

Review article

Current applications of poly(lactic acid) composites in tissue engineering and drug delivery

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ABSTRACT

Biodegradable poly(lactic acid) (PLA) presents suitable physicochemical properties and biocompatibility for biomedical engineering. However, PLA has some drawbacks, such as low cell adhesion, biological inertness, low degradation rate, and acid degradation by-products. In this review, recent progress on strategies to address these problems is summarized, including novel fabrication techniques, high-performance PLA composites, and their applications for tissue engineering and drug delivery. The scaffolds, especially for bone regeneration, blood vessels, organs, and skin regeneration are evaluated, in terms of in vivo and in vitro biocompatibility and biodegradability. The enhanced mechanical, thermal, and rheological properties of PLA biocomposites are analyzed in detail. PLA biocomposites for drug encapsulation, sustained release, and tumor-targeting are also reviewed. Furthermore, the challenges and future perspectives on PLA-based biocomposites are discussed.

1. Biodegradable polymer materials

Biodegradable polymer materials have already been widely used in clinic. Their properties are largely determined by their molecular weight, crystallinity, polydispersity, thermal transition, and degradation rate [1,2]. Biodegradable natural polymers have many medical applications, since their small variation between batches leads to high manufacturing reproducibility. However, natural polymers are difficult to form into desired shapes and impractical to supply in bulk quantities [3,4].

Biodegradable synthetic polymers mainly include PLA, polycaprolactone (PCL), poly(γ -glutamic acid) (PGA), polyanhydrides, polyphosphazenes, polyurethanes, poly(glycerol sebacate), and some synthetic hydrogels. The chemical structure of synthetic polymers determines their degradability, which therefore plays an important role in scaffold designing [5,6]. Researchers control the fundamental building blocks to obtain biodegradable synthetic polymers with different properties. Because synthetic polymers are easily tailored and chemically modified for design, they are versatile and have various applications in the clinic [7,8].

Compared to natural biodegradable polymers, synthetic biodegradable polymers lack differentiation properties, but they provide controlled mechanical properties while retaining biocompatibility [4,7]. In general, biodegradable synthetic polymers have tailororable porosity, degradation time and mechanical properties when used in biomedical applications. They are often manufactured under control in large quantities, have a long shelf life, and have a relatively low cost [1,2].

2. PLA in biomedicine

PLA is a linear aliphatic biopolymer, and can be produced from renewable resources like corn and sugarcane [9,10]. PLA exists in three stereochemical forms: poly (l -lactide) (PLLA), poly (D -lactide) (PDLA), and poly (DL -lactide) (PDLLA) (Fig. 1).

PLA is a leading material for biomedical applications and replacing conventional petrochemical-based polymers in industry [12–15]. The largest application for PLA is fiber and film manufacturing, because it is readily melt-spinnable, stress crystallizes upon drawing, and PLA films are transparent and have superior dead fold or twist retention for twist wrap packaging [16].

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PLA was used widely in clinical applications today [17–19]. They are all biocompatible and have controllable degradation rates *in vivo* [2, 11]. The elastic modulus of PLA is similar to that of human bone, so it is an ideal matrix for bone scaffolds [20–25]. The applications of PLA in biomedicine range from tissue engineering scaffolds, temporary and long-term implants, bone screws, anchors, spinal cages, prostheses, sutures, vascular grafts, drug encapsulation and delivery, and is constantly expanding to new fields [26–29].

Biodegradability is a major advantage of PLA; understanding the degradation process of PLA is essential. PLA degradation processes such as random or end scission, PLA chains crystallization, soluble oligomers diffusion, were studied. A cellular automaton algorithm which combined an accelerable reaction-diffusion model with coarse-grained kinetic Monte Carlo method was used in analysis. The molecular weight, mass, reaction number, cellular state, and soluble oligomer number generated by hydrolysis were found this way [2, 30, 31].

The Food and Drug Administration has approved fifteen direct human contact formulations using PLA carrier with a biological fluid, for controlled delivery of anticancer, antidiarrheal, antipsychotic, antibiotic, anti-inflammatory, antidiabetic drugs and opioid antagonists [9, 19, 32–34]. The hydrolysis product of PLA is L-lactic acid monomers. They are not bio-accumulative in vital organs and can be eliminated through renal excretion [35]. PLA products can achieve controlled adsorption and release of drugs because PLA scaffolds have tunable pore size and pore connectivity [19, 34, 36]. PLA has certain mechanical properties which are suitable for repairing small bone damage in non-load-bearing parts. In Europe and the United States, it had been used as an advanced orthopedic screw [34].

An idea biomaterial should have perfect biocompatibility, improved bioactivity, tailored degradation rate, non-toxic degradation products, and high mechanical property [37]. However, PLA has the disadvantages of low cell adhesion and low degradation rate, which is attributed to its hydrophobicity, biological inertness, and inflammation *in vivo* because of the acidic degradation products [9, 27–29]. These shortcomings hinder PLA's application in bone-regenerative treatments when specific interactions between cell and implants are needed [7, 22]. Specifically, the hydrophobicity of PLA prevents water and living cells from penetrating PLA, resulting in complications and necrosis [38]. Hydrophobic PLA surfaces also cause bacterial adhesion and form biofilms [34, 35]. In the earlier days of unmodified PLA implantation, the hydrophobicity and bioinertia of PLA resulted in poor response of osteoblasts. Soft tissue infiltrated into the interface between bone and implant, and ultimately led to insufficient osseointegration [7, 22]. Currently, to meet the requirements of the biomedical field, chemical modification,

composite technology, and novel fabrication technology are being developed to improve PLA properties [34, 39–41].

Chemical modification is used to change the structure (like chain extension, branching, and cross-linking) of PLA [42–44]. The traditional chemical modification mainly includes plasma and radiation treatment, chemical etching, copolymerization and grafting with monomers [34, 39–41]. The aim of these methods is to enhance the toughness, surface functionalities, topography, and hydrophilicity of PLA [37]. Composite technology was mainly used to improve properties which depend sensitively on the mechanical properties of the components, microstructure, and the interface between the phases [16, 45–49]. In comparison with chemical modified PLA, the PLA-based composites are expected to have better shock resistance, thermal, ecological, gas barrier properties, and cold crystallization behavior [37, 50, 51].

3. PLA biocomposites

Developing PLA based composites is one of the major methods to address the problems associated with PLA in biomedicine. Blend of other materials with PLA may provide balanced physical and biological properties. In recent years, incorporation of nanoparticles within PLA has been developed to achieve further performance improvement. Nanocomposites have attracted much attention due to their unique properties [24, 52]. Bionanocomposites are developed with a combined knowledge of materials science, nanotechnology, and biology [53–55]. Today, polymer nanocarriers have become a research hotspot in controlled local drug delivery applications due to their biocompatibility, bioavailability, drug encapsulation, and sustained drug release ability [56, 57].

The researchers aim to develop biodegradable polymer composites which can meet different practical requirements by adding appropriate nanofillers [19, 58]. If uniform dispersion and homogeneity is achieved, nanofillers can provide an exceptional surface area and result in property changes at low loadings. The lower the filler content, the smaller the impact on matrix biocompatibility [59–63]. One way to produce high performance PLA bionanocomposites is to combine PLA with nanoparticles like metallic nanofillers, cellulose nanocrystals (CNCs), and carbon-based nanoparticles [65–70].

The presence of metallic nanofillers (gold, silver, and platinum, etc.) provides high thermal conductivity for PLA composites, which increases PLA degradation. The uniform dispersion of metal nanoparticles on PLA surface can improve its surface roughness and enhance cell adhesion [9].

Recently, a magnesium alloy was coated with films containing ZnO nanoparticles, and then was embedded in PLA. *In vitro* and *in vivo*

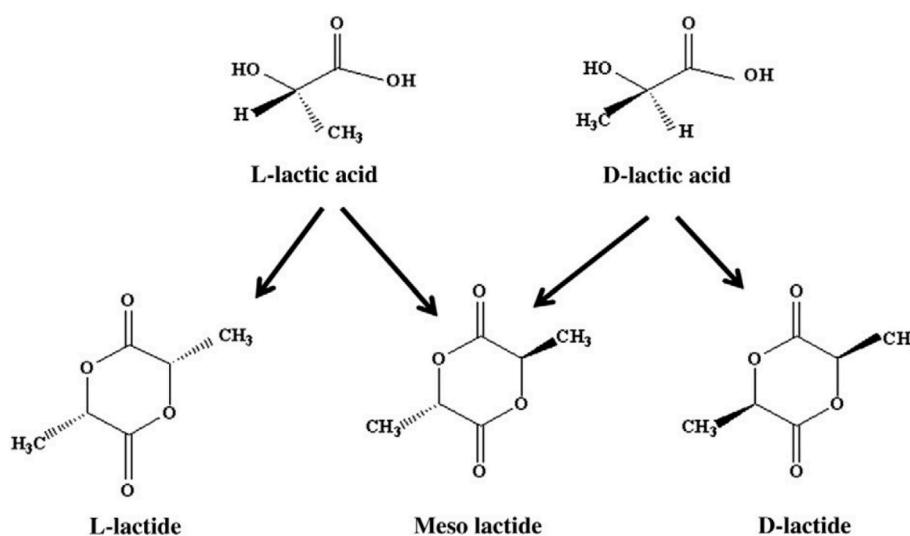


Fig. 1. Three stereo forms of PLA lactides [11].

experiments showed that the ZnO nanoparticles impacted the surface morphology and degradation rate of the composites. The coatings supported cell growth and inhibited bacterial growth [66,71]. In another example, hydrophilic hematite nanoparticles (α FeNPs) were assembled on the scaffold with a layer-by-layer method. Enhancements in osteogenic differentiation and increased minerals were found on scaffolds. The presence of α FeNPs nanoparticles led to improved surface topography, hydrophilicity, and interface stiffness of the scaffold [70]. Kim et al. introduced silver loaded dopamine modified mesoporous bioactive glass (Ag@pMBG) into a PLLA-PGA scaffold. The antibacterial mechanism of this Ag-loaded composite scaffold was shown in Fig. 2. Ag⁺ and Ag were released from the scaffolds. The Ag⁺ bound onto bacterial membranes and interacted with membrane proteins, which regulated membrane permeability and disrupted membrane integrity. Ag⁺ and Ag produced strongly oxidizing reactive oxygen species, which destroyed DNA, inhibited the replication and transcription of bacterial mRNA, antibacterial was achieved. After the bacteria were lysed, Ag and Ag⁺ were released and involved in the next killing. The bacteriostasis rate for *Escherichia coli* (*E. coli*) of the obtained scaffold was high (>99%), and the Ag⁺ exhibited a sustained release. Compared to PLLA-PGA, the silver loaded scaffold had improved mechanical properties, and better cell compatibility which promoted osteoblast adhesion and proliferation [72].

CNCs are nanobiomaterials which can be derived from natural resources like cotton seed hulls and corn stalks. CNCs have potential applications in sensors, packaging, biomedicine, and pharmaceutical engineering [17,18,73]. CNCs have drawn widespread interest in the nanocomposites field due to their high surface area and aspect ratio, good mechanical performance, biocompatibility, biodegradability, renewability, optical properties, and low costs [17,18]. Thus, CNCs are potential candidates to combine with PLA for biomedical applications. However, CNCs have inferior thermal stability, and when they are incorporated within PLA, dispersion is not homogeneous because CNCs and PLA have opposite hydrophilicity, which results in a significant decrease of mechanical properties of PLA composite [18]. To solve these problems, many recent studies have focused on grafting hydrophobic molecules onto CNC surfaces [2,17,21,73–75].

Hydrophobic PLA/CNC foams with cellular morphology were prepared by casting and leaching using sucrose as a porogen. The density of the composite foams could be reduced to ~10 fold compared to PLA granules. The crystallinity increased with increasing CNC content. The presence of CNCs reduced cell size, generated more nucleating sites, and enhanced cell density [17,76,77]. The thermal stability and hydrophobicity of CNCs were improved by grafting triazine derivative. Then the obtained CNCs was incorporated into PLA. The compatibility of CNCs with the PLA matrix was promoted while its transmittance was almost maintained [73,78]. It was proved that the thermal stability of PLA could be improved with microcrystalline cellulose fluids (MCCFs). The tensile strengths and the breaking elongation of PLA/MCCFs was also enhanced. The water contact angle for PLA/MCCFs was close to 0°, displaying the super-hydrophilicity. These PLA/MCCFs fabrics are candidates for sutures and dressings [79,80].

Some studies have shown that carbon-based nanomaterials (like carbon nanotubes (CNT) and graphene derivatives) can effectively enhance the mechanical properties and stability of PLA [59,64,81,82]. For example, ionic liquid modified graphene oxide (GO-g-IL) was synthesized and combined with PLA membrane. The obtained membranes had antimicrobial activity against *E. Coli* and *Staphylococcus Aureus* (*S. Aureus*). GO destroyed bacterial membranes with its sharp edges. The electrostatic interaction of positively charged IL and negatively charged phosphorus groups in bacterial membrane resulted in electrolyte loss and cell death [10,65,81,83].

4. PLA fabrication techniques

Porous PLA scaffolds with different morphologies can be synthesized with various techniques, including 3D printing, phase separation, electrospinning, injection molding, solvent casting, salt leaching, microsphere sintering, gas foaming, freeze-drying, and hydrogel, etc [84–98]. The selection of the preparation methods of scaffolds is usually based on its application requirements [99–108].

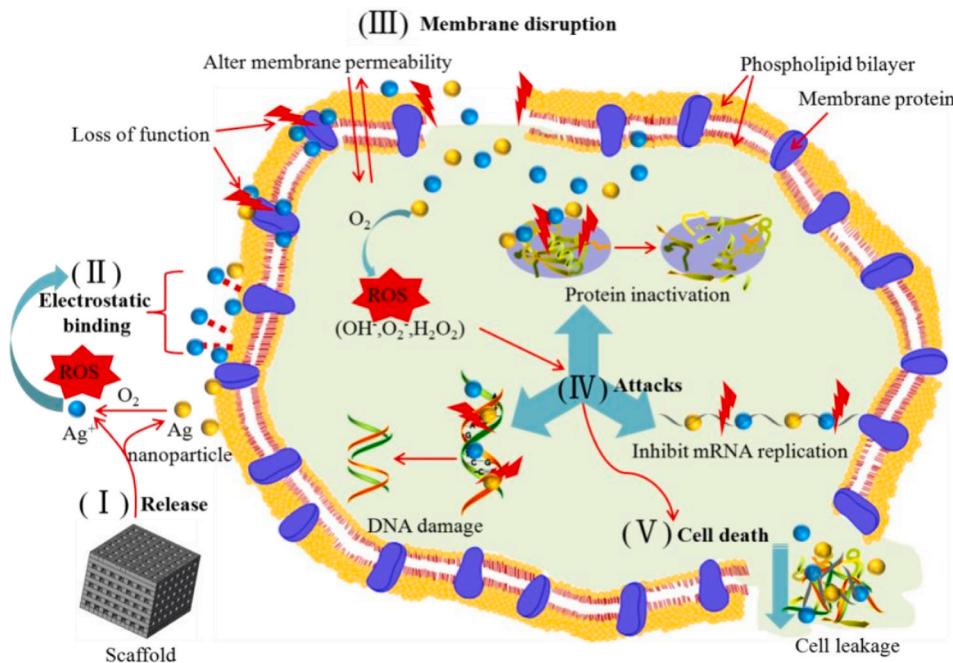


Fig. 2. The antibacterial mechanism of PLLA-PGA/Ag@pMBG: (I) Release of Ag and Ag⁺; (II) Ag⁺ binds to bacterial membranes by electrostatic interaction; (III) The interaction of Ag⁺ with the membrane destroys the integrity of the membrane, altering permeability; (IV) DNA is destroyed, transcription and synthesis of mRNA is inhibited, proteins are inactivated; (V) Ag and Ag⁺ are released from the lysed cells [72].

