Chapter 24
Application of Nanoparticles in Treating Periodontitis: Preclinical and Clinical Overview

Nathalia Mercado, Priyanka Bhatt, Vijaykumar Sutariya, Fernando Luis Esteban Florez, and Yashwant V Pathak

Abstract Periodontitis involves infection of the gums and other structures such as the periodontal ligaments, and the alveolar bone. The disease results in the formation of periodontal pockets and bone loss, and the tooth may fall out. Nanoparticles have gained a lot of use with various dental applications due to their unique properties that make them suitable for drug delivery. Due to the small size of nanoparticles, they are able to deliver the drug to particular tissues, cells or pathogens in the periodontal pockets. In addition, they display antimicrobial activity by destroying bacterial cell membranes and killing the bacteria. There are several different nanomaterials that are used to treat periodontal disease, such as liposomes, lipid and polymeric nanoparticles, and dendrimers. There has also been development of delivery systems for drugs, proteins, and cells. These include nanocapsules, nanoscaffolds, nanocoatings, and nanoshells. This chapter reviews the use of nanotechnology applications in dentistry and the different types of nanoparticles.

Keywords Chitosan nanoparticle · Drug delivery · Metal nanoparticles
Antimicrobial

N. Mercado · P. Bhatt · V. Sutariya
College of Pharmacy, University of South Florida, Tampa, FL, USA

F. L. E. Florez
Division of Dental Biomaterials, Department of Restorative Sciences,
University of Oklahoma College of Dentistry, Joint Appointment OUHSC Graduate College,
1201 N. Stonewall Ave., Suite 146B, Oklahoma City, OK 73117, USA

Y. V Pathak (✉)
College of Pharmacy, University of South Florida, Tampa, FL, USA

Adjunct professor at Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia
e-mail: ypathak1@health.usf.edu

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1 Introduction

Owing to the restrictions in dental instruments, nanoparticles have been used to prevent, diagnose, and treat various oral conditions. Additionally, an increase in antibiotic resistance has also led the medical field to use nanoparticles as an alternative. Nanoparticles have a unique combination of properties that make them suitable for various dental applications. They have a high surface area to volume ratio due to their small size, making them easy to manipulate and control on the atomic/molecular scale. They have an enhanced solubility, a quicker onset of therapeutic action and an increased rate of dissolution. Nanoparticles can also be used as drug delivery and ions agents [1]. In addition, they are able to interact closely with microbial membranes in order to treat dental caries and periodontal disease. Metal nanoparticles, such as copper, zinc, titanium, magnesium, silver, and gold, display antimicrobial properties. They can destroy the bacterial cell membrane and kill the bacteria. The antimicrobial activity of nanoparticles correlates with the particle size. Decreasing the size of the nanoparticle is beneficial because it increases their surface area, and allows for a greater contact and interactions with the surface and membranes of pathogenic microorganisms [2]. Particles ranging from 1 to 10 nm in size have shown to have a greater antimicrobial activity than larger particles [3]. Nanoparticles have also been combined with polymers for a variety of potential antimicrobial applications within the oral cavity. Different types of nanoparticles, such as chitosan, polymeric, quantum dot, liposomes, and metal nanoparticles, offer prominent features in the use of dental applications.

2 Periodontitis

Periodontal disease, also known as gum disease, is an infection that damages the soft tissue and structures around the teeth. These structures include the gums, the alveolar bone, and the periodontal ligament. The infection begins when bacteria stick to the surface of the tooth, which leads to the accumulation of bacterial plaque around the tooth. One way that it can lead to periodontitis is that the plaque can harden and form into tartar, or calculus. Plaque can also cause gingivitis, which is inflammation and irritation of the gums. Constant inflammation of the gums can eventually cause pockets to develop between your gums and teeth, which then fill with more bacteria and plaque. Without treatment, one is at high risk of tooth and tissue loss. Red, swollen, or tender gums that bleed easily; painful chewing; loose or shifting of teeth; receding gums; sensitive teeth or gums; and bad breath are major signs and symptoms of periodontitis. Several procedures have been used to treat periodontitis, such as bone grafting, scaling and root planing, use of bone substitutes, and guided tissue regeneration [4]. However, dental materials, instruments, and procedures are not very efficient or precise in targeting microbes; they lack the ability to reach the deep pockets. Nano drug delivery systems offer a more advanced drug delivery approach against periodontitis and are effective against resistant pathogens. Due to their small size they are able to reach sites that are not accessible

