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Review Article

# NOVEL BIOMATERIAL ASSISTED DRUG DELIVERY SYSTEMS FOR THE MANAGEMENT OF ORAL DISEASES–FUTURE THERAPEUTIC APPROACHES

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**ABSTRACT**

Oral health is integral to maintaining systemic health as the mouth and oral cavity connect our digestive system with the external environment. The incidence of oro-dental disorders has been emerging as a serious threat to the healthcare sector owing to the increasing complexity of oral microbiome. Conventional treatment modalities are often limited by drug resistance and unwanted inflammatory responses. Recently, therapeutic strategies that can reinstate microbial homeostasis in the oral microenvironment have been implicated in the management of odontogenic infections. Biomaterial-based drug delivery systems, including nanocarriers, dendrimers, hydrogels, oral thin films, oral patches, and other stimuli-responsive polymeric systems, facilitate targeted administration of antimicrobials and anti-inflammatory agents to the site of infection. Bio adhesivity of the polymeric carriers facilitates faster disintegration and accurate dosing of the pharmacological agent to the target site. Moreover, restorative dentistry has been revolutionized by the advent of bio-functional templates that offer improved osseointegration and long-term stability of implants. A comprehensive review of the potential applications of biomaterial-mediated therapeutic strategies in the management of caries, peri-implantitis, periodontitis, and other oro-dental infections is explored here.

**Keywords:** Drug resistance, Biomaterial, Drug delivery systems, Peri-implantitis, Periodontitis, Nanofibers, Dendrimers


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## INTRODUCTION

Oral diseases pose a major challenge to the healthcare sector affecting nearly 3.5 billion worldwide. The demineralization of enamel leads to caries, a disease affecting the periodontium, and other pathological conditions associated with various bacterial and viral infections, cancer affecting the oral cavity are the major dental disorders [1]. The incidence of oro dental infections inhabiting different compartments of the oral microenvironment has been provided by molecular studies [2]. Approximately 770 microbial species are identified and characterized as per the Human Oral Microbiome Database (HOMD) [3]. The oral flora mostly consists of aerobic microorganisms and obligate anaerobes, mainly *Streptococcus salivarius, Actinomyces odontolyticus, Neisseria, Veilionella,* and some yeasts. Also, anaerobic forms like *Prevotella, Fusarium*, etc inhabit the gingival tissue of the gum. The enamel surface is inhabited by microbes like *S. parasanguis* and *S. mutans* and the gingival epithelial surfaces and saliva are other major microbial niches [4]. Owing to dietary changes, inadequate oral hygiene, and systemic pathologies, transient changes in microbiota occur, leading to an imbalanced state. Derailment of microbial homeostasis in the oral microenvironment has been shown to contribute to a variety of systemic pathologies affecting the gastrointestinal system, neuronal function, endocrine system, and the immune defense mechanism [5].

The incidence of tooth decay shows individual variation depending upon immunological status and oral microbiome determined by various environmental and genetic determinants. The formation of dental biofilm in dormant areas of the teeth results in dental infections. Improper dental hygiene causes the progressive formation of sub-gingival biofilms [6, 7]. Dental caries often result from accumulated biofilms on the tooth surface. The high population of oral flora at the supra, subgingival, and marginal tissue can lead to periodontitis [8-10]. Inadequacies in dental implant procedures can lead to periimplantitis [11-13]. Although a multitude of treatment strategies are adopted for the management of oro-dental infections, dysbacteriosis, drug resistance, and other side effects severely limit their prognosis [14]. Drug delivery approaches in the management of oro-dental infections involve sustained and controlled release of therapeutic compounds at the site of tissue damage through the mediation of bioactive carrier templates [15-17]. Owing to the poor retention of different dosage forms in the oral cavity, precise targeting therapy is more significant [18]. The application of nanotechnological approaches for loading antibacterial agents, anti-inflammatory drugs, and biomolecules in toothpaste and other rinsing solutions has been instrumental in the management of dental caries and aids proper remineralization [19]. Management of periodontal diseases through regenerative strategies involves the application of polymeric carriers, including liposomes, nanoparticles, hydrogel films, injectable hydrogels, etc [20]. Hydrogel-based drug delivery systems offer biocompatible three-dimensional platforms for the controlled release of drugs. Injectable hydrogels loaded with drugs can function as bioactive matrices for periodontal regeneration [21]. This review presents an overview of the innovative strategies in drug delivery systems in dental therapeutics. This review presents an overview of the innovative strategies in drug delivery systems in dental therapeutics. The data for the review were based on the following criteria; Sources: PubMed, Scopus, Web of Science, Embase, and the websites of regulatory bodies like the Human Oral Microbiome Database (HOMD), Central Drugs Standard Control Organisation (CDSCO) and World Health Organisation (WHO). Keywords: Drug delivery systems (DDS); Micro/Nanoparticles (NPs), Hydrogels Dendrimers, Mucoadhesive drug delivery systems, Nano fibers, strips, Pharmaceutical industry; Drug development; Regulatory guidelines. Year: 2010-2023.

