International Journal of Innovative Research and Reviews, 6(1) 42-50

International Journal of Innovative Research and Reviews
ISSN: 2636-8919
Website: www.injirr.com
doi:
Research paper, Short communication, Review, Technical paper

REVIEW ARTICLE

Nanotechnological Drug Release Systems in Oral Diseases: A Review

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HIGHLIGHTS

- Nanotechnological drug delivery systems developed with nanotechnology have taken their place in many fields of medicine and provide numerous advantages such as optimum contact with mucosal surfaces and a long stay in the targeted tissue.
- Thanks to features such as biodegradable controlled release technology, regulation of local or systemic drug release rate, and elimination of absorption problems, patient compliance problems have been reduced.
- Nanotechnology, which is used in regenerative and restorative treatments in dentistry, is also involved in drug delivery systems in the treatment of periodontal diseases and oral cancers.

ARTICLE INFO

Received : 02.25.2022
Accepted : 05.16.2022
Published : 07.15.2022

Keywords:
Dentistry
Drug Release Systems
Nanotechnology
Oral Cancer
Periodontal Disease

ABSTRACT

Nanotechnology is an interdisciplinary field on the focus of most researches carried out in the field of health in recent years. Nanotechnological drug release systems developed with nanotechnology have gained ground in many fields of medicine and have brought about in numerous advantages. The small sizes and high surface areas of nano-scale particles provide chemically more reactive and superior electrical, magnetic, optical, biological, or mechanical properties compared to their macroscopic or microscopic counterparts. Thanks to their superior physicochemical and biological properties, nanotechnological drugs are involved in the diagnosis, prevention, and treatment of oral diseases such as dental caries, periodontal diseases, peri-implantitis, pulp, and periapical lesions, denture stomatitis, hyposalivation, oral cancer, and oral candidiasis. Nanotechnological drug delivery systems have taken an active role in the treatment of periodontal diseases and oral cancers, for they perform a long-term release in the mouth. This review study is aimed to explain the effects of nanotechnological drug delivery systems in the treatment of periodontal diseases and oral cancers, which will be examined under the title of oral diseases.

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1. Introduction

The utilization of nanotechnology in the studies conducted in recent years in the field of health and medicine involves a wide range of medical applications, including but not limited to, cancer therapy, drug delivery, tissue engineering,

Cite this article Sevinç Gül SN, Dilsiz A. Nanotechnological Drug Release Systems in Oral Diseases: A Review. *International Journal of Innovative Research and Reviews (INJIRR)* (2022) 6(1) 42-50
Link to this article: http://www.injirr.com/article/view/95

regenerative medicine, detection of biomolecules, and antimicrobial agents [1]. Nano-scale drug delivery systems developed with nanotechnology have gained ground in many fields of medicine and have brought about in numerous advantages. Biodegradable controlled release technology was reported to have reduced patient compliance problems thanks to features such as regulation of local or systemic drug release rate and elimination of absorption problems [2]. Furthermore, nanotechnological drug delivery systems have advantages such as optimum contact with mucosal surfaces and a long stay in the targeted tissue.

In addition to being used in regenerative and restorative treatments in dentistry, nanotechnology is also involved in drug delivery systems in the treatment of periodontal diseases and oral cancers, and effective long-term drug release tasks in the mouth can be performed with the use of nanotechnology.

In this review, the effects of drug delivery systems produced with nanotechnology in the treatment of periodontal diseases and oral cancers will be explained with the most up-to-date data.

2. Nanotechnological Drug Delivery Systems in Periodontal Disease

Periodontitis, which is one of the main causes of tooth loss in adults, is a chronic inflammatory disease characterized by periodontal tissue destruction, alveolar bone loss, and periodontal pocket formation, and causes mobility and tooth loss in the later stages [3, 4]. 15% to 20% of adults are known to have been affected by severe forms of the disease, and 35% to 60% of the population by less severe forms [5]. The main pathogenesis of periodontitis is said to be the interaction between the host immune response and pathogenic microorganisms in subgingival dental plaque [6]. Furthermore, periodontal pockets were reported to provide favorable conditions for the proliferation of microorganisms that have been proven to be associated with various systemic diseases such as cardiovascular disease, oral and colorectal cancer, respiratory diseases, rheumatoid arthritis, diabetes mellitus, and Alzheimer's disease [7, 8].

