UNIVERSIDADE ESTADUAL DE CAMPINAS
FACULDADE DE ENGENHARIA QUÍMICA

SARA CRIVELLIN

SYNTHESIS OF L-LACTIDE DIMER VIA REACTIVE DISTILLATION AND SYNTHESIS AND PROCESSING OF POLY (L-LACTIC ACID) (PLLA)

SÍNTESE DE DÍMERO L-LACTÍDEO VIA DESTILAÇÃO REATIVA E SÍNTESE E PROCESSAMENTO DE POLI (ÁCIDO L-LÁCTICO) (PLLA)

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Tese apresentada à Faculdade de Engenharia Química da Universidade Estadual de Campinas como parte dos Requisitos exigidos para a obtenção do título de Doutora em Engenharia Química

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Dedico este trabalho aos meus pais, Massimo e Carla, sempre presentes e ao meu namorado Gustavo que me apoia todos os dias.

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RESUMO

Esta proposta visa a produção de dímero de L-láctideo(LLT) em um processo de uma etapa. O dímero de lactídeo é um monômero importante produzido, normalmente, a partir da desidratação do ácido lático, seguida pelo processo de despolimerização do pré-polímero e posterior purificação. Como o ácido lático é uma molécula quiral, o lactídeo pode existir em três formas isoméricas: L-, D- e mesolactídeo. O dímero L- lactídeo é utilizado para sintetizar o polímero, Poli(L-ácido lático), de alta massa molar, por polimerização de abertura de anel (ROP). O interesse por este produto se deve aoalto valor no mercado mundial. Um dos itens que afeta este valor é o custo de produção e se deve a sua síntese demorada e a necessidade de controle rigoroso de temperatura e pressão, uso de catalisador, baixa seletividade, alto custo energético e racemização, o que permite chegar a um lactídeo de alta pureza. A rota inicial proposta para a produção de L-lactídeo é a destilação reativa, mas outras tecnologias para sintetizá-lo, como a produção do dímero via síntese de policondensação direta também foram estudadas. No cenário mundial, tem-se observado um grande número de publicações referentes tanto à produção do ácido lático (LA) e seus isômeros, como o LLA, quanto à síntese do poli(ácido lático) (PLA) e derivados (PLLA, PDLA, PLDLA), e pouco foi demonstrado sobre a síntese do dímero cíclico, lactídeo (LT). Esta é uma questão importante, pois para obter alguns produtos com características específicas, o processo de polimerização faz uso de lactídeo. Nos últimos anos, o grande potencial que os polímeros sintetizados em condições favoráveis possuem em termos de biodegradabilidade, biocompatibilidade e, em alguns casos, reabsorção, também tem sido amplamente divulgado. Dentre estes, o PLLA é conhecido por ser eficiente e utilizado em diversas áreas, desde a produção de embalagens até aplicações médicas, e também na impressão 3D (manufatura aditiva). A ausência de processo disponível na síntese de LT deixa uma lacuna que permite a avaliação de diferentes tecnologias para obtenção deste produto. Nesse sentido, este trabalho tem como ponto de partida desenvolver uma estratégia para obtenção do LLT. Para tanto, foram avaliadas a cinética de reação, o equilíbrio de fases e a influência das propriedades termodinâmicas para se chegar a um projeto de processo adequado. Os materiais obtidos são caracterizados por cromatografia de permeação em gel (GPC), calorimetria exploratória diferencial (DSC), espectroscopia de infravermelho por transformada de Fourier (FTIR) e microscopia eletrônica de varredura (MEV). Este trabalho propõe a apresentar uma rota viável de produção de LLT em uma etapa visando aumentar a produtividade do processo, a seletividade para o produto de interesse e a otimização do processo de síntese deste produto. Desta forma, em consonância com os objetivos, diferentes configurações foram propostas para a produção do dímero e do polímero PLLA, conseguindo apresentar um avanço no processo com aumento de escala na produção, passando de uma unidade de bancada para produção em uma planta piloto.

Palavras-chave: L-lactideo, Poli (L-Lactídeo), Processo de polimerização, Biomateriais.

ABSTRACT

This proposal aims at the production of L-lactide dimer (LLT) in a one-step process. Lactide dimer, normally is an important monomer produced from lactic acid dehydration, followed by the pre polymer depolymerization process, and subsequent purification. As lactic acid is a chiral molecule, lactide can exist in three isomeric forms: L-, D-, and meso-lactide. The dimer L-lactide is used to synthesize the polymer, poly (L-lactic acid), with high molar mass by ring-opening polymerization (ROP). The interest in this product is due to high value in the world market. This is due to the production cost with time-consuming synthesis and the need for strict temperature and pressure control, catalyst use, low selectivity, high energy cost, and racemization, to allows to obtain lactide of high purity. The initial proposed route for L-lactide production is reactive distillation, but other technologies to synthesize it, such as dimer production via direct polycondensation synthesis, have also been studied. In the world scenario it has been observed many publications referring both to the production oflactic acid (LA) and its isomers, such as LLA, and the synthesis of poly (lactic acid) (PLA) and derivatives (PLLA, PDLA, PLDLA), and little has been demonstrated about the synthesis of the cyclic dimer, lactide (LT). This is an important issue since to achieve some products with specific characteristics the polymerization process makesuse of lactide. In recent years the great potential that polymers synthesized under favorable conditions have in terms of biodegradability, biocompatibility, and, in some cases, reabsorption, has also been widely publicized. Among these, PLLA is known to be efficient and used in several areas, from packaging production to medical applications, and in 3D printing (additive manufacturing). The absence of available process on the synthesis of LT leaves a gap that allows the evaluation of different technologies to obtain this product. In this sense, the proposal of this project has as a starting point to develop a strategy to obtain LLT. To this end, the reaction kinetics, phase equilibrium, and the influence of thermodynamic properties will be evaluated to reach an adequate process design. The obtained materials will be characterized by gel permeation chromatography (GPC), differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), and scanning electron microscopy (SEM). In this work was proposed a suitable route to produce LLT in one step, aiming to increase the productivity of the process, the selectivity for the product of interest and the optimization of the synthesis process of this product. Taking these into account, different configurations were proposed to produce dimer and PLLA polymer, managing to present an advance in the process, and, therefore, an increase in scale production, with the use of a pilot plant.

Keywords: L-lactide, Poly (L-Lactide), Polymerization process, Biomaterials.

List of figures

List of Tables

List of abbreviations

LA	Lactic acid
LLA	L-lactic acid
LT	Lactide
LLT	L-lactide
PLA	Polylactic Acid
PLLA	Poly-L-Lactic Acid
ROP	Ring-Opening Polymerization
THF	Tetrahydrofuran
FTIR	Fourier Transform Infrared Spectroscopy
DSC	Differential Scanning Calorimetry
GPC	Gel Permeation Chromatography
XRD	X-ray Diffraction
SEM	Scanning Electron Microscopy
VPL	Net Present Value
IRR	Internal Rate of Return
CAPEX	Capital Expenditure
OPEX	Operating Expenditure
PTEA	Preliminary Techno-Economic analysis

Summary

Chapter 1

1.1 Introduction

Lactide (3,6-dimethyl-1,4-dioxane-2,5-dione) is indeed a cyclic dimer and a key intermediate in the production of poly (lactic acid) (PLA), a biodegradable polymer. It is commonly synthesized through the cyclic dimerization of lactic acid, resulting in the formation of a ring structure with two ester groups. There are two primary methods, which are normally used to produce lactide. The first one is dehydration of Lactic Acid (LA), in other words, lactic acid, which can be obtained from renewable resources like corn starch, sugarcane, or other biomass, undergoes a dehydration process to form lactide. The dehydration involves the removal of water molecules from lactic acid, resulting in the cyclic dimer Lactide(EHSANI; KHODABAKHSHI; ASGARI, 2014).

The second one is depolymerization of PLA; the polymer can be depolymerized, meaning it is broken down into its constituent lactic acid units. The lactic acid obtained through this depolymerization process can then be used to produce lactide, following the same dehydration process. Due to its time-consuming synthesis and the need for strict temperature and pressure control, catalyst use, low selectivity, high energy cost, and racemization, the value of a high purity lactide has a high cost in the market (CUNHA et al., 2022).

For this reason, to have an idea of the market and to see the trend in demand for this material, the price was checked as showed in Table 1.1. This was done because the aim is to propose possible production pathways focusing on industrial production, and so it is important to know the viability of the process. Normally, the production process is expensive due to factors such as racemization, and continuous control of temperature and pressure to produce the lactide cycle dimer (LT)(GHADAMYARI et al., 2018). It is also important to study the physical and chemical characteristics of the dimer through the experimental activities, possibly to develop a know-how which allows us to understand when the dimer is produced, and which are the most important variables to control.

	Price/gr (U$D) March 2022	Price/gr (U$D) July 2022	Price/gr (U$D) April 2023	var mar 22 - apr 23 USD
AK Scientific	1,81	2,63	14,00	672%
Alfa Aesar	3,74	3,89	4,20	12%
American Custom Chemicals Corporation	48,51	48,51	48,51	0%
Apollo scientific	4,60	4,60	3,35	-27%
Chem-Impex	2,02	2,60	2,67	32%
Crysdot	3,64	3,64	3,64	0%
Matrix Scientific	3,56	3,56	3,56	0%
Medical Isotopes, Inc.	8,80	8,80	8,80	0%
Sigma-Aldrich	2,92	5,71	6,65	128%
SynQuest Laboratories	7,36	7,36	7,36	0%
Polyscience	1,93	1,93	1,93	0%
TCI Chemical	2,77	3,64	3,64	31%
TRC	6,00	6,00	6,00	0%
Average	7,51	7,91	8,79	**15%**

Dolar price	mar-22	lug-22	apr-23
	4,739	5,173	5,072

Table 1.1 Lactide price in the market, according to the major selling industries [Author's source].

Moreover, there are reports and technologies that explain how can produce PLA and process improvements, but there is an absence of available materials for the synthesis of LT that leaves a gap in the literature.

Figure 1.1 shows how is found in scientific articles about the dimer lactide. It is possible to notice an increase in the last few years, at the same time there is little information about the synthesis and the processes to obtain the lactide; most of the works related to the synthesis of the dimer can be found in patents(CUNHA et al., 2022).

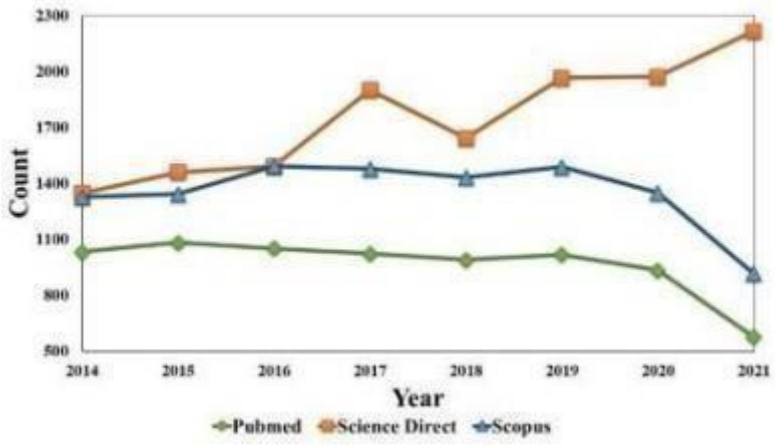

Figure 1.1: Publications about lactide in the last few years in common database research platforms for the search item “lactide” (CUNHA et al., 2022).

Another study was done in the Scopus search engine and Figure 1.2 shows how many articles have been found in the last few years in relation to the search for the item 'Reactive distillation' and 'Synthesis of lactide by reactive distillation'. It is noted that only two articles were found under the second item, one concerns a paper written in relation to this thesis and presented at the Naples congress, ICONBM-AIDIC, in 2022 (CRIVELLIN et al., 2022a). The second article found concerns the depolymerization of PLA for the production of the L-lactide(ALBERTI; ENTHALER, 2020).

In a national search, only two theses were found that delve into the work of lactide synthesis. The first focuses on the development of the synthesis and purification of the L-lactide and glycolide dimer for the production of poly(lactic-co-glycolic acid), (ELVIS et al., 2013): The second concerns a study of the synthesis process for the production of poly(lactic acid -co-glycolic) always starting from the two dimers (SOUZA, 2017).

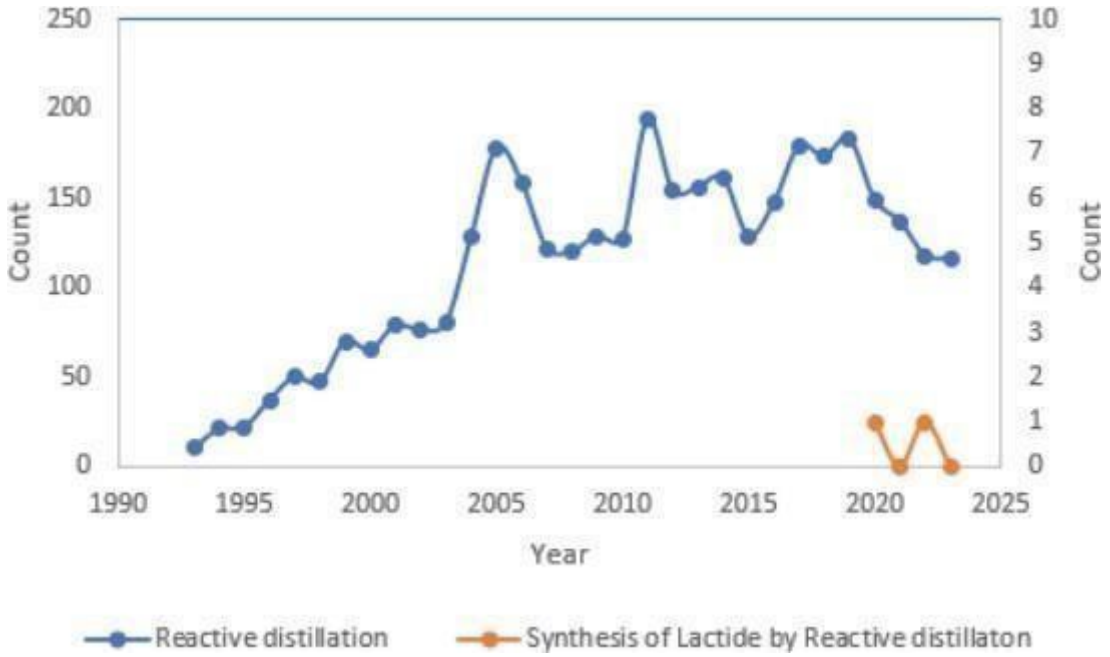

Figure 1.2: Research about items ‘Publications about Reactive distillation’ and ‘Synthesis of lactide by Reactive distillation’ in the last few years in database Scopus[Author’s source].

The attention regarding this dimer, L-lactide, is due to the fact that it allows to synthesize the final polymer, poly (L-lactic acid), through the route of the ring opening polymerization (ROP) in order to easily increase the molar mass.

The synthesis of PLA, an aliphatic polyester commonly obtained from α-hydroxy acids, is a multistep process that begins with the production of lactic acid (LA, 2-hydroxy propionic acid), normally produced by fermentation(KOMESU, 2015).

Fermentation to obtain lactic acid (LA) can be classified according to the bacteria used: the heterofermentative process means the equimolar production of lactic acid, acetic acid, ethanol, and carbon dioxide starting from hexose while the homofermentative process represents only the production of lactic acid by hexose metabolism (LASPRILLA et al., 2012a). The carbon source that enables the production of lactic acid can be sugar in the form of glucose, fructose, lactose, or from materials containing this sugar such as sugarcane bagasse, molasses, whey, and cassava bagasse. Normally the latter is used for an economic reason(MARTÍNEZ, 2011).

Whereas Brazil is expected to produce 661.4 million tons in 2023/2024, thus increasing by 6% from 2022/2023, due to favorable weather and rising sugar prices (SUGIARTI; MEYLINAH; OSINSKI, 2021). In addition, according to the United States Department of Agriculture Service, filed in April 2023, it said that the war in Ukraine had only a slight impact on the current sugar cane harvest because Brazil has managed to find alternative sources of fertilizers from beginning of the war, thanks also to the "diplomacy of fertilizers" 13 undertaken by the Brazilian Ministry of Agriculture (SUGIARTI; MEYLINAH; OSINSKI, 2021).

Although a characteristic was perceived in 2022, there was no negative impact on agricultural production or productivity because farmers used more efficient methods of applying the input (SUGIARTI; MEYLINAH; OSINSKI, 2021). Sugarcane is a raw material that is very abundant in Brazil according to FAO Statistics Division (2010) and for this reason, there is an interest and incentive for the production of lactic acid and its polymer (LASPRILLA et al., 2012a).

Normally sugar cane is used for the production of bioethanol and the waste material of the process is used for the production of the polymer, so it can be defined as a sustainable process (KWAN; HU; LIN, 2018).

Returning to the synthesis of LT and PLA, the interest lies mainly in the medical field. The two main synthesis routes determine a different molar mass. The synthesis through a direct polycondensation starting from L-lactic acid allows to obtain lower molar mass of the polymer compared to the polymerization synthesis through the opening of the cyclic Lactide ring. The molar mass of the former depends greatly on the reaction conditions and reaction time as the direct polymerization method concerns obtaining the

polymer, PLA, through condensation reactions between monomers without the formation of an intermediate oligomer. While the polymerization through ring opening, the lactide dimer, involves the formation of an oligomer starting from lactic acid, the consequent formation of the cyclic dimer and the opening of the same which allows to obtain the PLLA polymer with high molar mass (Mw> 100.00 Daltons) (JAMSHIDI; HYON; IKADA, 1988).

Depending on the synthesis route chosen, polymerization synthesis via direct polycondensation or polymerization via ring opening, it is possible to produce a polymer that can be used as a bio-healing, scaffold or even if it has a low molar mass as a facial filler, bio- ink(ANARAKI et al., 2015; NOFAR; SALEHIYAN; SINHA RAY, 2019).

According to the literature, PLA used as derma filler has a microparticles between 20 to 100 µm size and with a molar mass more or less between 70 to 500 kDa. (FERNEINI et al., 2014; PETER MORGAN; MACAKOVA, 2020).

PLA belongs to the class of synthetic biopolymers and in particular linear aliphatic polyesters also including poly (glycolic acid) (PGA), poly (lactide-glycolide) (PLGA), Poly (ε-caprolactone) (PCL), and poly (para-dioxanone) (PPDO). All these biopolymers and composites are used in the medical field, particularly in tissue engineering. In general, all these biopolymers have an advantage over those of natural origin, such as collagen, silk, and hyaluronic acid, to know, they can be produced on a large scale with easer processability and reproducibility and good mechanical characteristics depending on the synthesis variables (BALAJI et al., 2017).

Bearing all this in mind, the aim of this thesis is to try to synthesize l-lactide, LT, in a single step and to characterize it. With the aim of being able to synthesize the PLLA polymer through ring reopening synthesis and obtain a final high molar mass polymer for applications in the medical sector.

Furthermore, another important point is to use and study a process free of toxic and organic solvents and to support it with a 'green' theory. Normally, to increase the molar mass quickly during the synthesis process, many industries add diisocyanates(GHALIA; DAHMAN, 2017). These toxic compounds work in an effective way as an oligomer chain extender to modify and increase the molecular weight of biodegradable polymers.

1.2 Goals

This thesis aims to explain the synthesis and demonstrate the synthesis of L-lactide and PLLA through ring opening polymerization starting from an industrial L-lactic acid to produce a final polymer that meets the requirements of ANVISA and Food Drug Administration (FDA) for medical applications.

- Production of lactide by reactive distillation;
- Evaluation of the efficiency of different catalytic systems in the production of lactide by reactive distillation;
- Study and optimization of the catalysed reaction system using experimental planning;
- Determination of the lactide formation reaction and phase equilibria;
- Evaluation of the efficiency, selectivity, and yield of the process to obtain the L-lactide;
- Characterization of the lactide obtained by GC-MS, FT-IR, DSC, and TGA analysis;

1.3 Work organization

This work is divided into 8 chapters.

Chapter 1 presents a description of the topic and how it is presented on the market.

Chapter 2 presents the theoretical foundations with the main definitions of the topics necessary for the development of the work.

Chapter 3 presents a study relating to the thermodynamic and kinetic part in order to choose the parameters, mainly temperature, and pressure, to be used in the experimental part.

Chapter 4 presents the experimental part of the production of L-lactide in a single step and subsequently the synthesis of PLLA via ring-opening synthesis.

Chapter 5, the experimental part of L-lactide and PLLA production is presented at the same time via the direct polycondensation route, furthermore, in this chapter, the purification process is presented.

Chapter 6 presents the scale-up of the process shown in the previous chapter. the methodology and analysis for the characterization of the materials obtained.

Chapter 7, the application in the medical field, such as bio-inks, facial fillers, and, consequently, a business plan for a product in the cosmetic market.

Finally, Chapter 8, conclusions, and future ideas in relation to this thesis and the

doctoral path is presented.

The bibliographical references are presented at the end of this work.

1.4 The main contribution of this research

The primary objective of this thesis revolves around highlighting the significance of L-lactide and its production through a singular, one-step process. Another aspect also involves understanding the characteristic of this cyclic dimer, as its comprehensive characterization has been notably lacking within the existing literature.

That is another and no less important objective continue to improve the research done so far by my colleagues who have moved to the INCT-Biofabris laboratory, at the University of Campinas.

Furthermore, this doctoral thesis can be considered as a consequence of the study of the work done by Astrid Juliana Rancon,(JULIANA, 2011), who has already studied and explored the synthesis and synthesis parameters for the production reactions of L-lactide and PLLA, both through polycondensation both directly and via ring-opening polymerization.

Milena Lopes,(SAVIOLI LOPES, 2014), as a consequent work deepening both the synthesis and the purification part.

Ana Pattaro,(PATTARO, 2016) through copolymerization and the main study of PLLA obtained through ring-opening polymerization synthesis and applications, especially concerning electrospinning.

Finally, my current colleague Samuel Diogenes de Souza, (DE SOUZA, 2022), who has made it possible to significantly increase the knowledge of the synthesis through direct polycondensation and actively helping for the synthesis and results of this thesis on the production of L-lactide in a single step.

All processes were studied without using any type of solvent, continuing the laboratory's previous activities which focuses on 'Green' chemistry.

Chapter 2

2.1 Theoretical introduction

2.1.1 The cyclic dimer lactide

Lactide (LT) has different isomeric forms, namely (S,S)-L, (R,R)-D, and (S,R)/(R,S)-meso (as illustrated in Figure 2.1). Among these, L-lactide holds the distinction of being the most readily available in the commercial market(GUILLAUME et al., 2015; OVITT; COATES, 1999).

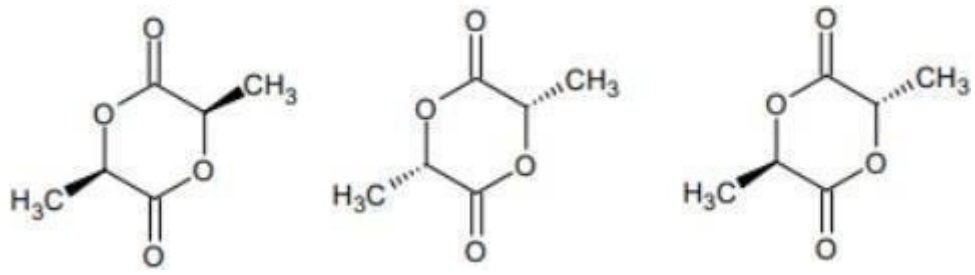

Figure 2.1: Chemical structure respectively of L-lactide, D-lactide, D, L-lactide, Source: Produced in ChemSketch based on(GROOT et al., 2010a).

The isomerism of the synthesized lactic acid is closely related to the optical activity of the lactic acid and this, in turn, significantly influences the properties of the resulting polymer. The melting temperatures (Tm) of the various lactide isomers vary: D- and L-lactide have a Tm range of 95-98°C, meso-lactide of 53-54°C, while rac-lactide has a Tm range of 122-126°C, as shown in Table 2.1 (CUNHA et al., 2022).

It is important to know what type of isomer are working with, because if start from enantiomerically pure monomers (L-lactide, D-lactide), the formation of a polymer with an isotactic structure occurs. However, if one starts from a meso-lactide, the resulting polymer acquires a syndiotactic structure, with an alternation of D-lactide and L-lactide monomers or even heterotactic, with an alternating sequence of two different monomers (STANFORD; DOVE, 2010). Ultimately, based on its solubility, lactide exhibits solubility in various solvents, including water, alcohols such as methanol and isopropanol, oxygenated solvents such as ethyl acetate, acetone, butanone, and tetrahydrofuran, as well as organochlorine solvents such as methylene chloride and chloroform. Furthermore, lactide shows solubility in organic solvents such as benzene, toluene, and xylene. In contact with water at room temperature, lactide undergoes

hydrolysis turning into lactic acid. Notably, the rate of hydrolysis is higher for meso-lactide than for D/L-lactide(JIN; TIAN; WANG, 2010; LIM; AURAS; RUBINO, 2008).

Physical Properties	L-Lactide	D-Lactide	Meso-lactide
Molecular weight (g/mol)	144.12	144.12	144.12
Optical rotation in degrees	-260	260	
Specific rotation (polarimetry toluene, 25 °C)	(-287)-(-300)	(+287)-(+300)	
Appearance	White crystal		
Melting point (°C)	95-100	95-100	53-54
Boiling point (°C)	255	142	
Heat of fusion (J/g)	146	118;128	120-170 (DSC 10 °C/min)
Heat of vaporization (kJ/mol)	63		
Solid density (g/mL)	1.32-1.38	1.32-1.38	
Liquid viscosity (mPas) (110 °C)	2.71		
Liquid viscosity (mPas) (120 °C)	2.23		
Liquid viscosity (mPas) (130 °C)	1.88		

Table 2.1: Lactide isomers properties (CUNHA et al., 2022).

In contact with water at room temperature, lactide undergoes hydrolysis turning into lactic acid. Notably, the rate of hydrolysis is higher for meso-lactide than for D/L-lactide(JIN; TIAN; WANG, 2010; LIM; AURAS; RUBINO, 2008).

According to Figure 2.2, starting from lactic acid, the most used route for the synthesis of lactide (LT) involves a pre-polymerization step through the dehydration of lactic acid (LA) (PARK et al., 2018).

This process includes the sequential addition of LA molecules, which leads to the formation of dimer (LA2) and trimer (LA3) species, which are then subjected to dehydration to yield L-lactide (L-LT) and meso-lactide (M- LT) with L and D configurations respectively. It should be noted that during heating, L-LT can easily convert to M-LT. The production of the dimer (LT) is particularly challenging and expensive aspect of this synthesis process. It requires high energy consumption, operates under high vacuum conditions, requires extended residence times, and involves high temperatures. Furthermore, obtaining optically pure LT presents difficulties and subsequent distillation/purification processes can introduce impurities into the final product, compromising its purity(HEO et al., 2019; PARK et al., 2018; VANWOUWE et al., 2016).

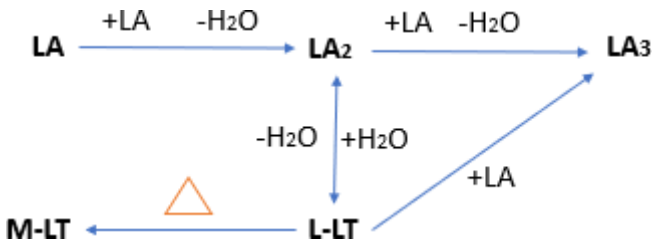

Figure 2.2: Pathways for synthesize LT adapted(PARK et al., 2018).

Consequently, when using different isomers for the synthesis of poly (lactide) through copolymerization, the resulting copolymers exhibit distinct thermal properties and unique macromolecular architectures(GROOT et al., 2010b; KOLSTAD, 1996; OVITT; COATES, 1999).

The differences observed in these copolymers depend on the specific reactions between the comonomers and the prevailing polymerization conditions, both of which significantly affect the conversion and distribution of the comonomers within the polymer chain(GROOT et al., 2010b; KOLSTAD, 1996). Ring-opening polymerization (ROP) offers better control over the distribution of comonomers in the polymer chain, thereby resulting in copolymers characterized by low polydispersity, high molar mass and abundant end groups, in contrast to polycondensation which results in a low molecular weight polymer(DECHY-CABARET; MARTIN-VACA; BOURISSOU, 2004).

2.1.2 Production of Lactide

The acquisition of lactide represents an interesting procedure to produce high molar mass polylactic acid (PLA) through ring-opening polymerization (ROP), as lactide serves as the fundamental monomer in this polymerization process. Regrettably, there is little research in the literature regarding the methodology for obtaining this crucial monomer. Numerous investigations have been undertaken to enhance the understanding of experimental parameters, as temperature, pressure, and quantity of catalyst, in addition to purification techniques.

