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Research review paper

Poly-lactic acid synthesis for application in biomedical devices — A review

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ABSTRACT

Bioabsorbable polymers are considered a suitable alternative to the improvement and development of numerous applications in medicine. Poly-lactic acid (PLA,) is one of the most promising biopolymers due to the fact that the monomers may produced from non toxic renewable feedstock as well as is naturally occurring organic acid. Lactic acid can be made by fermentation of sugars obtained from renewable resources as such sugarcane. Therefore, PLA is an eco-friendly product with better features for use in the human body (nontoxicity). Lactic acid polymers can be synthesized by different processes so as to obtain products with an ample variety of chemical and mechanical properties. Due to their excellent biocompatibility and mechanical properties, PLA and their copolymers are becoming widely used in tissue engineering for function restoration of impaired tissues. In order to maximize the benefits of its use, it is necessary to understand the relationship between PLA material properties, the manufacturing process and the final product with desired characteristics. In this paper, the lactic acid production by fermentation and the polymer synthesis such biomaterial are reviewed. The paper intends to contribute to the critical knowledge and development of suitable use of PLA for biomedical applications.

Contents

1. Introduction

The development of biomaterials (biodegradable and bioabsorbable) with the required characteristics to aid in the recovery of tissues damaged by accident or human disease is one of the greatest research challenges involving areas such as medicine and engineering. Biopolymers offer an alternative to traditional biocompatible materials (metallic and ceramic) and non-biodegradable polymers for a large number of applications (Chen et al., 2002; Nair and Laurencin, 2007; Peter et al., 1998; Temenoff and Mikos, 2000). Synthetic biodegradable poly-lactones such as poly-lactic acid (PLA), poly-glycolic acid (PGA), and poly-caprolactone (PCL) as well as their copolymers are now commonly used in biomedical devices (Cheng et al., 2009) because of their excellent biocompatibility. These polymers are degraded by simple hydrolysis of the ester bonds, which does not require the presence of enzymes and in turn prevents inflammatory reactions. The hydrolytic products from such degradation process are then transformed into non-

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toxic subproducts that are eliminated through normal cellular activity and urine.

On the other hand, synthetic degradable polyesters have been used in surgery as suture materials and bone fixation devices for about three decades. Back in 1973, lactic acid and glycolic acid were proposed as degradable matrices for the sustained delivery of bioactive substances (Auras et al., 2004). Likewise, Poly-lactic acid (PLA) has been demonstrated to be a suitable bioabsorbable polymer for fixation devices such as resorbable plates and screws (Lorenz, 2010). Bioabsorbable fixation devices have been extensively used as dissolvable suture meshes and recently, by orthopedic surgeons (Lovald, 2009; Waris et al., 2004). Absorbable systems are highly advantageous when compared with titanium plates or other metallic implants given that they do not erode bone when placed in the human body (Dearnaley et al., 2007; Lindqvist et al., 1992). In addition, bioabsorbable devices do not require a second surgery to remove the implant – which reduces medical costs – and allow for the gradual recovery of tissue function as the device is degraded. Moreover, synthetic bioabsorbable polymers can stimulate isolated cells to regenerate tissues and release drugs such as painkillers, anti-inflammatories and antibiotics, which has recently motivated their study as scaffolds for cell transplantation, both in vitro and in vivo (Chen et al., 2006; Dai, et al., 2010; Kulkarni et al., 2010). Another desirable feature of resorbable plates is that, once resorbed, they do not block computed tomography (CT) scans, which facilitates subsequent medical imaging evaluations.

Regarding PLA, it has an extensive mechanical property profile and it is thermoplastic with high biocompatibility and biodegradability properties (Auras et al., 2004; Gupta et al., 2007). PLA is obtained from lactic acid and converted back to the latter one when hydrolytically degraded. Lactic acid is a naturally occurring organic acid that can be produced by fermentation of sugars obtained from renewable resources such as sugarcane. Therefore, PLA can be produced and used in an environmentally friendly cycle.

Although there are multiple ways to fabricate PLA, none of them is simple or easy to execute. PLA synthesis requires rigorous control of conditions (temperature, pressure and pH), the use of catalysts and long polymerization times, which implies high energy consumption. In order to understand reaction behavior, kinetic studies of PLA synthesis have been conducted by means of modern simulators, which offer a powerful tool to determine the optimal conditions for obtaining the desired PLA polymer for a specific application. This review summarizes information about the properties and applications of poly-lactic acid as well as the different synthesis methods that are currently employed for its production. Lactic acid production process from renewable resources is also reviewed.

2. Lactic acid

Lactic acid (2-hydroxypropionic acid) is a simple chiral molecule that exists as two enantiomers, L- and D-lactic acid (Fig. 1), which differ in their effect on polarized light. The optically inactive D, L or meso form is an equimolar (racemic) mixture of D(−) and L(+) isomers (Gupta et al., 2007). It is considered the most potential monomer for chemical conversions because it contains a carboxylic and a hydroxyl group (Varadarajan and Miller, 1999).

