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# Mechanical and Biological Behaviour of 3D Printed PCL-Based Scaffolds Fabricated by Fused Deposition Modelling for Bone Tissue Engineering: A Review of Recent Advances

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**Abstract:** The imperative need for alternative approaches to organ transplantation, replacing or regenerating damaged tissues is the key driving force for the remarkable development in tissue engineering. It can be precious in saving people who suffer from the critical shortage of organ donation. Such a strategy can repair injured body parts and tissues by using biomaterials, cells, and bioactive agents. Even though numerous scaffold manufacturing techniques have been available for bone regeneration, the three-dimensional (3D) printing approach can provide scaffolding with delicate features that may not be obtainable in other manufacturing strategies. For instance, when a 3D printer is used, it is possible to easily adjust scaffold pore architecture and size, porosity, and material alignment, forming customizable and defect-fillable scaffolds, which helps control the mechanical behavior of cellular response. The most prominent material used in scaffolding and printing is polycaprolactone (PCL), owing to its considerable potential and capabilities. It has favorable properties for the fabrication of bone tissue engineering scaffolds, such as biocompatibility, viscoelasticity, and affordability. Nonetheless, some inherent drawbacks of this polymer that limit its use in this field are detected, including inadequate mechanical performance, cell adhesion, osteoinductive deficiency, hydrophobicity, and low degradation rate. The incorporation of other materials within this polymer to form composites, on the other hand, can contribute to alleviating the negative influence of the PCL's undesirable characteristics. Improving the mechanical and biological behaviors of PCL-based scaffolds allows these structures to be utilized for tissue engineering since such composites can promote cell adhesion and differentiation, mimic anatomical characteristics of native bone, and can have superior mechanical performance. In this review, the latest advancements in printing intricate geometries 3D PCL-based composites using bioactive ceramics and/or biopolymers by fused deposition modeling (FDM) for bone tissue engineering will be explored, particularly from a morphological, mechanical, and biological perspective.

**Keywords:** Bone Tissue Engineering, Biological, Mechanical, FDM, PCL, Scaffolds

## 1. Introduction

Tissue engineering (TE) is a multidisciplinary field that is currently receiving tremendous attention to replace or repair tissues and organs by combining cells and biomaterials [1, 2]. Now, bone transplantation is highly demanded due to the enormous incidence of bone defects, which are principally brought about by bone contagions, tumors, and trauma [3, 4]. Nonetheless, traditional bone grafts, namely, autografts, allografts, and xenografts, cannot be entirely satisfactory from a clinical point of view. For example, autografts are generally restricted by donor deficiency and site morbidity, while the other two methods are constrained by the prospective risk of immune response [5, 6]. Bone tissue engineering (BTE) is a profitable strategy for constructing bone replacements that could overcome the shortcomings mentioned above [7]. An optimal bone scaffold should offer structural support for seeded or encapsulated cells and generate a preferable environment for cell responses, osteogenesis, and eventually tissue repair [8]. On that account, the development of new bioactive materials to induce osteogenesis for BTE is highly desirable. BTE has three broad constituents: cells, bioactive molecules, and scaffold. The scaffold considerably influences nutrients and waste transport and induces cell attachment and proliferation [9, 10]. Regular strategies such as foaming [11], particle/salt leaching [12], freeze-drying [13], and

electrospinning [14, 15] have been utilized for scaffold manufacturing. One chief downside is that porous scaffolds produced by conventional approaches cannot be comprehensively adjustable in terms of the geometrical factors, including porosity and pore interconnection size. Furthermore, scaffolds with on-demand porosity for particular defects are challenging to fabricate with most of these strategies. Additive manufacturing is a versatile approach that makes it feasible to fabricate 3D structures from various materials with complex and precision engineering [16-18]. The application of 3D printed scaffolds for TE has gained substantial consideration in the last few years. 3D printing can provide a designed shape with superb 3D macroscopic and microscopic structures that are well-known to be advantageous for cell infiltration, transport of nutrients and metabolic waste, and individualised bone defect repair treatment [19-22]. Apart from that, with this approach, it is also possible to take advantage of the progress achieved in other means such as the finite element method in designing and producing scaffolding with the required specifications [23, 24].

It is alleged that the most common approaches in TE are scaffolds, which are 3D structures resembling extracellular matrix and allowing proper mechanical and biological support for the neo-tissue fabrication [25-28]. PCL is a biodegradable aliphatic synthetic polymer [29] that is mostly utilized as a 3D scaffold due to its nontoxicity, compatibility (it is an FDA-approved polyester), relatively low melting and glass transition temperatures; at normal human body temperature, the semi-crystalline PCL accomplishes a rubbery shape causing its remarkable toughness [30, 31]. PCL parts present a remarkably plastic deformation before fracturing. Figure 1 demonstrates various stages of the PCL tensile test; when necking is commenced, it will carry on to propagate along with the specimen, resulting in high strain levels [32].

