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Synthesis and Characterization of L-Lactide and Polylactic Acid (PLA) from L-Lactic Acid for Biomedical Applications

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Abstract. Lactide is the monomer for the polymer polylactic acid (PLA) from lactic acid through polycondensation and depolymerization process. The properties of PLA strongly depend on the quality of the lactide monomer from which it is synthesized. Optical purity of lactide produced in depolymerization process confirmed to be L-lactide. The highest yield of crude lactide was 38.5% at temperature 210 °C with average molecular weight (Mn) of oligomer was 2389. Ring opening polymerization of lactide using *Candida rugosa* lipase as biocatalyst to PLLA synthesis has been achieved to generate useful biomedical materials free from heavy metal.

Keywords: Biopolymers; *Candida rugosa* lipase; lactide; PLA; ring opening polymerization

INTRODUCTION

Lactic acid has high versatile applications in food, pharmaceutical, textile, leather and chemical industries [1] and becomes the monomer in the production of biodegradable polyester (PLA)[2]. PLA is a biodegradable polymer and derived from renewable resources. Because of these properties the PLA has become a good candidate for use in biomedical applications. It has extensive applications in biomedical fields, including suture, bone fixation material, drug delivery microsphere, and tissue engineering [1].

Low molecular weight PLA is used for drug delivery. Wichert and Rohdewald used 2000 gr mol^{-1} PLA as a polymer for microencapsulation [3] and Andreopoulos et al. used 2,000-20,000 gr mol^{-1} PLA as antibiotic releasing system [4]. PLA is normally made through ring opening polymerization (ROP) of lactide, a ring structure formed by self esterification of two lactic acid molecules. In commercial processes, synthesis of lactide by the depolymerization of oligomer and lactide polymerization through ROP method use high temperature and organo-metallic catalysts. However, residues of organo-metallic catalysts were not tolerated in biomedical applications due to their toxicity. Food and Drug Administrator (FDA) has regulated the maximum tolerance of tin in commercial and biomedical product for as much as 20 ppm [5]. As far as enzymatic polymerization has been investigated for metal-free PLA preparation, several lipase have been tested as the catalyst for the ROP of lactide. In this study, the lactide production should be done without catalyst and the polymerization process to open the lactide ring is using lipase catalyst. The benefits to use lipase catalyst are reducing the process temperature from 200-250 °C to 60 – 110 °C, thus the consumption of energy is also reduced [6], and lipase could be obtained from renewable resources and environmental-friendly from mesophyllic to thermophyllic lipase. The properties of PLA strongly depend on the optical purity of the lactide monomer. L-lactide from L-lactic acid is produced through polycondensation and depolymerization process. Polycondensation of L-lactic acid produces oligomers PLA and depolymerization of oligomer produces a cyclic ester, lactide. Characteristic of lactide is strongly influenced by temperature, pressure, molecular weight of oligomers and catalyst on the de-polymerization process. Previous studies have not yet reported the synthesis of L-lactide done without catalyst and lactide polymerization using *candida rugosa* lipase. The aim of

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this study is to determine the characteristic of lactide from de-polymerization process without catalyst and the characteristic of PLA produced using *candida rugosa* lipase.

THE OBJECT OF THE STUDY

The production of lactide from L-lactate acid in this research with various polycondensation temperature and polymerization of crude lactide yielded from the reaction using *candida rugosa* lipase as catalyst. The characteristic of lactide and PLA was analyzed using Fourier-Transform Infrared Spectroscopy (FT-IR, Agilent Technologies type Cary 630) and proton nuclear magnetic resonance (^{1}H NMR spectra recorded on a JEOL spectrometer operating at 500 MHz). The number-average molar mass (Mn, Mw) and polydispersity index (PDI) of the oligomer were determined by using GPC-8025.

The yield of crude lactide in the depolymerization process was calculated by using eq.1.

$$Yield\ of\ crude\ lactide\ (\%) = \frac{Crude\ lactide\ product\ (gr)}{Oligomer\ in\ reactor\ (gr)}\ x\ 100\% \qquad (1)$$

METHODS

Polycondensation of L-Lactic Acid

L-lactic acid was put in a four-necked flask equipped with a magnetic stirrer, a temperature controller and a condenser, which was connected to a distilled collector. The reaction was carried out at 120 °C for one hour with continuous nitrogen gas flow to push evaporative water into the condenser. Afterward, polycondensation was carried out with variation of temperature at 150, 180 and 200 °C for 4 hours and gradually at 150 °C for 2 hours and at 180 °C for 2 hours without nitrogen gas flow.

