**Novel drug delivery systems in dental care and periodontal disease**

**Abstract**

The field of drug delivery in dental care has witnessed significant advancements in recent years toward more effective and patient friendly treatment options. Novel drug delivery methods have been focused on improving the delivery of therapeutic agents in the oral cavity, enhancing treatment outcomes, and reducing the risk of oral infections, inflammation, and other complications associated with traditional treatment methods.

Various types of novel drug delivery systems, including nanoparticles, liposomes, and hydrogels have been introduced in the field of dental care and periodontal disease. These delivery systems can target specific oral tissues, provide sustained and controlled release of therapeutic agents, improve bioavailability. Furthermore, they have shown significant potential in preclinical and clinical studies for the treatment of various dental conditions.

This article provides an overview of recent advancements in the use of novel drug delivery systems in different fields of dental care and pathologic conditions of the oral cavity including periodontitis, oral carcinomas, oral candidiasis, xerostomia, aphthous stomatitis, lichen planus, and oral mucositis.

**keywords:** Novel drug delivery systems, Oral pathology, Nanofibers, Hydrogels, Nanoparticles

**1. Introduction**

Oralhealth is an essential part of people's quality of life and is an important item considered in the general health. Any discomfort or pathologic conditions in the oral cavity can highly affect daily functions of a person (like eating, tasting, smiling and etc.), and also their emotional and social quality of life [1]. Although most of oral disease are preventable but they are chronic and very prevalent and cause a lot of direct and indirect costs for people and health care system. Periodontitis, oral carcinomas, oral candidiasis, xerostomia, aphthous stomatitis, lichen planus, and oral mucositis are among the most common pathologic conditions in the oral cavity [2, 3].

According to the type and state of each pathologic condition, different treatment options and drug delivery systems have been developed and in most cases local delivery of the therapeutic agent is preferred to reduce systemic side effects. Although conventional local drug delivery systems such as oral gels, buccal tablets, and lozenges provide acceptable delivery of active agents, drawbacks such as short residence time at the site of action, low bioavailability, variations in oral conditions, accidental swallowing and possibility of side effects have limited their efficacy. In recent years, novel and nanostructured drug delivery systems have increasingly attracted the attention of researchers as a means of treatment for oral diseases because of their ability to provide higher drug absorption from oral mucosa, efficient drug targeting, reduced systemic toxicity, and higher patient compliance. Therefore, there is a demand for development of novel and more efficient drug delivery systems [4].

In recent years, a wide range of novel DDSs have been raised and proven to be advantageous in alleviation of pathologic oral and dental conditions. These novel delivery systems have shown higher drug absorption, efficient drug targeting, reduced systemic toxicity, and higher patient compliance, and can be an efficient alternative for delivery of therapeutic agents in oral cavity [4, 5].

This article presents a general review of different types of novel drug delivery systems investigated in the field of dental and oral care. Publications from the last 10 years investigating novel DDSs for oral conditions were browsed in a systematic search using the PubMed/MEDLINE, Web of Science, and Scopus databases. Studies investigating the applications of buccal mucoadhesive films, polymeric nanoparticles, electrospun nanofibers, liposomes, hydrogels and other novel and nanostructured drug delivery systems in different oral complications including periodontitis, peri-implintitis, oral carcinomas, oral candidiasis, oral mucositis and etc. are summarized in the following sections.

**2. Challenges of drug delivery in the oral cavity**

The main drug delivery approach in the oral cavity is local treatments. Because even in some cases like oral cancers that systemic administrations of chemotherapy and immunotherapy medications is needed, the drug is often diluted during systemic circulation [6].

The oral and maxillofacial regions have some unique anatomical and histologic properties that pose challenges in drug delivery and treatment. Dynamic changes in the oral environment, complex anatomical structure, the diversity of the oral microbiome and presence of digesting enzymes are some of these challenges that limit efficient delivery of therapeutic agents.

The oral cavity is situated at the entrance of the respiratory and digestive tracts and poses significant environmental fluctuations influenced by dietary habits and gas exchange. There is a wide range of variations in temperature and humidity levels in the oral cavity. The oral temperature can change from the ambient external temperature during respiration to about 37–40 degrees Celsius during food ingestion. Additionally, the humidity within the oral cavity typically falls within the range of 30–50%, which may vary due to the secretion of saliva. The residence time of drug delivery systems in the oral cavity is usually very short due to mechanical abrasion and dilution during mastication [7, 8].

There are complex anatomical structures with diverse tissue and muscles in the oral and maxillofacial region which have vital physiological and social functions, including speaking, chewing, and facial expression [9]. Nonetheless, the oral cavity harbors distinct types of stem cells and a keratinized layer that effectively protects the underlying tissues. These protective barriers also inhibit the penetration of therapeutic molecules across the oral mucosa to systemic blood circulation. Furthermore, the highly enzymatic environment of the oral cavity acts as a metabolic barrier and could have negative effects on the bioavailability of active agents [10, 11].

Rapid elimination of drugs due to the flushing action of saliva or the ingestion of food, the non-uniform distribution of drugs within saliva after release from buccal tablets and lozenges, and patient compliance in terms of taste are major problems associated with drug therapy within the oral cavity. Novel drug delivery systems can improve the residence time and permeation of drugs in the oral cavity. They have some advantages that can bypass these complex therapeutic challenges and enhance the efficacy of drug delivery [12].

