Nanoparticles in Dentistry

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In recent years, nanoparticles (NPs) have been receiving more attention in dentistry. Their advantageous physicochemical and biological properties can improve the diagnosis, prevention, and treatment of numerous oral diseases, including dental caries, periodontal diseases, pulp and periapical lesions, oral candidiasis, denture stomatitis, hyposalivation, and head, neck, and oral cancer. NPs can also enhance the mechanical and microbiological properties of dental prostheses and implants and can be used to improve drug delivery through the oral mucosa.

Keywords: nanoparticles ; drug delivery ; dental caries ; periodontal diseases ; dental prosthesis ; head and neck neoplasms ; hyposalivation

1. Introduction

Nanotechnology has become one of the most active research areas in the past decades, especially in health sciences [1]. Nanoparticles (NPs) are discrete clusters of atoms with a wide range of medical applications, including cancer therapy, drug delivery, tissue engineering, regenerative medicine, biomolecules detection, and also as antimicrobial agents [2]. NPs are generally classified into organic (dendrimers, micelles, liposomes, or polymers), inorganic (metal or metal oxide based), or carbon = based (fullerenes, graphene, or carbon nano tubes) [3].

One of the main challenges for dental researchers is to develop materials that can withstand the harsh conditions of the oral environment while remaining biologically sustainable and biocompatible [4][5]. NPs are gaining momentum in dentistry due to their physicochemical and biological properties, including biocompatibility, size, charge, large surface area, strength, solubility, chemical and surface reactivity, color, high stability, and thermal conductivity [6][7][8]. Such properties have allowed the development of new, innovative materials and the expansion and improvement of their functions [9]. Despite having countless advantages, some NPs also have limitations, including toxicity, limited delivery, and being difficult to handle [8].

2. Dental Caries

Dental caries is the most prevalent oral diseases among the population worldwide. For this reason, it is considered a public health problem, making the development of alternative treatments imperative [10]. Dental caries is a multifactorial disease and is usually caused by microbial colonization of the dental surface and the formation of biofilms. The microorganisms present in the oral cavity promote sugar metabolism generating acidic metabolites that drastically reduce the osral pH [10][11]. The acidification of the pH starts the process of demineralization of the teeth, that leads to the loss of calcium, fluoride, and phosphate ions, resulting in the formation of cavities [12].

This process can be reversed with fluoride application or by using toothpaste and mouthwashes containing fluoride. The use of NPs is an important tool and can help in this type of treatment [12][13]. NPs can be defined as ultra-dispersed supramolecular structures, with sizes from 10 µm to 1000 µm [14]. Drugs can be encapsulated, dissolved, trapped, or attached to the structure of NPs and this can be very useful in dentistry. For example, NPs with adequate amounts of fluoride can be applied in the oral cavity to increase fluoride levels. This application allows the remineralization of the teeth and avoids the process of caries formation [12]. Calcium fluoride nanoparticles (CaF_2NPs) have been widely used to increase the level of fluoride present in the oral cavity. According to Kulshrestha et al., CaF_2NPs are capable of inhibiting the production of exopolysaccharide by *Streptococcus mutans* [15]. These NPs have a dual effect: to promote the remineralization of tooth enamel and to prevent the development of biofilm. However, the residence time in the oral cavity of CaF_2NPs is short and, in order to improve this characteristic, the CaF_2NPs can be loaded in chitosan bioadhesive films [12][16][17]. Chitosan is a polymer widely used for oral applications because of its mucoadhesion, biocompatibility, low toxicity, and controlled release of drugs. A study conducted by Ghafar et al. incorporated CaF_2NPs in a bioadhesive chitosan film and the CaF_2NPs remained intact for up to 3 h. This approach provided an increase in the residence time of

CaF_2NPs in the oral environment, showing an advantage when compared to the use of toothpaste and mouthwashes, which remain for a few minutes in the oral cavity [12].

In addition to chitosan, pectin and alginate are examples of other polymers that also have mucoadhesion, biocompatibility, biodegradability, and low toxicity. For this reason, Nguyen et al. evaluated the capacity of these three polymers to produce nanoparticles loaded with sodium fluoride. The best results were obtained with chitosan NPs, while alginate was not able to form nanoparticles. Chitosan NPs showed slow and continuous fluoride release, with increased release in acidic conditions [13]. Despite requiring in vivo studies, chitosan was the best option for obtaining NPs and showed slow fluoride release.

Another alternative for dental caries treatment is the use of restorative materials with bioactive functions [18]. The addition of chitosan NPs in a glass ionomer cement (GIC) is one of these strategies [18][19][20]. Chitosan NPs have bactericidal effect and provide fluoride release from the material, promoting a dual effect in the prevention of dental caries. Kumar et al. demonstrated that the addition of 10 wt.% of chitosan NPs in GIC increased the material resistance and fluoride release [18]. However, Ibrahim et al. showed that the addition of more than 25% (*v*/*v*%) of chitosan NPs in the GIC improved its bactericidal effect against *S. mutans*, but decreased its physical properties, leading to ruptures and poor adhesion to dentin [19]. For this reason, these same authors added titanium oxide NPs (TiO_2NPs) to the GIC. The hybrid material showed antimicrobial activity with inhibition of biofilm growth. In addition, the TiO_2NPs improved some physical characteristics, such as flexibility and compressibility [20].