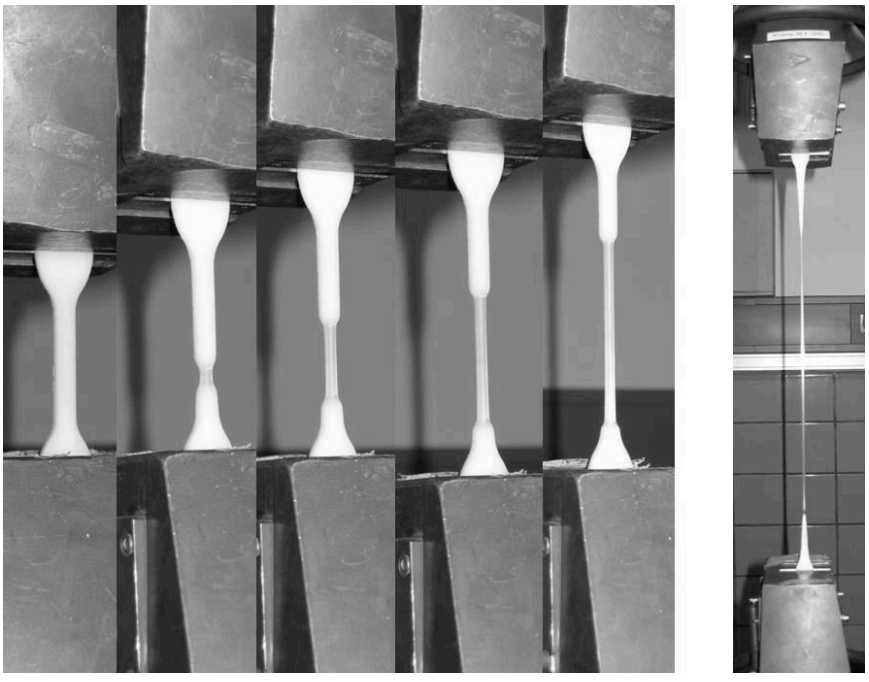

Fig. 1 PCL behavior during different stages of the tensile test [32].

The proper rheological and viscoelastic features of PCL allow the fabrication of a wide range of scaffolds using traditional and modern procedures [33-36]. Its scaffolds have been extensively examined for TE; nevertheless, they exhibit weak mechanical properties [37, 38], and their hydrophobic nature prevents cell adhesion and proliferation [38, 39]. Consequently, PCL-based composites have ameliorated the material characteristics, cellular activity, and degradation rate compared to neat PCL [40-43]. To enhance scaffold features, including mechanical and surface characteristics and biocompatibility, diverse kinds of additives have been applied to modify PCL. The advancement of composites allows fashion to

fashion, to a large degree, biomaterials with suitable mechanical and physiological behaviors and varying porosity inside complex geometries.

Additionally, adjusting the reinforcing phase's type, dimension, loading, morphology, and distribution promotes living cells' attachment, migration, proliferation, and differentiation within the scaffold [44]. To tune the mechanical property based on the required tissue (Figure 2), the fabrication method, porosity, and reinforcement can be chosen. For example, attributable to the presence of pores, porous and fibrous PCL structures are mechanically weaker than bulk PCL [45].

Furthermore, Górecka et al. found that the diameter of PCL fibres had a profound impact on microstructure and mechanical characteristics. The modulus of elasticity and strength decreased with increasing fibre diameter [46]. Besides, it was found that the 3D PCL honeycomb structure could have exceptional repeatability under compressive loads [47].