**3. Novel drug delivery systems in oral and dental pathologic conditions**

Conventional systemic treatments generally result in low accumulation in desired sites and require high amounts of active agents, which could lead to a higher probability of side effects and systemic toxicity. Targeted systemic DDSs could resolve these drawbacks; however, preparing efficient targeted systems faces significant complexity.

Novel drug delivery systems such as mucoadhesive gels, films, and patches, which allow for localized and sustained release of active ingredients, like antibiotics, anti-inflammatory agents, and analgesics, directly to the oral tissues, facilitating targeted and efficient treatment of dental conditions, such as periodontitis and dental caries, and also enable the treatment of other oral mucosal diseases, such as oral lichen planus and recurrent aphthous ulcers, allowing for improved management of symptoms and enhanced patient comfort [13]. Additionally, these novel drug delivery systems can be further classified into various categories, including nanotechnology-based approaches, such as nanoparticles that can be engineered to target specific cells or tissues in the oral cavity, ensuring optimal drug delivery and reducing the risk of adverse effects associated with systemic administration, and also hybrid systems that combine different materials and technologies, enabling the creation of personalized treatment plans tailored to individual patient needs and preferences. Furthermore, the development of novel drug delivery systems that incorporate bioresponsive materials, which can detect and respond to specific biological stimuli, enabling the creation of "smart" drug delivery systems that can adapt to changing physiological conditions, thereby optimizing drug release and promoting enhanced therapeutic outcomes. The integration of bioresponsive materials, such as pH-sensitive polymers and temperature-sensitive liposomes, has been shown to significantly improve the efficacy and safety of various dental treatments, particularly in the management of oral infections, where the bioresponsive materials can detect changes in the physiological environment and release therapeutic agents in a controlled and targeted manner, thereby reducing the risk of side effects and improving treatment outcomes [13-15].

**3.1. Mucoadhesive Buccal Films**

Mucoadhesive buccal films are retentive dosage forms that release the drug directly into the site of action. Mucoadhesive buccal films are one of the most common type of novel drug delivery systems because they possess appropriate physical properties to treat oral conditions and the main method of preparing films, film casting, is an easy and low-cost process. These films have shown high patient compliance due to their small size and reduced thickness, compared to conventional dosage forms like lozenges and tablets [16].

Buccal films have been proposed for local treatment of different oral lesions. They have been used for delivery of various drugs or natural plant based extracts for anti-inflammatory and healing purposes [17]. Buccal films can be formulated using different polymers either individually or in combination to obtain the required drug release profile [16, 17].

Some studies have shown proven in vivo and clinical efficacy in oral lesions. Enin et al. in 2017 [18], prepared a novel double-Layer buccal films consisting of HPMC, chitosan and sodium alginate and containing lidocaine hydrochloride and diclofenac potassium. They used nanoemulsion technique to mask the bitter taste of diclofenac. The prepared formulation exposed a strong anti-inflammatory effect from 61 to 87% inhibition with a strong analgesic effect when compared to simple drugs. The clinical study revealed that films were accepted by the patients, and the presence of lidocain on the outer side helped in reduction of pain and diclofenac in the inner side helped in relieving the inflammation.

In a study conducted by shao and zhou [19], the clinical effects of an oral mucosal film containing chitosan in treating recurrent aphthous stomatitis was evaluated through a randomized double blind clinical trial. The prepared buccal film was more effective than placebo in reducing the pain and ulcer size, and in accelerating the healing process. The results revealed that oral mucoadhesive films containing chitosan can be a promising alternative for both drug delivery and wound healing effect.

Gajdošová et al. [20] also introduced bilayer mucoadhesive buccal films containing ciclopirox olamine for treating oral candidiasis. They used poly(ethylene oxide) and Eudragit polymers to prolong drug release, and the effectiveness of the films were evaluated both *in vitro* and *in vivo* using rabbits. the ex vivo studies revealed that ciclopirox olamine does not pass through the porcine buccal tissue and accumulatesin the tissue which would be helpful in treating local lesions. All rabbits with stomatitis showed progressive healing after the treatment with the preopared buccal films without organ pathologies.

**3.2. Electrospun Nanofibers**

Electrospun nanofiber mats are one the most favorable novel drug delivery systems in pathogenic oral conditions. These nanofibers mats consist of 50-1000 nm sized fibres having large surface area, high porosity, small pore size, and low density. They can provide immediate, sustained, or responsive release of the entrapped drug. Different polymers can be used in preparation of nanofibers including biodegradable hydrophilic polymers, hydrophobic polymers and amphiphilic polymers, and they can be designed to be mucoadhesive using mucuadhesive polymers like chitosan (CS). The preparation method of nanofibers are usually flexible, cost-effective and easy to be scaled up [21, 22].

Electrospun nanofibers have been used widely for periodontitis because they can be designed to be biocompatible and biodegradable, completely fill the pockets, and have strong retention on the target site due to excellent mucoadhesion properties [5]. Chaturvedi et al. [23] evaluated the clinical efficacy of adding doxycycline-loaded nanofibers to the process of scaling and root planning in patients with chronic periodontitis. They reported sustained release of drug for up to 11 days and significant benefits compared to control group. Deepak et al. [24] used the electrospinning technique to prepare nanofibers enriched with layers of nanometric hydroxyapatite as a reinforcing filler and silver-metronidazole as periodontal pocket disinfectant. The *in vitro* and *in vivo* animal studies showed that broad-spectrum antimicrobial activity of the metal complex and the potential of biomimetic nano-hydroxyapatite for filling periodontal defects, alongside its compatibility, made this formulation a promising approach for treatment of periodontitis.

