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3D Bioprinting of Synthetic Based Scaffold for Pulp-Dentin Regeneration- Comparison of Physiochemical And Biological Behaviour.

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Abstract

Two structurally distinct scaffolds were fabricated using 3D printing technology for dentin–pulp complex regeneration. A polycaprolactone/nano-hydroxyapatite/graphene oxide (PCL/nHA/GO) composite scaffold was developed for dentin regeneration, whereas a PCL/gelatin methacrylate (GelMA) scaffold loaded with vascular endothelial growth factor (VEGF) was designed to promote pulp tissue regeneration. Comprehensive physicochemical characterization of the fabricated scaffolds was carried out using field emission scanning electron microscopy (FESEM) coupled with energy-dispersive spectroscopy (EDS), Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), atomic force microscopy (AFM), contact angle analysis, and compressive strength testing. The incorporation of nano-hydroxyapatite (nHA) and graphene oxide (GO) markedly improved the mechanical strength, surface roughness, and bioactivity of the dentin-mimetic scaffold, indicating its potential to support dentin regeneration. Moreover, the GelMA-based pulp scaffold exhibited enhanced hydrophilicity and superior cell adhesion, which can be attributed to its extracellular matrix–mimicking architecture and intrinsic angiogenic capability. Gene expression profiling demonstrated a marked upregulation of key odontogenic markers, including DSPP, OCN, and DMP-1, across both scaffold groups.A bilayered PCL/nHA/GO–PCL/GelMA construct was effectively fabricated and thoroughly characterized, confirming its structural and functional suitability for dentin–pulp complex regeneration. Collectively, these results indicate that the developed multifunctional scaffolds possess promising translational potential for applications in regenerative endodontics.

Keywords. 3d bioprinting,pulp-dentin complex regeneration,polycaprolactone composite,nanohydroxyapatite,graphene oxide,gelatin methacrylate , human dental pulpal cells,odontogenic differentiation

Introduction

Regenerative endodontics focuses on re-establishing the biological integrity and functional vitality of the pulp–dentin complex instead of simply substituting diseased

tissue with inert obturation materials [1]. While conventional root canal therapy is successful in eradicating infection, it leaves the tooth non-vital, thereby increasing its vulnerability to fracture and eliminating its inherent immune defense capacity [2]. As a result, biologically driven regenerative strategies have attracted considerable interest in contemporary dental research.Tissue engineering approaches rely on the fundamental triad of stem cells, bioactive signaling molecules, and scaffolding matrices [3]. Within this framework, scaffolds are particularly critical as they create a three-dimensional (3D) niche that facilitates cellular attachment, proliferation, migration, and differentiation, while also directing extracellular matrix formation [4]. For successful pulp–dentin regeneration, an optimal scaffold should exhibit excellent biocompatibility, a highly interconnected porous architecture, adequate mechanical stability, controlled degradability, and inherent bioactivity capable of stimulating odontogenic differentiation [5].

Additive manufacturing techniques, especially 3D printing, have transformed scaffold fabrication by allowing accurate regulation of pore size, structural geometry, and spatial distribution [6]. Polycaprolactone (PCL) has emerged as a commonly employed material in dental tissue engineering owing to its good mechanical strength, biodegradability, and superior printability [7]. Nevertheless, its inherent hydrophobicity and relatively low bioactivity require surface functionalization or the integration of bioactive additives to improve cellular interactions and biological performance [8].

Nano-hydroxyapatite (nHA), owing to its close compositional similarity to the mineral component of dentin, has been reported to improve scaffold bioactivity and stimulate odontogenic differentiation in dental pulp stem cells (DPSCs) [9]. In addition, graphene oxide (GO) has gained significant interest because of its high surface area, mechanical strengthening effect, and capacity to influence stem cell behavior and differentiation processes [10,11]. Therefore, the combined incorporation of nHA and GO within a PCL matrix may synergistically enhance mechanical properties, increase surface roughness, and boost bioactivity, thereby making the composite scaffold a promising candidate for dentin regeneration.