Nanotechnological drug delivery systems are among the most popular topics of current research for regenerative periodontal therapy. Over the last two decades, a significant number of nanotechnological drug delivery systems have been developed and yielded promising results [9]. Among the greatest advantages is optimum contact with the mucosal areas in the periodontium, staying for a long time in the targeted tissue like a periodontal pocket, and being in contact with the junctional epithelium so as to increase the epithelial transport of poorly absorbed drugs. Having these advantages, nanotechnological drug delivery systems are extremely promising for regeneration and periodontal disease treatment [10]. In order to enable sustained and controlled release to the intended targets, therapeutic molecules can be loaded onto carriers such as nanoparticles or scaffolds or be encapsulated [10]. Better penetration of the active ingredient into the junctional epithelium is among the key benefits of using nanotechnological delivery systems. Drug concentration in periodontal tissue can be achieved by controlled release systems that can be placed locally in periodontal pockets [11, 12]. It offers advantages such as the local administration of antimicrobial agents to periodontal pockets, reaching the target area at low doses, and hence not exposing the whole body to the drug [13, 14]. Furthermore, controlled drug release systems were reported to be beneficial for areas that are difficult to access due to anatomical irregularities such as furcation defects, or due to increased pocket depth [15]. In preventing the bacterial colonization, which is one of the most important causes of periodontal diseases, the use of antimicrobial nanoparticles (NPs) is reported to be an effective approach. Lee et al. [16] have used silver NPs loaded on nanofibers to develop antimicrobial surgical oral wound dressing to be used for drug delivery, and prevention of periodontitis and gingivitis.

On the other hand, it has been reported that gelatin and chitosan composite structures containing hydroxyapatite nanoparticles and antimicrobial peptide (Pac-525) loaded PLGA microspheres for use in directed tissue regeneration developed by He et al. have sustained release and antibacterial activity, over a long period of time against Staphylococcus aureus (*S. aureus*) and Escherichia coli (*E. coli*) [17].

In another study, polymeric electrospun nanofibers developed for rapid release of an antibacterial peptide (BAR) were reported to have had antimicrobial activity against Porphyromonas gingivalis (*P. gingivalis*) and Streptococcus gordonii (*S. gordonii*) and to have reduced release of Interleukin 17 (IL-17) [18]. Additionally, in another study, amino silane coated magnetic NPs functionalized with chlorhexidine were reported to have shown bactericidal and antifungal activity against microbial biofilm and that they can be used safely in the treatment of local infections in the mouth for they have increased efficiency with salivary proteins and low toxicity to human osteoblasts [19]. Examining the antibacterial effects of chitosan-based gold nanoparticles (AuNPs) (~15nm) were proved to have bactericidal activity against S. aureus and Pseudomonas aeruginosa (*P. aeruginosa*) [20]. Another study investigating the cytotoxicity of AuNPs on human periodontal ligament cells (hPDLCs) reported that 60 nm AuNPs at a concentration of 56 µM have been reported to effectively enhance the proliferation of hPDLCs [21]. Yu et al. [22] reported that AuNPs from 10 to 20nm was shown to strongly inhibit biofilm formation of pathogenic P. aeruginosa bacteria, despite not being observed to show any inhibitory effect on the growth of pathogens such as Candida albicans (*C. albicans*).

In a study by Madhumadhi and his colleagues, a tetracycline delivery system based on a calcium-deficient hydroxyapatite nanocarrier was developed, and in vitro and in vivo studies proved that tetracycline-loaded nanoparticles are biocompatible as an osteoconductive bone scaffold and that they have antibacterial and proliferative effects [23] . For the treatment of periodontitis, chlorhexidine-loaded calcium phosphate nanoparticles imparted adhesive property with carboxymethylcellulose, were attached to the tooth surface and suggested to be used against dental caries and periodontal disease by inhibiting E. coli and Lactobacillus casei (*L. casei*) bacteria [24] . In a study conducted by Kalia

et al. [25], it was reported that polymeric NPs synthesized for the release of BAR peptide showed antimicrobial activity on P. gingivalis and S. gordonii with a higher local peptide dose compared to free peptide formulations.

Another approach in the treatment of periodontal disease is to destroy the inflammation caused by the chronic form of the disease. Among the NPs employing antibacterial compounds to treat periodontal disease are nitric oxide-releasing silica NPs [26], polydopamine NPs [27] and silica and Larrea divaricata Cav. extract NPs [28]. After treatment with some of these NPs showed a higher antioxidant activity [27, 28]. Metformin hydrochloride-loaded PLGA NPs produced by Pereira et al. [29] also controlled inflammation and bone loss in an experimental periodontal disease model by successfully controlling blood glucose levels below what is considered as diabetes. Actually, preventing bone loss and promoting tissue repair are important factors in the treatment of chronic periodontal disease cases. Zambrano et al. [30] have reported that curcumin-loaded polymeric NPs could reduce inflammation and tissue destruction associated with periodontal disease. In a study wherein NP and doxycycline were used together, a significant decrease in inflammatory cell activation (through MPO measurements) was reported [31]. On the other hand, inflammation in periodontitis treated with metronidazole with NPs after 21 days was reported to be less in comparison to untreated periodontitis [32].

