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Advanced drug delivery systems for local treatment of the oral cavity

Good oral health is of major importance for general health and well-being. Several innovative drug delivery systems have been developed for the local treatment and prevention of various diseases in the oral cavity. However, there are currently few optimal systems and many therapeutic challenges still remain, including low drug efficacy and retention at targeted site of action. The present review provides an insight into the latest drug delivery strategies for the local treatment and prevention of the four most common oral pathologies, namely, dental caries, periodontitis, oral mucosal infections and oral cancer. The potential of bioadhesive formulations, nanoparticulate platforms, multifunctional systems and photodynamic methodologies to improve therapy and prophylaxis in future local applications for the oral cavity will be discussed.

The oral cavity (mouth) is the first section of the digestive system and consists of different anatomical structures, including teeth, gingiva (gum) and their supportive tissues, hard and soft palate, tongue, lips and a mucosal membrane lining the inner surface of the cheek. Apart from trauma from injuries, the most common acquired oral problems worldwide are dental caries, periodontal diseases, oral malignancies and oral infections [1]. Local therapy of these conditions has several apparent advantages than systemic drug administration, targeting directly to the diseased area while minimizing systemic side effects [2,3].

Conventional dosage forms for the local treatment of the oral cavity are summarized in Table 1 [4–7]. As can be seen, semisolid or liquid dosage forms are the most common mainly due to the ease of administration and patient acceptability. However, the major disadvantage with these traditional systems is poor retention in the oral cavity leading to suboptimal therapeutic effect. Many attempts have been made to overcome these challenges. The inclusion of mucoadhesive polymers to form viscous mouthwashes and gels that provide lubrication and physical protection for ulcerated oral mucosa appears to provide

some symptomatic relief. One successful example is Oraqix® periodontal gel which is a noninjectable local anesthetic containing a eutectic mixture of lidocaine and prilocaine for pain control during scaling and root planing (SRP). Oraqix is based on a thermosetting system which exists as a liquid at room temperature but thickens into an elastic gel when applied to the periodontal pockets (body temperature). The change in consistency due to the change in surrounding temperature enables the product to remain in place to produce anesthesia [8]. In the treatment of periodontitis, there has been a shift from systemic delivery of antibiotics to local drug delivery. The periodontal pockets are ‘easy’ accessible since the drug delivery systems can be placed directly into the pockets and serve as reservoirs for drug release. Many different drug delivery systems have been investigated and some products are commercially available, such as PerioChip® insert, a matrix of hydrolyzed gelatin with chlorhexidine, Actisite®, a polymer-based fiber with tetracycline, Atridox®, an injectable formulation with doxycycline and Arestin® dry powder microspheres of the biodegradable polymer poly(lactic-co-glycolic acid) (PLGA) and minocycline [9].

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Key term definitions

Bioadhesive drug delivery systems: Drug delivery systems with 'sticky' properties based on the concept of bioadhesion. Bioadhesion is a phenomenon where macromolecules, most often polymers, are able to adhere or attach to biological surfaces via chemical (electrostatic interactions, hydrogen bonding) and/or physical (entanglements) mechanisms.

Although these more modern products demonstrate that some obstacles can be overcome, many challenges still remain. Intensive research in the development of advanced drug delivery systems to the oral cavity is ongoing. The present review will focus on recent advances in the local treatment and prevention of the most prevalent oral diseases and conditions. In the first part, novel drug delivery systems for oral infections, including dental caries, periodontitis and oral mucosal infections, will be reviewed followed by the second part on new drug delivery systems for oral cancer. Finally, critical viewpoints on future directions will be discussed.

Oral infections

A healthy oral cavity is normally colonized by fungi, viruses and bacteria with the latter predominating. It has been estimated that over 700 bacterial species reside in the oral cavity; some may be pathogenic, others are symbiotic or commensal [10,11]. When the normal flora of the mouth is disrupted, for example, with tobacco use, pregnancy, diet, nutrition, age and oral hygiene, indigenous bacteria can convert to a pathogenic existence leading to tissue inflammation and disease of oral structures [12,13]. Oral infections can be divided into two main types; those that originate in the tooth or the closely surrounding structures (odontogenic) and those that are not (nonodontogenic).

Odontogenic infections

Dental caries and periodontitis are the two major odontogenic problems worldwide.

Dental caries

Dental caries (tooth decay) is one of the most prevalent diseases in humans. Even though the incidence of dental caries has decreased worldwide during the last decades, it is still a great problem in many communities [14]. Dental caries is caused by the production of acid originated from bacteria fermenting carbohydrates leading to demineralization of the dental enamel and the formation of cavities. The bacteria are part of the oral biofilm also called the dental plaque residing on the dental enamel. Calcium and phosphate present in saliva can counteract the demineralization effect. The amount of these agents and the amount of acid will decide whether a remineralization or a demin-

eralization will occur (Figure 1) [15]. One of the most well-known remineralization agents that can be given externally in order to prevent dental caries is fluoride. When fluoride is present at the dental surface, it can react with hydroxyapatite, the main mineral component of dental hard tissues, forming fluorapatite or fluoridated hydroxyapatite [16]. These substances have greater chemical stability and the teeth are better protected against acid attack and demineralization by cariogenic bacteria.

