

초임계 유체에서 L-Lactide의 Scale-up 중합

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Scale-up Polymerization of L-Lactide in Supercritical Fluid

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초록: 초임계 유체에서 poly(L-lactide) (PLLA)의 산업화 생산 공정 개발을 위한 예비 연구로, 1-dodecanol/stannous 2-ethyl-hexanoate (DoOH/Sn(Oct)₂)를 개시제로 하여 chlorodifluoromethane 초임계 용매 하에서 락티드의 개환 중합을 실시하였다. 중합은 3 L 반응기를 사용하였으며 중합시간, 온도, 압력 및 단량체와 초임계 용액 농도에 따른 중합 거동을 관찰하였다. 중합시간이 5시간 경과할 경우 얻어진 중합체의 반응 수율 및 분자량은 각각 72%, 68000 g/mol 이었다. 단량체의 농도가 증가할수록 중합체의 수율 및 분자량은 증가하였으며 최대 각각 97%, 144000 g/mol이 얻 어졌다. 반응기의 압력이 130에서 240 bar로 증가할 경우 PLLA의 수율 및 분자량이 증가하였다. 얻어진 중합체의 열 안정성을 향상시키기 위해 메탄올 처리 및 진공 처리를 실시하였다. 그 결과 두 가지 방법 모두 PLLA의 열안정성을 향상시켰다.

Abstract: For the purpose of the pre-industry production of poly(L-lactide) (PLLA) and full understanding of the supercritical polymerization system, large scale polymerization of L-lactide initiated by 1-dodecanol/stannous 2-ethyl-hexanoate (DoOH/Sn(Oct)₂) was carried out in supercritical chlorodifluoromethane under various reaction conditions (time, temperature and pressure) and reactants (monomer and supercritical solvent) concentrations. A 3 L sized-reactor system was used throughout this study. The monomer conversion increased to 72% on increasing reaction time to 5 h. The molecular weight of PLLA product also increased to 68000 g/mol over the same period. An increase in monomer concentration resulted in a higher molecular weight, up to 144000 g/mol and 97% of monomer conversion. Raising the reaction pressure from 130 to 240 bar also resulted in an increased monomer conversion and molecular weight. To increase heat resistivity of PLLA, methanol treatment and heat-vacuum methods were evaluated. Both of them successfully improved the heat resistivity property of PLLA.

Keywords: large scale polymerization, polylactide, supercritical fluid.

Introduction

Lactic acid derived from agricultural products by fermentation is nontoxic and harmless to animals, plants, and human beings. Poly(L-lactide) (PLLA) is an environmentally friendly-biodegradable material which recently gains much attention because of its widely application in biomedical fields such as carriers for drug delivery, absorbable sutures and scaffolds for tissue engineering.¹

Supercritical fluids have been utilized successfully in polymer development.^{2-5,15} Because of the simple and complete

removal from the polymer product, supercritical fluid was used as solvent in this study. This is a very important factor for the application of the polymer in the biomedical fields. One of the highlights of the supercritical fluids character is that these fluids may have the solubility of liquid and diffusivity of gas. Diffusion of material in supercritical fluid occurs more rapidly than in organic liquid solvents because supercritical fluids has a higher diffusion coefficient than liquid state solvents. Physical properties of supercritical fluids are also unique in comparison with other solvent. At supercritical state, the possibility to tune physical properties (such as density, viscosity, diffusivity and polarity) is wide open by adjusting only temperature and pressure compared to that of organic

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solvents.

Reports that supercritical chlorodifluoromethane (scR22) can be successfully utilized as homogeneous solvent for ring-opening polymerization of L-lactide (L-LA) have been published elsewhere.⁶⁻⁸ However, large scale production of PLLA was barely achieved, because of the complicated design of the polymerization system. Thus, the objective of this research was to produce PLLA of high molecular weight and furthermore to develop an optimized procedure to scale-up from laboratory scale (40 mL reactor volume) to 3 L mini-plant scale.