Khan and coworkers [25] prepared tinidazole-loaded biodegradable chitosan/poly (ε-caprolactone) mucoadhesive nanofibers for treatment of periodontitis. The prepared formulation could sustain the drug release up to 18 days, and inhibited bacterial growth *in vitro*. Moreover, preliminary clinical studies on patients revealed a significant decrease in clinical markers of periodontitis.

Samprasit et al. worked on the application of nanofiber mats for prevention of dental caries in their studies [26, 27]. They proposed thiolated chitosan-based nanofibers for delivery of α-Mangostin [27] and Garcinia mangostana extract [26] for prevention of dental caries. The results suggested that the prepared mats have mucoadhesive properties and are useful to maintain oral hygiene by reducing the bacterial growth that causes the dental caries.

Nanofiber mats were used for treatment of other oral complications like oral candidiasis, xerostoma, and lichen planus as well. Tonglairoum et al. [28] prepared clotrimazole sandwich nanofibers for oral candidiasis. They reported significantly faster antifungal effects on Candida than the commercial lozenges while they were safe after 2 h incubation.

A localized nanofiber formulation of pilocarpine was suggested by Muthumariappan et al. [29], targeting the salivary glands to overcome the limitations of existing pilocarpine formulations like its adverse side effects and multiple daily dosing. The results showed that salivary secretion was significantly increased 4.5 h after intradermal treatment with drug-loaded nanofibers *in vivo*.

Colley et al. [30] prepared clobetasol incorporated nanofibers and suggested the formulation for treatment of oral lichen planus and recurrent aphthous stomatitis as it can successfully release the drug and showed proper adherence to mucosal tissue without causing tissue damage *in vivo*.

Nanofiber mats were also proposed for treatment of oral carcinomas. Will et al. [31] examined the potentials of local treatment with diclofenac loaded in electrospun nanofibers made from poly(D,L-lactide-co-glycolide) polymer. Diclofenac was chosen as a cyclooxygenase inhibitor because this class of drugs have have shown great potential in their ability to directly inhibit tumor growth as well as suppressing inflammation-mediated tumor growth. The formulation was tested on the mouse resection model of oral carcinoma and the results showed 89% survival rate in this group compared to survival rates of 10%-25% in control groups.

**3.3. Nanoparticles**

Polymeric nanoparticles with a diameter range of 1 to 1000 nm can encapsulate the therapeutic agents or form chemical bonds with them [32]. These particles can improve the physicochemical and pharmacologic properties of drug molecules, and deliver the active agents to the site of action. Hence they can propose higher therapeutic efficacy with lower side effects and are good candidates for treatment of oral complications .

Nanoparticles have been proposed for treatment of different oral pathologies including periodontitis, malignancies, mocositis, and delivery of antibacterial and antifungal agents. Yao et al. [33] reported proper maintenance of minocycline in periodontal pocket after encapsulation into RGD-pepdtide conjugated nanoparticles. The prepared nanoparticles demonstrated significantly better anti-periodontitis effects compared to control. In another study conducted by Pramod and coworkers [34], eugenol-loaded nanocapsules could successfully prevent septal bone resorption in ligature-induced periodontitis model in rats. Lin et al. [35] also prepared nanospheres encapsulating metronidazole, an antibiotic, and N-phenacylthiazolium bromide, a host modulator, for treating periodontitis. The prepared nanoparticles could significantly reduce inflammation and increase collagen deposition relative to control groups.

Nanoparticles have shown great efficacy in cancer treatment due to their unique properties. Different types of nanoparticles have been proposed for delivery of various anticancer agents including doxorubicin [36], curcumin [37], TH287 (a MTH1 inhibitor) [38], all-trans retinoic acid [39], and Cu-carboxylate complexes [40] in treatment of oral malignancies. The result of these studies have shown higher cellular uptakes and cytotoxicities, enhanced tumor-targeting and penetrating efficiencies, effective inhibition of tumor growth, and inhibition of tumor recurrence by using nanoparticles in oral carcinoma cell lines and animal models.

Polymeric nanoparticles have been also investigated for topical therapy of oral lesions. Rençber et al. [41] proposed chitosan coated Eudragit mucoadhesive nanoparticles containing fluconazole for local treatment of oral candidiasis. The *in vitro* studies showed antifungal efficacy against Candida albicans for an extended period and the *in vivo* animal experiments showed successfully treatment of infected rabbits after local administration of the optimum formulation once a day.

Rebamipide-loaded PLGA nanoparticles coated with chitosan were also examined for treatment of chemotherapy-induced oral mucositis in rats by Takeuchi et al. [42]. The chitosan-coated nanoparticles could significantly decrease the ulcer area at day 9, 11, and 13 and also shortened the treatment period by 3.6 days compared to control groups.

**3.4. Vesicle-based drug delivery systems**

Another novel category of nanostructured carriers for treatment of unpleasant oral conditions are vesicle-based drug delivery systems including liposomes, proliposomes, niosomes, transferosomes and etc. Due to their excellent biocompatibility and controllable performance, the vesicular drug delivery systems are suitable options for drug delivery and controlled release and the recent developments in this field have provided ideal opportunities for the creation of multifunctional drug delivery platforms, demonstrating their potential for clinical implications [43].

