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Copolymerization of L-Lactide and ε-Caprolactone in Supercritical Fluid

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Abstract: Copolymerization of L-lactide and ε-caprolactone initiated by tin (II) octoate ($Sn(Oct)_2$) was carried out in supercritical chlorodifluoromethane (R22) with varying reaction conditions (time and temperature) and amounts of monomer and catalyst, under a pressure of 250 bar. The optimum conditions were a reaction time of 10 h and a temperature of 130 °C, which is similar to the temperature used in bulk copolymerization system. The conversion increased from 56% to 76% by increasing the reaction time from 1 to 10 h. The molecular weight also increased to 75,900 $g.mol^{-1}$ over the same period, while the increased monomer concentration resulted in a high molecular weight of 86,400 $g.mol^{-1}$ and a monomer conversion of 84%. Raising the reaction temperature from 90 to 130 °C increased the monomer conversion as well as the poly-L-lactide-*co*-ε-caprolactone (PLCL) molecular weight. The variation on the stannous octoate catalyst suggested that less catalyst would decrease the caprolactone content of the polymer.

Keywords: PLCL, biodegradable, copolymer, supercritical fluid.

Introduction

Interest in copolymers of L-lactide and ε-caprolactone has increased as their potential in a wide range of biomedical applications, such as drug delivery systems[1,2] and tissue engineering.[3-5] This copolymer may expand its applications compared to the homopolymer because with this material it becomes possible to fabricate a varied family of bioabsorbable materials with soft, elastic compositions. Moreover, the elongation characteristics of elastomeric copolymers make them suitable for applications where elasticity and degradability are required in the same product.[6,7] The syntheses of L-lactide and ε-caprolactone copolymers have been widely studied in recent years. Most studies have focused on random copolymers,[8-10] diblock copolymers,[11] triblock copolymers[12] and multiblock copolymers.[13]

The ease of solvent removal has been one of the major benefits of supercritical fluid solvents. The use of regular hydrocarbon solvents will limit the product's possibility for bio-related applications due to the solvent residue in the product. Supercritical fluid solvents are an alternative to incompressible organic liquid solvents because they can have liquid-like dissolving power while exhibiting the transport properties of a gas. They have been used in a variety of polymer processes such as extractions and separations, fractionations, and reactions. Particularly, this technology has recently gained attention in the particle formation of biodegradable polymers. On the other hand, the choice of supercritical solvents to dissolve polymers is limited. Carbon dioxide (CO_2) is the favorite solvent for supercritical fluid system. However, the applications of CO_2 have been limited by its solvent power, which lies somewhere between that of a nonpolar organic and perfluorinated solvent. It is not a good solvent for dissolving polar biodegradable polymers, as it was reported that poly(L-lactide) was not completely soluble in pure CO_2 at pressures as high as 800 bar and at temperatures up to 100 °C.[14] On the other hand, chlorodifluoromethane is an excellent solvent for dissolving poly(L-lactide) and has been used as solvent in L-lactide polymerization under supercritical conditions.[15]

This paper will describe the study of L-lactide and ε-caprolactone copolymerization, using chlorodifluoromethane in

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supercritical conditions. This will be the first attempt to synthesize high molecular weight PLCL copolymers in chlorodifluoromethane as supercritical media.

Experimental

Materials. L-Lactide was purchased from Purasorb. Tin(II)-bis(2-ethylhexanoate) and $Sn(Oct)_2$ (Sigma-Aldrich, 99%) were purified by distillation under reduced pressure and dissolved in dry toluene. Caprolactone and toluene (Sigma-Aldrich) were also distilled prior to use. R22 (99 wt%) was purchased from Solvey Gas Co. Toluene was dried by refluxing over benzophenone-Na complex and distilled under a nitrogen atmosphere just prior to use. $CDCl_3$ (Aldrich, 99.5 atom % D) was used as received.

