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Design of Peptide-Guided Mineralization towards Self-Enamel Regeneration and Its Translation Challenges in Dentistry

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ABSTRACT: This review critically examines peptide-guided biomimetic mineralization as a platform for autonomous enamel regeneration, with emphasis on amelogenin-derived peptides (P26, QP5, and LRAP), self-assembling peptide systems such as P11-4, and nanomaterial-assisted delivery platforms. Peptide systems regulate hydroxyapatite nucleation, crystal growth, and localized ion delivery, enabling the formation of enamel-like mineral within demineralized lesions. Injectable peptide hydrogels and nanocomposite mineralizing matrices are also discussed based on published literature. The review also discusses the principal translational barriers that currently limit clinical implementation, including peptide instability in saliva, uncontrolled ion release, incomplete enamel crystal orientation, weak adhesion to demineralized enamel, insufficient long-term mechanical durability, and the limited availability of high-quality randomized clinical evidence. Overall, amelogenesis-inspired smart biomaterials represent a promising strategy for autonomous enamel regeneration, although significant advances in biomaterial design, crystal organization, and clinical validation are still required for commercial production and clinical practice.

1. INTRODUCTION

Cementum, dentin, and enamel are three mineralized tissues that are essential for human tooth formation. In the human system, Sharpey's fibers are present and composed of collagen; they attach to the main fibers of the periodontal ligament. These attachments form the main structures and help anchor the cementum to the tooth root, securing the tooth generations. These fibers are crucial to tooth anchoring and are oriented roughly perpendicular to the cementum surface. Dentin's elasticity helps form the tooth's mass. Dentin is somewhat harder than bone but softer than enamel, featuring densely packed dentinal tubules. Dentin flexibility prevents the delicate enamel from cracking. At the dentin-enamel junction (DEJ), the two tissues are firmly bonded. [1-2]. Enamel covers the teeth as a crown to protect the dentin, and it is composed of hydroxyapatite crystals formed during amelogenesis; this tightly regulated biomineralization is a cascade process of amelogenin, enamelin, and ameloblastin, along with proteolytic enzymes such as metalloproteinase-20 (MMP-20) and kallikrein-related peptidase-4 (KLK4) [3–5].

The enamel layer covers the crown of the tooth and is unique because it is the only epithelial-derived calcified tissue in vertebrates. It is the hardest substance in the body. Its hardness is between that of iron and carbon steel, but it has higher elasticity [5]. Enamel hardness is a function of its high mineral content. Unlike bone and dentin (20–30% organic material by

weight), fully formed enamel contains very little protein (less than 1% organic material) [6, 7]. Therefore, within the body, teeth are the most resistant to deterioration and have provided important anthropological clues about how humans evolved. Although DNA analysis has taught us much about the migration patterns of our ancient ancestors, teeth have perhaps been more important in identifying our ancestors' food preferences and lifestyles. Their shape, wear patterns, and carbon isotope compositions are unique indicators of our past behaviors [8].

It's well known that human teeth are composed of three different mineralized tissues: cementum, dentin, and enamel. In the human body, enamel covers the teeth as a crown to products the fibres , and it is composed of hydroxyapatite crystals formed during amelogenesis; this tightly regulated biomineralization process is directed by amelogenin, enamelin, and ameloblastin, together with proteolytic enzymes such as metalloproteinase-20 (MMP-20) and kallikrein-related peptidase-4 (KLK4) [1–5]. These proteins regulate crystal nucleation, orientation, elongation, and maturation, ultimately generating the characteristic rod-like architecture responsible for the exceptional hardness and wear resistance of enamel [6–8]. Following tooth eruption, ameloblasts are lost, and mature enamel becomes acellular and incapable of intrinsic regeneration, making structural defects irreversible once the native mineral architecture is disrupted [9,10]. Current preventive and restorative approaches, including fluoride therapy and resin-based restorations, primarily arrest lesion progression or replace damaged tissue but do not reconstruct the hierarchical enamel structure or restore its original mechanical integrity [11,12].