Toothpastes have for decades been the most important delivery system of fluoride in the combat against dental caries, but other administration systems can also be found such as mouth rinses, varnishes, gels and tablets [16]. One major problem associated with the delivery of fluoride is the short time of action. Constant secretion of saliva acts to dilute and clear drugs, including fluoride, from the oral cavity despite the fluid's essential function to maintain oral health via rinsing, protection and lubrication of oral tissues. This often leads to reduced bioavailability, less drug efficacy, and frequent drug administration to maintain therapeutic dose. It has been shown that even a small increase in the amount of fluoride present in the mouth gives a significant reduction in the incident of caries in children [17]. However, fluoride must be present at the surface of the teeth to be able to protect them from acid attack; when it is swallowed or flushed by saliva the effect disappears. The use of **bioadhesive drug delivery systems** will therefore have a prominent advantage compared with conventional fluoride delivery systems. Some efforts have been done lately on developing new drug delivery systems for fluoride but according to the potential such new systems could represent, the amount of new studies are small. Microparticles composed of the bioadhesive polymer chitosan, the cross-linking agent glutaraldehyde and fluoride have been investigated [18]. The particles were prepared by spray-drying and tested for size distribution, encapsulation efficiency and drug release. The results showed that the particles prepared from a low concentration of chitosan were the most uniform, while a higher concentration of chitosan gave higher entrapment efficiency. The release of fluoride was biphasic indicating a fast burst release with a longer slow release phase giving a total release time of 6 h. Unfortunately, the particles had low bioadhesive properties probably because the fluoride ions present at the surface of the particles shielded the positive charges of chitosan leading to less attractive interactions with the dental surface. The authors suggested that the chitosan particles could potentially be loaded into a dentifrice, be aerosolized or be compressed into discs to improve the bioadhesive properties. Another

Table 1. Conventional dosage forms and some examples of commercially available products for the local treatment of the oral cavity.

Dosage form	Examples of local use in the oral cavity	Advantages	Limitations
Semisolid dosage forms (gels/creams/pastes)	Gelclair® oral gel contains sodium hyaluronate and glycyrrhetic acid for oral mucositis, pain relief and soothing of oral lesions/ulcers	More acceptable in terms of mouth feel	Poor retention at the site of application
	Daktarin® oral gel contains miconazole for treating oropharyngeal candidiasis	Localized action within the oral cavity	Difficulties in accurate drug dosing
	Biotene® oral gel contains various lubricating polymers for dry mouth symptom relief		
	Fluoride toothpastes under various brand names		
	Colgate Orabase® paste contains benzocaine as a local anesthetic		
Liquid dosage forms (solutions/suspensions)	Fluoride or various antiseptic (eucalyptol, menthol, methyl salicylate, thymol, chlorhexidine, cetylpyridinium chloride) mouthwashes from various brands	Patient acceptability	Not readily retained at the targeted site of absorption
	Colgate Peroxyl® mouth rinse contains hydrogen peroxide as an oral debriding agent	Ease of administration	Relatively uncontrolled and inconsistent drug delivery throughout the oral cavity (compared with single unit dosage forms) Palatability: drugs in solutions stimulate taste buds. Unpleasant taste may lead to poor patient compliance. May require taste masking
Medicated chewing gum	Fluoride gum under various brand names	Prolonged drug release	Due to involuntary swallowing, drugs may reach GI tract causing systemic effects
	Vitaflo CHX® containing the antibacterial agent chlorhexidine	Good patient compliance Patient-controlled dose titration	
Patches/films/strips	Canker Cover® oral patch contains menthol, a short acting and mild anesthetic, for the treatment of canker sores	Thin and flexible	Drug delivered to a small area of mucosa, thus limiting the dose delivered
	Listerine® Pocketpaks® breath strips contain menthol, thymol and eucalyptol that act as mouth fresheners killing bad breath germs	Less obtrusive and more acceptable to patient	Thinness may lead to increased susceptibility to overhydration and loss of adhesive properties
		Localized over a specified region, thus less inter- and intra-subject variability	Patches with nondissolvable backing need to be removed once the drug has been released

Figure 1. The balance between the re- and de-mineralization of the teeth.

type of microparticles has also been developed containing gelatin or ethylcellulose in combination with fluoride [19]. These particles were prepared either by spray-drying or by microencapsulation via emulsification. The spray-dried particles had superior entrapment efficiency compared with particles prepared by microencapsulation. Drug release from the gelatin particles was faster than the ethylcellulose particles; however, sustained release over a period of 8 h was observed for both matrices. Although these data were encouraging, the importance of the results needs to be further evaluated *in vivo*.

The use of **nanotechnology** in dentistry has received considerable attention the past decade [20]. Nanoparticles have a wide range of pharmaceutical applications since their physical and chemical characteristics, for example, shape, surface charge and hydrophobicity, can be adjusted accordingly to their target. Nanoparticulate formulations for local applications in the oral cavity can be delivered as an aqueous suspension or be incorporated into a gel or paste

