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Nanofibrous Scaffolds Functionalized with Serine for Dentin Mineralization: A Characterization Study

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ABSTRACT

OBJECTIVE Dentin repair and regeneration pose significant challenges in restorative dentistry due to its hierarchical structure and susceptibility to demineralization. Traditional approaches often fail to restore the natural architecture and functionality of dentin. The aim of this study was to develop and characterize a biomimetic polycaprolactone (PCL)/nanohydroxyapatite (nHA)/serine (Ser) scaffold to enhance dental mineralization and support tissue regeneration. The inclusion of serine, known for its ability to bind calcium and phosphate ions and guide hydroxyapatite crystal formation, could enhance nucleation and cell attachment, making the scaffold a promising biomaterial for dentin repair.

METHODS Nanofibrous scaffolds were fabricated using PCL, nHA, and Ser by the electrospinning method. The structural and functional properties of the scaffold were characterized through scanning electron microscopy (SEM), energy-dispersive x-ray spectroscopy (EDX), x-ray diffraction (XRD), and fourier transform infrared spectroscopy (FTIR). SEM and EDX were used to evaluate the morphology, porosity, and elemental composition. XRD analyzed the crystalline and amorphous phases, while FTIR analyzed chemical interactions among the components.

RESULTS SEM analysis revealed a uniform fibrous structure with interconnected porosity, mimicking the extracellular matrix. EDX confirmed the successful incorporation of calcium and phosphorus, indicating the presence of nHA. XRD analysis demonstrated a combination of crystalline and amorphous phases, highlighting the scaffold's structural stability and bioactivity. FTIR spectroscopy identified characteristic peaks corresponding to PCL, nHA, and Ser, validating their successful integration and interaction within the scaffold matrix.

CONCLUSIONS The nanofibrous scaffold exhibited structural and compositional properties, confirming the presence of PCL, nHA and Ser. The properties analyzed support its potential for biomineralization and tissue regeneration. The inclusion of Ser could enhance hydroxyapatite nucleation and cell attachment, making the scaffold a promising biomaterial for dentin repair. Further *in-vitro* and *in-vivo* studies are recommended to validate its clinical application.

KEYWORDS biomineralization, dentin regeneration, nanohydroxyapatite, polycaprolactone, serine, scaffolds, tissue engineering

INTRODUCTION

Dentin repair and regeneration remain persistent challenges in restorative dentistry due to its intricate hierarchical structure and susceptibility to demineralization. Conditions such as dental caries and erosion compromise the mechanical integrity of dentin, leaving it vulnerable to structural failure. While conventional restorative approaches such as dental fillings address these issues temporarily, they often fail to restore the natural functionality and microarchitecture of dentin. These limitations highlight the need for biomimetic strategies that replicate the biological processes underlying dentin formation and repair (1, 2). Dentin presents a greater challenge for remineralization than enamel due to its elevated organic composition (3). This challenge is largely attributed to the widely accepted notion that dentin remineralization does not proceed through spontaneous mineral precipitation or nucleation on its predominantly type I collagen organic matrix. Rather, it relies on the growth of existing crystals within the damaged regions (4, 5). Biomineralization, the biological process by which minerals are deposited onto organic scaffolds, governs dentin formation and repair. Central to this process is the interaction between collagen fibrils and non-collagenous proteins (NCPs). NCPs, such as dentin phosphoprotein (DPP), dentin matrix protein 1 (DMP1), and osteopontin, categorized as NCPs, actively regulate mineralization by drawing in calcium and phosphate ions and stabilizing amorphous calcium phosphate (ACP) precursors. These proteins guide the transformation of ACP into crystalline hydroxyapatite, forming an organized mineralized structure within the collagen matrix. Mutations or deficiencies in NCPs often result in impaired dentin mineralization, underscoring their critical role in this process (6, 7).