Liposomes are biocompatible and biodegradable particles with a phospholipid-based bilayer structure and flexibleformulation options that can encapsulate both hydrophilic and hydrophobic therapeutic agents and be administered through various routes [44]. Furthermore, the addition of targeting elements such as ligands to liposomes leads to site-specific delivery of active agents [45]. Niosomes are bilayered vesicular structures that are composed of non-ionic surfactants and cholesterol, rather than phospholipids, that provides better stability of these vesicles [46].

Liposomes have been suggested as local or systemic treatment option for different oral pathologies. There are successful examples of systemic administration of liposomal anticancer drugs in oral carcinomas [4, 47, 48]. However, vesicular systems were also investigated for local treatment of oral lesions.

In a study conducted by Figueiró Longo et al. [49], injection of liposomal aluminum-phthalocyanine chloride into the peritumoral area showed proper efficacy along with photodynamic therapy on chemically induced tongue tumors *in vivo*.

Heiser et al. [50], showed that clinical applications of sprays containing liposomal phospholipids can alleviate symptoms related to xerostomia in patients with head and neck cancer. They suggested Liopsaliva and Liponasal sprays to be used during cancer treatment to moisturize the mouth and nose, potentially reducing side effects like infections and improving the patient's quality of life.

In a clinical trial conducted by Azizi et al. [51] in 2018, he efficacy of liposomal triamcinolone in Orabase on 60 erythematous-ulcerative lichen planus patients was evaluated. The pain intensity and cross sectional area of the lesions were measured after two and four weeks administration of the formulation. The results revealed that liposomal formulation exhibited promising clinical results and was more effective compared with the non-liposomal form of the medicine.

Atorvastatin is a hypocholesterolemic drug that has shown promising antifungal efficacies. Nour et al. [52] proposed atorvastatin-loaded liposomes in a 3D-printed mucoadhesive polymer film for management of oral candidiasis. The prepared formulation showed sustained drug release, *in vitro* antifungal activity against fluconazole-resistant Candida albicans, and ameliorated the infection and associated inflammation in oral candidiasis rabbit model.

Abruzzo et al. [53] suggested loading of miconazole in a hydrophilic matrix by taking advantage of the amphiphilic nature of liposomes to maintain the drug release over an extended period of time and provide adequate concentration at the infection site. The drug-loaded liposomes were introduced in a polymeric matrix consisting of even chitosan, sodium hyaluronate, or hydroxypropyl methylcellulose. The results showed that chitosan and hyaluronate-based formulations completely inhibited Candida albicans growth after 24 h, and chitosan-based formulation was introduced as the most promising candidate for the local treatment of oral candidiasis as it exhibited the best mucoadhesive capacity.

Yadav et al. [54], prepared ketoprofen-loaded proniosomal gel and *in vivo* results showed better efficacy with preserved bone resorption process for the optimum formulation compared to marketed product for treatment of periodontitis.

In a study conducted by Arafa et al. [55], niosomes containing Propolis extract were inserted in a polymeric film to benefit from its antimicrobial properties in treating patient with oral recurrent aphthous ulcer. The clinical results on 24 patients showed that the ulcer size started to reduce in 2-3 days, complete healing was achieved within first 10 days of treatment and pain relief lasted for more than 4–5 h, in contrast to the placebo group.

Melatonin was also encapsulated in niosomes and embedded in a mucoadhesive gel formulation, to employ its anti-inflammatory and antioxidant activities in treatment of 5-FU-Induced Oral Mucositis in Mice. The results showed that the prepared formulation could potentially inhibit inflammation and lipid oxidative stress in 5-FU-induced oral mucositis [56].

**3.5. Hydrogels and Hydrogel embedded nanostructures**

Hydrogels are solid-like viscoelastic drug delivery systems, and due to their hydrophilic structure they can absorb high amounts of water and other biological fluids and to swell. Hydrogels can encapsulate various therapeutic agents and release them in a controlled manner or in response to environmental changes like temperature or pH [57]. Hydrogels imitate the biochemical properties of the extracellular matrix and can be used for the transport of drugs and cells, and are therefore considered as a potential biomaterial. They show great promise in the field of oral pathology making them suitable for drug delivery and tissue regeneration in the oral cavity. Hydrogels have been studied extensively for treating various conditions, including periodontal diseases, oral mucosal diseases, and even oral cancers [58].

Kong et al. [59] prepared hydroxypropyl methylcellulose (HPMC) hydrogel formulation for delivery of Histatin-5 with potent anti candidal activity. According to *in vivo* results, the prepared formulation not only exhibited significant antifungal activity against Candida albicans but they also could clear the existing lesions as well as associated inflamed tissue in mouse model.

Because of their stimuli responsive nature, hydrogels were examined for treatment of periodontitis as well. Chang et al. [60] investigated, a thermogelling and pH-responsive injectable hydrogel for naringin, a natural flavonoid compound with anti-inflammatory properties, to inhibit experimental induction of periodontitis *in vivo*. The prepared hydrogels were consistently fluidic at 4°C but rapidly gelled at 37°C and could significantly reduce the inflammation and pathologic signs of periodontitis after subgingival delivery.

Yu et al. [61] suggested pH-Responsive hydrogels containing N-phenacylthiazolium bromide, which cleaves the crosslinks of advanced glycation end products on the extracellular matrix, for periodontitis. The prepared chitosan-based hydrogels released the encapsulated compound faster at pH 5.5 to 6.5 and consistently slower at pH 7.4, led to a decrease in inﬂammation and collagen matrix loss *in vivo*.