In another study, Aliasghari et al. showed that chitosan NPs have anti-growth and anti-adherence effects against cariogenic bacteria in vitro [21]. Chitosan is a polymer with antimicrobial properties by itself. This potential can be increased by loading antibiotics in chitosan NPs [17][22]. Chitosan NPs are widely used in dentistry as hydrogels and nanofibers for application in the oral cavity [17][21][22]. The use of chitosan NPs is also reported by Ikono et al., who found antifungal action against *Candida albicans* [23]. Covarrubias et al. coated copper NPs with chitosan and proved that the bactericidal effect of the NPs against *S. mutans* increased and was equivalent to the traditional antimicrobials such as chlorhexidine and cetylpyridinium chloride [16]. Ren et al. produced a chitosan hydrogel incorporated with a peptide that promotes tooth remineralization. This peptide combined with chitosan hydrogel showed a dual effect with antibacterial effect and tooth remineralization properties [24].

Other polymeric NPs composed of poly(ethyleneglycol) (PEG) and polylactic-co-glycolic acid (PLGA) are used for the prevention and treatment of dental caries. These polymers are mucoadhesive, biocompatible, biodegradable, and suitable for promoting prolonged release [25][26][27]. Sebelemetja et al. produced polymeric NPs using PEG-PLGA that showed bactericidal and anti-biofilm effects against *S. mutans* [26]. Zhao et al. produced polymeric NPs loaded with chlorhexidine which were able to rapidly release the drug in acidic pHs [28]. The same strategy was also proposed by Liu et al. using the polymers PEG-b-PCL and PCL-b-PAE [25]. These polymeric NPs along with chitosan NPs and fluoride NPs are highly promising for dental caries therapy and can help to design other drug-delivery systems.

3. Periodontal Diseases

The cause of periodontal disease is the imbalance between the colonization of bacterial pathogens and the host immune response toward infection [29]. The first step in the development of periodontal disease is the formation of dental plaque and gingivitis, which consist in the inflammation of gingiva. The chronic stage occurs later, when the immune cells are recruited and activated. These cells release pro-inflammatory cytokines and reactive oxygen species (ROS) that cause alveolar bone and periodontal ligament destruction [29][30].

The use of NPs for the eradication of pathogenic bacteria is an effective approach to treat periodontal disease since bacterial colonization is one of the first steps to trigger this condition. Emmanuel et al. reported that silver nanoparticles (AgNPs) associated with azithromycin and clarithromycin have a synergistic antimicrobial efficacy against periodontal disease causing microorganisms [31]. The platinum nanoparticles (PtNPs) developed by Itohiya et al. have been shown to mediate antibacterial effects caused by *S. mutans*, *Enterococcus faecalis*, and *Porphyromonas gingivalis* [32]. These microorganisms are associated with dental caries, endodontic lesions, and periodontal diseases. Similarly, Vega-Jiménez et al. developed bismuth subsalicylate NPs with antibacterial effect against periodontal pathogens *Aggregatibacter actinomycetemcomitans*, *Capnocytophaga gingivalis*, and *P. gingivalis*, with low toxicity against human gingival fibroblast (HGF-1) cells [33]. In another study, Holden et al. produced glutathione-capped bimetallic NPs with great antibacterial potential against anaerobic oral pathogen *P. gingivalis* [34].

These nanoparticles can be used alone or in association with biomaterials to promote prolonged residence time in the oral cavity. Lee et al. loaded AgNPs into electrospun nanofibers to enhance its bio-functionality. This biomaterial has also been employed for oral drug delivery and for the development of an antimicrobial oral wound dressing to inhibit periodontitis and gingivitis [35]. Another example of biomaterial for dental application is the gelatin and chitosan composite guided tissue regeneration membrane containing hydroxyapatite nanoparticles and antimicrobial peptide (Pac-525)-loaded PLGA microspheres developed by He et al. This drug delivery system showed sustained release and antibacterial activity for a long period of time against *S. aureus* and *Escherichia coli* [36]. To promote a rapid release of an antibacterial peptide (BAR), Mahmoud et al. developed polymeric electrospun fibers to encapsulate it. The development of this platform could rapidly release the peptide and disrupt the dual-species biofilm formed by *P. gingivalis* and *Streptococcus gordonii* [37].

