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Biocompatible catalysts for lactide polymerization – catalyst activity, racemization effect and optimization of the polymerization based-on Design of Experiments.

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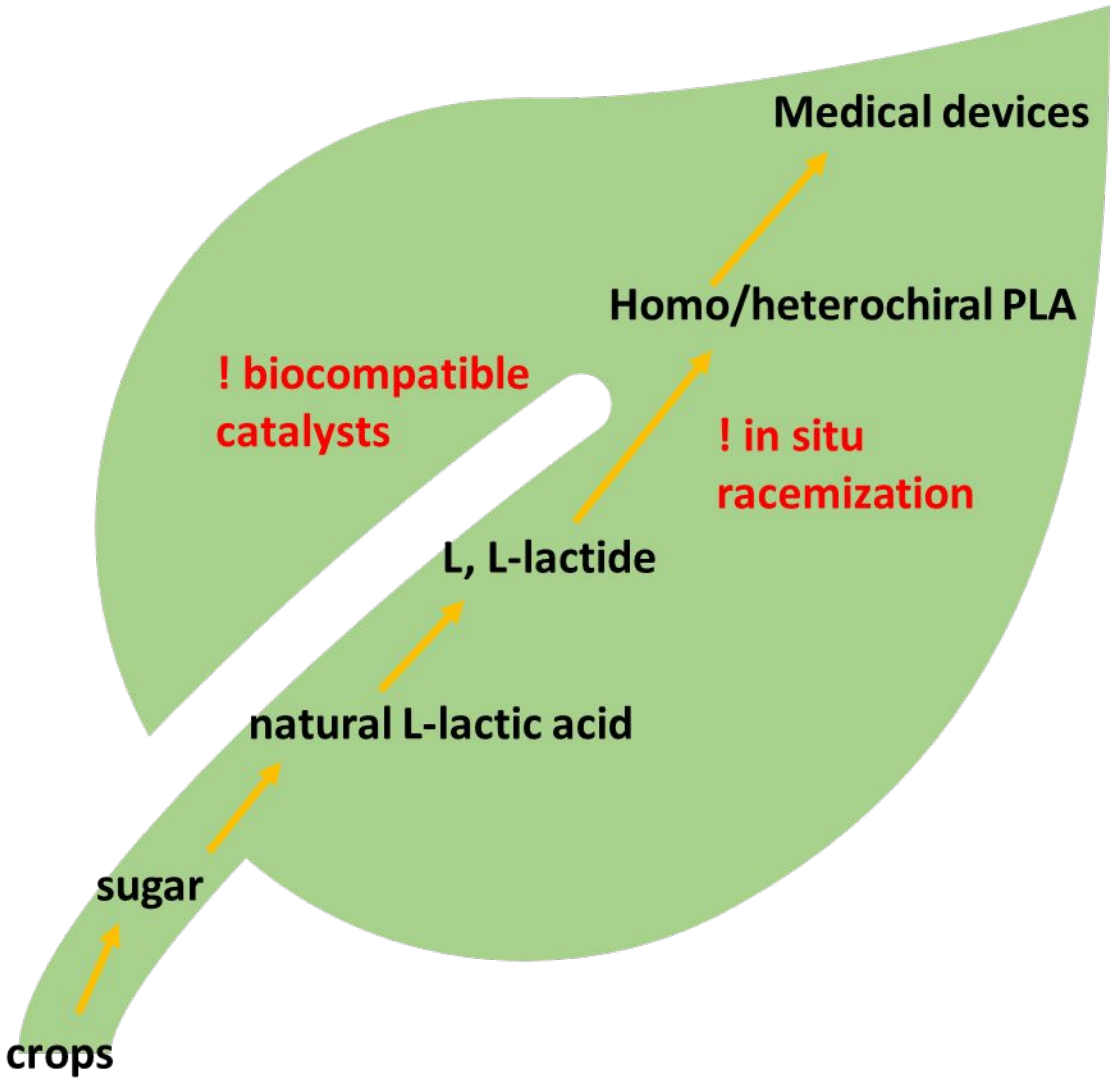


ABSTRACT: An original synthesis of Ca, Mg and Zn 2-ethylhexanoate (octoate) obtained by reaction between metallic powder with 2-ethylhexanoic acid was achieved. The activities of obtaining biocompatible catalysts of lactide polymerization were tested. The most active catalyst was zinc 2-ethylhexanoate ($ZnOct_2$), and the lowest activity had calcium 2-ethylhexanoate ($CaOct_2$). The ROP process was successfully optimized by using the design of the experiment. Polylactide with M_w=82.3 kg/mol with lactide conversion up to 85% and 8% content of D-lactic acid has been obtained. Thus obtained polylactides can be used in medical and pharmaceutical devices.