This biological limitation has stimulated the development of biomimetic dental materials that emulate key events of amelogenesis rather than functioning as passive restorative fillers. Recent reports have clearly indicated that nanotechnology-based studies have improved the mechanical properties of dental composites. Much effort has been devoted to designing new self-healing systems with clinical feasibility. Most of this design is based on biomimetic nanoparticles incorporating peptides, proteins, and minerals. [13–16]. In peptide-guided mineralization, bioactive materials containing calcium phosphate nanostructures are incorporated with stimuli-responsive biomaterials. This smart design is highly promising and shifts the field toward smart regenerative platforms capable of directing hydroxyapatite nucleation, controlling crystal organization, and promoting autonomous remineralization in response to the oral environment [17–20]. However, significant translational challenges remain, including reproducing the hierarchical organization of native enamel, maintaining bioactivity under salivary and biofilm conditions, and achieving durable clinical performance. This review critically examines amelogenesis-inspired smart biomaterials for autonomous enamel restoration, with emphasis on the molecular mechanisms of biomimetic mineralization, peptide-functionalized nanomaterial platforms, and the key barriers that must be overcome for clinical translation.

2. METHODOLOGY

This review was conducted as a focused narrative synthesis of studies related to amelogenesis-inspired biomaterials and autonomous enamel regeneration. Literature was retrieved from PubMed, Scopus, Web of Science, and Embase using combinations of the keywords “amelogenesis,” “enamel regeneration,” “biomimetic mineralization,” “self-assembling peptides,” “peptide-guided remineralization,” and “smart dental biomaterials.” Peer-reviewed original research articles, translational studies, and recent review papers published primarily between 2005 and 2025 were considered. Studies were selected based on their relevance to enamel biomineralization mechanisms, peptide-functionalized nanomaterials, and stimuli-responsive restorative systems. The retrieved evidence was critically synthesized to identify current biomaterial strategies, mechanistic advances, and key barriers to clinical translation in autonomous enamel restoration.

3. PEPTIDE-GUIDED BIOMIMETIC MINERALIZATION

Biomimetic enamel regeneration increasingly relies on peptide-guided mineralization strategies that replicate key molecular events of amelogenesis rather than merely depositing mineral onto demineralized enamel. During natural enamel formation, amelogenin-derived protein assemblies regulate hydroxyapatite nucleation, crystal orientation, and anisotropic crystal growth within a highly organized extracellular matrix [21–23]. Contemporary biomimetic systems therefore employ short functional peptides that direct calcium phosphate organization, stabilize amorphous precursor phases, and promote enamel-like mineral formation under physiological conditions. Unlike conventional remineralization therapies, peptide-guided systems aim to reconstruct the hierarchical mineral architecture and improve the structural integrity of early enamel lesions. A schematic representation of the mechanisms of peptide-guided biomimetic mineralization during enamel regeneration is shown in Figure 1. Peptide-guided biomimetic enamel remineralization can be understood as a hierarchical pathway that closely replicates the fundamental stages of natural amelogenesis, integrating the complementary functions of P26, QP5, leucine-rich amelogenin peptide (LRAP), and the self-assembling peptide P11-4[24,25]. The step-by-step mechanism is In **Step 1 (Peptide Application**

and Diffusion), the therapeutic peptide systems were applied directly to the affected tooth surface, allowing them to diffuse deep into the subsurface porosities of the demineralized enamel. In **Step 2 (Triggered Self-Assembly and Scaffold Formation)**, Environmental triggers like local pH changes cause P11-4 to self-assemble into a beta-sheet scaffold, forming a strong 3D structure within the lesion matrix. In **Step 3 (Calcium/Phosphate Ion Sequestration)**, specialized peptides such as P26 (functioning as a nucleation-promoting peptide) and QP5 (which stabilizes amorphous calcium phosphate or ACP) actively capture, bind, and retain essential calcium and phosphate ions sourced from saliva or supplemental remineralizing solutions. In **Step 4 (Oriented Hydroxyapatite Nucleation and Growth)**, guided by crystal growth modulators like Leucine-Rich Amelogenin Protein (LRAP) alongside the established peptide framework, the sequestered ions drive the oriented nucleation and epitaxial growth of new hydroxyapatite crystals, successfully restoring the structural integrity of the remineralized enamel. This hierarchical regeneration process increases mineral density, restores enamel surface microhardness, reduces lesion permeability, and enhances resistance to future acid attack, thereby providing a mechanistically integrated strategy for biomimetic self-enamel regeneration that bridges developmental enamel biology with clinically applicable peptide-based remineralization technologies.