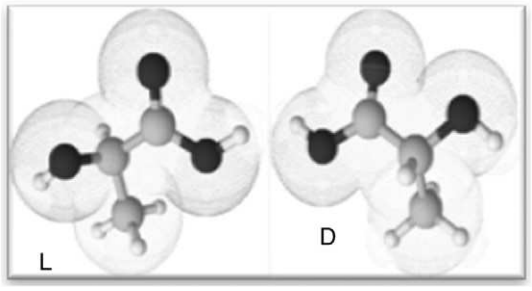

Fig. 1. L- and D-lactic acid.

Lactic acid production has a great worldwide demand due to its versatile applications in food, pharmaceutical, textile, leather, and chemical industries (John et al., 2009) and as monomer in the production of biodegradable polymers (PLA) (Adsul et al., 2007). Lactic acid can influence the metabolic function of cells in a variety of ways, as it can serve as an energy substrate and given its uncharged character and small size, it can permeate through the lipid membrane. Also, lactate is capable of entering cells via the monocarboxylate transporter (MCT) protein shuttle system (Philp et al., 2005). Once inside the cell, lactate is converted to glucose, serving as an energy source in the Cori cycle. In addition to its role as an energy substrate for cells, lactic acid has been shown to have antioxidant properties that may serve to protect cells from damage due to free radicals that are naturally produced throughout the cell life cycle (Lampe et al., 2009).

Lactic acid can be produced by fermentative or chemical synthesis. The chemical synthesis is mainly based on the hydrolysis of lactonitrile by a strong acid, where a racemic mixture of the two forms (D(−) and L(+)) lactic acid is produced. The biotechnological production of lactic acid has received significant interest, since it is an attractive process in terms of its environmental impact and its combination of low production cost from sugarcane fermentation, decreased fossil-based feedstock dependency, reduced CO2 emission, biocatalyst use, and high product specificity (Lunelli et al., 2010) and, additionally, production of optically pure L- or D-lactic acid, depending on the strain selected (Adsul et al., 2007).

Approximately 90% of the total lactic acid produced worldwide is made by bacterial fermentation and the remaining portion is produced synthetically by the hydrolysis of lactonitrile. The petrochemical scheme of monomer production was prevalent until 1990, when a more economic fermentation approach was developed (Adsul et al., 2007; Gupta et al., 2007).

The fermentation processes to obtain lactic acid can be classified according to the type of bacteria used. In the heterofermentative process, equimolar amounts of lactic acid, acetic acid, ethanol, and carbon dioxide are formed from hexose, whereas in the homofermentative process only lactic acid is produced from hexose metabolism (Auras et al., 2004; Garvie, 1980; Hofvendahl and Hahn-Hägerdal, 2000; Thomas et al., 1979). Fig. 2 shows the catabolic pathways for lactic acid production using lactic acid bacteria.

On the other hand, the carbon source for microbial production of lactic acid can be either sugar in pure form such as glucose, sucrose, lactose or sugar containing materials such as molasses, whey, sugarcane bagasse, cassava bagasse, and starchy materials from potato, tapioca, wheat and barley. Sucrose-containing materials such as molasses are commonly exploited raw materials for lactic acid production because they represent cheaper alternatives (John et al., 2007; Lunelli et al., 2010). Sugarcane bagasse is reported to be used as support for lactic acid production by *Rhizopus oryzae* and *Lactobacillus* in solid-state fermentation (SSF) by supplementing sugars or starch hydrolysates as carbon source (Rojan et al. 2005). Brazil is the world's largest sugarcane producer with 648,921.280 million tons per year in 2008, which generated about 130 million tons of bagasse on dry weight basis, according to FAO Statistics Division (2010), what may be an extra incentive to have a competitive lactic acid industry.

3. Poly-lactic acid

PLA is a highly versatile biodegradable polymer, which can be tailor-made into different resin grades for processing into a wide spectrum of products. Because lactic acid is a chiral molecule existing in L and D isomers, the term “poly-lactic acid” refers to a family of polymers: pure poly-L-lactic acid (PLLA), pure poly-D-lactic acid (PDLA), and poly-D,L-lactic acid (PDLLA) (Griffith, 2000). The L-isomer is a biological metabolite and constitutes the main fraction of PLA

