Recent advances in 3D-printed polylactide and polycaprolactone-based biomaterials for tissue engineering applications

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Abstract

The three-dimensional printing (3DP) also known as the additive manufacturing (AM), a novel and futuristic technology that facilitates the printing of multiscale, biomimetic, intricate cytoarchitecture, function-structure hierarchy, multi-cellular tissues in the complicated micro-environment, patient-specific scaffolds, and medical devices. There is an increasing demand for developing 3D-printed products that can be utilized for organ transplantations due to the organ shortage. Nowadays, the 3DP has gained considerable interest in the tissue engineering (TE) field. The AM of bioactive materials particularly biopolymers permits the manufacturing of implants at specific defective sites with tunable properties and controllable chemical composition. Polylactide (PLA) and polycaprolactone (PCL) are exemplary biomaterials with excellent physicochemical properties and biocompatibility, which have drawn notable attraction in tissue regeneration. Herein, the recent advancements in the PLA and PCL biodegradable polymer-based composites as well as their reinforcement with hydrogels and bio-ceramics scaffolds manufactured through 3DP are systematically summarized and the applications of bone, cardiac, neural, vascularized and skin tissue regeneration are thoroughly elucidated. The interaction between implanted biodegradable polymers, in-vivo and in-vitro testing models for possible evaluation of degradation and biological properties are also illustrated. The final section of this review incorporates the current challenges and future opportunities in the 3DP of PCL- and PLA-based composites that will prove helpful for biomedical engineers to fulfill the demands of the clinical field.

Keywords: Polylactic acid, Polycaprolactone, 3D printing, Biodegradability, Tissue engineering, Scaffolds

List of abbreviations

2D	Two-dimensional
3D	Three-dimensional
3DP	3D printing
AM	Additive manufacturing
Ag-NPs	Silver nanoparticles

Alg	Alginate
ALP	Alkaline phosphatase
AUP	Acrylate-terminated urethane-based polymer
BG	Bioactive glass
BMSCs	Bone marrow derived stem cells
BTE	Bone tissue engineering
CAD	Computer-aided design
CI	Chitin
CNF	Cellulose nanofiber
CNT	Carbon nanotube
Col	Collagen
COL-1	Type I collagen
CP	Calcium phosphate
CS	Chitosan
CT	Computed tomography
DAT	Decellularized adipose tissues
DES	Drug-eluting stents
dECM	decellularized extracellular matrix
DIW	Direct ink writing
DLP	Digital light processing
DMA	Dynamic mechanical analysis
DNA	Deoxyribonucleic acid
DPSCs	Dental pulp-derived stem cells
DX	Doxycycline
FEM	Finite element modeling
FFF	Fused filament fabrication
EBM	Electron beam melting
EC	Endothelial cell
ECM	Extracellular matrix
EHDP	Electrohydrodynamic printing
ELISA	Enzyme-linked immunosorbent assay
EUP	Ene-terminated urethane-based polymer
FDA	Food and drug administration
FDM	Fused deposition modeling
Gel	Gelatin
GelMA	Methacrylated gelatin
GNPs	Gold nanoparticles
HA	Hyaluronic acid
HACC	2-hydroxypropyltrimethyl ammonium chloride chitosan
HAp	Hydroxyapatite
hASCs	Human adipose stem cells
hAuCs	Human auricular chondrocytes
hMSCs	Human mesenchymal stem cells
HUF	Human uterine fbroblasts
HUVEC	Human umbilical vein endothelial cell
IJP	Inkjet printing

91	IR	Infrared
92	IVD	Intervertebral disc
93	LCD	Liquid crystal display
94	MC	Methylated collagen
95	MEW	Melt electrospinning writing
96	MPP	Multi-photon polymerization
97	MRI	Magnetic resonance imaging
98	mRNA	Messenger ribonucleic acid
99	MSCs	Mesenchymal stem cells
100	nFA	Nano-fluorapatite
101	nHAp	Nano-hydroxyapatite
102	NGCs	Nerve guidance conduits
103	PCL	Polycaprolactone
104	PDA	Polydopamine
105	PDLA	Poly (D-lactide)
106	PDLLA	Poly(D, L-lactic acid)
107	PEDOT	Poly(3,4-ethylenedioxythiophene)
108	PEG	Polyethylene glycol
109	PEI	Polyethyleneimine
110	PETA-4SH	Pentaerythritol tetrakis(3-mercaptopropionate)
111	PGA	Polyglycolic acid
112	PGS	Poly(glycerol sebacate)
113	PHA	Polyhydroxyalkanoate
114	PHB	Polyhydroxybutyrate
115	PLA	Polylactide
116	PLCL	Poly(l-lactide-co-ε-caprolactone)
117	PLGA	Poly(lactide-co-glycolide)
118	PLLA	Poly (L-lactide)
119	PP	Polypropylene
120	PPSu	Poly(1,3-propylene succinate)
121	PPy	Polypyrrole
122	PS	Polystyrene
123	PMMA	Poly (methyl methacrylate)
124	PNI	Peripheral nerve injury
125	PU	Polyurethane
126	PUA	Polyurethane acrylate
127	PVA	Polyvinyl alcohol
128	PVP	Polyvinylpyrrolidone
129	rhCol	Recombinant human type III collagen
130	RGO	Reduced graphene oxide
131	RGNP	RGD-conjugated bioactive gold nanoparticle
132	RT-PCR	Real-time polymerase chain reaction
133	SA	Sodium alginate
134	SABR	Stereotactic ablative body radiotherapy
135	SCs	Schwann cells
136	SE	Solution electrospinning

SF	Silk fibroin
SFF	Solid freeform fabrication
SEM	Scanning electron microscope
SLA	Stereolithography
SMC	Smooth muscle cell
SMSCs	Synovial mesenchymal stem cells
SS	Stainless steel
TCP	Tricalcium phosphate
TE	Tissue engineering
TEC	Triethyl citrate
TFNA	Tetrahedral framework nucleic acid
TISA	Thermally induced self-agglomeration
TPMS	Triply periodic minimal surface
UV	Ultraviolet
YUP	Vne-terminated urethane-based polymer
VG	Vascular graft
VMAT	Volumetric modulated arc radiotherapy
β-CD	β-cyclodextrin
μCP	Microcontact printing

Table of Contents

1 Introduction

Biomaterials are propitious materials, which play an important role in restoring the functions and facilitating the healing of different injuries and diseases [1]. The utilization of biomaterials such as wood and metal is found back in Egyptian times, when they used to employ sutures developed through animal sinew [2]. Modern biomaterials are extensively applied in clinical applications to support, enhance or substitute traumatized tissues or biological functions [3]. Even today, different non-degradable materials including stainless steel (SS), titanium, and chromium-cobalt (Cr–Co) alloys are extensively employed as temporary or permanent implanting materials, which reinstate functions by delivering support to the hard tissues [4]–[6]. However, these materials contain various alloying elements which harmfully influence their biocompatibility for tissue regeneration applications [7]. Additionally, swear inflammation and serious allergic reactions were noted with these elements during metallic implants [8]. It is due to ion release that occurs as a result of corrosion or excessive wear of

ions. Furthermore, the destruction of native tissues was also observed as a result of metallic implants [9].

Biomaterials can be developed through ceramics, metals, glass, plastics, as well as living tissues and cells. These materials are reengineered into machined or molded parts, fibers, films, coatings, fabrics, and foams to develop hip joint substitutes, dental implants, and heart valves [10]. Tissue engineering (TE) is an interdisciplinary field, which combines biomedical engineering and life sciences to generate biological substitutes through the implantation of suitable living cells onto scaffolds to enhance or restore tissue functions [11]–[13]. Biomaterials for TE applications must exhibit controlled porosity, surface chemistry, and biodegradability for promoting optimal cell proliferation, adhesion, differentiation, and migration of endogenous extracellular matrix (ECM) materials by the cells [14]. Furthermore, scaffolds must possess appropriate pore sizes for strong interconnection and nutrient distribution [15]–[17].

Scaffolds are usually developed by using different conventional fabrication routes including particulate leaching, thermally phase separation, solvent-casting, electrospinning, melt molding, gas foaming, and freeze-drying [18]–[20]. However, these techniques have their limitations in terms of minimal control over toxic solvent residues, scaffolds composition, architecture, micropore shape, interconnection, distribution, and pores size [21]. The additive manufacturing (AM), a rapid prototyping technology, also referred to as the three-dimensional printing (3DP) exhibits tremendous benefits in biomedical and other engineering fields [22]–[25]. In the contemporary world, the 3DP has become a widely applied technology by overcoming the limitations associated with the traditional manufacturing routes and facilitates to manufacture the high-quality scaffolds through the layer-by-layer stacking supported by computer-aided design (CAD) [26]–[29]. The rapid prototyping technology is seldomly called solid freeform fabrication (SFF) in which composite scaffolds of complex geometries and uniform thickness are prepared without using a particular mold or tooling [30]. This technology has grown continuously, over the four decades and has been recently applied in the clinical sector to develop novel 3D-printed biodegradable scaffolds and other medical instruments [31]–[33].

On the other hand, the 3D bioprinting approach manufactures highly intricate scaffolds, tissues, and biomedical devices [34]. This technique involves patterning and assembling non-living and living biomaterials onto a tissue or substrate through CAD modeling, which uses ordinary medical images including magnetic resonance imaging (MRI), X-rays, and computed tomography (CT) [35], as illustrated in Figure 1(a). The desired products are created using CAD software like AutoCAD®, SketchUp®, and SolidWorks®. Subsequently, these models are sliced into layers by using slicing software, like Simplify®, Slic3r®, and Cura®. These sliced models are imported into the 3D printer as STL files [36].

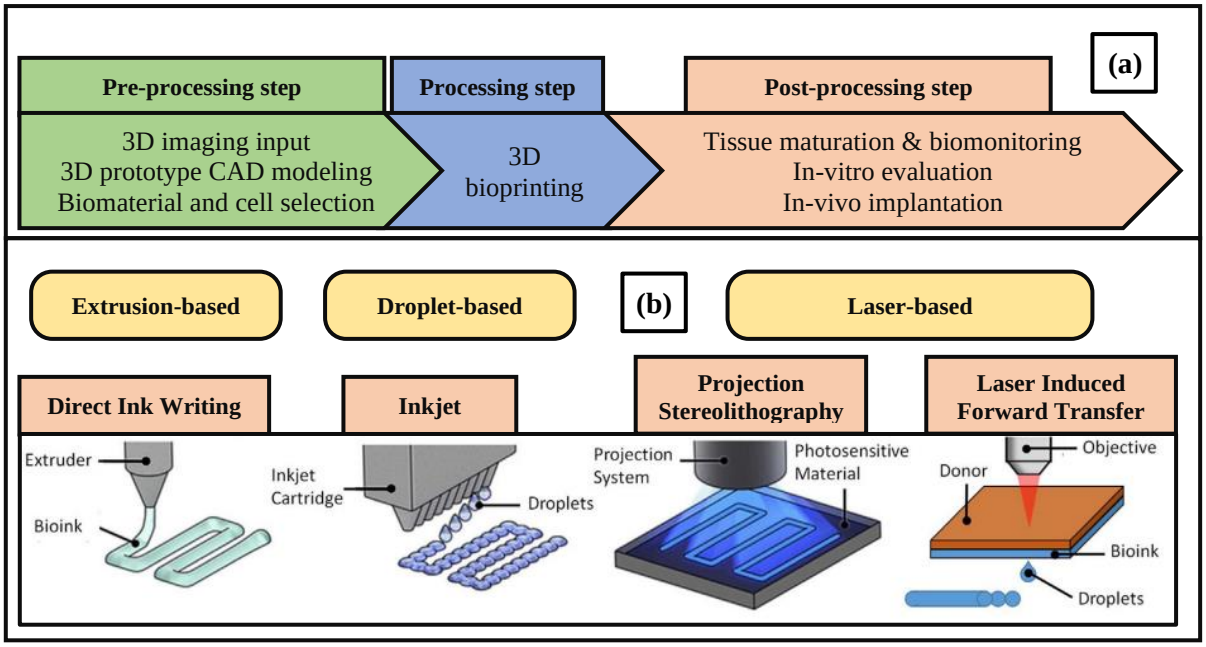


Figure 1 (a) Flow diagram showing different steps involved in 3D bioprinting; (b) Types of 3D bioprinting technologies employed for medical sectors (adapted with permission from ref. [37], copyright, 2017)

The complete degradation of biopolymeric composite materials is completely attained in the natural environment due to different microorganisms, ultraviolet (UV) light, or moisture [38]–[40]. The degradation process comprises the changes in crystallinity of the biopolymeric matrices and different natural residue or natural fibers [41]. Bioprinting technology offers high precision, easy manipulation, and fast production, that has been vastly explored to fabricate cell-laden scaffolds for tissue regeneration purposes with the ultimate aim to print organs [42]–[44]. Additionally, the bioprinting approach presents the flexibility to use different tissue-specific cells, biomaterials, and bioactive growth factors to fabricate organs/tissues [45]–[47].

1.1 Polymeric biomaterials for tissue engineering

The utilization of the non-biodegradable materials is limited due to their surgical excision, excessive mechanical properties of native tissues, and foreign body reactions [48]. Biodegradable behavior helps materials to eliminate from the body after performing their assigned tasks [49]. In the last few decades, the usage of naturally- or synthetically-derived biodegradable polymeric materials are continuously growing in TE, regenerative medicine, and wound healing applications due to their excellent biocompatibility, biodegradability, controllable mechanical characteristics, and inert nature. The properties of these polymers are determined through their crystalline structure, molecular weight, thermal transition, polydispersity, and degradation rate [50]–[52]. Natural biodegradable polymers including chitosan (CS), chitin (CI), gelatin (Gel), hyaluronic acid (HA), alginate (Alg), collagen (Col), cellulose, elastin, silk fibroin (SF), and their composites are resourceful bioactive materials with high biocompatibility and minimal immunological effects, which are predominantly applied to develop tissue constructs for the repairing of skin, tendon, bone, skeletal muscle, cartilage, ligament, neural, and vascular tissues [53]–[56]. These biodegradable materials are preferred over synthetic polymers due to their biocompatibility [57]. For instance, Alg-, Col-, SF-, and CS-based natural biopolymer composites are dominating the landscape of the TE sector [58]. These composites offer high biodegradability, biocompatibility, and hydrophilicity

under an optimum physiological environment [59]–[61]. Different conventional and modern manufacturing methods can be applied to develop Col-based scaffolds for bone tissue engineering (BTE) applications [62]–[64]. Alg is another naturally occurring polymer, which is continuously applied to develop biodegradable, biocompatible, and hydrophilic scaffolds. Furthermore, the incorporation of Alg into CS significantly increases the mechanical strength and integrity of the scaffolds [65]–[67]. Similarly, SF is fundamentally applied in wound healing applications due to its high angiogenic property and is an integral part of bone regeneration [68]. However, these scaffolds offer high degradation rates, high shrinking capacity, and low mechanical strength [69]. The only hindrance in developing natural biopolymer-based scaffolds is difficulty in molding these materials into desired shapes [70].

Biodegradable synthetic biopolymers contain a variety of macromolecules including polylactic acid (PLA), polyhydroxybutyrate (PHB), poly(lactide-co-glycolide) (PLGA), polyglycolic acid (PGA), polystyrene (PS), polyvinyl alcohol (PVA), polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), polyhydroxyalkanoate (PHA), polycaprolactone (PCL), poly(l-lactide-co-ε-caprolactone) (PLCL), polyurethane (PU), poly(glycerol sebacate) (PGS), and other synthetic hydrogels [71]–[75]. Figure 2 depicts that PCL and PLA are most commonly used biopolymers for TE applications. These polymers offer lower costs compared to natural biodegradable polymers and develop tailorable structures. The chemical structures of these polymers control the degradation mechanism, which plays a pivotal role in scaffold designing [76].

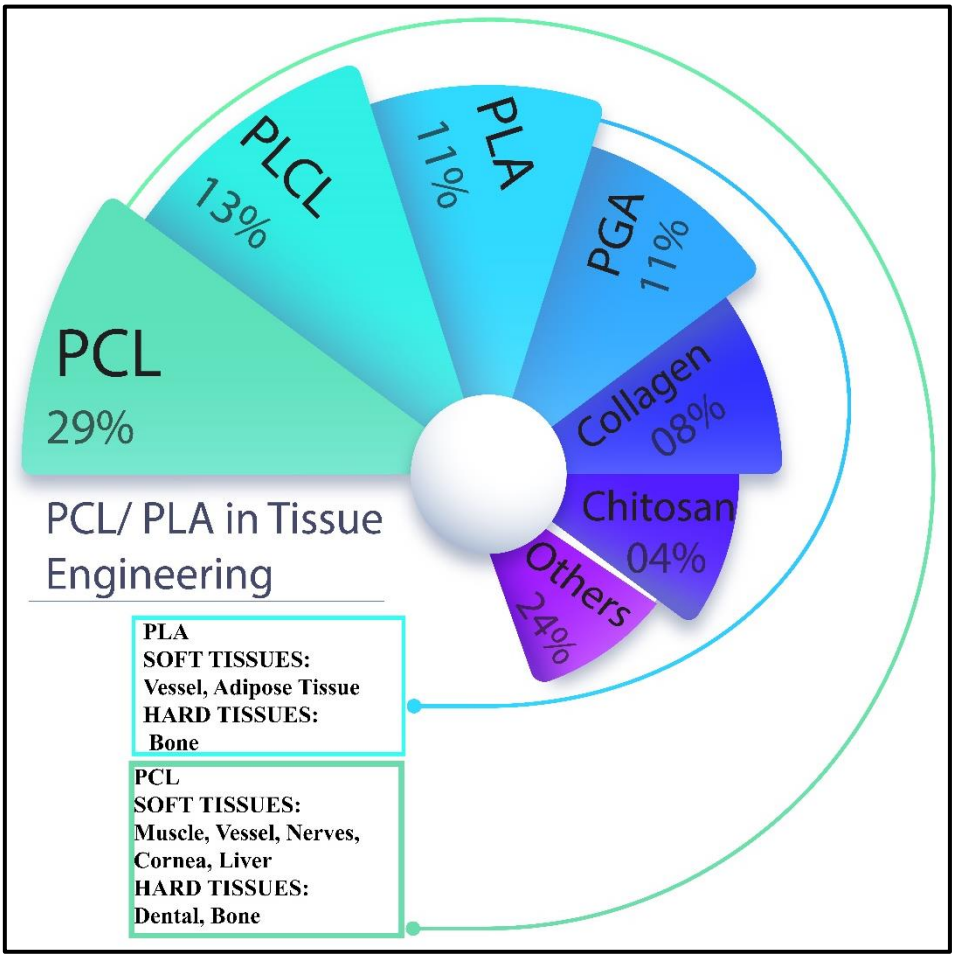


Figure 2. Different biopolymers used to fabricate scaffolds for tissue regeneration applications. The results are obtained by using "tissue engineering and biopolymer" term.

Biodegradable synthetic polymers with different characteristics can be developed by controlling the fundamental building blocks [158]. These versatile polymers are extensively applied in clinical applications due to their easy tailoring ability and can be chemically modified for design [77]. The United States Food and Drug Administration (FDA) approved some synthetic biopolymers including PCL, PLA, PGA, PGLA, and PEG for the biomedical sector. In the human body, the biopolymers release their payloads through a controllable non-toxic decomposition [78]. Though, some synthetic polymers like poly(methyl methacrylate) (PMMA) exhibit high-enduring strength and are applied in orthopedic surgeries for joint replacements [79]. However, aseptic loosening in these acrylic polymers results in damaging the bone tissues, and gradual wear is also observed due to the mismatch between the mechanical properties [80]. Figure 3 encapsulates some prominent factors important for the extensive use of PCL- and PLA-based biodegradable polymers in tissue regeneration applications.

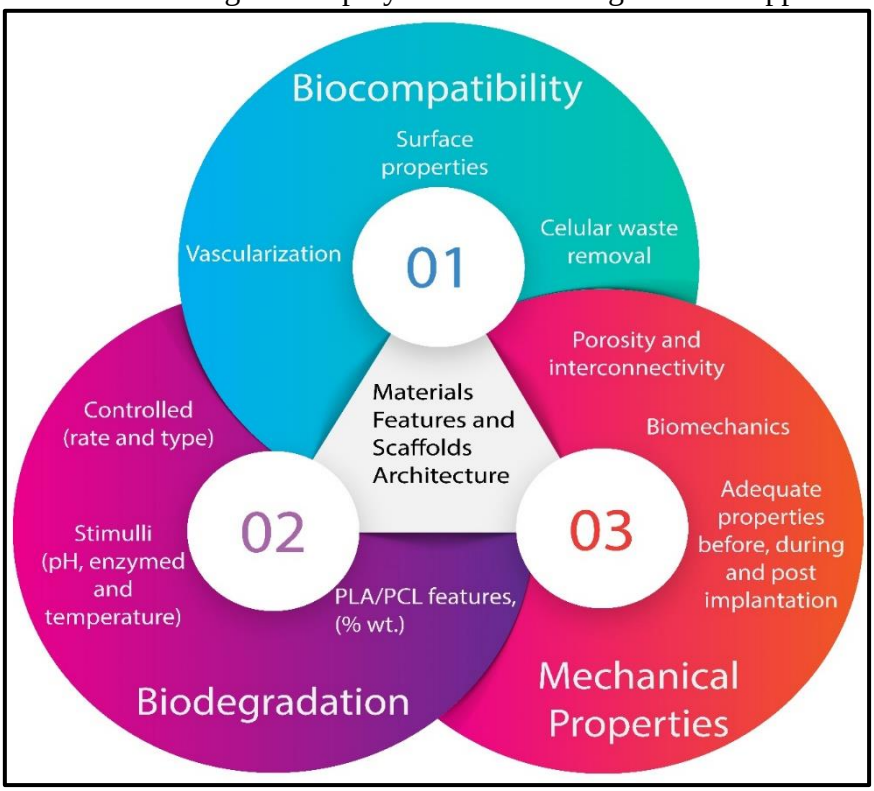


Figure 3. Main parameters that promote tissue regeneration applications of PCL- and PLA-based polymers

1.1.1 Polylactide

PLA is a linear aliphatic polyester and FDA-approved synthetic biodegradable polymer, which can be produced through renewable feedstock sugarcane and corn by using extrusion between 190^{o}C-230^{o}C [81]. PLA, a prominent material exhibit desirable mechanical characteristics, excellent thermal stability, degradability, processability, and biocompatibility, which advocates its applications in dentistry, musculoskeletal, and orthopedics sectors [82]. For instance, PLA-based filaments are applied in musculoskeletal TE applications, for substituting non-biodegradable fibers and ligaments [83]. PLA degradation generates acidic by-products and affects long-term compatibility by inducing tissue inflammation of orthotics and cell death of scaffolds [84]. Furthermore, this polymer exhibits poor stability and requires blending with other polymeric materials to increase its use in TE applications [85]. For instance, PCL/PLA blends are effective in increasing cranial bone regeneration [86]. PLA exhibits brittle nature

which reduces its overall strength and limits its utilization in TE applications [87]. Poor mechanical characteristics and hydrophilic nature of PLA debilitate cell adhesion, proliferation, and differentiation. The mechanical strength of this polymer can be enhanced by incorporating bio-ceramics, which increase compressive strength and mineralization [88]–[90]. Similarly, the addition of metallic nanoparticles (NPs) such as platinum, silver, and gold increase the thermal conductivity of PLA-based composites, which ultimately improves biodegradation [91]. Furthermore, the metallic NPs should be uniformly dispersed to enhance cell adhesion and to improve the surface roughness of PLA-based composites [92]. This polymer usually exists in the stereoisomeric forms of poly (D-lactide) (PDLA), poly (L-lactide) (PLLA), and poly(D, L-lactic acid) (PDLLA), as illustrated in Figure 4.