As to what was reported in the study conducted by Mou et al. [33] employing albumin microspheres containing minocycline and zinc oxide nanoparticles (ZnO NPs), gingival tissue could repair itself at certain ZnO NP concentrations, and antimicrobial activity, low toxicity and high safety were achieved. Calcium and zinc-loaded NPs were found in another study to promote periodontal regeneration, as well as showing nontoxic activity against oral mucosal fibroblasts [34]. Wijetunge et al. [35], additionally, found that ciprofloxacin and betamethasone-loaded agglutinin liposomes promoted potent antibacterial and synergistic anti-inflammatory effects for up to 24 hours. Bao et al. [27] reported that they achieved effectively ROS clearance, anti-inflammatory activity, biodegradability, high biocompatibility, and low systemic toxicity by means of the injectable antioxidant defence platform designed, based on poly(dopamine) nanoparticles as smart scavengers, for the removal of reactive oxygen species (ROS) in order to treat oxidative stress-induced periodontal disease. Vidal-Romero et al. [36] reported a 65.78% reduction in dentobacterial plaque index upon application of local drug delivery systems, which they synthesized using chlorhexidine-loaded nanospheres and nanocapsules, to the periodontal pocket to improve the treatment of periodontitis.

To summarize the in vivo studies conducted to investigate the effectiveness of nanoparticles-based release in the anti-inflammatory treatment of periodontitis; it was shown in the study conducted by Napimoga et al. [37] on the experimental periodontitis model that the 15d-PGJ2 drug loaded on PLGA nanocapsules (NC) had induced significantly lower alveolar bone loss in the group administered, and that the 15d-PGJ2 NC group had had lower lymphocyte infiltration, RANK-L and m-RNA expression, and myeloperoxidase activity. In a study wherein experimental periodontitis was induced in rats in order to examine the efficacy of ketoprofen nano-emulgel containing eugenol on periodontitis, the group treated with ketoprofen nanoemulgel was found to have had less bone loss, and that gingival index, tooth mobility, and cytokine expression were significantly lower than the group that was merely ligated [38] . In another study conducted by Khajuria et al. [39] , in the experimental periodontitis study induced by injecting P. gingivalis Lipopolysaccharide (LPS), it was reported that the alveolar bone loss was less in the dental film group, where chitosan-based risedronate/zinc hydroxyapatite nanoparticles placed in the pocket, and that the mineral density of the alveolar bone improved significantly. In a study investigating the effects of PLGA NPs loaded with metformin hydrochloride in the treatment of experimental periodontitis induced in rats with diabetes, fewer inflammatory cells; weak staining of receptor activator of nuclear factor kappa-B ligand (RANKL), cathepsin K, osteoprotegerin, and osteocalcin; a decrease in IL-1β and TNF-α levels; increased AMPK gene expression; decreased nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κB), p65, high-mobility group protein 1 (HMGB1) and transforming growth factor-*β*-activated kinase 1 (TAK-1) levels were reported [29]. It was reported in another study that gold NPs (AuNP) coated with L-cysteine have decreased alveolar bone loss in rats induced with experimental periodontitis, that the elastic and collagen fibers were tighter and more organized, as well as that the number of osteoclasts was less in the group with AuNP and that the inflammatory response and the iNOS level decreased [40].

Thanks to their nano-scale size, smart nanoparticles can be easily applied to periodontal pockets by injection. Injectable systems are an effective alternative for the release of antibiotic, anti-inflammatory, and antioxidant drugs in the periodontal pocket. These systems are extremely easy and fast to implement, significantly reducing the cost of treatment compared to other devices that require time and precision to insert into the periodontal pocket. The advantages of these smart nanoparticles are that they cover a large surface area, infiltrate easily into the gingival tissue, that a controlled release of drugs at different pH values can be made, and that they reduce the therapeutic dose and shorten the treatment time. Studies on the use of nanotechnological drug release systems in periodontal therapy are summarized in Table 1

3. Nanotechnological Drug Release Systems in Oral Cancers

It was reported by the International Agency for Research of Cancer that 19.3 million people were diagnosed with cancer in the world in 2020, and about 10 million people died from cancer [41]. Oral cancer is the 16th most common cancer type in the world [42]. Worldwide, 377 thousand people were diagnosed with oral cancer in 2020 and 177,000 died from oral cancer [41]. With early diagnosis and effective treatment, the survival rate can reach 70-90% [43]. However, treatment is often difficult due to late diagnosis, high risk of invasion, rapid metastasis, frequent relapses, and painful side effects [44, 45]. Considering the side effects of chemotherapy, radiotherapy, and surgical treatment of cancer and its adverse impacts on the quality of life of the patients, nanotechnology is expected to be able to provide advantages in diagnosis and treatment [45].

