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REVIEW PAPER

Biodegradable poly(lactic acid)-based scaffolds: synthesis and biomedical applications

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Abstract Biodegradable polymers are identified as substantial materials for biomedical applications. These polymers have the ability to deteriorate through an unpretentious hydrolysis and eliminated through kidneys' functions or metabolic processes. Among widely used biodegradable polymers in biomedical applications, poly(lactic acid) (PLA) is becoming one of the most paramount polymers. Synthesizing PLA through melt/solution polycondensation polymerizations makes it relatively easy to tailor properties of final product. However, their synthesis reactions are affected by several parameters such as polymerization time, temperature, pressure, catalysts, and the polarity of the solvent. Moreover, equilibrium reactions are controlled through utilizing a hydrophilic monomer such as ethylene glycol (EG). These factors can strongly impact final properties of PLA. Thus, it is indispensable to comprehend the effect of operating parameters during the polymerization process. Optimizing synthesis conditions can be accomplished through reducing side reactions. Furthermore, this can be achieved through racemization by utilizing chain extenders to build high molecular weight and enhance thermal stability. In this review, the design and fabrication of porous PLA scaffolds and their physicomechanical behavior are reviewed. Different PLA scaffold parameters were investigated thoroughly, which include biocompatibility, biodegradability, and mechanical properties for different porosity and pore sizes to mimic the complex architecture of the natural tissue regeneration.

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Keywords Poly(lactic acid) · Polycondensation · Regenerative medicine · Chain extenders

Introduction

Recent developments in the synthetic biodegradable polymers have substantial interest for macromolecular science in both environmental and biomedical perspectives. One of the most important polymeric candidates is the biodegradable poly(lactic acid) (PLA) that is described as an aliphatic polyester. It is produced from the renewable resources of agriculture via combined fermentation and polymerization processes, and therefore, its production needs fewer fossil resources in comparison with petroleum-based polymers. In addition, PLA has recently attracted attention due to its excellent biodegradable and biocompatible properties. In particular, PLA has been utilized extensively in the field of biomedical with significant focus on applications in tissue engineering and drug delivery [1–4]. However, the PLA manufacturing cost is high, compared to the cost of petroleum-based polymers due to the complicated synthetic steps. Industrial production of PLA usually occurs through ring-opening polymerization of the cyclic lactide dimer, which is economically undesirable, and limits its widespread application.

In order to simplifying the synthesis procedures of high molecular weight (MW) PLA, and expand its applications, chain extending techniques have been developed in which the homopolymer or copolymer of the lactic acid (LA) monomer is used as a prepolymer. LA is mainly polymerized via direct polycondensation to produce low molecular weight prepolymer after which chain extenders are employed to increase the molecular weight. Diisocyanates have an effective way as an oligomer chain extender to modify and increase the molecular weight of biodegradable polymers. That includes

toluene diisocyanate (TDI), hexamethylene diisocyanate (HDI), and methylene diphenyl diisocyanate (MDI) [5]. Some disadvantages of these processes include toxicity and side reactions during the chain extending reactions and a final product with a high content of urethane that possesses lower thermal stability. These drawbacks will limit the range of applications for PLA. One way to overcome these disadvantages was through the incorporation of multifunctional compounds that are used as principle chain-linking agents. These compounds can react with either of the end groups: –OH group or –COOH group of PLA. An example is Joncryl ADR (styrene-glycidyl acrylate copolymer) which generally consists of three to nine epoxide groups. Joncryl ADR has been employed for polymers which are synthesized during the polycondensation processes in order to rebuild a highly branched form of PLA with high molecular weight that is produced from LA instead of lactide. These branched chains not only increase the molecular weight but also have superior properties in comparison with linear polymers [6–8].

PLA is a hydrophobic polymer that has methyl side groups. It is relatively more unaffected to hydrolysis in contrast with other biodegradable polymers as a result of the steric shielding effect on the methyl side groups. The ideal glass transition temperature (T_g) for typical trade PLA is between 50 and 60 °C. The tensile strength is about 32.22 MPa, and the elongation at break is approx. 30.7% [9]. The limitation of PLA is its brittleness and poor thermal stability. However, the mechanical properties and crystallization behavior of PLA are very dependent on the molecular weight and the stereochemistry of the backbone. To achieve superior mechanical strength, PLA should possess higher molecular weight [10].

The ring-opening polymerization (ROP) can be performed in solution or bulk melt. The bulk melt polymerization of lactide using several zinc complexes, such as zinc L-lactate and zinc stearate, and zinc salts, such as $ZnCl_2$, $ZnBr_2$, or ZnI_2, has been employed as catalysts and methanol as a cocatalyst in the absence of solvents [11]. Meanwhile, the ROP of lactide requires purification to eliminate undesirable materials from the final product, which needs complex chemical units [12]. The utilization of nontoxic chain extenders has the capability of increasing the molecular weight of PLA. There are two different methods to achieve a high molecular weight PLA. Firstly, it can be directly added to single/twin screw extruder during melt processing. Secondly, it is to employ direct melt polycondensation to treat a low molecular weight PLA with chain extenders. The properties of PLA obtained using these methods can be tailored to different operating conditions. Another way to increase the molecular weight of PLA is to synthesize the copolymer of two monomers (such as LA with ethylene glycol (EG)) which reacts through hydroxyl and/or carboxyl terminal groups. The copolymer is further interacted with a chain extender to achieve a high molecular weight and provide appropriate mechanical features [13]. In a relevant study, Ren et al. [14] reported a direct condensation polymerization method for the synthesis of high molecular weight PLA. It was described in a two-step prepolymerization, molt state process, and chain extension reaction. First, the LA monomer was oligomerized to gain a low molecular weight hydroxyl-terminated prepolymer. The molecular weight was enhanced via chain extension and could reach up to 30 kDa through direct polycondensation polymerization. The results showed that the obtained PLA has an inherent viscosity about 1.0 to 1.5 dl/g.

The demand for materials that possess suitable biocompatibility, biological safety, and biodegradability is growing throughout the world. Biodegradable PLA has been extensively used in modern pharmaceutical science for controlled–released, targeted drug delivery, and biological tissue engineering such as surgical structures, fracture splints, bone screws, meniscus-repairing material, and bioactive scaffold materials [15, 16]. It is essential that the PLA used in the pharmaceutical and medicinal fields does not contain or metallic and toxic ingredients. The use of octoate ($Sn(Oct)_2$) as a catalyst for PLA synthesis has been permitted by the Food and Drug Administration (FDA) [17, 18] to be utilized in synthesizing PLA for pharmaceutical and biomedical applications since it is less toxic for the human body. Thus, the recent developments of synthesizing a green PLA with a target to increase molecular weight are reviewed. Several parameters are additionally discussed which are associated with the influence of biocompatible, biodegradable, and mechanical properties on the final PLA-based scaffold for applications in regenerative medicine.

Biodegradable polymers

Biodegradable polymers can be classified into two main groups and four subgroups based on their method of preparation: stepwise polycondensation or ring-opening polymerization (Fig. 1). The first group consists of agro-polymers such as polysaccharides and proteins. The second group contains biodegradable polyesters, including PLA, polyhydroxyalkanoate (PHA), aliphatic polyesters, and aromatic polyesters [19, 20]. Biodegradable polymers exhibit a broad range of properties and can be replaced with non-biodegradable polymers in a different fields of applications such as biomedical applications, textile applications, and packaging applications. Among these polyesters, PLA is currently one of the most favorable biopolymers. PLA has been addressed in a plentiful literature with several reviews and book chapters throughout the last decade [21]. Aliphatic polyesters such as PLA, poly(3-caprolactone) (PCL), and poly(glycolide acid) (PGA) gained more attention due to their biocompatibility and biodegradability in the human body. A logical significance has been the introduction of inorganic and organic nanofillers into biodegradable polymers to synthesize nanocomposites relying on hydroxylapatite, carbon nanostructures, or metal nanoparticles

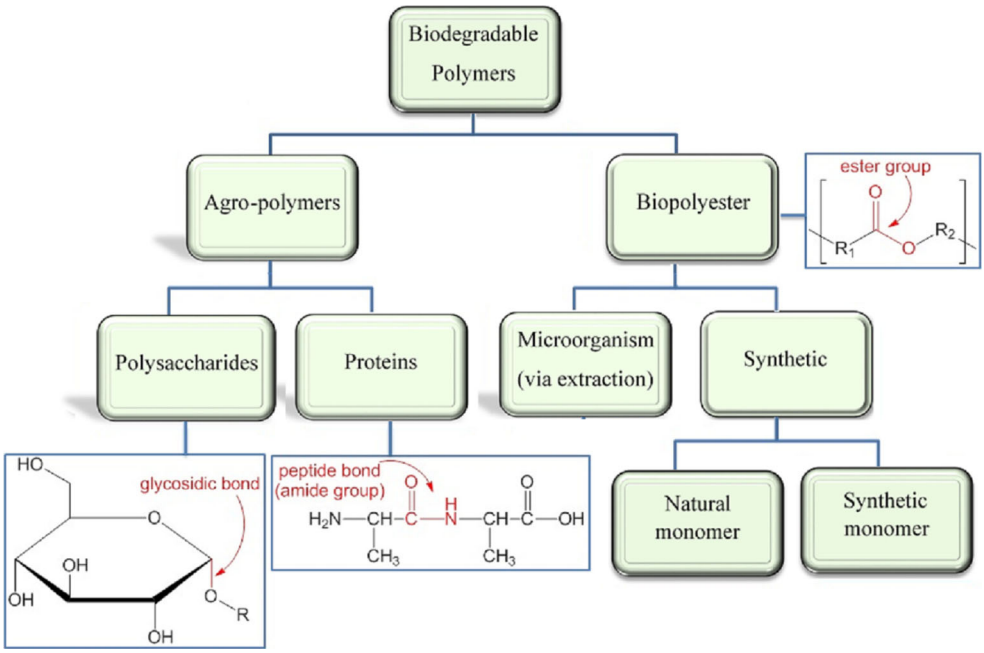

Fig. 1 Classification of the biodegradable polymers according to their method of preparation [22]

to formulate new classes of biomaterials with improved properties. Subsequently, the enhancement of interfacial adhesion between nanostructure polymers has become a key role in the nanocomposite method. There is no class of biodegradable polymer can be suitable for all the needs of biomedical scaffolds. However, before being chosen for any biomedical implementation, a biodegradable polymer requires significant examination of its synthesis, interaction method, and compatibility with the human body. Currently, both natural and synthetic polyesters are considered the best entirely developed class of biodegradable polymers [22].

Classification of biodegradable polymerizations

Biodegradable polymers can be synthesized by some methods including melt/solution direct condensation polymerization, ROP, and metal-catalyzed polymerization. A broad range of organometallic initiators has been used to start the polymerization of biodegradable polymers, including tin, zinc, and aluminum complexes. The most preferred initiator is tin(II) octanoate, and it has been approved in small quantities by the FDA. However, there are still concerns about applying the tin catalysts in the synthesis of a biodegradable polymer for biomedical applications in comparison to a green solvent and less toxic catalyst [23]. Different types of polymerization reactions are described below.

Ring-opening polymerization to form biodegradable PLA

PLA with high molecular weight is exclusively produced by the ROP of the corresponding cyclic monomer using a metal catalyst. The terminal end of the PLA chain acts as the reactive center, and further cyclic monomers are reacted by opening the ring system (e.g., epoxy polymerization) to produce a longer PLA chain. The mechanism of metal alkoxide-mediated lactide is designed to be a coordination–insertion method in which the Lewis acidic metal reacts to the ester carbonyl, boosting its electrophilicity through attacks on the carbonyl carbon and producing a tetrahedral intermediate. This fails by breaking the acyl carbon–OR bond in the ring (Fig. 2). The $Sn(OR)_2$ or (Oct)Sn(OR) acts as an initiator. The Sn(II) complex activates and coordinates each monomer unit. The process is intramolecular, and the coordination–insertion mechanism of ROP lactide is comparable to that of a transesterification process. These green characteristics of biodegradability and renewability of PLA open doors for different applications in the biomedical field as a biomaterial [24].