Polymerization Procedure in Supercritical R22. The experimental apparatus is schematized in Figure 1. Polymerization was conducted in a 40 mL stainless steel high-pressure cell equipped with a magnetic stirring bar and an electrical heating mantle. Lactide, caprolactone and $Sn(Oct)_2$ solution in toluene were added to the cell. The toluene was removed under vacuum. Before the reaction, the reactor was heated to 50 °C, and then purged with nitrogen for 5 min. The reactor was then connected to the R22 feed system and vacuumed again for 30 min. The reactor was filled with liquid R22 to 30 bar at 50 °C and then gradually heated to 130 °C to achieve a pressure of 250 bar. Polymerization was allowed to proceed for the predetermined times. After the polymerization, the reactor was cooled to room temperature. To quantify PLCL conversions, the product was dissolved in choloroform and the cell was rinsed with chloroform in order to dissolve traces of the polymer and monomer. Both chloroform solutions were then poured into a large volume of cold methanol. The precipitated PLCL was recovered by filtration and dried under vacuum at room temperature. The monomer conversion was determined gravimetrically.

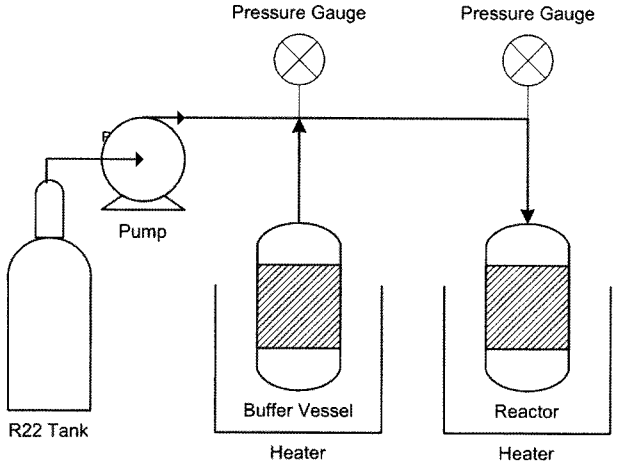

Figure 1. Supercritical polymerization instrument system.

Determination of Molar Masses (M_n) and Polydispersity Indexes (M_w/M_n). The molecular weight (M_n) and molecular weight distribution (M_w/M_n) were determined by gel permeation chromatography using a Viscotek GPC-System equipped with a pump and a degasser (GPCmax VE2001, flow rate 1.0 mL/min), RI detector (302 TDA). The column was eluted with $CHCl_3$ (flow rate of 1.0 mL/min at 30 °C) and calibrated with polystyrene standards over an M_n range of 1,000-350,000.

NMR Measurements. ^1H NMR spectra were measured in $CDCl_3$ at room temperature using a Varian Unity Plus 200 MHz spectrometer. TMS was used as an internal reference.

Results and Discussion

General Properties of the Polymer Product. ^1H NMR spectrum of PLCL showed signals at δ 1.57 (CH_3, PLA), δ 5.1 (CH, PLA), δ 1.35-1.67 ($CH_2CH_2CH_2$, PCL), δ 2.3 (CH_2CO, PCL), and δ 4.03 (CH_2O, PCL) as a characteristic of PLCL. The NMR spectrum is shown in Figure 2. The LA/CL ratio in the copolymers was calculated using the integration ratio of peaks at 5.1 ppm for the LA unit and at 2.3 ppm for the CL unit and was found to be similar to the feed ratio of the monomers. This is comparable to our previous study on multiblock copolymerization of PLCL in bulk system.[13] The thermal properties of PLCL thermogravimetry and differential scanning calorimetry analysis are shown in Figure 3. DSC thermogram showed a melting point of 145 °C. TGA showed a single step weight loss at 340 °C. The typical GPC diagram of PLCL is shown in Figure 4. The retention volume is at 14.96 mL.

Effect of Polymerization Time. A series of L-lactide and ε-caprolactone polymerizations initiated by $Sn(Oct)_2$ (Monomer to catalyst ratio ($[Mo]_0/[Sn]_0$ = 198)) were carried out in scR22 at 130 °C and 250 bar. The initial monomer concentration of LA to CL ratio was constant at 2:1. The results are shown in Table I. The highest molecular weight was achieved at 10 h reaction time, while the monomer conversion was relatively stable at temperature above 5 h. However, a further increase in the polymerization time, up to 15 h, resulted in lower molecular weight although there was only a slight

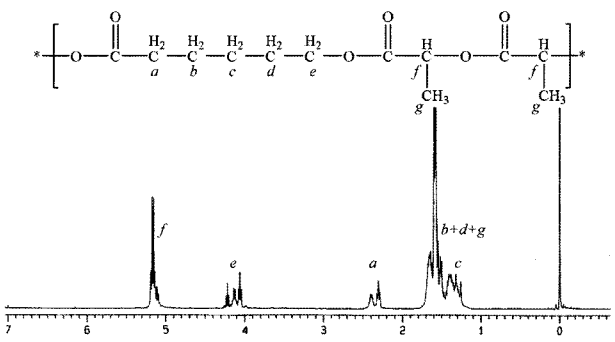

Figure 2. ^1H NMR spectrum of PLCL in $CDCl_3$.

