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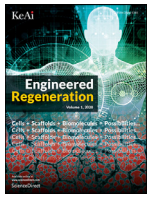

Applications of PLA in modern medicine

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ABSTRACT

Polylactic acid (PLA) is a versatile biopolymer. PLA is synthesized with ease from abundant renewable resources and is biodegradable. PLA has shown promise as a biomaterial in a plethora of healthcare applications such as tissue engineering or regenerative medicine, cardiovascular implants, dental niches, drug carriers, orthopedic interventions, cancer therapy, skin and tendon healing, and lastly medical tools / equipment. PLA has demonstrated instrumental importance as a three-dimensionally (3D) printable biopolymer, which has further been bolstered by its role during the Coronavirus Disease of 2019 (Covid-19) global pandemic. As an abundant filament, PLA has created desperately needed personal protective equipment (PPE) and ventilator modifications. As polymer chemistry continues to advance, so too will the applications and continued efficacy of PLA-based modalities.

1. Introduction

The polymer, polylactic acid, polylactide, or more commonly known by its abbreviation PLA, is a versatile biopolymer. PLA is biodegradable and exhibits thermoplastic behavior. While PLA has modern industrial uses, including textiles and packaging, it has emerged as a pertinent material for bioengineering. Relevant medical applications may vary from tissue engineering regenerative medicine to orthopedic, cardiac, and dental uses. The innate characteristics of PLA lend itself to rapid prototyping and efficient manufacturing in 3D printed constructs. This can be implemented to generate patient-specific tissue engineering scaffolds or rapidly manufacture medical equipment, such as the personal protective equipment (PPE) needed to keep healthcare workers safe during the Covid-19 pandemic. PLA consists of lactic acid monomers which compose its polymeric backbone. PLA monomers may also be referred to as 2-hydroxypropionic acid or cyclic diester lactide. The first recorded synthesis of PLA was in 1932 by Wallace Carother at DuPont laboratories. Since then, the usage of PLA has expanded tremendously. In 2016, the bioplastic market has experienced an 11% annual increase generating a revenue of more than 2.6 billion USD [1]. Engineers and scientists have capitalized on the many applications of this material's advantages [2]. Briefly, advantages include: environmentally friendly, ease of production, recyclable, compostable, biocompatible, and few to no reported carcinogenic effects [3]. PLA may be derived from renewable resources such as carbon dioxide, wheat, corn, and rice. PLA's degradation products are also non-toxic to humans and the environment. PLA uses 25-55% less energy to produce than petrol-based polymers [3]. Ease of PLA production is due to inexpensive and widely available source materials. PLA has been approved by the FDA for direct contact with biological fluids.

1.1. Mechanical properties

Mechanical properties of PLA may vary given the molecular weight of the polymer and degree of crystallinity [4]. Mechanical properties are also governed by the stereochemical configuration of the molecular structures of the PLA backbone. Given that lactide monomers are chiral, mechanical properties can be manipulated through the polymerization of D-lactide, L-lactide, D, L-lactide or meso-lactide. The molecular weight may also be changed through the addition of functional groups to the backbone. These functional groups may include the addition of hydroxyl species, lactic acid, and water [5]. As a result, the user may modify the configurations of the PLA polymer backbone so as to achieve the desired properties. Improved mechanical properties of PLA can be achieved with semi-crystalline PLA over an amorphous assembly of the polymer. Semi-crystalline PLA exhibits the following properties: approximate tensile modulus of 3 GPa, approximate tensile strength 50-70 MPa, flexural modulus of 5 GPa, and flexural strength of 100 MPa. PLA is an advantageous biopolymer with relatively high strength and high modulus. Further properties are presented in Table 1. PLA exhibits a proportional increase in tensile modulus and molecular weight. With an average molar mass increase from 50 to 100 kDa, the tensile modulus increases by a factor of 2^7 [6]. However, PLA in engineering applications may have mechanical limitations. PLA has poor toughness resulting in a quite brittle material displaying less than 10%

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Table 1
PLA physical and mechanical properties of isomers and biopolymers [3].

Properties	Units	PLA	PLLA	PDLLA	PGA	PDLLA/PGA 50/50	PCL	PHB
ρ	g/cm^3	1.21–1.25	1.24–1.30	1.25–1.27	1.50–1.71	1.30–1.40	1.11–1.15	1.18–1.26
σ	*MPa*	21.0–60.0	15.5–150	27.6–50.0	60.0–99.7	41.4–55.2	20.7–42.0	40.0
E	*GPa*	0.35–3.50	2.70–4.14	1.00–3.45	6.00–7.00	1.00–4.34	0.21–0.44	3.50–4.00
ε	%	2.50–6.00	3.00–10.0	2.00–10.0	1.50–20.0	2.00–10.0	300–1000	5.00–8.00
σ^*	*Nm/g*	16.8–48.0	40.0–66.8	22.1–39.4	40.0–45.1	30.9–41.2	18.6–36.7	32.0–33.9
E^*	*kNm/g*	0.28–2.80	2.23–3.85	0.80–2.36	5.00–4.51	0.77–2.14	0.19–0.38	2.80–2.97
T_g	°C	45–60	55–65	50–60	35–45	50–55	(−60–65)	15.0–5.00
T_m	°C	150–162	170–200	*am*[b]	220–233	*am*	58–65	168–182

ρ — polymer density, σ — tensile strength. E — tensile modulus, ε – ultimate strain, σ^* - specific tensile strain, E^* — specific tensile modulus, T_g — glass transition temperature and T_m — melting temperature, am — amorphous therefore no defined melt point.

Table 2
Physical characteristics of injection mold grade commercial amorphous PLA [2].

Characteristics	Unit	Amount
Molecular Weight (MW)	g/mol	66,000
Specific Gravity		1.27
Solid Density	g/cm^3	1.252
Melting Density	g/cm^3	1.073
T_g	°C	55
T_m	°C	165
Specific Heat (Cp)	J/kg °C	
190°C		2060
100°C		1955
55°C		1590
Thermal Conductivity	W/m °C	
190°C		0.195
109°C		0.197
48°C		0.111

elongation prior to breakage [7]. Given these toughness metrics, PLA toughness may result in failure at high-stress levels inducing plastic deformation. This may limit the orthopedic use of PLA in fixation plates and screws.

1.2. Physical properties

PLA embodies the physical characteristics and processability of a thermoplastic. Thermoplastic polymers may be heated or reheated and cooled to alter for the desired morphology. In contrast, a thermoset polymer has increased heat resistance and is irreversibly set upon hardening. PLA is a semi-crystalline polymer that exhibits a glass transition temperature (T_g) of 55°C and has a melting point (T_m) at 165°C. Both T_g and T_m are vital in describing PLA's physical parameters such as density, rheology, and heat capacity. Molecular weight, primary structure, optical characterization, as well as crystallinity are critical to PLA's physical properties [3]. PLA's physical properties are summarized in Table 2.

The widespread usage of PLA can be attributed to its versatility. Mechanical properties of PLA could potentially be tuned in several methods. Polymer crystallinity defines physical properties such as hardness, modulus, tensile strength, stiffness, and the melting point. Semi-crystalline PLA, specifically, may be modified through plastic additives, which can reduce T_g, T_m, and overall crystallinity. Semi-crystallinity of the polymer is usually characterized by the percent weight per volume of poly(l-lactic acid) (PLLA) in the sample: a 90% w/v of PLLA is deemed semicrystalline [8]. Lower values result in an amorphous polymer. PLA may also be blended with other polymers, including, but not limited to, polyethylene, polypropylene, chitosan, polystyrene, polyethylene terephthalate, and polycarbonates. Blending with PLA-based stereocomplexed polymers, such as PLLA and PLDA, has demonstrated improved thermal stability and decelerated degradation rate. As a polymer, PLA can also be altered structurally through branches, leading to the formation of, for examples, grafted and cross-linked polymers. Copolymerization with glycolic acid is a frequently used method known to yield favorable material properties. The hydrophilicity of PLA can be particularly enhanced through copolymerization with polyethylene glycol (PEG) [8].