Another method to prevent periodontitis is to treat the tissue inflammation caused by the chronic form of the disease. Nitric oxide-releasing silica NPs [38], polydopamine NPs [29], and silica NPs [30] are examples of NPs that used anti-inflammatory compounds for treating periodontal disease. After treatment with some of these NPs, it was possible to observe a decrease in local periodontal inflammation and a higher antioxidant activity [29][30]. The metformin hydrochloride-loaded PLGA NPs produced by Pereira et al. also controlled inflammation and bone loss in an experimental periodontal disease model by managing to control blood glucose levels below what is considered diabetes [39]. In fact, prevention of bone loss and promotion of tissue repair are important factors for the treatment of chronic cases of periodontal disease. Mou et al. produced albumin microspheres containing minocycline and zinc oxide nanoparticles (ZnONPs) and observed gingival tissue self-repairing, antimicrobial activity, low toxicity, and high security at certain concentrations of ZnONPs [40]. Osorio et al. observed periodontal regeneration by using calcium- and zinc-loaded NPs. These NPs can promote precipitation of calcium phosphate deposits and were found to be non-toxic against oral mucosa fibroblasts [41]. Despite the aforementioned promising results, further studies are needed to investigate these novel formulations with NPs, especially in vivo studies and controlled clinical trials.

Kalia et al. used polymeric NPs to deliver the BAR peptide to inhibit *P. gingivalis* and *S. gordonii* biofilm formation. These authors noticed a higher local dose of peptide compared to treatment with formulations of free peptide. The BAR-modified NPs also disrupted the preformed biofilms more effectively [42]. Zambrano et al. found that curcumin-loaded polymeric NPs may reduce inflammation and the connective tissue destruction associated with periodontal disease [43]. In addition, Wijetunge et al. found that wheat germ agglutinin liposomes loaded with ciprofloxacin and betamethasone promote potent antibacterial and synergistic anti-inflammatory effects for up to 24 h [44]. Liposomes were used by Moraes et al. to promote pain control during scaling and root planning treatment. The liposomes loaded with lidocaine/prilocaine could be a good option to increase patient compliance during this type of clinical treatment, especially anxious patients or those who have a fear of needles [45].

4. Pulp and Periapical Lesions

Exposure of the dental pulp is a challenging problem to treat successfully, regardless of the cause [46]. The primary goal of endodontic therapy is to eliminate microbial infection and promote periapical tissue healing [47]; however, complete eradication of intracanal microbial load is considered practically impossible and has yet to be achieved [48][49]. Endodontics can benefit from the emergence of nanotechnology due to its broad-spectrum antibacterial and anti-biofilm activity and biocompatibility [50].

Chitosan has many applications in endodontics. It can be successfully used as a chelating substance [51][52][53][54][55], as a scaffold for the delivery of growth factors [56], or medications [57]. Moreover, it can be used as an irrigant solution [47][58][59][60] with less toxicity than sodium hypochlorite or chlorhexidine [58][59], as an intracanal medication by itself [61], or as an adjunct to calcium hydroxide [62][63]. Chitosan can increase the antibacterial efficacy, bond strength, and penetration of root canal sealers, directly or indirectly [48][64][65][66]. In addition, some studies suggest that chitosan could be used as an auxiliary for procedures such as apexification [67], endodontic retreatment [68], pulp-capping [46][69][70][71], and pulpotomy [72], although it was not able to induce apexogenesis in immature necrotic permanent teeth [73] or to form new mineralized tissues along the root canal walls of immature dog teeth with apical periodontitis [74].

AgNPs are also widely used in this field. It has been shown that these NPs, combined or not with other substances, are effective against *E. faecalis* [75][76][77][78] and other endodontic-periodontal pathogens [79], are biocompatible [80], have low cytotoxicity and genotoxicity [81], and can be used as endodontic irrigants [75][82], chelating agents [83], root canal sealers [84], and/or repair cements [85]. However, some authors have reported that AgNPs can cause tooth discoloration when used as an intracanal medicament [86], while others have claimed otherwise [50]. Perhaps, the combination of AgNPs with calcium hydroxide might be the reason for these contrasting results, as it did not promote significant changes in tooth color [50].

Several different NPs have been investigated for endodontic therapy. The obturation properties of gutta percha can be enhanced with diamond NPs [87]. A randomized clinical trial with six months of follow-up reported that there was a decrease in the size of periapical lesions after obturation with modified gutta percha, with no adverse events [87]. Gold (Au) and iron oxide NPs can inhibit pathogenic biofilm formation [88][89] and invasion to dental pulp stem cells [88]. Some studies proposed propolis-loaded NPs of PLGA and NPs of amorphous calcium phosphate as endodontic sealers, given their antimicrobial activity [90][91], good bond strength to root canal [90], and/or cytocompatibility [91]. PLGA-moxifloxacin NPs and chlorhexidine hydrochloride nanoemulsions could be employed as irrigant solutions, considering their antibacterial activity against *E. faecalis* [6][92], cleansing ability [92], and/or sustained release [6]. Nanotechnology can also be used to promote pulp tissue repair and regeneration [93], a topic of great interest in dentistry.

NPs can have their properties improved by being conjugated with other substances and materials. The combination of photodynamic therapy and NPs can reduce the presence of *E. faecalis* in root canals [94][95][96] and remove the smear layer from the apical third of root canals [97]. The association of chitosan and EDTA can simultaneously disinfect root canals and remove the smear layer [98].