Step-growth polymerization (esterification reaction)

According to the biotechnological pathways shown in Fig. 1, synthetic polymers (i.e., PLA) are mainly produced in step-growth polymerization, which is different from chain-growth polymerization. The principle of step-growth polymerization is based on the type of functional groups that are involved in the polymerization process. Step-growth polymerization is a condensation reaction between two and more different functional groups existing in the monomers. Ethyl acetate is synthesized in the industry generally via the classic Fischer esterification process of acetic acid and ethanol. This turns to the ester group in about 65% yield at room temperature [25]. However, to synthesize polyester by step-growth polymerization, each monomer must have at least two functional groups (i.e., OH) to form a dimer with an ester bond, which is

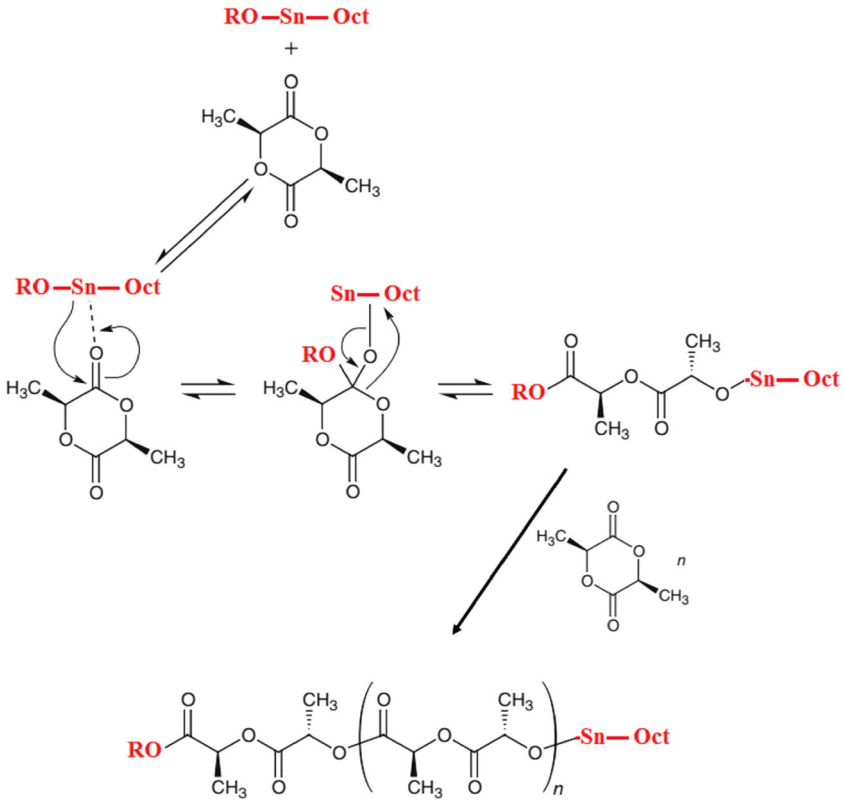

Fig. 2 Schematic ionic propagation for ring-opening polymerization [24]

followed by the reaction of the same groups to form a trimer till the final polyester is created. This reaction takes up a longer polymerization time to achieve the desirable polymer.

Polymerization of polyester

Polyester polymerization is a systematic process where the monomers consist of two reactive functional groups with other side functional groups, and consequently, the linear chain polymerization can be created. Alternatively, when the chemical reaction includes monomers with more than two functionalities, cross-linked or branched polymers might be formed. This type of polymerization is called polyesterification reaction. It mainly occurs between a dicarboxylic acid and a diol and includes water elimination and formation of a polycondensation product [26]. Most of the step-growth polymerizations produce small molecules (e.g., H_2O, NaCl, HCl) in the form of byproducts, called "condensation polymerization." These chains of repeating units combine to form the ester linkages.

Poly(lactic acid)

PLA is mainly produced either from the LA monomer during the fermentation processes of natural resources (corn, wheat) or as petrochemical derivatives under different routes of polymerization. The degradation products of PLA, specifically water and carbon dioxide, are neither carcinogenic nor toxic to the human body.

Lactic acid (monomer)

Lactic acid (2-hydroxypropionic acid) is defined as a type of chiral molecule that consists of two enantiomers, D- and L-LA, which are different under the influence of polarized light. The optically ineffectual L, D, or meso create is an equable (racemic) mixture of $L_{(+)}$ and $D_{(-)}$ isomers. It is described as the monomer that has a high potential for chemical transformations since it consists of a hydroxyl group and a carboxylic group. The manufacture of LA has significant worldwide demand because it is used in a broad range of applications in pharmaceutical, food, leather, textile, and chemical substances. The most important application of LA is being used as a monomer in the synthesis of biodegradable (PLA) [27]. LA can be metabolized by the human cells in an assortment of ways: it can be used as an energy substrate, and it can penetrate the lipid membrane due to its uncharged character and small size. Furthermore, lactate can enter cells through the monocarboxylate transporter (MCT) at certain transport processes [28]. After being inside the cell, lactate is turned into glucose and is used as an energy alternative for the Cori cycle. In addition to its main factor as an

energy substrate for cells, LA has been proven to be used as an antioxidant to preserve cells from getting destroyed by the free radicals which are naturally generated during the cell's life cycle [29]. LA can be synthesized by either fermentation or chemical process. It is mainly dependent on the hydrolysis of acetonitrile by a strong acid when the racemic mixture changed to LAs and $L_{(+)}$ and $D_{(-)}$ are produced (Fig. 3a). The biotechnological method involving LA has received a lot of interest. This process has a significant impact on the environment since it is made from sugarcane fermentation and thus involves lower production cost. It has several advantages, such as reduced fossil-based feedstock reliance, decreased CO_2 emissions, biocatalyst usage, high productivity [30], and production of optically pure D- or L-LA, depending on the strain chosen. About 90% of the total yield of LA worldwide is prepared by bacterial fermentation while the other portion is achieved synthetically through the hydrolysis of acetonitrile. The petrochemical patterns of monomer production were predominant till the year 1990 when a suitable commercial fermentation method was established. The fermentation processes of LA are described to be consistent with the type of bacteria employed. In the fermentative process, equal amounts of LA, acetic acid, carbon dioxide, and ethanol are produced from hexose. The fermentation method of hexose metabolism has the potential to yield LA [31–33].

Polymerization routes for PLA

The lactic acid has hydroxyl and carboxyl functional groups that react with difunctional groups and produce polyesters through a polycondensation reaction. Nevertheless, the traditional condensation process of LA does not have the capability to increase the molecular weight completely except if organic solvents are employed in the azeotropic distillation of water condensation, in which case, the polymerization process takes a long time. The yield of the conventional condensation reaction of LA produces a fragile glassy polymer that is not usable for plastic applications [34, 35]. Therefore, the most appropriate method to produce PLA with higher molecular weight is via the ROP of lactide [36–38]. The polymer scientific researchers proposed this two-step process, which produced a high molecular weight PLA. The intermediate, a cyclic LA dimer, lactide is created in the first step while the side product (water) is eliminated via evaporation throughout oligomerization. D-LA, L-LA, or together can be polymerized to a conforming low molecular weight PLA oligomer. The latter is then depolymerized by a transesterification reaction. Throughout depolymerization, three stereo forms of lactide are prospectively achieved: L-lactide, D-lactide, and meso-lactide. In the second method, a purified D-lactide, L-lactide, DL-lactide (50:50 of D- and L-isomers), or meso-lactide is turned into the corresponding high molecular weight polyester by catalytic ring-opening polymerization (Fig. 3b). The ROP has been obtained as

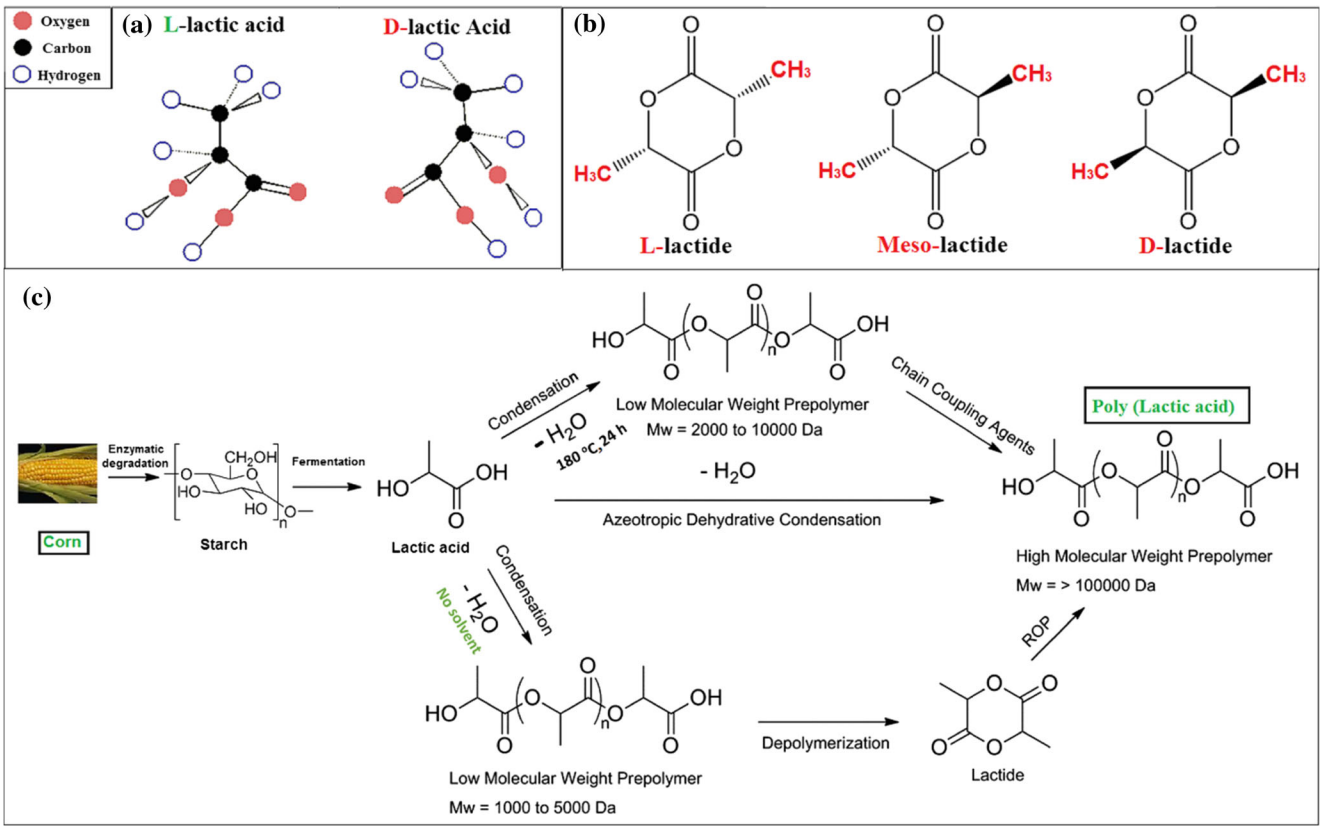

Fig. 3 (**a**) The stereoisomers of LA. (**b**) Chemical structures of dimeric D-lactide, L-lactide, and meso-lactide. (**c**) Synthesis methods of PLA

bulk, melt, emulsion, or solution polymerization by using $Sn(Oct)_2$ as an initiator and propargyl alcohol as a co-initiator. Based on the initiator and co-initiator system, the ROP is conducted by an insertion–coordination, cationic, anionic, active hydrogen, zwitterionic, or free radical polymerization.