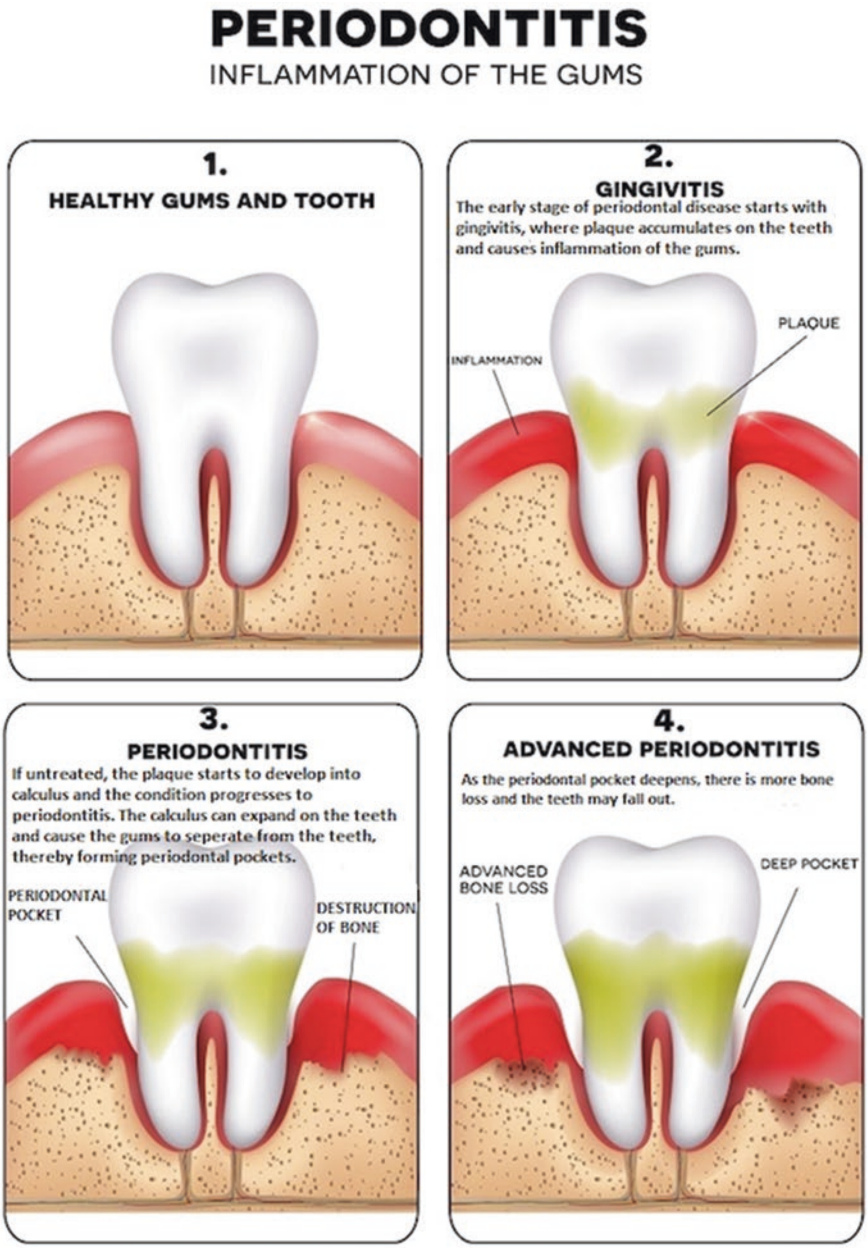

Fig. 24.1 Stages of periodontitis

to other devices, such as periodontal pockets. Additionally, nanoparticles offer a high stability and a controlled release rate. The drug dissolved in the nanoparticle matrix also has the advantage that it does not require a high dosage frequency since the drug is distributed for an extended period of time (Fig. 24.1).

3 Applications of Nanoparticles in Dentistry

The antibacterial activity of nanoparticles is directly proportional to the release of ions. With that said, the greater the concentration of nanoparticles, the more ions that can be released, and the higher toxicity to the bacterial cells. Other mechanisms also exist in the destruction of nanoparticles. One mechanism is through the binding of electrostatic forces. Once the nanoparticle binds to the bacterial cell membrane, it causes alterations in bacterial cell functions that subsequently lead to bacterial cell death [5]. The second mechanism involves the production of oxygen free-radicals that can hinder protein function and result in excess radical production (Fig. 24.2).

