ISSN Print: 2394-7489
ISSN Online: 2394-7497
IJADS 2020; 6(4): 81-84

www.oraljournal.com
Received: 08-09-2020
Accepted: 12-10-2020

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Current applications of chitosan nanoparticles in dentistry: A review

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DOI: https://doi.org/10.22271/oral.2020.v6.i4b.1050

Abstract
Nanotechnology is widely used in our day to day life including its use in medicine. Nanostructures are used in innovations or diagnosis of dentistry. Some nano-particles are used for oral disease preventive drugs, prostheses and for teeth implantation. Nano-materials further deliver oral fluid or drugs, preventing and curing some oral disease like oral cancer and maintain oral health care up to a high extent. The nanoparticle like chitosan has anti-microbial, anti-oxidant, and anti-tumor effects. The literature search was done by the online and text search. The data was conducted using different electronic databases and the articles published in the different journals were obtained. The nanoparticle like chitosan has anti-microbial, anti-oxidant, and anti-tumor effects. Therefore, the purpose of present review was to evaluate the different aspects of nano-particles like chitosan in the Dentistry.

Keywords: Dentistry, endodontic, nanoparticles, nanotechnology, review

1. Introduction
Nanotechnology, a technology which deals objects of nanometer size and the particles are called as nanoparticles (NPs). Silver is the frequently used NPs, used in various products in different form, which is followed by carbon and ion oxides. The nanoparticle can improve the quality of the products by adding many functional groups to it. Thus, nano-products are widely used in various industrial sectors, medicine and in the field of dentistry [1]. Nano material denotes a natural, incidental, or manufactured material containing particles in an unbound state or as an aggregate or agglomerate in which 50% or more of the particles in number, size, distribution, or 1 or more external dimensions is in the size range of 1-100 nm. Nano materials offer unique physicochemical properties, such as ultra-small sizes, large surface area/mass ratio, and increased chemical reactivity, compared with their bulk counterparts. The increased surface to volume ratio and increased number of atoms that are present near the surface compared with micro/macrostructures are suggested to contribute to the distinctly different properties of nanomaterials [2]. The scope of such strategies includes a wide variety of oral health–related issues such as treatment of dentin hypersensitivity, biofilm elimination, diagnosis and treatment of oral cancers, bone replacement materials, and so on. Currently, newer technologies are being tested in Endodontics, mainly towards overcoming the microbial challenge [3]. Natural biomaterials are known for a range of biological properties such as biocompatibility and biodegradation required for biomedical applications. A few examples of natural biomaterials include collagen fibrin, natural silk, and chitosan [4].
Chitosan is a natural biomaterial that is purified mainly from chitin. The major source of chitin remains the crustacean's (such as crab and shrimp) exoskeleton. Other sources include insects, fungi and certain plants such as mushrooms [5]. In the field of Endodontics, the nano-materials are focused on steps that would improve mechanical integrity, antimicrobial of previously diseased tissue regeneration, and dentin matrix. Currently, it is a new technology tested in Endodontics to have challenges over microorganisms. Chitosan (poly [1, 4-b-D-glucopyranosamine]), a DE acetylated derivative of chitin, is the second most abundant natural biopolymer. Nanoparticles of chitosan could be synthesized or assembled using various methods depending on the physical characteristics or end of application required on the nanoparticles.

Chitosan has many interest in biomedicine because of its versatility in various forms such as capsule (micro-and nanoparticles), powder, scaffolds, films, beads, hydrogels, and bandages. Chitosan nanoparticles have been developed mainly for drug/gene delivery applications and antibacterial purposes. Chitosan has excellent antiviral, antibacterial, and antifungal properties. Gram-positive bacteria are more susceptible than Gram-negative ones. The minimum inhibitory concentrations which are ranged from 18 to 5000 ppm depending on the organism, pH, and degree of deacetylation, molecular weight, chemical modifications, and presence of lipids and proteins [6]. The widespread recognition of microbial biofilm as the contributory factor for human infection and constant increase in antimicrobial resistance warrants the discovery of a reliable and effective antimicrobial strategy to combat infectious diseases. Treatment of infected root canals presents with a major challenge of bacterial persistence after treatment. Use of various antibacterial nanoparticles presents as a potential treatment strategy to improve the elimination of biofilm bacteria from the root canal system. Nanoparticles have been developed to improve the root canal disinfection as well as to seal the canal space during root canal treatment [7]. Therefore, the purpose of present review was to evaluate the different aspects of nano-particles in the Dentistry.

