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Antimicrobial Hydrogels: A Review

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Abstract

Hydrogels are three-dimensional networks created by crosslinking hydrophilic polymer chains. These networks, made from either natural or synthetic polymers, can absorb a significant amount of water, giving the material a soft consistency similar to living tissues. The rise in microbial infections, particularly those impacting wound healing and causing biomedical implant failures, has driven the innovation of new materials with antimicrobial properties. These specialized hydrogels incorporate antimicrobial agents or possess inherent antimicrobial properties, offering promising solutions for medical applications such as wound healing, infection prevention, and tissue engineering. Their biocompatibility makes hydrogels an ideal foundation for creating materials with targeted antimicrobial effects. Antimicrobial hydrogels can be achieved by incorporating or covalently attaching known antimicrobial agents, or by designing the hydrogel to have inherent anti-microbial capabilities. This review presents an overview of these innovative antimicrobial hydrogels, highlighting their applications, effectiveness, and limitations.

Keywords: *Hydrogels; Demineralized Dentin Matrix; Drug Delivery Systems; regenerative endodontics.*

Introduction

The oral cavity is a moist habitat that is constantly in contact with the air and food. There are no other bodily tissues that exhibit the same characteristics when it comes to being contaminated by microorganisms.
Because dental infections cause constant pain, suffering, and numerous other issues that are directly tied to their ongoing presence in the mouth and negatively impact patient's quality of life, they represent a global concern.
To accomplish the ultimate goal of dental regeneration, this circumstance focuses dental therapies on the first removal of infections. Treatments related to endodontics, such as regenerative endodontic therapy and vital pulp therapy (VPT) modalities (direct/indirect pulp capping, partial/full pulpotomy), require the use of appropriate carriers for the controlled release of disinfectants and bioactive molecules for pulp regeneration. Products with controlled release drug delivery are made to release the active components gradually over a longer period of time in a predictable manner.[3]Regenerative endodontic procedures (reps) based on hydrogel are thought to be extremely promising therapeutic approaches for restoring the dental pulp (DP) tissue in human teeth that have lost vitality. However, following the cleaning step, residual bacteria may still exist in the endodontic area, which limits the regeneration process's potential for success. [4] During the process of dental regeneration, multifunctional hydrogels are essential in preventing infections, inflammation, oxidative stress, and other problems.[1]
Hydrogels have been used as an ideal drug-delivery system for therapies, mostly for oral mucosal disorders, wounds, periodontitis, and cancer therapy, due to their biocompatible structure and unique stimulus-responsive characteristic. Hydrogels are also perfect scaffolds for periodontal tissue, bone, cartilage, and the dentin-pulp complex in regenerative engineering.[5]