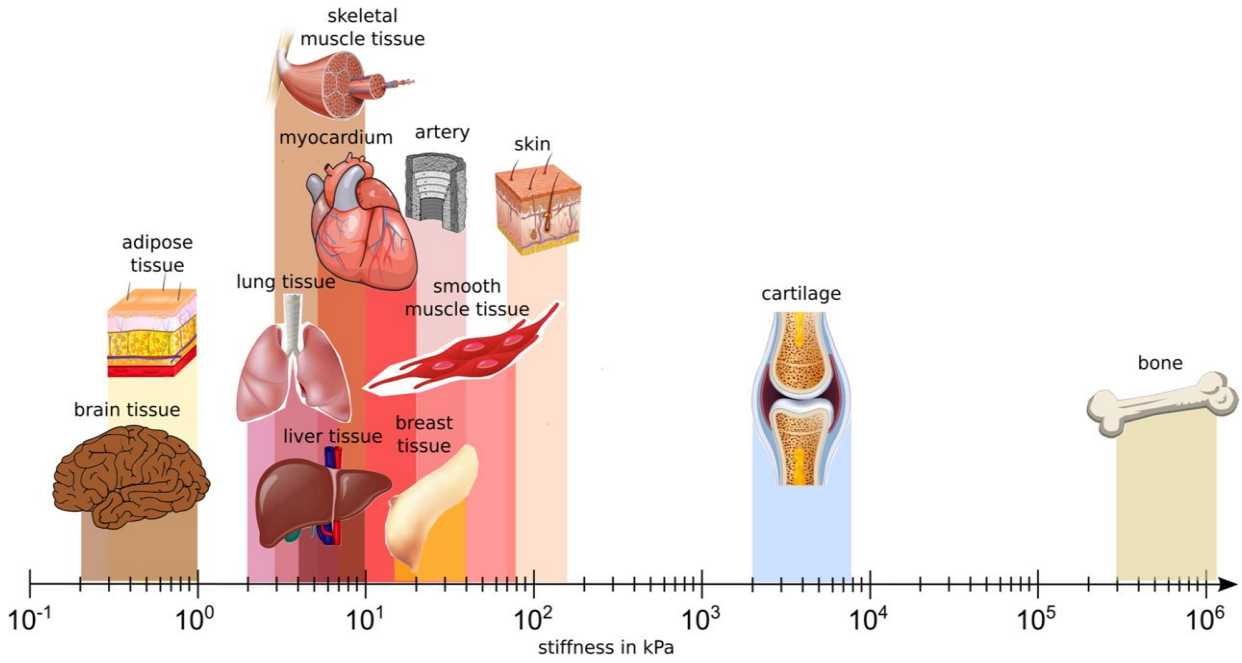


Fig. 2 Stiffness of various human tissues [48].

## 2. Fused Deposition Modelling (FDM)

Additive manufacturing or 3D printing has been extensively applied in diverse fields, including construction, biomechanical, and medicine [18, 20]. It is a computer-aided additive manufacturing procedure to produce a wider variety of complex geometry structures from 3D model data. The route comprises consecutive printing layers of materials that are made one over the other (layer by layer) [18, 49-51]. Charles Hull developed this technique in a method termed stereolithography, followed by the emergence of other types, including FDM and inkjet printing [18].

For medical and bioengineering applications, FDM has been of tremendous interest in 3D printing technology in recent years [50, 52]. Compared to other 3D printing methods, this technique is affordable, easy to use, small in size, and capable of manufacturing multifunctional parts [53, 54]. This approach is also frequently called fused filament fabrication (FFF) and has been commercially accessible for nearly three decades [55]. In this process, a thermoplastic filament is extruded from a nozzle; the nozzle contains a heater that assists in softening the filament [56, 57] (Figure 3). Such filament is then solidified and deposited due to a fan attached at the nozzle end [57, 58]. Compared with other 3D printing approaches, FDM offers the capability to use more than one type of material during the printing process (FDM printers with dual extruders) [58-60].

FDM is used to manufacture customized defect corresponding constructions for bone healing. It

provides personalized complex geometry scaffolds in various porosity and pore sizes to facilitate cell spreading and differentiation [61-64]. PCL is considered one of the predominant thermoplastics for benchtop FDM due to its low melting point at about 60  and proper fiber diameter. It sustains high crystallization and adequate mechanical behaviors after fabrication [50, 65, 66].

