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Applications and Research Progress of Multifunctional Hydrogels in Periodontal Tissue Regeneration

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Abstract

Hydrogels, as a novel class of biomaterials, exhibit broad application prospects and are widely used in tissue engineering. In the field of periodontology within dental medicine, hydrogels can be employed for periodontal tissue regeneration to repair the damage caused by periodontitis. At present, various hydrogels have been developed to control periodontal inflammation and repair periodontal tissues. This article, based on domestic and international literature, provides a brief review of hydrogels used in periodontal tissue regeneration.

Keywords

Hydrogel, Periodontal Tissue Regeneration, Scaffold Material, Bone Defect Repair

1. Introduction

Periodontal tissue refers to the supporting structures of teeth, including the alveolar bone, gingiva, and periodontal ligament. When periodontal tissues are subjected to inflammatory damage, chronic inflammatory conditions such as gingivitis, periodontal pocket formation, and alveolar bone resorption may occur. Severe periodontitis can lead to the destruction and loss of periodontal tissues [1]. Currently, the treatment of periodontitis primarily focuses on antibacterial, anti-inflammatory, and tissue regeneration strategies, with tissue regeneration being the ultimate goal of periodontal treatment. However, due to the complexity of the inflammatory mechanisms in periodontitis, the outcomes of periodontal regeneration treatments often fall short of expectations, leaving many issues unresolved.

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Hydrogels, with their three-dimensional network structure and hydrophilic nature, can serve as suitable scaffolds for drug delivery and the encapsulation of other active components. At present, hydrogels have been applied in various research areas of oral medicine. Smart hydrogels, which can respond to environmental stimuli, have been developed for applications such as tissue regeneration, controlled drug release, and wound healing. These smart hydrogels have been widely applied in periodontal tissue regeneration research. This article reviews the applications of hydrogels in periodontal tissue regeneration, aiming to contribute valuable insights into achieving successful periodontal tissue regeneration.

2. Hydrogels

Hydrogels were first discovered in 1960 by Wichterle and Lim [2]. They prepared the earliest hydrogel using hydroxyethyl methacrylate as the monomer and ethylene glycol dimethacrylate as the crosslinking agent. This hydrogel was initially used as a material for contact lenses and was synthesized mainly through simple chemical crosslinking. In the 1970s, research shifted towards environmentally responsive hydrogels, which could swell in response to environmental stimuli (e.g., temperature, pH, and biomolecule concentration), making them suitable for controlled drug delivery [3]. By the 1990s, more researchers began to employ physical crosslinking methods to improve the performance of hydrogels. In the 2010s, hydrogels were further improved by using covalent crosslinking of complementary functional groups under physiological conditions, significantly enhancing the properties of smart hydrogels and expanding their application potential.

Based on their composition, hydrogels can be classified into three types: natural polymer hydrogels, synthetic polymer hydrogels, and hybrid hydrogels that combine natural and synthetic polymers.

- **Natural Polymer Hydrogels**: These include polysaccharides (e.g., chitosan, alginate, cellulose), biological polymers (e.g., nucleic acids and DNA), and polyamides (e.g., collagen) [4].
- **Synthetic Polymer Hydrogels**: Composed of materials such as polyethylene glycol, polyacrylic acid and its derivatives, polyvinyl alcohol, and polyoxyethylene, these hydrogels exhibit excellent physical and chemical properties.
- **Hybrid Hydrogels**: These hydrogels combine the advantages of both natural and synthetic polymers, improving mechanical strength and biocompatibility. For example, Zang *et al.* [5] developed a thermosensitive hybrid hydrogel from chitosan/β-glycerophosphate (CS/β-GP) loaded with BMP-7 and ornidazole. This hydrogel demonstrated improved physicochemical properties, stable release of BMP-7 and ornidazole, significant antibacterial activity, reduced osteoclast numbers, increased osteoblast numbers, and promoted periodontal tissue regeneration in Class III furcation defects.

Hydrogels possess several advantages:

1) Hydrogels can swell to absorb and retain large amounts of water without dissolving.

2) They exhibit mechanical strength and viscoelasticity, allowing them to maintain structural stability under external forces, such as those exerted during mastication and swallowing.

3) They possess excellent biocompatibility and biodegradability, decomposing into harmless final products.