3.1 Amelogenin-derived peptides

Amelogenin-derived peptides represent the most extensively investigated biomimetic molecules for enamel regeneration because they preserve key functional domains involved in hydroxyapatite regulation. P26 promotes nucleation of calcium phosphate nanocrystals and supports the formation of elongated apatite structures resembling early enamel crystallites [26]. QP5 enhances crystal growth and promotes a more ordered mineral layer through selective interactions with calcium and phosphate ions, thereby improving mineral density within demineralized enamel [27]. In contrast, leucine-rich amelogenin peptide (LRAP) exhibits a broader regulatory role by influencing crystal orientation, matrix organization, and mineral maturation through supramolecular self-association [28,29]. Comparative studies indicate that P26 primarily initiates nucleation, QP5 accelerates crystal growth, and LRAP contributes most effectively to structural organization and enamel-like crystal alignment, suggesting complementary rather than redundant functions in biomimetic mineralization.

3.2 Self-assembling peptide systems

Among clinically relevant biomimetic technologies, the self-assembling peptide P11-4 has demonstrated the strongest translational potential. P11-4 remains soluble under physiological conditions but undergoes triggered self-assembly within subsurface carious lesions to form a three-dimensional nanofibrillar scaffold that resembles the transient protein matrix of developing enamel [30,31]. This system concentrates calcium and phosphate ions from saliva and local fluids, promoting in situ hydroxyapatite nucleation throughout the lesion body rather than only at the enamel surface [32]. Clinical studies have reported significant remineralization of non-cavitated enamel lesions, increased surface microhardness, and reduced lesion progression following P11-4 treatment, although the regenerated mineral remains structurally distinct from fully mature enamel and long-term durability data are still limited [33–35].

3.3 Nanomaterial-assisted peptide delivery

Nanostructured carriers have emerged as effective platforms for bioactive peptide-based remineralization. These nanomaterials serve as stabilizing and protective carriers against enzymes and also regulate mineralization. Recent research indicates that mesoporous silica nanoparticles provide a high surface area and a tunable pore architecture, enabling sustained peptide loading and release while protecting peptides from enzymatic degradation in saliva [36,37]. Another well-reported example is calcium phosphate nanoparticles; they perform dual functions as both delivery vehicles and mineral reservoirs. They supply calcium and phosphate ions that synergize with peptide-mediated nucleation to enhance apatite formation [38]. Bioactive glass nanoparticles release calcium, phosphate, and silicate ions that stimulate biomineralization and improve mineral density and interfacial bonding with demineralized enamel [39]. Peptide-functionalized nanomaterials therefore integrate molecular guidance with localized ion delivery, enabling more homogeneous mineral deposition, promoting deeper lesion remineralization, and improving control over crystal growth compared with plain peptide and ion therapy alone [40].

3.4. Scientific challenges

Despite substantial progress over the last few years, peptide-guided biomimetic mineralization has not yet achieved complete regeneration of the native enamel architecture. The principal challenges are (i) reproducing the highly anisotropic orientation of enamel prisms and the hierarchical organization generated during amelogenesis [41]; (ii) mineral deposition often remains

shallow, limiting the depth and mechanical benefits of remineralization in advanced subsurface lesions [42]; (iii) bioactive peptides are susceptible to enzymatic degradation and dilution within the dynamic salivary environment, reducing their residence time and therapeutic efficacy [43]; (iv) most available evidence derives from in vitro or short-term clinical studies, and long-term resistance to cyclic loading, acidic challenges, biofilm activity, and wear remains insufficiently established [44,45]; and (v) future biomimetic systems must be designed to regulate the orientation of minerals deposition with the peptide and also to prevent infections.

4. BIOMATERIAL PLATFORMS FOR ENAMEL REGENERATION

The current generation of enamel-regenerative biomaterials is designed not only to study passive remineralization agents but also to develop multifunctional platforms that combine peptide-guided mineralization, ion delivery, antibacterial activity, and structural control of hydroxyapatite growth. The most promising systems are currently reported based on integrated polymer networks combined with bioactive nanomaterials [46–48]. This multifunctional system creates artificial microenvironments that emulate selected aspects of the enamel extracellular matrix. This polymer network works not only as a bulk restorative material, but it also functions like biomimetic peptides at the lesion site, regulates calcium and phosphate availability, and promotes the formation of organized, enamel-like mineral in physiological conditions.