creating products with high patient acceptance and ease of administration. With respect to dental caries, nanoparticulate metals and metal oxides with bactericidal effects have been of great interest. A new strategy for preventing dental caries is by eradicating the bacteria responsible for producing the dental plaque. A major challenge is to kill the bacteria in the lower layer of the biofilm [21]. *Streptococcus mutans* is the most common bacteria hosting the oral biofilm and many studies have evaluated different active substances that can inhibit or kill these specific bacteria. Metal ions have proven effect against these bacteria [22] and especially silver has been used for decades against bacterial infections. Silver nanoparticles can penetrate the bacterial cell walls and damage the cells. It has been shown that the smaller the silver particles are, the better is the bactericidal effect [23]. This is mainly due to better contact with the surface of the bacteria. In spite of the beneficial effects in caries prophylaxis, the use of silver, for instance, in the form of nano silver diamine fluoride, has some serious drawbacks such as tooth staining [24]. Other forms of silver have therefore been investigated. A new formulation composed of nano silver fluoride in combination with chitosan has recently been developed [25]. Chitosan was chosen due to its stabilizing effect on the silvery nanoparticles but also for its inherent antimicrobial effect and bioadhesive properties. These newer type of particles were not cytotoxic and had a lower minimum inhibition concentration than the silver diamine fluoride particles. In a clinical trial, the nano silver fluoride particles were tested for its potential in preventing dental caries in children [26]. The particles did not stain the teeth and were found effective in preventing dental caries.

Key term definition

Nanotechnology: The science, engineering, and technology of materials at nanoscale, typically less than 100 nm. Owing to the extremely small size, nanoscaled particles have unique properties, such as high surface-to-volume ratio, and different chemical reactivity and biological activity than larger particles.

Biomimetic: Refers to man-made materials, structures, or processes that imitate biological systems or simulate natural processes. The basis for finding inspiration from nature is that biological systems have evolved well-adapted structures over time through natural selection and, thus, by looking at biological solutions; scientific problems can be solved.

Another nanoparticulate drug delivery system that has been proposed for caries therapy is micelles. Formulations composed of biodegradable micelle-forming polymers (Pluronic® 123) with tooth binding moieties and the antimicrobial agent triclosan have been investigated [27]. In order to target the teeth, two new tooth binding agents, diphosphoserine and pyrophosphate, were examined. Diphosphoserine resembles statherin which is a substance with known high affinity for hydroxyapatite. Both types of micelles showed great affinity toward hydroxyapatite (HA) powder and triclosan was released in a sustained manner over a period of 24 h both in phosphatebuffer and saliva. The micelles were also tested for its binding capacity toward HA discs pretreated with saliva. The results indicated a competition between the components of saliva and the micelles in binding to the HA discs; however the formulations were still able to reduce the growth of a biofilm. Discs with an oral biofilm present were also tested, and still the micelle formulations showed antibacterial effect against the biofilm. The authors suggested that the two types of micelles have potential in preventing growth of the oral biofilm, most preferably if administered straight after brushing the teeth to minimize the competitive binding of salivary components on the dental surface.

Nanotechnology coupled with **biomimetic** strategies is the latest approach in caries therapy and prophylaxis [28]. Enamel repair of early caries lesions by casein phosphopeptide-amorphous calcium phosphate nanocomplexes (CPP-ACP) [29] and the manipulation of nanoparticles to form structures resembling natural enamel (biomimetic enamel synthesis) [30] are areas that have been explored. Noncollagenous proteins, such as CPP and amelogenin, chelate with calcium ions and play an important role in the biomineralization of dental hard tissues. In this regard, chitosan has been investigated for its potential as a biomaterial with cariogenic [31] and chelating properties [32]. Zhang *et al.* synthesized stable phosphorylated chitosan-ACP nanocomplexes that can remineralize the enamel subsurface lesion by mimicking the biomineralization process [33]. Ruan and Moradian-Oldak developed an amelogenin-chitosan hydrogel for enamel reconstruction to prevent the development of tooth decay and promote enamel restoration [34]. These two recent reports reflect a new, highly interesting remineralizing strategy that offers a great potential with minimal intervention by dentists. Another biomimetic approach using nanotechnology has been explored by Nguyen *et al.* [35,36]. *In vivo*, the enamel surface is covered by a thin layer called the acquired enamel pellicle that serves as a protective barrier against tooth wear. The formation of this pellicle involves selective adsorption of salivary proteins, asso-

ciated into micelle-like globules, onto the enamel surfaces. Analogously, Nguyen *et al.* prepared nanosized liposomes that resemble these vesicular structures to mimic the adsorption onto enamel surfaces and, thereby, provide a physical, protective barrier to the dental enamel. Still in its infancy, this concept needs further validation in clinical studies to determine its potential in caries prevention.

Periodontitis

Periodontitis is another huge public health problem. WHO claims that 10–15% of the population worldwide has this disease [1]. Periodontitis is a local inflammation in the periodontal pockets and is caused by dental plaque. The pockets can be found in the area between the teeth and the gum. The progression of the inflamed pockets takes several years; initially the inflammation is only localized to the gum, but with time the inflammation protrudes deeper and the pockets where anaerobic bacteria are residing are formed [37,38]. Untreated, this will lead to bacterial infection and, in severe occurrences, loss of teeth and bone resorption.

Conventional treatment program for periodontitis is by mechanical removal of dental plaque via SRP followed by systemic use of antibiotics via peroral administration. Lately, the trend has been shifted more toward local delivery of antibiotics due to the disadvantages with systemic drug use. The ideal drug delivery system to the periodontal pockets is composed of a biodegradable scaffold and the drug can be slowly released over several weeks from a bioadhesive entity. A wide range of new drug delivery systems are under investigations, such as fibers, strips, inserts/implants, films, gels, microparticles and nanoparticles.