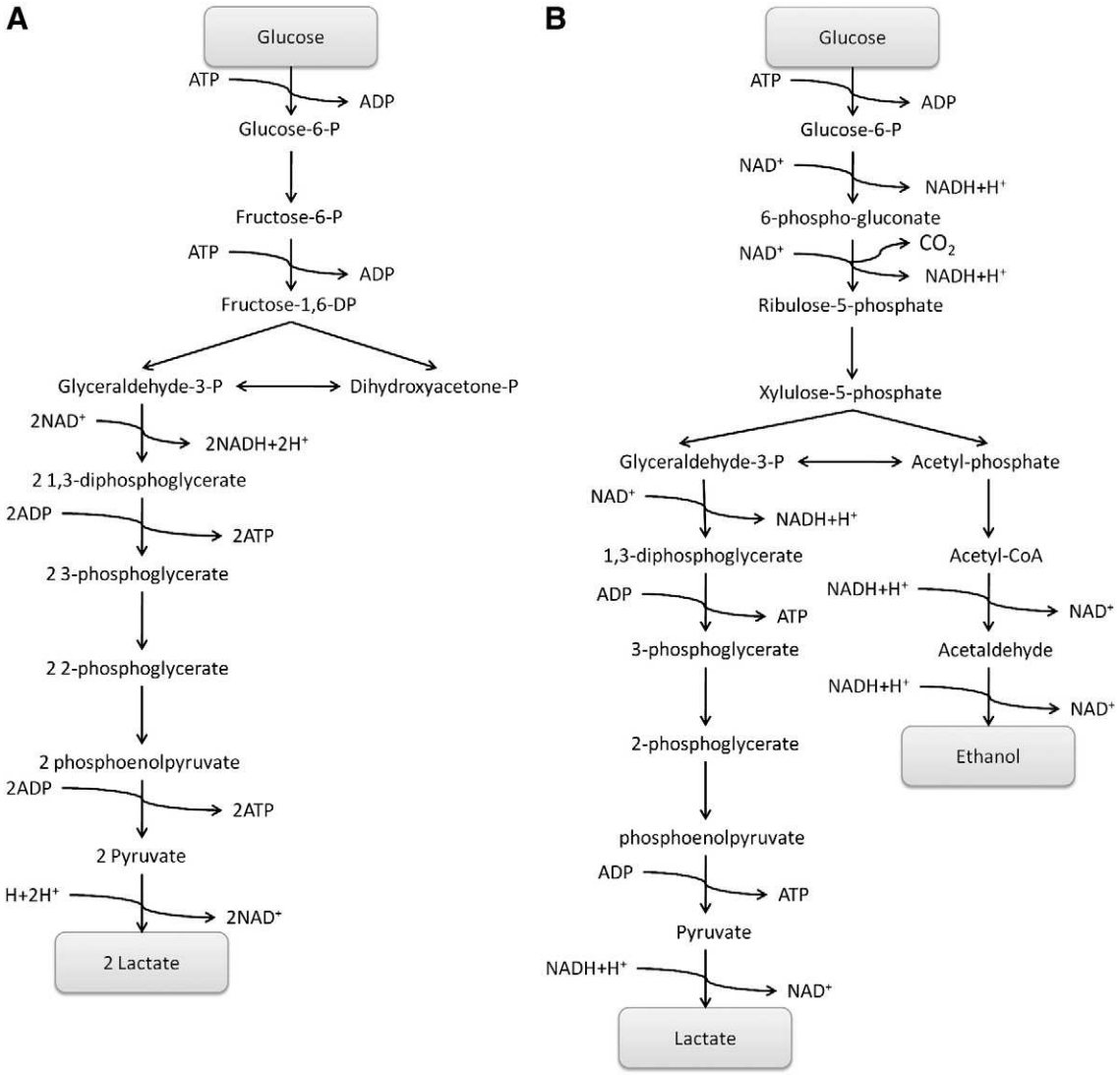

Fig. 2. Metabolic pathways for lactic acid production. (A) Embden–Meyerhof–Parnas; (B) 6-phosphogluconate/phosphoketolase (adapted from Axelsson, 2004).

derived from renewable sources since the majority of lactic acid from biological sources exists in this form. Depending on the composition of the optically active L- and D, L-enantiomers, PLA can crystallize in three forms (α, β, and γ) (Lim et al., 2008).

PLA was discovered in 1932 by Carothers (DuPont) who produced a low molecular weight product by heating lactic acid under vacuum. In 1954 Du Pont produced and patented a polymer with higher molecular weight. In 1968 Santis and Kovacs reported on the pseudo orthorhombic crystal structure of PLLA, which was a left-handed helix conformation of the α-form (Södergard and Stolt, 2002). Lactic acid based polymers first became commercially successful as fiber materials for resorbable sutures. After this, a number of different prosthetic devices have been developed (Auras et al., 2004). Nowadays, PLA resins are approved by the US Food and Drug Administration (FDA) and European regulatory authorities for all food applications and some chirurgical applications such as drug releasing systems (Lampe et al., 2009).

Likewise, PLLA has gained great attention because of its excellent biocompatibility and mechanical properties. However, its long degradation times coupled with the high crystallinity of its fragments can cause inflammatory reactions in the body. In order to overcome this, PLLA can be used as a material combination of L-lactic and D, L-lactic acid monomers, being the latter rapidly degraded without formation of crystalline fragments during this process (Fukushima and Kimura, 2008).