Wang et al. [62] investigated the incorporation of doxycycline as an antimicrobial and lipoxin A4 as anti-inflammatory agent, into thermo-reversible hydrogel as a treatment option for periodontitis. They hypothesized that thermo-reversible nature of the material allow its application into the periodontal pocket. The hydrogel exerted no local or systemic adverse effects in dogs and reduced the subgingival bacterial load and pro-inflammatory mediators, and also improved gingival clinical attachment compared with conventional periodontal treatment.

Rezazadeh et al. [63] developed a thermally sensitive trimethyl chitosan-based mucoadhesive gel on to deliver erythropoietin as an anti-inflammatory, antioxidant, and wound-healing agent in Oral mucositis. The formulation exhibited proper characteristics and antimicrobial properties *in vitro*, and tested on Sprague-Dawley rats with chemotherapy-induced mucositis *in vivo*. Erythropoietin was released from hydrogels during 8 h, and more than 30% of the drug still remained on the mucosa after 3 h of washing the buccal mucosa with phosphate buffer.. The EPO hydrogel demonstrated in vitro/in vivo wound-healing properties

In a clinical trial conducted by Qataya et al. [64] it was shown that topical administration of selenium hydrogel in patients with erosive oral lichen planus could significantly reduce pain scores compared to conventional topical corticosteroids and antifungal treatment.

Hydrogels were also utilized for administration of other nanostructured drug delivery systems in oral cavity. Hydrogels can increase the residence time at the site of application because of their rheology and swelling properties and would be beneficial for the stability of the nanosystem [65, 66]. In a study conducted by Mou et al. [67] minocycline and zinc oxide-loaded albumin nanoparticles were incorporated into Carbopol pH-responsive hydrogel networks to be used in periodontitis. The prepared formulation exhibited broad spectrum antimicrobial activity, sustained release, and tissue-repairing, and adhesive properties. It also showed obvious treatment progression and gingival tissue self-repairing in a periodontitis rat model compared to 2% minocycline ointment.

Alkhalidi et al. [65] proposed fluconazole-loaded sesame oil containing nanotransfersomes that were embedded in cross-linked hyaluronic acid hydrogels. The optimum formulation showed higher *ex vivo* permeation in sheep buccal mucosa, enhanced *in vitro* antifungal activity, and proper ulcer index values in immunocompromised rats with Candida infection, compared to fluconazole suspension and hyaluronic acid hydrogel.

Hydrogels containing cyclosporine A-loaded solid lipid nanoparticles were examined for treatment of aphthous stomatitis by Karavana et al. [66]. The results revealed that bioadhesive gel provides a protective layer over the lesion and the addition of cyclosporine A solid lipid nanoparticles led to a significant decrease in lesion size and rapid mucosal tissue repair.

El-Wakeel et al. [68] evaluated the efficacy of topical insulin-liposomes embedded in chitosan-based hydrogels in a clinical study on patient with recurrent aphthous ulcers. The pain scores were significantly reduced in the insulin-liposomal gel group compared to control groups.

**4. Conclusion**

Novel drug delivery systems had brought a wide range of advantages in dental drug delivery. They can increase the residence time of therapeutics at the site of action, deliver the therapeutic agents directly to the site of infection or inflammation, increase bioavailability and provide controlled release of drug. Some of these formulations can release the drug in response to environmental change that can provide release of drug at the inflammation site due to pH or temperature changes. The novel drug delivery systems can be designed to be bioadhesive and biodegradable which bring a lot of advantages for their application in the oral cavity.

Novel drug delivery systems including buccal films, nanofibers, polymeric nanoparticles, vesicular systems and hydrogels have been proven to be advantageous in different pathologic conditions in the oral cavity including periodontitis, oral mucositis, oral bacterial and fungal infections, aphthous stomatitis, lichen planus, and oral carcinomasvarious *in vitro* and *in vivo* studies, as well as clinical trials.

**5. References**

1. Spanemberg JC, Cardoso JA, Slob E, López-López J. Quality of life related to oral health and its impact in adults. Journal of stomatology, oral and maxillofacial surgery. 2019;120(3):234-9.

2. Sroussi HY, Epstein JB, Bensadoun RJ, Saunders DP, Lalla RV, Migliorati CA, et al. Common oral complications of head and neck cancer radiation therapy: mucositis, infections, saliva change, fibrosis, sensory dysfunctions, dental caries, periodontal disease, and osteoradionecrosis. Cancer medicine. 2017;6(12):2918-31.

3. Peres MA, Macpherson LMD, Weyant RJ, Daly B, Venturelli R, Mathur MR, et al. Oral diseases: a global public health challenge. Lancet (London, England). 2019;394(10194):249-60.

4. Taneja N, Alam A, Patnaik RS, Taneja T, Gupta S, K SM. Understanding Nanotechnology in the Treatment of Oral Cancer: A Comprehensive Review. Critical reviews in therapeutic drug carrier systems. 2021;38(6):1-48.

5. Joshi D, Garg T, Goyal AK, Rath G. Advanced drug delivery approaches against periodontitis. Drug delivery. 2016;23(2):363-77.

6. Zupančič Š, Preem L, Kristl J, Putrinš M, Tenson T, Kocbek P, et al. Impact of PCL nanofiber mat structural properties on hydrophilic drug release and antibacterial activity on periodontal pathogens. European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences. 2018;122:347-58.

7. Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. Nature reviews Immunology. 2015;15(1):30-44.

8. Graves DT, Li J, Cochran DL. Inflammation and uncoupling as mechanisms of periodontal bone loss. Journal of dental research. 2011;90(2):143-53.