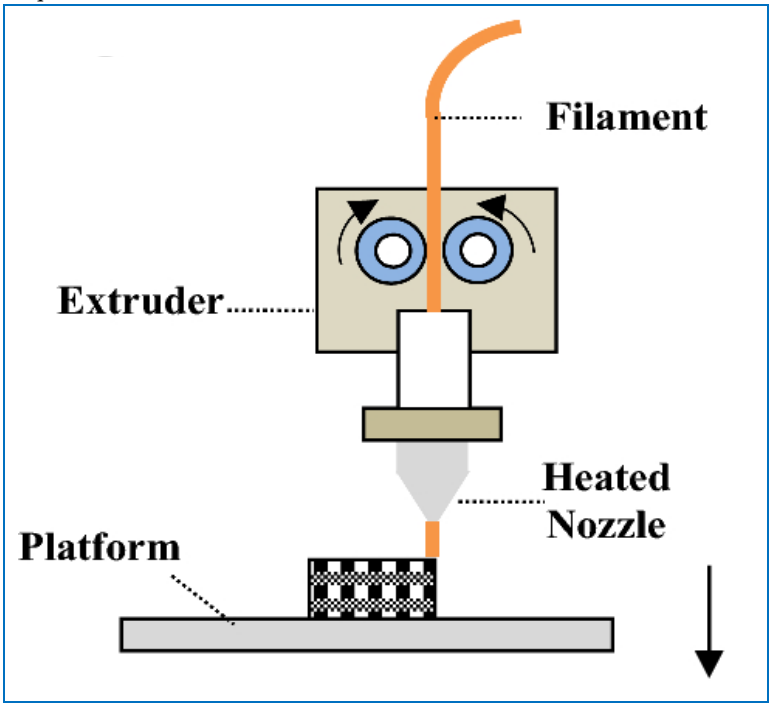


Fig. 3. Schematic of FDM [67].

## 3. 3D Printed PCL-Based Scaffolds Manufactured by FDM for BTE

Many biomaterials have been assessed as scaffolds for healing or repairing disordered bone, including metallic, bioactive ceramic, and biopolymer materials [68, 69]. PCL has potential applications for bone repair for the considerable pore volume of PCL scaffolds that affords greater bone regeneration. Owing to its low degradation rate (more than two years), PCL seems more favorable compared with the other biodegradable polymers [70]; degradation occurs typically by microbes or by hydrolysis of its ester linkage under physiological circumstances [71]. The PCL-based structures offer appropriate biomechanical aspects, can be easily printable, and is inexpensive [72-75]. The interaction between mesenchymal stem cells (MSCs) and PCL has been investigated for attaining scaffolds through 3D printing predominantly in tissue with a long regeneration period, which entails mechanically sufficient performance 3D supports [76]. In this regard, several studies have been carried out to form PCL-based composites for the engineering of bone tissue. Such composites have been fabricated by incorporating bioceramics, biopolymers, or both within PCL.

### *3.1. 3D Printed PCL-Bioceramic Composite Scaffolds*

As long as they have chemical and structural features comparable to the mineral phase of bones, bioceramics have been broadly evaluated for bone treatment [77, 78]. Nonetheless, their poor physicochemical properties [78, 79] and brittle nature impede their bone restoration applications [79, 80]. On the other hand, the problem with PCL is hydrophobicity and the lack of tendency for cell adhesion [81, 82]. From a biological standpoint, cells typically require a rigid substrate to be attached and increased [83]. Therefore, these issues can be overcome when combined with PCL bioactive ceramics. The fabricated composite could perform better than the unreinforced structure to serve as TE scaffolds [36]. Several bioactive ceramics have been utilized with PCL, including Beta-tricalcium phosphate (β-TCP) and hydroxyapatite (HA), all of which have a comparable bone mineral phase [84]. HA exhibits unique biological aspects such as osteoinductivity and biocompatibility [85, 86] due to its chemical

composition that promotes rapid and strong attachment of proteins and amino acids to its surface, resulting in efficient hard tissue regeneration [87, 88]. Filaments made of PCL/HA created scaffolds and testbeds for mimicking bone anatomy (Figure 4) [73]. 3D PCL/HA could be used to heal load-bearing disordered bone [89]. The size of HA particles was revealed to have a key role in governing the composite scaffold's overall properties; the HA particles in the nHA/PCL were consistently dispersed while agglomerated in the microsized scaffold. The tensile and flexural strength of the nHA/PCL structures were higher than those of neat PCL and micro-HA/PCL scaffolds [90]. An opposite correlation between porosity and compressive modulus was demonstrated, with compressive properties that could match human trabecular bone [91].

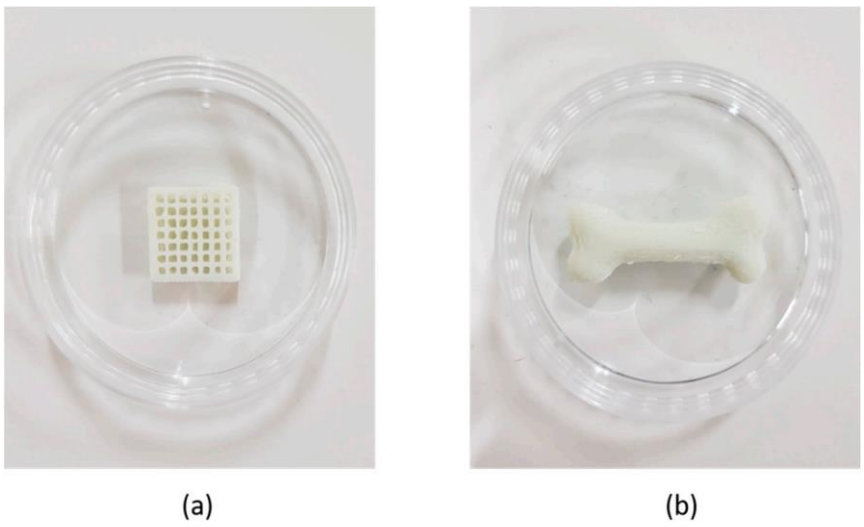


Fig. 4 (a) FDM 3D printed bone scaffolding and (b) structure of bone mimetic [73].