In situ forming implants are interesting drug delivery systems since they have some superior advantages, including ease of administration and low cost. The formulation is placed in the periodontal pocket by a syringe and then the implant is formed [39,40]. However, burst release of the drug and low volume of the gingival crevicular fluid may negatively influence the drug release characteristics. Both poly(DL-lactide) (PLA) and poly-(DL-lactide-co-glycolide) (PLGA) are potential polymer candidates in an implant intended for the periodontal pocket since they have low toxicity and are biodegradable. An *in situ* forming implant composed of PLA and tinidazole has been investigated and tested on beagle dogs [41]. The study showed that the burst release of drug could be avoided by adjusting the composition of the solvent under preparation. The drug was released (65%) during 7 days. The formulation with the highest amount of the drug decreased the symptoms of periodontitis in the tested dogs.

Another study investigated *in situ* forming implants composed of PLGA and metronidazole and, in addition, either sodium carboxymethyl cellulose (NaCMC) or carbopol (CP) was added to the formulation in order to increase the bioadhesive properties of the formulation and modify the drug release [42]. The formulation composed of the highest amount of polymer showed the longest duration of drug release lasting 10 days. The NaCMC increased the bioadhesive properties of the implant; however, this resulted in faster drug release for some of the formulations. CP did not affect the bioadhesion, but the viscosity of the solution was increased and this may influence the injectability of the formulation. The inserts/implants are interesting platforms for further studies with other drugs.

Polymeric microspheres may also be a viable alternative in delivering drugs to the periodontal pockets due to their possible bioadhesive and biodegradable properties. Microspheres composed of zein from corn starch, PLGA, and tetracycline compressed to a monolithic device were recently investigated [43]. This study revealed zein to be a good candidate for sustaining the release of tetracycline. The formulation was successful in releasing a concentration of tetracycline above the minimum inhibition concentration for *Staphylococcus aureus* during the 15 days of study. The formulation showed no *in vitro* cytotoxic effect.

Fibers also composed of polymers seem to have a potential to serve as drug reservoirs because they can easily be inserted into the periodontal pockets. Electrospun PLA fibers with metronidazole have been investigated for their effect against different oral bacteria [44]. Again, PLA seems suitable as a drug carrier since this polymer is bioresorbable and does not have to be removed from the oral cavity when the treatment has ended. Different concentrations of the drug were loaded in the fibers and, depending on the thickness of the fibers, an initial burst release of the drug was observed, however, a linear release of metronidazole over 6 days was observed. The fibers showed antibacterial effect against different types of pathogenic periodontal bacteria and were not cytotoxic. These fibers seem to meet many of the requirements for a drug delivery system intended for the periodontal pockets.

Since periodontitis also involves other oral complications than infections caused by bacteria, such as inflammation and bone loss, it could be an advantage to load combinations of drugs into one formulation and, as such, obtain a dual or synergistic action of the treatment. Multilayered films have been investigated for their potential use in the treatment of periodontitis [45]. Individual casted films of cellulose acetate phthalate and Pluronic F-127, each loaded with different drugs (metronidazole, ketoprofen, doxycycline

and simvastatin), were sealed together with acetone in order to produce one multilayered film. The drug release was dependent on the erosion of the films with the drug in the outer layer being released first. The rate of drug release could be adjusted by the thickness of the film, and the lag time before releasing the next drug could be increased by including films without drugs in-between the loaded films. Multilayered films seem to have a potential due to its relatively easy production and the possibility to release different types of drugs in a sequential manner.

Since bone loss is a complication of periodontitis, a gel composed of 1% alendronate was investigated in a clinical trial for its ability to act as an inhibitor of osteoclast mediated resorption and as a potential stimulator of osteoblasts [46]. The gel was composed of poly(acrylic acid) (PAA) and alendronate. In addition, triethanolamine was added in order to form the gel. The gel was placed in the periodontal pocket by a syringe. By investigating the gingival crevicular fluid, the drug could be detected even 1 month after placement. This indicates that the drug is resistant to degradation (hydrolysis) and that the mucoadhesive properties of the PAA may be beneficial. The group treated with the drug showed improved bone fill compared with the group receiving placebo. This gel may be an alternative approach to the drug delivery systems loaded with antimicrobials; however, additional interventions such as SRP is still necessary in the management of periodontitis.

Another very interesting study investigated the possibility of formulating a drug delivery system with both mineralizing and antibacterial effect. By this approach, both dental caries and the formation of the dental plaque, by such periodontitis, could potentially be prevented [47]. Calciumphosphate nanoparticles loaded with chlorhexidine were prepared. The particles were coated with CMC in order to achieve bioadhesive properties. The drug release experiments showed that chlorhexidine was released during one day while calcium phosphate had a release of 72% during two days. The nanoparticles adhered in sufficient amount both to the enamel and the dentin, and were able to inhibit bacterial growth (*Escherichia coli* and *Lactobacillus casei*). These multifunctional nanoparticles could be promising in the combat against both dental caries and periodontitis.