Amino acids, particularly serine (Ser), play a pivotal role in mimicking the functions of NCPs. Ser, a polar amino acid, facilitates hydroxyapatite nucleation by electrostatically binding calcium and phosphate ions, creating localized supersaturation conditions that are essential for mineral formation. Furthermore, Ser adsorbs onto mineral surfaces, influencing crystal morphology and growth patterns. These interactions are critical for achieving the structural and mechanical properties of natural dentin, making Ser an ideal candidate for incorporation into biomimetic scaffolds (6).

Electrospun nanofibrous scaffolds have emerged as promising biomaterials for replicating the extracellular matrix in dentin regeneration. These scaffolds provide high surface area, interconnected porosity, and mechanical flexibility, facilitating cell adhesion, proliferation, and biomineralization. Polycaprolactone (PCL), a biodegradable polymer, is widely used in scaffold fabrication due to its mechanical resilience and compatibility with bioactive agents. However, PCL exhibits hydrophobic properties. In contrast, materials like hydroxyapatite and calcium phosphate, known for their hydrophilicity, can be blended with PCL to produce electrospun composite fibers. HA, being both hydrophilic and osteoconductive, offers advantages over PCL alone. Incorporating nanohydroxyapatite (nHA) into PCL fibers can enhance their overall properties compared to using PCL fibers on their own (8). Hydroxyapatite is limited in its application for load-bearing purposes due to its poor biomechanical properties, including brittleness, low fatigue strength, and lack of flexibility (9). Consequently, increasing attention has been directed towards developing hydroxyapatite particles in various shapes and sizes and embedding them within biodegradable polymer frameworks (10). The integration of bioactive ceramics with degradable polymers to construct highly porous 3D scaffolds has proven to be an innovative method for creating composite systems tailored to bone tissue engineering (11). The incorporation of nHA further augments the biomineralization potential of these scaffolds. With its structural and compositional similarity to the inorganic phase of dentin, nHA enhances the bioactivity of scaffolds by releasing calcium and phosphate ions, promoting mineral deposition. Functionalization of PCL scaffolds with Ser enhances their capacity to emulate natural biomineralization processes, making them highly effective for regenerative dental applications (2, 12). The synergistic combination of PCL, nHA, and Ser provides a robust platform for creating scaffolds that mimic native dentin environments and support effective tissue repair (13).

This study investigates the development and characterization of a Ser-incorporated nanofibrous

scaffold designed to enhance dentin mineralization. This research aims to contribute to the growing field of biomimetic scaffolds for dental tissue engineering by offering insights into their potential applications for regenerative therapies. In our previous work, glutamic acid-loaded PCL nanofibrous scaffolds were shown to promote controlled calcium phosphate nucleation and dentin mineralization, suggesting that amino acid modification could enhance the regenerative potential of synthetic scaffolds (14). The aim of the study was to develop and characterize a biomimetic PCL/nHA/Ser scaffold which can potentially enhance dental mineralization and support tissue regeneration. The objectives were to evaluate the structural, compositional and elemental analysis using scanning electron microscopy (SEM), energy-dispersive X-ray spectroscopy (EDX), fourier transform infrared spectroscopy (FTIR), and x-ray diffraction (XRD).

METHODS

Materials

PCL (molecular weight: 80,000), nHA 200 nm were procured from Sigma-Aldrich (Bangalore, India) and Ser were obtained from Southern India Scientific Corporation (Chennai, India). Dimethylformamide (DMF), chloroform ($CHCl_3$) and 1% antibacterial-antifungal solutions, purchased from HiMedia Laboratories (Thane, India), were used as solvents for scaffold preparation. All the chemicals utilized in this study were of analytical grade and employed directly without undergoing any additional purification processes.

Scaffold fabrication

Ser was incorporated into the scaffold by dissolving 2 wt% Ser in water and adding it to the PCL/nHA solution, followed by stirring for an additional 12 hours to ensure uniformity. The concentration of 2 wt% Ser was selected based on previous studies that demonstrated effective ion binding and bioactivity at low amino acid loading, without compromising fiber integrity or electrospinning efficiency (15).