9. Kassebaum NJ, Smith AGC, Bernabé E, Fleming TD, Reynolds AE, Vos T, et al. Global, Regional, and National Prevalence, Incidence, and Disability-Adjusted Life Years for Oral Conditions for 195 Countries, 1990-2015: A Systematic Analysis for the Global Burden of Diseases, Injuries, and Risk Factors. Journal of dental research. 2017;96(4):380-7.

10. Zhang H, Zhang J, Streisand JB. Oral mucosal drug delivery: clinical pharmacokinetics and therapeutic applications. Clinical pharmacokinetics. 2002;41(9):661-80.

11. Harris D, Robinson JR. Drug delivery via the mucous membranes of the oral cavity. Journal of pharmaceutical sciences. 1992;81(1):1-10.

12. Chinna Reddy P, Chaitanya KS, Madhusudan Rao Y. A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods. Daru : journal of Faculty of Pharmacy, Tehran University of Medical Sciences. 2011;19(6):385-403.

13. Zhang Y, Jiang R, Lei L, Yang Y, Hu T. Drug delivery systems for oral disease applications. Journal of applied oral science : revista FOB. 2022;30:e20210349.

14. Makvandi P, Josic U, Delfi M, Pinelli F, Jahed V, Kaya E, et al. Drug Delivery (Nano)Platforms for Oral and Dental Applications: Tissue Regeneration, Infection Control, and Cancer Management. Advanced science (Weinheim, Baden-Wurttemberg, Germany). 2021;8(8):2004014.

15. Nguyen S, Hiorth M. Advanced drug delivery systems for local treatment of the oral cavity. Therapeutic delivery. 2015;6(5):595-608.

16. Morales JO, McConville JT. Manufacture and characterization of mucoadhesive buccal films. European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik eV. 2011;77(2):187-99.

17. Yan Y, Yan W, Wu S, Zhao H, Chen Q, Wang J. Oral Patch/Film for Drug Delivery-Current Status and Future Prospects. Biopolymers. 2024;115(6):e23625.

18. Abo Enin HA, El Nabarawy NA, Elmonem RA. Treatment of Radiation-Induced Oral Mucositis Using a Novel Accepted Taste of Prolonged Release Mucoadhesive Bi-medicated Double-Layer Buccal Films. AAPS PharmSciTech. 2017;18(2):563-75.

19. Shao Y, Zhou H. Clinical evaluation of an oral mucoadhesive film containing chitosan for the treatment of recurrent aphthous stomatitis: a randomized, double-blind study. The Journal of dermatological treatment. 2020;31(7):739-43.

20. Gajdošová M, Vetchý D, Muselík J, Gajdziok J, Juřica J, Vetchá M, et al. Bilayer mucoadhesive buccal films with prolonged release of ciclopirox olamine for the treatment of oral candidiasis: In vitro development, ex vivo permeation testing, pharmacokinetic and efficacy study in rabbits. International journal of pharmaceutics. 2021;592:120086.

21. Joshi D, Garg T, Goyal AK, Rath G. Development and Characterization of Novel Medicated Nanofibers Against Periodontitis. Current drug delivery. 2015;12(5):564-77.

22. Kapahi H, Khan NM, Bhardwaj A, Mishra N. Implication of nanofibers in oral drug delivery. Current pharmaceutical design. 2015;21(15):2021-36.

23. Chaturvedi TP, Srivastava R, Srivastava AK, Gupta V, Verma PK. Doxycycline poly e-caprolactone nanofibers in patients with chronic periodontitis - a clinical evaluation. Journal of clinical and diagnostic research : JCDR. 2013;7(10):2339-42.

24. Deepak A, Goyal AK, Rath G. Development and Characterization of Novel Medicated Nanofiber for the Treatment of Periodontitis. AAPS PharmSciTech. 2018;19(8):3687-97.

25. Khan G, Yadav SK, Patel RR, Kumar N, Bansal M, Mishra B. Tinidazole functionalized homogeneous electrospun chitosan/poly (ε-caprolactone) hybrid nanofiber membrane: Development, optimization and its clinical implications. International journal of biological macromolecules. 2017;103:1311-26.

26. Samprasit W, Kaomongkolgit R, Sukma M, Rojanarata T, Ngawhirunpat T, Opanasopit P. Mucoadhesive electrospun chitosan-based nanofibre mats for dental caries prevention. Carbohydrate polymers. 2015;117:933-40.

27. Samprasit W, Rojanarata T, Akkaramongkolporn P, Ngawhirunpat T, Kaomongkolgit R, Opanasopit P. Fabrication and In Vitro/In Vivo Performance of Mucoadhesive Electrospun Nanofiber Mats Containing α-Mangostin. AAPS PharmSciTech. 2015;16(5):1140-52.

28. Tonglairoum P, Ngawhirunpat T, Rojanarata T, Panomsuk S, Kaomongkolgit R, Opanasopit P. Fabrication of mucoadhesive chitosan coated polyvinylpyrrolidone/cyclodextrin/clotrimazole sandwich patches for oral candidiasis. Carbohydrate polymers. 2015;132:173-9.

29. Muthumariappan S, Ng WC, Adine C, Ng KK, Davoodi P, Wang CH, et al. Localized Delivery of Pilocarpine to Hypofunctional Salivary Glands through Electrospun Nanofiber Mats: An Ex Vivo and In Vivo Study. International journal of molecular sciences. 2019;20(3).