Smart nanoparticles have features that will facilitate cancer treatment thanks to their size, morphology and distribution

[46]. Drug-loaded nano-systems, together with elements of the immune system such as antibodies and cytokines, play an important role in the fight against cancer [47] . By targeting the tumor directly, these systems eliminate the undesirable side effects of traditional cancer treatments and play a role in protection and treatment with the therapeutic effects they provide [48] .

The most effective cytotoxic agents used in the treatment of head and neck cancers are doxorubicin and paclitaxel. Doxorubicin (DOX) nanoparticles synthesized to eliminate the existing side effects of these drugs showed a higher apoptotic effect on (Centre Antoine Lacassagne-27) CAL-27 cells, and a greater increase in caspase-3 level was obtained compared to doxorubicin [49]. On the other hand, the use of doxorubicin-loaded nanoparticles (n-Dox) was reported to have increased its biological efficacy and therapeutic effects, and to have reduced hematological side effects in treatments [50].

By means of the HN-1 and PEGylated DOX (PD) (HNPD) nanoparticles synthesized by Wang et al [51], a significantly higher cellular uptake and cytotoxicity were observed compared to PD nanoparticles, and the HNPD nanoparticles were selective for CAL-27 and squamous carcinoma cell -25 (SCC-25) cells. Other than that, the (PDPN Ab)-AuNP-DOX nano-drug delivery system synthesized by Liu et al., (PDPN Ab)-AuNP-DOX was shown to exhibit enhanced antitumor activity, both in vitro and in vivo, by having low toxicity and high drug loading capacity [52].

In another study, it was reported that the hybrid paste produced from liposome and alginate facilitated the death of cancer cells thanks to its mucoadhesion feature and continuous liposome release [53]. Xiong et al. [54] developed multifunctional targeted polymeric nanoparticles (NPs) loaded with DOX using indocyanine green for targeted photoacoustic imaging and photo-thermal ablation of oral cancer cells, and argued that the combination of chemotherapy and photo-thermal therapy in oral cancer treatment is more effective. Endo et al. [55] have shown, by synthesizing cisplatin-loaded polymeric micelles containing poly(ethylene glycol) (PEG)-poly(glutamic acid) block copolymers, that cisplatin-loaded nanoparticles have an inhibitory effect equivalent to free drugs besides having lower nephrotoxicity. In comparison to DOX alone, MSNP-PEI-DOX/MDR1-siRNA synthesized in a study was reported to have increased the effect of cancer chemotherapy for the treatment of multidrug-resistant cancer [56].

Solid nanoparticles loaded with paclitaxel in combination with solid nanoparticles loaded with ascorbic acid were reported to be more effective than the nanoparticles loaded with 5-fluorouracil in the in-vivo treatment of oral squamous cell carcinoma [57]. As well as curcumin loaded on PLGA NPs has been reported to induce cell apoptosis without showing cytotoxic effects on healthy gingival fibroblasts and oral keratinocytes [58]. In addition, catechol (Cat) modified chitosan/hyaluronic acid (HA) nanoparticles, (Cat-NPs), have been developed as a new carrier to deliver DOX to oral cancer cells. The Ca t portion of the NPs makes use of the carrier's adhesion to the oral mucosa and sustained local release of DOX into the oral cavity. It was shown that DOX-loaded Cat-NPs (DOX-NPs) inhibited the growth of the cell lines of HN22 oral squamous cell carcinoma with a low IC and that DOX-NPs induced apoptosis in cells compared to free DOX [59].

In a study conducted on the treatment and diagnosis of oral squamous cell carcinoma (OSCC) with synthesized superoxide paramagnetic iron oxide nanoparticles (SPION), the effect of SPIONs on OSCC mitochondria was investigated. SPIONs were shown to have decreased cell viability and to have increased lipid peroxidation level and caspase-3 activity in OSCC cells. Furthermore, SPIONs have been reported to have selective toxic effects only on OSCC and not on mitochondria in healthy cells [60].

Synthetic composite sponges comprised of decorated polycaprolactone (PCL) and chitosan solution (CS) were evaluated in cell proliferation and survival, cell motility, and autophagic effects of 5-fluorouracil-loaded nanoparticles in head and neck cancer human cell lines (CAL27 and HSC3) in a vivo mouse model (AT84). Compared to control group, significant inhibition of cancer cell proliferation was observed with CS-decorated PCL NPs, based on metabolic and colony formation assays. In addition, significant increases in autophagy and cell death were reported, as assessed by cell protein analysis, LC3-II expression, and PARP1 cleavage, respectively [61].

It was reported in a study conducted by Wang et al. [62] that ALA-PDT adequately destroyed DOK and CAL-27 cells in a dose- and time-dependent manner in vitro in the development and treatment of OSCC. Furthermore, the new CS-ALA-shGBAS they synthesized by creating a mitochondrial-targeted drug co-delivery system for combined photodynamic therapy (PDT) and gene therapy was reported to have a superior mitochondrial-targeted killing efficiency on OSCC, both in vitro and in vivo [63].