3.1 In Diagnosis

The use of nanodevices provides higher accuracy when performing diagnostic tests in the mouth by marking specific bacteria. Once marked, the bacteria can be easily identified and removed. There are several different tools that help detect and diagnose oral conditions. Cantilevers are tools that can attach to carcinogenic molecules, or altered DNA sequences. Nanopores can also detect carcinogenic molecules. Nanotubes can be used for analyzing dentin collagen network, dentin pores and their effects on tooth hypersensitivity, the surface of dental implants, and colonies formed on tooth surfaces. Nanowire sensors were developed to detect proteins or viruses in saliva samples [6]. Nanosystems, such as the oral fluid nanosensor test,

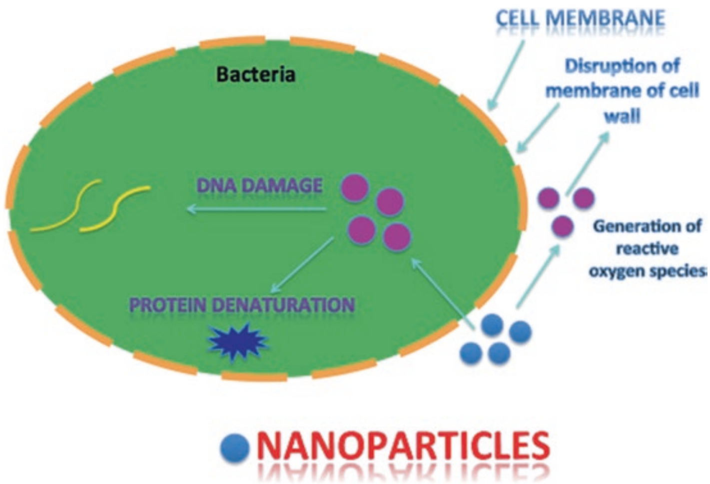

Fig. 24.2 Mechanism of interaction of nanoparticle with bacterial cell

are effective in detection of salivary proteomic biomarkers and nucleic acids specific for oral cancer. Several other tests, such as the oral fluid nanosensor test and the optical nanobiosensor test, are also useful for diagnosis of oral cancer.

3.2 In Treatment

The use of nanomaterials has allowed new treatment opportunities to arise in dentistry. These opportunities include local anesthesia, dentition renaturalization, a cure for hypersensitivity, orthodontic realignment in just one visit to the office, and more [4].

Several nanoparticles, such as zinc oxide and silver, are being used to inhibit bacterial growth by incorporating the nanoparticles into dental composites or dental adhesives [7]. For example, resin composites containing silver ion-implanted fillers have shown to be effective against oral streptococci [8]. Due to their large surface-to-volume ratio, they have better interaction with the bacterial cell membrane, thereby destroying it. Other ways they can inhibit bacterial growth is by blocking the transport and metabolism of sugars, by producing reactive oxygen species, inhibiting the electron transportation across the bacterial membrane, and blocking DNA replication [2].

Some nanodevices can be used for both diagnostic and therapeutic purposes. Dendrimers, for example, are synthetic polymers that have the ability to simultaneously carry one molecule for the removal of cancer cells in the oral cavity and one molecule for diagnosis. Research has also proven that solutions of chlorhexidine mixed with hexametaphosphate (HMP) nanoparticles are significantly effective in inhibiting fungal infestation by blocking the metabolic activity of *Candida albicans* [9].

For orthodontic treatment, brackets can be coated with CuO (copper oxide) and ZnO (zinc oxide) nanoparticles in order to inhibit the growth of *S. mutans* [10]. Coating orthodontic wires with inactive fullerene-like tungsten disulfide nanoparticles can reduce friction that may be caused when sliding a tooth along an arch wire [11]. When straightening or rotating a tooth, orthodontic nanorobots can be used for a painless correction of misaligned teeth [12].

Dental implants have failed due to a lack of bone formation around the implant. However, there have been improvements by the addition of nanoscale deposits of hydroxyapatite crystals and calcium phosphate, which has created a better implant surface for osteoblast formation [13].

When administering local anesthesia, nanotechnology solution can be used to administer anesthesia without pain. This method works by filling the patient's gingiva with micron-sized analgesic dental robots. The nanorobots would reach the dentin and move toward the pulp, and once they have reached the pulp, the nanorobots would block all sensation in the tooth [2].

Nanorobots have also been incorporated in toothpastes and mouthwashes in order to prevent the accumulation of calculus (Tables 24.1, 24.2 and 24.3).