Electrospinning was carried out using a Holmarc Opto-Mechatronics electrospinning apparatus (Model: HO-NFES-040). The polymer solution was loaded into a syringe fitted with a metallic needle, and the process was optimized with the following parameters: a flow rate of 500 µL/h, an applied voltage of 10-15 kV, and a needle-to-collector distance of 7.5 cm. Aluminum foil was used to cover the collector plate, which was grounded to collect the nanofibers. The electrospinning process was conducted at room temperature for 3 hours. After the fibers were collected, the scaffolds were dried under vacuum in a desiccator overnight to remove residual solvents and ensure complete solvent evaporation. PCL and PCL/nHA scaffolds were fabricated as described above and were utilized as controls for this new investigation (16). The structural and compositional analysis of these scaffolds provided a comparative baseline to evaluate the performance of the newly developed PCL/nHA/Ser scaffold. These results establish the structural and compositional properties of the PCL and PCL/nHA scaffolds as reliable controls for assessing the enhanced functionality and biomineralization potential of the PCL/nHA/Ser scaffolds.

Characterization

SEM

The surface characteristics of the electrospun scaffolds were examined through SEM (JSM IT800, JEOL Ltd., Tokyo, Japan). The scaffolds were cut into small sections and attached to aluminum bases with a conductive carbon adhesive. To enhance the conductivity of the samples, a fine gold layer was deposited using a sputter coater. SEM analysis was performed at an accelerating voltage of 5-15 kV to visualize the fiber surface characteristic, morphology, surface texture, and distribution of nHA particles within the fibers. Images were captured at multiple magnifications, and ImageJ software was utilized for analyzing the samples.

EDX

The elemental composition of the scaffolds was investigated using the EDX detector attached to the SEM system. EDX was utilized to visualize the spatial distribution of these elements throughout the fiber network.

XRD

The crystalline phases and structural composition of the scaffolds were analyzed with XRD (Bruker diffractometer, Singapore). The scans covered 2θ angles from 10° to 80° with CuKα radiation (λ = 1.5406 Å). A scanning interval of 0.1° and a speed of 1 step per second were applied. Char-

acteristic peaks corresponding to nHA (at ~26° and ~32°) and PCL crystallinity (~21.5° and ~23.8°) were evaluated. The degree of crystallinity was calculated to assess the impact of Ser and nHA on the structural integrity of the scaffolds.

FTIR

FTIR analysis was carried out to identify the chemical interactions between PCL, nHA, and Ser within the scaffolds. The spectral data were obtained with a JASCO 4100 spectrometer, covering the range of 400 to 4,000 cm^{-1}, at a resolution of 4 cm^{-1} with 32 scans for each sample. Specific peaks corresponding to the functional groups of PCL (C = O stretching at ~1720 cm^{-1}), nHA (P-O stretching at ~1045 cm^{-1}), and Ser (O-H and N-H stretching at ~3200-3500 cm^{-1}) were analyzed to confirm their incorporation and interactions within the scaffold matrix.

This is a descriptive observational study hence statistics are not included.

RESULTS

SEM

The surface structure of the PCL/nHA/Ser scaffolds were analyzed using SEM to evaluate fiber formation, distribution, and the incorporation of nHA and Ser. The SEM micrographs revealed that the electrospun scaffolds exhibited a uniform fibrous structure with interconnected porosity, closely resembling the extracellular matrix as shown in Figure 1 A and B. The fibers displayed a smooth surface, with minimal bead formation, indicating optimized electrospinning parameters. The distribution of nHA was uniform throughout the scaffold, with no significant agglomeration observed, suggesting effective dispersion during the electrospinning process. Additionally, the scaffold fibers maintained structural integrity and flexibility, crucial for replicating the mechanical characteristics of natural tissue. The presence of Ser in the scaffold was indirectly confirmed through morphological changes in the fiber surface. The fibers showed slightly rougher textures compared to pure PCL fibers, which may be attributed to the functionalization of the polymer matrix with Ser and nHA. This enhanced surface roughness is expected to improve cell attachment and promote mineralization. Overall, the SEM analysis confirmed that the PCL/nHA/Ser scaffolds possess a highly porous and fibrous structure, with uniform incorporation of nHA and Ser. These characteristics make the scaffold suitable for supporting cell proliferation, nutrient diffusion, and biomineralization in tissue engineering applications.