4) Smart hydrogels exhibit environmental responsiveness, meaning they can sense external physical and chemical changes and adjust their swelling or volume accordingly to adapt to external conditions [6].

These features make hydrogels suitable materials for tissue regeneration engineering.

3. Periodontal Tissue Regeneration

The ideal goal of periodontal tissue regeneration is to achieve the formation of new cementum, new alveolar bone, and periodontal ligament fibers connecting both the alveolar bone and cementum [7]. At present, the primary techniques for periodontal tissue regeneration are guided tissue regeneration (GTR) and guided bone regeneration (GBR). Traditional GTR and GBR techniques use graft materials and membranes, but these often lack sufficient mechanical strength, exhibit volume instability under external forces, and are limited in their applicability to cases of extensive tissue defects [8]. To overcome these drawbacks, tissue engineering techniques have been introduced. Periodontal tissue regeneration through tissue engineering requires the following components:

1) Stem cell populations with differentiation potential;

2) Scaffold materials or matrices to maintain space and serve as carriers for active substances;

3) Growth factors;

4) Adequate blood supply [9].

Hydrogels are widely applied in periodontal tissue regeneration due to their three-dimensional porous structure, making them suitable for use as biomembranes and scaffold structures. By adjusting the composition and ratio of polymers, the surface porosity of hydrogels can be tailored to meet specific needs. Hydrogel scaffolds with controlled pore structures can support the adhesion and proliferation of human periodontal ligament fibroblasts (HPDLFs) and human gingival fibroblasts (HGFs) [10].

In addition, hydrogels serve as excellent carriers for encapsulating stem cells, maintaining their viability within the scaffold. For instance, when encapsulated in hydrogel scaffolds, stem cells such as dental pulp stem cells (DPSCs) and mesenchymal stem cells (MSCs) derived from cranial neural crests can be delivered to bone defect sites, providing space and a microenvironment for proliferation and osteogenic differentiation [11]. Moreover, hydrogels are effective carriers for drug delivery systems, allowing for antibacterial and anti-inflammatory properties while promoting tissue regeneration.

For example, Koch *et al.* [12] demonstrated that two self-assembling peptide

hydrogels (SAPs), P11-28 and P11-29, exhibited significant antibacterial activity against *Porphyromonas gingivalis*, a key periodontal pathogen. Furthermore, these hydrogels enhanced the osteogenic differentiation potential of human dental follicle stem cells (DFSCs), suggesting that P11-SAP hydrogels could be used as promising therapeutic strategies for periodontal treatment.

4. Hydrogels for Periodontal Tissue Regeneration

4.1. Thermosensitive Hydrogels

Thermosensitive hydrogels exhibit sol-gel phase transitions in response to temperature changes. Below a critical temperature, they exist in a liquid state, while above this temperature, they solidify into a gel. This property makes them widely applicable in the field of dentistry, especially in controlled drug release and delivery of active components, offering great potential for applications.

For example, Liu *et al.* [13] developed a thermosensitive hydrogel using polyethylene glycol diacrylate (PEG-DA) as a scaffold material, with dithiothreitol (DTT) and stromal cell-derived factor-1 (SDF-1) as carriers. When applied to a rat periodontitis model, the hydrogel demonstrated excellent therapeutic effects, including reducing reactive oxygen species (ROS) damage, activating the Wnt/β-catenin signaling pathway, alleviating inflammatory responses, and promoting periodontal bone regeneration.

Chitosan-based thermosensitive hydrogels undergo sol-gel transitions when the temperature increases. Their flexibility allows them to effectively fill bone defects and serve as scaffolds for delivering drugs and active components [14]. Chen Xi *et al.* [15] prepared an injectable thermosensitive hydrogel using chitosan, β-glycerophosphate, gelatin, and tacrolimus. This hydrogel was applied to a rat model of periodontitis. The results showed that the hydrogel significantly reduced alveolar bone destruction caused by periodontitis and promoted the formation of new bone tissue, demonstrating its potential for anti-inflammatory and periodontal tissue regeneration applications.