As clearly shown in Fig. 3c, ROP is a key role to obtain high molecular weight [39]. This process achieved through opening the cyclic dimer (lactide) in the existence of a catalyst. The polymerization proceeds in three steps: condensation reaction, depolymerization, and ROP. This process requires further steps of purification, which are comparatively expensive and complicated. The catalytic ROP of the lactide intermediate produces PLA with controlled molecular weight [40]. By controlling temperature and residence time associated with catalyst activity and concentration, it is possible to manipulate the ratio and arrangement of L- and D-LA units in the final PLA. In general, the synthesis of lactide via ROP requires several complicated steps to tailor the PLA properties. An alternative method to obtain a high molecular weight PLA is to react in the polycondensation process with chain extenders [41]. Chain extenders are generally a bifunctional group with low molecular weight compounds, which increases the molecular weight of biopolymers in a rapid reaction [42]. The chain extender for PLA can be suitably and economically achieved in an extruder when the reaction rate is high [43]. Several researchers have extensively studied hydroxyl-reactive and carboxyl groups with different types of chain extenders to produce appropriate polyesters. In the aliphatic polyester, the hydroxyl end group normally links with the carboxyl end group. The carboxyl-reactive group appears to be further advantageous due to the decrease of the acid amount, which results in enhanced thermal stability and, subsequently, an increase in molecular weight of PLA. However, hydroxyl end groups are sometimes influenced by the carboxyl end groups as a result of comparatively low molecular weight PLA particularly when it is synthesized via the melt polycondensation process. Hence, a hydroxyl-reactive chain extender has an effective way of increasing molecular weight [44].

Chain extension has the capability to obtain the high molecular weight of PLA based on the polycondensation conditions. Gu et al. [45] reported a high molecular weight PLA that was completely synthesized in two stages. First, the LA was oligomerized to produce a low molecular weight hydroxyl-terminated PLA, and then the molecular weight was elevated by using a chain extender, 1,6-hexamethylene diisocyanate. The outcomes demonstrated that the molecular weight of PLA reached to 116.9 kDa at 180 °C and after 40 min of adding the chain extender.

Synthesis of PLA via condensation polymerization

The main advantage of synthesizing PLA via polycondensation of LA is that it is an easy process applied to produce PLA through a bifunctional monomer that undergoes self-esterification through a reversible step-growth polymerization mechanism. Furthermore, the PLA can be synthesized in the absence of solvent, which is essential for further applications as a biomaterial. In this mechanism, PLA chains react together and lead to longer chains with water as a byproduct. Water should be eliminated from the polymerization reacting with the purpose of shifting the chemical equilibrium to the right and enhancing the polycondensation reaction. Water removal is a key aspect that limits the extent of the reaction and, thus, the polymer's molecular weight. Due to the increase in viscosity during polymerization, water removal efficiency decreases and only low molecular weight polymers can be produced by polycondensation. Moreover, several aspects are considered, such as reaction temperature, pressure, concentration, the addition of a catalyst, and the role of water mass transport [46]. A wide variety of metal-based catalysts, such as tin and Zn compounds, are substantially effective in enhancing the polycondensation of LA. An additional consideration is in regard to the possible discoloration of the final polymer. During polycondensation, PLA undergoes side reactions leading to discoloration from yellow to brown and, in the end, to black. These side reactions occur specifically at high reaction temperatures and high reaction times but are still not well known. The addition of cocatalysts, such as the *p*-toluenesulfonic acid (TSA) is reported to be more efficient than single metal catalysts regarding molecular weight achieved and the effective prevention of the polymer discoloration [47]. The LA polycondensation was investigated with different catalysts: non-metallic and metallic, inorganic and organic, and heterogeneous and homogeneous as shown in Table 1. These results found out that chloride and tin oxide were principally useful in increasing the molecular weight of poly(L-lactic acid) (PLLA) among the metal oxide and metal catalysts considerably adopted for regular esterification reactions, despite the PLLA yield was fairly low. The activity of both the chloride and tin oxide was practically identical when it was carried out in the polycondensation reaction. The equilibrium reaction between the pressure and reaction temperature was also essential for controlling the evaporation of L-lactide that was formed in symmetry with PLLA. A high molecular weight PLLA (molecular weight ≥100 kDa) was obtained by the melt polycondensation of LLA with an existence of Sn(II) catalysts initiated via proton acids in a short reaction time. Moreover, the polycondensation process was carried out in above melting temperature of PLLA at low pressure. The PLLA yield converted approximately 60% of the initial L-LA due to the vaporization of lactide that formed through the ring L-lactide and PLLA chain equilibrium.

Liu et al. [48] attempted to produce high molecular weight by direct polycondensation followed by a chain extender with HDI. PLA prepolymer with a viscosity average molecular weight (M_{η}) of 2×10^4 Da was synthesized from L-lactide using $Sn(Oct)_2$ as the catalyst. After 20 min of adding the

Table 1 Various types of catalyst used in direct polycondensation [47]

Run	Catalyst	Catalyst/OLLA (wt%)	Temperature (°C)	Time (h)	Pressure (Torr)	MW (g/mol)	Yield (%)
1	GeO_2	0.8	180	20	10	28,000	73
2	Sb_2O_3	0.1	200	30	20	20,000	25
3	ZnO	0.1	200	30	20	36,000	35
4	Fe_2O_3	0.1	200	8	1	20,000	23
5	Al_2O_3	8.5	200	30	20	27,000	42
6	SiO_2	0.8	180	20	10	11,000	58
7	TiO_2	0.8	180	20	10	11,000	64
8	SnO	0.2	180	20	10	50,000	36
9	$SnCl_2{\cdot}2H_2O$	0.4	180	20	10	41,000	43
10	TSA	0.34	180	10	10	17,000	70

OLLA oligomer lactic acid, *TSA* toluenesulfonic acid

chain extension under 175 °C, the resulting prepolymer had M휂 of 20.3×10^4 g/mol.

Synthesis of prepolymer from lactic acid and ethylene glycol

Poly(ethylene glycol) (PEG) is considered as a biodegradable polymer with no reported toxic records [49]. PEG is synthesized by the oxidation of ethylene in the presence of oxygen to form ethylene oxide under an exothermic polymerization. The molecular weight obtained is in the range from 1 to 20 kDa, and PEG will either be in liquid form or wax. Also, the crystalline polymer has a T_g range of 60 to 75 °C. The water solubility and T_g are both functions of the molecular weight. The higher the molecular weight achieved molecularly, the lower the solubility of the PEG [50]. PEG can be dissoluble in benzene, alcohol, acetone, and chloroform. Presently, PEG is used as a binder, carrier, lubricant, and coating in the pharmaceutical, food, and textile industries. In PEG/PLA blends, PEG is used to improve the PLA hydrophilicity and to increase its degradation rate and the rate of drug release. Furthermore, PEG/PLA blends exhibit better strength with lower deformity than neat PLA, and the PEG functions as a plasticizer for PLA. PEG/PLA blends can be produced either by melt blending or solvent casting. Kim and Kim [51] reported that the solvent casting technique consists of more than 20 wt% of polymer that can be crystallized, and the resulting blends are semi-miscible. The PLA/PEG blend degradation was apparently more than that of pure PLA. When the PEG quantity was equivalent or lesser than 30 wt%, mass loss occurred mostly because of the enzymatic degradation. With more than 30 wt% of PEG, the mass loss principally happened due to the PEG dissolution. Hiltner et al. [52] stated that the low PEG content in the PLA/PEG blends led to an accelerated hydrolysis process (buffer solution at pH 7.4 and 37 °C).

A recent study of Junjie et al. [53] prepared the PLA/PEG/PLA triblock copolymer and PLA/PEG diblock in the presence of acryloyl groups at PEG end chains and PLA chains, respectively. These PLA/PEG copolymers can create micelles in aqueous solution throughout self-assembly with a hydrophilic PEG shell and hydrophobic PLA core. Furthermore, the PLA/PEG, SCL micelles, PLA/PEG/PLA, and core cross-linked (CCL) micelles were synthesized by chemical cross-linking and photo cross-linking, to improve the stability of micelles. The structure of PLA/PEG shell-cross-linked micelles and PLA/PEG/PLA core-cross-linked micelles is illustrated in Fig. 4. These forms are essential for controlled hydrophobic drug release.

Factors affecting the properties of PLA

Various factors of synthesis conditions can dramatically affect the performance of PLA, such as the catalyst mechanism during polymerization of PLA, the polarity of the solvent, the isomeric purity, and the incorporation of multifunctional groups of chain extenders to enhance molecular weight. The sensitivity of these factors can impact the molecular weight and, consequently, the mechanical properties of PLA.

Effect of solvent in polymerization of PLA

PLA has high solubility in solvents such as chloride, benzene, methylene, chloroform, and dioxane. Each solvent affects the film properties of the PLA. Solvents such as chloroform induce a greater PLA chain mobility. Moreover, dioxane induces a tough surface to form because of the slow evaporation rate. PLA film cast with acetone, toluene, and ethyl acetate exhibited an enhanced surface segregation and hydrophobicity [54]. However, the hydrophilicity of LA shows a different behavior with solvents. Zhang et al. [55] reported that the compounds of rare-

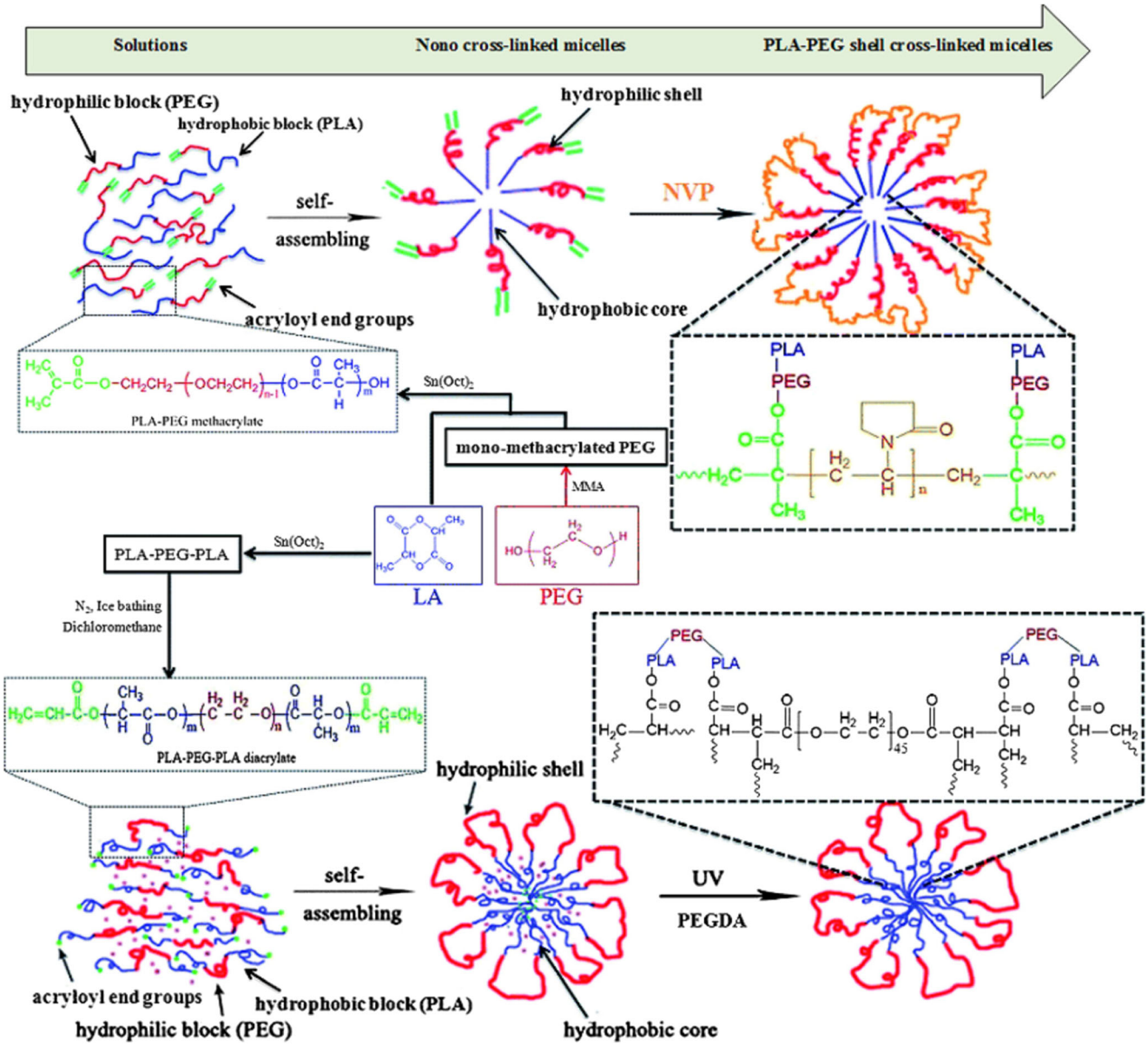

Fig. 4 Schematic structure of PLA blends with PEG shell-cross-linked micelles and PLA/PEG/PLA core-cross-linked micelles [53]