Another growing area of interest in dentistry is the use of so-called antibacterial **photodynamic therapy** (PDT) [48,49]. The insistent increase in antibiotic resistance across the world has stimulated the search for novel antimicrobial strategies that can kill multi-drug resistant microorganisms, and PDT is a treatment modality that is least likely to lead to the devel-

opment of drug resistance [50]. Nanoparticles seem to have a great potential as delivery vehicles for photosensitizers, the active components in PDT, probably due to their small size [51]. Methylene blue, a photosensitizer, was loaded into different PLGA nanoparticles and was investigated for its photodynamic effects on dental plaque bacteria [52]. The study showed that the phototoxic effect of methylene blue loaded into cationic PLGA particles was effective against bacterial suspension and biofilm. It should be noted that the effect in the suspension was higher than the effect in the biofilm where only 48% of the bacteria were killed. This may be due to the difficulty of the photosensitizer in penetrating into deeper layer of the biofilm. In order to verify the positive effect of PDT in the treatment of periodontitis, more investigations are needed. Another study investigated a rather new photosensitizer rose bengal for potential use in infected root canals [53]. Rose bengal was loaded into chitosan nanoparticles and was tested against *Enterococcus faecalis* with known potential inhibitors of disinfectants present. The study showed that these particles were effective in reducing the amount of bacteria even in the presence of pulp and BSA and also in the absence of light; however when illuminated, the bacteria were completely eliminated. This study shows that with the right formulation (photosensitizer and drug delivery system) PDT has a great potential in root canal disinfections.

Nonodontogenic infections

Oral mucosal infections

The etiology of nonodontogenic oral infections may vary widely and may be associated with almost any microorganism. Infections of the oral mucosa, either of bacterial, fungal or viral origin, are of particular importance. Due to the escalation of human immunodeficiency virus (HIV)-infections and other immunodeficient conditions in recent years, the resurgence of oral mucosal infections as trivial illnesses has been observed [54–56]. It has been estimated that approximately 50% of people who are HIV-positive acquire oral coinfections [57]. Although the introduction of highly active antiretroviral therapy (HAART), has made some oral manifestations less common, HIV-associated oral lesions still remain significant with oral candidiasis as the most typical lesion [58]. Oral candidiasis, classically known as thrush, has a great number of other predisposing factors: the use of broad spectrum antibiotics, steroid inhalers or systemic steroids; hypopendocrine disorders; Sjögren's syndrome; malignancies; malnutrition and old age, all of which collectively identify different immunocompromised patient groups [55,59].

Apart from HIV, oral mucosal infections may also arise secondary to chemotherapy and irradiation in cancer patients [60]. Oral candidiasis, oral viral infections, including herpes simplex virus, varicella zoster virus, Epstein–Barr virus and cytomegalovirus, and oral bacterial infections are commonly seen in cancer patients undergoing chemotherapy. Due to the immunosuppression, seemingly harmless mucosal lesions can become aggressive and life-threatening if the infection invades and gains access to the circulation causing bacteremia and sepsis. The opportunistic oral infections that emerge due to impaired host resistance, thus, significantly contribute to increased mortality and morbidity in cancer patients receiving treatment. On the other hand, persistent viral infection of the oral mucosa caused by human papillomavirus (HPV) has recently been associated with increased risk of oral cancer [61]. HPV can cause malignant transformations of the epithelial cells of oral mucosa by integrating into the host genome and causing aberrant gene expression and accumulation of mutational events.

The management of oral mucosal infections has traditionally been via topical administration of antimicrobial agents of which the most are antifungal products. Currently, there are no intraoral products available for the local treatment of oral viral infections; the closest are creams for labial (lip) herpes. In these cases, dermatologic preparations are used in the mouth but have not been designed to be bathed in and flushed by saliva. Thus, formulations specifically designed for the intraoral environment are necessary for more efficient therapy. Similar to odontogenic infections, one of the main approaches of designing drug delivery systems for oral mucosal infections is to retain the formulation on oral surfaces, in this case the oral mucosa, for a sufficient period of time to achieve adequate anti-infective effect [62].

Based on the principles of **mucoadhesion**, hydrogels have received considerable attention in this regard [63–65]. Hydrogels are 3D, hydrophilic, polymeric networks that are capable of imbibing large amounts of water and act as semisolid dosage forms

Key term definition

Photodynamic therapy: Light is used to activate light-sensitive compounds (photosensitizers) to form reactive oxygen species (ROS). These ROS have the ability to cause oxidative damage to malignant cells and also kill bacteria. When light is used in combination with photosensitizers to generate fluorescence to detect or localize malignant and premalignant tissues, it is called photodynamic diagnosis.

Mucoadhesion: Refers to a distinct form of bioadhesion where macromolecules are able to specifically attach to mucosal surfaces, such as on the mucosal linings of the gastrointestinal tract, nose, rectum, vagina, and oral cavity.

for drug delivery. Owing to the swelling ability in aqueous media and binding to mucosal surfaces via hydrogen bonds, hydrogels are particularly useful to provide mucosal adhesiveness and increase the residence time of the dosage form in the oral cavity. More recently, hydrogel-based systems are becoming more advanced combining other new concepts and technologies, such as stimuli responsive systems, micro- and nanogels [64].

Mendes *et al.* chose the hydrogel dosage form to improve local delivery of the broad spectrum antifungal agent miconazole for the treatment of oral candidiasis [66]. However, miconazole is poorly water soluble and, hence, difficult to incorporate directly into the hydrogel. The researchers encapsulated miconazole in nanostructured lipid carriers (NLC), which are lipid nanoparticles based on a blend of solid and liquid lipids, to provide high drug loading capacity and gel embodiment. They observed a controlled release of miconazole from both NLC and NLC-based hydrogel formulations. Hydrogel containing miconazole loaded NLC yielded the same antifungal activity compared with a commercial oral gel, however, using a 17-fold lower dose. The researchers concluded that the new formulation could enhance therapeutic efficacy of miconazole owing to the NLC to reduce the amount of drug administered and decrease dosage frequency.