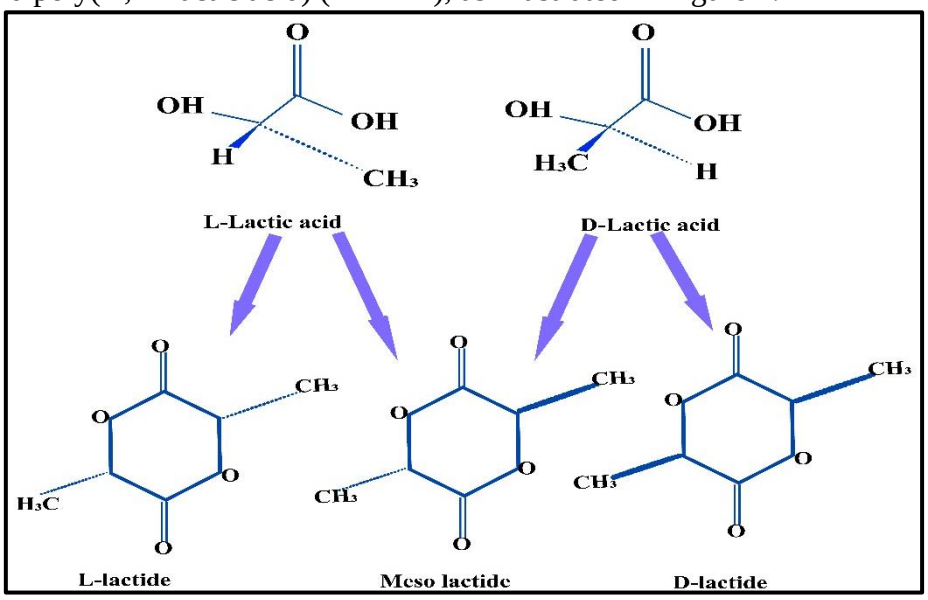


Figure 4. Different stereoisomeric forms of PLA-based lactides

PLLA, a propitious semicrystalline biomaterial exhibits excellent biodegradability, biocompatibility, elasticity, bio-stimulatory, and mechanical properties [93]. It is a suitable polymer for drug delivery in TE due to its non-toxicity and rapid degradation [94]. The degradation rate of PLLA-based polymer is stabilized by forming composites with other bioactive materials such as PCL, which also help in sustained drug release. This increases the utilization of PLLA-based composites to develop drug release in tissue injury repair [95]. It is also used in combination with other polymers/additives to construct high performance hybrid scaffolds for tissue regeneration applications [96].

PDLA is a semicrystalline polymer, which offers much higher degradation than PLLA polymer. This polymer possesses low biocompatibility compared to PLLA, however, PDLA polymer is vastly applied in biomedical applications including bone fixation supports and biodegradable sutures, due to its high mechanical strength [97]. Fibrous scaffolds developed by blending PLLA with PDLA resulted in high compressive and tensile strength [98]. PDLLA is an amorphous polymer with a lactide origin, which exhibit excellent biocompatibility, hydrophobicity, and biodegradability. This polymer is highly suitable to construct porous and biocompatible scaffolds for BTE applications. Furthermore, PLLA offers stabilized degradation due to its hydrophobic nature [99].

1.1.2 Polycaprolactone

Similar to PLA polymer, PCL is another FDA-approved synthetic biodegradable aliphatic polymer, which can be degraded through bulk erosion or hydrolysis and exhibits a low melting

temperature (60°C) [100]. PCL contains repeating hexanoate entities and is extensively applied in clinical applications due to excellent features including biocompatibility, stiffness, mechanical elasticity, biodegradability, non-toxicity, thermal stability, rheological, and viscoelastic properties [101]. However, intracellular resorption pathways and long-term degradation are a few limitations of resorbable PCL polymer. PCL exhibits stable nature within the living body and does not show any considerable degradation for a period of six months. The material takes two years for complete degradation [102]. However, the porosity, molecular weight, and surface area significantly affect the degradation duration. The blending of PCL with other functional polymers during scaffold preparation incorporates excellent characteristics in the composite by overcoming its limitation [103]. The incorporation of tricalcium phosphate (TCP) and hydroxyapatite (HAp) into PCL-based scaffolds improves osteoconductive and osteoinductive characteristics [104]. Table 1 summarizes the salient features and prominent applications of PCL and PLA-based polymers.

Table 1. Properties and salient features of PCL, PLA, and PLA's lactides

Polymer	**Properties**	**Melting point**	**Advantages**	**Disadvantages**	**Prominent applications**	**Ref.**
PCL	Compressive strength: 216 MPa Young modulus: 343.9–363.4MPa	60°C	**(1)** Extraordinary viscoelastic, rheological, and mechanical properties. **(2)** Highly biocompatible **(3)** Minimal inflammability **(4)** Low cost	**(1)** Low cell adhesion **(2)** Slow degradation	Bone, skin, retina, and vascular tissue engineering	[105]
PLA	Compressive strength: 230 MPa Young modulus: 4.107GPa	175°C	**(1)** Excellent mechanical characteristics **(2)** Highly flexible **(3)** Low cost **(4)** Excellent thermal stability	**(1)** Long-term biocompatibility **(2)** High inflammability **(3)** Low bioactivity and porosity **(4)** Brittle nature **(5)** Poor hydrophilicity which limits cell adhesion without modification **(6)** Slow degradation kinetics	Bone, neural, skin, cartilage, ligament, and vascular regeneration	[106]
PDLA	Tensile strength: 40–70 MPa	160 °C	**(1)** Highly flexible **(2)** Excellent mechanical properties	**(1)** Slightly harmful degradation	Bone fixation devices and augmentation devices	[107]
PLLA	Mechanical strength: 4.8 GPa,	173 °C	**(1)** Non-toxic degradation **(2)** High strength **(3)** Excellent processability **(4)** Excellent biocompatibility	**(1)** Low cell intrusion **(2)** Long degradation time	Bone and dermis tissue regeneration, ligament replacement, absorbable orthopedic fixation devices, augmentation devices, and drug delivery devices	[108]

PDLLA	-	No melting point-amorphous	**(1)** Excellent mechanical properties	**(1)** Slightly harmful degradation	Ligament replacement, tissue fixation devices, augmentation devices, and coating of surgical sutures	[109]

1.2 Scope to develop PLA/PCL-based tissue constructs

Based on chemical composition, materials employed for biomedical applications are further categorized into ceramics, metals, glass ceramics, synthetic polymers, natural polymers, and their composites [110]–[112]. In the contemporary world, state-of-the-art 3D-printed biodegradable synthetic polymer materials such as PCL and PLA are enormously used in TE and scaffolds manufacturing [113]. Figure 5 depicts different vital implantation locations in the human body where the repairing of soft and hard tissues is done through a synthetic 3D-printed model. The metallic elements are mostly used in joint replacement, cardiovascular stents, remodeling of bone, and fracture fixation owing to their excellent corrosion behavior and other mechanical properties [114]–[116]. Figure 5 also depicts different grafting sites using various kinds of implanting materials including non-biodegradable polymers, biodegradable polymers, metals, and ceramics [117]. In comparison, 3D-printed PCL- and PLA-based biodegradable biopolymers can reduce prolonged inflammation which is generally observed with non-biodegradable materials that are permanently fixed at defective sites [118]–[120].

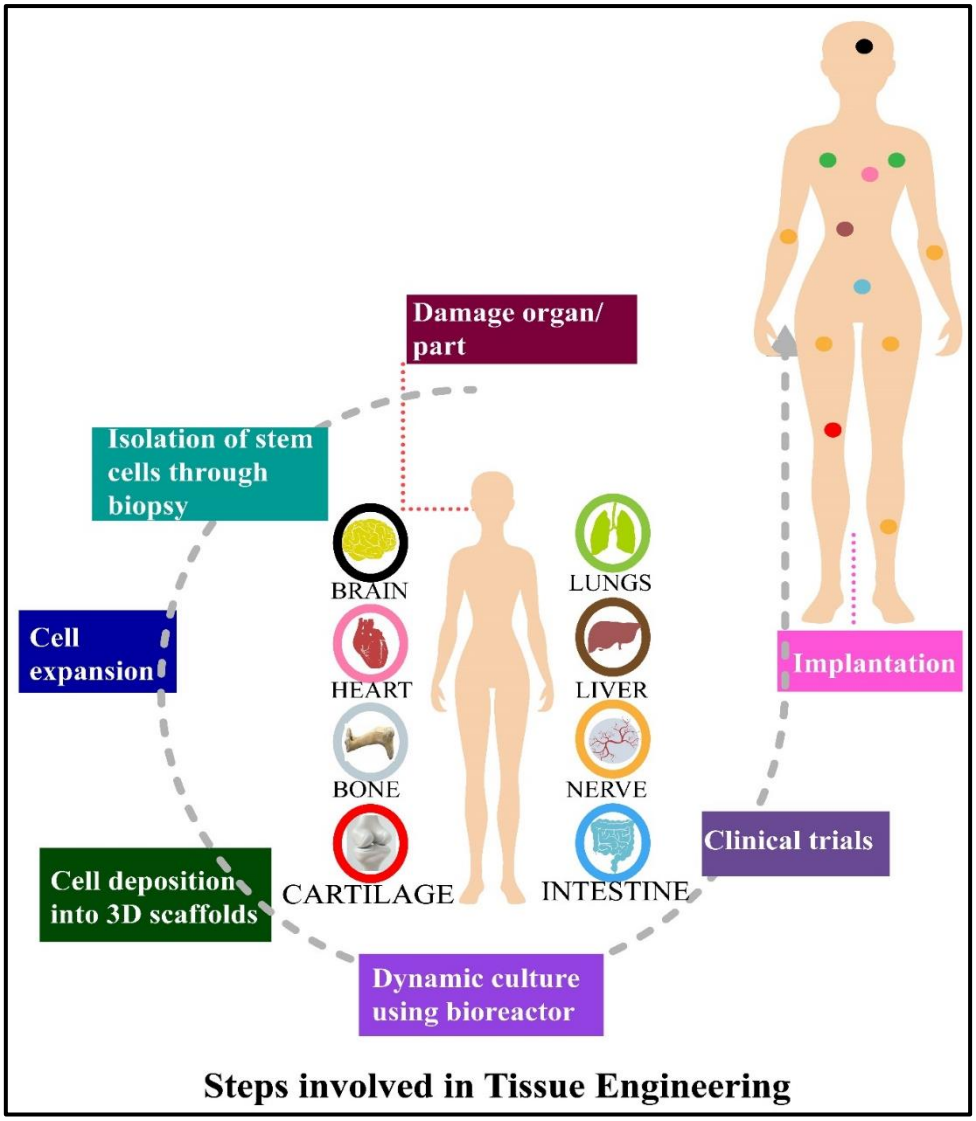


Figure 5. Main implantation locations in the human body where biomaterials are applied to repair or regenerate tissues.

The paper presents the most recent advancements in 3D-printed PLA and PCL-based biodegradable polymer and their applications in the biomedical fields, especially in TE applications. The article elucidates the most innovative 3DP technologies employed for 3DP of the PLA- and PCL-based scaffolds for TE including cartilage, bone, nerve, skin, and cardiovascular. This article also incorporates the effect of the incorporation of bio-ceramics into PCL- and PLA-based biopolymeric scaffolds. This review also contains in-vitro and in-vivo responses of different 3D-printed scaffolds. Furthermore, current challenges and future perspectives of the PCL- and PLA-based 3D-printed biodegradable polymers in the biomedical sectors are also outlined. Lastly, this review provides a new pathway for their successful commercial utilization in clinical practices. In summary, this encapsulates the recent developments in the PCL- and PLA-based biopolymers 3DP by keeping in view their biomedical applications.

1.3 Scaffolds requirements

Growth factors, cells, or biologically active molecules are three important components of tissue regeneration. Scaffolds usually act as artificial supporting platforms to mimic the

characteristics of native tissues. These temporary matrices promote cell growth, adhesion, proliferation, and differentiation [121]–[124]. Nowadays, scaffolds are fabricated through myriad biomaterials and manufacturing techniques. However, it is essential to evaluate their suitability and design for tissue regeneration and repair applications [129]. Figure 6 incorporates the important scaffold requirements and properties. Few design considerations for ideal scaffolds are biodegradability, biocompatibility, mechanical properties, and interconnected porous structure. In addition to this, scaffolds must provide the hierarchical structure, biomechanical and physiological micro-environment to avoid immune reactions as well as replace scaffolds with repaired tissues, and must enable infiltration and migration of cells and diffusion of nutrients [125]–[127]. It is a daunting task to mimic tissues without compromising other unique features of biopolymer-based scaffolds [128].

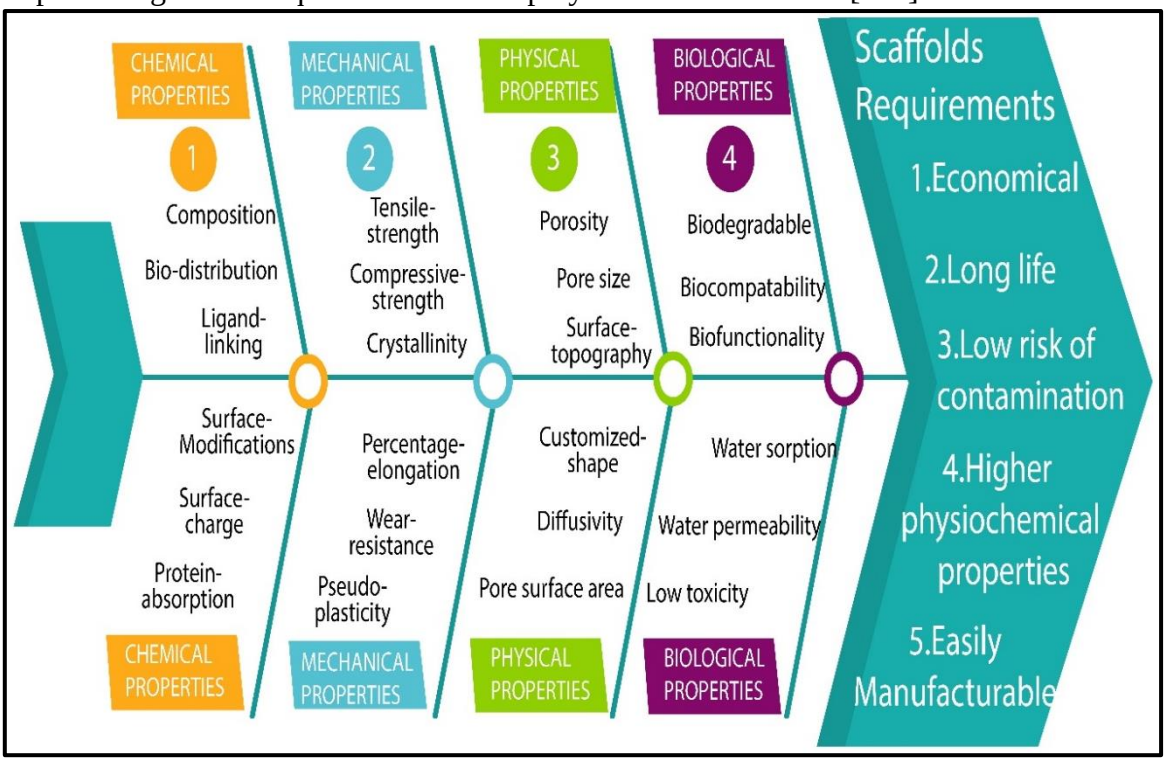


Figure 6. Desirable PCL- and PLA-based scaffolds properties

The successful biomimetic scaffold should exhibit comparable micro-architecture and physicochemical properties. These properties play a pivotal role in regulating cell growth, adhesion, differentiation, migration, and proliferation. Both PCL and PLA biodegradable polymers exhibit excellent physicochemical characteristics [129]. Figure 7 shows the dependence of physicochemical characteristics on the chemical structure of these polymers and these physicochemical characteristics influence biocompatible properties.

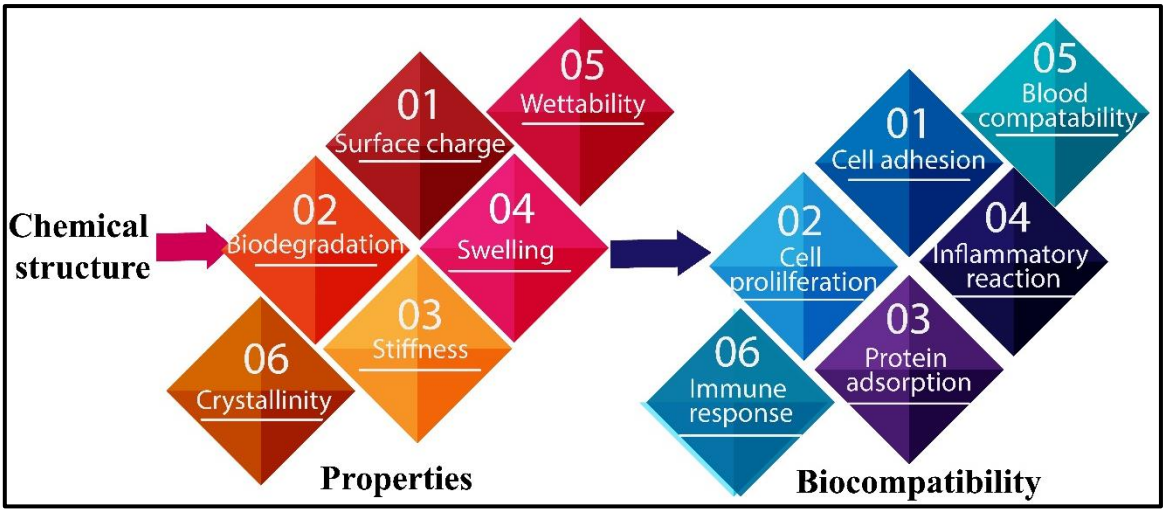


Figure 7. Physicochemical properties of PLA- and PCL-based polymers, which are controlled through their chemical structure and influenced their biological responses

2 Bio-fabrication processes for developing PLA- and PCL-based scaffolds

PLA- and PCL-based composite scaffolds can be developed by using different conventional manufacturing techniques including salt leaching, fiber bonding, phase separation, solvent casting, microsphere sintering, fiber mesh assembly, injection molding, gas foaming, and freeze-drying [130]–[132]. With the recent technological advancement, scaffolds can be synthesized through electrospinning and 3DP techniques. The choice of manufacturing technique used to develop scaffolds depends upon the application requirement [133]. This section illustrates the modern manufacturing techniques, which are used to develop scaffolds for TE applications.

2.1 Electrospinning technique

Electrospinning, an electrohydrodynamic process is a widely adopted propitious method to formulate ultrathin nano-fiber scaffolds and these nanofiber-based scaffolds are highly beneficial due to their high mechanical stability, high porosity, and large surface-to-volume ratio [134]–[136]. This technique uses an electric field or high voltage to extrude micron- to nano-scaled fibers from polymer melt or solution through an orifice [137]. Electrospinning uses high voltage for polymeric melt or solution to generate an electrified jet near the capillary tip, followed by elongation due to stretching for developing nano-fibers [138]. Such process induces enhanced mechanical properties to fibrous scaffolds due to nano-diameter, which cannot be achieved through conventional processes like phase separation, gas foaming, self-assembly, freeze-drying, and solvent casting [139]–[141]. It induces interconnectivity of porosity, and can permit the development of circular-shaped cross-sections with a variety of lengths and smooth surfaces. This technique can be applied to develop highly porous scaffolds with a maximum thickness of 1 mm, which makes them cell-friendly. Furthermore, this process requires a solvent to disperse NPs and dissolve polymers [142]. The influencing factors of the electrospinning technique are flow rate, solution viscosity, polymer concentration, work distance, electric field intensity, and air humidity [143]–[145].

The electrospinning technique produces tissue scaffolds of desired hierarchy by controlling the various parameters such as fiber diameter, alignment, and nanostructure [146]. In the last few decades, this technique has gained significant attraction and multitude studies were dedicated to design electrospun non-fibrous PLA- and PCL-based scaffolds for different tissue regeneration applications [147]. For instance, Miszuk et al [148] used the electrospinning-

based thermally induced self-agglomeration (TISA) technique to develop a PCL/HAp-based 3D nanofibrous ECM composite scaffold. The results indicated that these scaffolds were fitted into different defect configurations and encapsulated multiple drugs release, even after their high elasticity and porosity, as shown in Figure 8(a). These press-fit composite scaffolds are suitable for drug delivery systems and TE applications.

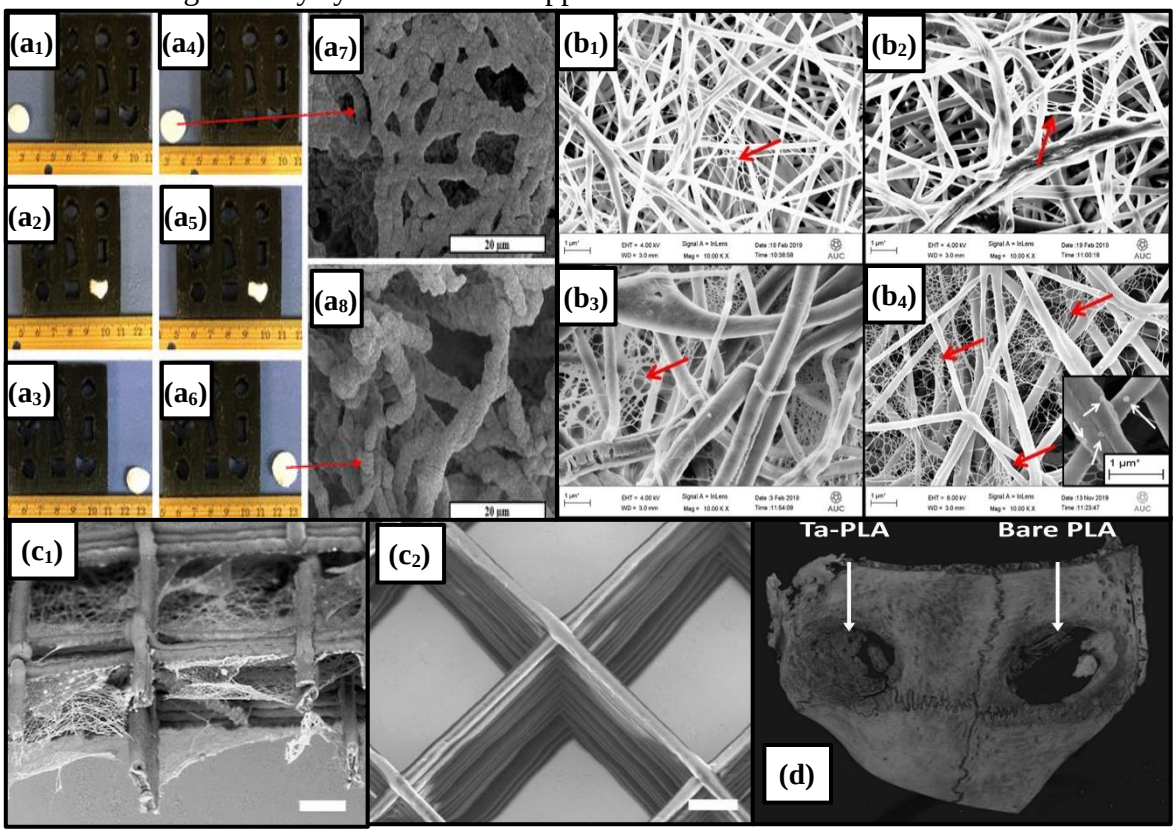


Figure 8. TISA-PCL before compressing; (a_1) Fitting into different defect shapes; (a_2) Scaffold during fitting into defect; (a_3) After removal from the defect; (a_4-a_8) Same procedure for TISA-PCL/HAp-based composite scaffolds (adapted with permission from ref. [148], copyright 2021, American Chemical Society); (b) SEM images of distributions of nanonets into the (b_1) PCL, (b_2) PCL/Gel, (b_3) PCL/Gel/BG, and (b_4) PCL/BG nanofibers. The arrows show the incorporation on nanonets in the PCL/BG (adapted with permission from ref. [149], copyright 2021, Springer Nature); (c) SEM photograph of multi-layered scaffolds; (c_1) Multi-layer PCL/Gel composite scaffold; (c_2) Multi-layer MEW PCL-based scaffold (adapted with permission from ref. [150], copyright 2021, Elsevier); (d) Micro CT 3D images of calvarial defects covered with electrospun/DC sputtered Ta-PLA and Bare PLA (adapted with permission from ref. [123], copyright 2019, Elsevier).

The incorporation of different NPs into electrospun polymer produces scaffolds, which mimic characteristics of the native tissues [151]. Nowadays, NP-reinforced electrospun scaffolds have gained ascending trend for TE applications [152]. For instance, Elkhouly et al. [149] fabricated bilayer PCL/Gel/BG-based electrospun scaffolds with accelerated mechanical, biological, and physical properties. The formation of uniform fibers, as well as BG incorporation into the fibers, were analyzed by using the scanning electron microscope (SEM) machine, as shown in Figure 8(b). The results indicated that PCL/Gel/BG-based scaffolds exhibited higher surface area, total pore volume, swelling rates, degradation rates, and cytotoxicity, compared to PCL scaffolds. Thus, these bilayer scaffolds have the potential to be applied in TE applications.