earth 2,6-dimethyl-aryloxides are successful initiators for the ROP. PLA with a molecular weight about 4.5 × 104 g/mol and over 90% yield can be obtained with $Ln(ODMP)_3$ as an initiator at 100 °C in a 45-min polymerization reaction. Table 2 shows the effect of solvent polarity on lactide polymerization. The LA monomer converting and resulting molecular weight of PLA in the presence of THF and chloroform is lower compared to toluene. It proves that polar solvents are not useful for the lactide polymerization with 2,6-dimethylaryloxide ($Ln(ODMP)_3$). This is similar to the coordination mechanism. It has been proved that the conversion and molecular weight of PLA could be tailored simply via varying monomer concentration, and the molar ratio of monomer to initiator, in addition to polymerization temperature and time [56]. Therefore, it is clear that solvent has the capability to change PLA properties by changing its crystallinity.

Table 2 Effect of solvent on the polymerization of PLA [56]

S/No.	Solvent	$Ln(ODMP)_3$[a]	Conversion (%)	$Mv^b \times 10^4$
1	Toluene	La	97.2	4.51
2	Chloroform	La	50.0	1.47
3	THF	La	79.4	3.58
4	Toluene	Sm	79.4	3.58
5	Chloroform	Sm	41.7	1.56
6	THF	Sm	32.5	1.13

Reaction conditions: [LA] = 2.0 mol/l, [LA]/[Ln] = 1000, at 100 °C, 45 min; La and Sm are block element compounds

[a] 2,6-Dimethylaryloxide

[b] Viscosity average molecular weight

Effect of catalyst on synthesis of PLA

LA polycondensation in the existence of a tin catalyst and reduced pressure were found to produce PLA of no more than 10 kDa. Alternatively, the binary catalyst such as $SnCl_2$/*p*-TsOH demonstrated the relatively high molecular weight of 16 kDa within 30 min under a vacuum of around 30 mmHg. It has been shown (Table 3) that the two catalysts comprised of metal compounds activated with proton acids that are more efficient than a single metal compound [57]. The two catalysts are effective catalysts to obtain PLA with high molecular weight. The reaction system polarity significantly altered the progress of the polycondensation, resulting in a great deterioration of catalyst activity. Thus, TSA as a catalyst is usually added to further catalyze the second step, polycondensation (oligomerization), after the completion of the first step of melt polycondensation [58].

The PLA is either divided into two stereo forms or a combination of various ratios [59]. One of the drawbacks of direct polycondensation is that a low molecular weight PLA shows deterioration in mechanical properties followed by an increase in the melt elasticity at higher temperature condition. Until 1995, it was evident that a large molecular weight of PLA is difficult to achieve by the direct polycondensation due to the ester linkage and the activated hydrated form, which require a long time to obtain high molecular weight. Nevertheless, recent reports proved that the stannous octoate obtained a reasonable molecular weight for a short polymerization time.

Selection of catalyst

A selection of catalysts for PLA synthesis should be appropriate for targeted applications. Several investigators reported the impact of catalysts used for the prepared PLA [60]. They have either employed catalysts synthesized from transition metal substances or a combination that contains transition metal substance accompanied by protonic acid as a cocatalyst, as presented in Table 4. Tin compounds possess significant effectiveness to produce a high molecular weight PLA [61]. Inorganic tin compounds are proved to be less toxic than tin(IV) compounds and organic tins, as shown in Table 4. Hence, inorganic tin is a better selection as a catalyst when compared to organic tin. It is important to note that toxicity rises because of increasing tin concentrations. Tetraphenyl tin is a catalyst permitted by the FDA and thus can be employed safely for the synthesis of PLA for biomedical applications. A few reports investigated the effects of binary catalysts. The results demonstrated that stannous octanoate is one of the most efficient catalysts used to produce PLA molecular weight with high yield. Nonetheless, as many other catalysts, it is still relatively uneasy to eliminate the catalyst from the PLA, which results in cytotoxicity, thus restricting its application. On the other hand, some researchers have incorporated metal–salen Schiff base complexes as an initiator for ROP [62], and no results have been recorded in the literature for the utilization of other catalysts in polycondensation polymerization. It can be seen in Table 4 that the tin metal, tin oxide, $Ni_{(II)}$, and $tin_{(II)}$ halide produce a high molecular weight PLA. Apparently, substituted distannoxane catalysts are considerably hydrophobic due to the bulky alkyl groups coordinated with the tin atoms and, thus, it can act as tolerant catalysts. Tin atoms used in the catalytic centers led to delayed hydrolysis of ester linkages to an extent. Studying variations of substituents (X = Cl, R = n − Bu, NCS, OH) on the distannoxane ladder structure, it was reported that the molecular weight of synthesized PLA is comparatively unresponsive to the nature substituents [63].

Table 3 Effect of catalyst on the polymerization of PLA [58]

Catalyst	Reaction time (h)	Yield	Molecular weight (kDa)	Color
p-Toluenesulfonic acid	20	80	14.4	Medium
Sb_2O_3	27	93	48	Medium
SnO	20	80	16.7	Poor
Sn	16	85	35	Poor
Stannous octoate	12	71	48	Medium
Dibutyl tin oxide	20	60	12	Medium
Tetraphenyl tin	71	80	17	Medium
$SnCl_2{\cdot}2H_2O$ (0.5), TSA (0.4)	24	82	57	Good
Titanium isopropoxide	55	85	37	Poor
$Zr(OBu)_4$	20	70	14.2	Medium

Stannous octoate for polymerization of PLA

Growing interest in the synthesis of sustainable biodegradable PLA has alerted scientific awareness in deeply considering the mechanisms and kinetics of lactone polymerization, especially the role of the controlling a catalyst employed in the

Table 4 Molecular weights of PLA synthesized with different catalysts [73]

Catalyst	Molecular weight		
	10^4	10^5	10^6
Protonic acids	H_3PO_4 Nafion	H_2SO_4 MSA	*p*-TSA
Metal compounds Metals	MgTiAl	Zn	Sn
Oxides	Ge(IV)Zr(IV)	Zn(II)	Sn(II)
Halides	Cu(II)Al(III)	Zn(II)	Sn(II)
Organic acid salts Others	$Al(PrO)_3$	Mn(II)Zn(II) $Ti(BuO)_4$	Fe(II)Sn(II)Ni(II)
Binary catalyst		Sn(II)-*p*-TSA	

reactions. Stannous octoate (SO) is considered as one of the most useful catalysts, selected for lactone polymerization due to a variety of causes, primarily for the little toxicity, low cost, and high efficiency. The recent patent by Aminuddin and Belcheve [64] reported the use of stannous octoate surface-induced ring-opening polymerization for medical device applications. There are two fundamental types of mechanisms that have been suggested. The first mechanism uses a direct catalyst type [65–67], where the catalyst assists to initiate a monomer by coordination with regards to the carbonyl oxygen. In this type, catalysis uses stannous octoate as the initiator and propargyl alcohol as the co-initiator, and lactide coordinates with the tin atom of the catalyst to generate a stannous oxide bond. In the second mechanism, Kowalski et al. [68] and Duda et al. [69] published a kinetic mechanism that strongly suggests that SO acts as a co-initiator and lauryl alcohol (1-dodecanol) is added as an initiator during lactide polymerization. It has occurred through stannous alkoxide excite centers originated by the reaction from stannous octoate with an alcoholic initiator. In particular, the system involves a caprolactone as a monomer in tetrahydrofuran at 80 °C. In previous work by Hans and Kricheldorf [70], they used the direct spectroscopic indication of tin that is covalently linked to the PLA chain end and the mechanistic focus on the interaction of various alcohols and alcohols/ester with a catalyst such as stannous octoate. The mechanism of the functional group can affect the activation of the catalyst–alcohol interaction. Later, Kricheldorf et al. [71] described how the chemical structure of the initiator impacts the activation of the alcohol–catalyst interaction. Per their analysis, this mechanism in the first steps of the reaction handles the creation of the initiator species, followed by the ring opening and the formation of the propagating chain end. As presented in Fig. 5a, the functional hydroxyl linked with SO to form a free 2-ethylhexanoic acid and a stannous alkoxide species.

Additional reaction with alcohol forms the stannous dialkoxide initiator and releases 2-ethylhexanoic acid with undesirable water, as shown in Fig. 5b. In the meantime, the catalyst deactivates through a reversible reaction, thus reducing the initiator concentration and generating a stannous alcohol; see Fig. 5c. The stannous alcohol derivative has been proven to be more thermodynamically stable than the stannous dialkoxide and less efficient as an initiator. The interaction of ethylene glycol with SO in Fig. 5d is particularly strong due to the subsequent five-member cyclic compound that is kinetically preferred compared to the six-member cyclic compound. Also, several parameters have a significant impact on polycondensation conditions. Recent progress has been made in achieving a high molecular weight PLA via sequential melt/solid polycondensation. Table 5 summarizes the potential advantages and drawbacks of the different synthesis methods [72].

Chain extender for PLA

PLA biodegradable polymers have several advantages, mainly for being renewable and degradable while their products are compostable. The degradation ability of synthetic PLA in a controlled manner was developed for environmental purposes in the late 2010s [73]. Utilizing PLA in biomedical applications rapidly grew. Research still attempts to design novel materials that could be tailored to the specific needs and properties required by various applications. However, it is hard to achieve a very high molecular weight PLA with relatively high melt strength. There are limitations such as its inherent brittleness and low thermal stability. Processing techniques, where melt strength is an essential parameter, include sheet thermoforming extrusion, injection blow molding, film blowing, profile extrusion, extrusion blow molding, and sheet foam extrusion mostly combined with thermoforming. The addition of chain extender resin builds a higher molecular weight of the resulting PLA bioplastic [73].