Mucoadhesive polymeric nanoparticles have also been proposed for the delivery of antibacterials in the oral cavity. Tiyaaboonchai *et al.* prepared such nanoparticles by complexation of the two polymers polyethylenimine and dextran sulfate (DS) [67]. Polyethylenimine and DS are both hydrophilic macromolecules and are able to form hydrogen bonds with mucosal surfaces allowing intimate contact with the oral mucosa. The mucoadhesive property of the nanoparticles was evaluated by an *ex vivo* wash off test using porcine buccal mucosa which was exposed to a continuous flow of artificial saliva at a rate similar to the flow rate of human saliva. Strong mucoadhesion was found even at stressed conditions mimicking the shear forces from salivary secretion in the mouth. The researchers claimed that the observed mucoadhesion was attributed to the ionic interaction between the positively charged nanoparticles and the negatively charged mucosal surface. Moreover, the nanoparticles were loaded with pomegranate peel extract as the model drug substance because it has been shown to have antibacterial activity. The drug release profile of the nanoparticles showed an initial burst release within 5 min followed by a second, sustained release phase over several hours, thus, demonstrating prolonged drug release characteristics.

Overall, the results on the use of mucoadhesive systems for drug retention on the oral mucosa are promising; however, clinical studies remain to be explored in order to establish the locoregional anti-infective efficacy of the nanoparticles in the oral cavity.

Oral cancer

Oral cancer pertains to the cancer of the mouth itself, of the oropharynx and on the exterior part of the mouth (lip). Globally, oral cancer is ranging as the sixth most common cancer with high incidence rates in specific parts of the world (South and Southeast Asia). Tobacco use, heavy alcohol consumption and the chewing of betel quid (a stimulant traditionally used in parts of Asia) have been identified as significant risk factors in these areas [68,69]. In recent times, the incidence of oropharyngeal cancer seems to increase in the Western countries despite the decrease in tobacco use in these regions. HPV infection has often been observed in patients with no history of tobacco or alcohol use, and now HPV is recognized as a causative agent for a subgroup of head and neck cancers [70]. More than 90% of oral cancers are squamous cell carcinomas [71]. These epithelia-derived cancers often develop from a group of oral conditions called potentially malignant disorders. Malignant transformation in oral precancerous lesions may be prevented if correct diagnosis and timely treatment are provided. Thus, early stage oral cancer is highly curable; however, recurrence, delayed diagnosis and rapid metastasis can make the treatment highly challenging.

Current treatment modalities of oral cancer are radiation, surgery and chemotherapy. Radiation and surgery are effective in treating cancer in localized areas; however, these treatment protocols result in post-therapeutic complications and high treatment-related morbidity in survivors. Patients may develop osteonecrosis, salivary gland damage, oral mucositis and increased risk of infections. Chemotherapy, either used alone or in conjunction, is a less invasive method and more efficient in treating widespread metastatic cancer. Nonetheless, the high incidence of serious adverse effects induced by systemic chemotherapeutic agents represents a limiting factor in the overall success of the treatment.

Aggressive treatment regimens with the cytotoxic agent 5-fluorouracil (5-FU) is associated with myelosuppression and gastrointestinal toxicity. Another problem reported with 5-FU and other chemotherapeutic agents is the phenomenon of hypoxic conditions at solid tumors due to limited blood supply from surrounding tissues leading to the development of drug resistance. In order to increase drug levels at tumor

sites in oral squamous cell carcinomas (OSCCs) and simultaneously decrease drug resistance and systemic side effects, buccal matrix tablets to deliver 5-FU locally and directly to the cancerous tissues were designed [72,73]. The tablets were prepared by direct compression of the matrix consisting of the drug and the biocompatible polymer Eudragit® RS-100. The researchers showed reproducible 5-FU release from the matrix tablets in a buccal-like environment [72]. Apoptotic effects on cancer cells were demonstrated following topical administration of 5-FU matrix tablets on a 3D outgrowth model of OSCC; indicating that locoregional chemotherapy of OSCC could be effective [73].

Another popular approach is to develop tumor-targeted nanoparticulate systems that can minimize the undesirable side effects but at the same time maintain or, even better, enhance the therapeutic effects [74]. Due to the small size of nanoparticles and the enhanced permeability and retention effect seen in tumor tissues, nanoparticulate platforms tend to selectively accumulate in tumors with reduced distribution in normal, healthy tissues (passive targeting). Cisplatin is one of the most effective cytotoxic agents in the treatment of head and neck squamous cell carcinoma; however, its use has been limited due to the dose-dependent toxicities affecting the ear, and the gastrointestinal, renal, neurological and hematological systems [75]. Endo *et al.* encountered this issue by developing cisplatin loaded polymeric micelles comprising poly(ethylene glycol) (PEG)-poly(glutamic acid) block copolymers with the hydrophilic PEG moiety granting stealth properties, in other words, longer circulation time, to the formulation. They found that both free cisplatin and cisplatin loaded nanoparticles exhibited equivalent growth-inhibitory effect in oral carcinoma-bearing mice; however significantly less nephrotoxicity was observed with the cisplatin loaded nanoparticles [76]. With noticeable antitumor activity and superior safety profile, the encouraging results of the nanoparticles have paved their way to the next phase of the drug development process and into clinical trials.