The chemistry of PLA involves the processing and polymerization of lactic acid monomer. PLA is a chiral polymer containing asymmetric carbon atoms with a helical conformation. It has stereocenters in its repeating unit, which can exhibit two structures of maximum order, that is, isotactic and syndiotactic. Isotactic polymers contain sequential stereocenters of the same relative configuration, while syndiotactic polymers contain sequential stereocenters of opposite relative configuration (Auras et al., 2010). Isotactic and optically active PLLA and PDLA are crystalline, whereas relatively atactic and optically inactive PDLLA is amorphous (Bouapao et al., 2009). Monomer dyads in the PLA chain may contain identical stereocenters (L:L or D:D) or enantiomeric stereocenters (L/D).

3.1. Poly-lactic acid properties

PLAs properties have been the subject of extensive research (Malmgren et al., 2006). The stereochemistry and thermal history have direct influence on PLA crystallinity, and therefore, on its properties in general. PLA with PLLA content higher than 90% tends to be crystalline, while the lower optically pure is amorphous. The melting temperature (Tm), and the glass transition temperature (Tg) of PLA decrease with decreasing amounts of PLLA (Auras et al., 2010). Physical characteristics such as density, heat capacity, and mechanical

and rheological properties of PLA are dependent on its transition temperatures (Henton et al., 2005).

For amorphous PLA, the glass transition temperature (Tg) is one the most important parameters since dramatic changes in polymer chain mobility take place at and above Tg. For semicrystalline PLA, both Tg and melting temperature (Tm) are important physical parameter for predicting PLA behavior (Auras et al., 2004; Bouapao et al., 2009; Yamane and Sasai, 2003). The melt enthalpy estimated for an enantiopure PLA of 100% crystallinity (ΔH°_{m}) is 93 J/g; it is the value most often referred to in the literature although higher values (up to 148 J/g) also have been reported (Södergard and Stolt, 2002).

The density of amorphous and crystalline PLLA has been reported as 1.248 g ml^{-1} and 1.290 g ml^{-1}, respectively. The density of solid polylactide was reported as 1.36 g cm^{-3} for l-lactide, 1.33 g cm^{-3} for meso-lactide, 1.36 g cm^{-3} for crystalline polylactide and 1.25 g cm^{-3} for amorphous polylactide (Auras et al., 2004). In general, PLA products are soluble in dioxane, acetonitrile, chloroform, methylene chloride, 1,1,2-trichloroethane and dichloroacetic acid. Ethyl benzene, toluene, acetone and tetrahydrofuran only partly dissolve polylactides when cold, though they are readily soluble in these solvents when heated to boiling temperatures. Lactid acid based polymers are not soluble in water, alcohols as methanol, ethanol and propylene glycol and unsubtituted hydrocarbons (e.g. hexane and heptane). Crystalline PLLA is not soluble in acetone, ethyl acetate or tetrahydrofuran (Nampoothiri et al., 2010). Some of PLAs properties are cited in Table 1.

Few stereocomplex such as PLA can be produced by enantiomers with the identical chemical composition but with different steric structure. Since discovery in 1987, the stereocomplex between poly (L-lactide) (PLLA) and poly(D-lactide) (PDLA) have been intensively studied by preparations, structural, functional properties and applicability (Quynh et al., 2008). The PLA properties may be controlled through the use of special catalysts isotactic and syndiotactic content with different enantiometric units (Gupta et al., 2007).

PLA also can be tailored by formulation involving co-polymerizing of the lactide with other lactones-type monomers, a hydrophilic macromonomers (polyethylene glycol (PEG)), or other monomers with functional groups (such as amino and carboxylic groups, etc.), and blending PLA with other materials (Cheng et al., 2009). Blending can radically alter the resultant properties, which depend sensitively on the mechanical properties of the components as well as the blend microstructure and the interface between the phases (Broz et al., 2003). Broz et al. (2003) prepared a series of blends of the biodegradable polymers poly(D,L-lactic acid) and poly(ε-caprolactone) by varying mass fraction across the range of compositions. Polymers made from ε-caprolactone are excellent drug permeation products. However, mechanical and physical properties need to be enhanced by copolymerization or blending (Auras et al., 2004; Wang et al., 1999).

PLA degrades primarily by hydrolysis, after several months exposure to moisture. Polylactide degradation occurs in two stages. First, random non-enzymatic chain scission of the ester groups leads to a reduction in molecular weight. In the second stage, the molecular weight is reduced until the lactic acid and low molecular weight oligomers are naturally metabolized by microorganisms to yield carbon dioxide and water (Oyama et al. 2009: Auras et al., 2004).