Table 24.1 Delivery systems used for drugs, proteins, and cells [4]

Delivery systems	Description
Nanocapsules	Encapsulation of drugs into nanoparticle shells allows a sustained release of drugs once the capsule disintegrates at specific locations
Nanoscaffolds	These materials also deliver drugs to the target sites. They have the advantage of disintegrating without triggering an immune response in the body. They are used in dentistry for, regeneration of the alveolar bone, periodontal ligament, dental pulp, and enamel
Nanocoatings	These materials can be used to combat endodontic and periodontal diseases that are caused by pathogenic microorganisms. They may be used in combination with other treatments to lower the sub gingival microbial count
Nanoshells	When infrared light is applied to these materials, they produce heat and can destroy the bacteria, cancer cells, and ligature of the vessels. They can be loaded with antibodies, or other proteins and used for drug delivery

Table 24.2 Applications of nanoparticles in dentistry

Antimicrobial nanoparticles	Therapeutic nanodevices
Chitosan	Nanopores
Copper based nanoparticle-metal nanoparticle	Dendrimers
Zinc based nanoparticle-metal nanoparticle	Nanotubes
Silver nanoparticle-metal nanoparticle	Nanoshells
Titanium oxide-metal nanoparticle	Quantum dots

Table 24.3 Incorporation of nanoparticles into dental materials

Nanoparticles	Dental material
SiO2, ZrO2-SiO2	Resin-based composites
ZnO	Cements
Ag-nanoparticles	Adhesives
Apatite and Ti nanoparticles	On dental implants

4 Types of Nanoparticles

4.1 Chitosan Nanoparticles

Chitosan is the second most abundant biopolymer that can be obtained through partial deacetylation of chitin. It is composed of glucosamine units and *N*-acetylglucosamine. Chitosan exhibits antibacterial properties due to its positive charge, making it an ideal candidate for use in root canal treatments. It has various unique properties for drug delivery applications, such as mucus adhesion, hydrophilicity, biocompatibility, biodegradability, healing wounds quickly and a broad antibacterial spectrum. Owing to the many favorable properties of chitosan, it has been used as a suitable material in dental applications.

4.2 Polymeric Nanoparticles

Poly(lactic-co-glycolic acid) is copolymer of poly-lactic acid (PLA) and poly-glycolic acid (PGA). In the presence of water, PLGA undergoes hydrolysis of its ester linkages, resulting in the monomers lactic acid and glycolic acid, which are by-products of different metabolic pathways in the body [14]. The production of PLGA nanoparticles has been beneficial in various fields of dentistry, such as endodontic therapy, dental caries, dental surgery, dental implants, or periodontology. For periodontal treatment, PLGA implants, disks, and dental films are beneficial in local administration of antibiotics. They also reduce the systemic side effects of general antibiotic delivery [15].

4.3 Quantum Dot

Quantum dots are made of semiconductor materials with fluorescent properties and can be used as photosensitizers and carriers. Quantum dots are beneficial in diagnosing oral cancer by, binding to cancer cells. Once they bind, UV light is radiated to them and starts UV light emission, making it easier to detect oral cancers. They can also be used as drug or gene carriers. Thus, quantum dots are useful in prevention of oral cancer.

4.4 Metal Nanoparticles

Metal nanoparticles have large surface area to volume ratios and good antibacterial properties, thereby making them ideal candidates in deterring growth of various microorganisms. Metal nanoparticles are beneficial because they can act on a wide range of microorganisms. For example, silver nanoparticles have a greater affinity for gram-negative and anaerobic bacteria. Various others metal nanoparticles, such as copper oxide, also displays unique properties that make them suitable in the use of dental applications.

4.5 Silver Nanoparticles

Silver was incorporated into dental composites in order to introduce antimicrobial properties and improve biocompatibility of the composites [16]. Silver is very favorable because it displays a strong antibacterial activity and it has anti-inflammatory effects. Due to its large surface area, the silver nanoparticles have better contact with microorganisms, thereby making their antimicrobial activity more efficient.

Silver is very reactive in its ionized form. The silver ions interact with the peptidoglycan cell wall, the plasma membrane, bacterial DNA, and bacterial proteins [16]. That interaction ultimately causes structural changes in bacterial cells, which leads to cell death.

4.6 Copper Oxide Nanoparticles

Copper nanoparticles have antibacterial activity, along with antifungal activity and are beneficial in controlling biofilm formation within the oral cavity. It has been demonstrated that copper oxide nanoparticles can be beneficial in dental coating to inhibit dental infections. Researchers reported that copper oxide nanoparticles inhibit bacterial growth by the process of passing through nanometric pores on the cellular membranes of most bacteria. Their size, stability, and concentration influence the bactericidal activity of the copper oxide nanoparticles.