Depolymerization of Oligomer

The oligomer yielded from the polycondensation process was reheated with temperature experiments at 210°C for 3 hours and vacuum pressure 76 torr. The flask was equipped with a magnetic stirrer, a temperature controller, and a distillation column, which was connected to a vacuum pump. The oligomer was heated until it stopped producing distillate. Subsequent to the depolymerization process completed, the vacuum valve was closed slowly. Then the lactide was collected on the sample container.

Polymerization

Lactide produced from depolymerization process was diluted with toluene while heated at 70 °C, then the lipase catalyst was added with various concentration 10, 15 and 20% (w/w). The mixture was heated at atmospheric pressure, temperature 45 °C for 72 hour. PLA produced from the process was diluted with chloroform, then separated with lipase through centrifugation. The precipitation from centrifugation process was filtered and the liquid was then heated to evaporate the solvent and chloroform. The final liquid product was further analyzed.

RESULTS AND DISCUSSION

Polycondensation of L-Lactic acid

L-lactic acid polycondensation was carried out without catalyst at 150, 180, 200 °C for 4 hours each and one process with gradually increased the temperature to 150 °C for 2 hours to 180 °C for 2 hours. Oligomer was a solid translucent white, brittle, and unhygroscopic at room temperature. The FTIR spectra of oligomer at variation temperature of polycondensation is shown in Fig. 1.

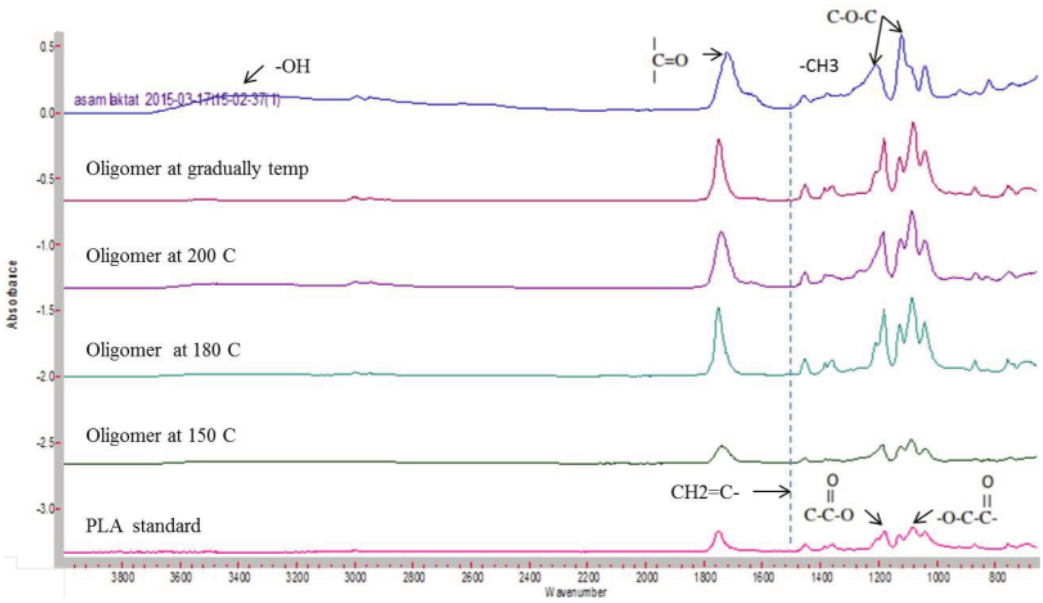


FIGURE. 1. The FT-IR spectra of oligomer at variation temperature of polycondensation

The FTIR spectrum of oligomer is similar with spectrum of PLA standard. In the FTIR spectrum of oligomer consists of carbonyl group (C=O), C-H bending vibration and C-O stretching were found at 1735 to 1749, 1451 to 1454 and 1180 to 1185 cm^{-1}, respectively. The difference spectrum of oligomer with L-lactic acid is that the spectrum L-lactic acid showed the existence of the -OH stretching vibration at 3403 cm^{-1} wave number, and significant reduce of the –OH stretching vibration in the oligomer. This is due to the polyesterification reaction that used -OH to react with acid and form ester. The final statement is similar as described by Nikolic et al [7].