The polymer degradation rate is mainly determined by polymer reactivity with water and catalysts. Any factor which affects the reactivity and the accessibility, such as particle size and shape, temperature, moisture, crystallinity, % isomer, residual lactic acid concentration, molecular weight, water diffusion and metal impurities from the catalyst, will affect the polymer degradation rate (Auras et al., 2004; Bleach et al., 2001; Cha and Pitt, 1990; Drumright et al., 2000; Tsuji and Ishida, 2003). The *in vivo* and *in vitro* degradation have been evaluated for polylactide surgical implants. *In vitro* studies showed that the pH of the solution does play a role in the *in vitro* degradation, and that, an *in vivo* study can be used as a predictor of the *in vivo* degradation of PLA (Auras et al., 2004; Mainil-Varlet, 1997).

Table 1
Lactid acid polymers properties (adapted from Nampoothiri et al., 2010 and Södergard and Stolt, 2002).

Lactic acid polymers	Glass transition temperature Tg (°C)	Melting temperature Tm (°C)	Density (g/cm^3)	Good solubility in solvents
PLLA	55–80	173–178	1.290	Chloroform, furan, dioxane and dioxolane.
PDLLA	43–53	120–170	1.25	PLLA solvents and acetone, ethyl lactate, tetrahydrofuran, ethyl acetate, dimethylsulfoxide, N,N xylene and dimethylformamide.
PDLA	40–50	120–150	1.248	

3.2. Poly-lactid acid synthesis

Polymers based on lactic acid (PLA) are a most promising category of polymers made from renewable resources (Auras et al., 2010). PLA can be prepared by different polymerization process from lactic acid including: polycondensation, ring opening polymerization and by direct methods like azeotopic dehydration and enzymatic polymerization (Garlotta, 2001). Currently, direct polymerization and ring opening polymerization are the most used production techniques. Fig. 3 shows the main methods for PLA synthesis.

Condensation polymerization (polycondensation) includes solution polycondensation and melts polycondensation, and is the least expensive route. However, it is very difficult to obtain a solvent-free high molecular weight poly-lactic acid for these routes (Auras et al., 2004). In direct polycondensation, solvents and/or catalysts are used under high vacuum and temperatures for the removal of water produced in the condensation. The resultant polymer is a low to intermediate molecular weight material, which can be used as is, or coupled with isocyanates, epoxides or peroxide to produce a range of molecular weights (Gupta et al., 2007). Achmad et al. (2009), report the synthesis of PLA by direct polymerization without catalysts, solvents and initiators by varying the temperature from 150 to 250 °C and the pressure from atmosphere pressure to vacuum for 96 h. The Mitsui Toatsu Chemical Company polymerized poly-DL-lactic acid (PDLLA) using direct solution polycondensation, in which lactic acid, catalysts, and organic solvent with high boiling point were mixed in a reactor. The resultant product shows a molecular weight (MW) of about 300,000 (Cheng et al., 2009).

Polycondensation method produces oligomers with average molecular weights several tens of thousands and other side reactions also can occur, such transesterification, resulting in the formation of ring structures as lactide. These side reactions have a negative influence on properties of the final polymer (Auras et al., 2010). That subproducts production cannot be excluded, but can be controlled by the use of different catalysts and functionalization agents, as well as by varying the polymerization conditions (Mehta et al., 2005).

Lactid acid direct condensation is carry out in three stages: removal of the free water, oligomer polycondensation and melt condensation of high molecular weight PLA. In first and third stages, the removal of water is the rate-determining step. For the second one, the rate-determining step is the chemical reaction, which depends on the catalyst used (Auras et al., 2010). The direct polycondensation of lactic acid in bulk is not applied on a large scale, because of the competitive reaction of lactide formation and the simultaneously occurring degradation process (Dutkiewicz et al., 2003).

In the sequential melt/solid-state polycondensation, besides the three mentioned steps (i. e., removal of the free water content, oligomer polycondensation, and melt polycondensation) is utilized an additional fourth stage. In the fourth stage, the melt-polycondensated PLA is cooled below its melting temperature, followed by particle formation, which

