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ADVANCES IN 3D PRINTING OF POLY(E-CAPROLACTONE) (PCL)-BASED SCAFFOLDS FOR BONE TISSUE ENGINEERING: A MINI REVIEW

Idris Oladimeji Junaid[1], John Tsado. Mathew[2], Ngozi M. Uzoekwe[3], Osarhieme Tinuade Okugbo[4], Gregory E. Onaiwu[3], Nyaknno U. Udokpoh[6], Aireguamen I. Aigbodion[3], Samuel E. Ugheighele[5], Ikhazuagbe H. Ifijen*[6]

[1]Quality Assurance Department, Senior QA Specialist, Catalent, 7555 Harmans Rd, Harmans, MD 21077, USA
[2]Department of Chemistry, Ibrahim Badamasi Babangida University, Lapai, Niger State, Nigeria
[3]Department of Physical Sciences, Chemistry Unit, Benson Idahosa University, Benin City, Nigeria
[4]Department of Medical Biochemistry, Faculty of Basic Medical Sciences, College of Medical Sciences, Benson Idahosa University, Benin City, Nigeria.
[5]Department of Biological Science, Faculty of Science, Benson Idahosa University, Benin City, Nigeria
[6]Department of Research Outreach, Rubber Research Institute of Nigeria, Iyanomo, Benin, Nigeria

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***Correspondent Author:** Dr Ikhazuagbe. H. Ifijen (larylans4u@yahoo.com; ORCID: https://orcid.org/0000-0003-4165-5639, Tel: +234 703 642 6776)*

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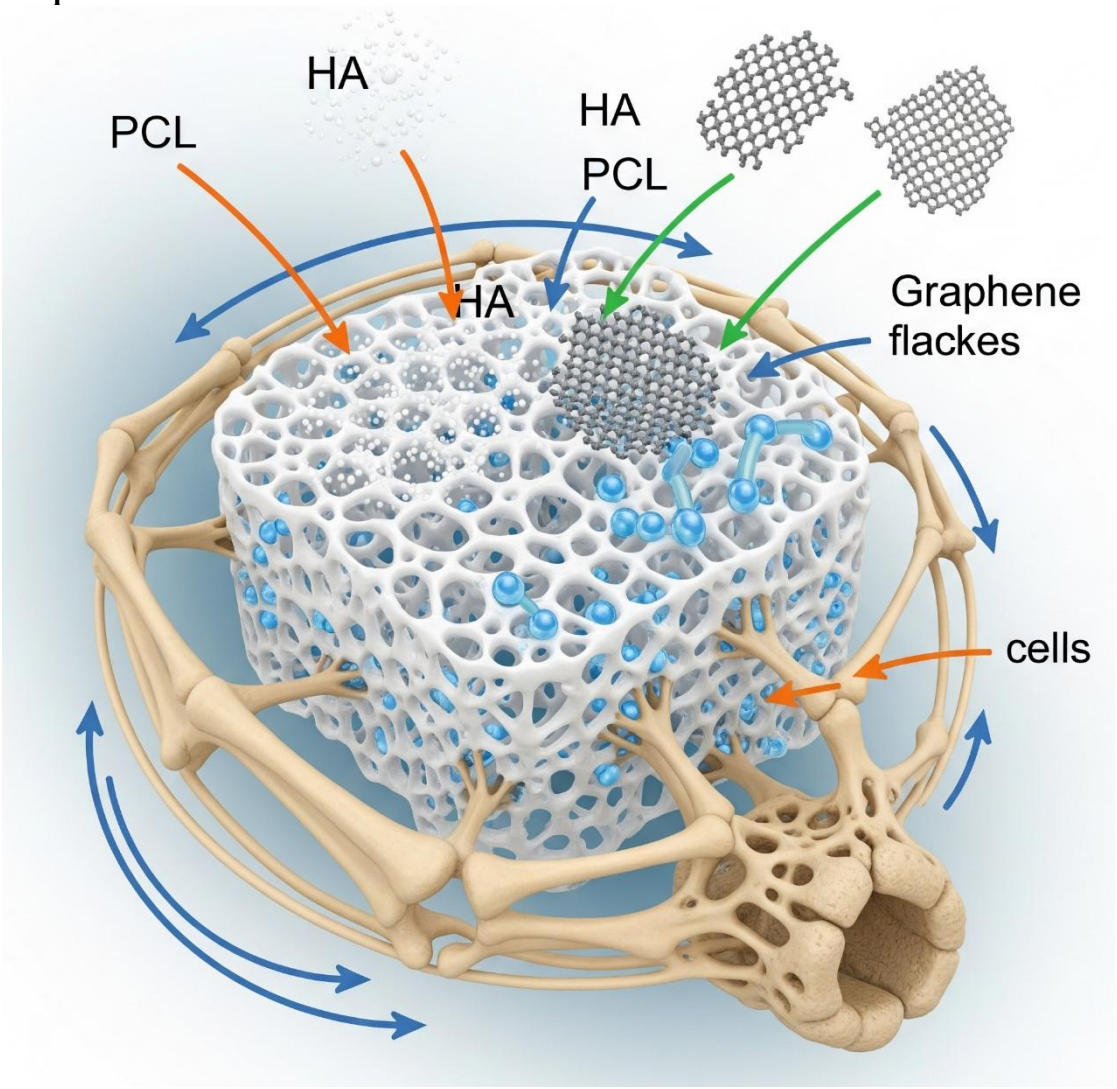
Abstract