30. Colley HE, Said Z, Santocildes-Romero ME, Baker SR, D'Apice K, Hansen J, et al. Pre-clinical evaluation of novel mucoadhesive bilayer patches for local delivery of clobetasol-17-propionate to the oral mucosa. Biomaterials. 2018;178:134-46.

31. Will OM, Purcz N, Chalaris A, Heneweer C, Boretius S, Purcz L, et al. Increased survival rate by local release of diclofenac in a murine model of recurrent oral carcinoma. International journal of nanomedicine. 2016;11:5311-21.

32. Akhlaghi MF, Daeihamed M, Jafari SM. Regulatory principles on food nano-particles legislated by North and South American countries. Safety and Regulatory Issues of Nanoencapsulated Food Ingredients: Elsevier; 2021. p. 239-50.

33. Yao W, Xu P, Zhao J, Ling L, Li X, Zhang B, et al. RGD functionalized polymeric nanoparticles targeting periodontitis epithelial cells for the enhanced treatment of periodontitis in dogs. Journal of colloid and interface science. 2015;458:14-21.

34. Pramod K, Aji Alex MR, Singh M, Dang S, Ansari SH, Ali J. Eugenol nanocapsule for enhanced therapeutic activity against periodontal infections. Journal of drug targeting. 2016;24(1):24-33.

35. Lin JH, Feng F, Yu MC, Wang CH, Chang PC. Modulation of periodontitis progression using pH-responsive nanosphere encapsulating metronidazole or N-phenacylthialzolium bromide. Journal of periodontal research. 2018;53(1):22-8.

36. Wang Y, Wan G, Li Z, Shi S, Chen B, Li C, et al. PEGylated doxorubicin nanoparticles mediated by HN-1 peptide for targeted treatment of oral squamous cell carcinoma. International journal of pharmaceutics. 2017;525(1):21-31.

37. Mazzarino L, Loch-Neckel G, Bubniak Ldos S, Mazzucco S, Santos-Silva MC, Borsali R, et al. Curcumin-Loaded Chitosan-Coated Nanoparticles as a New Approach for the Local Treatment of Oral Cavity Cancer. Journal of nanoscience and nanotechnology. 2015;15(1):781-91.

38. Shi XL, Li Y, Zhao LM, Su LW, Ding G. Delivery of MTH1 inhibitor (TH287) and MDR1 siRNA via hyaluronic acid-based mesoporous silica nanoparticles for oral cancers treatment. Colloids and surfaces B, Biointerfaces. 2019;173:599-606.

39. Chen XJ, Zhang XQ, Tang MX, Liu Q, Zhou G. Anti-PD-L1-modified and ATRA-loaded nanoparticles for immuno-treatment of oral dysplasia and oral squamous cell carcinoma. Nanomedicine (London, England). 2020;15(10):951-68.

40. Lin M, Wang D, Liu S, Huang T, Sun B, Cui Y, et al. Cupreous Complex-Loaded Chitosan Nanoparticles for Photothermal Therapy and Chemotherapy of Oral Epithelial Carcinoma. ACS applied materials & interfaces. 2015;7(37):20801-12.

41. Rençber S, Karavana SY, Yılmaz FF, Eraç B, Nenni M, Özbal S, et al. Development, characterization, and in vivo assessment of mucoadhesive nanoparticles containing fluconazole for the local treatment of oral candidiasis. International journal of nanomedicine. 2016;11:2641-53.

42. Takeuchi I, Kamiki Y, Makino K. Therapeutic efficacy of rebamipide-loaded PLGA nanoparticles coated with chitosan in a mouse model for oral mucositis induced by cancer chemotherapy. Colloids and surfaces B, Biointerfaces. 2018;167:468-73.

43. Maeki M, Kimura N, Sato Y, Harashima H, Tokeshi M. Advances in microfluidics for lipid nanoparticles and extracellular vesicles and applications in drug delivery systems. Advanced drug delivery reviews. 2018;128:84-100.

44. Daeihamed M, Dadashzadeh S, Haeri A, Akhlaghi MF. Potential of Liposomes for Enhancement of Oral Drug Absorption. Current drug delivery. 2017;14(2):289-303.

45. Fazel M, Daeihamed M, Osouli M, Almasi A, Haeri A, Dadashzadeh S. Preparation, In-Vitro Characterization and Pharmacokinetic Evaluation of Brij Decorated Doxorubicin Liposomes as a Potential Nanocarrier for Cancer Therapy. Iranian journal of pharmaceutical research : IJPR. 2018;17(Suppl2):33-43.

46. Arzani G, Haeri A, Daeihamed M, Bakhtiari-Kaboutaraki H, Dadashzadeh S. Niosomal carriers enhance oral bioavailability of carvedilol: effects of bile salt-enriched vesicles and carrier surface charge. International journal of nanomedicine. 2015;10:4797-813.

47. Yang G, Yang T, Zhang W, Lu M, Ma X, Xiang G. In vitro and in vivo antitumor effects of folate-targeted ursolic acid stealth liposome. Journal of agricultural and food chemistry. 2014;62(10):2207-15.

48. Li M, Li Z, Li J, Jin L, Jin C, Han C, et al. Enhanced antitumor effect of cisplatin in human oral squamous cell carcinoma cells by tumor suppressor GRIM‑19. Molecular medicine reports. 2015;12(6):8185-92.

49. Figueiró Longo J, Muehlmann L, Velloso N, Simioni A, Lozzi S, de Oliveira Cavalcanti C. Effects of photodynamic therapy mediated by liposomal aluminum-phthalocyanine chloride on chemically induced tongue tumors. Chemotherapy. 2012;1(103):2.