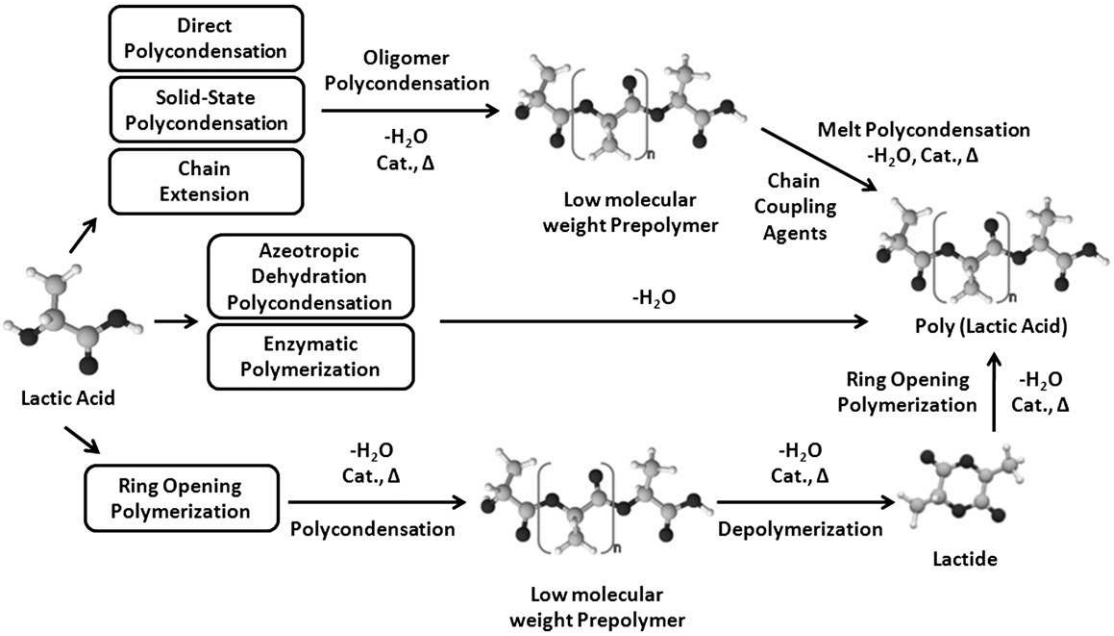

Fig. 3. Synthesis methods for Poly(Lactic Acid) (adapted from Garlotta, 2001 and Auras et al., 2010).

then subjected to a crystallization process (Auras et al., 2010; Fukushima and Kimura, 2008).

Chain extension is effective way to achieve high molecular weight lactic acid-based polymers by polycondensation (Gu et al., 2008). In this method the intermediate low molecular weight is to treat polymers with chain extenders which link the low molecular weight prepolymer into a polymer of high molecular weight. Gu et al., 2008, obtained polymer with a molecular weight (Mv) of 27 500 g mol^{-1} after 40 min of chain extension at 180 °C using 1,6-hexamethylene diisocyanate as the chain extender.

Ring-opening polymerization (ROP) is the most commonly route to achieve high molecular weight (Auras et al., 2010). This process occurs by ring opening of the lactic acid cyclic dimmer (lactide) in the presence of catalyst. The process consists of three steps: polycondensation, depolymerization and ring opening polymerization (see Fig. 3). This route requires additional steps of purification which is relatively complicated and expensive. Catalytic ring-opening polymerization of the lactide intermediate results in PLA with controlled molecular weight (Kim et al., 2009). By controlling residence time and temperatures in combination with catalyst type and concentration, it is possible to control the ratio and sequence of D- and L-lactic acid units in the final polymer (Gupta et al., 2007).

On the other hand, ring-opening polymerization of lactide can be carried out in melt, bulk, or in solution and by cationic, anionic, and coordination-insertion mechanisms depending on the catalyst. Various types of initiators have been successfully tested, but among them, stannous octoate is usually preferred because it provides high reaction rate, high conversion rate, and high molecular weights, even under rather mild polymerization conditions (Mehta et al., 2005).

Azeotropic dehydration is a direct method for synthesis of high molecular weight PLA (Garlotta, 2001). In this route, the removal of water formed from the reaction medium becomes relatively easier and a higher molecular weight of the PLA is achievable (Auras et al., 2010). Kim and Woo (2002) obtained PLA of Mv about 33 000 through the azeotropic dehydration at 138 °C for 48−72 h using a molecular sieve as a drying agent and m-xylene as a solvent.

Enzymatic polymerization emerges as one of the most viable alternatives and is an environmentally benign method that can be carried out under mild conditions. This methodology can provide adequate control of the polymerization process (Cheng et al., 2009), but the literature about enzymatic polymerization is poor. Chanfreau et al. (2010), reported the enzymatic synthesis of poly-L-lactide using a liquid ionic (1-hexyl-3-ethylimidazolium hexafluorophosphate [HMIM][PF6]) mediated by the enzyme lipase B from Candida antarctica (Novozyme 435). The highest PLLA yield (63%) was attained at 90 °C with a molecular weight (Mn) of 37.8 9 103 g/mol (Chanfreau et al., 2010).

3.3. Kinetics and modeling of PLA

In contrast with the extensive experimental work about polymerization reactions, only few publications deal with the mathematical modeling of such reactions or at least on the evaluation of the corresponding rate coefficients (Yu et al., 2009). PLA production can be carried out from both lactic acid and its dimer cyclic (lactide) as the monomer.