The last part of this paper discussed about the purification method for the PLLA product to improve its heat resistivity. Methanol recrystallization method is the most common method used for PLLA, which is technically simple but is not preferred for the bio-related field due to the use of organic solvent. Thus this method was compared with heat and vacuum treatment methods. Another solvent option for PLLA crystallization is water-ethyl acetate.⁹ While the more complex one is melt crystallization method for PLLA crystal formation and purification.¹⁰

Experimental

Materials. Large scale polymerization system of L-LA in supercritical fluid was conducted based on our earlier study on small scale reaction system.⁷ Thus for comparison with the previous study, all the materials; R22 as supercritical fluid, and Tin(II)bis(2-ethylhexanoate) ($\text{Sn}(\text{Oct})_2$)/1-dodecanol (DoOH) as initiator, was identical with the previous study.⁷

L-LA was purchased from Purac. $\text{Sn}(\text{Oct})_2$ (Sigma Chemical Co., St. Louis, MO, 99%) and DoOH (Aldrich, 99.5%) were purified by distillation under reduced pressure and dissolved in dry toluene. R22 was purchased from Foosung 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.

Large Scale Polymerization Procedure. The polymerization apparatus is shown in Figure 1. This apparatus design was based on our small scale system.⁷ The buffer vessel was omitted in the large scale system for more efficient solvent use. Thus R22 was pumped directly to the reactor chamber, then heated up to the desired temperature. The reactor itself is a 3 L stainless steel high-pressure cell equipped with a magnetic stirring system and an electrically heating mantle.

L-LA (200 g), DoOH solution (20 mL of a 0.11 M solution in toluene; 2.2×10^{-3} mol of DoOH), and $\text{Sn}(\text{Oct})_2$ solution (28.7 mL of 0.12 M solution in toluene; 3.5×10^{-3}

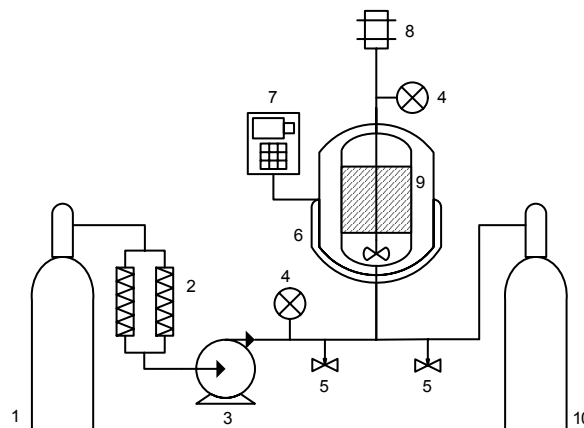


Figure 1. Polymerization apparatus: 1. R22 solvent tank, 2. water absorbent, 3. solvent feed pump, 4. pressure gauge, 5. valve, 6. heater, 7. heater controller, 8. electronic stirrer controller, 9. polymerization reactor, 10. nitrogen tank.

mol of $\text{Sn}(\text{Oct})_2$) were added to the reactor. Then toluene was removed under vacuum, the reactor was heated to 50 °C, and was purged with nitrogen for 10 min. The reactor was then disconnected from the nitrogen line and then connected to the R22 feed system. The reactor was filled with liquid R22 to 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 200 bar. Polymerization was allowed to proceed for the predetermined times. After the polymerization, the reactor was cooled to room temperature, and R22 was vented out through a needle valve. To quantify L-LA conversions, the product was dissolved in chloroform then poured into a large volume of methanol. The precipitated PLLA was recovered by filtration and dried under vacuum at room temperature. Monomer conversion was determined gravimetrically. Heat-vacuum treatment was used to purify the polymer product. The unpurified PLLA product was put in the vacuum chamber which was set at 10 torr, then heat was applied at 100 °C.

For kinetic study, a time based experiment was conducted with variation on reaction time, up to 300 min. The L-LA was fixed at 200 g with the addition of DoOH solution (2.2×10^{-3} mol of DoOH), and $\text{Sn}(\text{Oct})_2$ (3.5×10^{-3} mol). Pressure and temperature was constant at 200 bar and 130 °C, respectively.

