A Study on modification of polylactic acid and its biomedical application

Yi Huang[1, a, *, †], Yu Wang[2, b, *, †], and Jiarui Wen[3, c, *, †]

[1]Shenzhen University, Nanshan Distract, Shenzhen, China
[2]Henan University of Technology, Zhongyuan District, Zhengzhou, China
[3]Nanchang Hangkong University, Honggutan District, Nanchang, China
[†]These authors contributed equally.

Abstract. Polylactic acid (PLA) is one of the most extensively studied biodegradable materials. PLA is a versatile material with excellent bio-compatibility, bioabsorbability, biodegradability, and low toxicity. As an environmentally friendly polymer, PLA is favored by researchers and has explored many commercial applications, playing an important role in medicine and industry to replace many traditional petrochemical-based polymers. However, the strength and mechanical properties of PLA need to be improved to meet the practical application of multiple scenarios. The purpose of this review is to explore the modification methods of grafted copolymerization and block co-polymerization to improve the performance of PLA. This review also focuses on the medical applications and covers some non-medical applications of PLA.

1 Introduction

The huge circulation of traditional petroleum-based plastics in everyday life results in millions of tons of plastic waste each year worldwide, most of which is sent to landfills where it takes a long time to degrade in the soil. There is also a large amount of plastic discarded at random, leading to serious "white pollution", causing great damage to the ecological environment. Therefore, alternatives to traditional plastics need to be developed urgently [1]. With the enhancement of people's awareness of environmental protection, biodegradable materials begin to enter consumers' lives. Compared with traditional plastics, biological materials have better resource utilization and environmental protection [2]. Biodegradable polymer materials refer to the transformation of macromolecular materials into small molecular materials under the action of microorganisms and catalytic enzymes, which are finally metabolized into water and carbon dioxide. This material makes up for the defects of other polymer materials, has a unique degradation function of its own, reduces the pressure on the environment caused by the failure to decompose after use, and fundamentally solves the environmental pollution caused by waste. Biodegradable polymer materials can be divided into natural biodegradable polymer materials, microbial synthetic polymer materials, and chemical synthetic biodegradable polymer materials, which have their own biodegradability, biocompatibility, and non-toxicity, so it has a great development potential and application prospects [3].

Polylactic acid (PLA) is a biodegradable polymer prepared by chemical synthesis from renewable plant resources such as corn and sugar beet. It is a kind of biodegradable thermoplastic alipid polyester. PLA is rich in raw materials. Polysaccharides and starches in biomass resources are saccharified and fermented to produce lactic acid, which is further polymerized to form PLA. Finally, different processing technologies are used to manufacture products. The whole production process does not produce any pollution, and the energy consumption is only 20% to 50% of that of conventional petrochemical products. The carbon dioxide and water generated by degradation after waste is returned to nature and re-enter the ecosystem to participate in photosynthesis and maintain the carbon balance of the ecosystem, with good circularity [4]. At present, when petroleum resources are scarce and white pollution is serious, polylactic acid (PLA) has become the most potential substitute for petroleum-based plastics.

PLA, also known as polylactide, is a linear aliphatic polyester polymer material synthesized by condensation of lactic acid or lactide as monomers. Lactide is a cyclic dimer of lactic acid. There are two chiral centers in the lactide monomer, which can form three different three-dimensional configurations: L-Lactide, D-Lactide, and D,L-Lactide (LLA, DLA, and DLLA). Thus, their corresponding polymers, L-PLA, DL-PLA, and meso-lactic acid (PLLA, PDLA, and PDLLA), are chiral polymers with asymmetric carbon atoms and helical conformations with different chain configurations [5]. The crystallinity of PLA is about 0-37 %, the glass transition temperature (Tg) is 55-65 ° C, and the melting point (Tm) is 160-190 ° C due to the difference of conformation and molecular weight. The best solvent of PLA is chloroform. Other good solvents are chlorinated or fluorinated organic

[*]Corresponding author's e-mail: [a]2018201003@email.szu.edu.cn,
[b]201926020104@stu.haut.edu.cn, [c]19012224@stu.nchu.edu.cn

compounds, dioxane, furan, xylene, etc. PLA is hydrophobic with a static water contact angle of 80 ° and surface energy of 49 mJ / m^2 [6]. At present, the chemical synthesis of polylactic acid mainly has two ways: lactic acid direct condensation polymerization (direct method) and lactide ring-opening polymerization (indirect method). The direct polycondensation method, also known as a one-step method, refers to the direct dehydration condensation of lactic acid under heating conditions to form polylactic acid. Although this method is simple and easy to do, the relative molecular weight is low. In industrial production, ring-opening polymerization is preferred. First, lactide is synthesized from lactic acid through two-step polymerization, and then lactide is purified, and ring-opening polymerization is used to prepare polylactic acid with high molecular weight [7]. Polylactic acid has non-toxic, non-irritating, good biocompatibility, biodegradability, and the advantages of good mechanical strength and processability. They are widely used in surgical sutures, drug-controlled release materials, orthopaedics internal fixation materials, and biomedical fields such as tissue engineering materials. They are also used as biodegradable farm film, food packaging materials, automobile interior trim materials environmental protection high polymer material. With the development of technology, it can also be used as green fiber material in the textile industry and used as engineering plastic in the electronics industry, which has a wide range of uses [5]. Polylactic acid (PLA) is an eco-friendly bioplastic with good biocompatibility, processability, and less energy dependence. However, it has some shortcomings that limit its application in some fields. (1) Poor toughness PLA has helical arranged molecular chains. There is only one methylene group in the repeated unit of the main chain, and there is no flexible methylene group, which leads to the poor activity of the molecular chain. Secondly, PLA's Tg is between 55-65℃, so PLA is rigid and brittle at room temperature, elongating at a break of less than 10%, and poor ductility [8]. The tensile strength and Young's modulus of PLA are close to PET, but the defect of poor toughness limits its wide application. (2) ***Low heat-resistance*** Due to the poor crystallization ability, it is difficult to crystallize the injection molding cycle of polylactic acid in traditional melt processing. So, the PLA products treated by melt always remain amorphous [9]. The thermal deflection temperature (HDT) of amorphous PLA is as low as 50 ~ 65 °C, while high crystallinity PLA is more than 100 ~ 120 °C [9]. Therefore, to improve the heat resistance of polylactic acid products, the key is to improve their crystallization rate to obtain higher crystallinity. (3) ***Hydrophobicity*** PLA is relatively hydrophobic, and the static water contact angle is about 80°. This leads to low cell affinity and can cause inflammatory reactions from living hosts to directly contact biological fluids, limiting the biomedical application of PLA to some extent. Therefore, modification of the defects of polylactic acid is a research hotspot for researchers. Modification of polylactic acid by different methods is conducive to expanding the application range of polylactic acid.