The use of lactide as monomer or intermediate product leads to a "Ring Opening Polymerization" (ROP), which refers to the opening of dimer rings in order to form polymer chains. Several authors have worked in the modeling of catalyzed lactide ROP (Puaux et al., 2007; Yu et al., 2009). According to Yu et al. (2009), the first systematic kinetic analysis of PLA ROP catalyzed by Sn(Oct)2 was reported by Eenink (1987), although impurities were not accounted for in such kinetic models. Later on, Zhang et al. (1994), found that hydroxyl and carboxylic acids strongly affect reaction rates. On the other hand, reversible reactions were included in the lactide polymerization model proposed by Witzke et al. (1997). More recently, researchers have developed models based on the cationic mechanism, which involves irreversible initiation and propagation steps as well as irreversible chain transfer to monomer and impurities (Mehta, 2007; Puaux et al., 2007).

The following reactions (R1–R3) represent the polymerization models for PLA synthesis by ring opening proposed by Mehta (2007). This type of reaction is also considered a chain-growth polymerization, and therefore, it is divided into three mains steps: initiation, propagation and termination, having each one of them a different rate constant.

$$M + I \xrightarrow{k_0} P_1 \quad \text{(R1)}$$

$$P_j + M \xrightarrow{k_j} P_{j+1},\ j = 1, 2, 3, \ldots \quad \text{(R2)}$$

$$P_j + M \xrightarrow{k_t} M_j + P_1 \quad \text{(R3)}$$

where k_0 is the initiation rate constant, M is the monomer, I is the initiator and P_1 is the activated polymer of one unit. P_j is the active polymer chain of j units and the rate constant of propagation reaction is k_j, which refers to the jth propagation step on a chain. M_j is the deactivated polymer of j repeat units that will not react any further, and k_t is the termination rate constant. Regarding the termination step, Mehta (2007), proposed two alternative ways, being water-like impurities considered in the first method and intermolecular chain transfers accounted for in the second one. The mass balance equations for a batch reactor were written for the above kinetic scheme as follows:

$$\frac{d[M]}{dt} = -[M]\left\{k_0[I] + \sum_{j=1}^{n} k_j\left[P_j\right] + \sum_{j=1}^{n} k_{tj}\left[P_j\right]\right\} \quad \text{(Eq.1)}$$

$$\frac{d[I]}{dt} = -k_0[I][M] \quad \text{(Eq.2)}$$

$$\frac{d[P_1]}{dt} = k_0[I][M] - k_1[P_1][M] + \sum_{j=2}^{n} k_{tj}\left[P_j\right][M] \quad \text{(Eq.3)}$$

$$\frac{d\left[P_j\right]}{dt} = [M]\left\{k_{(j-1)}\left[P_{j-}1\right] - k_j\left[P_j\right] - k_{tj}\left[P_j\right]\right\},\ j\ N\ 1 \quad \text{(Eq.4)}$$

Seavey and Liu (2008), developed a PLA synthesis simulation in Aspen Polymers (ASPEN PLUS) with the polymerization mechanism described in the following equations. The reactions (R4–R6) represent the oligomers oblation; they are esterification reactions that produce low molecular weight PLA molecules and their respective reversible reactions (hydrolysis).

$$LA + LA \leftrightarrow P_2 + W \quad \text{(R4)}$$

$$P_n + LA \leftrightarrow P_{n+1} + W \quad \text{(R5)}$$

$$P_n + P_m \leftrightarrow P_{m+n} + W \quad \text{(R6)}$$

where LA is lactic acid, W is water and, Pn is an oligomer with n acid lactic units. In the presence of the appropriate stannous catalyst, the two end groups of the linear oligomer can also react with each other forming a closed ring structure, reaction that is especially favorable for linear dimers because of the high stability of the resulting molecule (Lactide). The reaction (R7) represents this reaction and its reverse reaction (hydrolysis).

$$P_2 \leftrightarrow C_2 + W \quad \text{(R7)}$$

where P2 is a linear dimer, C2 is a cyclic dimer and W is water. In the polymerization steps, lactide is polymerized through ring opening and ring addition reactions in the presence of catalyst and trace amounts of water and lactic acid. This is represented in reactions (R8–R9).

$$LA + C_2 \leftrightarrow P_3 \quad \text{(R8)}$$

$$P_n + C_2 \leftrightarrow P_{n+2} \quad \text{(R9)}$$

Due to the absence of large amounts of water and lactic acid, the Pn molecule has a high repeat unit amount, which in turn leads to a high molecular weight polymer. Seavey and Liu (2008) used the step–growth reaction kinetics model in Polymers Plus to predict the reaction rates involved in each step of the PLA process. According to Seavey and Liu (2008), the step–growth model generates a reaction network based on user-specified functional groups. In this way, the role of the user is limited to defining the structure of the reactants in terms of nucleophilic and electrophilic functional groups in order to select the type of reactions to be generated by the model, which is able to find all possible ways, in which, the various species can react with each other. This implemented model generates forward- and reverse- condensation reactions (e.g., esterification and hydrolysis) as well as subsequent rearrangement reactions (polymerization) (Seavey and Liu, 2008).