KEYWORDS: PLA, racemization, medical devices, DOE, scale-up

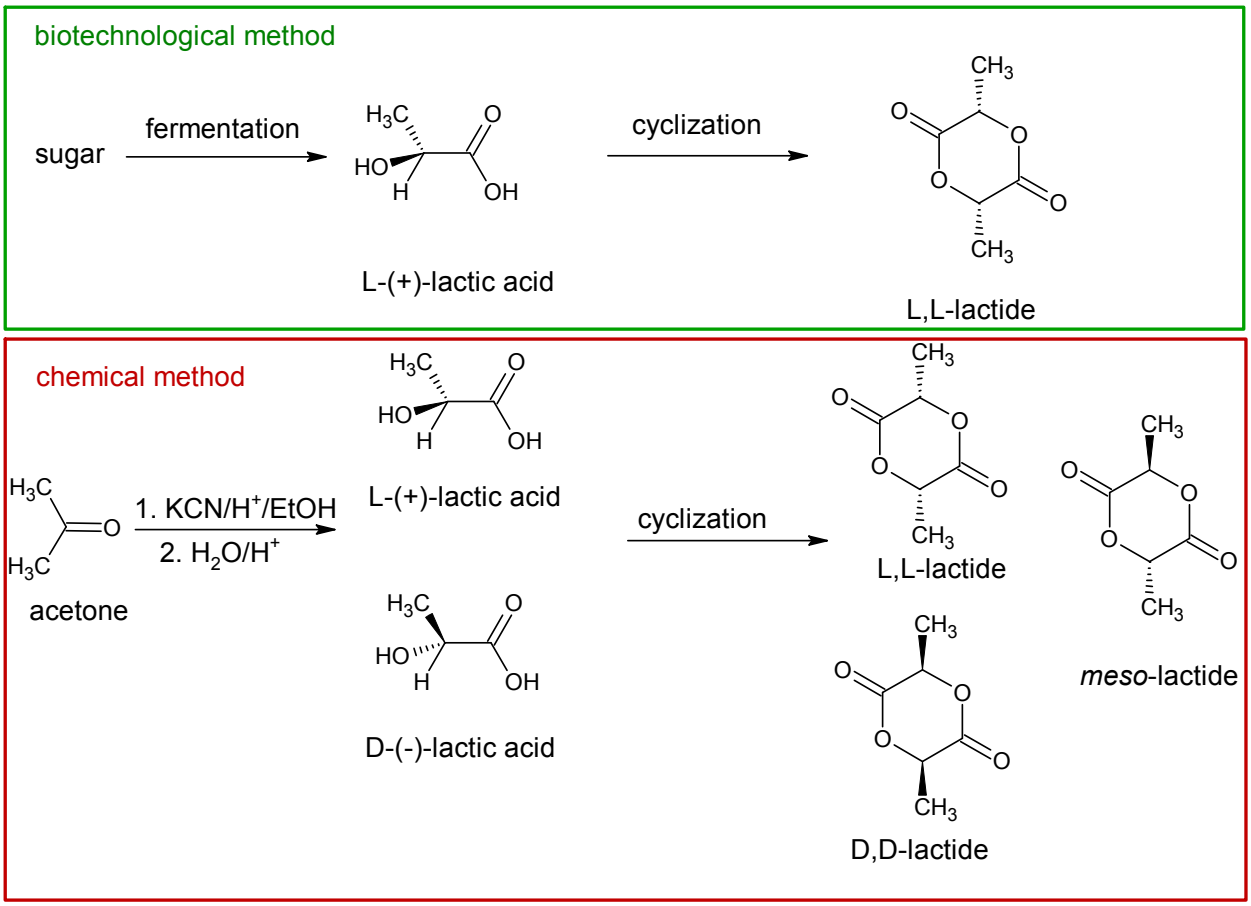
INTRODUCTION

Polylactide is a "double green" polymer with high application potential.[1,2] Raw materials for its production can be obtained from renewable resources.[3] After using the product, it can be composted, where it decomposes into non-toxic products (CO_2 and H_2O).[4] Non-toxic and biocompatible PLA can be used in regenerative medicine for damaged tissues.

Also, PLA has found many applications: packaging materials,[1,5] textiles,[6] composites.[68] Medicine,[7,8] and pharmacy[9,10] are continually looking for new applications for polylactide. Researchers focused on developing new forms of drug delivery systems (DDS) and developing materials for regenerative medicine.[11,12,13,14,15]

The monomer in PLA is lactic acid (LAc) (Scheme. 1). It is a weak, water-soluble organic acid with an asymmetric carbon atom.[16] Lactic acid may exist in the form of two enantiomers: D-(-)-LAc or L-(+)- LAc. L-(+)- LAc is present in living organisms as a product of various metabolic changes.[17] Lactic acid can be obtained as a result of chemical synthesis and biotechnological methods.[18,19]

Scheme 1. Synthesis of chiral lactic acid and chiral lactide



In chemical synthesis, a racemic LAc mixture is obtained. Biotechnologically, however, both optically active enantiomers can be selectively obtained as a result of bacterial (e.g. using the Lactobacillus strain[20,21,22]) fermentation of starch and other carbohydrates derived from corn, sugar beet or potatoes.[23]

The properties of PLA depend on the stereochemical composition of the repeat units and their distribution along the chain.[24] Homochiral PLA (PLLA or PDLA) (Fig. 1) is an isotactic, stereoregular and semicrystalline polymer (degree of crystallization up to 40%),

with T_g 55–65 °C and T_m 170–183 °C.[25] Atactic PLA is made of heterochiral PLDLA units. It is an amorphous polymer with T_g = 59 °C, without melting point.[26] A mixture of homochiral, isotactic PLLA and PDLA chains creates stereocomplexes with a melting point of approx. 230 °C.[27,28]