In this paper, the biodegradable polymer polylactic acid was comprehensively reviewed, and its structural characteristics and synthesis methods of mainstream applications were introduced. The physical and chemical characteristics of polylactic acid were introduced in detail, and the biodegradation characteristics of polylactic acid were emphatically introduced. At the same time, aiming at the defects of polylactic acids, such as poor toughness, poor heat resistance, and hydrophobicity, the recent research results of modified polylactic acid are introduced, especially the chemical modification method, namely copolymerization modification. Finally, the application of polylactic acid was summarized. Due to its good biodegradability and biocompatibility, the application of polylactic acid in the biomedical field was mainly introduced. The future of polylactic acid and its related research was prospected.

2 Synthetic methods

The monomer lactic acid of PLA has two kinds of optical isomers, which are left-lactic acid and right-lactic acid. The lactic acid of two different optical isomers corresponds to the cyclic dimers of three different isomers, namely, lactide namely, L-lactide, D-lactide, and Meso-lactide, respectively.

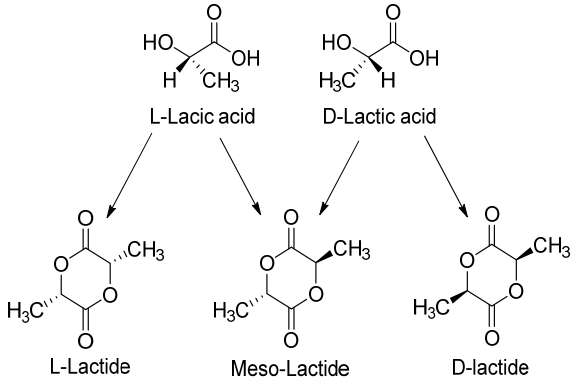

Figure 1. There are two main methods for PLA preparation, namely direct polycondensation of lactic acid and ring-opening polymerization of lactide according to different process steps.

2.1 Direct polycondensation of lactic acid

There are hydroxyl and carboxyl groups in lactic acid, which can be directly synthesized by polycondensation. The by-products such as distilled water were continuously removed in the condensation reaction, and finally, brittle, glassy PLA polymers were obtained. The advantage of this method is that the process is simple, and the tedious steps such as intermediate purification are omitted, so the production cost is low. However, conventional polycondensation of lactic acid does not increase the product's molecular weight unless organic solvents are azeotropically distilled with condensed water, and the polymerization takes a long enough time. Due to the viscosity of polymer melt, the existence of water and impurities in the reaction process, and the low concentration of active end groups, only low molecular weight polymers can be obtained by polycondensation [10]. Low molecular weight PLA has poor mechanical properties and no good application value, except adding a

molecular chain coupling agent or esterification accelerator to increase the molecular weight of PLA.

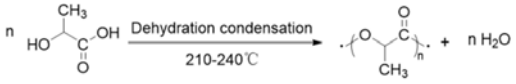

Figure 2. The process of the dehydration condensation

2.2 Ring-opening polymerization of lactide

PLA with high molecular weight and uniform distribution can be prepared by ring-opening polymerization of lactide with mature technology. Compared with the stepwise polycondensation method, this process route does not involve the use of mechanical solvents, nor does it require water removal operation under high temperature and high vacuum. It is economical and environmentally friendly and is the main process route for the production of polylactic acid. But this method also has many disadvantages, such as complex processes, various steps, high technical content, and cost. In the ring-opening polymerization of lactide, oligomers were synthesized by dehydration and condensation of lactic acid. The oligomers were cracked to lactide under the action of the initiator, and finally, the lactide was ring-opening polymerized to PLA.

So far, four ring-opening polymerization mechanisms of lactide have been proposed: Cationic ring-opening polymerization [11], anion ring-opening polymerization [12], coordination-insertion ring-opening polymerization [13], enzyme-catalyzed ring-opening polymerization [14]. The use of less catalyst characterizes cationic ring-opening polymerization, but it is difficult to obtain high molecular weight PLA. High reactivity and high speed characterize the anionic ring-opening polymerization. However, the product is toxic when too many catalysts are used. Coordination ring-opening polymerization is suitable for preparing high molecular weight PLA. The internal structure of bioenzyme is complex, and the mechanism of its catalytic polymerization is not mature, which needs further study. The relationship between catalytic mechanism and enzymatic degradation mechanism needs further study. Enzyme catalysis is clean and reactive. The advantages of high performance and reusability are incomparable to synthetic catalysts.

3 Properties

Due to the different chemical activity of lactic acid and lactide in the synthesis of PLA, the properties of the products are also very different, namely poly (D-lactic acid) (PDLA), poly (L-lactic acid) (PLLA), and poly (D, L-lactic acid) (PDLLA).

Table 1. Result of the different chemical activity of lactic acid and lactide in the synthesis of PLA

Sample	Solid structure	Melting Point(℃)	elongation at break(%)	Tensile strength(MPa)	Tg(℃)	Td(℃)	Melting Heat(J·g)
PLLA	hypocrystalline	170-190	3-5	50-70	55-65	-200	931
PDLA	crystal	180	3	50	50-60	-200	-
PDLLA	hypocrystalline	-	2.6	53	50-60	180-200	142

3.1 Mechanical properties of PLA

Mechanical properties of PLA-based polymers vary greatly from soft and elastic plastics to rigid and high strength materials depending on crystallinity, polymer structure, molecular weight, and processing methods. Semicrystalline PLA has better mechanical properties than amorphous PLA. The tensile modulus (Young's modulus) of semi-crystalline PLA is about 3GPa, the tensile strength is 50-70MPa (equivalent to non-biodegradable conventional plastics [15]), the flexural modulus is about 5GPa, the flexural strength is about 100MPa, and the elongation at break is about 4 % [1].