These studies aim to evaluate their impact on the yield, selectivity, and purity of the resultant lactide. In the available literature, historical accounts reveal that

Carother(CAROTHERS; BOROUGH; NATTA, [s.d.]), was among the first to explore the reversible formation of lactide (LT) through the polycondensation reaction of lactic acid (LA). This exploration highlighted the potential use of temperature and pressure to favor the formation of the desired lactic product and, consequently, the production of LT. However, the presence of various coexisting species, such as lactic acid, water, higher oligomers, and other impurities, necessitates a purification process (potentially involving solvent-assisted purification, crystallization from the melt, or purification in the gas phase) for the crude LT. This purification step becomes indispensable to render LT suitable and applicable for ring-opening polymerization (ROP) reactions, and these steps are very expensive(LIM; AURAS; RUBINO, 2008; TSUJI, 2014), impacting the product final costs.

In the patent filed by Sinclair et.al,(SINCLAIR, 1992), is mentioned how produce lactide starting from Lactic acid. The feed for this production is composed by mixture of one or more of LA, L2A, and L3A, optionally with lactide (LT) being present. In addition, this patent claimed that the production of the dimer occurs through an "end-biting" reaction. They also suggested the recovery of the lactide from the low molar PLA mixture, ignoring the step in which the back-biting reaction occurs. They also pointed out that high temperatures are necessary for distillation the lactide to increase viscosity and molar mass. This technological process is due to the fact that if lactic acid presents higher oligomeric LAn species during the synthesis part of the production of LT, it could compromise the yield of the reaction of the production of the dimer. Furthermore, it must be taken into consideration that the removal of water presents the main force of this reaction. As Sinclair et.,(SINCLAIR, 1992), showed, if the removal of water is stopped from the moment that an oligomer is formed with two repeating units of lactic acid, the yield can be maximized and the reaction shifted towards the production of the product, i.e. LT.

Another process is the production of lactide through PLA depolymerization. The most important step for producing lactide (LT): (i) thermo-catalytic depolymerization of polylactide to produce lactide in the presence of cocatalyst; (ii) vaporization of the product during the reaction stage; (iii) product recovery through condensation; (iv) separation of L-, D-, or meso-lactide(EHSANI; KHODABAKHSHI; ASGARI, 2014).

The utilization of metal complexes in the lactide synthesis has been the subject of investigation(EHSANI; KHODABAKHSHI; ASGARI, 2014). Specifically, the implementation of tin-based catalysts under elevated temperature and reduced pressure

conditions led to a decrease in lactide yield, accompanied by an improvement in its purity(DONG; KIM; DOO, 2006).

This phenomenon is attributed to the higher depolymerization reaction rate observed at elevated temperatures and the acceleration of basic impurities' elimination facilitated by the low pressure, consequently minimizing racemization(EHSANI; KHODABAKHSHI; ASGARI, 2014).

2.2 Industrial production of lactide

At the moment, according to the literature, the first step of the industrial process, is when water is extracted from lactic acid to produce a low molar mass prepolymer (oligomer) without the need of solvents. Next, the second step involves catalysed depolymerization of the oligomer, resulting in the formation of the cyclic dimer (lactide), which is then purified via distillation (VINK et al., 2003).

Both of these steps require rigorous heating and vacuum conditions to facilitate continuous water and lactide removal. To ensure optimal results, the L-lactide selectivity should be maintained between 60 and 70% to prevent racemization and undesired by-products. Nevertheless, these conditions are energy-intensive, requiring extensive recycling and downstream purification steps, thus rendering the overall process to be expensive. In other words, because water must be removed in the most efficient way possible in order to move the reaction towards the products, i.e. in the production of the lactide(DE CLERCQ et al., 2018).

On an industrial scale, the conventional two-step lactide synthesis process is performed at 200°C, 5 mmHg, and with a 0.25%wt catalyst concentration (Sn(Oct)2) (NOFAR; SALEHIYAN; SINHA RAY, 2019), as illustrated in Figure 2.3. During this process, reactor R-1 drives lactic acid dehydration and polymerization under low pressure (50-200 mmHg) and high temperature (200°C). The formation of oligomers occurs through a self-catalysed esterification reaction, wherein equilibrium exists among monomers, oligomers, and water due to the reversibility of these reactions. To enhance lactic acid conversion, the water vapor is extracted from the reactor (stream 6) and directed to the water removal column (C-1) (HEO et al., 2019). According to Figure 2.3, the lactic acid oligomers formed in R-1 are fed into R-2, where a catalytic depolymerization reaction occurs, producing lactide. This reactor operates at vacuum pressure (10–50 mmHg) and high temperature (200–240 ◦C) to facilitate the reaction, vaporize and remove the

lactide(HEO et al., 2019). The unreacted oligomers are recycled (stream 11), and the high molecular weight oligomers are discarded (stream 13). Lastly, the crude lactide goes to the purification column (C-2), where the lactide is purified.

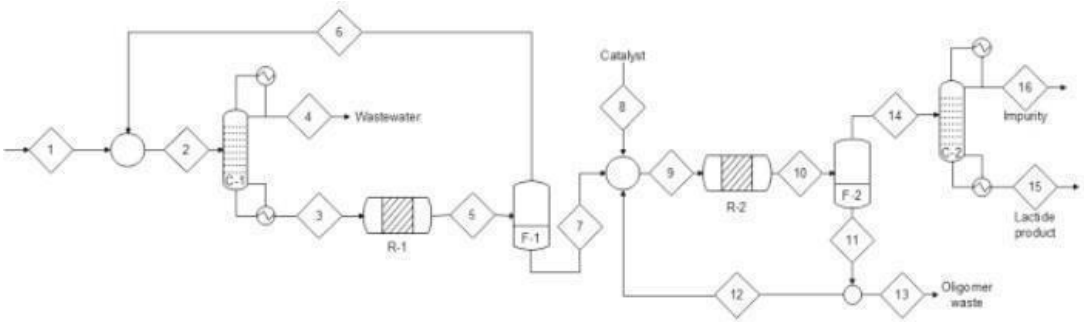

Figure 2.3: Two characteristic steps for the production of lactide where: (1) lactic acid stream, (2) lactic acid + reflux mixed stream, (3) dehydrated lactic acid stream, (4) wastewater, (5) dehydrated lactic acid stream, (6) lactic acid recovery, (7) R-1 liquid phase, (8) catalyst feed stream, (9) lactic acid + catalyst mixed stream,(10) oligomers stream, (11) unreacted oligomers stream, (12) unreacted oligomer recovery, (13) high molar mass oligomers, (14) crude lactide stream, (15) purified lactide stream, (16) 30 not purified lactide stream, (C-1, C-2) distillation columns, (R-1, R-2) polycondensation and depolymerization reactors, respectively, (F-1, F-2) heating duties (HEO et al., 2019).

The same author, Heo et al., (HEO et al., 2019) studied the one-step lactide production process as shown in Figure 2.4(HEO et al., 2019). The one-step lactide synthesis process commences with the combination of lactic acid and nitrogen, aiming to minimize the formation of oligomers. The mixture undergoes boiling in the preheater, H-1, before being directed into the reactor, R-1(HEO et al., 2019). The reactor, supported by SiO2/Al2O3 catalyst, operates at a high temperature range of 220–240 ◦C and can operate effectively under atmospheric pressure. Subsequently, the reactor product is routed to the first flash drum, F-1, where the separation of nitrogen and water from other compounds takes place. The wastewater is condensed and discarded in F-2, while a portion of the nitrogen gas is recycled and purged. The remaining crude lactidein F-1 is then sent to the distillation unit, C-1, which yields purified lactide as the final product(HEO et al., 2019).

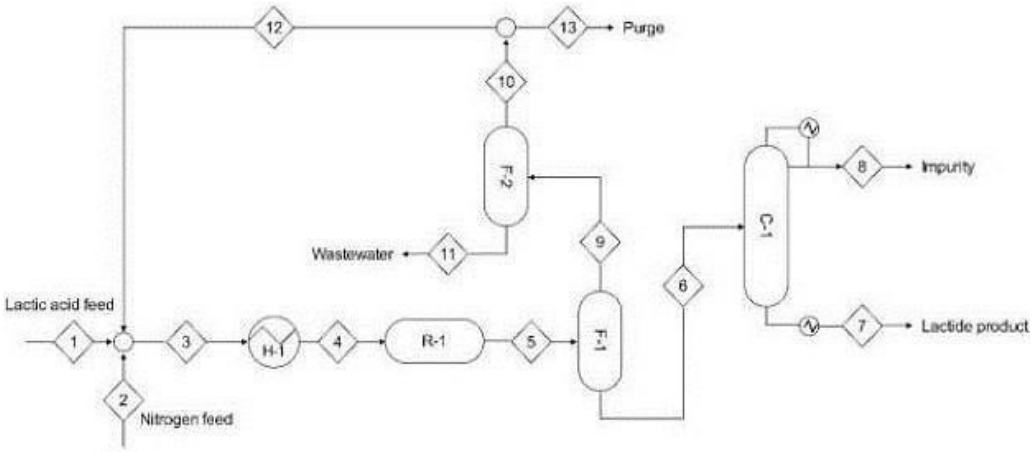

Figure 2.4: One-step lactide synthesis process: (1) lactic acid feed stream, (2) nitrogen stream, (3) lactic acid + N2 mixed stream, (4) vaporized mixed stream, (5) reactor outlet, (6) crude lactide stream, (7) purified 31 lactide, (8) not purified stream, (9) vapor outlet of the F-1 flash drum, (10) gas outlet, (11) waste water, (12) N2 gas recycling, (13) N2 purged, (R-1) fixed-bed plug flown reactor filled with SiO2/Al2O3, (H-1, F-1, F-2) heating duties, (C-1) distillation column(HEO et al., 2019).

At the end, Figure 2.5 depicts the Natureworks TM (Cargill Dow) plant design to produce lactide and PLA using a solvent-free process. The production of lactic acid, lactide and PLA, using food residues as an input stream and also mass balance demonstrated the feasibility of sustainable lactide production cycle with high yields for desired products, estimating a minimum selling price for lactide of about $2073 metric tons (TM)(KWAN; HU; LIN, 2018).

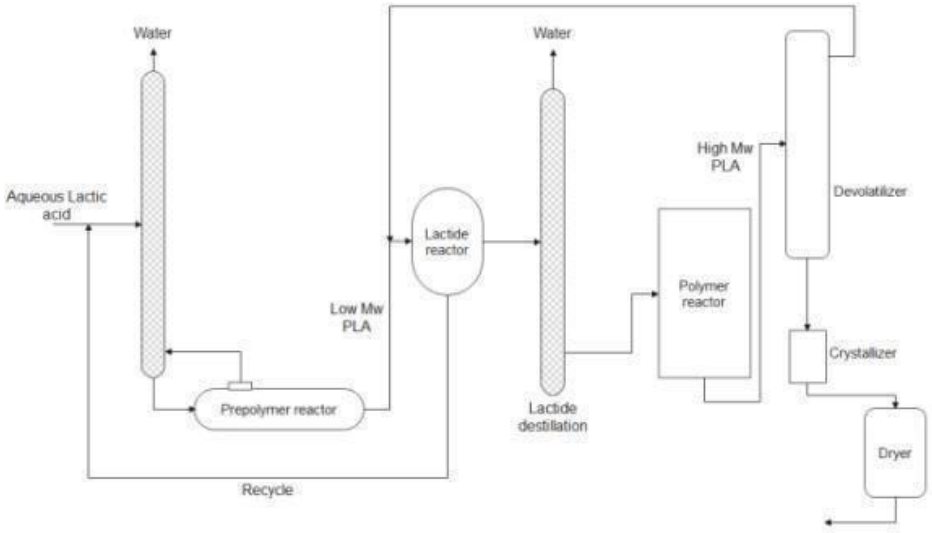

Figure 2.5: The scheme shows the NatureworksTM (Cargill Dow) plant design to produce lactide and PLA (KWAN; HU; LIN, 2018).

2.3 Reactive Distillation

Reactive distillation presents an interesting approach that enables chemical reactions and separation to occur simultaneously in a single step. Over the recent years, this distillation method has gained popularity in the process industry due to its ability to integrate chemical reactions with thermal separation, and in the end, decrease the design system complexity effectively. In this type of distillation, reactive solvents are introduced to facilitate selective reactions with specific components within the column, coexisting with fractional distillation in some or all stages of the process. Consequently, the desired products are formed and can be easily separated from the column.

This integrated approach proves advantageous as it reduces production and equipment design costs while enhancing process productivity. However, it's essential to note that this integration also brings some about increased complexity, with intricate considerations concerning liquid-vapor equilibrium, liquid-vapor mass transfer, liquid-solid mass transfer, intra-particle diffusion (heterogeneous catalysis), adsorption on the catalyst, and reaction kinetics (KISS et al., 2006).

Furthermore, reactive distillation was initially used in various processes because it allows solving problems in relation to reversible reactions: shifting the equilibrium towards the desired reactions, leading to high selectivity, facilitating separation for

azeotropic mixtures, shorter reaction times and finally reduction of process costs (BRAVO, 2022; HE; SINGH; THOMPSON, 2006; REEPMEYER; REPKE; WOZNY, 2004).

According to the patent number: 5,368,691, Roi et. Al in 1994, (ROI et al., 1994), patented the reactive distillation process which allows carrying out a catalytic reaction and isolating the required product by distillation, in which the liquid phase containing the reactants passes from the bottom upwards through at least one catalytic bed, without the vapor phase of the distillation passing through catalytic beds. According to Figure 2.6, these operating characteristics occur in a reactive distillation zone (C) comprising an alternation of distillation cells (D). Each reaction cell (R) is physically separated from the adjacent distillation cell(s) (D). The patent concerned the interest to be applied to the synthesis reactions of tertiary alkyl ethers by adding aliphatic mono 33 -alcohols (methanol, ethanol) on iso-olefins (isobutene, isopentene) (ROI et al., 1994).

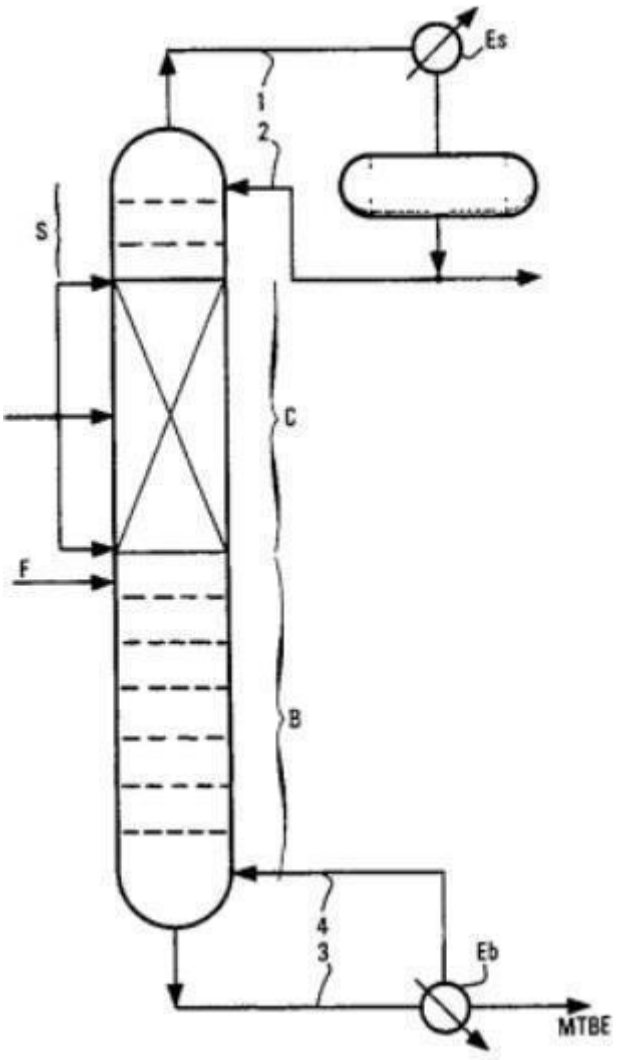

Figure 2.6: The reactive distillation scheme presented by Roi et. al, in the patent number 5,368,691 (ROI et al., 1994).

Regarding the reactive distillation in the synthesis of lactic acid (LA), Lunelli et.al,(LUNELLI, 2010), studied the process of esterification and purification of LA with ethanol to produce ethyl lactate. After this, Komesu et al,(KOMESU, 2015), in the 2015 studied the esterification process of LA with ethanol and the hydrolysis of the ethyl lactate formed in a reactive distillation system using the ASPEN PLUS® simulator was performed to recover LA with high purity. Furthermore, in the study carried out by Komesu,(KOMESU et al., 2015), an investigation was conducted to evaluate and optimize LA purification.

The experiments were performed using a reactive distillation system, focusing on assessing the impact of three key factors: the ethanol: LA molar ratio, reboiler temperature, and catalyst amount. The main goal was to produce ethyl lactate, which

could later be hydrolysed to obtain concentrated LA. The study identified the molar ratio of the reaction components as a significant influential variable(KOMESU et al., 2017). In their study, Dusselier et al., (DUSSELIER et al., 2015), introduced an innovative one-step liquid phase catalytic process for synthesizing LT using zeolite as a catalyst. The process employed a reactive distillation configuration with a unique water removal approach(DUSSELIER et al., 2015). The setup includes a stirred tank reactor, a condenser, a phase decanter, a liquid-liquid extraction apparatus (for solvent-water separation), an oligomer hydrolysis reactor (for process feedback), and an evaporator to facilitate solvent removal and crystallization LT(DUSSELIER et al., 2015). This new process enabled the direct synthesis of LT from an aqueous solution of LA by condensation, without the need for transesterification. Simultaneously, the removal of water took place during the LT ring-closing reaction. The study emphasized the complementarity of extraction and catalyst selectivity, which contributed to efficient water removal via solvent distillation and facilitated LT crystallization. As a result, this process integration has reduced the number of unit operations in the system, simplifying the whole procedure(DUSSELIER et al., 2015). In particular, the zeolite-based catalyst has shown remarkable regenerative capacities. It maintained its catalytic activity and selectivity up to 6 consecutive reactions, without any loss of performance(DUSSELIER et al., 2015). Finally, Alberti and Enthaler et al.,(ALBERTI; ENTHALER, 2020), used reactive distillation to obtain LT from the depolymerization of PLA products using zinc catalysts, establishing a catalysed chemical recycling method(ALBERTI; ENTHALER, 2020). A peculiarity of high molar mass PLA is that it has little flexibility. Therefore, any subsequent modifications to the processing to obtain films, with the use of electrospinning, should be taken into account(SEDUSH; CHVALUN, 2015).

2.4 Polymer synthesis

The synthesis of PLLA is usually a multi-step process that begins with the production of lactic acid (LA, 2-hydroxypropionic acid) via fermentation. For producing the final polymer, it is possible to opt for two main synthesis routes. The synthesis via direct polycondensation involves a condensation reaction that obtains PLLA by continuously eliminating the water molecule. This type of synthesis allows us to obtain a low molar mass polymer, depending on the reaction time. The longer the time, the more it is

possible to increase the polymer chain(LASPRILLA et al., 2012a; VANWOUWE et al., 2016).

If the objective is to achieve high molar masses, ring-opening polymerization synthesis (ROP) is the one that allows through a pre-polymerization, the synthesis of an oligomer and subsequently the synthesis of the cyclic dimer, L-lactide, to obtain a much greater molar mass, Mw > 100,000 Da. Figure 2.7 shows the two synthesis routes.

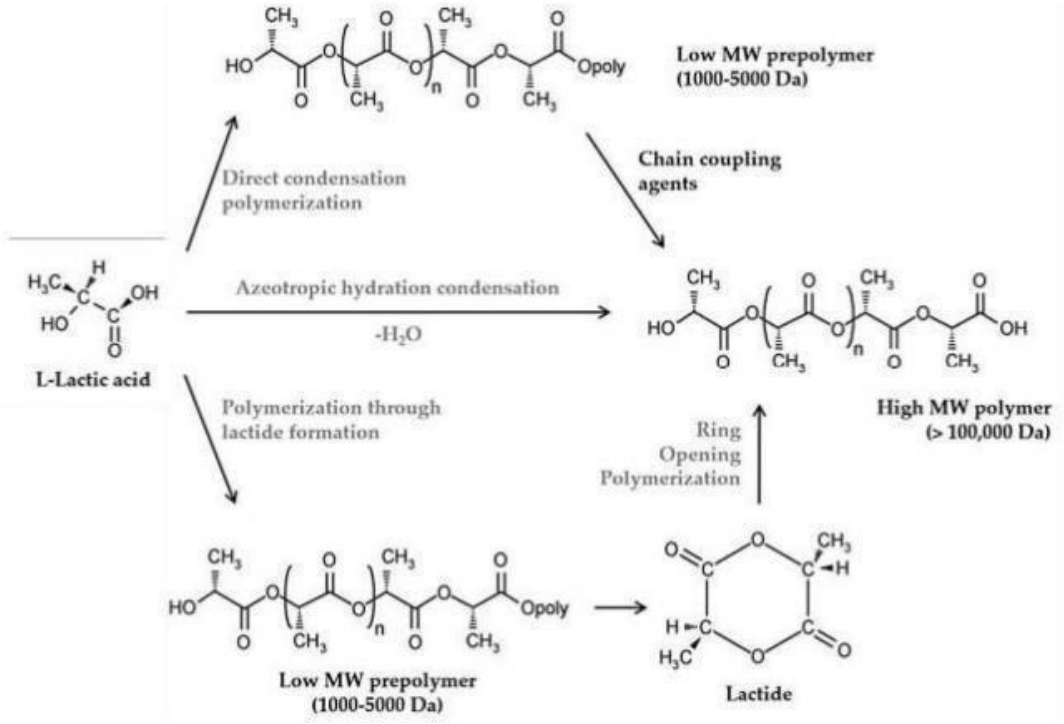

Figure 2.7: Productive routes for the synthesis of PLLA (LUNT, 1998)

For producing PLLA via the ROP route, mechanism chain as showed in Figure 2.8, the crucial objective is to control the LLT's optical purity as it directly impacts the properties of the eventual polymer. Therefore, achieving a high optical purity of LLT is essential for the production of PLLA with desirable characteristics (HEO et al., 2019; LASPRILLA et al., 2012a; SAVIOLI LOPES, 2014). The optical properties of the lactic acid utilized in lactides synthesis play a crucial role in determining the isomerism, ultimately influencing the properties of the final polymer(KOLSTAD, 1996).

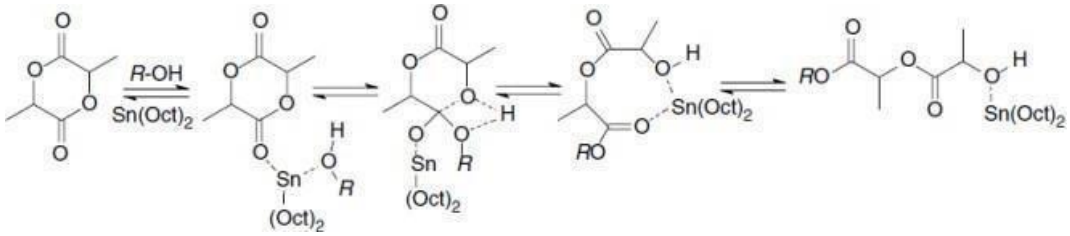

Figure 2.8: General mechanism of PLA chain growth by ROP (HENTON et al., 2005).

Although the physic or chemical properties of lactide do not vary significantly among its isomeric forms, they have a profound impact on polymerization reactions, resulting in poly(lactide) (PLA) with diverse properties and characteristics. These properties encompass tactile structures, melting point (Tm), mechanical properties, degradation rate, crystallization rate, extent of crystallization, and more (BOUYAHYI et al., 2011; CUNHA et al., 2022; DECHY-CABARET; MARTIN-VACA; BOURISSOU, 2004).
Among these characteristics, the Tm of lactide holds particular importance in polymer synthesis(SEDUSH; CHVALUN, 2015). This is because ring-opening polymerization (ROP) occurs at temperatures above the Tm of lactide and below the thermal degradation temperature of PLA(GROOT et al., 2010b; LIM; AURAS; RUBINO, 2008), thus, exerting a significant influence on polymer processing. The control of LLT production is essential to allow the synthesis of PLLA, in particular of the levorotatory stereoisomer(GROOT et al., 2010b).
Furthermore, PLLA can be synthesized using lactic acid produced through a fermentation process. Sugarcane bagasse serves as the feedstock for this production, where Rhizopusoryzae and Lactobacillus are added in solid-state fermentation (SSF) with sugar or hydrolysed starch as carbon sources(ROJAN et al., 2005). As Brazil boasts abundant sugarcane resources, according to the FAO Statistics Division (2010), there is considerable interest and incentive for lactic acid and its polymer production(LASPRILLA et al., 2012a). In particular, the process can be considered sustainable since sugar cane is commonly employed for the production of bioethanol and the waste material of this process is used for the production of polymers(DE OLIVEIRA, 2019; LASPRILLA et al., 2012b).

2.5 Biocompatible polymers

Poly (L-lactic acid) stands out as a crucial biopolymer in medical applications due to its exceptional biological, chemical, and physical properties. One of its remarkable features

is its excellent thermal processability, allowing it to undergo conventional polymer processing methods such as injection, extrusion, thermoforming, and spinning. Compared to petroleum-based polymers, its production demands significantly less energy, making it an environmentally favorable choice (CUNHA et al., 2022). PLA exists in different stereoisomers, specifically PDLA and PLLA, which are determined by the isomers of lactic acid (LA): L-lactic acid (L-LA) and D-lactic acid (D-LA). The specific stereoisomer used in the synthesis of the polymer plays a pivotal role in its production, effectively controlling the resulting isomer. This monomer's significance lies in its ability to influence the processing, crystallization, and degradation behavior of PLA, with the stereochemical structure of PLA being profoundly impacted by both Lactic acid isomers and lactide isomers(AURAS; HARTE; SELKE, 2004).

The PLA and other polymer can be defined ad biopolymers, and this means all those polymers that are produced from natural resources including plants and animals.

Polymers which are used to replace biological structures, which are used as supplements for tissue healing and to speed up the regeneration of the latter, are defined as biocompatible(BALAJI et al., 2017; SHIROUD HEIDARI et al., 2023).

Finally, those polymers that break down into smaller, biologically acceptable molecules are classified as biodegradable. Based on these definitions, there are polymers that are biodegradable and biocompatible which in turn can be classified into natural and synthetic polymers(BALAJI et al., 2017; SHIROUD HEIDARI et al., 2023).

Natural polymers for instance collagen, gelatin, silk, and hyaluronic acid are widely used in tissue engineering. Natural polymers have excellent characteristics in relation to cell attachment and differentiation and mimic the native extracellular matrix (ECM), but unlike artificial ones, it is complicated to control their synthesis(BALAJI et al., 2017; SHIROUD HEIDARI et al., 2023). The most important synthetic biopolymers are the aliphatic polyester family: polylactide (PLA), poly (glycolic acid) (PGA), poly (lactide-co-glycolide) (PLGA), Poly (ε-caprolactone) PCL, and poly (para -dioxanone) (PPDO) (BALAJI et al., 2017; SHIROUD HEIDARI et al., 2023).

Unlike natural biopolymers, the latter can be easily synthesized and manufactured on a large scale, are simpler to process and reproduce, have good mechanical characteristics, and moreover, controlled degradation (SHIROUD HEIDARI et al., 2023).

These polymers can normally be synthesized according to different techniques which are shown in Figure 2.9.

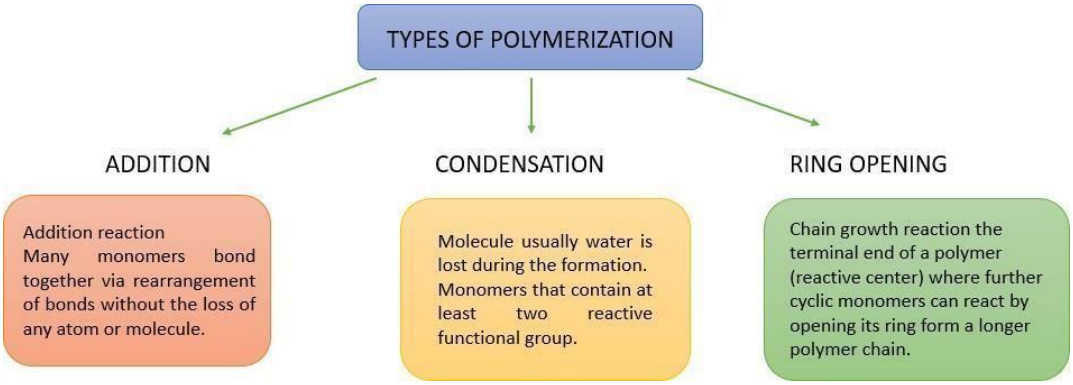

Figure 2.9: Definition on different polymerization techniques (BALAJI et al., 2017).

In this thesis, would like to test the possibility the synthesis of PLLA via the ROP pathway starting from L-lactide which is synthesized in a single step, furthermore attention is paid to the L- isomer, as it specifically starts from L-lactic acid.

Remember that several stereoisomers are found, specifically PDLA and PLLA, which are determined by the isomers of lactic acid (LA): L-lactic acid (L-LA) and D-lactic acid (D-LA). The specific stereoisomer used in the synthesis of the polymer plays a pivotal role in its production, effectively controlling the resulting isomer. This monomer's significance lies in its ability to influence the processing, crystallization, and degradation behaviour of PLA, with the stereochemical structure of PLA being profoundly impacted by both Lactic acid isomers and lactide isomers (AURAS; HARTE; SELKE, 2004).