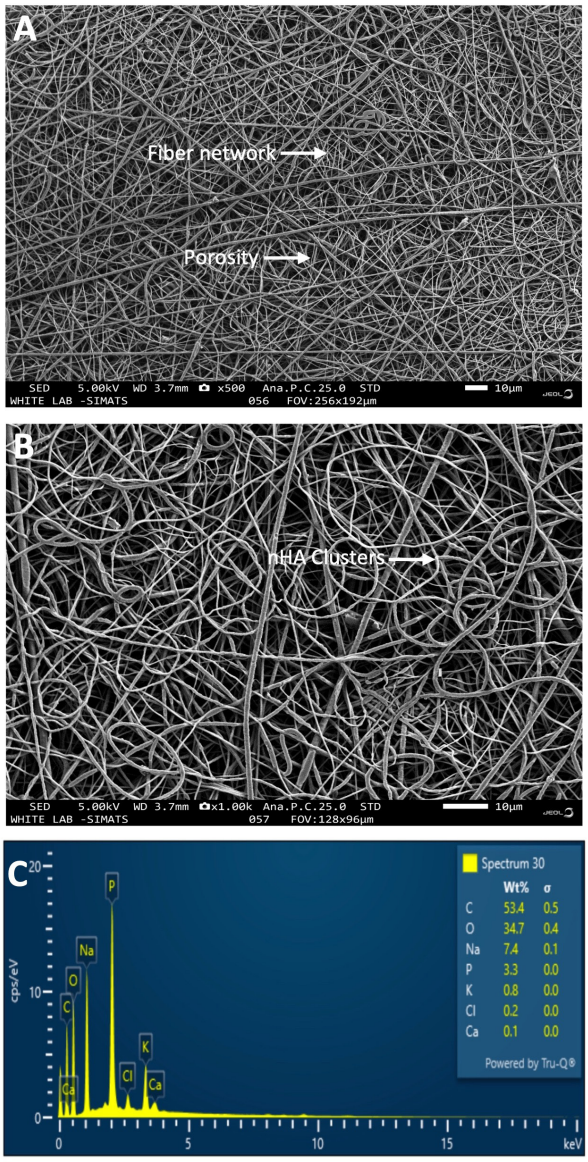

Figure 1. SEM images of electrospun nanofibrous scaffold (A and B) PCL/nHA/Ser at two different magnifications and their EDX spectrum (C)

EDX

The elements present in the PCL/nHA/Ser scaffold were examined through EDX to verify the effective integration of nHA into the fibers. The EDX spectra indicated the existence of characteristic elements, including carbon (C) and oxygen (O), which are attributed to the PCL polymer matrix, as shown in Figure 1C. Additionally, calcium (Ca) and phosphorus (P) were detected, confirming the incorporation of nHA within the

scaffold. The Ca/P ratio observed in the scaffold exhibited a deviation from the stoichiometric ratio of hydroxyapatite, which can be attributed to the dynamics of the electrospinning process (17). Sodium (Na) was also observed, indicating its presence as a component of the synthetic nHA. The elemental distribution suggests effective blending of nHA and Ser within the PCL matrix during the electrospinning process. These findings complement the SEM observations, confirming that the PCL/nHA/Ser scaffold is a composite system with well-distributed nHA and Ser, highlighting its potential as a biomimetic scaffold for tissue engineering applications.