### Drug delivery systems for the treatment of oral cavity disease

Controlled and sustained delivery of drugs, growth factors, cytokines, etc to the site of infection for repair and regeneration can be accomplished by the use of carrier systems, generally known as drug delivery systems (DDS). Moreover, the DDS shows higher restorative efficiency and fewer side effects. Technological advancements in biomaterial science have led to the fabrication of nanocarriers, hydrogels, and dendrimers as suitable platforms for targeted drug delivery [22]. Biomaterials have been employed as carriers of bio-active ion coatings, which lead to increased osteo integration and prevent soft tissue inflammation and bone resorption. The application of metallic nanoparticles to treat or prevent bacterial colonization on implant surfaces is of great concern due to its cytotoxic effect on human cells [23]. Besides the use of locally administered antibiotics, the idea of biomaterials for the controlled and directed delivery of specific drugs and for reducing microbial resistance has been envisaged as a potential approach for the management of peri-implantitis [24]. Antimicrobial peptides are another class of bioactive substances with profound immunomodulatory properties and recently localized delivery systems loaded with such peptides have been implicated as potential therapeutic agents in inflammatory conditions associated with dental caries and periodontal infections [25]. A novel antimicrobial peptide, ZXR-2 has been reported to attenuate the growth of pathogenic bacteria associated with dental caries [26].

**Micro/Nanoparticles (NPs)**

Nanomaterials are promising candidates for drug delivery owing to their smaller particle size, ease of synthesis, and biocompatibility. Therapeutic applications of nanoparticles (NPs) in dentistry can be attributed to their ability to inhibit bacterial growth by disrupting the cell membrane integrity [fig. 1, fig. 2]. Nanoparticles in conjugation with biopolymers have been reported to manifest significant antimicrobial activity against oral pathogens [27]. Microparticles derived from metals and polymers have been extensively used in dentistry for the management of dental infections [28]. The application of nanoparticles in managing dental caries involves the use of resin composite agents incorporated with inorganic antibacterial NPs that inhibit biofilm formation [29]. An adhesive containing a low concentration of silver nanoparticles (AgNPs) was found to be cytotoxic and inhibited the growth of *S. mutans* [30]. Several studies have demonstrated the efficacy of inorganic Nanoparticles like colloidal metal oxide NPs, metaphosphate NPs added to glass ionomer cement, and titanium oxide NPs in reducing secondary caries [31]. It is also reported that organic NPs mediate the mineralization of infected dental structures. Yuncong Li *et al.* developed a dental adhesive based on magnetic nanoparticles conjugated with dimethyl amino hexadecyl methacrylate (DMAHDM), and amorphous calcium phosphate nanoparticles (NACP), which significantly inhibited biofilm formation and has been implicated in the prevention of secondary caries by facilitating improved dentine bonding [32]. The addition of titanium oxide NPs to mouthwash solutions displayed enhanced bactericidal activity *in vitro* [33]. Sodium fluoride incorporated with silver nanoparticles was shown to inhibit the progression of dental caries *in vitro* and aided remineralization [34].

