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Review

Local treatment of the dental caries using nanomaterials

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ABSTRACT

Targeted therapy as well as reduced adverse effects are the advantages of local drug delivery in dental caries. The application of nanotechnology in this context has gained increasing momentum during last years. A literature search here has provided a brief overview to present the recent developments in using nanoparticles for local treatment of dental caries. Nanoparticles as delivery systems, can entrap substances/drugs and use the advantages of small size and better penetration. They can also profit from biomimetic approaches to provide more effective treatment. Thoroughly, nanotechnology-based treatment of dental caries in situ, may introduce a novel aid in the field of dentistry.

1. Introduction

The oral cavity as the first section of the gastrointestinal system is exposed to different injuries in which dental problems are the second cause of acquired diseases after trauma. The local treatment serves as a targeted therapy in the diseased area while minimises side effects [1,2].

Regarding dental problems, tooth decays, or dental caries is among the most common disease in the human defined by local damage susceptible dental hard tissues by acidic by-products from the bacterial fermentation of dietary carbohydrates [3]. The generation of acid initiates this problem originated from bacteria fermenting carbohydrates that leads to the demineralization of the dental enamel and the formation of cavities. Calcium and phosphate supplementations can attenuate teeth demineralization to prevent dental caries. Also, these ions are present in the saliva, and their salivary concentration will determine whether remineralization or a demineralization will occur [4] (Fig. 1).

Fluoride is the simplest anion of fluorine that has an important role in the industrial chemicals. It is a well-known remineralization agent in the prevention of dental caries in early stages. Fluoride in the topical and systemic forms can react with hydroxyapatite and form fluorapatite or fluoridated hydroxyapatite [4,5].

The most common dosage forms for dental caries are liquid or semisolid products that possess the ease of administration and patient acceptability. The main drawback of these forms is poor retention in the oral cavity that results in the suboptimal therapeutic outcome [6].

For years toothpaste have been the main delivery systems for fluoride against dental caries. Also, some other administration structures also have been used like gels, tablets and mouth rinses [7]. Constant secretion of saliva which dilutes and degrade fluoride-enriched is the main hurdle that constraints their therapeutic efficacy. Thus, it seems that fluoride is needed to be existent on the surface of the teeth to be safe from saliva acid attack [4,8].

The application of nanotechnology in dentistry has grabbed significant attention in recent years. Nanoparticles are a class of materials with particulate physicochemical properties and a wide range of applications including pharmaceutical applications. The efficiency of dental materials such as antimicrobial dental adhesives, dental implants, aesthetic restorative materials and denture bases has been revolutionized via the aid of nanotechnology [9–12]. Different types of oral and dental nano-formulations have been investigated by researchers so far. Nanoparticle-based formulations for local delivery in the oral cavity can be presented as an aqueous suspension or be incorporated into a gel or paste [13].

A literature review here has presented a brief sight to present the recent developments in using nanoparticles for local treatment of dental caries.

1.1. Nanomaterials in dental caries

Nanoparticles are a class of materials with size range between 1 and 100 nm possessing particulate physicochemical properties and a wide

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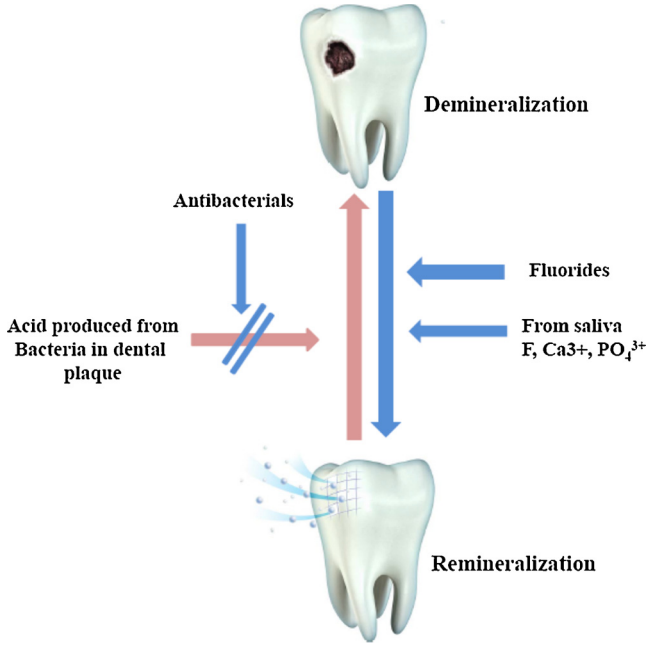

Fig. 1. The re- and de-mineraleralization process of the teeth.

range of applications [14,15]. Reduced particle sizes from micrometers to nanometers is concomitant with altered chemical and biological properties of particles such as hardness, chemical reactivity and active surface area [16]. Nanocarriers are also nanomaterials being used as a transport unit for another substance, such as a drug/gene. Commonly used nanocarriers include micelles and liposomes. Nanocarriers are currently being considered for their use in dentistry and their unique features establish potential use in antimicrobial agent's delivery.