Poly(ε-caprolactone) (PCL) is a widely used, FDA-accepted, slow-degrading polyester well suited to 3D printing via extrusion methods for bone tissue engineering. Recent years have seen rapid development of PCL-based printed scaffolds combined with osteoinductive fillers (hydroxyapatite, β-TCP, doped-HA), surface modifications (polydopamine, collagen), and multifunctional additives (graphene/GO, magnetic or plasmonic particles) to improve osteogenesis, mechanical performance and biological activity. Low-temperature and solvent-assisted workflows, hybrid printing with hydrogels, and post-print functionalization have expanded the design space and preserved bioactivity. Although promising preclinical outcomes are reported, key barriers remain matching mechanical properties to host bone, controlling degradation while enabling timely bone in-growth, achieving reliable vascularization, and navigating regulatory/scale-up challenges. Targeted strategies now focus on hierarchical porosity, composite formulations (PCL/HA, PCL/β-TCP, PCL/GO), and clinically relevant case reports that point toward near-term translational opportunities.

Keywords: *Poly(ε-caprolactone) (PCL), 3D printing, Bone tissue engineering, Scaffold fabrication, Hydroxyapatite (HA).*

Graphical Abstract



1.0 Introduction

Polymer scaffolds are fundamental components in bone tissue engineering, serving as temporary frameworks that support cell attachment, proliferation, and new tissue formation [1-3]. Their design must balance mechanical strength, biocompatibility, and degradation rate to effectively guide bone regeneration [4-6]. Among the polymers used, polycaprolactone (PCL) has gained significant attention due to its unique combination of properties. With a low melting point of approximately 60 °C, high flexibility, and a degradation period that spans several months to years, PCL can be processed easily via advanced manufacturing techniques such as fused deposition modelling (FDM) and extrusion-based 3D printing. These characteristics enable the fabrication of scaffolds suitable for both load-bearing and non-load-bearing applications in bone repair [7-8].

Compared to other biodegradable polyesters, such as poly(lactic-co-glycolic acid) (PLGA), which degrade more rapidly, PCL's slow resorption provides long-term mechanical support critical in cases where bone healing is prolonged. However, this extended degradation time can be a limitation, necessitating the incorporation of bioactive fillers or the design of composite materials to better tailor the scaffold's degradation profile to the natural pace of bone regeneration. Advances in composite scaffold development, including the integration of hydroxyapatite (HA), β-tricalcium phosphate (β-TCP), and bioactive nanoparticles, have demonstrated improvements in osteoconductivity and mechanical properties, addressing some of these challenges [9-11].

The versatility of PCL in 3D printing has further accelerated its application in bone tissue engineering, enabling the precise fabrication of patient-specific scaffolds with controlled porosity and architecture. Recent reviews have emphasized the potential of PCL-based composites to support mesenchymal stem cell adhesion, proliferation, and differentiation, fostering enhanced mineralization and extracellular matrix deposition. Despite these promising in vitro and in vivo findings, translating such technologies to clinical practice requires addressing issues related to

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scaffold degradation, biological performance, and regulatory compliance [12-14].

This study aims to explore the development and characterization of PCL-based composite scaffolds incorporating bioactive components, focusing on their structural, mechanical, and biological properties relevant to bone regeneration. By evaluating the effects of composite formulations and 3D printing parameters, we seek to optimize scaffold design to better support bone healing and facilitate future clinical translation.

2. Fabrication Methods for PLC Scaffolds

2.1 Melt extrusion / FDM

Melt extrusion, particularly fused deposition modelling (FDM), remains the predominant method for fabricating polycaprolactone (PCL) scaffolds due to PCL's relatively low melting temperature and ready availability of filaments, allowing precise control over scaffold macro-architecture such as strut size, pore geometry, and infill patterns, along with excellent reproducibility [7, 11]. Yazdanpanah *et al.* (2023) demonstrated this by fabricating PCL scaffolds reinforced with 30% nano-hydroxyapatite (nHAp) designed to mimic trabecular bone, with porosities varied systematically and internal structures arranged as either lattice or staggered (interlayer offset) configurations [7]. Their mechanical testing revealed that pore architecture and porosity critically influence scaffold mechanical properties: lattice structures displayed higher elastic modulus at porosities above 55%, while staggered structures performed better below this threshold. Importantly, all scaffolds exhibited mechanical parameters within ranges comparable to natural trabecular bone illustrating how fine-tuning pore design and internal offsets can optimize scaffold stiffness and strength to better match native bone tissue.

Complementing this, Wang *et al.* (2025) employed FDM to fabricate PCL/hydroxyapatite scaffolds with gyroid architectures across a range of infill densities, emphasizing the importance of pore size and interconnectivity for biological function [11]. The scaffold with 55% infill density had a pore size around 465 ± 63 µm, falling within the ideal 300–600 µm range often cited for facilitating vascular infiltration and bone ingrowth. This group confirmed that such interconnected porous structures support cell bridging, alkaline phosphatase activity, and calcium deposition, key indicators of osteogenic potential [11]. Their results highlight the delicate balance between porosity and mechanical integrity, with geometric designs like gyroid structures mimicking cancellous bone microarchitecture more effectively than simple rectilinear lattices, influencing both mechanical performance and biological outcomes.