Methods

In the present review, the literature search was done by the online search regarding chitosan nanoparticles. The comprehensive literature search was conducted using different electronic databases like PubMed, Medline, Embase, EBSCOhost, Web of Science, Google etc. and the articles published in the different journals were obtained. The keywords used for the computer-based search were like ‘Nanoparticle’; ‘Nanotechnology’; ‘Dentistry’; ‘Review’; ‘Endodontics’; etc. Further articles were sought by manually searching reference lists of the relevant article publications. The articles which were published only in the English language were selected. The review data consisted of different original articles, reviews, textbooks, etc. were documented. There was no patient involvement in the review.

Classification of Nanoparticles in Dentistry

The NPs can be classified under three main categories as follows [7].

On the basis of origin, NPs can be classified as

a. Natural
b. Artificial

On the basis of dimension

a. Zero-dimensional or nanostructures such as NPs
b. One-dimensional or nanorods and
c. Two-dimensional or thin films

On the basis of structural configuration

a. Carbon-based NPs
b. Metal NP
c. Dendrimers
d. Composites

Synthesis of nanoparticles

There are two different types of approaches by which we can prepare NPs

1. **Top-down approach.**
2. **Bottom-up approach.**

The top-down approach reduces the size of the material from bulk to nanoscale utilizing special treatments such as grinding/ablation/etching/sputtering. The bottom-up approach is preparation of NP/nanostructures utilizes mostly chemical reactions. There are various methods that have been employed in synthesis of nanoparticles. They are as follows: chemical, electrochemical, wet chemical, pyrolytic, microwave, hydrothermal, mycosynthesis, sonochemical, solution-gel, co-precipitation, biosynthesis, etc [8].

What Makes Nanoparticles Different from the Bulk Materials?

When compared with bulk materials, the NPs provide greater benefits as they are relatively low stability molecules having low coordination and unsatisfied bonds that allow them to interact with other particles effectively and with ease. Added to this, they exhibit quantum confinement effects in materials with delocalized electrons. Moreover, the high surface area to volume ratio plays a major role in determining the energy statistics of the particles. The concept of NPs as antimicrobial agents is very novel and utilizes quite different mechanisms which are in contrast to antimicrobial mechanisms of the antibiotics. Therefore, antibiotic resistance becomes a redundant issue. Not only do they disrupt the process of cell wall synthesis as done by the conventional bulk materials, but NPs also have the potential of inhibiting various enzymes, such as DNA-dependent RNA polymerase and DNA gyrase. Furthermore, chemical, magnetic, electrical, mechanical, and optical alterations and modifications can be undertaken to attain more benefits [8].

Chitosan

Chitosan has anti-microbial, anti-oxidant, and anti-tumor effects. Bone formation is accelerated by chitosan through increasing osteoblasts formation in bone tissue, and it has also the capability of connective tissue regeneration. Chitosan has been recognised as an antimicrobial agent, however its ability to act in this way is not completely elucidated as several different mechanisms have been attributed to this nature of chitosan. One theory suggests that when exposed to bacterial cell wall, chitosan promotes displacement of Ca^{++} of anionic sites of the membrane, resulting in cellular destruction. It is also known to exhibit a potent antiplaque activity against several oral pathogens such as Porphyronomas gingivalis, Prevotella intermedia and Actinobacillus actinomycetem comitans. Chitosan has a high degree of biocompatibility in animal models and can be conveniently adapted for the development of implantable biomaterials. In addition, chitosan can be chemically functionalized using various compounds [9]. Nanoparticles of chitosan could be synthesized or assembled using different methods depending on the end application or the physical characteristics required in the nanoparticles. Chitosan nanoparticles (CS NPs), by virtue of their charge and size, are expected to possess enhanced antibacterial activity. In addition, chitosan possesses several characteristics such as being nontoxic toward mammalian cells, colour compatibility to tooth structure, cost effectiveness, availability, and ease of chemical modification. CS NPs can be delivered within the anatomical complexities and dentinal tubules of an infected root canal to enhance root canal disinfection. Despite tremendous efforts in investigating the suitability of chitosan in drug delivery and the large number of chitosan manufacturers, it is still very difficult to obtain chitosan which is fully standardized with respect to molecular weight and degree of deacetylation for pharmaceutical research [10].

