

Poly(lactic Acid) and Its Synthesis

Subjects: Polymer Science

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Biomaterials are natural or engineered substances that interact with components of living systems that can be exploited for a medical purpose, either as therapeutic or diagnostic agents. Poly-(lactic Acid) (PLA) is a compostable polymer derived from corn sugar, potato, and sugar cane whose promising physicochemical properties are comparable to those of petroleum-based polymers, such as polyethylene, polypropylene, polystyrene, polycarbonate, and polyethylene terephthalate. PLA is a semicrystalline polymer that hydrolyses in physiological media, yielding lactic acid, a non-toxic component that is eliminated via the Krebs cycle as water and carbon dioxide. The biocompatibility, biodegradability, and resorbability characteristics of PLA have promoted its use in the biomedical field for a wide range of applications (suture threads, bone fixation screws, drug delivery systems, etc.), offering an alternative to conventional biocompatible materials such as metals and ceramics.

Keywords: polylactide ; stereocomplex ; ROP

1. Poly-(lactic Acid) (PLA)

Poly(lactic acid) is a poly- α -hydroxy acid synthesised from lactic acid (LA; 2-hydroxypropanoic acid) which exists in two optically active stereoisomers, namely, L-LA and D-LA (S and R in absolute configuration, respectively) ^[1]. Approximately 90% of the total lactic acid produced worldwide is made by bacterial fermentation, which offers advantages in both the utilisation of a renewable source and the production of optically pure L- and D-lactic acid, depending on the strain selected (the chemical synthesis of lactic acid always results in a racemic mixture). The dehydrated cyclic dimer of lactic acid is commonly called lactide (3,6-dimethyl-1,4-dioxane-2,5-dione). Lactide exists in three different forms due to the presence of two asymmetric carbon atoms in the molecule: L-lactide, D-lactide, and meso-lactide. In addition, a racemate of D-lactide and L-lactide exists as rac-lactide ^[1]. The chirality of Poly-(lactic Acid) (PLA) adds new functionality to PLA applications such as the specific recognition and interaction with chiral molecules (drugs, proteins, DNA, etc.) ^[2].

The polymerisation of optically pure L- and D-lactide yields isotactic homopolymers of Poly-(L-lactide) (PLLA) and Poly-(D-Lactide) (PDLA), respectively. Both PLLA and PDLA are semicrystalline polymers, showing a melting temperature (T_m) around 170 °C ^{[3][4]} and a thermal degradation temperature around 200 °C ^[5]. The PLA derivative crystallinity as well as their melting and glass transition temperatures (T_g) usually decrease with the diminishing optical purity of the lactate units ^{[6][7]}. PLLA polymers with a D-lactide content lower than 10% tend to be crystalline (or PDLA with L-lactide content), whilst homopolymers with a lower optical purity are amorphous ^[8]. The random insertion during the polymerisation of D- and L-LA units of both rac- and meso-lactide monomers generates an atactic polymer, Rac-PLA, which is completely amorphous. Moreover, syndiotactic PLA is obtained when D- and L-lactic acid units are placed alternatively along the chain, whereas a heterotactic chain architecture is attained when D- and L-lactide units are inserted alternatively on the polymer chain ^[9]. Syndiotactic PLA is a semicrystalline polymer exhibiting higher T_c than isotactic PLA but lower T_m , whilst heterotactic PLA is amorphous ^[10]. Furthermore, the one-pot sequential addition polymerisation method ^[11] of D- and L-lactide monomers yields stereo-block copolymers with blocks of opposite chirality, featuring melting temperatures 50 °C higher than those of isotactic homopolymers (220 °C) ^[12].

PLA displays different crystalline phases (α , α' , β , γ) established by the chain architecture and the specific crystallisation mechanism or thermo-mechanical history imposed during its processing, which define the properties of the final product ^[13]. The α -phase is the more stable PLA homocrystal structure that corresponds to an orthorhombic unit cell in which the helices are packed in a hexagonal fashion, containing two antiparallel chains per unit cell. The α -phase is normally obtained when isotactic PLLA or PDLA are crystallised from the melt above 130 °C or by crystallisation from the solution, characterised by a melting temperature of around 170 °C ^{[14][15]}. The α' -phase (or δ -phase) is the disordered form of the α -phase that is generated either from crystallisation from the melt at temperatures below 110 °C or by cold-crystallisation after quenching PLA to the glassy state. The α' -phase is also organised in the orthorhombic crystallographic unit cell;