The presence of either L- or D-monomers significantly affects the physical characteristics of the final polymer. For instance, PLLA polymer exhibits the highest melting point among various types of PLA due to its crystalline nature. Conversely, when the D-isomer is incorporated into the PLA chain, it reduces the polymer' s crystallinity, leading to lower melting points in PLA copolymers until they become amorphous with D contents exceeding 12% (CUNHA et al., 2022).

2.6 Preliminary comments

After a bibliographic search, a lack was noticed relating to the topics of reactive distillation and above all in relation to the L-lactide dimer. The production and synthesis of the dimer and above all the synthesis conditions such as pressure and temperature are not clear. As a result, we do not see many works related to the synthesis of poly (L-lactic acid) via ring opening, recognizing this biopolymer as a potential material

especially in the medical field.

Chapter 3

3.1 Introduction

In chapter 3 the kinetic mechanism relating to the synthesis of PLLA via the ring-opening route and using L-lactide as an intermediate is described. Attention is paid to the production of L-lactide, and an analysis is done in the commercial software Aspen Plus to see what the optimal variables are for synthesizing the cyclic dimer, LLT. Furthermore, this analysis is deepened by the Differential Scanning Calorimetry (DSC) analysis which allows the analysis of physical processes, such as the melting temperature, cold crystallization and vitreous transition of polymeric materials.

3.2 Preliminary investigation on L-lactide formation reaction

At the beginning of the experimental part, several studies were carried out to understand the best parameters to start the production reaction of L-lactide starting from the L-isomer of lactic acid.

It was initially based on the work of Rueda's Master Degree, (MARTÍNEZ, 2011), who simulated in the commercial software AspenPlus, the production of the PLLA polymer starting from a lactic acid obtained through fermentation.

As regards the kinetic part, it was taken into consideration that follows the model of step growth polymerization, used by Seavey et al, (SEAVEY C. KEVIN, 2008) also known as condensation polymerization. It is a process of formation of a polymer in which reactive molecules, often bifunctional or multifunctional, come together through condensation reactions to form covalent bonds and create the polymer(ROGERS; LONG; TURNER, 2003).

The kinetic mechanism is represented by:

$$LA + LA \leftrightarrow P_2 + W \quad (1)$$

$$P_n + LA \leftrightarrow P_{n+1} + W \quad (2)$$

$$P_n + P_m \leftrightarrow P_{m+n} + W \quad (3)$$

$$P_2 \leftrightarrow C_2 + W \quad (4)$$

$$LA + C_2 \leftrightarrow P_3 \quad (5)$$

$$P_n + C_2 \leftrightarrow P_{n+2} \quad (6)$$

The first three equations represent the formation of the oligomer, where note esterification reactions that produce PLA molecules with low molecular weight, and their respective reversible reactions (hydrolysis). Pn is an oligomer with n lactic acid units when n=2 is the oligomer of the linear dimer. In the presence of tin octanoate, the catalyst, the two terminal groups of the linear oligomer can also react with each other, forming a closed-ring lactide dimer, this reaction is particularly favored for linear dimers, dilactic acid, therefore equation (4) represents this reaction, and its reverse reaction (hydrolysis)(MARTÍNEZ, 2011).

This study proved how important the elimination of water was during the reaction and also how important it was to use high temperatures and low pressures for the production of L-lactide. In the work done by Rueda,(MARTÍNEZ, 2011), a temperature of 200°C in vacuum was chosen in the simulation for the production of the cyclic dimer, with a liquid/vapor phase reactor.

For this reason, a simulation was started in Aspen to reorganize Rueda's simulation and Seavey's study to block the synthesis at the LLT cyclic dimer.

Components of the reaction under examination were introduced such as L-lactic acid, water, the catalyst, the L-lactide dimer and the linear dimer which allows the closure of the molecule and the formation of the desired product.

Some parameters of the lactide component are not present in the AspenPlus database, so it was not easy to obtain a complete simulation. However, to study the optimal parameters to be able to start the experimental part, a simulation was carried out where the behaviour of the binary mixture L-lactic acid and l-lactide was investigated, taking into account temperature and liquid/vapour mole fraction of the components.

Figure 3.1, relating to temperature, shows exactly how for 0.005 moles of LLT fraction in the LLA-LLT mixture the first drop of vapor occurs at exactly 225°C while Figure 3.2, relating to pressure, shows exactly that for LLT to evaporate in the mixture requires a very low pressure tending towards vacuum. This agrees with Rueda's simulation that found that temperature of 200°C in the L-lactide formation reactor and a pressure close to vacuum were suitable operational conditions.

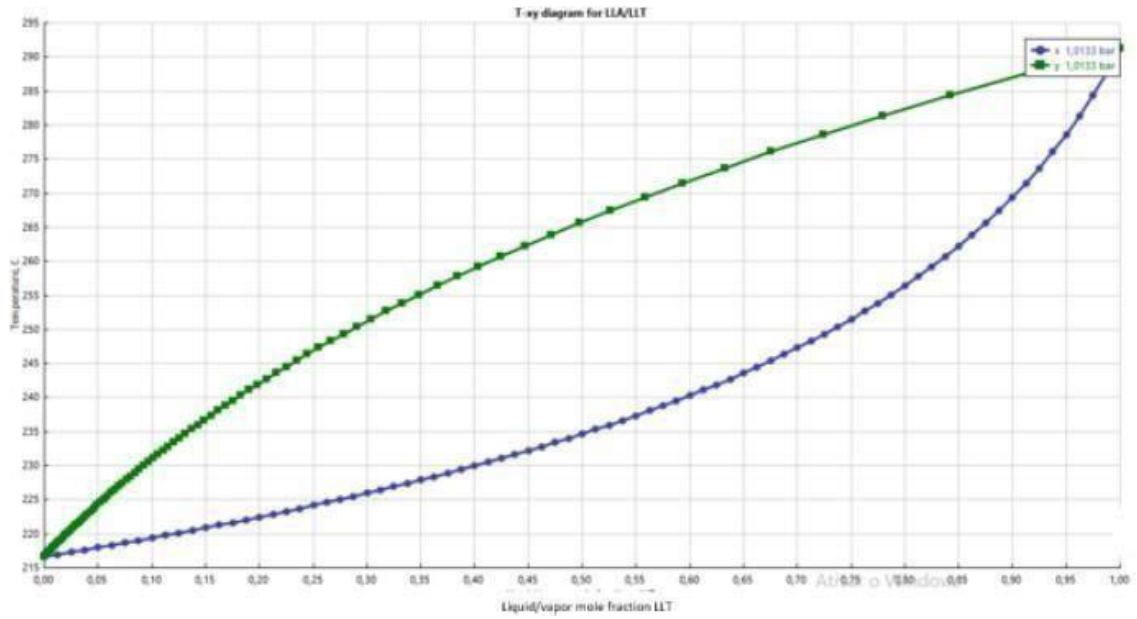

Figure 3.1: Binary mixture liquid/vapor mole fraction with the LLT vary VS temperature [Author's source].

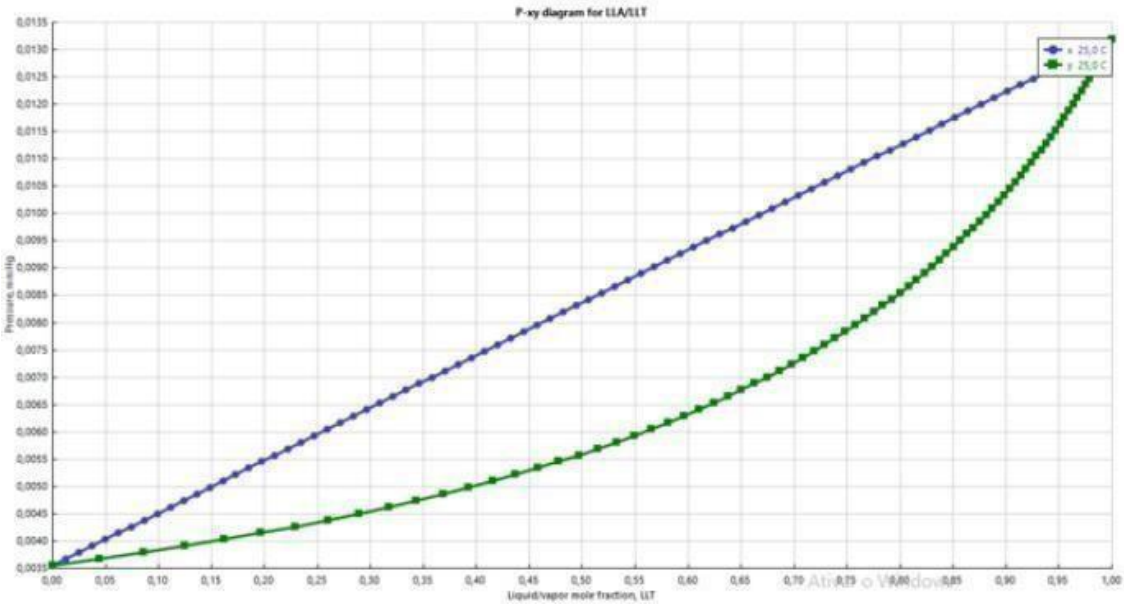

Figure 3.2: Binary mixture liquid/vapor mole fraction with the LLT vary VS pressure [Author's source].

This information is important to define the operational conditions of the experimental process.

3.3 Study of the process synthesis to produce L-lactide via Differential Scanning Calorimetry (DSC)

The Differential Scanning Calorimetry (DSC) technique is used to analyse the physical processes of melting, crystallization, and vitreous transition of a polymeric material. Furthermore, it is also used to analyse a chemical process, such as the polymerization and degradation of a material(VYAZOVKIN, 2006)

For this last reason, this technique was used to visualize some kinetic parameters of the production reaction of L-lactide starting from L-lactic acid.

For the analyses, a Mettler Toledo model DSC1 was used in the Recursos Analíticos e de Calibração (LRAC) laboratory, located in the Universidade Estadual de Campinas (UNICAMP).

A small amount of L-lactic acid containing the catalyst (EstahnoOctanoate II) should be collected with the help of a glass paste pipette and weighed in containers of Al (40 uL) using a microanalytical balance, placing between 3-10 mg of material. Afterwards the cadens were sealed with a perforated lid and attached individually to the equipment for analyses.

The samples were subjected to temperature variations at different heating rates, 10 and 20 °C/min, under a nitrogen atmosphere (50 mL/min), to simulate the L-lactide synthesis reaction.

Knowing the boiling temperature of L-lactic acid of 140°C, the formation temperature of L-lactide within 220-240°C and the degradation temperature of PLLA between 280°C-300°C, it was taken into consideration a range between 25°C and 350°C to carry out the analyses.

Table 3.1 presents the different phases of analysis; cooling was carried out to clear the thermal history of the first heating.

Ratio rate	Heating	Isotherm	Cooling	Isotherm	Heating
10 °C/min	25 - 350°C	350°C for 2 min	350 - 25 °C	25°C for 2 min	25 - 200 °C
20 °C/min	25 - 350°C	350°C for 2 min	350 - 25°C	25°C for 2 min	25 - 200 °C

Table 3.1: the different phases of analysis done in the DSC equipment to view the steps of L-lactide synthesis [Author's source].

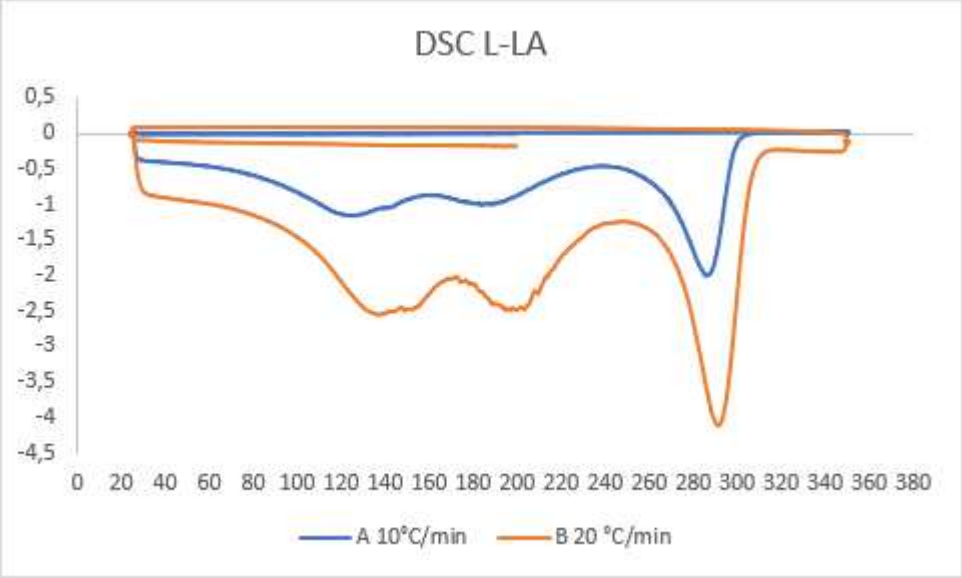

Figure 3.3: DSC analysis for the synthesis of L-lactide [Author's source].

It can be observed, according to Figure 3.3, that at approximately 140°C there is a phase transition relating to the fusion of L-lactic acid and immediately afterwards, at the beginning of 200°C a variation which probably presents the starting of the formation of cyclic dimer while in the last peak between 280°C and 300°C a probable degradation of the material is noted.

It can be seen how in the graph during cooling it returns to the starting point, proving the reversibility of the reaction, and finally, again from the graph, the speed of production of L-lactide is depicted since at 140 °C, the fusion of L-lactide begins leading the lactic acid to react with action of the catalyst.

3.4 Preliminary comments

In relation to the kinetic study carried out, it is necessary to note the importance of a simultaneous control of pressure and temperatures for the formation of L-lactide, respectively of a temperature close to 220°C and a pressure close to vacuum.

Furthermore, from the

kinetics we note that the formation of the cyclic dimer is linked to the formation of the linear dimer which with the continuous withdrawal of water allows cyclization.

Finally, from the DSC diagram it is concluded that at a temperature of 220°C the formation of the dimer is noted. This preliminary study helps to define the initial parameters for the experimental investigation. The complete simulation of Aspen was not carried out due to the lack of all properties in the Aspen database, which would require the establishment of a methodology to predict such properties. This activity is suggested as a future work to be developed by anybody else.

Chapter 4

4.1 Introduction

In chapter 4 the experimental part is presented because of the previous chapter. Thanks to the analyses carried out, the pressure and temperature parameters studied were used in the following chapter. In particular, the synthesis of L-lactide is presented starting from L-lactic acid in a single step, trying to optimize the reaction and subsequently be able to synthesize the PLLA polymer via ring opening to synthesize the high molar mass polymer.

4.2 Experimental part

In this Chapter the production of L-lactide was studied experimentally through reactive distillation based on the study done in Chapter 3 as well as based on the theoretical and literature information described in Chapter 2. The goal is to not only generate the cyclic dimer efficiently in one way, but also to do so without the use of any toxic solvents. Additionally, the quantity of solvent and catalyst should adhere to the guidelines set forth by the FDA and Anvisa for materials utilized in the medical field.

4.3 Material

The material used is L-lactic acid (LLA) 85% (Synth), Tin-Octanoate 2 (OctSt-II) (Sigma Aldrich), 1-dodecanol (Vetec), as catalyst and co-catalyst respectively.

4.4 Methods

4.4.1 Reactive Distillation

As a first proposal to produce L-lactide in one step, the reactive distillation column was proposed.

The equipment, as showed in Figure 4.1, is composed of a single column where the separation process takes place and a reactive part where the production of the dimer should happen.

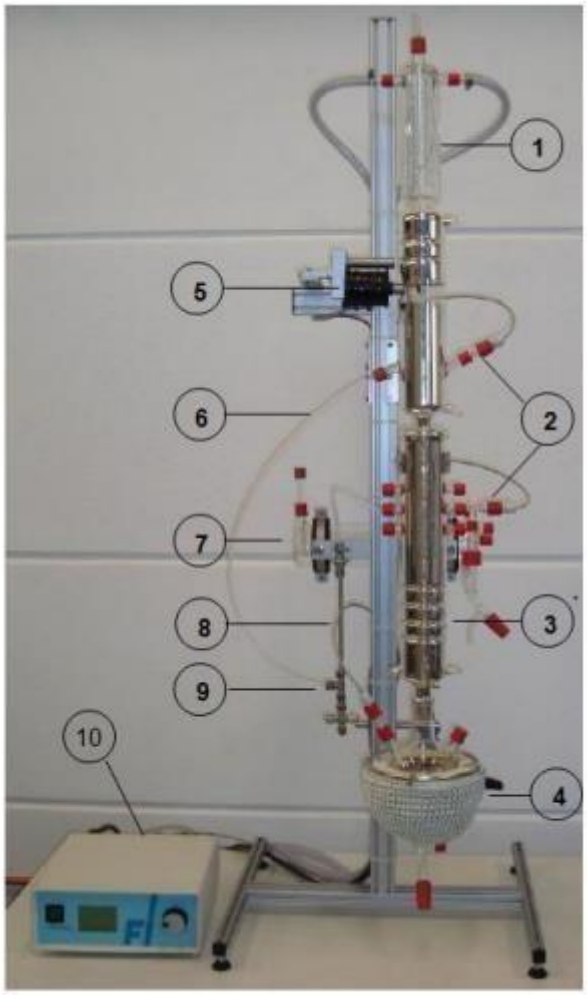

Figure 4.1: Reactive distillation system. (1) condenser, (2) thermocouples, (3) reactive distillation column, (4) reboiler, (5) solenoid valve, (6) recycle, (7) decanter, (8) pre-reactor, (9) mixer, (10) controller [Author's source].

The described column is built up with perforated borosilicate glass plates, with a plate distance of 30 mm. The column is equipped with a vacuum jacket to ensure thermal insulation and temperature control is achieved using thermocouples to measure the temperature in several parts of the rig. The catalyst employed for this reaction is SnOct(II), which is the same catalyst used in another synthesis route for PLLA

production, namely the synthesis via direct polycondensation route. The column operates under atmospheric pressure.

Before stating the equipment operation, a thorough cleaning process was undertaken to remove residues resulting from a biomass purification process from other studies carried out in another research. Additionally, some electrical components were replaced due to extended periods of activity.

The initial test involved feeding L-lactic acid along with the appropriate amount of catalyst stands co-catalyst, namely 1 wt% and 0.0025 wt%, respectively, as approved by Anvisa and the FDA. The feeding process was facilitated by a peristaltic pump.

During the start-up period of the equipment, an accurate check was carried out on the various components and a problem was noted relating to the control of the thermocouples. To resolve the problem, the electrical system was inspected. Furthermore, during the first test it was noted that the column operated only at atmospheric pressure which would not be ideal relative to the preliminary study presented in Chapter 3.

It has been shown how important the simultaneous control of pressure and temperature is, respectively a pressure close to vacuum and a temperature between 200 and 240°C. During the experiment, thanks to a safety control of the equipment itself, it was not possible to work under pressure or vacuum and to reach the minimum temperature, thus making impossible to reach the synthesis conditions previously identified. was deduced. This reactive distillation does not allow, due to its configuration, to achieve the required vacuum, probably due to the fragility of the internal components and so we began to study a similar configuration with other glass units that could allow to obtain synthesis conditions.

The aim was to synthesize the dimer, L-lactide, and subject the system to pressure to obtain the formation of the desire product, as show Figure 4.2.

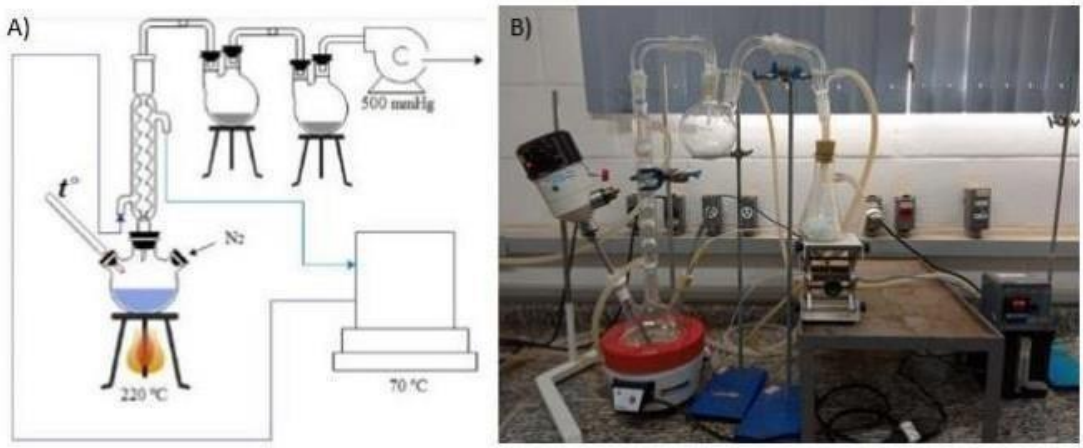

Figure 4.2: the part a) represents the scheme done introducing o N2 and, the part b) represents the scheme with glass experimental units without N2 [Author's source].

The feed to the first reactor is with L-lactic acid, kept under constant stirring, with a stream of N2 which allows to increase the conversion of the reaction and with a temperature not lower than 220, because L-lactide is formed at a temperature between 220 and 240°C with a pressure between -500/-550 mmHg, and the formation is very fast, by controlling the pressure, to be able to remove water more efficiently and thus increase the conversion of the system.

The same simulation is done without the N_2 stream, it has been noted that the use of N_2 does not increase the efficiency of water removal from the system, but rather does not allow rapid evaporation, given by the contrast between the evaporation of the water and of particles of L-lactic acid with N_2 top pressure being applied, resulting in a lactide with yellow colour, as showed a Figure 4.3a, and with water, instead of crystals, as showed the Figure 4.3b.

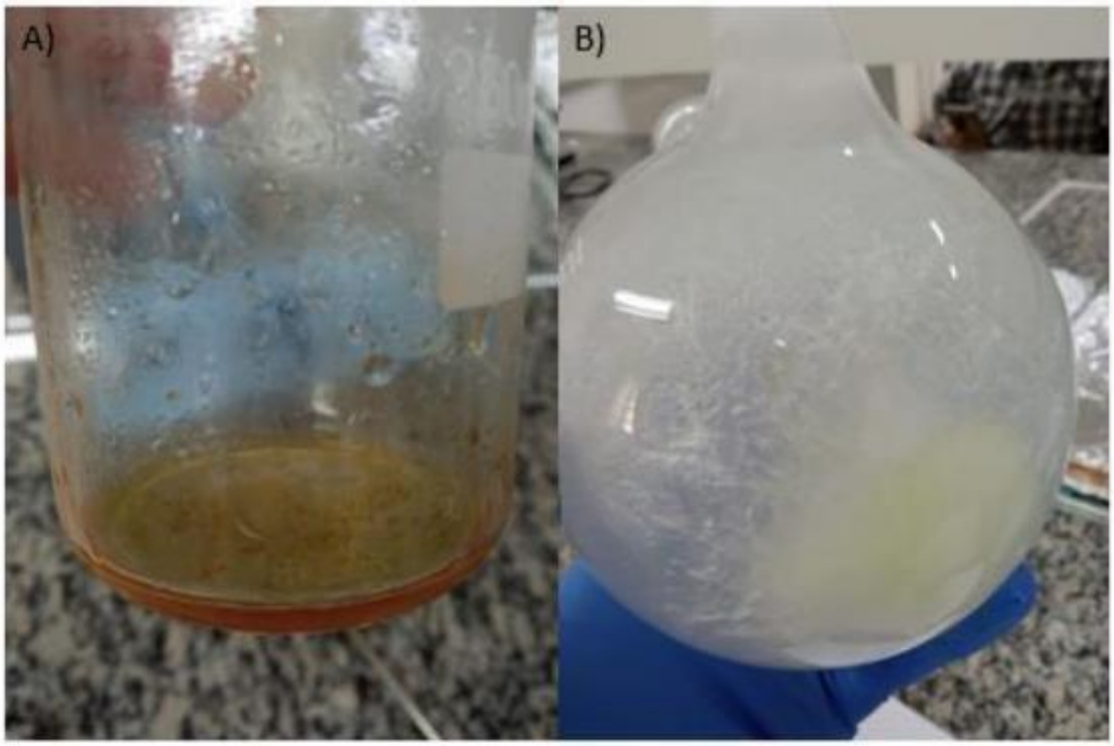

Figure 4.3: The part a) represents the L-lactide produced with N2 and the part b) represent the L-lactide produced without N2 [Author's source].

For this reason, this experimental study demonstrates that it is not necessary to use the inert gas N_2 which is helpful to reduce the production cost. The aim is not only to synthesize L-lactide in a single step but also to try to find a solution as simple as possible with as lower as possible environmental impact.

4.4.2 Production of L-lactide without catalyst

For the second experimental part, a study was carried out on the use or otherwise of the catalyst during the synthesis of L-lactide.

The SnOct(II) catalyst during direct polycondensation synthesis and ring-opening synthesis is used for the purpose of increasing the polymer chain and not for forming the cyclic dimer. It is known that the formation of L-lactide occurs mainly thanks to only two monomers of L-lactic acid which, due to the continuous elimination of water, allows the formation of the cyclic dimer, as shown in Figure 4 according to Park et. al (PARK et al., 2018).

A new configuration was studied to increase the efficiency and conversion of the reaction; the studied system is represented in Figure 4.4.

This system was designed with glass units which helps the retreat of water thanks to the difference in height and the activation of the bomb in order to be able to concentrate L-lactide in the appropriate reservoir.

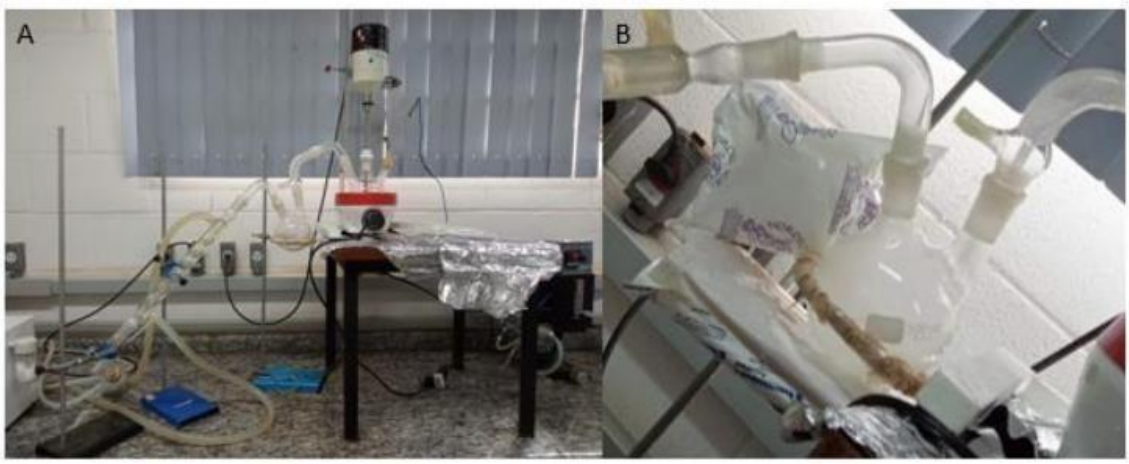

Figure 4.4: The part a) represents the scheme for L-lactide production; The part b) details of the configuration, especially the L-lactide reservoir where the ice was placed [Author's source].

Three syntheses were carried out, two with the catalyst and one without. The formation of L-lactide was noted even without the catalyst, but for the same quantity introduced of L-lactic acid, the formation of the dimer was noted in twice the time than with the catalyst.

The synthesis conditions for the three reactions are presented in Table 4.1. Furthermore, from the table 4.1 the quantity of L-lactide produced is the same, what changes is the reaction time to have the same conversion at the same temperature and pressure.

Configuration	Pressure [mmHg]	Temperature °C	Feed L-lactic acid [g]	Formation time of L-lactide [h]	L-lactide produced [g]
Without catalyst	-550	240	84,455	1	25,19
First with catalyst	-550	240	97,889	0,5	25,228
Second with catalyst	-550 ÷ -600	240	98,200	0,5	25,000

Table 4.1: Synthesis conditions for the three reactions (without and with catalyst) for producing L-lactide [Author's source].

In the first reactor where there is constant agitation, already dehydrated L-lactic acid was introduced, ready for synthesis. In the second configuration, unlike the first, aluminium sheets were placed to have a better heat exchange. As can be seen from Figure 4.5, in the second reservoir, due to the aluminium foil and the ice introduced, the

formation of L-lactide crystals can be perceived. The dimer begins to form in the vapor phase and crystallizes immediately, if the poor nucleation of the crystals can be noticed, as soon as a temperature lower than the synthesis temperature is perceived. In fact, due to rapid cooling, crystallization was successful achieved.