Table 1 shows the molecular weight of oligomer which produced from variation temperature of polycondensation process of L-lactic acid.

TABLE 1. Molecular weight of Oligomer

T policondensation	Mw	Mn	PDI
150 °C	1080	380	2.85
180 °C	1736	893	2.92
200 °C	2487	1375	1.80
gradually	2820	2389	1.18

Polycondensation temperature highly determined the molecular weight and degree of oligomer polydispersion. Lactic acid polycondensation reaction took place at higher rate at higher temperature, hence molecular weight of oligomer increased as the temperature increased. Polydispersion degree decreased at polycondensation temperature 200 °C and the molecular weight showed the similarity at step up polycondensation process. Molecular weight generated from this study is much higher than the research by Pravin et al (2014) which produced oligomers with Molecular weight in 1380 and total oligomerization time was 9 hours [8]. Gradual temperature of polycondensation produced higher molecular weight of oligomers than the polycondensation at 150, 180, and 200 °C and the oligomer consisting of monodisperse molecules was characterized by the value of PDI 1.18.

Depolymerization Process

Oligomer PLA on depolymerization process will be degraded to cyclic ester (lactide) through intramolecular trans-esterification reaction. In intramolecular trans-esterification reaction, the carbon atom in the carbonyl group of PLA is attacked by the OH end group. Depolymerization process in this research was done without catalyst, with various number of average molecular weight of oligomer, temperature at 210 °C and 76 torr pressure. The lactide produced is transparent and hygroscopic powder, as can be seen in Fig. 2.

FIGURE. 2. Lactide from depolymerization process

The ^{1}H NMR spectrum of lactide consisted of two patterns of segregation, doublet and quartet. Fig. 3 shows that the spectrum quartet of lactide consists of four peaks that are on the proton shift 5.07-5.02 ppm and the spectrum doublets consist of two protons shift peak at 1.65-1.68 ppm. Result of this study is different from that reported by Yoo (2009). The use of SnO catalyst produced D,L-lactide with the-CH signal at 1.72 ppm [9]. The third doublet spectrum of ^{1}H NMR proved the methyl group consisted of L, L / D, D-lactide, meso-lactide and oligomer, thus can be seen in sequential chemical shift at 1.65-1.68; 1.70-1.75; and 1.45-1.64 ppm [7]. Based on the literature, the crude lactide contains lactide at stereoisomers L, L / D, D-lactide and impurities such as lactide acid and oligomer/lactic acid dimmer. ^{1}H NMR spectrum could not distinguish the form of L- or D-lactide as the two types of these isomers have the same spectrum. L-lactic acid is used as raw material for making lactide in this experiment, thus it stands to the reason that the product is L-lactide. ^{1}H NMR spectrum of L-lactide produced in this study was similar to the spectrum of L-lactide reported by A.C. Silvino et al [10].