however, it contains two parallel helices per unit cell, which increase the lattice parameters when compared to the ordered α phase. A mixture of α - and α' -phases is obtained when PLA is crystallised between 110 °C and 130 °C, although the α' -phase recrystallises into the α -phase when heated near the T_m (150–160 °C) [14]. Moreover, the β -phase is developed by stretching PLA fibres in the α -phase at a high temperature (130–140 °C) and high draw ratios as well as by casting thin films from the solution [15][16]. The chain conformation of the β -phase is a threefold helix in a trigonal unit cell containing three chains per unit cell, and its T_m is ca. 10 °C lower than α -phase T_m [17][18]. In addition, the β -phase exhibits piezoelectricity that allows for the interchange of mechanical and electrical energy [18], broadening its potential applications. Finally, the γ -phase is produced by the epitaxial crystallisation of PLA on hexamethylbenzene, forming two antiparallel threefold helices in an orthorhombic unit cell [19].

Furthermore, a new crystal structure, the stereocomplex (SC) phase, is formed from the co-crystallisation of the two stereoisomers of PLA (PLLA and PDLA) that feature a trigonal unit cell comprised of six threefold helices per unit cell. The structural peculiarity of the SC phase, with the nearest neighbours of any stem being of a different polymeric chain, provides them easy access to the growth front for both enantiomeric species. In addition, the specific C-H...O-H hydrogen bonds within the crystal lattice that stabilise the structure [20] endow stereocomplexes with a higher melting point (220 °C) and degradation temperature (220–260 °C) [5]. The SC phase was first found by casting a mixed solution of both enantiomers [21], and since then, the SC phase has typically been obtained intentionally from the blend of both enantiomers in the solution (in an appropriate solvent such as dichloromethane or chloroform at room temperature or acetonitrile around boiling temperature [22]) or in the solid-state from the melt [23]. However, the SC crystallisation of the blended enantiomers diminishes for high-molecular-weight (HM_w) PLA, and enantiomeric homocrystals (HC) in the α -phase are obtained instead [24]. Additionally, the critical M_w to exclusively obtain SC crystallisation is lower for blends obtained from the melt than those obtained from the solution [25], which hampers its industrial application. The optical purities of the polymers and the mixing ratio of the isomeric chains also affect the obtained ratio of SC-to-HC crystallites, and thus, the preparation of pure SC-PLA requires meticulous specific conditions [26]. SC crystallites can also be generated through the synthesis of block copolymers by the one-pot sequential monomer addition to a truly living polymerisation catalyst, which allows for the retention of the SC crystallisation in HM_w polymers [27][28].

The new synthetic approach affords a wide range of chain architectures that can be generated through different ratios of L- and D-Lactide monomers that offer the possibility to tailor the properties of the final polymeric product depending on the intended application. Furthermore, understanding the advantages and drawbacks of the different synthetic processing methods to obtain PLA is crucial to tailoring the foreseen applications. Moreover, since PLA still exhibits performance drawbacks such as low mechanical properties, a low thermal resistance, and a low hydrophobicity, which limit its applications in some biomedical fields, novel materials with unique properties can be obtained through the blend or copolymerisation of PLA with other biodegradable or non-biodegradable polymers, such as polyethylene (PE), polypropylene (PP), Polyhydroxyalkanoates (PHA), PMMA, Poly(ethylene-co-vinyl acetate) (PEVA), etc. [29][30][31]. In addition, nanocomposites can be fabricated by mixing PLA with other complementary compounds such as silk [32], gelatin [33], collagen [34], tungsten disulfide [35][36][37], natural fibres (flax, jute, hemp,) [38], ceramics (ZnO, TiO₂) [39][40], etc. to enhance their performance.

2. Synthesis of Poly-(lactic Acid)

PLA was first synthesised by polycondensation by Théophile-Jules Pelouze in 1845. In 1932, Wallace Hume Carothers developed a novel synthetic method based on the ring-opening polymerisation (ROP) of the cycle lactide monomer to synthesise PLLA. ROP was later patented by Du Pont in 1954 to synthesise vinyl fluoride (U.S. Patent No. 2674632, 1954). However, HM_w PLA by ROP on an industrial scale was only attained by the mid-1990s [4].