Nanomaterials implementation in dentistry could be classified into two main categories: preventative and restorative dental care [17]. According to the recent knowledge, nanotechnology has provided novel approaches in prevention and treatment of tooth decay in particular via the control of plaque related biofilms and remineralization of primary dental caries [18,19].

In spite of the abundance of different bacteria in oral cavity, only a few distinct species such as *Streptococous mutans* and *Lactobacillus* species are assumed to cause tooth decay. *Streptococcus mutans* (S. *mutans*) which are the most common bacteria hosting in the oral biofilm was first found in human caries lesions by Clarke in 1924. However, more distinct connections between this bacteria and dental caries were identified later by Keyes in 1960 [20], and it is now considered a primary etiological agent of dental caries in both humans and animals. Nanotechnological developments as novel drivers of innovation have also offered advantages in this subject. Natural biomineralization which is an intrinsic repaired process has been shown to be stimulated via the use of nanotechnology. Application of nanomaterials in toothpaste and other rinsing solutions has been observed to substantially improve oral health through prevention of dental caries. In addition, nanomaterials utilized in polishing agents and dental filling materials prevent caries. Antimicrobial nanoparticles per se could prohibit bacterial growth and thus dental caries [14,21].

Nanotechnology treats dental caries in two main approaches. In the first approach, the nanomaterials with fluoride and calcium release ability such as calcium phosphate, calcium fluoride, hydroxyapatite and fluorohydroxyapaptite are used in a process calls remineralization. Implementation of antibacterial nanomaterials such as silver, quaternary ammonium polyethyleneimine and zinc oxide nanoparticles is the second approach [22,23]. A combination of these two approaches may also use to present better outcomes. The new types of nanomaterials which have been designed for avoiding dental caries by eradicating the bacteria responsible for the dental plaque are presented below [24].

1.2. Nanosilver fluoride particles

Tens of thousands of researches have revealed the effectiveness of metal ions in the reduction of bacterial infections. According to reports, silver (Ag) ion have shown potent antimicrobial activity against S. *mutans* [25]. Recent advances have d out the outstanding antibacterial activity of metal and metal oxide nanoparticles in optimal treatment of dental caries.

Antibacterial activity of Ag nanoparticles has been posed to occur via two main mechanisms: a)

Free Ag ions toxicity arising from the dissolution of the metals from the surface of these nanoparticles and b) oxidative stress via the generation of reactive oxygen species (ROS) on surfaces of the nanoparticles [26]. The interaction of Ag ions with disulfide and sulfidryl groups of enzymes afterwards gives rise to metabolic disruption and consequent cell death. Ag nanoparticles may also induce pits in the bacterial membrane causing cell fragmentation [26–28]. It has been revealed that the smaller Ag nanoparticles have better contact with the surface of the bacteria and then better antibacterial activity compared to the larger particles.

According to the data above, some forms of nanosilver-fluoride products have been investigated so far. Nano-silver-diamine-fluoride is one of these products that possess useful properties in caries prophylaxis despite some reported drawbacks such as tooth staining [28]. Burns et al. tested nano- silver- fluoride formulations for preventing dental caries in school children with active caries in primary teeth and no pulpal exposure, fistula or decay in permanent teeth. They used two drops of the prepared formulation (as a test group and two water drops as a control group) to the tooth with a microbrush for two minutes, once in a 12-month period. Their test on 130 five-month follows up eight teeth in 60 children (mean age of 6.31) showed no losses after one week. At the 12-month period, there was a 33.3% test group failure rate and 65.3% control failure rate. The authors concluded that the yearly utilization of nano-silver-fluoride solution showed more efficiency in strengthening and also arresting dentine caries in primary teeth than the placebo. Furthermore, this product showed superiority in comparison with silver diamine fluoride because it neither had a metallic taste nor stained the dental tissue. Besides, ease of synthesis, being cost-effective and not depending on clinical settings hold promise in the application of the latter formulation [29].

Nano-silver-fluoride-chitosan is another novel formulation that has recently been presented [30].

Chitosan itself has been reported to have inhibitory effects of *S. mutans* growth gaining importance in prevention of tooth decay. For instance, chitosan supplementations in chewing gums have shown to reduce the amount of oral bacteria unequivocally [31]. Moreover, it can act as a barrier against acid penetration and thus prohibit enamel demineralization in vitro [32].

Chitosan is a bio-adhesive and safe polysaccharide which improves drug delivery and helps to the dental binding. It also possesses inherent antimicrobial effect according to previous reports. However, the most important reason for chitosan application in this composition is due to its stabilizing impact on the Ag nanoparticles [32,33].

Freire et al. tested the antimicrobial effect and cytotoxicity of 4 chitosan–silver–fluoride nanocomposites in different shapes and sizes. The outcomes revealed that the smaller the size particle is, the safer is the formulation on murine macrophages. However, the differences in the size and shapes of the aforementioned samples did not produce any significant discrepancies in the antibacterial and antifungal effects. Also, the samples did not alter the growth curves of both grams negative and positive bacteria. The authors concluded that the prepared nano-composites offer encouraging outlook on the control of multiple-drug-resistant microorganisms and do not signify considerable risks to

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