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DRUG DELIVERY SYSTEMS FOR CARIES DISEASE

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Abstract

Dental caries is a multifactorial, dynamic disease that affects dental hard tissues, being initiated by acidic products from oral biofilms. The etiology and pathophysiology of dental caries are extremely complex. It is widely accepted that changes in the local microecology and disruption of tooth re/demineralization could cause dental caries. Moreover, saliva, fluoride application, dietary sugars and preventive behaviors could also influence it. In recent decades, a combination of drug-release and controlled-release systems for the purpose of caries prevention has gradually attracted attention. These could help maintain the concentration of anti-caries agents in situ through sustained drug release. Such local application has many advantages, such as high efficacy and few systemic effects. Thus, in recent years, there has been an increasing amount of research on drug delivery systems for different stages of dental caries.

Keywords: dental caries, drug-release system, anti-caries agents

INTRODUCTION

Dental caries is one of the most widespread chronic diseases worldwide. The Global Burden of Disease study conducted in 2016 demonstrated that carious disease of permanent teeth ranks 1st with the highest prevalence and 2nd with the highest incidence [1]. As a common oral infectious disease that could occur at all ages, dental caries is the major cause of oral pain and tooth loss and poses a serious threat to human oral health. WHO has recognized that caries is a major health problem in most industrialized countries [2].

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Moreover, saliva, fluoride application, dietary sugars and preventive behaviors could also influence it [3, 4]. Given the harmfulness of dental caries, timely treatment and prevention are essential. It has been found that with proper treatment, dental caries can be initially reversed or stopped [5,6].

Over time, efforts have been made to prevent and control this form of dental hard tissue disease. Since plaque formation and tooth demineralization are the major processes of dental caries development,

antibacterial and remineralizing agents have been widely researched [7,8].

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1. DRUG DELIVERY SYSTEMS FOR EARLY DENTAL CARIES

1.1. Drug release systems with antibacterial action

In terms of prevention and therapy of early dental caries, non-invasive and drug therapy is the main treatment. Antibacterial drug delivery systems have been widely investigated to reduce dental plaque, the initiating factor of dental caries.

Different types of antibacterial agents such as peptides, chlorhexidine, quaternary ammonium salt have been loaded for biofilm removal.

Antibacterial drug delivery systems were also applied for local drug delivery in these studies, among which chlorhexidine-loaded bioadhesive systems were the most studied [9]. Chlorhexidine-loaded varnish usually used ethylcellulose matrix or other biocompatible copolymers that could release chlorhexidine sustainably.

Some products have already been applied in clinical trials and have demonstrated significant antibacterial effects lasting from a few days to a few weeks.

Other drug delivery systems with antibacterial action for dental caries such as chitosan-based propolis formulations have also been investigated. Franca J.R et al., 2014 [10] reported that propolis sustained-release caries antibacterial drug delivery systems for one week showed similar or better antimicrobial activity than chlorhexidine varnish.

In recent years, nanoscale drug delivery systems have attracted increasing attention from researchers. Liposomes, micelles and other copolymeric nanoparticles have been used as carriers to induce local release of antibacterial agents such as peptides, triclosan, chlorhexidine [11,12,13].

Several studies have reported lipid-based carriers such as liquid crystals or liposomes loaded with antimicrobial peptides. Such types of antibacterial drug delivery systems could spontaneously form thermodynamically stable lipid bilayers at the bio-interface having a number of characteristic elements: biodegradability, excellent biological adhesion, high drug loading and sustained drug release [14].

Bernegossi et al., 2015 [15] reported a mucoadhesive liquid crystalline system (LCS) loaded with decapeptides. The mixture of PPG-5-CETETH-20, oleic acid and Poloxamer 407 dispersion could aggregate as microemulsions and form a liquid crystalline lamellar phase [15].

The peptide KSL-W (F2-P) was incorporated and showed significant effects against salivary biofilms. Similarly, peptides such as D1-23 and p1025 have also been

reported with high viscosity and bioadhesion when diluted with artificial saliva and significant antibacterial effects against Steptcoccus mutans [16,17,18].

Chen L. et al., 2013 [19] designed a novel pGJA-P/VAX DNA vaccine-loaded nanoparticle system that exhibited pH-mediated DNA release and improved mucoadhesive properties. pGJA-P/VAX could encode a GLU domain of GTF enzymes as well as the A and P regions of a surface protein antigen (PAc) of S. mutans and thus reduce S. mutans colonization, inducing effective immune responses to mucosal level.

1.2. Drug delivery systems with remineralization action

Fluoride as a remineralizing agent has been widely used in the clinic or at home for years, and fluoride drug delivery systems were one of the first applications in the prevention of early dental caries.

It can form a fluorapatite structure on the tooth surface, with low acid solubility and thus inhibits demineralization and promotes remineralization [20]. Different types of fluoridated products have been available for local fluoride delivery (eg: toothpaste, mouthwash, gels, varnishes, etc.) [21]. Such delivery systems demonstrate limited control of sustained release, which could be easily diluted or eliminated by saliva so that bioavailability is greatly reduced [22]. Therefore, long-term release intraoral systems have been investigated, especially for people at high caries risk [23].