4.1 Injectable peptide hydrogels

Injectable peptide hydrogels provide a minimally invasive strategy for localized enamel regeneration by acting as temporary biomimetic matrices. Self-assembling peptide hydrogels, particularly those based on P11-4 and ELR-related peptide systems, undergo in situ nanofibrillar assembly after application to demineralized enamel, generating a three-dimensional network that resembles the transient protein framework present during amelogenesis [49,50]. This hydrated matrix retains calcium and phosphate ions, facilitates peptide-mediated nucleation, and supports mineral deposition throughout the subsurface lesion rather than only on the enamel surface [51]. The principal advantage of injectable hydrogels is their ability to infiltrate early enamel lesions and maintain prolonged contact with the mineralizing interface while remaining compatible with minimally invasive clinical protocols [52].

4.2 Nanocomposite mineralizing matrices

Nanocomposite-based mineralizing matrices are made with a combination of bioactive peptides and functional nanomaterials to improve mineralization efficiency and structural stability. Mesoporous silica nanoparticles enable sustained peptide loading and controlled release, while calcium phosphate nanoparticles simultaneously function as mineral precursors and peptide carriers [53,54]. Bioactive glass nanoparticles contribute additional calcium, phosphate, and silicate ions that enhance hydroxyapatite formation and increase mineral density within demineralized enamel [55]. These hybrid matrices provide both molecular guidance and localized ion delivery, producing deeper remineralization and more homogeneous enamel-like mineral deposition than peptide-only formulations [56].

4.3 Surface-guided enamel-like crystal growth

A critical objective of biomimetic enamel regeneration is not simply mineral deposition but reconstruction of the oriented crystal architecture characteristic of mature enamel. Surface-guided mineralization strategies employ peptide-functionalized nanoparticles, mineral-binding polymers, and nanostructured templates that direct anisotropic hydroxyapatite growth along preferred crystallographic orientations [57,58]. Amelogenin-derived peptides adsorbed onto engineered surfaces can organize amorphous calcium phosphate precursors and promote the formation of elongated apatite crystallites with improved structural alignment [59]. Although current systems have partially reproduced enamel prism-like organization, complete restoration of native hierarchical architecture remains a major challenge, particularly under the dynamic mechanical, chemical, and biological conditions of the oral environment [60,61].

5. TRANSLATIONAL BARRIERS

Despite significant advances in peptide-guided biomimetic mineralization, the translation of enamel-regenerative biomaterials from laboratory research to routine clinical practice remains limited. Current systems can promote hydroxyapatite formation under controlled conditions, but they have not yet achieved predictable regeneration of native enamel architecture within the complex oral environment. The principal translational barriers involve peptide stability, controlled mineral delivery, crystal organization, interfacial adhesion, mechanical durability, and limited quality of clinical evidence.

5.1 Stability of bioactive peptides in saliva

Bioactive peptides derived from amelogenin and related enamel proteins are highly susceptible to enzymatic degradation, dilution, and clearance within saliva and dental biofilms. Proteolytic enzymes present in the oral cavity can reduce peptide residence time and diminish their ability to regulate hydroxyapatite nucleation and crystal growth [62,63]. Strategies such as peptide cyclization, incorporation into self-assembling hydrogels, and nanoparticle-mediated protection have improved stability, but sustained biological activity under clinically relevant conditions remains insufficiently established [64].

5.2 Controlled ion release

Effective enamel regeneration requires coordinated delivery of calcium and phosphate ions throughout the lesion body rather than rapid surface precipitation. Many experimental systems exhibit burst ion release, resulting in superficial mineral deposition that restricts diffusion into deeper demineralized regions [65]. Nanostructured carriers, including mesoporous silica, calcium phosphate nanoparticles, and bioactive glass, have been developed to provide sustained and localized ion release, yet achieving temporally controlled mineralization comparable to natural amelogenesis remains a major challenge [66,67].

5.3 Crystal orientation comparable to native enamel

The defining feature of mature enamel is its highly anisotropic prism architecture, generated through precisely regulated crystal orientation during amelogenesis. Most biomimetic systems produce hydroxyapatite crystals with limited long-range alignment, and regenerated mineral often lacks the hierarchical organization required for native mechanical performance [68,69]. Reproducing enamel prism orientation and inter-prismatic organization is therefore one of the most critical unresolved scientific problems in biomimetic enamel regeneration.