The molecular weight and structural composition of PLA will affect its mechanical properties:

1. The higher molecular weight, PLA has higher mechanical strength. When the weight-average molecular weight (Mw) increased from 50 kDa to 100 kDa, the tensile modulus of PLLA increased by 2 times. When Mw increased from 50 kDa to 150 kDa, the tensile strength increased from 15.5 MPa to 80 MPa [1].

2. The crystallinity and mechanical properties of PLA can be precisely controlled by controlling the chemical composition of PLA.

The mechanical properties of PLA are also affected by the crystallinity, lamellar thickness, spherulite size, and molecular chain orientation of PLA [16].

Compared with some bio-based materials such as PEG and PC, PLA has better tensile strength and thermal processing properties. It can be used for injection molding, film extrusion, blow molding, thermal molding, fiber spinning, and film forming, but the product does not have good elongation. Comparison with traditional plastics such as polyethylene terephthalate (PET) and polystyrene (PS). The tensile strength and modulus of PLA are similar to those of PET and PS, but the elongation at break of PLA is less than that of PS, proving that PLA is more brittle than PS. It can be seen that PLA has great commercial potential to replace conventional petroleum-based polymers, but further modification is needed to meet practical application requirements.

Table 2. The properties of PLA, PET, PS

Property	PLA	PET	PS
Tensile strength (MPa)	59	54	45
Elastic Modulus (GPa)	3.4	2.8	2.9
Elongation at break (%)	6	5.5	7
Impact Strength, (J/m)	26	59	21
Tg(℃)	58	79	98

3.2 The thermal performance

Like traditional thermoplastic polymers, PLA is a semi-crystalline polymer with typical melting behavior and glass transition behavior during heating. The glass transition temperature (Tg) of PLA is about 50-60℃, the melting temperature (Tm) is about 170-190℃, and the melting enthalpy (Δ) is 93.1J / g. The content and molecular weight of PDLA are the main factors affecting the Tg and Tm of PLA. When the molecular weight of PDLA is high but not greater than the critical value, the Tg and Tm of PLA increase with the molecular weight of PDLA. With the increase of PDLA content, the χc, Tm, and crystallization rate of PLA decrease. The possible reason is that the increase of PDLA content reduces the regularity of the PLA molecular chain, reduces its crystallinity and melting point. Also, it may be that PDLA is excluded from the orderly folding of the PLA molecular chain to form crystallization [17].

3.3 Crystallization properties

According to the different optical isomers of lactic acid or lactide, PLA can form three kinds of crystals with different helical conformation, namely α, β, and λ crystal [18]. The α-crystal is stable and formed by melt crystallization, cold crystallization, and solution crystallization. The melting point is about 185℃ [19]. The β-crystal is more unstable and is usually formed from the more stable α-crystal under high tensile stress, with a slightly lower melting point of about 175°C [20]. The λ- crystal can be epitaxially grown on a hexomethylphenyl substrate. Due to the high glass transition temperature of PLA, the crystallization rate of PLA is usually slow, and the crystallinity is low. The crystallinity of PLA has an obvious effect on its properties, such as melting temperature, mechanical strength, primary property, barrier property, degradation property, etc.

3.4 Biodegradability

The ester groups in PLA molecular chains are sensitive, and the molecular chains are prone to hydrolysis or enzymatic cleavage. During the degradation of PLA, the main chain of PLA was broken, and oligomers and lactide were formed. The intramolecular and intermolecular transesterification of lactide resulted in the formation of monomer lactic acid, which was further decomposed into CO_2 and H_2O.

The degradation of PLA involves two processes: non-biodegradation and biodegradation. The non-biodegradation process is the chemical hydrolysis of the ester bond in the main chain of PLA in the presence of high temperatures and water [21]. Biodegradation is the microbial decomposition of polymer, which produces carbon dioxide and water under aerobic conditions and methane and hydrocarbons under anaerobic conditions [22].

Overall, the biodegradation process of polymer mainly includes the following important steps [23]: (1) Biodegradable polymers are affected by water, humidity, and other factors in the natural environment to break the molecular main chain. At the same time, microorganisms grow and reproduce on the surface or inside the polymer, resulting in changes in the polymer's chemical, physical and mechanical properties. Finally, the polymer material is decomposed into small fragments. (2) Microorganism secretes enzymes that can degrade polymer molecular chains, and polymer fragments are further degraded under the catalysis of enzymes and converted into oligomers, dimers, and monomers. (3) Some of the degraded molecules can be recognized by the receptors of the microbial cell and can cross the cell membrane. Some of the degraded molecules are left outside the microorganism. The microorganism metabolizes the molecules that cross the cytoplasm to produce energy, new biomass, and many primary and secondary metabolites. This process is called microbial assimilation. (4) Some metabolites (such as organic acids, aldehydes, antibiotics, etc.) can be excreted by microorganisms to the extracellular environment and eventually converted into C02, N2, CH4, H20, and biomass salts, etc. This stage is called microbial mineralization.

Polymer degradation is usually divided into main chain fracture, side-chain fracture, and crosslinking point fracture. PLA degradation usually occurs through the cleavage of ester bonds, which can be attributed to two steps: (1) It is believed that chemical hydrolysis is the initial step of PLA degradation. Ester bonds can be destroyed by absorbing water at high temperatures and high humidity, resulting in molecular chain rupture and molecular weight reduction. At the same time, the carboxylic acid end groups on the PLA molecular chain and a small amount of PLA oligomers can further catalyze the hydrolysis of ester bonds, resulting in the gradual acceleration of the degradation rate (free radical self-catalysis) [24]. (2) Acidic lactic acid oligomers are then degraded through microbial fragmentation, releasing carbon dioxide and water[3]. In other words, the degradation of PLA is a biochemical process, including the chemical hydrolysis process of the PLA molecular chain and the biodegradation process caused by microorganisms in soil [25]. Due to the role of hydrated hydrogen ions, the ester bond of the PLA molecular chain breaks to form carboxyl and hydroxyl groups. Still, the whole hydrolysis process requires a lot of time and energy.