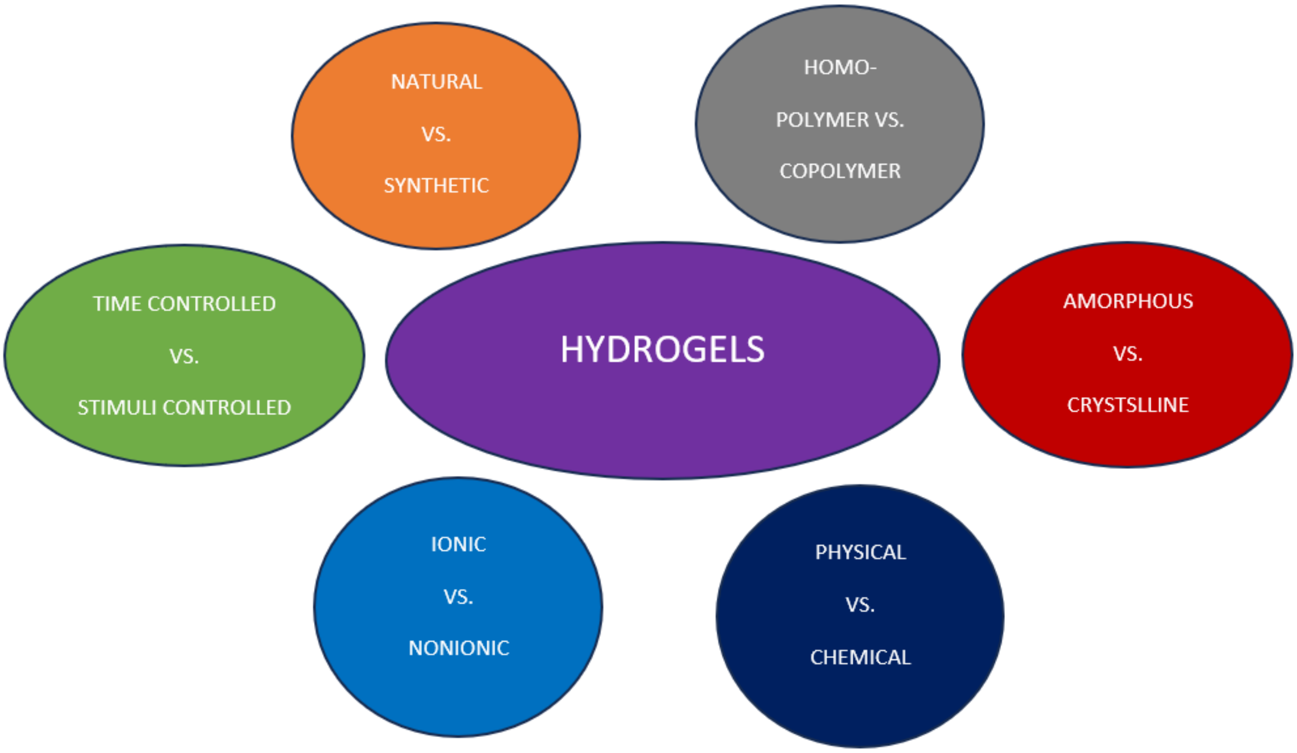
Types of Hydrogels

A wide variety of hydrogels have been developed for biomaterial applications. These hydrogels are either natural or modified natural polymers or synthetically derived. Commonly studied natural and synthetic hydrogels are listed in the table below -

Natural polymers	Synthetic polymers
Fibrin	Poly (ethylene glycol)
Collagen and gelatin	Poly (acrylic acid)
Hyaluronic acid	Poly (vinyl alcohol)
Alginate	Polypeptides
Agarose	Polyphosphazene
Chitosan	Poly (hydroxyethyl methacrylate) Dextran
Poly (NIPAAM)	

Hydrogels Classification

1-According to **Ghasemiyeh P, Mohammadi-Samani S**. [6]



2-According to **Haugen HJ, Basu P, Sukul M, Mano JF, et al** [7]

Hydrogels are classified as -

1.According to source-
- Natural
- Synthetic
- Hybrid

2. According to physical properties-
- Smart hydrogels
- Conventional hydrogels

3. According to preparation-
- Copolymeric hydrogels
- Homo-polymeric hydrogels
- Interpenetrating network

4. According to ionic charge-
- Cationic charge
- Anionic charge
- Non-ionic charge

5. According to cross-linking-
- Physically crosslinked
- Chemically crosslinked

6. According to degradability-
- Biodegradable
- Non-biodegradable

7. **According to response-**

A. Chemically responsive
- PH responsive
- Glucose responsive
- oxidant responsive

B. Biochemical responsive
- Antigens responsive
- Enzymes responsive
- Ligands responsive

C. Physically Responsive
- Temperature
- Pressure
- Light
- Electric field
- Magnetic field

Advantages of Hydrogels

1. **Viscoelasticity**: Among the various biomaterials used in tissue engineering scaffolds, hydrogels (i.e. Hydrophilic three-dimensional (3D) natural or synthetic polymers with a huge water-holding capacity) are considered favourable scaffolds for both endodontics and periodontics.
   Due to their viscoelastic properties, hydrogels can mimic the native extracellular matrix (ECM) of soft tissues; which encapsulates the cells and contains a huge amount of water, which enables the active transport of biological molecules/cells and the transport of bioactive substances loaded into the hydrogels.[1]

2. **Accessibility and Applicability**: The injectability of hydrogel is another problem in the treatment of small 3D defects in endodontics and periodontics. Such injectables, which fully reach void /spaces, are better than predetermined scaffolds, which often do not enter irregular pulp cavities, root canals, and periodontal pockets.
   Injectable hydrogels with optimal viscoelastic properties are considered one of the ideal materials with the lowest penetrability and highest sterility due to their injectability.[1]

