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Review Paper: Novel Drug Delivery Systems in Dentistry: Applications in Periodontal and Oral Mucosal Diseases

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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.

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1. Introduction

Oral health 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, and smiling), and also their emotional and social quality of life (1). Although most oral diseases are preventable, 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).

Depending on 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 developed and proven to be advantageous in managing 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 represent 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-implantitis, oral carcinomas, oral candidiasis, oral mucositis and other conditions are summarized in the following sections.

The main drug delivery approach in the oral cavity is local treatments. Even in conditions such as oral cancers, where systemic administration of chemotherapy or immunotherapy is required, drug concentrations are often significantly reduced due to systemic dilution (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 digestive 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 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 tissues 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 enhance drug residence time and permeation in the oral cavity. These platforms offer distinct advantages that help overcome complex therapeutic barriers and improve the overall efficacy of drug delivery (12).

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 allow for localized and sustained release of active ingredients—such as antibiotics, anti-inflammatory agents, and analgesics—directly to oral tissues. These systems facilitate targeted and efficient treatment of dental conditions such as periodontitis and dental caries, and also enable effective management of oral mucosal diseases including oral lichen planus and recurrent aphthous ulcers, thereby improving symptom control and enhancing 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, novel drug delivery systems incorporating bioresponsive materials—capable of detecting and responding to specific biological stimuli—have enabled the development of "smart" platforms that can adapt to changing physiological conditions, thereby optimizing drug release and enhancing 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).

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 types 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 in vivo and clinical efficacy in oral lesions. Enin et al. (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 lidocaine 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 was 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 accumulates in the tissue which would be helpful in treating local lesions. All rabbits with stomatitis showed progressive healing after the treatment with the prepared buccal films without organ pathologies.

Electrospun nanofiber mats are one of the most favorable novel drug delivery systems in pathogenic oral conditions. These nanofiber 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 is 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 et al. (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 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.

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 provide 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, mucositis, and delivery of antibacterial and antifungal agents. Yao et al. (33) reported proper maintenance of minocycline in periodontal pocket after encapsulation into RGD-peptide 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 results 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 also been 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 successful 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.

Another novel category of nanostructured carriers for treatment of unpleasant oral conditions is vesicle-based drug delivery systems including liposomes, proliposomes, niosomes, transferosomes 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 flexible formulation 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).

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 accordingly. 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 anticandidal activity. According to *in vivo* results, the prepared formulation not only exhibited significant antifungal activity against Candida albicans but it 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.

2. Conclusion

Novel drug delivery systems have introduced numerous advantages in the management of oral and dental pathologies. These systems enhance the residence time of therapeutic agents at the site of action, improve bioavailability, allow for controlled and sustained drug release, and reduce systemic side effects by delivering medications directly to the targeted oral tissues. Some formulations are also capable of responding to environmental stimuli—such as changes in pH or temperature—enabling smart, site-specific drug release, particularly in inflamed or infected areas. Moreover, their potential for bioadhesion and biodegradability makes them especially suitable for use in the oral cavity. Various delivery platforms, including mucoadhesive buccal films, electrospun nanofibers, polymeric nanoparticles, vesicle-based systems, and hydrogels, have shown promising results in the treatment of a wide range of oral conditions—such as periodontitis, oral mucositis, fungal and bacterial infections, aphthous ulcers, oral lichen planus, and oral carcinomas—as demonstrated in in vitro studies, animal models, and clinical trials.

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Authors' Contributions

Masoud Faghih Akhlaghi: Methodology, Investigation, Writing – Review and Editing **Marjan Daeihamed:** Conceptualization, Writing – Original draft, Supervision.

Conflict of Interests

The authors declare no conflict of interest.

Availability of data and material

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References

1. Spanemberg JC, Cardoso JA, Slob E, López-López J. Quality of life related to oral health and its impact in adults. J Stomatol Oral Maxillofac Surg. 2019;120(3):234-9. [DOI: 10.1016/j.jormas.2019.02.004] [PMID]
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 Med. 2017;6(12):2918-31. [DOI: 10.1002/cam4.1221] [PMID]
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. [DOI: 10.1016/S0140-6736(19)31146-8] [PMID]
4. Taneja N, Alam A, Patnaik RS, Taneja T, Gupta S, K SM. Understanding nanotechnology in the treatment of oral cancer: a comprehensive review. Crit Rev Ther Drug Carrier Syst. 2021;38(6):1-48. [DOI: 10.1615/CritRevTherDrugCarrierSyst.2021036437] [PMID]
5. Joshi D, Garg T, Goyal AK, Rath G. Advanced drug delivery approaches against periodontitis. Drug Deliv. 2016;23(2):363-77. [DOI: 10.3109/10717544.2014.935531] [PMID]
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. Eur J Pharm Sci. 2018;122:347-58. [DOI: 10.1016/j.ejps.2018.07.024] [PMID]
7. Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. Nat Rev Immunol.. 2015;15:30-44. [DOI: 10.1038/nri3785] [PMID]
8. Graves DT, Li J, Cochran DL. Inflammation and uncoupling as mechanisms of periodontal bone loss. J Dent Res. 2011;90(2):143-53. [DOI: 10.1177/0022034510385236] [PMID]
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. J Dent Res. 2017;96(4):380-7. [DOI: 10.1177/0022034517693566] [PMID]
10. Zhang H, Zhang J, Streisand JB. Oral mucosal drug delivery: clinical pharmacokinetics and therapeutic applications. Clin Pharmacokinet. 2002;41(9):661-80. [DOI: 10.2165/00003088-200241090-00003] [PMID]
11. Harris D, Robinson JR. Drug delivery via the mucous membranes of the oral cavity. J Pharm Sci. 1992;81(1):1-10. [DOI: 10.1002/jps.2600810102] [PMID]
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. 2011;19(6):385-403. [PMID]