Strontium-containing HA (SrHA) has also the capability of bone repair or replacement as a consequence of similar inorganic constituents with native bone; therefore, it can promote osteoblast and alkaline phosphatase (ALP) activity [92, 93]. The presence of SrHA within the scaffold markedly enabled the BMSCs proliferation; these scaffolds prompted greater osteo-related gene expressions and *in vivo* cranial bone restoration compared to SrHA-free scaffolds [94]. MicroCT analysis for this type of composites revealed porosity within the levels of human cancellous bone. The SrHA-containing constructs were shown to have higher levels of mineralization and osteogenesis for hTERT-MSCs contrasted to loaded-free PCL and PCL/HA scaffolds [95].

Bioactive glasses (BG) are also used in BT applications for their marked ability to bond with bones and their stimulating impacts on neo-bone creation [96, 97]. On the other hand, they are not as applicable in load-bearing structures due to their low flexibility and strength. Nonetheless, incorporating them with polymers could raise the osteoconductivity and degradation rate of the resulting composite. The addition of BG to PCL could also compensate for its hydrophobicity and deficient cell response [98]. Incorporating BGS-7 into PCL could overcome the mechanical shortcoming of using this kind of bioglass scaffolds alone, particularly the brittleness. BGS-7/PCL displayed an enhancement in toughness compared to that of the blank bioglass scaffold with a comparable porosity. The *in vitro* biological activity of blank PCL, BGS-7, and composite scaffolds revealed that increasing the weight fraction of BG caused a significantly enhancement in the MC3T3-E1 cells proliferation and osteoconductivity, and appropriate mechanical properties [99]. The interaction of HA, BG, or both bioceramic on PCL critically facilitates cellular activity and improves osteogenic differentiation in the formed scaffolds [100].

β-TCP has also been revealed to have the ability to support osteoinductivity and osteoconductivity. Concomitantly, bone tissue scaffolds formed with β-TCP effectively healed bone in animal models [101]; thus, PCL–β-TCP composites have been commonly applied in bone reformation. The fabricated PCL–β-TCP scaffolds containing 20 wt% of β-TCP exhibited a square pore-shaped structure with 100%

interconnected pores. The offset scaffolds revealed superior mechanical and biological enhancements, including high bending modulus, osteoblast-like cell (MG63)-seeding effectiveness, and calcium deposition [102]. In another work, Bruyas et al. examined the influence of electron beam (E-beam) sterilization on PCL/β-TCP properties. They found that such irradiation was not shown to tailor the scaffold's surface characteristics, while stiffness and strength were observed to enhance.

Moreover, the modified scaffolds had faster degradation and did not influence the viability and differentiation of cells implanted on these composites [103]. β-TCP could control the degradation rate and enhance the osteogenic differentiation of C3H10 [104]. The 3D PCL/β-TCP scaffold was also fabricated (Figure 5) and modified by amine plasma-polymerization to increase the MC3T3-E1 cell activity *in vitro*. Amine plasma-polymerization led to a considerable rise in the hydrophilicity of the composite surface while it did not affect surface roughness. In addition, amine plasma-polymerization on 3D PCL/β-TCP [105] and oxygen plasma treatment on 3D PCL [106] were observed to positively influence cell proliferation and differentiation.