Further advancing the concept of biomimicry, Yang *et al.* (2024) integrated 3D-printed PCL scaffolds with multi-layer mineralized graphene oxide-collagen-hydroxyapatite (GO-Col-HAp) microscaffolds to replicate hierarchical nano- and micro-structures of natural bone extracellular matrix (ECM) [12]. Their composite scaffolds maintained robust mechanical strength due to the PCL framework, while the mineralized microscaffolds enhanced water retention, cell adhesion, proliferation, and osteogenic differentiation. The architecture featured cubic disks and square pores designed to facilitate nutrient transport and vascularization. In vivo implantation in mandibular bone defects demonstrated successful regeneration, showcasing the benefits of combining a mechanically stable FDM-printed PCL macrostructure with bioactive nanoscale features [12].

Together, these studies underscore the crucial role of melt extrusion in creating PCL-based scaffolds with controlled macro- and micro-architectures. Optimal pore sizes between approximately 300 and 600 µm, along with interconnected lattice or gyroid designs, enhance vascular and cellular infiltration essential for bone regeneration. Variations in lattice geometry (e.g., lattice vs staggered or gyroid vs rectilinear) markedly influence mechanical properties such as elastic modulus and yield strength, which can be fine-tuned to closely mimic trabecular bone, as shown by Yazdanpanah *et al.* (2023) [7] and Wang *et al*. (2025) [11]. Meanwhile, integrating ECM-inspired mineralized components within these frameworks further promotes biological functionality without compromising structural integrity.

2.2 Solvent-assisted extrusion & low-temperature printing

Solvent-based inks, co-printing with sacrificial components, and low-temperature approaches enable incorporation of heat-sensitive biomolecules or cell-laden hydrogels alongside PCL frameworks. These hybrid strategies permit fabrication of mechanically robust PCL frames with soft, bioactive interstices (e.g., collagen or gelatin methacryloyl (GelMA) inks), improving cell viability and in vitro maturation [12].

The study by Yang *et al.* (2024) presents a compelling hybrid fabrication approach that aligns well with recent trends in incorporating soft, bioactive materials within mechanically robust 3D-printed frameworks for tissue engineering applications [12]. In particular, their integration of a 3D-printed polycaprolactone (PCL) scaffold with multi-layer mineralized graphene oxide-collagen-hydroxyapatite (GO-Col-HAp) microscaffolds (MLM GCH) resonates with ongoing advances in solvent-based inks, co-printing with sacrificial components, and

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low-temperature strategies that preserve bioactivity during scaffold formation.

As illustrated in Figure 1, the design starts with a cubic PCL framework that replicates the macrostructure of native bone ECM. This step highlights the mechanical backbone of the scaffold, a characteristic feature of thermoplastic materials like PCL that are widely favored for their strength and biocompatibility. However, PCL's lack of intrinsic bioactivity necessitates the incorporation of softer, biofunctional components. Yang *et al.* [12] address this limitation by embedding MLM GCH microscaffolds into the PCL lattice, an approach conceptually similar to co-printing or post-printing infusion of bioactive hydrogels such as collagen or gelatin methacryloyl (GelMA) into PCL matrices. This hybridization reflects the benefit of low-temperature or solvent-compatible processes that preserve sensitive biomolecules or cells while enhancing the biological milieu of the scaffold.

Importantly, the MLM GCH component of the scaffold contributes features akin to soft interstices seen in hybrid systems using bioinks. The multi-layer structure provides not only hierarchical porosity but also improved hydration, mimicking the natural bone ECM's nano- and microscale architecture. These properties are crucial for promoting cell viability, proliferation, and differentiation—core outcomes of bioactive ink incorporation noted in emerging biofabrication strategies. As seen in Figure 1, the integration of these microscaffolds within the PCL grid produces a composite that supports both mechanical integrity and a biologically active microenvironment.

Furthermore, the observed success of the MLM GCH/PCL scaffold in promoting in vivo bone regeneration mirrors the advantages of combining structurally stable frameworks with soft bioactive regions, as seen in GelMA- or collagen-infused systems. The use of materials like GO-Col-HAp, which possess high surface area and bioactivity, parallels the rationale behind integrating sacrificial or functional hydrogel components within thermoplastic lattices to create biomimetic, osteoinductive environments.

In sum, Yang *et al.* (2024) exemplify a strategic convergence of hard-soft material integration, echoing the principles underlying co-printing with sacrificial components and solvent-based bioinks [12]. The detailed schematic in Figure 1 captures the essence of this modular assembly: a rigid, printable backbone (PCL) complemented by soft, ECM-like fillers (MLM GCH), ultimately yielding a scaffold system capable of enhanced in vitro cell behavior and in vivo bone regeneration.