13. Zhang Y, Jiang R, Lei L, Yang Y, Hu T. Drug delivery systems for oral disease applications. J Appl Oral Sci. 2022;30:e20210349. [DOI: 10.1590/1678-7757-2021-0349] [PMID]
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. Adv Sci. 2021;8(8):2004014. [DOI: 10.1002/advs.202004014] [PMID]
15. Nguyen S, Hiorth M. Advanced drug delivery systems for local treatment of the oral cavity. Ther Deliv. 2015;6(5):595-608. [DOI: 10.4155/tde.15.5] [PMID]
16. Morales JO, McConville JT. Manufacture and characterization of mucoadhesive buccal films. Eur J Pharm Biopharm. 2011;77(2):187-99. [DOI: 10.1016/j.ejpb.2010.11.023] [PMID]
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. [DOI: 10.1002/bip.23625] [PMID]
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. [DOI: 10.1208/s12249-016-0533-z] [PMID]
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. J Dermatolog Treat. 2020;31(7):739-43. [DOI: 10.1080/09546634.2019.1610548] [PMID]
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. Int J Pharm. 2021;592:120086. [DOI: 10.1016/j.ijpharm.2020.120086] [PMID]
21. Joshi D, Garg T, Goyal AK, Rath G. Development and characterization of novel medicated nanofibers against periodontitis. Curr Drug Deliv. 2015;12(5):564-77. [DOI: 10.2174/1567201812666141205131331] [PMID]
22. Kapahi H, Khan NM, Bhardwaj A, Mishra N. Implication of nanofibers in oral drug delivery. Curr Pharm Des. 2015;21(15):2021-36. [DOI: 10.2174/1381612821666150302153306] [PMID]
23. Chaturvedi TP, Srivastava R, Srivastava AK, Gupta V, Verma PK. Doxycycline poly e-caprolactone nanofibers in patients with chronic periodontitis - a clinical evaluation. J Clin Diagn Res. 2013;7(10):2339-42. [DOI: 10.7860/JCDR/2013/5858.3519] [PMID]
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. [DOI: 10.1208/s12249-018-1177-y] [PMID]
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. Int J Biol Macromol. 2017;103:1311-26. [DOI: 10.1016/j.ijbiomac.2017.05.161] [PMID]
26. Samprasit W, Kaomongkolgit R, Sukma M, Rojanarata T, Ngawhirunpat T, Opanasopit P. Mucoadhesive electrospun chitosan-based nanofibre mats for dental caries prevention. Carbohydr Polym. 2015;117:933-40. [DOI: 10.1016/j.carbpol.2014.10.026] [PMID]
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. [DOI: 10.1208/s12249-015-0300-6] [PMID]
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. Carbohydr Polym. 2015;132:173-9. [DOI: 10.1016/j.carbpol.2015.06.032] [PMID]
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. Int J Mol Sci. 2019;20(3):541. [DOI: 10.3390/ijms20030541] [PMID]
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. [DOI: 10.1016/j.biomaterials.2018.06.009] [PMID]
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. Int J Nanomedicine. 2016;11:5311-21. [DOI: 10.2147/IJN.S109199] [PMID]
32. Akhlaghi MF, Daeihamed M, Jafari SM. Regulatory principles on food nano-particles legislated by North and South American countries. In: Safety and Regulatory Issues of Nanoencapsulated Food Ingredients: Elsevier; 2021:239-50. [DOI:10.1016/B978-0-12-815725-1.00007-0]
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. J Colloid Interface Sci. 2015;458:14-21. [DOI: 10.1016/j.jcis.2015.07.032] [PMID]
34. Pramod K, Aji Alex MR, Singh M, Dang S, Ansari SH, Ali J. Eugenol nanocapsule for enhanced therapeutic activity against periodontal infections. J Drug Target. 2016;24(1):24-33. [DOI: 10.3109/1061186X.2015.1052071] [PMID]
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. J Periodontal Res. 2018;53(1):22-8. [DOI: 10.1111/jre.12481] [PMID]
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. Int J Pharm. 2017;525(1):21-31. [DOI: 10.1016/j.ijpharm.2017.04.027] [PMID]
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. J Nanosci Nanotechnol. 2015;15(1):781-91. [DOI: 10.1166/jnn.2015.9189] [PMID]
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 Surf B, Biointerfaces. 2019;173:599-606. [DOI: 10.1016/j.colsurfb.2018.09.076] [PMID]
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 (Lond). 2020;15(10):951-68. [DOI: 10.2217/nnm-2019-0397] [PMID]
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 Appl Mater Interfaces. 2015;7(37):20801-12. [DOI: 10.1021/acsami.5b05866] [PMID]
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. Int J Nanomedicine. 2016;11:2641-53. [DOI: 10.2147/IJN.S103762] [PMID]