Killing all cancer cells without affecting or destroying healthy cells is the primary goal of cancer treatment. In order to reach the maximum therapeutic potential, the targeted and site-specific drug release of chemotherapeutic drugs in the body must be achieved. These drugs synthesized as or within nanoparticles have advantages such as lower cytotoxicity and systemic toxicity thanks to the site-specific drug delivery, as well as higher therapeutic efficacy, a higher percentage of apoptotic cells, less hematological complications, more active substance accumulation in the tumor, and thereby the inhibition of tumor.

These advantages are expected to facilitate the clinical use of anticancer drugs synthesized with nanoparticles in the future. As a result, nanoparticle-based drug delivery systems are regarded as an unmatched and potential alternative for solving the problems associated with drugs and traditional formulations. Further in vitro and in vivo studies on animal models are considered to be useful in elucidating possible mechanisms for the treatment of life-threatening diseases such as oral cancer, at both molecular and cellular levels. Studies on the use of nanotechnological drug delivery systems in the treatment of oral cancers are summarized in.

Table 1 In vitro and in vivo studies using nanotechnological drug delivery systems in the treatment of periodontitis and oral cancer.

Ref	Aim of study	Drug Tested	Main Results
[16]	Develop antimicrobial surgical oral wound dressing to be used for drug delivery and prevention of periodontitis and gingivitis.	AgNP	The developed oral wound dressing showed excellent antibacterial activity as increasing content of the AgNPs
[17]	Obtain nanofibrous membrane with osteogenic and antibacterial activities	Gelatin/Chitosan composite GBR membrane containing hydroxyapatite nanoparticles (nHAp) and (Pac-525)-loaded PLGA microspheres	The antimicrobial peptide-loaded gelatin/chitosan nanofibrous membrane had sustained release and antibacterial activity, over a long period of time against Staphylococcus aureus (*S. aureus*) and Escherichia coli
[18]	Develop and characterize a rapid-release platform, composed of polymeric electrospun fibers (EFs) that encapsulate BAR, and evaluate fiber safety and functionality against *P. gingivalis*/*S. gordonii* biofilms in vitro	BAR	BAR had antimicrobial activity against Porphyromonas gingivalis (*P. gingivalis*) and Streptococcus gordonii (*S. gordonii*) and reduced release of Interleukin 17 (IL-17)
[19]	Determine the activation and cell cytotoxicity of the amino silane-coated nanoparticle form of CHX in body fluids.	Amino silane-coated magnetic nanoparticles functionalized with chlorhexidine (MNP@CHX)	MNP@CHX showed greater antimicrobial activity against planktonic and biofilm-forming microorganisms than free CHX.
[20]	Synthesize non-cytotoxic nanocomposites films that are either colloidal or exhibit high antibacterial activity	Chitosan-based gold (Au) nanoparticles (AuNPs)	AuNPs were proved to have bactericidal activity against S. aureus and Pseudomonas aeruginosa (*P. aeruginosa*).
[21]	Investigate the effects of different sizes and concentrations of AuNPs on cell proliferation and differentiation.	Gold (Au) nanoparticles (AuNP)	60 nm AuNPs at a concentration of 56 µM have been reported to effectively enhance the proliferation of hPDLCs.
[22]	Test the inhibitory effect of Au nanoparticles (AuNPs) on pathogenic growth, biofilm formation, and invasion	Gold (Au) nanoparticles (AuNP)	AuNPs from 10 to 20nm was shown to strongly inhibit biofilm formation of pathogenic P. aeruginosa bacteria.
[23]	Synthesize and characterize calcium-deficient hydroxyapatite (CDHA) nanocarriers with different Ca/P ratios. Investigate the antibacterial effect of nanocarriers (TC-CDHA) by loading tetracycline on synthesized CDHA and examine the biocompatibility of TC-CDHA nanocarriers.	Tetracycline loaded Calcium deficient hydroxyapatite (TC-CDHA)	Tetracycline-loaded nanoparticles were biocompatible as an osteoconductive bone scaffold and they had antibacterial and proliferative effects
[24]	Synthesize carboxymethyl cellulose (CMC) to combine the antibacterial effect of chlorhexidine with calcium phosphate nanoparticles with mineralization ability and to achieve an optimal loading with chlorhexidine and improve the adhesion properties on the tooth surface.	Chlorhexidine-loaded carboxymethyl cellulose-functionalized calcium phosphate nanoparticles (CaP-CMC-CHX)	The CaP-CMC-CHX paste stuck well to the root surface and closed dentin tubules.
[25]	Develop drug delivery vehicles for potential use in the oral cavity containing BAR-modified poly(lactic-co-glycolic) acid (PLGA) nanoparticles (NPs)	A synthetic peptide (BAR)	BAR was effective in controlling periodontitis by limiting *P. gingivalis* colonization in the oral cavity.
[26]	Synthesize nitric oxide-releasing silica NPs and investigate the antibacterial activity of nitric oxide-releasing NPs.	Nitric oxide-releasing silica NPs	Antibacterial action was observed against the periodontopathogens Aggregatibacter actinomycetemcomitans and Porphyromonas gingivalis.
[27]	Develop polydopamine NPs and test the antioxidant effect of polydopamine NP by in vitro and in vivo study	Polydopamine (PDA) NP	PDA NPs were effective in removing multiple ROS and deactivating ROS-induced inflammatory reactions, and in an in vivo experimental model of periodontitis, PDA NPs removed ROS and diminished periodontal inflammation.
[28]	Develop biopolymer silica composites with Larrea divaricata Cav. Extract and investigate the antioxidant activity, cell proliferation	Chitosan (Chi)-Carboxymethylcellulose (CMC)-Silica (SiO2) loaded with aqueous *Larrea divaricate* Cav. extract (Ld)	Chi-CMC-SiO2 composites showed the highest incorporation and reached 100% of extract release in almost 4 days while they preserved their antioxidant properties
[29]	Investigate the effect of metformin hydrochloride-loaded Poly (d,l-Lactide-co-glycolide) (PLGA)/(MET-loaded PLGA) on a ligature-induced periodontitis model in diabetic rats.	Metformin hydrochloride-loaded PLGA NPs	Metformin hydrochloride-loaded PLGA NPs produced also controlled inflammation and bone loss in an experimental periodontal disease model by successfully controlling blood glucose levels.
[30]	Assess the biological effect of the local administration of curcumin in a nanoparticle vehicle in an experimental periodontal disease model.	Curcumin NPs	Curcumin-loaded polymeric NPs could reduce inflammation and tissue destruction associated with periodontal disease.