The recent emergence of biopharmaceuticals (nucleic acids, antibodies, proteins and peptides) has shown very promising therapeutic results in cancer therapy [77,78], however, the clinical advancement has been limited by the sensitive nature of this new class of drugs. Currently, the delivery of these macromolecules is only achieved by injection due to enzymatic degradation when administered perorally. Local administration to the oral cavity may also expose them to enzymatic activity of saliva. Further, mucosal penetration may be poor due to the large size

and other inherent physical properties of the macromolecules, thus, significantly reducing the drugs' bioavailability.

Another critical step in the drug development process of these biopharmaceuticals is the need to deliver them directly into cancer cells, in other words, transfer across the cell membrane, in sufficiently high concentrations to exert their therapeutic effects inside the malignant cells. Intracellular targeting and the implementation of delivery vectors are, thus, vital in this context. Viral vectors, dendrimers, liposomes, lipid and polymeric nanoparticles are just some of the nanoscaled delivery vehicles that have been investigated for intracellular applications [79,80]. Recently, polymersomes have been of particular interest. Polymersomes are self-assembled vesicles comprising synthetic, amphiphilic block copolymers. Similar to liposomes, they can entrap lipophilic molecules within their membrane and hydrophilic molecules within their aqueous interior. However, polymersomes possess improved properties, such as higher drug loading capacity, better drug retention and formulation stability than liposomes. A new generation of polymersomes for intracellular drug delivery into OSCC cells have recently been developed [81,82]. The polymersomes consisted of one part conferring stealth features to the structure, poly-2-(methacryloyloxy)ethyl phosphorylcholine (PMPC), and the other part, poly-2-(diisopropylamino)ethyl methacrylate (PDPA), was a pH-sensitive copolymer. PDPA is hydrophobic at pH above 6.4 and self-assembles into membrane enclosed polymersomes. At pH below 6.4 corresponding to the pH in the endosomal compartments of cells, the vesicular structure quickly dissolves into unimers. The rapid conversion ruptures the endosomes due to osmotic shock resulting in the release of polymersome content into the cytosol. The researchers were able to demonstrate that PMPC-PDPA polymersomes could penetrate and distribute within OSCC cells *in vivo* suggesting that polymersome-based systems are highly promising for the intracellular delivery of drugs, proteins or genes, to cancerous cells of the oral cavity.

Oral cancer is an excellent target organ for chemoprevention because the oral cavity is visibly accessible and the progression of oral cancer from premalignant oral lesions has a highly characteristic and recognizable presentation. Chemoprevention has been defined as the use of natural and synthetic chemical agents to inhibit, delay or reverse the carcinogenic process in tissue at risk for the development of invasive cancer [83]. Typical classes of chemopreventive agents for local delivery to the oral cavity are vitamin A derivatives (retinoids), nonsteroidal anti-inflammatory drugs (NSAIDs, in particular cyclooxygenase (COX)-inhibitors) and natu-

ral products such as green tea extract and black raspberries. The therapeutic efficacy of these agents and, thus, the success of oral cancer prevention have been said to be governed by the effectiveness of the delivery vehicles.

Holpuch *et al.* have investigated various delivery strategies for chemopreventive compounds. In a proof-of-concept study, they prepared solid lipid nanoparticles with the intention to locally deliver poorly water soluble and unstable agents, whose nature is typical for chemopreventive compounds, to human oral tissues [84]. Acting as drug reservoirs, the prepared solid lipid nanoparticles could both penetrate to the basal layer cells of normal oral epithelium and also be internalized by OSCC cells in order to increase intracellular drug levels at the target cells.

In another work, Holpuch *et al.* evaluated a novel mucoadhesive patch for local delivery to the oral cavity of the chemopreventive vitamin A analog fenretinide [85,86]. This drug was dispersed in Eudragit, a poly(meth)acrylate-based polymer, with a surrounding adhesive layer consisting of polycarbophil and hydroxypropyl methylcellulose, all well-known mucoadhesives. Because the buccal epithelium is the target of chemoprevention in oral cancer, the design of a mucoadhesive patch is a logical approach in order to allow localized, intimate and prolonged contact between the mucoadhesive and the absorbing tissue. This, in turn, will provide high drug influx and increase the drug's bioavailability. Holpuch *et al.*'s investigation showed that the mucoadhesive patches were able to retain on the oral mucosa sufficiently to deliver therapeutically relevant fenretinide levels at site of action by first using rabbit oral tissues following with human oral tissues and cultured oral keratinocytes. Based on the collected data, they concluded that the described mucoadhesive patch is a viable delivery strategy for potent chemopreventive agents with dose-limiting toxicities such as fenretinide.

Several other researchers are exploring the use of mucoadhesive drug delivery systems for chemoprevention of oral cancer [87,88]. Cid *et al.* [89] explored chitosan gels for buccal delivery of the highly lipophilic celecoxib, a COX-2 inhibitor, for oral cancer chemoprevention. Laurocapram (Azone®), a nonionic surfactant, was added to this formulation as a penetration enhancer in order to increase uptake of the drug in the buccal mucosa. The main idea was to combine the strong mucoadhesive character of chitosan with laurocapram's capacity to increase drug permeation and retention in the buccal mucosa in order to improve overall drug bioavailability at the desired tissue. The researchers demonstrated that chitosan gels containing laurocapram increased celecoxib retention on buccal tissues through the increased mucoadhesion and mucosa retention exhibited by these formulations and, hence, acting

as deposits for continuous and gradual absorption of the drug. The intervention with active compounds to inhibit malignant progression is now extensively studied and continues to hold promise with the search for novel and more efficient delivery opportunities.