Polymer Characterization. M_v of the PLLA was determined from the intrinsic viscosity in chloroform at 25 °C by using the following equation.¹¹

$$[\eta] = 4.41 \times 10^{-4} M_v^{0.72}$$

Heat resistivity of PLLA was analyzed isothermally at 200 °C by thermal-gravimetry analyzer (TGA) TA Instrument TGA-2950.

Results and Discussion

Effect of Time. A series of L-LA polymerizations initiated by $\text{Sn}(\text{Oct})_2$ were carried out in scR22 at 130 °C and 200 bar, where $[\text{LA}]_0$ is the initial L-LA concentration and $[\text{Sn}]_0$ is the initial $\text{Sn}(\text{Oct})_2$ concentration.

The reaction time dependences of monomer conversion and PLLA molecular weight growth are shown in Figure 2. The monomer conversion increased to ca.70% on increasing the reaction time to 5 hrs. The molecular weight of the product also increased to ca.70000 g/mol over the same period. This result is comparable with our previous study using small scale polymerization system which also achieved optimum reaction time at 5 hrs.⁶ There is a slight decrease in conversion and molecular weight at 10 hrs of reaction time, most probably due to the thermal degradation of the PLLA product.

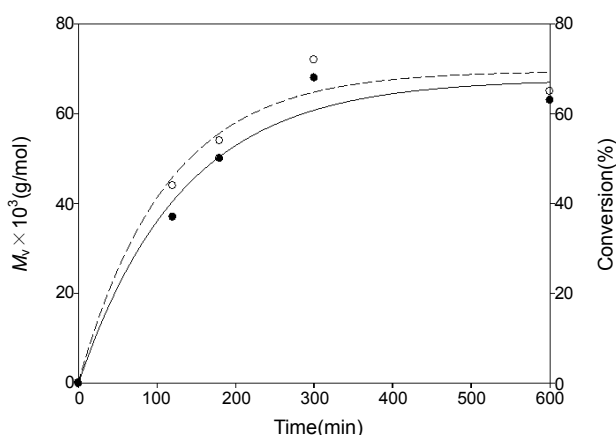


Figure 2. Relation between PLLA molecular weight (●) and monomer conversion (○) with polymerization time. Polymerization conditions: $C_{\text{LA}}=4$ wt%, $[\text{LA}]_0/[\text{Sn}]_0=200$, at 130 °C and 200 bar in scR22.

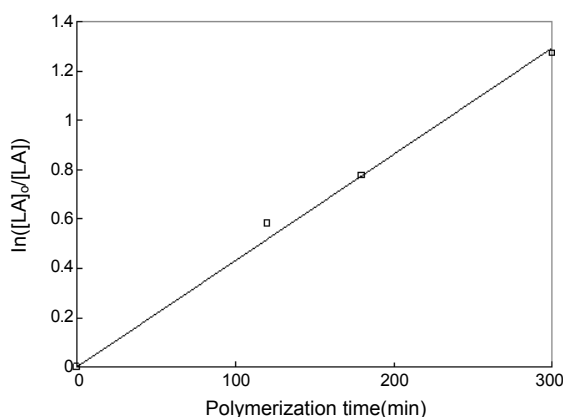


Figure 3. Plot for determining the rate constant of L-LA polymerization in supercritical chlorodifluoromethane initiated by tin(II) octoate at 130 °C under 200 bar with monomer concentration of 4 wt% and $[\text{LA}]_0/[\text{Sn}]_0=200$.

The kinetics of L-LA large scale polymerization was also studied. From Figure 3, the kinetic data and plots obtained for the $\text{Sn}(\text{Oct})_2$ -initiated polymerization produced a linear relationship in semi-logarithmic coordinates within experimental error, where $[\text{LA}]_0$ and $[\text{LA}]$ are the monomer concentrations at time zero (t_0) and t , respectively. Figure 3 also indicates that this large scale polymerization is a living process.

The relative polymerization rate constant is defined as

$$k_p = -d[\text{LA}]/([\text{LA}] dt) = \ln([\text{LA}]_0/[\text{LA}])/t$$

where, t denotes the polymerization time. The polymerization rate of $4.3 \times 10^{-3} \text{ min}^{-1}$ was achieved in this set of experiment. This result is comparable to the small scale polymerization of L-lactide.⁷ A continuous increase in the rate would be expected to happen if the higher monomer concentration is used.