Ref	Aim of study	Drug Tested	Main Results
[31]	Test the efficacy of a locally applied 8.5% nanostructured doxycycline (DOX) gel in preventing alveolar bone loss in experimental periodontal disease	Doxycycline nanostructured gel	NP and doxycycline were used together, a significant decrease in inflammatory cell activation (through MPO measurements) was reported
[32]	Develop pH-responsive polylactide-glycolic acid copolymer and chitosan (PLGA/chitosan) nanosphere as an inflammation-responsive vehicle and assess the potential of the nanosphere encapsulating metronidazole, an antibiotic, and N-phenacylthiazolium bromide (PTB)	Polylactide-glycolic acid copolymer and chitosan (PLGA/chitosan) nanosphere	Inflammation in periodontitis treated with metronidazole with NPs after 21 days was reported to be less in comparison to untreated periodontitis
[33]	Synthesize serum albumin microspheres containing minocycline and zinc oxide nanoparticles (ZnO NPs) by incorporation into the hydrogel and compare them with 2% minocycline ointment	Serum albumin microspheres containing minocycline and zinc oxide nanoparticles (ZnO NPs)	Albumin microspheres containing minocycline and zinc oxide nanoparticles (ZnO NPs), gingival tissue could repair itself at certain ZnO NP concentrations, and antimicrobial activity, low toxicity and high safety were achieved.
[34]	Synthesize calcium and zinc-loaded bioactive and cytocompatible nanoparticles for periodontal therapy	Zinc and calcium loaded PolymP-*n*Active nanoparticles	Calcium and zinc loaded NPs were found in another study to promote periodontal regeneration, as well as showing nontoxic activity against oral mucosal fibroblasts
[35]	Investigate the effect of encapsulation of two physiochemically different drugs (ciprofloxacin and betamethasone) on continuous adjuvant release with surface grafted cyclodextrin (WGA-liposome-CD) and wheat germ agglutinin (WGA) conjugated liposomes.	Ciprofloxacin and betamethasone-loaded Wheat germ agglutinin liposomes	Ciprofloxacin and betamethasone-loaded agglutinin liposomes promoted potent antibacterial and synergistic anti-inflammatory effects for up to 24 hours.
[36]	Develop and evaluate pH-dependent systems based on nanospheres (NSphs) and nanocapsules (NCs) loaded with chlorhexidine (CHX) base as a novel formulation for the treatment of periodontal disease	NSphs-CHX and NCs- CHX	A 65.78% reduction in plaque index upon application of local drug delivery systems, which they synthesized using chlorhexidine-loaded nanospheres and nanocapsules, to the periodontal pocket to improve the treatment of periodontitis.
[37]	Check a nanotechnological formulation as a carrier for 15d-PGJ(2), and to investigate the immunomodulatory effects of this formulation in a mouse periodontitis model.	15d-PGJ2-loaded nanocapsules	The 15d-PGJ(2)-NC had induced significantly lower alveolar bone loss in the group administered, had lower lymphocyte infiltration, RANK-L and m-RNA expression, and myeloperoxidase activity
[38]	Test the efficacy of a locally applied 2%w/w nanoemulgel (NEG) of Ketoprofen (KP) in preventing the periodontitis, and was also checked NEG without KP to ensure the effect of eugenol in NEG as an oil phase.	2%w/w nanoemulgel (NEG) of Ketoprofen (KP)	The group treated with ketoprofen nanoemulgel was found to have had less bone loss, and that gingival index, tooth mobility, and cytokine expression were significantly lower than the group that was merely ligated
[39]	Develop a chitosan-based risedronate/zinc-hydroxyapatite intrapocket dental film (CRZHDF) for applications in the treatment of alveolar bone loss in an animal model of periodontitis	Chitosan-based risedronate/zinc-hydroxyapatite intrapocket dental film	The alveolar bone loss was less in the dental film group, where chitosan-based risedronate/zinc hydroxyapatite nanoparticles were placed in the pocket and the mineral density of the alveolar bone improved significantly.
[40]	Regulate the inflammatory response and the subsequent differentiation of periodontal cells under the condition	45 nm gold nanoparticles (AuNPs)	Decreased alveolar bone loss in rats induced with experimental periodontitis, the elastic and collagen fibers were tighter and more organized, as well as that the number of osteoclasts was less in the group with AuNP, and that the inflammatory response and the iNOS level decreased
[49]	Investigate the apoptotic effect of Doxorubicin and its nano-formulated form (Doxil) on oral squamous cell carcinoma CAL-27 cells.	Doxorubicin nano-formulated form (Doxil)	Doxil showed a higher apoptotic effect on CAL-27 cells, and a greater increase in caspase-3 level was obtained compared to doxorubicin.
[50]	Asses the efficacy of the injectable form of the n-Doxon blood parameters and cardiac and liver enzymes compared to the commercial form of Dox in OSCC-induced by 4NQO in rats	Doxorubicin-loaded nano-particles (n-Dox)	n-Doxon increased its biological efficacy and therapeutic effects, and to have reduced hematological side effects in treatments
[51]	Detection of morphology, size and in vitro drug releases of HNPD nanoparticles, evaluation of OSCC targeting capacity and therapeutic efficacy of HNPD nanoparticles both in vitro and in vivo	PEGylated DOX (PD) mediated by HN-1 peptide	A significantly higher cellular uptake and cytotoxicity were observed compared to PD nanoparticles, and that the HNPD nanoparticles were selective for CAL-27 and SCC-25 cells.
[52]	Design and fabricate a multifunctional drug-delivery nanoplatforms for oral cancer therapy	Polyethylene glycol-stabilized, PDPN antibody (PDPN Ab)- and doxorubicin (DOX)-conjugated gold nanoparticles (AuNPs)	(PDPN Ab)-AuNP-DOX was shown to exhibit enhanced antitumor activity, both in vitro and in vivo, by having low toxicity and high drug loading capacity