XRD

The XRD examination of the PCL/nHA/Ser scaffold revealed a combination of crystalline and amorphous phases, which are key to its structural and functional properties. Distinct diffraction peaks at 21.43°, 23.63°, and 29.42° (2θ) were observed, corresponding to the crystallographic planes as shown in Figure 2. The sharp peaks at 21.43° and 23.63° are characteristic of the semi-crystalline nature of PCL. These peaks confirmed the retention of PCL's crystallinity during the fabrication process. Similarly, the peak at 29.42° (2θ) is attributed to nHA, indicating the effective integration of hydroxyapatite within the polymer matrix. In contrast to the crystalline peaks, the broader background signal observed in the XRD pattern is indicative of the amorphous regions within the scaffold. The amorphous phase is associated with the presence of Ser, which disrupts the regular packing of the crystalline lattice and contributes to the flexibility and bioactivity of the composite. The broader FWHM values of 0.359° and 0.392° at 21.43° and 23.63°, respectively, suggest the coexistence of both crystalline and amorphous domains. This combination of crystalline and amorphous phases provides the scaffold with a balance of mechanical strength and bioactive properties. The crystalline domains ensure structural integrity and stability, while the amorphous regions promote interactions with biological tissues, facilitating cell attachment and biomineralization. These results confirm the suitability of the PCL/nHA/Ser scaffold for applications in tissue engineering.

FTIR

The FTIR spectrum of the PCL/nHA/Ser scaffold was analyzed to confirm the successful incorporation of nHA and Ser into the polymer matrix. The spectrum displayed characteristic peaks corresponding to the functional groups of PCL, nHA, and Ser, demonstrating the composite nature of the scaffold, as seen in Figure 3. The PCL com-