The lactic acid monomer can be converted to PLA through a polycondensation process by the reaction of the hydroxyl (–OH) and carboxylic acid (–COOH) groups with the removal of the detrimental byproducts such as water. Generally, catalysts are added to polymerisation to increase the reaction rate. The removal of water, enhanced under vacuum pressure, is critical to producing HM_w polymers due to the increased viscosity of the reaction mixture as the reaction proceeds. However, side reactions, such as transesterification, can also occur during the polycondensation of lactic acid, resulting in the formation of ring structures of different sizes, such as lactides. Transesterification reactions lower the overall M_w and the stereocontrol over the chain architecture, decreasing the physical properties of the PLA afforded as well as reducing the reaction yield [7]. The HM_w PLA is mainly synthesised by ROP due to the accurate chemical control in terms of molecular weight, polydispersity, polymer chain-ends, and tacticity. Moreover, ROP requires relatively mild conditions (130 °C) when compared to polycondensation (180–200 °C) [7][41]. Three reaction mechanisms have been proposed for ROP of lactide: anionic, cationic, and coordination-insertion mechanisms. In both anionic and cationic polymerisations, a monomer-activation mechanism occurs first, which permits the catalyst to be independent of the

propagating polymer and can thus be easily removed as the polymerisation finishes. However, undesirable side and racemisation reactions are likely to occur due to the highly activated monomers. On the contrary, coordination-insertion polymerisation attains HM_w PLA with higher control over the M_w distribution [7][42]. Metal complexes of several metals have been widely employed as the catalysts for the ROP of lactides [7], of which the most studied are stannous 2-ethylhexanoate [Sn(Oct)₂], aluminium isopropoxide [Al(O i-Pr)₃], and zinc(II) lactate [Zn(Lact)₂] [41]. Sn(Oct)₂ is the catalyst utilised for the industrial synthesis of PLA, largely due to its approval by the FDA for use in medical (<20 ppm [43]) and food applications. Moreover, lauryl alcohol (1-dodecanol) is usually added as an initiator [7].

The polymerisation is induced by a coordination-insertion three-step mechanism supported by the catalyst [41], which was first formulated in 1971 by Dittrich and Schulz [42]. Firstly, Sn(Oct)₂ reacts with the lauryl alcohol to form a tin alkoxide. Subsequently, the exocyclic carbonyl oxygen of lactide temporarily coordinates with the tin atom of the catalyst in the alkoxide form. The formed coordination system enhances the nucleophilicity of the alkoxide part of the initiator as well as the electrophilicity of the lactide carbonyl group that enables the reaction to each other. Finally, the acyl-oxygen bond of lactide is disrupted, and the generated linear chain of the lactide turns into the alkoxide part of the catalyst, promoting the coordination with a new lactide molecule and, thus, the polymerisation propagation [7]. Finally, the active metal-alkoxide bond is hydrolysed as the monomer is entirely consumed, and the formation of a hydroxyl end-group occurs [41]. In the last stage of the propagation step, as the monomer concentration becomes significantly lower (~80%), both intra- and inter-molecular transesterification reactions occur, and the molecular weight distribution increases. However, the degrees of racemisation and chain scrambling achieved by metal complexes that follow coordination-insertion mechanisms are notably lower than those obtained by anionic or cationic catalysis [7]. The microstructure of the final polymers depends both on the initial monomers added to the reaction mixture and the catalyst stereocontrol. The control exerted by the catalyst over the nanostructure of the PLA, particularly to synthesise the PLA stereo block copolymers of HM_w, is essential to tailor the properties of the final product, and the synthesis of novel catalysts, particularly metal-based catalysts, for polymerisation by the coordination mechanism has attracted much attention since the pioneering work of Kleine et al. in the 1950s [41][44][45]. However, several drawbacks to controlling the synthesis of stereoblock HM_w PLA have emerged since then, such as the decrease in the living character of the catalyst due to the increase in the reaction heterogeneity [46], the detrimental side reactions due to the multiple nuclearities exhibited by the catalysts [47], as well as the long reaction time required to achieve the desired architectures and molecular weight [42]. Recently, novel catalysts that fulfil the synthetic requirements whilst exhibiting low toxicity for the application of the PLA derivatives in the biomedical and pharmaceutical fields were just attained [28][48][49], which offer the possibility to design multiblock copolymers simultaneously featuring the PLA stereoblock to attain higher physicochemical properties with other complementary blocks to tackle the PLA limitations.

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