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REVIEW

POLYLACTIC ACID: SYNTHESIS, PROPERTIES AND TECHNICAL AND BIOMEDICAL APPLICATIONS

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Abstract. Polylactic acid (PLA) is one of the common aliphatic polyesters synthesized from lactic acid monomer (2-hydroxyl propionic acid) by fermentation or chemical synthesis. Due to its high strength, high modulus, biodegradability, compostability and well-known safety profile, PLA becomes a very useful material for both fundamental researches and practical applications. However, awareness of PLA manufacturing knowledge combined with understanding of its physico-chemical properties is essential for fruitful applications of PLA. This review article presents the synthesis, characteristics, properties and applications in technique and biomedicine fields of PLA. Among them, main synthesis methods of PLA will be mentioned. The physical, mechanical, thermal, gas permeable, electrical, and chemical properties of PLA will be described. The applications of PLA in packaging materials, agriculture, or other technique fields and biomedicine also help readers have a better overview of PLA.

Keywords: polylactic acid, properties, degradation, application, biomedicine.

Classification numbers: 1.4.2, 2.9.3.

1. INTRODUCTION

Polylactic acid or polylactide (PLA), a biodegradable hydrolyzable aliphatic semi-crystalline polyester having no aromatic structure, was discovered in the 1920s by Wallace Corothers. It is produced from renewable agricultural sources such as corn, rice, wheat, sugar beets, and other starchy products, thus it is known for its eco-friendliness. In general, PLA is produced through the direct condensation reaction of its monomer, lactic acid, as an oligomer, and followed by a ring-opening polymerization of the cyclic lactide dimer. Its chemical structure can be seen in Figure 1. Its properties vary to a large extent depending on the ratio between, and the distribution of two stereoisomers or other co-monomers. For industrial applications (films, fibers, bottles, etc.), the chain length (*n)* of PLA should be between 700 and 1400 [1, 2]. Since lactic acid is a chiral molecule with L-type and D-type isomers, PLA can be formed in three forms, namely poly-L-lactic acid (PLLA), poly-D-lactic acid (PDLA), and poly-D,L-lactic acid

(PDLLA) (Figure 2). PLLA has high crystallinity and slow degradation rate while PDLA can be decomposed more quickly. Both low molecular weight PLA and high molecular weight PLA have been synthesized, however, low molecular weight PLA is less stable, so this synthesis was considered unsuccessful [2]. Therefore, high molecular weight PLA is mainly produced in industry and widely applied in various fields of life and industry.

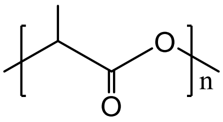
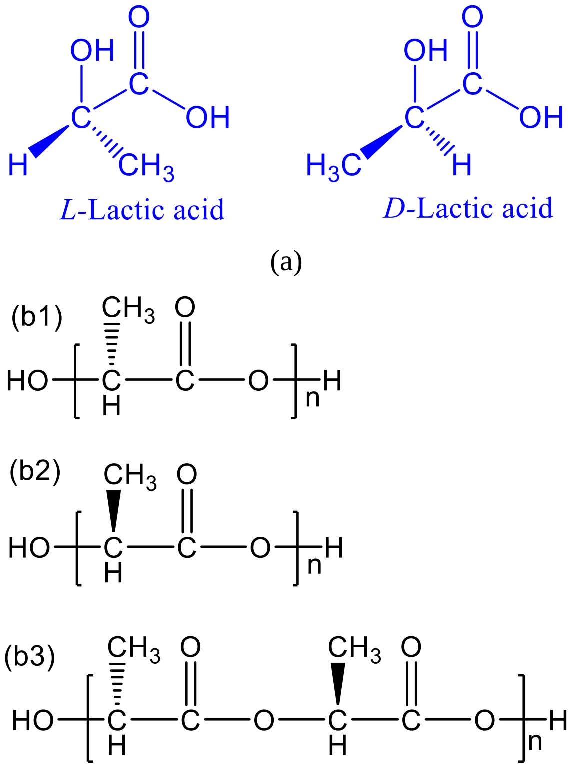


Figure 1. Chemical structure of PLA.



(a)

(b)

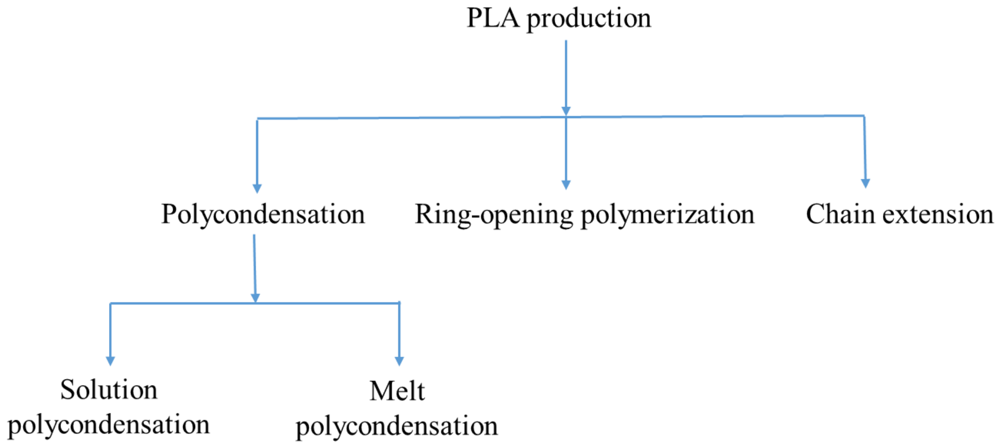
Figure 2. (a) The stereoisomers of lactic acid and (b) Chemical structure of PLLA (b1), PDLA (b2) and PDLLA (b3).

PLA is the one of most important bioplastics in terms of consumption volume in the world. Some largest PLA producers are NatureWorks (Joint-venture between Cargill (US) and PTT (Thailand)), WeforYou, Evonik, Total-Corbion (Joint-Venture between Total (France) and Corbion (Netherlands)). The production and use of PLA reduce greenhouse gas emissions and environmental impact compared to alternative polymers including polycarbonate, polystyrene, polyethylene terephthalate, polypropylene, low density polyethylene [3]. PLA can be processed at 170-230 ^{o}C by injection molding, sheet blow molding, thermoforming, sheet extrusion, fiber spinning, injection stretch blow molding or non-woven spinning, and spun bonding [1]. It is primarily hydrophobic because of the presence of methyl groups of the LA monomers. It can be completely degraded into carbon dioxide and water by microbes. It has good biocompatibility, hence, it has been approved by the U.S. Food and Drug Administration (FDA) and European regulatory authorities for use in drug-delivery systems and food.

2. MAIN SYNTHESIS METHODS OF POLYLACTIC ACID

On an industrial scale, manufacturers have developed some synthesis methods for high molecular weight PLA (M_w> 10,000 g/mol). These are lactide ring opening polymerization (ROP), structural co-monomers in high boiling solvents/direct polymerization, and chain extension (Scheme 1). The majority of commercial producers find that ROP is preferable for better process control and better production quality. Therefore, most of PLA products on the market have been produced according to ROP route. Only minor amounts of PLA have come from other routes.

ROP route includes a three-step reaction: polycondensation, lactide formation and lactide ring-opening polymerization. In the first stage lactide is formed, which – after fine purification – is converted by ROP to PLA. Firstly, lactic acid was evaporated or distilled to remove water and concentrate lactic acid, followed by pre-condensation to form pre-polymer. Next, the pre-polymer converts to a cyclic dimer (crude lactide). Then, the lactide was purified to obtain highly purified lactide before it was ring opening polymerized to form PLA. After that, the demonomerisation or stabilization was carried out to obtain high purity polylactide [1]. PLA obtained in this way has high molecular weight, higher than 100,000 Daltons [4].



Scheme 1. Synthesis scheme of PLA by different methods.

Lactide can be polymerized in melt, bulk, solution or suspension state. Some parameters that can affect PLA processing through ROP route are racemization, lactide purity and residual monomer content. The metallic catalysts which have been typically used in ROP to produce PLA include tin-based catalysts, aluminum alkoxides, etc. due to their solubility in molten lactide, low rate of racemization of the polymer and high catalytic activity [1, 2]. The above efficient catalysts based on Ca, Fe, Mg, Zn and K showing less toxicity than tin compounds have been used in lactide and lactone polymerization. In addition, metal-free catalysis including organocatalytic (cationic, nucleophilic, bifunctional) or enzymatic approaches has been developed for ROP to form PLA. Depending on the catalyst, the ROP of lactide can occur according to one of three mechanisms: anion, cation and coordination/insertion. Among the above catalysts, tin (II) di-2-ethyl hexanoic acid (typically tin (II) octoate or stannous octoate) was approved by the FDA because it has high catalytic activity, low toxicity and is a highly suitable inducer. The advantage of this route is that PLA has a high molecular weight, however, it requires strict purity of the LA monomer and has high cost.