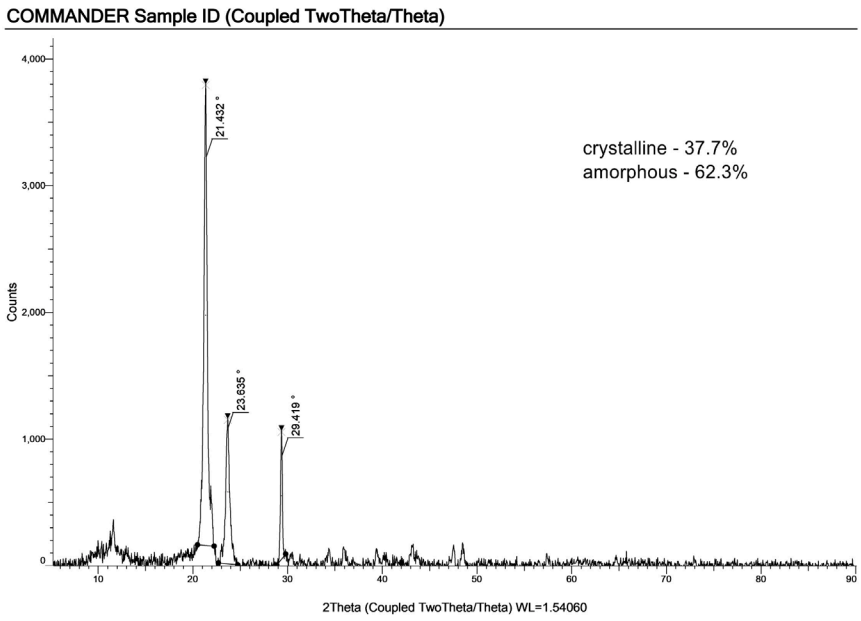

Figure 2. XRD spectrum of PCL/nHA/Ser scaffold

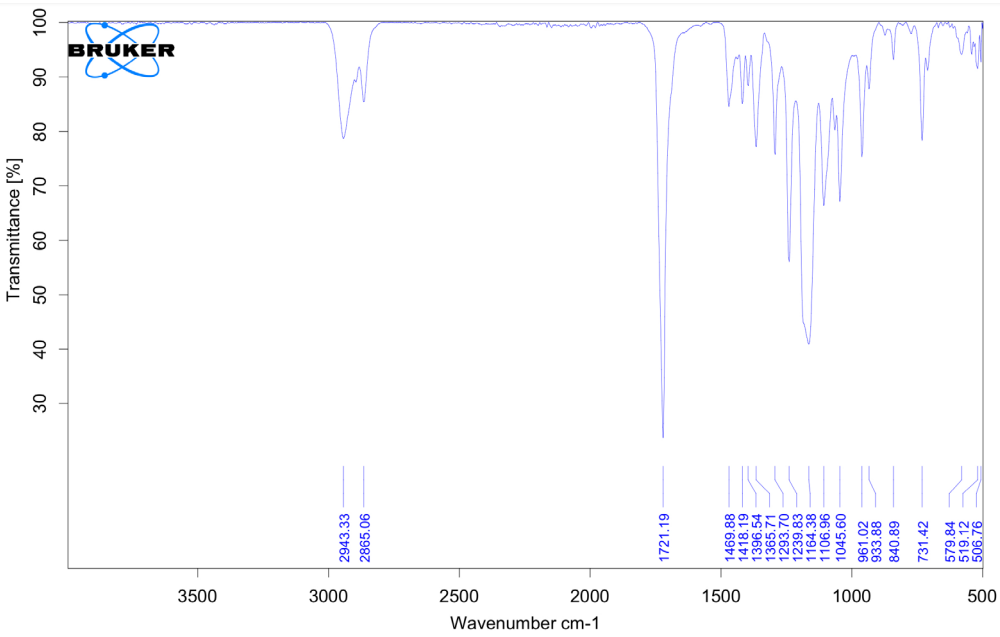

Figure 3. FTIR analysis of PCL/nHA/Ser scaffold

ponent showed prominent peaks at 1,721.19 cm^{-1}, attributed to the C = O stretching vibration, and at 2,943.33 cm^{-1} and 2,865.06 cm^{-1}, corresponding to CH_2 asymmetric and symmetric stretching, respectively. These peaks confirmed the presence of PCL as the base polymer in the scaffold.

The contribution of nHA was evident from the strong absorption band at 1,106.96 cm^{-1}, corresponding to the P-O stretching vibration, and the peaks at 579.84 cm^{-1} and 519.12 cm^{-1}, characteristic of phosphate bending vibrations. These features are consistent with the hydroxyapatite structure, validating its incorporation within the scaffold. Serine incorporation was confirmed by the presence of distinct peaks at 1,469.88 cm^{-1} and 1,365.71 cm^{-1}, corresponding to C-H bending and C-N stretching vibrations, respectively. Additionally, the sharp peak observed at approximately 933.88 cm^{-1} can be associated with the C-O stretching of the hydroxyl group in serine, while the region around 840.89 cm^{-1} corresponds to out-of-plane O-H bending, further supporting the presence of serine. Notably, the absence of a broad O-H/N-H band in the range of 3,200-3,500 cm^{-1} may be attributed to hydrogen bonding interactions or overlapping with polymer signals, yet the distinct peaks observed in the fingerprint region confirm the successful incorporation of serine.

The overlapping of characteristic peaks from PCL, nHA, and Ser within the FTIR spectrum indicates effective blending and molecular interactions between the scaffold components. The incorporation of serine is particularly significant, as its functional groups are expected to enhance scaffold bioactivity by promoting cell adhesion and mineralization processes. These findings confirm that the PCL/nHA/Ser scaffold integrates all components effectively, supporting its potential for application in tissue engineering.

DISCUSSION

The development and characterization of the PCL/nHA/Ser scaffold have demonstrated its potential as a biomimetic material for applications in tissue engineering. The results from SEM, EDX, XRD, and FTIR analyses provide compelling evidence of the scaffold's structural, compositional, and functional properties, highlighting its suitability for promoting mineralization and supporting cellular activity.