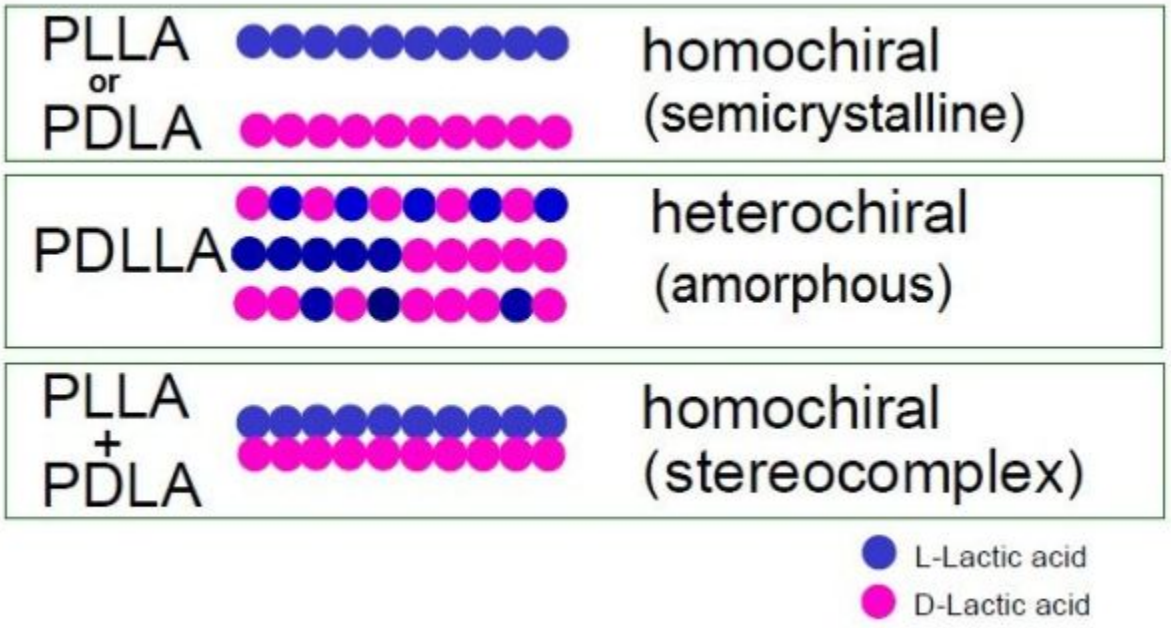


Figure 1. Chemical structure of polylactide, stereochemistry and properties

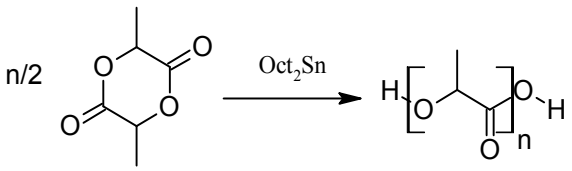
Mechanical properties characterize materials made of PLA. It can be a soft and flexible or hard and durable plastics.[29] For homochiral PLA, as the average molar mass increases, the flexural strength increases, and the tensile strength does not change.[30]

However, as the PLDLA average molar mass increases, the flexural and tensile strength increases.[31]

Polylactide with strictly defined chirality can be obtained using optically active catalysts or mixtures of D,D-lactide and L,L-lactide with defined stoichiometry.[32] The cost of purchasing D,D-lactide is about twice as high as L,L-lactide.[33] The price of *meso*-lactide is challenging to determine because there are no suppliers of this raw material.[34] Therefore, many groups are working on catalysts that racemize lactide in situ in polymerization.[35]

Direct lactic acid condensation on tin or zinc oxide leads to PLA under 5 kg/mol.[36] High molecular weight PLA is obtained by ring-opening polymerization (ROP).[37] The most popular catalyst is tin(II) 2-ethylhexanoate ($SnOct_2$).[38] The high molecular weight polymer (M_w> 100 kg/mol) is obtained with high lactide conversion (> 95%).[39,40]

Scheme 2. **The synthesis of polylactide with tin(II) octoate.**



1 2

The production of PLA with tin(II) catalysts[41,42], disqualify such obtained material from medicinal applications. Acceptable content of tin(II) residue in medical devices should not exceed 20 ppm of tin.[43] The practical exclusion of tin content in medical devices is a premise to research the search for new biocompatible catalysts for lactide polymerization.[44,45,46,47]

In the synthesis of medical PLA, it is recommended to use zirconium[48] and titanium[49,50,51] catalysts. Zirconium and titanium are used to production of bone implants, so they should also be non-toxic to humans in other applications. However, it has been found that some people may have an allergic effect. Zr and Ti catalysts are more expensive than the commonly used $SnOct_2$, which increases the cost of PLA production.

The latest trend in catalyst synthesis is the use of molecules found in metabolic pathways, i.e. magnesium,[52,53] zinc[54,55,56,57,58,59,60] and calcium.[61,62] To date, scientists have developed dozens of catalysts based on zinc. [54,55,56,57,58,59,60] Unfortunately their use leads to low molecular weight PLA (M_w <15 kg/mol). Less scientific work concerns catalysts of magnesium and calcium.[52,53] Polymerizations catalyzed with Ca and Mg salts have a long time of reaction (1–4 days) and polymer molar mass under 13 kg/mol.

Our research aimed to find new non-toxic catalysts for lactide polymerization. The next step was examined catalysts activity and determine optimal reaction conditions.[43] Additionally checking whether racemization of the chiral center in lactic acid occurs due to the use of strongly basic metals in catalysts.

Presently the most effective ROP catalyst is $SnOct_2$. We tried to obtain its magnesium, zinc and calcium analogue $MOct_2$ (M is metal).

Several methods can obtain magnesium (calcium or zinc) octoate (**4**). The first method is the reaction between 2-ethylhexanoic acid (**3**) and a metal oxide.[63,64] The water formed in the reaction is azeotropically separated. The second method is the reaction between metal chloride[65,66] and 2-ethylhexanoic acid (**3**). In this reaction, hydrogen chloride is formed in addition to the desired catalyst. The presence of hydrogen chloride is unfavorable due to its strong corrosive effect on steel apparatus.

We used the design of experiments to optimize process conditions. Three variables in the rotatable factorial plan were examined. We tested the significance of the equation coefficients with the Student's test. The MS Solver add-on predicted the optimal conditions of polymerization.[67]

EXPERIMENTAL SECTION

All solvents (toluene, dichloromethane) and other reagents (magnesium, zinc, calcium) were used without any purification.

L,L-lactide (Boehringer Company) with high purity >99.5%, water content <80 ppm and free acids content under 0.3 mmol/kg was used. IR spectra were measured using a BRUKER ALPHA II Platinum ATR spectrometer (in ATR technics). ^{1}H or ^{13}C NMR spectra were measured using a Mercury-400BB spectrometer (400 MHz). Elemental analysis was measured by Perkin Elmer, model PE Seria II CHNS/O. A gel permeation chromatography measured molecular weights of PLA samples. The apparatus UltiMate 3000 Dionex, with refractometric detector RIn-101 Shodex and with two Jordi Gel DVB Mixed Bed columns was used. Conversion of lactide was predicted using the calibration curve method.

The specific rotation of the product was measured with a polAAr 32 automatic polarimeter.

The content of D centers in the PLA chain was calculated from the formula:

$$\%D = \frac{[\alpha] + \alpha_w}{2 \cdot \alpha_w} \cdot 100\%$$

where:% D - the percentage of centers -D; [α] - specific rotation of the tested polymer α_w - specific rotation of poly-D-lactide (+161.0 °)

Synthesis of calcium 2-ethylhexanoate ($CaOct_2$, 4a). 2-ethylhexanoic acid (11 mL, 10 g, (0.07 mol)), pellets of calcium (1.40 g, 0.035 mol, the particle size of calcium <5 mm) and toluene (70 mL) were agitated (200 rpm) and heated under reflux for 24 hours. Unreacted calcium was filtered out from the hot solution. Product was filtered at room temperature and washed with toluene (15 mL).