The direct polymerization of LA monomers is also used to produce PLA. This way can be carried out in bulk followed by chain extension with reactive additives or by solid state post-condensation to reach high molecular weight PLA. The direct polycondensation can be divided into solution polycondensation method (using solvents) and melt polycondensation method (non-solvent). The advantages of this route are one-step, ease to control and economical cost. However, the disadvantages of solution polycondensation method are impurities, side reactions, pollution, and low molecular weight PLA, while the limitations of melt polycondensation method are high reaction temperature, sensitivity to reaction conditions, and low molecular weight PLA. The melt condensation polymerization includes three stages: removal of free water, oligomer polycondensation and melt polycondensation of high molecular weight PLA. In the first stage, hydroxyl and carboxylic acid groups of LA monomers react together and water has been removed during the condensation reaction (Eq. 1).

$$HO\text{-}(CH(CH_3)COO)_n\text{-}H + HO\text{-}(CH(CH_3)COO)_m\text{-}H \leftrightarrow HO\text{-}(CH(CH_3)COO)_{n+m}\text{-}H + H_2O \quad (1)$$

where n and $m \geq 1$.

During condensation process, the ring structure such as lactide can be formed. This can make a negative effect on the properties of obtained PLA. The temperature of reaction should be below 200 ^{o}C to avoid the formation of lactide. However, this causes an effect on the removal of water.

In the second stage, the low molecular weight PLA or lactide oligomers which converted from LA was obtained. Strong acidic organometallic compounds based catalysts are used to improve the reaction rate in this stage.

In the third stage, the removal of water reaches critical. The melt polycondensation should be carried out to enhance both mass and heat transfer of water. The reactive additives have been added to chain extension of PLA. After melt polycondensation, the melt polycondensated PLA was cooled and particles were formed. These particles can be subjected to a crystallization process. The PLA obtained by this route has molecular weight as high as 130,000 g/mol or 100,000 g/mol or 63,000 to 79,000 g/mol depending on the type of catalyst used [2]. In some cases, drying organic agents were used in the azeotropic dehydration reaction, the PLA can retain the optical purity. However, these solvents are flammable causing safety risks. Besides, the chain extenders and polymer impurities are toxic and non-biodegradable, thus, the obtained PLA by this route cannot apply in biomedicine field [4].

When using catalysts or adding dried organic agents during polycondensation process, the obtained PLA has a high molecular weight, the process is more efficient and has no pollution.

Another route for PLA synthesis is chain extension using linking agents such as diisocyanates, bis-2-oxazoline, dual (2,2’-bis(2-oxazoline) and 1,6-hexam-ethylene diisocyanate), or bis-epoxies. In the presence of linking agents, it is possible to control PLA branching [2]. In addition, PLA can be biosynthesized in one-step. The obtained PLA has high molecular weight and high degradable capacity.

3. CHARACTERISTICS, PROPERTIES OF POLYLACTIC ACID

3.1. Physical properties

PLA is a white or opaque yellow polyester thermoplastic. It has high gloss and transparency. The specific weight of PLA is 1.25 g/cm^3. The physical and other properties of PLA depend on two isomers of LA monomers, L-lactic and D-lactic (produced by the fermentation of carbohydrates by homofermentative bacteria and heterofermentative bacteria, respectively), with three optical isomers of LA [5]. In addition, lactide purity also affects the properties of PLA. The solubility of PLA depends on the molecular weight, crystallinity and content of co-monomers in the polymer. PDLA, PLLA and PDLLA have crystal, hemi-crystal and amorphous structures, respectively [6]. PLA can be dissolved in fluoride or chloride organic solvents, dioxane, furan, acetone, pyridine, ethyl lactate, tetrahydrofuran, xylene, ethyl acetate, dimethylsulfoxide, N,N-dimethylformamide, and methyl ethyl ketone. It is insoluble in water, alcohols (methanol, ethanol, propylene glycol), and unsubstituted hydrocarbons (hexane, heptane) [7]. The specific viscosity or intrinsic viscosity of PLA can be determined in chloroform or benzene using a Ubbelohde viscometer at 30 °C. The molecular weight of PLA could be calculated according to the Mark-Houwink equation [8-10]:

$$[\eta] = KM^{\alpha} \qquad (2)$$

$$\ln[\eta] = \ln K + \alpha \ln M \qquad (3)$$

where, K and α are constants, depending on nature of solvent and temperature, the value of α ranges from 0.5 to 0.8, M is molecular weight, and [η] is intrinsic viscosity (in dL/g).

The polydispersity of isotactic PLA (S-PLA) and racemic/atactic PLA (r-PLA) given in Table 1 was calculated using the Mark-Houwink equation and reported by Schindler *et al.* [8].

Table 1. Mark-Houwink parameters and polydispersity of isotactic PLA (S-PLA) and racemic/atactic PLA (r-PLA) in chloroform and benzene [8].

Polymer solvent	**S-PLA benzene**	**S-PLA chloroform**	**r-PLA benzene**	**r-PLA chloroform**
K x 10^4	5.72	5.45	2.27	2.21
α	0.72	0.73	0.75	0.77
M_w/M_n	1.87	1.87	1.88	1.89

3.2. Mechanical properties

PLA has high mechanical properties like common thermoplastics. It has high hardness, easy to fold when folded, wear resistance, high elastic modulus, high tensile strength, low elongation at break and low flexibility as compared to polyethylene or polypropylene. The mechanical properties of PLA are similar to those of poly (ethylene terephthalate) (PET) synthesized from fossil fuels. The mechanical properties of PLA can vary widely from soft, elastic to hard. They depend on the composition, molecular weight and crystal structure of PLA as mentioned above. PLLA has Young modulus of 2.7 GPa while PDLA has Young modulus of 1.9 GPa [11]. As the molecular weight increases, the mechanical properties of PLA are enhanced. For instance, when the molecular weight of PLLA increases from 23,000 to 67,000 g/mol, its flexural strength increases from 64 to 106 MPa and the tensile strength reaches 59

MPa. For PDLLA, when its molecular weight increases from 47,500 to 114,000 g/mol, its tensile strength and torsional force vary from 49 MPa to 53 MPa and from 84 MPa to 88 MPa, respectively [6]. Since PLLA has a semi-crystalline structure, it has better mechanical properties than PDLLA which is in amorphous state. The conversion process can produce PLA in either oriented or non-oriented form. The orientation can affect the mechanical properties of PLA. Table 2 shows a clear difference in critical tensile strength, tensile strength, Young modulus, elongation at break and impact strength of oriented PLA as compared to non-oriented PLA. This is caused by the degree of orientation as well as the content of the – stereostructure of the two PLAs above. However, those factors do not affect the Rockwell hardness, density, and glass transition temperature of these two PLA types [12].

Table 2. Mechanical properties of high molecular weight PLA with oriented and non-oriented macromolecular chains [12].

Properties	Non-oriented	Oriented
Ultimate tensile strength (MPa)	47.6–53.1	47.6–166
Tensile yield strength (MPa)	45.5–61.4	N/A
Tensile modulus (MPa)	3447–4000	3889–4137
Notched izod impact (ft-lb./in.)	0.3–0.4	N/A
Elongation at break (%)	3.1–5.8	15–160
Rockwell hardness	82–88	82–88
Specific gravity (g/cm^3)	1.25	1.25
Glass transition temperature (^{o}C)	57–60	57–60

Table 3. Effect of stereostructure and crystallinity on the mechanical properties of some PLA types [13 - 14].

Properties	PLLA	Annealed PLLA	PDLLA
Tensile strength (MPa)	59	66	44
Elongation at break (%)	7.0	4.0	5.4
Modulus of elasticity (MPa)	3750	4150	3900
Yield strength (MPa)	70	70	53
Flexural strength (MPa)	106	119	88
Unnotched Izod impact (J/m)	195	350	150
Notched Izod impact (J/m)	26	66	18
Rockwell hardness	88	88	76
Heat deflection temperature (^{o}C)	55	61	50
Vicat penetration (^{o}C)	59	165	52

Table 3 presents the effect of molecular weight and crystallinity on the mechanical properties of three types of PLA (amorphous PLLA, annealed PLLA and amorphous PDLLA). Thanks to the incubated process which leads to a crosslinking effect of the crystalline regions and stereo-regulation of polymer macromolecular chains, the elongation and impact strength of PLLA have been improved significantly [13 - 14].

Table 4. Mechanical properties of PLA plasticized with PEG [15].

