High Molecular Weight Poly(L-lactide) and its Microsphere Synthesized in the Supercritical Dimethyl Ether

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Summary: The ring-opening polymerization of L-lactide initiated by stannous octoate was carried out in supercritical dimethylether(scDME) at various reaction conditions (time and temperature). The monomer conversion increased to ca. 90% on increasing the reaction time to 1hr. The molecular weight of the poly(L-lactide)(PLLA) also increased to ca. 160,000 $g \cdot mol^{-1}$ over the same period. Increasing reaction temperature from 118 to 135 °C or reaction pressure from 280 to 520 bar resulted in increased monomer conversion and molecular weight. After the polymerization, PLLA microspheres were prepared in situ by using a continuous supercritical anti-solvent process without residual organic solvent.

Keywords: DME; microsphere; PLLA; polymerization; supercritical fluid

Introduction

Much attention has been placed on the use of supercritical fluids as solvents in a variety of polymer processes including extractions, separations, fractionations, particle formations, and other reactions. Interest stems primarily from the ability to change the bulk properties of supercritical fluids (e.g., density and solubility) dramatically with small variations in temperature and pressure such that supercritical fluids have liquidlike dissolving power while exhibiting the transport properties of a gas.[1–5] For example, the use of supercritical carbon dioxide ($scCO_2$) as a solvent for polymerization is attractive because of its low toxicity and cost. Also, $scCO_2$ is a viable 'green' alternative and can be removed without trace.

Lactic acid derived from agricultural products by fermentation is nontoxic and harmless to animals, plants, and human beings. Moreover, polylactides, the polymers of lactic acid, have significant applications in the environmental and medical fields.[6–11] However, stringent requirements must be fulfilled before a polymer can be used for biomedical applications. The purity of the polymer product is of concern, because residual monomers, catalysts, and solvents pose risks when such materials are in contact with biological fluids or tissues.[12] The solution polymerization of L-lactide (L-LA) in regular hydrocarbon solvents, such as methylene chloride, chlorobenzene, benzene, or toluene, is not favored because these solvents must be thoroughly removed before use. In addition, when poly (L-lactide) (PLLA) is synthesized by the ROP of L-LA, it is almost inevitable that the polymer obtained contains residual monomer, which was reported to enhance polymer hydrolytic degradation.[13] In this respect, the production of polylactides under solvent-free conditions, combined with the possible extraction of residual monomer, by using processes like the supercritical antisolvent (SAS) recrystallization process,[14] shows great promise. Therefore, the use of supercritical fluids

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as a solvent for polymerization is attractive because of its low toxicity and need not collect.

Production and application of dimethyl ether (DME) have attracted the attention of many researchers in the past years due both to environmental protection and to the increased price of crude oil. DME and fluoro-dimethyl ether are environmentally friendly aerosol sprays and green refrigerants because of their zero ozone depletion potential (ODP) and their lower globe warming potential (GWP) compared with the traditional chlorofluorocarbons (CFCs, Freon) and newer R-134a (HFC-134a).[15–19]

In this study, we prepared high molecular weight PLLA using scDME as polymerization media. PLLA microspheres were prepared in situ by using a continuous supercritical anti-solvent process without residual organic solvent. Also, the effects of reaction conditions (time and temperature) and reactant concentrations (initiator, monomer, and solvent) on monomer conversion and PLLA molecular weight, in the stannous octoate initiated polymerization of L-LA in scDME were investigated.

Experimental Part

Materials

L-Lactide (L-LA) was purchased from Purac Biochem BV (Gorinchem, The Netherlands). It was recrystallized from ethyl acetate and dried in a vacuum (0.2 mmHg) over P_4O_{10}. Tin(II)bis(2-ethylhexanoate) ($Sn(Oct)_2$) (Sigma Chemical Co., St. Louis, MO, 99%) and 1-dodecanol (DoOH) (Aldrich, 99.5%) were purified by distillation under reduced pressure and dissolved in dry toluene. DME was purchased from the Messer Griesheim Co. and had a certified purity of 99.9%, and used as received. Toluene was dried by refluxing over the benzophenone-Na complex and distilled in a nitrogen atmosphere just prior to use. $CDCl_3$ (Aldrich, 99.5 atom % D) was used as received.