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 Surf B Biointerfaces. 2018;167:468-73. [DOI: 10.1016/j.colsurfb.2018.04.047] [PMID]

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. Adv Drug Deliv Rev. 2018;128:84-100. [DOI: 10.1016/j.addr.2018.03.008] [PMID]

44. Daeihamed M, Dadashzadeh S, Haeri A, Akhlaghi MF. Potential of liposomes for enhancement of oral drug absorption. Curr Drug Deliv. 2017;14(2):289-303. [DOI: 10.2174/1567201813666160115125756] [PMID]

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. Iran J Pharm Res. 2018;17(Suppl2):33-43. [PMID]

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. Int J Nanomedicine. 2015;10:4797-813. [DOI: 10.2147/IJN.S84703] [PMID]

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. J Agric Food Chem. 2014;62(10):2207-15. [DOI: 10.1021/jf405675g] [PMID]

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. Mol Med Rep. 2015;12(6):8185-92. [DOI: 10.3892/mmr.2015.4423] [PMID]

49. Figueiró Longo J, Muehlmann L, Velloso N, Simioni A, Lozzi S, de Oliveira Cavalcanti C, et al. Effects of photodynamic therapy mediated by liposomal aluminum-phthalocyanine chloride on chemically induced tongue tumors. Chemotherapy. 2012;1(2):1000103. [Link]

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. [DOI: 10.1002/hed.24198] [PMID]

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. Eur J Integrat Med. 2016;8(3):275-80. [DOI:10.1016/j.eujim.2015.09.138]

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 Deliv Transl Res. 2023;13(11):2847-68. [DOI: 10.1007/s13346-023-01353-4] [PMID]

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. Int J Pharm. 2024;661:124461. [DOI: 10.1016/j.ijpharm.2024.124461] [PMID]

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. [DOI: 10.1208/s12249-016-0665-1] [PMID]

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. Sci Rep. 2018;8:18056. [DOI: 10.1038/s41598-018-37157-7] [PMID]

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. Curr Drug Deliv. 2021;18(2):199-211. [DOI: 10.2174/1567201817666200525151848] [PMID]

57. Conte R, Valentino A, Romano S, Margarucci S, Petillo O, Calarco A. Stimuli-responsive nanocomposite hydrogels for oral diseases. Gels. 2024;10(7):478. [DOI: 10.3390/gels10070478] [PMID]

58. Dongwen L, Dapeng M, Jiazhi Y, Xiaoguang L. Hydrogels in oral disease management: a review of innovations in drug delivery and tissue regeneration. Med Sci Monit. 2025;31:e946122. [DOI: 10.12659/MSM.946122] [PMID]

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. Antimicrob Agents Chemother. 2016;60(2):881-9. [DOI: 10.1128/AAC.02624-15] [PMID]

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. J Periodontol. 2017;88(2):190-6. [DOI: 10.1902/jop.2016.160189] [PMID]

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. J Periodontol. 2016;87(6):742-8. [DOI: 10.1902/jop.2016.150542] [PMID]

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 Biomater. 2020;116:259-67. [DOI: 10.1016/j.actbio.2020.09.018] [PMID]

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 Deliv Transl Res. 2018;8(5):1226-37. [DOI: 10.1007/s13346-018-0566-9] [PMID]

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 Dis. 2020;26(4):789-804. [DOI: 10.1111/odi.13285] [PMID]

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):27. [DOI: 10.3390/pharmaceutics13010027] [PMID]

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. Int J Nanomedicine. 2012;7:5693-704. [DOI: 10.2147/IJN.S36883] [PMID]

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 Deliv. 2019;26(1):179-87. [DOI: 10.1080/10717544.2019.1571121] [PMID]

68. El-Wakeel NM, Dawoud MHS. Topical insulin-liposomal formulation in management of recurrent aphthous ulcers: A randomized placebo-controlled trial. J Investig Clin Dent. 2019;10(4):e12437. [DOI: 10.1111/jicd.12437] [PMID].