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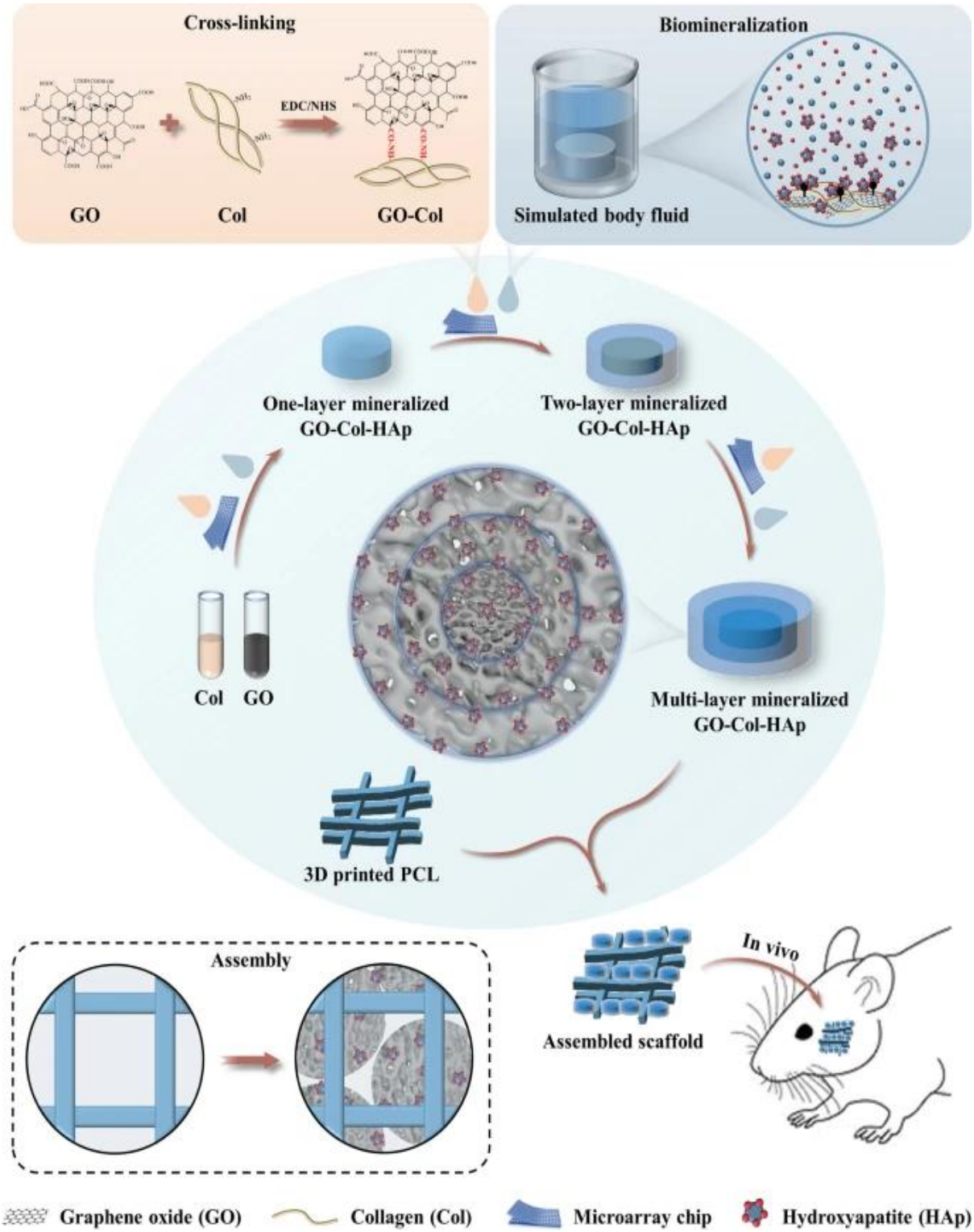

Figure 1. Schematic illustration of the fabrication of 3D-printed polycaprolactone framework assembling ECM-inspired multi-layer mineralized GO-Col-HAp microscaffolds and its application in mandibular bone regeneration [12]

2.3 Multimaterial & hybrid printing

Combining PCL with inks that deliver growth factors, ceramics, or hydrogels in a single print run (multi-nozzle printers) creates hierarchical scaffolds with spatially controlled mechanics and biology. Translational case reports indicate successful patient-specific implants made from 3D-printed PCL frameworks combined with biological fillers.

The study by Özdemir *et al.* (2023) offers a practical example of how 3D-printed PCL scaffolds combined with bioactive components like hyaluronic acid can be used in clinical settings, aligning well with strategies involving multi-nozzle printing of growth

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factors, ceramics, or hydrogels [13]. These combinations enable the fabrication of hierarchical scaffolds with spatially controlled mechanical and biological properties tailored to patient-specific defects.

In this case, a CE-marked PCL-hyaluronic acid scaffold (*Bloocell*) was used in two patients—one with a glenoid defect due to rheumatoid arthritis and another with a chronic radius non-union. The scaffold was printed using extrusion-based 3D printing under GMP-certified conditions, illustrating its readiness for clinical use. Notably, the glenoid reconstruction demonstrates how PCL provides the structural framework while hyaluronic acid contributes to a bioactive environment supporting regeneration. Figure 2 illustrates the intraoperative placement of the scaffold into the glenoid defect, confirming its anatomical fit and integration with the prosthetic components. Postoperative imaging and 9-month follow-up outcomes showed excellent implant stability and full, painless range of motion, underscoring the translational success of combining rigid PCL with biological fillers.