The biodegradation of PLA is a complex process. There are a series of influencing factors in this process, including the characteristics of PLA, the environmental conditions exposed to PLA, and the characteristics of microorganisms in soil. Molecular chain structure, molecular weight, chemical structure, crystallinity, morphology, size, and additives of PLA are important factors affecting the biodegradation rate of PLA. The effects of environmental factors on the biodegradation rate

of PLA mainly include the temperature, humidity, pH value, oxygen content, and species and distribution of microorganisms in the soil environment.

4 Modification

The modification of PLA makes it possible to put it into commercial application on a large scale. The following will cover toughening modification, heat resistance modification, hydrophilic modification.

4.1 The toughening modification

PLA has helical molecular chains. There is only one methylene group in the repeating unit of the main chain, and there is no flexible methylene group, which leads to the poor activity of the molecular chain. Secondly, the Tg of PLA is between 55-65 °C, so PLA shows rigidity and brittleness at room temperature. The elongation at break is less than 10 %, and the ductility is poor [26]. The tensile strength and Young's modulus of PLA are close to PET's, but the poor toughness limits its wide application.

From the perspective of microscopic molecular structure, the copolymerization modification can improve the toughness of PLA by introducing flexible chain segments into PLA side chains or main chains to reduce the chain regularity. It also reduces the crystallization performance or weakens the interaction between chains. The copolymerization is divided into graft copolymerization and block copolymerization.

4.1.1 block copolymer

PLA block copolymerization mainly refers to the copolymerization of PLA with polyester, polyolefin, etc., to prepare block copolymer with a specific structure. Generally speaking, after PLA block copolymerization, due to the introduction of flexible chain segments and the reduction of intermolecular forces, the toughness of PLA will be improved accordingly.

Jorge et al. introduced different content (3-39 %) of ethylene brassylate (EB) as the copolymerization monomer of DL-lactide, synthesized random copolymers by ring-opening polymerization, with higher thermal stability (degradation temperature close to 450 ° C) and better ductility. When the mole fraction of EB was 5 %, the elongation at break increased to 87 %, and the elastic modulus remained at about 1 GPa. The copolymer with EB mole content of 16 % showed a clear elastomer curve, and at the elongation of 1400 % (without fracture of the sample), it had a positive secant modulus of 2.0 MPa and tensile strength of 0.3 MPa [27].

Bedo and his colleagues used MDI as a coupling agent to prepare block copolymer PLA-b-PU by coupling reaction of polyurethane (PU) containing PTHF soft chain with PLA. PLA-b-PU has good elongation (elongation > 200 %) and high modulus, yield stress, and tensile strength. The properties of the two different processing methods are different: conventional mixing (PLA / PU) of PU and PLA and block polymerization (PLA-b-PU). The interfacial adhesion of block polymers can be observed under large deformation, and coupling leads to a more uniform dispersion of PU particles in the matrix, resulting in better mechanical properties. So reactive polymerization with good compatibility has better processability than conventional physical blending [28].

M. A. Ghalia et al. used PEG to copolymerize PLA. They synthesized polyethylene glycol-polylactic acid copolymer (PLA-co-PEG) by the melt polycondensation method. It was found that when the volume ratio of PLA to PEG was 80: 20 and 1.25% chain extender was added, the tensile strength and impact strength of the copolymer was increased to 70 MPa and 7.9 kJ/m2, respectively, and the elongation at break was increased by 17% [29].

Zhang et al. blended PLLA, PBS, and PLLA-PBS triblock copolymers by melt blending. They added reactive $(PLLA\text{-}b\text{-}PGMA)_3$ as a macromolecular chain extender to prepare block branched PLA toughness resin. The structure promotes the compatibility of the three and improves the toughness of the mixture. When the ratio of the three is 70 / 30 / 30, the fracture elongation reaches 95 %, and the fracture strength and modulus of the material can remain at a high level. The method also improves the overall melt strength of the material. Rheological experiments showed that the viscosity and storage modulus of the blend were significantly higher than those of pure PLLA. Tensile viscosity measurement shows strong strain hardening behavior. The tensile test showed that the tensile properties were significantly improved, and the tensile strength remained at a high level [30].

4.1.2 Graft copolymer

Graft copolymerization of PLA refers to the grafting of active groups on the PLA mainchain and then graft copolymerization of other monomers to generate copolymers with specific functions to improve the PLA resilience.

Kaynak et al. prepared graft polymer (PLA-G-MA) by grafting maleic anhydride (MA) on PLA skeleton through reactive extrusion molding and then added it into the melt blend system of PLA and thermoplastic elastomer to study the influence of PLA-G-MA on the toughness of the blend. The results of the infrared harmonic analysis show that MA reacts with the functional groups in the hard segment of the thermoplastic elastomer, which further improves the compatibility. The results of scanning electron microscopy (SEM) show that the addition of PLA GMA reduces the size of the elastomer microregion and increases the surface area, which is conducive to the enhancement of interfacial interaction. The blends' impact strength and fracture toughness increased significantly, and the mechanical and thermal properties did not decrease [31].

Liu et al. synthesized lignin-grafted polylactic acid copolymers (LG-g-PDLA, LG-g-PDLLA, and lg-g-plla) by ring-opening polymerization of D-, DL- and l-lactic acid, and prepared poly (l-lactic acid) / lignin-grafted polylactic acid (PLLA / LG-g-PDLA, / LG-g-PDLA and / LG-g-PLLA) complex films. The tensile test showed that when 1 % LG-g-PDLA was added to the PLLA matrix, the tensile strength and strain increased by 11.6 % and 38.6 %,

respectively. What is more, previous studies have shown that the increase of tensile strength and strain of PLA / lignin blends usually sacrifices tensile modulus. Liu et al. found that compared with pure PLLA film, the tensile strength (1 % and 3 % LG-g-PDLA) and strain of PLLA / LG-g-PDLA stereocomplex films were slightly increased the tensile modulus was not sacrificed [32].