The increased population of anaerobic microbes contributed to inflammatory conditions leading to dental implant-associated infections. Accumulation of plaque biofilm in titanium implants causes chronic side effects. In 2016, Peiyuan Li *et al.* developed a bio-functionalized titanium implant loaded with AgNPs with enhanced antibacterial properties, substantiating its plausible use in regenerative dentistry [35]. Zhong *et al.* studied the antibacterial efficacy of a nanosilver-incorporated chitosan-based composite scaffold. The composite matrix demonstrated sustained release of silver nanoparticles to suppress bacterial invasion and prevent implant-associated secondary infections [36]. Chitosan nanoparticles incorporated with glass ionomer cement and titanium oxide exhibited enhanced mechanical strength, implicating its long-term applications in biofilm inhibition and restoration of oral health [37].

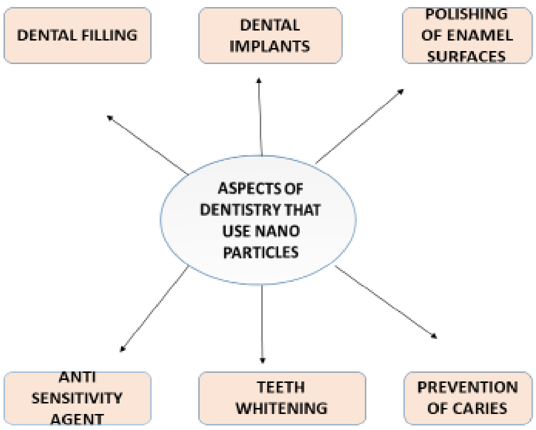


**Fig. 1: Application of nanoparticles in dentistry**

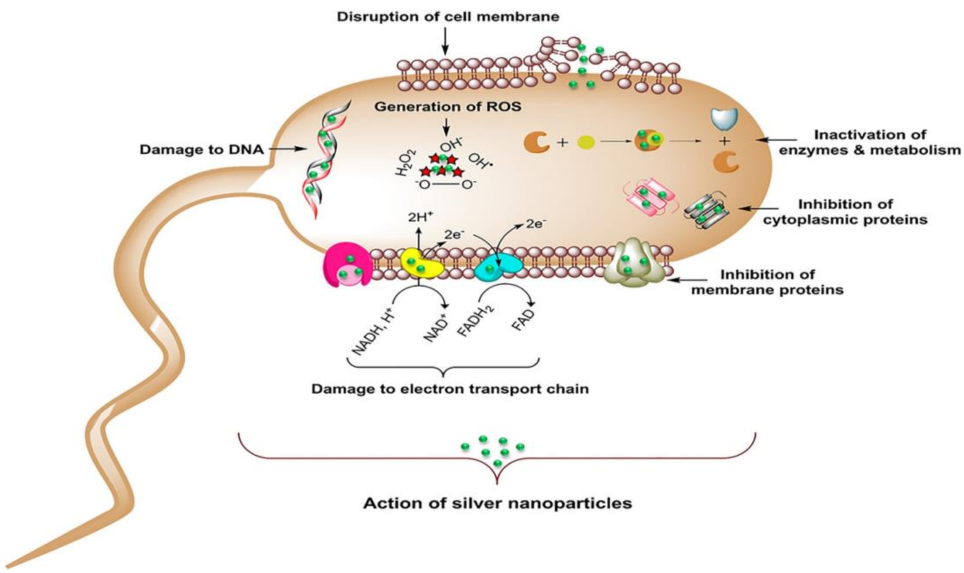


**Fig. 2: Antibacterial activity of AgNPs [38]**

**Hydrogels**

Hydrogels are characterized by their hydrophilicity and water-imbibing capacity that enables the formation of a three-dimensional network that can act as a carrier matrix for drug loading. The inherent porosity and structural integrity of hydrogels make them ideal systems for drug delivery [39]. The superior biocompatibility is owed to their high water content with excellent bio-adhesive potential [40]. Hydrogel properties can be fine-tuned to deliver macromolecular drugs as well as growth factors for the management of periodontal infections and per-implantitis [fig. 3]. Injectable hydrogels can be directly