Materials	Tensile strength (MPa)	Elongation at break (%)	Young modulus (GPa)
PLA	66.0	1.8	3.3
PLA containing 12.5 wt.% of PEG400	18.7	115.0	0.5
PLA containing 12.5 wt.% of PEG1,500	18.5	194.0	0.7

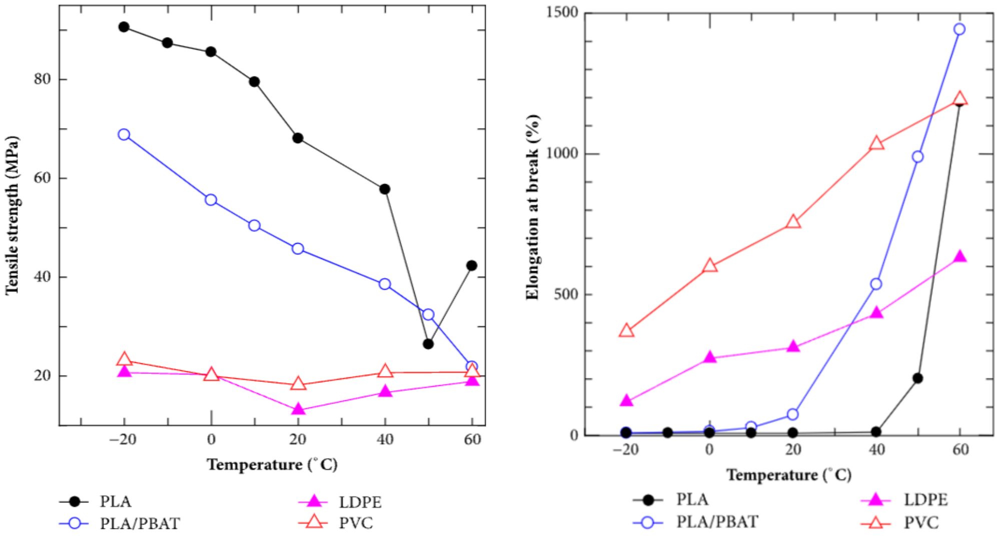


Figure 3. Tensile strength and elongation at break of PLA, LDPE, PVC, and PLA/PBAT blend [16] (Reprinted from Katsuyoshi S. by permission of Hindawi Limited).

As PLA is combined with another polymer, its mechanical properties of PLA can be enhanced. For example, a blend of poly(glycolic acid) and PDLA (75/25 wt.%) has a Young modulus of 2.0 GPa, 0.1 higher than neat PDLA (1.9 GPa) [11].

To increase the elongation at break and elasticity of PLA, some low molecular weight and biodegradable compounds including lactite monomer, glucose monoesters, fatty acid partial esters, citrate esters (triacetin citrate, tributyl citrate), epoxidized soybean oil (ESO), and acetyl tri-n-butyl citrate (ATBC) as well as polymers such as polyethylene glycol (PEG) and polycaprolactone (PCL) are used to plasticize PLA [15]. These above materials have low glass transition temperatures, thus, they can reduce the glass transition temperature of PLAwhen mixed, resulting in PLA becoming softer. The elongation at break of PLA increased when plasticizers were introduced into PLA macromolecules, reducing the interaction and bonding of PLA chains. For example, when mixing PLA with PEG (two PEG types with different molecular weight, PEG 400 and PEG 1,500), the tensile strength of PLA decreased rapidly from 66 MPa to 18.5- 18.7 MPa while its elongation at break increased by more than 100 times (Table 4) [15]. As a result, PLA becomes more flexible and it can be applied to packaging and film products.

The mechanical properties of PLA depend on temperature. When increasing the temperature from -20 ^{o}C to 40 ^{o}C, the tensile strength of PLA decreased while its elongation at break did not change (Figure 3). The tensile strength of PLA was higher than that of low density polyethylene (LDPE), poly(vinyl chloride) (PVC) or blend of PLA and polybutyrate adipate terephthalate (PBAT) [16].

3.3. Thermal properties

PLA has a higher melting temperature (T_m) and crystallization temperature (T_c) than LDPE and high-density polyethylene (HDPE). It is difficult for PLA to degrade by heat or thermal – oxidation as compared to LDPE and HDPE. At temperatures greater than the glass transition temperature (T_g), PLA changes from the glassy to the rubbery state. When PLA is heated to a temperature greater than T_g, it gradually changes to a viscous form. At temperatures below T_g, PLA is in the glassy state and is capable of stretching when cooled down to a second transition or β-transition temperature of about -45 °C. Below this temperature, PLA is a rather brittle polymer. The thermal properties of PLA are highly dependent on the stereostructure (Table 5). PLLA has a T_m of 170 - 183 ^{o}C and a T_g of 55 - 65 ^{o}C while PDLLA has a T_g of 59 ^{o}C. The T_m of PLLA can increase from 40 - 50 ^{o}C and this temperature also increases to 60 - 190 ^{o}C when it has been blended with PDLA. Melt enthalpy of 100 % crystalline PLA (ΔH°_m) is 93 J/g. The T_m and the degree of crystallization of PLA depend on the molecular weight, purity, crystallization kinetics, etc. [17]. The thermal stability of PLA decreases rapidly under high temperature and humidity conditions. The oriented PLA and non-oriented PLA have the same T_g value, around 57 - 60 ^{o}C [12]. For PLA combined with poly(glycolic acid), the T_g of PLA decreased slightly (5 - 10 ^{o}C) [11] while for PLA blended with PEG, the T_g of PLA decreased sharply, from 60 ^{o}C to 22 ^{o}C [15].

Table 5. Thermal properties of some PLA types [13, 17].

Properties	**PDLA**	**PLLA**	**PDLLA**
Melting temperature (T_m, ^{o}C)	~180	170–183	Variable
Glass transition temperature (T_g, ^{o}C)	50 - 60	55 - 65	Variable
Degradation temperature (T_d, ^{o}C)	200	200	185-200

Due to its high moisture permeability index and low T_g, PLA is difficult to mold at high temperatures compared to PE and PLA having low stability. Carrasco *et al.* studied the chemical structure, degree of crystallinity, thermal stability and other properties of PLA after processing on industrial plastic processing machines (injection and extrusion after post- injection) with or without annealing process (Table 6) [18].

Table 6. DSC parameters and XRD results of PLA samples [18].

Sample	**Heating cycles**	**T_g (°C)**	**Cool crystallization**		**Melting**		**XRD**
			T_c (°C)	**X_{c-c} (%)**	**T_c (°C)**	**X_{c-c} (%)**	**X_c (%)**
PLA-I	First cycle	65	125	4.1	154	4.5	-
PLA-I	Second cycle	64	133	0.3	156	0.3	-
PLA-EI	First cycle	67	-	-	154	33	45.1
PLA-EI	Second cycle	64	128	8.4	154	7.8	-
PLA-EIA	First cycle	64	133	2	156	1.9	-
PLA-EIA	Second cycle	68	-	-	154	34.5	47.3

The authors found that PLA processing caused a reduction in the molecular weight of PLA (determined by gel permeation chromatography) by breaking the PLA macromolecular chains. The degree of crystallinity of PLA was determined by differential scanning calorimetry (DSC) and X - ray diffraction (XRD) methods. The rapid cooling process of the PLA sample after injection molding hardly or less causes a re-arrangement in the crystalline structure of PLA. In contrast, after annealing, a crystalline structure of PLA was formed. By using the DSC method, the authors determined the degree of crystallinity of injection PLA (PLA - I), extrusion after post - injection (PLA - EI), and annealed PLA (PLA - EIA) to be 4 %, 8 %, and 33-35 %, respectively. By using the XRD method, the degree of crystallinity of annealed PLA was determined to be 45-47 %. PLA had a higher thermal stability (~331 °C) than processed PLA (323-325 °C) [18].

Mohamed *et al.* also reported the effect of annealing process on the thermal properties of PLA. Increasing PLA annealing time of PLA from 0 to 24 hours could lead to an increase in the degree of crystallization of PLA (Table 7). The PLA sample annealed for 24 hours had a thermal conductivity of 0.0904 W/(m.K) and a T_g of 59.0 ^oC, an increase of 40.59 % and 11.33 %, respectively, compared to the unannealed PLA. An annealing time from 1 to 3 hours at 90 ^oC was suitable for PLA to apply as a green thermal insulation material (with thermal conductivity of 0.0798-0.0865 W/(m.K)) [19].

Table 7. Thermal properties of some PLA types [19].

Annealing processing interval (h)	**T_g (°C)**	**T_c (°C)**	**T_m (°C)**	**ΔH_c (J/g)**	**ΔH_m (J/g)**	**χ_c (%)**
Fast (0)	53	89.9	168.4	19.2	50.6	33.8
0.5	57.6		168.7		48.8	52.5
1	56		168.6		47.7	51.3
3	56.4		168.5		50.3	54.1
10	57.6		168.8		54.5	58.6
17	56.6		168.3		60.3	64.8
24	59		169.7		54.3	58.4

The coefficient of linear thermal expansion (CTE) is an important parameter to evaluate the thermal deformation of polymers and plastics, especially polymers with a large CTE index. Two PLA discs prepared using 3D printing technology had a filling degree of 20 % (PLA 20) and 40 % (PLA 40). The CTEs of PLA 20 and PLA 40 were 4.17×10^{-4} [mm/mm.^oC] and 4.55×10^{-4} [mm/mm.^oC], respectively [20].

3.4. Gas permeability

PLA has good gas permeability. Table 7 presents the gas permeability of some common thermoplastics [21, 22]. The gas permeability of PLA, especially for N_2 and O_2, is much lower than that of PE. The CO_2 permeability of PE is many times higher than that of PLA. This means that PLA shields the air much better than PE. In addition, PLA has good odor retention [21, 22].