In Park's study [33], soda lignin derived from an herbaceous plant was fractionated with five different organic solvents - ethyl acetate(F1), 2-butanone(F2), methanol(F3), acetone(F4), and dioxane/water(F5), Some of these fractions were grafted with l-lactide to synthesize lignin grafted polylactic acid by ring-opening polymerization. At the same time, lignin-polylactic acid composite PLA 2002D and lignin-g-PLLA copolymer were prepared by mixing. Compared with neat PLA, the tensile strength of lignin-PLA composites containing SL, F1, F3, and F5 copolymers were 60.0-68.5 MPa, similar to neat PLA (66.7 MPa). The elastic modulus of the composites varied with the lignin content, from F1 (2197.7 MPa) to F5 (2503.4 MPa). At the same time, the elastic modulus of the research surface increases with the increase of the chain length of PLA [34]. Therefore, the elastic modulus of the F1-g-PLLA composite with the shortest polylactic acid chain is the lowest, while that of the F5-g-PLLA composite with the longest chain length is relatively high.

In Lyu's study [35], the PLA-g-GMA, an effective compatibilizer of PLA / PBAT blends, was synthesized by a one-step method with DCP as initiator. The biodegradable high-performance PLA / PBAT / PLA-g-GMA blends were obtained, and the samples with excellent mechanical properties were successfully printed by 3 D printing. With the increase of compatibilizer PLA-g-GMA, the tensile strength and elongation at the break of the injection and 3D printing samples gradually increased during the longitudinal deposition. The increased tensile strength of 3D printing samples during transverse deposition showed that PLA-g-GMA promoted the interfacial adhesion between filament layers. For the longitudinally deposited 3D printing sample, the tensile strength of PLA / PBAT / 10(70wt%PLA, 30wt%PBAT, 10wt%PLA-g-GMA) was 42.6 MPa, and the elongation at break exceeded 200 %.

4.2 Heat resistant modification

The heat resistance of PLA is poor. The thermal deformation temperature (HDT) of amorphous PLA materials is only about 55 ℃, lower than that of PP, PS, and other commonly used plastics, limiting the use range of PLA at a higher temperature. The basic reason for PLA's poor heat resistance is that its crystallization rate is slow, and the products obtained by injection molding and other molding methods are almost amorphous. When the temperature reaches above the glass transition temperature of PLA, the molecular chain segments in the amorphous region begin to move freely, leading to the softening deformation of the material. On the other hand, simply increasing the crystallinity of PLA is usually difficult to improve its toughness, so simultaneously improving the toughness and heat resistance has become a focus of PLA research.

Deng et al. annealed the PLA / ethylene-methacrylate-glycidyl methacrylate (E-MA-GMA) and HDT of the blends and proposed that the possible toughening mechanism was that the asymmetric thermal shrinkage between the PLA matrix and the E-MA-GMA dispersed phase gave the “negative pressure effect” of the E-MA-GMA phase [36]. Wu et al. prepared PLLA / EVM GMA composites by reactive blending. The epoxy group in EVM GMA reacted with the carboxyl group of PLLA, which improved the compatibility between PLLA and elastomer and then improved the material's mechanical properties. On this basis, the material was simply heat-treated to improve its HDT to more than 90 °C. At the same time, the composite maintained excellent toughness, such as elongation at break more than 60 % and notched impact strength more than 60 kJ / m2. It can be seen that annealing treatment can improve the crystallinity and heat resistance of PLA / elastomer series blends. However, due to the slow crystallization rate of PLA, it takes a long annealing time to obtain higher crystallinity [37]. Wu et al. also introduced a small amount of PDLA and EVM-g-PDLA copolymers in situ into the above system to shorten the annealing time. Through simultaneous stereocomplexation in the PLLA matrix, Wu et al. increased the interfacial force between PLLA and EVM-g-GMA and the melt viscosity ratio. They improved the crystallization rate of the PLLA matrix. By adjusting the interfacial force and melt viscosity ratio, the bicontinuous structure and supertoughness modification of the composites were realized, such as notched impact strength increased by 84 times compared with PLLA. Moreover, after rapid annealing treatment, the composites can obtain excellent heat resistance (HDT > 100 °C) and toughness (elongation at break > 80 %, notch impact strength > 70 kJ / m^2) [38]. Similarly, Deng et al. found in situ formations of ethylene-acrylate-glycidyl methacrylate terpolymer graft PLA (E-MA-g-PLA) not only can be used as a compatibilizer can also improve the stability of PLLA/PDLA melt to obtain both excellent toughness and heat resistance of composite materials. In addition, the composite of PLA and inorganic fillers can also improve the heat resistance of PLA composites to some extent [39].

4.3 The hydrophilic modification

Because polylactic acid has a wide range of applications in biology and biomedicine, it is expected to improve its hydrophobic properties. For example, polylactic acid's hydrophobicity leads to faster uptake of drug-loaded nanoparticles (NPs) through the mononuclear phagocytic system (MPS), resulting in a shorter duration in circulation and a decrease in drug availability in the body. To prolong the circulation time of hydrophobic PLA-based NPS in blood, it is necessary to improve its hydrophilicity. Copolymers (ABPs) containing amphiphilic blocks can be used in drug delivery systems. These ABPs self-assemble in water to form core/shell micelle NPs. The hydrophobic core can carry various hydrophobic drugs and hydrophilic nanoparticles, ensuring water solubility and

biocompatibility of NPs [40].

Zhang et al. reported synthesizing functionalized cyclic lactide monomer 3, 6-bis (benzyloxymethyl) -1, 4 - dioxane-2, 5 - dione (BnLA) by an advanced synthetic route. With BnLA as raw material, water-soluble hydroxyl functionalized homopolylactide (P (OH) LA) was synthesized by ring-opening polymerization (ROP), and the hydrogenation deprotection reaction was carried out. Amphiphilic diblock polylactic acid (P (OH) LA-PLA) was synthesized by ROP reaction with dl-lactide as initiator, and then dehydroprotection was carried out. P (OH) LA-PLA can form polymer micelles with a diameter below 100 nm. This material has potential applications in biomedicine [41].