The SEM analysis revealed a uniform fibrous structure with interconnected porosity, closely mimicking the extracellular matrix of natural tissues. The smooth yet slightly roughened fiber surfaces, due to the incorporation of nHA and Ser, suggest enhanced bioactivity, which is critical for cell adhesion and proliferation. The homogeneous distribution of nHA within the fibers, observed through SEM and EDX mapping, ensures consistent mechanical properties and effective biomineralization across the scaffold.

The EDX analysis confirmed the presence of calcium and phosphorus, which are characteristic of nHA, indicating the successful integration. The calculated Ca/P ratio aligned with the theoretical values for hydroxyapatite, suggesting that the nHA maintains its structural integrity within the composite scaffold. This uniform elemental distribution further emphasizes the scaffold's ability to emulate the mineralized matrix of dentin and bone.

XRD analysis revealed the coexistence of crystalline and amorphous phases within the scaffold. The distinct peaks for PCL and nHA confirmed the retention of their structural identities, while the broadening of peaks suggested interactions with Ser, leading to partial disruption of crystalline order. The balance between crystalline and amorphous phases is particularly advantageous, as it provides mechanical stability while enhancing bioactivity. The crystalline regions contribute to the scaffold's strength, whereas the amorphous regions facilitate biological interactions and mineral deposition.

FTIR spectroscopy further validated the incorporation of PCL, nHA, and Ser into the scaffold. Characteristic peaks for PCL (C=O and CH_2 stretching), nHA (P-O and phosphate bending), and Ser (O-H and N-H stretching) were identified, confirming the composite nature of the scaffold. The overlapping peaks indicate interactions between these components, which could enhance the scaffold's ability to support biomineralization and promote tissue integration.

The incorporation of Ser into the PCL/nHA scaffold is particularly significant. Ser mimics the function of noncollagenous proteins (NCPs) in natural mineralization processes, enhancing hydroxyapatite nucleation and controlling crystal growth. This bioactive modification positions the scaffold as a superior alternative to conventional polymer-based materials, offering enhanced mineralization potential and cell compatibility.

The combination of PCL, a biodegradable polymer, with nHA and Ser addresses key limitations of individual materials. While PCL provides mechanical flexibility and a suitable platform for fiber formation, nHA improves osteoconductivity and mineral release, and Ser introduces bioactivity critical for tissue regeneration. This synergistic approach ensures that the scaffold not only mimics the structural and functional properties of the extracellular matrix but also facilitates cellular responses necessary for effective regeneration.

Negatively charged amino acids, including Ser through phosphorylation, play a crucial role in binding calcium and phosphate ions, facilitating nucleation and guiding the conversion of ACP into organized hydroxyapatite in Ser-incorporated scaffolds (18). The phosphorylation of Ser residues in proteins such as ameloblastin (AMBN) plays a critical role in enamel formation, acting as a post-translational modification necessary for proper mineralization and crystal organization (19). This underscores the potential of Ser in biomimetic scaffolds to mimic natural processes, stabilizing precursor minerals and guiding the deposition of hydroxyapatite.

Amino acid-functionalized scaffolds, such as those incorporating serine, have been shown to mimic NCPs and regulate nucleation, crystal growth, and signaling pathways crucial for dentin-pulp regeneration (20).

Electrospun scaffolds incorporating biofunctional molecules like amino acids offer promising results in dentin-pulp tissue engineering due to their controlled degradation, high porosity, and ability to promote mineralized tissue formation (21).