Product was obtained with 64% yields (7.3 g, 0.022 mol) and 95.3% purity.[47]

$CaOct_2$: white solid; IR (ATR, cm^{-1}): 2962, 2936, 1685, 1561; ^1H NMR (400 MHz, DMSO-*d6*) δ/ppm: 0.82 (2t, 6H) 1.22 (m, 4H) 1.28 (m, 2H) 1.45 (m, 2H) 1.87 (s, 1H); elemental analysis (%): cal. C 58.86; H 9.26; anal. C 59.87; H 9.22.

Synthesis of magnesium 2-ethylhexanoate ($MgOct_2$, 4b). 2-ethylhexanoic acid (22 mL, 20 g, (0.14 mol), powdered magnesium (1.68 g, 0.07 mol, the particle size of magnesium <5 μm) and toluene (100 mL) were agitated (200 rpm) and heated under reflux for 20

hours. Unreacted magnesium was filtered out from the hot solution. Product was filtered at room temperature and washed with toluene (15 mL).

Product was obtained with 80% yields (17.4 g, 0.11 mol) and 99.8% purity.[68]

$MgOct_2$: yellow solid; IR (ATR, cm^{-1}): 2960, 2934, 1692, 1603; ^1H NMR (400 MHz, DMSO-*d6*) δ/ppm: 0.84 (m, 6H) 1.26 (m, 4H) 1.59 (m, 4H) 1.89 (m, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ/ppm: 12.1; 14.0; 22.8; 25.4; 29.7; 31.8; 47.6; 183.9; elemental analysis (%): cal. C 61.8; H 9.73; anal. C 61.5; H 9.71.

Synthesis of zinc 2-ethylhexanoate ($ZnOct_2$, 4c). 2-ethylhexanoic acid (11 mL, 10 g, (0.07 mol)), powder of zinc (2.246 g, 0.034 mol, the particle size of zinc <1 μm) and toluene (70 mL) were agitated (200 rpm) and heated under reflux for 8 h. Unreacted zinc was filtered out from the hot solution. Product was filtered at room temperature and washed with toluene (15 mL).

Product was obtained with 87% yields (10.4 g, 0.03 mol) and 99.5% purity.[47]

$ZnOct_2$: transparent syrup; IR (ATR, cm^{-1}): 2962, 2933, 1628, 1592; ^1H NMR (400 MHz, DMSO-*d6*) δ/ppm: 0.80 (m, 6H) 1.23 (m, 4H) 1.35 (m, 2H) 1.45 (m, 2H) 2.02 (dq, 1H); elemental analysis (%): cal. C 54.62; H 8.59; anal. C 54.63; H 8.62.

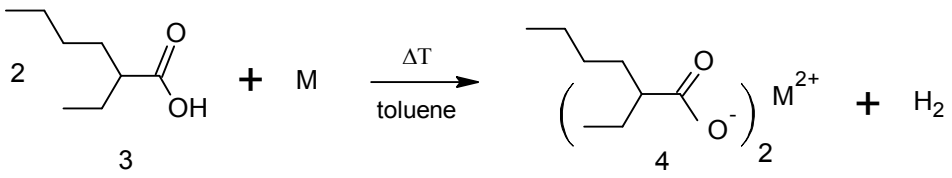
Polymerization of L-lactide. L-lactide (8.64 g, 0.06 mol) was melted in an argon atmosphere with magnetic stirring (160 rpm) in a temperature range from 120 °C to 200 °C (start of polymerization). 0.06–0.7 mL of 0.12 M solution of catalyst ($MgOct_2$, $CaOct_2$, $ZnOct_2$) in CH_2Cl_2 was added (0.05–1.5 $\%_{mol.}$ catalyst/lactide ratio). reactions were carried out in t = 1–32 h. The reaction products were cooled down to room temperature in an argon atmosphere and analyzed. Polylactides were obtained with the conversion of lactide 2–98.0% and M_w 1.2–34.1 kg/mol, *DI* 1.4–2.4, *%D* 0–13%.

PLA: white or yellow solid; IR (ATR, cm^{-1}): 1749, 1181, 868; ^1H NMR (400 MHz, $CDCl_3$) δ/ppm: 1.54 (d, 3H) 5.18 (q, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 16.7; 20.5, 52.3, 69.0, 170.3

RESULTS AND DISCUSSION

Catalyst's synthesis The catalyst synthesis was carried out in the direct reaction of an acid (**3**) with metal (Scheme 3). The merit of this method is the lower price of metal than its oxide or chloride. The second reaction product is hydrogen, which is removable from the reaction mixture.[47]

Scheme 3. **Obtaining of calcium, magnesium and zinc 2-ethylhexanoate**



M=Ca (a); Mg (b); Zn (c)

The reaction between acid **3** with metal was carried out in reflux of toluene. The substrates were mixed using a magnetic stirrer for 8–24 h (yield 64–87%). The viscosity of the reaction mixture acid **3** to metal in molar ratio 2:1 was too high. To reduce them was necessary to add an appropriate volume of toluene. This treatment allowed for better mixing of the reaction mixture in the final stage of the process. The unreacted metal particles were selectively separated by hot filtration. The yellow product is crystallized from the toluene solution at room temperature. Then it could be separated by subsequent

filtration. The last step was washing a product with toluene and drying at room temperature. The catalyst was obtained with sufficient good purity. The most importantly was low content of water (<400 ppm). The presence of water in the catalyst is disadvantageous because it cannot be used for ring-opening polymerization.

Table 1. Results of synthesis of calcium, magnesium and zinc octoate

2-ethylheksanoate	time (h)	yields (%)	purity (%)	water content (ppm)
zinc	8	87.0	99.5	350
magnesium	20	80.0	99.8	280
calcium	24	64.0	95.3	300

Catalysts activity in lactide polymerization.