PLA maleation has proven to be an effective method to modify the properties of PLA/ poly(ε-caprolactone) (PCL) immiscible blends. Peroxide compounds may be added to PLA/PCL to induce chemical interfacial cross-links, which in turn improve blend component compatibilities [9]. Shin et al. utilized the compatibilizing agent, glycidyl methacrylate (GMA), such that GMA acted as a monomeric compatibilizer and a reactive agent interfacing PLA and PCL phases [10]. Interfacial adhesion was also improved by the addition of PLA-g-MA to blends of PLA and starch improving the compatibility of blend constituents [10]. These additions are conducted through the addition of carbon nanotubes, ceramic nanoparticles, natural fibers, and cellulose. Manufacturing techniques may take advantage of the strong interactions between PDLA and PLLA blocks, which result from the formation of stereocomplex crystallization as well as improved mechanical properties and thermal stability. Moreover, slower degradation rates, which can be essential in drug delivery applications, may be achieved. Modulation in the synthesis of PLLA and PDLA blocks may aid in the production of hydrogels, nanoparticles, and micelles.

The following physical properties must be considered for tuning PLA biodegradability. Polymer degradation rate will increase with an increasingly hydrophilic material, and thus, PLLA has a slower degradation rate than poly(d,l-lactic acid) (PDLLA) due to crystalline regions. The geometry of an implantable or PLA derived device will affect the biodegradation rate as it will directly relate to the surface area present to the solution of the bulk material. Degradation rate will further decrease with an increase in molecular weight, which in turn implies a lower concentration of carboxyl end groups. Semicrystalline PLA is less susceptible to degradation than amorphous configurations as crystalline PLA is less subject to hydrolysis. The hydrolysis rate can be increased with the addition of acidic compounds. Basic molecules may neutralize carboxyl end groups and enhance degradation through base catalysis. Plasticizers increase water diffusion increasing the degradation rate. Sterilization is of particular importance for PLA manufactured for implantation and can be accomplished through beta or gamma irradiation techniques. These irradiation techniques result in reactions such as chain scission or cyclization, lowering the molecular weight and thereby increasing the degradation rate. It must be considered that bulk PLA fabricated through extrusion, injection molding, or other processing techniques may decrease the molecular weight and thus enhance degradation [8].

Degradation rate is a major property of PLA as the kinetics of its breakdown dictate its performance in a variety of applications. First and foremost, it is important to mention that PLA possesses the ability to degrade naturally *in situ*, which benefits medical operations for several reasons, such as the reduction of surgical interventions. Prolonged degradation could also be achieved for the purpose of controlled drug

release. Degradation rate is dependent upon a number of factors: polymer composition, pH, device geometry, molecular weight, crystallinity, addition of drugs and/or additives, sterilization, mechanical stress, and fabrication processing [8].

PLA solubility affects manufacturing and processing characteristics. PLA is noted to be soluble in dioxane, acetonitrile, chloroform, methylene chloride, 1,1,2-trichloroethan, and dichloroacetic acid. PLA exhibits partial solubility when heated to boiling temperatures in ethylbenzene, toluene, acetone, and tetrahydrofuran. PLA is not soluble in water, alcohols, ethyl acetate, or linear hydrocarbons [8].

Oksman et al. reported utilizing cellulose whiskers to modulate PLA properties. Microcrystalline cellulose (MCC) and PLA were used to develop novel nanostructured composites through compound extrusion. MCC treated with N,N-dimethylacetamide in combination with lithium chloride aided in the swelling of MCC and separation of cellulose whiskers. These suspended cellulose whiskers were injected into the PLA melt during the extrusion process. PEG was utilized as a processing aid. This material combination demonstrated an 800% increase in elongation to break. Oksman et al. noted future studies will investigate process optimization to avoid thermal degradation of the composite [11].

PLA processing may result in a group of polymers, which include homopolymers PLLA and poly(d-lactic acid) (PDLA), which are synthesized from mixtures of pure L- or D-lactic acid. The copolymer PDLLA will result in a racemic mixture. Predictably this varying stereochemistry impacts material properties where PLLA and PDLA are generally semicrystalline, while the copolymer PDLLA is generally amorphous. Polymer crystallinity modulates mechanical properties such as hardness, tensile strength, stiffness, and melting points [8].

1.3. Chemical properties

The constituent monomer of PLA is the optically active molecule, lactic acid (CH_3-CHOHCOOH). PLA can be found in two chiral configurations, L-lactic acid and D-lactic acid. Stereoisomers provide variation in PLA types. PLA is a degradable substance, whereby breakdown occurs through hydrolysis of the polymer chain. The rate of hydrolysis is dependent upon molecular weight, crystallinity, morphology, and rate of water diffusion. The mechanism of PLA autocatalysis is propagated by terminal carboxylic acid groups. Due to its relatively slow degradation rate, PLA can remain in vivo for typically 3-5 years. Degradation rate may be accelerated with increased temperature as well as with heightened acidity. Molecular weight is also reported to influence PLA degradation [7]. Proteins and cells exhibit limited surface interaction with PLA given its hydrophobicity. This may reduce the potential of PLA scaffolds to promote cell ingress. PLA's hydrophobic nature may also instigate an inflammatory response of local tissue [12]. Moreover, given its relatively inert chemical nature, side-chain additions, bulk modifications, and surface manipulations are difficult to achieve.

1.3.1. Manufacturing

The synthesis of PLA occurs through the polymerization of lactide monomers. The lactide stock is obtained through bacterial fermentation of a renewable source such as corn starches, sugarcane, or beet sugar. Synthesis procedures can entail direct oligomer polycondensation, solid-state polycondensation, or simply by addition polymerization of the primary chain, which yields low molecular weight intermediates that can later be processed to obtain PLA [10]. Direct polymerization may be carried out through azeotropic dehydration polycondensation or enzymatic polymerization. These processes facilitate the direct production of PLA from lactide monomers. Ring-opening polymerization techniques are commonly used to create PLA from low molecular weight pre-polymer, followed by depolymerization resulting in a lactide molecule. The site of ring-opening results in the formation of PLA [11] The polymerization of PLA facilitated through ring-opening yields higher molecular weight products. This synthesis procedure requires high purity lactide and heavy metal catalysts which increase the cost of production.

The company Mitsui Toatsu Chemicals creates PLA in industrial quantities utilizing azeotropic dehydration, reacting 90% L-lactic acid and tin catalysts. These reactants are added to an organic solvent in a distilling reactor. High heat reactions require the use of an organic solvent with a high boiling point. This process is carried out for 2 hrs at 140°C, vaporizing water. A 3Å molecular sieve allows for the reuse of the distilled solvent. Water levels diminish to 3 ppm as polymerization occurs for 20-40 hours at 130°C. The final product has a molecular weight of $3^{\circ}10^{5}$ kDa. The PLA end product can be used for injection molding, film extrusion and forming, blow molding, thermoforming, and fiber spinning. The resulting PLA is superior for thermal processing over its counterparts, poly-hydroxyl-alkanoate (PHA), PEG, and PCL [13].

1.3.2. Crystal structure

PLA crystallinity may vary upon manufacturing processes. The polymer is generally an amorphous thermoplastic. Amorphous molecular geometry is a result of PLA chains with variable cross-linkages. Consequently, it is optimal to synthesize PLA as a copolymer of both the L and D stereoisomer configurations. The L configuration of PLLA accounts for the majority of crystalline properties. PLA is entirely amorphic when the polymer has greater than 10% of the D stereoisomer configuration (PDLA) by weight [14]. Despite PLA's relatively low crystallinity, homopolymer PDLA and PLLA structures constitute a variety of crystal types. PLA can be configured in an α-crystalline structure (the most common configuration) which is composed of an ortho, pseudo-orthorhombic arrangement, existing in 3(10) helical form of PLA chains. While a variety of forms can be generated above 100°C (α-crystalline structure included), only the α-form can be synthesized at temperatures below 100°C. An alternative molecular framework exists in α'-crystallinity which is fabricated at 100-120°C. The α'-crystalline structure has comparable molecular geometry to the α-crystalline form, however, the defining contrast being α'-crystallinity exists in looser packing of crystal fibers [14]. As a result, α'-crystallinity displays decreased modulus, as well as barrier properties. Differential scanning calorimetry (DSC) conducted on PLA samples revealed that the α'-crystallinity structure displays a brief exotherm just prior to the melting peak. This exothermic behavior preceding melting indicates a conformational change from α'-crystallinity structure to α-form. Additionally, ß-crystalline molecular structures have been fabricated in a comparable methodology to hot-drawing, which elongates the material while exposed to high temperatures. ß -form structures are unique in that they have a 3(1) helical configuration which permits trigonal molecular arrangements. ß -structures have diminished molecular stability in comparison to their α-form counterparts, indicated by a 10°C depression in melting point temperature. The ß -form unit cell composition preserves density, however, there is a substantial reduction in unit cell volume from 1.92 g/cm^3 to 0.84 g/cm^3. Given the unit cell volume changes between α-form and ß -molecular structures, new steric relationships may be introduced that yield less thermodynamically stable products.