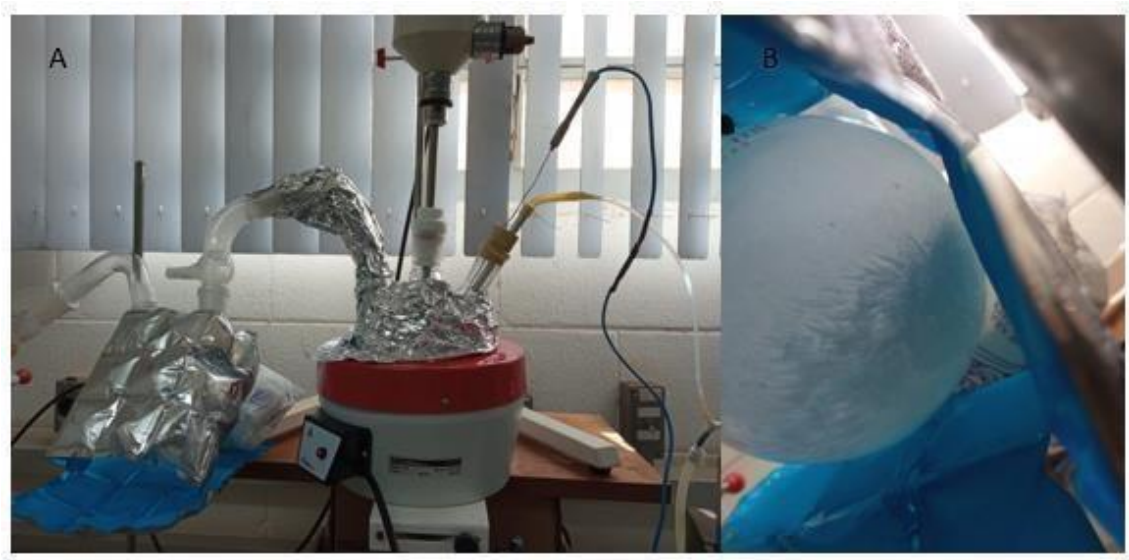

Figure 4.5: The part a) represents the scheme for L-lactide production with aluminium; The part b) represents the details of the production of L-lactide crystals [Author's source].

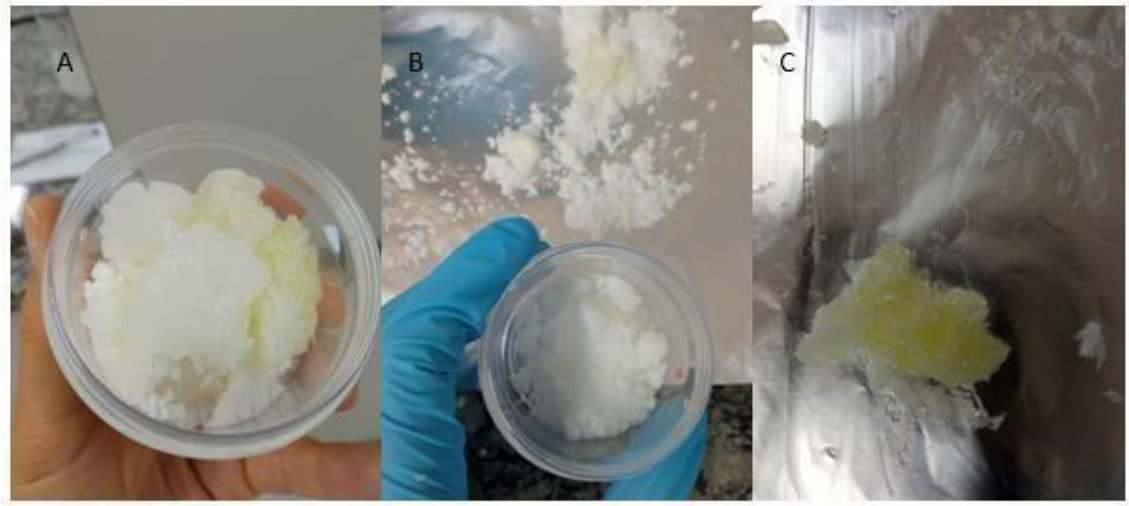

Figure 4.6: The part a) and b) represent the L-lactide produced dry; The part c) represents L-lactide with water. It can be observed the formation of crystals, but it is possible to notice that ~~a~~ part of it is still moist [Author's source].

Figure 4.6 represents the cyclic dimer formed during synthesis with the catalyst. It is noted that there are parts of the system in which there is not yet an efficient withdrawal of water and for this reason not all L-lactide is completely dry.

Furthermore, the conditions tested represent the ideal conditions to produce L-lactide in a single step and the system appears to be the most efficient.

In the reactor where the reagent, L-lactic acid with the catalyst, was placed, during the synthesis time, the PLLA polymer begins to form via the direct polycondensation route. Since the objective is not the production of the polymer, the reaction time used does not represent the optimal time for the growth of the polymer chain.

After synthesizing L-lactide, as the dimer is unstable, a lyophilization process was employed to ensure optimal storage by completely removing all water content, as shown in Figure 4.7.

This technique, also known as freeze-drying, initially eliminates water through vacuum-induced sublimation. This causes the frozen water to transition directly from the solid phase to the gas phase, bypassing the liquid phase(KASPER; FRIESS, 2011).

It has been calculated that, following the freeze-drying process, and considering the quantity of L-lactide produced with the catalyst, a total of 3.429g of water was removed, according to Figure 4.7. This result also confirms the efficiency of the constructed system, as the dimer has been successfully produced under suitable conditions with appropriate pressure and temperature, enabling efficient water removal.

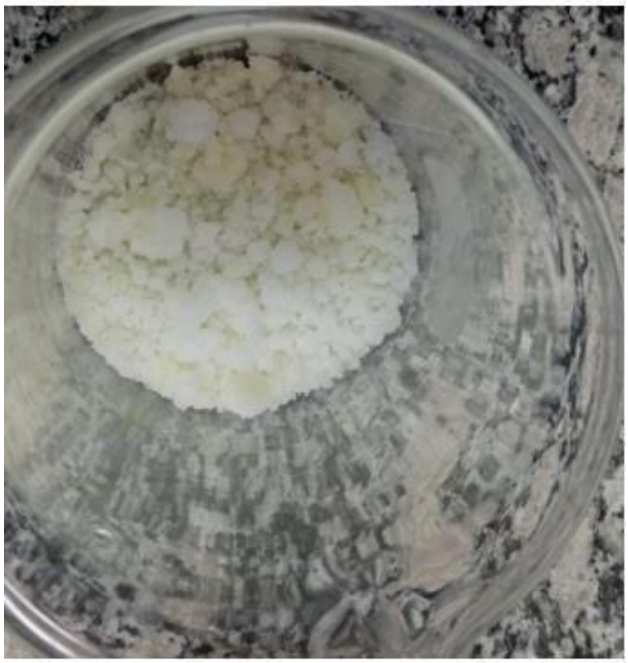

Figure 4.7: L-lactide produced after lyophilization process [Author's source].

4.4.3 Synthesis of PLLA starting from L-lactide

The same L-lactide dimer produced via a single step was used as the raw material to synthesize the PLLA polymer via ring-opening polymerization synthesis (ROP), as shown in Figure 4.8.

This synthesis mechanism allows us to obtain a high molar mass polymer, Mw greater than 100,000 Da, despite direct polycondensation synthesis. This is because the ROP allows greater control in relation to the polymer chain. The control of the synthesis conditions, i.e. 140 °C and atmospheric pressure, allow to control average degree of polymerization (DP) of the resulting polymer, considering which is usually equal to, or at least proportional to, the monomer conversion time the molar ratio between monomer and initiator(DECHY-CABARET; MARTIN-VACA; BOURISSOU, 2004).

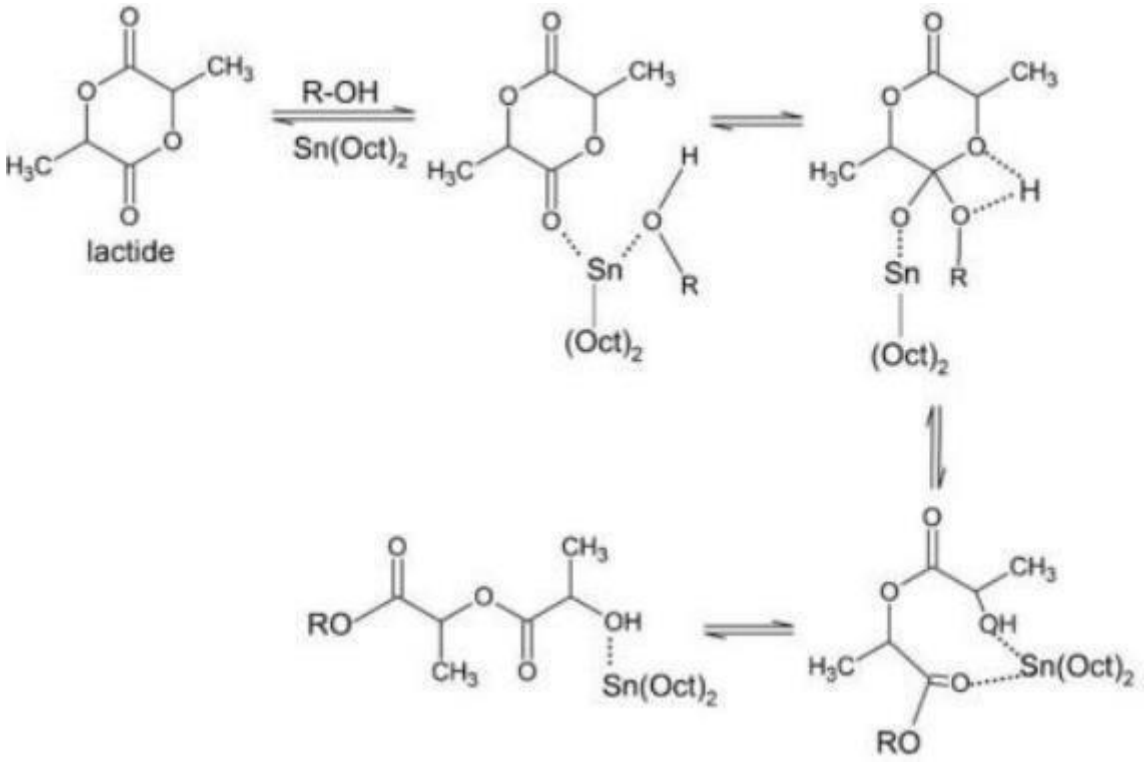

Figure 4.8: Reaction mechanism of the polymerization of PLLA starting from the cyclic dimer LT (CUNHA et al., 2022).

For the synthesis process, a fired glass reactor was used, heat-resistant for temperature control, a mechanical stirrer maintained for the first 15 minutes of reaction and N_2 gas during the reaction, as shown in Figure 4.9.

Figure 4.9: System for PLLA synthesis via ROP route [Author's source].

The procedure and the parameters of the synthesis derive from the study previously made by Pattaro(PATTARO, 2016) and the work of Kaihara et. al (KAIHARA et al., 2007).

The synthesis was carried out by maintaining a glycerin bath at a constant temperature of 140°C, a becker containing L-lactide was added and the quantity of catalyst and cocatalyst always equal to the experiments carried out previously, in particular 1 wt% SnOct(II) and 0.0025 wt% 1-dodecanol.

Since the becker was introduced, the synthesis started, and constant stirring was maintained for the first 15 minutes, after stirring was stopped, the reactor was closed and the N_2 line kept operating.

In these constant conditions, two experiments were carried out: the first synthesis lasted

two hours also in relation to the conditions previously posed by Pattaro,(PATTARO, 2016), and the second synthesis was extended by five hours; Table 4.2 shows the quantities of- PLLA that was obtained.

ROP	Feed LLA [gr]	Product PLLA [gr]
First synthesis	15,031	10,342
Second synthesis	25,000	22,459

Table 4.2: Represents the amount of L-lactic acid used as feed and how much PLLA polymer was produced via ring-opening (ROP) synthesis [Author's source].

The produced PLLA polymer, as shown in Figure 4.10, immediately after polymerization was allowed to cool to ambient temperature for approximately one hour and then placed in a freezer inside a desiccant, which did not allow it to come into contact with humidity; this thermal shock was to help complete solidification.

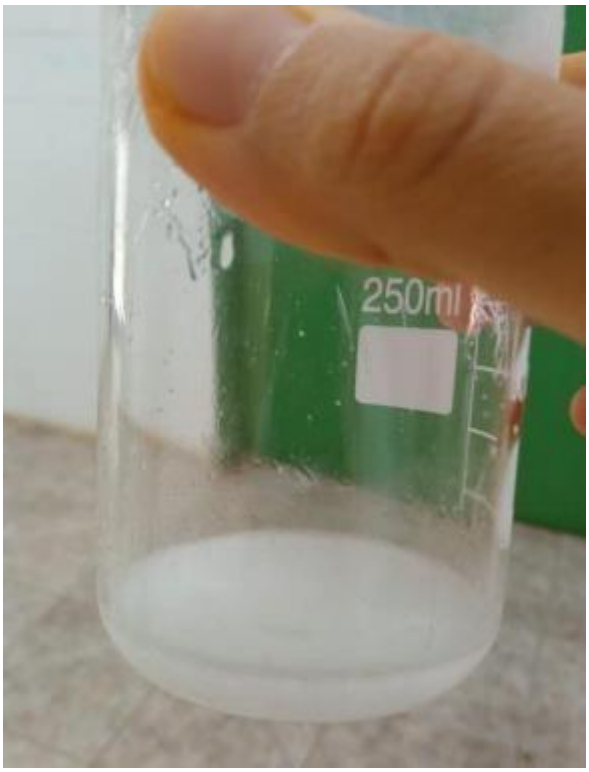

Figure 4.10: PLLA produced from ring-opening route [Author's source].

The polymer did not solidify completely, the material was very viscous. but not solid. This could be explained in relation to the purity of the L-lactide because even a small

quantity of water does not allow complete polymerization and there could be a quantity of unreacted monomer and therefore this would hinder the synthesis of the final polymer.

In industry, normally after the production of L-lactide with the addition of organic solvents, a recirculation is provided in the plant to remove unreacted monomers and dimers; the recirculation should be added directly via a mixer into the main line before entering the cyclic dimer production reactor(HEO et al., 2019; KAIHARA et al., 2007).

4.5 Electrospinning with PLLA obtained in the Ring-opening polymerization.

Despite the difficulty in polymerizing the material through ring-opening synthesis, electrospinning apparatus was used to verify possible membrane formation by this procedure.

Electrospinning is a technique, patented by Fohrmals, in 1934,(AHMADIAN et al., 2021), and used with the aim of forming fibers via a continuous filament of nanometric or micrometric scales. Fohrmals utilized for the first-time cellulose acetate ~~was used~~ and subjected to an electrostatic force that allowed spinning.

This process, as show Figure 4.11, uses a syringe pump, a high voltage pump, and a collector(PHAM; SHARMA; MIKOS, 2006; THAKKAR; MISRA, 2017; WILLIAMS; RAIMI-ABRAHAM; LUO, 2018).

Polymer filaments are formed due to two charged electrodes with opposite polarity, placed one in contact with the solution and the other with the collector. The solution is ejected out of the metal spinneret with a small hole, the solution evaporates leaving the solid fibers which are collected on the collector. The distance between the spinneret and the collector is important because if it is not enough there is incomplete solvent evaporation. The potential difference depends on the properties of the spinning solution: polymer molecular weight and viscosity(DE SOUZA, 2022; GUPTA et al., 2005)

The process to carry out the fiber processing through electrospinning is available in the Biofabris laboratory (National Institute of Science and Technology for Biomanufacturing), at the State University of Campinas (UNICAMP).

The PLLA obtained was solubilized in chloroform in an 80% solution. It was left to dissolve for approximately 24 hours(INAI; KOTAKI; RAMAKRISHNA, 2005; XAVIER et al., 2016).

As shown in Figure 4.11, there are several variables that must be considered for the

electrospinning process.

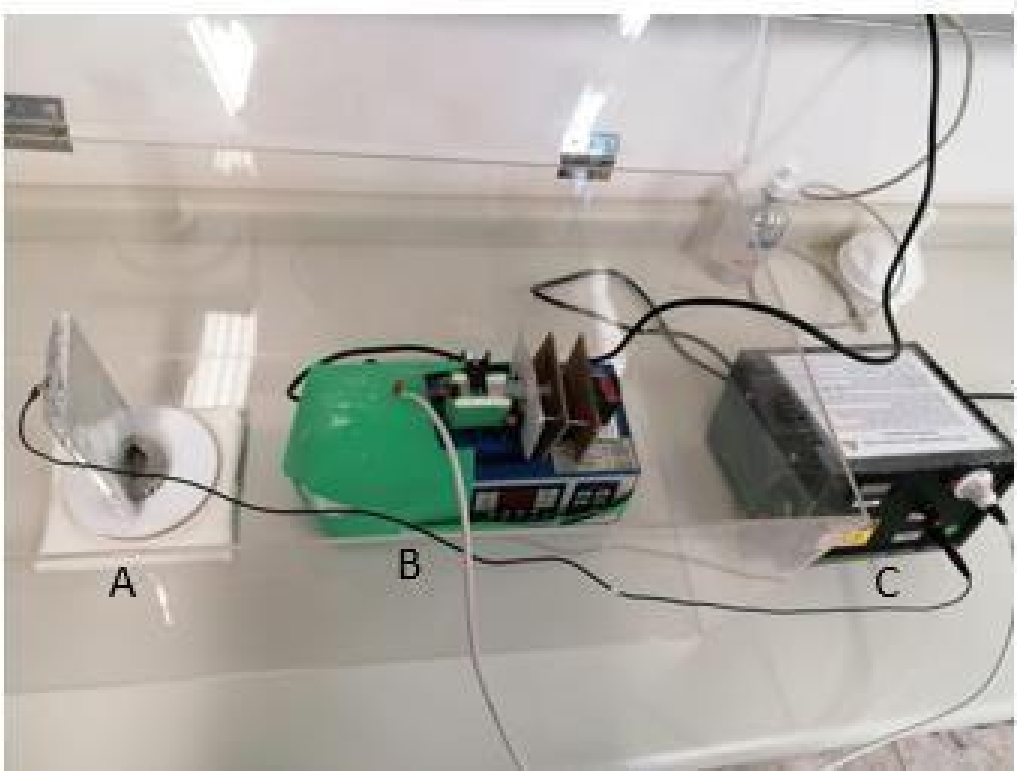

Figure 4.11: Electrospinning equipment parts: A) collector with aluminium part; B) infusion bomb C) High voltage source [Author's source].

As shown in Figure 4.11, there are several variables that need to be considered for the electrospinning process, after the PLLA and chloroform solution was placed in a 10 mL syringe, the collector was placed at a distance of 15 cm from the tip of the syringe, the voltage chosen was 15 kV.

With these characteristics, a membrane was produced which on the aluminium collector which was subsequently analysed using an optical microscope and how humid it was. Before analysing it with Scanning Electron Microscopy (SEM), was placed in an oven at around 105° C to be able to eliminate all the humidity.

4.6 Results

The lactide obtained from the single-step synthesis and the material obtained from the ring-opening polymerization synthesis were analysed via the different characterization techniques, in particular Fourier-transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC) and Gel Permeation Chromatrography (GPC). All analyses

were carried out by the Recursos Analíticos e de Calibração (LRAC) laboratory, located in the Universitá Estadual de Campinas (UNICAMP).

4.6.1 Fourier-transform Infrared Spectroscopy (FTIR)

The L-lactide dimer and PLLA polymer produced as described in this Chapter were characterized using the FTIR technique. FTIR measurements were performed using a Thermo Scientific spectrometer with a Nicolet Continuum model (Madison/USA). The sample was prepared by placing 0.2 mg of active material in a KBr pellet. The studied region ranged from 500 to 4000 cm^-1, allowing the determination of vibrational absorption bands for PLLA and LLT.

According to the studies reported by Motta et.al,(MOTTA; DUEK, 2006), and Fang et.al,(FANG et al., 2009) it is noted that the two spectra relating to PLLA and L-lactide, respectively Figure 4.12 and Figure 4.13, reflect the characteristics and absorption bands relating to the materials .

Table 4.3 shows the band characteristics reported in the work of Motta et. al, (MOTTA; DUEK, 2006), and also used in Pattaro's thesis, (PATTARO, 2016).

Absorbance [a.u]	Chemical bond
2995,24	CH axial movement
2950,88099	CH asymetric axial movement
1758,95651	C=O stretch
1450,36765	CH3 asymetric axial movement
1382,86384	CH3 asymetric axial movement
1201,56788	C=O stretch
1130,2067	C=O stretch
1101,2765	O-CH stretch
1099,34782	C=O stretch
935,41	CH

Table 4.3: Absorbance band relative PLLA and L-lactide [Auhtor’s source].

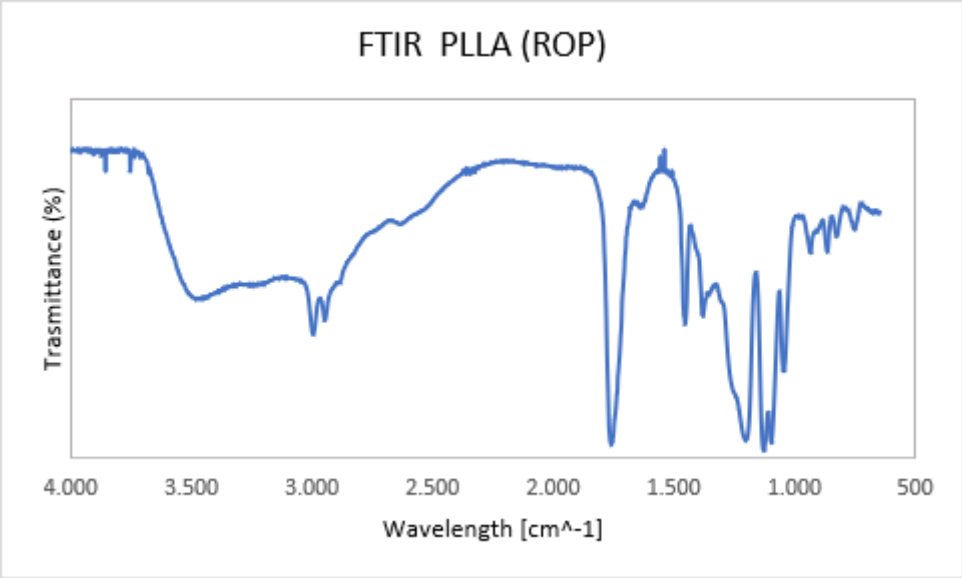

Figure 4.12: FTIR of PLLA produced [Author's source].

According to Figure 4.12, is possible to observe an absorbance peak at 935.32 cm^-1 relating to the -CH group, and also it was ~~we~~ noted the peaks 1099.24, 1130.10 cm^-1 and also 1758.79 cm^-1 which are characteristic of the -CO group, the absorption band that includes the asymmetric axial movements of the -CH3 group, respectively 1380.80 and 1456.02 cm^-1. Also, it was observed 2993.03 group relating to the axial and asymmetric movements of the group -CH.

As a difference, note a band around 3750 cm^-1 which, according to the work presented by Motta et.al,(MOTTA; DUEK, 2006), defines this band as the characteristic of –OH. Therefore, it can be deduced that there could be non-polymerized components which would explain the lack of solidification of the polymer obtained.

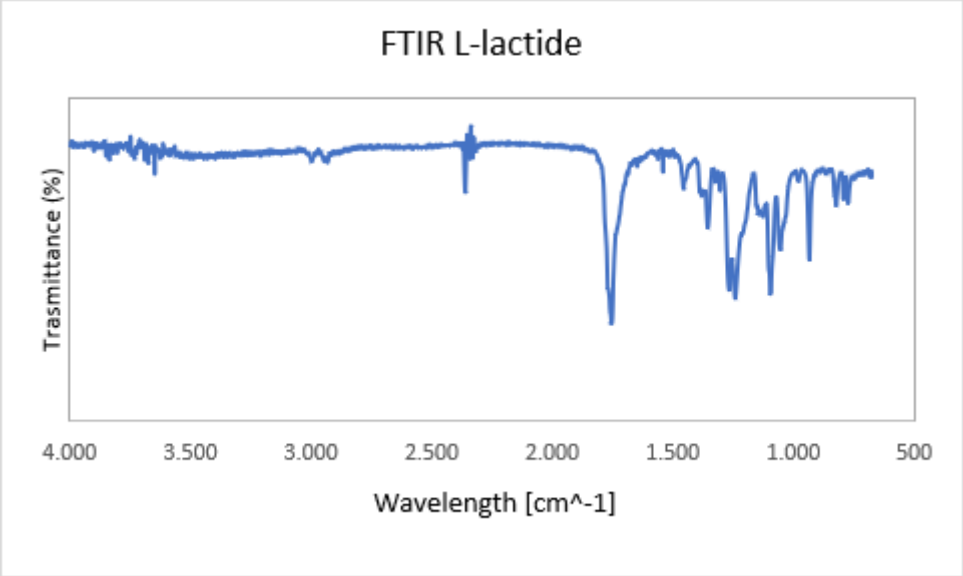

Figure 4.13: FTIR of L-lactide produced [Author's source].

Regarding Figure 4.13 related to LLT, it is possible to notice the characteristic band of the dimer at 933.39 cm^-1 -CH which refers to the bonding of the L-lactide ring(FANG et al., 2009).

Furthermore, there is a peak at 1753.00 cm^-1 which is related to the -C=O bond strength.

It can be concluded that the two materials obtained are L-lactide and PLLA which managed to polymerize completely, however there exist inside the monomers or oligomers which have not polymerized, thus also explaining the lack of solidification.

4.6.2 Differential Scanning Calorimetry (DSC)

The produced L-lactide was analysed by DSC to study the thermal transitions of the produced dimer. For analysis, a XPR2 model Mettler Toledo was used. A small amount of each sample (~7 mg) can be collected with the help of a micro spray or even metal and weighed in a container of Al (40 uL) on the microanalytical balance.

The method used includes a first quenching of 25-220°C, then a cooling of 220-25°C at a rate of 10°C/min and subsequently a final quenching of 25-220°C, always carried out at a rate of 10 °C/min and 50 mL into inert atmosphere N_2.

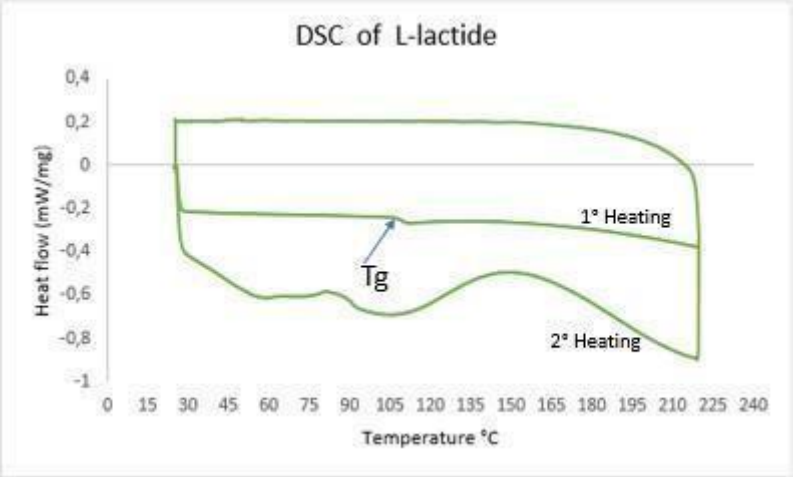

Figure 4.14: DSC analysis of the L-lactide product [Author's source].

From this analysis, as show Figure 4.14, it is possible to see a glass transition temperature of 111.26°C; it is not possible to see the temperature of cold crystallization at constant temperature, probably due to the lack of purity of the cyclic dimer. Normally the melting temperature of the 'L-lactide is between 240-255 °C, but the analysis is carried out if it is reached at 220 °C and it is not possible to determine it.

Usually, in DSC analysis, it is possible to observe the physical changes in polymers such as melting temperature, cold crystallization, and glass transition. However, in this analysis, only the glass crystallization temperature was identifiable. This is likely due to the L-lactide produced not being very pure.

In the future it is better to study the post-processing part without using toxic solvents to ensure the right polymerization through the ring-opening polymerization path(YU; STORTI; MORBIDELLI, 2011).

4.6.3 Thermogravimetric analysis (TGA)

TGA analysis was carried out to measure the change in mass with an increase in temperature, thermal stability, and maximum degradation temperature for the L-lactide and the PLLA obtained. These analyses were done in the XPR2 model Mettler Toledo equipment. Samples in the form of particles or viscous liquid can be transferred with the help of a metal pin or micro metallic foam for alumina particles (70 uL), ready for analysis.

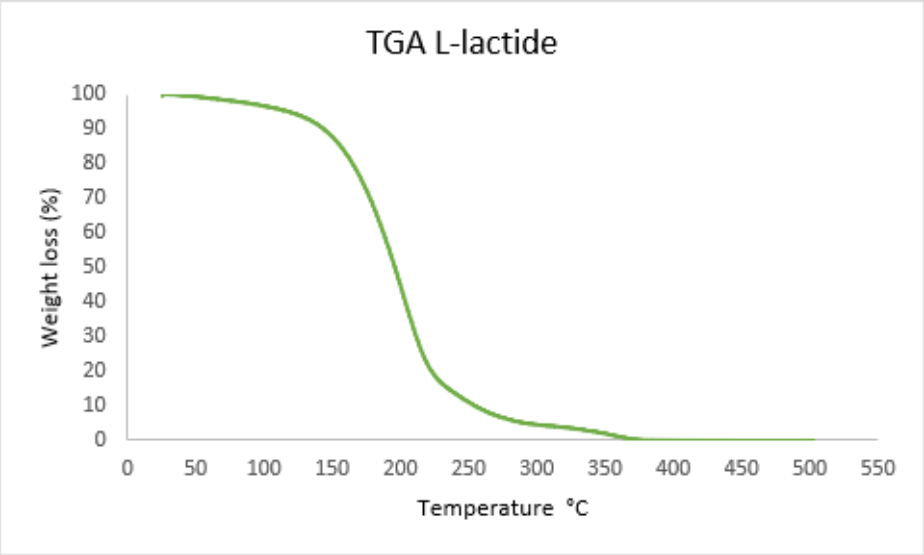

Figure 4.15: TGA curve about cyclic dimer (LLT) produced [Author's source].