Despite the aforementioned advantages, NPs can also have some limitations. For example, one randomized, double-blind, clinical trial did not find significant differences between a liposomal bupivacaine formulation and bupivacaine alone in the management of symptomatic patients with pulpal necrosis experiencing moderate to severe preoperative pain [99]. Another clinical trial from the same group did not find significant differences between the same liposomal bupivacaine formulation and 2% lidocaine with 1:100,000 epinephrine for pain reduction in untreated symptomatic irreversible pulpitis [100], indicating that there are some situations where NPs are not as effective as the free, conventional drug.

5. Peri-implantitis and implant failures

Implant-prosthetic rehabilitation has become the preferred therapy for tooth loss and the gold standard in modern dentistry because of its ability to integrate with the surrounding alveolar bone [101][102][103]. Peri-implantitis is one of the most common causes of implant loss and is caused by a microbial biofilm surrounding the surface of the implant that leads to inflammation [104].

Many NPs have been studied aiming to reduce surface contamination and the occurrence of peri-implantitis. Studies have shown the antimicrobial activity of NPs against pathogens related to peri-implantitis, including *S. gordonii* [104], *S. mutans* [105][106], *P. gingivalis* [107][108], *Staphylococcus aureus* [109], *C. albicans* [110], *E. coli* [111][112], *Streptococcus sanguinis*, and *A. actinomycetemcomitans* [113]. NPs can prevent or treat the infection through alternative means, such as by using a chitosan brush to perform the debridement [114][115]; by applying a chitosan-based thermosensitive hydrogel, which reportedly has antibacterial properties and could act as a lubricant and sealant simultaneously [116]; by delivering drugs or proteins to the target tissue via a liposome-modified titanium surface [117]; by brushing the implant surfaces with an implant-paste based on two-dimensional nanocrystalline magnesium phosphate gel and hydrated silica NPs [101]; or by coating the implant surface with a chitosan matrix containing gelatin nanospheres loaded with antibiotics [118].

Inorganic NPs have many different roles in periodontology, especially in the prevention and treatment of peri-implantitis. Copper and AgNPs present antibacterial properties [119][120][121][122], AuNPs can be used as a bone inductive adjuvant [103], bismuth NPs can improve the treatment of peri-implantitis and peri-implant mucositis [122], titanium NPs prevent fungal and bacterial adhesion to the implant surface [123][124], and hydroxyapatite NPs can be combined with AgNPs, aiming to enhance their biocompatibility [125].

The clinical success of titanium implants depends on their surface characteristics, which can influence cell adhesion, proliferation, differentiation, and their integration with surrounding tissues [126][127]. Using hydroxyapatite nanocrystals to treat titanium surfaces can increase cell proliferation, differentiation, and spread and contribute to the synthesis of bone matrix, and consequently, osseointegration [126]. Hydroxyapatite NPs seem to be an excellent scaffold for bone implant integration, considering the high cell adhesion and osteoblast viability presented in the study conducted by De Lima Cavalcanti et al. [127]. Hydroxyapatite NPs can also be combined with chitosan and graphene oxide to fabricate a composite coating, which greatly heightened the cell–material interactions in vitro and enhanced osseointegration in vivo [128]. AuNPs were used to coat titanium surfaces, which showed significantly enhanced osteogenic differentiation and influence on the osseous interface formation [129].

Chitosan has many applications in this field, as it can be used to coat surfaces in order to increase their biocompatibility and bioactivity [130]. Chitosan can also be conjugated with other substances, including AgNPs [131][132], hyaluronic acid [131][133][134], poly(dopamine) and hydroxyapatite [135], collagen [136], silica [137], and poly(acrylic acid) [138]. These substances,

alongside chitosan, can prevent the surface adhesion of bacteria [131][132][133][134][138], increase the proliferation of cells [137][138], and improve osseointegration [134], soft tissue integration [135], and peri-implant tissue attachment [136].

NPs can also be used for sinus floor elevation and augmentation procedures. Nanocrystalline and nanoporous hydroxyapatite were tested during a clinical study and proved to support bone formation, with no clinical and histological signs of inflammation in the augmented sites [139]. The use of hydroxyapatite NPs for augmentation with simultaneous implant placement was compared to a graftless tenting technique in another clinical trial, and both showed successful results regarding implant stability [140].

Patients with special needs can benefit from the advances of nanotechnology as well. Chitosan-AuNPs facilitated PPARγ gene delivery on dental implants and contributed to osseointegration, new bone formation, and mineralization in diabetic-induced rats, suggesting it can be used as a therapeutic approach in diabetic patients. This gene consists of transcription factors and is closely linked to the metabolism of glucose homeostasis [141]. Chitosan-AuNPs were also able to deliver c-myb, a transcription factor involved in the control of cell proliferation, differentiation, survival, and death, to the target area and consequently enhance bone formation in the osteoporosis [142]. Another option for osteoporotic patients might be implants coated with gelatin/chitosan and insulin-like growth factor 1, a strategy that promoted osseointegration in osteoporotic conditions both in vivo and in vitro [143]. A liposomal bupivacaine formulation might help those who are more sensitive to pain to experience a significant reduction of postsurgical pain and opioid consumption [144].