2. Applications

2.1. Tissue engineering

2.1.1. Tissue engineering (HA)

PLA plays a pivotal role in fulfilling various tissue engineering and regenerative medicine treatment strategies. One example is its capability to foster hard tissue regrowth in bone grafting procedures. The approach of current technologies focuses on the integration of tissue-engineered bone with native bone. The synthesized material is reported to encourage osteogenesis and angiogenesis with the neighboring tissues. However, several publications agree that the material utilized in these modalities suffer from a lack of physiological function [15]. Complications arise largely from a broad array of biological factors that must

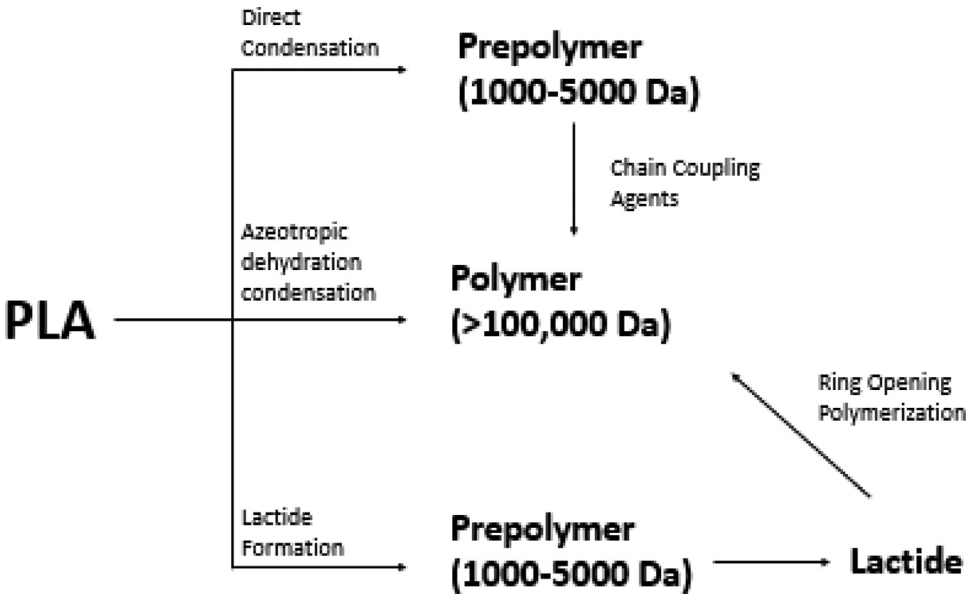

Fig. 1. Synthesis pathways for PLA [3].

be considered before implantation of the biomaterial. For instance, scaffolds are intended to induce cell processes, including, but not limited to, migration, delivery, proliferation, and differentiation. Concurrently, the material has to demonstrate an ability to integrate with the surrounding environment. Moreover, optimal performance is achieved when it can withstand immune responses and circumvent degradation into deleterious by-products [15].

PLA combined with hydroxyapatite (HA) has shown promise in this field. HA can independently stimulate osteogenesis through activation of osteoblasts and pre-osteoblastic cells [16,17]. HA is normally blended with macro-materials as micro- or nano-sized crystals. A composite of PLA and HA affects the unique properties of each substance. PLA is already known to influence the physical and mechanical characteristics of HA, and, concomitantly, HA can enhance the flexural strength of PLA. Previous studies have explored the applications of PLA/HA blends. Hatano et al., for example, evaluated the mechanical nature of a PLA/HA composite. The material was synthesized in accordance with an affordable, user-friendly hot-pressing technique. Results suggested a PLA/HA blend that was 80% HA by weight possessed an elastic modulus comparable to the value seen in human cortical bone - roughly 10 GPa. Nonetheless, unpredicted shortcomings were experienced and documented. Increasing the concentration of HA above 80%, however, undermined the inherent structural parameters [18]. One potential explanation may be due to the dearth of PLA polymers that HA crystals may aggregate or bind to. Additionally, the blend portrayed very poor structural integrity and mechanical function under in vitro stresses. PLA/HA blends were subjected to solutions that emulated physiological pH and isotonic salt content, which consequently reduced measurements. Hatano et al. conjectured pH and salt triggered the blends to dissolve, providing more mobility, thus, less fixation on the polymer, for HA crystals [18]. It is worth mentioning that this study did not perform in vivo experimentation, which leaves the impact of osteoblasts, osteoclasts, and other cells on the material unaddressed.

PLA offers excellent bioresorption capabilities which allows the polymer to integrate with host cells and tissues. This feature is particularly useful for bone grafting. As a result of the defects associated with PLA-based bone substitutes, efforts have shifted to tailor PLA properties for regenerative therapies. Indeed, the current paradigm focuses on the design of tissue-engineered bone in lieu of a complete artificial replacement. Findings in this regard have given way to optimism. PLA loaded with high molecular weight HA particles accelerates osteoblast development from precursor cells. Several other effects of HA on the interaction of PLA with cells have been reported. For example, Russias et al. investigated changes in the physical properties of PLA generated by HA insertion [17]. PLA was combined with HA through a high-velocity stream containing micro-HA-particles. This methodology led to a homogenous distribution of HA across the PLA surface. Data indicated a 5-fold increase in surface roughness of PLA/HA composites compared to PLA. In addition, a 21% reduction in the water contact angle was observed [17]. These modifications are interpreted as of high importance as they enhance protein adsorption and interaction with the extracellular environment. Improved wettability leads to greater hydrophilicity, giving way to the aforementioned advantages. Moreover, the rough topography demonstrated greater pre-osteoblast proliferation and differentiation. The authors mentioned this phenomenon most likely occurred from heightened integrin bindings between native cells and the biomaterial. Most of all, Russias et al. showed a viable method of fabrication that increases osteoblastic activity, while decreasing osteoclastic-related breakdown - two qualities favorable for bone growth [17].

2.1.2. Tissue engineering (Bone-Glass)

The capabilities of PLA can be further explained through their utility in forming new bone [19]. Specifically, scaffolds of PLA may reach this outcome from the assistance of glass such as calcium phosphate glass. Calcium phosphate glass has a chemical composition capable of alteration, which enables the rate of degradation to be tailored to that of bone. Further features include being highly biocompatible due to low cytotoxicity [19].

Fig. 1.

PLA/calcium phosphate glass scaffolds have been manifested through the following procedure [19]. The foam formation process may be used to create these scaffolds. This process entails the insertion of the glass into a PLA solution to enable the union of these two components. As a result, calcium phosphate glass can be developed in a homogeneous fashion. Additionally, the PLA/calcium phosphate glass provides the desired mechanical strength as well as the appropriate interaction for the cells and the material (Fig. 2) [19].