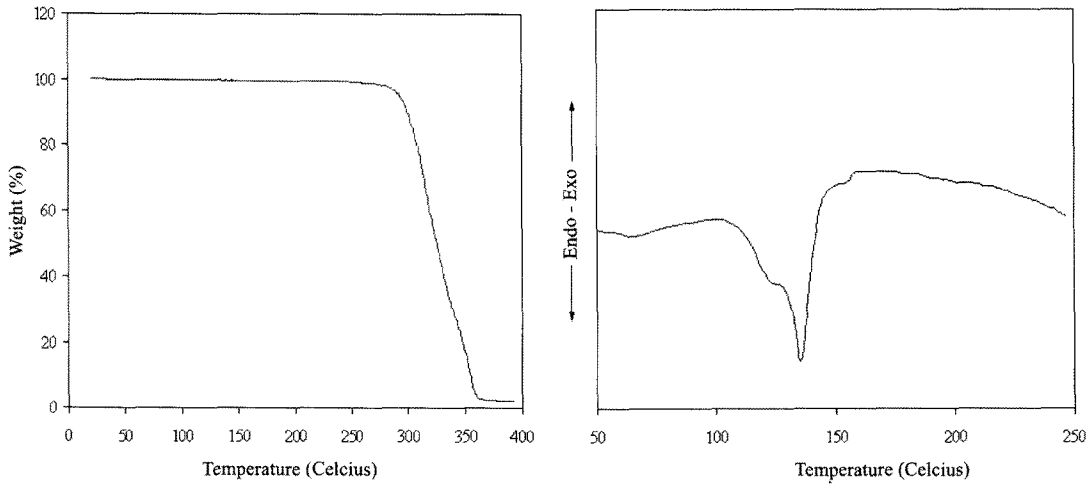

Figure 3. TGA and DSC diagram of PLCL.

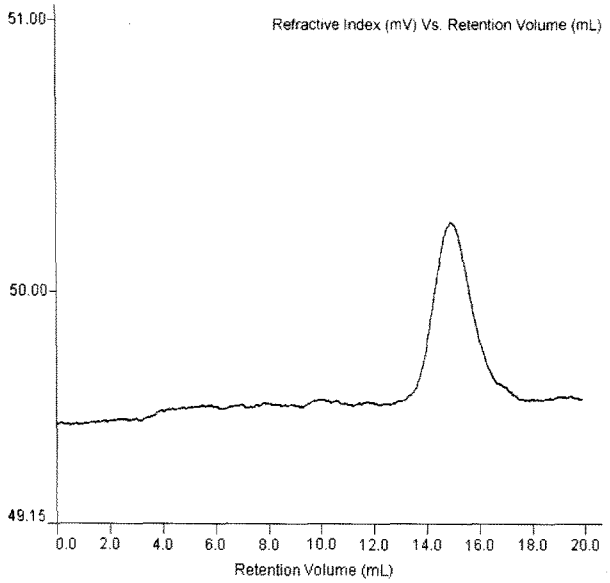

Figure 4. GPC diagram of PLCL.

decrease in the monomer conversion and caprolactone content. Prolonged reaction time at a high temperature is an important factor, leading to the degradation of PLCL, as it is known, PLCL is an easily degradable polymer material. Another factor is probably due to that the transesterification side reaction in the polymerization as it intensifies over a prolonged time.[16] The prolonged reaction time was also reported to cause the decrease of M_n in lactide polymerization.[17,18] The maximum conversion of 76% can be obtained after 10 h of reaction time. Over that same period, the polymer composition can also get the exact number as the monomer ratio. The small amount of the caprolactone content attained in the short reaction time is due to the low reactivity of the caprolactone in comparison with the lactide monomer.