Conventional electrospinning usually develops densely-packed sub-micrometer fibers and an increase in electrospinning time enables the development of a scaffold with a specific

thickness. However, electrospinning time enhances the thickness of scaffolds due to the loss of electrostatic force [153]. Nowadays, electrospun scaffolds are manufactured through advanced electrospinning technologies including self-assembly electrospinning, template-assisted electrospinning, melt electrospinning writing (MEW), wet electrospinning, and layer-by-layer electrospinning [154]. Recently, these newly emerging fabrication electrospinning techniques have been used to fabricate tissue scaffolds. MEW is a novel 3DP, which uses electrostatic force to develop highly fibrous scaffolds with 3D structures. This technique demonstrated excellent potential to develop scaffolds, and the pore distribution and geometry of these scaffolds can be regulated by controlling the design of the printing path [155]. However, PCL-based MEW scaffolds exhibit worse hydrophilicity and little bioactivity to support cell growth and adhesion. The combination of solution electrospinning (SE) and MEW can be applied to counter this problem. For instance, Wang et al. [150] developed PCL/Gel micro/nano hierarchical scaffolds by combining the MEW and solution electrospinning (SE) techniques for tissue regeneration applications. Composite scaffolds were fabricated by alternative stackings of SE Gel-based nanofibers and well-ordered MEW PCL-based microfibers. SEM images of both multi-layer PCL/Gel composite and multi-layer PCL-based scaffolds are depicted in Figure 8(c). The results showed that the PCL/Gel composite scaffold not only increased the hydrophilicity, cell adhesion, and proliferation but also helped in osteogenesis.

Scaffolds for tissue regeneration applications can be manufactured through a combination of electrospinning and other fabrication processes. This approach develops intricate architectures with enhanced biomechanical properties. For instance, Hwang et al [143] developed PLA/tantalum (Ta)-based scaffolds by using electrospinning and DC sputtering processes, as illustrated in Figure 8(d). The in-vivo results revealed that PLA/Ta-based scaffolds exhibited excellent bone regeneration properties. Thus, polymer-based electrospun fibrous membrane coated with Ta is the propitious approach to enhance osteogenic functionality of membranes.

2.2 3D printing techniques

Since the inception of 3DP technology in 1984, it has gained an ascending trend and has revolutionized the TE, regenerative medicine, and rehabilitation fields by permitting the development of dental molds, patient-specific scaffolds, craniofacial implants, organ printing, prothesis, orthoses, and implantable biosensors with excellent design flexibility and high structural complexity [156]. All these developments have become possible due to different 3DP technologies and bioactive materials. Biopolymers especially PLA- and PCL are usually employed as feedstock in 3DP technologies for generating intricate scaffolds, however, low bio-affinity caused obstructions in the actual implementation in biomedical applications [157]–[159].

3DP technology is categorized into four major classes: solid-based, liquid-based, gas-based, and powder-based. The slurry-based technique which includes stereolithography (SLA), digital light processing (DLP), fused deposition modeling (FDM), inkjet printing (IJP), selective laser melting (SLM), and selective laser sintering (SLS) are extensively applied for the 3DP of biopolymers owing to their adaptability, porosity, controlled chemistry, and intricate product's generation [160]–[162]. This has ultimately helped the world to utilize these approaches for the 3DP of polymeric materials to enhance their relevance in biomedical sectors. These processes use PLA and PCL in the form of pellets, powder, filament, or dissolved in solvents [163]–[165].

The usability and versatility of 3DP technology have ultimately permitted the implementation of biopolymeric materials by considering the significance of scaffold systems [166]. Several

technologies are employed to develop intricate 3D scaffolds. Conventional 3DP approaches involve the development of the products through layer-by-layer deposition, whereas, scaffolds are additively manufactured using a two-step process of acellular scaffolds. These scaffolds are seeded with cellular structure and cell-laden constructs generated to imitate natural tissues. The acellular scaffolds are manufactured through SLA, FDM, and SLS technologies [167].

2.2.1 Stereolithography

SLA is one of the most versatile and straightforward UV-assisted 3DP technologies, which uses photocurable resins as printing inks in which curing is controlled spatially by considering the digital data of design upon exposure to UV light [168]–[170]. This technique offers high printing speed, quality, and cell viability, compared to other 3DP techniques [171]. Recently, it was observed that UV light source is highly pernicious for deoxyribonucleic acid (DNA) cells and can cause dermal cancer. This problem can be solved by using visible light during SLA bioprinting [172]. It is essential to wash scaffolds for removing the uncured resin after the development of 3D constructs. The method can be utilized to synthesize biopolymers and ceramic reinforced biopolymer-based composite scaffolds [173]. For instance, Asikainen et al. [174] fabricated drug-releasing PCL-based scaffolds through SLA technique, as depicted in Figure 9(a), and found that porosities did not affect the drug release profiles.

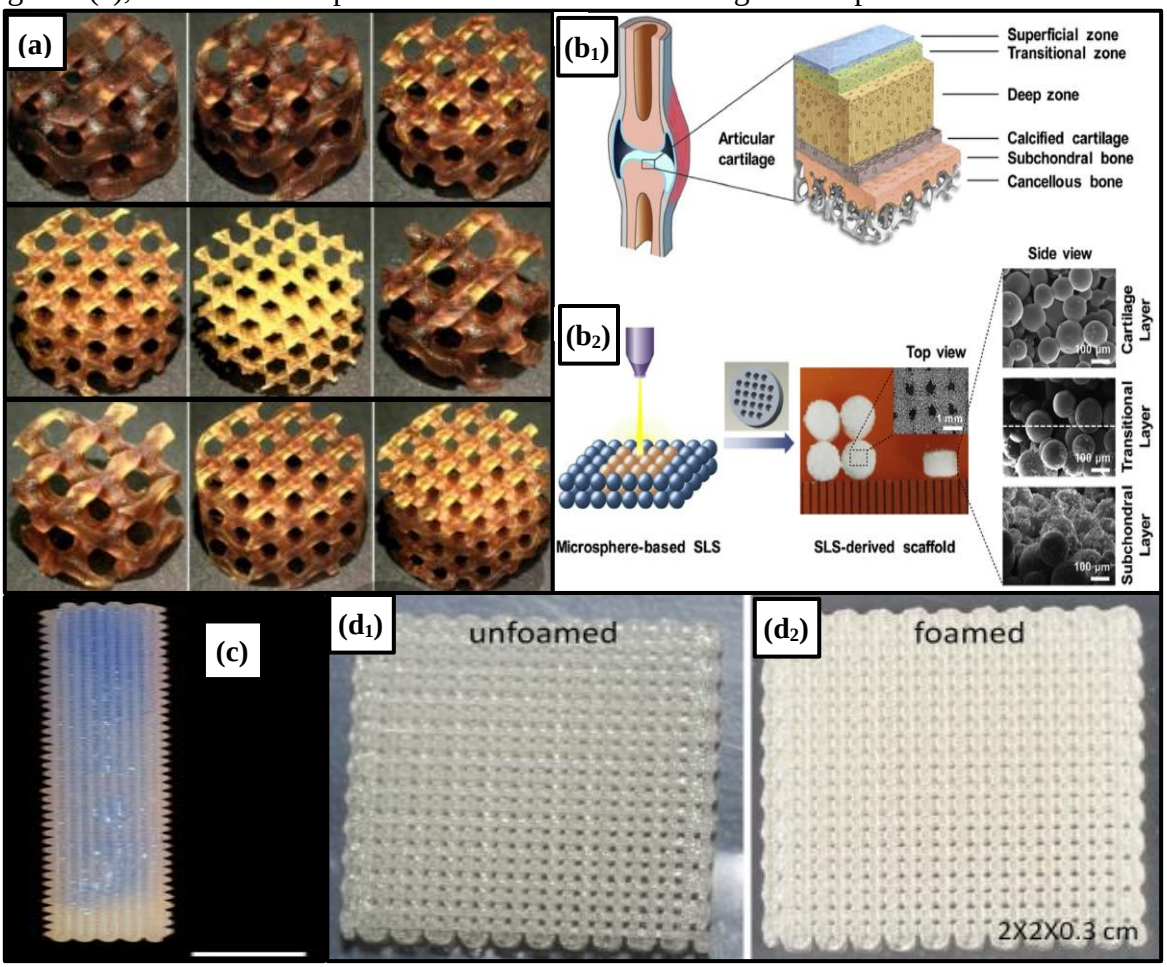


Figure 9. SLA-printed PCL-based scaffolds with different varying porosities (adapted with permission from ref. [174], copyright, 2019 IOP Publishing); (b) Hierarchical structure of natural osteochondral unit and its biomimetic replication; (b_1) Natural osteochondral unit comprised of a variety of tissue layers including middle calcified cartilage, superficial cartilage, deep subchondral bone, and transitional zones between layers; (b_2) SLS-printed PCL microspheres and PCL/HAp-based composite

microspheres, which were used as building blocks to develop multi-layered scaffolds (adapted with permission from ref. [175], copyright, 2017 Elsevier); (c) PCL/Col-based FDM-printed chemical gradient scaffolds (adapted with permission from ref. [176], copyright, 2017 John Wiley and Sons); (d) PLA-based FDM-printed scaffolds; (d_1) Without gas foaming; (d_2) With gas foaming approach (adapted with permission from ref. [177], copyright, 2016 Elsevier).

It is a useful technique for constructing intricate scaffolds of microscale resolution. Furthermore, sub-micrometer features to the developed products can be imparted by using its distinct types: direct ink writing (DIW) and multi-photon polymerization (MPP) [178]. Usually, MPP technique is not practically applied to fabricate tissue scaffolds for implantation due to the development of a smaller volume size part (< 1 mm^3). However, this process can help to understand cell-scaffold interactions. 3D-printed products developed through the SLA technology provide better control over the intricate scaffolds geometries involving porosity, pore size, and patterns, along with the ability to possess high resolution and eliminate unnecessary polymer resin [179]. However, photo-initiators can result in cytotoxicity due to moieties, likely entrapment of residual photo-initiators and monomers as well as poor mechanical characteristics of the photocured resins, which are challenges in the TE applications of SLA-based scaffolds [180].

2.2.2 Digital light processing

DLP is another 3DP technique, which uses a projection of visible or UV light from a digital micromirror device to project single image of the layer or designed pattern [181]. This technique offers higher printing speed and lower intrinsic accuracy compared to SLA technique. This process does not require any post-curing due to its ability to cure the whole layer simultaneously [182]. DLP uses a variety of biopolymers and bio-ceramics to develop biopolymer composites/nanocomposites for TE applications [183]. Similar to SLA, this process uses vinyl polymerization or acylate chemistry and host of crosslinkers, monomers, photosensitizer, initiators, and special fillers in the mixture [184]. For instance, Chen et al. [185] fabricated PCL/polyurethane acrylates (PUA)-based intricate tissue scaffolds by using DLP technique. DLP-printed scaffolds exhibited tailorable mechanical properties, degradability, and cytotoxicity.

2.2.3 Selective laser sintering

SLS technology employs high laser density which successively fused ceramics, metals, polymers or composites to develop the 3D intricate structure, thus, enhancing the surface quality and mechanical characteristics of the scaffolds. 3D-printed products developed through SLS are highly porous and can be employed in TE applications [186]. This technology is widely applied to develop nanocomposite-based bioactive scaffolds for tissue regeneration applications. However, two different powdered materials respond differently to processing parameters, during the formation of SLS-based objects [187]. This leads to the development of microspheres of different materials, which enables the uniform response of powders to the processing parameters. Consequently, SLS technique provides excellent control over the porosity of scaffolds. For instance, Du et al. [175] employed the SLS approach to develop PCL/HAp-based gradient scaffolds for repairing osteochondral bone defects, as illustrated in Figure 9(b). Likewise, SLM technique is extensively applied to develop metal-based porous scaffolds for orthopedic applications [188]–[190].

2.2.4 Fused deposition modeling

FDM uses the low temperature-controlled extruding device to heat and squeezes the biopolymer-based composites. The final 3D product is built onto the substrate through layer-by-layer deposition [191]. FDM is usually applied to fabricate robust scaffolds with predefined configurations [192]. Biopolymers are not commonly prepared through FDM due to the high-melting temperature associated with this technology. Despite this, FDM has found its application in the manufacturing of scaffolds for the TE sector by performing post-processing strategies [193]. For example, Chen et al. [194] fabricated PCL-based macro-porous scaffolds through FDM technology and embedded them in the matrix of methylated collagen (MC), HA, and terpolymer through polyelectrolyte complex/coacervation. The results indicated that embedded scaffolds exhibited higher cellular seeding efficiency, distribution, proliferation, and osteogenic differentiation, compared to naked PCL-based scaffolds.

PCL and PLA are the most common biocompatible and degradable materials used in FDM technique to develop scaffolds for TE purposes. This technique also develops a variety of PLA- and PCL-based composite materials by incorporating BG, HAp, and TCP [195]. Direct printing of ceramics is impossible by using contemporary FDM printers due to their high melting temperature (> 2000^{o}C). This problem can be solved by using powder additives in biopolymer-based composites [196]. The interface between bone and cartilage requires varying proportions of nutrients for optimal function. Recently, FDM technology has found its application to develop chemical gradient scaffolds for interface TE applications. D'Amora et al. [176] employed FDM technology to develop PCL-based scaffolds by using heterogeneous Col concentration, as shown in Figure 9(c). The results indicated that 3D-printed chemical and morphological gradient scaffold exhibited appropriate porosity and controlled geometry.

It is quite a challenging task to develop intricate cell-laden architectures through FDM by applying heat. However, the use of multiple printing heads for extruding different materials simultaneously or sequentially can alleviate this issue [197]. For instance, Kundu et al. [198] fabricated cell-printed scaffold by using PCL, and chondrocytes-encapsulated Alg hydrogel for cartilage TE applications, which exhibited excellent ECM formation. Optimal printing resolution (200 μm) of FDM technique is one of its major drawbacks. However, the recent emergence of MEW technique that develops nanofibers and this technique can be combined with FDM to fabricate intricate scaffolds with high-resolution [199]. This combinational approach increases the effectiveness and micro-porosity of the 3D-printed scaffolds. Likewise, Zhou et al. [177] combined gas foaming and FDM techniques to fabricate PLA-based multi-hierarchical micro/macro-porous biopolymer scaffolds, which are shown in Figure 9(d). These hierarchical scaffolds can be potentially applied in BTE applications.

2.2.5 Electrohydrodynamic printing

Nowadays, electrohydrodynamic printing (EHDP), an emerging IJP technology, gains immense interest in the manufacturing of tailored micro-/nano-scaled scaffolds. This process uses ejection of droplets driven through a high voltage electric field, that is developed between the substrate and the nozzle [200]–[202]. However, the printed scaffolds usually possess low mechanical properties, biodegradability, and biocompatibility. This technique is further classified into solution EHDP and melt EHDP, based on the printing materials [203]. The precision of solution EHDP varies from 500 nm to 3 μm. On the contrary, the precision of melt EHDP ranges from 3 μm to100 μm. This process is highly suitable to develop highly precise and accurate micro/nano-sized capillaries, arteries, or veins. Different biopolymers in the form of ink are employed in the EHDP technique [204]. Recently, PLA- and PCL-based biopolymers are successfully applied in melt EHDP technique to develop high resolution tissue regeneration

scaffolds [205]. For instance, Liu et al. [206] developed PCL/Gel-based scaffolds by using EHDP for treating peripheral nerve injury. EHDP-printed PCL filaments help to develop highly precise intricate architecture of triple-layered conduits with tailorable directionality, as illustrated in Figure 10(a). In another study, Li et al. [207] fabricated PVP/PCL-based composite scaffolds through EHDP technique, as shown in Figure 10(b). Thus, EHDP has gained ascending trend and employs as an auxiliary technique to manufacture scaffolds for TE applications.

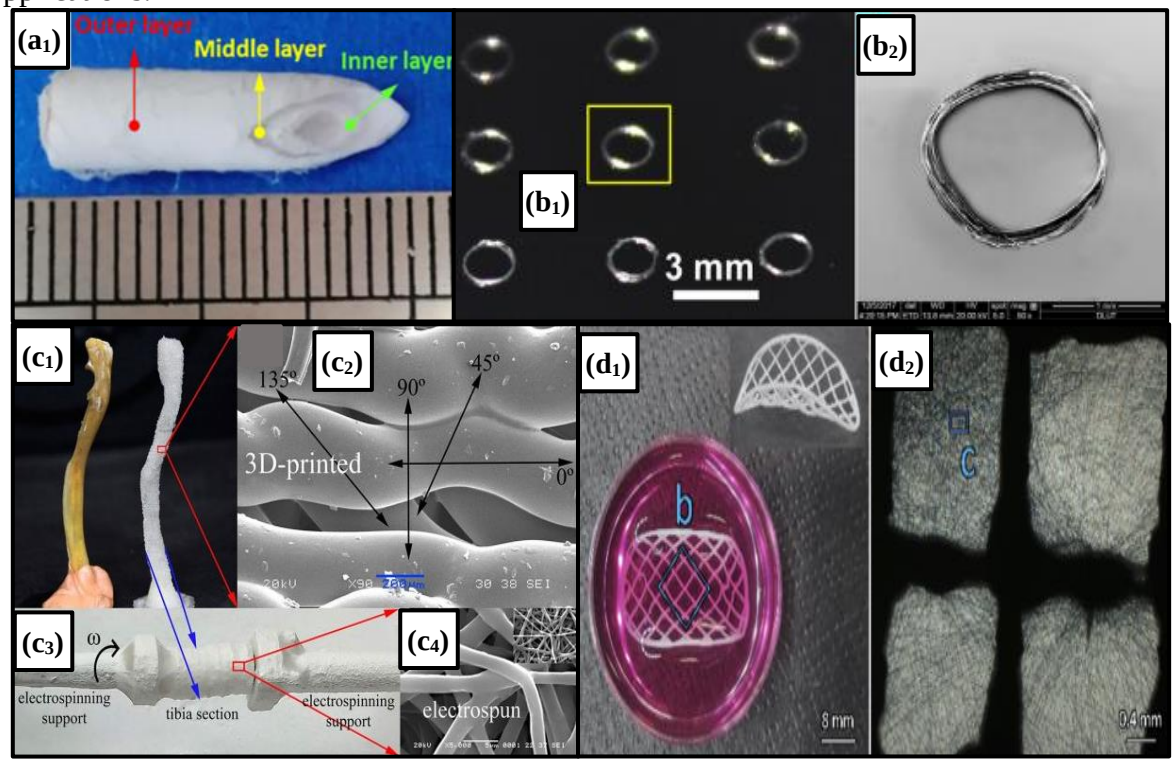


Figure 10. (a) PCL/Gel-based scaffold developed via EHDP for neural tissue regeneration applications (adapted with permission from ref. [206], copyright, 2020 Elsevier); (b_1-b_2) PVP/PCL-based 3D-printed rings of 800 µm radius (adapted with permission from ref. [207] , copyright, 2021 Elsevier); (c_1) Actual tibia of a rabbit on the left side, 3D-printed PCL scaffold in the shape of the tibia on the right side; (c_2) SEM picture of the surface; (c_3) 3D-printed PCL section was set up on the electrospinning supports; (c_4) SEM picture of electrospun PCL microfibers (adapted with permission from ref. [208], copyright 2022, Springer Nature); (d) PCL-based 3D-printed vascular scaffold; (d_1) 3D patch geometry and gross strands developed through FDM; (d_2) Microscopic image, which permits the visualization of electrospun nano-fibers (adapted with permission from ref. [209], copyright, 2022 Elsevier).

2.2.6 Electron beam melting

Another type of 3DP process is the electron beam melting (EBM), which is a powder-based process widely applied to develop scaffolds for tissue regeneration applications [210]. This process uses a focused electron beam to heat and melts powdered metallic materials or alloys. Vacuum conditions for this process are necessary to avoid the risk of the electrostatic charge of the powdered material [211]. A variety of conductive materials including alloys and metals are extensively applied to develop scaffolds for the TE sector. For instance, Surmeneva et al. [212] successfully fabricated Ti6Al4V/$CaCO_3$-based scaffolds through EBM technology. The results indicated that these scaffolds improved surface hydrophilicity and exhibited excellent antimicrobial behavior. Thus, these scaffolds possessed the excellent potential to be applied in BTE applications.

2.2.7 3D-printed/electrospun-based combinational approach

The combination of electrospinning and 3DP technology developed 3D scaffolds, which exhibit excellent cell adhesion, proliferation, and differentiation. Furthermore, these scaffolds enable infiltration and migration of cells and diffusion of nutrients due to loosely packed nanofibers and high pore size [213]–[215]. Zhao et al. [216] observed that scaffolds with excellent micro-/macro-scaled precision and enhanced biomechanical characteristics can be produced by combining different 3DP techniques with other conventional techniques like electrospinning. Additionally, the development of 3D-printed/electrospun composites helps to reduce the length of nanofibers and formulates mesh-layered 3D-printed scaffolds [217]. These composite scaffolds possess excellent cell migration, biocompatibility, and mechanical properties. For instance, Rosales et al. [208] studied electrospun/3D-printed PCL scaffolds in the shape of a rabbit tibia, as presented in Figure 10(c). Gel molecules were grafted onto the PCL to improve the cell proliferation, and adhesion and further facilitated the cells with the human adipose stem cells (hASCs) culture environment, which is beneficial for bone regeneration and other TE applications.

In another study, Chou et al. [218] employed FDM and electrospinning techniques to fabricate bioresorbable nano-fibrous drug-eluting cuboid frames for repairing alveolar bone defects. The cuboid frames were comprised of PLA, ketorolac, and amoxicillin–loaded PLGA nanofibers, which mimicked the morphology of natural ECM of bone tissues. Thus, this combined 3DP and electrospinning-assisted approach are suitable for various maxillofacial applications. Similarly, Mayoral et al. [209] developed a PCL-based cardiovascular patch by using hybrid 3DP and electrospinning techniques, as illustrated in Figure 10(d). FDM technique develops geometrical shape and supporting architecture and electrospinning generated a network of nano-fibers, which mimicks interstitial structure. The in-vitro study indicated that this mesenchymal stem cells (MSCs)-loaded scaffold exhibited excellent mechanical properties, adequate porosity for infiltration of cells, and appropriate resistance to physiological aortic pressure. Thus, the combination of FDM and electrospinning exhibits excellent potential to develop intricate vascular grafts.

2.2.8 Cellular bioprinting

Nowadays, different cellular bioprinting technologies have also been employed to construct 3D scaffolds tissues. These technologies are further classified into extrusion-based, droplet-based, and laser-based 3D bioprinting techniques, as illustrated in Figure 1(b).

Droplet-based printing also commonly called inkjet bioprinting is a drop-on-demand and non-contact technology, which precisely releases less viscous biopolymer droplets coming through the nozzle head by using electrostatic, piezoelectric, or thermal actuating units onto the substrate surface, constructing less contaminated 3D-printed scaffolds [219]. However, the heated printer head affects the viability of cells and this issue can be eliminated by using an electrostatic inkjet system [220]. Similarly, the excessive clogging of the biopolymers also limits the utilization of this process. Zhong et al. [221] fabricated chitin macro/nano-based architectures by using nanofiber inked solution via microcontact printing (μCP), replica molding, and airbrushing. In another study, Tao et al. [222] printed SF ink solution on multiple surfaces that changed colors in the presence of bacteria. Similarly, Ardelean et al. [223] printed Col/HAp-based polymer composites for fabricating scaffolds. Additionally, the utilization of IJP technology for controlling cell binding and proliferation also gained significant attention [224].

Laser-based 3D bioprinting techniques are non-contact printing technologies that employ high-power infrared (IR) or UV light directed on the photocurable bioink deposited onto the substrate to develop 3D constructs. This process permits high resolution deposition of bioink material in liquid or solid phase. This technique does not clog the bioink due to the absence of a nozzle and can be utilized for the 3DP of highly viscous materials [225], [226]. Bioink materials usually exhibit ideal features including biocompatibility, adhesive properties, cytocompatibility, biodegradability, and low surface tension, and usually contain synthetic, natural, or hybrid polymers [227].

Extrusion-based printing also known as DIW bioprinting is a contact technology that draws highly viscous bioink from the nozzle through the solenoid, pressure, or piston drives and deposits it iteratively. This method has the flexibility to use multiple cartridges for dispensing heterogeneous cells, thus, developing intricate scaffolds, organs, or tissues with excellent mechanical and structural integrity, and cell density [228]–[230]. In this technique, hydrogels should exhibit thixotropic nature and resin chains should be oriented in the direction of flow. Furthermore, the hydrogel-based bioink must be cross-linked with other materials for obtaining low wetting properties and excellent surface roughness [231]. Natural and synthetic-based hydrogels are used separately or in combination for the manufacturing of bioink material. Furthermore, the impregnation with different nanomaterials including nano-hydroxyapatite (nHAp), cellulose nanofibers (CNFs), and carbon nanotubes (CNTs) as well as synthetic biopolymer-based nanostructures can help in tailoring the printability, stiffness, and elasticity of hydrogels [232].