4.7 Liposomes

Liposomes are lipid-based nanoparticles composed of amphipathic phospholipids that are made up mainly of phosphatidylcholines. Liposomes can be categorized into cationic, anionic, and neutral nanoparticles. They have unique advantages, such as nontoxic, nonimmunogenic nature, protecting drugs or siRNA-based therapeutic agents from degradation, and offering passive and active delivery of genes, proteins, peptides, and various other substances [17], [18]. Additionally, they can increase the half-life of various therapeutic agents. Liposomes are widely used to encapsulate drugs for use against various periodontal pathogens.

4.8 Solid Lipids

Solid lipid nanoparticles have some excellent properties, such as a high drug loading capacity, a large surface area, and immediate biodegradability. Solid lipid nanoparticles are made from physiological lipids, thereby diminishing the danger of toxicity [19].

4.9 Hydrogels

Hydrogels are natural or synthetic polymers with various favorable properties. These properties include a high water-absorbing capacity, ability to mimic natural living tissue, and a high porosity. The porous structure of hydrogels makes them suitable for carrying and releasing drugs (Fig. 24.3 and Table 24.4).

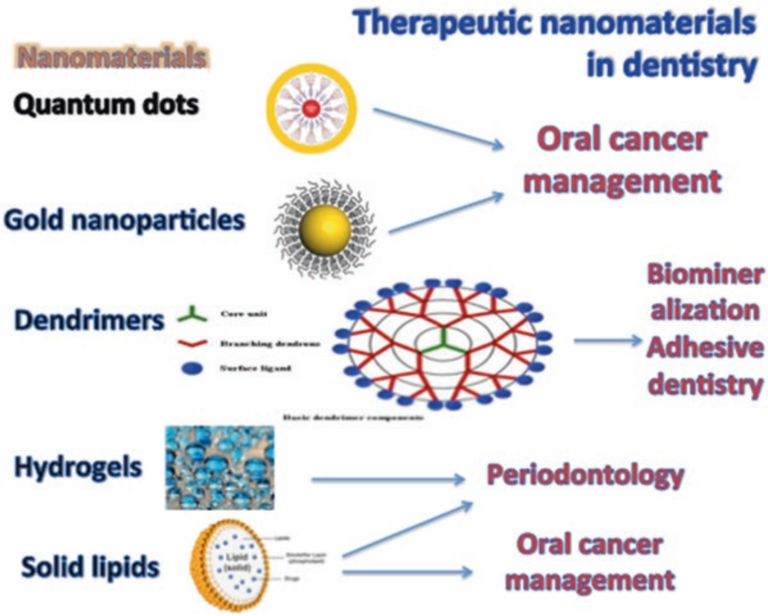

Fig. 24.3 Various types of nanoparticles and their use in dentistry

Table 24.4 Nanoparticles in dentistry

Nanoparticles	Drug	Dental application	Description	References
Chitosan	Triclosan	Local drug delivery for treatment of periodontal diseases	Local therapeutic application in periodontal diseases	[20]
PAA-poly(acrylic acid)	Penicillin		Antibacterial activity against penicillin-resistant bacteria is enhanced	[21]
PLGA	Nanohydroxyapatite and nanocollagen	To treat periodontal disease	Bone regeneration and tissue collagen regeneration	[21]
Chitosan	Silver nanoparticles		Used for infected areas, such as open wounds	[21]
Chitosan	Metronidazole	Local drug delivery for treatment of periodontal diseases	Effective against anaerobic organisms by disrupting bacterial DNA synthesis	[21]
PLGA	Methylene blue	Antimicrobial endodontic treatment	Display significant killing of *Enterococcus faecalis* biofilm species that infect root canals	[22]
PLGA	Minocycline	Drug delivery for treatment of periodontitis	To improve drug loading and treat periodontitis	[15]

5 Properties of Chitosan Nanoparticles

5.1 *Antimicrobial Properties*

Chitosan nanoparticles have antimicrobial activity against gram-negative and gram-positive bacteria. The molecular weight of chitosan influences its solubility and antibacterial activity. In small molecular weight, chitosan nanoparticles are successful in hindering the colonization of bacteria (such as *Streptococcus mutans*) on the surface of teeth while still preserving the normal oral flora. Chitosan nanoparticles of small molecular weight are able to damage the physiological activities of bacteria by penetrating the bacteria. In contrast, chitosan nanoparticles of high molecular weight have the ability of blocking the entry of nutrients by forming a film around the bacterial cells. Chitosan possesses a positive charge that interacts with the anionic groups on the bacterial cell wall, thereby causing damage to the cell wall. That interaction blocks the exchange of nutrients between the bacterial cell and the extracellular matrix. The electrostatic charges compete for calcium for specific sites in the membrane, which then leads to the leakage of cell contents and cell death. Chitosan is effective in controlling plaque in vitro by obstructing dental plaque pathogens such as *Actinobacillus actinomycetemcomitans, P. gingivalis* and *S. mutans*.