4.1. 3D printing

3D printing is widely used for pharmaceutical products. 3D printing is a computerized method, and has important applications in personalized dose medicine due to its low cost and accurate free form. It can fabricate scaffolds with designed shapes and precisely controlled micro/nano structures [109–113]. For tissue regeneration, 3D polymeric scaffolds as alternatives should have hierarchical structures, proper mechanical and biological properties [68,114,115]. The main 3D printing technologies currently being used are FDM, polyjet, selective laser sintering, direct ink writing, stereolithography, and digital light processing [68]. They can design reproducible scaffolds with interconnected macropores structure. Individualized implants are designed to match the size of the defect closely, and to fit the anatomical structure of an individual patient [114,116].

The main challenge of 3D printing is to improve the mechanical properties of scaffolds while maintaining their appropriate porosity. Moreover, typically 3D printing cannot print products with microporosity smaller than 10 µm [111,117]. By comparison, gas foaming can fabricate micro-porosity products with several microns. It is a flexible and clean method to prepare multifunctional microporous scaffolds for bone tissue engineering [58,86,118,119].

The 3D printing scaffolds usually have poor biological activity, which needs to be improved through some surface modification technology. To solve this problem, some methods like surface roughening, surface peptide modification, hyaluronic acid and collagen surface modification, etc. have been studied [114,120].

3D printed PLA and macrostructures of apatite-wollastonite (AW) were combined to form PLA/AW composite through thermal bonding. The properties of the obtained PLA/AW matched cortical and cancellous bone properties. It led to many new bones, fibrous connective tissues, and blood vessels, which penetrated the AW after implantation (Fig. 3). Bone growth in larger pores of PLA was promoted by the AW [121,122].

PLA was combined with gellan gum-poly(ethylene glycol) diacrylate hydrogel (GG-PEGDA) to form a dual printed scaffold by 3D printing.

The filling mode and density of PLA frameworks was controlled to adjust the mechanical performance and degradation of the PLA/GG-PEGDA. These PLA/GG-PEGDA scaffolds are expected to be used to regulate cell function and treat intervertebral disc tissue defects [105,123].

FDM is a method of making 3D models by extruding thermoplastic materials. It is the commonly used 3D printing method. FDM is a low-cost and easy to operate method which can make hollow objects. It has been widely used in the design of pharmaceutical preparations [68,124]. The FDM technology can control the pore size and porosity of its products. The porous structure enables cells to bind to thin polymer scaffolds, thus making it easier for cells to colonize, proliferate and differentiate. Large 3D structures can be formed when the internal organization of the scaffold by FDM is stacked together, which can improve the cell communication and the interactions between cells and implants [125–128].

PLA is a thermoplastic polymer which can be selected for FDM. Its glass transition temperature is low (55 °C–65 °C), and decomposition temperature is high (350 °C). The temperature range of PLA for heated extrusion is wide [25]. Normally, drug components are added to polymer filaments before FDM printing. However, FDM has low drug loading. The drug release profiles of FDM printed tablets are easily influenced by geometry, selected polymer, and drug loading. Therefore, FDM printing is not an option for thermally sensitive drugs [5,117,124].

PVA was blended into PLA to prepare PLA/PVA filament for FDM. Fig. 4 is the novel combined fabrication technology of hierarchical PLA/PVA composites with designed macro/micro-porous structures. A PLA/PVA scaffold with macropores (>100 µm) was prepared via the FDM method, then the micropores (<10 µm) were created via gas foaming. To further create open pores, PVA was extracted subsequently through solvent etching [111,129,130].

4.2. Phase separation

Phase separation method was also used as a method to prepare 3D scaffolds [29,72]. It can be classified into NIPS, TIPS, and vapor induced

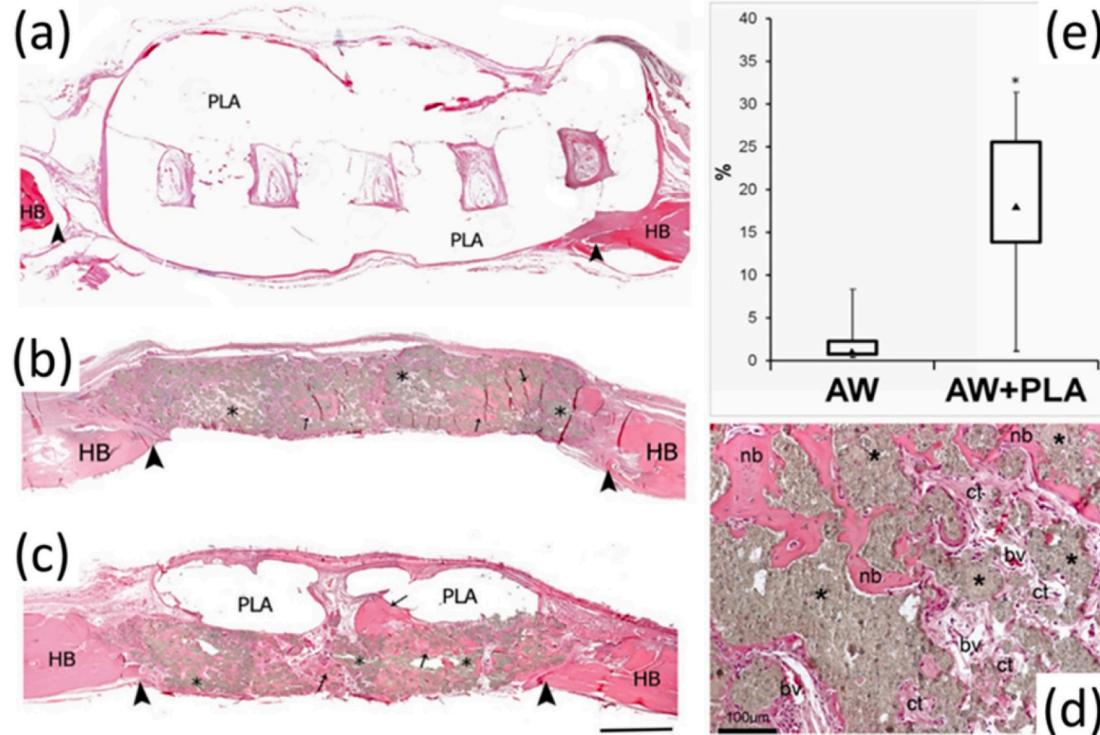


Fig. 3. The morphological images of the calvarial repair. (a) PLA; (b) AW; (c) PLA/AW; (d) enlarged AW area (nb-new bone, bv-blood vessel, ct-connective tissue); (e) proportion of new bone in the calvaria defects by AW or PLA/AW [121].

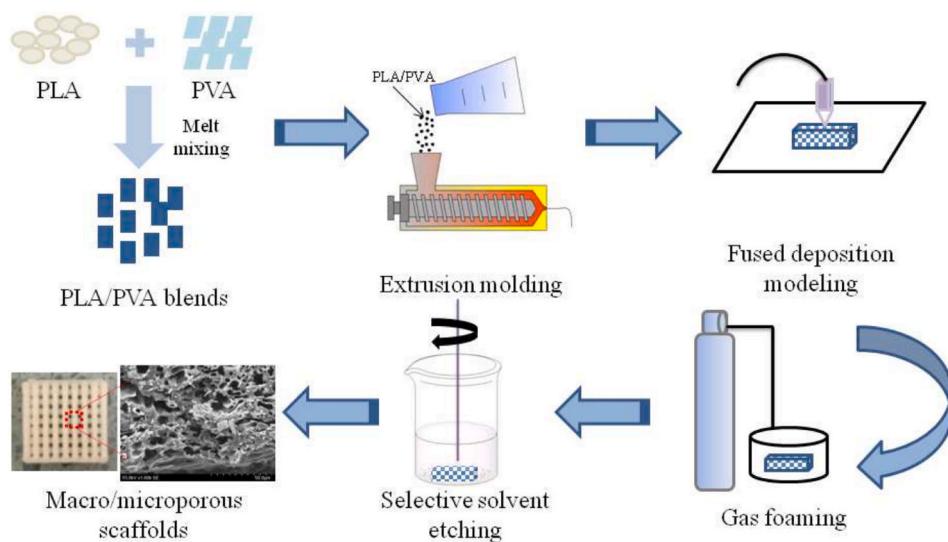


Fig. 4. Fabrication method of hierarchical PLA/PVA scaffolds with a designed macro/micro-porous structures [111].

phase separation (VIPS). With phase separation using porogen leaching, a 3D porous architecture with interconnected macro-pores is created in scaffolds. It often allows cell adhesion and proliferation; however, there are some limitations in the phase separation method, which restrict its further application in scaffolds. For example, the products have low biological activity; the preparation is time-consuming; the available polymer raw materials is limited; the removal of porogens is an additional required step in the manufacturing process; the pore diameters of the products ranging from nanometer to micrometers, sometimes is too small for cell penetration [29,77,131].

By adjusting the ternary solution (polymer, solvent, non-solvent) through changing the solvent, concentration of polymer, cooling rate, or phase separation path, the TIPS technique can prepare scaffolds with various morphologies [132]. Its products are beneficial for cell adhesion, migration, proliferation, and differentiation. The TIPS technique shows good control of scaffolds structure, including porosity, pore diameter and pore interconnectivity. The TIPS process may follow two mechanisms, solid-liquid phase separation (SLPS), and liquid-liquid phase separation (LLPS) as Fig. 5 illustrated [133,134].

A conductive nanofibrous PLA/PANI scaffold was prepared through a combination of in-situ polymerization and TIPS methods. This method can prepare composite scaffolds on a large scale. The dispersion and distribution of PANI was enhanced by in situ polymerization, which further improved the conductivity of the composite. The conductivity of

the obtained scaffold was close to that of spongy bone [22,135].

Poly(lactic-co-glycolic acid) (PLGA) is a typical PLA based copolymer, it has been approved by FDA for clinical uses [51]. PLGA filled with TiO₂-OA (oleic acid) nanoparticles were prepared by TIPS method. The PLGA/TiO₂-OA nanocomposite scaffolds was a potential drug carrier material [24,136].

Novel HA nanowhiskers were synthesized in situ at the surface of GO (HA@GO) with the assistance of microwave mineralization in stimulated body fluid. Then, the PLA/HA@GO nanocomposites were fabricated through a solution coagulation method (Fig. 6). The HA@GO exfoliated and dispersed well in the PLA because of the strong interactions between HA@GO and PLA, and the abundance of oxygen functional groups [65,137].

4.3. Electrospinning

Electrospinning is a convenient and versatile method to fabricate polymer fibers with diameters from several nanometers to micrometers [138–141]. In an electric field, the polymer solutions flow in the form of a charged jet before entering a collector. The solvent is evaporated to produce polymer filaments [35,83,110]. Scaffolds prepared by electrospinning have a large surface area and high porosity, which is beneficial for cell attachment and proliferation. Moreover, the electrospun fibers enhance oxygen permeability, fluid accumulation, and wound healing

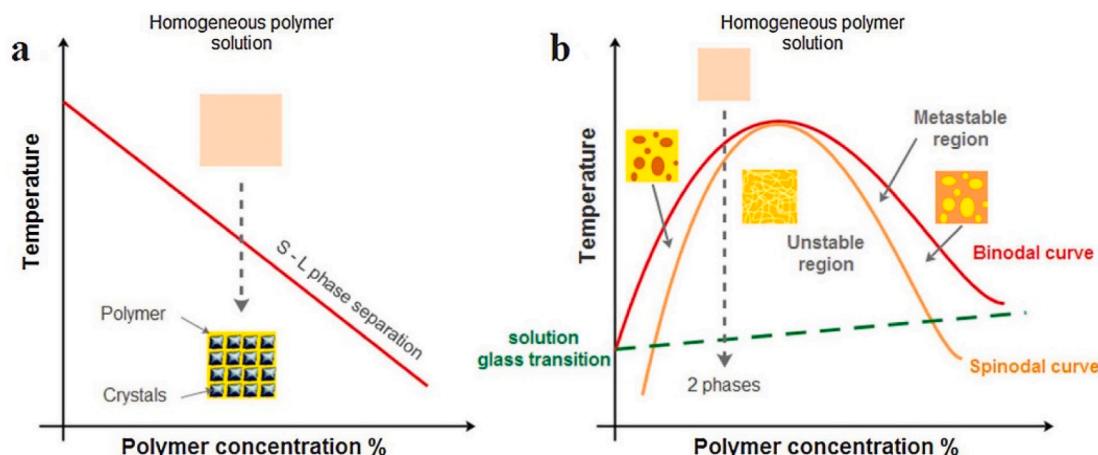


Fig. 5. The mechanisms of TIPS process in polymer solutions (a) SLPS; (b) SLPS [133].

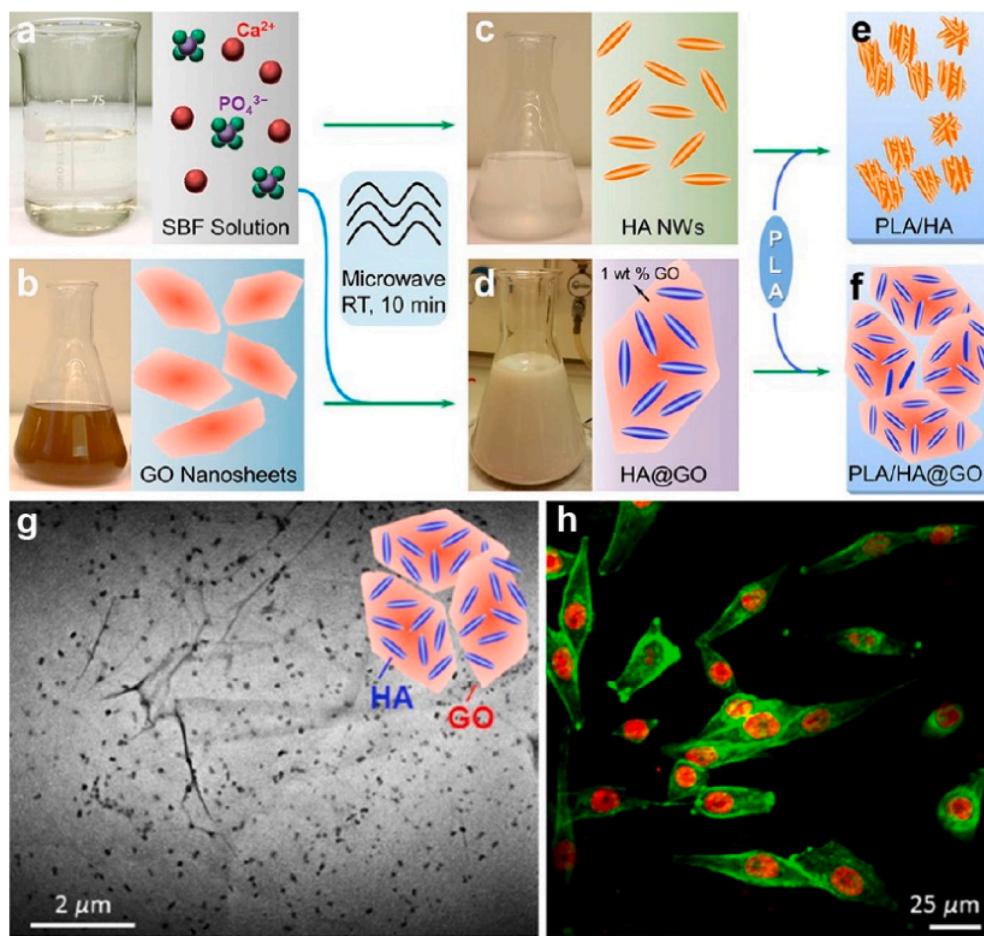


Fig. 6. (a–f) The fabrication processes of HA@GO and PLA/HA@GO composites; (g) TEM image of HA@GO; (h) F-actin and nuclei stained in MG-63 cells on PLA/HA@GO [137].

with their large surface area [69,83,142]. The nanofibrous can mimic the architecture and morphology of ECM around cells. It acts as a mechanical support and a regulator to improve cell activity before the host cells refill and synthesize a new matrix [143,144].