Toxicity and safety of chitosan:

Chitosan is biodegradable and the process occurs either by chemical or enzyme catalysis. Degradation of chitosan is dependent on the degree of deacetylation and the availability of amino groups. Additionally, chitosan is approved as safe by US-FDA (Food and Drug Administration) and EU (European Union) for dietary use and wound dressing applications. However, the toxicity of chitosan increases by increasing charge density and degree of deacetylation. We have not found any published data showing human toxicity of chitosan based formulations or questioning the safety of chitosan for human use. However, there are several animal toxicity studies reporting good safety *in vivo* and *in vitro* [11].

Applications of chitosan materials

Applications of chitosan materials were seen in different methods such as in parentral drug delivery, in per-oral administration, in mucosal drug delivery, in controlled drug delivery, in insulin delivery, in ocular drug delivery, in non-viral gene delivery, in vaccine delivery, in brain targeting, in tissue engineering, in electrodeposition, in stability improvement, etc [12].

Applications of chitosan materials in Dentistry:

The chitosan-based materials have been explored extensively for a wide range of dental applications as follows [13].

Oral Drug Delivery

Chitosan-based composites (CBCs) can be used to design a robust local drug delivery system with the required mechanical properties, contact time, a sustained release profile, while maintaining an intimate contact with the oral mucosa. CBC leads to enhance the bioavailability for treating various oral pathologies. Oral administration of CHS is non-toxic. Chitosan in the form of nano-particles and resorbable films can be used to deliver antibiotics (such as metronidazole, chlorhexidine and nystatin) to periodontal tissues in situ, against fungal infections and oral mucositis. In dentistry, CHS has displayed effective plaque control *in vitro* by inhibiting specific dental plaque pathogens (Actinobacillus actinomycetemcomitans, P. gingivalis and S. mutans). A comprehensive understanding of the antibacterial activity of CHS-based materials remains elusive to date.

Guided Tissue Regeneration

There is an increasing level of interest in developing regenerative periodontal therapeutic strategies vis-à-vis the concept of guided tissue regeneration (GTR) or guided bone regeneration (GBR). The underlying strategy in GTR involves isolating the periodontal defect with a suitable membrane (resorbable or non-resorbable) that acts as a physical impediment to gingival tissue infiltration into the osseous defects, thereby encouraging bone regeneration and preventing spaces for fibrous tissue proliferation simultaneously. In order to achieve this objectively in an efficient and clinically viable manner, it is imperative for the template to possess certain biological, physical, chemical and bioactive characteristics that encourage favourable host tissue response in a self-contained temporal system amenable to tissue regeneration. The spectrum of properties desirable in a comprehensive GTR membrane therapy system ranges from robust constructs (smart, bio-integrative and conducive) to drug delivery applications. An optimal particle size and biological behaviour of the inclusive elements improves the receptiveness to cellular and extracellular matrix cues. Due to the compliance with the aforementioned properties, chitosan has been pinned as a favourable substrate material for periodontal tissue regeneration

Modifications of Dentifrices

The commercially available chitosan-based dentifrice (Chitodent (B&F)), that is a non-fluoride formulation, and highlighted a significant reduction of tissue loss.