Polymerization

The polymerization apparatus is shown in Figure 1. Polymerization was conducted in a 52 mL stainless steel high–pressure cell equipped with a magnetic stirring bar and an electrically heating mantle. L-LA (6.0 g), DoOH solution (0.019 mL of a 1.07 M solution in toluene; 2.0×10^{-5} mol of DoOH), and $Sn(Oct)_2$ solution (0.25 mL of a 0.20 M solution in toluene; 6.2×10^{-5} mol of $Sn(Oct)_2$) were added to the cell. The toluene was removed under vacuum, the reactor heated to 50 °C, and purged with nitrogen for 5 min. When the reactor was cooled to room temperature, it was evacuated for 2 h using a liquid nitrogen cooled trap and then purged with nitrogen for an additional 10 min. The cell was then disconnected from the nitrogen line, evacuated, and connected to the DME feed system. The cell was filled with liquid DME to ca. 50 bar at 50 °C by using an air-driven gas compressor (Maximator Schmidt Kranz & Co. GmbH) and then gradually heated to 130 °C to achieve a pressure of 400 bar. Polymerization was allowed to proceed for the predetermined times. After the polymerization, the reactor was cooled to room temperature, and DME was vented through a needle valve into chloroform in order to collect both unreacted monomer and polymer. To quantify L-LA conversions, the cell was rinsed with chloroform in order to dissolve traces of polymer and monomer. Both chloroform solutions were then poured into a large volume of cold methanol. The precipitated PLLA was recovered by filtration and dried under vacuum at room temperature. Monomer conversion was determined gravimetrically.

Preparation of PLLA particles

The experimental apparatus used for the supercritical antisolvent precipitation process is shown in Figure 2. It consists of a CO_2 supply system, a polymerized solution feeding system, a precipitator with injector, filters, a pressure regulator, and a gas-liquid separation section. Carbon dioxide was compressed using a high-pressure metering pump (Milton Roy, U.S.A) and

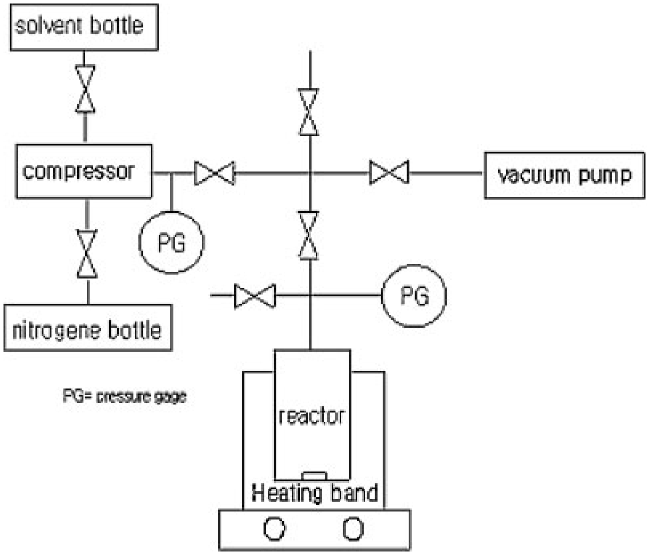


Figure 1.
Polymerization apparatus.

fed into the side of the precipitator vessel (Jerguson Gage, 34 mL) as a continuous phase; its temperature and pressure were maintained at 40 °C and at 100 bar using a PID temperature controller and a back-pressure regulator (Tescom; 26-1721-24). After a steady state CO_2 flow rate of 8 $L \cdot min^{-1}$ had been achieved, the reaction mixture containing polymers and unreacted monomers in DME was pumped using another high-pressure metering pump (Milton Roy, U.S.A) into the precipitator through a nozzle (stainless steel, 0.03″ I.D., 1/16″ O.D.) at a flow rate (0.30 mL/min). The nozzle was mounted on the top of the precipitator to introduce the solution as dispersed liquid droplets into the CO_2 antisolvent. Upon injection into the precipitator, PLLA particles were formed and a fluid mixture of CO_2 and DME including