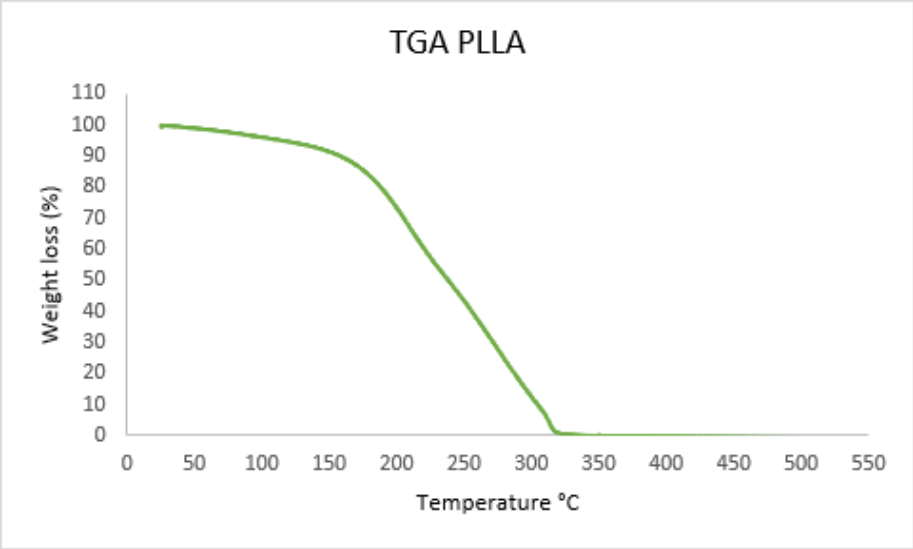

Figure 4.16: TGA curve about PLLA produced [Author's source].

Through the analysis of Figure 4.15 and 4.16, it is possible to see the onset of temperature in which a loss of mass begins. The onset of temperature normally defines the upper limit of the thermal stability of the material mass loss and often defines the upper limit of the material's thermal stability. However, it should be appreciated that extensive degradation of the polymer may already occur before the point at which detectable changes in mass occur(NG et al., 2018)

The degradation of polymers is affected thanks to phenomena such as humidity or the presence of monomers or when the material does not have a high degree of

purity(YUJIANG FAN, HARUO NISHIDA, YOSHIHITO SHIRAI, 2003)

According to Figure 4.15 relating to L-lactide, an initial mass loss is noted at a temperature of 106.66°C, close to the temperature of the L-lactide produced by Purac®, analysed in Pattaro's thesis work, (PATTARO, 2016).

As regards the max temperature and final temperature, it differs from industrial l-lactide probably due to the presence of humidity and lack of a high degree of purity. The difference between the two temperatures is not negligible, no other tests were carried out, a lack of purity in the dimer obtained is assumed, and therefore a loss in mass of the product considering the proven reversibility over time of the reaction which involves the reaction starting from the monomer L-lactic acid.

As regards PLLA, Figure 4.16, from Table 4.4, it can be seen that the initial mass loss temperature is lower and the range between the final temperature and the final temperature is very wide, probably due to the lack of polymerization and quantity of monomers and oligomers that have not polymerized(JAMSHIDI; HYON; IKADA, 1988; MOTTA; DUEK, 2006)

Table 4.4 shows the values relating to the degradation temperatures.

	Ti [°C]	Tmax [°C]	Tf [°C]
L-lactide produced	106,66	137,73	229,538
L-lactide Purac	110	224	233
PLLA produced (ROP)	135,9	174,36	321,74

Table 4.4: Summary regarding the temperatures of TGA for L-lactide and PLLA [Author's source].

4.6.4 Scanning Electron Microscopy (SEM)

After the electrospinning process the membrane formed on the collector was analysed.

First it was analysed in an optical microscope, Leica brand, model DMLM (Wetzal, Germany).

The exhibit placed on a glass plate and subsequently analysed with an expansion of 100 and 500 times, as shown in Figure 4.17.

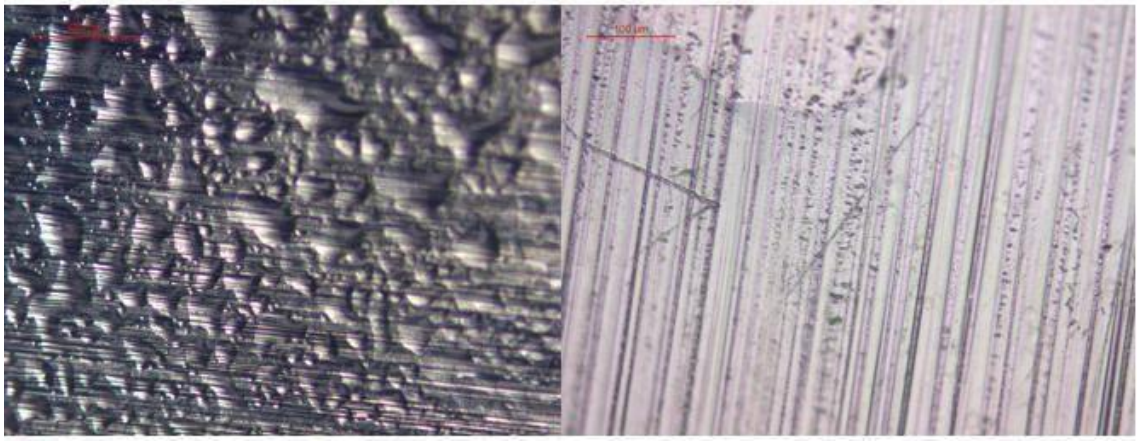

Figure 4.17: Analysis related to the optical microscope for the membrane: the first with a resolution of 500 times and the second with a resolution of 100 times [Author's source].

Humidity was noted from the optical microscope images and before analysing it via Scanning Electron Microscopy (SEM), the sample was placed in an oven at 105°C for 16 hours.

Subsequently the sample was analysed with High Resolution Electronic Microscope with X-ray Dispersive Energy Detector, of the TermoFisher Scientific brand, model Quattro S, as show Figure 4.18.

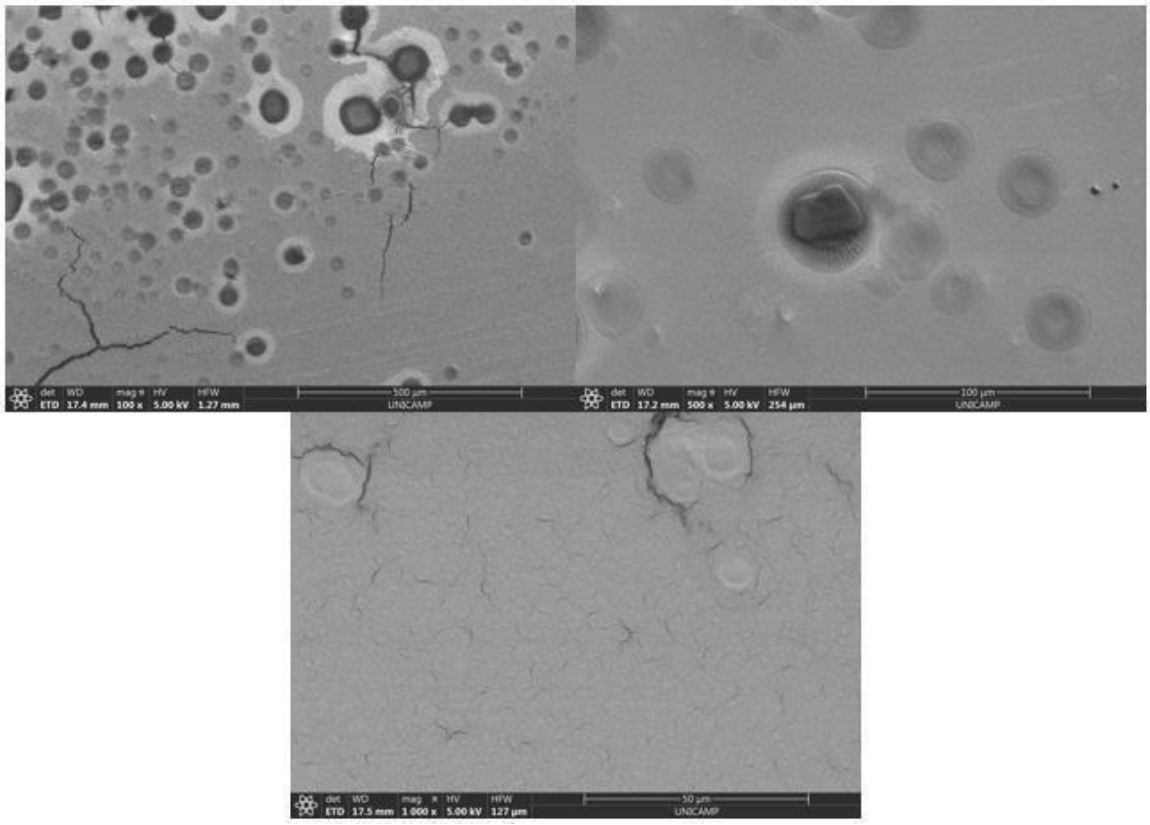

Figure 4.18: Analysis by Scanning Electron Microscopy (SEM), respectively of 500 µm, 100 µm, 50 µm [Author's source].

4.7 Partial conclusion

In relation to Chapter 4, it can be concluded that thanks to a simultaneous control of temperature and pressure, respectively 220°C and -550 mmHg, it was possible to synthesize L-lactide in a single step. Furthermore, it was analysed that L-lactide is formed exactly in the vapor phase since the temperature of 220°C is reached and to allow the solidification of the dimer it is necessary, to have pressure control and a quick cooling system (lower temperature than the reactor one), to be able to collect the cyclic dimer into crystals.

Ice was introduced into the system to lower the temperature, which thanks also to the but if there is control of the pressure and temperature, the ambient temperature allows the formation of crystals. The crystals obtained are elongated crystals due to incomplete nucleation and rapid cooling.

It was observed that for the synthesis of the PLLA polymer starting from L-lactide, it is necessary to achieve a high level of purity of the latter because otherwise during the polymerization via ring-opening the PLLA does not polymerize completely and therefore does not solidify.

Normally, as shown by the work carried out by Kaihara et.al,(KAIHARA et al., 2007) toluene is used for the recrystallization of the L-lactide and subsequently for the synthesis of the final polymer.

Chapter 5

5.1 Study of synthesis to produce L-lactide in one way and PLLA via the direct polycondensation route.

In this Chapter 5, a continuation of the study done in Chapter 4 is presented.
According to the system presented in Figure 18, it was perceived that not only the formation of L-lactide occurs, but also in the reactor where constant agitation is present there is the formation of PLLA polymer via direct polycondensation synthesis. For this reason, in this chapter different configurations will be analysed which will allow not only to obtain the cyclic dimer, which is the main objective of this thesis, but also the polymer.
The aim will be to study a system to obtain maximum efficiency, both in collecting the cyclic dimer and the polymer. It is important to remember that L-lactide is the reactant for a third product, i.e. PLLA synthesized via ring-opening polymerization synthesis which allows to obtain a polymer with high molar mass.

5.2 Materials

The material used is L-lactic acid (LLA) 85% (Synth), Tin-Octanoate 2 (OctSt-II) (Sigma Aldrich), 1-dodecanol (Vetec) and, Chloroform (Synth), and Ethanol (Sigma-Aldrich) for purification process.

5.3 Methods

This part of the project includes several experimental configurations with glass units.
This study, which will be presented, will serve to consolidate the appropriate variables, such as pressure and temperature, for the synthesis of L-lactide as well as, at the same time, the PLLA. The second aim, but not less important, is the choice of the best

process to be able to obtain an efficient and as defined 'Green' process free of toxic solvents and with the minimum waste.

5.4 Study and optimization of the catalysed reaction system

5.4.1 Initial configuration

The study with experimental glass units starts from a preliminary study by Souza,(DE SOUZA, 2022), who used this type of process to produce Poly(L-lactic acid) via the direct polycondensation route.

The experiment to obtain the polymer and subsequently L-lactide was conducted at the INCT-Biofabris laboratory, University of Campinas, as showed in Figure 5.1. Prior to commencing the polymerization, a dehydration step was performed as the L-lactic acid used contained 15% water. The reactor was heated to 130 ºC for 3 hours to completely eliminate the water(CRIVELLIN et al., 2022a). The second step involved initiating the actual synthesis, where in SnOct2 and 1-dodecanol were added at 1% and 0.0025% respectively, following ANVISA and FDA guidelines. The reaction took place at a temperature of 160º C, a pressure of approximately -400 mmHg, for approximately 72 hours, with constant agitation maintained throughout the process(AURAS; HARTE; SELKE, 2004; CRIVELLIN et al., 2022a; DE SOUZA, 2022).

Figure 5.1: The first Experimental unit at INCT-Biofabris laboratory, University of Campinas (DE SOUZA, 2022).

During the synthesis, some deposits, as depicted in Figure 5.2, were observed between the reactor exit and the condenser inlet due to the rapid temperature change, as the condenser was set to 5 ºC. The fouling material was L-lactide, which is other product of the reaction. The synthesis process was halted at 8 hours and even at 12 hours to collect the reaction by-product. According to the literature, it has been reported that the formation temperature of L-lactide falls within the range of 160 ºC to 240 ºC. The sudden temperature change caused by the condenser facilitated the solidification of the L-lactide(CRIVELLIN et al., 2022a; LASPRILLA et al., 2012a).

The fouling forced to block the reaction and open the system, allowing the entrance of oxygen, considering that the entrance of O_2 affects the yield of the reaction because it breaks the polymeric chain. In this initial configuration, a temperature of 160°C was chosen to facilitate the formation of the polymer in according to the literature (ACHMAD et al., 2009; DE SOUZA, 2022; LUNELLI, 2010; SAVIOLI LOPES, 2014).

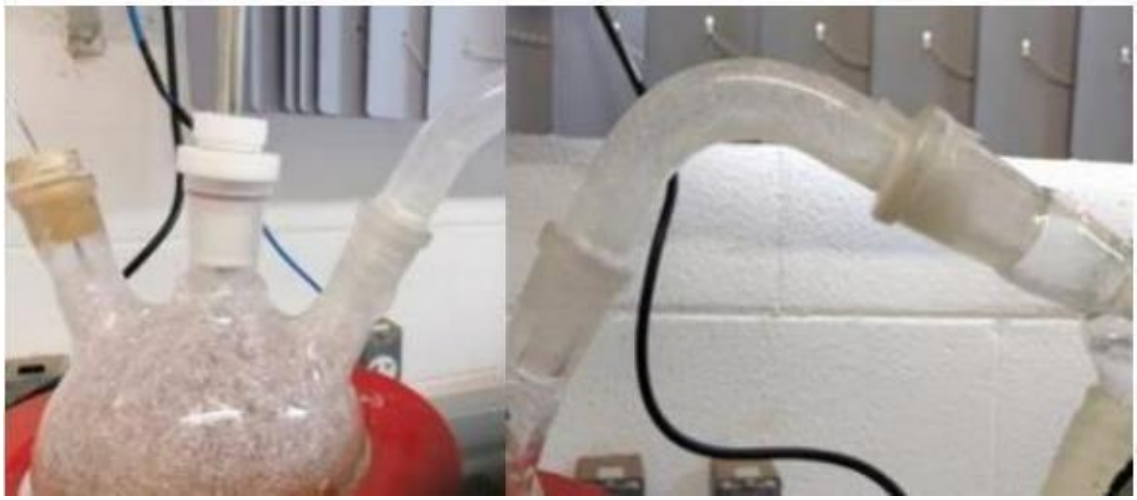

Figure 5.2: Encrustation obtained in 12 h and 8 h respectively (CRIVELLIN et al., 2022a).

5.4.2 Second configuration

After the initial configuration, the configuration for the L-lactide production and, the simulation with reactive distillation, considering the errors and low reaction yield, it has explored the impact of some changes in the system.

Specifically, the first step was to design a continuous system without the need for manual intervention, thereby controlling the oxygen input and increasing the final molecular mass. Consequently, the objective was to reduce the synthesis time. A new configurations system was proposed, and it was thought to use a reaction temperature of 220 ° C, - 500 mmHg of pressure, and lower the reaction time to a minimum of 24 h, which allows you to have an industrial perspective for producing in the same time the dimer l-lactide and the PLLA, because only 2 hours it is not adequate to have a polymer via the direct polycondensation route, but only an oligomer.

This new configuration system is shown in Figure 5.3. Then, it was reproduced on the bench to effectively verify if the analysed and studied conditions were suitable, as shown in Figure 5.4. It allows to make a continuous system that would lead to greater efficiency and a greater molecular mass of the final polymer (PLLA). Furthermore, the increase in pressure guarantees the formation of the other product (LLT) in the second reservoir (R2) and therefore would limit the fouling seen in the initial system presented previously, Figure 5.3. The control of pressure and temperature is essential to allow maximum conversion, considering that the reaction for producing LLT reaction is

reversible, which makes this dimer an unstable material, considering that the increase in temperature from the first to the second system helps the increase of the polymer chain and the formation of LLT.

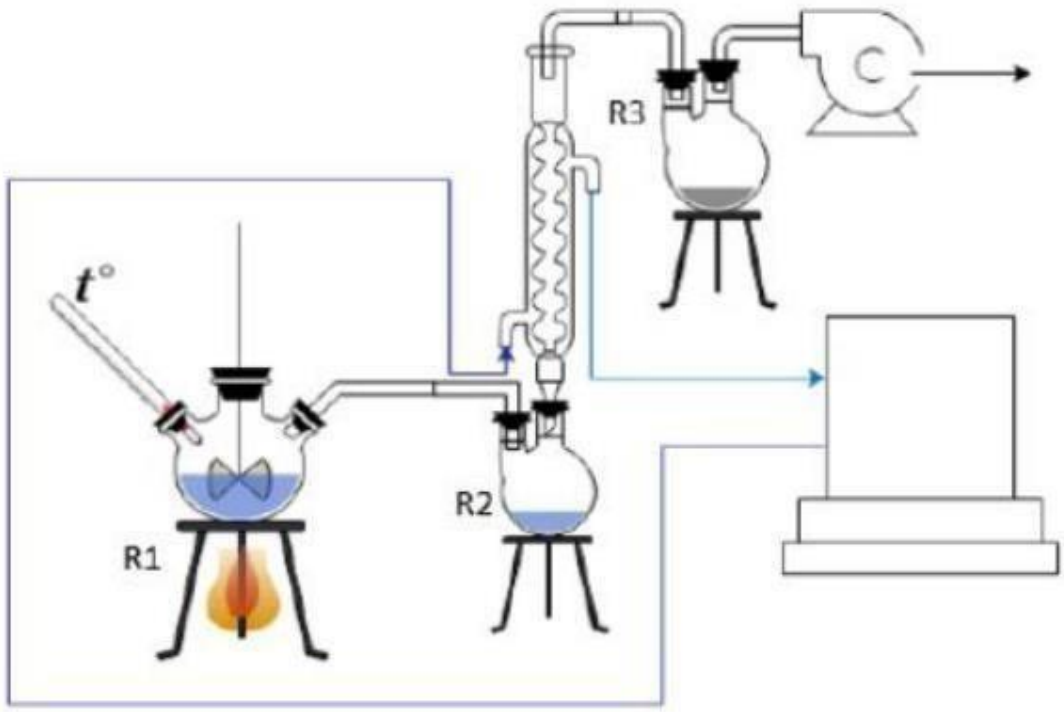

Figure 5.3: Diagram of the system for increased efficiency and conversion of polymer (PLLA) and L-lactide production reaction: R1 represents the reactor of PLLA production, R2 represents L-lactide reserve, and R3 water reserve [Author's source].

Figure 5.4: The second configuration done for producing PLLA and L-lactide. [Author's source].

In this case the experiments were started with an already dehydrated L-lactic acid to reduce the total time and avoid opening the system for adding the catalyst and the co-catalyst, always in the same quantities, 1% and 0.0025%, respectively. The system, as shown in Figure 5.4, comprises the jacketed reactor with the stirrer where the LLA is introduced and immediately after the L-lactide tank. Since the reaction under examination is reversible, a third tank is positioned allowing to collect water during the synthesis reaction; while, in theory, a dehydrated LLA without excess water has already been introduced into the system at the beginning of the reaction.

The process parameters were changed, the temperature was increased to 220°C, the pressure was adjusted to -400 mmHg, and, in addition, the water bath temperature was significantly increased to 70°C to avoid thermal shock and to allow water to be removed more efficiently. This increase is also to avoid encrustations at the reactor outlet and a correct collection of L-lactide in the second reservoir. The formation of L-lactide necessarily occurs since it is extracted at a temperature of 240 °C and the pressure increases, considering that the formation of LLT can also occur at lower temperatures provided that a pressurized system is used. It should be remembered that the boiling point of the L-lactide is 255°C. The reaction was carried out for 24 hours, but still having fouling at the outlet of the main by-product reactor; the start of the formation of

the L-lactide it was again observed when the temperature of 220°C was reached, and the system needed to be opened again.

5.4.3 Third configuration

In this third configuration, as illustrated in Figure 5.5, all the elements from the second configuration are included. However, a notable difference is that the collector between the main reactor, housing the agitator, and the second reservoir has been replaced with a Vigreux column. This modification enabled the continuous operation of the reaction for a duration of 24 hours without the need to interrupt the process or open the system. The substitution of the collector by the Vigreux column led to a significant improvement in reactor design, making it feasible to sustain the reaction without compromising the system's integrity. This breakthrough not only improved the overall efficiency of the process, but also reduced the need for frequent monitoring and intervention by operators, contributing to enhanced safety and reduced human error. The system parameters remained partially unchanged throughout the experimental process. Specifically, the operating temperature was maintained at 220°C, with pressures between -400 and -500 mmHg. The idea was to lower the pressure as much as possible, but working with very high temperatures, it was not possible to maintain a stable pressure that touched -500 mmHg. Furthermore, the water bath temperature was set at a constant 70°C. To further study the water removal process, two condensers were incorporated after the second tank. The decision to introduce the additional condensers was motivated by the need to gain a deeper understanding of the water removal dynamics during the reaction, considering that dehydrated L-lactic acid was introduced as the initial feed.

Efficient water removal is essential to control the equilibrium of the reaction and maximize the yield of the product. Using these condensers, an attempt was made to optimize the separation of water from the reaction mixture, ensuring better process control and potentially increasing the overall efficiency of the reaction.

Figure 5.5: The third configuration done for producing PLLA and L-lactide [Author's source].

As shown in Figure 5.6, the encrustations reappeared; however, this time, they did not hinder the success of the reaction, allowing for a continuous process lasting 24 hours. In this third configuration, it was observed that the collection of L-lactide in the designated reservoir remained challenging. Additionally, it was noticed that the formation of the dimer occurred in the vapor phase and crystallized upon a decrease in temperature. The crystals exhibited an elongated morphology, as illustrated in Figure 5.7, attributed to rapid cooling and the absence of nucleation. The reappearance of encrustations, though present, did not impede the continuous flow of the reaction, leading to a significant improvement over previous setup. This continuous operation for 24 hours presents promising prospects for large-scale and prolonged production of the desired product.

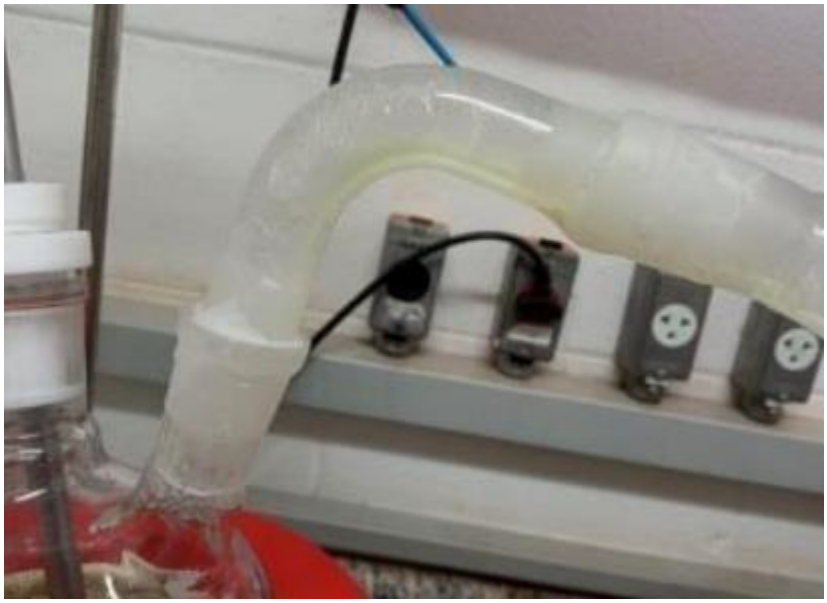

Figure 5.6: LLT fouling that occurred in the third setup [Author's source].

Figure 5.7: Crystals of LLT [Author's source].

L-lactide is a highly unstable dimer; that is, if the system does not allow to remove water adequately, crystallization does not occur, and the dimer reverts to L-lactic acid, as the conversion from L-lactic acid to L-lactide is reversible, as pointed out earlier in the study presented in Chapter 3.

In this Thesis, the focus on the instability of L-lactide emphasizes the critical role of proper water removal during the reaction. This knowledge serves as a foundation for designing more efficient processes and controlling the synthesis of L-lactide and related compounds.

5.4.4 The Fourth configuration

The fourth configuration, as illustrated in Figure 5.8, represents the final setup and demonstrated the highest level of efficiency for producing L-lactide and PLLA.

The system assembled was the same as described in the third configuration; however, following several considerations regarding pressure and temperature, aluminium insulator was introduced to improve temperature control between the reactor and the L-lactide reservoir, as was done in the production of L-lactide in one way.

This adjustment resulted in a homogenous temperature distribution, facilitating the collection of L-lactide in the second reservoir. The applied temperature ranged from 220 to 240°C, with a pressure of -500 mmHg. In the L-lactide tank, ice, as shown in Figure 33, has been incorporated to allow for rapid cooling within the system, aiding crystallization in that specific location only. This synthesis was conducted over a 24-hour period, during which fouling still occurred, but with no negative impact on reaction time. In contrast to previous attempts, no L-lactide formation wasn't observed on the surface of the main reactor, as illustrated in Figure 5.9. From this observation, it can be concluded that effective control of temperature and pressure was achieved, and the crystals was obtained as show Figure 5.10.

Table 5.1 represents a summary of the various configurations used to produce the LLT dimer and polymer PLLA. Note that all configurations synthesize PLLA polymer, as shown in Figure 5.11, the colour is more amber than that obtained with ring opening synthesis.

Figure 5.8: The fourth configuration done for producing PLLA and L-lactide [Author's source].

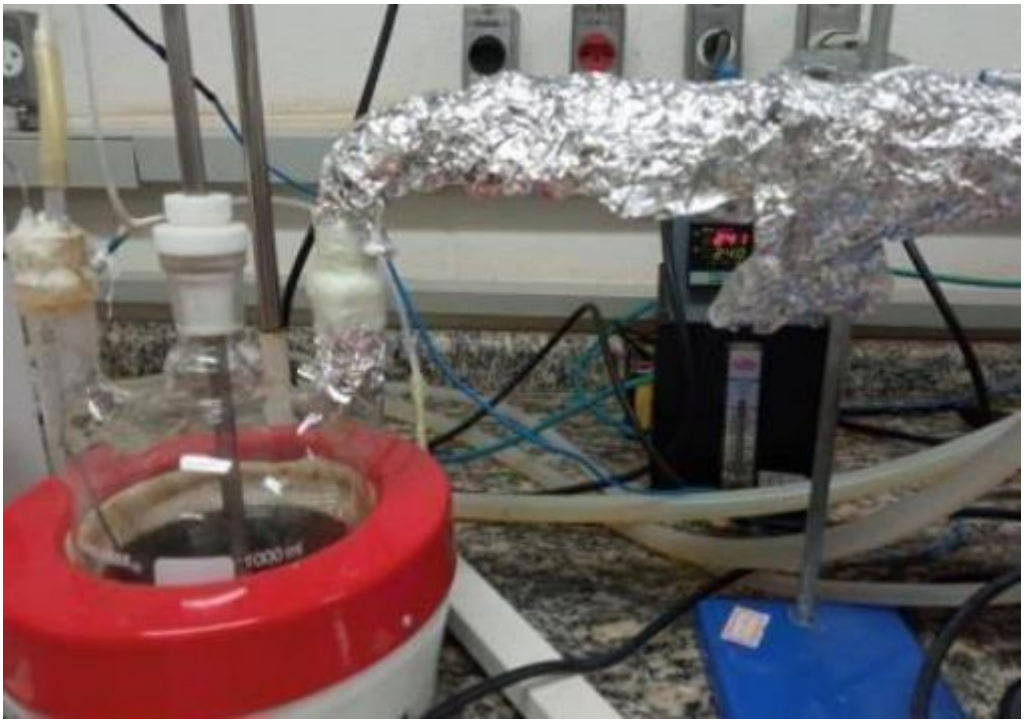

Figure 5.9: System details, no L-lactide formation occurred during synthesis. [Author's source].