The choice of bioink for 3D bioprinting technologies depends upon viscoelasticity, printability, bioresorbability, permeability, and biocompatibility with targeted cells and organs [233]. Additionally, bioink materials should mimic indigenous ECM-based tissues structurally and functionally by adding cellular cytokines, motifs, and growth factors [234]. The rheological, biological, and mechanical characteristics of the bioink affect the functionality of 3D-printed organs and scaffolds. The influencing factors of 3D-printed extrusion-based technologies for biopolymers are illustrated in Figure 11. The better regulation of these parameters is essential for achieving high-quality 3D-printed scaffolds [235]. For instance, rheological characteristics play an integral role in regulating the shape fidelity and resolution of the printed architecture [236]. Therefore, it is essential to consider rheological measurements for the evaluation of the printing conditions [237]. Likewise, the quality of 3D-printed scaffolds also depends upon the bioprinter-based parameters that include extrusion rate, nozzle diameter, nozzle height, printing speed, and nozzle moving speed [238]. Additionally, some parameters are also related to the biopolymers including printing temperature and bioink formulation [239]. Therefore, the proper adjustment of these material-based and bioprinter-based parameters is the main requirement for developing intricate scaffolds [240].

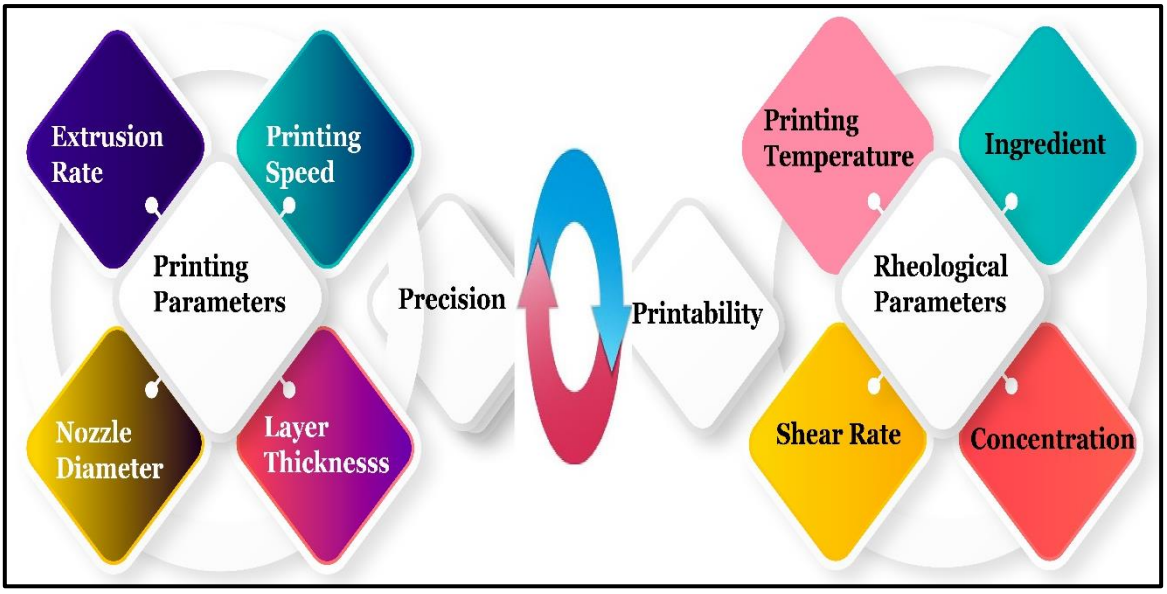
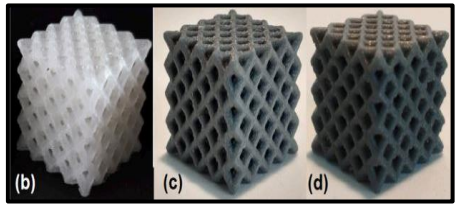
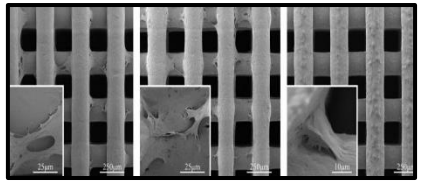
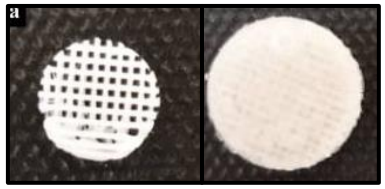
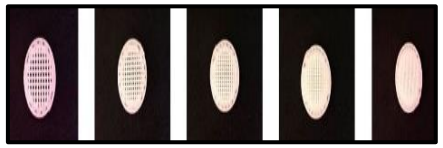
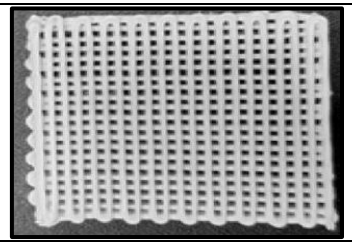
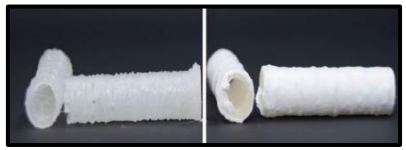
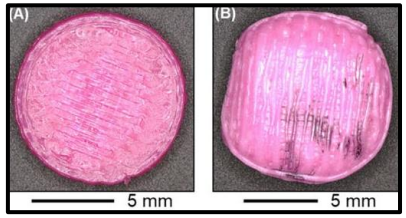
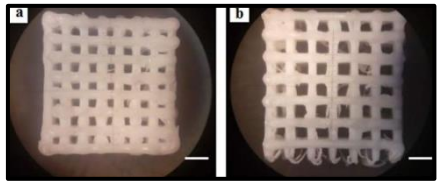
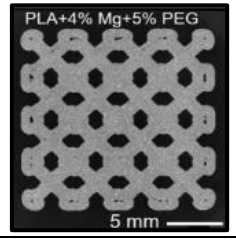


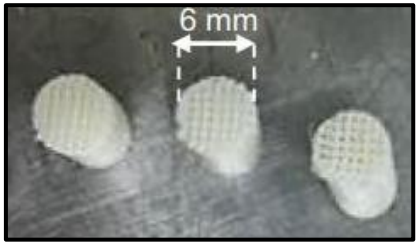
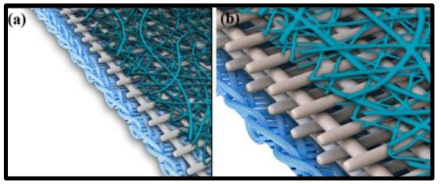
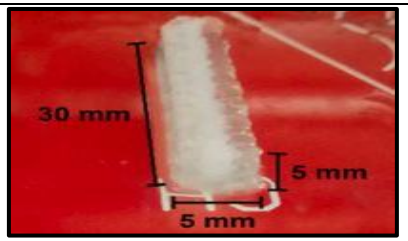
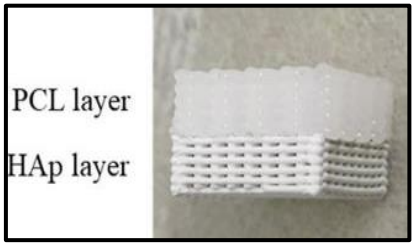
Figure 11. Figure depicting the relationship between the processing parameters and rheological properties

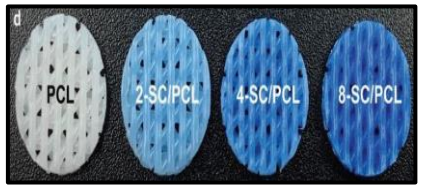
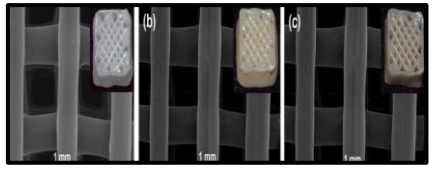
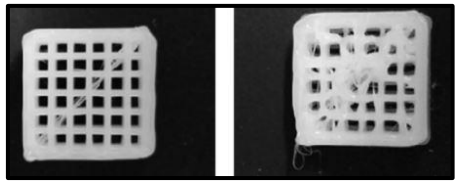
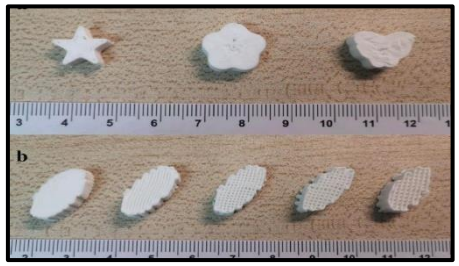
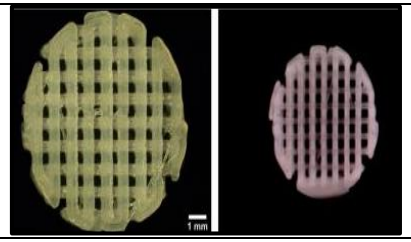
Table 2 provides the summary of recent work on 3DP of PLA- and PCL-based biodegradable composites along with their mechanical properties.

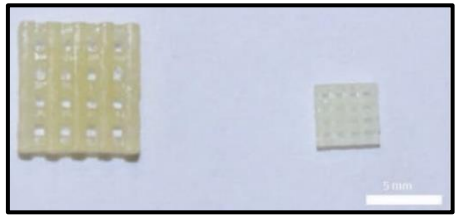
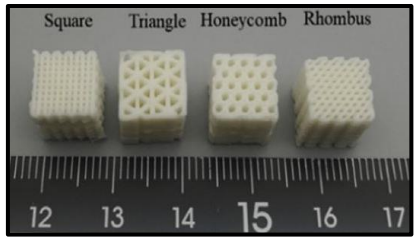
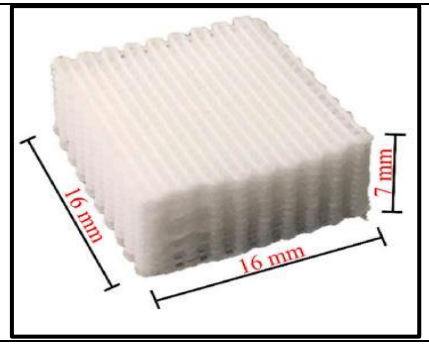
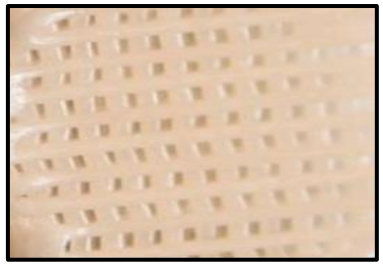
Table 2. A summary of recent work on 3DP of PLA- and PCL-based biodegradable composites along with their mechanical properties along with their different physio-chemical and mechanical properties.

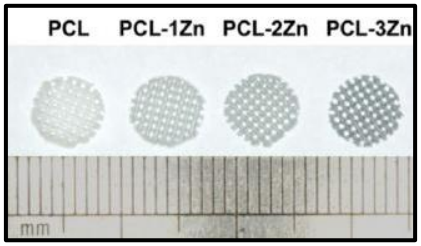
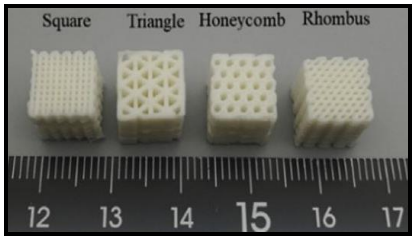
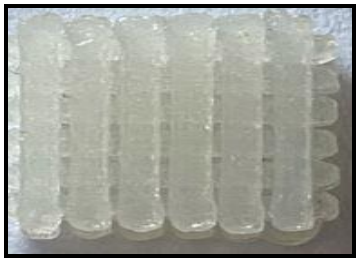
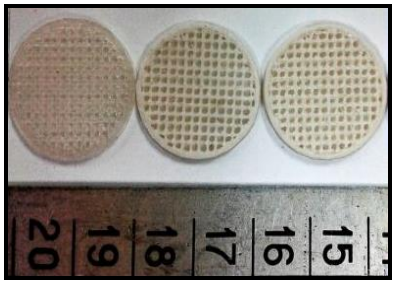
Fabrication technique details	**Scaffold's material composition**	**Porosity (%)**	**Pore size**	**Maximum mechanical properties**	**Fabricated model/design**	**Key findings**	**Ref.**
FFF Printing speed: 5 mm/s. Printing temperature: 190-210 ºC. Nozzle diameter: 400 µm	PLA PLA-3.5% Zn PLA-7% Zn PLA-10.5% Zn	-	5 µm	Compressive strength: 16 MPa Elastic modulus: 675 MPa		The addition of Zn particles caused the limited changes in the physiochemical properties of the PLA. Furthermore, window temperature for 3DP and the melt flow index remain unchanged.	[241]
FFF Printing speed: 15 mm/s. Layer thickness 270 µm Printing temperature: 95 ºC. Nozzle diameter: 300 µm	Different molecular weight of PCL	40.78 - 50.63	350 µm	Compressive strength: 2.9 MPa Elastic modulus: 104.81 MPa		The results showed that scaffolds with lower molecular weight offered better bio-mechanical properties.	[242]
FDM Printing speed: 6 mm/s. Printing temperature: 86 ºC. Nozzle diameter: 4 mm	PCL/dECM/Alg sulfate	-	600 µm	Compressive strength: ~ 6.18 MPa Compressive elastic modulus: ~ 0.27 MPa		The printed scaffold with 1% dECM demonstrated better viscosity, chondrogenic differentiation, cell viability, and proliferation for nasal cartilage tissue regeneration applications.	[243]
Extrusion-based 3DP Layer thickness: 0.05 mm. Nozzle diameter: 0.4 mm	PLA with varying filling rates	3.11-35.11	100-550 µm	Compressive strength: ~1200 MPa Compressive elastic modulus: 10000 MPa		PLA-based scaffold with 60 % filling rate exhibited extraordinary properties for BTE applications, compared to the other filling rate scaffolds.	[244]

FFF -	PCL/nFA-based scaffolds	-	-	Tensile strength: 19 MPa Tensile elastic modulus: 650 MPa		The addition of the nano- nFA filler inside the PCL matrix improved the mechanical properties of scaffolds and PCL/20 wt.% nFA exhibited extraordinary mechanical properties.	[245]
3DP with air-jet-spinning	PLA	-	-	Maximum strength: 150 MPa Elastic modulus: 839.1 MPa		The fiber coating produced micro-retentive surface cues for enhancing the biological response of cells.	[246]
FDM Printing speed: 150 mm/s. Printing temperature: 215 °C. Layer height: 200 µm Nozzle diameter: 400 µm	PLA	78	120 µm	Compressive strength: ~0.18-0.2 MPa		Microwave foaming technique of PLA-based 3D-printed scaffolds resulted in highly porous structure, which is highly suitable for tissue regeneration applications.	[247]
FDM and electrospinning: Printing speed: 5 mm/s. Nozzle diameter: 400 µm	PLA/PVA/HA	-	500-900 µm	Maximum tensile strength: 6.56 MPa Elastic modulus: 19.25 MPa		3D-printed PLA was coated with electrospun PVA/HA fibers to improve the mechanical and biological properties of PLA/PVA/HA scaffolds for cartilage applications.	[248]
FFF Printing speed: 5 mm/s. Layer thickness: 0.2 mm Printing temperature: 170-210 °C	PLA/Mg/PEG	-	-	Compressive strength: 16 MPa Compressive elastic modulus: 650 MPa		Face-centered cubic shape-based scaffolds were printed with good dimensional accuracy and mechanical properties.	[249]

FFF Printing temperature: 180°C. Nozzle diameter: 0.4 mm	PCL/HAp	-	400 µm	Maximum tensile strength: 9.13 MPa Elastic modulus: 340.72 MPa Compressive strength: ~ 20 MPa Compressive elastic modulus: 62.67 MPa		The addition of HAp in the PCL matrix improved biocompatibility. Furthermore, PCL/20 wt.% HAp-based scaffold demonstrated nobler mechanical properties than the other scaffolds for BTE applications.	[250]
Extrusion-based 3DP and electrospinning: Extrusion temperature: 205°C. Layer thickness: 0.1 mm. Nozzle diameter: 0.8 mm	PLA electrospinning / knitted fabric composite scaffolds	-	350.2-750.8 µm	Maximum strength: ~ 30 MPa		The different multi-scale nano/micro fiber scaffolds with various topological morphologies and properties offer mechanical and support structural for potential TE applications.	[251]
Extrusion-based 3DP and freeze dying: Extrusion temperature: 25°C. Printing speed: 3 mm/s. Nozzle diameter: 0.5 mm	DX/HAp/PCL	-	90.4-196.6 µm	Compressive strength: ~ 90 kPa Compressive elastic modulus: ~77 kPa		3D-printed DX/HAp/PCL-based scaffolds with loaded core shell had osteogenic potential and showed efficient bio-resorption, immune tolerance for bone tissue defect healing application.	[252]
DIW Printing Speed: 6 mm/s and 1.5 mm/s Nozzle diameter: 0.4 mm and 0.3 mm	PCL/HAp	44.6 and 55.8	-	Compressive strength: ~ 25 MPa Compressive elastic modulus: ~155 MPa		3D-printed scaffold had excellent toughness and strength biomimetic to articular cartilage.	[253]

Extrusion-based 3DP: Printing speed: 1-3 mm/s.	Strontium copper tetrasilicate/PCL	-	-	Maximum elastic modulus: 138.89 MPa		3D-printed strontium copper tetrasilicate/PCL-based composite scaffold showed an efficient antitumor platform due to its remarkable biocompatibility, and photothermal characteristics.	[254]
FDM: Nozzle diameter: 400 µm Layer thickness: 300 µm Nozzle temperature: 90 °C Printing speed: 10 mm/s	PCL/GNPs	50-75	300 µm	Maximum compressive strength: 26.5 MPa Maximum compressive modulus: 43.4 MPa		3D-printed PCL/0.5wt.% GNPs-based scaffold demonstrated superior mechanical and physical properties for myocardial TE applications.	[255]
FDM: -	HAp/PCL	-	-	Compressive modulus: 160.1 MPa		Increasing HAp content in various improved properties such as printability, mechanical strength of scaffolds, compared to pure PCL scaffold.	[256]
Extrusion-based 3DP Extruding speed along the z-axis: 0.0016 mm/s	PLA/nHAp	50.39-73.46	-	Maximum compressive modulus: 11.56 MPa		3D-printed scaffolds with composition PLA/nHAp demonstrated better morphology, porosity, mechanical properties, and hydrophilicity, and have promising applications in bone defect repairing.	[257]
FFF: Printing speed: 20 mm/s. Layer thickness: 0.1 mm Nozzle diameter: 0.25 mm	PLA/PEI/ceria NPs	68.04	516-471 µm	Compressive modulus: 26.8 MPa		Ceria-functionalized PLA-based scaffolds showed better combination of properties, compared to NaOH-treated/PLA scaffolds for BTE applications.	[258]

DLP	AUP/PCL AUP/PCL/PETA-4SH, EUP/PCL/PETA-4SH YUP/PCL/PETA-4SH	-	250-500 µm	Maximum tensile strength: 21.3 MPa Tensile elastic modulus: 93.4 MPa		Photocross-linkable different PCL scaffolds particularly EUP/PCL/PETA-4SH, demonstrated excellent tensile properties which is approximately tenfold higher compared to the current state-of-the-art.	[259]
FDM: Printing speed: 60 mm/s. Layer thickness: 0.2 mm	PLA/nHAp composite	60%	-	Compressive strength: 44.02 MPa Elastic modulus: 43 MPa		The effect of increasing nHAp content was significant for improving the acidity of PLA degradation products, modifying the bioactivity, and biodegradation rate.	[260]
Extrusion-based 3DP: Printing speed: 300 mm/min. Nozzle diameter: 400 µm	PCL/β-TCP/PEG	>85	400-550 µm	Maximum compressive strength: 2.11 MPa Maximum compressive modulus: ~ 36 MPa		PEG coating and β-TCP structure of PCL/β-TCP/PEG scaffolds enhanced the hydrophilicity, cell proliferation, mineralization properties and osteogenic differentiation, for promising bone defect repair applications.	[261]
FDM: -	PCL/corncob-derived cellulose, PCL/wood cellulose	54.24	~300 µm	Maximum compressive modulus: ~63.31 MPa		At 2% corncob-derived cellulose addition in PCL scaffold enhanced its porosity cell infiltration and migration properties.	[262]

FDM Printing speed: 500 mm/min. Nozzle diameter: 300 μm	PCL/Zn	43.53	~300 μm	Maximum compressive strength: 75.35 MPa Maximum flexural strength 141.15 MPa		Increasing Zn contents up to 2 wt.%, in PCL/Zn scaffolds gradually improved osteoclastogenesis.	[263]
FDM: Printing speed: 60 mm/s. Layer thickness: 0.2 mm	PLA/nHAp composite	60%	-	Compressive strength: 44.02 MPa Elastic modulus: 43 MPa		The effect of increasing nHAp content was significant for improving the acidity of PLA degradation products, modifying the bioactivity, and biodegradation rate.	[260]
Extrusion-based 3DP: Printing temperature: 210 °C Printing speed: 80 mm/s	PLA/CS PLA/keratin	-	-	Storage modulus: 2550 MPa at 30°C		CS and keratin improved cell growth in a PLA matrix for developing effective scaffolds for TE applications.	[264]
FDM Nozzle diameter: 0.2 mm Layer thickness: 50 μm	PLLA/HAp	-	1.096 mm	Young's modulus: 9.39 GPa		The reported Young's modulus for 50 wt.% of HAp in PLLA/HAp scaffolds matched with the modulus of human femur and tibia.	[265]

3 Blending of PCL- and PLA-based polymers with different biomaterials

In comparison to ECM-derived natural biopolymers, PCL and PLA scaffolds are not biologically active. Moreover, these scaffolds exhibit poor cell adhesion, proliferation, and growth due to their poor hydrophilicity, which is the main issue in developing successful cell culture followed by tissue formation [266]. Thus, the blending of PCL and PLA scaffolds with natural polymers, synthetic polymers, bioceramics, and other hydrogels can improve biocompatibility and modulate the rate of degradation. Additionally, copolymerization is another approach, which is used to improve the physicochemical properties of these polymers [267]. This section illustrates the blending of PCL or PLA with natural biopolymers and bioceramics.

3.1 Blending with natural biopolymers

Hybrid scaffolds can be developed by combining PCL- or PLA-based polymers with other natural polymers. These scaffolds have gained ascending trend in the biomedical field and provide controllable and benign environment for growth, proliferation, and differentiation of cells. To develop hybrid scaffolds, the optimized contents of these biomaterials are essential for TE applications.

3.2 Blending with bioceramics

PLA- and PCL-based scaffolds exhibit poor cellular attachment, proliferation, and differentiation, which are the most critical and basic criteria for scaffold implantations. The developed scaffolds should possess excellent interaction between the implant surface and cells. Therefore, it is necessary to enhance the surface properties of fabricated scaffolds before being implanted in traumatized tissues [268]–[270]. The surface and biomechanical properties of the scaffolds can be enhanced by incorporating inorganic non-metallic materials including bioactive glasses (BGs) and bio-ceramics [271].

Bio-ceramics such as calcium phosphate (CP), zirconium oxide, tricalcium phosphate (TCP), and hydroxyapatite (HAp) release ions upon interacting with surrounding tissues, which trigger osteogenic gene expression. These customized composite scaffolds exhibit great potential in the tissue regeneration field due to good tissue binding, high compression strength, excellent antimicrobial properties, lack of toxic reaction, and pH changing features of bioactive ceramics [272]. However, these bio-ceramics exhibit low ductility, biodegradability and biocompatibility, which are limiting their utilization in tissue regeneration field [273]–[275]. The integration of synthetic biopolymer-based materials and bio-ceramics helps to improve scaffold characteristics and tissue interaction, which permits controlled degradation [276]. Additionally, bio-ceramics-based polymer materials repair biological tissues and improve biocompatibility and mechanical strength of the scaffolds [277]. For instance, Cao et al. [278] proposed 3D-printed PCL/PEG/HAp-based scaffolds for calvarial defects. The results indicated that scaffolds with higher HAp content (90 wt.%) improved matrix formation. The in-vivo study of rat calvarial defects revealed that the new bones and blood vessels were generated within the pores of 3D-printed scaffolds via intramembranous ossification, as presented in Figure 12(a).