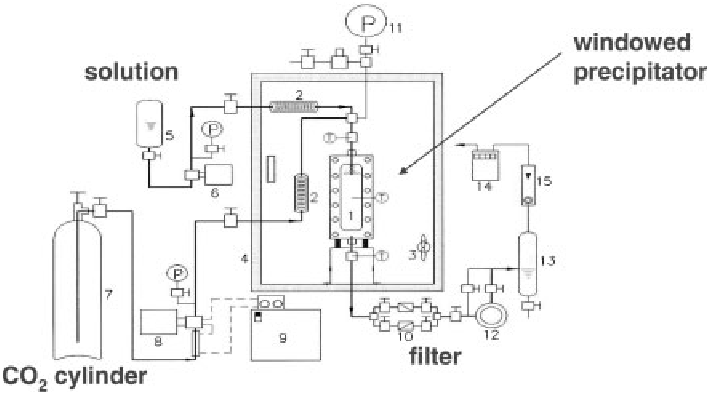


Figure 2.
Scheme of the apparatus used for preparation of PLLA microsphere: 1. precipitator 2. preheater 3. fan 4. bath 5. solution 6. solvent Feed Pump 7. CO_2 cylinder 8. CO_2 Feed Pump 9. Circulator 10.Filter 11. Pressure Gauge 12. Back Pressure Regulator 13. Separator 14. Gasmeter 15. Flowmeter.

unreacted monomers flowed out of the precipitator. To remove residual solvent and unreacted monomer from the recrystallized particles, the precipitator was filled with CO_2 for several minutes, and the PLLA particles were collected on filters (tee-type filter, 0.5 μm), which were located between the precipitator and the back-pressure regulator.

These filters were situated on both sides using a tee-type union in order to avoid sudden pressure reductions in the precipitator and to investigate continuous experiment. The line from the back-pressure regulator to the depressurizing tank was heated by electrical band heaters to prevent freezing due to adiabatic CO_2 expansion.

The effluent mixture was depressurized and allowed to expand to atmospheric pressure as it passed through a depressurizing tank (SUS 316; 300 mL). The instantaneous and the accumulated flow rates of CO_2 were measured using a rotameter (Metheson 604 SUS ball, U.S.A) and a dry gas meter (Taekwang Energy S/T-3, Korea), respectively.

Polymer Characterization

Mv of the PLLA was determined from the intrinsic viscosity in chloroform at 25 °C by using the following equation.

$$[\eta] = 4.41 * 10^{-4} MV^{0.72}$$

^1H NMR spectra were recorded at 25 °C using a Varian Unity Plus 300 MHz spectrometer in $CDCl_3$. Morphological evaluations of the microparticles were conducted by scanning electron microscopy (SEM) (HITACHI S-4200).

Results and Discussion

Effect of Time

A series of L-LA polymerizations initiated by $Sn(Oct)_2$ ($[LA]_0/[Sn]_0 = 1000$) were carried out in scDME at 130 °C and 380 bar, where $[LA]_0$ is the initial L-lactide concentration and $[Sn]_0$ is the initial $Sn(Oct)_2$ concentration. The reaction time dependences of monomer conversion and PLLA MW growth are shown in Figure 3. The monomer conversion increased to ca. 90% on increasing the reaction time to 30 min. The molecular weight of the product also increased to ca. 160 000 g/mol over the same period. However, a further increase in the polymerization time to 1 h had little effect on either monomer conversion or on PLLA MW.

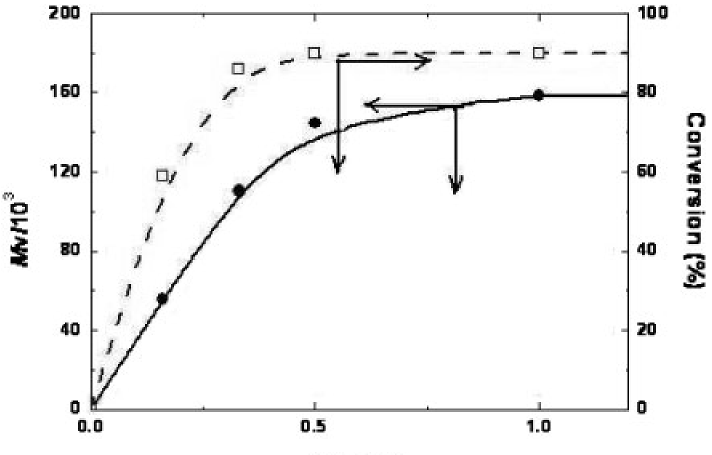


Figure 3.
Relation between monomer conversion (□) and poly(L-lactide) molecular weight (●) by viscometer at different times. Polymerization condition: $[LA]_0 = 1.54$ mol/L, $[LA]_0/[Sn]_0 = 1000$, at 130 °C and 380 bar in supercritical DimethylEther.