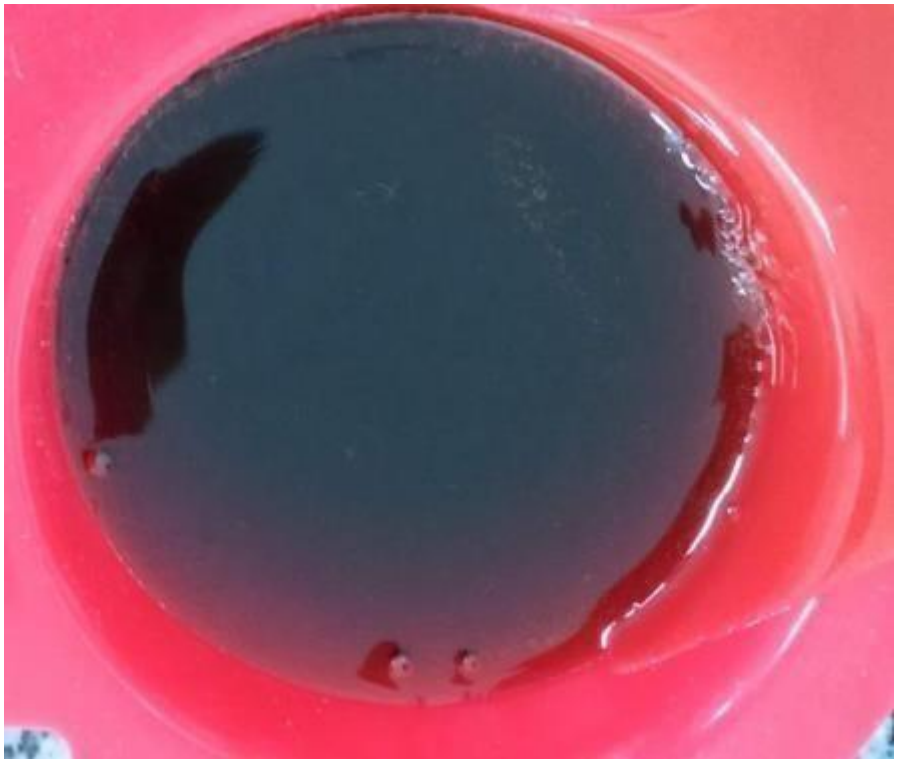

Figure 5.10: Raw PLLA obtained in all configurations [Author's source].

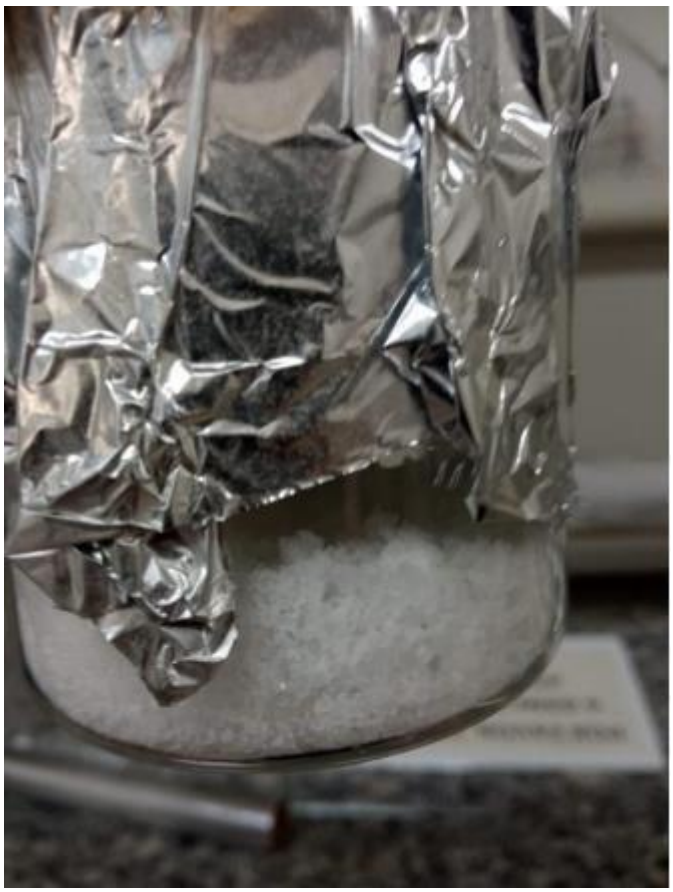

Figure 5.11: Crystal about L-lactide collected in the fourth configuration [Author's

source].

Configurations	T [°C]	P [mmHg]	Considerations
Initial configuration	160	-400	L-lactide encrustations and opening the system twice, the bath temperature was setup in 5°C
Second configuration	220	-500	L-lactide encrustations but there is not opening the system,the bath temperature was setup in 70°C
Third configuration	220	-400 to -500	The addition of 'Vigreaux column' helps to reduce encrustation but it isn't the better optimization,l-lactide does not complete collected in the second resevoir
Fourth configuration	240	-500	The best dipped system with the best yield in relation to the l-lactide produced. The addition of the aluminum and the ice allowed for greater thermal control.

Table 5.1: Summary of the configurations presented in the experimental part in Chapter 5 [Author's source].

5.5 Post processing

5.5.1 Purification

According to the process done by Lopes, (SAVIOLI LOPES, 2014), was done the purification process about the raw polymer collected in the fourth configuration.

The main goal of this purification was to effectively remove any impurities that may have been retained during the synthesis, explicitly targeting the remaining L-lactide and unreacted L-lactic acid.

Interestingly, the system presented does not use organic solvents or toxic substances, guaranteeing a more ecological and environmentally friendly approach. The motivation behind this purification effort stemmed from the intended applications of the resulting product in the medical area. Therefore, ensuring a high degree of purity is very important to meet FDA and Anvisa standards.

The process of purification of the raw material includes the addition of high purity reactants, including 99.9% chloroform PA (Synth) and 99.8% ethanol PA (Sigma Aldrich). These meticulously selected solvents ensured the efficacy of the purification procedure while maintaining the utmost precision in the subsequent analysis.

The purification steps for the polymer are depicted in Figure 5.12, illustrating the sequential stages in this process.

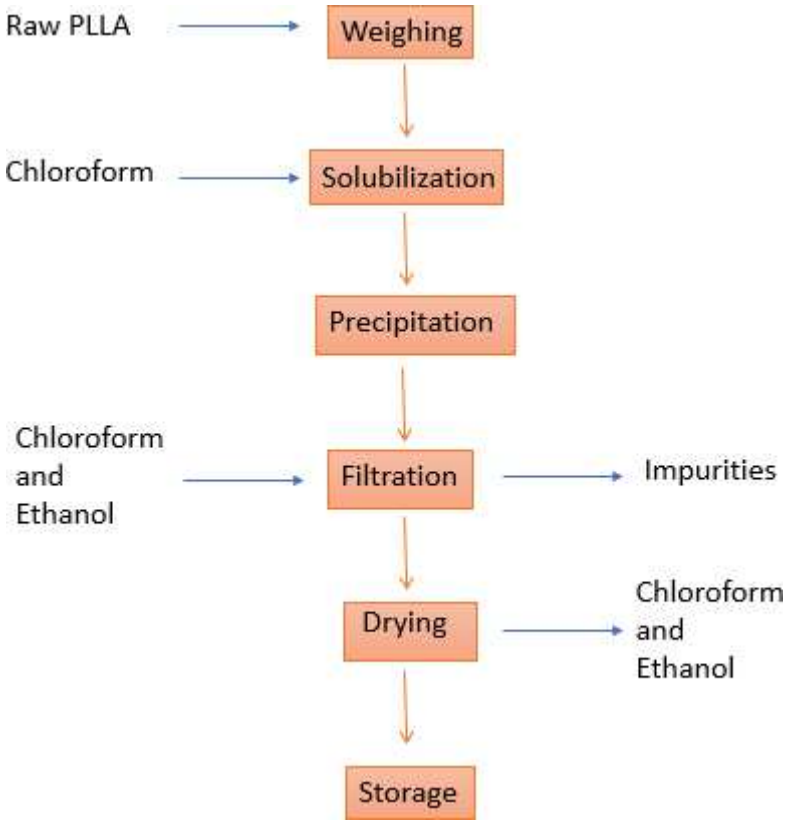

Figure 5.12: PLLA purification steps [Author's source].

The purification steps used were as follows:

1. The sample is weighed and solubilized following the ratio of 20g of polymer to 60 mL of chloroform (Figure 5.13);
2. After complete dissolution, for a period of 24 hours under constant agitation, the solution is precipitated with ethanol until it becomes cloudy (Figure 5.14);
3. The solution must be kept for 24 hours, and later, it can be filtered, and after drying, the PLLA is transferred to the mortar and macerated (Figure 5.15);
4. After being completely macerated, refined PLLA presents the morphology of a clarified white powder (Figure 5.16);

Figure 5.13: Solubilization of PLLA in the chloroform [Author's source].

Figure 5.14: Solution with PLLA and chloroform precipitated with ethanol [Author's source].

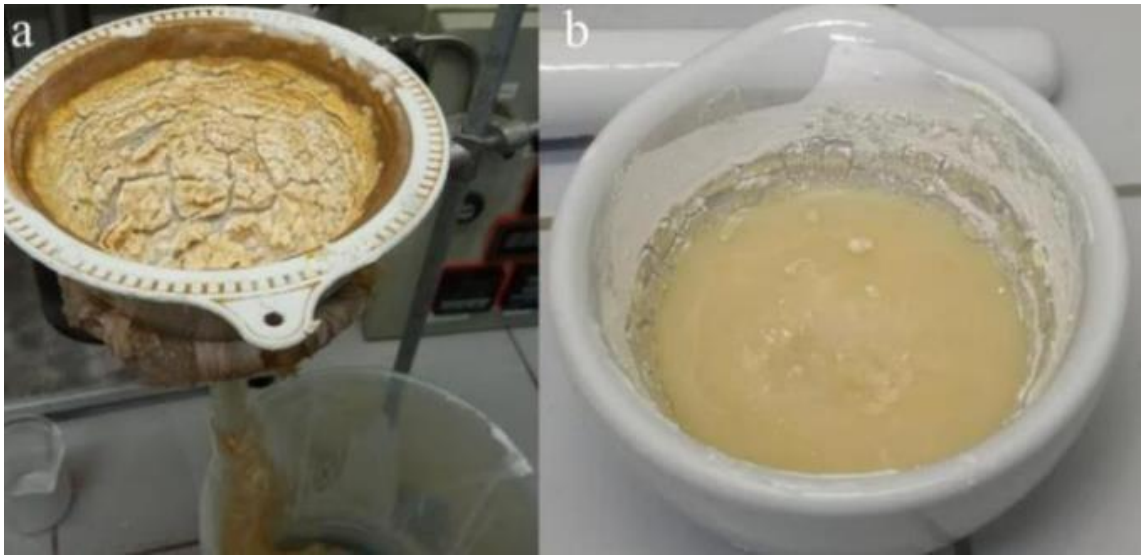

Figure 5.15: Filtered solution (a) and transferred purified PLLA (b) [Author's source].

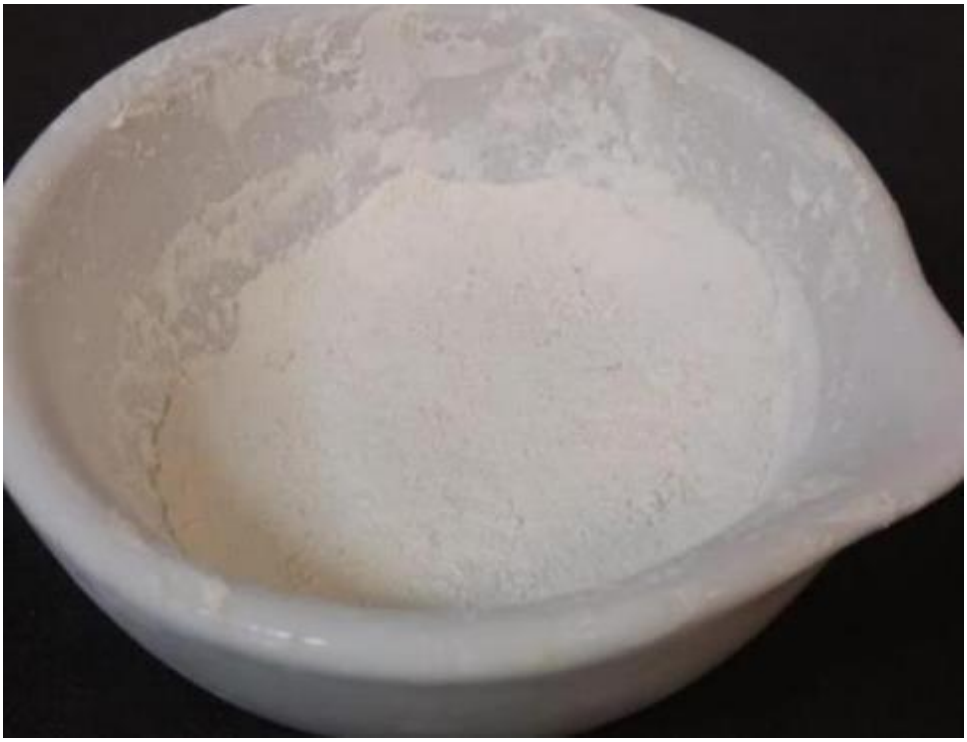

Figure 5.16: Refined PLLA [Author's source].

5.5.2 Purification Yield

After PLLA was purified according to the steps described above, the yield is calculated as a percentage (η%), which is defined as a percentage ratio from the ratio between the real yield (or the obtained quantity) to the theoretical yield (or the expected quantity), as expressed in Equation 7:

$$\eta\% = (\text{Real yield}/\text{Theoretical yield}) * 100 \quad (7)$$

The yields of the PLLA obtained in the initial configuration and in the fourth configuration have been calculated and they are depicted in Table 5.2.

Experimental Unit where the PLLA was obtained	Synthesis time [h]	Inicial mass [g]	Final mass [g]	η%
1	72	111,21	82,39	74,08
4	24	107,27	98,38	91,71

Table 5.2: Percentage yield of PLA obtained in the first and fourth configuration [Author's source].

5.6 Results

In this Chapter ~~5~~, not only was the priority given to the synthesis of L-lactide but the experimental part with the glass units led to the definition that there is not only one product, L-lactide, but also the PLLA polymer obtained through direct polymerization synthesis.

Due to these considerations and the market price of L-lactide, as shown earlier in Market Price Table 1, in Chapter 1, it was decided to study and design the system to pay attention to the two final products: L-lactide and, PLLA. Considering that, L-lactide has a significant market interest, making it a highly valuable raw material for synthesizing poly (lactic acid) (PLLA) through the ring-opening mechanism (ROP). Consequently, at the industrial level, having both low molecular weight PLLA, which is suitable for medical applications as a film, and high molecular weight PLLA, which allows the formation of scaffolds or prostheses, is of great importance in the medical field.

In the diagram presented, Figure 5.17, can see the various syntheses that can be done starting from L-lactic acid and furthermore, to increase the shelf-life of the products obtained, a purification and freeze-drying process was carried out.

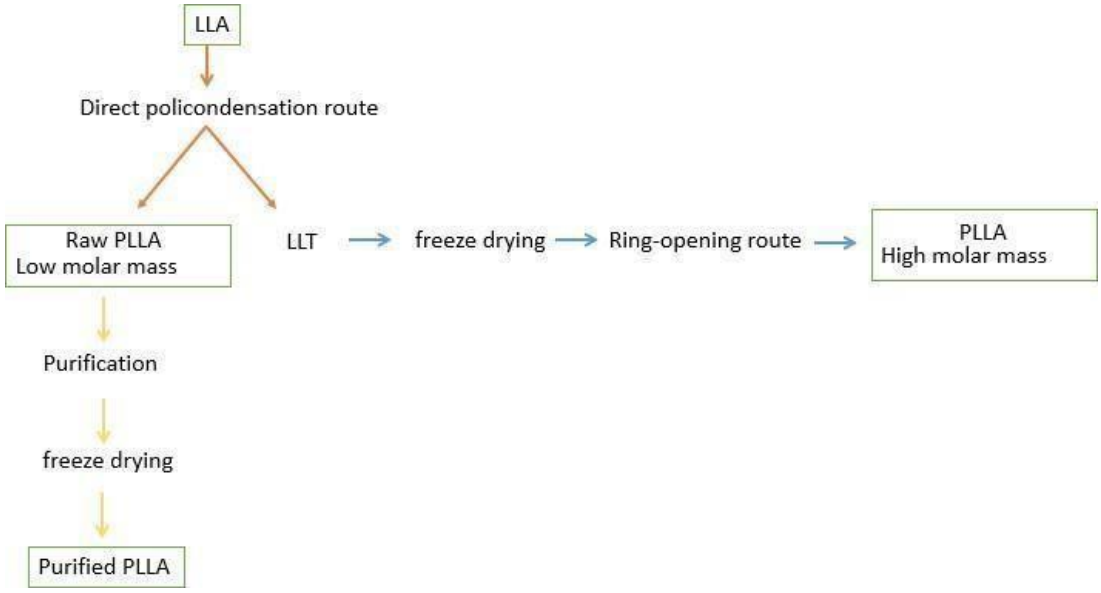

Figure 5.17: Outline of the various stages of the process [Author's source]

5.6.1 Mass balance concerning the Fourth configuration.

After conducting the synthesis in the context of this fourth configuration, a

comprehensive mass balance analysis was performed to quantify the yield of the reaction, with particular emphasis on the production of L-lactide (LLT).

The mass balance of the fourth configuration is presented because it was the best in terms of synthesis and collection of L-lactide in the second tank and for the polymer obtained.

The scheme under consideration is presented in Figure 5.8.

In the context of this project, the mass balance, shown in Figure 5.18, according to the fourth configuration, provides valuable information on the reaction efficiency and specific L-lactide production, clarifying the performance and reliability of the designed system. These quantitative results further validate the potential industrial applicability of the continuous-flow process for the synthesis of LLT and PLLA.

The processes and configurations were initially designed to give more relevance to LLT, but as low molar mass PLLA was also synthesized, it began to look like a product for different applications. A third product can be obtained starting from L-lactide itself using ring-opening synthesis.

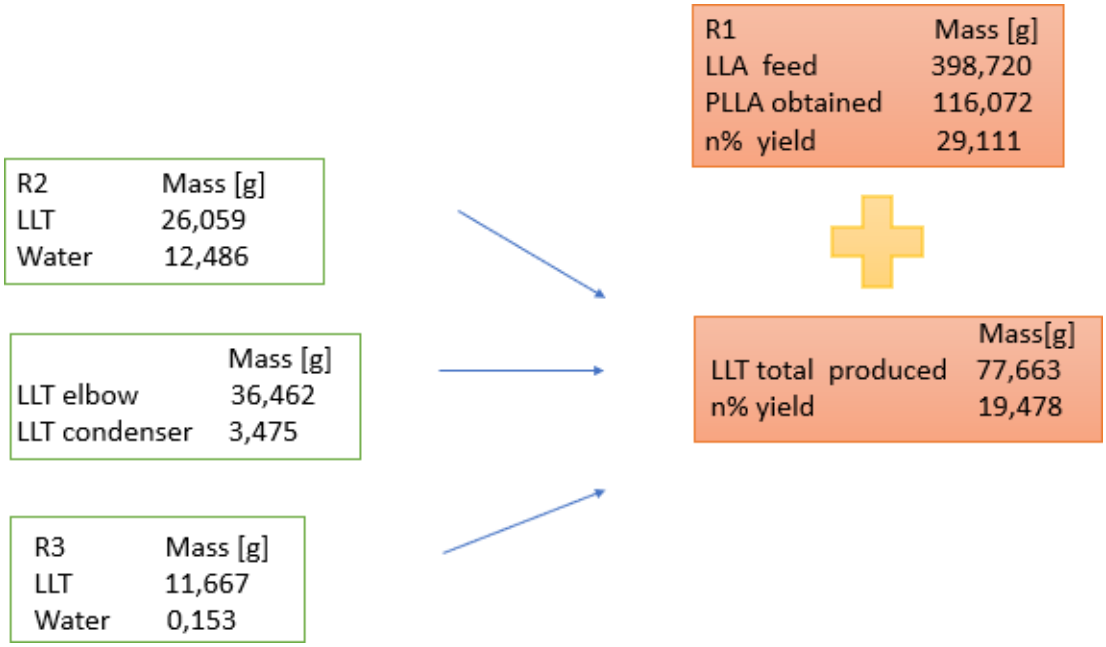

Figure 5.18: Scheme of Mass balance for the Fourth configuration [Author's source].

5.6.2 Fourier-transform Infrared Spectroscopy (FTIR)

The L-lactide dimer and the PLLA polymer produced in the fourth configuration were

characterized through the FTIR technique. The measurements of FTIR were carried out using a Bruker VERTEX 70v spectrometer in transmission mode with a 633 nm wavelength laser radiation. The sample was prepared by placing 0.2 mg of active material in a KBr pellet. The studied region ranged from 500 to 4000 cm^-1, allowing the determination of vibrational absorption bands for PLLA and LLT. FTIR analysis was performed on raw and purified PLLA in the fourth configuration, resulting in characteristic polymer functions. When overlaid, it was possible to observe that purification enhanced the resolution of bands for understanding chemical functions, as shown in Figure 5.19. In the subsequent Figure 5.20, the result for LLT was represented, yielding the characteristic function of the dimer. The relative results for PLLA and LLT were compared using Table 4.3, which correlates each absorbance with the characteristic chemical bond.

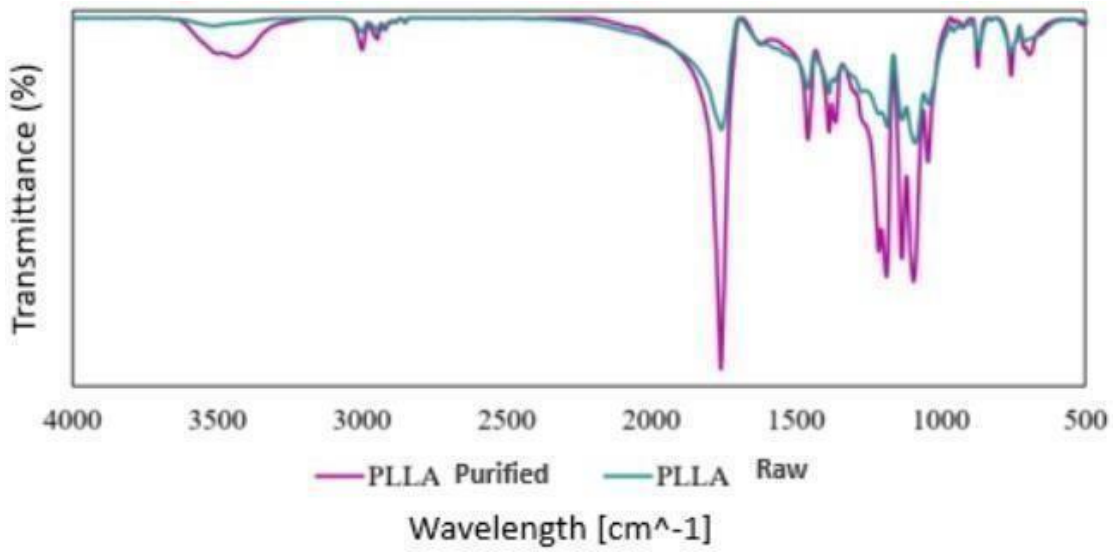

Figure 5.19: FTIR of PLLA obtained from polycondensation in the Fourth configuration before and after the purification process [Author's source].

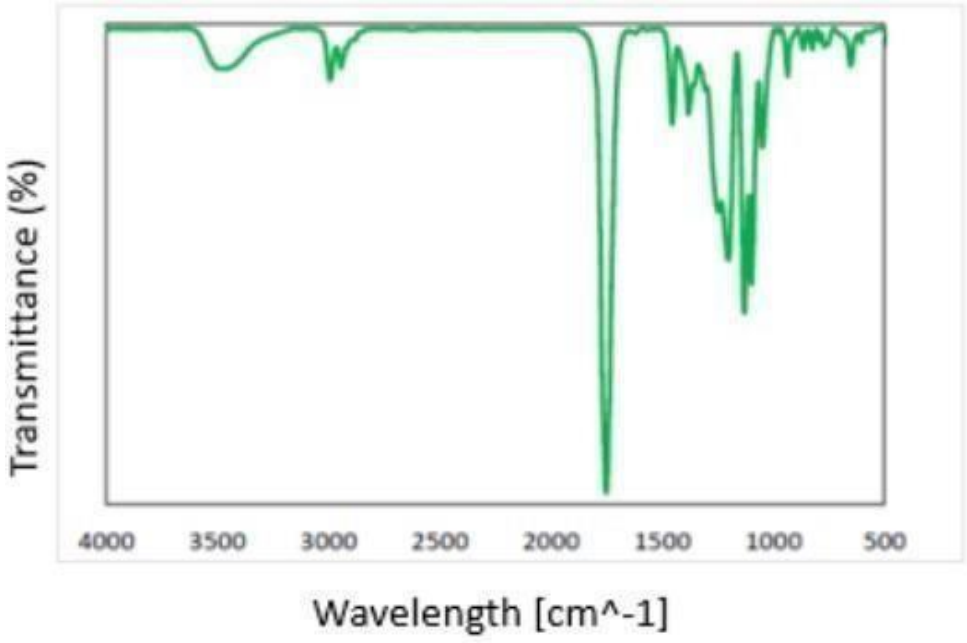

Figure 5.20: FTIR of LLT produced in the Fourth configuration [Author's source].

The absorption bands observed in the spectra can be classified: from 3000 cm-1 to 2800 cm-1 refer to the stretching of CH and CH3 bonds; 1745 cm-1 corresponds to the stretching of the C=O bond; 1455cm-1, absorption due to deformation of the CH3 bond; 1385 cm-1, deformation of CH bonds and CH3 and; 1275 cm -1 corresponds to the stretching of the C-O (ester) bond.

According to Motta, (MOTTA; DUEK, 2006) and the work done by Pattaro, (PATTARO, 2016), it is verified that the spectrum coincides exactly with PLLA and L-lactide, as show in Table 4.3 (Chapter 4) used to analyse the spectrum of L-lactide and the polymer obtained from the synthesis via ring-opening polymerization (ROP).

Also, at the end, comparing the two spectra relative to the raw polymer and the purified polymer, it can be observed that the two are coincident and that only the resolution changes because the purified one has a larger area.

5.6.3 X- Ray Diffraction (XRD)

The DRX technique uses expansion of X-ray radiation through structures organized (crystals), allowing the realization of morphological elements in matter, determining its crystalline structure and its crystalline fraction (percentage), so to visualize the crystallinity of the synthesized polymers, XRD analyses were performed, as showed the

Figure 5.21.

The X-ray diffractor used for the characterization of the PLLA was the Rigaku model MiniFlex 300/600 located at the Federal University of São Paulo (Campus Diadêma). The radiation used was copper kα (λ=1.5 Å), the voltage of 40 kV, current of 40 mA, 2θ scan from 2° to 90° and scan speed of 5°*min^-1.

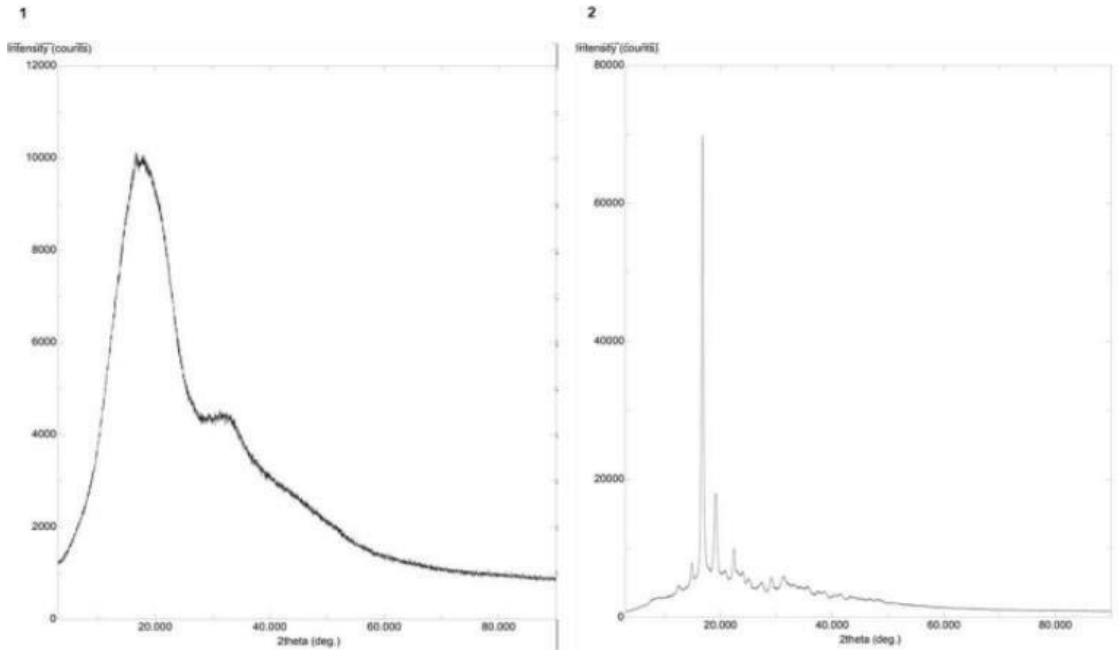

Figure 5.21: XRD of crude (1) and purified PLLA (2) [Author's source].