Additionally, hydrogels can be combined with various components for drug release. Wang *et al.* [16] designed a thermosensitive hydrogel incorporating mesoporous silica nanoparticles into a PDLLA-PEG-PDLLA hydrogel. This hydrogel enabled continuous release of stromal cell-derived factor-1 (SDF-1) and metformin to simulate the "recruitment-osteogenesis" cascade of mesenchymal stem cells (MSCs) for diabetic periodontal bone regeneration. The results showed that this hydrogel could restore inhibited migration and osteogenesis of rat bone marrow mesenchymal stem cells (rBMSCs) under high-glucose conditions, recruit rBMSCs to periodontal defect sites, and significantly promote periodontal bone regeneration in type 2 diabetic rats.

4.2. pH-Sensitive Hydrogels

pH-sensitive hydrogels respond to changes in environmental pH by undergoing volume changes. These hydrogels contain acidic or basic groups that ionize as the

pH changes, causing the hydrogel to swell or contract [17].

In periodontitis, the microenvironment of periodontal tissues becomes acidic due to bacterial aggregation and metabolic activities. pH-sensitive hydrogels can function effectively in this acidic environment. For instance, Bako *et al.* [18] developed a pH-sensitive nanocomposite hydrogel (NCHG) drug delivery system to release mineral trioxide aggregate (MTA) and chlorhexidine. The system released MTA within 12 hours and sustained chlorhexidine release for over 7 days, demonstrating significant antibacterial effects and reducing systemic side effects.

Similarly, Yu *et al.* [19] investigated a chitosan-based pH-sensitive hydrogel loaded with N-phenyl bromothiazole (PTB) and applied it to a rat model of periodontitis. The hydrogel significantly reduced inflammatory cell infiltration and collagen matrix loss during the induction phase and increased collagen deposition during the recovery phase. These results suggest that PTB-loaded chitosan-based pH-sensitive hydrogels can delay the onset of experimental periodontitis and promote its recovery.

Furthermore, researchers have used pH-responsive nanospheres to encapsulate metronidazole (MTZ) or N-phenyl bromothiazole ammonium bromide (PTB) for subgingival delivery in periodontitis treatment. These pH-sensitive nanospheres demonstrated excellent drug release properties and significantly reduced inflammatory responses in experimental periodontitis models [20].

Currently, research on pH-sensitive hydrogels has primarily focused on controlled drug release to manage periodontitis progression, while studies on their role in periodontal tissue regeneration have largely been limited to observing inflammatory responses. Additionally, dual-responsive hydrogels sensitive to both temperature and pH have been developed. For example, Li *et al.* [21] synthesized a smart temperature-pH-sensitive nanohydrogel using nanocellulose, thermosensitive monomers (NIPAM), and pH-sensitive monomers (AA and AM). This hydrogel released higher levels of 5-fluorouracil under acidic conditions and at 40˚C. However, such dual-responsive hydrogels have yet to be clinically applied in oral medicine and require further research.

4.3. Photosensitive Hydrogels

Photosensitive hydrogels undergo sol-gel phase transitions under prolonged light exposure, enabling the release of encapsulated active components. Ma *et al.* [22] encapsulated periodontal ligament stem cells (PDLSCs) in an injectable, photocrosslinkable composite hydrogel made of methacrylated gelatin (GelMA) and polyethylene glycol diacrylate (PEGDA). When injected into alveolar bone defects and exposed to light, the hydrogel significantly promoted bone tissue formation and completely filled the defect area. Goto *et al.* [23] evaluated the *in vitro* feasibility of a visible-light-cured riboflavin-gelatin-based hydrogel (GelMA-RF) as a scaffold material for bone regeneration. Under osteogenic induction conditions, osteoblasts encapsulated in the GelMA-RF hydrogel exhibited significantly increased expression of late-stage osteogenic genes, indicating that GelMA-RF

hydrogels are excellent scaffolds for osteoblast encapsulation. Furthermore, these hydrogels not only aided bone regeneration but also showed potential for treating complex bone defects associated with periodontitis and other destructive bone diseases.

Photosensitive hydrogels can also serve as barrier membranes for guided periodontal tissue regeneration. Wei *et al.* [24] used digital light processing technology and photocrosslinkable hydrogels to develop a novel biphasic layered structure consisting of a non-stoichiometric silicon-calcium phosphate scaffold and a GelMA/silanized hydroxypropyl methylcellulose (GelMA/Si-HPMC) hydrogel membrane. This personalized hydrogel membrane demonstrated excellent cell viability and osteogenic potential *in vitro* and showed strong periodontal regenerative capacity in vivo in canine models with periodontal defects.