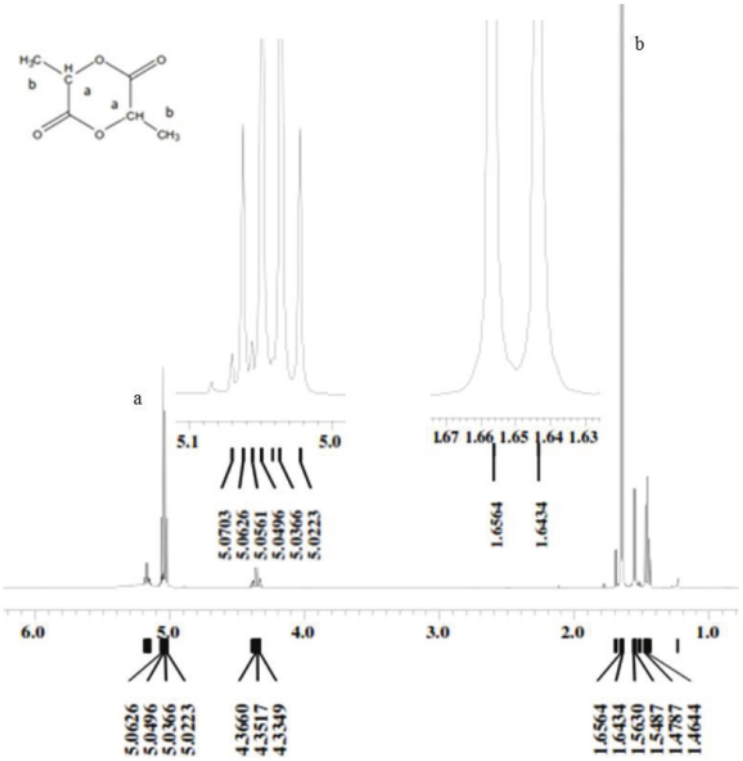


FIGURE. 3. The [1]H NMR spectrum of lactide

The differences between spectrum of L-lactide and L-lactic acid was as shown in Table 2.

TABLE 2. The differences [1]HNMR spectrum of L-Lactide and L-lactic acid

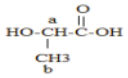
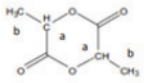
Compound	Molecular structure	H-doublet	H-quartet
L-Lactic Acid		b = 1.49-1.48	a = 4.38-4.36
L-Lactide		b = 1.65-1.68	a= 5.07-5.02

Fig. 4 shows the effect of different number average molecular weight (Mn) of oligomer when depolymerization reaction was conducted at temperature 210 °C. The yield of lactide increased with increasing of Mn of oligomer. This is due to the higher molecular weight oligomers (Mn), the concentration of hydroxyl groups of the lower and so the reaction of depolymerization increases. The highest yield of lactide using molecular weight number of oligomer of 2389 (gr/mol) gained was 38.5%.

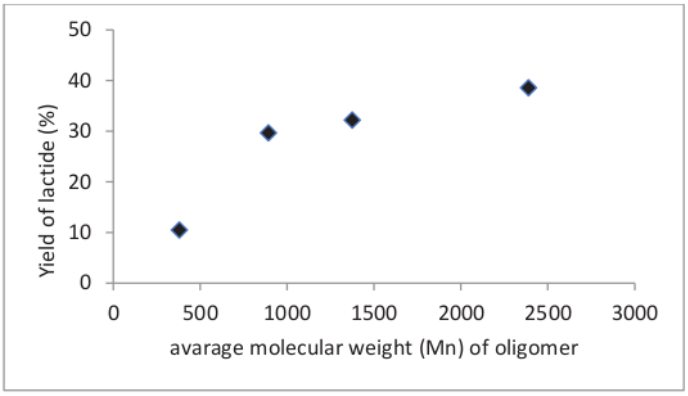


FIGURE. 4. Yield of lactide with depolymerization without catalyst

Polymerization of Lactide Using Candida Rugosa Lipase as Biocatalyst

L-lactide produced was further polymerized using *Candida rugosa* lipase as catalyst to yield free metal PLA. The weight of lipase used in the polymerization were 10, 15, and 20% (w/w). The FTIR spectrum shows similarity with the standard PLA functional group, as can be seen in Fig. 5.