Table 1.
Molar ratios, and molecular weights for the polymerization of L-LA initiated by $Sn(Oct)_2$ in ScDME at Various Temperatures.

Entry	*T* °C	Time (hr)	*Mv*/10^3 (g/mol)	conversion (%)
1[a)]	110	1	–	–
2	118	1	161.0	84.4
3	125	1	161.0	87.1
4	135	1	158.0	87.1
5	145	1	110.0	84.2
6	155	1	71.0	81.9

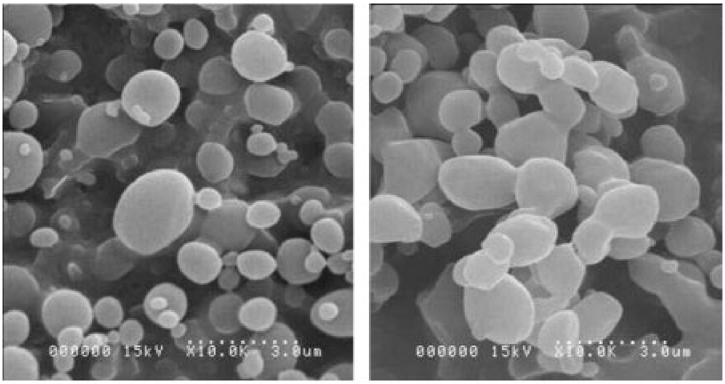
Reaction carried out at 380 bar using $[LA]_0/[Sn]_0 = 2000$. $C_{LA}/C_{DME} = 26\%$. $[LA]_0$ is the initial L-lactide concentration, $[Sn]_0$ is the initial $Sn(Oct)_2$ concentration;
a) Oligomer obtained.

Effect of Temperature

The effect of temperature on monomer conversion and PLLA MW was investigated in a series of polymerizations conducted at temperatures ranging from 105 to 155 °C and at a constant pressure of 380 bar. In all of these experiments, the ratio of monomer to DME concentration was held constant at 26%. Results are summarized in Table 1. Increasing the reaction temperature from 118 to 135 °C resulted in increased monomer conversion from 82.4 to 87.1%. The MWs of the resulting product also increased from 141 000 to 161 000 g/mol over the same temperature range. However, a further increase in the polymerization temperature to 155 °C resulted in a slightly reduced monomer conversion and MW to 81.9% and 71 000 g/mol, respectively. This may have been due to thermal depolymerization reactions and catalyst instability at the elevated temperature. Such reductions in MW and monomer conversion were consistent with the thermal degradation, described elsewhere for $Sn(Oct)_2$ catalyzed lactone polymerization.[20] Teyssié et al.[21] observed similar MW limitation behavior in aluminum isopropoxide initiated polymerization of lactides in toluene. They attributed their result to inter- and intramolecular transesterification reactions at higher temperature. The MWD was rather narrow at low temperature, but increased as the temperature increased.

Preparation of PLLA Microspheres

After the polymerization, the DME solution, containing polymer and unreacted monomer, was atomized in a high-pressure precipitator vessel, which was swept with CO_2 antisolvent at 0.7 kg/hr; 35 °C and 100 bar, through a nozzle at 55.2 mL/hr. Upon injecting the mix into the precipitator, PLLA particles were formed and a mixture of CO_2 and DME, including unreacted monomers, flowed out of the precipitator. To remove residual solvent and unreacted monomer from the recrystallized



100 bar 200 bar

Figure 4.
SEM photographs of Poly(L-lactide) microspheres prepared at 35 °C, 1.0 wt/wt%(PLLA+DME), 0.03″ nozzle diameter, 55.2 mL/min solution flow rate, and 0.7 kg/hr CO_2 flow rate.

particles, the precipitator was filled with CO_2 for several minutes. Typical ^1H NMR spectra for the PLLA synthesized before and after the SAS process suggested that residual monomers were removed efficiently by the SAS process.

Since both DME and CO_2 are gases at normal pressure, it is expected that very little residual solvent remained in the PLLA microspheres. Nevertheless, we measured residual solvent by gas chromatography using the headspace method,[22] but found no solvent in the PLLA microspheres at the ppb level. Most of the particles were found to be spherical and to have a smooth surface (see Figure 4). Mean particle sizes fell in the range about 0.1–2 μm at a precipitator pressure of 100–200 bar. Therefore, PLLA microspheres can be prepared directly without residual organic solvent and monomer to yield highly purified microspheres for environmental and biomedical applications.