Additionally, researchers [25] designed glucose-sensitive photocrosslinked hydrogels for the treatment of periodontitis in diabetic patients. Using photocrosslinking methods, glucose oxidase was immobilized on a chitosan-based hydrogel. This hydrogel responded to changes in blood glucose concentration to release drugs and supported the adhesion of osteoblasts (MC3T3-E1), providing a promising approach for localized drug delivery and bone formation in diabetic patients with periodontitis.

4.4. Enzyme-Sensitive Hydrogels

Enzyme-sensitive hydrogels are hydrogels that undergo sol-gel phase transitions under enzymatic action [26]. The relatively constant temperature of the oral cavity provides favorable conditions for enzymatic reactions, allowing enzyme-sensitive hydrogels to exhibit significant effects in periodontal therapy and tissue regeneration.

Guo *et al.* [27] developed a matrix metalloproteinase-8 (MMP-8)-responsive polyethylene glycol hydrogel for oral drug delivery. MMP-8 is closely related to bone metabolism and increases in concentration during periodontitis progression. The hydrogel, composed of a polyethylene glycol scaffold containing diacrylate groups and a cysteine-terminal peptide crosslinker (CGPQG↓IWGQC), could be degraded by MMP-8, releasing encapsulated drugs such as minocycline hydrochloride, bovine serum albumin, or antimicrobial peptides. This hydrogel allowed slow drug release in response to increasing MMP-8 concentrations, effectively controlling periodontitis progression.

Similarly, Liu *et al.* [28] synthesized a smart gingipain-responsive hydrogel (PEGPD@SDF-1) using polyethylene glycol diacrylate (PEGDA), dithiothreitol (DTT), and functional peptide modules (FPM). The hydrogel responded specifically to gingipain, a key protease in periodontitis, releasing short antimicrobial peptides to inhibit *Porphyromonas gingivalis* growth. In addition, this hydrogel promoted the proliferation, migration, and osteogenic differentiation of PDLSCs and recruited $CD90^+/CD34^-$ mesenchymal cells, inducing bone formation. These results highlight the significant applications of enzyme-sensitive hydrogels in

drug delivery, antibacterial activity, and periodontal tissue regeneration.

The different types of hydrogels, along with their components and main findings, are summarized in Table 1, while Table 2 provides a summary of their mechanisms of action, applications, advantages, and limitations in periodontal regeneration.

Table 1. Summary of hydrogel types, components, and main findings in periodontal regeneration.

Types	Components	Main findings	Ref.
Thermo-sensitive hydrogels	PEG-DA/DTT/SDF-1	Reduced ROS damage; activated Wnt/β-catenin; enhanced bone regeneration	[13]
	CS/β-GP/Gel/FK506	Reduced alveolar bone destruction; promoted new bone formation	[15]
	PDLLA-PEG-PDLLA/MSN/SDF-1/MET	Restored RBMSCs activity; enhanced diabetic periodontal bone regeneration	[16]
pH-sensitive hydrogels	NC hydrogel/MTA/CHX	Sustained release >7 days; significant antibacterial effects	[18]
	CS/PTB	Delayed periodontitis; increased collagen deposition	[19]
	PLGA/CS/MTZ/PTB	Reduced inflammatory response	[20]
Photo-sensitive hydrogels	GelMA/PEGDA/PDLSC	Promoted bone tissue formation; complete defect filling	[22]
	GelMA-RF	Enhanced osteogenic gene expression	[23]
	NCSI/GelMA/Si-HPMC	Good cell viability; barrier function	[24]
	CS/GOx	Enhanced cell attachment; suitable for diabetic patients	[25]
Enzyme-sensitive hydrogels	PEG/CGPQG↓IWGQC/drugs	Controlled periodontitis progression	[27]
	PEGDA/DTT/FPM/SDF-1	Promoted PDLSC proliferation and osteogenic differentiation	[28]

Abbreviations: PEG-DA, poly(ethylene glycol) diacrylate; DTT, dithiothreitol; SDF-1, stromal cell-derived factor-1; CS, chitosan; β-GP, β-glycerophosphate; Gel, gelatin; FK506, tacrolimus; MSN, mesoporous silica nanoparticles; MET, metformin; NC, nanocomposite; MTA, mineral trioxide aggregate; CHX, chlorhexidine; PTB, N-benzyl benzothiazolium bromide; PLGA, poly(lactic-co-glycolic acid); MTZ, metronidazole; GelMA, gelatin methacryloyl; PEGDA, poly(ethylene glycol) diacrylate; PDLSC, periodontal ligament stem cells; RF, riboflavin; NCSI, non-stoichiometric silicate; Si-HPMC, silanized hydroxypropyl methylcellulose; GOx, glucose oxidase; MMP-8, matrix metalloproteinase-8; FPM, functional peptide module.