Kalellar et al. prepared a three-component amphiphilic brush-graft copolymer (PLA-g-POEGMA) of poly (lactic acid) -poly (OEGMA) by atom transfer radical polymerization (ATRP) using poly (lactic acid) bromide (Br-PLA) as multi-site initiator. Br-PLA was prepared by free radical bromination of PLA with n-bromosuccinimide (NBS). Amphiphilic brush copolymer was self-assembled to form particles with a diameter less than 100 nm, without any additional stabilizer or surfactant, and without additional purification steps. Nanoparticles showed good absorption and release of curcumin and dye molecules in buffer and serum conditions, and their toxicity to mammalian cells was negligible. Therefore, these nanoparticles as carriers for intravenous injection of hydrophobic drugs and imaging agents showed promising results [42].

Using L-, d-lactic acid, and glucose as raw materials, Qi et al. synthesized equal amounts of poly (L-lactic acid) (PLLA) and poly (d-lactic acid-co-glucose) (PDLAG) by melt polycondensation. They prepared poly (lactic acid) stereocomplex of poly （lactic acid containing glucose group by solution blending method(sc-PLAG). To study the hydrophilicity of sc-PLAG samples, the water contact angle of sc-PLAG during feeding with different glucose contents was tested. The water absorption rate of the sample was calculated. The results show that the glucose-containing polylactic acid ternary complex can effectively improve the hydrophilicity of polylactic acid materials and has broad application prospects in biomedical fields such as drug delivery systems and tissue regeneration [43].

5 The application of PLA

The PLA plays an important role in biomedicine due to its biodegradability, biocompatibility, and eco-friendliness. PLA can be metabolized by the human body and is non-toxic. Therefore, it can be used in drug delivery. Biocompatibility ensures PLA entering the body without causing inflammation. In addition, PLA is also an environmentally friendly polymer. Because of its reproducibility, transparency, and mechanical properties, it can be made into a widely used film in food packaging. The following sections describe the application of the PLA in drug delivery, tissue engineering and implants.

5.1 Drug delivery

With the development of medicine, targeted therapy began to rise to reduce the damage to the body. One promising application is the use of nano-drug carriers, such as lipids, polymer nanoparticles, dendrites, micelles. Compared with systemic chemotherapy, the delivery of therapeutic drugs via small nanocarriers results in higher concentrations of drugs at the tumor site and lower toxicity due to permeability and retention (EPR) effects [44]. The liver and kidneys quickly clear other low-molecular weight drugs. The bioavailability and anti-tumor effect were significantly improved.

Currently, most cancer drugs have poor permeability through the blood-brain barrier. So the development of implantable anticancer drugs with biodegradable polymerizations allows the continuous release of these therapeutic drugs. PLGA is used to deliver drugs to malignant glial tumors. Camptothecin encapsulated in PLGA indicates increased tolerance of normal toxic compounds. Experimental results showed that the growth of intracranial glial tumors in mice was slow and the median survival rate was increased, and nanoparticles penetrating the brain were formed. When there was convection transmission, intracranial distribution was increased [45].

To develop the next generation of cancer drugs that can deliver drugs over time. Nanoparticles prepared by PLA have great potential, and the biodegradability of PLA is more suitable. Nanoparticles are usually in the range of 1-100 nanometers in diameter. PLA nanoparticles have been applied in many clinical anti-tumor hydrophobic drugs. For example, PLA nanoparticles have been studied for the treatment of leukemia. Bovine sperm ribonuclease is adsorbed to the PLA and has demonstrated spermatogenic and anti-embryo effects in vivo [46].

Nanoparticles can significantly improve drug delivery and have a variety of application options. Sticky drugs allow therapeutic drugs to pass through mucus-covered upper epidermises, such as the eyes, mouth, and nose, to treat many health problems [46]. In addition, it has broad application prospects in central nervous diseases, such as stroke, Parkinson's disease, Alzheimer's disease, and mental diseases [47].

In addition, the PLA based on drug delivery systems has been used for drug delivery of different durations, including contraceptives, narcotic antagonists, local anesthetics, vaccines, peptides, and proteins. Polymerized drugs are released in three ways: erosion, diffusion, and swelling. For PLA, ester bond rupture occurs randomly through hydrolytic ester cleavage, leading to subsequent device erosion. PLA particles were prepared by solvent evaporation technology, and the ideal candidate for system design was found.

5.2 Implants

Synthetic conduits made of PLA and other biomaterials offer chemical and mechanical flexibility, ease of use, and bioabsorbability. Cai et al. demonstrated that in a rat model, the high permeability and degradability of the conduit composed of PLA induced axon migration and

maturation [48]. And the permeable PLA catheter increases axon regeneration in the damaged space. PLA catheters can also support myelin, comparing with conventional silicone catheters.

At the fracture site, metal screws are often used to restore mechanical and stability. But these metals tend to cause symptoms such as bone shrinkage and infection. It has been reported that between 7% and 26% of internal fractures are refractured due to screw luminal resection [49]. PLA screws have been extensively studied for degradation kinetics and decay products in vitro and in vivo. The results suggest that a compound formulation may be the best solution to ensure proper degradation time and maintenance of mechanical and tensile strength [50]. In addition, PLA materials have broad application prospects in meniscus repair, guided bone regeneration, skin grafting, and other fields and are polymers with excellent comprehensive properties.

5.3 Tissue engineering

Tissue engineering is one of the most exciting interdisciplinary areas of research. As the research went on, the use of the PLA grew exponentially. Such as scaffolding materials. The PLA's bioabsorbability allows the scaffold to disappear from the transplant site over time, leaving a perfect piece of natural tissue. The PLA bracket will maintain its mechanical properties until it is no longer needed. The scaffold degrades and is absorbed into the body in a continuous sequence, leaving no trace.

6 Conclusion and outlook

With their high mechanical strength, high melting temperature, good biodegradability, and good sustainability, the PLA can be prepared to apply for medicine. This paper aims to summarize the preparation of PLA, the selection of modification, and the application of PLA and to introduce the improvement of PLA properties by modification in detail. For example, to overcome PLA's own shortcomings, graft copolymerization, block copolymerization, and hydrophilic modification is used to improve PLA's mechanical properties and hydrophilicity. This review also covers the mechanical properties, thermal properties, crystallization properties, biodegradation, and other aspects of PLA.

The improvement of the properties of polylactic acid by modification is discussed, and the application of polylactic acid in medical and non-medical fields is discussed. With the deepening of the research, it is believed that the shortcomings of direct polylactic acid polymerization and open-loop polymerization can be solved in the future. Polylactic acid has been improved continuously by modification and has been widely used in more fields by virtue of its excellent properties.

