]/[SnOct] = 5000, and a polymerization time of 30 hours. A heterogenous structure was also observed for these polymerized billets. The intrinsic viscosity decreased with increasing CL content (Fig. 5). For example, the intrinsic viscosity decreased from 5 dL/g for PDLLA to about 2 dL/g for P(DLLA-*co*-CL) with a 9 wt% CL content. It then leveled off to around 2 dL/g for a CL content in the 9 to 55 wt% range. This intrinsic viscosity change for the copolymer might be due to a change in its conformation in dilute chloroform.

TABLE 1. Polymerization Conditions and Results of PLLA Samples in Figure 4

Figure	T_p, °C	[M]/[SnOct]	Time, hours	Yield, %	MW × 10^{-4}
a	103	1,000	5	60.4	7.52
b	103	1,000	10	81.3	10.9
c	103	1,000	30	95.4	14.5
d	103	10,000	30	56.0	15.8
e	103	10,000	50	70.4	19.4
f	103	10,000	88	77.7	17.4
g	145	5,000	96	93.1	14.8
h	103	5,000	54	92.3	22.0
i	145	10,000	75	98.6	16.1

Enhancing Polymer Tensile Strength by Die-Drawing

It was found in our experiments that enhancing the mechanical strength of PLLA cylinders by die-drawing [26] was difficult, even at a temperature as high as 140°C. The PLLA cylinders broke before a significant degree of drawing could take place. This was apparently due to the brittle nature of PLLA. Since poly(ϵ-caprolactone) is an elastomer, we speculated that by adding ϵ-caprolactone to the PLLA main chain, the brittleness of PLLA should decrease. In the die-drawing studies, we found that a copolymer containing only 3 wt% ϵ-caprolactone signifi-

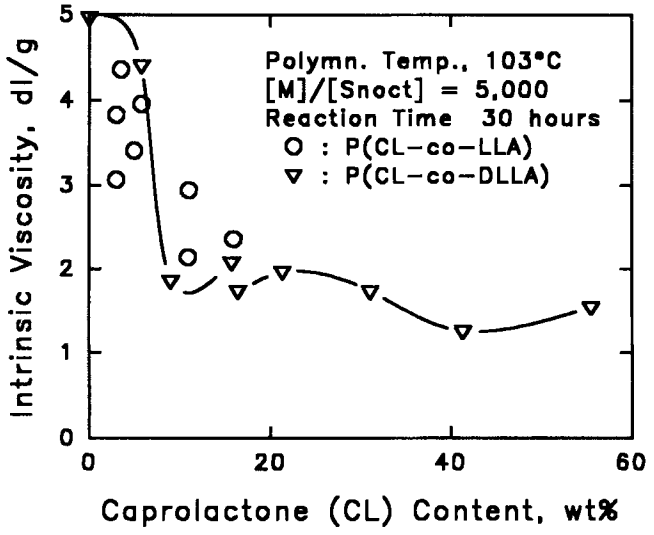


FIG. 5. The intrinsic viscosities of poly(ϵ-caprolactone-*co*-DL-lactide) and poly(ϵ-caprolactone-*co*-L-lactide) decrease with increasing ϵ-caprolactone content.

cantly increased the flexibility of the polymer at a temperature between T_g and T_m, without apparent loss in PLLA stiffness at room temperature. Unlike pure PLLA cylinders, the die-drawing was easily performed on this copolymer (Table 2). The tensile strength increased greatly by die-drawing. For example, the tensile strength increased from 52.8 MPa for an undrawn cylinder to 190 MPa for a drawn cylinder at a drawing temperature of 82°C and a drawing speed of 500 mm/min. These results are comparable to those obtained for fiber reinforcing PLLA, PGA, and their copolymers [7]. The material appears to be promising for use in orthopedics due to its good mechanical strength, biocompatibility, biodegradability, and processability.

Decreasing the Melt Processing Temperature of PDLLA

Three methods were employed to investigate the PDLLA melt process temperature: decreasing the molecular weight of PDLLA, adding DL-lactic acid oligomer to high molecular weight PDLLA, and copolymerizing DLLA with ϵ-caprolactone.

Since PDLLA is an amorphous polymer, no melting point can be detected. However, the glass transition temperature can be employed to indicate the melt process temperature required. The lower the T_g, the lower the melt process temperature required. The glass transition temperature of PDLLA increased dramatically between MW = 4,800 and 46,900, going from 38 to 51°C, respectively. Beyond MW = 100,000 it leveled off at 56°C (Fig. 6).

The DL-lactic acid oligomer, a viscous liquid at room temperature, was synthesized by polycondensation at 200°C for 5 hours. Adding it to PDLLA significantly decreased the T_g (Fig. 7). The T_g decreased from 47°C for pure PDLLA with a MW of 32,300 to 22°C for this PDLLA with 12.5 wt% oligomer in it. Further addition of oligomer, to 50 wt%, did not bring down the T_g as much as for the first 12.5 wt%.