There are four main factors that influence the antimicrobial action of chitosan [23]:

- The microbial species.
- The molecular weight of chitosan, the density of the positive charge, and the hydrophobicity and hydrophilicity of chitosan.
- The soluble and solid state.
- Environmental factors such as pH, ionic forces, temperature, and time.

5.2 *Mucoadhesive Properties*

Chitosan mucoadhesion is due to the interaction between the positive charge of chitosan and the negative charge of mucous membranes. That interaction increases the adhesion to the mucosa and the time of contact for penetration of drug molecules through it. It also provides a controlled rate drug release in order to improve therapy. Additional advantages of using mucoadhesive chitosan drug delivery systems are reduced administration frequencies and a constant mucoadhesiveness. Other possible factors that play a role in chitosan mucoadhesion are, its wettability, entanglement, Van der Waal's forces, hydrogen bonding, and hydrophobic interactions.

5.3 Drug Delivery Properties

Chitosan nanoparticles can be loaded with various antibiotics, such as metronidazole, chlorhexidine, and nystatin, to distribute to periodontal tissues and treat against fungal infections and oral mucositis. Due to their high surface area and reactivity, the drug is released with more ease. Chitosan is an efficient drug delivery system due to its stability, solubility, and bioavailability, and its ability to deliver the drug to a specific site. Another advantage of using chitosan as a drug carrier is its easy elimination by metabolic degradation in the body. However, this is only applicable for chitosan nanoparticles of small molecular weight. Enzymes must degrade the large molecular weight chitosan nanoparticles. There are various mechanisms for releasing the drugs. The loaded drug can be released from chitosan by diffusion, erosion, or degradation of the chitosan nanoparticle.

5.4 Dental Applications of Chitosan Materials

Chitosan possesses unique properties that have enabled it to emerge as a material for a wide range of dental applications. Due to its nontoxicity, biodegradability, hydrophilicity, biocompatibility, and compatibility to mix with other materials, Chitosan is a favorable material for periodontal tissue regeneration because it can deliver the drug to the periodontal pocket and sustain and/or control the concentration of the drug. It has also been beneficial in modifications of dentifrices, enamel repair, adhesion and dentine bonding; for coating dental implants; and for modification of dental restorative materials [24]. Due to its ability to support viable osteoblasts, chitosan can be used as a template for bone defect restorations [25]. Furthermore, chitosan nanoparticles have been incorporated into root canal sealers in order to inhibit the penetration of microbes and to reduce biofilm formation at the dentin–root filling interface [26].

Chitosan has also been combined with various polymeric and organic substances for bone regeneration purposes. For example, chitosan–gold nanoparticles have shown to enhance osseointegration of dental implants [26]. Chitosan–gold nanoparticles conjugated with PPAR have also been used to modify dental implants, and this has led to the formation of new bone with improved mineral density and a reduction in inflammation.

In prosthetic dentistry, chitosan has also been utilized to modify glass ionomer restoratives. Other uses include antibacterial activity of dental adhesive, and antibacterial activity of composites [23].

In endodontics, chitosan has several useful applications. In vitro, chitosan was shown to improve the stability of dentin collagen, provide a sustained release of calcium ions in the root canal system, and regulate stem cell differentiation from apical papilla [23] (Table 24.5).

Table 24.5 Results of clinical study

Clinical trial phase	Treatment	Indication	Patients in trials	Response in trials and clinical status	References
IV	Scaling and systemic moxifloxacin	Aggressive periodontitis	40	Completed	NCT02125812
IV	Combination of metronidazole and amoxicillin in type 2 diabetes patients with periodontitis	Periodontitis	58	Completed	NCT02135952
II and III	Compare the efficacy of locally delivery of 1% metformin (MF), 1.2% simvastatin (SMV)	Chronic periodontitis	98	Greater pocket probing reduction (PPD) and clinical attachment level (CAL) in SMV group than MF	NCT02372656
I and II	Gingiva mesenchymal stem cell therapy	Periodontitis	30	Completed	NCT03137979
I and II	*Effectiveness of probiotic Saccharomyces boulardii*	Chronic periodontitis	31	Completed	NCT03516370
II	Effectiveness of azithromycin	Chronic periodontitis	80	Completed	NCT01921738
N/A	Evaluation of nanocrystalline hydroxyapatite silica gel	Chronic periodontitis	30	Recruiting	NCT02507596
N/A	Tooth brushing with dentifrice, and turmeric massaging	Chronic periodontitis	91	Completed	NCT02890771
II	*Nigella sativa* (Kalonji) oil	Chronic periodontitis	25	Not yet recruiting	NCT03270280
N/A	Drug delivery of *Garcinia mangostana* gel	Chronic periodontitis	50	Completed	NCT02880397