Utilization of chain extenders for PLA

Chain extension is a method to build a higher molecular weight of polymer chains. This can be achieved in post-polymerizations, which can be either in the terminal polymerization processing step, during compounding extrusion, or injection molding of the final product. Likewise, properties and structure of PLA can be

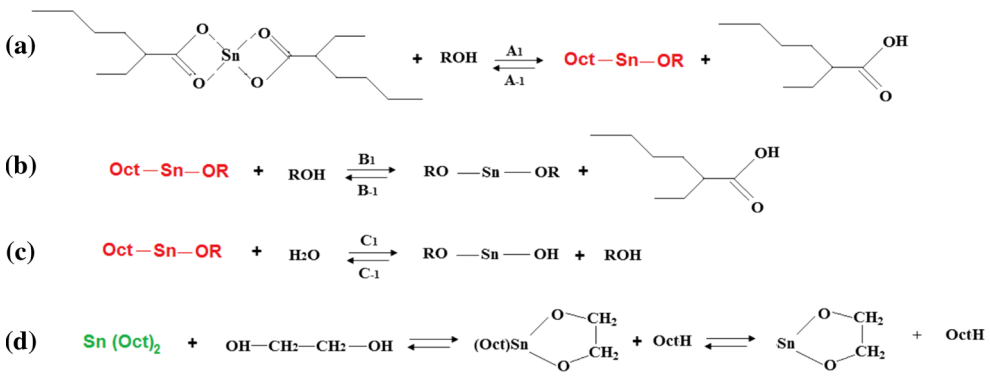

Fig. 5 Reaction mechanism of initiation induced by polymerization of stannous octoate, including (**a**, **b**) creation of initiator (stannous alkoxide), (**c**) deactivation of the catalyst caused by the water, and (**d**) interaction of stannous alkoxide with ethylene glycol

Table 5 Variation of operating parameters on output variables during the synthesis of PLA under different polymerization conditions

Amount of monomer	Parameters					Output		Ref	Remarks
	Reaction (h)	Temp (°C)	Catalyst	Pressure (Pa)	Monomer	Yield (%)	Molecular weight (Da)		
NA	10	170	$SnCl_2$ (0.5 wt%	70	D,L-LA	NA	4100	[72]	
NA	12	180	$SnCl_2$/*p*-TSA	1333.3	L-LA	42	30,000	[71]	BC was more efficient than the MP used
NA	30	177	Naphthalenesulfonic	101.325	D-LA	NA	33,300	[78]	SPM was used
NA	40	180	$Ti(OBu)_4$	133.3	L-LA	NA	1.3×10^5	[70]	DPM was used
10 g	23	160	Sn(II)Oct	1333.3	D,L-LA	80	8.2×10^3	[73]	MP was used
			$Al(O_4Pr)_3$	1333.3	L-LA	13	2.7×10^4	[74]	
			$Ti(O_4Pr)_4$	1333.3	L-LA	38	5.7×10^4		BC and MP were used
			$Si(OEt)_4$	1333.3	L-LA	78	2.2×10^4		
			$Ge(OEt)_4$	1333.3	L-LA	65	3.7×10^4		
30 g	24	150	NA	NA	D,L-LA	NA	1×10^5	[75]	MP was used
36.2 g	20–40	140	Sn powder (0.14 g)	NA	L-LA	NA	1.4 × 105	[79]	DPM was used
200 g	14	180	$SnCl_2$/*p*-TSA	1333	L-LA	67	1×10^5	[76]	MP and BC were used
1000 ml	30	170	Sn(II)Oct at 0.05	101.325	L-LA	NA	1.6×10^4	[77]	MP was used

BC binary catalyst, *MP* melt polycondensation, *SPM* solution polycondensation method, *DPM* direct polycondensation method, *LA* lactic acid, *TSA* toluenesulfonic acid, *Sn(II)Oct* stannous octanoate, *NA* not available

controlled through the improvement of the molecular weight by reacting molecular units of oligomers with a considerable reactive monomer content. The most commonly used chain extenders are diisocyanates, such as TDI and 1,6-hexamethylene diisocyanate (HMDI) [74]. Despite the higher molecular weight that PLA can reach, the chain extension reaction of PLA is uneasy to control. Furthermore, the polymers treated by diisocyanates cannot be employed in biomedical fields because of the harmfulness of diisocyanates. Experimentation with the polymerization process, including modification treatment and biodegradation rate of poly(ester-urethanes), has demonstrated that the LA-based low molecular weight PLA can be incorporated with other different chain extender groups. The chain extenders include the epoxy group, which can react with both hydroxylic and carboxylic (–OH and –OOH) end groups. The chain extenders studied in the literature are difunctional such as –COOH/isocyanate, –COOH with an amine, –OH with pyromellitic dianhydride (PMDA), –OH/–COOH, and –OH with triglycidyl isocyanurate (TGIC). The first experiment of chain extension with PLA was carried out with a diisocyanate substance [75]. The difunctional groups have restricted properties, and these substances have limited uses because of its high volatility and toxicity. Lately, a multifunctional styrene acrylic random oligomer (Joncryl) has been offered as a chain extender material for PLA during an extrusion process [76, 77]. In a recent study, Al-Itry et al. [78] presented an enhancement in the thermal properties of PLA by using a single/twin extruder with various quantities of multifunctional epoxides, thus, to improve the mechanical properties and viscoelastic. In this case, the functional groups can interact with either –COOH or –OH of PLA. This leads to a high molecular weight PLA with relatively branched chains, while less cross-linking of PLA might be obtained when less than 2 wt% of multifunctional groups are used [79]. The branched PLA has an effective way to increase molecular weight and tailor different properties of PLA compared to the linear PLA.

Reaction mechanism of PLA and multifunctional groups

Chain extenders are useful compounds used to reconstruct chain scission reactions that occur from the degradation during bulk polycondensation. In Fig. 6(A), the epoxide groups can theoretically react with both –COOH and –OH groups of the PLA. In Fig. 6(B), the styrene acrylic multifunctional groups appear to react specifically with –COOH and –OH groups [78–80]. In the case of PLA, esterification reactions of –COOH end groups precede –OH end group etherification. This latter reaction contends with the etherification of second OH groups and the central chain transesterification. The resulting couplings include ring-opening epoxide reactions and the formation of covalent bonds through hydroxyl side group creation.

Effect of chain extender on PLA properties

In a recent study by Dong et al. [81], two chain extenders—Joncryl (ADR-4370) and 1,6-hexanediol diglycidyl ether (HDE)—reacted with PLA and poly(butylene adipate-*co*-terephthalate) (PBAT) was studied. The influence of chain

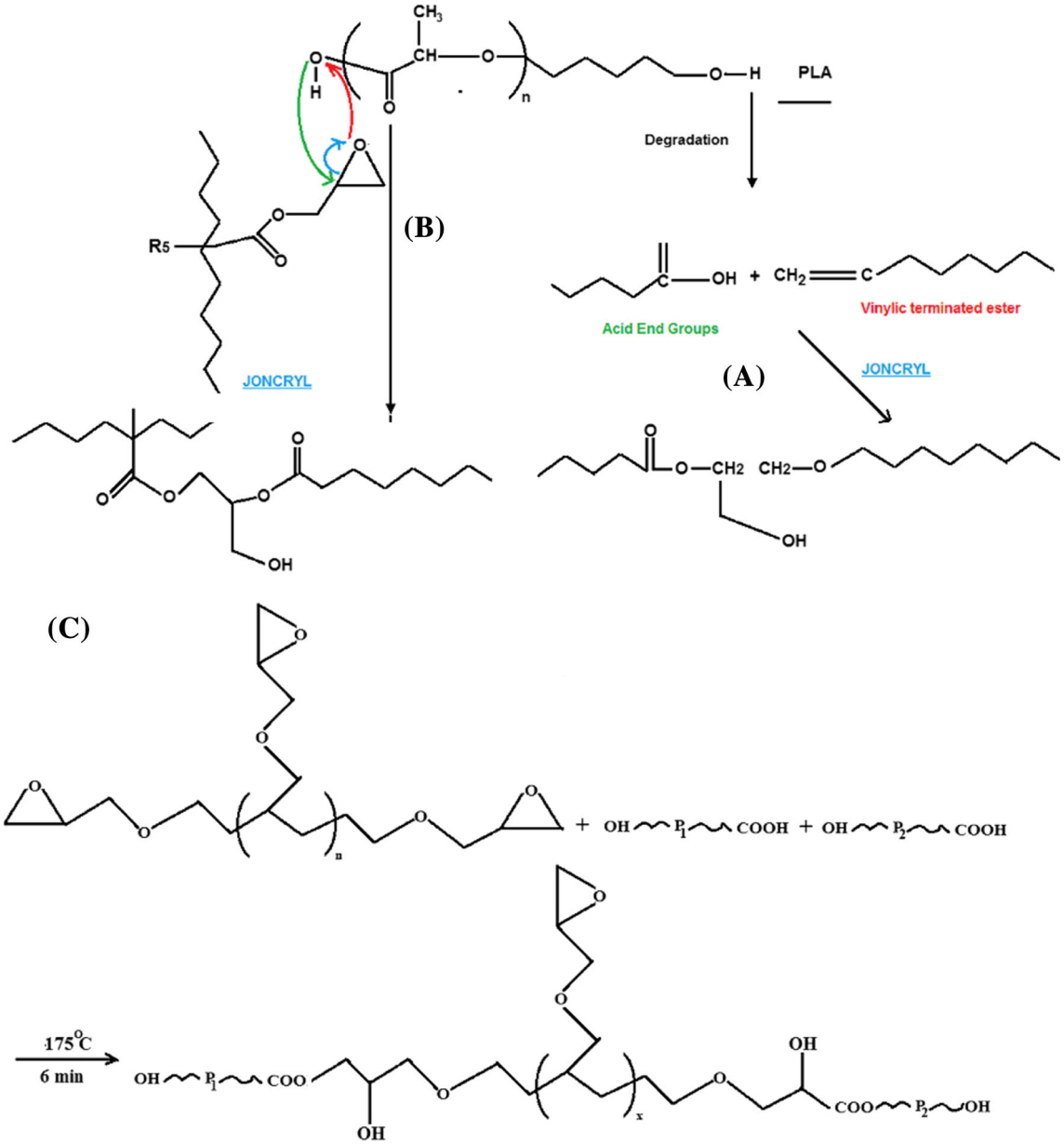

Fig. 6 *(A)* Mechanism of the reaction between PLA and functionalized epoxy. *(B)* Reaction mechanism of epoxy with PLA under degradation of PLA. *(C)* The proposed reaction between the polyester and the chain extenders P1 and P2 shows PLA chains. *X* illustrates reacted PLA chains (P1 and P2) [81]

extenders on the mechanical properties, morphology, thermal stability, and biodegradation of the PLA/PBAT blends was investigated, and their result is presented in Table 6. In addition, Fig. 6(C) illustrates the mechanism of the reactions between the polyesters and the chain extenders that can be conducted during the polycondensation process for 6 min before terminating polymerization.

Another study conducted by Volker et al. [82] used a chain extender for improving specific properties. Their results confirmed that the suitable reaction temperature was 180 °C, and the suitable reaction time was 30 h for the polycondensation. On the other hand, stannous chloride/*para*-toluenesulfonic acid ($SnCl_2 \cdot 2H_2O$/TSA) as a catalyst showed the best catalytic effect. The molecular weight of products is increased as the ratio of ADR is increased; the molecular weight reached 360 kDa when the ratio of ADR achieved 1.5 wt% and then the final product converted to cross-linking once the ratio of ADR reached 2.0 wt%. Similar findings that were published by Najafi et al. [83] highlighted results on the control of hydrolytic degradation of PLA/clay nanocomposites using chain extenders (styrene acrylic multifunctional group) (ADR-4368). The highest molecular weight reached was 50 kDa with a broad of PDI 2.85 at 1.0 wt% of ADR-4368. Corre et al. [84] reported the impact of the chain extension on the

Table 6 Molecular weight analysis of PLA as a function of various chain extenders

Sample	Mn (kDa)	MW (kDa)	PDI	Tensile strength (MPa)	Elongation at break (%)	Ref
Neat PLA	90	150	1.7	60	10 ± 1.3	[81]
PLA/PBAT (80:20, *w*/*w*)	60	130	2.2	29	210 ± 1.5	[81]
PLA/PBAT/ADR (80:20:1, *w*/*w*)	100	330	3.3	40 ± 2.1	65 ± 2.1	[81]
PLA/PBAT/HDE (80:20:1, *w*/*w*)	70	160	2.3	35 ± 3.2	50 ± 3.1	[81]
PLA/PBAT (70:30)/20% OL/1% ADR	50	142	2.85	40 ± 1.1	16.8 ± 0.2	[80]
PLA/PBAT (70:30)/20% OL/2% ADR	NA	NA	NA	41 ± 2	18 ± 4.6	[80]
PLA/1.5% ADR	133	218	1.59	68 ± 5.4	NA	[85]
PLA/1.2% ZnO/0.4 CCA/1.5% ADR	109	175	1.6	43 ± 1.3	NA	[85]

ADR = chain extender

OL organosolv lignin, ADR, *CCA* copper chlorophyll acid, *NA* not available

crystallization property of PLA. The molecular weight increased from 211 kDa at 1 wt% ADR-4368 to 290 kDa at 2 wt%, respectively. The step mechanism of hydroxyl-terminal prepolymers is used to accelerate the biodegradability of PLA. This can be achieved by introducing different quantities of hydrophilic EG and LA monomers with a small quantity of chain extender during the condensation copolymerization of poly(LA-*co*-EG) matrices.