The shielding ability and the gas permeability coefficient (including oxygen and CO_2) of PLA are smaller than those of polystyrene (PS) but almost similar to those of PET (Table 9). It is noteworthy that the water-vapor permeability of PLA does not change significantly with relative humidity even though PLA is a polar polymer. The decrease in water-vapor permeability of PLA with increasing temperature is an advantage of PLA for use as a multilayer structural encapsulation material [23].

Table 8. Gas permeability of PLA, HDPE, LDPE, and PET [21-22].

Gas permeability (10^{-10} gm/m^{2}sbar)	**PLA**	**HDPE**	**LDPE**	**PET**
CO_2	27.7	62	160	12
O_2	1.21	10	28	0.76
N_2	-	2.6	7.2	0.041

Table 9. Water-vapor transmission rate and oxygen transmission rate of PLA, PET and PS [23].

Sample	**Thickness (mm)**	**Water-vapor transmission rate [g(m^2/d)]**	**Water-vapor permeability coefficient [kg/m/(m^2/s/Pa)]**	**Oxygen transmission rate [cc(m^2/d)]**	**Oxygen permeability coefficient [kg/m/(m^2/s/Pa)]**
PET	18	3.48	2.82×10^{-15}	9.44	6.95×10^{-19}
PS	18	5.18	4.18×10^{-15}	531.58	3.91×10^{-17}
PLA	20	15.30	1.34×10^{-14}	56.33	4.33×10^{-18}

3.5. Electrical properties

Electrical properties of PLA such as dielectric constant, recovery intensity (calculated from the difference of dielectric constant at very low frequencies and dielectric constant at very high frequencies) and recovery time depend on crystallinity content in PLA, time of thermal impact on the PLA sample, etc. Table 10 gives dielectric constant values at very low frequencies (ε_{r0}), dielectric constants at very high frequencies ($\varepsilon_{r\infty}$), recovery intensity ($\Delta\varepsilon$) and recovery time (τ) of the original PLA sample with 5% crystallinity, before heat treatment (denoted as PLA-0) and the PLA sample with 42 % crystallinity, after 15 minutes of heat treatment at 80 °C (denoted as PLA-A). It can be seen that the recovery intensity value of PLA-0 decreased significantly after heat treatment, from 2.15 to 0.88. This can be explained by the crystallization process after heat treatment which restricts/prevents the orientation of the dipoles. In addition, the τ value of the PLA-A sample increased very strongly, 7 times higher than that of the PLA-0 sample. Thus, crystallization in PLA after heat treatment contributed to the suppression of dipole orientation [24].

Table 10. Dielectric constant, recovery intensity and recovery time of PLA before and after treating at 80 ^{o}C [24].

Sample	**$\varepsilon_{r\infty}$**	**ε_{r0}**	**$\Delta\varepsilon$**	**τ (μsec)**
PLA-0	2.72	5.24	2.15	56.8
PLA-A	2.03	3.97	0.88	379.9

Table 11 presents some electrical properties (dielectric constant and dielectric loss angle tan (tanδ)) of PLA (transparent) and PLA added TiO_2 pigment (white), compared with acrylonitrile - butadiene copolymer – styrene (ABS) (transparent) fabricated by 3D printing method. It can be seen that the dielectric constants of both PLA and ABS were relatively small. The dielectric constant of transparent PLA was 2.7 - 2.9, which was smaller than that of transparent ABS. When adding TiO_2 into PLA, the dielectric constant of PLA increased to 3.1 - 3.2. TiO_2 had a significant effect on the dielectric constant of PLA. Transparent ABS had the largest tanδ. This value varied when compared with transparent PLA or white PLA. As sample thickness changed, the tanδ of PLA changed more than its dielectric constant. This can be explained by the air voids appearing more between the layers in the PLA structure. However, there was no difference in tanδ between the transparent and white PLA samples [25].

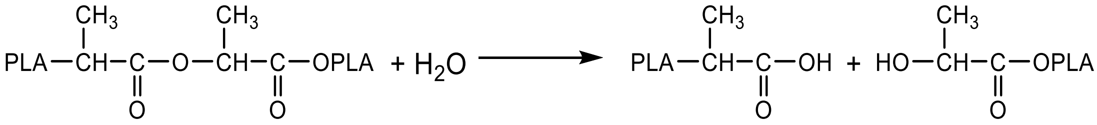
Table 11. Dielectric constant and dielectric loss tanδ of PLA and ABS [25].

Sample	**PLA**				**ABS**
Color	White		Transparent		Transparent
Thickness (mm)	0.5	1	0.5	1	0.5
Dielectric constant (-)	3.1094	3.2107	2.6699	2.8514	3.0856
Tanδ (-)	0.0053	0.0073	0.0050	0.0075	0.0269

The breakdown voltage or breakdown strength of PLA was temperature dependent, reaching about 4 MV/cm in the temperature range of 0 - 50 °C, which was equivalent to that of LDPE. At temperatures higher than 50 °C, the breakdown voltage of PLA decreased sharply with increasing temperature and it had a value of 2.5 MV/cm at 80 °C. Below 0 °C, the breakdown voltage of PLA dropped to 2.5 MV/cm at −20 °C, which was equivalent to that of PVC. In the range of 0 – 50 °C, PLA/PBAT blend had a breakdown voltage of 1 MV/cm, smaller than PLA and equivalent to PLA in the range of −20 – 10 °C. Blending PLA with PBAT can help PLA become more flexible but reduce the breakdown voltage of PLA. However, the breakdown voltage of polymer blend PLA/PBAT was still higher than that of PVC in the range from −10 to 60 °C [16].

3.6. Chemical properties

PLA is a saturated polyester which is easily hydrolyzed by chemical agents and enzymes of microorganisms. It is also easily decomposed under the influence of high temperature, sunlight radiation, etc. In a humid environment, especially when in the presence of acids and bases, PLA is hydrolyzed and the ester groups of its main chain were cleaved, leading to a decrease in the molecular weight of PLA. In aqueous media, PLA degradation is mainly due to hydrolysis of ester bonds and occurs randomly along the polymer chain:

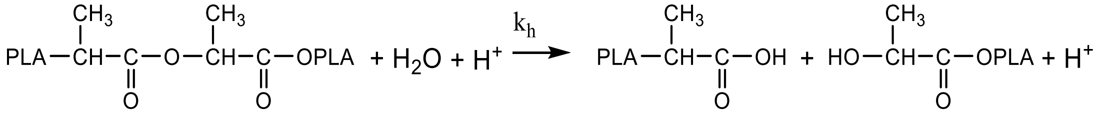


$$\text{PLA}-\overset{CH_3}{\overset{|}{CH}}-\underset{O}{\underset{\|}{C}}-O-\overset{CH_3}{\overset{|}{CH}}-\underset{O}{\underset{\|}{C}}-\text{OPLA} + H_2O \longrightarrow \text{PLA}-\overset{CH_3}{\overset{|}{CH}}-\underset{O}{\underset{\|}{C}}-OH + HO-\overset{CH_3}{\overset{|}{CH}}-\underset{O}{\underset{\|}{C}}-\text{OPLA} \quad (4)$$

The end-chain carboxylic acid groups can catalyze and promote faster the hydrolysis process of PLA (self-catalyzed mechanism). This mechanism is evident when the PLA sample was immersed in pH 7.4 buffer at 37 °C: the pH at the sample surface was maintained at 7.4

while the pH in the deeper layer inside the sample decreased because of the formation of end-chain acid groups of PLA [26]. The dispersion ability of the oligomers into the buffer medium was difficult due to the sample thickness. PLA oligomers containing the end-chain carboxyl groups can escape from the sample when the sample thickness was about 200-300 μm. Samples with thickness thinner than 200 μm could degrade much more slowly due to the rapid escape of oligomers containing the end-chain carboxyl groups into the medium, reducing the autocatalytic effect [27]. The self-catalyzed PLA hydrolysis reactions take place as follows:

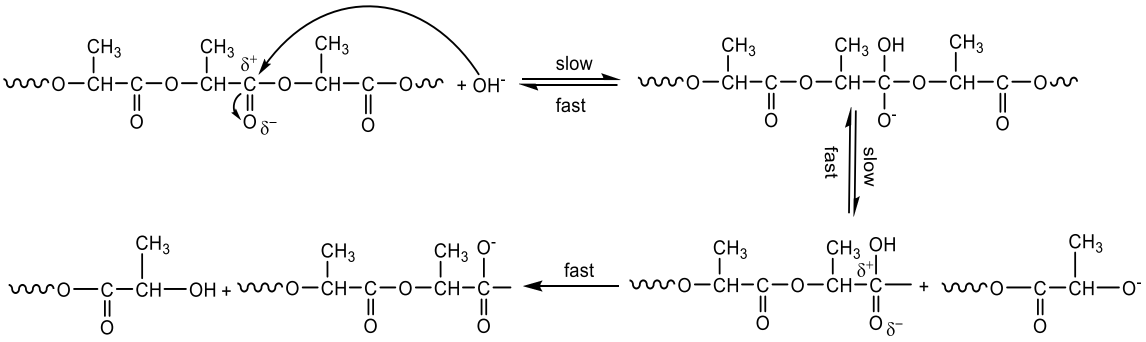
$$\mathrm{RCOOH} \overset{K_a}{\rightarrow} \mathrm{RCOO^-} + \mathrm{H^+} \qquad (5)$$



$$\mathrm{PLA{-}CH(CH_3){-}C({=}O){-}O{-}CH(CH_3){-}C({=}O){-}OPLA} + H_2O + H^+ \xrightarrow{k_h} \mathrm{PLA{-}CH(CH_3){-}C({=}O){-}OH} + \mathrm{HO{-}CH(CH_3){-}C({=}O){-}OPLA} + H^+ \qquad (6)$$

Acid and base catalysts can promote the hydrolysis process of PLA. The results of PLA hydrolysis in the media with pH = 2.0 (0.1 N HCl solution or D,L-lactic acid solution), pH = 7.4 (phosphate buffer) and pH = 12 (0.01 N NaOH solution) showed that the hydrolysis of PLA in alkaline medium occurred faster than in neutral medium. In acidic media, the PLA hydrolysis occurred at a rate equal to that in neutral media [28, 29]. In alkaline media, OH^- ion is a very strong nucleophile agent that easily attacks the carbon atom in the carbonyl bond of PLA, making PLA hydrolysis faster as presented in Scheme2.