A number of devices made of copolymers or glass, bioadhesive polymers, micro/nanoparticles, etc., have been used as delivery and delivery supports. A membrane-controlled reservoir was first reported in 1970, which was a hydrogel copolymer support composed of 50/50 hydroxyethyl methacrylate (HEMA)/methyl methacrylate (MMA) copolymer as a fluorine-loaded inner core and a membrane of copolymer 30/70 HEMA/MMA. Hydration of the device caused the release of fluoride ranging from 0.02 to 1.0 mg per day, with release lasting up to 180 days [24].

Later, other copolymer and glass device carriers with different fluoride concentrations and release rates were developed [25]. Such types of drug delivery systems have typically been attached to the tooth surface by resin-based adhesives. To improve comfort and simplify surgery, bioadhesive drug delivery systems have been investigated [26,27]. As early as the 1980s, bioadhesive tablets with sustained release of fluoride over several hours were reported by researchers [28].

Keegan et al., 2012 [29] synthesized a new type of chitosan/fluoride bioadhesive microparticles with 6-hour sustained release of fluoride and acceptable mucosal adhesion. Nguyen S. et al., 2017 [30] investigated fluoride-loaded nanoparticles based on chitosan, pectin and alginate biopolymers. An increased and constant release of fluoride was observed for 4 hours. Such a type of bioadhesive nano-system for drug delivery could help to improve patient acceptability and compliance, but more research on fluoride-sustained release as well as in vivo tests are needed. Zhou Y. et al., 2014 [31] showed also the long-term release of antibacterial drug and remineralization of

dentin, which provides a novel strategy to repair dental caries and dentin at the same time.

2. DRUG RELEASE SYSTEMS FOR SECONDARY CARIES

When tooth decay has progressed to cavitary lesions, remineralization treatment or other drug therapy cannot help reverse the situation. So, a restorative treatment is required. However, dental restoration faces many problems, such as the high rate of secondary caries and the threat of pulp damage.

In the last decades, dental restoration modified by local drug release systems has demonstrated beneficial effects: anti-biofilm, anti-inflammatory and/or remineralization effect. Adhesives and composite resins could be loaded with antibacterial nanoparticles (such as Ag and ZnO) and remineralizing agents such as Nano-ACP.

Chlorhexidine is still widely used in resin modified drug delivery systems [32,33]. Nonparticles, spheres, capsules, etc. were designed as carriers. Luo D. et al., 2017 synthesized resin-embedded chlorhexidine spherical particles with a controlled release for 650 h [34].

Boaro L. et al. reported the particulate form of chlorhexidine/montmorillonite, which could release chlorhexidine for 10 days [35].

Metal particles are the main antibacterial agents for modifying dental resin. The most used are silver particles, with broad-spectrum antibacterial properties [36,37]. Researchers have incorporated them into restorative resins and adhesives. The main disadvantage of silver particles is the tooth staining effect.

Thus, other metal particles such as colorless ZnO were added into the composite material. Meanwhile, it was reported that ZnO acted as an opaque filler within the resin [38]. Chen H. et al., reported ZnO@m-SiO2 modified composite resin, which had improved mechanical properties and antibacterial activity [39].

Some researchers have combined silver with ZnO. Previous studies have found this combination to be more effective than the individual components. Other antibacterial agents such as triclosan and cationic agents have also been loaded [40].

In order to reduce the inflammatory response of the pulp caused by deep dental caries, anti-inflammatory agents (ex: indomethacin) were included in the dental resin [41]. Genari B. et al., reported indomethacin-loaded nanocapsules for reducing nociceptive and inflammatory response in vivo [42]. They also combined antibacterial agents, obtaining a modified dental resin with drug release systems, bifunctional, controlled release of indomethacin and triclosan, with a significant antimicrobial effect, without compromising its physicochemical properties [43,44].

Incorporation of remineralizing agents is also extremely important in dental resin modified with drug delivery systems. Calcium phosphate (CaP) composites have demonstrated the controlled release of Ca and P ions for remineralization in acidic media.

Incorporation of calcium phosphate nanocomposites (Nano-ACP) into dental restorative systems without affecting

mechanical properties has been reported. Some presented a combination with antibacterial drug delivery systems, which demonstrated a favorable anticariogenic effect [45].

CONCLUSIONS

Drug delivery systems for the prevention and treatment of dental caries have been widely reported. Antibacterial and remineralizing agents were loaded into different carriers for sustained and controlled local release.

Multifunctional drug delivery systems have attracted much attention and with the development of nanotechnology, the modification of dental resin by drug delivery systems has also been widely studied.

Great efforts have already been made for the long-term anticariogenic effect of drug delivery systems. However, in recent years, more and more emphasis has been placed on the balance of the oral environment. Maintaining microbial eubiosis instead of destroying all biofilms has attracted much attention.

Smart materials that respond to the changing oral environment could be an excellent solution. Research in this direction is still limited, so there is great potential for future studies.

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