6. Dental prosthesis failures

Although dental implants are becoming more accessible and affordable, in many cases, for medical and financial reasons, a conventional denture is still the preferred treatment for edentulous patients [145][146].

Dentures are usually made with conventional heat-polymerized polymethylmethacrylate (PMMA) [147] due to its biocompatibility, esthetics, stability in the oral environment, ease of repair, tasteless and odorless properties, high polishability, low cost, acceptability by the patients, light weight, and low water sorption and solubility levels [145][148][149][150]. However, PMMA has poor mechanical properties, such as low flexural and impact strength, low fracture resistance, insufficient surface hardness, fatigue failure, and surface roughness, which allows microbial adhesion [147][149][151][152][153][154].

Given the aforementioned limitations of conventional dental prostheses and the fact that PMMA is a clear polymer capable of being modified, new technologies have been developed in order to improve its physicochemical properties [147]. The ideal material must balance its achieved properties while still managing to be biocompatible, readily available, cost effective, antimicrobial, easy to manipulate, capable of maintaining sufficient bond strength with artificial teeth and lining materials, functionally efficient, and esthetically pleasing [150][155][156]. The incorporation of organic and inorganic NPs into acrylic resins has been proposed with this aim.

Zirconium oxide (ZrO_2) NPs were one of the most common types of NPs tested in this field in the past years. The addition of ZrO_2NPs can significantly increase the dimensional accuracy, decrease the impact strength [155], and increase the tensile strength of the denture base acrylic [150], while the translucency of the PMMA can be reduced as the concentration of nano-ZrO_2 increases [150]. Incorporation of ZrO_2NPs can also improve the flexural and transverse strength and reduce *Candida* adhesion to repaired denture bases [157][158][159]. By mixing these NPs with glass fibers, the flexural and impact strengths of PMMA can significantly improve [149].

The effect of incorporating silica NPs into PMMA has also been described in the literature. The silica incorporation into acrylic resin decreased its flexural strength when compared to PMMA alone [148]. Furthermore, Karci et al. found lower flexural strength values in the groups with silica NPs when compared with those of titanium and aluminum NPs [152]. When silica aluminum borate whiskers were combined with Novaron AG300, tetra-needle-shaped zinc oxide whisker, and silanized ZrO_2NPs, the composites presented substantially higher antibacterial activity, flexural strength, and surface hardness, without compromising their cytotoxicity [153]. By silanizing SiO_2NPs with γ-methacryloxypropyltrimethoxysilane, the PMMA specimens presented adequate flexural strength, flexural modulus and fracture toughness, with a clinically acceptable color [160].

Zinc oxide (ZnO) NPs have also been receiving attention recently. In some concentrations, these NPs can present antifungal properties [9][161], increase the hardness, thermal stability, glass transition temperature, and the hydrophilicity of PMMA composites, and do not compromise the properties of acrylic resin in a way that could disqualify its clinical use [162][163]. However, some studies report the opposite, stating that ZnONPs are not capable of inhibiting biofilm formation nor

increasing the glass transition temperature [164]. When silanized with methacryloxypropyltrimethoxysilane, ZnONPs can present greater antifungal effect, fewer color differences, and opacity compared to nonsilanized NPs [165].

Moreover, other NPs have been investigated. The addition of nanodiamonds to acrylic denture base improved its flexural strength and surface roughness at low concentrations, but its impact strength was compromised [147]. Prepolymer incorporation resulted in increased flexural strength of acrylic resins when compared to silica addition [148]. The incorporation of AgNPs affected the transverse strength of the denture base acrylic resins in a concentration-dependent manner and decreased the glass transition temperature in the study conducted by Koroglu et al. [154]. The concentration of AuNPs added to PMMA can have significantly different effects on PMMA flexural strength [151]. The addition of titanium dioxide NPs can considerably modify the acrylic resin color and decrease its flexural strength, but it can also significantly increase the impact strength, tensile strength, and microhardness, depending on the concentration of NPs [166][167].

Regarding the prevention of denture-related infections, incorporation of titanium dioxide or AgNPs in PMMA was proved to have antimicrobial activity, especially in higher concentrations and against *Candida* species [145][168][169]. High concentrations, however, could result in lower mechanical parameters [145]. The addition of nanostructured Ag vanadate can provide acrylic resins with antibacterial activity but reduces their impact strength [170]. By adding nano-chitosan particles to acrylic resins, biofilm formation of *Candida* species can be significantly reduced [171]. The incorporation of platinum and diamond NPs into a silica coating agent can improve its hydrophilicity and longevity, helping prevent microorganisms from adhering to the denture surface [156].

7. Oral candidiasis and denture stomatitis

Oral candidiasis is an opportunistic fungal infection that affects approximately 2 million people around the world annually, especially those who are immunocompromised [171][172][173], and it is characterized by patches of creamy white exudate with a reddish base covering the mucous membrane of the tongue, cheeks, palate, and oropharynx [173]. Denture stomatitis, on the other hand, manifests as palate and alveolar ridge erythema [174] and it is the most prevalent form of oral candidiasis [175].