In acidic medium, the hydrolysis of PLA has additional stages of protonation and proton separation. The protonated ester groups make the carbon atom in the carbonyl bond becomes more active and susceptible to attack by the nucleophile (H_2O) [30]. Then, acyl-oxygen cleavage forms lactic acid oligomers or PLA molecules containing terminal -COOH groups. These groups in turn catalyze the hydrolysis of PLA following the "self-catalysis" mechanism as described above [26, 31].



Scheme 2. Hydrolysis reaction of PLA.

When packaging films, bags, and boxes made from PLA contact with food, lactic acidosis may occur during storage time because PLA decomposes in high humidity condition. The major compounds degraded from PLA are LA, lactide and oligomers. The survey results show that PLA is stable at 40 °C for 6 months, decomposes at 60 °C or above T_g and the degree of lactic acidosis increases. Regarding the toxicity of lactic acid, the Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO/Expert Committee on Food Additives (JECFA)) states that both D-lactic acid and (DL)-lactic acid leached from PLA should not be used in infant food packaging [23].

PLA is susceptible to microbial effects. The decomposition process of PLA by microorganisms consists of two stages. In the initial stage, microorganisms secrete enzymes that catalyze the hydrolysis of PLA into short-chain fragments of a size small enough for the microorganisms to use as a source of nutrients limited size of PLLA oligomers that microorganisms can digest is 11,000) [32]. In the later stage, microorganisms digest the above hydrolysis products to produce biomass, CO_2 and H_2O. PLA is degraded by some bacteria, such as *amycolatopsis* sp. One of the most effective PLA-degrading enzymes is *proteinase* K.

Table 12 indicates the cleavage of PLLA macromolecules and PLLA hydrolysis mechanism under different pH and temperature conditions, with and without enzymes. It is noteworthy that a random cleavage of the PLLA macromolecules occurred in all investigated conditions. The enzymatic hydrolysis and degradation of PLA in the microbial media are also greatly influenced by the molecular weight and crystallinity of PLA [33]. The smaller the molecular weight of PLA, the greater the rate of biodegradation. As the crystal content of PLLA increased, the strength of PLA also increased. PLA obtained by LA polymerization had a low molecular weight and contained many end-chain carboxyl and hydroxyl groups, so they can react with monomers or polymers containing terminal functional groups such as carboxyl, hydroxyl, amino, anhydride acid, etc. As a result, the PLA circuit was extended, increasing the molecular weight of PLA.

Table 12. Cleavage of PLLA macromolecules and hydrolysis mechanism of PLLA film under different conditions [33].

pH	**Temperature (^oC)**	**Enzyme**	**Hydrolysis mechanism**	
			Cleavage	**“Corrosion” mechanism**
2.0	37	-	Random in the amorphous region	Crevice
7.4	37	-	Random in the amorphous region	Crevice
12.0	37	-	Random in the amorphous region	Surface
7.4	37	*proteaza* K	Circuit cleavage predominates in free-terminal chains and these chains were compacted in the amorphous region	Surface
7.4	97	-	Random in the amorphous region	Crevice

PDLA and PLLA are more resistant to saline than PDLLA. The half-life of PDLA and PLLA at 37 ^oC in normal saline is 4 – 6 months and that of PDLLA is 2 – 3 months [13]. The thermal decomposition of PLA occurs in the temperature range of 325 - 375 °C to form lower molecular weight chain-cut products (oligomers), volatile organic compounds, and CO [34].

4. TECHNICAL APPLICATIONS OF POLYLACTIC ACID

4.1. Packaging materials

PLA is used in food packaging, including direct contact applications where it is classified as safe (GRAS). The packaging films based on PLA is very effective for products such as fresh fruits, coffee, foods, confectionery, cold drinks, etc. It is used as high-transparency bottles to replace PET bottles, as food and beverage containers, cups, spoons, overwrap, etc. [23, 35–37]. Table 13 presents the potential applications of PLA as a packaging material for various foods.

Table 13. Potential applications of PLA as a packaging material [23, 35 - 37].

Kind of food	Properties of packaging material	Producer
Bottled water	Shielding gases, moisture and light resistance	Biota^{TM}
Bottled soft drinks	Shielding gases, moisture and light resistance, inert with fragrance contamination	Noble^{TM}
Milk	Shielding gases, moisture and light resistance	
Yogurt	Mechanical strength, shielding oxygen, CO_2, moisture and fat resistance	Dannon^{TM}
Cheese	Shielding gases, moisture and light resistance	
Butter/Margarine	Mechanical strength, shielding gases, and moisture resistance	

PLA is also known as a green food packaging material because it can keep the smell and freshness of food after processing, including processing at high pressures (350, 450, 650 MPa for 15 minutes). Some modifiers can be added to PLA to improve its mechanical properties, gas and UV shielding properties, anti-microbial ability, and anti-oxidation ability, especially, modified PLA in the form of nanocomposites [35]. PLA blends with starch, protein and biopolymers have been studied and developed for biodegradable and renewable packaging materials. Packaging materials based on a combination of PLA with organic acids, antibiotics made from bacteria - bacteriocins (e.g. nisin), extracts from fruits such as lemon and grapefruit, essential oils, enzymes (e.g. lysozyme), and metals (e.g. silver zeolites) are potential antimicrobial packaging materials. They showed inhibitory effects on *Listeria monocytogenes*, *Escherichia coli*, *Staphylococcus aureus*, and *Micrococcus lysodeikticus*. Native antibacterial substances were also coated on the surface of antibacterial packaging products from PLA [38].

Recently, Purac Company (Netherlands) has developed heat-stable PLA fabrication technology to make products such as cups, bottles, and jars for hot foods and beverages. These products can operate in a temperature range of 80 - 120 °C. Purac PLA cups held boiling water and hot coffee without distortion compared to amorphous PLA cups [39].

The multilayer film of PLA coated with SiO_2 has good shielding ability, thus it is suitable for cheese packaging. This film can keep the quality of cheese for 65 days [40]. Polymer blends based on PLA, namely cellulose nanofibers and casein were very suitable for producing thermoformed packaging materials with tensile strength higher than the original PLA films [40-41]. Reis *et al.* fabricated beeswax-coated trays based on PLA and thermoplastic starch by flat extrusion techniques, rolling and heat processing. The water-vapor permeability of PLA/thermoplastic starch trays was significantly reduced due to the hydrophobic nature of the beeswax coating. It is very suitable for preserving fresh fruits and vegetables [42].

4.2. Agriculture

PLA is used as a biological membrane to accelerate fruit ripening on crops, retain fertilizers and moisture, inhibit the growth of mold, weeds and insect damage, and help plants cope with changes in weather. Modified PLA is also used as nursery pots, pots and a number of other items. It has the ability to decompose into low molecular products, which gradually enter the soil after a certain period of use. These decomposition products can become a source of nutrients for plants [43].

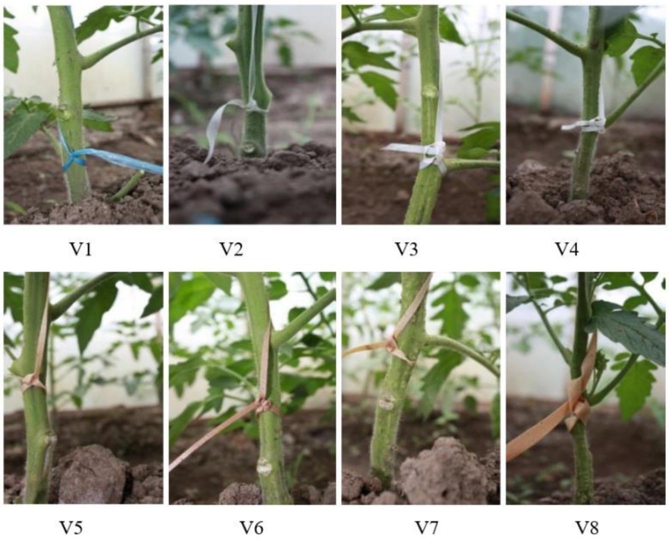


Figure 4. Behavior of tomato yarns in green house trials. V1: Romanian market – PP, V2: Incerplast – PVC, V3-V8: PLA composite fibers (UNIPIX) [44] (Reprinted from Maria *et al.* with permission from Romanian Biotechnological Letters).