3. **Biodegradability:** In order not to prevent regeneration, the implanted hydrogel should gradually degrade and be replaced by newly formed tissue while the reconstruction of the native tissue progresses.
   Tailoring the biodegradability of hydrogels is possible by methods such as cross-linking. In case of infections, the defective environment becomes acidic, so an acidic pH must regulate the stability of the hydrogel. Alternatively.
   PH-sensitive hydrogels can be designed to induce degradation and thus drug release at a lower PH after implantation in the presence of pathogens.[1]

4. **Antimicrobial properties**: Antimicrobial properties should be added to the hydrogels since infections can significantly delay the healing process at the defect site.
   Especially for dental tissue technologies, after disinfecting the diseased area, residual pathogens can cause recurrent infection by contaminating both the surrounding tissue and the implanted biomaterial in a scenario.
   Thus, antimicrobial properties added to these types of biomaterials may play a critical role in promoting tissue regeneration.[1]

Application of Hydrogels for Dental Pulp Regeneration

Pulp tissue is mostly made up of odontoblasts, which are positioned on the pulp's outer periphery and are responsible for producing dentin, as well as nerves, blood vessels, and lymphatic and connective tissues. The preservation of blood flow and homeostasis, sensory transmission, and dentin regeneration all depend on dental pulp.[8]

The pulpless teeth lose their natural biological defence following traditional root canal therapy because of permanent pulpitis and pulp necrosis. This may increase the likelihood of severe caries, apical periodontitis, and eventually tooth loss. To restore tooth function and enhance the prognosis of a pulpless tooth, the theory of dental pulp regeneration was therefore proposed.[9]

With the use of histology techniques, biomimetic ideas, developmental biology, and molecular and developmental biology, pulp regeneration with hydrogels is now a reality.[10]

The notion that an injectable hydrogel based on hyaluronic acid, licensed by the Food and Drug Administration, could be a promising scaffold material for regenerative endodontics was evaluated by Chrepa. et al.[11]

It has also been discovered that chitosan, a naturally occurring biopolymer produced from chitin, can stimulate the growth and development of dental pulp stem cells (DPSCs). Chitosan hydrogel has strong conductivity and can serve as an appropriate template.[12]

Injectable composite hydrogels are now a viable choice for pulp tissue engineering applications. Tissue-engineered pre-vascularized dental pulp-like constructions have been made using UV light-crosslinked gelatin meth-acryloyl (GelMA) hydrogel.
Injectable GelMA for DPSCs (Dental Pulp Stem Cells) can stimulate angiogenesis while also promoting cell adhesion and proliferation. In various investigations, the survival rates of dental pulp cells encapsulated in GelMA ranged from around 80% to 90%.[13]

Application of Hydrogels for Periodontal Tissue Regeneration

Patients are negatively impacted by periodontal disease, a global health issue. The devastation of tooth-supporting structures is a hallmark of periodontitis, a chronic inflammatory disease of the periodontal tissue brought on by pathogenic bacteria. The ultimate goal of treating periodontal disease should be to regenerate periodontal tissue to restore its structures and functions. Hydrogels have been used extensively recently in periodontal tissue regeneration studies as scaffold materials and as a sustained-release technology. [14]
Several approaches have been employed to enhance the mechanical properties of hyaluronic acid (HA)--based hydrogels in the context of alveolar bone regeneration. Hybrid chitosan (CS)-HA hydrogel scaffold that integrated the benefits of both constituents was made in Miranda's study by using modified hyaluronic acid (HA) and chitosan (CS).[15]
GelMA and polyethylene glycol (PEG) have been combined to bioprint periodontal tissue regeneration. [16]
By providing adequate and consistent stimulation, the bioactive substances (VEGF, platelets-derived growth factors) released from hydrogels facilitated the repair of periodontal tissue in the rat model. In the future, these hydrogels may replace periodontically accelerated osteogenic orthodontics and bone transplantation in clinics. [17]