6 Future Perspectives of Nanoparticles

With nanoparticles gaining more and more popularity, it is expected to find its use in all the specializations of dentistry. In the future, there will be improvements in the diagnosis and treatment of oral cancers, in the production of nanorobotic dentifrices delivered by toothpaste or mouthwash, local anesthesia, in hypersensitivity cure and complete orthodontic realignments [27]. Nanotweezers are currently under development for the future, which can be used for cell surgery.

In future, it is believed that all dental procedures will be performed using nanorobots.

7 Conclusion

The emergence of nanotechnology in the dental field has improved dental materials and devices for oral health care. Different nanoparticles are used to prevent the attachment of biofilm to the tooth surface, which is the main cause for the development of plaque and calculus. Nanomaterials are also used in dental fillings, and as implant materials. Nanoparticles have excellent properties and some display antimicrobial properties that allow it to interact with bacteria and kill it. Nanotechnology is quickly evolving and there will be more improvements in the near future.

References

1. Camacho-Flores, B. A., Martínez-Álvarez, O., et al. (2015). Copper: Synthesis techniques in Nanoscale and powerful application as an antimicrobial agent. *Journal of Nanomaterials, 2015*, 10.
2. Bhardwaj, A., Bhardwaj, A., Misuriya, A., Maroli, S., Manjula, S., & Singh, A. K. (2014, February 26). Nanotechnology in dentistry: Present and future. *Journal of International Oral Health: JIOH, 6*(1), 121–126. PubMed PMID: PMC3959150. Received October 10, Accepted December 11.
3. Sánchez-Sanhueza, G., Fuentes-Rodríguez, D., & Bello-Toledo, H. (2016). Copper nanoparticles as potential antimicrobial agent in disinfecting root canals: A systematic review. *International Journal of Odontostomatology, 10*, 547–554.
4. Abiodun-Solanke, I. M. F., Ajayi, D. M., & Arigbede, A. O.. (2014, September–October). Nanotechnology and its application in dentistry. *Annals of Medical and Health Sciences Research, 4*(Suppl. 3), S171–S177. PubMed PMID: PMC4212373.
5. Ibrahim, A. I. O., Moodley, D. S., Petrik, L., & Patel, N. (2017). Use of antibacterial nanoparticles in Endodontics. *South African Dental Journal, 72*, 105–112.
6. Mitra, S. B., Wu, D., & Holmes, B. N. (2003, October 1). An application of nanotechnology in advanced dental materials. *The Journal of the American Dental Association, 134*(10), 1382–1390.
7. Abou Neel, E. A., Bozec, L., Perez, R. A., Kim, H. W., & Knowles, J. C. (2015). Nanotechnology in dentistry: Prevention, diagnosis, and therapy. *International Journal of Nanomedicine, 10*:6371–6394. PubMed PMID: 26504385. Pubmed Central PMCID: PMC4605240. Epub 2015/10/28. eng.
8. AlKahtani, R. N. (2018, April 1). The implications and applications of nanotechnology in dentistry: A review. *The Saudi Dental Journal, 30*(2), 107–116.
9. Schmalz, G., Hickel, R., van Landuyt, K. L., & Reichl, F.-X. (2017, November 11). Nanoparticles in dentistry. *Dental Materials, 33*(11), 1298–1314.
10. Wang, L., Hu, C., & Shao, L. (2017). The antimicrobial activity of nanoparticles: Present situation and prospects for the future. *International Journal of Nanomedicine, 12*, 1227–1249. PubMed PMID: 28243086. Pubmed Central PMCID: PMC5317269. Epub 2017/03/01. eng.
11. Sivaramakrishnan, S. M., & Neelakantan, P. (2014). Nanotechnology in dentistry—What does the future hold in store? *Dentistry, 4*, 198. https://doi.org/10.4172/2161-11221000198.
12. Shetty, N. J., Swati, P., & David, K. (2013, January 17). Nanorobots: Future in dentistry. *The Saudi Dental Journal, 25*(2), 49–52. PubMed PMID: PMC3723292. Received August 9, Revised November 20, Accepted December 17.
13. Verma, S. K., & Chauhan, R. (2014, August 1). Nanorobotics in dentistry—A review. *Indian Journal of Dentistry, 5*, 62–70.