Scaffolds may be improved through the modulation of the following characteristics: porosity, mechanical strength, and bioactivity. The PLA/calcium phosphate composite was biocompatible in that it effectively integrated with host tissues [19]. PLA controls demonstrated poor cell adherence. The depth and diameter of porous interconnected veins, in the PLA/calcium phosphate composites, encouraged the ingress and proliferation of osteoblasts. These composites demonstrated superior an-

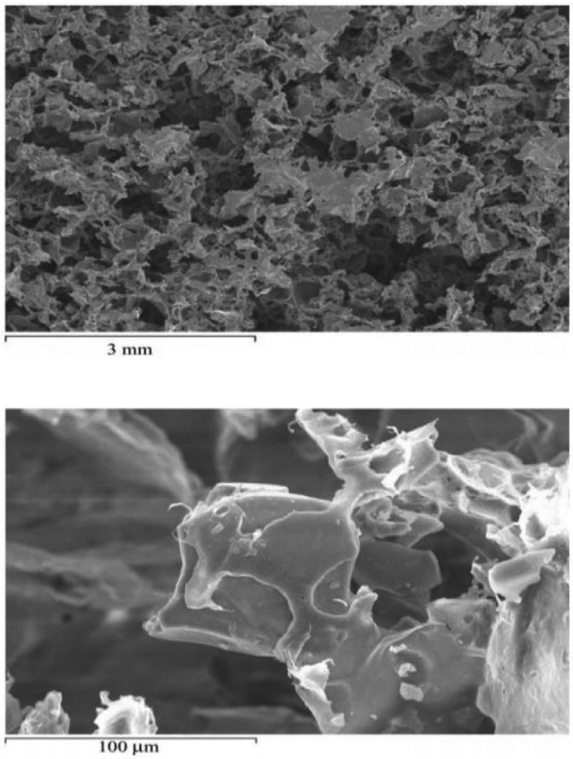

Fig. 2. SEM images of PLA only composite (top) and PLA/calcium phosphate composite (bottom) [16].

giogenesis and nutrient sequestration when compared to unmodified PLA. Upon addition of bioglass to the PLA composite, there was a 4% increase in porosity from 93% to 97% [19]. Compressive yield testing revealed that PLA/calcium phosphate composite demonstrated superior properties compared to the PLA control. The test resulted in 120 MPa for glass infused composite compared to 74.5 MPa for the PLA foam. This 61% increase represented a successful transfer of the desired calcium phosphate glass traits. The composite also exhibited a higher level of resistance to failure, as well as an increase in compressive modulus, which may be attributed to the glass's ample adhesion. The PLA/calcium phosphate composite was able to achieve a value of 20.2 MPa, whereas the PLA control presented 17.5 MPa [19].

2.1.3. *Tissue engineering, epithelial & cardiovascular*

PLA tissue engineering scaffolds may also be used to regenerate epithelial cells. Polyglycolic acid (PGA)/PLA blends have drawn interest in the treatment of Short Bowel Syndrome [20]. In this disease state, the jejunal-ileal length is truncated by an average of 33% and may result in nutrient deficiencies. The efficacy of tissue grown in this manner may

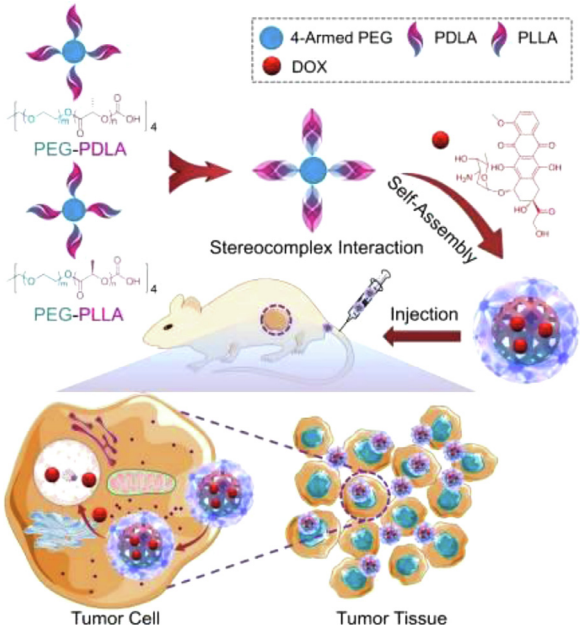

Fig. 4. Schematic of design of doxorubicin-loaded stereocomplex micelle and administration to mouse subject [41].

be tested through electrophysiology and histology. PLA coating of PGA sheets can be treated to experimental stents. These stents were placed into cardiovascular disease rat models, whereby success was observed through type I collagen integration of 28 of the 61 total scaffolds. The organoid units themselves were made of a core of mesenchymal stromal cells surrounded by an epithelium [20]. Results indicated 47 out of 61 scaffolds contained notable cyst dimensions, 26 of which were coated with collagen [20]. Authors proposed that these outcomes may be related to the immunogenicity and high permeability of collagen type I [21]. Electrophysiological testing indicated active ion-transport of scaffold grown mucosal cells, and comparable epithelium barrier strength. Histological evaluation is demonstrated in Fig. 3. Crypt presence and adequate epithelial morphology suggest the potential future utility of PGA/PLA scaffolds for epithelial regrowth [20]. PGA/PLA composite scaffolds thus demonstrate experimental success in the proliferation and robustness of epithelial cells within the intestinal epithelium [20].

Figs. 4–9.

Novel forms of PLA-based scaffolds, intended for vasculature, have also been researched due to their tunable bioresorption. PLGA has been successful in experimental cardiac patches [22]. These patches are capable of anisotropic electrophysiological functions of native tissue and may provide relief in conditions such as myocardial infarctions [23]. Electrospun PLA/chitosan copolymers have demonstrated promise in fostering the growth of cardiomyocytes. Efficacy was demonstrated through phe-

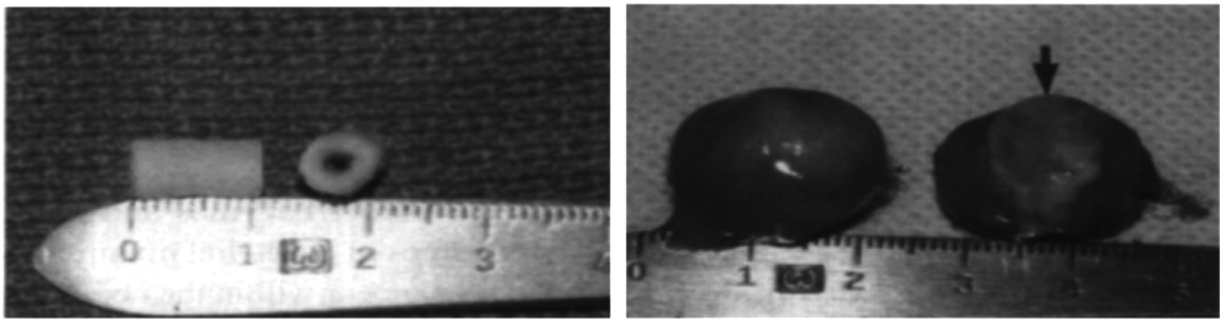

Fig. 3. Sizes of the cysts for histological examination (right) relative to scaffolds (left) [20].

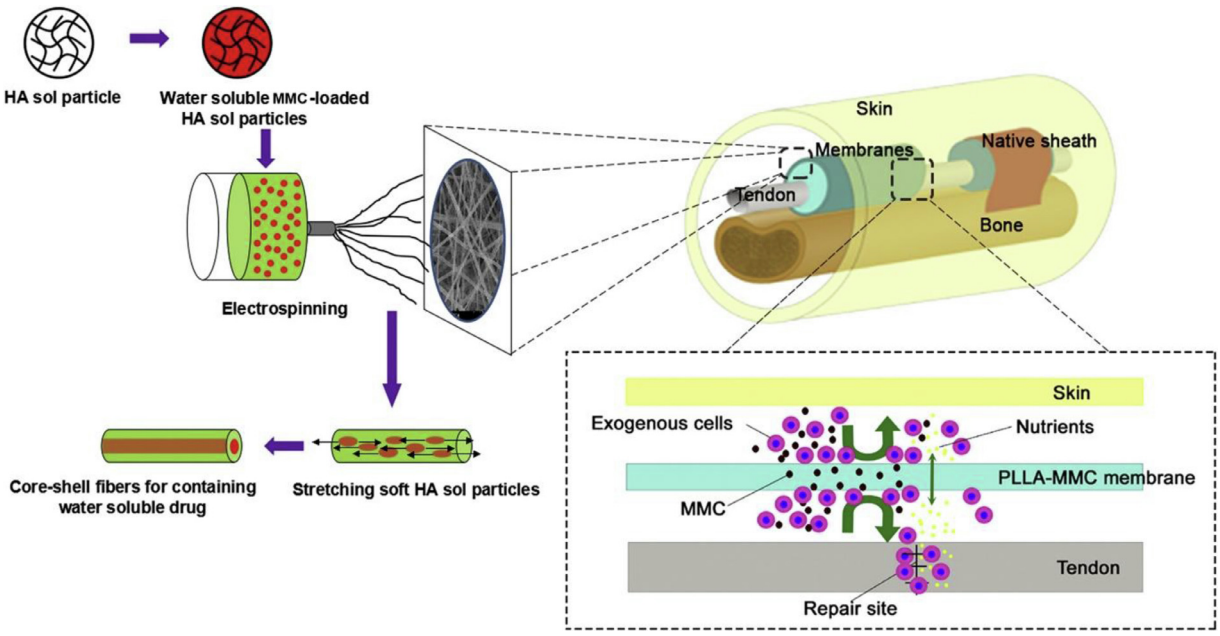

Fig. 5. MMC-loaded PLLA membrane formed based on the electrospinning technique outlined by Zhao et al. [43].