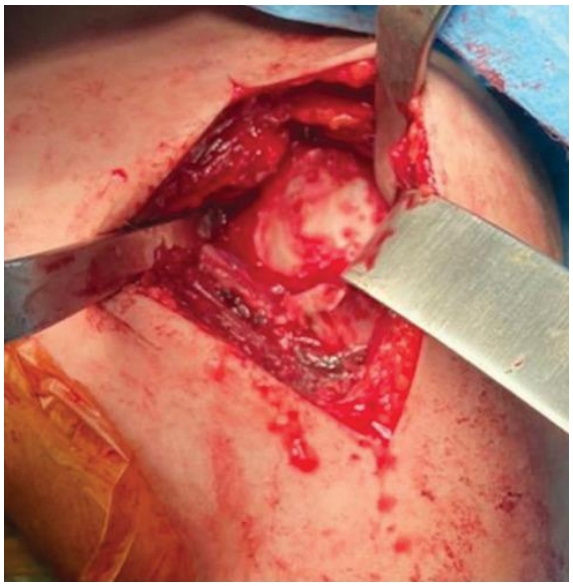

Figure 2. Intraoperative appearance of glenoid confirming central glenoid defect [13].

3.0. Strategies for Enhancing Polycaprolactone (PCL) Scaffold Performance in Bone Tissue Engineering

3.1 Ceramic fillers: HA, β-TCP and doped-HA

Integration of hydroxyapatite (HA), β-tricalcium phosphate (β-TCP) or doped HA (e.g., Sr, Zn, Se dopants) into PCL filaments improves stiffness, bioactivity and osteoconductivity. Multiple groups report enhanced osteogenic differentiation of MSCs on PCL/HA or PCL/HA/collagen scaffolds and improved in vitro mineralization and ALP activity compared with neat PCL. For example, 3D-printed PCL/HA/COL scaffolds increased osteogenic markers and mineral deposition in vitro (enhanced ALP and calcium deposition).

The studies by Ebrahimi *et al.* (2022) [14] and Petousis *et al.* (2024) [15] strongly support the integration of hydroxyapatite (HA) and collagen (COL) into polycaprolactone (PCL) scaffolds to improve their mechanical, biological, and osteogenic performance—directly aligning with the strategy of doping PCL with HA, β-TCP, or composite fillers to enhance bioactivity and osteoconductivity.

Ebrahimi *et al*. [14] focused on modifying 3D-printed PCL scaffolds with HA and type I collagen to address the inherent limitations of neat PCL, particularly its hydrophobicity and lack of osteoinductivity. Their results showed that while PCL alone supports mesenchymal stem cell (MSC) proliferation, the addition of HA and COL—especially in combination—significantly enhanced osteogenic differentiation. Notably, the PCL/HA/COL scaffolds demonstrated increased alkaline phosphatase (ALP) activity and calcium deposition, two key markers of osteogenesis, confirming that composite scaffolds create a more osteosupportive environment than neat PCL. These outcomes mirror other findings in the literature where PCL/HA or PCL/HA/COL scaffolds outperformed pure PCL in promoting bone-related gene expression and mineralization.

Complementing these biological findings, Petousis *et al.* [15] examined the mechanical and structural enhancements gained by incorporating varying concentrations of HA into PCL filaments. Using a rigorous process that included filament extrusion, bioplotting, and multiple material characterization techniques, the study showed that PCL/HAp composites—especially at 6.0 wt.% HA—exhibited a significant 14.6% increase in mechanical strength compared to pure PCL. This improvement in structural integrity is critical for scaffolds intended for load-bearing applications, where mechanical stability must be balanced with bioactivity. As detailed in Figure 3, the study methodically follows each step of scaffold fabrication and characterization, from raw material preparation to micro-CT imaging and mechanical testing, illustrating the systematic approach taken to optimize the PCL/HA composite.

Together, these two studies underline the dual benefit of integrating HA and collagen into PCL: enhanced biological performance from Ebrahimi et al., and improved mechanical and structural properties from Petousis et al. The findings presented in Figure 3 especially reinforce the technical feasibility of incorporating HA into PCL for robust scaffold production using bioplotting methods. This integrated strategy of compositional tuning not only strengthens the scaffold but also creates an osteoconductive surface that better supports MSC differentiation, mineralization, and tissue regeneration.

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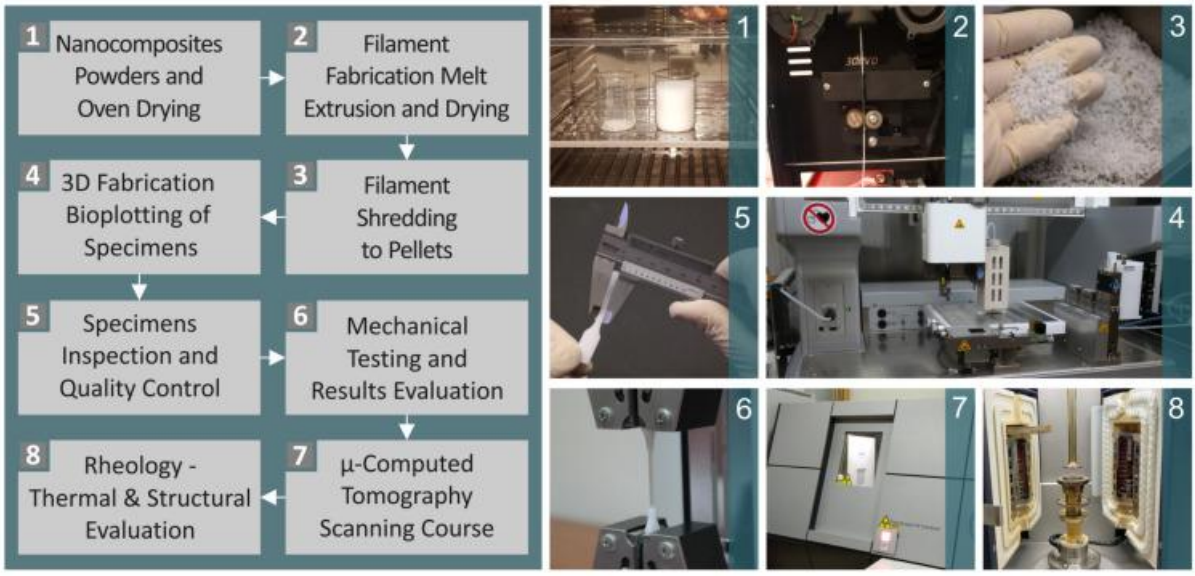