L-LD polymerization was provided out at 200 °C for 24 h with 0.05%$_{mol}$ catalyst (Fig. 2.). The lowest LD conversion was obtained with a calcium catalyst (58%). The conversion at the same high level (92%) was achieved in the case of magnesium (91.5%) and zinc (92.8%) catalysts. The lowest molecular weight, 19.5 kg/mol, was obtained against $CaOct_2$. The polylactide obtained against $MgOct_2$ had an average molar mass of

about 31 kg/mol. The highest molar mass (64 kg/mol) was obtained in a $ZnOct_2$ catalyzed reaction.

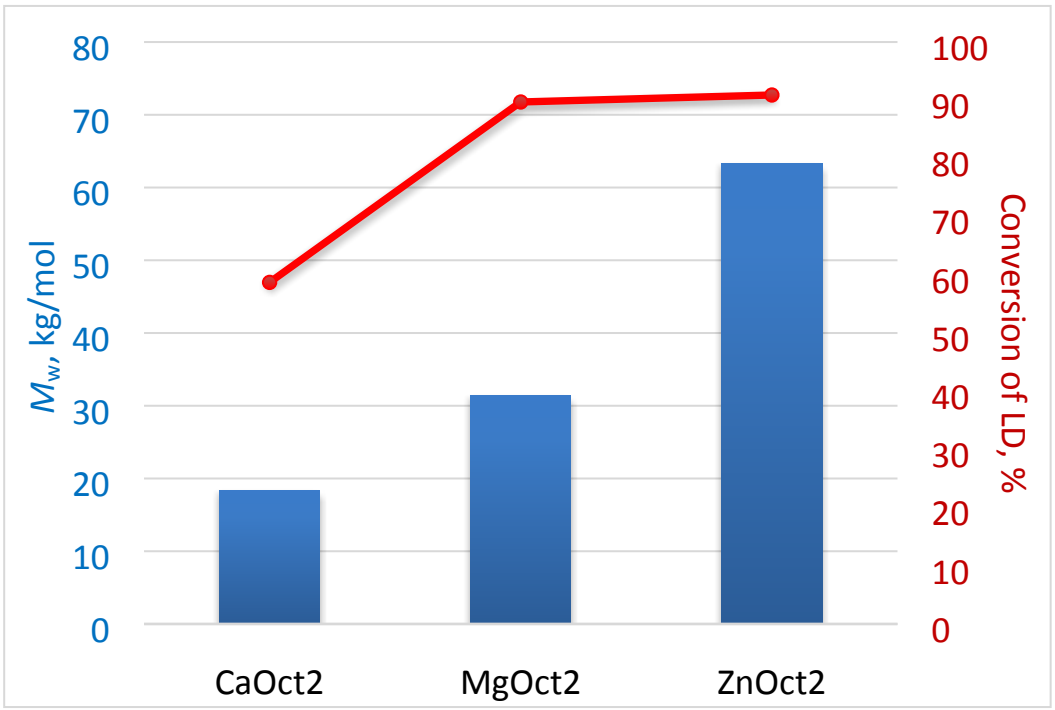


Figure 2. **The influence of catalyst on lactide conversion and molecular weight**

Racemization of lactide in ROP.

Two methods determined the degree of racemization of lactic acid in polylactide. The signal surface ratio of 169.3 ppm (heterochiral PLA) to 169.5 ppm (homochiral PLA) was determined in the ^{13}C NMR spectrum (Figure 3).

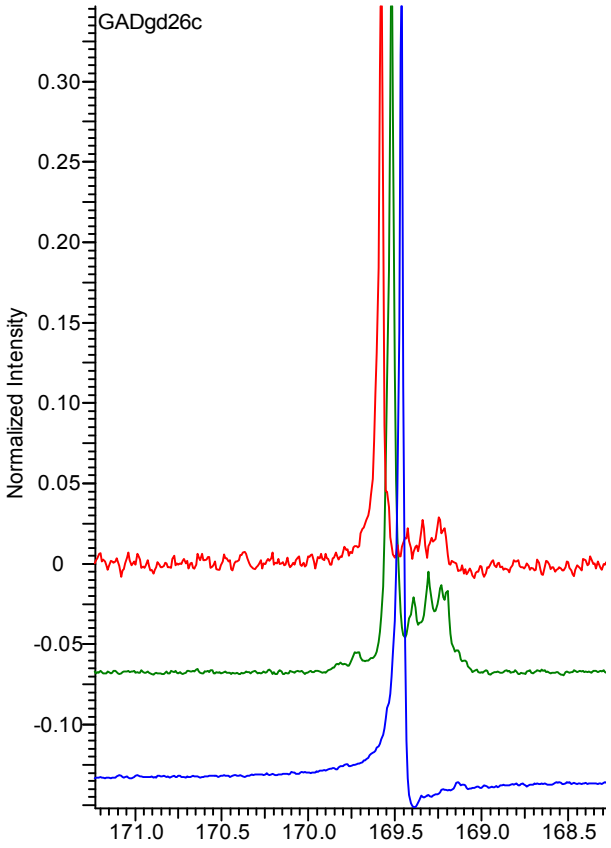


Figure 3. The fragment of ^{13}C NMR spectrum of polylactides obtained against $SnOct_2$ (blue), $CaOct_2$ (green), $MgOct_2$ (red) (169.3 ppm – PDLLA, 169.5 ppm - PLLA)

Table 2. The degree of racemization of lactic acid in PLA determined by ^{13}C NMR and specific rotation measurement

CATALYST	RACEMIZATION DEGREE OF LACTIC ACID, %	
	^{13}C NMR	specific rotation

$SnOct_2$	0	0
$CaOct_2$	32.0	31.9
$MgOct_2$	20.3	20.8
$ZnOct_2$	14.5	13.9

Optimization of L,L-lactide polymerization. High conversion of lactide in PLA is necessary for the material to be used in medicine. When residual lactide concentration in PLA is high, additional steps to remove it are required. This prolongs the process and increases its cost.[69,70,71] The molecular weight of PLA significantly affects the potential application. The higher M_w PLA is used for implants and the lower molecular weight for DDS. Thus, it seems useful to link the synthesis conditions to M_w of the polymer. The content of D centers in PLA (% D) should not exceed 15%.[72]