14. Patel, J., Amrutiya, J., Bhatt, P., Javia, A., Jain, M., & Misra, A. (2018, March). Targeted delivery of monoclonal antibody conjugated docetaxel loaded PLGA nanoparticles into EGFR overexpressed lung tumour cells. *Journal of Microencapsulation, 35*(2), 204–217. PubMed PMID: 29542378. Epub 2018/03/16.eng.
15. Kashi, T. S., Eskandarion, S., Esfandyari-Manesh, M., Marashi, S. M., Samadi, N., Fatemi, S. M., et al. (2012). Improved drug loading and antibacterial activity of minocycline-loaded PLGA nanoparticles prepared by solid/oil/water ion pairing method. *International Journal of Nanomedicine, 7*, 221–234. PubMed PMID: 22275837. Pubmed Central PMCID: PMC3263414. Epub 2012/01/26.eng.
16. Mohamed, H. I. (2012, May). Current perspectives of nanoparticles in medical and dental biomaterials. *Journal of Biomedical Research, 26*(3), 143–151. PubMed PMID: 23554743. Pubmed Central PMCID: PMC3596063. Epub 2013/04/05.eng.
17. Bhatt, P., Lalani, R., Vhora, I., Patil, S., Amrutiya, J., Misra, A., et al. (2018, January 30). Liposomes encapsulating native and cyclodextrin enclosed paclitaxel: Enhanced loading efficiency and its pharmacokinetic evaluation. *International Journal of Pharmaceutics, 536*(1), 95–107.
18. Bhatt, P., Lalani, R., Mashru, R., & Misra, A. (2016). Abstract 2065: Anti-FSHR antibody Fab' fragment conjugated immunoliposomes loaded with cyclodextrin-paclitaxel complex for improved in vitro efficacy on ovarian cancer cells. *Cancer Research, 76*(14 Supplement), 2065.
19. Jain, S., Jain, S., Khare, P., Gulbake, A., Bansal, D., & Jain, S. K. (2010, August). Design and development of solid lipid nanoparticles for topical delivery of an anti-fungal agent. *Drug Delivery,17*(6), 443–451. PubMed PMID: 20486871. Epub 2010/05/22.eng.
20. Pragati, S., Ashok, S., & Kuldeep, S. (2011). Recent advances in periodontal drug delivery systems. *International Journal of Drug Delivery, 1*(1), 1–14. Epub 2011-04-20.
21. Sneha, B. (2014, January). Applications of nanotechnology in dentistry. *Research Journal of Pharmacy and Technology, 7*(1).
22. Pagonis, T. C., Chen, J., Fontana, C. R., Devalapally, H., Ruggiero, K., Song, X., et al. (2010, December 16). Nanoparticle-based endodontic antimicrobial photodynamic therapy. *Journal of Endodontics, 36*(2), 322. PubMed PMID: PMC2818330.
23. Kmiec, M. P. L., Tedesco, M. F., et al. (2017). Chitosan-properties and applications in dentistry. *Advances in Tissue Engineering and Regenerative Medicine: Open Access, 2*(4), 205–211. https://doi.org/10.15406/atroa.2017.02.00035.
24. Husain, S., Al-Samadani, K. H., Najeeb, S., Zafar, M. S., Khurshid, Z., Zohaib, S., et al. (2017, May 31). Chitosan biomaterials for current and potential dental applications. *Materials, 10*(6), 602. PubMed PMID: PMC5553419. Received May 1, Accepted May 27.
25. Jazayeri, H. E., Fahmy, M. D., Razavi, M., Stein, B. E., Nowman, A., Masri, R. M., et al. (2016, August) Dental applications of natural-origin polymers in hard and soft tissue engineering. *Journal of Prosthodontics,25*(6), 510–517. PubMed PMID: 27003096. Epub 2016/03/24.eng.
26. Virlan, M. J., Miricescu, D., Radulescu, R., Sabliov, C. M., Totan, A., Calenic, B., et al. (2016, February 9). Organic nanomaterials and their applications in the treatment of oral diseases. *Molecules, 21*(2). PubMed PMID: 26867191. Epub 2016/02/13.eng.
27. Narang, R. S., & Narang, J. K. (2015, July–September). Nanomedicines for dental applications-scope and future perspective. *International Journal of Pharmaceutical Investigation, 5*(3), 121–123. PubMed PMID: 26258052. Pubmed Central PMCID: PMC4522860. Epub 2015/08/11.eng.