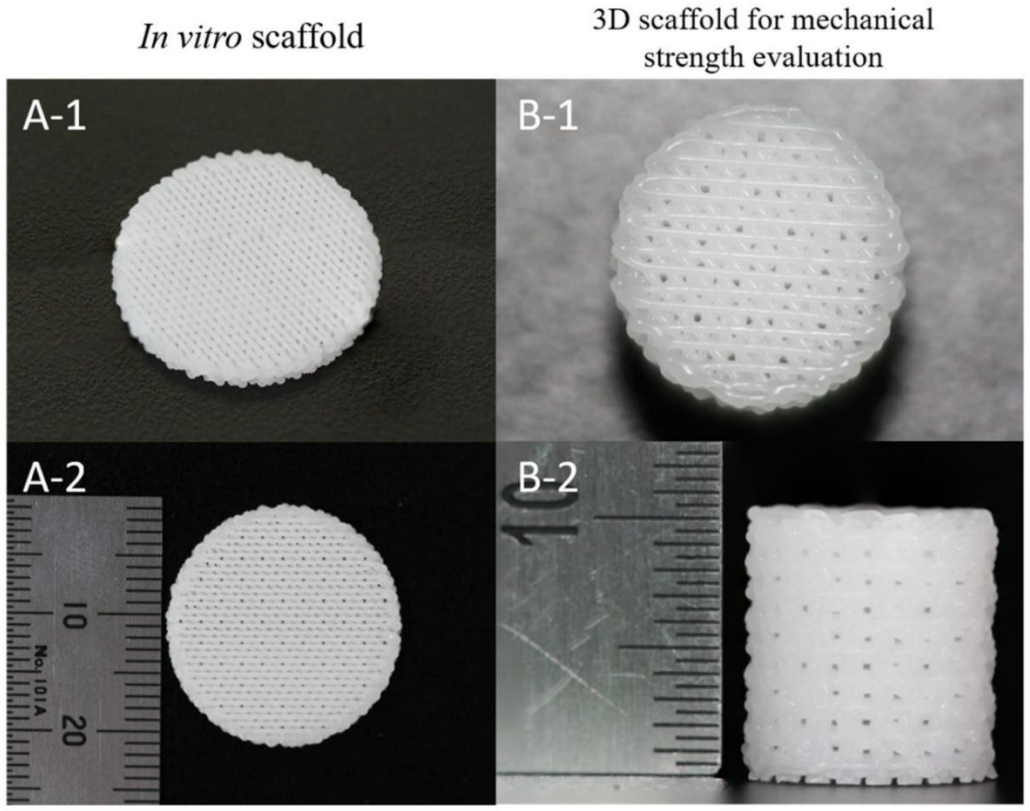


Fig. 5 (A-1) and (A-2) plane and side view photographs for 3D PCL-based scaffold, respectively for *in vitro* test; (B-1) and (B-2) plane and side view photographs for 3D PCL-based scaffold, respectively for mechanical strength assessment [105].

3D printed porous PCL scaffolds were also functionalized with broadly used clinically minerals, namely TCP, HA, Bio-Oss (BO), or decellularized bone matrix (DCB). The incorporation of such additives did not considerably reduce the compressive graft modulus. Calcium content, Collagen type1, and osteocalcin expression of adipose-derived stromal stem cells indicated that PCL-BO and PCL-DCB composite might be preferred for bone treatment over PCL-HA or PCL-TCP [107]. NaOH treatment improved hydrophilicity and roughness of FDM 3D hollow cage-shaped PCL scaffolds, which promoted hBMSCs activity. Additionally, PCL-BO presented osteogenic capacity *in vivo* (Figure 6) [108]. PCL-BO and PCL-DCB exhibited a better bone healing capacity *in vivo* than PCL-HA or PCL-TCP [107].

Biomedical uses of calcium carbonate ($CaCO_3$) have attracted special interest owing to its enormous potential and capabilities. Such material is affordable, non-toxic, osteoconductive [109, 110], and has a low degradation rate [111]. Neumann et al. incorporated $CaCO_3$ in different concentrations into highly

porous PCL scaffolds to enhance their osseointegration, mechanical behavior, and degradation rate. It was pointed out that 33% $CaCO_3$-PCL-based scaffold could have a higher *in vitro* apatite formation [112].

When 3D printed PCL/graphene scaffolds were used to remedy a rat calvaria critical-sized defect, this scaffold allowed an increment in cell migration, causing neo-tissue creation and effective bone remodeling [113]. Contrary to graphene, which enhances mechanical properties, and cell proliferation, graphene oxide demonstrates some cytotoxicity, particularly at great loading [114]. For the same purpose but with other materials, Nigoghossian et al. [115] and Zhang et al. [116] combined PCL with upconversion nanoparticles (UCNPs)-apatite and pearl powder, respectively. For both these composites, the mechanical property was revealed to improve with the increase concentration of reinforcement used.