Along with PDT, another growing area of interest in oncology is photodynamic diagnosis [48]. Oral cancer is particularly amenable for this new diagnostic mode because the oral cavity enables easy access for the application of a light source and photosensitizing agents. As early detection of oral cancer is an essential measure to improve survival rates and prevent metastases, a diagnostic method that permits minimal invasiveness, selectivity, *in situ* monitoring and better tolerance for the patient is preferred.

Within this context, effective delivery of the photosensitizers is of great concern and has therefore led to the use of carrier systems to improve the detection process. High-performance chitosan-based nanoparticles as carriers for 5-aminolevulinic acid (ALA) for oral cancer have been developed [90,91]. Serving as a prodrug, ALA is converted to the photosensitive fluorophore protoporphyrin IX in the cell mitochondria. Following illumination, intracellular accumulation of protoporphyrin IX increases tissue fluorescence and facilitates the distinction between nonmalignant and malignant lesions. One disadvantage with ALA-mediated photodynamic diagnosis is that ALA is highly hydrophilic and has poor affinity toward the lipophilic cell membrane. Therefore, a suitable carrier system is needed. Chitosan was modified to form nanoparticles with improved targeting and release characteristics. Cancerous cells, including oral epithelial cancer cells, exhibit an overexpression of folate receptors with folic acid as a ligand with high affinity. To enable active targeting to oral cancer cells, folic acid-conjugated chitosan nanoparticles were therefore prepared. Furthermore, N-succinyl chitosan was incorporated within the nanoparticle structure. Introduction of negatively charged molecules to positively charged nanoparticles has shown to enhance drug release or transfection efficiency by reducing the intensity of interactions between the nanoparticles and the entrapped material (drug/DNA). Based on these principles, it has been successfully shown that modified chitosan nanoparticles loaded with ALA were taken up by oral cancer cells via folate-receptor-mediated endocytosis. ALA was released in the lysosomes resulting in the conversion and accumulation of protoporphyrin IX for fluorescent endoscopic detection [90].

Conclusion

Due to many various diseases that find place in the oral cavity in combination with the difficulty of obtaining high concentration of the drug at the dis-

eased area, there is no doubt a great demand for new drug delivery systems for the local treatment of the oral cavity. The most successful research has been toward novel systems for the treatment of periodontitis where several new products have entered the market. This is probably due to the ease of getting access to and remaining in place in the periodontal pockets.

Future perspective

In the future, probably even more products will be approved for marketing based on advanced drug delivery platforms, such as fibers and *in situ* gel forming systems for treatment of periodontitis. For the other oral conditions, odontogenic as well as non-odontogenic, there seems to be increased research toward the use of nanoparticulate formulations. As delivery vehicles, nanosized particles can entrap a wide range of substances, from synthetic compounds to biomacromolecules, while having the advantage of being small and therefore easy to penetrate and overcome barriers of the body. They can also quite easily be given bioadhesive or stimuli-responsive properties producing intelligent systems that can provide more efficient pharmacologic therapy of oral pathologies. Nanoparticulate formulations coupled

with PDT seem also to be a very promising technique in treating oral infections. Hence, due to the versatility and multifunctionality of nanoparticulate formulations, the authors anticipate that there will be new nanoparticle-based products for local drug delivery to the oral cavity on the market in a 10 year perspective as long as the particles are nontoxic and biodegradable/biocompatible.

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Executive summary

Background

- The oral cavity is a complex environment for drug delivery consisting of several distinct anatomical structures, is constantly flushed by saliva, and is inhabited by a myriad of diverse microorganisms often existing in resistant biofilms.

Diseases related to the oral cavity

- The most common diseases that can find place in the oral cavity are oral cancer and oral infections. The latter can be divided into two main types; those that originate in the tooth or the closely surrounding structures (odontogenic), such as dental caries or periodontitis, and those that are not (non-odontogenic), such as mucosal infections.

Local drug delivery to the oral cavity

- By delivering drugs directly to the oral cavity, therapeutic efficacy at the locoregional, targeted site of action can be enhanced, systemic drug delivery can be avoided, and the dose of the drug can potentially be lowered leading to fewer side effects.
- The greatest challenge for local drug delivery is the short residence time in the oral cavity due to the secretion of saliva and physiological functions such as eating, drinking, and swallowing.

Recent advances in local drug delivery to the oral cavity

- The most successful research on local drug delivery to the oral cavity has been towards novel systems for the treatment of periodontitis where several new products have managed to enter the market. This is probably due to the ease of getting access to and remaining in place in the periodontal pockets. For periodontitis, many different drug delivery systems have been evaluated; ranging from films, fibers, and strips to *in situ* forming gel systems, micro- and nano-particles.
- For the other oral diseases, there has been an increased research towards nanoparticulate formulations. Nanoparticles have the advantage of being more effective than larger particles, can be given bioadhesive or stimuli-responsive properties, and in addition have the potential of attaining drug targeting for treatment of oral cancer. The potential of combining nanoparticles with photodynamic treatment also seems very promising. This is due to the possibility of killing malignant tissues while reducing cytotoxicity to healthy tissues in cancer and killing the bacteria residing in the oral biofilm which is the cause of many of the oral infections. Photodynamic therapy is also least likely to lead to the development of antibiotic resistance.

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