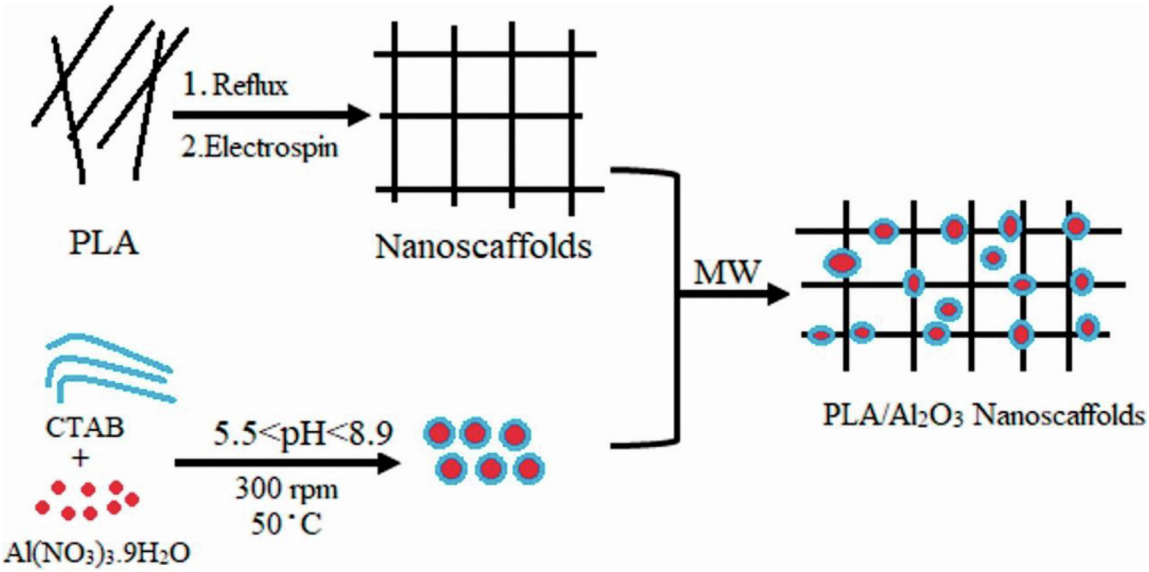

Fig. 6. Illustration of the fabrication process of PLA/Al_2O_3 nanoscaffolds for resin composites [44].

notypically appropriate cell elongation, as well as the presence of troponin I and sarcomeric α-actin [24].

Patients suffering from coronary artery disease may require bypass surgery which requires an autograft of saphenous arteries or veins [25]. Moreover, autografts impose risks of patient infection and donor site pain. Cardiovascular implant failure may result in restenosis 10 years post-operation. As a result, these obstacles provide for an opportunity to create a novel treatment, or improved implant to mitigate current shortcomings [25]. Synthetic PLA grafts can provide appropriate mechanical support and offer versatile biodegradable qualities favorable for healing periods [25]. The degradation of PLA endothelial grafts resulted in 0.77% mass loss after 25 days and 1.93% loss after 50 days of in vitro testing. PLA grafts maintain mechanical support despite gradual resorption, thus enabling appropriate cell growth [25]. Endothelial cell viability was observed when exposed to PLA extract, further confirming PLA meets biocompatibility requirements for arterial grafting [25]. Additionally, PLA facilitated the growth of human adipose stem cell monolayers. Through MTT analysis, significant variability in PLA cellular viability was not found [25].

2.2. Drug carriers

With the evolution of pathologies and antibiotic-resistant bacteria, the need for new pharmaceuticals is as dire as ever. Drug discovery, however, has not progressed mainly due to the abundance of failed clinical trials [26]. As a result, researchers are more inclined to explore delivery strategies that enhance drug efficiencies rather than create novel medications [26]. The performance of a drug is principally dictated by the physiological responses of the body following administration [27]. Once in the body, the drug must overcome metabolic and immune processes [28]. These challenges have led to the design of novel drug carrier systems that transport pharmaceuticals through biological barriers. Drug delivery systems usually consist of a biodegradable polymer loaded

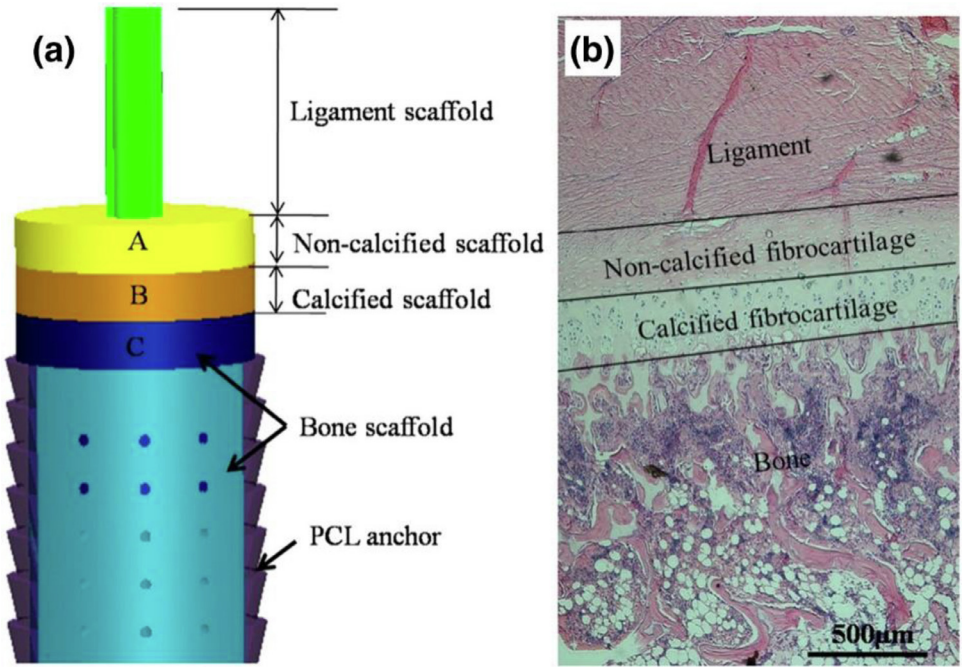

Fig. 7. Illustration of the components of the scaffold designed for ligament, cartilage, and bone regeneration [35].

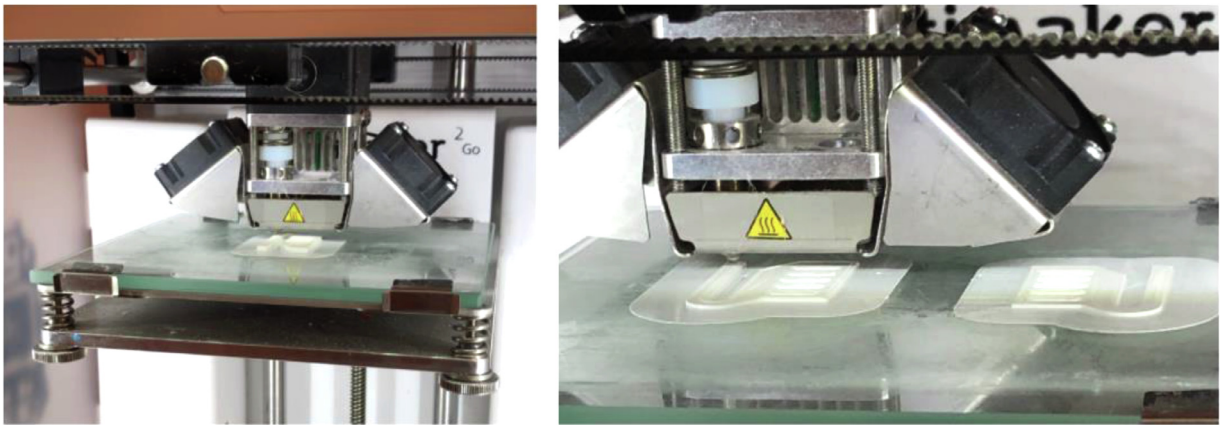

Fig. 8. A 3D printer performing the fabrication of an object using PLA as the filament.