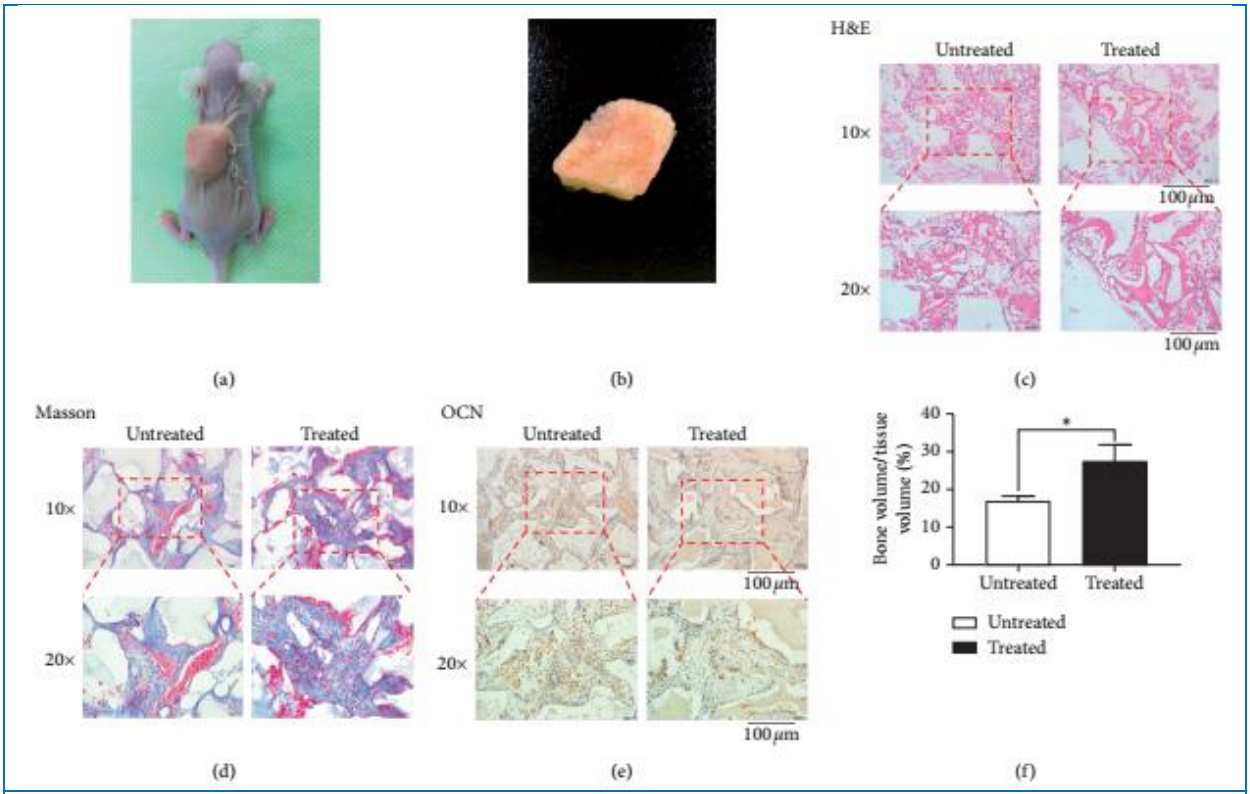


Fig. 6 NaOH treated PCL-BO composite scaffolds with hBMSCs encapsulated to promote osteogenic differentiation *in vivo*. (a) A scaffold was implanted inside a nude mouse. (b) Scaffolds were harvested after two months of culture. (c) Hematoxylin and Eosin staining of modified and unmodified scaffolds. (d) Masson's trichrome staining of modified and unmodified scaffolds. (e) Immunohistochemistry staining for osteocalcin of modified and unmodified scaffolds. (f) Semi-quantitative analysis [108].

### *3.2. 3D Printed PCL-Biopolymer Composite Scaffolds*

Biopolymers are presently utilized to create bone scaffolds due to their biocompatibility, biodegradation, and uncomplicated processability [117-120]. FDM 3D printing was used to form a composite scaffold produced from PCL with other biopolymers such as sodium alginate [121] and biodegradable continuous PGA suture yarn [122]. A considerable improvement in the tensile strength and modulus of the strengthened PCL was obtained compared to those of PGA-free scaffolds. The composite substrate degraded twenty times faster than additive-free PCL, and it did not exhibit any sign of cytotoxicity. 3D printed PCL containing PLGC copolymer scaffold encapsulated with dental pulp stem cells was shown to promote bone repairing [123]. Bombyx mori silk microparticles (SMP) were also loaded in various mass fractions into PCL. These microparticles enhanced the shear thinning, the storage modulus, and the compressive elastic modulus, and the hydrophobicity of the scaffolds. On day 21, the scaffold containing ten wt% of SMP showed noticeably high human adipose derived MSCs viability and proliferation. Calcium mineral deposits were detected to growth with SMP weight fraction [40].

Microcrystalline cellulose (MCC)/PCL [124] and bacterial cellulose (BC)/PCL [125] composite scaffolds and printed PCL platforms containing aspirin-loaded liposomes and bone-forming peptide-1 [126] were revealed to have enhanced biocompatibility and cell proliferation. Wang et al., in another work, formed PCL/osteogenic growth peptide (OGP) scaffolds by adding OGP to PCL. Such constructs had hydrophilic properties, suitable surface features, induced osteogenesis, and ability to the restorative bone in a rat cranial bone defect model [127].