Treating oral candidiasis and denture stomatitis can be challenging, as it involves the improvement of oral and/or denture hygiene, relining or replacing the prostheses, avoiding overnight use of dentures, and the topical and/or systemic administration of antifungal drugs [174]. However, the effectiveness of treatment can be compromised by the cost of medication [176], its unpleasant taste, toxicity, and possible side effects, including nausea, mouth irritation, vomiting, and diarrhea [173][174], poor oral absorption [177], drug resistance [176], and the cleansing effect of saliva [173]. Nanotechnology has been proposed to overcome such obstacles, given that unconventional antimicrobial agents hold great potential in the treatment of infectious diseases [178].

The powerful fungicide effect of chitosan and its capacity to inhibit *C. albicans* adhesion and biofilm formation have been described by many authors [179][180][181][182]. Fabio et al. evaluated the possible enhancive effect of chitosan on the photosensitizer methylene blue. Although chitosan has a strong antifungal action, it does not improve the methylene blue activity during photodynamic therapy [183]. The effect of other NPs combined with antimicrobial photodynamic therapy have also been assessed. Cationic curcumin-polymeric NPs can reduce *C. albicans*, even in the absence of light [184], and chloro-aluminum phthalocyanine encapsulated in cationic nanoemulsions seems to be an effective photosensitizer agent to use [185].

The efficacy of chitosan along with its inherent biocompatibility also makes it a promising candidate for use as a mouthwash [174]. Some authors have developed mouthwashes with chitosan alone [174] or in combination with curcumin [186][187]. Chitosan mouthwash significantly decreased the erythematous area, burning sensation, time required for clinical improvement, and number of blastospores and mycelia in a clinical trial [174], while the combination with curcumin presented a favorable clinical response with no local or systemic adverse events neither in animals [186], nor in humans [187].

Mucoadhesives, gels, toothpastes, buccal tablets, and buccal films have been proposed as treatments for oral candidiasis. Such formulations were developed with NPs for improved local delivery of drugs like miconazole [176][188][189][190], nystatin [173][177], amphotericin B [191], and fluconazole [192], or plant-derived products, such as stigmasterol [193] or *Glycyrrhiza glabra* L. extract [194]. Some of these formulations presented enhanced antifungal activity, reduced cytotoxicity, faster drug release rate, improved dissolution rate, and better prolonged release than marketed products or the non-loaded drug [176][188][189][190][191], while others, despite not being compared to commercialized products, have shown promising results [173][177][192][193][194].

One alternative therapy for denture stomatitis is the incorporation of NPs, such as chitosan and ZnO-Ag, into tissue conditioners or soft liners. These modified materials present a significant antifungal and antibacterial activity and are not cytotoxic [195][196][197][198]. The incorporation of such NPs into tissue conditioners or soft liners did not compromise some mechanical properties, such as shore A hardness, surface roughness, and tensile bond strength, in a clinically relevant manner [195][199]. Chitosan has also shown properties suitable for development into an antifungal denture adhesive that could inhibit *C. albicans* adherence to denture base acrylic resin [200].

NPs have been employed to protect antimicrobial peptides from degradation in the oral cavity as well. Histatin 5 was encapsulated by liposomes [201] or combined with amphotericin B and coated with chitosan [202], with very positive results. Antimicrobial molecules cathelicidin LL-37 and ceragenin CSA-13 were developed with magnetic NPs and presented high antifungal activity and biocompatibility, resistance to inhibitory factors present in body fluids, and effective inhibition of fungal biofilm formation [178].

8. Head, neck, and oral cancer

Around half a million people are diagnosed with oral cancer worldwide, and approximately 150,000 patients pass away yearly [203]. Early and accurate diagnosis allows a proper treatment, resulting in less morbidity and better prognosis [204]. However, treatment is usually challenging due to late diagnosis, high risk of invasion, rapid metastasis, frequent relapses, and painful side effects [205][206]. Considering the adverse effects of traditional anticancer treatment and their impact in the quality of life of the patients, nanotechnology has a great potential to improve early diagnosis and therapy [205].

A wide variety of NPs were proven to be effective against a number of oral cancer cell lines, including human Caucasian dysplastic oral keratinocytes (DOK) [205][207], mouth epidermoid carcinoma (KB) [203][208][209][210][211][212], murine AT-84 oral squamous carcinoma cells [213], oral squamous cancer cell lines of Asian origin (ORL-48 and ORL-115) [214], human oral squamous cell carcinoma lines (PE/CA-PJ15 [215], OEC-M1 [216], HSC2 [217], YD-9 [218], SAS [219][220], HSC4 [1][220], KOSC [220], HSC3 [204][221][222], HSC-3-M3 [7], Ca9-22 [223], CAL 27 [222][223][224][225][226][227], SCC131 [228], SCC4 [222][228], VB6 [229], and H357 [229][230][231]), human tongue carcinoma cell lines (SCC-9 [232][233][234], SCC-25 [224][230][233][235], SCC-15 [236], and SCC-090 [237]), and multidrug-resistant oral carcinoma cells (KB-Ch^{R}-8-5) [238]. Despite the promising results, most of these studies were conducted in vitro, thus, further in vivo studies are necessary to confirm the efficacy of these nanomaterials.