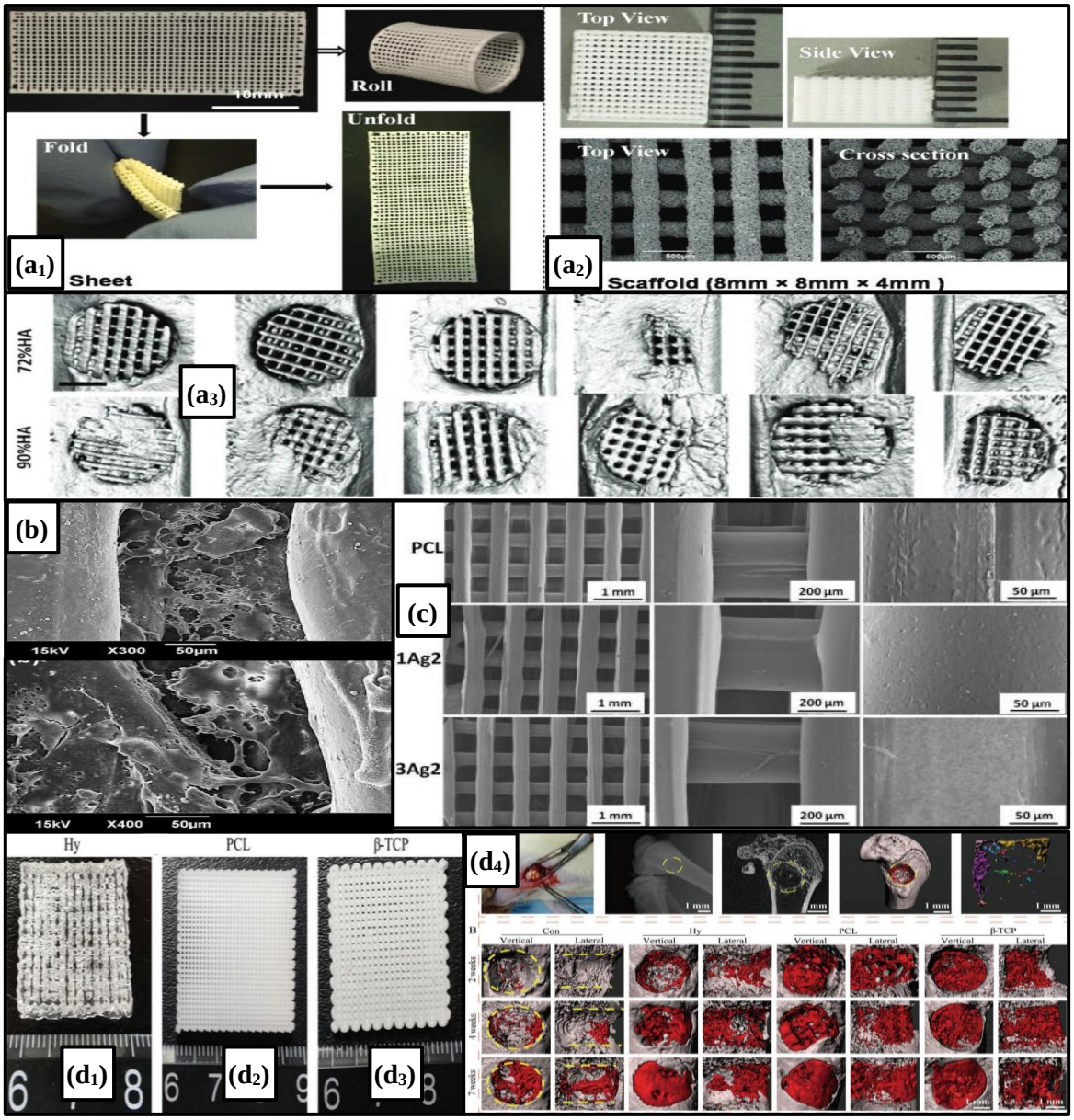


Figure 12. (a_1) 3D-printed PEG/PCL/HAp composite struts in scaffold and sheet forms depicting rolling, folding and unfolding behavior; (a_2) Macro and micro photographs of a 3D-printed thick scaffold; (a_3) Photographs of scaffolds after 12 weeks implantation in rat (adapted with permission from ref. [278] , copyright, 2022, The Royal Society of Chemistry); (b) SEM micrographs depicting the cell attachment and proliferation over PLA/HAp-based scaffolds (adapted with permission from ref. [279], copyright, 2019,Elsevier); (c) SEM analysis of Ag-NPs reinforced PCL-based 3D-printed scaffolds (adapted with permission from ref. [280], copyright, 2021,Elsevier); (d) Different 3D-printed scaffolds models; (d_1) GelMA-based hydrogel; (d_2) PCL; (d_3) β-TCP in cubic shape; (d_4) The implantation of scaffolds at distal femur site, and monitoring and analysis of new bone formation of hydrogel, PCL, and β-TCP-based scaffold groups at 2, 4, and 7 weeks through Imaris software (adapted with permission from ref. [281], copyright, 2022, John Wiley and Sons).

In another study, Mondal et al. [279] fabricated PLA/HAp-based scaffold through 3DP technique and exhibited excellent porosity, cell adhesion, proliferation, and differentiation. Scanning electron microscope (SEM) images in Figure 12(b) illustrated that the incorporation of HAp-based into PLA matrix improved cell attachment, which absorbed nutrients and facilitated cell activity.

CP-based bio-ceramics are bioresorbable and osteoconductive, however, these ceramics exhibit brittle nature in tension and shear, and are highly advantageous to develop scaffolds for tissue repairing applications due to their similarity with the mineral phase of bone and high stiffness (393 GPa) [282]. TCP-reinforced PCL- and PLA-based polymer composites improve the long-term degradation, high biocompatibility, and appropriate mechanical properties [283]–[285]. For instance, Ji et al. [281] developed methacrylated gelatin (GelMA)-, PCL-, and β-TCP-based 3D-printed scaffolds and explored the regulating effect of the symbiotic microenvironment during bone healing, as presented in Figure 12(d). The in-vivo results revealed that all three scaffolds improved bone healing mechanisms. Furthermore, PCL scaffolds regulated cell proliferation and differentiation through supporting cell cycle, cellular senescence, and accelerating the process of endochondral ossification.

The addition of NPs especially gold, silver, copper or platinum and other carbon nanomaterials (nanotubes, nanofibers, and graphene nanosheet) into PCL- and PLA-based matrices alters the inherent characteristics of scaffolds to widely expand medical utility of biodegradable polymer nanocomposites [286]. These nanocomposite-based interconnected and porous scaffolds possess excellent cell adhesion, differentiation, and growth as well as flow of nutrients. Furthermore, nano-fibrous scaffolds should maintain their structural integrity and mechanical characteristics, during in-vivo and in-vitro cell growth [287]. The incorporation of these metallic NPs into PCL- and PLA-based biopolymers produces 3D-printed tissue of antibacterial characteristics. For instance, Radhakrishnan et al. [280] fabricated PCL-based porous scaffolds by incorporating silver nanoparticles (Ag-NPs) and evaluated its biomechanical performance. SEM study revealed that the incorporation of Ag-NPs developed scaffolds with uniform architectures, as illustrated in Figure 12(c). Furthermore, Ag-NPs reinforced PCL scaffolds exhibited good stiffness, enzymatic stability, cytocompatibility, and antimicrobial properties.

3.3 Metamaterials

Auxetic structures, popular metamaterials with unique cellular and repeated patterns, exhibit a negative Poisson's ratio. These metamaterials sophisticatedly change their volume through stress redistribution due to distinct structural patterns [288]. Such materials possess distinct mechanical characteristics including resilience, toughness, flexibility, and vibration control [289]. Nowadays, these metamaterials are gaining a lot of attraction in the TE field for developing scaffolds. Scaffolds with tailorable auxetic behavior possess an extraordinary ability to mimic the biophysical behavior of ECM. Furthermore, these auxetic scaffolds are highly propitious for the elimination of metabolic waste, and transportation and infiltration of nutrients, similar to native tissues [290]. Additionally, biopolymeric materials are fabricated to develop 3D scaffolds due to their specific functional and structural properties [291].

The intervertebral disc (IVD) is an important part of living creatures due to its various biomechanical functions such as supporting the weight of the body and allowing motion. Sometimes imperative treatments are required for IVD degeneration such as disc replacement and lumbar fusion, which causes adjacent segment disease. This problem was overcome by Marshall et al. [292]. The authors produced a viscoelastic PLA-based flexible scaffold with tunable biomimetic mechanics for complete spine motion segment applications through 3DP, as illustrated in Figure 13(a). The biodegradation study of the fabricated scaffold demonstrated a lower degradation rate, which resulted in superior mechanical stability, compared to the pure PLA scaffold. Furthermore, this flexible PLA scaffolds was highly biocompatible, stable and biomaterial for engineered disc replacement.

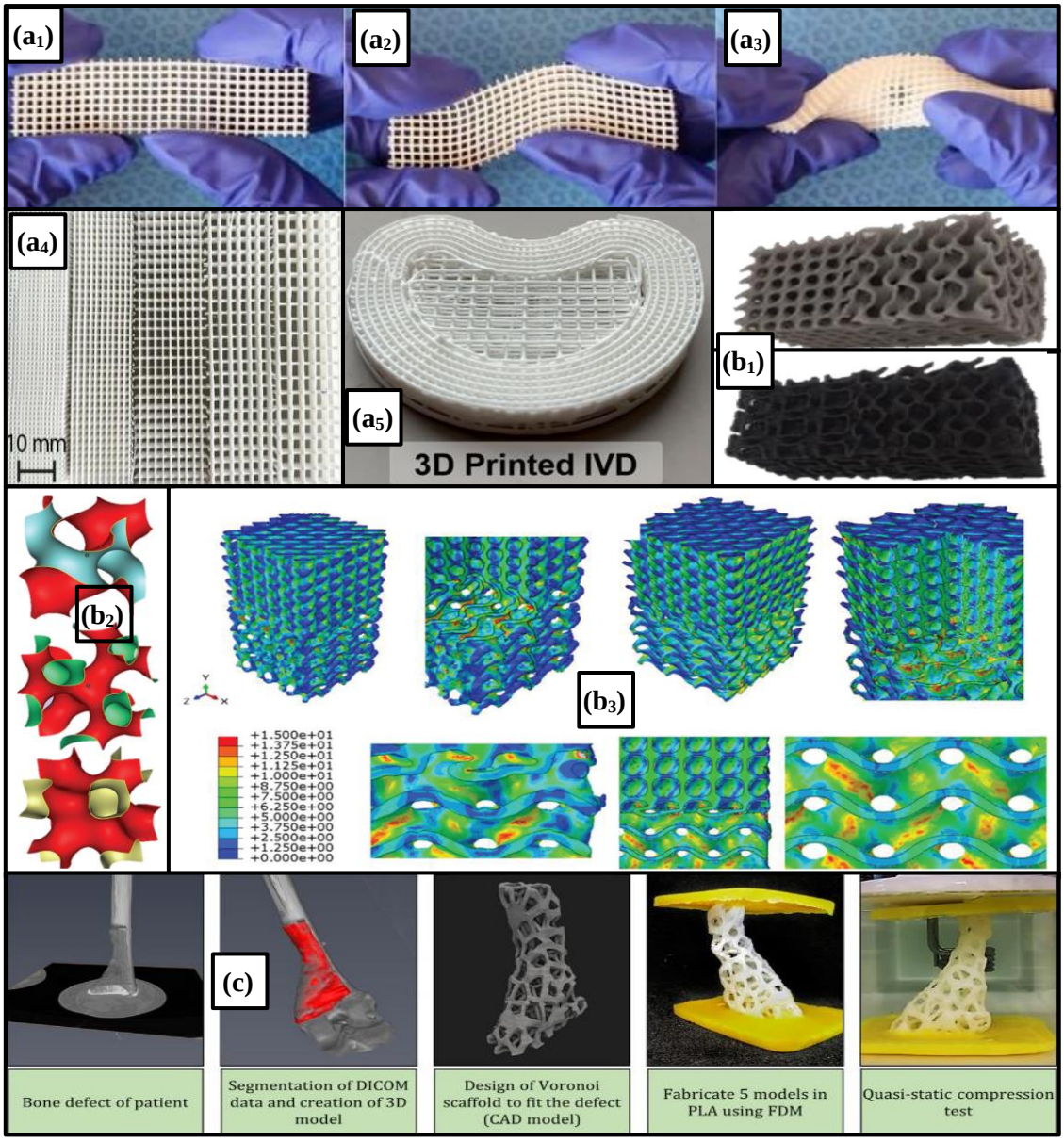


Figure 13. (a_1) Flexible PLA sheet; (a_2) Flexible PLA sheet during bent view; (a_3) Flexible PLA sheet during twisting; (a_4) Flexible PLA scaffolds with 1, 1.5, 2, 2.5, and 3 mm fiber spacings; (a_5) 3D-printed scaffold in anatomically disc shaped (adapted with permission from ref. [292], copyright 2021, American Chemical Society); (b_1) Printed PLA-based multi-morphology scaffolds; (b_2) Gyroid, diamond, and Schoen I-WP (from top to bottom); (b_3) Simulation results (adapted with permission from ref. [293], copyright 2022); (c) Different stages in Voronoi design-based scaffolds for the bone defect of the patient (adapted with permission from ref. [294], copyright 2021, Elsevier).

In addition to auxetic structures, which have distinct mechanical properties, other structures have been taken into consideration by researchers due to their unique mechanical and biological properties. One of these structures is the triply periodic minimal surface (TPMS), which has extensive application in the biomedical sector due to its excellent properties, such as excellent mechanical properties, nutrient transportation, oxygen diffusion, and ion exchange, and has become an ideal choice in TE applications [295]–[297]. These structures are defined with mathematical equations, and their parameters can be changed to generate desired structures with specific biological and mechanical properties, which can be used in patient-specific applications.

These function-based structures have been developed by a plethora of researchers for different biomedical applications. For instance, in a study by Noroozi et al. [293], the multi-morphology PLA-based bone scaffolds were printed through the FDM method, and the effect of different parameters on the mechanical properties of scaffolds was investigated. They also evaluated the effect of the transition zone, which can be defined as a zone where one pattern starts to change to another pattern, on the mechanical properties of printed scaffolds. The author observed that porosity is more important than the transition zone, and in the same transition zone pattern, the scaffolds with smaller porosity showed higher mechanical properties. Furthermore, they used the micro-CT technology to obtain the real geometry of 3D-printed bone scaffolds and compared them with their nominal geometry and ~~this vein~~ they were able to show the anomalies geometry that happen during printing. Moreover, they developed finite element modeling (FEM) for both nominal and real geometries of bone scaffolds and showed that micro-CT finite element simulation can improve simulation results, as illustrated in Figure 13(b).

Parametric designs like Voronoi are usually using standardized algorithms to develop reproducible structures. Voronoi design is an effective strategy to optimize the porous scaffolds for TE applications. Herath et al. [294] employed a novel Voronoi design concept to develop a 3D model of the biodegradable polymer. FEM results revealed that this model design produced scaffolds with macropore sizes (> 4 mm) while keeping the structural stability, as illustrated in Figure 13(c). For experimental purposes, the authors fabricated PLA-based polymers through a FDM technology. The experimental results showed that biodegradable polymer achieved ~71 % porosity with macropore sizes ranging from 4 mm to 11.8 mm. Additionally, the built FEM model successfully not only helped to assess the mechanical characteristics but also predicted the fracture sites of the bone scaffolds. Thus, the novel Voronoi design concept can be applied to mimic the geometry of the cancellous bone.

4 Role in biomedical applications

3D-printed PCL and PLA-based biodegradable polymers have been playing a vital role in different biomedical sectors including surgical training, 3D anatomical models, surgical equipment, implants, and prosthetics [298]–[300]. Porous biodegradable polymer scaffolds propose many advantages for biomedical applications. The contemporary 3DP techniques have exhibited excellent control in automation, customized parts, reproducibility, and complex geometries as well as the processing of medical digital images [301]–[304]. These techniques are captivating for many clinical practices and applications such as bone graft models, urogenital, TE, cardiovascular, medical stents, and neurological surgeries. Figure 14 depicts that PCL- and PLA-based polymer composites are extensively applied in hard tissue (dental and bone) and soft tissue (skin, liver, tendon, cartilage neural, ligament, muscle, and cardiovascular) engineering applications. This section elucidates a variety of soft and hard tissue regeneration applications of PCL- and PLA-based composite scaffolds.

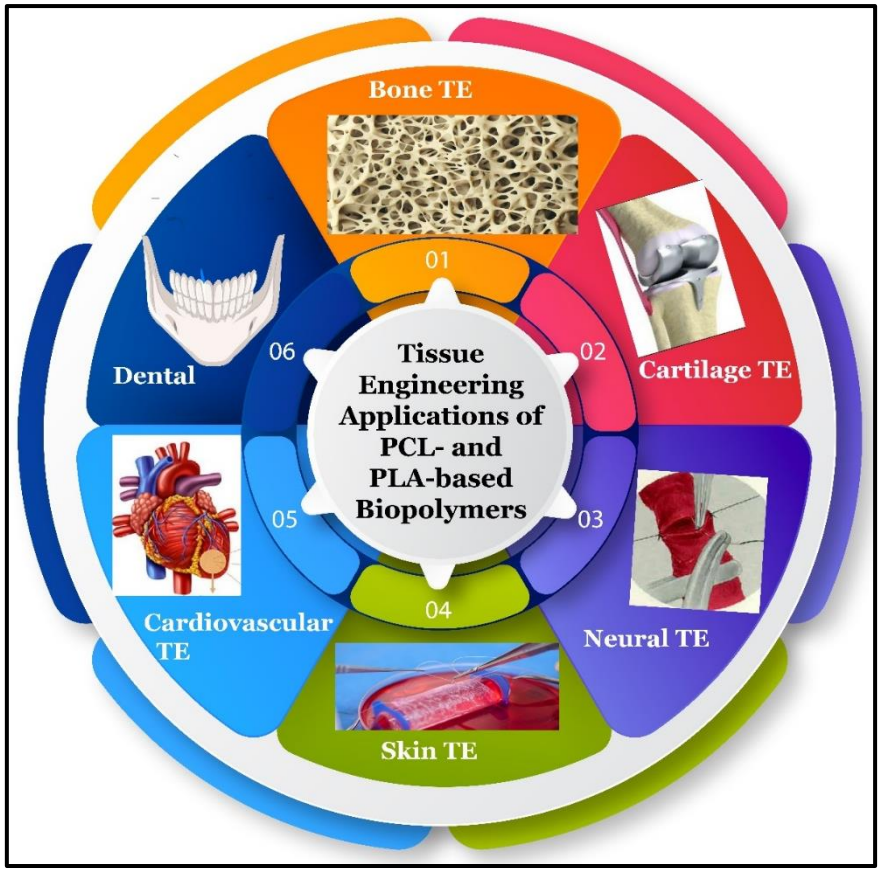


Figure 14. 3D-printed PCL- and PLA-based biodegradable polymer composites in different medical disciplines

4.1 Bone tissue engineering

The bone is a connective tissue that performs several vital responsibilities, such as providing a framework for bodies, supporting other tissues, and storing and hematopoiesis functions in bodies [305]. The bone ECM consists of several components, including inorganic mineral components, organic components, and water, among which the inorganic elements with 69 wt.% constitute the main part of the bone. About 90% of organic components are Col type-1, which provides bone with tensile strength [306]. Furthermore, HAp and CP exist in the bone as inorganic mineral components, which give rigidity to the bone and act as precursors to apatite [307]–[309]. Moreover, bone cells have a critical role in bone function, which can be classified into four groups: osteogenic, osteoblasts, osteocytes, and osteoclasts, as depicted in Figure 15(a). Bone and related diseases are among the most important clinical challenges as the number of orthopedic surgeries around the world reached 22.3 million in 2017 and is estimated to reach 28.3 million by 2022 [310]–[312]. In general, bone can heal itself on small size defects such as cracks and some types of fractures, but in many cases, when bone defects exceed the critical size defects, the bone loses such a feature, and the bone regeneration is not complete and requires treatment [313]–[315]. The normal treatments of bone tissue damage and diseases are transplantation of tissue that has been obtained from the patient (the gold standard for surgeons) or compatible donors. However, these approaches have some limitations and difficulties, such as covering only small size defects, not covering special shapes, insufficiency of autogenous bone, infections, morbidities, and chronic pain at the donor or acceptor site [316]. Therefore, new approaches should be employed to address these concerns.

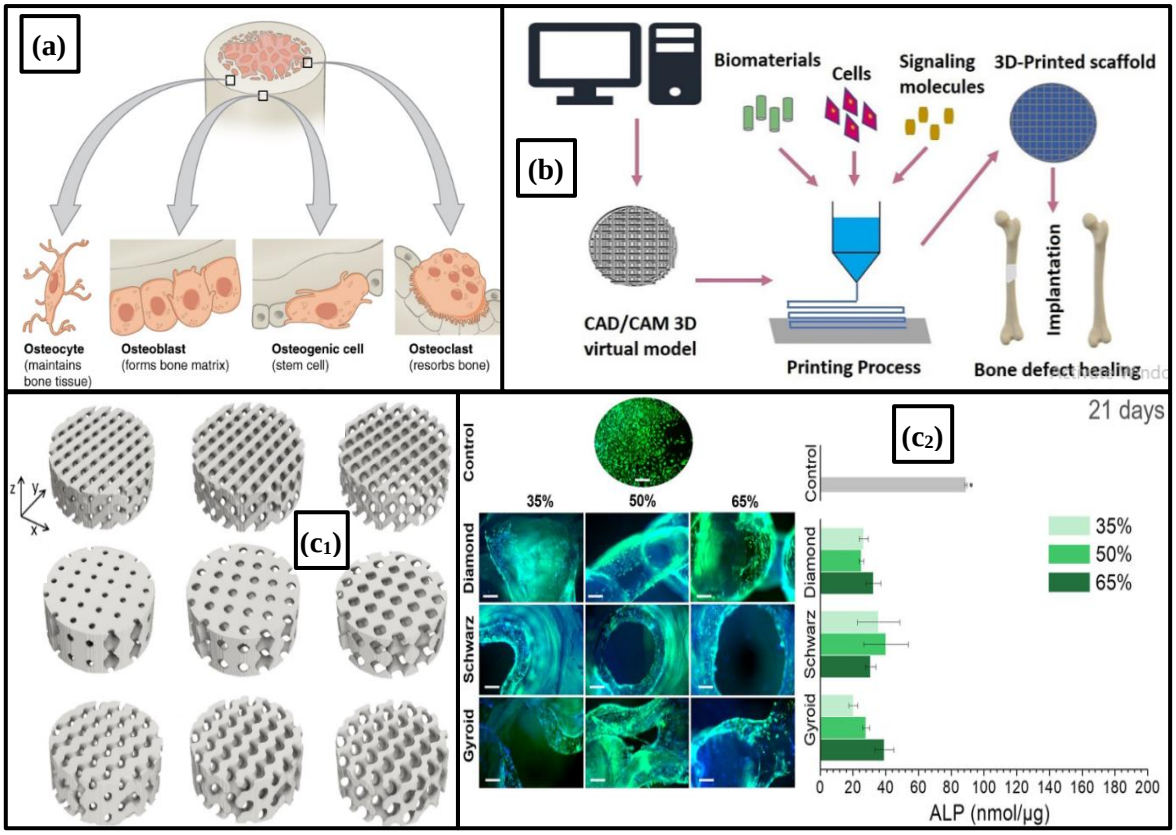


Figure 15. (a) Four types of cells in bone tissue (adapted with permission from ref. [317], copyright, 2017, Elsevier); (b) 3D-printed based BTE approach (adapted with permission from ref. [65], copyright, 2021, Elsevier); (c_1) Different bone scaffolds with different porosities; (c_2) Fluorescent stained images of osteoblast-like cells cultured on the different geometries and porosities over 21 days (adapted with permission from ref. [318], copyright, 2022, SAGE Publications Ltd).

BTE is an interdisciplinary and novel approach that combines cells and biomaterials to repair and regenerate bone tissues, which has been able to overcome the limitations of conventional treatment [197]. Biomaterials are a key element in the BTE approach because they act as ECMs and must provide bone-like conditions for cells [319]. To meet this goal, several parameters, including biocompatibility, mechanical strength, biodegradability, and anti-bacterially, are important [67]. Figure 16 depicts the essential features of synthetic bone scaffolds. The scaffold morphology has a prominent role in the biological characteristics of the tissues including cell proliferation, cell migration, cell growth, and cellular adhesion as well as mechanical properties [320]. The combination of biomaterials with 3DP technology has also drastically changed the applicability of BTE so that some of the limitations that existed in traditional methods, such as limitations in special shapes of tissue, were generally overcome by 3DP technology, as illustrated in Figure 15(b).