Effect of Temperature. The effect of temperature on the monomer conversion and PLCL molecular weight was investigated in a series of polymerizations conducted at temperatures ranging from 90 to 170 °C and at a constant pressure of 250 bar. The results are shown in Table II. Increasing the reaction temperature from 90 to 130 °C resulted in an increased molecular weight of the resulting product from 55,300 to 76,200 g · mol^{-1}. However, a further increase in the polymerization temperature to 150 °C resulted in a slightly reduced molecular weight to 62,200 g · mol^{-1}. Due to the low reactivity of the caprolactone, the caprolactone content on the polymer product showed lower value at low temperature. While at higher temperature, the caprolactone content is relatively high. When 170 °C was employed, the product color changed to brownish and conversion went down to zero.

An optimum temperature is needed for the solvent to be at a certain point where it can dissolve the reactant. A low temperature will increase the viscosity of the polymerization system which reduces the activity of the macromolecular propagation of the species. On the other hand, a high

Table I. Results of the Copolymerization of L-Lactide and ε-Caprolactone at Various Times, 250 bar and 130 °C, $[Mo]_0/[Sn]_0$=198, Monomer to Solvent Weight Ratio=0.84

Time (h)	Feed (mol %)		Polymer Product (mol %)		Conversion (%)	$M_n \times 10^{-3}$ (g.mol^{-1})	M_w/M_n
	L	CL	L	CL			
1	66.7	33.3	80.6	18.5	56	53.9	1.43
3	66.7	33.3	70.2	28.5	66	59.9	1.70
5	66.7	33.3	68.5	31.0	73	70.0	1.55
10	66.7	33.3	64.9	35.0	76	75.9	1.65
15	66.7	33.3	67.0	33.0	70	48.6	1.67

Table II. Results of the Copolymerization of L-Lactide and ε-Caprolactone at Various Temperatures, 250 bar and 10 h, $[Mo]_0/[Sn]_0$=200, Monomer to Solvent Weight Ratio=0.84

Temperature (°C)	Feed (mol %)		Polymer Product (mol %)		Conversion (%)	$M_n \times 10^{-3}$ (g.mol^{-1})	M_w/M_n
	L	CL	L	CL			
110	66.7	33.3	73.9	26.1	66.5	55.3	1.72
130	66.7	33.3	66.9	33.1	80.2	76.2	1.78
150	66.7	33.3	67.8	32.2	78.6	62.2	1.75

Table III. Results of the Copolymerization of L-Lactide and ε-Caprolactone at Various Monomer Concentrations, with 250 bar, 130 °C and 10 h, $[Mo]_0/[Sn]_0$=200

Monomer to Solvent Weight Ratio	Feed (mol %)		Polymer Product (mol %)		Conversion (%)	$M_n \times 10^{-3}$ (g.mol^{-1})	M_w/M_n
	L	CL	L	CL			
0.35	66.7	33.3	77.5	22.5	58.9	60.6	1.50
0.48	66.7	33.3	70.8	29.2	77.5	68.8	1.65
0.62	66.7	33.3	67.0	33.0	75.3	73.3	1.60
0.84	66.7	33.3	66.9	33.1	80.2	76.2	1.78
1.10	66.7	33.3	68.5	32.5	84.3	86.4	1.68
1.34	66.7	33.3	66.8	33.2	82.4	82.3	1.72
2.68	66.7	33.3	76.8	23.2	79.1	64.4	1.78

temperature intensifies the possible occurrence of intermolecular and intramolecular transesterification, 'backbiting' of the active chain-end that causes degradation and formation of cyclic oligomers, which, consequently, may produce a decrease in molecular weight.[19] This also may be due to thermal depolymerization reactions and catalyst instability at the elevated temperature of 150 °C for 10 h in scR22. Such reductions in M_n and monomer conversion were consistent with previous research on lactide polymerization,[18,20] and another study on lactone polymerization.[21] The optimum temperature commonly used in bulk copolymerization is 130 °C.[22]