PLA composite scaffolds prepared by electrospinning have potential applications in bone and cartilage tissue restoration, blood vessels, nerves, liver and kidney stroma, and drug delivery [40,131]. However, their low hydrophilicity and poor mechanical properties lead to poor cell adhesion and osteogenic differentiation [70,110,145]. Moreover, despite the high opening porosity of products from electrospinning, the small fiber diameter leads to small pore size and low porosity. The pores are smaller than cells, which greatly limit cell infiltration and migration, and also limits the penetration growth of cells inside the fibrous scaffolds [110,146]. Furthermore, residual solvents from electrospinning may inhibit cell activities [103,147]. The scaffold surface is essential to induce osteogenic differentiation, since cells adhere to the surface, osteogenic differentiation is facilitated by a micro-nano surface structure and a rigid interface, which is like the collagen environment of bone. Thus, many methods have been developed by researchers to improve the surface structures and morphologies of the scaffolds [70, 148].

During electrospinning, the mechanisms of pore formation mainly include breath figures, thermal and humidity-induced phase separation [149]. NanoMatrix3DVR (NM3DVR) is an advanced electrospinning method. It provides a longer culture and a larger space for cell proliferation. The product of NM3DVR are mainly used for exploring the process of cell adhesion, differentiation, expansion, and cultivation in vitro [150,151].

Porous and rough PLA fibers were prepared by electrospinning of binary and ternary systems of PLA, dichloromethane, and hexane. After solvent exchange, cold crystallization and α' to α recrystallization occurred in the system, the surface porosity decreased except for the fibers from the ternary system with higher PLA concentrations [99,152]. Fig. 7 shows the images of PLA products from ternary systems during phase separation [99].

MCCFs were synthesized by grafting polyethylene glycol-substituted tertiary amines on microcrystalline cellulose. Then the PLA/MCCFs were fabricated through solution electrospinning technology (Fig. 8). In the process of solvent evaporation, MCCFs migrated rapidly into micropores before solidification. The surface micropores of PLA/MCCFs decreased or even disappeared, with the increasing of MCCFs [79,80].

Polymer supports were obtained from PLA/starch using the electrospinning technique, then they were combined with arginine-glycine-aspartic acid peptides (RGD) by physical absorption. The results showed that the surface became more irregular with the increase of starch content. RGD enhanced the wettability of the composite, which was beneficial to the adhesion, proliferation, and proliferation of osteoblasts. The obtained composite was biocompatible and no inviable cells were found [35,120].

Thermoplastic polyurethane (TPU) and lecithin (Lec) were spiked into the PLA electrospun solution by one-step emulsion electrospinning to fabricate scaffolds for hepatocyte culture in bioreactors (Fig. 9). The flexibility, hydrophilicity, and bioactivity of PLA were enhanced. The adhesion and proliferation of HepG2 cells was found on the PLA/TPU/Lec fibers, and toxin-damage among hepatocytes was decreased [153, 154].

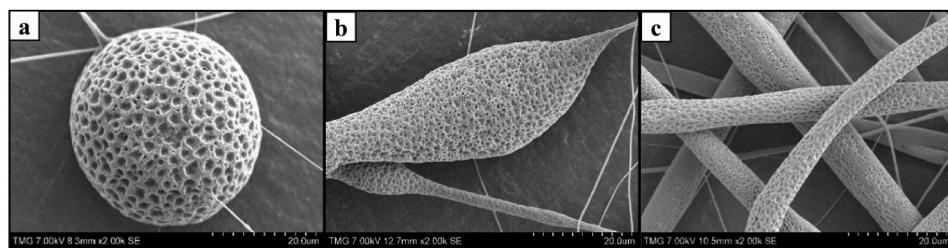


Fig. 7. SEM of the products from the ternary system with 9.1 wt% PLA during phase separation at (a) 5 h; (b) 7 h; and (c) 20 h. Image c is the beginning of the electrospinnability window [99].

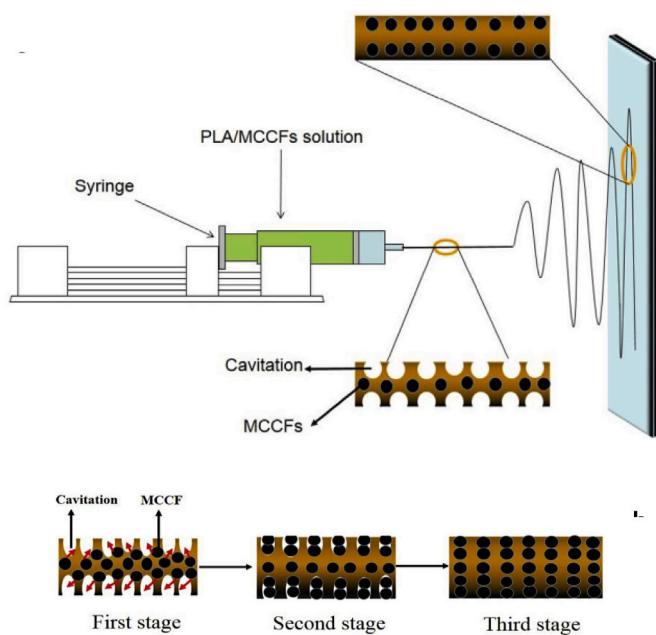


Fig. 8. (a) The fabrication of solution electrospun PLA/MCCFs composites; (b) the morphology evolution of PLA/MCCFs in electrospinning [79].

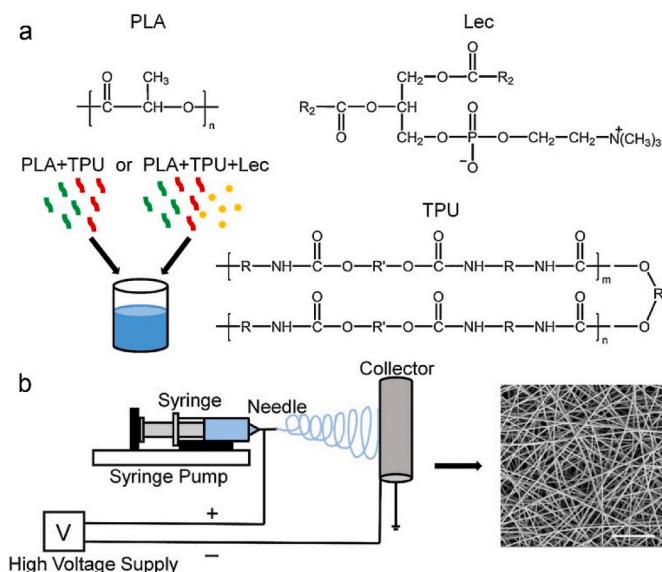


Fig. 9. (a) The fabrication of PLA/TPU/Lec by electrospinning solution; (b) the process of electrospinning [153].

Electrospun PLLA scaffolds are used to extend the axons of neural engineering directly. The combination of PLLA and PLA-poly (pentadecalactone) (PLLA-PPDL) increased the neurite extension of dorsal root ganglia on PLLA. Compared to PLLA, the surface nanotopography of PLLA-PPDL-PLLA composite was increased [101,155]. PLLA/gelatin fibers were fabricated by electrospinning. Compared to PLLA, the water contact angle of PLLA/gelatin was changed from 120° to 0°, the number and average area of adhered cells had doubled by the immobilization of gelatin on PLLA. The obtained PLLA/gelatin coating was stable in water for one month [115].

Cotton-like nonwoven PLA were fabricated via centrifugal melt-spinning. The PLA fibers had 3D porous structures with diameters from the nanoscale to several tens of micrometers. Compared to the PLA fibers form electrospinning, these fibers had lower cytotoxicity and higher cell proliferation [103,156]. A PLA melt spun scaffold was fabricated through the hot-pressing method. The morphology, porosity, fiber arrangement, and the water absorption of the obtained PLA were influenced by the processing temperature [104].

A sputtering-based PIII (S-PIII) technique was used to implant osteoinductive biometal Ta on PLA surfaces (Fig. 10). The Ta-implanted PLA had sufficient interfacial strength. The incorporation of Ta by S-PIII treatment improved the hydrophilicity of PLA and the interaction between cells and PLA. Compared to Ta-coated PLA in the same conditions, the surface roughness of the Ta-implanted PLA doubled [6,41].

4.4. Others

Low-pressure microcellular injection is a method to produce materials with high porosity, but the growth and coalescence of cells are hard to control in the micro-foaming process due to shear stress. By comparison, high-pressure microcellular injection can easily control nucleation, growth, and coalescence of cells. However, it is difficult to obtain high porosity [157,158].

PLA surface was modified with dual peptides arginine-glycine-aspartic acid (dual RGD peptides) by atmospheric pressure plasma jet (APPJ). After treatment by APPJ, the surface hydrophilicity and water absorption of PLA was improved, and enhanced cell proliferation and gene expression were found [30,41,159]. PLA membrane scaffolds were also fabricated by air jet spinning. The average fiber diameter of PLA by air jet spinning was 0.558 mm (7% w/v of PLA) and 0.647 mm (10% w/v of PLA) [20]. A rough PLA scaffold was fabricated via rotary jet spinning. It was used to deliver stem cells into ischemic mouse brain cortex suffering from thermocoagulation damage. No inflammatory response was found. The damaged area was reduced by mesenchymal stem cells (MSCs) transplantation. The PLA microfibers increased MSCs retention at the damage area [160,161].

High concentration solvent casting, particulate leaching, and compression molding were combined to fabricate a PLA/HA/ethyl cellulose (PLA/HA/EC) scaffold as a weight-bearing bone substitute (Fig. 11). The porous PLA/HA/EC composite had dimensional stability in hydrolysis, and enhanced mechanical properties and hydrophilicity [21,162].

Melt extrusion and tube-drawing (MD) methods were combined to

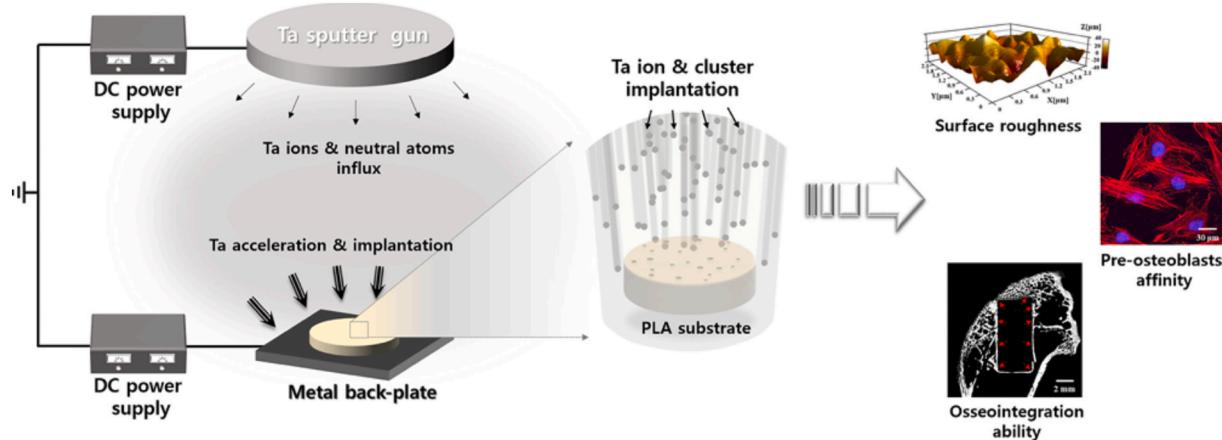


Fig. 10. The Ta S-PIII treatment for surface of PLA, and the surface roughness, pre-osteoblasts affinity, osseointegration ability of the obtained composites [6].

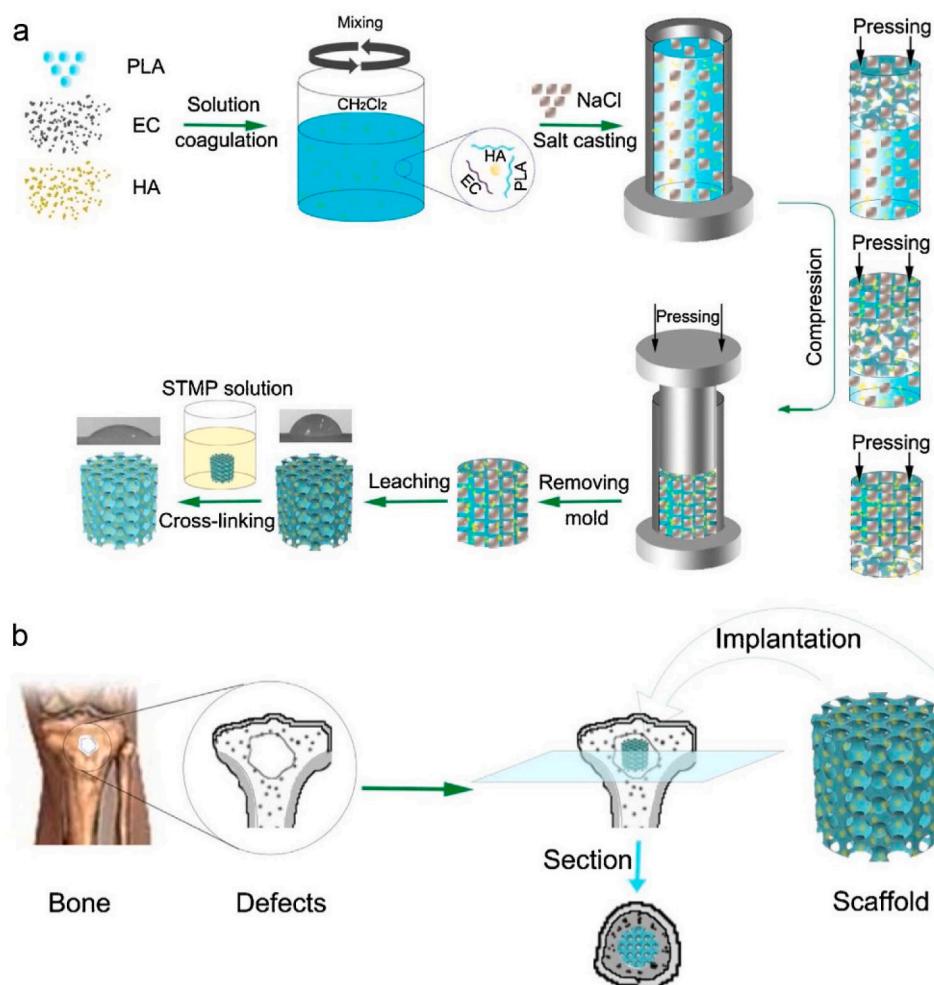


Fig. 11. (a) Preparation of PLA/HA/EC composites by the combination of solvent casting, particulate leaching, and compression molding; and (b) bone grafting [21].

prepare a PLA scaffold as a vascular scaffold. The obtained PLA tubular scaffold had high compressive strength and recovery ability. The MD tube products had chain orientation and increased crystallinity. It is an ideal method to produce biodegradable vascular scaffold with high mechanical properties [163,164].