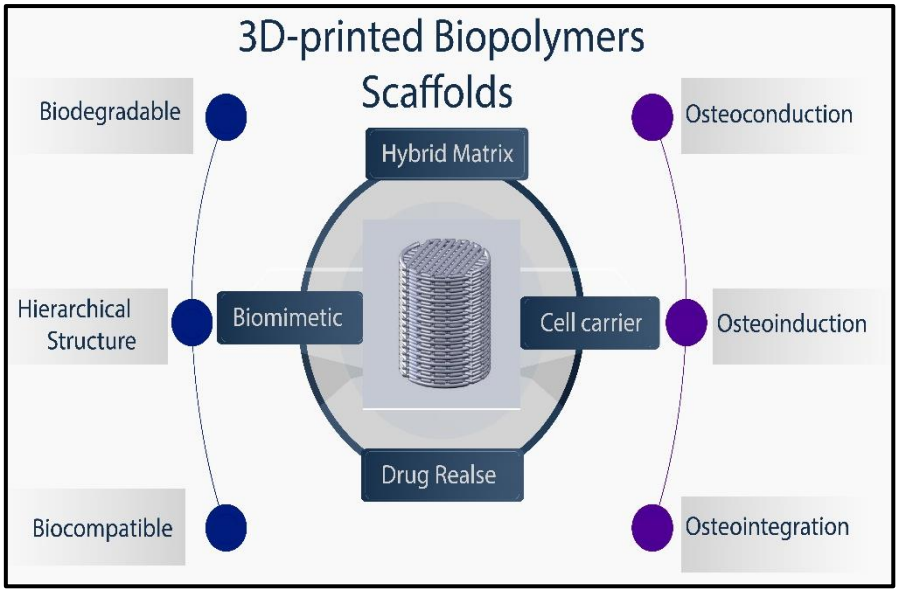


Figure 16. Different Features of 3D-printed biodegradable polymers scaffolds for BTE

Nowadays, 3D-printed polymers have been extensively used as bone tissue biomaterial, among which PLA and PCL, due to their excellent properties, have been taken into consideration by many researchers. In a study, an implicit function was used to design and print PLA-based bone scaffolds [318]. The authors used different types of structures, including diamond, Schwarz, and gyroid structures with different pore sizes. The mechanical response of the printed scaffolds was evaluated and showed that the PLA-based printed scaffolds could provide sufficient value of mechanical resistance for BTE applications. In addition, the in-vitro study was performed to prove scaffolds' biocompatibility and cell proliferation ability. Furthermore, the biological study showed that the PLA-printed scaffold could promote the differentiation of pre-osteoblastic cell lines, as depicted in Figure 15(c).

Noroozi et al. [321] printed PLA-based TPMS scaffolds filled with cell-laden Alg hydrogel as a natural polymer. They evaluated the mechanical properties of these bone scaffolds, numerically and experimentally. Additionally, the biological response of fabricated bone scaffolds was also evaluated by using the in-vitro model in which static and dynamic cell culture techniques were applied. The results showed that the PLA/Alg bone scaffold has a better biological response, including cell adhesion and proliferation. In another study, the PCL biomaterial was employed to print TPMS-based bone scaffolds by melt extrusion. SEM technique was used to determine the geometrical features such as pore size and strut thickness. The compressive test was employed to determine the mechanical response of printed scaffolds, and it was shown that primitive scaffolds have the highest modulus and gyroid the highest yield strength. Moreover, the biological assay was used to determine the biological response of printed scaffold, which showed primitive scaffolds has the highest value of cell attachment and cell proliferation compared to others [322].

In addition to pure PLA and PCL, bioceramic materials such as HAp, TCP, and biphasic calcium phosphate, which belong to the CP family are widely used in bone tissues, due to their high ability in bone regeneration, biocompatibility, integration with the bone, and their similarity to bone tissue compositions. There are other types of bioceramics, including calcium silicate and BGs, which due to their unique features are widely used in BTE [323]–[325]. Therefore, 3DP of a combination of PCL, PLA, and bioceramics has been considered by researchers for BTE [310]. In a study, Zhang et al. [260] successfully prepared scaffolds of

the optimized nHAp/PLA composite through FDM technology for bone tissue regeneration. The authors observed that nHAp/PLA-based composites exhibited excellent compressive strength, which was considerably better than those of cancellous bone and HAp-based ceramic scaffolds. The 3D-printed biopolymer-based scaffold was implanted at the bone fracture site of white rabbits, as depicted in Figure 17(a). Additionally, bone-like apatite was developed on the surface during the in-vitro degradation method, and excellent osteogenic properties were further verified through in-vivo experimentation.

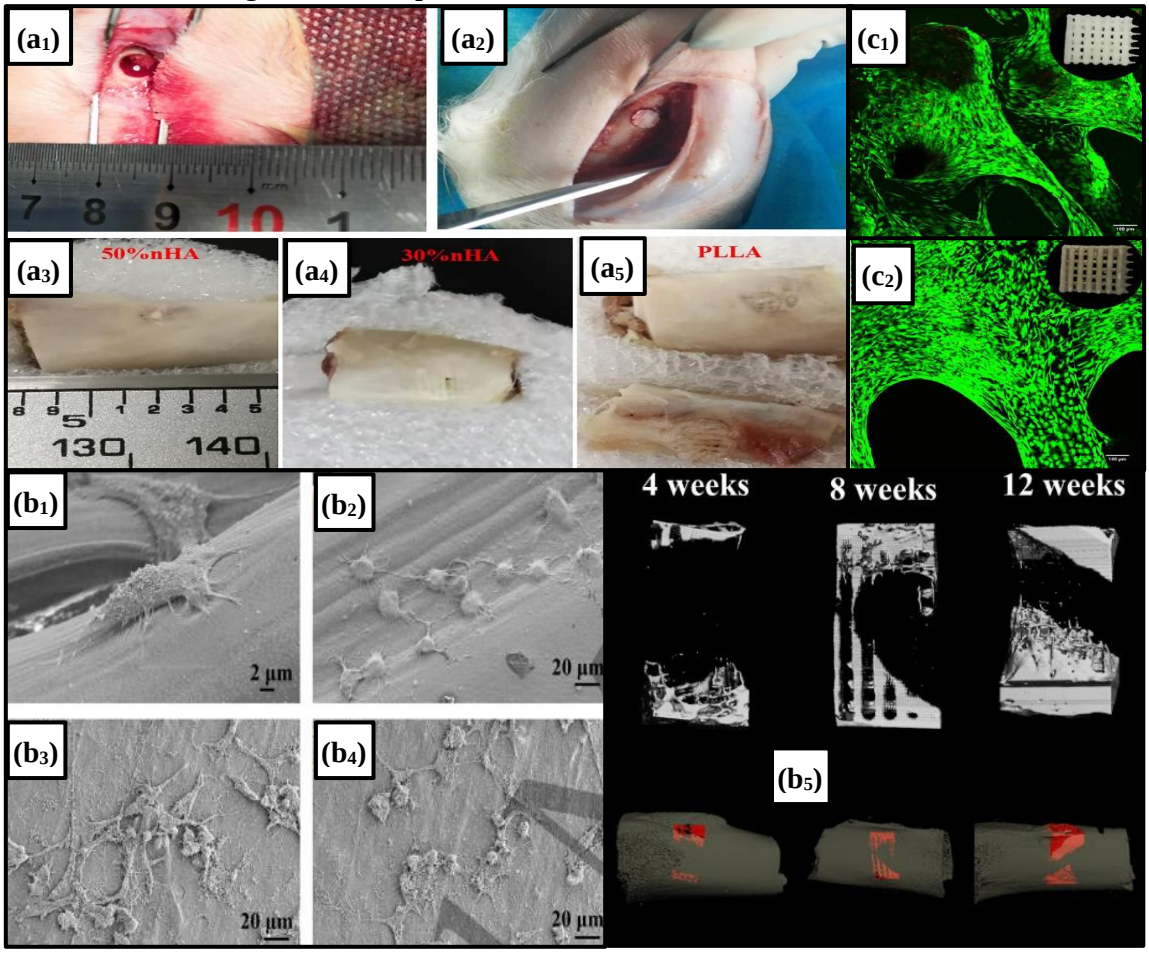


Figure 17. (a_1) 3D-printed in-vivo model of bone ruptures; (a_2) PLA/nHAp-based composite were implanted at the bone rupture location; (a_3-a_5) Figure showing that scaffolds were harvested after 30 days (adapted with permission from ref. [260], copyright, 2021, Elsevier); SEM images of cell-seeded on printed scaffolds; (b_1, b_2) For 1 day; (b_3, b_4) For 3 days; (b_5) Micro-CT 3D images of bone formation after 4,8, and 12 weeks (adapted with permission from ref. [326], copyright, 2019, IOP Publishing Ltd); (c) Cell viability study; (c_1) Pure 3D-printed PLA bone scaffold; (c_2) 3D-printed PLA bone scaffolds coated with PDA and COL-1, Live cells are shown in green, and dead cells are shown in red (adapted with permission from ref. [327], copyright, 2018, John Wiley and Sons).

In another similar study, Chen et al. [326], by employing FDM printing, fabricated a bone scaffold based on a combination of PLA and nHAp. The authors homogeneously dispersed nHAp into PLA-based scaffolds. The mechanical property of printed scaffolds was measured in terms of compressive strength, which showed that printed scaffolds have a compressive strength in the range of human trabecular bone. In addition to confirming the antibacterial feature of this scaffold, the authors also evaluated the cytocompatibility of these 3D-printed scaffolds, and for this purpose MG-63 cell line was used. Moreover, the in-vivo response of introduced bone scaffolds was evaluated by implanting printed scaffolds into a rat model and

evaluating their osteogenesis and osteoconductivity for 4,8, and 12 weeks, as illustrated in Figure 17(b).

In another study, 3DP technology was employed to fabricate PCL/BG bone scaffolds [328]. The contact angle study showed that adding BGs increased the hydrophilicity of PCL. The in-vitro results improved the cell adhesion and cell proliferation of PCL/BG-based bone scaffolds. Moreover, the in-vivo rat model was used to evaluate the bone regeneration potential of introduced scaffolds, which showed that increasing the BG amount could improve bone defect repairing. In addition to using PCL, PLA, and bioceramics, some researchers have used other biomaterials to enhance the biological performance of bone scaffolds. In a study by Peng et al. [329], the oxygen-releasing bone scaffolds were fabricated with 3DP technology. The authors used MgO_2 as the oxygen-releasing element, PCL, and β-TCP and evaluated the performance of printed scaffolds by using in-vitro and in-vivo analysis. Results showed that printed scaffolds in terms of cell survival, proliferation, migration, adhesion, and osteogenic differentiation performed better than the control group. Moreover, the mechanical properties of printed scaffolds were evaluated, which showed good mechanical properties. The oxygen-releasing data showed that printed scaffolds could have a sustained release of O_2 over two weeks.

Besides the suitable features of 3D-printed PLA and PCL scaffolds, hydrophobicity is one of the deficiencies which prevent the optimal biological response of these bone scaffolds. Hydrophobicity leads 3D-printed bone scaffolds to low bioactivity features [330]. Surface modification of 3D-printed bone scaffolds is an effective alternative approach, which can be used in BTE applications [331]. In this approach, the covering materials modify the cell attachment and improve biological responses [332]. Many researchers have done the surface modification of 3D-printed PCL bone scaffolds, and for this purpose, cellulose nanofibrils material [333], and nanobioceramic [334] are used. Furthermore, extortionate researchers have employed this method on 3D-printed PLA scaffolds, in which they used dopamine [335], nHAp [336], PLA nanofiber [337], Gel, and mucic acid [338]. In a study by Teixeira et al. [327], 3D-printed PLA-based bone scaffolds were coated with polydopamine (PDA) and type I collagen (COL-1). They investigated the effect of coating on surface smoothness and the result showed that the PDA coating could create a smoother surface than pure PLA scaffolds and COL-1 coated scaffolds. Additionally, they investigated the effects of these coatings on cell adhesion and metabolic activity of 3D-printed PLA bone scaffolds. The authors seeded MSCs on pure 3D-printed scaffolds and surface-treated scaffolds and observed that these coatings could increase cell viability and cell-biomaterial attachments, as illustrated in Figure 17(c).

In another study, the 3D-printed PLA-based bone scaffolds were surface modified via CS- and HAp-based coating [339]. Fourier transform infrared technique was used to evaluate bonding between PLA, CS, and HAp. The in-vitro study showed that the proposed surface-modified scaffold could increase cell adhesion and proliferation, compared to pure PLA. Similarly, Li et al. [340] studied the effect of the various pore size of 3D-printed PCL/PEG/HAp-based bioactive scaffolds on the immune response and bone-biomaterial integration by using in-vivo analysis. Scaffolds of various pore sizes 209.9 ± 77.1 μm [P200], 385.5 ± 28.6 μm [P400], and 582.1 ± 27.2 μm [P600] were fabricated, as presented in Figure 18(r-s). These results indicated that P600 remarkably reduced the foreign body response and caused more M2 macrophage infiltration, vascular ingrowth, and the development of new bone. Thus, PCL/PEG/HAp-based porous scaffolds have promising applications in the repair of bone defects.

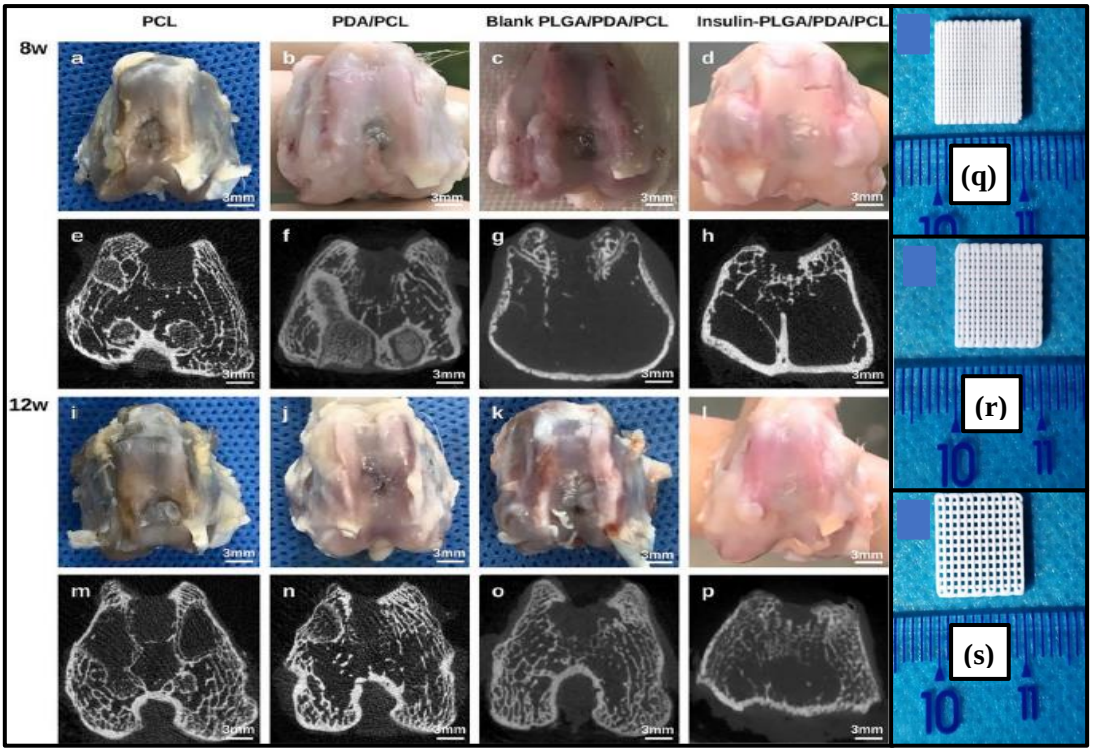


Figure 18. Gross visuals of femoral condyle samples; (a-d) 8 weeks; (i-h) 12 weeks after implantation of PCL, PCL/PDA, blank PCL/PLGA/PDA, and insulin-PCL/PLGA/PDA scaffolds. Micro-CT images of bone regeneration; (a-d) 8 weeks; (i-h) 12 weeks after implantation of PCL, PCL/PDA, blank PCL/PLGA/PDA, and insulin-PCL/PLGA/PDA scaffolds. Quantitative value of micro-CT bone remodeling (adapted with permission from ref. [341], copyright, 2021 Elsevier); (q-s) Images of various 3D-printed scaffolds; (q) P200; (r) P400; (s) P600 (adapted with permission from ref. [340], copyright, 2022, American Chemical Society).

Some researchers have used the surface modification technique for dual purposes. These surface modifications not only modified the biological and mechanical properties of scaffolds, but also use it for drug-delivery purposes. In a study, Wei et al. [341] used the insulin-releasing PLGA to modify the surface of 3D- printed PCL-based bone scaffolds for osteochondral repair. The authors used a double-emulsion solvent evaporation technique to generate insulin-coated PLGA-based NPs, and after that, they coated PDA and insulin-coated PLGA NPs on the surface of PCL-based printed scaffolds. Results showed that the presence of PDA and PLGA on the surface of PCL scaffolds did not affect the physicochemical characteristics of the PCL, while the hydrophilicity of PCL scaffolds was improved. The insulin release curve showed that this technique can provide a sustained drug release after the initial burst of insulin-releasing. The in-vitro study illustrated that surface-modified scaffold can significantly improve osteogenic differentiation of rabbit bone MSCs and the proliferation of chondrocytes. Furthermore, the in-vivo study with a rabbit model confirmed the ability of fabricated scaffolds in improving the repair of cartilage and subchondral bone after 8 and 12 weeks, as shown in Figure 18(a).

4.2 Cardiovascular tissue engineering

Cardiovascular regeneration is a propitious method, which refers to the repairing of blood vessels for restoring the function and structure of traumatized organs and tissues [342]. A variety of techniques like the implantation of stents, tissue-engineered grafts, angioplasty, and bypass surgery through grafting are usually applied in vascular regeneration, to produce

biologically structural and functional vessels from stem cells, smooth muscle cells, endothelial cells (ECs), biomaterials, bioactive molecules, and corresponding cell spheroids and aggregates [343].

Recently, tissue engineering vascular grafts (VGs) exhibited excellent potential to substitute synthetic and biological grafts [344]. Vessel repairing methods include the development of VGs, decellularization of vessels, formation of self-assembly VGs, and other vessel maturation techniques [345]. In recent years, the demand for VGs has been increased rapidly. However, it is impossible to obtain vascular tissues of patient-specific function and shape through traditional allograft transplantation and autologous implantation [346]. This problem can be solved by 3DP of microporous tubular structure, as cardiovascular scaffolds with a suitable diffusion barrier for cell seeding [347]. 3DP of engineered vascular tissues with intricate hierarchical architectures enable the development of new blood vessels [348]. These vascular scaffolds are printed through extrusion-based, UV-assisted, or inkjet-based 3D printing technologies. These vascular scaffolds exhibit complete degradation after angiogenesis [349]. For instance, Yeo et al. [350] developed PCL/Col-based micro/nano-hierarchical scaffolds for co-culturing human umbilical vein endothelial cells (HUVECs) and C2C12 myoblasts. The results implied that co-culturing of myoblasts and HUVECs, as well as aligned nano-/micro-fibers, induced myogenic differentiation with vascularization. Furthermore, these intricate architectures with aligned patterns allowed the growth of cells in desirable morphology, as illustrated in Figure 19(a).

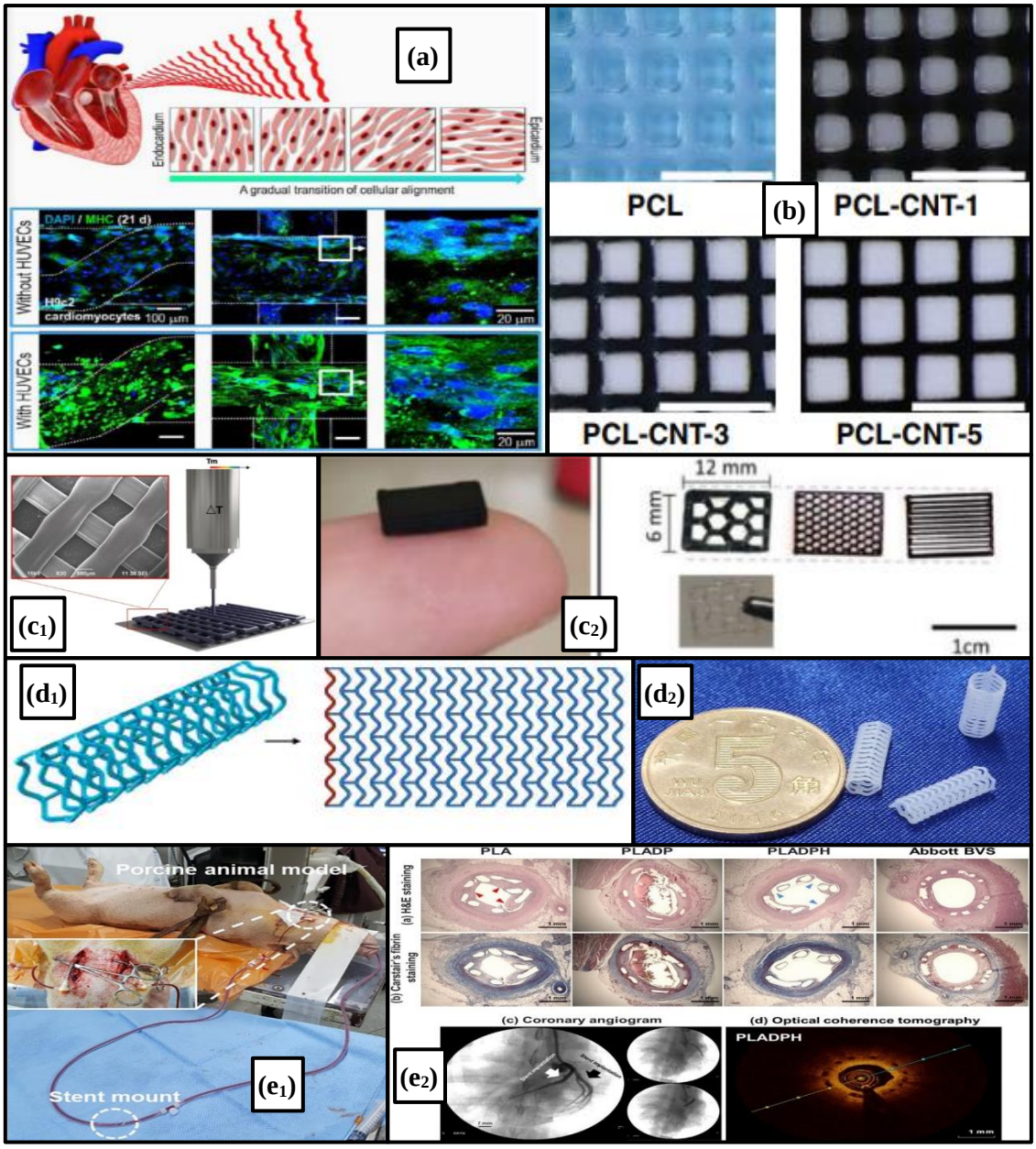


Figure 19. (a) A schematic representation and fluorescence photographs of cardiac muscle structure (adapted with permission from ref. [350], copyright, 2020, Elsevier); (b) Microscopic images of 3D-printed PCL and PCL/CNTs-based composite scaffolds (adapted with permission from ref. [351], copyright, 2016, John Wiley and Sons); (c_1) SEM photographs of micro-scaled pattern; (c_2) Different configurations of 3D-printed PEDOT-g-PLA patterns employed for biocompatibility test (adapted with permission from ref. [352], copyright, 2021, John Wiley and Sons); (d_1) 3DP trajectory of stent; (d_2) 3D-printed PCL-based bioresorbable stents (adapted with permission from ref. [353], copyright, 2020); (e_1) Porcine animal model arteriovenous shunt blood circulation system during in-vivo study; (e_2) Porcine coronary arteries analysis during vivo histological study (adapted with permission from ref. [354], copyright, 2019, Elsevier).