Figure 3. The conducted procedures of the present work namely the (**1**) preparation and drying process of the PCL and HAp raw materials, (**2**) filament extrusion and drying process, (**3**) shredding process of the produced filaments, (**4**) bioplotting for the 3D specimens' manufacturing, (**5**) quality inspection of the specimens, (**6**) mechanical test of the samples and outcome evaluation, (**7**) µ-CT, and (**8**) rheology, thermal, and structure investigation [15].

3.2 Carbon-based additives (graphene, graphene oxide)

Graphene oxide (GO) and reduced graphene derivatives incorporated into PCL have been used to boost mechanical strength and surface bioactivity; several recent studies report improved cell adhesion, osteogenic differentiation and electrical/thermal functionalities for PCL/GO scaffolds. However, concentration-dependent cytotoxicity and dispersion stability require optimization.

The study by Amini-Mosleh-Abadi *et al.* (2025) directly supports the growing body of research exploring the integration of graphene oxide (GO) into polycaprolactone (PCL) scaffolds to enhance mechanical performance and surface bioactivity for bone tissue engineering applications [16]. As reported in other studies, the addition of GO to PCL composites offers significant improvements in compressive modulus and biological response, though careful attention must be paid to concentration-dependent effects and dispersion stability—issues that are also addressed in this work. In this study, composite scaffolds were created by incorporating either 3% or 9% (w/v) GO into PCL and further refined into hybrid forms using an alginate/gelatin hydrogel blend. The investigation of pore sizes (400, 1000, and 1500 µm) alongside material composition allowed for a nuanced analysis of how both structural and compositional variables influence scaffold function. The results showed that both the 3D architecture and GO concentration significantly impacted swelling, degradation, and mechanical performance. Specifically, scaffolds containing 9% GO with a 400 µm pore size achieved the highest compressive modulus (~48 MPa), placing them within the mechanical range of trabecular bone. This aligns with prior observations that GO enhances the stiffness of PCL scaffolds, supporting their use in load-bearing bone repair scenarios.

Biologically, cell viability assays revealed generally favorable biocompatibility across most composite and hybrid formulations, though notably, the PCL/3% GO scaffold showed slightly reduced viability—highlighting the need for optimization of GO content and dispersion. This echoes broader concerns in the literature about GO's concentration-dependent cytotoxicity, where suboptimal loading or poor dispersion may compromise cell compatibility. Nevertheless, the study confirmed that scaffolds with higher GO content (9%) supported both mechanical performance and acceptable cell survival (>70%), underlining GO's potential when properly formulated. Amini-Mosleh-Abadi et al. provide valuable insight into the dual benefits and challenges of GO integration into PCL scaffolds. Their findings reinforce that GO can significantly enhance mechanical strength and bioactivity, as observed in other PCL/GO systems, but that precise control over concentration and distribution is critical to avoid cytotoxic effects. This work thus contributes to refining design parameters for PCL/GO scaffolds in bone tissue engineering.

3.3 Bioactive coatings and functional brushes

Surface modification—polydopamine (PDA) coatings, collagen or peptide grafting (e.g., RGD), growth factor immobilization—enhances protein

adsorption and cell attachment. PDA-modified 3D-printed PCL scaffolds, for instance, show improved hydrophilicity and cell spreading in vitro [17].

The study by Zhong *et al.* (2025) offers strong evidence for the effectiveness of surface modification—specifically polydopamine (PDA) coatings—in improving the biological performance of 3D-printed polycaprolactone (PCL) scaffolds [17]. This directly supports the broader strategy of enhancing scaffold bioactivity through techniques like PDA coating, collagen or peptide grafting (e.g., RGD motifs), and growth factor immobilization, all aimed at promoting protein adsorption, cell adhesion, and osteogenic differentiation.

Zhong *et al.* [17] fabricated PCL scaffolds using 3D printing and then applied PDA coatings of varying thicknesses by immersing the scaffolds in dopamine solutions for different durations (0, 3, 6, and 24 hours). Their findings demonstrated that PDA coating significantly altered the surface properties of PCL, particularly by improving hydrophilicity—a key factor that influences protein adsorption and cell attachment. Among the modified groups, the PDA-PCL-6 scaffold (6-hour immersion) showed the most pronounced improvement in biological performance, including enhanced proliferation, adhesion, and osteogenic differentiation of bone marrow mesenchymal stem cells.