Effective pulp regeneration further depends on the development of a well-vascularized soft connective tissue capable of healing with adequate nutrient delivery and maintaining long-term vitality [12]. Gelatin methacrylate (GelMA), a photocrosslinkable gelatin derivative, closely

replicates the native extracellular matrix environment and facilitates cell encapsulation, proliferation, and tissue formation [13]. In addition, the incorporation of pro-angiogenic growth factors such as vascular endothelial growth factor (VEGF) has been shown to stimulate neovascularization and enhance regenerative outcomes in pulp tissue engineering [14].Nevertheless, achieving the concurrent regeneration of both dentin and pulp tissues remains complex because of their differing structural compositions and biological functions [15]. To address this challenge, a bilayered scaffold approach—combining a mineralized, dentin-mimetic layer with a hydrophilic, angiogenic pulp-supportive layer—may more effectively replicate the hierarchical architecture of the natural pulp–dentin complex [16].

Accordingly, the present investigation was designed to fabricate and characterize two structurally distinct 3D-printed scaffolds: a PCL/nHA/GO composite scaffold intended for dentin regeneration and a PCL/GelMA scaffold functionalized with VEGF for pulp tissue regeneration. Furthermore, a bilayered construct combining both scaffold systems was developed to examine its suitability for integrated pulp–dentin complex regeneration. The scaffolds were systematically evaluated for their physicochemical and biological characteristics to determine their potential translational applicability in regenerative endodontic therapy.

Materials and Methods

Materials

1.polycaprolactone (PCL; Mw 80,000), nano-hydroxyapatite (nHA), and graphene oxide (GO) were sourced from certified commercial suppliers. Gelatin methacrylate (GelMA) and the photoinitiator Irgacure 2959 were employed for hydrogel synthesis, while recombinant human vascular endothelial growth factor (VEGF) was incorporated as the angiogenic signaling molecule. All reagents used were of analytical grade. Human dental pulp stem cells (hDPSCs) were isolated from premolars extracted for orthodontic indications [17].

2. Fabrication of 3D-Printed Scaffolds

2.1 PCL/nHA/GO Composite Scaffold (Dentin Layer)

PCL pellets were heated to 70–80 °C until fully liquefied, after which nHA (15 wt%) and GO (0.5 wt%) were blended into the molten polymer under continuous mechanical stirring to ensure homogeneous distribution. The composite material was subsequently loaded into a temperature-controlled extrusion-based 3D printing system. Scaffolds were fabricated using a

CAD-generated grid design with a nozzle diameter ranging from 200–400 μm, strand spacing of 300–500 μm, and a layer thickness of approximately 200 μm [18].

2.2 PCL/GelMA/VEGF Scaffold (Pulp Layer)

GelMA (7% w/v) was prepared by dissolving it in phosphate-buffered saline (PBS) containing 0.5% photoinitiator. Subsequently, VEGF (100 ng/mL) was incorporated into the solution and mixed under aseptic conditions to obtain a homogeneous hydrogel bioink. This bioink was either printed onto or cast over the pre-fabricated PCL framework and then photocrosslinked using UV irradiation (365 nm for 20 s) to stabilize the hydrogel network [19].

Figure 2. Fabrication of the PCL/GelMA/VEGF hydrogel layer over the PCL scaffold.

2.3 Bilayer Scaffold

A bilayer scaffold was developed through sequential fabrication, beginning with the printing of the PCL/nHA/GO dentin-like layer followed by deposition of the PCL/GelMA/VEGF hydrogel as the pulp-supportive layer. Special attention was given to optimizing the interfacial bonding to promote structural integrity and effective integration between the two layers [20].

Figure 3. Schematic illustration of the bilayer scaffold combining dentin-mimetic (PCL/nHA/GO) and pulp-supportive (PCL/GelMA/VEGF) components.

3. Physicochemical Characterization

Field emission scanning electron microscopy (FESEM) coupled with energy-dispersive spectroscopy (EDS) was employed to evaluate scaffold surface morphology, pore architecture, and elemental distribution of incorporated components such as nHA and GO. Fourier transform infrared spectroscopy (FTIR) was utilized to verify chemical interactions among PCL, nHA, GO, and GelMA, while X-ray diffraction (XRD) analysis was conducted to assess scaffold crystallinity and phase composition [21].

3. Physicochemical Characterization

Atomic force microscopy (AFM) was employed to quantify the surface roughness (Ra) of both PCL/nHA/GO and PCL/GelMA scaffolds. Scaffold wettability was assessed through contact angle measurements using a goniometer to determine hydrophilic behavior. Mechanical

performance, including compressive strength and elastic modulus, was evaluated using a universal testing machine to determine the structural stability of the fabricated scaffolds [22].

Figure 5. Live/dead staining of hDPSCs on (A) PCL/nHA/GO and (B) PCL/GelMA/VEGF scaffolds at day 3.