administered to the site of infection which further stabilizes by sol-gel transition for sustained release of drug [41]. A plethora of hydrogel-based drug delivery systems for the management of oral pathologies based on natural polymers like chitosan, hyaluronic acid, alginic acid, carrageenan, collagen and synthetic polymers like polyethylene glycol (PEG), poly lactic acid (PLA), poly lactic-co-glycolic acid (PLGA), polyvinyl alcohol (PVA), polyethylene glycol di acrylate(PEGDA), polycaprolactone (PCL) have been reported [42].

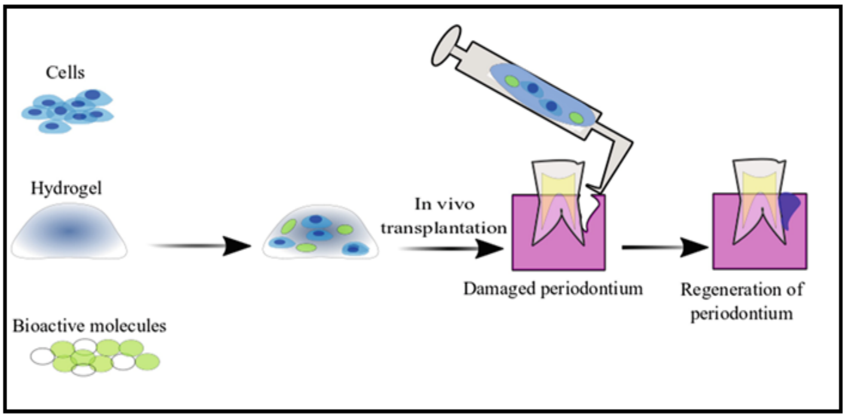


**Fig. 3: Regenerative applications of hydrogels [43]**

A hydrogel-based delivery system consisting of miconazole-loaded nanostructured lipid carriers was developed by Mendes *et al.* to inhibit the growth of *Candida albicans*. Incorporation of the drug in the hydrogel network facilitated sustained release of the drug and exhibited significant anti-fungal activity *in vitro* [44].

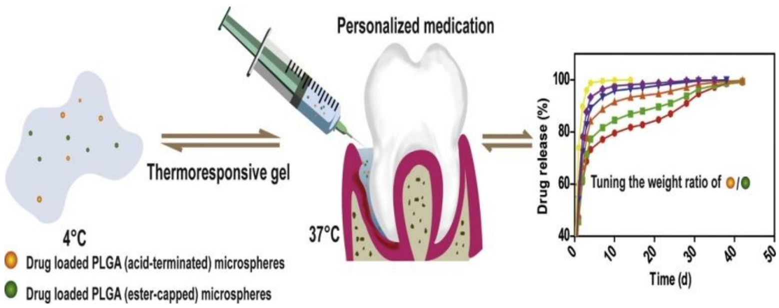


**Fig. 4: Application of Injectable hybrid hydrogels [45]**

An RGD-coupled alginate hydrogel combined with silver lactate has been shown to function as an efficient medium for the delivery of gingival mesenchymal stem cells (GMSCs). The hydrogel also exhibited significant antimicrobial properties by the controlled release of silver ions and the study pointed out its potential application in peri-implantitis [46]. Another category of hydrogels utilized for personalized medication as curative agents for periodontal and endodontic infections include injectable hybrid hydrogels owing to the tunable physicochemical properties that enable them to function as localized carriers for antibiotics and cytokines [fig. 4] [47].