Effect of Pressure. L-LA polymerizations initiated by $\text{Sn}(\text{Oct})_2$ were carried out at pressures ranging from 130 to 240 bar at a constant temperature of 130 °C. The results of this experiment were summarized in Table 1. In all of these experiments, the ratio of monomer (L-LA) to R22 was held constant at 4.

Increasing the reaction pressure from 130 to 240 bar resulted in increased monomer conversion from 56.3 to 75.1%. The molecular weight of the resulting product also increased from 43200 to 72000 g/mol over the same pressure range. The reaction pressure dependences of monomer conversion and PLLA molecular weight growth are shown in Table 1.

As previously studied,⁸ the polymerization of L-LA occurs with a negative volume of activation. The relation of pressure, volume of activation and rate constant is given by¹²

$$\left(\frac{d \ln k}{dP} \right)_T = \frac{-\Delta V^\ddagger}{RT}$$

Where $\Delta V^\ddagger$ is the volume of activation, i.e., the difference in the partial molar volumes (cm^3/mol) between reactants and the transition state. The negative volume of activation indicates that an increase in pressure causes an increase in

Table 1. Experimental Conditions and Results of L-LA Polymerizations Initiated by $\text{DoOH}/\text{Sn}(\text{Oct})_2$ in scR22 at Various Pressures. Polymerization Conditions: $C_{\text{LA}}=4$ wt%, $[\text{LA}]_0/[\text{Sn}]_0=200$, at 130 °C and 5 hrs in scR22

Pressure (bar)	$M_n \times 10^{-3} (\text{g/mol})$	Conversion (%)
130	43.2	56.3
160	58.3	64.7
200	67.8	72.2
240	72.0	75.1

Table 2. Results of L-LA Polymerization Initiated by DoOH/Sn(Oct)₂ in scR22 at Various Concentrations of L-LA. Polymerization Conditions: [LA]₀/[Sn]₀=200, at 130 °C, 200 bar and 5 hrs in scR22

C_{LA} (wt%)	$M_n \times 10^{-3}$ (g/mol)	Conversion(%)
4	68.0	72.0
8	72.0	82.0
12	82.0	89.0
16	128.0	94.0
20	142.0	98.0
25	145.0	96.0
30	144.0	97.0

the reaction rate.^{13,14} Thus the higher molecular weight and conversion which are resulted from higher pressure applied on the large scale polymerization of L-LA are in accordance with this.

Effect of L-LA Concentration. The effects of monomer concentration on monomer conversion and polymer molecular weight were investigated in a series of polymerizations conducted at various monomer concentrations. The polymerization was conducted at 130 °C and 200 bar for 5 hrs. The molar ratio of monomer to initiator in the feed was 200.

With increasing monomer concentration, PLLA molecular weight and conversion were increased. When the L-LA concentration was increased from 4 to 30 wt%, the monomer conversion and the PLLA molecular weight gradually increased from 72% and 68000 g/mol to 97% and 144000 g/mol, respectively. The reaction monomer concentration dependences of monomer conversion and PLLA molecular weight growth are shown in Table 2.

In this scale-up polymerization system, the PLLA molecular weight is relatively higher than our previous study using small scale polymerization system.⁶ At monomer concentration higher than 15%, the conversion was always above 90%. The typical discussion for this is related to catalyst efficiency. In small scale polymerization system, catalyst is diluted with large amount of toluene compared to scale-up polymerization system. This process may deactivate catalyst at some degree leading to the decrease of conversion.