Table 2. Comparison of different types of hydrogels: mechanisms and applications in periodontal regeneration.

Hydrogel Type	Mechanism of Action	Applications in Periodontal Regeneration	Advantages	Limitations
Temperature -Sensitive	Sol-gel transition occurs above or below a critical temperature, enabling injectable forms that solidify in situ.	Drug delivery (e.g., SDF-1, metformin), filling bone defects, reducing inflammation, promoting bone regeneration.	- Injectable and adaptable to irregular defects. - Controlled drug release. - Suitable for minimally invasive procedures.	- Limited stability in dynamic oral environments. - Risk of premature gelation or drug release.
pH-Sensitive	Swelling or deswelling in response to environmental pH changes.	Responsive drug release in acidic environments of periodontitis, controlled inflammation, and antimicrobial activity.	- Precise release in pathological microenvironments. - Prolonged drug activity with reduced systemic effects.	- Primarily focuses on drug release. - Limited application for tissue regeneration beyond inflammation control.

Continued

Light-Sensitive	Gelation or drug release triggered by specific wavelengths of light.	Scaffolding for bone and periodontal ligament regeneration, barrier membranes for guided tissue regeneration (GTR).	- Precise spatial and temporal control. - Enhanced encapsulation of stem cells or growth factors.	- Requires external light source. - Limited penetration depth of light in biological tissues.
Enzyme-Sensitive	Degradation or sol-gel transition in response to specific enzymes like MMP-8, often overexpressed in periodontitis.	Controlled drug release, antibacterial effects, and bone regeneration by leveraging enzymatic activity in periodontal disease.	- Highly specific drug release. - Synergistic control of inflammation and tissue regeneration.	- Dependence on enzyme activity variability. - Potential off-target effects in non-enzymatic environments.

5. Hydrogels and the Molecular and Cellular Mechanisms in Periodontal Tissue Interaction

5.1. Effects of Hydrogel Properties on Periodontal Tissue Regeneration

The repair of periodontal bone defects remains one of the greatest challenges in periodontal tissue regeneration therapy. For tissue regeneration scaffolds, porosity plays a crucial role in bone regeneration as it allows nutrient and oxygen exchange, waste removal, and inward growth of bone tissue and blood vessels. The porosity and interconnectivity of scaffolds affect their permeability, thereby influencing the rate of de novo tissue formation, while pore size and geometry control osteogenesis. Researchers often choose hydrogels with high porosity as scaffold materials to mimic the natural microenvironment of bone tissue. By replicating the extracellular matrix (ECM) of real bone tissue, hydrogels create an ideal environment for cell proliferation, adhesion, and differentiation, ultimately promoting new bone formation. Increased porosity leads to a larger surface area, providing additional attachment and growth sites for cells. Franziska *et al.* [29] studied the effects of two single-component and two complementary β-sheet-forming self-assembling peptide (SAP) systems on hydrogel performance, finding that single-component systems had approximately 30% higher porosity compared to complementary systems. The single-component P11-SAP system demonstrated 1.7 times higher cell adhesion and growth, making it a promising scaffold for periodontal regeneration therapy due to its tunable ECM-mimicking nanofibrous structure and favorable cell interactions. Other studies have also shown that appropriate porosity positively influences the regeneration of alveolar bone in periodontitis. For instance, a β-TCP/CTS/SBA-15 scaffold loaded with MET was implanted in the alveolar bone defect regions of periodontitis-induced rats. After 12 weeks, micro-CT and histological analyses revealed healing and mineralization of the alveolar bone in the rat periodontitis model [30].