Application of Hydrogels for Drug Delivery in Oral Science

Hydrogels can absorb large amounts of water and swell due to their excellent hydrophilic properties, good viscoelasticity, and long residence times. This was introduced as a new drug delivery system for the introduction and delivery of various pharmaceuticals/compounds in a controlled manner.[18] Several researchers have validated agarose hydrogel systems for the mineralization and biomimetic characterization of teeth.[19] Muşat's group was the first to report the simultaneous use of chitosan (CS) and agarose (A) in biopolymer hydrogels for biomimetic remineralization of acid-based cartilage surfaces.[20] Ren's group outlined a more clinically capable anti-caries treatment by combining amelogenin-derived peptide QP5 with antibacterial chitosan in a hydrogel (CS-QP5 hydrogel), and detailed a hindrance of cariogenic microscopic organisms and the advancement of remineralization of introductory caries injuries.[21] Aksel et al. found that the antibiotic-loaded chitosan-fibrin hydrogel improved the antibacterial properties against E. faecalis biofilm.[22]
Metronidazole and ciprofloxacin-loaded chitosan were found more reasonable due to their idealize antibacterial property whereas keeping up cellular work. Yan et al. connected GelMA hydrogel as a carrier of metronidazole (MTR) and chlorhexidine (CHX).[23]
A comparative application with GelMA and CHX was taken by Ribeiro et al, they defined injectable chlorhexidine (CHX)-loaded nanotube-modified GelMA hydrogel which given the supported discharge of CHX for dental disease removal against E. faecalis.[24]
In a later medicate conveyance ponder, photocrosslinkable chlorhexidine-loaded methacrylated gelatin (GelMA) hydrogels were arranged with a wide range of antimicrobial activity against endodontic pathogens. It is worth noticing that it is significant to center on the disposal of the profoundly determined bacterium Enterococcus faecalis which might occupy the most minor spaces such as dentinal tubules due to its estimate and remain there with a prominent continuance to long-term starvation indeed after sterilization strategies connected.
The agar dissemination measure appeared that GelMA stacked with 2 and 5% of chlorhexidine feast displayed factually higher antimicrobial movement against Enterococcus faecalis and came to the level of control in 24 hr.[1]

Limitations

Antimicrobial hydrogels have many drawbacks despite their many benefits, as previously discussed. As a result, while many of these compounds have demonstrated encouraging in vitro results, they have not been thoroughly investigated in preclinical settings, and only a small number of these compounds are commercially or therapeutically accessible.
High biocompatibility and bioactivity are two benefits of naturally generated biomaterials; nevertheless, batch variability and challenging processing are drawbacks.
The immunogenicity of the biomaterials themselves and the immune response connected to their delivery are examples of immunity-related problems that remain unresolved.
Antibiotic-containing hydrogels run the danger of encouraging the emergence of new, resistant microorganisms. The majority of metal or metal oxide nanoparticles have low biocompatibility and are unstable both chemically and physically.[25]
Hydrogel formulations have some limits about their applicability, clinical practices, and sustainability, based on prospective and continuing research.
Their limited non-biodegradable and biocompatible qualities limit their biomedical applications. To get over these restrictions, poly (ester)-based copolymers are a good substitute, but further investigation is still needed.
Furthermore, local drug carriers such as PEG and poly(ester)-based hydrogels are ineffective for long-term treatments. The FDA has cleared them for in vivo implantation, but their oral and nasal route administrations are inappropriate.[26]

Conclusion

Antibacterial hydrogels are materials designed to prevent bacterial infections. They consist of a network of water-soluble polymers capable of retaining a substantial amount of water while preserving their structural integrity. Natural polymer-based hydrogels, including starch, cellulose, chitosan, and peptides, are gaining significant attention in the realm of antimicrobial hydrogels.
Nowadays, a variety of smart antimicrobial hydrogels have been developed that respond to external stimuli such as pH, temperature, and light. Hydrogels infused with antibiotics, metal nanoparticles, antimicrobial polymers, and peptides are capable of releasing antimicrobial agents in a controlled, sustained manner. This is crucial for effectively treating infections and preventing the formation

of biofilms. To ensure future clinical applications, it is essential to test antimicrobial hydrogels against clinically isolated microbes, particularly multidrug-resistant strains. Additionally, evaluating the in vitro and in vivo biocompatibility of the hydrogels is crucial.

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