Improving Heat Resistivity. PLLA synthesized using supercritical fluid will have low heat resistivity due to the remained monomer. To improve the heat resistivity of the polymer, two methods were studied to remove the unreacted monomer. The first is methanol treatment method. PLLA which is not soluble in methanol will precipitate, while the methanol-soluble impurities, such as monomer and oligomer can be easily separated through filtration. The TGA analysis conducted isothermally at 200 °C showed that the PLLA residue without the methanol treatment was at 90.8%. After the

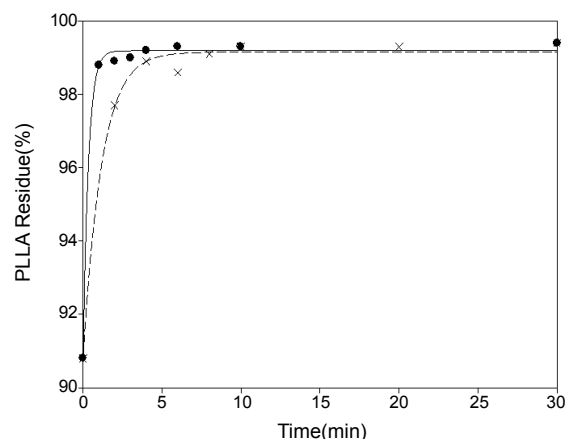


Figure 4. PLLA residue change with time; methanol treatment (●) and vacuum treatment (x). The methanol treatment was conducted at room temperature. The vacuum treatment was conducted at 100 °C and 10 torr. Heat resistivity measurement was isothermal at 200 °C.

methanol treatment, this value increased to 99.2%. Since methanol is an organic solvent and the solvent removal process is not simple, heat-vacuum treatment was used to purify the polymer product. Heat was applied at 100 °C to evaporate residual methanol from the polymer inside a vacuum chamber with 10 torr pressure. It was found that PLLA treated with those methods have PLLA residue up to 99.2%, as summarized in Figure 4. PLLA with higher heat resistivity will have good thermal stability: thus would have higher residue on the TGA analysis.

Conclusions

In this study, a successful large scale supercritical fluid polymerization of lactide is presented with 97% of monomer to polymer conversion and molecular weight of 144000 g/mol. It is found that this large scale polymerization could resemble the smaller scale system, in terms of conversion, molecular weight and reaction kinetic. For the polymer product to obtain high heat resistivity, the unreacted monomer was removed from the PLLA product. Both methanol treatment method and heat-vacuum method can successfully improve the PLLA heat resistivity.

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References

1. J. C. Middleton and A. J. Tipton, *Biomaterials*, **21**, 2335

- (2000).
2. A. I. Cooper, *J. Mater. Chem.*, **10**, 207 (2000).
 3. D. L. Tomasko, H. Li, D. Liu, X. Han, M. J. Wingert, and L. Lee, *J. Ind. Eng. Chem. Res.*, **42**, 6431 (2003).
 4. S. Alsoy and J. L. Duda, *Chem. Eng. Technol.*, **22**, 971 (1999).
 5. J. L. Kendall, D. A. Canelas, J. L. Young, and J. M. De Simone, *Chem. Rev.*, **99**, 543 (1999).
 6. J. W. Pack, S. H. Kim, S. Y. Park, and Y. W. Lee, *Macromol. Biosci.*, **4**, 340 (2004).
 7. J. W. Pack, S. H. Kim, S. Y. Park, Y. W. Lee, and Y. H. Kim, *Macromolecules*, **36**, 8923 (2003).
 8. J. W. Pack, S. H. Kim, S. Y. Park, Y. W. Lee, and Y. H. Kim, *Macromolecules*, **37**, 3564 (2004).
 9. Z. H. Zhou, X. P. Liu, and L. H. Liu, *Int. J. Polym. Mater.*, **57**, 532 (2008).
 10. Y. He, Z. Fan, J. Wei, and S. Li, *Polym. Eng. Sci.*, **46**, 1583 (2006).
 11. Y. Doi and K. Fukuda, *Proceedings of the Third International Scientific Workshop on Biodegradable Plastics and Polymers*, Japan, p.464 (1994).
 12. A. A. Clifford, *Fundamentals of Supercritical Fluids*, Oxford University Press, Oxford, p.189 (1998).
 13. T. Asno and W. J. le Noble, *Chem. Rev.*, **78**, 407 (1978).
 14. R. Van Eldik, T. Asno, and W. J. le Noble, *Chem. Rev.*, **89**, 549 (1989).
 15. H. S. Byun, *Polymer(Korea)*, **23**, 181 (1999).