Maria Rapa *et al.* fabricated composite fibers based on PLA, wood fiber, and aliphatic-aromatic copolyester (ECOFLEX F BX 7051) from 1,4-butandiol, adipic acid and terephtalic acid monomers (UNIPIX) by melt extrusion method. These fibers were applied as yarns (a thickness of 0.3-0.5 mm, minimum resistance of 24 N) to support tomato plants during their growth in greenhouse trials (Figure 4). The authors showed that the tomato yarn products V3, V4, V6, V8 and control V1 have good quality and proper staking [44].

In recent years, FkuR Kunststoff GmbH Company has manufactured BIO-FLEX® in particular from co-polyester and PLA. Packaging films made from these blends have a high barrier against moisture, oxygen and aromas with an adequate permeability ("breathability") [45].

4.3. Textiles

Due to its small moisture absorption, low flammability, and UV resistance, PLA is very suitable for applications in the textile industry (yarns, nonwovens, blankets, carpets, mattress, sportswear, sanitary products, diapers, etc.) [35, 46 - 51]. Table 14 shows a comparison between nature, recyclability and biodegradability of PLA fiber and PET fiber. PLA was produced from LA which was fermented from corn flour. This monomer is both renewable andnon-polluting. PET was synthesized from petroleum sources, and it is not biodegradable, easily causing environmental pollution [45 - 47].

Karst *et al.* investigated the washing process of PLA fabrics for 50 cycles at different pH solutions (8 or 10), washing temperature (35 ^{o}C or 55 ^{o}C), line drying conditions (21 ^{o}C/65 % relative humidity or in a rotary dryer at 50 ^{o}C or 70 ^{o}C). The obtained results show that the residual mechanical properties of PLA fabrics washed at pH 8 and 35 ^{o}C, dried at 21 ^{o}C, 65%

relative humidity, were greater than those of the samples washed at pH 10 and 55 ^{o}C, dried in a rotary dryer at 70 ^{o}C. The authors recommended washing and drying conditions for PLA fabrics as follows: mixing detergent with a solution of pH 8, cold washing at 35 ^{o}C and line drying. If drying in a rotary dryer is required, it should be kept at a low temperature or maintained at 50 ^{o}C [47].

Table 14. Nature, recyclability and biodegradability of PLA fiber and PET fiber [46].

Comparison index	**PLA fiber**	**PET fiber**
Nature	Natural source and renewable	Petroleum source and non-renewable
Recyclability	Fully recyclable	Fully recyclable
Biodegradability	Complete	Completely non-degradable

The FIBFAB project finished in 2019 achieved its goal of producing PLA based fabrics (PLA/wool fibers and PLA/cotton fibers) for men and women clothing applications. This project selected the optimal parameters for obtained fibers to be thinner (less than 3 dtex) and special attention in mechanical spinning process (the friction between the fibers must be checked carefully when spinning at high speeds). Fabrics made from PLA fiber combined with cotton or wool fibers had outstanding advantages such as better breathability, more hydrophobicity, more UV resistant, better flame resistant, suppression and lower density as compared with the polyester fibers (PES) [48, 49]. A new fiber material – FIBFAB – based on commercial PLA and additives such as crystallization agent, processing aid and hydrolytic stabilizer has been fabricated. The mechanical properties of FIBFAB were reduced from 29 cN/tex to 18 cN/tex after some washing and drying cycles [49].

4.4. Transportation

Currently, PLA and PLA-based composites are widely used in the field of transportation due to their good mechanical properties, lightness, and environmental friendliness. In 2012, Fiat Automobile Company (Italy) developed "green" composite materials based on PLA to replace petroleum-based polymers for several parts and components in cars. In the near future, PLA-based composite materials will be applied more in human- and environment-friendly automobiles [51].

In 2003, Toyota Company (Japan) used PLA-based composite reinforced with kenaf fibre to manufacture car tires using a die-casting technology. Compared with conventional car tires, tires made of PLA-based composite reinforced with kenaf fibre had greater durability. In addition, this composite has also been used to manufacture other car parts and components such as seats, floor coverings, handles, etc. [52].

Amani Bouzouita *et al.* prepared PLA/poly(methyl methacrylate) (PMMA) blend by melt mixing method. This blend had a heat deformation temperature guaranteed for injection-molded parts and components in the automotive or electronic industries. To improve the strength of this blend, some modifiers have been added such as Biomax® Strong 120 (BS) (an ethylene acrylate containing epoxy groups), Ultranox 626A, etc. Tables 15 and 16 present the composition of PLA/PMMA blend samples and their mechanical properties. It can be seen that the elongation at break of the blend was significantly enhanced in the presence of BS [53].

By 3D printing technology, PLA has been used to manufacture a number of car parts and components (the largest application is car covers). The shape of the parts or their components will be designed by a computer software [54].

Table 15. Composition of PLA based blend samples [53].

Sample	PLA (wt.%)	PMMA (wt.%)	BS (wt.%)
PLA	100	0	0
PLA/BS	83	0	17
PLA80/PMMA20/BS	66.4	16.6	17
PLA70/PMMA30/BS	58	25	17
PLA50/PMMA50/BS	41.5	41.5	17
PLA30/PMMA70/BS	25	58	17
PLA20/PMMA80/BS	16.6	66.4	17
PMMA/BS	0	83	17
PMMA	0	100	0

PLA/fibrous flax composites containing 30 wt.% and 40 wt.% of fibrous flax were fabricated by melt extrusion on a twin-screw extruder. These composites had good mechanical properties, met the requirements and were suitable for automobile panels [55]. In another report, PLA/fibrous hemp composites with honeycomb sandwich core structure were fabricated using 3D printing technology. These honeycomb cores had a high durability. In the flatwise direction, the honeycomb cores had a compressive modulus of 850 MPa and a compressing strength of 47 MPa. In the edgewise direction, they had a compressive modulus of 625 MPa and a compressing strength of 15 MPa. Therefore, they could be used to fabricate small aerospace parts and automobile prototypes such as car fog light covers and unmanned aerial vehicle (UAV) frame [56].

Table 16. Mechanical properties of PLA based blend samples [53].

Sample	Tensile strength (MPa)	Young modulus (GPa)	Elongation at break (%)
PLA	68± 2	3.2 ± 0.1	2,8 ± 0.2
PLA/BS	44 ± 2	2.3 ± 0.1	148 ± 28
PLA80/PMMA20/BS	46 ± 1	2.4 ± 0.1	133 ± 11
PLA70/PMMA30/BS	49 ± 3	2.5 ± 0.1	116 ± 4
PLA50/PMMA50/BS	52 ± 1	2.6 ± 0.1	66 ± 26
PLA30/PMMA70/BS	53 ± 1	2.5 ± 0.1	44 ± 7
PLA20/PMMA80/BS	52 ± 1	2.4 ± 0.1	33 ± 5
PMMA/BS	23 ± 5	1.7 ± 0.2	2 ± 0.3

PLA/carbon composites fabricated with 3D printing technology had good elongation at break and were suitable for application in parts and components of automobiles, aircraft and spacecraft [57]. Ford Company (USA) has manufactured car roof systems and car mats from PLA based composites combining PLA with some suitable additives [58]. In 2007, Mitsubishi Co. Ltd. (Japan) applied PLA and nylon 6 fiber to produce car mats [58].

4.5. Electrical and electronic engineering

PLA based materials have been applied in electrical and electronic fields. Carolin Henning *et al.* have prepared composites based on PLA, cellulose acetate and zinc pyrophosphate (ZnPP) as flame retardants. These materials have been used to fabricate wire junction panels [59]. PLA fabrics have been developed for piezoelectric textiles. Elastic, transparent piezoelectric films have been also prepared by interlacing PLLA and PDLA [60].

PLA combined with various additives is increasingly used to fabricate products in the electrical, electromagnetic and electronic fields by 3D printing technology [61], for example, conductive PLA/multi-walled carbon nanotube materials [62]. PLA was mixed with medium-sized carbon nanopowder to fabricate 3D-printed wires for use in robots, unmanned aerial vehicles (UAVs) with high mechanical strength [63].

A low-cost 3D - printed PLA plastic conical antenna with conductive paint coating was fabricated to radiate or receive electromagnetic waves [64]. This antenna had a radiation efficiency of more than 90 % up to 5 GHz and an impedance bandwidth of 20:1. In 2002, Mitsubishi Plastics Co. Ltd. (Japan) manufactured heat-resistant PLA by injection molding technique and applied it to the housing of the Sony Company "Walkman" music player [65].