These results reflect how PDA acts as a bioadhesive interface, mimicking the mussel-inspired mechanism of surface binding. By enhancing wettability and providing abundant functional groups for protein interaction, PDA facilitates more efficient cellular responses. The PDA-PCL-6 group, in particular, also demonstrated superior in vivo outcomes. Micro-CT imaging, histological staining, and immunohistochemical analyses for bone morphogenetic protein 2 (BMP-2) and type I collagen (COL-I) confirmed significantly improved bone regeneration and tissue integration compared to uncoated controls. Importantly, this study highlights the need for optimizing coating parameters—such as immersion duration—to balance coating thickness with bioactivity. Over- or under-coating can diminish cell compatibility or interfere with scaffold porosity and function. The 6-hour PDA coating emerged as a critical window for maximizing biofunctionality without compromising structural integrity.

4.0 Biofunctionalization and controlled release

Embedding growth factors (BMP-2, VEGF), antibiotics, or osteoinductive ions into PCL composites, or loading PCL microspheres into printed constructs, enables local delivery with temporal control. PCL's slow degradation suits long-term release but may require core-shell or particulate strategies to tune kinetics. Several studies integrate growth factor reservoirs or drug-eluting ceramics within the PCL frame to stimulate angiogenesis and bone formation while minimizing burst release.

The review by Gharibshahian *et al.* (2023) aligns well with emerging strategies that embed growth factors, drugs, or bioactive ions into polycaprolactone (PCL) composites to enable localized, temporally controlled delivery within 3D-printed scaffolds [18]. As the authors highlight, PCL's inherent qualities—such as its high biocompatibility, slow degradation rate, and mechanical robustness—make it an excellent base material for long-term release systems in bone tissue engineering (BTE).

A central theme in the review is the multifunctionality achieved by combining PCL with other bioactive agents, including growth factors like BMP-2 and VEGF, antibiotics, and ceramic particles. These combinations are key for overcoming PCL's biologically inert nature, especially when engineered into 3D-printed scaffolds that offer spatial precision in delivering therapeutics. The incorporation of such components into PCL matrices supports critical regenerative functions—stimulating angiogenesis, promoting osteogenesis, and reducing infection risk at the defect site.

The review also acknowledges the need for fine-tuning release kinetics in PCL-based systems. PCL's slow degradation makes it ideal for sustained delivery, but this characteristic can hinder timely therapeutic action if not engineered appropriately. To address this, the integration of core-shell architectures, particulate drug carriers, or PCL microspheres within scaffold designs has gained traction. These strategies help mitigate the initial burst release and allow more controlled, stage-specific release profiles—crucial for growth factors whose timing and dosage directly influence bone healing. Gharibshahian et al. further note that advancements in 3D printing techniques—such as co-axial extrusion, multi-material printing, and microfabrication—are making it increasingly feasible to embed these functional reservoirs directly into the scaffold. By controlling scaffold porosity, compartmentalization, and distribution of loaded agents, these technologies are pushing printed PCL composites closer to clinical translation. Importantly, this approach combines mechanical support with localized bioactivity, addressing both structural and biological requirements for bone regeneration.

5.0 Mechanical Properties And Degradation

Polycaprolactone (PCL) is widely recognized in tissue engineering for its favorable processing characteristics, flexibility, and biocompatibility. However, its mechanical performance—particularly its relatively low elastic modulus—limits its application in load-bearing scenarios without modification [7]. This limitation becomes more pronounced in porous scaffold designs, where

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mechanical integrity is compromised by the necessary introduction of voids to support cell infiltration and vascularization. As such, the inherent mechanical properties of PCL must be carefully balanced with architectural design to achieve functional constructs.

To mitigate these issues, PCL is often reinforced with bioactive fillers such as nano-hydroxyapatite (nHAp), as demonstrated in the study by Yazdanpanah *et al.* (2023). The inclusion of 30% (wt.) nHAp significantly enhances stiffness and bioactivity, though at the cost of some ductility—a common trade-off in polymer-ceramic composites [7]. The resulting mechanical properties of the PCL/nHAp scaffolds—elastic modulus ranging from 14 to 165 MPa and yield strength from 0.9 to 10 MPa—fall within the range of human trabecular bone, making them suitable for applications in non-cortical regions.

In terms of degradation, PCL is characterized by its slow hydrolytic breakdown, typically taking 1–3 years in vivo. While this extended degradation profile is advantageous for maintaining mechanical support during early healing, it may delay full tissue regeneration if scaffold persistence outlasts the remodeling phase. Although Yazdanpanah *et al*. [7] did not directly engineer degradation kinetics, their composite design and architectural optimization likely contribute to more balanced scaffold resorption by promoting early biological integration. Future scaffold strategies might incorporate faster-degrading co-polymers, enzymatically cleavable linkers, or porogens to synchronize degradation with the natural timeline of bone healing.

6.0 In Vitro and in Vivo Evidence

6.1 In vitro

Multiple groups report that PCL/HA and PCL/HA/COL scaffolds support MSC adhesion, proliferation, ALP activity and mineralization better than PCL alone (e.g., enhanced osteogenic gene expression, extracellular matrix deposition). PCL composites with LAP (laponite) or ordered mesoporous calcium silicate also demonstrate osteoinductive behavior and sustained bioactivity in vitro.