Traditional electrospun scaffolds produced by electrospinning has typically nanoporous structures, which can negatively affect cell infiltration. For that reason and to address the low resolution of 3D printing techniques, PCL/gelatin nanofibers were infused into the meshes of PCL to produce a composite scaffold. It had a higher compressive modulus than that of the lyophilized electrospun scaffold. The 3D scaffolds were noticed to have proper biocompatibility, and MC3T3-E1 cells revealed higher infiltration within the composite than on the gelatin-free substrate, which could result from the microporous structure [128]. In recent work, the compressive strength and biocompatibility of PCL/gelatin/Halomonas levan (HLh) scaffolds decreased and increased, respectively, with the increasing HLh amount in PCL/gelatin composites [129].

### *3.3. 3D Printed PCL-Bioceramic-Biopolymer Composite Scaffolds*

3D printing scaffolds made of various components, namely PCL, PCL/ polyvinyl acetate (PVAc), PCL/HA, and PCL/PVAc/HA, were evaluated for bone repair. Porous channel structures were achieved in scaffolds with a pore size and porosity up to 475 mm and 76.1%, respectively. The addition of HA and PVAc had an opposite influence on scaffolds' compressive modulus. In contrast, the former led to an improvement in the modulus; the latter resulted in a decrease in it. Cell proliferation and bone formation rates were higher for the PCL/PVAc/HA than for other scaffolds [130]. A gene-activated bioink was formed by combining Arg-Gly-Asp-g-irradiated alginate and nHA complexed to plasmid DNA. BMSCs-laden ink was co-printed with PCL supporting mesh. These constructs were demonstrated to support high rates of vascularisation and mineralization instead of non-cell-containing structures [131]. Cellulose nanofibrils material (CNF) was shown to support the development of a well-organized actin cytoskeleton on the surfaces of TCP/PCL scaffolds. Besides, ALP, collagen type1, and mineral production were induced within CNF-coated surfaces [132]. Likewise, 3-poly-L-lysine (EPL) polypeptide was utilized for surface alteration of FDM printed PCL/HA scaffolds. Such composites with interconnected pores displayed rough surfaces, to some extent, and enhanced mechanical performance because of loading HA fillers. Following being modulated by EPL, favorable osteoconductivity, and antibacterial activity of EPL/PCL/HA composites were observed [64]. With nHA and continuous biodegradable PGA suture yarn, PCL-based scaffolds displayed a distinguished increase in tensile strength, modulus of elasticity, compressive strength, and cell adhesion compared to unmodified PCL [133]. Computer tomography data can be utilized to make 3D PCL porous cages using various kinds of polymer spools: PCL, PCL- PLA, and PCL/HA. Log-pile scaffolds could be permeated with a blend of cells and gelatin hydrogel to remedy complex bone defects [44]. In a study by Goncalves et al., printable carbon nanotubes (CNT)/HA/PCL composite scaffold was shown to have an interconnected network of square pores and compressive strength compatible with the trabecular bone, and proper cell adhesion [134].

## 4. Conclusions and Future Prospects

3D bioprinting has become a promising route to manufacture bioengineered scaffolds to treat patient-specific bone defects. This technique produces well-organized predefined, highly porous microarchitecture and biomimetic scaffolds that can have enhanced functionality and adequate mechanical behavior. This can be achievable by controlling various printing factors that provide an aseptic environment for bone regeneration. PCL-based scaffolds have been extensively utilized to engineer bone tissue in combination with other bioactive organic and/or inorganic compounds. Incorporating such bioactive materials into PCL can provide scaffolds that mimic the intricate construct, composition, and biomechanics of bone tissue leading to improvement in cellular response, osteoconductive and mechanical performance of PCL-based composites. For instance, PCL/HA/BG scaffold was a prospective candidate for engineering bone tissue in terms of having better mechanical and biological properties than that of unreinforced PCL.

Even though numerous studies have examined the capability of 3D printing to produce bone tissue substrates, the renewal of complex bone defects is a substantial clinical challenge. Despite being one of the utmost practiced additive manufacturing to fabricate affordable intricate 3D structures for bone repair, the layer thickness and appearance, filament dimension and orientation, void creation, and interlayer distortion can cause mechanically weak FDM 3D printed substrates. Besides, the deficiency of resolution, the inadequate surface quality of the printable inks with mass production, and the narrow range of utilized printable materials are chief challenges that arise in 3D printed composites, all of which require more work for further advancement in FDM 3D printed bone tissue scaffolds.

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