Ref	Aim of study	Drug Tested	Main Results
[53]	Synthesize a new oral mucoadhesive delivery system based on the combination of alginate and liposomes	Three hybrid alginate/liposomes delivery systems; a hybrid paste, a hybrid hydrogel, and a hybrid cross-linked paste.	The hybrid paste produced from liposome and alginate facilitated the death of cancer cells thanks to its mucoadhesion feature and continuous liposome release
[54]	Synthesize a chemokine (SDF-1)-modified, sterically stabilized system to co-deliver doxorubicin and indocyanine green	SDF-1 / Indocyanine green / Perfluorohexane / Doxorubicin PLGA Nanoparticles	Multifunctional targeted polymeric nanoparticles loaded with doxorubicin using indocyanine green for targeted photoacoustic imaging and photo-thermal ablation of oral cancer cells, and argued that the combination of chemotherapy and photo-thermal therapy in oral cancer treatment is more effective
[55]	Develop cisplatin (NC-6004)-bearing polymeric micelles to enhance their antitumor effects and reduce such toxicity problems, evaluate the efficacy and safety of NC-6004 for oral squamous cell carcinoma	Cisplatin (NC-6004) -bearing polymeric micelles	Cisplatin-loaded nanoparticles had an inhibitory effect equivalent to free drugs besides having lower nephrotoxicity
[56]	Synthesize a new nanoparticle that could carry both MDR1-siRNA to block MDR1 expression and doxorubicin (DOX)	Mesoporous Silica Nanoparticles (MSNP)-Polymerpolyethylenimine (PEI) - DOX/ MDR1 -siRNA	Synthesized MSNP-PEI-DOX/MDR1-siRNA increased the effect of cancer chemotherapy for the treatment of multidrug-resistant cancer
[57]	Prepare paclitaxel (PTX), 5-fluorouracil (5-FU) and ascorbic acid (AA) entrapped SLN to achieve sustained release of drug at desired concentration and evaluate SLN trapping PTX, 5-FU and AA both in vitro and in vivo to obtain the best combination for effective therapeutic efficacy.	Paclitaxel (PTX), 5-fluorouracil (5-FU), and ascorbic acid (AA) loaded solid lipid nanoparticles (SLN)	SLN with PTX in combination with SLN with AA was more effective than the nanoparticles loaded with 5-FU in the in-vivo treatment of oral squamous cell carcinoma.
[58]	Research the molecular mechanisms triggered by Cur-NPs in CAR (CAL27-cisplatin-resistant) cell line which was established in our laboratory	Water-soluble PLGA curcumin nanoparticles (Cur-NPs)	Curcumin loaded on PLGA NPs induced cell apoptosis without showing cytotoxic effects on healthy gingival fibroblasts and oral keratinocytes
[59]	Develop Cat-functionalized NPs as a mucoadhesive system for the local treatment of oral cancers	Doxorubicin (DOX) loaded Catechol (Cat)-modified chitosan/hyaluronic acid (HA) nanoparticles (NPs)	DOX-loaded Cat-NPs (DOX-NPs) inhibited the growth of the cell lines of HN22 oral squamous cell carcinoma with a low IC and DOX-NPs induced apoptosis in cells compared to free DOX
[60]	Evaluate the effects of SPIONs on OSCC mitochondria because of the usefulness of the application of these nanoparticles in cancer treatment and diagnosis.	Superparamagnetic iron oxide nanoparticles (SPIONs)	SPIONs had decreased cell viability and to have increased lipid peroxidation level and caspase-3 activity in OSCC cells. SPIONs had selective toxic effects only on OSCC and not on mitochondria in healthy cells
[61]	Characterize and evaluate the anti-neoplastic activity of a composite of chitosan (CS) and polycaprolactone (PCL) coating 5-fluorouracil (5-FU) in HNSCCC	Composite of chitosan (CS) and polycaprolactone (PCL) coating 5-fluorouracil (5-FU	Significant inhibition of cancer cell proliferation was observed with CS-decorated PCL NPs, based on metabolic and colony formation assays. Significant increases in autophagy and cell death were reported, as assessed by cell protein analysis, LC3-II expression and PARP1 cleavage, respectively
[62]	Compare the effects of ALA-PDT on a human oral precancerous cell line (DOK) and an oral squamous cell carcinoma cell line (CAL-27)	5-aminolevulinic acid-mediated photodynamic therapy (ALA-PDT)	ALA-PDT effectively killed DOK and CAL-27 cells in a dose- and time-dependent manner in *vitro*
[63]	Confirm whether the novel mitochondria-targeted gene can enhance the tumor suppression efficacy of ALA-PDT	5-aminolevulinic acid (ALA) photosensitizer loaded chitosan (CS) / the GBAS gene plasmid DNA (shGBAS) (CS-ALA-shGBAS)	The new CS-ALA-shGBAS they synthesized by creating a mitochondrial-targeted drug co-delivery system for combined photodynamic therapy (PDT) and gene therapy had a superior mitochondrial-targeted killing efficiency on OSCC, both in vitro and in vivo