For example, Furtado *et al.* (2025) demonstrated that 3D-printed PCL scaffolds infused with nanosized laponite (LAP) showed improved microporosity, mineralization, and osteogenic differentiation of mesenchymal stem cells (MSCs) without cytotoxic effects, even at high LAP concentrations—highlighting LAP's role in sustained bioactivity and in vitro osteoinduction [8]. Similarly, Mirzavandi *et al.* (2024) reported that scaffolds composed of PCL, gelatin, and 10% ordered mesoporous calcium-magnesium silicate (om-CMS) supported enhanced cell attachment, proliferation, and ALP activity, with no structural compromise [10]. These findings align with broader evidence that PCL-based composites with bioactive ceramics such as HA, collagen, LAP, and om-CMS outperform PCL alone in promoting MSC adhesion, proliferation, osteogenic gene expression, and extracellular matrix deposition, reinforcing their potential in bone tissue engineering.

6.2 In vivo / translational reports

Preclinical studies using critical-size defect models consistently show that PCL composites—particularly PCL/HA or PCL/β-TCP—outperform unmodified PCL in promoting bone formation, with enhanced osteoconductive and osteoinductive properties. Translating this into clinical contexts, Özdemir *et al.* (2023) presented two orthopedic cases utilizing a 3D-printed PCL + hyaluronic acid scaffold for bone regeneration: a glenoid defect in a rheumatoid arthritis patient undergoing shoulder arthroplasty, and a radius non-union in a young adult with a neglected fracture-dislocation [9]. In both cases, the customized scaffolds supported successful bone healing, functional recovery, and showed no signs of implant loosening or degradation over mid-term follow-up. These outcomes support the emerging trend of combining PCL scaffolds with biologics or bioactive hydrogels for patient-specific applications in cranial, maxillofacial, and orthopedic defect repair. However, consistent with the broader literature, such promising case reports underscore the need for larger-scale animal studies and well-controlled clinical trials to validate safety, efficacy, and long-term outcomes.

7.0 Challenges and Regulatory Considerations

Challenges in developing PCL-based scaffolds for bone regeneration primarily revolve around balancing material properties with biological demands and regulatory compliance. One major issue is controlling PCL's inherently slow degradation rate to align with the pace of natural bone healing, which often requires the use of composite materials or multi-phase scaffold designs to fine-tune resorption kinetics. Achieving a uniform dispersion of ceramic or nanoscale fillers within the polymer matrix is critical to ensure consistent mechanical strength and biological performance, yet this remains technically challenging. When incorporating biomolecules through hybrid printing methods, there is also a risk of thermal or shear-induced degradation that can diminish bioactivity. Another key hurdle is promoting vascularization within thick scaffold constructs; strategies such as designing internal channels, co-printing endothelial cell-laden bioinks, and delivering angiogenic factors are being explored to overcome diffusion limitations and support tissue integration. From a regulatory perspective, standardizing printing parameters, sterilization processes, and establishing robust quality control during scale-up are essential but complex steps for

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clinical translation. Recent reviews highlight the necessity of interdisciplinary collaboration and standardized reporting protocols to address these challenges effectively and accelerate the path from bench to bedside.

8.0 Future directions and recommendations

Future directions in PCL-based scaffold development point toward increasingly sophisticated designs and manufacturing approaches to enhance clinical outcomes. Hierarchical scaffolds that integrate macro-porous PCL frameworks with micro- and nano-porous bioactive fillers, along with hydrogel cores for effective cell delivery, show great promise for mimicking the complex bone environment. Smart composites, such as ion-doped hydroxyapatite and controlled-release microparticles, offer dual functionality by promoting osteogenesis while providing antibacterial protection, addressing common challenges in bone repair. Advances in multimaterial 3D printing technology will enable simultaneous deposition of PCL and cell-laden hydrogels, facilitating the fabrication of pre-vascularized constructs to improve scaffold integration and vascularization. Additionally, establishing standardized preclinical pipelines—including the use of large animal models and long-term evaluations—and adopting GMP-compliant production of filaments and inks are critical steps to transition these innovations into controlled clinical trials and, ultimately, therapeutic applications.

9.0 Conclusion

3D printing of PCL and PCL-based composites has matured into a versatile platform for bone tissue engineering. By combining architectural control with ceramic fillers, surface functionalization and hybrid printing, researchers have created scaffolds that better recapitulate bone microenvironments and stimulate osteogenesis in vitro and in vivo. To fully realize clinical translation, ongoing work must harmonize scaffold design with controlled degradation, vascularization strategies, robust manufacturing protocols, and rigorous long-term biological validation.

Declarations

Conflict of Interest

The authors declare no conflicts of interest related to this work.

Data Availability Statement

The data that support the findings of this review are available from the corresponding author upon reasonable request.

Authors' Contributions

Idris Oladimeji Junaid, John Tsado Mathew, Ngozi M. Uzoekwe, and Osarhieme Tinuade Okugbo contributed to the literature search, data organization, and initial drafting of the manuscript. Gregory E. Onaiwu, Nyaknno U. Udokpoh, and Aireguamen I. Aigbodion critically revised the manuscript for intellectual content and contributed to the conceptual framework. Samuel Ugheighele participated in data validation and content review. Ikhazuagbe Hilary Ifijen supervised the study, conceptualized the review, coordinated the writing process, and finalized the manuscript. All authors reviewed and approved the final version of the manuscript.

Ethical Declarations – Human/Animal Studies

Not applicable.

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