Fig. 9. Face shields printed through Stony Brook University iCreate for healthcare workers at Stony Brook Medical Center.

with therapeutic agents [29]. PLA boasts several advantages that have led to the design of effective drug delivery strategies.

One of the primary attributes that make PLA favorable for drug carriers is its biodegradability. PLA can dissolve readily in extracellular environments [30]. In addition to this capability, the degradation rate may be modulated to yield a desired effect. Particularly, for drug carrier systems, the kinetics of this breakdown may be prolonged to sustain a continuous release of medicinal agents [30]. This provides sufficient time for the drug to induce its effect, which is pivotal as this therapeutic strategy could potentially be diminished by metabolic processes. Drugs low

in molecular weight are of primary concern given their increased likelihood to be filtered from the bloodstream through the hepatic and renal systems [30]. To overcome these challenges, drugs have been loaded onto carriers, which target specific sites in the body. PLA has been reported to be an excellent drug delivery material as it can withstand dissolving over an extensive period of time. This quality of PLA has been demonstrated in anti-cancer drug compounds. Maji et al. evaluated the performance of tamoxifen encapsulated in poly(lactic-co-glycolic acid) (PLGA) nanoparticles [31] Results indicated an enhanced bioavailability compared to non-loaded control samples [31]. In addition, tamoxifen/PLGA composites were shown to improve the anti-tumor effects of the drug [31]. Similar findings were reported by Hrkach et al. in a study that observed the delivery capability of docetaxel loaded on PLA [32]. Data suggested a greater concentration of docetaxel within targeted tumors in comparison to free-docetaxel administration [32]. Consequently, the anticancer performance of the drug was improved, leading to reduced tumor growth. While PLA shows promise in various cancer treatments, PLA is also utilized in a variety of implant procedures [33]. With an adaptable degradation rate, PLA can deliver antibiotic agents to sites of implantation. This modality is particularly useful to limit risks of infection post-operation, decreasing the probability of implant failure [33].

PLA is a versatile biomaterial that possesses the capability to have its properties modified. As a polymer, PLA assumes several structural isomers, each with unique characteristics [34]. Additionally, PLA molecules can be altered chemically through interactions with adhesive proteins. Adsorption of certain proteins determines the cells and tissues the polymer may come into contact with once placed in situ [35]. This property has been beneficial in drug delivery applications. Post-intake, physiological responses inevitably dictate the fate of the drug molecules. With PLA, pharmaceuticals may target specific cells and avoid biological obstacles. Lv et al. demonstrated advanced chemotherapy against drug-resistant leukemia cells using daunorubicin-loaded PLA nanoparticles [36]. Some leukemia cells secrete agents that stymie anti-cancer drug performance. Combined with PLA, daunorubicin is able to bypass said inhibitors [36]. Moreover, PLA aids the transport of medications across membranes and physiological barriers [30]. As a result, intake of the drug in targeted cells is improved. Additionally, PLA has demonstrated potential in bypassing the blood brain barrier (BBB) [30]. Diffusion of drug particles across the BBB has been reportedly increased by PLA composites [30].

PLA is also well known for its positive impacts on drug specificity. Although drug particles have an intended medicinal purpose, unforeseen side effects may transpire. This may occur as a consequence of interactions between the drug and non-targeted cells. PLA can be coupled with drug particles to curtail the incidence of side effects and improve drug efficiency, which could potentially lead to lesser dosages. A recent study demonstrated increased drug specificity when the particles were loaded onto PLA containing magnetite (Fe_3O_4) [36]. The magnetic PLA composite was then subjected to a magnetic field, which improved drug accuracy [36]. The publication conveyed promising findings that may aid in the development of highly specific medications. Given the widespread cautions concerning a myriad of drugs, it is vital that this research area continues to be explored.

Even with the above advantages of PLA-based drug delivery systems, the therapeutic efficiency of such strategies can still be improved through manipulation of associated microparticles. Zhao et al. demonstrated the potential of this approach using pomegranate-structured composite microspheres composed of ibuprofen-loaded mesoporous silica nanoparticles (MSN) inserted into PLLA microspheres [29]. Results suggested drug release rates may be regulated through adjustment of the MSN and ibuprofen concentrations. Consequently, prolonged drug release using this technique may be fruitful especially for treatments involving long-term therapeutic effects. In another study, Zhao et al. showed favorable outcomes may be obtained through modifications of the loading strategy onto the polymer matrix. According to the results, programmable release of anti-inflammatory agents and anti-tumor agents on a short-term and long-term scale, respectively, can be simultaneously performed in the same drug delivery system [37]. Findings as such prove to be of high value due to the enhanced efficiency of the pharmaceutical effects.

2.2.1. Cancer therapy

PLA-based drug delivery systems have shown promise for therapeutic strategies in cancer treatments. Due to its adaptable degradation rate, PLA scaffolds offer a highly desirable feature for drug delivery systems: long-term drug release.

Given the understanding that inflammation may lead to tumor regrowth, it is critical to mitigate inflammatory responses post-tumor resection operations [38,39]. Dual-drug delivery polymer scaffolds are an effective method to induce more favorable tumor microenvironments. Early inhibition of inflammation can help optimize the performance of antitumor agents. Yuan et al. demonstrated the advantageous usage of an electrospun composite PLLA fibrous scaffolds immobilized with bicarbonate, doxorubicin, and ibuprofen for hepatic cancer therapy. Electrospun fiber-based scaffolds have previously been limited against hepatocellular carcinoma for two reasons: (1) a dearth of control over the release of drugs at specific time periods; and (2) minimal responsiveness to extracellular pH changes. Yuan et al. addressed the latter issue through incorporation of sodium bicarbonate-loaded mesoporous silica particles into the PLLA scaffold. These modified particles provide a degree of sensitization within the polymer to acidic environments, which triggered drug release. Strategic loading of ibuprofen on the scaffold surface offered control of inflammation at an early time frame. The reduced inflammation contributed to enhanced efficiency of the antitumor agent doxorubicin. Insertion of doxorubicin deeper within the scaffold led to sustained release of the antitumor drug. Results from Yuan et al. indicated the potential of pH-sensitive mediated drug release PLLA scaffolds in tumor recurrence prevention. Dual-drug delivery could potentially lead to improved anti-inflammatory and anti-tumor outcomes. Moreover, temporal manipulation of drug release can create environments suitable for more profound therapeutic effects [38,40]. Similar findings were reported by Pan et al. and in a study that investigated the inhibition of inflammation capability of implanted electrospun PLA fibers loaded with ibuprofen [40]. Sustained release of ibuprofen from the fibers led to increased efficiency in later-stage inflammation inhibition. Thus, short- and long-term modulation of inflammation via drug-loaded delivery systems may be attained.

Cervical carcinoma is a major causation of cancer-related deaths amongst females on a global scale [41]. Current treatment options, including chemotherapy, have proven success in clinic, however, patient complications from side effects are well-documented. In addition, chemotherapeutic agents suffer from several shortcomings, such as low bioavailability and subpar delivery efficiency. The advent of nano drug delivery systems has garnered tremendous attention as a possible solution to address these concerns. This is likely due to the controlled drug release and enhanced anti-tumor effects seen in doxorubicin-loaded PLA-based scaffolds, such as the one described by Niu et al. PLA stereocomplexes displayed drug delivery capabilities in cervical carcinoma mouse models and in vitro analyses. Sustained doxorubicin release contributed to improved tumor cell uptake of the anti-tumor agents. As a result, tumor cell activity was decreased with the drug delivery system compared to non-loaded drug performance. Increased tumor inhibition rates were also exhibited by doxorubicin-loaded stereocomplex micelles [41].