4. Conclusion

This review study lays bare the capacity and limitations of nanotechnology in the treatment of oral diseases. It will enable comprehensive oral health maintenance, including nano dentistry, nanomaterials, biotechnology, tissue engineering. Nanotechnological drug delivery systems are a treatment strategy that yields positive results in the treatment of periodontal diseases and oral cancers, such as minimizing systemic effects and maximizing effectiveness thanks to being applied locally. Despite the advantages of applying nanotechnology to drug delivery, there are still some challenges associated with the clinical application of nanotechnological drug delivery. Understanding the mechanism underlying intracellular uptake control and the fate of nanomaterials are the biggest challenges. To meet all these challenges, experts from different disciplines must work together to transform new laboratory innovations into new technologies, with the joint efforts of scientists in various disciplines including medicine, materials science, engineering, physics, and biotechnology. In the near future,

this technology may become a cornerstone in dentistry and medical science, and initiatives in this field may bring on positive results in economic and social terms by offering healthier oral health for people. Finally, preclinical data on the use of nanoparticles as an adjunct to the treatment of periodontal disease and oral cancers are encouraging, but particularly comprehensive clinical studies are needed as there is no strong evidence for their clinical efficacy. However, further studies based on more evidence are required due to safety concerns.

Acknowledgment

The authors received no financial support for the research, authorship, and/or publication of this article

Declaration of Conflict of Interest

Authors declare that they have no conflict of interest with any person, institution, or company.

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