Recently, Ribeiro *et al.* fabricated an injectable photo cross-linked gelatin methacryloyl (GelMA) hydrogel vehicle for ciprofloxacin release and was effective in attenuating biofilm formation *in vitro* [40]. Hydrogel systems based on chitosan have been extensively reviewed as bio-functional platforms for periodontal drug delivery [48]. A thermo-sensitive hydrogel made up of chitosan, β glycerol phosphate pentahydrate, and povidone-iodine with antimicrobial properties was studied for possible therapeutic implications in the management of denture implant abnormalities [49]. A cytocompatible composite hydrogel based on Chitosan and Zinc Oxide was found to be effective against *S. mutans* biofilm formation and has been recommended as a potent antimicrobial system against cariogenesis [50]. An adhesive hydrogel formulation derived from an antimicrobial peptide, Histatin-5, showed remarkable efficacy in the management of oral candidiasis as evidenced by *in vivo* experimental studies [51].

Recently, fibronectin-loaded collagen/gelatin hydrogel was investigated for its application in endodontic therapies as a bio-functional scaffold for dental pulp regeneration [52]. The PLGA-based hydrogel was developed as an in situ implant for the controlled release of metronidazole and is effective in managing periodontal infections [53]. Hydrogels are successfully employed as suitable carriers to deliver antimicrobial peptides (AMPs), for the ablation of biofilms in the oral cavity. Even though AMPs possess bacteriostatic and immunoregulatory properties, susceptibility to protease degradation limits their efficacy. Encapsulating them in stable hydrogel networks greatly enhances their longevity and sustained release at the site of infection [54]. A bio-adhesive hydrogel comprising (gelatin) and an antimicrobial peptide (AMP) prepared by photo-crosslinking showed significant anti-microbial properties. The bio functionality of the hydrogel as a suitable template for regenerative applications in combating peri-implant diseases has been demonstrated [55, 56].

**Dendrimers**

Dendrimers are a unique class of polymeric nanocarriers, which are hierarchically organized micellar structures enclosing a central core comprising chemical species that can conjugate therapeutically active components [57]. The core is surrounded by concentrically arranged polymeric building blocks with variable functional groups, which confers adhesive properties and biocompatibility to the nanocarrier [58]. These bio-functional complexes are particularly employed as agents for the remineralization of dentin and enamel as well as for the controlled release of antimicrobial drugs for treating periodontitis and other complications arising from dental implant procedures [59]. Recently, Fan *et al.* studied the remineralization efficacy of polyaminoamine (PAMAM) dendrimers in an invitro-simulated model consisting of sub-surface demineralized enamel [fig. 5] The carboxyl-conjugated PAMAM dendrimer was found to be more efficient in stimulating biomineralization of the treated enamel [60]. A phosphoryl-terminated poly (amide amine) dendrimer was modified for the incorporation of apigenin, a water-insoluble bacteriostatic agent. The dendrimers exhibited potent inhibitory effects against *Streptococcus mutants and* also induced mineralization *in vitro* [61]. Recently dendrimers have been arising as suitable delivery vehicles owing to their bio-adhesive properties and drug loading capacity and can form stable drug delivery systems in dentistry.