2.2.2. Skin and tendon regeneration

PLA can also serve a significant role in tissue regenerative medicine. Similar to drug delivery systems targeting carcinomas, PLA scaffolds may hold bioactive drugs that facilitate wound healing. Drug-loaded PLA scaffolds, however, could potentially be limited due to unintended

changes in the properties of the scaffold and/or drugs during the synthesis process. Moreover, surface modification of the scaffolds can be difficult to achieve given the relatively inert nature of PLA. The latter issue is of large importance as the polyesters may compromise the therapeutic strategy. Thus, the surface requires a stimulus to increase the polymer's overall cytocompatibility and function in vivo. Various biofunctionalization methods have been developed to improve these drawbacks. Based on results published by Cheng et al., bioactive ginsenoside-Rg3 was effectively combined with biomolecules, such as basic fibroblast growth factor (bFGF), in an electrospun PLGA scaffold through mussel-inspired poly(dopamine) (PDA) coating [42]. Incorporation of bio-signaling compounds led to enhanced cell adhesion and cell proliferation on the scaffold. Improved interactions between the scaffold and cells developed a favorable environment that mediated drug-therapy. The composite drug-biomolecule scaffold demonstrated a synergistic effect that encouraged early wound healing of rabbit ear wounds as well as long-term inhibition of hypertrophic scar formation. PLA scaffolds loaded individually by either the drug or growth factor showed less efficient healing and inhibition capabilities compared to the composite scaffold. Cheng et al. also mentioned the preservation of the original scaffold properties. Though the polyesters' chemical stability is not conducive for optimal cellular interactions, their adjustable biodegradability, mechanical properties, and porosity remain favorable, and thus, should not be altered [42]. The methodology presented by Cheng et al. is a promising approach in tissue regenerative medicine as enhanced tissue repair may be achieved compared to single-drug-loaded scaffolds.

Proper tendon repair is a crucial aspect of post-tendon surgery healing. However, adhesions and scar formation are a natural part of the healing process, which may lead to several complications, including hindered joint mobility. Due to its tunable degradation rate, PLLA provides advantages that may serve well in tendon repair. However, the hydrophobicity of the polymer reduces the drug efficiency of hydrophilic particles loaded into its structure. Micro-sol electrospinning offers a solution that combines hydrophilic mitomycin-C (MMC) into hyaluronan (HA) hydrosols loaded onto PLLA fibers. This technique, outlined by Zhao et al., created a drug delivery system that protects the function of MMC [43]. Most importantly, the novel approach led to the development of a scaffold that provided controlled release of MMC, stimulating intrinsic tendon healing, while concomitantly inhibiting scar tissue formation. Zhao et al. exemplify the versatility of PLA in terms of its applications [43]. Modifications to its structure and addition of various molecules refine its function for desirable outcomes.

2.3. Dental

Due to its structural adaptability and biocompatibility, PLA has attracted much attention to dentistry-based applications. PLA stimulates successful osseointegration of dental implants with native oral hard tissue [30]. While PLA is not the standard material for dental implantology, implants designed to hold drug loaded PLA polymers have demonstrated beneficial outcomes. Bone regeneration, for example, is possible using PLA-containing composite materials [30]. PLA also plays a role in dental resins essential for several restoration procedures. Resins are evaluated based on their mechanical function, stability, and appearance. Improved mechanical properties may be achieved using PLA composite scaffolds in resin. Ranjbar et al. observed increased flexural strength, modulus, and compressive strength in PLA/Al_2O_3 nano-scaffolds compared to traditional resins [44]. The composite material was synthesized through crosslinking the polymer with Al_2O_3 nanoparticles. Moreover, PLA combined with other polymers has been utilized to address post-operative complications. PLGA membranes have reportedly provided enhanced oral bone regeneration in rats. Similarly, PLGA membranes facilitated improved bone healing in calvarial defects in rabbits. PLGA scaffolds have also shown regeneration of damaged oral tissue. The drug delivery capabilities of PLA have been applied to clinical purposes in dental medicine [45]. PLGA particularly is able to serve an endodontic role through sustained delivery of antibiotics during root canal procedures [45].

2.4. Orthopedic

PLA offers potential advantages for biodegradable orthopedic devices. PLA suture devices were first patented in 1973, and have since found uses in resorbable fracture fixation plates [33]. Polymer fixation enables higher quality imaging due to radiolucent properties thus reducing potential artifact formation. PLA copolymers can be generated to modulate degradation properties, such as the introduction of chitosan-based materials [35]. PLA / chitosan-based copolymers offer increased material strength and prolonged degradation time. *In vivo* studies indicate sufficient PLA strength is demonstrated for 8-12 weeks post-implantation. These findings suggest PLA may be used effectively for internal bone fixation. PLA has also proven to maintain robust sterility which helps to mitigate infection. Orthopedic implantables composed of PLA may be infused with osteogenic or anabolic bioactives to encourage cell proliferation. Biodegradable fixation devices offer a remedy to potential osteopenia that may result from stress shielding that occurs with metallic implants. PLA based scaffolds may be 3D printed and precisely tailored for porosity sizes / depth, as well as connectivity to optimize osteoinductive capabilities. PLA copolymer degradation products are non-toxic, however, degradation products may increase resorption site acidity [46]. Chitosan copolymers are effective in neutralizing byproduct acidification. PLA biodegradation is advantageous in that no further surgeries are required for implant removal. PLA degradation rates can be modified to provide for the gradual transition of loading from implant to bone [33].

Orthopedic implants composed of PLA have demonstrated tremendous success in animal models. PLA copolymers integrated with proteolipid (mucopeptide N-acetyl muramoyl hydrolase phosphatidylinositol 3,4-diphosphate) has promoted osteogenesis in rats and dogs [33]. Furthermore, sutures and fixation rods composed of PLA have excelled in mending mandibular fractures in dogs. Rabbit osteotomies have been successfully reduced via resorbable self-reinforced, fibrillated PLA (96L/4D)/ (SR-PLA96) fixation rods [47].

With a tensile strength between 11.4-82.7 MPa and flexural strength between 45-145 MPa, L-PLA is an excellent biomaterial candidate for orthopedic implants [47]. Furthermore, L-PLA with a molecular weight of at least 100 kDa has routinely demonstrated adequate mechanical strength for implantation. L-PLA rods have improved hydrophobicity which may serve to retard degradation rates. Ultra-high-strength PLA has demonstrated effectiveness in osteochondral reconstruction and healing in soft tissue cases. These high strength PLA blends have proven efficacy in enhanced fixation and repair of tendons and ligaments. Pins, suture anchors, and screws composed of PLA and copolymers have facilitated anterior cruciate ligament (ACL) reconstruction, where suture anchors serve to reattach tendons and ligaments to bone [35]. PLA has been manufactured into highly specific and modified porous scaffold or cell carriers tasked with rebuilding extracellular ligamentous matrix components. Flexibility in manufacturing provides for permeable scaffolds that adequately sequester nutrients and promote cellular ingress while leaving exit pathways for cellular waste removal [47].

A challenge of PLA orthopedic scaffolds is that PLA surfaces lack a viable epitope for cell attachment. PLA surfaces must undergo modification to promote specific cell or protein attachment. It is imperative to increase surface bioactivity within the pore channels. While PLA embodies various advantageous characteristics, it may struggle with orthopedic applications due to low fatigue strength, creep, poor adhesion, and potentially poor biocompatibility in specific cases. PLA's brittle nature is a result of its slow crystallizing nature. Inadequate reactivity in the pores of PLA scaffolds may fail to promote cell ingress and may also need an autograft to see scaffolds. Autografts are not without complications as they may result in increased donor site pain, bleeding, necrosis, extended healing times, and an increased risk of infection. Lastly, if scaf-

folds are seeded with poor donor site stock they may compromise the effectiveness of scaffold treatment [35].