It was checked that essential process variable, e.g. temperature and reaction time, catalyst concentration and mixing efficiency. During polymerization, it is challenging to keep the mixing speed constant. A significant increase in viscosity during the process is

responsible for this effect. So we established this variable at a constant level. The quality of the L,L-lactide substrate used in reaction determines the molecular weight of polymer. Too high water content (>150 ppm) and/or lactic acid decrease a molecular weight of PLA. Before each reaction, the content of water and free acids in the lactide was tested.[68]

The optimization carried out was to indicate a relationship of lactide conversion ($\hat{y}_1$) and average molecular weight (M_w) ($\hat{y}_2$) and content of D centers in PLA ($\%D$) ($\hat{y}_4$) on reaction time (z_1) catalyst concentration (z_2) and temperature (z_3), respectively. The second-degree equation can be obtained using a rotatable compositional plane:

$$\hat{y}_i = b_0 + \Sigma b_i x_i + \Sigma b_{ij} x_i x_j + \Sigma b_i x_i^2$$

The criteria of optimization were to maximize of conversion of lactide ($\hat{y}_1$) and molecular weight of polylactide ($\hat{y}_2$). The percentage of the content of D centers in PLA should be below 15%, $\hat{y}_4$. We tested the effect of the time z_1 (1.3–4.7 h), catalyst/LD ratio z_2 (0.08–0.42 $\%_{mol}$) and reaction time z_3 (143.2–176.8 °C) (Table 3).

Table 3. **Polymerization of L-lactide with $ZnOct_2$. Factorial 2^3 and rotatable designs: variables at maximum and minimum levels.**

x_i	natural variable	(–1.682)	(-1)	(0)	(+1)	(+1.682)
x_1	time (h)	1.3	2.0	3.0	4.0	4.7
x_2	catalyst/LD ratio ($\%_{mol}$)	0.08	0.15	0.25	0.35	0.42
x_3	temperature (°C)	143.2	150	160	170	176.8

A rotatable 20-run design was used. This plan contains a 2-level factorial part (eight runs with three input variables at all combinations of the +1 and –1 levels). The next part is a star points (six runs with each of the three input variables at –1.682 and +1.682, while the other two were at (0)). The last is replicates at the center of the design (six runs with all three variables at 0). In all experiments, the remaining variables were constant (Table 4). The experiments were performed in random order, and for each experiment, all four of the response variables, y_i, were measured. Table 4 shows the design matrix, along with the measured responses.

To shorten the discussion, without the statistical analysis details are presented in this paper. We present here only the selected quadratic models (without insignificant coefficients) and the most important diagrams.

Table 4. L-lactide polymerization with $ZnOct_2$. Factorial rotatable design: experimental matrix[a] and results[b]

no.	Coded variables			Conversion (%)		M_w (kg/mol)		M_n (kg/mol)	%D (%)	
	x_1	x_2	x_3	y_1	$\hat{y}_1$	y_2	$\hat{y}_2$	y_3	y_4	$\hat{y}_4$
1	-1	-1	-1	25.6	26.4	58.1	53.7	42.9	11.0	10.6
2	+1	-1	-1	77.4	71.0	69.6	70.3	39.0	5.5	6.6
3	-1	+1	-1	48.3	40.5	50.5	49.9	35.5	4.9	4.7
4	+1	+1	-1	81.6	85.2	61.9	66.5	37.4	3.7	3.6
5	-1	-1	+1	30.4	26.1	33.9	30.5	31.4	2.2	2.9
6	+1	-1	+1	57.2	60.0	43.4	47.2	22.2	3.3	4.1
7	-1	+1	+1	45.6	47.0	27.7	34.3	19.9	3.9	3.4
8	+1	+1	+1	82.4	80.9	49.3	50.9	24.3	6.5	7.5
9	-1.682	0	0	19.3	23.0	13.8	16.2	12.8	3.2	3.4
10	+1.682	0	0	90.3	89.0	49.3	44.2	25.4	4.5	3.4
11	0	-1.682	0	34.0	37.4	59.8	65.6	28.2	3.6	2.6
12	0	+1.682	0	65.2	66.9	73.0	65.6	44.8	0.3	0.5
13	0	0	-1.682	50.5	57.9	73.2	74.3	49.9	12.8	12.9
14	0	0	+1.682	51.7	54.1	45.5	41.7	30.8	10.6	9.7
15	0	0	0	55.5	56.0	67.4	65.6	34.1	4.7	4.8
16	0	0	0	55.9	56.0	65.4	65.6	36.9	5.1	4.8

17	0	0	0	56.8	56.0	68.7	65.6	37.5	4.8	4.8
18	0	0	0	57.3	56.0	64.6	65.6	32.5	4.7	4.8
19	0	0	0	53.7	56.0	62.5	65.6	32.4	4.9	4.8
20	0	0	0	57.7	56.0	64.7	65.6	36.5	4.4	4.8

[a] Constant conditions: all experiments were performed using the same raw materials; scale: 8.64 g (0.06 mol) of L-lactide (purity >99.5%, contents of water <80 ppm and free acids 0.3 mmol/kg; stirring rate 160 rpm, in an argon atmosphere.

[b] All $\hat{y}_i$ have been calculated from the quadratic model.

Conversion of lactide, $\hat{y}_1$ (%).

$$\hat{y}_1 = 56.0 + 19.6\, x_1 + 8.77\, x_2 - 1.12\, x_3 - 2.69\, x_1x_3 - 1.69\, x_2x_3 - 1.37\, x_2^2$$

Figure 4 shows the effect of conversion of lactide, $\hat{y}_1$ depends on the reaction time x_1 and catalyst concentration x_2, at the reaction temperature x_3 = +1.