Doxorubicin (DOX) and paclitaxel are two of the most commonly used chemotherapeutic drugs [239]. Taking their adverse effects into consideration, studies have proposed alternative forms of drug delivery, such as liposome formulations [239], solid lipid NPs [240], mucoadhesive alginate pastes with embedded liposomes [241], methotrexate-loaded stimuli responsive silica-based NPs [242], polymers [243], PEGylated NPs [244][245], mesoporous silica NPs-polymerpolyethylenimine [246], multifunctional targeted polymeric NPs [247], and a multifunctional Au nanoplatform [248]. In comparison to the free drugs, these new systems showed a higher percentage of apoptotic cells [239][247], fewer hematological changes [242], significant therapeutic efficacy [243][248], significant inhibitory effects on tumor growth [245], lower cytotoxicity and systemic toxicity, and higher tumor accumulation of DOX [244].

AuNPs and nanorods have many applications in diagnosis and tumor margin determination. These nanomaterials have been associated with different diagnostic tools and systems, including air scanning electron microscopy [249], enzyme-linked immunosorbent assay (ELISA) [250], optical coherence tomography [251], surface enhanced Raman spectroscopy (SERS) [252][253][254], an electrochemical immunosensor [255], indirect computed tomography and magnetic resonance lymphography [256], and a biosensor consisting of an upconversion nanoparticle, MMP2-recognized polypeptides, and quenchers [257]. Such methods were proven to be reproducible [250], sensitive [250][257], specific [250][255][257], stable [255], accurate [253], reliable [252], and/or capable of detecting early-stage cancer [251].

Other NPs can be used with similar aims: carbon NPs were able to track occult lingual lymph nodes in early-stage tongue squamous cell carcinoma with accuracy [258]; AgNPs were used as a substrate for SERS, which showed specificity and sensitivity above 90% [259]; nanostructured zirconia on reduced graphene oxide exhibited a wide linear detection range, excellent sensitivity, and a remarkable low detection limit when used as an immunosensor [260]; a SERS substrate was made up of leaf-like titanium oxide nanostructures decorated with AgNPs and presented rapid and accurate detection of solid tumors [261]; and nanostructured yttrium oxide was used for the fabrication of a biosensing platform, which showed a high linear range and remarkable sensitivity [262].

Head and neck squamous cell carcinoma is the sixth most common cancer worldwide [263]. Considering the side effects of chemo and radiotherapy, it is necessary to develop more effective and safe treatments [264]. Several NPs can be

employed in the treatment of head and neck cancer, as they reportedly can enhance the efficacy of treatment [263], reduce or inhibit tumor growth [264][265][266][267], increase overall survival in animals [266], enhance tumor radiosensitization [265], suppress metastasis [268], induce cell apoptosis [206][264][269] and cell cycle arrest [269], and/or increase antiproliferative bioactivity [269]. AuNPs can be combined with X-ray irradiation to induce apoptosis [270], and PDT can be combined with lipid–calcium–phosphate NPs to deliver a vascular endothelial growth factor in order to decrease tumor volume [271].

Oral mucositis is one of the most common side effects induced by high-dose chemotherapy and/or radiation [272]. It not only compromises the quality of life of patients, but also affects compliance to treatment [272]. Studies suggest that different types of nanoformulations can be used to assess the risk of and treat chemotherapy- and radiotherapy-induced oral mucositis, including chitosan [272][273][274], PLGA [272], and hydroxypropyl methylcellulose [274]. These NPs can potentially be used in the development of muco-adhesive wound dressing materials [273] or sustained drug release systems [272][274].

9. Hyposalivation

Hyposalivation is the condition of having reduced or insufficient saliva production [275][276]. The use of some medication or radiation therapy for head and neck cancer treatment and autoimmune disorders (e.g., Sjogren's syndrome) can lead to hyposalivation [276][277]. There is a clinical concern that hyposalivation decreases oral health and overall health in many patients [277]. Oral lesions, dental caries, dental demineralization, periodontal disease, and fungal infections are some of the consequences caused by the decrease of salivary flow [278]. It also contributes to difficulties in speaking, chewing, and swallowing [279].

Current treatments for hyposalivation are limited to medications such as the muscarinic receptor agonists, pilocarpine and cevimeline [276][277]. Therefore, the development of new therapeutics is essential for the prevention and treatment of this condition. It is also important to create alternatives to provide relief from dry mouth condition, one of the consequences of hyposalivation, in order to improve the quality of life of patients with this problem. The use of nanoparticles can be extremely useful for the maintenance of the oral mucosa hydration. Adamczak et al. demonstrated the effectiveness of liposomes in water adsorption, desorption, and diffusion, even in environments with high humidity as the oral cavity [279]. To improve the residence time of liposomes in the oral cavity, liposomes can be coated with mucoadhesive polymers like pectin, chitosan, and hydroxyethyl cellulose [279]. The stability of liposomes can be improved by coating them with some of these polymers. This approach can also provide prolonged moisture protection in the oral cavity [280][281].