Hierarchically tri-continuous PLA/PS-OX/LLDPE composites were prepared from dually co-continuous ternary polymer blends. The obtained PLA/PS-OX/LLDPE had high porosity and pore accessibility. In

PLA/PS-OX/LLDPE composite, micron-sized pores allowed cell penetration and tissue entry, while submicron-sized pores were beneficial to express ECM and store growth factors for cell differentiation [84].

A rigid foam was prepared by melt blending of PLLA/PCL and SAP consisting of crosslinked particles of sodium polyacrylate, then the obtained materials were immersed in water. The SAP swelled and leached from the composite when the composites were immersed in water. It formed a rigid PLLA/PCL foam structure with interconnected tunable

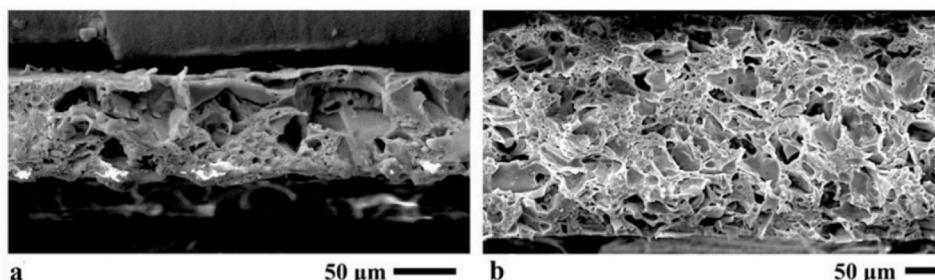


Fig. 12. (a) The morphology of PLA/PCL/SAP with thickness 0.1 mm; (b) the morphology of the obtained PLA/PCL with thickness 0.3 mm after water immersion [7].

porosity without organic solvents or chemical foaming agents (Fig. 12) [7,165].

5. Mechanical, thermal, and rheological properties of PLA

The microstructure and porosity of scaffolds determines their abilities for cell attachment, proliferation, differentiation, and migration. Nevertheless, increased porosity often leads to decreased mechanical properties of scaffolds [125,166]. The material type, porosity, pore shape, pore size, and pore orientation are the main factors influencing mechanical behaviors [25,167].

A successful biomimetic scaffold should have comparable micro-architecture and physicochemical properties to natural bone [168]. A scaffold with proper mechanical properties and porosities can act as a container for the transplanted cells in a bioreactor [25]. It is a major challenge in bone tissue engineering to develop biomimetic scaffolds which have suitable mechanical strength and porosities [21,108].

Rheology is the subject of fluid deformation and flow. It is related to the processability of materials, because it associates viscosity with temperature and shear rate. The rheological properties, especially the shear viscosity, are essential to thermal process like fiber spinning, injection molding, sheet forming, paper coating, and film blowing [76,169,170]. PLA remains a non-Newtonian pseudoplastic fluid under high shear conditions. The rheological properties of PLA were studied by rheological models, such as the Cross-WLF model and the Carreau-Yasuda model [158,169]. Thermodynamics is the study of the transfer and conversion of energy [72,133,144]. The study of PLA rheological and thermal properties is essential to understand of the processability of PLA [55,158,169].

PLA scaffolds were fabricated via air jet spinning method. 10% w/v scaffold was suitable for soft tissues, while 7% w/v scaffold was less rigid and more resistant to stress, which is a good candidate in hard tissue application [20,111]. PLA scaffolds were also produced with FDM technique. The molecular weight and degradation temperature of PLA was decreased by 3D printing process, but its semi-crystalline structure had not been changed. The influence of pore size of PLA scaffolds on the mechanical properties was not observed [23,80].

PLA scaffolds with tetragonal, hexagonal, and wheel-like structures were prepared via FDM method under a consistent porosity. All the scaffolds showed good biocompatibility of cells. The tetragonal structure scaffold had better mechanical strength both in theory and in experiment (Fig. 13). It also had less significant viscoelasticity and a better anti-fatigue performance [25,171].

Micron-sized HA spheres were prepared using spray drying (sHA). PLA/sHA scaffolds were then fabricated via FDM. The incorporation of sHA did not change the crystallinity and glass transition temperature of PLA [102]. A highly porous HA was prepared by a biomimetic approach from the cuttlefish bone, then a thin PLA/PCL was coated on the HA. The Young's modulus of the obtained scaffold increased 18 times, compared to the HA [7,172].

A PLA/HA/ethyl cellulose (PLA/HA/EC) scaffold was fabricated by

the combination of high concentration solvent casting, particulate leaching, and room temperature compression molding. The mechanical properties of the scaffold increased largely because of its compact and intact porous structure. After 8 weeks, the structure and properties (such as porosity, contact angle, compressive yield strength, and weight loss) of the scaffold with 20 wt% HA had met the physiological requirements of guiding bone regeneration [21]. A 3D PLA/HA/lignocellulose/58S bioactive-glass (PLA/HA/LG/BG) scaffold was prepared using a combination method of solvent casting/particle leaching and sol-gel. The biocompatibility and bioactivity of the scaffold was enhanced by the hydrophilic HA and BG. The mechanical properties of the scaffold had satisfied the demand of human trabecular bone [2,168].

A PLA/HA@GO nanocomposite was fabricated by solution coagulation method. Compared to PLA/HA, PLA/HA@GO with 30 wt% HA@GO exhibited a 2 fold and 7.9 fold increases in tensile strength and toughness, respectively [64,137]. A PLA/graphene-nanoplatelet/dibutyl-phthalate (PLA/GNS/DBP) composite with DBP as a plasticizer was fabricated via the solvent casting method. GNS had positive and negative storage modulus responses under an electric field. The bending and dielectrophoresis force mechanisms of PLA/GNS/DBP was demonstrated in Fig. 14. The PLA/GNS/DBP with 0.1% v/v GNS had the highest storage modulus sensitivity value. The storage modulus response of PLA/GNS/DBP with 1.0% v/v GNS became negative definite [10,81,173,174].

For PLA/CNCs composites, previous studies have shown that the compatibility of hydrophobic PLA and hydrophilic CNCs is poor. So CNCs can not be dispersed homogeneously in PLA, which deteriorates the mechanical properties of PLA/CNCs composites. To overcome this challenge, many advanced studies have been done [17,18].

PLA/CNCs nanocomposite mats were fabricated through electro-spinning. The thermal stability and mechanical properties of PLA/CNCs were largely enhanced by aligning fibers. The elongation at break was tunable by controlling the porous microstructure of composite. The performance improvement resulted from the ordered arrangement of fibers, increased crystallinity, and efficient stress transfer [79,146]. A triazine derivative was synthesized and introduced to CNCs, then the modified CNCs were incorporated into PLA as reinforcements. The incorporation of triazine improved the thermal stability and weakened the hydrophilicity of CNCs. The interfacial interactions of modified CNCs and PLA were improved, which increased the thermal stability and mechanical properties of PLA/triazine modified CNCs [73,78].

Bio-based PLA/CNCs foams using sucrose as porogens were prepared by casting and leaching. The obtained foams had cellular morphology and hydrophobicity. Compared to PLA, the storage modulus of PLA/CNCs had almost ~1.7 fold increase for the compressive mode, and ~2.2 fold increase for the tensile mode [17,77]. Maleic anhydride (MA) grafted CNCs was incorporated into PLA using MA as crosslinker by in-situ crosslinking to improve the mechanical properties of PLA (Fig. 15) [18]. Compared to PLA/CNCs, the tensile strength and Young's modulus of PLA/MA/CNCs with 5 wt% MA/CNCs loading had 73.2% and 122.7% increase, respectively [18,175].

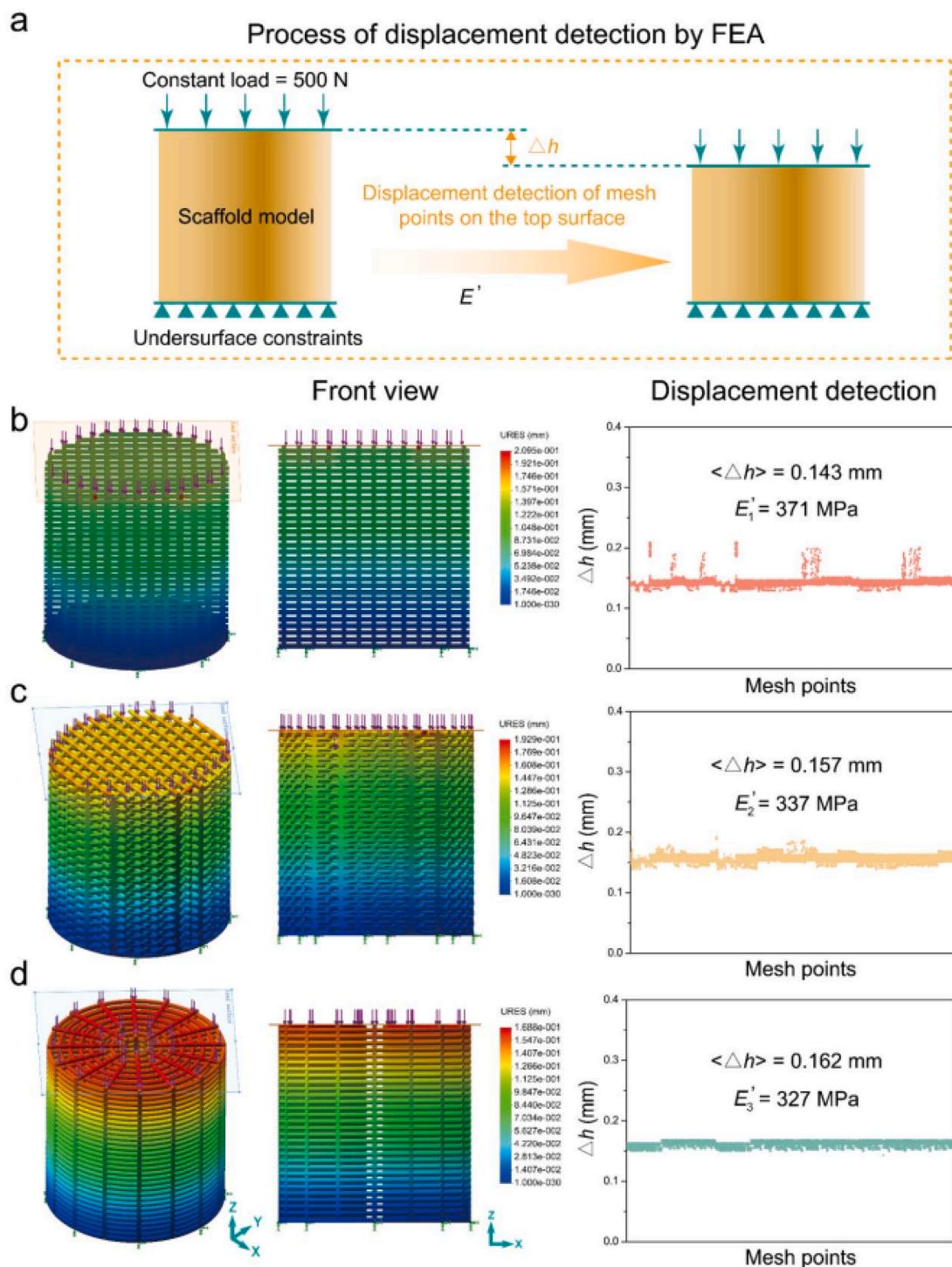


Fig. 13. Finite element analysis modelling on the top surface of 3D-printed PLA. (a) The process for displacement detection of meshing points. Corresponding mean value ($\langle \Delta h \rangle$) of and compression modulus (E') of scaffolds with (b) tetragonal; (c) hexagonal; and (d) wheel-like structures [25].

Polyethylene glycol-substituted tertiary amines were grafted onto microcrystalline cellulose to synthesis solvent-free MCCFs. PLA/MCCFs were then fabricated by electrospinning. With 10 wt% MCCFs, the tensile strength and breaking elongation of PLA/MCCFs had 218% and 192% increases respectively, compared to those of PLA [79,80].

The PLA fibrous membranes were produced with a wet-lay fabrication process, and then they were infiltrated with a gelatin hydrogel. The tensile strength, modulus, and toughness of PLA/gelatin increased with increasing PLA fiber length and concentration [138,176]. The PLA electrospun nanofibrous membrane was modified by tetracycline

hydrochloride/Fe₃O₄-COOH nanoparticles (TCH/Fe₃O₄-COOH). Compared to electrospun PLA, the Young's modulus, tensile strength and toughness of PLA/TCH/Fe₃O₄-COOH increased by 191%, 150% and 223%, respectively [177].

Biocompatible Ti3C2Tz-enhanced PLA membrane was fabricated. The interface between Ti3C2Tz and PLA was enhanced by n-octyl-triethoxysilane. The tensile strength of the composite was also enhanced. The incorporation of Ti3C2Tz improved the biological properties of PLA, including adhesion, proliferation, and differentiation of MC3T3-E1 (mouse preosteoblasts) in vitro [178,179]. Gelatin was

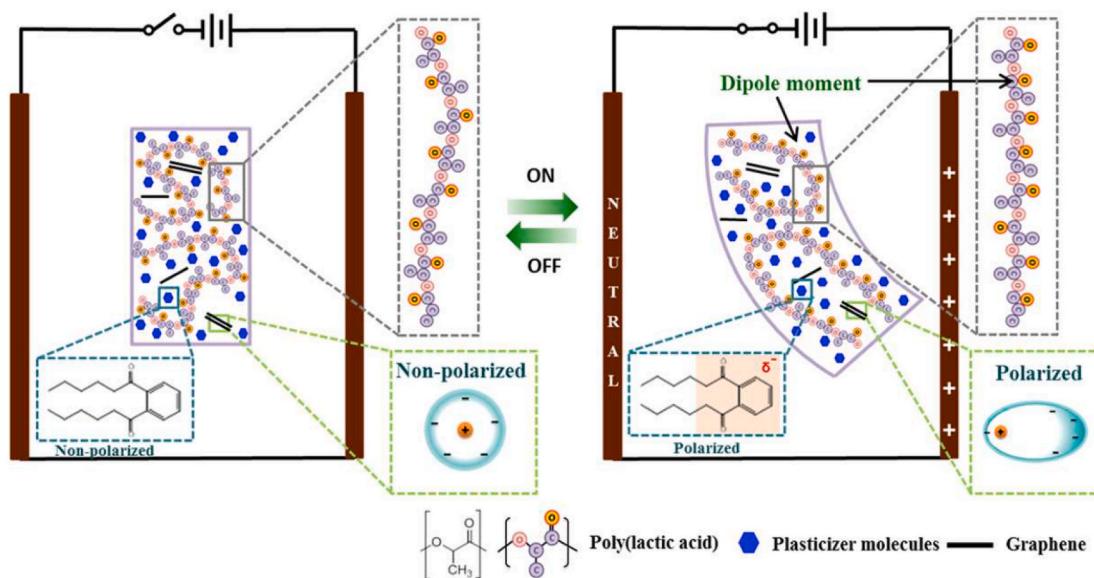


Fig. 14. Schematics of bending and dielectrophoresis force mechanisms of PLA/GNS/DBP under electric field [10].