Mechanical properties, such as hardness, elastic modulus, and viscoelasticity, are critical factors affecting the effectiveness of hydrogels in periodontal tissue

regeneration. Periodontal tissues possess a complex mechanical environment; therefore, the mechanical properties of hydrogels must match the physiological requirements of periodontal tissues to support regeneration and restore functionality. By fine-tuning parameters such as cross-linking density and molecular chain length, and incorporating reinforcing components like nanofibers or nanoparticles, the mechanical properties of hydrogels can be customized to closely mimic the mechanical characteristics of natural bone. Danilo *et al.* [31] prepared a nanocomposite hydrogel by combining lipid nanoparticle-loaded grape seed extract, simvastatin, and chitin nanocrystals. This hydrogel was 3D printed into a bilayer membrane with antimicrobial properties and multiscale porosity for periodontal tissue regeneration. The addition of chitin nanocrystals significantly enhanced the mechanical performance of the structure. Similarly, Hu *et al.* [32] designed a Nap-Alen/HAP supramolecular hydrogel composite with an appropriate hydroxyapatite (HAP) ratio. The incorporation of HAP not only enhanced mechanical properties but also formed a 3D sparse porous network structure that effectively promoted periodontal bone regeneration.

The degradation rate of hydrogels plays an essential role in periodontal tissue regeneration. A rational degradation rate ensures that the scaffold provides mechanical support while regulating cellular behavior by controlling the microenvironment, ultimately achieving a dynamic balance between tissue regeneration and scaffold degradation. The degradation rate of hydrogels must align with the repair timeline of periodontal tissues. For example, the regeneration of alveolar bone typically requires weeks to months, necessitating an extended scaffold degradation rate to provide sufficient mechanical support. If the scaffold loses its mechanical strength prematurely, it may collapse or reduce cell adhesion. Hydrogels with moderate degradation rates maintain scaffold porosity, facilitating the migration and differentiation of periodontal fibroblasts (HPDLFs) and osteoblasts. Nileshkumar *et al.* [33] reported a fiber-reinforced hydrogel incorporating a highly porous 3D poly(ε-caprolactone) (PCL) fiber network manufactured via melt electrospinning. The integration of PCL grids delayed hydrogel degradation, prevented soft tissue invasion, and provided a mechanical barrier, allowing slow-migrating progenitor cells sufficient time to participate in bone regeneration. This made it an excellent material for guided bone regeneration (GBR) membranes. Similarly, Liu *et al.* [34] developed multifunctional periodontal membranes by electrospinning biodegradable polymers with magnesium oxide nanoparticles (nMgO). These membranes modulated the degradation rate to match the periodontal regeneration timeline. Additionally, the acidic degradation products of PLA were neutralized by the alkaline ions released from nMgO hydrolysis, creating a pH microenvironment conducive to cell proliferation.

5.2. Regulation Mechanisms of Drug-Loaded Hydrogels on Periodontal Tissue Regeneration

Drug-loaded hydrogels effectively regulate the microenvironment of periodontal

tissue regeneration through the controlled release of anti-inflammatory factors, antimicrobial agents, and growth factors. These hydrogels exhibit multifunctional properties, such as anti-inflammatory, antimicrobial, and tissue repair-promoting effects.

First, hydrogels act as drug carriers, enabling sustained drug release by modulating porosity and degradation rates, thereby maintaining effective drug concentrations in the lesion area. For example, an injectable hydrogel system, CC-B-CAPE@CY-NPs, was developed for the treatment of periodontitis, where caffeic acid phenethyl ester (CAPE) and chrysin (CY)-loaded nanoparticles were incorporated into the hydrogel. *In vitro* studies demonstrated the hydrogel's ability to scavenge excess reactive oxygen species (ROS) and modulate M1 macrophage polarization, highlighting its anti-inflammatory efficacy [35]. Tang *et al.* [36] utilized the total flavonoids in propolis-loaded cubic liquid crystal hydrogels (TFP-CLC) for periodontal delivery, constructing an in situ thermosensitive reservoir system. TFP-CLC alleviated inflammation by regulating the TLR4/MyD88/NF-κB p65 and RANK/NF-κB signaling pathways, promoting alveolar bone repair, reducing inflammatory cell infiltration, and suppressing the expression of ROS, NF-κB, and IL-1β inflammatory cytokines.