Adamczak et al. also noted that liposomes coated with chitosan and pectin improve their water sorption capacity and mucoadhesion [279]. In another study, Adamczak et al. found that the alginate-coated liposomes have high mucoadhesion without being cytotoxic [280]. Nanostructured systems, such as liposomes, are promising alternatives to promote dry mouth relief because they are composed by phospholipids that bind water in their aqueous compartment [279][280][281].

Nanoparticles can also be used for preventive purposes, through the use of some compounds to protect the salivary glands from radiation-induced damage and concomitant hyposalivation [278].

10. Oral mucosa drug delivery

In recent years, the buccal administration of mucoadhesive formulations has had the greatest interest in the pharmaceutical and dentistry areas. This route of administration is useful due to many advantages, including easy accessibility, patient compliance, and limited enzymatic activity [282]. The administration of drugs in buccal mucosa can also minimize side effects and avoid degradation in the gastrointestinal tract. Another advantage that should be considered is the faster onset of action compared to oral ingestion. One portion of the drug is absorbed through the blood vessels directly to the systemic circulation when administered via the buccal mucosa [282][283].

However, the administration of drugs through the oral mucosa presents some barriers that must be overcome. The short residence time due to the salivary flow may lead to involuntary swallowing. Moreover, only small doses can be administered and drug permeability, controlled drug release, and targeting remain a challenge [282][283]. A promising approach to overcome these challenges is the use of NPs to promote the buccal delivery. NPs are able to improve water solubility and drug dissolution rates, can carry a high drug concentration, and protect drugs from degradation in biological fluids. Furthermore, the ability to improve the mucoadhesive properties of formulations can lead to a prolonged residence time in the oral cavity.

There are many systems that can promote and improve the buccal administration of drugs. In the past years, a great number of new formulations for this administration route have been developed. Tran et al. classified these systems in three groups: (i) nanoparticle-delivered mucoadhesive films; (ii) nanoparticle-delivered mucoadhesive gels; and (iii) nanoparticle-delivered mucoadhesive solid matrix forms [282].

The most commonly used systems are the mucoadhesive films. In these systems, the drug is loaded into nanoparticles and then are incorporated into a mucoadhesive film. Polymeric NPs [284][285][286], liposomes [287][288], chitosan NPs [289][290], lipids and polysaccharides can be used for this aim. These films can also be produced by using hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose sodium (SCMC), eudragit, carpobol, and ethyl cellulose. These materials provide mucoadhesion for the formulation and can increase the residence time once in contact with the oral mucosa.

Castro et al. incorporated PLGA nanoparticles into a mucoadhesive film composed of guar gum [286][291]. This system was developed aiming to allow the buccal application of bioactive peptides that undergo extensive enzymatic degradation. The authors found an increased buccal and intestinal permeation and a significant increase in the mucoadhesive properties [286][291].

The buccal mucosa is one of the most promising routes for protein and peptide delivery. There are many studies aiming for the development of non-invasive systems capable to promote the buccal administration of insulin. Insulin is commonly administered through syringes with needles which may lead to low treatment compliance [289]. Al-Nemrawi et al. developed chitosan NPs loaded with insulin, which were dispersed in a film composed by HPMC, SCMC, and carpobol. In vivo studies with diabetic rats showed that the prepared films were able to reduce blood glucose levels when applied buccally [289].

In addition to mucoadhesive films, mucoadhesive gels are also a promising strategy. These gels can be composed of hydroxyethyl cellulose [292], hyaluronic acid-based gel [176], carbopol, and polycarbophil [293][294]. In many cases, the use of nanostructured hydrogels for intraoral administration is better than the commercial products available on the market. Abozaid et al. produced an acyclovir-loaded lipid nanocapsules gel with an enhanced permeation in an ex vivo chicken pouch membrane model compared to a commercial cream [292]. The same results were observed by Muniz et al., who loaded lidocaine and prilocaine into a poly(ε-caprolactone) nanocapsule gel. The developed formulation provided effective and longer-lasting superficial anesthesia in vivo compared to a commercial product [294].

Marques et al. developed a mucoadhesive buccal gel containing nanostructured lipid carriers loaded with ibuprofen [293]. This gel presented great residence time on the buccal mucosa and the NLC demonstrated the ability to promote a sustained release of the drug [293]. In the same way, Hosny et al. observed higher ex vivo skin permeability and enhanced antifungal activity with a miconazole self-nanoemulsion in a hydrogel composed of hyaluronic acid [176]. These results demonstrate that it is feasible to use the buccal mucosa for drug administration and it is also possible to reduce the number of daily applications, because these systems present a prolonged drug release.

Mucoadhesive solid matrix forms are another way to promote the buccal administration of some drugs. Chitosan [295], solid lipids NPs [296], and silymarin NPs [297] can be incorporated in solid matrix to improve mucoadhesion and permeation across the buccal mucosa. Furthermore, solid dosage forms like tablets, sponges, or patches can promote prolonged residence time in the oral cavity when compared to mucoadhesive gels, which can be easily removed by saliva [298].

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