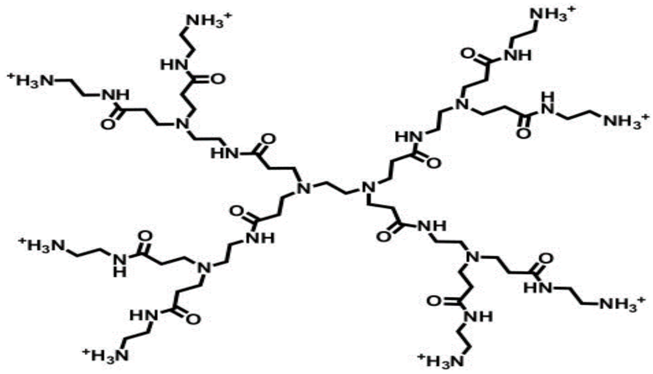

**Fig. 5: Chemical structure of cationic PAMAM Dendrimer [62]**

**Mucoadhesive drug delivery systems**

Bio-adhesive polymers in the form of films, gels, patches, and tablets form a novel therapeutic option for the management of periodontitis, dental caries, oral cancer, and others, owing to their suitability for targeted delivery of antibiotics, nutrients, and growth factors for assisted healing [21]. Polymer-based Oral thin films easily disintegrate and release the therapeutic ingredient into the oral cavity. Bio adhesivity of the polymeric carriers facilitates faster disintegration and accurate dosing of the pharmacological agent to the target site [63, 64]. The oral microbiome is constantly subjected to large-scale variation that contributes to the unregulated growth of pathogenic species. The introduction of probiotics to the oral microenvironment can facilitate the growth and sustenance of healthy bacteria owing to their immunomodulatory effect. A mucoadhesive film for the controlled delivery of *Lactobacillus fermentum* NCIMB 5221, a probiotic bacterium with remarkable anti-inflammatory properties, has been developed for the management of periodontitis, dental caries, and oral candidiasis. Carboxymethyl cellulose-based oral thin film exhibited significant bioadhesivity and sustained release of the bacterium into the oral cavity effects [65].

Therapeutic applications of *Lactobacillus brevis*, a probiotic bacterium in modulating chronic inflammatory conditions of the oral cavity as in periodontitis, biofilm pathogenesis have been immensely studied by several researchers. Abruzzo *et al.* developed a mucoadhesive buccal biofilm for the sustained release of probiotic bacterium *L. brevis* CD2 with strong anti-inflammatory potential [66]. Ciprofloxacin-loaded mucoadhesive biofilms were shown to exhibit significant drug-releasing profile and mucoadhesive properties for their application in periodontal drug delivery [67]. Recently, a bilayer drug delivery vehicle consisting of Gellan gum with Moxifloxacin hydrochloride and clove oil showed sustained drug release properties for managing chronic periodontitis [68].

**Nanofibers**

Owing to their porous architecture and biocompatible properties, nanofibers have been employed in regenerative dentistry for managing oral infections. Several researchers have developed such bio-functional platforms for targeted delivery of antimicrobial peptides [69]. Recently, Poly (D-L) lactide-co-glycolide (PLGA) and poly ε-caprolactone (PCL) nanofibers loaded with metronidazole and amoxicillin were fabricated for treating periodontal infections *in vivo* studies exhibited the biocompatibility of the drug-loaded fibers as suitable matrices with potent anti-inflammatory activity [70] [fig. 6]. Polycaprolactone nanofibers incorporated with Oxytetracycline and Zinc oxide were shown to attenuate the growth of Gram-positive bacteria that cause periodontitis and the fibers also exhibited rate-controlled delivery of the drugs [71]. Electrospun nanofibers developed from Polyvinylpyrrolidone/Hydroxypropyl β-cyclodextrin loaded with Clotrimazole have been shown to possess significant antifungal activity and were formulated as a suitable drug delivery matrix in the management of Oral candidiasis. The extracellular matrix mimicking property integrated with the drug-releasing efficacy of nanofibers offers novel strategies for tackling dental pathologies [72, 73]. The incorporation of remineralization agents like Calcium phosphate nanocomposites (Nano-ACP) demonstrated the controlled release of Calcium and Phosphate ions in dental restoration systems without affecting mechanical properties and showed an anti-caries effect [19].