Enamel Repair

Tooth enamel is a non-vascular and the hardest tissue of human body hence the repair or regeneration of enamel is challenging. A number of chitosan-based restorative formulations have been explored and are under consideration for achieving human enamel regeneration through successful delivery of organic amelogenin at the site of enamel defects. Recently, a chitosan-based hydrogel as a delivery medium for amelogenin with the aim of rejuvenating the aligned crystal structure.

Adhesion and Dentine Bonding

The dentine-restoration interface and durability of bond strength have captured the interest of researchers. Currently, the dentine replacement materials have issues such as technique sensitivity of acid etching and removal of the smear layer. The incomplete removal of the smear layer often gives rise to poor penetration of the resin monomer resulting in an unstable hybrid layer that is prone to nano leakage. Hence, the area of bioadhesive polymers in general and chitosan-based dentine replacement materials in particular merits special attention. Antioxidant chitosan hydrogels with propolis, β carotene and nystatin were investigated and translated significant grounds towards delivering robust dentine bonding systems with a concomitant increase in shear bond strength.

Modification of Dental Restorative Materials

Among restorative materials, glass ionomers (fluoroaluminosilicate glass powder with poly (acrylic) acid liquid) form a chemical adhesion with the calcified tooth tissues. Glass ionomer cements (GICs) have been presented with various modifications such as with resin or nano-additives and are commonly used for applications such as cementation of prosthesis and restorations.

Chitosan for Coating Dental Implants

The clinical success of dental implants is based on degree of osseointegration of implant materials and alveolar bone. A number of studies have reported promising results for chitosan coating of dental implants. The chitosan coating may affect the surface and bone interface by altering biological, mechanical and morphological surface properties.

Stem-Based Regenerative Therapeutics

The rapid advancements in stem cell field have led to the use of chitosan as a carrier for chitosan-mediated stem cell repair. The regeneration of dentine-pulp complex has been investigated by exploiting the regenerative potential of mobilised dental pulp stem cells. Also, the use of dental pulp stem cells cultured on a collagen-chitosan complex and were also able to form a dentine-pulp complex. The regeneration of entire tooth is also expected to be a goal of current research clusters. Tooth engineering to form dental structures *in vivo* has been established using different stem cells. Moreover, stem cell technology for regenerative therapies is already available as mesenchymal stem / stromal cells already have been introduced in the clinic for alveolar bone augmentation [4, 6, 20].

Limitations of chitosan

Chitosan has low solubility in neutral and alkaline pH. Its mucoadhesion and permeation enhancer properties are strongest in the duodenal area, which can be modulated with chitosan derivatives. The toxicological profile of chitosan derivatives is still under investigation. Chitosan has shown little or no toxicity in animal models and there have been no reports of major adverse effects in healthy human volunteers but clinical data are lacking. Even though chitosan is approved in dietary use, wound dressing applications and cartilage formulations, as of this writing there is not yet a chitosan-based drug formulation approved for mass marketing. Issues regarding scale up of fabrication methods will likely be informed by that of other polymeric formulations [14].

Conclusion

Chitosan is a new biomaterial for dental applications ranging from restorative dentistry to tissue engineered scaffolds for the alveolar bone to periodontal complex healing. Although it has gone through rigorous investigations for its biocompatible nature, antimicrobial properties, and adjustable degradation characteristics according to the application, there still remain certain issues that need addressing, such as the fact that extracted chitosan may vary in terms of structure and molecular weights from low, medium to high, resulting in inconsistent physiochemical characteristics and variability. These variations, especially when looking at dental applications, are an issue as the molecular weight range varies, and reproducibility of the correct molecular weight is still a challenging task. Nevertheless, this ever-evolving field of dentistry can use this naturally derived polymer to its advantage in numerous other prosthetic, orthodontic and implant-related fields as well. Therefore, there is excellent potential for expanding its biological applications in future. However, very little clinical data is available regarding the clinical dental applications of chitosan-based materials. In order to translate chitosan-based materials from research to clinical applications, there is need for further research, particularly *in vivo* studies and clinical trials.

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