5.4 Adhesion to demineralized enamel

Successful clinical regeneration requires durable integration between newly formed mineral and the existing demineralized enamel substrate. Conventional remineralization approaches frequently produce weakly bonded surface deposits that are susceptible to mechanical removal and acidic dissolution [70]. Peptide-functionalized nanomaterials and biomimetic interfacial coatings have improved mineral adhesion and continuity across the enamel interface, but long-term interfacial stability under salivary, thermal, and biofilm conditions remains inadequately characterized [71,72].

5.5 Long-term mechanical durability

Most experimental studies evaluate remineralization using short-term outcomes such as surface microhardness, mineral density, or crystal formation. However, regenerated enamel must withstand cyclic occlusal loading, thermal fluctuations, acidic challenges, and wear over prolonged periods [73]. The fatigue resistance, fracture toughness, and abrasion behavior of biomimetically regenerated enamel remain insufficiently understood, and standardized long-term durability studies are still lacking [74].

5.6 Lack of randomized clinical evidence

Although early clinical studies of self-assembling peptide systems have reported favorable outcomes for non-cavitated enamel lesions, high-quality randomized controlled trials remain limited [75]. Most available evidence is derived from in vitro studies, ex vivo models, or small clinical cohorts with relatively short follow-up periods. Robust multicenter randomized clinical trials comparing biomimetic peptide therapies with established remineralization and restorative treatments are required before these technologies can be incorporated into routine clinical practice [76].

6. CONCLUSION

Amelogenesis-inspired biomaterials are redefining enamel repair by shifting the field from passive remineralization toward biologically guided mineral regeneration. The strongest evidence currently supports peptide-directed strategies, particularly amelogenin-derived peptides and self-assembling peptide systems, which can regulate hydroxyapatite nucleation, promote crystal growth, and generate enamel-like mineral within early demineralized lesions. Integration of these peptides with nanostructured delivery platforms, including mesoporous silica, calcium phosphate nanoparticles, and bioactive glass, has further improved peptide stability, controlled ion release, and the spatial regulation of biomineralization. Despite these advances, current technologies do not yet reproduce the hierarchical prism architecture, mechanical performance, and long-term durability

of native enamel. Major translational barriers include peptide degradation in saliva, limited depth of remineralization, incomplete crystal orientation, insufficient adhesion to demineralized enamel, and the lack of robust randomized clinical trials. Future progress will depend on biomaterial platforms that combine sustained peptide activity, programmable ion delivery, and precise control of enamel crystal organization under clinically relevant oral conditions. Rather than simply repairing restorative materials, next-generation smart biomaterials should aim to recapitulate the fundamental principles of amelogenesis and enable autonomous regeneration of functional enamel.

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M.Latha Mala Priyadharshini and K.Chitra Priya Pandiyan – Supervision and Data Collections.

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Figure caption

Figure 1. Mechanisms of peptide-guided biomimetic mineralization during enamel regeneration. Schematic illustration of P26, QP5, LRAP, and P11-4 in enamel-like hydroxyapatite nucleation, crystal growth, and organization.

Figure 2. Biomaterial platforms enabling biomimetic enamel regeneration. Integrated peptide-delivery systems using hydrogels and bioactive nanomaterials for controlled enamel remineralization.

Figure 3. Translational barriers limiting clinical implementation of amelogenesis-inspired enamel regeneration. Key biological, material, and clinical barriers affecting the translation of biomimetic enamel regeneration into routine practice.

Figure 1.