4. In Vitro Biological Evaluation

4.1 Cell Culture

Human dental pulp stem cells (hDPSCs) were maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% antibiotic–antimycotic solution. Cells were incubated at 37 °C in a humidified atmosphere containing 5% CO_2 to ensure optimal growth conditions [23].

4.2 Cell Viability and Proliferation

Cellular viability and proliferation on the scaffolds were examined using the MTT assay along with live/dead fluorescence staining at predetermined time points (days 1, 3, and 7) to evaluate cell attachment and metabolic activity [24].To evaluate cellular attachment and spreading behavior, hDPSCs were stained with phalloidin to visualize F-actin cytoskeletal filaments and DAPI to label cell nuclei. The stained samples were examined using confocal laser scanning microscopy to assess cytoskeletal organization and morphology on the respective scaffold surfaces [25].

Figure 6. Confocal images showing cytoskeletal arrangement of hDPSCs cultured on (A) dentin-mimetic scaffold and (B) pulp-supportive scaffold.

4.4 Odontogenic Differentiation

For assessment of odontogenic differentiation, hDPSCs seeded on the scaffolds were cultured in odontogenic induction medium for 14 days. Total RNA was subsequently isolated, and quantitative real-time polymerase chain reaction (qRT-PCR) was conducted to evaluate the expression of odontogenic markers, including dentin sialophosphoprotein (DSPP), dentin matrix protein-1 (DMP-1), and osteocalcin (OCN). Relative gene expression levels were normalized to the housekeeping gene GAPDH and calculated using the $2^{-\Delta\Delta Ct}$ method [26].

5. Statistical Analysis

All experimental procedures were conducted in triplicate, and the obtained data were expressed as mean ± standard deviation. Statistical comparisons were performed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test, with a p-value < 0.05 considered indicative of statistical significance [27].

Results

1. Scaffold Fabrication and Morphology

Both PCL/nHA/GO and PCL/GelMA/VEGF scaffolds were successfully produced through extrusion-based 3D printing. The PCL/nHA/GO scaffolds demonstrated a highly organized porous grid architecture with consistent layer deposition (Figure 1). The addition of nHA and GO did not adversely affect printability, and the composite scaffolds retained their structural stability following fabrication.The PCL/GelMA/VEGF hydrogel was homogeneously applied onto the PCL framework, generating a continuous pulp-supportive layer (Figure 2). Moreover, the bilayer scaffold exhibited strong interfacial bonding without evidence of delamination, confirming effective integration between the dentin-mimetic and pulp-supportive components (Figure 3).FESEM observations indicated interconnected pore networks in both scaffold systems. The PCL/nHA/GO scaffolds showed increased surface roughness attributable to the incorporation of nHA and GO, whereas the GelMA hydrogel displayed a relatively smooth and hydrated surface morphology (Figure 4A–B). Elemental mapping via EDS verified the homogeneous presence of calcium and phosphorus within the PCL/nHA/GO scaffold, thereby confirming successful nHA incorporation [28].

2. Physicochemical Properties

FTIR analysis demonstrated distinct spectral peaks corresponding to PCL, nHA, GO, and GelMA, confirming preservation of their chemical structures without degradation during the fabrication process. XRD findings further indicated that nHA maintained its crystalline phase within the PCL matrix, whereas the incorporation of GO did not significantly influence PCL crystallinity. AFM evaluation revealed greater surface roughness in the PCL/nHA/GO scaffold ($Ra \approx 150$ nm) compared with the PCL/GelMA scaffold ($Ra \approx 40$ nm), suggesting a favorable surface topography for improved cellular attachment.Contact angle measurements showed enhanced wettability of the PCL/GelMA/VEGF scaffold (approximately 62°), while the PCL/nHA/GO scaffold exhibited comparatively hydrophobic characteristics (approximately 98°). Mechanical assessment through compressive testing demonstrated superior strength of

the PCL/nHA/GO scaffold (5.2 ± 0.3 MPa) relative to the hydrogel layer (0.8 ± 0.1 MPa), indicating its suitability for dentin-like structural support [29].

3. In Vitro Biological Evaluation

3.1 Cell Viability and Proliferation

MTT and live/dead staining confirmed high viability of hDPSCs cultured on both scaffold systems at days 1, 3, and 7. However, cells grown on the PCL/GelMA/VEGF scaffold exhibited greater spreading and enhanced proliferation compared with the PCL/nHA/GO scaffold, which may be attributed to its increased hydrophilicity and extracellular matrix–mimicking characteristics (Figure 5A–B) [30].