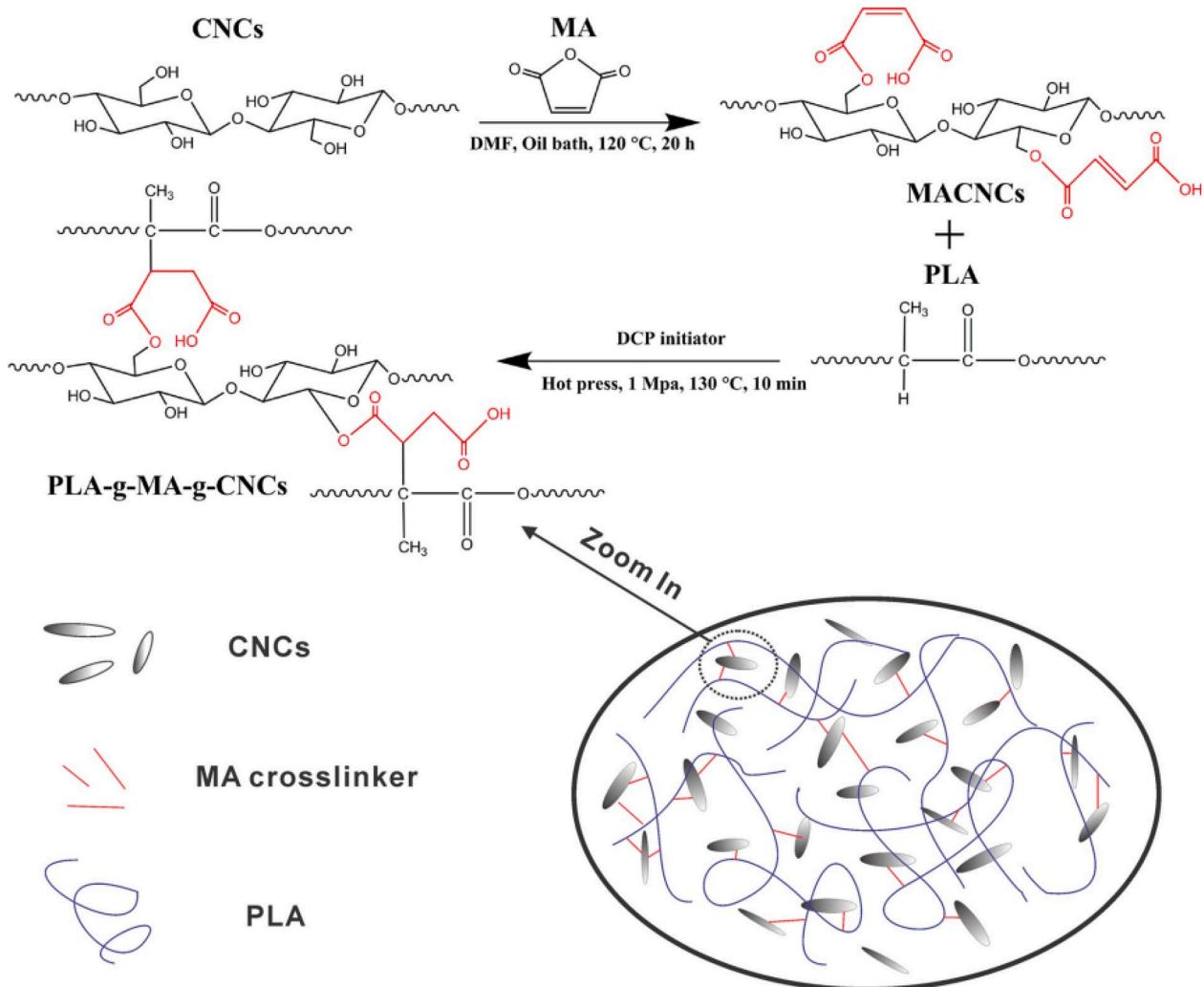


Fig. 15. Preparation of MA-grafted CNCs and the interfacial interactions between MA-grafted CNCs and PLA backbone [18].

immobilized on PLLA electrospun fibers. Compared to PLA, gelatin immobilization improved the composite scaffold strength by up to 50%, and doubled the number and average area of adhered cells [176].

PLA/PVA composites with PLA core and PVA shell were fabricated by coaxial electrospinning. The tensile strength and strain of PLA/PVA nanofibers had around 254% and 175% increase compared with that of PLA [109,180].

PLA/CNT/poly (ethylene oxide) nanocomposites (PLA/CNT/PEO) were produced. The storage modulus of obtained PLA/CNT/PEO depended on the networked CNT loading, the modulus of networks, and the interphase. To predict the constant storage modulus, a theoretical model was developed. The experimental data supported the theoretical calculations [181,182].

6. PLA for tissue engineering

Tissue engineering uses engineering principles and life sciences to develop biologically active substitutes with the aim of restoring damaged tissues and improving their functions. An engineered tissue starts by a scaffold able to support the migration and growth of cells that will originate the new tissue. Those porous scaffolds able to guide the implanted cells to form a new tissue showing a well-integrated structure after scaffold degradation. The scaffold therefore is a very important component for tissue engineering [183]. Tissue engineering offers a promising approach for regenerative medicine. For example, bone tissue cannot regenerate by itself when critically sized defects occur. In these situations, tissue engineering regenerates tissues by repairing large defects caused by trauma and surgery, and stimulates new cell growth [7, 184]. This is the current approach to restoring damaged bone [183,185], what is also a future approach to treat certain diseases. For example, new tissue-engineering technologies are being explored as treatment for congenital disorders, infections, and cancers [2].

Biological substitutes in tissue engineering are selected according to their applications. Biomaterials should have good cytocompatibility and not induce immunogenic, cytotoxic or inflammatory responses [184]. Moreover, biodegradability is required to remove the substitutes after tissue healing [186]. The ideal degradation products of substitutes are non-toxic, easily metabolized and naturally eliminated. The degradation time should allow tissue regeneration and material disintegration, but should not be too long to prevent tissue ingrowth to the damaged zone [184,186].

Tissue-engineered biomaterials should have three-dimensional (3D) structures with appropriate pore volume and pore size, and idea surface topography for cell migration and new tissue growth. Nutrients, soluble factors, and byproducts should be able to diffuse through the 3D pores easily. The mechanical properties of biological substitutes should be similar to or even better than the tissues to be restored, to support the implantation process and activities of patients after surgical operation [1,184].

Porous scaffolds loaded with specific cells and growth factors are commonly used in tissue engineering, to promote new tissue formation. The scaffolds should also have appropriate mechanical properties, and promote cell adhesion, proliferation, differentiation and secretion extracellular matrix (ECM) [1,183].

PLA, PGA, PCL, poly(hydroxyl alkanoate) (PHA), poly(hydroxybutyrate) (PHB), polyetheretherketone (PEEK), poly(glycerol sebacate) (PGS) are commonly used in tissue engineering [2,166,187,188]. PGA is used as suture material because of its high tensile strength and melting temperature. However, its high hydrolyzability limited its processing. Moreover, PGA lack sufficient mechanical integrity, so there may not be sufficient time for adequate regeneration of certain tissues [189]. PCL is used as scaffold material because it has good organic solvent solubility. PCL is suitable for long-term *in vivo* systems because it takes much longer to degrade compared with PLA and PGA [56,82,152]. PHB is used as scaffold material because of its high biocompatibility and non-toxic degradation products. But its brittleness, hydrophobicity, poor

stiffness, and slow degradation rate are drawbacks compared with other biopolymers [190]. PEEK is used for orthopedics, because it has high resistance to wear, mechanical properties, chemical resistance and radiolucency closely matching those of bone. But it is difficult to form strong attachments to native tissues because of its chemical inertness [191]. PGS is completely bioresorbable and is used in soft-tissue engineering, but it can generate acidic local environments [189,190].

In comparison to other biopolymers such as PHA and PCL, PLA has better thermal processability [16]. It is suitable for both *in vitro* and *in vivo* applications where long-term mechanical integrity is critical. However, PLA is brittle, and the implementation of PLA relies not only on mechanical integrity and processability, but also on controlled surface properties, so PLA has been modified to improve its toughness, degradation rate, hydrophilicity, and chemically inertness [189,190].

6.1. PLA for bone regeneration

Bone defects mainly result from trauma, osteoarthritis, osteoporosis, cancer, or congenital malformations. Research and development of bone substitute materials for bone repair are prevalent in clinical research today [21,185,192]. Combining biomaterials with autologous cells is a promising approach for bone regeneration in biomedical engineering [22]. For example, grafting biomaterials is critical for repairing endodontic lesions, bone trauma, atrophies, and tumors [132,193,194]. A guided bone regeneration membrane has been successfully used to keep the healing bone from the influence of soft tissue [178,187].

As an alternative to autogenous, xenogeneic or allograft bone grafts, bone tissue engineering is an effective method to repair or replace bone by combining implanted cells, bioactive molecules, and porous scaffolds [21,127]. The scaffolds transport cells to injuries and allow them to grow and retain space to form new tissue, so the porosity is critical for the scaffold's success [20,195,196]. In order to maintain cell adhesion, growth, migration, proliferation, vascularization, and eventually tissue reconstruction in an appropriate environment, simulating the native ECM structure is one of the main difficulties in bone tissue engineering [7,25,111,131,145,197]. To implement this function, bone scaffolds should provide topography and create chemical stimulation for cell growth, and should also act as temporary matrices to proliferate living cells and to deposit ECM [7,25]. Another challenge is using biodegradable scaffolds to load drugs, and to achieve sustainable and controlled drug release within the expected time [198–201].

An ideal bone regeneration scaffold should satisfy certain criteria, including (i) biocompatibility; (ii) a 3D interconnected macroporous structure to form a mimetic host tissue; (iii) sufficient mechanical properties similar to natural bone tissue; (iv) osteoconductivity and osteoinductivity; (v) biodegradability; (vi) a sustainable manufacturing process [193,197]. A 3D interconnected macroporous structure can maximize the contactable surface for the cell in growth, and to permit the nutrients transportation. The scaffold should absorb and hold liquid to provide metabolism for bone growth, which is also the key to drug delivery. The scaffold should also have sufficient mechanical properties to support the complete tissue regeneration and reconstruction, and to transmit loading. The degradation products are not toxic and should not cause inflammation. The degradation rate of scaffolds should match with new bone formation rate. The resorption of scaffolds during new bone formation is preferable, which can avoid surgical removal [147, 202–206].

To obtain scaffolds with specific shapes to meet clinical needs, the elasticity, stiffness, and topography are also needed to be considered. A variety of synthetic biomaterials are explored using metals, ceramics, natural and synthetic polymers. Metals have excellent mechanical properties which make them suitable for load-bearing. Ceramics have good biocompatibility and bioconductivity, which are similar to minerals in bone. However, both metals and ceramics exhibit poor biodegradability. In contrast, biodegradable polymers exhibit the necessary physicochemical and biological properties, so they are good candidates

for bone regeneration scaffold application [32,56,66,207–210].

The properties of fillers are one of the decisive factors to improve the properties of composites [168,211]. Hydroxyapatite (HA) is widely used as a filler in bone tissue engineering, because it is a major inorganic component of natural bone with similar biological activity and bone osteoconductivity [145,212–214]. HA plays an important role in organization and homeostasis of the ECM. It can interact with proteins, which makes it biologically functional. The mechanical properties and cell interaction of the composite scaffold can be improved by combining HA with PLA [132,184,215]. But sometimes, HA degrades quite slow, by which limits scaffold's absorption and its effects on cell interaction [168].

The application of PLA/HA nanocomposite scaffolds depends largely on their biominerization behavior, so it has been widely studied [203]. The ideal scaffold should have a mineralization rate matched with the formation of new tissues and bone regeneration. Mismatched mineralization ratio and speed will lead to inflammation and decreased mechanical properties of surrounding tissues [168,216].

PLA scaffolds have also been functionalized with polyethyleneimine (PEI) and citric acid (CA), and then were modified with calcium phosphate mineral deposits. These calcium-deficient HA deposits presented a bone-like environment to the cells. The PLA-PEI-CA/HA scaffolds exhibited sustained release of Ca^{2+} , and showed improved wettability and nanoscale roughness. Compared to an unmodified PLA scaffold, the mineral deposition of obtained PLA-PEI-CA/HA was nearly twice as high, and human mesenchymal stem cells adhesion and proliferation was ~50% higher [114,132].

Two PLLA/HA composites with different architectures were prepared through a combination of solvent casting and salt-leaching methods. PLLA/HA mineralization in simulated body fluid followed a zero-order kinetic model. By comparison, it followed a second-order model when the PLLA/HA degraded in phosphate-buffered saline solution, indicating the mineralization medium should be chosen cautiously in different situations [203]. PLLA/HA porous scaffolds were also obtained by thermally induced phase separation technique (TIPS) from a polymer/solvent/non-solvent solution in another study [132]. The mouse preosteoblastic MC3T3-E1 cell viability was not affected by HA. Compared to PLLA, the PLLA/HA scaffold had a higher alkaline phosphatase activity, and an alkaline phosphatase leveled off more than twofold was observed after 21 days of culture [132,217].

A novel PLA/PCL/HA scaffold was prepared by coating cuttlefish bone aragonitic structure with a PLA/PCL film in another study [172]. It combined the brittleness and fast degradation of PLA and ductility of PCL. The scaffold has good bioactivity. It promoted cell attachment and proliferation, and supported calcium phosphate deposition [172,218–223]. PLA/HA/lignocellulose/58S bioactive glass (PLA/HA/LG/BG) scaffold was prepared using solvent casting, particle leaching and sol-gel technology. The obtained scaffold combined the high stiffness of HA, formability of LG, and bioactivity of BG. The scaffold degradation rate was adjusted by changing the content of BG to match the growth of new bone [21,168].

HA nanowhiskers were synthesized on GO surface (HA@GO) by microwave-assisted mineralization. The method allowed homogeneous doping of biologically beneficial ions in the apatite structure. Then a novel PLA/HA@GO nanocomposite was fabricated. The obtained PLA/HA@GO had cytocompatibility with osteoblasts. Compared to normal PLA/HA, PLA/HA@GO had a high increase (>85%) in cell viability at 30 wt% HA@GO [65,68,137].

PLA/Col/nano-HA/Chitosan (PLA/Col/nHA/CS) composite scaffold was fabricated with the assistance of sonication and amidation (Fig. 16). The obtained scaffold had similar micro-nano morphologies to natural ECM. It was biocompatible and could maintain cell growth. The polymer matrix regulated the nHA crystallization, which enhanced the mechanical properties and the mineralization capacity of the scaffold [224,225].