Conclusions

Supercritical DME can be successfully utilized as a solvent for the ring-opening polymerization of L-LA, and the following in situ preparation of PLLA microspheres, without any residual monomer and solvent, by using a continuous supercritical anti-solvent process. The monomer conversion increased to ca. 90% on increasing the reaction time to 1hr. The molecular weight of the poly(L-lactide)(PLLA) also increased to ca. 160,000 $g \cdot mol^{-1}$ over the same period. Increasing reaction temperature from 118 to 135 °C or reaction pressure from 280 to 520 bar resulted in increased monomer conversion and molecular weight. Most of the prepared PLLA particles were found to be spherical and to have a smooth surface. Mean particle sizes fell in the range about 0.1–2 μm at a precipitator pressure of 100–200 bar. Therefore, this process presents advantages compared to the traditional polymerization in organic solvents or in $scCO_2$ for preparing PLLA microspheres.

[1] J. A. Pratt, S. H. Lee, M. A. McHugh, *J. Appl. Polym. Sci.* **1993**, *49*, 953.

[2] X. Zhao, R. Watkins, S. W. Barton, *J. Appl. Polym. Sci.* **1995**, *55*, 773.

[3] J. H. Kim, T. E. Paxton, D. L. Tomasko, *Biotechnol. Prog.* **1996**, *12*, 650.

[4] R. Bodmeier, H. Wang, D. J. Dixton, S. Mawson, K. P. Johnston, *Pharm. Res.* **1995**, *12*, 1211.

[5] L. Benedetti, A. Bertucco, P. Pallado, *Biotechnol. Bioeng.* **1997**, *53*, 232.

[6] R. Langer, *Science* 1990, *249*, 1527.

[7] U.S Patent 6,509,440, (**2003**), M. Sakane, M. Nakai, K. Shimizu, Y. Kajikawa, M. Ito.

[8] J. W. Pack, S. H. Kim, S. Y. Park, Y. W. Lee, Y. H. Kim, *Macromolecules* **2003**, *36*, 7884.

[9] J. W. Pack, S. H. Kim, S. Y. Park, Y. W. Lee, Y. H. Kim, *Macromolecules* **2003**, *36*, 8923.

[10] J. W. Pack, S. H. Kim, S. Y. Park, Y. W. Lee, Y. H. Kim, *Macromolecules* **2004**, *37*, 3564.

[11] J. W. Pack, S. H. Kim, S. Y. Park, Y. W. Lee, Y. H. Kim, *Macromol. Biosci.* **2004**, *4*, 340.

[12] N. A. Peppas, R. Langer, *Science* **1994**, *263*, 1715.

[13] S.-H. Hyon, K. Jamshidi, Y. Ikada, *Polymer International* **1998**, *46*, 196.

[14] T. W. Randolph, A. D. Randolph, M. Mebes, S. Yeung, *Biotechnol. Prog.* **1993**, *9*, 429.

[15] B. Herman, *Aerosol Spray Rep.* **1994**, *33*, 385.

[16] S. Bobbo, R. Camporese, *J. Chem. Thermodynam.* **1998**, *30*, 1041.

[17] D. B. Bivens, B. H. Minor, *Int. J. Refrig.* **1998**, *21*, 567.

[18] D. A. Good, Y. Li, J. S. Francisco, *Chem. Phys. Lett.* **1999**, *313*, 267.

[19] M. He, H. Li, T. Li, J. Wu, Z. Liu, *J. Xi'an Jiaotong Univ. (Chn.)* **2003**, *37*, 10.

[20] J. W. Pack, S. H. Kim, I.-W. Cho, S. Y. Park, Y. H. Kim, *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 544.

[21] Ph. Dubois, C. Jacobs, R. Jérôme, Ph. Teyssié, *Macromolecules* **1991**, *24*, 2266.

[22] A. L. Theis, A. J. Waldack, S. M. Hansen, M. A. Jeannot, *Anal. Chem.* **2001**, *73*, 5651. S. Zilker, *J. Chem. Phys. Chem.* **2000**, *1*, 72.