References

1. Abi-Akl, R., Ledieu, E., Enke, T. N., Cordero, O. X., Cohen, T., Physics-based prediction of biopolymer degradation. Soft Matter 2019, 15 (20), 4098-4108.
2. Arjmandi, M., Ramezani, M., Mechanical and tribological assessment of silica nanoparticle-alginate-polyacrylamide nanocomposite hydrogels as a cartilage replacement. J. Mech. Behav. Biomed. Mater. 2019, 95, 196-204.
3. Luckachan, G. E., Pillai, C. K. S., Biodegradable Polymers- A Review on Recent Trends and Emerging Perspectives. J. Polym. Environ. 2011, 19 (3), 637-676.
4. Vink, E., Davies, S., Life Cycle Inventory and Impact Assessment Data for 2014 Ingeo Polylactide Production.
5. Pan, P.; Inoue, Y., Polymorphism and isomorphism in biodegradable polyesters. Prog. Polym. Sci. 2009, 34 (7), 605-640.
6. Sangeetha, V. H., Deka, H., Varghese, T. O., Nayak, S. K., State of the art and future prospectives of poly(lactic acid) based blends and composites. Polym. Compos. 2018, 39 (1), 81-101.
7. Vink, E. T. H., Rabago, K. R., Glassner, D. A.; Gruber, P. R., Applications of life cycle assessment to NatureWorks (TM) polylactide (PLA) production. Polymer Degradation and Stability 2003, 80 (3), 403-419.
8. Lim, L. T., Auras, R.; Rubino, M., Processing technologies for poly(lactic acid). Prog. Polym. Sci. 2008, 33 (8), 820-852.
9. Li, H. B.; Huneault, M. A., Effect of nucleation and plasticization on the crystallization of poly(lactic acid). Polymer 2007, 48 (23), 6855-6866.
10. Slomkowski, S., Penczek, S., Duda, A., Polylactides-an overview. Polym. Adv. Technol. 2014, 25 (5), 436-447.
11. Kohn, F. E., Vanommen, J. G.; Feijen, J., THE MECHANISM OF THE RING-OPENING POLYMERIZATION OF LACTIDE AND GLYCOLIDE. Eur. Polym. J. 1983, 19 (12), 1081-1088.
12. Kricheldorf, H. R.; Boettcher, C., POLYLACTONES .26. LITHIUM ALKOXIDE-INITIATED POLYMERIZATIONS OF L-LACTIDE. Makromolekulare Chemie-Macromolecular Chemistry and Physics 1993, 194 (6), 1665-1669.
13. Kohn, F. E., Vandenberg, J. W. A., Vanderidder, G.; Feijen, J., THE RING-OPENING POLYMERIZATION OF D,L-LACTIDE IN THE MELT INITIATED WITH TETRAPHENYLTIN. J. Appl. Polym. Sci. 1984, 29 (12), 4265-4277.
14. Kricheldorf, H. R., Syntheses and application of polylactides. Chemosphere 2001, 43 (1), 49-54.
15. Auras, R. A., Harte, B., Selke, S.; Hernandez, R., Mechanical, physical, and barrier properties of poly(lactide) films. J. Plast. Film Sheeting 2003, 19 (2), 123-135.
16. Huang, T., Yamaguchi, M., Effect of cooling

conditions on the mechanical properties of crystalline poly (lactic acid). J. Appl. Polym. Sci. 2017, 134 (24), 7.