The incorporation of Ser into biomimetic systems for dentin and enamel remineralization demonstrates its critical role in stabilizing ACP and guiding its transformation into hydroxyapatite. As highlighted in previous studies, Ser's ability to form strong electrostatic interactions with calcium ions enhances the stability of ACP, mimicking natural biomineralization pathways such as those involving dentin sialophosphoprotein (DSPP) (22). When combined with carboxymethyl chitosan (CMC), Ser significantly prolongs the stability of ACP nanocomplexes, facilitating their sustained use in clinical applications. Additionally, Ser enhances the structural organization of remineralized layers, forming highly aligned, enamel-like crystals that resemble native tissue. These findings align with the current study, where Ser-incorporated PCL/nHA scaffolds promoted the deposition of orderly mineralized structures, demonstrating their potential as effective platforms for dentin repair.

The role of Ser-rich sequences in biomimetic remineralization is well-supported, as demon-

strated by the Aspartate-Ser-Ser (DSS) sequence in DPP. Peptides like 8DSS effectively bind to demineralized dentin collagen via electrostatic interactions, promoting hydroxyapatite nucleation and nano-crystal deposition on dentin surfaces and within tubules (23). This process significantly enhances the mechanical properties of demineralized dentin. The use of self-assembling peptides like P11-4, which promote enamel remineralization through a biomimetic approach (24), highlights the need for similar strategies in dentin. These peptides scaffold hydroxyapatite formation, a process potentially beneficial for the complex microstructure of dentin. This underscores the importance of researching biomimetic compounds tailored specifically to target dentin's unique properties.

Recent studies also highlight that phosphorylated amino acids such as phosphoserine can promote osteogenic differentiation and calcium deposition in nanohydroxyapatite-based scaffolds, underscoring the role of amino acid signaling in enhancing mineralization pathways (25).

Furthermore, biomimetic mineralized collagen-hydroxyapatite scaffolds engineered using synthetic analogues of noncollagenous proteins have shown enhanced intrafibrillar mineralization and osteogenic potential, supporting the rationale for amino acid-modified scaffolds in dental applications (26).

These findings highlight the potential of Ser to stabilize mineral precursors and direct organized crystal formation, aligning with the goals of this study to leverage Ser-incorporated scaffolds for biomimetic dentin remineralization.

Research highlighting the synergistic interaction between casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) and fluoride for enamel remineralization (27) indicates a promising strategy that might be extended to dentin. Considering dentin's higher organic composition and increased porosity, it becomes essential to develop methods capable of penetrating deeply and reinforcing the collagen framework. Accordingly, exploring the capability of CPP-ACP to enhance the intradentinal deposition of calcium and phosphate ions warrants comprehensive evaluation.

Limitations and future directions

While the current study successfully demonstrates the scaffold's potential, additional investigations are warranted to fully validate its performance. Future studies should explore the scaffold's behavior in biological environments, such as *in-vitro* and *in-vivo* mineralization assays, to assess its long-term stability, biocompatibility, and degradation profile. Furthermore, understanding the influence of Ser concentration on the scaffold's mechanical and biological properties could provide valuable insights for optimizing its design.

Future investigations should also evaluate the scaffold's antimicrobial efficacy and mechanical stability under simulated oral conditions, including dynamic loading and exposure to salivary enzymes, to better replicate clinical performance.

CONCLUSIONS

The nanofibrous scaffold exhibited structural and compositional properties, confirming the presence of PCL, nHA and Ser. The properties analyzed support its potential for biomineralization and tissue regeneration. The inclusion of Ser could enhance hydroxyapatite nucleation and cell attachment, making the scaffold a promising biomaterial for dentin repair. Further *in-vitro* and *in-vivo* studies are recommended to validate its clinical application.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article.

AUTHOR CONTRIBUTION

A.K.: conceptualization, methodology, software, writing & editing, data curation, writing - original draft preparation, visualization, investigation,

supervision, software, validation; S.R., J.S.: conceptualization, methodology, software, writing, review & editing, data curation, writing- original draft preparation, visualization, investigation, supervision, software, validation

DATA AVAILABILITY STATEMENT

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

INSTITUTIONAL REVIEW BOARD STATEMENT

Not applicable. This study did not involve human or animals.

INFORMED CONSENT STATEMENT

Not applicable. This study did not involve humans.

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