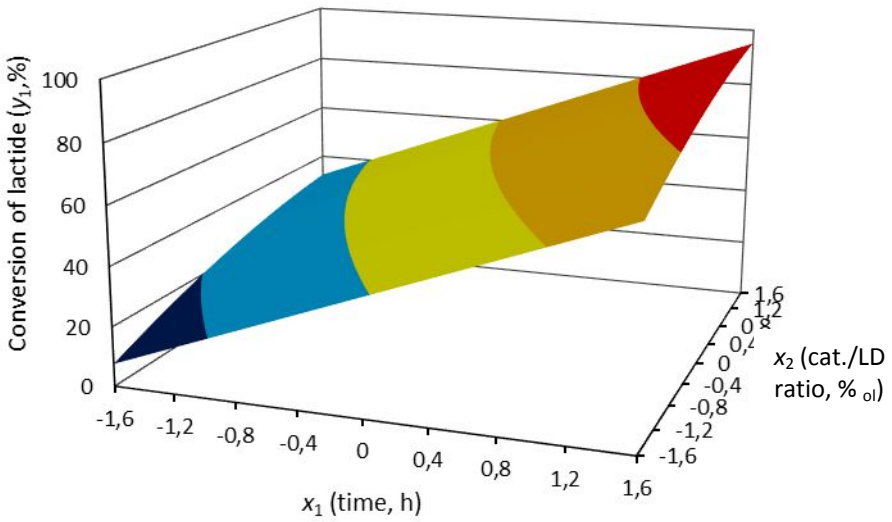


Figure 4. **The L-lactide conversion ($\hat{y}_1$) effect on the reaction time (x_1), and concentration of catalyst, (x_2); temperature (x_3) = +1.**

The molecular weight of PLA (M_w) $\hat{y}_2$, (kg/mol).

$$\hat{y}_2 = 65.6 + 8.32\ x_1 - 9.69\ x_3 + 1.88\ x_2x_3 - 12.5\ x_1^2 - 2.69\ x_3^2$$

Figure 5 shows the influence of PLA molecular weight ($\hat{y}_2$) depends on the reaction time (x_1) and temperature (x_3), at the catalyst concentration x_2 = +1.

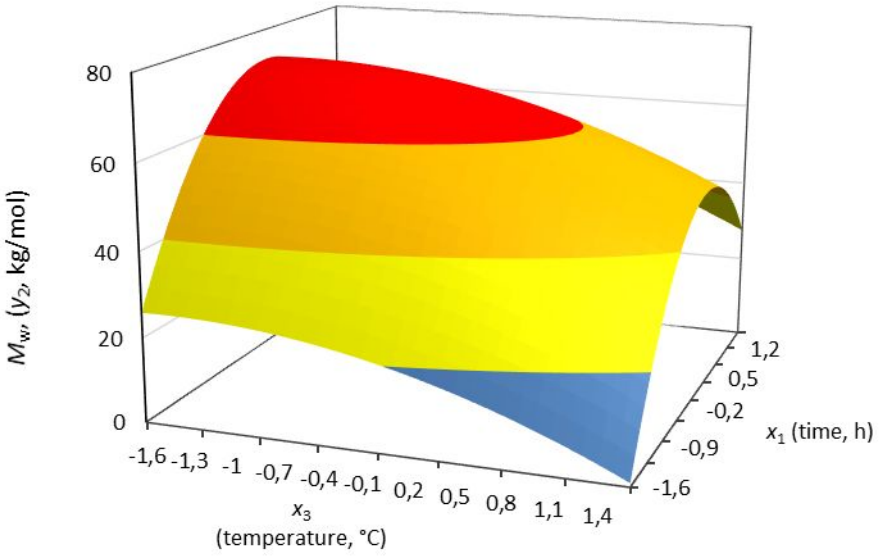


Figure 5. **The polylactide molecular weight ($\hat{y}_2$) in function on the reaction time (x_1) and temperature (x_3); catalyst concentration (x_2)=+1.**

Content of D centers in PLA (*%D*) ($\hat{y}_4$).

$$\hat{y}_4 = 4.79 - 0.63\ x_2 - 0.94\ x_3 + 0.73\ x_1x_2 + 1.30\ x_2x_3 + 1.60\ x_2x_3 - 0.49\ x_1^2 - 1.16$$

$$x_2^2 + 2.29\ x_3^2$$

Figure 6 shows the influence of the content of D centre in PLA (%D) ($\hat{y}_4$) on the catalyst concentration x_2 and temperature x_3, at the reaction time x_1 = +1.

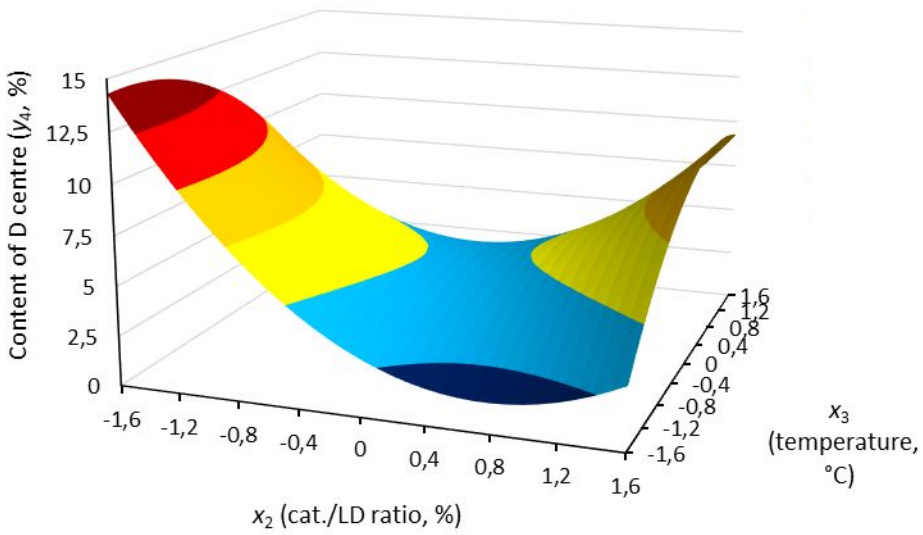


***Figure 6*. The content of D centre ($\hat{y}_4$) on the concentration of catalyst (x_2) and the temperature (x_3); reaction time (x_1)=+1**