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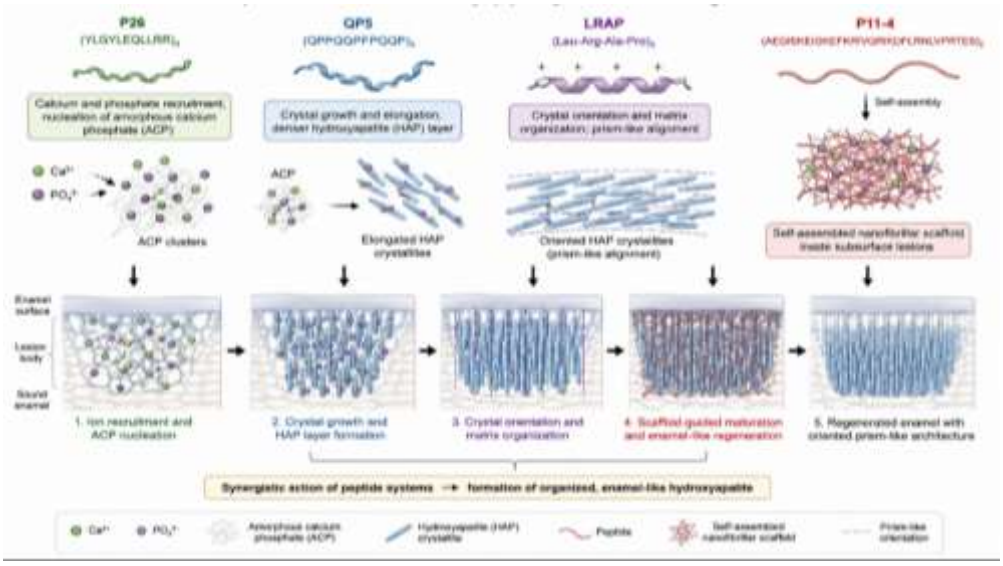
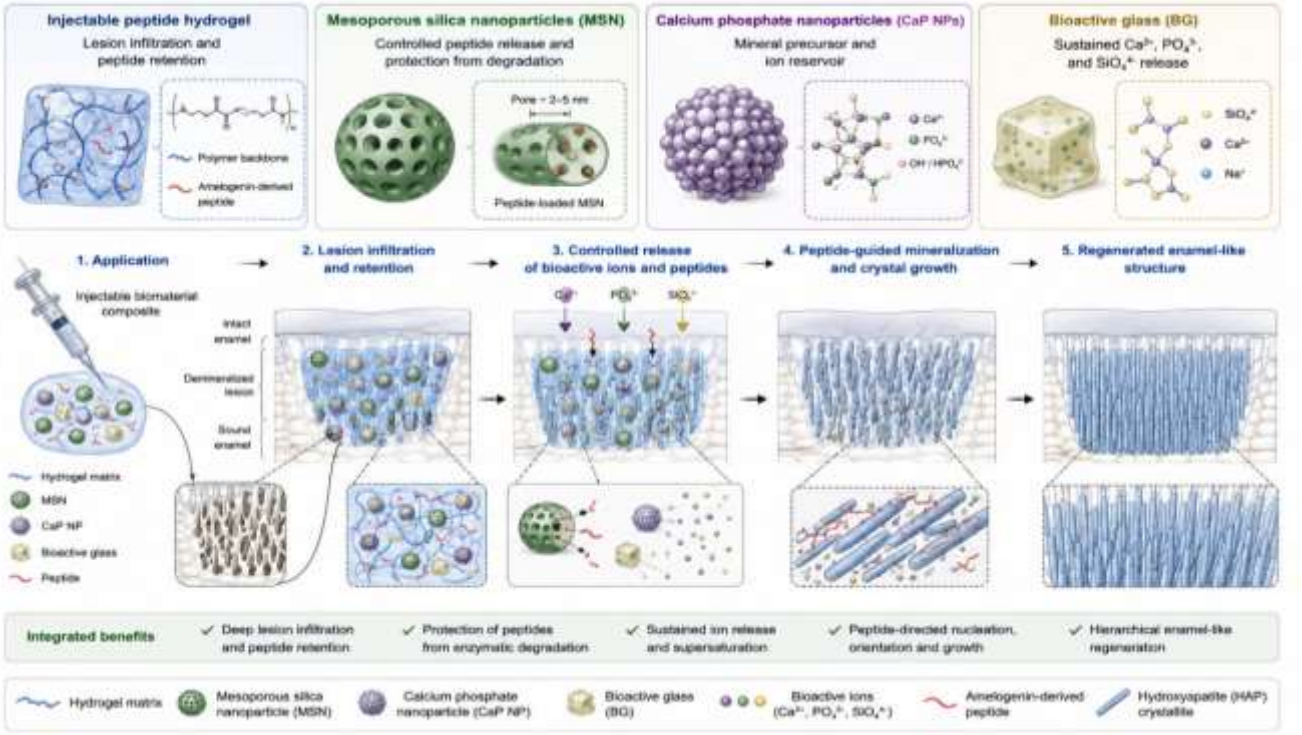


Figure 2.



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Figure 3.