A mineral ion-loaded HA was prepared from the fish scale, then in

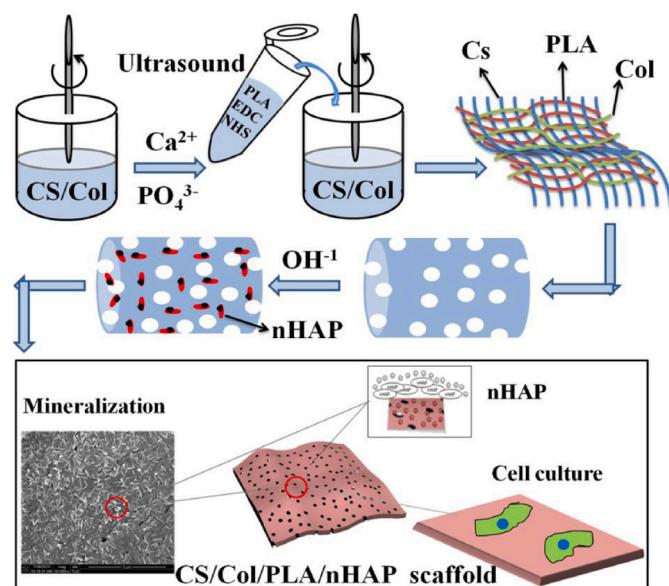


Fig. 16. The fabrication processes and mineralization image of a PLA/Col/nHA/CS hybrid scaffold [224].

situ blending was used to fabricate a PLA/chitosan/HA scaffold. HA increased the cell viability and alkaline phosphate (ALP) activity. The adhesion and proliferation of UMR-106 cells on the obtained scaffold surface was found in vitro [207,226,227]. A nano HA synthesized from pectin (nHAp) in bitter gourd fruit was created. Initially, Ca^{2+} were chelated and reacted with carboxyl group of pectin from plant extracts (GP) to form calcium pectinate complex. The Ca^{2+} get immobilized in the pectin surface. The addition of $(\text{NH}_4)_2\text{HPO}_4$ causes the nucleation of GP/nHAp. The nHAp particles were obtained by the calcinations of nHAp/GP composite. The honeycomb-like PLA/nHAp films was obtained by breath figure method (Fig. 17). The PLA/nHAp had high survival rate for human normal cell line (L929) and had inhibited human cervical cancer cell line (HeLa) growth by 63% [21,27].

Hyaluronan has emerged recently to prepare multi-functional PLA composites [29,184]. Hyaluronan is a glycosaminoglycan, which is a major constituent of human tissue ECM. It has the main advantages of being nonimmunogenic and commercially available in biomedical quality. Moreover, hyaluronan is bioactive, and is usually used for biological regulation [29,184,228]. For example, PLA was aminolyzed by hexane-1,6-diamine, and then was functionalized by hyaluronan through electrostatic interactions. The presence of hyaluronan led to high mesenchymal stem cells proliferation due to its chain mobility and conformational freedom. The bioactivity depended on the surface interaction between the bioactive species and the cells [184,229]. Asymmetric PLA films were fabricated according to the non-solvent induced phase separation (NIPS) method. The PLA membrane surface was then functionalized with hyaluronan. Hyaluronan enhanced cell proliferation. The MSCs colonized the entire film thickness after 7 days of culture. Pore size and surface functionalization by hyaluronan has a strong effect on cell colonization and proliferation, and also on cell membrane morphology [29].

The Ta-implanted PLA was fabricated by plasma immersion ion implantation (PIII), owing to the biocompatibility, corrosion resistance, and osteogenic/osseointegration abilities of Ta. The obtained Ta-implanted PLA had higher adhesion stability than Ta-coated PLA. Compared to PLA, the osseointegration and osteogenesis of a rabbit femur around the Ta-implanted PLA was improved (Fig. 18) [6,230]. In another study, PLLA scaffold was combined with porous β -tricalcium phosphate (β -TCP). The water uptake ability, biominerization, and bioactivity of the PLLA was improved by β -TCP. The biocompatibility and osteogenic differentiation of human MSCs was also enhanced [110].

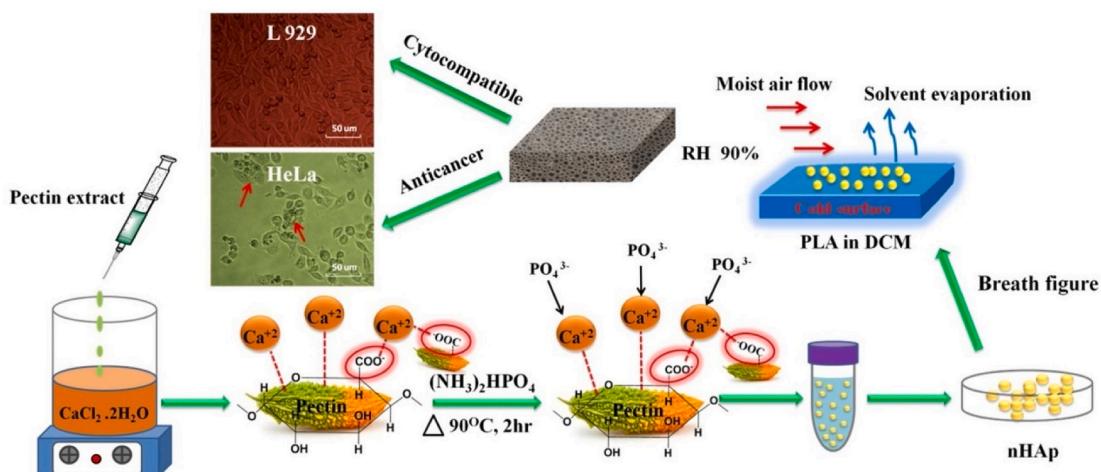


Fig. 17. Mechanistic pathway for pectin assisted synthesis of nHAp and PLA/nHAp nanocomposite. Initially, Ca^{2+} were chelated and reacted with carboxyl group of GP to form calcium pectinate complex. The addition of $(\text{NH}_4)_2\text{HPO}_4$ causes the nucleation of GP/nHAp. The nHAp particles were obtained by the calcinations. The honeycomb-like PLA/nHAp films was obtained by breath figure method. The images are PLA/nHAp with 4 wt% nHAp loading seeded on L929 and HeLa cells [27].

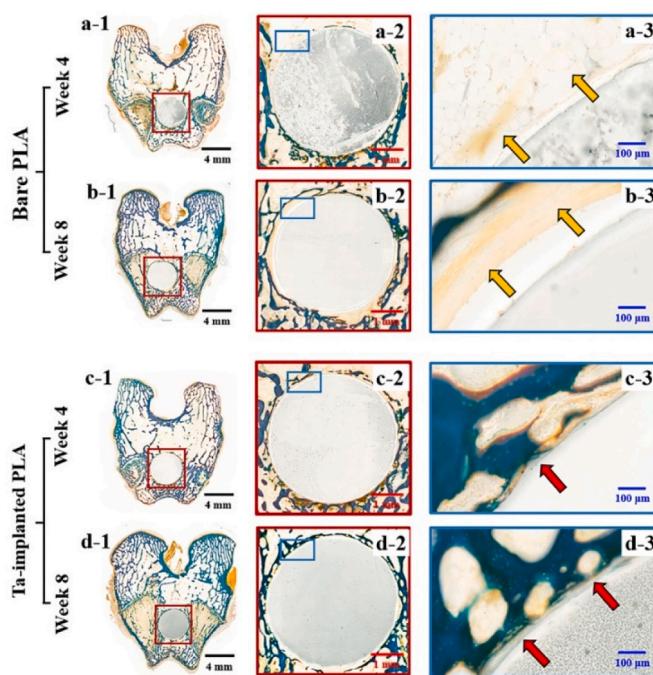


Fig. 18. Images of the tissues and implants in rabbit femur. Yellow and red arrows display the direct contacts between bones and implants are not forming and forming, respectively [6]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

PLA/dicalcium phosphate dihydrate/hydraulic calcium silicate (PLA/DCPD/CaSi) scaffold was prepared by TIPS. The acid degradation products of PLA were neutralized by deposition/nucleation of apatite. The presence of CaSi and DCPD improved the cell adhesion and growth of PLA, and the obtained scaffold was biocompatible and bioactive [128, 193, 222]. A PLA/polyaniline (PLA/PANI) scaffold was fabricated by a in-situ polymerization/TIPS technology. The obtained 3D nanofibrous scaffold had no cytotoxicity, good cell adhesion, and similar conductivity to bone. The cell proliferation, osteogenic differentiation and calcium mineralization was improved compared to PLA [22, 72].

A PLA/apatite-wollastonite (PLA/AW) composite matching the properties of cortical and cancellous bone was prepared through 3D printing. The AW had excellent osseointegration with new bone

formation and vascularization in rat calvarial injury. Layered PLA/AW showed promoting new bone formation, and it showed no delamination in vitro or in vivo [121]. Another 3D-printed PLA scaffold was immersed into polydopamine (PDA) and/or type I collagen solutions. In many stages of cell culture, the cell adhesion, osteoinductivity, and the metabolic activity of porcine bone MSCs seeded onto the scaffold was improved by the PDA/collagen coating [183, 231].

6.2. PLA for blood vessels and organs

In addition to bone regeneration, PLA has also been used in the treatment of blood vessels and organs such as coronary stents, dental implants, acute hepatic failure, glomerular and tubules reconstruction, and ocular diseases, etc.

For example, PLA was coated on the surface of Fe, and the obtained composite was implanted into the porcine artery. The PLA accelerated the corrosion of Fe. Intimal coverage, moderate inflammatory responses, and stent degradation were observed. The Fe/PLA stent exhibited excellent operability in the interventional treatments of cardiovascular diseases; its safety and efficacy were also preliminarily confirmed using the large animal model [232].

A drug delivery system (Mg/MgO/PLA-ferulaic acid) was fabricated by anodic oxidation and dip coating process. The anticorrosion capacity was improved because of the dense MgO/PLA layer. The released ferulaic acid decreased platelets adhesion and aggregation during the early stage of implantation. The Mg/MgO/PLA-ferulaic acid have the possibility for the treatment of coronary Artery Stenosis [233]. The co-implantation of spherical PLA/Mg microparticles in combination with dental implants of either titanium or PEEK was also studied [191].

A PLA/PCL foam vascular scaffold was prepared with supercritical carbon dioxide. Then the PLA phase of the scaffold was etched off with NaOH to make open pores and to improve its hydrophilicity. The obtained scaffold had excellent suture retention and fracture resistance. The cell culture of the scaffold was also improved [160, 234]. A PLA/PCL foam was also fabricated by introducing superabsorbent polymer (SAP) particles and on their swelling and leaching in the presence of water. The obtained foam had good cell adhesion and proliferation because of the interconnected pores [7, 235].

Another PLA/PCL scaffold for liver tissue engineering was combined with polyacrylamide, tumor necrosis factor- α , and insulin-like growth factor 1 to form PLA/PCL/PAAm/IGF-1/TNF- α scaffolds. The scaffold had strong inhibitory effect on BMSC senescence in vitro. It could be efficiently induced BMSCs differentiation into hepatocytes. The co-immobilized IGF-1/TNF- α biomaterial is the promotion for the

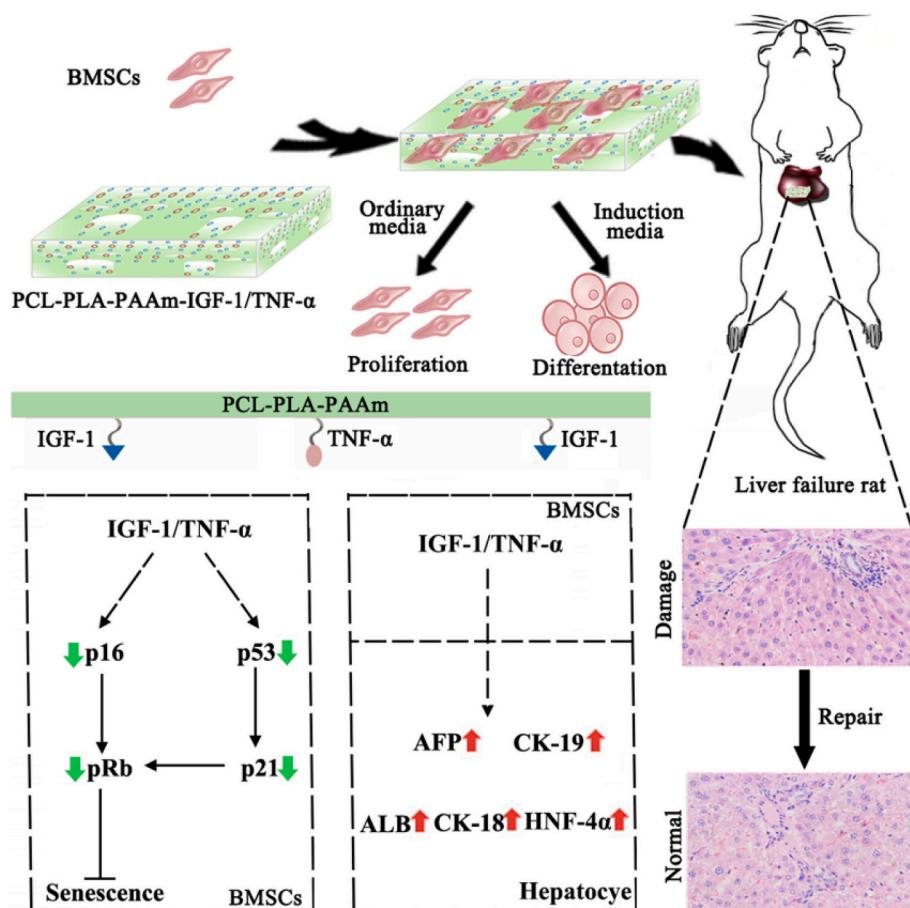


Fig. 19. The regulation mechanism of BMSCs differentiation and senescence by PLA/PCL/PAAm/IGF-1/TNF- α scaffolds [210].

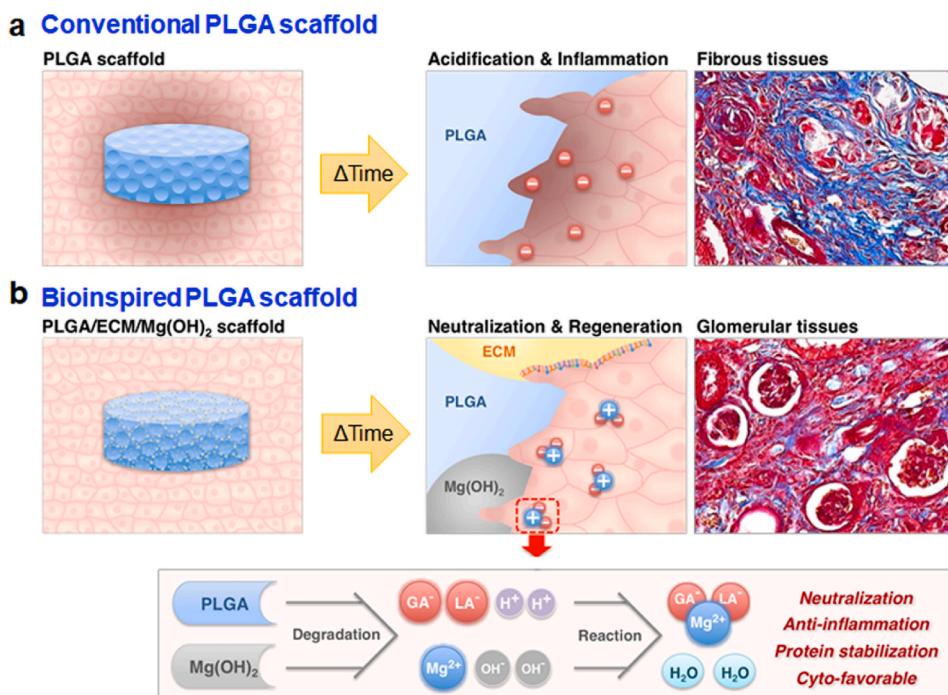


Fig. 20. (a) PLGA scaffold caused inflammation and fibrosis because of its acidic degradation products; (b) PLGA/Mg(OH)₂/ECM scaffold induced glomerularization of kidney cells [241].

hepatocyte differentiation of BMSCs. The obtained scaffold promoted treatment of acute hepatic failure (Fig. 19) [3,236].