2.5. Antibacterial

Bacterial colonization and subsequent biofilm formation may result in detrimental infections which require surgical debridement. PLA films reinforced with magnesium (Mg) have demonstrated osteogenic properties and promote bone cell ingress. Despite bone promoting properties, PLA integrated with Mg may allow for the inception of biofilms. González-Martin et al. reported an initial reduction in bacterial biofilm formation in PLA films integrated with 10% Mg. However, this ratio of PLA and Mg is merely deemed bacteriostatic and not bactericidal, as after 24 hours of incubation biofilm formation of PLA/Mg scaffolds surpass that of PLA control [48].

Karakurt et al. attempt to mitigate PLA's poor antibacterial surface properties through the addition of immobilized saccharides. Utilizing plasma post-irradiation grafting techniques, immobilized glucosamine (GlcN) and chondroitin sulfate (ChS) are added to modulate surface properties, chemical composition, surface topography, and hydrophilicity. Following these modifications, PLA films displayed bactericidal effects against *Escherichia coli* and *Staphylococcus aureus* strains. It was found that the integration of ClcN and ChS into PLA films was bactericidal yet no synergistic effects were reported. Optimal antibacterial effects for ChS were seen against E. coli, while GlcN was superior against S. aureus. This proposed surface modification may hasten the emergence of PLA based medical devices to market [49].

2.6. Three-dimensional printing

Three-dimensional (3D) printing has emerged as a promising fabrication modality with a broad array of applications in the field of medicine. 3D printing may be characterized as an additive manufacturing process that gives way to rapid prototyping [50]. The profound contributions of this state-of-the-art technology to medicine are tied to its ability to produce a tangible model from a preliminary virtual model [51]. This capability is frequently utilized for pre-operative planning as well as educational purposes [52]. 3D printed organ models aid surgeons develop an effective treatment strategy as the analogs are designed with a morphology and anatomy according to diagnostic images [52]. Device testing and medical training are also well-documented benefits provided through this technique. Due to its widespread accessibility, ease of use, low cost, and speed, 3D printing offers the opportunity to design customized devices, addressing complications associated with patient variance. The growing popularity of this modality in addition to efforts to personalize medicine is likely to expand its usage across extreme scenarios. Recent studies have already explored the significance of 3D printing within organ printing and personal protective equipment manufacturing [53,54].

Equally important to the function of a 3D printer is the filament of choice. Various materials possess unique properties that may be exploited to fulfill a specific outcome. PLA is one of the most common filaments available for 3D printing [55]. PLA offers several advantages that bolster the effectiveness of additive manufacturing.

Vardhan et al. reported a novel technique of fused deposition modeling (FDM) where alternate layers of sprayed aluminum and PLA produce higher tensile strength than native PLA. The authors indicated the importance of infill density and the number of stacked layers of metal spray, where increased material strength is proportional to infill density while inversely proportional to the number of layers. Vardhan et al. proposed this technique may improve the mechanical properties of 3D printed PLA with minimal additional resources. Encouraging results suggested increased infill density and a single layer of aluminum spray significantly increased the tensile strength of PLA parts made by FDM. Mechanistically, increased infill density provides for strong bonds between PLA layers, while added aluminum improves thermal conductivity. Future studies will investigate PLA aluminum 3D printed composites for their wear resistance [56].

2.6.1. Surgical tools

PLA has demonstrated sufficient strength and mechanical characteristics suitable for a variety of clinical applications. PLA has demonstrated an ability to withstand external loads experienced by surgical retractors. Rankin et al. produced a PLA-based surgical retractor using 3D printing methods. The fabricated retractor tolerated 133 N of tangential force. Additional results suggested the PLA instrument exhibited adequate durability to support forces presented during operation [50]. PLA has also been the desired filament for other tools, including needle drivers, hemostats, forceps, and scalpel handles [57]. Due to its low allergenicity and safety, PLA can be used as a solution to a broad range of clinical circumstances with minimal adverse physiological reactions. Moreover, PLA may be repeatedly sterilized without significant compromise of its physical and chemical properties. As a result, the cost of production for several 3D printed instruments is substantially low compared to their pre-existing counterparts. Rankin et al. estimated the price of their 3D printed retractor may be a tenth of the cost for the stainless steel equivalent. Furthermore, when under duress, PLA fractures in a predictable manner. Rankin et al. loaded five 3D printed retractors till failure [50]. Data indicated each retractor failed at the same stress value as well as in the same position. This quality is particularly useful for 3D printed materials that may be inserted or implanted into the body.

3D printing combined with computer-aided design (CAD) software can produce replicable components or whole tools intended for clinical performance. Moreover, rapid prototyping permits the development of customizable instruments tailored to patient anatomical measurements. The surgical relevance of 3D printed models using PLA has been illustrated by a great number of studies describing self-produced prototypes. For example, PLA-based space holders designed for esophageal retraction demonstrated adequate functionality in porcine models [58]. The space holders widened the aperture of the esophagus to provide enhanced exposure of lesions [58]. The larger field of view aided suture placement, which could potentially lead to higher quality closure of wounds.

2.6.2. Severe acute respiratory syndrome coronavirus 2

Given its prevalence, 3D printing may serve pivotal roles in times of disaster. Historically, 3D printing has led to the development of models, prostheses, surgical aids, implants, and scaffolds [59]. Modern technological advancements have expanded its applications to critical care equipment. In response to the Covid-19 pandemic, 3D printing has been utilized to create ventilators that could potentially accommodate more than one patient. Clarke reported a 3D printed circuit splitter that enabled ventilation of two patients using a single ventilator [54]. The findings demonstrated in this publication convey the value of care feasible from 3D printing during emergency situations. Moreover, unprecedented demands on the healthcare system could lead to protective personal equipment (PPE) shortages. 3D printing offers a rapid means for mass production of protective gear. In addition, PPE may be customized to the sizes and shapes of wearers. Cai et al. demonstrated a swift, effective protocol for the fabrication of personalized N95 masks [60]. While supply restoration is of large importance, quality gear that may be tailored to an individual's unique features is a breakthrough development that could potentially maximize comfort and fit on top of personal safety. Modular 3D printed PPE designs can be readily found on the NIH 3D Print Exchange. As a commonly printed filament, PLA has played a fundamental role in the rapid manifestation of these designs. As a result, PLA should be considered for future manufacturing of personal equipment.

Bottlenecks

Reports have documented deficiencies associated with PLA in biomedical applications. Particularly, brittleness has been cited pervasively as a defect to the material's mechanical nature. As a result, stud-

ies have focused on methods to obtain adequate functional capability as well as robustness throughout implantation and industrial transportation, respectively. PLA also exhibits low toughness and delayed crystallization [3].

Despite widely available raw materials to synthesize PLA, none of the manufacturing techniques are simple with straightforward execution. PLA synthesis requires controlled reaction conditions such as temperature, pressure, and pH to ensure proper catalyst function. PLA requires long polymerization times which results in high energy consumption. As a result, a criticism put forth in the literature is PLA manufacturing, in some instances, may result in high costs [3].

While PLA is biodegradable, the application of this biomaterial can be limited by slow degradation kinetics. The PLA interface has poor hydrophilicity prior to degradation. While PLA is versatile, once formed, PLA exhibits poor mechanical ductility. PLA has also displayed poor thermal stability. PLA's degradation can also be a disadvantage if an implant is intended as a permanent fixture. PLA has the potential to spread communicable pathologies. PLA may also undergo denaturation when exposed to alcohol. Despite these challenges, current research has shown that PLA deficits can be addressed, and when modified for one of the aforementioned applications, PLA may be a useful tool in biomedical science [2,3].

3. Conclusion

Polylactic acid, PLA, has an exemplary history as a biomaterial. As a thermoplastic, users have demonstrated an ability to manufacture highly specific products for key problems in healthcare. Provided PLA's uses in 3D printing, as well as its eco-friendly traits, it is likely PLA will be a contributing biomaterial for the foreseeable future. The Covid-19 pandemic has made clear the usefulness of bulk thermoplastics that can be printed into any desired product. Perhaps these principles will take root in field hospitals in distressed countries, military hospitals, disaster relief, or medicine practiced in space.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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