Second, antimicrobial drugs, such as metronidazole and antimicrobial peptides, inhibit the growth of major pathogenic bacteria like *Porphyromonas gingivalis* through sustained-release mechanisms, thereby reducing inflammatory responses. For instance, thermosensitive hydrogels were prepared by mixing 28% w/v Pluronic F127 with various concentrations of methylcellulose (MC) and silk fibroin (SF) for local delivery of the antibiotic metronidazole (MTZ) to oral infection sites [37]. Hydrogels have inherent antibacterial properties, such as those crosslinked with chitosan (CS) and antimicrobial peptide-modified polyethylene glycol (PEG), form dual antibacterial hydrogels (CS-PA). When curcumin-loaded biodegradable nanoparticles (CNP) were added, the system exhibited long-term anti-inflammatory activity. In a periodontitis-hypertension mouse model, CS-PA/CNP applied to the gingival sulcus demonstrated optimal therapeutic effects for both periodontitis and hypertension [38].

Lastly, growth factor-loaded hydrogels, such as those containing BMP-2 or VEGF, release active factors gradually during degradation, activating osteogenesis and angiogenesis signaling pathways like Wnt/β-catenin and PI3K/AKT, thus promoting alveolar bone and periodontal ligament regeneration. Studies have shown that SDF-1 and BMP-2 co-assembled supramolecular hydrogels (SDF-1/BMP-2/NapFFY) enable the sustained release of bioactive factors, significantly enhancing periodontal bone regeneration and reconstruction [39]. In another study, an injectable silk hydrogel was used as a carrier for VEGF and BMP-2 in maxillary sinus floor elevation procedures. Results indicated that the hydrogel's slow release of growth factors promoted angiogenesis and new bone formation, demonstrating a synergistic effect in bone regeneration [40].

Through these mechanisms, drug-loaded hydrogels not only provide precise

treatment at the lesion site but also optimize the microenvironment for periodontal tissue repair, exhibiting significant potential for clinical applications.

6. Challenges and Opportunities in Clinical Translation

Hydrogels exhibit significant potential in periodontal tissue engineering due to their unique physicochemical properties and biocompatibility. However, several challenges remain in their clinical translation.

The primary challenge lies in the precise regulation of mechanical properties and degradation dynamics. The complex biomechanical environment of periodontal tissues demands hydrogels with adequate mechanical strength to withstand masticatory forces while ensuring that their degradation rate aligns with the pace of new tissue formation. Another critical issue is stability in the oral environment. The presence of enzymes and pH fluctuations in blood and saliva can lead to premature degradation or structural changes in hydrogels, compromising their scaffolding function. Furthermore, the coordinated regeneration of multiple tissue interfaces remains a significant hurdle. Periodontal tissues comprise various components, including alveolar bone, periodontal ligament, and cementum, necessitating the design of hydrogels with spatial chemical gradients to promote the targeted differentiation of different tissue types.

Nevertheless, these challenges also present opportunities for innovation. The incorporation of nanomaterials or the construction of dynamic chemical bonds offers the potential for dynamically tunable mechanical properties. Surface modification and biomineralization strategies can enhance the stability of hydrogels in the oral environment. Additionally, advanced 3D printing technologies can fabricate hydrogels with precise microstructures and multilayered scaffolds, enabling the spatial and temporal delivery of bioactive molecules to regulate cell fate.

As material science, stem cell biology, and micro/nanofabrication technologies continue to advance, the application prospects for hydrogels in periodontal tissue regeneration are expected to become even more promising.

7. Conclusions

In summary, smart hydrogels have demonstrated broad and diverse applications in periodontal tissue regeneration. Various types of responsive hydrogels, including temperature-sensitive, pH-sensitive, and dual-responsive hydrogels, are continually being developed. By re-engineering and modifying hydrogel components, their physical, chemical, and biological properties can be further optimized to better suit the treatment needs of periodontal diseases such as periodontitis.

However, the application of hydrogels in periodontal tissue regeneration still faces many challenges:

1) Better control of the sol-gel transition of hydrogels;

2) Optimization of drug release rates to achieve the best therapeutic outcomes;

3) Maintenance of the bioactivity of encapsulated biological factors during release;

4) Addressing issues related to hydrogel degradation.

Currently, most studies on hydrogels for periodontal tissue regeneration are limited to *in vitro* and animal experiments, with limited clinical translation. Future research should focus on improving hydrogel performance, enhancing its anti-inflammatory properties and tissue regeneration capabilities, and ultimately promoting its clinical application to provide better solutions for the treatment of periodontitis.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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