3.2 Cell Adhesion and Morphology

Confocal microscopy demonstrated that hDPSCs seeded on PCL/nHA/GO scaffolds adopted an elongated morphology with well-defined actin filament organization, reflecting effective adhesion and mechanotransduction activity (Figure 6A). In contrast, cells cultured on the PCL/GelMA/VEGF layer displayed a more dispersed and branched morphology, resembling the phenotype of pulp-like connective tissue cells (Figure 6B) [31].

3.3 Odontogenic Differentiation

Quantitative RT-PCR analysis revealed significant upregulation of odontogenic markers DSPP, DMP-1, and OCN in hDPSCs cultured on both scaffolds relative to controls ($p < 0.05$).</mark> Importantly, the bilayer scaffold demonstrated further enhancement of gene expression levels, suggesting a synergistic regenerative effect achieved by integrating dentin-mimetic and pulp-supportive components (Figure 7) [32].

Discussion

The present study confirms the successful development of a bilayered 3D-printed scaffold designed to replicate both dentin and pulp tissue compartments. The PCL/nHA/GO composite scaffold demonstrated superior mechanical performance, increased surface roughness, and enhanced bioactivity, which is in agreement with earlier studies reporting the positive influence of nHA and GO on osteogenic and odontogenic differentiation pathways [1–3]. The modified surface topography, along with the incorporation of bioactive nanofillers, likely enhanced cellular mechanotransduction mechanisms, thereby contributing to the upregulation of

odontogenic markers such as DSPP and DMP-1 in hDPSCs.The PCL/GelMA/VEGF hydrogel layer provided a hydrophilic and extracellular matrix–like microenvironment conducive to cell adhesion, spreading, and proliferation. The addition of VEGF may have stimulated early angiogenic signaling, a critical requirement for successful pulp tissue regeneration [4]. The enhanced proliferation and branched cellular morphology observed on the GelMA layer further support its suitability as a soft tissue–mimetic scaffold.

The integration of dentin-mimetic and pulp-supportive layers into a single bilayer construct effectively reproduced the hierarchical organization of the native pulp–dentin complex. Importantly, the bilayer system preserved structural cohesion while further promoting odontogenic gene expression, suggesting a synergistic interaction between biochemical cues (VEGF, nHA, GO) and topographical stimuli. These observations are consistent with previous reports indicating that hierarchical or multiphasic scaffolds enhance regenerative outcomes by providing tissue-specific microenvironments [5–7].

Physicochemical analyses further validate extrusion-based 3D printing as a dependable technique for producing scaffolds with tailored pore geometry, mechanical strength, and biofunctional properties. The reinforced mechanical characteristics of the PCL/nHA/GO scaffold make it appropriate for dentin-like structural support, whereas the softer and more hydrophilic PCL/GelMA hydrogel layer favors pulp-like connective tissue formation without compromising overall scaffold stability.Collectively, these findings demonstrate that multifunctional bilayer scaffolds integrating a mineralized dentin layer with an angiogenic pulp-supportive layer can effectively facilitate cell attachment, proliferation, and odontogenic differentiation, thereby offering a promising strategy for functional pulp–dentin complex regeneration.

Conclusions

The present investigation successfully achieved the fabrication and comprehensive characterization of bilayered 3D-printed scaffolds intended for pulp–dentin complex regeneration. The PCL/nHA/GO layer functioned as a mineralized and mechanically stable framework with increased surface roughness and bioactivity, thereby facilitating odontogenic differentiation of hDPSCs. In contrast, the PCL/GelMA/VEGF hydrogel layer provided a hydrophilic, extracellular matrix–like microenvironment that promoted cellular attachment, proliferation, and angiogenic signaling essential for pulp tissue regeneration [1].The

combination of these two distinct layers into a single bilayer construct effectively reproduced the hierarchical organization of the natural pulp–dentin interface. Moreover, the bilayer scaffolds demonstrated synergistic enhancement of odontogenic marker expression, underscoring the significance of integrating structural support with biochemical and topographical cues to achieve tissue-specific regeneration [2].In summary, the developed multifunctional bilayer scaffolds exhibit considerable translational potential as a regenerative endodontic platform, offering an innovative strategy to restore both mineralized dentin and vascularized pulp tissues. Nevertheless, further in vivo investigations and long-term functional studies are warranted to validate their therapeutic efficacy and support future clinical translation [3].

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