Spherical FK506 (tacrolimus)/NH₂-PEG-b-PLA/hydroxypropyl methylcellulose nanomicelles were prepared by solvent evaporation process. The micelles enhanced the ocular surfaces retention and corneal penetration of FK506, and the sustained FK506 release provided a long period effective anti-rejection in vivo. The micelles have great potential for immuno-related ocular diseases [237]. Nifedipine is a hydrophilic vasodilator. The nifedipine-loaded PLA/PEG micelles showed biocompatibility and bioavailability. PLA/PEG improved the solubility and bioavailability of Nifedipine. The micelles improved the anticataract ability through the inhibition of extracellular calcium ions influx. The micelles may have potential applications in cataract treatment [238].

Core-shell PLA/poly(vinyl alcohol) (PLA/PVA) composite nanofibers were fabricated by coaxial electrospinning technique. The obtained PLA/PVA nanofiber mat was hydrophilic. The tensile strength of the PLA/PVA increased by 254% compared to pristine PLA. The obtained PLA/PVA nanofiber mat also showed suitable properties for proliferation, and attachment of human embryonic kidney cells (HEK-293) [180, 239].

The heparin was coated onto the amino-groups of PDA/PEI/PLA stent. The heparinized PLA stent showed thromboresistance and hemocompatibility, and modulation of smooth muscle cell and endothelial cell proliferation. Moreover, in vivo assessment, it exhibited the widest lumen area with less neointimal hyperplasia and without atherosclerosis or thrombosis [240].

A scaffold was fabricated for renal tissue regeneration with a combination of PLGA, Mg(OH)₂, and decellularized renal ECM. The Mg(OH)₂ neutralized the acidic degradation products of PLGA and inhibited inflammation. The ECM influenced cell attachment and differentiation and exchange of metabolites, and enhanced the cytocompatibility. The PLGA/Mg(OH)₂/ECM composite enhanced the reconstruction of glomerular and tubules (Fig. 20) [241,242].

Methotrexate (MTX) is hydrophilic and it is used to treat selected vitreoretinal diseases. The PLGA/PLA coated CS-based MTX micro-implants administered a therapeutic release rate of 0.2–2.0 µg/day of MTX, for an extended period of ~3–5 months. The drug release is caused by polymer swelling and diffusion of loosely bound MTX particles. The mechanism of drug release may be a combination of polymer diffusion and hydrolysis [243].

6.3. PLA for skin regeneration

Skin is the largest organ in the human body. When the skin is disrupted, some physiochemical processes takes place to repair the wounds. However, chronic wounds cannot heal through the normal healing process and have further complications due to bacterial infection [49,244,245]. Traditional antibiotics are rarely effective in reducing chronic wound infections because weak blood flow and dead tissue prevent antibiotics from penetrating the wound [246]. Hence, it is important to develop wound dressing that can prevent bacterial infection, promote tissue regeneration, and act as a barrier against mechanical trauma. PLA composites-based scaffolds are proved to be ideal matrices for wound healing [49,245,246].

PLA nanofibers encapsulating Doxycycline (DCH) as a matrix metalloproteinases inhibitor were fabricated by electrospinning for the treatment of chronic wounds. DCH/PLA had positive antibacterial activity against *E. coli*, and had no obvious toxicity to L929 mouse fibroblasts. It promoted the chronic wound healing of diabetic rats, and possessed great superiority over topical coating of DCH because of the sustained release of DCH [247].

The antimicrobial agent, thymoquinone (TQ) was incorporated into the PLA/cellulose acetate (PLA/CA) scaffolds. Because of the hydrophilicity of CA and its ability to form hydrogen bonding with PLA, the TQ-loaded PLA/CA wound dressings showed an antibacterial activity against *Staphylococcus aureus* (*S. aureus*) and *E. coli*, and it maintained

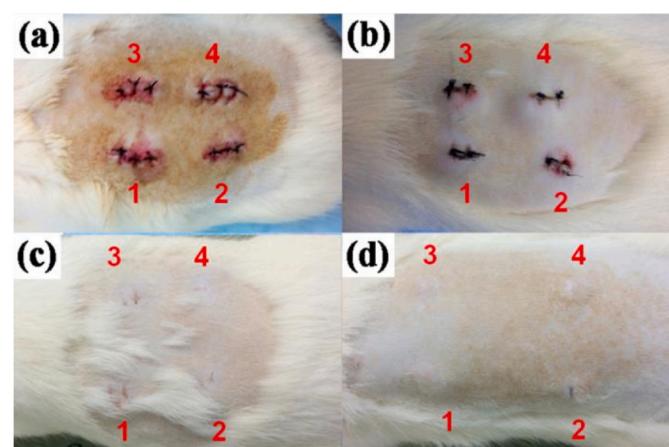


Fig. 21. The PLLA/CSMs composites with (1) 0 wt% CS; (2) 5 wt% CS; (3) 10 wt% CS; and (4) 20 wt% CS were implanted into rat's subcutaneous for (a) 24 h (b) 1 w (c) 2 w (d) 6 w [186].

the sustained release of TQ for 9 days [49]. PLLA/CS microspheres (PLLA/CSMs) composites were fabricated. CSMs accelerated PLLA degradation and neutralized the acidity of the degradation products. pH value of composite was around 7.50 in vitro until six weeks when it was implanted subcutaneously in a rat (Fig. 21) [186,207,208].

A Ag₂[1,3,5-benzenetricarboxylate]-imidazole-PLA electrospun fibrous mat was fabricated. The bacterial killing performance against *E. coli*, *S. aureus*, *Pseudomonas aeruginosa* (*P. aeruginosa*), and *Mycobacterium smegmatis* in vitro was observed at the bacteria inhibition rate of more than 95.0% [246]. Green synthesized silver nanoparticles (AgNPs) using Teucrium polium extract were embedded in PLA/PEG. The AgNPs has antioxidant activity. The obtained Ag/PLA/PEG film exhibited antimicrobial activity against *P. aeruginosa* and *S. aureus*, which showed a suitable safety profile in human macrophage cells. This film with simultaneous antimicrobial and antioxidant activity has potential as a wound dressing [244].

A PLA/poly(trimethylene carbonate) (PLA/PTMC) composite was fabricated. It reduced infections because it formed a thin and breathable film on the skin surface. It promoted the proliferation of L6 rat myoblasts, fibroblasts and epidermal stem cells within the skin wound, and it was harmless to the liver and kidneys [48].

PGA/PLA was fabricated by coaxial electrospinning with a PGA core and PLA shell. The composite scaffold was hydrophobic and biocompatible, which was beneficial to cell proliferation and wound healing. More than 90% re-epithelialization was observed [69,248].

A Cu-doped borate-bioactive-glass/PLGA (PLGA/BG-Cu) dressing loaded with vitamin E (VE) was prepared. The Cu²⁺ and VE were proved to be controlled release. The dressing promoted angiogenesis and repaired skin defects. It improved the epithelialization of wound closure and promoted vessel formation and collagen remodeling. Fig. 22 shows the preparation of PLGA/BG-Cu-VE dressing and the wound healing processes [67,185,199].

7. PLA for drug delivery

Drug delivery describes the method to delivering drugs and other xenobiotics to their site of action within an organism. The challenges for drug delivery systems include the development of a drug carrier that can maintain sustained drug release and targeting drug delivery, methods to regulate the bioavailability of associated drug once it has reached the target tissue, methods to enhance the specificity for target cells, and methods to deliver macromolecules more efficiently to their sites of action in the interior of target cells [249]. The micro- or nano-encapsulation of pharmaceutical ingredients is a promising way for drug delivery [123,126,250,251]. Biodegradable polymers with a

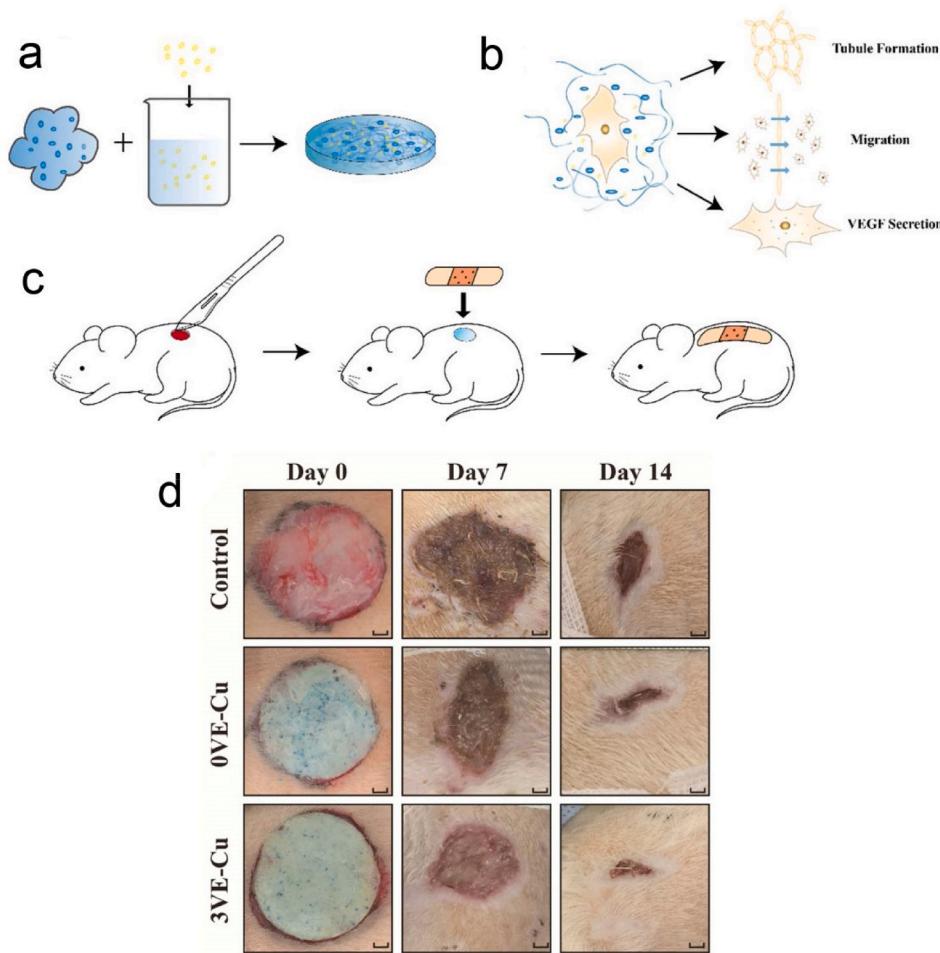


Fig. 22. (a) PLGA/BG-Cu-VE dressing fabrication (Blue spot: Cu²⁺; Yellow spot: VE; Blue line: BG); (b) tubule formation, migration, and VEGF secretion; (c) the experimental process of using dressing in rodents; (d) skin defects in rodents, untreated or treated with PLGA/BG or PLGA/BG-Cu-VE [67]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

nanostructure are potential candidates for biomedical applications such as drug delivery, cell carriers, and medical imaging agents [58,198]. Biological microcapsules can be used as carriers with controlled drug release function, it can enhance the accuracy of drug release to a specific site of action, and prolong the effective time of active drug ingredients. Moreover, encapsulation prevents contact of protein from cells or enzymes in surrounding tissues, until it has been released [218–220].

Ideal drug carriers should release drugs at specific locations and prevent drug decomposition during blood circulation. Biological functionalization is a basic requirement for carriers to ensure targeting. Moreover, ideal drug release systems should have a constant release rate and drug concentration in the plasma *in vivo* for the required treatment length. In order to improve the therapeutic effectiveness and dose management, researchers are focus on more advanced sustained release systems to deliver drugs at a specific rate to targets [31,74,177,241,252].

7.1. PLA for drug encapsulation and sustained release

Drugs with different hydrophobicity were encapsulated in PLA/PLGA composites (Fig. 23) prepared by ring-opening polymerization. The obtained composites had narrow weight distribution compared to the industrialized products. With the change of lactide content, the hydrophilicity of the composite was tunable. Moreover, the size and stability of these drug carriers depended on the solvents and stabilizers [250,253].

Core-shell structures of PVA/PLA were also obtained via coaxial

electrospinning while the parameters were optimized (Fig. 24). By changing parameters like voltage, internal and external flows that influence fiber morphology, the burst effect of coaxial electrospinning was eliminated. The optimal fibers showed controlled protein release with the presence of shell. The mouse preosteoblastic MC3T3-E1 proliferated and differentiated by the combination of human bone morphogenetic protein-2 (BMP-2) [109,115,254].

Rifapentine and PLA were used as the drug and carrier to formulate sustained-release microsphere. The microsphere was integrated into HA/β-TCP or allogeneic bone as implants for the treatment of osteo-articular tuberculosis. The encapsulation and drug loading efficiency were ~78% and ~36%, respectively. It had a long-term antibacterium effect and excellent osteoconductive and osteoinductive properties [255]. Recombinant human insulin-like growth factor 1 (rhIGF-1) loaded PLA/HA@Eudragit double-layer microspheres (PLA/HA@Eu) with core-shell structure were formulated with an oil-in-water-in-oil technique. Long-term controlled release of rhIGF-1 was maintained at a constant rate from the microspheres over 180 days *in vitro*, which was in line with the rhIGF-1 release patterns *in vivo*. It provides a promising therapeutic approach to delay osteoporosis and articular degeneration [109,217]. Prefabricated electrospun PLA/HA/gelatin was fabricated into a scaffold and immobilized with BMP-2 peptides via a PDA assisted coating method, forming a sustained release scaffold. The scaffold had desirable biocompatibility and osteoinductivity both *in vitro* and *in vivo*. The HA and BMP-2 peptides synergistically promoted osteogenic differentiation of bone mesenchymal stem cells [131,225].