Synthetic PLA-based scaffolds for tissue engineering

Synthetic PLA remains the most suitable polymer for scaffold fabrication. Due to the nature of its rate of degradation and mechanical properties that is similar to those of proteins in hard and soft tissue engineering, PLA has several advantages in the development of synthetic vascular and bone scaffold. Through utilizing the reinforced elements, it is possible to tailor and improve mechanical properties of the PLA matrices. The purpose of the reinforced material is to compensate for the deterioration of mechanical properties because of the development of the porous structure in the PLA matrices. This porous structure is essential for the propagation and metabolism of the cells. However, that will lead to a drastic decline in the mechanical properties, such as modulus of elasticity (Young's modulus), tensile strength, and flexural modulus. It is expected that tailoring parameters such as the composition of the polymeric matrices and the weight content of the reinforced elements will produce a class of biomaterials with a wide range of mechanical properties. Table 7 summarizes

Table 7 Properties of PLA scaffold nanocomposites based on reinforced elements

Initial polymers	Reinforce element	Porosity % (pore size)	Methods	Process condition	Strength (MPa)	Modulus (MPa)	Ref
PLLA	None	87.37 (64 μm)	Thermally induced, phase separation	Freeze-dry at 200 °C for 72 h	1.8	2.2	[85]
PLA	Nano-HA	85.06	Solvent casting	160 °C	8.7	14.9	[86]
PLLA (70)	AB (30)	92 (62 μm)	Supercritical CO_2	1,4-Dioxane (15 MPa, 35 °C)	0.05	NA	[87]
PLA	Nanoclay	73	Screw extruder/injection molding and leaching method	200–220 °C, 100–200 rpm	NA	3.5	[88]
PLA	MFC	90	Compression molding at 180 °C and 10 MPa	High-speed blender at 20,000 rpm for 60 min	38.7	3.1	[89]
PLA	Epoxy	74	Electrospinning	Dissolved in chloroform methanol (2:1)	4.3	2.7	[90]
PLA	HA fibers (70 wt%)	NA	Hot pressing	175 °C, 10 MPa	40	11	[91]
PLA	BCN (5%)	92	Solvent casting and freeze-drying	1,4-Dioxane (1:19) at 45 °C for 8 h	1.03	36.84	[92]
PDLLA	HA/β-TCP	69 ± 5	CO_2 foaming with a solvent infiltration method	Room temp under vacuum	0.36	0.22	[93]

AB ammonium bicarbonate, *MFC* microfibrillated cellulose, *BCN* bacterial cellulose nanowhiskers, *NA* not available

the physical and mechanical properties of PLA scaffolds incorporated with reinforced elements and their fabrication techniques.

- The pore size should measure between 100 and 400 μm.
- Interconnected open porosity for in vivo tissue in-growth
- Sufficient mechanical strength and controlled degradation kinetics for proper load transfer to the adjacent host tissue

Design and fabrication of PLA scaffold

Bone is a natural structure of hydroxycarbonate apatite and collagen with a 10–30% porous hard outer layer such as cortical bone and a 30–90% porous internal as an example of cancellous bone. The achievement of appropriate bone tissue scaffold has to gain mechanical properties of polymer scaffolds that mimic a human bone and to be tailored to a broad range of soft tissue (cancellous) to the hard tissue (cortical bone) under controlled processing parameters. Whereas one of the hindrances in creating a design, an ideal scaffold is related to the control aspect ratios of the scaffold associated with the types of scaffolding techniques used. The main factors for an ideal scaffold for bone regeneration are described below:

Properties design for PLA in tissue engineering

PLA is considered as a biodegradable biomaterial which provides the substantial advantage of being capable to break down by the process of hydrolysis. The host's response in both drug carrier and tissue engineering is based on the biological, physical, and chemical properties of the biomaterials. Once these biomaterials are biodegradable, there is a further step of continuing changes in the biomaterial properties caused by degradation as a function of time. These variations induce long-term host's response to the biomaterials to be different from the original response. A broad range of natural and synthetic biodegradable PLA has been examined for biomedical

Table 8 Properties and fabrication of PLA copolymer in biodegradable PLA for applications as biomaterials

Polymers	Modulus (GPa)	Elongation (%)	Solvent	Crystallinity (%)	Degradation time (Weeks)	Applications	Ref
Poly(L-lactide)	2.7	–	Benzene, THF, dioxane	37	12–19	Interference screws, suture anchors, meniscus repair	[94]
Poly(D,L-lactide)	3.0	Poly(D,L-lactide)	Methanol, DMF	Amorphous	11–14	Orthopedic implants, drug delivery	[95]
Poly(D,L-lactide-*co*-glycolide) (85:15)	2.0	3–10	Chloroform, acetone, THF	Amorphous	5–7	Interference screws, suture anchors, ACL	[96]
Poly(D,L-lactide-*co*-glycolide) (50:50)	2.0	2–8	Chloroform, acetone, DMF, THF	Amorphous	1–3	Orthopedic implants, drug delivery	[97]
Polyglycolide/polyglactine	7.0	13–21	Hexafluoroisopropanol	60–60	6–11	Suture anchors, meniscus repair, medical devices	[98]
PLLA	1.2–3	2–5	Toluene, xylene	Amorphous	>24	Orthopedic implants	[99]
Poly(lactic acid) (PLA)/polyamide 6 blends	1.6–1.65	8–10	No	53	12	Orthopedic implants	[100]
PP/PLA (60:40)	1.5	32	PP-*g*-MA compatibilizer	38	>12	Medical packaging application	[101]
PLA/PCL (80:20)	1.117 ± 52	3–10	Chloroform	Amorphous	12–18	Soft tissue engineering	[101]
Poly(L-lactide-*co*-D,L-glycolide) (75:25)	1.9	3–10	Benzene, acetone, DMF	Amorphous	4–5	Orthopedic implants, coatings, data	[102]
Poly(D,L-lactide-*co*-glycolide) (85:15)	2.0	3–10	Ethanol, benzene	Amorphous	5–6	Interference screws, suture anchors, ACL reconstruction	[103]
Poly(D,L-lactide)	1.9	3–1	Hexafluoroisopropanol	Amorphous	12–16	Bone tissue engineering	[103]
PLA	1.5–2.7	–	Chloroform, dioxane, dichloromethane	Amorphous	12–18	Fracture fixation, interference screws, suture anchors	[104]
PLA/hydroxylapatite	4.7 ± 0.01	36 ± 0.9	2,2,2-Trifluoroethanol (TFE)	Amorphous	6	Tissue regeneration	[105]

implementation with novel PLA continuously being developed to meet required biomaterial demands. The PLA properties are critically affected by some features. These features of PLA biomaterials include the polymerization process, hydrophobicity, molecular weight, water adsorption, surface charge, erosion mechanism, and rate of biodegradation. The PLA biomaterials can be prepared and designed to meet the standard specifications of the anticipated biomedical as a function of PLA. With the support of computer-aided technology, it is possible to form nanoparticles and PLA scaffolds with complicated architectures to imitate their biological counterparts. Table 8 summarizes the results of recent research on the properties and fabrications of PLA with other biodegradable polymer blends for the application as biomaterials.

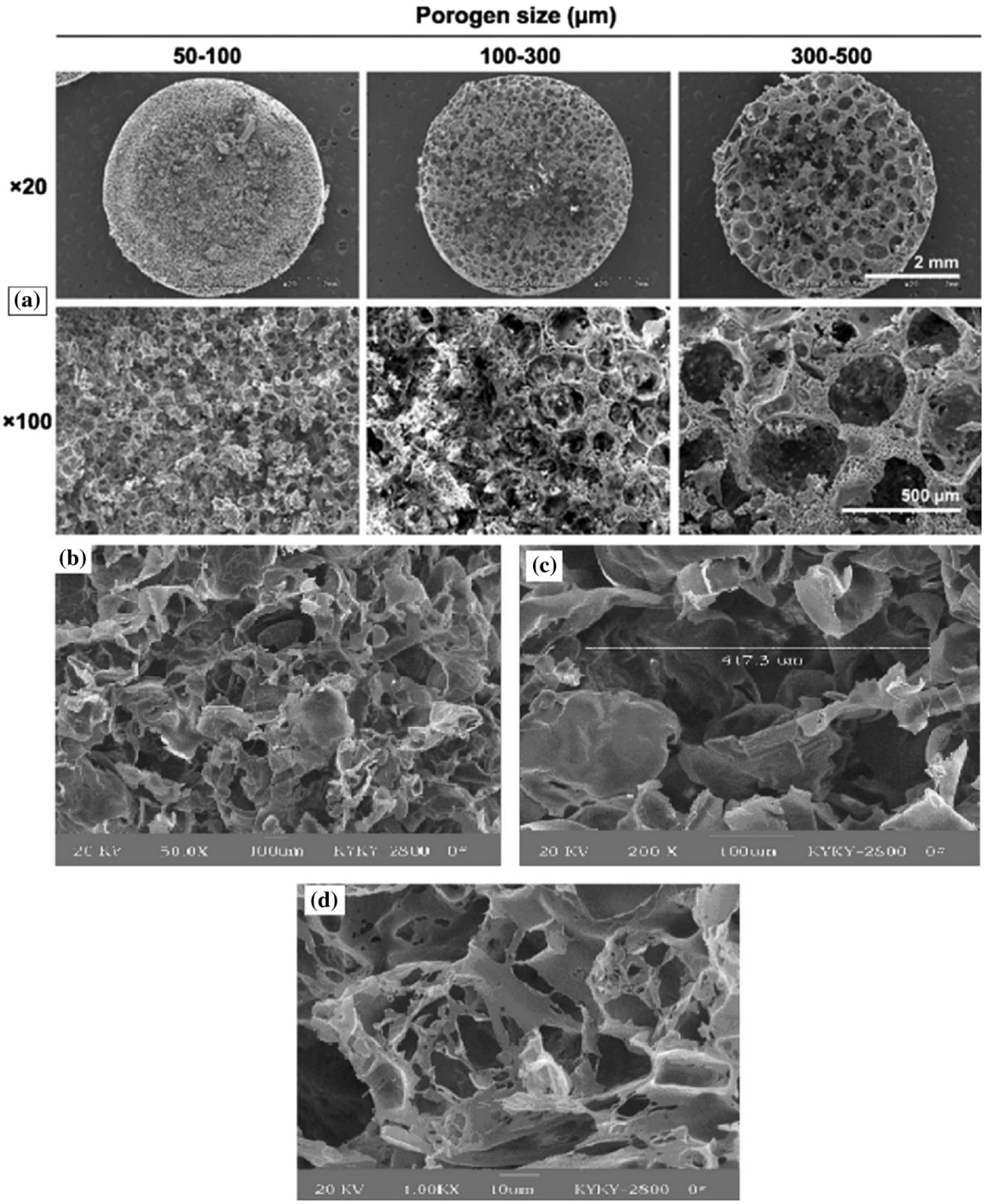

Fig. 7 (**a**) SEM of BSM–PLGA composite scaffolds with varying pore sizes. (**b**) SEM images of PLA prepared through sodium hydrogen carbonate particulates. (**c**) Low magnification. (**d**) High magnification of macroporous structure [112, 113]

Biocompatibility

Biocompatibility is one of the substantial properties that should be considered when designing soft and hard tissue scaffolds. The biocompatibility of a scaffold is designated to replace a part of a living system and to enhance cellular activity. The molecular systems should not be toxic and cause immunological rejection by the host tissue [106]. Typical bone PLA scaffold can be osteoconductive, and the scaffold allows the cells to attach, propagate, and create an extracellular matrix on its pore and surface. The scaffold has the capability to generate a novel bone creation by biosignaling and recruiting progenitor cells. The typical polymer scaffold is successful in creating blood vessels on the implant during a short time of implantation for active support of oxygen, nutrient, and waste transportation [107].