17. Saeidlou, S., Huneault, M. A., Li, H.; Park, C. B., Poly(lactic acid) crystallization. Prog. Polym. Sci. 2012, 37 (12), 1657-1677.
18. Lopes, M. S., Jardini, A. L., Maciel, R., Poly (lactic acid) production for tissue engineering applications. In Chisa 2012, Kluson, P., Ed. Elsevier Science Bv: Amsterdam, 2012; Vol. 42, pp 1402-1413.
19. Chen, X., Kalish, J., Hsu, S. L., Structure evolution of alpha'-phase poly(lactic acid). Journal of Polymer Science Part B Polymer Physics 2011.
20. Di Lorenzo, M. L., Crystallization behavior of poly(L-lactic acid). Eur. Polym. J. 2005, 41 (3), 569-575.
21. Elsawy, M. A., Kim, K. H., Park, J. W.; Deep, A., Hydrolytic degradation of polylactic acid (PLA) and its composites. Renew. Sust. Energ. Rev. 2017, 79, 1346-1352.
22. Kale, G., Auras, R.; Singh, S. P., Comparison of the degradability of poly(lactide) packages in composting and ambient exposure conditions. Packag. Technol. Sci. 2007, 20 (1), 49-70.
23. Lucas, N., Bienaime, C., Belloy, C., Queneudec, M., Silvestre, F.; Nava-Saucedo, J. E., Polymer biodegradation: Mechanisms and estimation techniques. Chemosphere 2008, 73 (4), 429-442.
24. Auras, R., Harte, B.; Selke, S., An overview of polylactides as packaging materials. Macromol. Biosci. 2004, 4 (9), 835-864.
25. Qi, X., Ren, Y. W., Wang, X. Z., New advances in the biodegradation of Poly(lactic) acid. Int. Biodeterior. Biodegrad. 2017, 117, 215-223.
26. Lim, L. T., Auras, R.; Rubino, M., Processing technologies for poly(lactic acid). Prog. Polym. Sci. 2008, 33 (8), 820-852.
27. Fernández, J., Montero, M., Etxeberria, A., Sarasua, J.-R., Ethylene brassylate: Searching for new comonomers that enhance the ductility and biodegradability of polylactides. Polymer Degradation and Stability 2017, 137, 23-34.
28. Bedő, D., Imre, B., Domján, A., Schön, P., Vancso, G. J., Pukánszky, B., Coupling of poly(lactic acid) with a polyurethane elastomer by reactive processing. Eur. Polym. J. 2017, 97, 409-417.
29. Ghalia, M. A., Dahman, Y., Investigating the effect of multi-functional chain extenders on PLA/PEG copolymer properties. Int. J. Biol. Macromol. 2017, 95, 494-504.
30. Zhang, B., Sun, B., Bian, X. C., Li, G.; Chen, X. S., High Melt Strength and High Toughness PLLA/PBS Blends by Copolymerization and in Situ Reactive Compatibilization. Ind. Eng. Chem. Res. 2017, 56 (1), 52-62.
31. Kaynak, C., Meyva, Y., Use of maleic anhydride compatibilization to improve toughness and other properties of polylactide blended with thermoplastic elastomers. Polym. Adv. Technol. 2014, 25 (12), 1622-1632.
32. Liu, R., Dai, L., Hu, L. Q., Zhou, W. Q., Si, C. L., Fabrication of high-performance poly(L-lactic acid)/lignin-graft-poly(D-lactic acid) stereocomplex films. Mater. Sci. Eng. C-Mater. Biol. Appl. 2017, 80, 397-403.
33. Park, S. Y., Kim, J. Y., Youn, H. J.; Choi, J. W., Utilization of lignin fractions in UV resistant lignin-PLA biocomposites via lignin-lactide grafting. Int. J. Biol. Macromol. 2019, 138, 1029-1034.
34. Yoon, J. T., Lee, S. C., Jeong, Y. G., Effects of grafted chain length on mechanical and electrical properties of nanocomposites containing polylactide-grafted carbon nanotubes. Compos. Sci. Technol. 2010, 70 (5), 776-782.
35. Lyu, Y., Chen, Y. L., Lin, Z. W., Zhang, J. M., Shi, X. Y., Manipulating phase structure of biodegradable PLA/PBAT system: Effects on dynamic rheological responses and 3D printing. Compos. Sci. Technol. 2020, 200, 15.
36. Deng, L., Xu, C., Wang, X. H., Wang, Z. G., Supertoughened Polylactide Binary Blend with High Heat Deflection Temperature Achieved by Thermal Annealing above the Glass Transition Temperature. ACS Sustain. Chem. Eng. 2018, 6 (1), 480-490.
37. Wu, B. G., Xu, P. W., Yang, W. J., Hoch, M., Dong, W. F., Chen, M. Q., Bai, H. Y.; Ma, P. M., Super-Toughened Heat-Resistant Poly(lactic acid) Alloys By Tailoring the Phase Morphology and the Crystallization Behaviors. J. Polym. Sci. 2020, 58 (3), 500-509.
38. Wu, B. G., Zeng, Q. T., Niu, D. Y., Yang, W. J., Dong, W. F., Chen, M. Q., Ma, P. M., Design of Supertoughened and Heat-Resistant PLLA/Elastomer Blends by Controlling the Distribution of Stereocomplex Crystallites and the Morphology. Macromolecules 2019, 52 (3), 1092-1103.
39. Deng, S. H., Bai, H. W., Liu, Z. W., Zhang, Q.; Fu, Q., Toward Supertough and Heat-Resistant Stereocomplex-Type Polylactide/Elastomer Blends with Impressive Melt Stability via in Situ Formation of Graft Copolymer during One-Pot Reactive Melt Blending. Macromolecules 2019, 52 (4), 1718-1730.
40. Niu, X. F., Liu, Z. N., Hu, J., Rambhia, K. J., Fan, Y. B.; Ma, P. X., Microspheres Assembled from Chitosan-Graft-Poly(lactic acid) Micelle-Like Core-Shell Nanospheres for Distinctly Controlled Release of Hydrophobic and Hydrophilic Biomolecules. Macromol. Biosci. 2016, 16 (7), 1039-1047.
41. Zhang, X. J., Dai, Y., A Functionalized Cyclic Lactide Monomer for Synthesis of Water-Soluble Poly(Lactic Acid) and Amphiphilic Diblock Poly(Lactic Acid). Macromol. Rapid Commun.

2017, 38 (2), 5.

42. Kalelkar, P. P., Collard, D. M., Tricomponent Amphiphilic Poly(oligo(ethylene glycol) methacrylate) Brush-Grafted Poly(lactic acid): Synthesis, Nanoparticle Formation, and In Vitro Uptake and Release of Hydrophobic Dyes. Macromolecules 2020, 53 (11), 4274-4283.
43. Qi, L. Y., Zhu, Q. J., Cao, D., Liu, T. T., Zhu, K. R., Chang, K. X., Gao, Q. W., Preparation and Properties of Stereocomplex of Poly(lactic acid) and Its Amphiphilic Copolymers Containing Glucose Groups. Polymers 2020, 12 (4), 17.
44. C. Oerlemans., W. Bult., M. Bos., G. Storm., F.W. Nijsen., W.E. Hennink., Polymeric milcelles in anticancer therapy: targeting, imaging and triggered release, Pharm. Res.2010, 27 (12), 2569–2589.
45. G. Strohbehn., D. Coman., L. Han., R.R. Ragheb., T.M. Fahmy., A.J. Huttner., F. Hyder., J.M.Piepmeier., W.M. Saltzman., J. Zhou., Imaging the delivery of brain-penetrating PLGA nanoparticles in the brain using magnetic resonance, J. Neuro-Oncol. 2015, 121 (3), 441–449.
46. E. Fröhlich., E. Roblegg., Mucus as barrier for drug delivery by nanoparticles,J. Nanosci. Nanotechnol. 2014, 14 (1), 126–136.
47. J.J. Lochhead., R.G. ThornE., Intranasal delivery of biologics to the central nervous system, Adv. Drug Deliv. Rev. 2012, 64 (7), 614–628.
48. J. Cai., X. Peng., K.D. Nelson., R. Eberhart., G.M. Smith., Permeable guidance channels containing microfilament scaffolds enhance axon growth and maturation,J. Biomed. Mater. Res. A. 2005, 75 (2), 374–386.
49. F.A. Barber., D.A. Coons., Midterm results of meniscal repair using the BioStinger meniscal repair device, Arthroscopy 2006, 22 (4), 400–405.
50. J.H. Chang., H.C. Shen., G.S. Huang., R.Y. Pan., C.F. Wu., C.H. Lee., Q. Chen., A biomechanical comparison of all-inside meniscus repair techniques, J. Surg. Res. 2009, 155 (1), 82–88.