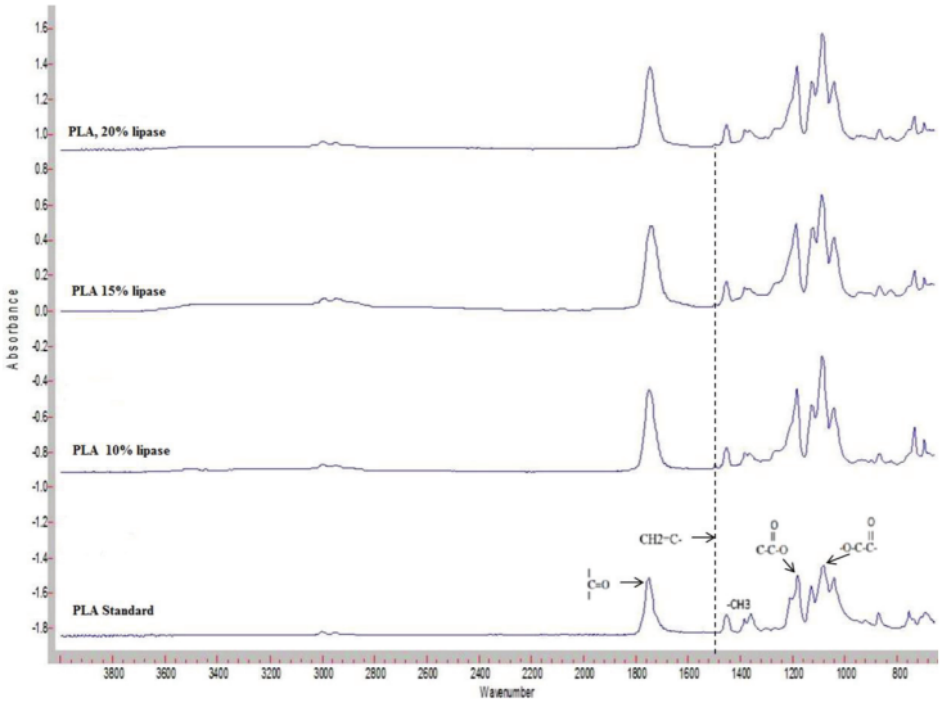


FIGURE 5. The FT-IR spectra of PLA using candida rugosa lipase as biocatalyst

In the FTIR spectrum, PLA consists of carbonyl group (C=O), CH_3 bending vibration and C-O stretching. The very strong peak at 1740-1746 cm^{-1} assigned to the carbonyl group (-C=O) stretching vibration; the peak at 1451

and 1264 cm^{-1} assigned –CH3 symmetric and -CH3 asymmetric; the peak at 1182-1264 cm^{-1}, 1041-1084 cm^{-1} dan 733-866 cm^{-1} attributed to the asymmetric –C-O-C- vibration, the symmetric –C-O-C- vibration and –CO bending vibration, respectively. This result has similarities with the research results by Achmad et al. (2009) [11] and Ding et al.(2011) [12] .

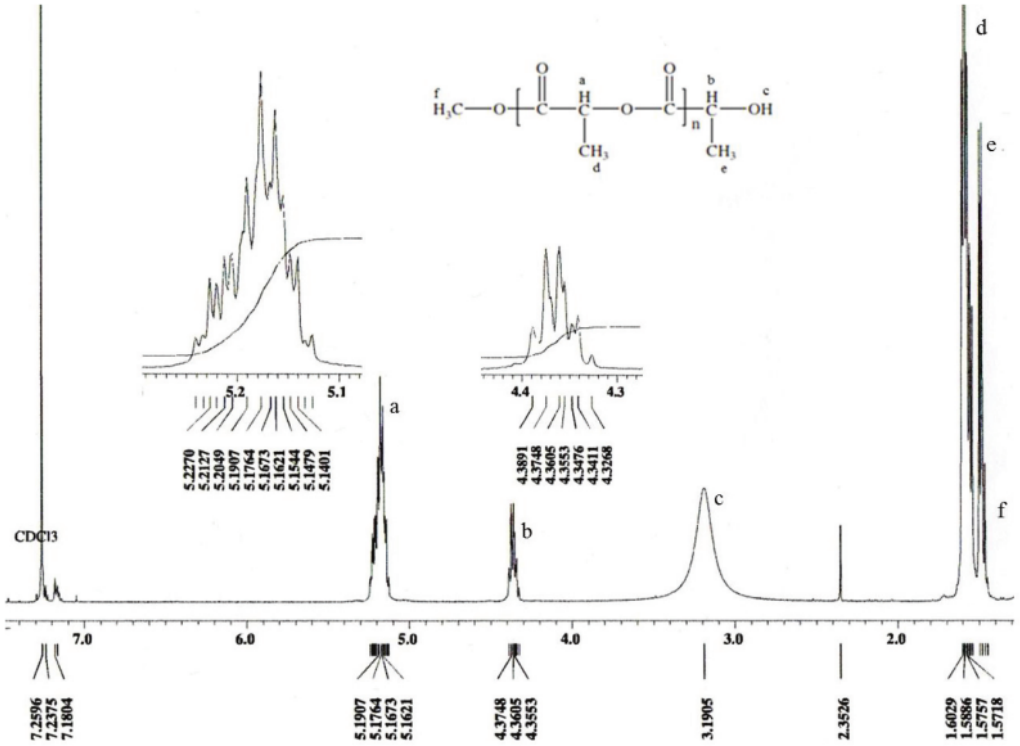


FIGURE. 6. The ^{1}H NMR spectrum of PLLA

The Fig. 6 shows the ^{1}H NMR spectrum of PLA obtained at 45 °C for 72 hours using *Candida rugosa* lipase as biocatalyst. Result of the ^{1}H NMR analysis in this study is the obtained spectrum of H doublet for methyl group at 1.59 ppm and H quartet in the main chain of PLLA at 5.18 ppm. The additional signals appearing at 4.37, 3.19, and 1.57 ppm was assigned to the methine proton, the hydroxyl end group and the methyl proton of PLLA, respectively. This result is similar with spectrum of PLLA that reported by Choubisa et al, (2013) [13]; Ding L, et al (2011) [12] and Umare et al, (2007) [14].