The experimental data was described very well by obtained equations. An optimal point was calculated using the Microsoft Solver. The optimization criteria were to obtain the maximum molar mass with lactide conversion >80% with the content of D centre <15%. The coordinates of the optimal point are the following: z_1 = 4.7 h, z_2 = 0.08%$_{mol}$, z_3 = 176.8 °C. The result of the reaction under these conditions should be a polymer with M_w = 81.1

kg/mol and conversion of 84.5% and *%D*=8%. The PLA with M_w = 82.3 kg/mol and 85.0% conversion and *%D*=8.4% (Table 5) was obtained in a confirmatory experiment. The obtained result, in line with the forecast, testifies to the correctness of the equations obtained. The average molar mass of polymers was increased from 20.0 up to 70.0 kg/mol.[68]

Table 5. **Experimental and predicted results of polylactide synthesis with $ZnOct_2$ in optimal conditions**

Results	conversion (%)	M_w (kg/mol)	*%D* (%)
calculated	84.5	81.1	8.0
experimental	85.0	82.3	8.4

Scale-up of lactide polymerization

In determining optimal conditions, a large scale laboratory process was carried out at 50 g lactide. The reaction conditions were as follow: temperature – 175 °C, catalyst concentration – 0.08% and reaction time – 5 h. The reaction was conducted for 5 hours.

The scale of the process has been increased six times (Fig.6). The results were similar to those of optimization were obtained. The conversion of lactide differed approx. 1% (Table 6) and M_w by approx. 0.4 kg/mol. High compliance was also observed on the content of D centers (about 0.2%).

The scale was increased 25 times. The experiment was carried out at 2 L metal reactor. This apparatus can be used on a post-production medical PLA scale. The same proportions were tested as on the large laboratory scale. The results that were obtained also matched very well to those of smaller scales (lab and large laboratory). A polymer with a high 89.2% conversion and a higher molecular weight of 86.9 kg/mol was obtained. The content of D centers (9.6%) was similar to the one predicted by the optimization model. It can be concluded that the received models also work well on a larger scale.

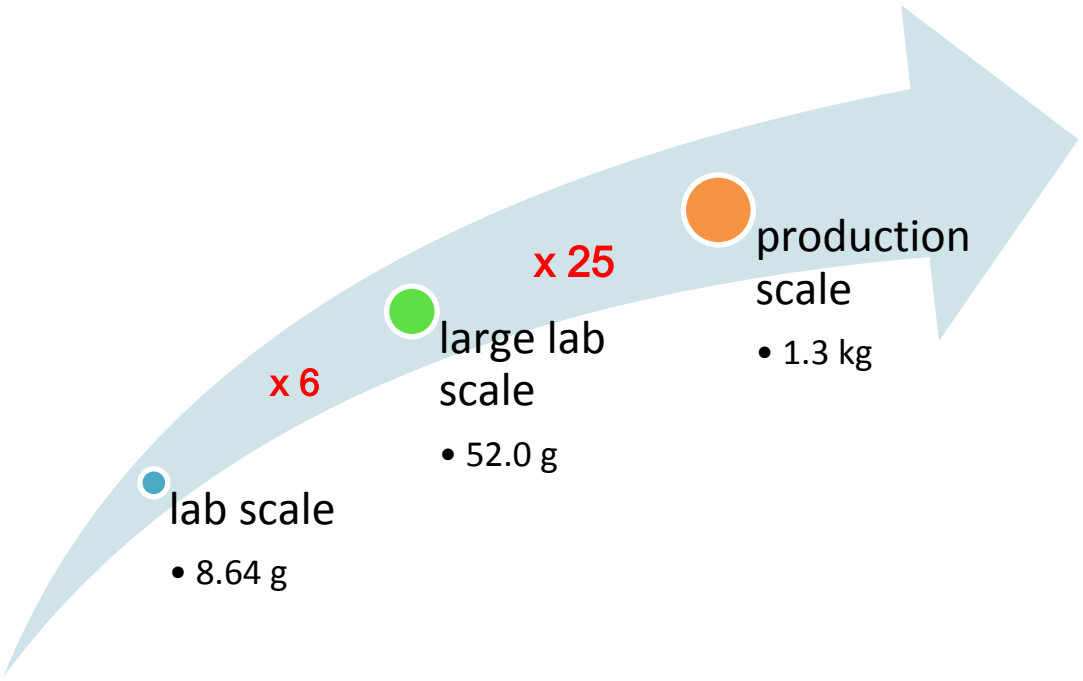


Figure 7. Process scale-up diagram

Table 6. Obtained results of L-lactide polymerization at different scales

Scale	LD mass (g)	conversion (%)	M_w (g/mol)	*%D* (%)
lab	8.64	85.0	82.3	8.4
large lab	52.0	85.9	81.9	8.6
production	1300	89.2	86.9	9.6

CONCLUSIONS

An original method for synthesis biocompatible catalysts was developed. It is based on the reaction of 2-ethylhexanoic acid with metals, e.g. zinc, calcium and magnesium. It was shown that $ZnOct_2$ is a very good, non-toxic catalyst for PLA production. The adequate mathematically models (conversion of lactide, PLA molecular weight and contents of D centre in the polymer) for lactide polymerization catalyzed by $ZnOct_2$ were obtained. Polymerization conditions with $ZnOct_2$ as catalyst were developed. The PLA was obtained with 85% lactide conversion and an average molecular weight of 82.3 kg/mol, and $D\%$=8.4%, without tin (II) residues. The obtained models have been shown to work well, even when scale-up. Convergent results were obtained with a 6- and 25-fold increase in scale. It has been shown that the developed process conditions can be transferred to a production scale.

ABBREVIATIONS

DoE, Design of Experiments; PLA, polylactide; $SnOct_2$, tin 2-ethylhexanoate; $CaOct_2$, calcium 2-ethylhexanoate; $MgOct_2$, magnesium 2-ethylhexanoate; $ZnOct_2$, zinc 2-ethylhexanoate; M_n, number average molecular weight; M_w, weight average molecular weight.

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Notes

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