Novel biodegradable PLA- and PCL-based composite scaffolds intended for vascularization exhibits tailorable bioresorption and appropriate morphology [355]. These scaffolds behave as substrate for cardiomyocyte maturation and growth. The fulfillment of two conditions including biological controllability and mechanical characteristics is necessary for effective vascularization [356]. These two requirements can be satisfied by combining PCL and PLA

with suitable biomaterials and additives. For instance, Dominguez-Alfaro et al. [352] synthesized biocompatible and conductive poly(3,4-ethylenedioxythiophene) (PEDOT)/PLA-based copolymer by using the melt extrusion technique, as presented in Figure 19(c). The developed tissue architectures (cardiomyocytes with cardiac fibroblast) in PEDOT-g-PLA exhibited excellent biocompatibility, maturation, and growth of cells.

In another study, Ho et al. [351] developed PCL and PCL/CNTs-based composite scaffolds for cardiac TE by using the 3D printing technique, as illustrated in Figure 19(b). These scaffolds were tailored in terms of biodegradability and cell compatibility by varying CNT contents. The in-vitro study indicated excellent growth, proliferation, adhesion, and migration of H9C2 myoblast cells.

PLA- and PCL-based biopolymers are also employed to develop drug-eluting stents (DESs) for curing blocked coronary arteries [357]. For instance, Qiu et al. [353] developed PCL-based bioresorbable polymeric stents through the 3DP technique, as shown in Figure 19(d). The surface of PCL was successfully modified through sulfated CS. The in-vivo results revealed that these stents possessed excellent cell compatibility, blood compatibility, and non-cytotoxicity. Additionally, the modification through sulfated CS enhanced cell viability, growth, and proliferation.

In another study, Lee et al. [354] developed a 3D-printed PLA-based biodegradable polymeric stent through polyethyleneimine (PEI), PDA, and heparin chemistry for the prevention of thrombosis and restenosis with good blood compatibility and anticoagulation. The results from the biological testing demonstrated that the fabricated PLA-based stent possessed outstanding anti-coagulant activity including thromboresistance and hemocompatibility, along with regulation of smooth muscle cells (SMCs) and endothelial cells (ECs) proliferation. Additionally, upon in-vivo experiment, the heparinized PLA-based 3D-printed stent displayed the largest lumen area without thrombosis or atherosclerosis and with minute neointimal hyperplasia, as illustrated in Figure 19(e).

4.3 Cartilage tissue engineering

Cartilage, a type of connective tissue appears in different parts of the human body and is more flexible and softer than bone. These connective tissues are filled with synovial fluid containing nutrients and oxygen, and encapsulate the synovial membrane around the joint [358]. Articular cartilage is a type of cartilage, which bears load and shock, and performs lubrication function in the joints as well as covers the long bone's junctions [359]. Furthermore, cartilage controls the structure of the surrounding tissues and provides minimal friction against external loads. Osteochondritis, traumatic injuries, age-related diseases, and congenital anomalies are the main factors, which cause defects in cartilage tissues. Cartilage tissues do not depict any regenerative capacity due to the lack of vasculature. Therefore, chondrocytes and their progenitor cells cannot be migrated toward the trauma site for generating the matrix. To overcome this problem, biomedical engineers around the world diverted their attention to fabricate scaffolds for cartilage TE applications [360].

Extortionate researchers have tried to develop PLA- and PCL-based biodegradable scaffolds due to their excellent degradation properties, porosity, and biocompatibility. For instance, Dong et al. [361] co-cultured human mesenchymal stem cells (hMSCs) with human auricular chondrocytes (hAuCs) on 3D-printed PLA scaffolds to promote healthy elastic cartilage formation by simulating and implanting auricular helical-shape rim in nude rats. Cartilaginous tissue was developed within scaffolds after 3 months, as presented in Figure 20(a). Thus, the co-implantation of hAuCs and hMSCs in Col within an external scaffold effectively produced

human elastic cartilage and has potentials in auricular TE applications. Likewise, Blum et al. [362] fabricated PCL-based scaffolds for cartilage regeneration by using the 3DP technique and findings suggested excellent non-toxicity, cell adhesion, and proliferation.

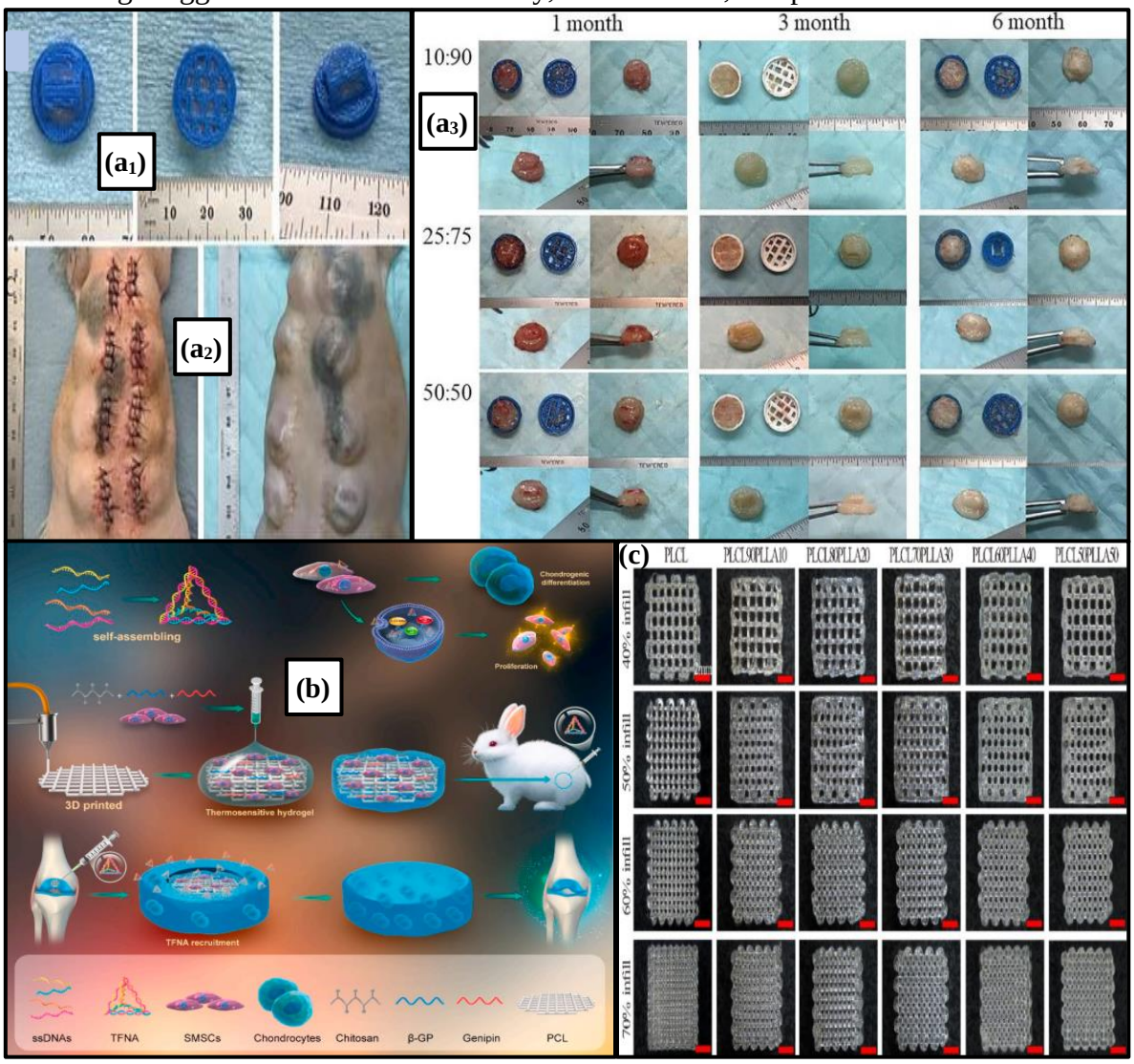


Figure 20. (a_1) Different views of 3D-printed ridged PLA containing injection molded HAuCs/hMSCs-seeded Col; (a_2) Visual representation and explanation of implanted scaffolds at implantation site; (a_3) 3D-printed scaffolds in various ratio after 1-, 3-, and 6-months in vivo pink. After 1 month, construct changed to pink color whereas it changes to appear pearly white, more like cartilage after 3 months (adapted with permission from ref. [361], copyright, 2022, John Wiley and Sons); (b) A schematic illustration of study which fabricate CS/PCL-based scaffolds for articular cartilage injury (adapted with permission from ref. [363], copyright, 2022, Elsevier); (c) 3D-printed PLCL/PLLA-based scaffolds with varying filling rates and mass ratio (adapted with permission from ref. [364], copyright, 2021, American Chemical Society).

Similarly, Li et al. [363] developed CS/PCL-based hybrid scaffold for cartilage tissue regeneration applications by incorporating tetrahedral framework nucleic acid (TFNA) and synovial mesenchymal stem cells (SMSCs). A schematic illustration is shown in Figure 20(b) presents the methodology adopted during the study. The results revealed that PCL-based cartilage scaffold exhibited excellent mechanical support and TFNA induced a good micro-environment for the chondrogenic differentiation and proliferation of delivered SMSCs and repaired cartilage.

PLCL, an amorphous copolymer, is a propitious candidate for developing scaffolds for cartilage tissue regeneration applications, and this copolymer exhibit excellent ductility, elasticity, and toughness [365]. For instance, Duan et al. [364] developed PLCL/PLLA-based scaffolds by using the 3DP technique, as illustrated in Figure 20(c). The authors developed various scaffolds by varying the mass ratios of PLLA. The results revealed that PLCL-based scaffolds with low percentage of PLLA exhibited appropriate complex viscosity, compression modulus, tensile modulus, and relaxation times for cartilage TE applications.

4.4 Neural tissue engineering

Peripheral nerve injury (PNI) occurs due to tumors, traumatic injuries, and other diseases, which may cause partial or complete paralysis. The conventional repair approach for PNI is nerve transection, which involves suturing the proximal and distal nerve ends without incorporating tensile force. Furthermore, this method has the limitation to be applied for small gap nerve injuries [366]. Moreover, it is a highly challenging task to regenerate and repair PNI due to the inherent non-dividing behavior of neuron cells [367]. Autograft is another possible approach to treat larger PNIs, however, it requires surgical invasive procedures, and branched nerves, diametral, and length mismatch limited the use of this option. As a result, there is a need to develop possible substitutes for autografting with excellent biological performance and design flexibility. The design of these guides can be improved by incorporating internal structure for directing regenerating axons through fibers or channels [368].

Different natural (COL-1, CS, HA, and silk) and synthetic polymeric materials (PGA, PCL, PLGA, and PLA) are used to fabricate nerve guidance conduits (NGCs) with versatile manufacturing techniques including electrospinning, film rolling, injection molding, micro-drilling, coaxial extrusion, and dip coating. However, these methods cannot help in attaining the diverse requirements of NGCs [369]–[371]. In the contemporary world, 3DP technology has gained significant interest in the nerve tissue regeneration field and can develop functionalized nerve repairing scaffolds, imitating anatomical nerve intricate structures with high resolution, unique customizability, and scalability for nerve TE [372]. Various 3DP techniques allow for designing a versatile and wide range of NGCs, including branched conduits, hollow conduits, and conduits with multiple micro-channels, which are illustrated in Figure 21(a).

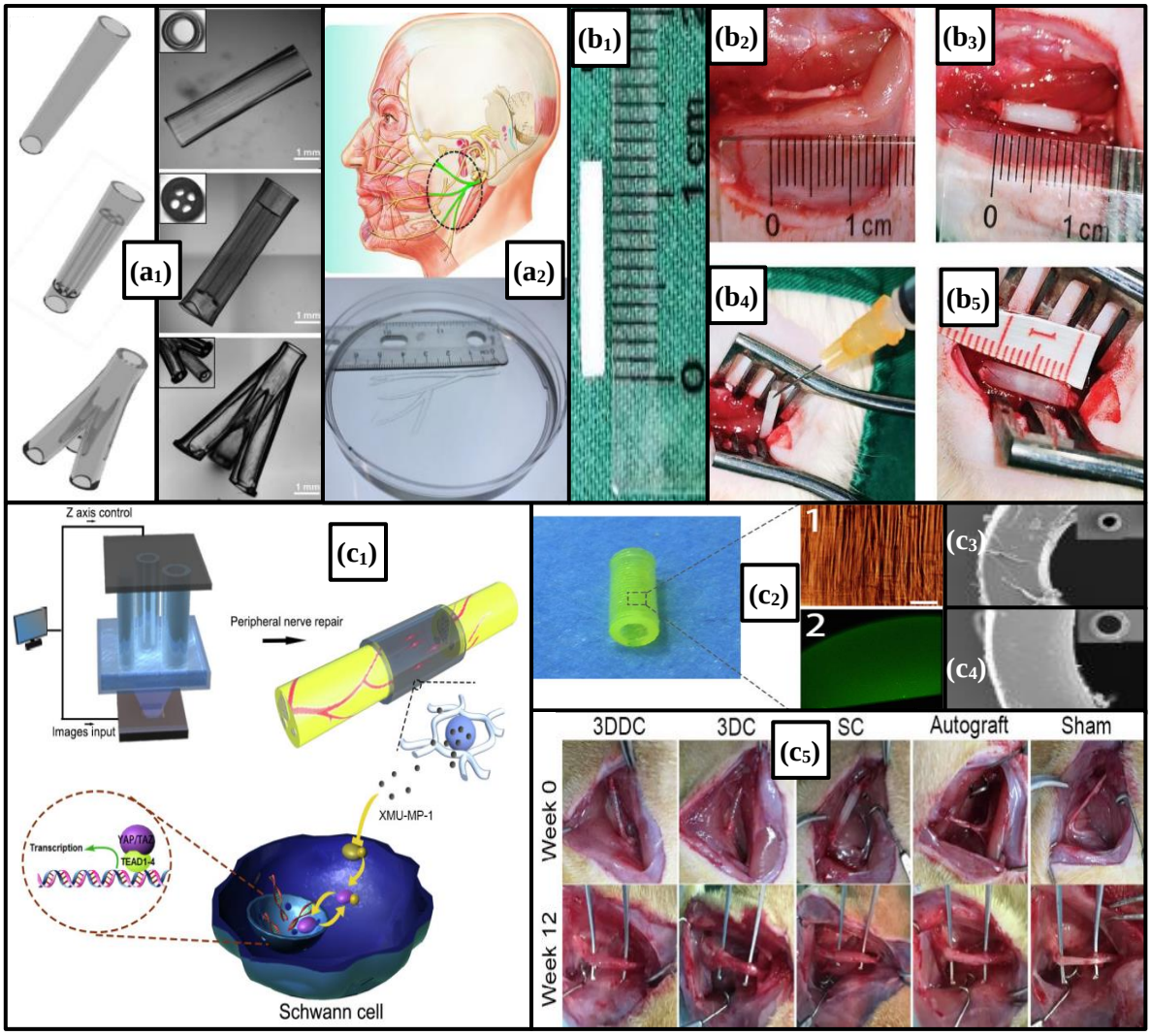


Figure 21. (a_1) Figure depicting different CAD designs and their corresponding 3D-printed NGCs; (a_2) Schematic illustration of human facial nerve and 3D-printed NGCs (adapted with permission from ref. [373], copyright, 2018, Elsevier); (b_1) PCL-based NGC with 2mm diameter and 12 mm length; (b_2-b_5) Surgical implantation procedures of repairing of a nerve defect though autografts (adapted with permission from ref. [374], copyright, 2022, John Wiley and Sons); (c_1) A schematic figure showing 3DP of NP-enhanced NGCs. The NPs in conduits released inhibitor to promote peripheral nerve repair by targeting Hippo pathway; (c_2) Figure showing microstructure and NPs distribution of the conduit; (c_3-c_4) SEM photographs of 3D-printed conduits with different size; (c_5) In-vivo analysis of regenerated sciatic nerve without or with conduits (adapted with permission from ref. [375] copyright, 2019, Elsevier).

PLA- and PLA-based biodegradable polymeric conduits exhibit great potential for neural tissue regeneration applications [376]. For instance, Tao et al. [375] fabricated PEG/PCL/GelMA-based nerve guiding scaffolds by using the 3DP technique, as illustrated in Figure 21(c). The findings suggested that NGC provided excellent drug-releasing performance and facilitated peripheral nerve regeneration through the Hippo pathway. Some studies have illustrated the efficiency of matrix-filled NGCs for nerve regeneration compared to hollow NGCs. For instance, Singh et al. [377] fabricated PCL-based aligned cryomatrix-filled biomimetic nerve conduits through a 3DP technique, and in-vivo results revealed that this conduit helped in successful nerve regeneration. Similarly, Yao et al. [374] developed PCL-based guidance conduits filled with Mg^{+2}-releasing hydrogel bioactive scaffold for peripheral nerve

regeneration. The results indicated that Mg^{+2} improved neurite outgrowth after 12 weeks of successful implantation in rats with nerve defects, as presented in Figure 21(b). Thus, 3D-engineered PCL conduit with Mg^{+2}-releasing hydrogel stimulates peripheral nerve regeneration applications.

4.5 Skin tissue engineering

Skin, the largest body organ which regulates moisture and body temperature, prevents the loss of body fluid and facilitates a barrier against thermotaxis and pathogenic bacterium [378]. The loss of skin tissues occurs due to chronic wounds, burns, lesions, and diabetic ulcers [379]. Furthermore, wound sites become highly susceptible to microbial infections arising from mucous membranes, surrounding skin, or exogenous sources [380]. Micro-organisms introduced attack deeper and surrounding tissues, thus, developing severe infections, which delay wound healing [381]. Skin grafting is limited due to the shortage of artificial dermal tissues and antigenicity, which has boosted the demand to develop scaffolds for skin regeneration [382]. The thickness of human skin ranges from 1 to 4 mm and exhibits elastomer-like characteristics. Therefore, skin scaffolds must possess excellent durability and high elasticity to permit suturing [383]. Additionally, wall thickness and porosity are other important factors, which must be considered for the development of scaffolds. By keeping in view, the normal healing time of incision, skin scaffolds must possess the ability to degrade within 25 days [384].

Different synthetic polymers including PVA, PLA, PCL, PEG, PLGA, PU, and PMMA are applied to develop wound dressing and scaffolds for skin TE applications [385]. However, PLA-based skin scaffolds exhibit hydrophobicity, low cell adhesion, growth, and proliferation [386]. Recently, a plethora of researchers have developed PCL-based scaffolds for dermal tissue regeneration applications, due to their excellent elastic properties, biocompatibility, and cytotoxicity. For instance, Afghah et al. [387] applied a melt-plotting approach to fabricate PCL/poly(1,3-propylene succinate) (PPSu)-based skin scaffolds by incorporating anti-microbial silver NPs. The findings suggested that PCL/PPSu/Ag-based scaffolds are propitious bioactive materials for skin regeneration applications.

The incorporation of Zn, Cu, and Ag into PCL-based wound dressing improves the anti-microbial characteristics. For instance, Muwaffak et al. [388] employed 3D scanning to fabricate 3D models of ear and nose for individual patients. In the study, the hot-melt extrusion 3DP technique was utilized to extrude pellets attained from vacuum dried PCL-based biopolymers along with various metals for manufacturing the metal-homogeneously loaded filaments, as demonstrated in Figure 22(a). The results confirmed that Cu-PCL and Ag-PCL dressings exhibited promising bactericidal characteristics against Staphylococcus aureus bacterium that generally causes skin infections and can be potentially applied for wound healing applications.

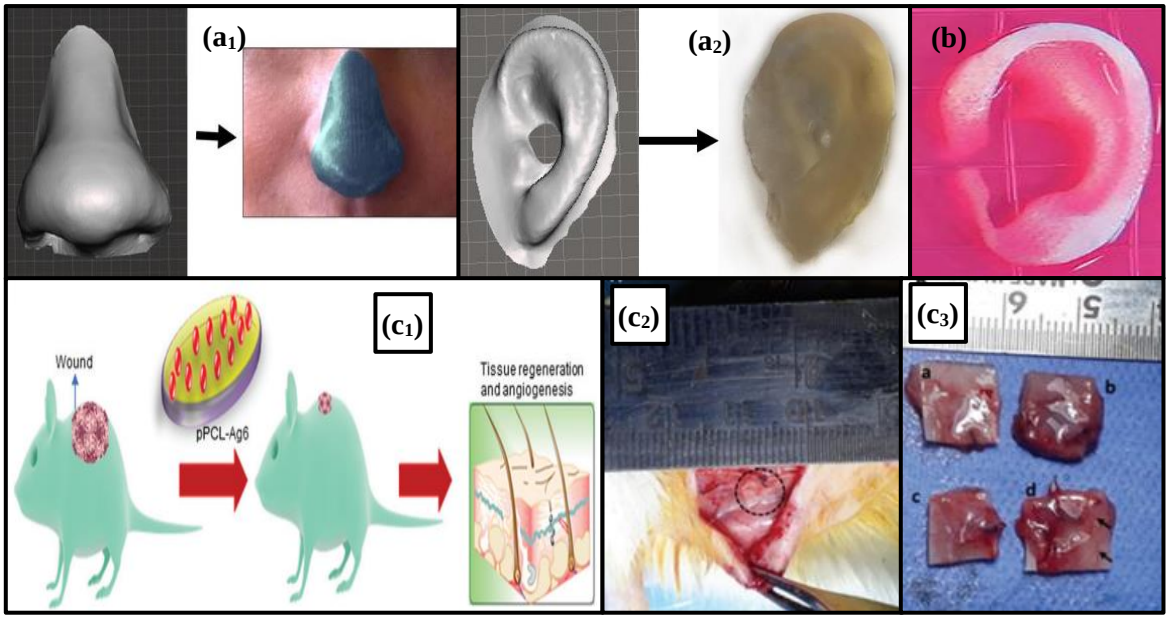


Figure 22. (a_1) 3D scan nose model and Cu/PCL-based 3D-printed wound dressing model; (a_2) 3D scan ear model and Ag/PCL-based 3D-printed wound dressing model (adapted with permission from ref. [388], copyright, 2017, Elsevier); (b) 3D-printed ear by Cellink company (adapted with permission from ref. [389]); (c_1) Schematic diagram depicting the in-vivo performance of PCL/Ag-based dermal scaffold; (c_2) 3D-printed scaffold embedded into native tissues; (c_3) Native tissues integrated with PCL-based scaffolds containing varying content of silver. Angiogenesis is evident in PCL/Ag (c, d) tissues (adapted with permission from ref.[390], copyright, 2021, The Royal Society of Chemistry).

In another study, Ninan et al. [390] proposed a plasma nano-engineering approach to develop PCL-based scaffolds by incorporating Ag NPs, as illustrated in Figure 22(c). The findings suggested that PCL-based dermal scaffolds exhibited excellent antibacterial, biocompatible, and mechanical properties, due to the immobilization of Ag-based NPs. To recapitulate this, PCL-based 3D-printed dermal scaffolds exhibit excellent wound healing and skin regeneration applications.

4.6 Other tissue engineering applications

Besides bone, cardiac, vascular, neural, skin, and cartilage tissue engineering applications, PCL- and PLA-based biopolymeric composites have also found their applications in various other soft (urethra and breast) and hard (jaw, dental, and musculoskeletal) tissue repairing applications [391]. For instance, Xu et al. [392] fabricated PCL/PLGA/triethyl citrate (TEC)-based urethra scaffolds developed through 3DP, as shown in Figure 23(a). The in-viva results of scaffolds exhibited excellent biocompatibility, porosity, and interconnection for transportation and infiltration of nutrients. Similarly, Hu et al. [393] prepared PCL/PVA/soybean peptide-based degradable patch with an antiadhesive layer for hernia repair through 3DP and electrospinning techniques, as depicted in Figure 23(b). The developed patch has adequate mechanical properties as compared to the commercial polypropylene (PP) patches. In-vivo and in-vitro studies indicated that these prepared patches showed excellent biocompatibility and good adhesion with HUVECs. The surgical implantation of prepared patches was performed on defective rat model, as presented in Figure 23(b_6). These 3D-printed regenerative biological patch have huge scope in hernia repair through the development of novel biomimetic biodegradable patches.