According to Figure 5.21, it can be noted that the characteristic peaks of PLLA were found in the range of 2θ (14.5; 16.3; 18.7 and 21.9°) as in the literature de França et.al(DE FRANÇA et al., 2022).

Furthermore, it can be noted that the XRD of the purified polymer has more accentuated peaks, because, after the purification process, the PLLA has a higher degree of purity, How XRD analysis allows to visualize crystallinity it is related to the purification process since it involves the removal of monomers or dimers that did not participate in the polymer chain growth. This is the reason that the peaks of purified PLLA appear more pronounced, while those of crude PLLA show a greater area.

5.7 Partial conclusion

In this Chapter, it was focused the production of two products, L-lactide and PLLA with

low molar mass, and possibly a third which has l-lactide as its raw material which, through ring-opening synthesis, allows us to obtain a PLLA with a high molar mass. The conclusion was reached that the fourth configuration is the most efficient one and furthermore a synthesis is presented that does not involve waste and does not use organic solvents. We managed to lower the reaction time, to get closer to industrial production, as shown in Table 5.1.

Furthermore, the importance of the simultaneous control of temperature and pressure was demonstrated, respectively reaching temperatures of 220°C and pressure of -550 mmHg, in order to form the cyclic dimer. Remembering that L-lactide is formed in the vapor phase and therefore it is very important to be able to collect the crystals in the second reservoir through thermal control. This control still needs to be improved. The purification process of the PLLA obtained in the reactor is also important because in the studied process a higher temperature is used than the ideal temperature of the synthesis via direct polycondensation, normally a range from 140 to 160°C is used.

All the syntheses studied always involve the same quantity of catalyst and co-catalyst, respectively 1% of SnOct(II) and 0.0025% of 1-dodecanol, which are authorized by Anvisa and FDA for medical applications.

Chapter 6

6.1 Introduction

This chapter studies the production of L-lactide and PLLA via direct polycondensation, always starting from L-lactic acid.

The system described represents a consequence of the fourth configuration (Chapter 5) but in a pilot plant, starting to focus on production on a larger scale (pilot-plant).

6.2 Scale-up of the fourth configuration

After conducting extensive experimental studies, considering the acquired results and advances in understanding L-lactide and crucial synthesis parameters, such as temperature and pressure, a viable process know-how was developed. This was driven by the absence of alternative processes to simultaneously produce PLLA biopolymer

and cyclic LLT dimer. The primary focus was then shifted towards scaling up production and attempting to synthesize both the polymer and the dimer on a pilot plant, as a consequence relating to Chapter 5 and in particular to the fourth configuration studied.

Another crucial consideration is to prioritize a "Green" process, one that avoids the use of toxic solvents while ensuring the appropriate quantities of catalysts, Tin Octanoate 2 (OctSt-II) (Sigma Aldrich), and cocatalyst 1-dodecanol (Vetec). These should be maintained at 1 wt% and 0.0025 wt%, respectively, following the guidelines set by Anvisa and FDA.

6.3 Description of process

The proposed process is a continuous process where there is no interference of oxygen gen during the synthesis period, its presence causes the polymer chain to crack. The process involves the synthesis of PLLA and L-Lactide from lactic acid. The polymerization process starts with the dehydration of lactic acid for at least three hours, followed by the addition of the catalyst SnOCt (II) and the respective cocatalyst (1-dodecanol) to initiate its synthesis, while constantly stirring.

Pressure and temperature control are crucial as they increase the system's efficiency, thus reducing the reaction time, an essential parameter for industrial production. Maximum polymerization efficiency, mean that depending on the control of reaction variables, it is possible to achieve the desired final product (PLLA) with a desired molar mass and at the same time produce the lactide dimer (LLT). The production of PLLA is done through direct and continuous polycondensation synthesis, which differs from those found in the literature, where lactide is commonly produced in different steps.

With this technology, it is possible to produce lactide directly, considering that the cyclic dimer has a high market value, as shown in Table 1.1, and is also the raw material for the production of high molar mass PLLA through the opening route (ROP).

Therefore, the process yields two products with high purity: PLLA and L-lactide. Additionally, the system avoids wasting inputs, and the post-consumption products are degradable through hydrolysis, with the final process residue (water) being reusable, contributing to a green logistics process. Finally, it has been designed, described in this know-how, the process that allows, by setting pressure and temperature, to obtained, from lactic acid, PLLA and LLT using SnOct (II) and 1-dodecanol as catalysts, feed

them into a reactor operating in the temperature range of 180 to 250 °C and a pressure of -550 to -600 mmHg.

Figure 6.1 depicts the components that are part of the process, including: a main reactor (4) and a secondary reactor (6); thermal controllers (3 and 7); reagent feeding zone (2); thermal exchange system (1, 5, and 8); reservoir (9); trap (10); and a vacuum and pressure pump (10).

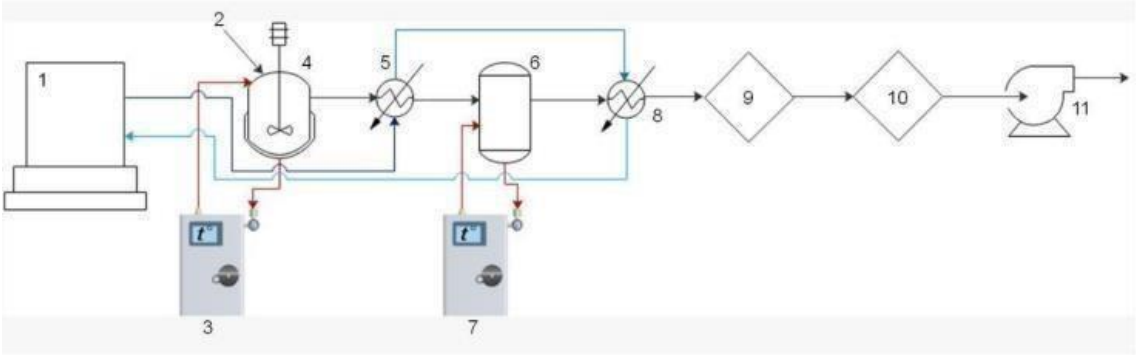

Figure 6.1: The scheme that represents what has been described in the know-how [Author's source].

It is worth noting that the obtained products can be refined to achieve a higher degree of purity. The molar mass can also be customized through process unit variables, thereby producing polymers suitable for various applications and lactide of specific classes that can be used to produce high molar mass polymers.

6.4 Pilot Plant

The used pilot plant is shown in Figure 6.2. A retrofit was implemented to automate the process and facilitate parameter selection and control, as shown in the control screen in Figure 6.3. In addition, the bomb was replaced to ensure conditions effective vacuum, allowing a pressure of -550/-600 mmHg. This, combined with a temperature range of 180-220°C, facilitates the smooth production of the dimer. Pressure control is a very important factor because having vacuum control during the reaction allows the process to collect L-lactide (LLT) in the second tank and not foul the condenser which connects it to the main reactor where the PLLA polymer synthesis takes place. A detail added to favor the production of the cyclic dimer is the shape of the stirrer which, by rotating counter clockwise during the reaction time, would help to make the vapor phase rise

again in the top part of the reactor, shown in Figure 6.4. This vapor phase would be exactly the section where L-lactide would begin to form.

Figure 6.2: Pilot plant for the production of PLLA and LLT [author's source].

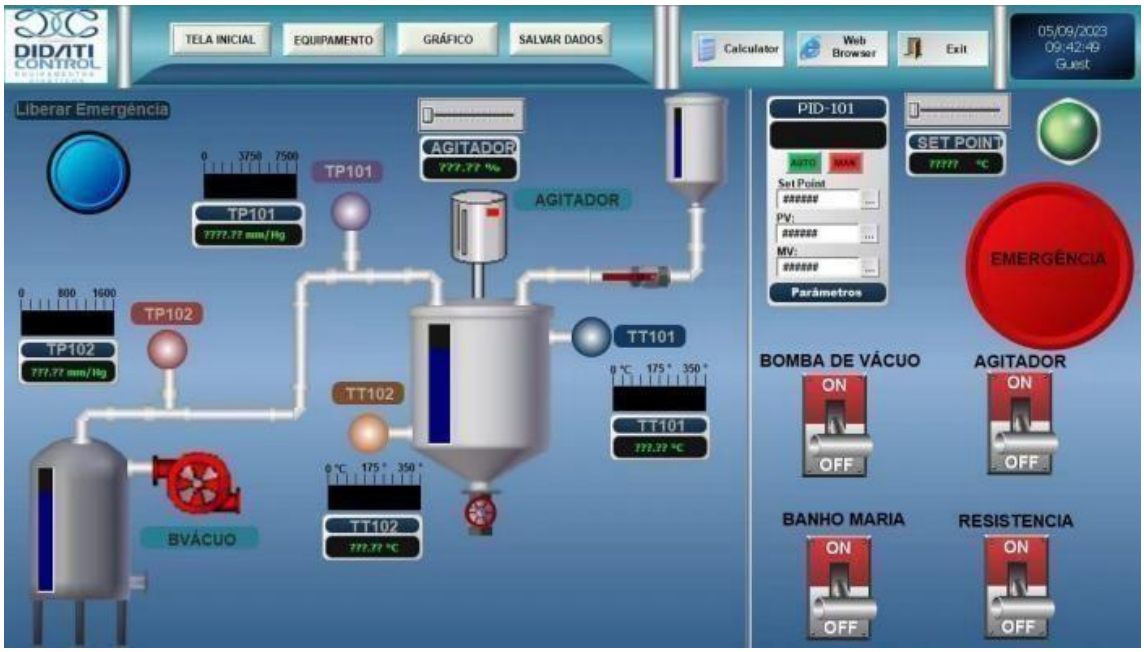

Figure 6.3: Screen control for the pilot plant [Author's source].

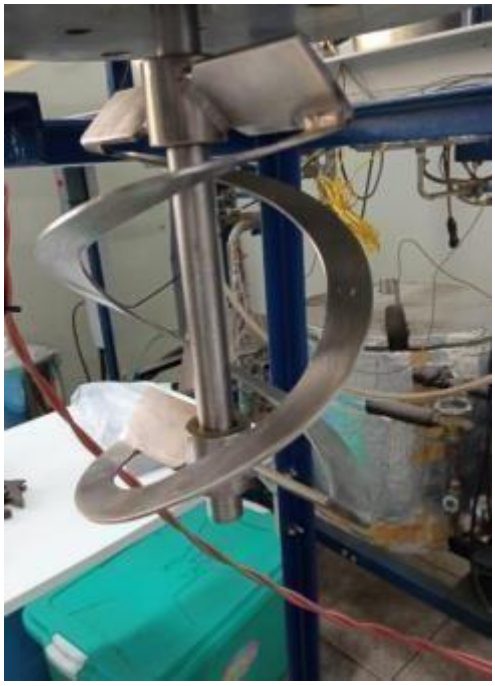

Figure 6.4: Mixer shape to aid LLT formation [Author's source].

According to Figure 6.2, the pilot plant is composed by:

1. Principal reactor where is produced PLLA;
2. L-lactide reservatory;
3. Mechanical stirrer;
4. Pressure controller;
5. Water bath;
6. Pump of vacuum;
7. Condenser;

6.5 Materials

The materials used for the synthesis are the same used also in the configurations made with laboratory units. The material used is L-lactic acid (LLA) 85% (Synth), Tin Octanoate 2 (OctSt-II) (Sigma Aldrich), 1-dodecanol (Vetec).

6.6 Methods

The reaction carried out was a polycondensation reaction. In the main reactor, L-lactic acid was fed, in a quantity of 3 Kg.

The selected L-lactic acid has a concentration of 85%. The established reactions parameters are 180°C and a pressure of -580 mmHg, the chosen reaction time was 4 hours. Before counting the beginning of the reaction, therefore the 4 hours chosen, the first dehydration step was carried out as L-lactic acid has 15% of water. Since the reactor was started, the mechanical stirrer has been activated at 30% intensity. The temperature has been steadily raised until reaching 180°C, and subsequently, the bomb has been ignited to assess heat exchange 79 efficiency and ensure a vacuum of -580 mmHg. Additionally, aluminium paper and parafilm tape to work as insulator have been introduced into the system. Also, a hose handle that passes water at a temperature of 70°C is taken from an aluminium base to be able to maintain the temperature and control the thermal trough, as depicted in Figure 6.5.

Figure 6.5: Detail of pilot plant, addition of aluminium paper[Author's source].

The dehydration step began once the temperature reached 120°C. It can be observed that 450 ml of water, corresponding to 15% of the content in the L-lactic acid used as feed, was removed from the system, Figure 6.6. After completing this step, catalyst and co-catalyst were added, specifically SnOct2 at 1% and 1-dodecanol at 0.0025%, following ANVISA and FDA guidelines. The reaction started upon the introduction of the catalyst and co-catalyst, maintaining a fixed temperature of 180°C and a pressure of -580 mmHg for 4 hours.

Figure 6.6: Details of the water retreat [Author's source].

After the 4 hours of operation, the system was powered off, and the resulting polymer was extracted from the main reactor, specifically measuring a weight of 1.5 kg of PLLA poly (L-lactic acid), according to Figure 6.7.

Additionally, the system was carefully opened, and upon inspection inside the repository, as shown in Figure 6.8, could be observed the successful production of LLT (L-lactide), which not only confirmed the initial hypothesis, but also demonstrated the achievement of the objective to produce the dimer in a single step.

Evidently, crystalline structures of the dimer were visible, even if in relatively small quantities could be discerned a small quantity of water. During the synthesis, a total of 279.794 g of L-lactide was successfully produced, and in addition to this achievement, 400 ml of water was effectively removed from the process.

Figure 6.7: PLLA produced in the pilot plant [Author ‘s source]

Figure 6.8: L-lactide produced in the pilot plant [Author’s source].

6.6.1 Post processing of L-lactide

After the reaction occurred in the pilot plant, the formation of the l-lactide was noted with still a quantity of water present inside, as shows Figure 6.9. The quantity of water could be noted thanks to the viscosity of the product.

Figure 6.9: LLT produced in the pilot plant [Author's source].

Filtration was done with a simple filter, as shown in Figure 6.10, in order to remove water, the l-lactide weighed after the filtration was 57.739 g. Therefore, an elimination of 222.058 g was noted, with the need to further improve the withdrawal of water to be able to collect the dimer in a more stable condition.

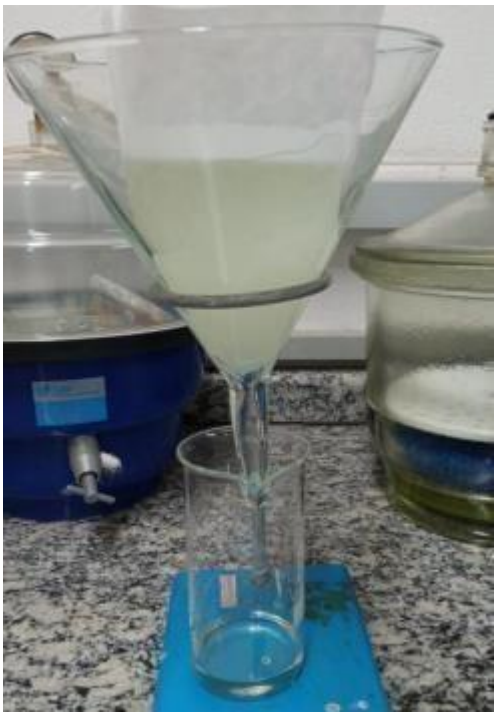

Figure 6.10: Filtration of l-lactide collected in the pilot plant [Author's source].

Furthermore, a second step was done to see if a distillation helped the water to evaporate and so a system was assembled and a temperature of 120°C was maintained

to ensure evaporation, as shown in Figure 6.11. It was noted that the l-lactide, Figure 6.12, returned to a yellow colour, and to a liquid form; it is probable that a reversibility of the reaction was noted, therefore returning to have a composition of LLA monomer with some LLA dimer.

Figure 6.11: Distillation column for the purification of l-lactide [Author's source].

Figure 6.12: L-lactide collected after these two steps of purification[Author's source].

6.7 Results regarding Pilot Plant

Consistent with the outlined procedure, the results obtained during the reaction are presented in Table 6.1.

In particular, PLLA obtained through direct polycondensation and L-lactide were characterized Fourier-transform Infrared Spectroscopy (FTIR), and it was possible to analyse the molar mass of the polymer obtained through Gel Permeation Chromatography analysis (GPC).

Feed	Step reaction	Temperature °C	Pressure [mmHg]	Time [h]	Product
LLA 3 Kg	Dehydration	Up to 120°C	-580	0,5	LLA dehydrated 2,460 Kg
LLA dehydrated 2,4 Kg	Direct Policondensation	180°C	-580	4	PLLA 1,5Kg LLT 279,794 g

Table 6.1: Result about Pilot Plant [Author's source].

6.7.1 Fourier-transform Infrared Spectroscopy (FTIR)

After the synthesis of the polymer and the dimer, an analysis of the material was always carried out in the same equipment used for the characterization of the materials synthesized in the experimental units.

The measurements of FTIR, as showed in Figure 6.13 and Figure 6.14, were carried out using a Bruker VERTEX 70v spectrometer in transmission mode with a 633 nm wavelength laser radiation. The sample was prepared by placing 0.2 mg of active material in a KBr pellet. The studied region ranged from 500 to 4000 cm^-1, allowing the determination of vibrational absorption bands for PLLA and LLT.

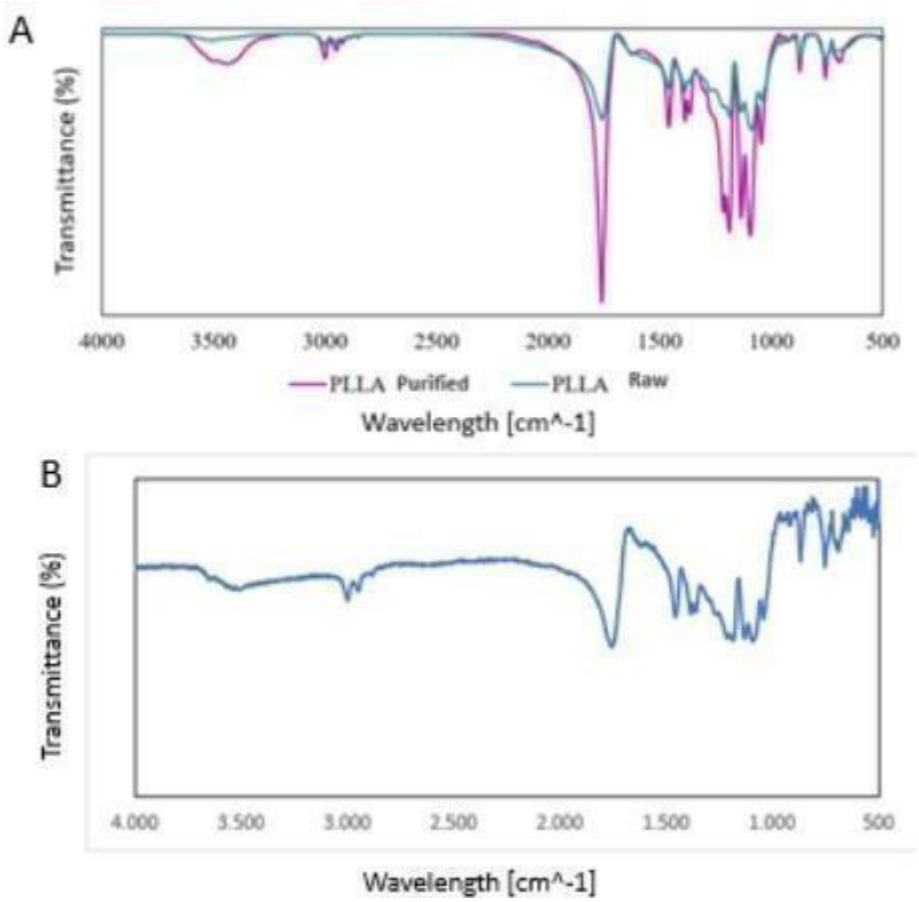

Figure 6.13: the part A showed the FTIR done for the PLLA in the experimental unit and the part B shows the FTIR of PLLA produced in the Pilot Plant [Author's source].

According to Figure 6.13, the spectrum of PLLA synthesized in the pilot plant corresponds to the spectrum of raw PLLA synthesized in the experimental unit. Greater uncertainty is found in graph close to the wavelength at 500 cm^-1, probably due to some uncertainty in the measurement.

According to Lopes'thesis,(SAVIOLI LOPES, 2014), and thanks to the study done by

Pattaro, (PATTARO, 2016), also compared the absorption bands of an industrial PLLA, Table 6.2, with that obtained in the pilot plant and it can actually be noted that the absorptions are characteristic of the polymer.

Absorption band symmetrical/asymmetrical	Industrial PLLA [cm^-1]	Pilot Plant PLLA [cm^-1]
Vibrations of -CH and -CH3	2999,47 / 2948,81	2994,91 / 2944,77
Vibrations -C=O of -COO	1754	1754,91
Flex vibrations -CH of -CH3	1387,86 / 1452	1384,64 / 1459,85
Vibrations -C-O of -COO	1130,42 / 1044,95	1186,01 / 1043,3
Alongside vibrations of -COO	872,98	871,67

Table 6.2: Characteristic absorption bands of the PLLA polymer: industrial VS produced in the pilot plant [Author's source].

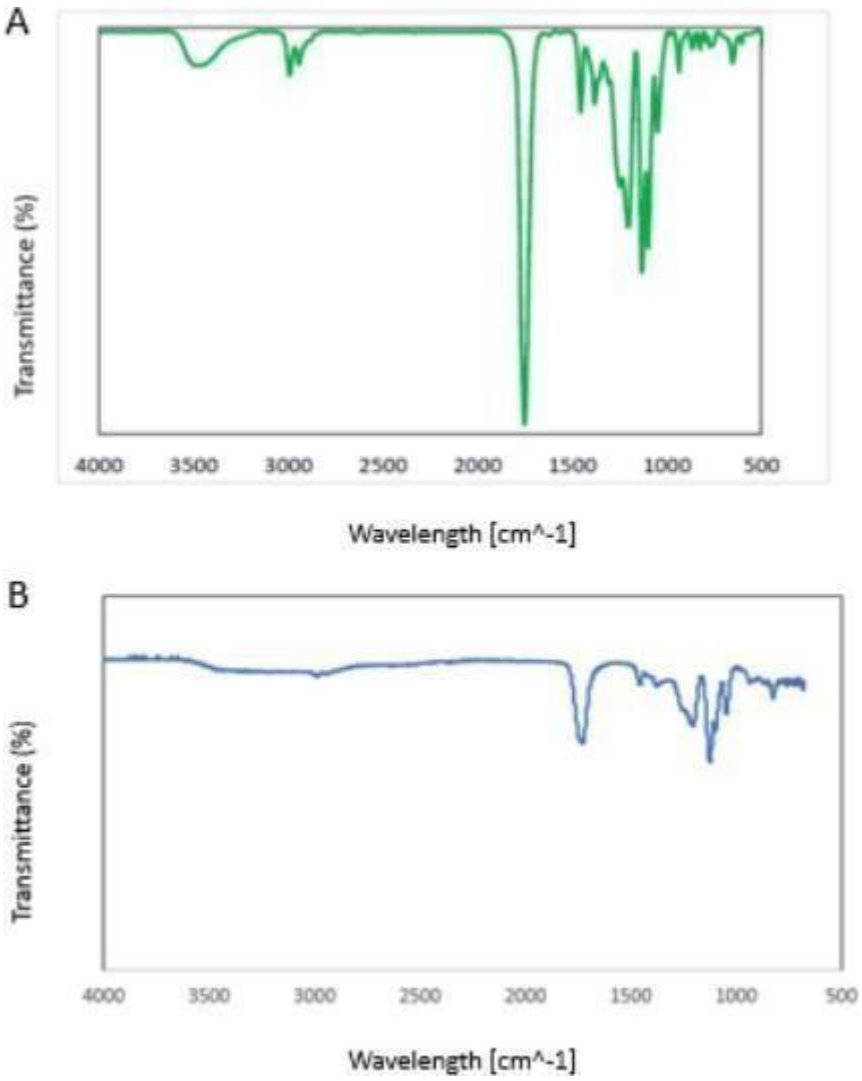

Figure 6.14: the part A showed the FTIR done for the LLT in the experimental unit and the part B shows the LLT of PLLA produced in the Pilot Plant [Author's source].

The same thing was done for L-lactide. In the same equipment, the analysis of the infrared spectrum was made. As can be seen in Figure 6.14, graph B, which represents LLT produced in the pilot plant, has a spectrum very similar to the LLT produced in the experimental glass units.

The peaks coincide, but what differs from each other is the area under it. This can be explained in relation to the degree of purity, in the collected LLT as shown in Figure 60a.

Furthermore, according to Pattaro's thesis, (PATTARO, 2016), the absorption bands that characterize L-lactide are the vibrations corresponding to an absorption band of 936 cm^-1 -CH which in the studied spectrum is 825 cm^-1 continuing with a stretching of

the -C=O characteristic in the bands of 1720 cm^-1 and 1120.66 cm^-1.

6.7.2 Gel Permeation Chromatography (GPC)

The gel permeation chromatography (GPC) technique made it possible to analyse the molar mass of the polymer obtained.

From this analysis three indicators can be obtained: Mn, Mw and finally the ratio between two Mw/Mn(CODARI et al., 2010; TERRA et al., 2022)

Mn is defined as the molar mass of the entire polymer chain, divided by the polymer chains present, therefore not different from a numerical average. Mw is another way to calculate the molar mass because it takes into account the weight of each fraction of the chain present within the polymer, thus giving a definition of a weighted average(TERRA et al., 2022)

Lastly, the ratio between the two is defined, Mw/Mn, or Polydisperse Index, IP, refers to a measure of the distribution of molecular weights within a polymer sample. It quantifies the spread of polymer chain lengths. IP value of 1 indicates a monodisperse sample, meaning all polymer chains have nearly the same molecular weight. Conversely, a higher IP value suggests a broader range of molecular weights, indicating a more polydisperse sample. In practical terms, a lower IP is desirable in many applications, as it signifies a more uniform and consistent polymer product.

As this analysis is very expensive, because it uses solvents to solubilize the various materials, it was not carried out on all the synthesized samples. In this case the synthesized PLLA was dissolved in Tetrahydrofuran (THF), respectively 30mg of materials per 10 mL of solvent and then left to rest for 24h. The equipment used is Viscotech brand, model TDA 302 (Houston).

Table 6.3 shows the results of this analysis, and the graphs are placed as an appendix I.

Sample	Mn [Dalton]	Mw [Dalton]	IP [Mw/Mn]
PLLA	40152,00	142762,00	3,55

Table 6.3: Results from the GPC analysis of the PLLA produced [Author's source].

According to the analysis of Motta in 2002,(MOTTA, 2022) it is noted that the Mw = 100000.00 and IP = 1.7, and the polymer obtained by us has a similar molar mass and what is certainly different is the polydispersity index, which is equal to 3.55; this would

explain a lower purity than the industrial one and a presence of monomers or oligomers within the analysed polymer chain.

6.8 Partial conclusion

These results demonstrate and confirm the hypotheses related to the scale-up and further underline the achievement of L-lactide production through a single step, and in the same time the synthesis of PLLA through direct polycondensation.

It can be noted that, being able to reach a pressure very close to vacuum, it is also possible to lower the formation temperature of the L-lactide. It was decided to use 180°C in order to be able to produce the dimer and also the polymer. It must be considered that the ideal temperature to produce PLLA by direct polycondensation is 160°C.

As can be seen from Figure 6.7, the colour of the raw polymer is very dark, the ideal would be to collect a much lighter coloured polymer. The aluminium added to the reactor outlet is essential to prevent the dimer from crystallizing and encrusting that part of the system, causing a stop of the synthesis. As soon as the reaction parameters are reached, the dimer begins to form in the vapor phase in the top part of the reactor and if the outlet tubing does not have a temperature close to the internal temperature of the reactor, the LLT crystallizes. For this reason, it is essential to have a thermal control of the whole system and in the lactide reservoir a lower temperature already causes the formation of the dimer, ice was added to the glass unit to guarantee this heat exchange.