Mechanical properties

The design of PLA scaffolds must be tailored to a wide range of mechanical properties ranging from cancellous to cortical bone and matched to host bone properties. As an example of Young's modulus, the value has to be in the range 15 to 20 GPa for hard tissue and 0.1 to 2 GPa for soft tissue. Likewise, the compressive strength should be between 100 and 200 MPa for cortical bone and between 2 and 20 MPa for cancellous bone. However, considerable variations in the mechanical properties and scaffold design dimensions make it difficult to optimize typical bone scaffolds [108]. The mechanical properties of PLA scaffolds depend on the molecular weight and crystallinity of PLA, and these properties impact the rate of biodegradation and reaction mechanism. The loss of mechanical properties remains a barrier to the effective use of PLA. Thus, the incorporation of nanoparticles in the PLA matrices also provides a rise in the improvement of the mechanical properties and the biological response.

Pore size

The pore size is defined as one of the scaffold properties that is formed to the interconnected porosity that favors tissue integration. Pore size should not be less than 100 μm in diameter for the complete diffusion of oxygen and nutrients to support cell survivability [109]. Nevertheless, there are some specific requirements for pore sizes in hard tissues that are in the range of 200–350 μm. Furthermore, several studies revealed that multiscale porous PLA scaffolds were linking either micro- or macroporosity and that may achieve superior results than purely macroporous PLA scaffolds [110]. The reduction in compressive and tensile properties is one of the drawbacks of increasing porosity; various porous scaffolds employing PLA matrices, ceramics, nanocomposites, and metals have been investigated. Particularly, the mechanical properties of bioceramic materials are comparable to those of cortical bone. Moreover, the synthesis of polymer scaffolds regarding pore size, porosity, and biodegradation can be designed to meet the requirements of cancellous bone. Blends of scaffolds varying in quantities of ceramic/PLA nanocomposites are potentially advantageous to control the specific requirements of bone tissue. On the other hand, porous metallic scaffolds are appropriate regarding mechanical properties but are still unsuccessful in providing substantial implant tissue integration [111]. Kim et al. [112] developed a nanocomposite scaffold using collagen matrices extracted from poly(lactide-*co*-glycolide) (PLGA) and porcine bladder submucosa matrix (BSM) as demonstrated by SEM in Fig. 7a. Composite scaffolds exhibited an irregularly oriented, open, three-dimensional porous structure of interconnectivity. This kind of network structure could provide a stage for cell adherence and propagation.

In a relevant study, Ruan et al. [113] investigated the SEM of PLA porous materials. The macropore size in the range from 300 to 500 μm can be observed in Fig. 7(B) and (C), which is appropriate for hard tissue. High magnification of the SEM image in Fig. 7(D) confirms that the open pore size and interconnected wall network are appropriately dispersed in the PLA scaffolds. Furthermore, it is possible to vary the pore size of PLA scaffold for designing tissue material by tailoring the aspect ratio of the foaming agent.

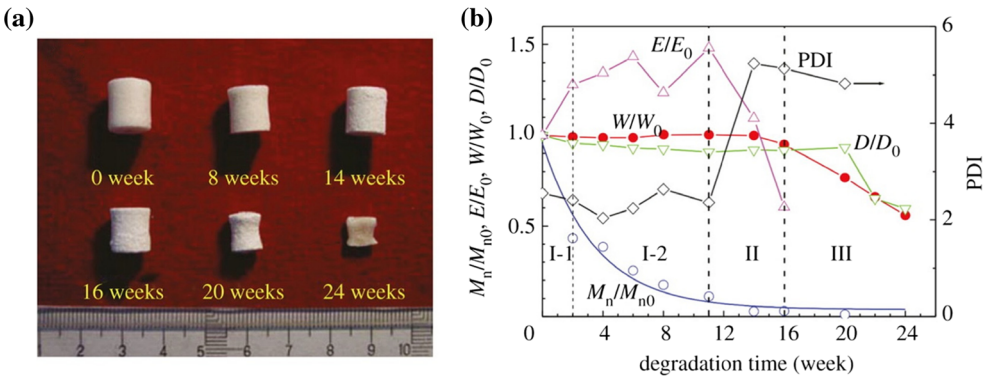

Fig. 8 (**a**) PLGA85/15 scaffolds biodegraded in PBS solution at 37 °C, indicating the period. (**b**) Three steps of biodegradation examined by change molecular weight, PDI, and compressive modulus [114]

Biodegradability

Biodegradability is an indispensable property in designing scaffolds for bone tissue regeneration. Typical scaffolds should possess comparable mechanical properties to that of the host tissue. However, the rate of biodegradation is another key factor that requires an in vivo study. The control of biodegradation in polymer scaffolds depends on properties such as molecular weight and crystallinity to manipulate a broad range of maxillofacial applications within the week to months and years. Future research will be done that emphasizes a variety of parameters such as polymerization conditions, compositions, and scaffolding techniques that need to optimize and control desired applications in bone tissue engineering [94, 113]. Wu and Ding [114] investigated the PLGA porous scaffold in vitro degradation in PBS solution at 37 °C; the result showed that the molecular weight of PLGA decreased exponentially with time. Three steps of biodegradation were analyzed by the control of the number of average molecular weight, polydispersity index (PDI) of a PLGA, and the

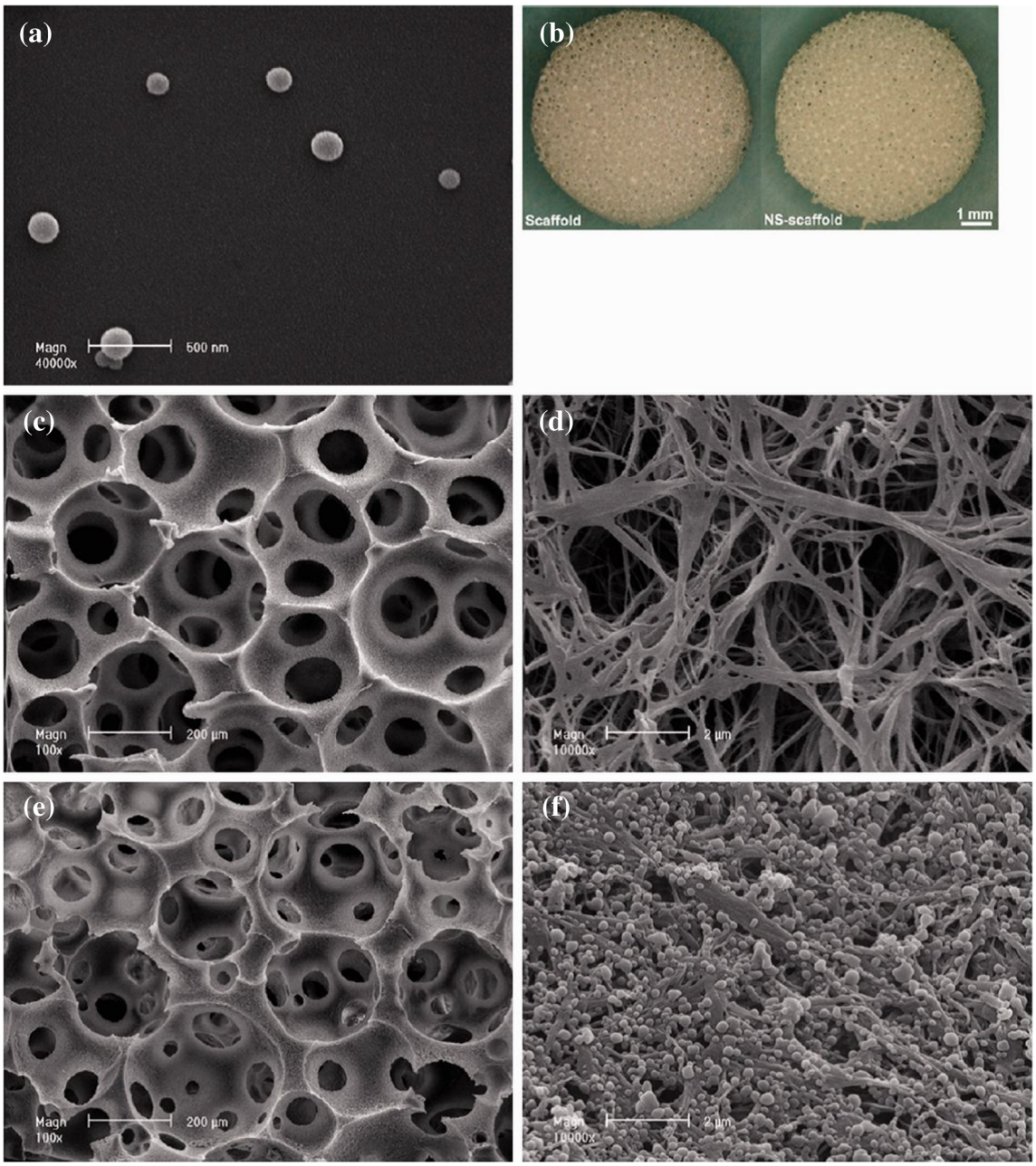

Fig. 9 Investigation of PLGA (50)/64 K nanospheres (NSs) reinforced into PLLA nanofiber scaffolds. (**a**) SEM of rhBMP-7 consisting of PLGA (50)/64 K nanospheres. (**b**) SEM of PLLA scaffolds prior to (*left side*) and after (*right side*) nanosphere incorporation. (**c**) SEM of PLLA nanofibers before nanosphere reinforcement at ×100, and ×10,000 (**d**). SEM of PLLA nanofibers after PLGA (50)/64 K nanosphere reinforcement at ×100 (**e**) and ×10,000 (**f**) [117]

compressive modulus of the PLGA scaffold (*E*). The remaining weight (*W*) and diameter (*D*) indicate simultaneous biodegradation on the surface and in the interior of the material (Fig. 8). These outcomes are an important characteristic of the bulk biodegradation mechanism of PLGA matrices.