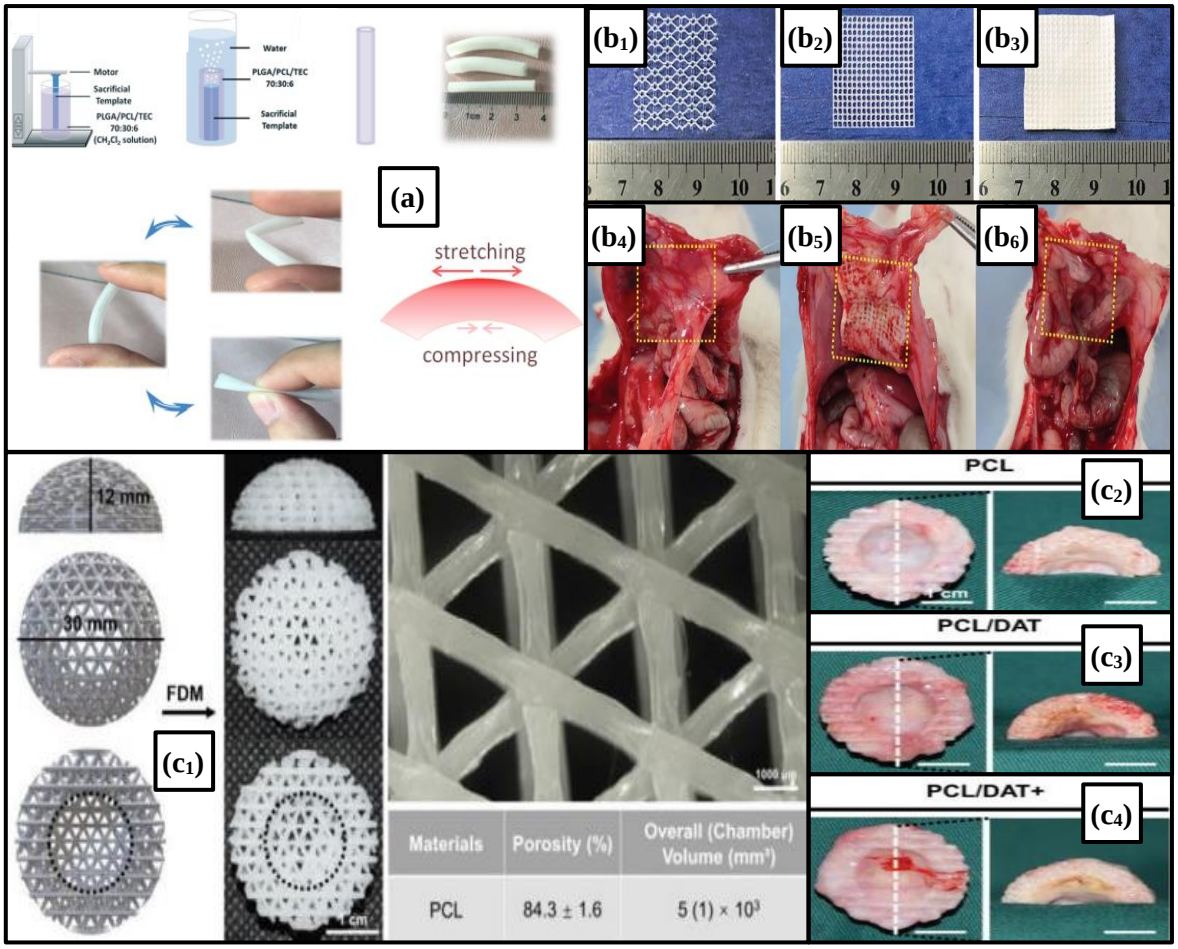


Figure 23. (a) 3D-printed PCL/PLGA/TEC-based urethra scaffolds for urethra tissue repair and showing bending and compressing deformations (adapted with permission from ref. [392], copyright, 2020, American Chemical Society); (b) Macrograph of various patches; (b_1) PP-based patch; (b_2) PCL-based patch; (b_3) Composite patch. Photographs of wound healing 4 weeks after patch implantation; (b_4) PCL-based patch group; (b_5) PCL/PVA-based patch group; (b_6) Composite patch group (adapted with permission from ref. [393], copyright, 2022, John Wiley and Sons); (c_1) Optical and SEM Images characterizing PCL chambers; (c_2-c_4) Optical images of explanted specimens, dotted lines representing the sectioned. (c_2) PCL; (c_3) PCL/DAT; (c_4) PCL/DAT+ (adapted with permission from ref. [394], copyright, 2022, Elsevier).

Zhang et al. [394] studied the TE chamber technique for constructing soft tissues using PCL/decellularized adipose tissues (DAT). PCL miniaturized porous chamber was constructed through estimating the scaling differences between human and rabbit chests. Further studies under different weeks of implantation are depicted in Figure 23(c). Thus, the newly constructed tissue had remarkably high expressions of adipogenic genes, in comparison to the endogenous adipose tissue and potential application in clinically breast TE applications.

The musculoskeletal system imparts the body with support, shape, movement, and stability. It plays a pivotal role in the homeostatic and biomechanical functions of the human body [395]. Musculoskeletal tissue injuries are common and require scaffolding strategies to regenerate and repair tissues. Nowadays, PLA- and PCL-based biomaterials are extensively applied to regenerate musculoskeletal tissues [396]. For instance, Leonov et al. [397] developed an anthropomorphic phantom from real patient data obtained by CT and MRI scans through FDM and liquid crystal display (LCD)-based 3DP, as illustrated in Figure 24(a). Different parts such as brain tissue, temporal acoustic windows, and acoustically opaque parts of the skull were

stimulated using different materials including PLA, photopolymer resin, PVC plastisol, and zinc oxide. In another study, Jeong et al. [398] evaluated the efficacy of 3D-printed PCL/β-TCP scaffolds in the treatment of complex zygomaticomaxillary defects for different patients. Different patients performed maxillary reconstruction surgery using PCL/β-TCP-based 3D-printed scaffold through various reconstructive procedures such as bone grafting, fat graft, and fasciocutaneous free flaps. Post-treatment results after a specific period are presented in Figure 24(b_5) and revealed that PCL/β-TCP-based scaffolds offered strong support and improved bone formation in complex zygomaticomaxillary defects.

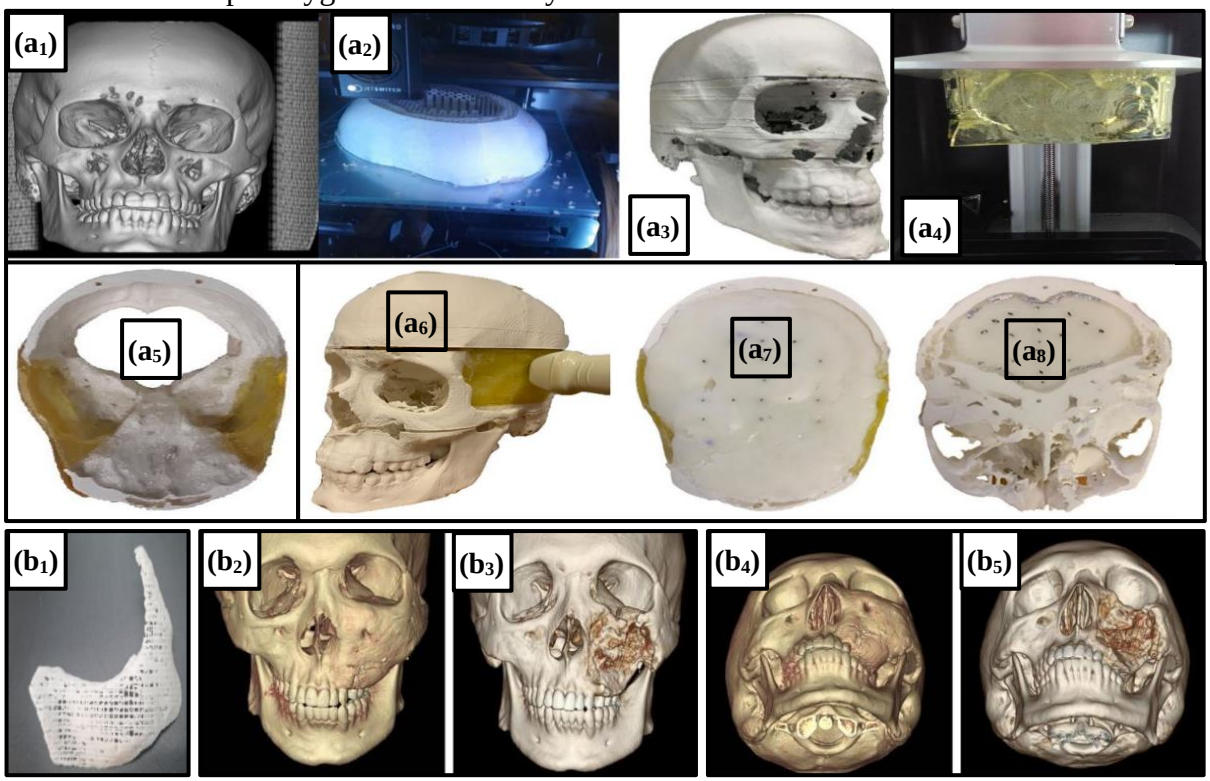


Figure 24. (a_1) Bone segmentation during CT scan; (a_2) FDM-based3DP of the phantom; (a_3) Final assembled skull model; (a_4) Temporal bone model from LCD printing; (a_5) Central part of the phantom printed having fixed acoustic windows; (a_6) Photo of phantom during ultrasonic probe placed onto the acoustic window; (a_7) Image of its central section taken from above; (a_8) Image of the central section from below (adapted with permission from ref. [397], copyright, 2022, Springer Nature); (b_1) Image of 3D-printed PCL/β-TCP scaffolds of 500 µm pore size and 50% of porosity; (b_2-b_5) 3D CT images of same patient during pre- and post-operative 6-month; (b_2, b_3) Frontal views; (b_4, b_5) Basal views (adapted with permission from ref. [398]).

Hydrogels are not suitable candidates repairing for musculoskeletal tissues [399]. To solve this issue, Heo et al. [400] developed a 3D-printed model and simulated the stiffness of the mandibular condyle, as illustrated in Figure 25(a). The results of the in-vivo study revealed that biodegradable PLA-based thermoplastic with photocurable hydrogels acted as the enveloped matrix for cyclic RGD-conjugated bioactive gold nanoparticles (RGNPs) and the addition of RGNPs resulted in the improvement of the cell proliferation and cellular adhesion, which enhanced gene-expression osteogenic specific growth factors. Thus, hydrogels with composite reinforcement can be applied for controlling stem cell differentiation and TE applications.
In another study, Ilhan et al. [401] developed synthetic patches through 3DP for repairing the perforations in the tympanic membrane, as illustrated in Figure 25(b). The authors used PLA scaffolds and incorporated sodium alginate (SA) and CS in varying weight fractions to print

eardrum patches. The results indicated that SA/PLA and CS/PLA scaffolds were successfully fabricated through 3DP technology. Furthermore, the mechanical characteristics of pure PLA-based scaffolds were maximum and the incorporation of SA and CS lowered their mechanical strength. However, PLA/CS-based scaffolds exhibited excellent biocompatibility and cytotoxicity after 1 week of incubation. Additionally, these scaffolds also enhanced the permeability and cellular adhesion of MSCs. Thus, PLA/CS-based composites can be utilized for the bioprinting of artificial patches, which proves helpful to treat eardrum injuries/perforations.

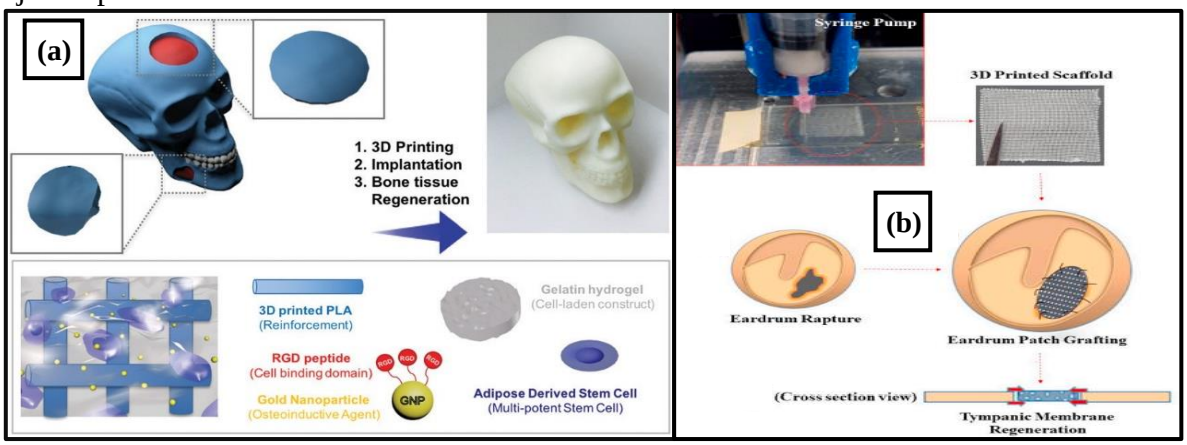


Figure 25. (a) 3D-printed PLA-based thermoplastic with photocurable hybrid hydrogels contained GNPs and adipose stem cells to be employed in patient-specific bone tissue regeneration (adapted with permission from ref. [400], copyright, 2017, The Royal Society of Chemistry); (b) A schematic diagram depicting different steps involved in the 3DP of PLA-based scaffold for eardrum injury (adapted with permission from ref. [401], copyright, 2017, Elsevier).

Table 3 provides the summary of different 3D-printed PLA/PCL biodegradable polymer composites employed in different TE applications.

Table 3. A summary of PLA/PCL biodegradable polymers and polymer composites manufactured through 3DP technology for biomedical applications

Biofabrication technique	**Material composition**	**Biological assessments**	**Features / characteristics**	**Biomedical applications**	**Ref.**
FFF	PCL/PLGA	Monitoring the degradation behavior through pH	Degradation rate of PLGA was faster than PCL.	BTE	[402]
Electrospinning and extrusion-based 3DP	PCL/PLA SA/PVA/HACC	In-vitro cell culture study Antibacterial study	SA/PVA/HACC layer provided a porous structural template and kept a moist wound environment. Furthermore, these scaffolds exhibited excellent water absorption ability as well as inhibited the bacterial growth.	Skin wound repairing	[403]
Extrusion-based 3DP	PLA/PDA-RGO	In-vitro cytotoxicity assay In-vitro cellular behavior In-vivo biocompatibility	The fabricated scaffold demonstrated excellent antioxidant, pro-angiogenic and osteoinductive properties.	Bone tissue regeneration	[404]

FFF	PLA/nHAp/β-CD/ chlorhexidine clathrate	Cell proliferation assessment, Cell osteogenic differentiation assay	The 3D-printed scaffold showed good biocompatibility and promoted cell (MC3T3-E1) proliferation and osteogenic differentiation by enhancing cell viability, ALP activity, and the mineralization content.	Repairing of regenerative jaw defects	[405]
Extrusion-based 3DP	PLA/PCL	HUVEC viability	The results of cross-sectional HUVEC culture demonstrated that the scaffolds were biocompatible and improved the permeability, adhesion and migration of HUVECs.	Vascular repairing	[406]
Electrospinning	Collagen/PLA	Isolation and culture of BMSC Cell viability and proliferation	The greater diffusion of BMSC along Col-modified electrospun fibers produced better biocompatibility of the scaffolds.	Nerve regeneration applications	[407]
FFF	PLA and iron reinforced PLA	VMAT	Film dosimetry results revealed that 2D gamma passing rates for lung and spine SABR were over 98% and 90%, respectively.	Bone and lung tissue engineering applications	[408]
-	rhCol/PLA	Histopathological evaluation and tissue structure	rhCol/PLA-based scaffold has demonstrated weight-adaptive properties, which offered better the regenerating tissue performance compared to other biomaterial scaffolds.	Repairing of articular cartilage	[409]
Electrospinning and extrusion-based 3DP	Pamidronate loaded layered double hydroxides/PCL	In-vitro cellular response ALP activity	3D scaffolds showed improved cell adhesion and ALP activity.	BTE	[410]
Extrusion-based 3DP	$CaCO_3$/PCL	Cell culture and cell viability assay In-vitro osteogenic differentiation	mRNA sequencing indicated that cell proliferation was inhibited and cell death was induced due to the reactive oxygen species.	Tissue regeneration	[411]
Electrospinning and FDM	PLA/PLGA	Biomechanical and histological assays	The histological analysis showed good biocompatibility of the PLA bars with animal tissues.	Pectus excavatum treatment in humans	[412]
Extrusion-based 3DP	PCL/PPy	Cell seeding, Cellular proliferation and viability assay Gene expression analysis by RT-PCR and ELISA	3D-printed PCL/PPy conductive scaffold helped in the differentiation of Olfactory ecto-MSCs into SCs-like phenotypes to promote neurite outgrowth.	Neural tissue engineering applications	[413]
Electrospinning	PGS/PLA	Blood compatibility assays Cell compatibility assays	The mechanical properties of PGS/PLA scaffolds were almost similar to the natural vessels.	Vascular tissue regeneration applications	[414]
FDM	PLA/HAp	RNA isolation and RT-PCR MSC differentiation on scaffolds In-vitro degradation	PLA/HAp scaffolds effectively induced osteogenic differentiation of hMSCs.	BTE	[415]

Electrospinning	PCL/Gel	In vitro cell morphology and proliferation Cell viability	During in vitro study, using L929 mouse fibroblasts, it was found that multilayered scaffold showed cell infiltration and proliferation from the innermost to the outermost and effective for vascular wall regeneration.	Vascular regeneration	[416]
Electrospinning	PCL/fibroin	In vitro cell study	In vitro study showed that addition of low-molecular weight fibroin with KUSA/A1 mesenchymal cells improved the formation of mineralized deposits.	Bone healing and regeneration application	[417]
FDM	PCL/HA/Col	In vitro cell study, Metabolic activity	HUF cells on PCL scaffold were demonstrated remarkable cell viability.	Treatment of stress urinary incontinence	[418]
Electrospinning	PCL/Gel/PGS,	In vitro cell study,	The rat C6 glioma cells exhibited excellent attachment and proliferation on scaffolds.	Nerve TE applications	[419]
Electrospinning/air-blowing	PCL/Col nanofibers	-	PCL/Col-based nanofibers scaffolds exhibited highly porous structure and novel micro/ nanofibrous architecture.	Regeneration of tissue defects	[420]
Electrospinning	PCL/CS/PEO	Cytotoxicity assays, Cell attachment and morphology,	Cytotoxicity and bioactivity studies on human dermal fibroblast cells have shown the cytocompatibility of the PCL/CS/PEO scaffolds.	Skin tissue regeneration	[421]
Electrospinning	PCL/Alg	In-vitro cell culture	PCL/Alg scaffolds support the adhesion and proliferation of hMSCs and also improved their chondrogenic differentiation.	Cartilage tissue engineering	[422]
Extrusion-based 3DP	Calcium silicate/PCL	Cell culture, attachment and morphology Cell viability assay ALP activity assay	PCL-impregnated scaffolds improved proliferation and osteogenic differentiation of BMSCs.	Tissue regeneration	[423]
Electrospinning	PCL	Cell culture, Cell seeding of PCL culture plates	Human ECs and MSCs perfectly adhered to PCL fibers uncoated surfaces for the generation of tissue-engineered heart valves	TE of heart valves	[424]
Electrospinning	PLA/Gel/SiO_2	In vivo evaluation of scaffolds	PLA/Gel/SiO_2 aerogel scaffolds demonstrated high cell survival rate and promoted osteogenic differentiation of BMSCs.	BTE	[425]
Extrusion-based 3DP	PLA/CS PLA/SA	In-vitro cytotoxicity Cell attachment investigation	MSCs exhibited appropriate cell adhesion, proliferation and spreading on all prepared scaffolds.	Eardrum perforation repair	[401]
Electrospinning	PCL/PLA/Zeolite	Cell culture Cell adhesion assay	The viability of human DPSCs on the PCL/PLA/Zeolite scaffolds improved significantly.	Dental tissue regeneration	[426]

5 Current challenges and future opportunities/perspectives

Recent advancements in PCL- and PLA-based scaffolds fabricated through novel 3DP techniques and their combinational approaches have ushered in new avenues of treatment of hard and soft traumatized tissues. However, different challenges exist during the fabrication of PCL- and PLA-based scaffolds manufactured through traditional routes. These challenges include incomplete removal of residual material especially porogen from the biopolymers, long fabrication time, and the use of hazardous organic solvents. The recent developments in 3DP technologies and biopolymer-based composites depict that these composites could be employed to develop composite scaffolds. Biodegradable PLA- and PCL-based polymers have been additively manufactured through many technologies, however, there are still many challenges that exist in terms of the viability of PCL- and PLA-based biopolymers in 3DP technologies. For instance, the utilization of the SLA technology for developing scaffolds is limited owing to its curing influence.

Similarly, PCL- and PCL-based synthetic polymers porous TE scaffolds are manufactured through SLS technology by placing the polymers in a powder bed system. Different challenges including powder processing approaches, appropriate material systems, and part characteristics are needed to be addressed before the utilization of this technology. Additionally, it is not viable to place the mixture of PCL/PLA and other biopolymeric materials in the powder bed system, therefore, the researchers should consider employing a uniform and homogeneous bed of these biomaterials.

Similarly, the combination of 3DP and electrospinning techniques to fabricate hierarchical PCL- and PLA-based highly porous and multifunctional tissue scaffolds. These cutting-edge combinational approaches are guiding biomedical engineers towards developing diverse and high-performance scaffolds by using PCL- and PLA-based biomaterials.

Emerging 3DP technology has significantly changed the production of complex and customized shapes, and tailored structures. Developing BTE owes advances in the 3DP technology. The challenges of BTE can be divided into two classes: geometrical and material challenges. Mimicking precisely the hierarchical structures of natural bone is one of the most important challenges that the 3DP technology has tried to solve. However, limitations in 3DP resolution cause mimicking bone structure to be a challenge. Moreover, printing of these tissues is associated with many challenges due to the radial gradient nature of cortical bone and cancellous bone. In addition to geometrical challenges, biomaterials challenges play a key role in BTE. However, the development of modern 3DP technologies including μCP and phase change printing can be helpful in the fabrication of hierarchal structured scaffolds and tissue regenerative systems. μCP technology is similar to image transfer ink or regular stamp which develops patterns on the substrate surface through an inked polymeric material with sub-micrometric resolution. These array patterns of biopolymers developed on the substrate have ensured controllable immobilization of biological cells as well as cellular adhesion.

Pure PCL and PLA in BTE cannot provide a suitable biological condition. Therefore, the modification of PLA and PCL through the incorporation of additives, hydrogels, and other biopolymers will enhance the biological and mechanical properties of these biomaterials in BTE. Some researchers use surface modification, and others use blending methods to incorporate the new materials into PCL and PLA biomaterials. The additive materials can be bioceramics or biopolymers, or these materials can be mixed to obtain an optimized biomaterial with acceptable properties in different aspects, including mechanical and cell adhesion, antibacterial feature, degradation rate, and promoting cell proliferation.

In addition to BTE, several vital organs perform key activities in the human body including, skin, cartilage, vessels, and cardiac, which their repairing and reconstruction with PCL- and PLA-based scaffolds also require insightful exploration, and the incorporation of other

biopolymers or additives must be investigated to improve cell growth, adhesion, and proliferation. In order to use these biodegradable scaffolds in actual clinical practices, safety evaluations of these biomaterials by using in-vivo trials are needed. Furthermore, there is a need to repair/cure large gap PNI through neural tissue scaffolds. The different combinations of PCL and PLA with different biomaterials along with design approaches to develop high-performance, multi-channel, and nano-structured NGCs.

To overcome some limitations in the 3DP technology, including their constant shape over time, and not responding to environmental stimuli, the 4D printing technology can be used. 4D printing technology uses specific stimuli like pH, light, temperature, electric field, and magnetic field to transform the shape of 3D-printed objects in a controlled fashion. It is the propitious approach to develop highly intricate and dynamic tissue structures of micro-/macro-scaled size. In the near future, 4D printing will be another research spotlight, which could allow the integration of physical or chemical-responsive materials into PLA or PCL matrices to develop dynamic tissue constructs.

6 Concluding remarks

3D-printed PLA- and PCL-based biodegradable polymers are extensively investigated as potential biomimetic scaffolds for TE and regenerative medicine, particularly for ruptures occurring in the bone, cartilage, skin, nerve, heart, tendon, dental, and blood vessels. These composite scaffolds are highly suitable for TE applications due to their ease of processing, sustainable nature, thermal stability, viscoelastic, and rheological properties. Printed scaffolds not only eliminate the stress concentration phenomenon but also reduces the inflammation which is usually observed in titanium, SS, and Co-Cr alloys. The reinforcement of PCL- and PLA-based biopolymer through bioceramics and BGs can also help to fabricate composite scaffolds that promote the formation of tissues for regenerative medicines.

It is envisaged that further advancements in the PCL- and PLA-based polymer composites manufactured through 3DP techniques and the evolution of 4D printing will eventually replace the utilization of metallic medical implants with these biodegradable polymers and will open new avenues to develop next-generation tissue constructs, which will further revolutionize the biomedical sector.

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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