To finalize it can be concluded that it is necessary to improve this water withdrawal step in order to improve the production of the cyclic dimer because the formation of the L-lactide during the reaction is very rapid and like the reaction which has LLA as a reactant ~~reagent~~ it is reversible and therefore the simultaneous control of pressure and temperature is essential, in order to collect the crystals that form the cyclic dimer. In addition, it can be noted that not only the parameters are important, but also the design of the system, such as the mixer, in order to aid the synthesis and move the desired reaction towards the product, L-lactide.

Chapter 7

7.1 Possible applications

PLLA is a widely used material in various techniques such as electrospinning and 3D printing due to its practicality and renewability(BARDOT; SCHULZ, 2020; ZHANG et al., 2021). For example, the monomer used in the production of PLLA polymers can be derived from the fermentation of sugar cane waste. Currently, even on the market, there is growing interest in using PLLA as a collagen stimulator. This demonstrates the material's ability to be absorbed and promote collagen formation, a process that typically diminishes with age. In business environments, this feature is recognized as filler. Furthermore, the PLLA produced in the experimental setup was used to produce a bio-ink using a 3D printer. The article is shown in the Appendix and the work will be further developed by my colleague Samuel Diogenes de Souza in his PhD project(CRIVELLIN et al., 2022b; DE SOUZA, 2022).

3D bioprinting, an emerging technology, allows for the precise placement of living cells and biomaterials in a layer-by-layer manner to create intricate composite tissue structures. Functioning as an additive manufacturing technique, it holds great promise for tissue engineering and regenerative medicine (SAVIOLI LOPES, 2014). In contrast to traditional scaffold fabrication methods, 3D bioprinting excels at mimicking the intricate microstructures of biological tissues and accurately controlling cell distribution.

Instead, electrospinning is a technique used in materials science and engineering to create fibers or microfibers from a polymer solution or melt. The process involves using an electric field to deliver a charged polymer solution or melt through a needle or nozzle. As the polymer solution is expelled, it forms a thin jet that stretches and solidifies into ultra-fine fibers as the solvent evaporates or cools. These fibers are collected on a target surface, typically forming a non-woven knitted membrane with a high surface area to volume ratio(RAFAELA BOHACZUK VENTURELLI, 2017).

In this thesis project, until now, it was not possible to study a possible membrane produced by PLLA synthesized starting from L-lactide due to the complexity and control of the reaction. Even a small amount of water present in the cyclic dimer does

not allow the correct polymerization for final PLLA polymer. Efforts have been made to focus on the synthesis process, aiming for the optimal level of purity while employing a solvent-free system to avoid the inclusion of harmful substances.

7.2 Future Application in the market

In recent times, the presence of polymers, in particular biopolymers, has been observed in real beauty and cosmetic treatments. The initial exploration of PLLA as a facial-filler dates back to 2004, when it was used to address lipoatrophy in HIV-infected patients receiving highly active antiretroviral therapy (HAART). The approval of poly-L-lactic acid (PLA) under the trade names New-Fill® and Sculptra™ marked the first filler, being the first by the FDA(COSTA et al., 2022).

Initial studies show significant efficacy, but the importance of injection depth became apparent soon after.

A study involving 14 patients reveals improvements, especially for those who had experienced lipoatrophy in a relatively short time. Furthermore, it was specified that the injection of diluted PLLA material should be performed in the subcutaneous tissue (JÉRÔME ASIUS, MAUGUIO (FR); HATEM FESSI; ELISABETH; LAUGIER-LAGLENNE, 2004; PETER MORGAN; MACAKOVA, 2020).

The PLLA used as a bio-stimulator is defined as a semi-permanent filler, with a duration of up to 24 months. The produced PLLA microspheres are hydrated, typically 120 mg of material with 6-8 mL of deionized water and 2% anesthetic, with a resting time of 24 to 72 hours before application to prevent nodules or needle blockages. Hydration can be performed directly by the physician who injects it into the patient, and the product can be sold in powder form and kept in the refrigerator until application. It is studied that PLLA stimulates neo-collagenesis, meaning the injected PLLA particles attract many macrophages. Since they cannot phagocytize the particles, they come together to form a larger type of inflammatory cell called a Multinuclear Giant Cell, along with lymphocytes and fibroblasts. A capsule forms around each individual microsphere as the PLLA is metabolized, resulting in increased collagen fiber deposition by fibroblasts, ultimately leading to a subsequent increase in dermal thickness(JOHL; BURGETT, 2006).

As the final polymer in the PLLA product undergoes an environmentally friendly purification process, the decision was made to investigate and explore the potential

applications of the product in the medical field. According to the patent disclosed by Galderma (2022),(PETER MORGAN; MACAKOVA, 2020), relating to the aforementioned product, the currently available product has the following characteristics: 150 mg of PLLA microparticles or microspheres, 10 mM phosphate buffer (with pH 6.2), isotonic sodium chloride, 0.5% polysorbate 80 and 180 mg of carboxymethylcellulose (CMC). Before injection, the product must remain in solution for 24 hours to ensure complete solubilization in water and to avoid nodule formation upon injection (PETER MORGAN; MACAKOVA, 2020; RAFAELA BOHACZUK VENTURELLI, 2017).

Using the methodological framework described previously in Chapter 5, refining the purification procedure through careful analysis could exploit the potential of the material, in the medical and especially aesthetic fields. This could lead to the introduction of a new filler product, potentially enhanced by incorporating an adequate amount of hyaluronic acid. This addition could allow for gelation, eliminating the need for a 24-hour solubilization period and making the product immediately usable (CABRAL et al., 2020).

For this reason, the PLLA produced in the experimental part, material produced with the experimental units described in Chapter 5, was diluted in water, as shown in Figure 7.1 according to the proportions presented in the Galderma patent(PETER MORGAN; MACAKOVA, 2020).

PLLA with a high molecular weight, in this case starting from L-lactide and using ROP synthesis, is not recommended for this application due to the degradation time which would be much longer and could cause damage during absorption. As shown by US patent 7,731,758 B2, which demonstrates that the PLLA polymer for subcutaneous applications should have a molar mass between 120,000 and 170,000 Da, because it allows the formation of the microparticles and degradation within 2 months, the time necessary for the formation of the fibroses which stimulate the production of collagen(JÉRÔME ASIUS, MAUGUIO (FR); HATEM FESSI; ELISABETH; LAUGIER-LAGLENNE, 2004).

Figure 7.1: Derma-filler with the PLLA produced [Author's source].

7.3 Preliminary Techno-Economic analysis (PTEA)

During the final phase of the project, following the study carried out, the production scale moved from laboratory glassworks to a pilot plant. An evaluation was conducted to evaluate the economic feasibility of the process. Economic analysis includes evaluating the economic feasibility of a project or process. This includes estimating the expenses and earnings associated with the project, together with an examination of the risks and uncertainties. PTEA aims to evaluate the feasibility of a project and determine the optimal efficient strategy, considering the costs to achieve a specific objective. This tool has a very important meaning for guiding the decision-making process of companies, and various other organizational entities.

Therefore, an economic investigation was conducted, starting with the following main steps:

1. Problem or Opportunity Decision: precisely outlines the problem or opportunity that will be the focus of the economic analysis;
2. Exploration of options: identify different alternatives available to address the problem or seize the opportunity, such as various technologies, processes and strategies;
3. Estimated Expenses and Earnings: Calculate the expected costs and benefits

associated with each option. This includes potential capital expenditures (CAPEX), operating expenses (OPEX), revenue projections and other relevant economic indicators;

7.4 Problem or Opportunity decision

In line with the progress of the project, the market-related expenses have been continuously documented since the beginning of the development of this thesis.
Two main avenues have been examined:

1. The potential commercialization of the polymer, with a focus on production costs.
2. The exploration of a feasible product, such as a filler for applications in the medical and cosmetic industries, considering the PLLA obtained in the Chapter 6.

This involves a thorough assessment of the regulatory complexities surrounding the marketing of pharmaceutical products.
From the knowledge and devolvement of this project, the interest to develop an economic analysis was born. This helped to provide a preliminary understanding of the investment required for a potential start-up company. Subsequently, a detailed analysis of the cash flow implications was conducted. The know-how implies the production of PLLA and L-lactide polymer through a green process that has no waste and toxic solvents during the synthesis time, this was the strategy.
The pilot plant used has been adapted to the process, the design costs and the annual wear costs have been considered in relation to the operation of the plant, furthermore other parameters have been considered in order to calculate the flow of case related to the production process in the medical field.

7.5 Parameters considered for the production of the cash flow.

Cash flow refers to the movement of money in and out of a business or financial entity over a specific period of time. Cash flow is essential because it monitors and studies from which sources money comes in, such as sales, investments, and loans, and also from which sources money comes out for expenses such as operating costs, repayments

and investments. Thus, a positive cash flow indicates that more money is flowing in than is leaving, while a negative cash flow suggests that more money is being spent than is being earned. Cash flow monitoring is essential to understanding an organization's financial health and its ability to meet its financial obligations.

CAPEX is capital expenditure and refers to the funds a company invests in acquiring, upgrading or maintaining assets over the long term that are expected to generate revenue benefits. Examples of CAPEX include plant and equipment (PP&E), such as buildings, machinery, vehicles and technological infrastructure, construction or renovation of plants, investments in research and development (R&D) projects and, finally, acquisition of other companies or interests in joint ventures. Furthermore, CAPEX refers to the continuous costs that a company incurs during the year and that is why it affects the income and exit flows.

OPEX refers to operating expenses, it refers to the ongoing costs that a company incurs as part of its day-to-day business operations. These expenses are typically incurred in a single accounting period and are essential to maintaining the business. Examples of OPEX include employee salaries, rent and office bills, marketing and advertising expenses, maintenance and repair costs, general and administrative costs, and also ongoing operational research and development costs which are different from the investments that are presented in the CAPEX, as capital investments OPEX is recorded as an expense in the company's income statement and directly affects its profitability for the reporting period. It is deducted from the company's revenue to calculate net income.

A substantial difference between CAPEX and OPEX, that the former can be seen as strategic decisions and often require careful evaluation, as they involve significant initial investments, while the latter are inevitable and routine costs in order to complete business activities daily.

Considering the definitions of CAPEX and OPEX, annual expenses were hypothesized taking into consideration a newly opened company, a start-up for the production of PLLA and the sale of the final product as a derma filler.

Furthermore, it was based on the law Lei 4.950-A/66 amended in 1966 which determines the salary of the professional engineer at the head of the company.

These considerations are shown in Table 7.2 and Table 7.3.

CAPEX					
Quality control test	Cost	CAPEX	Consumables	R$	21.385,20
Laboratory equipment	Cost	CAPEX	Third-party services	R$	100.000,00
Project Direct Infrastructure Cost	Cost	CAPEX	Daily expenses	R$	30.000,00
Construction pilot plant	Cost	CAPEX	Pilot plant	R$	400.000,00
Pilot Plant Technician Salary	Cost	CAPEX	Pilot plant	R$	57.000,00
Total				**R$**	**608.385,20**

Table 7.1: CAPEX capital expenditure in the project [Author's source].

OPEX				
Reagents and laboratory material in general	cost	OPEX	Consumables	R$ 120.000,00
Energy	Cost	OPEX	Energy	R$ 15.000,00
Engineer salary	Cost	CAPEX	Salary	R$ 141.700,00
Annual company rent	Cost	OPEX	Rent	R$ 56.581,20
Annual accountant	Cost	OPEX	Third party services	R$ 8.640,00
Annual maintenance	Cost	OPEX	Maintenance	R$ 90.000,00
Total				R$ 431.921,20

Table 7.2: OPEX operational cost in the project [Author's source].

7.6 Cash flow

The cash flow projection has been developed while considering a potential product for market placement. Given the evolving market landscape and the notable surge in cosmetic surgery, our selection centered on fillers. This product was opted for due to its ongoing market expansion and the escalating worldwide demand for injectable procedures, driven by various factors including convenience, minimal downtime, perceived risk, social influences across networks, and competitive pricing. Positive results regarding the effect on facial rejuvenation have also been proven (JÉRÔME ASIUS, MAUGUIO (FR); HATEM FESSI; ELISABETH; LAUGIER-LAGLENNE, 2004; ZARGARAN et al., 2023).

Firstly, the pilot plant's production cost for PLLA is determined using the mass balance presented in Chapter 6. The findings reveal that this l-lactide and PLLA, crafted through environmentally friendly technology exhibits a cost respectively, of R$ 10.00/g for l-lactide of R$ 1.12/g for PLLA in the market context. This evaluation takes into consideration a prominent brand like Sigma-Aldrich, where the same gram is marketed for R$ 392.21 for PLLA and R$ 37.72 for LLT. Notably, the underlying PLLA has a purity level appropriate for medical applications.

Table 14 underscores the viability of the process, indicating a robust market demand for both PLLA and L-lactide. Consequently, a thorough market analysis and corresponding

cash flow assessment has been initiated. The scope entails producing a refined batch reliant on PLLA, wherein each unit comprises 120 mg of polymer meticulously blended within 120 mL of water. This solution is used as a filler for injection, further complemented by 0.8 mL of lidocaine, an anesthetic agent.

	Price/gr	Links
LLA (Synth)	R$ 0,10	https://www.lojasynth.com/loja/produto-243435-2752-acido_lactico__l_85_paacs
PLLA purified (Sigma Aldrich)	R$ 397,80	https://www.sigmaaldrich.com/BR/pt/product/aldrich/764698
LLT (Sigma Aldrich)	R$ 37,72	https://www.sigmaaldrich.com/BR/pt/product/aldrich/367044
Raw PLLA in Pilot Plant	R$ 1,12	
LLT in Pilot Plant	R$ 10,00	

Table 7.3: Pricing about the market and the L-lactide and the PLLA produced in the pilot plant [Author's source].

In order to see the viability of the product, indicators have been calculated by constructing the cash flow, presented Table 7.3. The indicator calculated for the profitability and viability of investment projects are:

1. Net Present Value (VPL);
2. Payback Time;
3. Internal Rate of Return (IRR);

Net Present Value (NPV) is a financial metric used to assess the profitability of an investment by comparing the present value of expected future cash flows to the initial investment cost (CAPEX). It takes into account the time value of money, which means that future cash flows are discounted back to their present value using a specified discount rate, which was chosen as 8%.

The formula for NPV is:

$$NPV = \Sigma [CF\_t / (1 + r)^t] - \text{Initial Investment}$$

Where:

CF_t = Cash flow in time period t;

r = Discount rate;

t = Time period;

Initial Investment = Initial cost of the project;

If the NPV is positive, it indicates that the investment is likely to be profitable, as the expected returns exceed the initial investment, while if NPV io negative suggested the opposite. Payback time is a simple measure of the amount of time it takes for an investment to generate enough cash flow to cover the initial investment. It does not take into account the time value of money or cash flows beyond the repayment period.
The formula for payback time is:

$$\text{Payback Time} = \text{Initial Investment} / \text{Annual Cash Flow}$$

Where:

Initial Investment = Initial cost of project;
Annual Cash Flow = Expected annual cash flow generated by the investment;

The shorter the payback time, the quicker the initial investment is recovered.
The Internal Rate of Returns is the discount rate at which the NPV of an investment becomes zero. In other words, it's the rate that makes the present value of expected cash flows after the initial investment. The IRR reflects the annualized rate of return an investment is expected to generate over its lifetime. It helps determine whether the investment's returns are higher than the cost of capital. The formula for IRR involves solving for the discount rate that equals the sum of the discounted cash flows to zero.

Cash flow	2023	2024	2025	2026	2027	2028
Gross revenue	R$ 480.000,00	R$ 720.000,00	R$ 960.000,00	R$ 960.000,00	R$ 960.000,00	R$ 960.000,00
Variable cost	R$ -	R$ -	R$ -	R$ -	R$ -	R$ -
Fixed cost	R$ 431.921,20	R$ 431.921,20	R$ 431.921,20	R$ 431.921,20	R$ 431.921,20	R$ 431.921,20
Investiment	R$ 608.385,20	R$ -	R$ -	R$ -	R$ -	R$ -
Total cost	R$ 1.040.306,40	R$ 431.921,20	R$ 431.921,20	R$ 431.921,20	R$ 431.921,20	R$ 431.921,20
Gross profit	-R$ 560.306,40	R$ 288.078,80	R$ 528.078,80	R$ 528.078,80	R$ 528.078,80	R$ 528.078,80
Depreciation	R$ -	R$ 25.000,00	R$ 25.000,00	R$ 25.000,00	R$ 25.000,00	R$ 25.001,00
Profit before Financial result	-R$ 560.306,40	R$ 263.078,80	R$ 503.078,80	R$ 503.078,80	R$ 503.078,80	R$ 503.077,80
Tributes	R$ 129.120,00	R$ 193.680,00	R$ 258.240,00	R$ 258.240,00	R$ 258.240,00	R$ 258.240,00
Net Income=cash flow	-R$ 689.426,40	R$ 69.398,80	R$ 244.838,80	R$ 244.838,80	R$ 244.838,80	R$ 244.837,80

Table 7.4: Cash flow about the filler until 2028 [Author's source].

With this Table 7.4, previously calculated CAPEX and OPEX are included. the NPV, as shown in Table 7.5, was calculated for each year, according to formula (2)

Present value	-R$ 689.426,40	R$ 64.258,15	R$ 209.909,81	R$ 194.360,93	R$ 179.963,83	R$ 166.632,49
Accumulated Present Value	-R$ 689.426,40	-R$ 625.168,25	-R$ 415.258,44	-R$ 220.897,51	-R$ 40.933,68	R$ 125.698,81

Table 7.5: NPV calculated each year until 2028 [Author's source].

According to the study by Grover et. al,(GROVER et al., 2023; ZARGARAN et al., 2023), the popularity of nonsurgical facial aesthetics (NSFA) continues to grow.

The authors also cite a report by McKinsey & Company, a consulting firm, which predicts that the use of aesthetic injectables will become more widespread in the future, causing great interest and continued increases in market prices as demand increases (FERNEINI et al., 2014; JÉRÔME ASIUS, MAUGUIO (FR); HATEM FESSI; ELISABETH; LAUGIER-LAGLENNE, 2004).

In order to determine our payback period, we took into account the initial investment. Considering that every product sold to customers, whether dentists or cosmetic surgeons, consists of 120 mg of polymer, a price of R$ 1200 for 120 mg reals has been assumed per 400 bottles projected to be sold within a year, as given in Table 7.7. Through this assessment, we calculated a payback time of two and a half years, as presented in Table 7.6.

VPL 5 year	R$ 125.698,81
IRR (Internal Rate of Return)	14%
Payback	4,25
Profitability Rate	12,1%

Table 7.6: Payback time calculated [Author's source].

Production	2023	2024	2025	2026	2027	2028
Production quantity per unit	400	600	800	800	800	800
Sale value	R$ 1.200,00	R$ 1.200,00	R$ 1.200,00	R$ 1.200,00	R$ 1.200,00	R$ 1.200,00

Table 7.7: Pricing about filler [Author's source].

7.7 Partial conclusion

The PTEA was made to be able to evaluate the viability of the process and it know-how. The cash flow has been simplified as marketing costs and any employee placements are not included. In addition to producing a filler, it is obviously necessary for future marketing to carry out various in vivo, in vitro, and subsequently clinical tests required by Anvisa for sale on the Brazilian market. Furthermore, it is necessary to

consider and hypothesize the logistics of distribution and what will be the material to be able to produce the packaging for sending to the customer. The customers intended for this product are mainly cosmetic surgeons, dentists in private practices. Finally, Figure 7.2 encloses the cash flow result as it shows exactly the payback time, which is represented by the red line that intersects the zero line exactly after two and a half years.

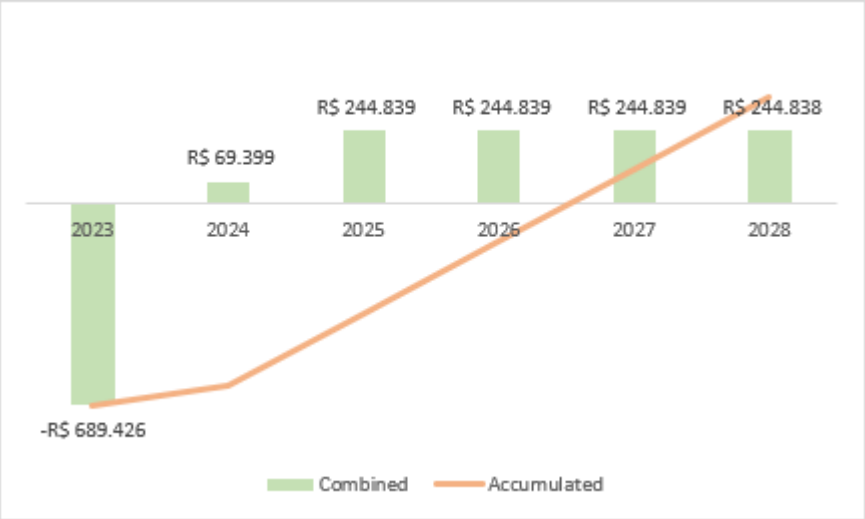

Figure 7.2: Graph that represent the result of cash flow [Author's source].

The cash flow relating only to the production of the polymer has not been made, due to the low price of production which already demonstrates the viability. The intention was to emphasize the product and also take into account the costs and expenses associated with the process at the conclusion of the production chain. The interest in the derma filler is due to the increase in demand and to an increasing interest in the market by expanding the marketing not only through the branch of aesthetic surgery but also the odonatological one.

Chapter 8

8.1 Conclusions and Future Work

In this last chapter the conclusion of this thesis is presented and furthermore in future work that could be done to improve the synthesis of the cyclic dimer, L-lactide.

8.2 Conclusions

At the beginning of this project, a long study was made regarding the physical and chemical characteristics of the L-lactide dimer extensively treated during the development of the thesis.

The first step would have been to synthesize this dimer with reactive distillation, a suitable equipment for treating and controlling reversible reactions such as the one involving the production of the dimer, starting from the L-enantiomer of lactic acid. This was not possible due to some problems found in the column and above all due to the synthesis conditions: temperature not lower than 200°C and pressure very close to a vacuum of -550 mmHg; parameters that the column was unable to work with ~~draw on~~.

Furthermore, the formation time is very rapid, the formation of the crystals is perceived 20 minutes after the start of the syntheses, and mainly the formation occurs in the vapor phase. This feature is not highlighted in the literature. Considering these first tests, we started designing a system that could focus on the production of the dimer in a single step and draw on the parameters to maximize production.

The experimental tests made with glass units managed to obtain good results. Still, the design of the pilot plant with the addition of a more performing pump and an automatic control ensured the success of the production of the dimer and at the same time of the polymer. This allows to control two products with a single synthesis what is an interesting point. The production of the PLLA polymer, as a secondary product, it made it possible to think about possible applications in the medical field market, such as derma fillers or 2D or 3D membranes as healing.

The production of the dimer and the control of the synthesis allows, in turn, to use of L-lactide as a reactant for the production of PLLA with a higher molecular mass and therefore for applications such as prostheses which require a longer degradation time. This was a very complex part due to the purity of the L-lactide.

The minimal presence of water, or monomers that were unable to react, do not help the synthesis by ring-opening. This also explains the high price on the market and the lack

of clarity in terms of the literature of the synthesis of the same dimer.

Furthermore, an added value is that the deposited know-how does not provide for any addition of solvents other than the reagents and the catalyst and co-catalyst, in quantities suitable for Anvisa and FDA standards, for the production of L-lactide and PLLA. It is worthwhile mentioning that the only way out is water.

Therefore, it can be defined to all intents and purposes as a 'Green' process. Another point to which it is necessary to pay attention is to try to increase the efficiency of the pilot plant to be able to eliminate water more easily during the synthesis and therefore to obtain an anhydrous L-lactide crystal, to increase the shelf life and consequently increase the efficiency of PLLA production via ring-opening route.

Initially this thesis aimed to use the reactive distillation column to be able to synthesize L-lactide, during the study it was possible not only to produce L-lactide in a single step but also to increase the efficiency of the process starting from the monomer L-lactic acid, allowing to have two products in a single reaction, L-lactide and low molar mass PLLA via the direct polycondensation route.

The main objectives achieved are summarized in this list:

1. Investigate a process similar to reactive distillation to produce L-lactide;
2. Synthesize L-lactide in a single step, starting directly from the LLA monomer;
3. Optimize the process on a laboratory scale and synthesize PLLA and L-lactide in a single reaction to then be able to design a scale-up relating to this process;

8.3 Future suggestions

The project investigated obtaining the L-lactide dimer in a single step and synthesizing the PLLA polymer from the dimer via ring opening.

Furthermore, various configurations have also been studied to be able to obtain dimer PLLA and at the same time low molar mass through direct polycondensation synthesis.

To give continuity to this work, some suggestions are presented:

1. Continue to increase the efficiency of obtaining L-lactide in the pilot project by increasing the conversion and amount of dimer collected;
2. Analyse and study a purification process that does not use organic solvents such as toluene. However, still using the 'Green' philosophy it is possible to reach a higher degree of purity to subsequently obtain PLLA through the ring-opening route;

3. Evaluate the addition of a distillation column to the second tank in order to increase the withdrawal of water from the system;
4. A continuous simulation study for the production of L-lactide;
5. Detailed simulation of the reactive distillation to evaluate its poten

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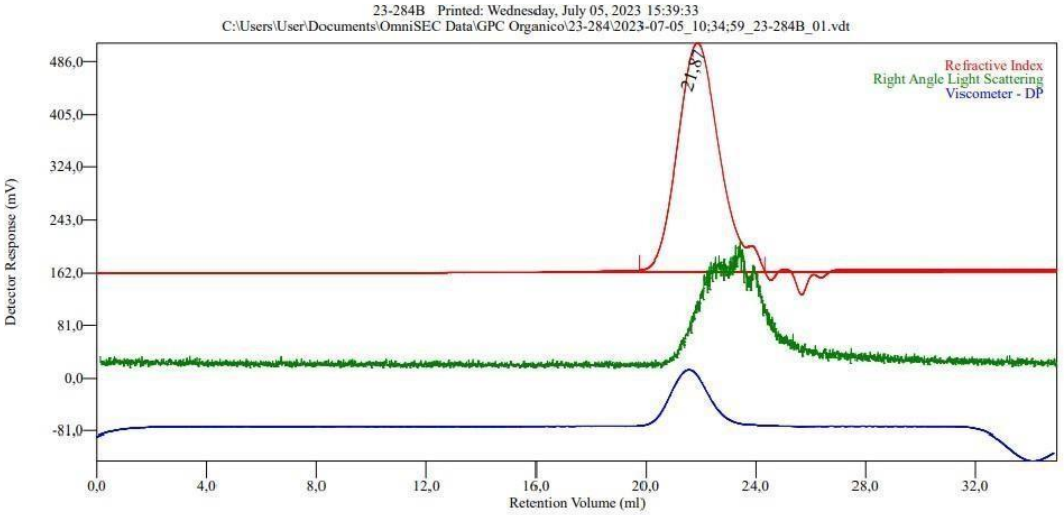
Appendix

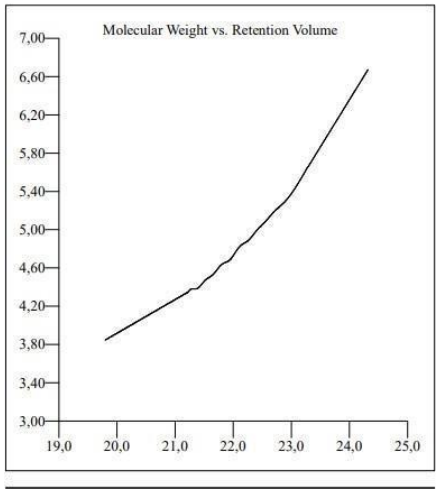
Appendix I : The gel permeation chromatography



Multi-Detectors - Homopolymers : Results

Peak RV - (ml)	21,870
Mn - (Daltons)	40.152
Mw - (Daltons)	142.762
Mz - (Daltons)	1,039 e 6
Mp - (Daltons)	45.592
Mw / Mn	3,555
Percent Above Mw: 0	100,000
Percent Below Mw: 0	0,000
IV - (dl/g)	0,5585
Rh(w) - (nm)	7,980
Wt Fr (Peak)	1,000
Mark-Houwink a	-0,519
Mark-Houwink logK	2,154
Branches	0,000
Branch Freq.	0,000
RI Area - (mvml)	630,65
UV Area - (mvml)	0,00
RALS Area - (mvml)	469,32
LALS Area - (mvml)	0,00
IVDP Area - (mvml)	145,25

Sample Parameters	Input	Calculated
Sample Conc - (mg/ml)	3,000	2,753
Sample Recovery (%)	0,000	91,774
dn/dc - (ml/g)	0,2599	0,0000
dA/dc - (ml/g)	1,0000	0,0000



Annotation	
Method File	Unsaved Method (23-284-0006.vcm)
Limits File	
Date Acquired	Jul 05, 2023 - 10:34:59
Solvent	THF
Acquisition Operator	admin : Administrator
Calculation Operator	admin : Administrator
Column Set	2 x Shodex KF806M
System	GPC Organico
Flow Rate - (ml/min)	1,000
Inj Volume - (ul)	100,0
Volume Increment - (ml)	0,00333
Detector Temp. - (deg C)	30,0
Column Temp. - (deg C)	30,0
OmniSEC Build Number	406