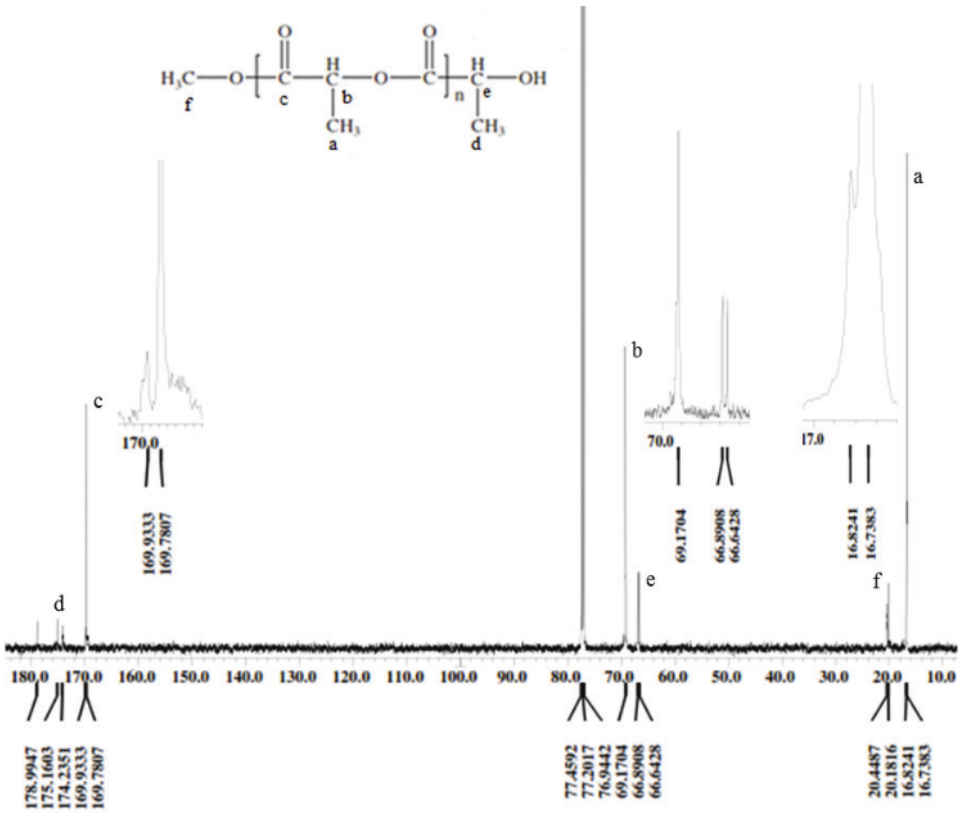


FIGURE. 7. the ^{13}CNMR spectrum of PLLA

Fig. 7 shows the ^{13}CNMR spectrum of PLA. The ^{13}CNMR spectrum shows the signal of methyl carbon, methane carbon and ester carbon in main chain were at 16.73; 69.17 and 169.78 ppm, respectively. The ^{13}CNMR spectrum of PLLA from this study was similar with Ding et al (2011) which used Ni(II) and Ni(II)-Ln(II) complexes as catalyst.

CONCLUSION

Lactic acid polycondensation reaction produces oligomer PLA with the highest molecular weight of oligomers at 2389 by gradual temperature of polycondensation. Lactide produced through depolymerization without catalyst has L-lactide stereoform. The yield of lactide increases with increasing Mn of oligomer. The highest yield of l-lactide was 38.5% at 210 °C of the depolymerization process. By means of ^{1}H NMR and ^{13}CNMR spectrum, polymerization of L-lactide using *candida rugosa* as catalyst at temperature 45 °C for 72 hours formed polyester with stereoform of PLLA. Metal-free PLLA produced in this process can be used for biomedical purposes such as drug delivery and polymer material for production of microcapsule.

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