4.6. Other fields

PLA combined with zeolites, hydrophilic additives, superhydrophobic additives, and lipophilic additives can be used as adsorbents for phosphorus-containing compounds, oils in the process of wastewater treatment [66, 67]. Permeable membranes, super-hydrophilic, superhydrophobic, and super-oleophilic porous fabrics fabricated by 3D printing technology can be used to separate oil/water systems. Yan C. *et al.* prepared PLA/Fe composite hydrogels to separate oil/water systems with a separation efficiency of 85 % [68]. The 3D printed hybrid porous filter material based on PLA, graphene oxide and chitosan can adsorb crystal violet dye quite well [69]. Similarly, metallic-organic PLA framework (MOF) materials can remove Malachite blue - triphenylmethane (residues in fish) from wastewater [70]. The porous 3D printed PLA/black coal composite can be used to adsorb volatile organic substances (benzene, toluene, ethyl benzene) in water [71]. PLA fibers can be used to fabricate gears, worm gears, school and office things by 3D printing technology [72, 73]. Composites based on PLA and basalt fibers can be applied for preparation of texture materials in the field of construction [74].

5. APPLICATIONS OF POLYLACTIC ACID IN BIOMEDICINE

5.1. Tissue engineering

Since the 1980s, tissue transplantation has been widely applied in the biomedical field thanks to the regeneration of living tissues by linking living cells to a scaffold system using biological materials. The requirements of an ideal scaffold which is used for tissue engineering are biocompatibility (not inducing any immune response), porosity (allowing cell or tissue growth and the removal of metabolic waste), good mechanical properties (archiving local stress and maintaining pore structure for tissue regeneration), and biodegradability. Many types of biological materials have been studied in clinical trials, including metallic and inorganic materials. However, these materials are not biodegradable and could be stored in the body causing adverse reactions. Biopolymer based scaffold systems are typically in 3D structure with high biocompatibility, low toxicity, biodegradability, sufficient porosity, great design flexibility, and suitable mechanical properties and size so that cells or tissues can grow and develop well on them under special physiological conditions and eliminate toxins in the process of metabolism. Biopolymers and their copolymers, especially PLA and modified PLA, are potential polymers for this application [35, 75-78].

PLA scaffolds have been used in tissue engineering to regenerate dead epithelial cells. PLA/poly (glycolic acid) (PGA) blend is used in treatment of short bowel syndrome [75]. PLA coated PGA sheets can make stents (a plastic tube that expands narrowed or blocked blood vessels). The PLA/PGA stents are used in the treatment of cardiovascular disease. Electrophysiological testing results showed that active ion transport in PLA/PGA scaffolds contributed to the promotion of proliferation of mucosal cells. These polymer blends have been approved by the FDA for clinical application in humans. Some cases of scaffolds in clinical use are the PGA/PLA blends, polydioxanone namely BioSeed®-B and BioSeed®-C (Biotissue Technologies AG, Freiburg, Germany) applied for cartilage repair [13]. Qiong Li *et al.* have fabricated a PGA/PLA scaffold (20 wt.% of PLA) with the shape of human nose (Figure 5) [79]. The nose-shaped scaffold achieved a precise shape compared to its positive mold.

Yue Long Wang *et al.* have developed PLA/poly(ε-caprolactone)-poly(ethyleneglycol)-poly(ε-caprolactone) (PCEC) hybrid fibers that create bone tissues suitable for human pulmonary mesenchymal stem cells (hPMSC) with high self-renewal ability. The PLA/PCEC fibers were fabricated by electrospinning method with nano- to micro-sized fibers with many nanopores on the single fiber surface. As the PCEC content increased from 0 wt.% to 50 wt.%, the mean fiber diameter and water contact angle of the PLA/PCEC fibrous scaffold decreased while their mechanical properties and thermal stability increased sharply. The PLA/PCEC fibrous scaffold is suitable for hPMSC cell attachment and proliferation thanks to the porous three-dimensional (3D) extracellular structure. The hPMSCs cells can interact and integrate well with surrounding PLA/PCEC fibers, proliferate and spread evenly over the fibers. However, after 2 weeks of culture in bone tissue, the hPMSCs cells on PLA/PCEC fibrous scaffold showed a mineralized background with red alizarin dye. Thus, the PLA/PCEC fibrous scaffold has good cell compatibility and is suitable for *in vitro* bone tissue generation and potential applications in bone tissue engineering [76]. A 3D microfibrous PLLA scaffold has been fabricated using electrospinning method. The level of osteoblast proliferation was enhanced 1.8-fold when using this scaffold as compared to that of 2D nanofibrous membranes. The results of the *in vivo* test on rabbits indicated the cell infiltration and bone formation on the 3D PLLA scaffold after 2 and 4 weeks of testing [80]. The 3D printed PLGA scaffolds can support the proliferation and osteogenic differentiation of osteoblasts. These scaffolds can be used for bone regeneration [81].

Research on technological conditions to fabricate PLA based scaffolds using different techniques such as 3D printing, electrospinning, plasma, etc. still attracts the attention of experts. In addition, studies on improving the porous and mechanical properties of PLA based scaffolds are necessary for optimal tissue engineering applications of these biomaterials.

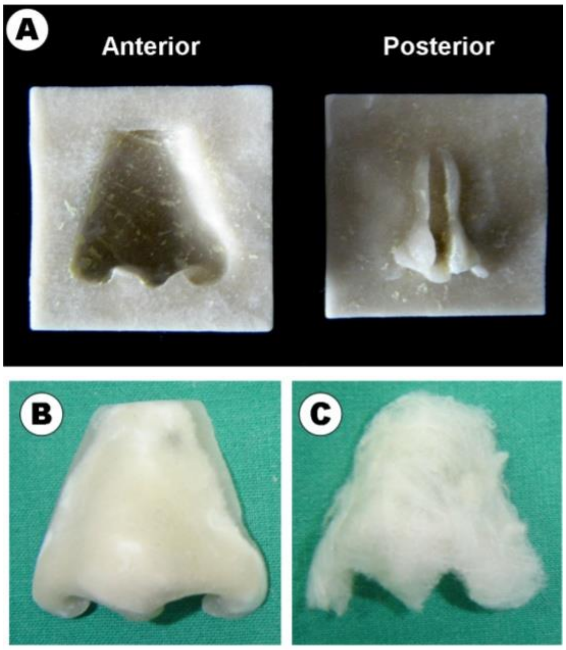


Figure 5. Mold preparation and fabrication of nose-shaped scaffolds. (A): Resin negative mold: anterior part and posterior part; (B): Resin positive mold; (C): Nose-shaped PLA/PGA scaffold [79] (Reprinted from Li *et al.* with permission from IntechOpen).

5.2. Drug delivery

PLA has high biocompatibility. After a period of use, it is biodegraded and does not cause toxicity to the human body. It has the ability to control the rate of drug release and to deliver drugs on usage requirements. Normally, a small amount of PLA is introduced into the human body to slow down the release of the drug and prolong its effects for a long time [82]. PLA is used to deliver tetanus drugs, insulin for type 2 diabetes, paclitaxel and 5 FU for cancer, etc.

PLA has been modified or combined with other polymers to enhance the ability to control drug release as well as drug's bioavailability. PLA based materials were fabricated in various dosage forms: pellets, microcapsules, microparticles and nanoparticles (Table 17) [83].

Table 17. Application of PLA, modified PLA and PLA based copolymers in drug delivery [83].

Materials	Application	Efficiency
PLA- PEG particles	Drug delivery for tetanus treatment	Increase in the drug transport through the nasal mucosa
PLA-b-pluronic-b-PLA copolymer	Insulin delivery for type 2 diabetes treatment	Good control of blood glucose levels
PLA microspheres	Paclitaxel delivery for cancer treatment	Reduction of inflammation
PEO-PLA copolymer	Paclitaxel and 5 FU delivery	Carry of drugs and good control of drug release process
PLA-PEG-PLA copolymer	Paclitaxel and 5 FU delivery	Good control of drug release process
AP-PEG-PLA copolymer	Drug delivery for cancer treatment	The ability to inhibit the growth of cancer cells

C. Liu *et al.* fabricated PLA/ginsenoside Rg3 (extracted from the roots of *panax notoginseng*) microspheres. Ginsenoside Rg3 can be released from the microspheres in pH 7.4 phosphate buffer solution at 37 °C. Its release content reaches 68 % after 2 hours and 89 % after 6 hours of testing. However, the release rate of ginsenoside Rg3 decreased after 6 hours of testing. The ginsenoside Rg3 release process from the microspheres consists of two stages: immediate release and controlled release. The first stage occurs due to the adhesion of the active substance to the microspheres which will release immediately. Thereafter, the release of the active substance slows down due to the diffusion of the active substance inside the microspheres to the solution [33].