Functionalized PLA scaffolds for tissue engineering

The availability of a wide range of applications of PLA in tissue engineering resulted in introducing different fabrication pathways to produced functionalized polymer matrices for targeted applications. Functionalized scaffolds have no effect on the regeneration process and can participate in the tissue neo-genesis process. With the recent advancement of synthesis biology in the scarcity of nanotechnology, current development on PLA scaffolding has further emphasized on the benefit of the multifunctional group into the PLA scaffolds that can prompt required cell–matrix interactions to direct cell orientation and improve novel tissue development. In general, bioactive materials can be integrated onto PLA scaffolds after being functionalized through the surface of bulk modification. In the bulk modification process, bioactive materials interact with PLA matrices prior to developing scaffold fabrication [115, 116]. Several surface treatments have been upgraded to integrate bioactive molecules onto the PLA scaffold. Bioactive molecules have an effective way throughout tissue regeneration. The localized and interim controlled delivery of bioactive molecules as a result of drugs and growth factors may be improving the clinical efficacy. The further quantity of bioactive molecules into PLA scaffold can dramatically tailor the ability of hard tissue regeneration. An earlier study by Wei et al. [117] investigated the improvement of osteogenesis by PLLA nanofiber scaffolds reinforcing recombinant human Bone Morphogenetic Protein-7 (rhBMP-7) nanospheres. As

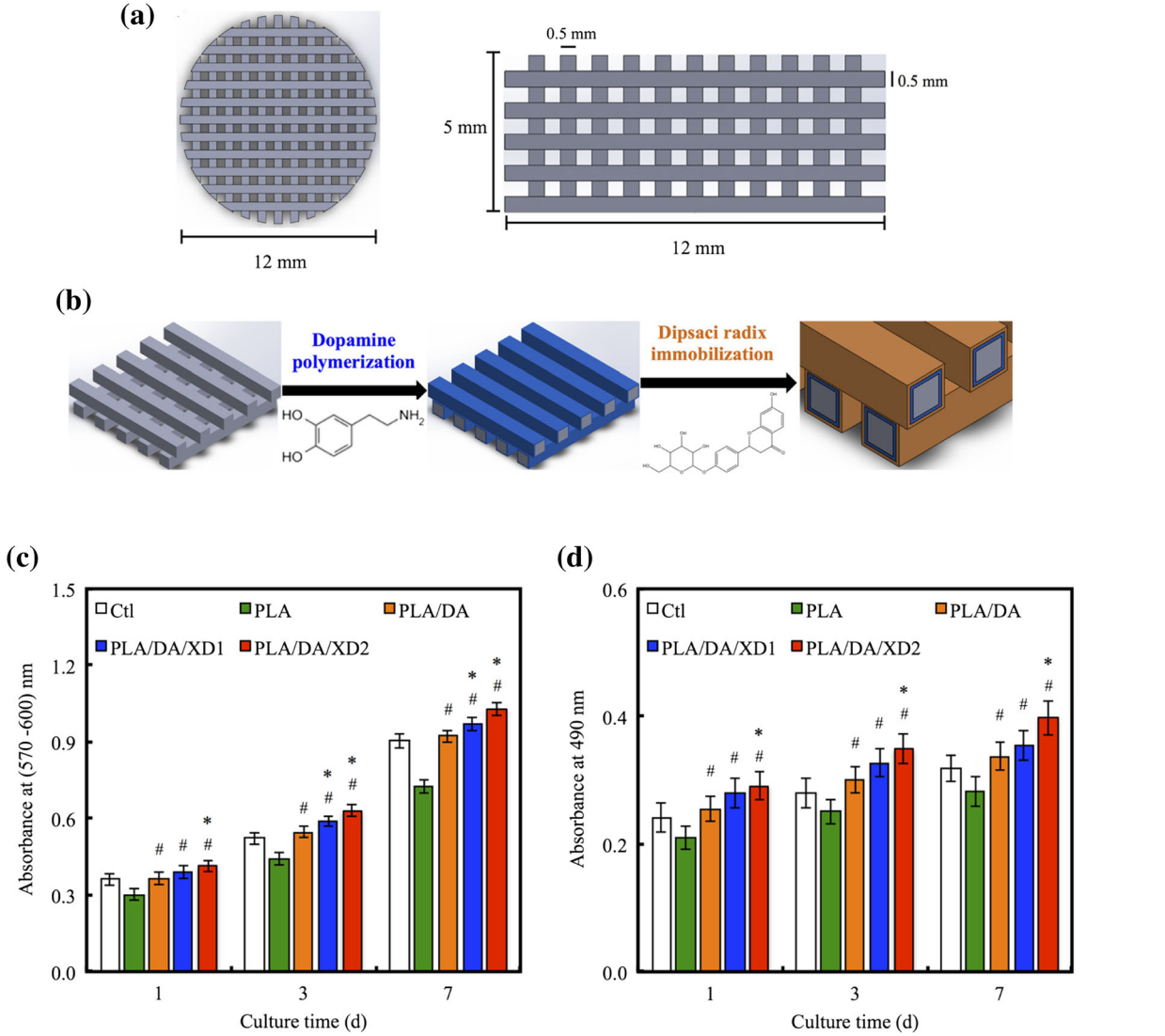

Fig. 10 (**a**) Three-dimensional printed images of PLA scaffold. (**b**) Schematic of dopamine-assisted immobilization of XD on surfaces. (**c**) Presto-Blue® assay. (**d**) Lactate dehydrogenase (LDH) assay of hBMSCs cultured on different specimens as a function of time [118]

shown in Fig. 9, three-dimensional PLLA macroporous and nanofiber scaffolds were synthesized with a high porosity. The diameter of PLLA nanofibers was in the range from 50 to 500 nm that are similar to a class of type I collagen fibers in size (Fig. 9b–d). The morphology of nanofiber PLLA scaffolds after being blended and incorporated with PLGA (50–64 K) nanosphere is shown in Fig. 9e, f. Compared to the neat PLLA scaffolds, prior nanosphere (NS) reinforced. The pore size of the scaffolds was affected by the nanofibers and nanospheres and distributed consistently. Therefore, rhBMP-7 proves to have a significant impact on prompting ectopic hard tissue via the scaffold generated. The NS scaffold can be employed as a drug carrier for several bioactive molecules or as an inductive tissue scaffold for different regenerative medicine applications.

Fang et al. [118] developed functionalized three-dimensional printed PLA scaffolds and employed a mussel-inspired surface coating to control cell attach, differentiation, and proliferation of human bone marrow mesenchymal stem cells (hBMSCs). The three-dimensional printed PLA scaffolds were designed to obtain the suitable height of 5 mm and the diameter of 12 mm. Furthermore, the accuracy of *Z*-axis was 0.1 mm as presented in Fig. 10a, b. The results in Fig. 10c indicate that the rate of proliferation of hBMSCs regularly increased and associated with the quantity of Xu Duan (XD) immobilization on polydopamine (PDA)-coated PLA that showed a significant variance compared to PDA-coated PLA specimens. The activity of lactate dehydrogenase (LDH) in the medium released from hBMSCs cultured on the specimens was used as an index of cytotoxicity. The hBMSCs were cultured on the scaffolds at an initial density of 10^4 cells per scaffold for 1, 3, and 7 days, and subsequently, the culture medium was collected and centrifuged. The LDH activity in the supernatant was estimated by a spectrophotometer measured at 490 nm absorbance (Fig. 10d). The outcomes of the PDA- and XD-coated PLA scaffolds revealed that no cytotoxic was recorded. It indicates appropriate cell viability and high biocompatibility for both XD- and DA-coated scaffolds.

Applications of PLA in regenerative medicine

The application of PLA in regenerative medicine assigned since 1966 when Kulkarni et al. [119] discovered that PLLA has a non-toxic tissue response when implanted in pigs and rats. Later, Cutright and Hunsuc [120] defined PLA new applications in sutures and orthopedic fixation. Nowadays, the PLA biomedical applications such as drug carrier system, surgical implants, and a porous scaffold for tissue regeneration are widely investigated (see Fig. 11). These applications are due to the synthetic biodegradable PLA that has special characteristics such as biodegradability and biocompatibility, in addition to thermal plasticity and flexible mechanical properties. Adjusting degradation rate and mechanical properties can

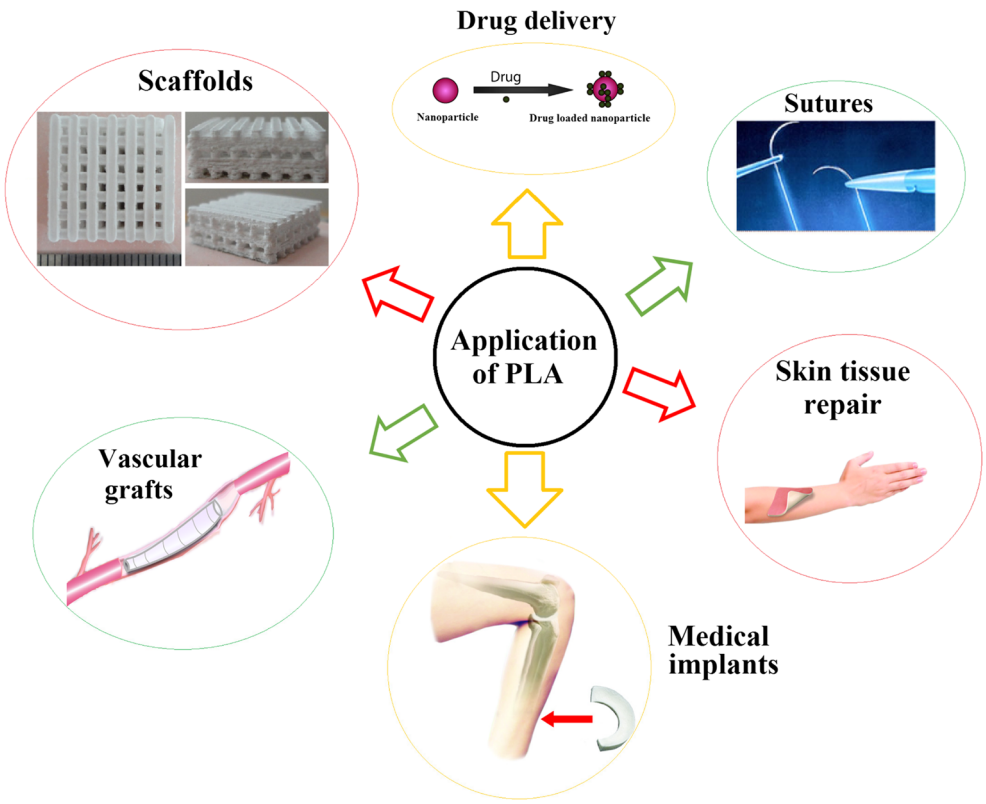

Fig. 11 Application of PLA in regenerative medicine

be achieved through reinforcing agents such as nanofibers. When implanted in vivo, it is degraded easily by a hydrolytic process without the need of either catalysts or enzymes; hence, a second surgical elimination of the implant is considered needless. Lactic acid is produced via the fermentation of sugars collected from natural resources such as sugarcane. Despite the fact that there are several methods of fabricating PLA, none of them is simple to perform. Due to the poor ductility and low hydrophilicity, the application of PLA is restricted to tissue engineering. The PLA blends with other polymers such as PEG, PLGA, and PEG have an effective approach to improve biocompatibility, enhance hydrophilicity, and accelerate biodegradation rate. In addition, the porous structure caused by the nanofiber in a fabricated PLA scaffold provides a suitable environment for incorporating drugs and therapeutic cells [121]. A fiber orientation into PLA matrices has a substantial benefit over conventional synthetic biodegradable polymer. Particularly, in the high porosity, it provided a high surface area for the cell–matrix interaction and increased both interconnectivity and cell adhesion [122]. The fabrication of three-dimensional PLA porous scaffold has gained a substantial interest in applications associated with bone and muscle tissues and cartilage regeneration, in addition to other cardiovascular diseases.

Conclusion

Synthetic PLA biodegradable polymers are used substantially in pharmaceutical and tissue engineering products. PLA is the material that has been selected for the design and clinical use of biodegradable implants and can be prepared with chemical structures that are tailored to optimize the physical properties of the biomedical material. Most biomedical applications possess specific requirements and are made of highly superior materials which are essential to perform in a dependable and expectable way. Consequently, the performance of the PLA polymer has to be designed and synthesized for a narrow molecular weight distribution, a low residual monomer, minimal impurities, and a well-defined chemical structure. The desired parameters can be controlled via polycondensation processes to achieve polymers with unique properties. Thus, synthesis of LA by polycondensation significantly depends on several parameters, including polycondensation, temperature, pressure, the polarity of the solvent, as well as types of catalysts and prepolymers' degree of polymerization. These conditions require being controllable for accomplishing a high conversion of PLA and minimizing racemization for desired applications in the biomedical field. The design of the PLA as a biomaterial with requisite characteristics depends entirely on the properties of the host tissue such as suitable pore size, porosity, adequate mechanical properties, and degradation rate. Thus, these synthetic PLA scaffolds must be designed to conform to a specific set of requirements. Several aspects of the synthesis conditions, chain extenders, and scaffold designs are considered to enhance potential applications of PLA. Future investigations will include blends of PLA, copolymerization, and a safe novel catalyst in the absence of solvents to impact-modified products, which will cover a broad range of biomedical applications, in addition to the beneficial properties of incorporating bioactive molecular drugs and certain growth factors in the PLA scaffolds to induce cell growth into a specific tissue formation.

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