Collagen functionalized hydroxyapatite was embedded into PLA

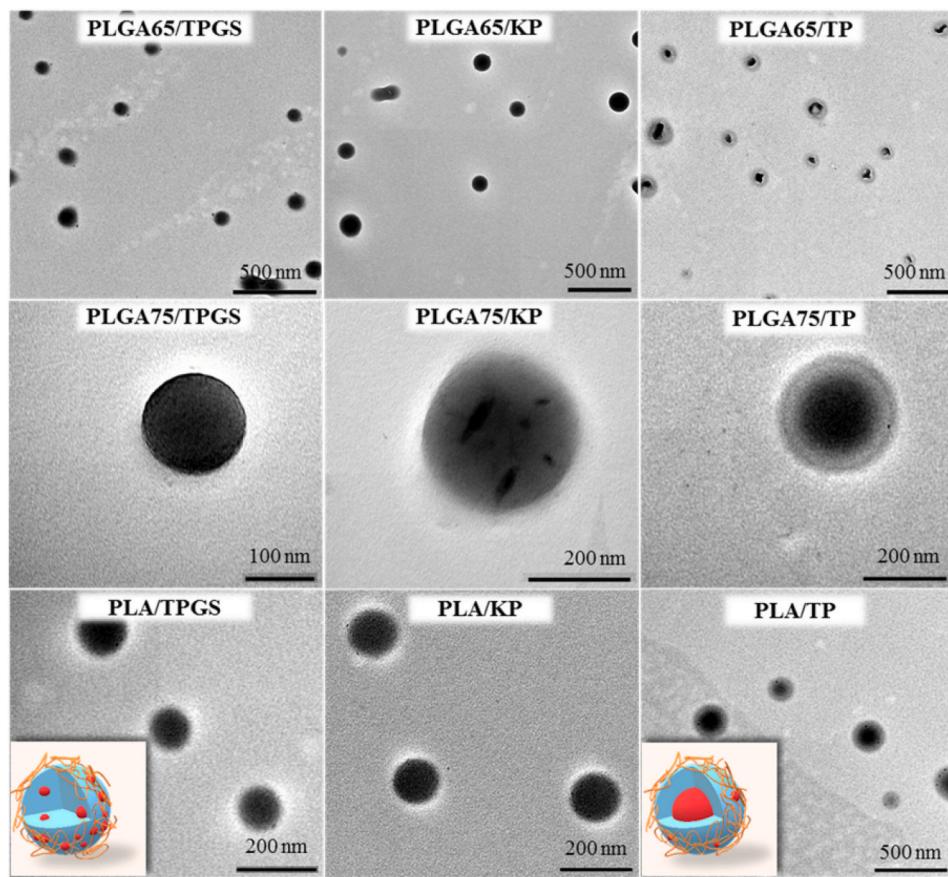


Fig. 23. TEM images and schematic of PLGA/PLA nanoparticles containing different drugs [250].

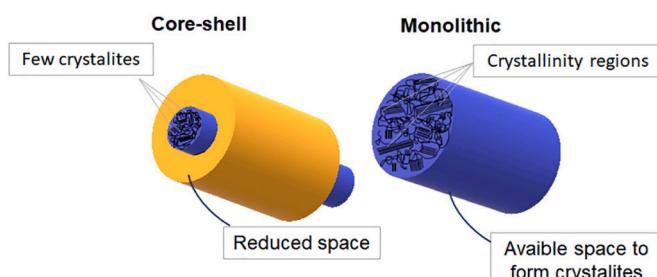


Fig. 24. Available volume in monolithic and coaxial electrospinning technique [115].

matrix, and subsequently covered with self-assembled collagen layer. The obtained composite was used for coating Ti implants to assess bone consolidation in orthopedic surgery [256,257]. A 3D printed PLA scaffold was combined with collagen, minocycline (MH) and citrate-HA (cHA). The obtained scaffold had a high compressive strength and adequate wettability. The MH led to an adequate antibiotic release profile that by being compatible with local drug delivery therapy was translated into antibacterial activities against *S. aureus*. Meanwhile, the adhesion, proliferation, and differentiation of precursor stromal populations was stimulated by cHA [34,188].

A vitamin E (VE) loaded bi-layered electrospinning membrane, based on an upper of PLA and a lower of PCL layer, was fabricated. The PLA/PCL/VE membrane showed sustained drug release pattern which followed non-fickian release behavior. The membrane supported cell adhesion, proliferation, and viability without necrotic behavior. Angiogenesis was also observed [142,258]. PLA microchamber arrays were prepared by dip-coating a PDMS stamp into PLA solution.

Rhodamine B as a model drug substance was loaded into PLA microchambers and released within 13 days in a phosphate buffer saline solution at 37 °C. The PLA microchamber arrays can be applied as the cover for implantable endovascular stent [259].

Layer-by-layer nanocoating consists of vancomycin/PLA/vancomycin-loaded noisome was designed. The niosomes-coated bone plates had superior antibacterial activity and no cytotoxic effects towards L929 mouse fibroblast cells. This coating is useful for medical devices which are prone to bacterial infections, such as orthopedic implants and dental implants [260].

The bilayered PLA/chitosan scaffold was fabricated by electrospinning, then NaX/Fe₃O₄ and Doxorubicin (DOX) were incorporated into the scaffold as anticancer drugs. The drug loading rate of DOX was higher than 90% and the drug release followed Fickian diffusion. After 7 days in the magnetic field, the DOX loaded PLA/chitosan/NaX/Fe₃O₄ killed 82% of H1355 cells [225,261].

Two PLA-hyperbranched polyglycerols nanoparticles (PLA-HPG NPs); nonadhesive PLA-HPG nanoparticles (NNPs) and surface-modified bioadhesive nanoparticles (BNPs)-loaded with the antiretroviral elvitegravir (EVG) were fabricated. After intravaginal administration, BNP distribution was widespread throughout the reproductive tract, and retention was nearly 5 times higher than NNPs after 24 h (Fig. 25). Moreover, BNPs were found to be highly associated with submucosal leukocytes and epithelial cell populations for up to 48 h after topical application, and EVG was retained significantly better in the vaginal lumen when delivered with BNPs as opposed to NNPs over a 24 h period [195].

7.2. PLA for tumor-targeting

Chemotherapy is conventional treatment against tumors. But it is far

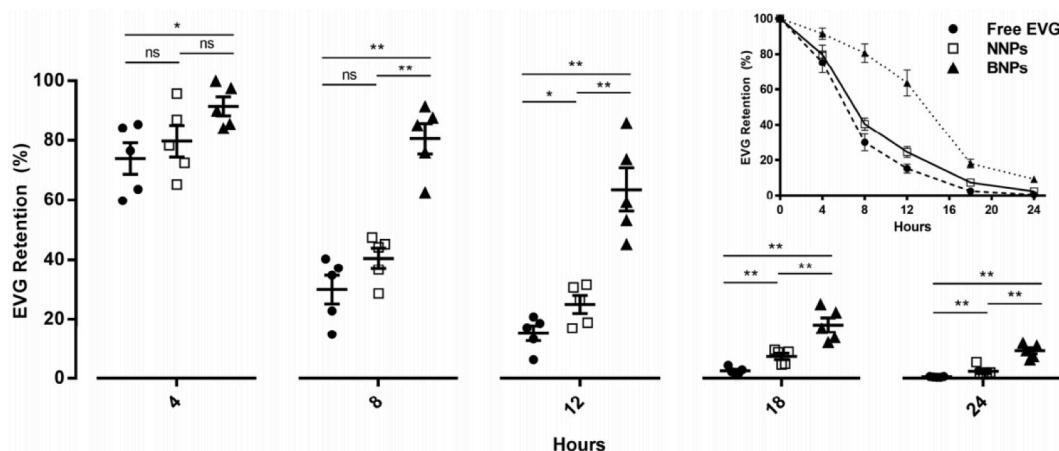


Fig. 25. Comparison of in vivo EVG retention percentages between free EVG, NNPs and BNPs at 4 h, 8 h, 12 h, 18 h and 24 h. The insert shows the 24 h EVG retention profile of free EVG, NNPs and BNPs [195].

from satisfactory because of side effects, poor bioavailability, chemoresistance, tumor heterogeneity, undesirable immune reactions between exogenous carriers and specific cell receptors, and wrong evaluation on realtime therapeutic effect [57]. To advance the therapeutic effects, targeting drug delivery, which can carry drugs to specific organs or tissues hold great promise for improving the efficacy and safety compared to traditional chemotherapy [262].

Polymeric nanoparticles (NPs) have been used as promising carriers of anticancer drugs, functioning as sustained, controlled and targeting drug delivery systems to improve the therapeutic effects and to reduce the side effects on normal organs. PLA based nanocomposite is often used for targeting drug delivery [262,263].

Polydopamine-modified NPs was synthesized using D-a-tocopherol polyethylene glycol 1000 succinate-poly(lactide) (pD-TPGS-PLA/NPs). Then galactosamine was conjugated on it (Gal-pD-TPGS-PLA/NPs) as a carrier for liver tumor-targeted drug delivery. Dopamine and galactosamine barely changed the zeta potential and drug release profile of NPs. The in vivo experiments showed that the Gal-pD-TPGS-PLA/NPs had a strong hepatoma-targeting property in nude mice. In Fig. 26, a strong signal was detected in the tumor tissue at 6 h after injection. The signal intensity was much stronger in tumor tissue than that in liver at 24 h after injection for all three groups. So Gal-pD-TPGS-PLA/NPs has liver- and hepatoma-targeting capability [262]. In another study, barbaloin (BBL)-loaded formulations was developed with pD-modified NPs, which was synthesized by PLA-TPGS (pD-PLA-TPGS/NPs). Then galactosamine was conjugated on it (Gal-pD-PLA-TPGS/NPs) for targeting the gastric cancer cells. BBL-loaded Gal-pD-PLA-TPGS/NPs showed a higher cellular uptake efficacy in gastric cancer cells, and displayed a stronger gastric tumor-targeting property in vivo. Gal-pD-PLA-TPGS/NPs more significantly reduced the gastric cancer cell viability. Greater apoptosis, autophagy and ROS generation was induced by Gal-pD-PLA-TPGS/NPs in gastric cancer cells [263].

Polymeric micelles have also been widely studied for targeting delivery of cytostatic drugs [264]. PLA stereocomplex interaction-assisted polymeric micelles have attracted increasing attention. As compared with the conventional micelles, PLA stereocomplex micelles have good biocompatibility, enhanced stability and reduced degradation rate. Furthermore, there is no need for introducing special functional groups into the blocks to stabilize the micelles in comparison with other non-covalent interactions. The above-mentioned advantages make PLA stereocomplex micelles with great promising applications for targeting drug delivery [264,265].

Paclitaxel-loaded biodegradable PLA/PEG micelles functionalized with folic acid and biotin were fabricated. The micelles showed low critical micelle concentration, high loading capacity of paclitaxel, and prolonged in vitro drug release. The cytotoxicity of the micelles against folate- and biotin-receptor positive OVCAR3 cells was observed, which indicates their potential for targeting delivery of cytostatic drug [264]. In another study, docetaxel (DTX)-loaded polymeric micelles (DTBM) were formulated using PEG-PLA-PEG triblock copolymer. DTBM showed a stable formulation of anticancer nanomedicine that could be reconstituted after lyophilization (DTBM-R). DTBM-R showed a particle size less than 150 nm and greater than 90% of DTX recovery after reconstitution. The micelles might minimize systemic toxicity due to their sustained drug release and maximize antitumor efficacy through increased accumulation and release of DTX [266]. Photodynamic therapy is a method to treat ovarian cancer, so photosensitizer Hypocrellin

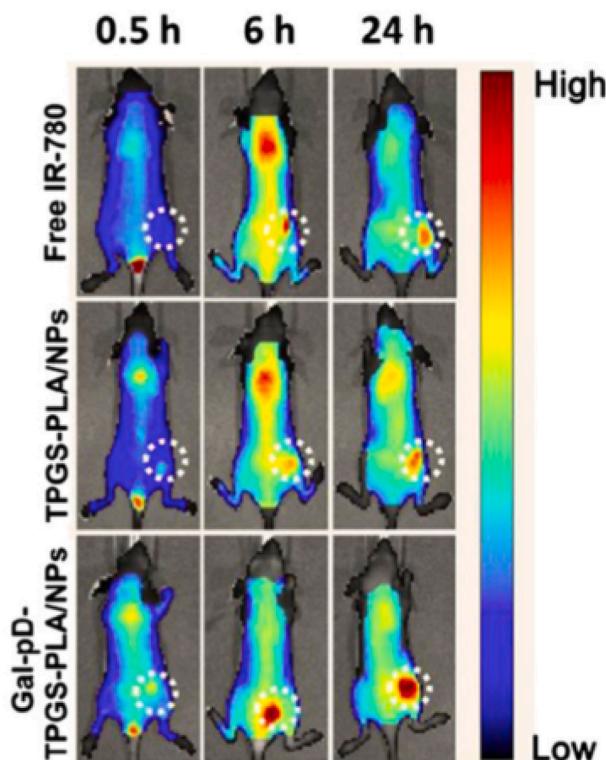


Fig. 26. In vivo imaging and biodistribution analysis of nude mice bearing HepG2 tumors after tail vein injection of free IR-780, IR-780 loaded TPGS-PLA/NPs and Gal-pD-TPGSPLA/NPs (Time-lapse NIR fluorescence images of nude mice. The tumors are circled with dotted line) [262].

B/folate-PEG-PLA micelles was prepared. It had a high drug loading capacity, good biocompatibility, controlled drug release, prolonged blood circulation of Hypocrellin B, and enhanced targeting and anti-tumor effect against ovarian cancer [267].

A 3D PLGA/PLA/PCL composite nanofiber implant was fabricated. It could release anti-glioma drug Temozolomide at a constant rate, continuously for one month into the brain tumor. The prolonged drug release in the brain tumor is critical in inhibiting the recurrence of glioblastoma [268].

PLLA microspheres also have been employed as drug carriers. PLLA microspheres lack cohesive force, so they might be easily to soft tissue space. To overcome this disadvantage, PLLA was modified by superparamagnetic Fe₂O₃ nanoparticles assisted with oxidative dopamine polymerization. The obtained microspheres have the potential of carrying cells to designated locations in a magnetic field [126,158].

8. Conclusions, challenges, and perspectives

PLA is a U.S. Federal Drug Administration approved polymer. It can be used for tissue reconstruction and drug delivery. However, PLA has limitations such as low toughness, low degradation rate, low cell adhesion because of its hydrophobicity, biological inertness, acidic degradation products, and inflammation *in vivo*. This review summarized and analyzed recent progress and research, including novel fabrication techniques, high-performance PLA composites and their applications.

Developing PLA based composites is a major method to address the problems associated with PLA scaffolds. The diversity of components and potential applications of biomaterials are greatly expanded by the integration of composite techniques. Blend of other materials with PLA may provide balanced physical and biological properties. However, a common problem of this strategy is that the thermal and mechanical properties of each component of the composite can vary greatly, potentially weakening the interfacial strength, and resulting in coating delamination, and implant loosening and poor osseointegration.

Nowadays, traditional fabrication methods for PLA based composites are facing many challenges while producing, challenges of 3D printing include how to enhance mechanical properties while maintaining porosity, and how to improve the reproducibility and reduce costs. Their low printing speed, the lack of quality control, and the risk of cyber-attacks on the printing process are also worthy of note. Scaffolds by phase separation processes usually have pores which are too small to allow cell penetration [269]. PLA scaffolds from conventional electro-spinning have poor mechanical properties and low thermal stability. They also have small pore size and tightly packed fibrous layers, which hinders the cultured cells' penetration and proliferation. A wider understanding of new and effective fabrication strategies to solve these problems will be the focus of future research.

Combined fabrication technologies have been employed to prepare PLA scaffolds with improved properties, such as the combination of FDM, gas foaming and solvent etching; the combination of in-situ polymerization and TIPS; the combination of microwave-assisted mineralization and solution coagulation; and the combination of solvent casting, particulate leaching, and compression molding. Combined fabrication technologies are worthy of further investigation and may offer a new strategy for designing high-performance biomaterials.

The authors believe that PLA composites have a promising future as bone tissue engineering and as carriers that can maintain a constant drug release rate and deliver drugs to precisely targeted tissue. It can be anticipated that future developments of PLA will keep including combined fabrication technologies and PLA based composites, which will improve the biofunctionality and physicochemical properties of PLA, and will also further expand the applications of PLA as scaffolds of bone tissue engineering and as carriers for drug delivery.

Declaration of competing interest

The authors declared that we have no conflicts of interest to this work.

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