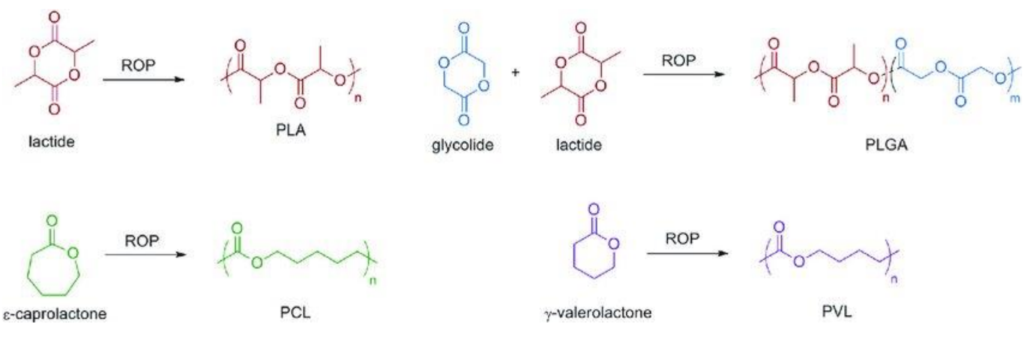


**Fig. 6: Synthesis of PLGA-PCL Nanofibers by ring-opening polymerization method [70]**

### Strips

Oral strips have been advantageous owing to their increased patient compliance and are a user-friendly technology for localized drug delivery, especially among children and the elderly population [74]. In dental therapeutics, drug-loaded polymeric strips have been developed for controlling microbial growth in infected periodontal pockets, as they provide a sustained concentration of antimicrobials to arrest the growth of microbes. Cefixime-loaded ethyl cellulose strips demonstrated potent antimicrobial activity *in vitro* and have been proven as an efficient drug delivery vehicle for insertion in periodontal pockets [75]. Clinical studies with Tetracycline hydrochloride strips demonstrated significant outcomes in patients with advanced periodontal diseases [76]. A biodegradable matrix of hydrolyzed gelatin has been developed commercially for controlled delivery of Chlorhexidine gluconate [77].

**Table 1: Drug delivery systems in dental therapeutics**

| Drug delivery platforms | Applications |
|---|---|
| Fluorinated bioactive glass | Antibacterial effect and prevention of demineralization [78] |
| Poly(amido amine) and calcium phosphate | Long-term dentin mineralization [79] |
| Ethylcellulose microparticles | Caries prevention by fluoride release [80, 81] |
| Silver lactate-loaded Alginate hydrogels | Peri-implantitis [46] |
| Chitosan-based nanocarriers | Periodontitis [48] |
| Calcium silicate loaded Chitosan Scaffold | Dental pulp regeneration [82] |
| Poly(amidoamine) (PAMAM) dendrimers | Dentin remineralization and dentinal tubule occlusion [54] |
| Pectin and Gellan gum-based muco adhesive buccal biofilms loaded with triamcinolone acetonide | Canker sores in oral cavity [83] |
| Cetylpyridinium chloride on chitosan blended with polyvinyl alcohol and hydroxyl ethyl cellulose | Anti-microbial activity against *S. mutans*-treatment of pediatric oral diseases [84] |
| Mucoadhesive buccal tablet containing metronidazole | Periodontitis and Gingivitis [85] |
| Isoguanosine-borate-guanosine hydrogels | Suppress oral tumor growth [86] |
| Triclosan Liposomes loaded with Dimethyl octadecyl ammonium bromide, cholesterol, and dimyristoyl phosphatidylcholine. | Inhibition of growth of the mixed biofilms of the oral bacteria [87]. |
| Catechol-modified chitosan/hyaluronic acid nanoparticles loaded with doxorubicin. | Apoptosis of oral cancer cells [88] |
| Nanosilver-doped titanium implants | Peri-implantitis [89] |
| Tetrahydro curcumin integrated mucoadhesive nanocomposite κ-carrageenan/xanthan gum sponges | Treatment for oral cancerous and precancerous lesions [90] |
| Clindamycin phosphate loaded chitosan/alginate polyelectrolyte complex film-muco adhesive delivery system | Periodontitis [91] |