It was observed that with an increase in the caprolactone content of the copolymer, the material changed from a brittle polymer to a rubberlike elastomer. Actually, Schindler et al. [10] found that the T_g of P(LA-*co*-CL) was between that of PLA and PCL. Furthermore, they showed that the relationship between T_g of

TABLE 2. Die-Drawing for Poly(L-lactide-*co*-ϵ-Caprolactone)[a] with 3 wt% ϵ-Caprolactone[b]

Temperature, °C	Draw speed, mm/min	Draw force, kg	Draw ratio[c]	Tensile strength, MPa
116	1000	22	4.5	157
104	1000	22	6.1	175
93	1000	30	6.1	185
82	200	32	5.6	190

[a]PLLA cylinders could not be die-drawn.
[b]Tensile strength of undrawn sample was 52.8 ± 9.0 MPa.
[c]Ratio of cylinder cross-section area before drawing to that after drawing.

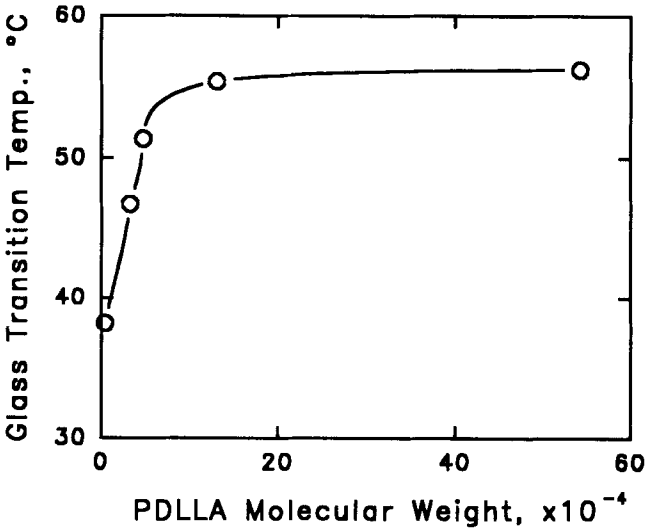


FIG. 6. Increasing the glass transition temperature of PDLLA with the increasing polymer molecular weight. The PDLLA with the lowest molecular weight was obtained from the polycondensation of DL-lactic acid. The other polymers were synthesized by the ring-opening polymerization of DL-lactide.

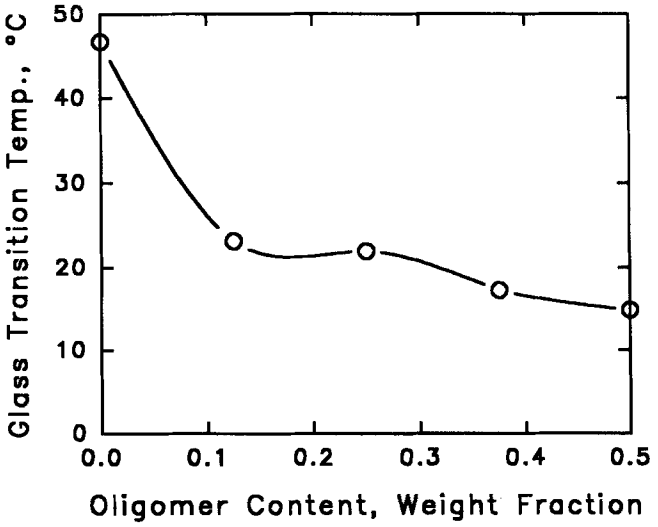


FIG. 7. Decreasing glass transition temperature with increasing oligomer content in PDLLA.

P(LA-*co*-CL) and its composition followed the Fox equation [27], $1/T_{1,2} = (w_1/T_1) + (w_2/T_2)$, where $T_{1,2}$ is the T_g of a copolymer, and w_1 and w_2 are weight fractions of the components in the copolymer.

Low molecular weight PDLLA, high molecular weight PDLLA containing DL-lactic acid oligomer, and P(DLLA-*co*-CL) with ϵ-caprolactone contents above 30 wt% were found to be melt extrudable below 100°C. We can speculate that controlled drug release devices may be melt processed much easier by employing these polymers rather than using high molecular weight PDLLA.

CONCLUSIONS

The polymerization temperature was found to be a critical factor affecting PLLA molecular weight. A high temperature of 184°C resulted in a polymer molecular weight of only 10×10^4, lower by a factor of 2 than that obtained at temperatures of 103 and 145°C. Stannous octoate concentration in the range of [M]/[SnOct] 1,000 to 10,000 was not found to have a significant effect on PLLA molecular weight. A heterogeneous structure of polymerized PLLA cylinders was observed. This structure was affected by polymer yield, polymerization temperature, and initiator concentration. Drawability of poly(L-lactide) at a temperature between its T_g and T_m was greatly improved by copolymerizing L-lactide with a small amount of ϵ-caprolactone. Poly(L-lactide-*co*-ϵ-caprolactone), due to its good mechanical strength, biocompatibility, biodegradability, and processability, is a promising material for orthopedic applications such as fixation of prosthetic devices. The glass transition temperature of PDLLA was significantly decreased by reducing the PDLLA molecular weight, adding DL-lactic acid oligomer and copolymerizing DLLA with ϵ-caprolactone.

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