50. Heiser C, Hofauer B, Scherer E, Schukraft J, Knopf A. Liposomal treatment of xerostomia, odor, and taste abnormalities in patients with head and neck cancer. Head & neck. 2016;38 Suppl 1:E1232-7.

51. Azizi A, Dadras OG, Jafari M, Ghadim NM, Lawaf S, Sadri D. Efficacy of 0.1% triamcinolone with nanoliposomal carrier formulation in orabase for oral lichen planus patients: A clinical trial. European journal of integrative medicine. 2016;8(3):275-80.

52. Nour EM, El-Habashy SE, Shehat MG, Essawy MM, El-Moslemany RM, Khalafallah NM. Atorvastatin liposomes in a 3D-printed polymer film: a repurposing approach for local treatment of oral candidiasis. Drug delivery and translational research. 2023;13(11):2847-68.

53. Abruzzo A, Corazza E, Giordani B, Nicoletta FP, Vitali B, Cerchiara T, et al. Association of mucoadhesive polymeric matrices and liposomes for local delivery of miconazole: A new approach for the treatment of oral candidiasis. International journal of pharmaceutics. 2024;661:124461.

54. Yadav NK, Nanda S, Sharma G, Katare OP. Systematically Optimized Ketoprofen-Loaded Novel Proniosomal Formulation for Periodontitis: In Vitro Characterization and In Vivo Pharmacodynamic Evaluation. AAPS PharmSciTech. 2017;18(5):1863-80.

55. Arafa MG, Ghalwash D, El-Kersh DM, Elmazar MM. Propolis-based niosomes as oromuco-adhesive films: A randomized clinical trial of a therapeutic drug delivery platform for the treatment of oral recurrent aphthous ulcers. Scientific reports. 2018;8(1):18056.

56. Uthaiwat P, Daduang J, Priprem A, Settasatian C, Chio-Srichan S, Lee YC, et al. Topical Melatonin Niosome Gel for the Treatment of 5-FU-Induced Oral Mucositis in Mice. Current drug delivery. 2021;18(2):199-211.

57. Conte R, Valentino A, Romano S, Margarucci S, Petillo O, Calarco A. Stimuli-Responsive Nanocomposite Hydrogels for Oral Diseases. Gels (Basel, Switzerland). 2024;10(7).

58. Dongwen L, Dapeng M, Jiazhi Y, Xiaoguang L. Hydrogels in Oral Disease Management: A Review of Innovations in Drug Delivery and Tissue Regeneration. Medical science monitor : international medical journal of experimental and clinical research. 2025;31:e946122.

59. Kong EF, Tsui C, Boyce H, Ibrahim A, Hoag SW, Karlsson AJ, et al. Development and In Vivo Evaluation of a Novel Histatin-5 Bioadhesive Hydrogel Formulation against Oral Candidiasis. Antimicrobial agents and chemotherapy. 2016;60(2):881-9.

60. Chang PC, Chao YC, Hsiao MH, Chou HS, Jheng YH, Yu XH, et al. Inhibition of Periodontitis Induction Using a Stimuli-Responsive Hydrogel Carrying Naringin. Journal of periodontology. 2017;88(2):190-6.

61. Yu MC, Chang CY, Chao YC, Jheng YH, Yang C, Lee N, et al. pH-Responsive Hydrogel With an Anti-Glycation Agent for Modulating Experimental Periodontitis. Journal of periodontology. 2016;87(6):742-8.

62. Wang B, Booij-Vrieling HE, Bronkhorst EM, Shao J, Kouwer PHJ, Jansen JA, et al. Antimicrobial and anti-inflammatory thermo-reversible hydrogel for periodontal delivery. Acta biomaterialia. 2020;116:259-67.

63. Rezazadeh M, Jafari N, Akbari V, Amirian M, Tabbakhian M, Minaiyan M, et al. A mucoadhesive thermosensitive hydrogel containing erythropoietin as a potential treatment in oral mucositis: in vitro and in vivo studies. Drug delivery and translational research. 2018;8(5):1226-37.

64. Qataya PO, Elsayed NM, Elguindy NM, Ahmed Hafiz M, Samy WM. Selenium: A sole treatment for erosive oral lichen planus (Randomized controlled clinical trial). Oral diseases. 2020;26(4):789-804.

65. Alkhalidi HM, Hosny KM, Rizg WY. Oral Gel Loaded by Fluconazole‒Sesame Oil Nanotransfersomes: Development, Optimization, and Assessment of Antifungal Activity. Pharmaceutics. 2020;13(1).

66. Karavana SY, Gökçe EH, Rençber S, Özbal S, Pekçetin C, Güneri P, et al. A new approach to the treatment of recurrent aphthous stomatitis with bioadhesive gels containing cyclosporine A solid lipid nanoparticles: in vivo/in vitro examinations. International journal of nanomedicine. 2012;7:5693-704.

67. Mou J, Liu Z, Liu J, Lu J, Zhu W, Pei D. Hydrogel containing minocycline and zinc oxide-loaded serum albumin nanopartical for periodontitis application: preparation, characterization and evaluation. Drug delivery. 2019;26(1):179-87.

68. El-Wakeel NM, Dawoud MHS. Topical insulin-liposomal formulation in management of recurrent aphthous ulcers: A randomized placebo-controlled trial. Journal of investigative and clinical dentistry. 2019;10(4):e12437.