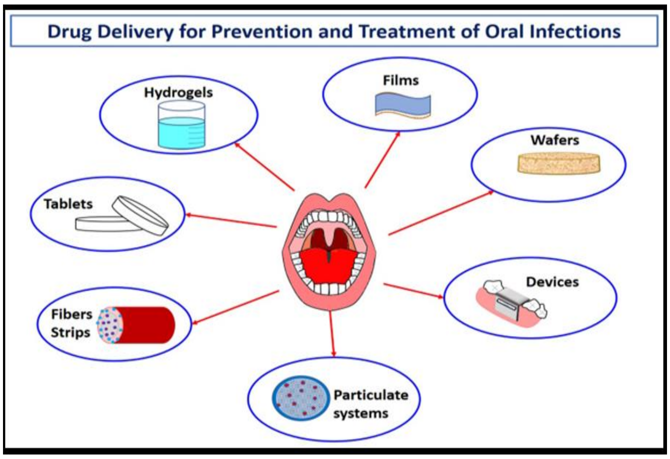


**Fig. 7: Drug delivery systems for oral infection [92]**

### Current and future perspectives

The application of drug delivery systems has been considered an appropriate strategy to improve the therapeutic effects of drugs. The advantages of DDS include controlled and targeted drug release patterns to improve the drug pharmacokinetics, bioavailability, selectivity, and, ultimately, improvement in the treatment outcome. Researchers suggest that (i) using nanoparticles could release the loaded drugs/agents in a pH-dependent manner to achieve targeted drug delivery, enhance the antibacterial properties of the restorative materials, and improve the antibacterial and antifungal activity of the loaded drugs (ii) using hydrogels could enhance the half-life of the loaded antibiotics and improve the antifungal and antibacterial activity of the drugs (iii) using microparticles could enhance the antibacterial activity of the drugs and (iv) strips/fibers have excellent mucoadhesion properties and could improve the antimicrobial activity.

Caries treatment now deals with controlling pathogenic bacteria, inhibiting demineralization, and improving re-mineralization by combining amelogenin-derived peptide with an antibacterial agent in a hydrogel. Dental treatment with dual action, like cariogenic bacteria inhibition and remineralization, would be of great interest in the future. An adhesive and photo-responsive microparticle drug delivery system is developed to treat periodontitis through microfluidic electrospray technology. Such microparticles are developed by ionic cross-linking of sodium alginate together with photo-curing of poly (ethylene glycol) diacrylate of the distorted microfluidic droplets. These microparticles are firmly adhesive and can release drugs promptly on the tooth. Anti-microbial peptides offer exciting opportunities for new therapeutic initiatives in regenerative endodontics. However, antimicrobial peptides constitute many key issues in design and delivery applications that need to be resolved immediately. By understanding the complex physiological conditions of AMP using animal experiments and with the aid of molecular informatics, chemistry, and pharmacy, AMP could be explored efficiently to treat periodontal diseases.

## CONCLUSION

Drug delivery systems have formed an integral part of therapeutic interventions in the management of dental pathologies. Incidences of periodontitis, dental caries, peri-implantitis, etc, have been steadily increasing globally and innovative approaches that minimize undesirable side effects and enhanced efficacy are instrumental in the management and prevention of such conditions. Targeted drug delivery strategies facilitate the controlled and sustained release of drugs for inhibiting microbial growth and facilitating tissue repair in periodontal and endodontic infections. Extensive studies are being performed for deriving multifunctional drug delivery systems for combating odontogenic infections comprising hydrogels, dendrimers, and nanoparticles. Optimisation of such systems for clinical translation remains a challenge and the current pace of technological innovations in dental therapeutics holds great promise in this respect. Advanced drug delivery matrices coupled with technological advancements in Robotics and Artificial intelligence are currently emerging as promising approaches in dentistry. Shortly, many products will be available in the market after the approval. Modifiable structure and selective properties such as bio-adhesive behavior or stimuli-responsive ability are important when we bring to commercialization. These properties may be challenging during drug formulation, particularly for treating oral diseases. In this aspect, we represent good examples of effective strategies to obtain the specific outcome in terms of drug release properties. Many biological mechanisms related to drug delivery systems in the human body are still largely unknown and require clinical studies.

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## AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

## CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

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