Effect of Monomer Concentrations. Monomer concentration is defined by monomer-to-solvent weight ratio. The ratio was varied from 0.35 to 2.68 in order to investigate the effect of the monomer concentration upon the PLCL produced. The results are shown in Table III. Increased monomer content resulted in an increase of the polymer molecular weight and achieved highest molecular weight at a monomer-to-solvent ratio of 1.10. When the monomer content was increased, the monomer conversion and the M_n of PLCL gradually increased to 84% and 86,400 g.mol^{-1}, respectively. Thus, this series of experiments showed that the monomer conversion and the PLCL molecular weight depended on the R22 concentration. This could be explained by the intermolecular interaction between the solvent and the propagating active species. There should be preferential solvation of the tin alkoxide by R22, thereby increasing the solvent concentration at the tin alkoxide. Increased scR22 concentration and/or decreased monomer concentration made the competing interaction between the monomer and R22 for coordination of the tin alkoxide shift in favor of the R22-tin alkoxide coordination.[20] As a consequence, the hindered nucleophilic attack of the monomer on the tin-alkoxide would lead to a low degree of polymerization. The molecular weight distribution also increased upon increasing the monomer concentration. However, at a monomer-to-solvent ratio of 2.68, M_n decreased due to the small amount of solvent involved in the reaction. This will cause low solubility of the monomer and less solvating power of R22. The low solvent concentration will also result in low caprolactone content in the polymer product.

Effect of Catalyst. The effects of the $Sn(Oct)_2$ catalyst concentration on the monomer conversion and the PLCL molecular weight were investigated in a series of polymerizations conducted at various catalyst concentrations. The experiments were carried out in scR22 at 130 °C and 250 bar, where variation was applied on the monomer-to-catalyst ratio. The initial monomer concentration of LA to CL ratio was constant at 2:1. Results are summarized in Table IV.

When the initial $Sn(Oct)_2$ concentration increased from a monomer-to-catalyst ratio of 125 to 200, M_n of PLCL also increased from 70,400 to 76,200 g.mol^{-1}. A typical coordination insertion mechanism, which usually occurs for lactide polymerization with $Sn(Oct)_2$ as the catalyst, has been assumed; this involves a covalent tin alkoxide bond formation and cleavage of the lactone acyl-oxygen bond.[23-26] This catalyst system was also known for its use as an initiator in polymerization of ε-caprolactone.[27-29] As previously stated, $Sn(Oct)_2$ also has interaction with the solvent, which is a coordinative bond between alkoxide and R22.[18,30] The competition between monomer and solvent for coordination to alkoxide required more catalyst to be applied in this system. From Table IV, we can see that the less catalyst applied to the reaction, the more difficult for caprolactone to polymerize. It is known that ε-caprolactone is less reactive in bulk system polymerization using $Sn(Oct)_2$ compared to L-lactide.[31,32] It

Table IV. Results of the Copolymerization of L-Lactide and ε-Caprolactone at Various Catalyst Concentrations, with 250 bar, 130 °C and 10 h, Monomer to Solvent Weight Ratio=0.84

Molar Ratio	Feed (mol %)		Polymer Product (mol %)		Conversion (%)	$M_n \times 10^{-3}$ (g.mol^{-1})	M_w/M_n
Monomer/Catalyst	LA	CL	LA	CL			
125	66.7	33.3	66.7	33.3	60.1	56.2	1.95
175	66.7	33.3	67.0	33.0	79.2	60.3	1.90
200	66.7	33.3	66.9	33.1	80.2	76.2	1.78
250	66.7	33.3	75.3	24.7	78.4	75.6	1.83
400	67.7	33.3	84.6	15.4	79.8	73.3	1.86
500	66.7	33.3	87.5	12.5	80.0	72.5	1.67
800	66.7	33.3	88.0	12.0	79.1	70.4	1.64

is also known in another system with a different catalyst, such as diphenylzinc, the ε-caprolactone conversion rate is much lower, and will be copolymerized after most L-lactide is depleted.[33] On the other hand, there is an increase in molecular weight by decreasing the catalyst content. This phenomenon is mostly due to the formation of polylactide.

Conclusions

Polymerization of L-lactide-ε-caprolactone can be successfully synthesized in supercritical chlorodifluoromethane. The copolymers produced have a maximum molecular weight of 86,400 g.mol^{-1}. The optimum conditions of this study are a reaction time of 10 h, and a temperature of 130 °C, which is the common temperature used in bulk copolymerization system. This work will open possibilities to utilize supercritical technology in synthesizing biodegradable copolymers.

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