PLA-based materials in combination with chitosan (CS) have been used to carry nifedipine - a drug for the treatment of hypertension and cardiovascular disease [84 - 89]. These systems were prepared by solvent casting or microemulsion method. The products were obtained in the form of nanoparticles, films or with a core-shell structure. PLA/CS/nifedipine (PCN) nanoparticles prepared by microemulsion method had drug loading efficiency from 60.96 % to 90 %, depending on the initial content of nifedipine. Observing the scanning electron microscopy (SEM) images of PLA/CS and PCN20N nanoparticles, it can be seen that most of the PLA/CS and PCN20N nanoparticles were spherical in shape. PLA/CS nanoparticles had sizes ranging from 40 to 500 nm and PCN20N nanoparticles had sizes ranging from 40 to 300 nm, in which small nanoparticles (40 - 50 nm) were dominant. However, these nanoparticles tend to agglomerate together. Nifedipine is released from PCN20N nanoparticles in simulated body fluids having different pH values in two stages: a rapid-release stage followed by a controlled, slow-release stage. The nifedipine content released from PLA/CS/nifedipine nanoparticles in different pH buffer solutions was arranged in the order: pH 7.4 > pH 6.8 > pH 2 ≈ pH 1.2. In pH 7.4 solution, the nifedipine content released from PCN20N nanoparticles reached 59.06 % after 8 hours of testing. In acidic solutions (pH 6.8, 2 and 1.2), the nifedipine content released after 8 hours of testing reached 55.29 %, 36.07 % and 35.32 %, respectively. This can be explained by the fact that in an acidic media, the amine groups in chitosan can be protonated, which limits the diffusion of nifedipine from the nanoparticles into solution. As a result, the nifedipine content released from PCN20N nanoparticles in acidic medium was smaller than in neutral medium [85].

Using an *in-vivo* test, PLA/CS/nifedipine nanoparticles showed a more positive effect on the blood pressure of rats than nifedipine alone. These nanoparticles were not toxic to rats. PLA/CS/nifedipine capsules were stable in content and solubility during storage at below 30 °C. The shelf-life of the capsules is expected to be over 24 months under storage conditions at below 30 °C [88].

PLA based materials can be used to prepare stimuli-responsive nano-carrier systems which can be sensitive to pH, heat, light, electric signal or other environmental conditions [13]. Clinical trials of PLA based materials have been still limited in study. This is of fundamental importance for real applications in biomedical therapy. Therefore, the development of PLA based nano-carrier systems with *in vitro, in vivo* tests and clinical trials is very necessary.

5.3. Bond implant

Due to its high strength, similar to that of animal bones, PLA can be used to fabricate or cover 3D structural products such as screws, fixing joint-plates, pins, anchors, cages, etc.). These parts are used to replace metal parts that can corrode in harsh environments (such as human body fluids). PLA-based implants can be used in case of ankle, knee, ulnar fractures, at the foot, pelvis, wrist, cheekbone, and in spondylodeis, etc. [58, 90]. Table 18 lists several commercial products used to fix bones made of PLA materials in the world [58].

Dinh Thi Mai Thanh *et al.* fabricated a nanocomposite based on PLA, magnesium and zinc-doped hydroxyapatite (d-HAp), poly(ethylene oxide) (PEO) and xenetic with PLA/d-HAp/PEO/xenetic ratio of 70/30/5/10 (wt.%/wt.%/wt.%/wt.%) for bone implant applications [91]. The nanocomposite had a Young modulus of 550 MPa and a tensile strength of 18 MPa. Using this nanocomposite, the authors carried out *in vitro* test in simulated body fluids (SBF) and *in vivo* test on femur of dogs. *In vivo* test results showed that most of the dog's parameters returned to normal after surgery. The material in the femur did not cause any inflammatory response, or structural and morphological abnormalities. There was proliferation and growth of bone in the area of implantation, and no image of bone inflammation. X-ray image of the femur of a dog implanted with the nanocomposite 3 months after surgery showed that the surrounding medulla had grown into the material area. However, the density of bone in the material area was lower than that in the surrounding medulla and outer bone cortex. This proves that a certain amount of PLA and HAp in the nanocomposite was gradually absorbed over time.

Table 18. Commercial products made of PLA materials for bone fixation [58].

Producer	**Materials**	**Products**	**Country**
Gunze	Drawn PLLA	Battery, Screw, Miniplate, Rod, Interference screw	Japan
Centerpulse orthopedics	PDLLA	Interference screw	USA
Takiron	Drawn PLLA	Battery, Screw, Miniplate, Rod	Japan
Arthrex	Drawn PLLA	Interference screw	USA
Phusis	P(LLA/DLLA)	Interference screw	France
Linvatec	Drawn PLLA	Suture anchor	USA
Biomet orthopedics	Drawn PLLA	Mini screw	USA
Geistlich biomaterial	P(LLA/DLLA)	Fixation pins for GTR and GBR membranes	Switzerland
Linvatec	PLLA	Drawn Suture anchor	USA
Conmed (bionx implants)	SR-PLLA Drawn PLLA	Battery, Screw, Meniscus arrow	USA
J&J (codman, Depuy and Mitec)	PLLA Drawn PLLA	Rivet for skull Suture anchor	USA

The PLA-PGA copolymer at the site of implant installation has been tested on rabbits to evaluate bone-implant interface. Thanks to its biocompatibility, the copolymer enhanced bone healing, and osseointegration. The presence of the copolymer improved the contact between bone and implant. The PLA-PGA copolymer is potential for application as a bone substitute [92]. PLGA and its composites with carbon fibers and hydroxyapatite were evaluated for their biodegradability in rabbit femoral bone. The modifiers (carbon fibers, hydroxyapatite) promoted regeneration of treated bone tissue and degradation of polymer [93]. PLLA and PDLLA were used as an additional support for titanium plate in fixation of chin fragment. The plate was bendable with forceps at room temperature and maintained the desired position [94]. Self-reinforced drawn poly-l/DL-lactide 70/30 (SR-PLA70) composite rods were implanted in the distal femur of rats from 1 week to 1 years. After 52 weeks of testing, the shear strength and flexural modulus of the rods decreased by 41 % and 43 %, respectively, from their initial values. It can be recorded bone osteotomies and no signs of inflammatory or foreign-body reactions. These rods are suitable for fixation of cancellous bone osteotomies [95].

PLA and its composites-based implants remain attractive in research and development because the use of biomaterial-based implants in bone surgery is a new trend nowadays. The creation of PLA composite implants by new methods and techniques to improve the desired qualities of osseointegration and to control the biodegradation of the implants are very necessary.

5.4. Other biomedical applications

PLA can be applied in the dental field because it is removable and biocompatible. It can be used as an implant material, supporting dental restorations thanks to the osseointegration. PLA also plays the role of dental composite or dental cement in the restoration and sealing process of teeth [96]. Ranjbar *et al*. have fabricated PLA/Al_2O_3 nanoscaffolds as dental resins with higher flexural strength, bending modulus, and compressive strength than composite materials made from traditional plastics [97]. PLA has the effect of skin, tendon, ligament regeneration and wound healing after surgery [96].

PLA sutures could be absorbed by the human body, thus they have been widely applied in modern surgery operators. Thanks to high degradation rate and good mechanical properties, nanofibrous PLGA mats which were prepared by electrospinning and modified with electron beam irradiation can be applied in soft tissue engineering [98]. Shuqiang Liu *et al.* conducted a study on the *in vitro* degradation behavior of sutures based on PLA/carbon nanotubes (CNTs) composites [99].

PLA has high strength and mechanical properties and ability to withstand the impact of external forces, so it is suitable for production of medical instruments. Rankin *et al.* fabricated PLA-based instruments by 3D printing method that can withstand a tangential force of 133 N and these instruments were durable during surgery [100]. In addition, PLA can be sterilized many times without affecting its physical and chemical properties [100]. Because it is virtually hypoallergenic and safe, PLA can be used as a solution in medicine with minimal impact by physiological reactions. It is also suitable for various medical instruments such as needle clamps, hemostatic instruments, forceps and scalpel handles [101].

CONCLUDING REMARKS

PLA has a lot of valuable properties and characteristics including biocompatibility, renewability, transparency, high mechanical strength, thermoplasticity, biodegradability, electrical insulation, high gas permeability, and compostability. The stereostructure of PLA depends on configuration of LA monomers. PLA is mainly synthesized by ROP in industry with the presence of tin(II) bis(2-ethylhexanoate) catalyst. The exploration of novel and well-defined catalysts for PLA synthesis are now being worked on by scientists and producers. This helps to find new catalysts which have good biocompatibility, low toxicity, great stereoselectivity, and excellent catalytic activity to open the application of PLA in biomedicine and infant packaging. Several modification strategies of PLA or blending of PLA with other polymers could enhance PLA properties. However, large opportunities and challenges remain in terms of exploring the modification and characteristics of modified PLA based materials. The development of PLA based materials with excellent properties and characteristics which are suitable for application in technique fields such as packaging, agriculture, textiles, transportation, electronics and electricity would be best to focus future research work with the aim of replacing petroleum based plastics. The increasing application of biomaterials in biomedicine demonstrates the importance of research and development of effective PLA material systems for tissue engineering, drug delivery, implantation and others.

CRediT authorship contribution statement. Nguyen Thuy Chinh: conceptualization, methodology, data analysis, and writing; Thai Hoang: conceptualization, formal analysis, writing, review and editing.

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