4. PLA biomedical applications

During the last decades, biodegradable materials have been studied extensively for medical applications, because they have advantages over nondegradable biomaterials include eliminating the need to remove implants and providing long term biocompatibility.

The most common synthetic biodegradable polymers in medical applications are the poly(α-hydroxyacid)s, including poly(glycolic acid) (PGA), poly(lactic acid) (PLA), and polydioxanone (PDS) (Middleton and Tipton, 2000). Poly-lactic acid offers unique features of biodegradability, biocompatibility, thermoplastic processability and eco-friendliness that offer potential applications as commodity plastics, as in packaging, agricultural products, disposable materials and medical textile industry. Because of its favorable characteristics, PLA has been utilized as ecological material as well as surgical implant material and drug delivery systems, and also as porous scaffolds for the growth of neo-tissue (Gupta et al., 2007; Yamane and Sasai, 2003). The use of poly-lactic acid in these applications is not based solely on its biodegradability nor because it is made from renewable resources. PLA is being used because it works very well and provides excellent properties at a low price (Drumright et al., 2000). Various devices have been prepared from different PLA types including degradable sutures, drug releasing microparticles, nanoparticles, and porous scaffolds for cellular applications.

The diversification of PLA applications is such that a single polymer may prove useful in many applications by simple modifications of its physical-chemical structure. In many cases the polymer can be blended or copolymerized with other polymeric or non-polymeric components to achieve the desired behavior (Cheng et al., 2009; Gupta et al., 2007). The surface properties of materials play a critical role in determining their applications, especially for biomaterials in biocompatibility. Different surface modification strategies, such as physical, chemical, plasma, and radiation induced methods, have been employed to create desirable surface properties of PLA biomaterials.

Because biodegradable polymer implants temporarily remain in the body and disappear upon degradation, and it is no necessary a secondary operation to remove them after the defect site is repaired, they have an important application in the medical field. As a fiber the PLLA is not suitable for sutures, due to its degradation rate is very slow. On the other hand, in applications that require long retention of the strength, such as ligament and tendon reconstruction, and stents for vascular and urological surgery, PLLA fibers are the preferred material (Durselen et al. 2001). Three-dimensional porous scaffolds of PLA have been created for culturing different cell types, using in cell-based gene therapy for cardiovascular diseases; muscle tissues, bone and cartilage regeneration and other treatments of cardiovascular, neurological, and orthopedic conditions (Coutu, et al., 2009; Kellomäki et al., 2000; Papenburg et al. 2009). Osteogenic stem cells seeded on scaffolds of this material and implanted in bone defects or subcutaneously can recapitulate both developmental processes of bone formation: endochondral ossification and intramembranous ossification (Behonick et al., 2007; Caplan, 2009). Due to the high strength of PLLA mesh, it is possible to create 3D structures such as trays and cages (Kinoshita et al., 2003).

An exciting application, for which the PLA offer tremendous potential, is bone fixation devices, since the metallic fixations have several disadvantages. Recently, biodegradable materials have been replacing metallic ones for the fixation of fractured bones in the forms of plates, pins, screws, and wires. Since materials for bone fixation require high strength, similar to that of bone, PLA has a large application in this field.

One application of PLLA in the form of injectable microspheres is temporary fillings in facial reconstructive surgery. PLLA microspheres have also been used as an embolic material in transcatheter arterial embolization, which is an effective method to manage arteriovenous

fistula and malformations, massive hemorrhage, and tumors (Eppley et al., 2004; Imola and Schramm, 2009). Microspheres and microcapsules have been widely applied in drug delivery systems (DDS) for the prolonged administration of a wide variety of medical agents such as contraceptives, narcotic antagonists, local anesthetics, and vaccines. DDS with peptides and proteins have also gathered much attention, since they are specifically effective with comparatively low doses (Tan et al., 2010). Release of drugs from these systems is based on several mechanisms that include diffusion and polymer degradation (hydrolysis or enzymatic degradation) (Valantin et al., 2003).

5. Conclusion

According to the text reported above it is possible to observe that the biodegradable and bioabsorbable polymer synthesized from renewable resources for biomedical devices application has attracted much attention of researchers and industry. Lactic acid, a product of industrial importance for production of several chemicals and as monomer for PLA production, can be produced by fermentation of the sucrose contained in sugarcane molasses, a by-product of sugar manufacture, and from sugarcane bagasse that is a waste available in abundance in Brazil. PLA is a well-known synthetic polymer, and it is one of the most promising biodegradable polymers used for various biomedical applications due to its biocompatibility and biodegradability. The diversification of PLA applications is such that a single polymer may prove useful in many applications by simple modifications of its physical–chemical structure, resultant of chirality of lactic acid molecule with two asymmetric centers existing in four different forms.

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