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# Nanoparticles in Endodontic Irrigation - A Review

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**Abstract:** ***The main goal of the root canal treatment is the elimination of the infection from the root canal system. The complete disinfection of the root canals is challenging due to its complex anatomy. The inaccessible anatomic aberrations solely depend on irrigation for disinfection. The use of nanoparticles in the irrigants enhances the efficiency of disinfection due to their ultra small sizes, large surface area/ mass ratio, and increased chemical reactivity. This article presents a comprehensive review on the scientific knowledge that is available on the application of nanoparticles in endodontic irrigation.***

**Keywords:** Disinfection, Nanoparticles, Irrigants, Root canal treatment, Dental pulp cavity

## 1. Introduction

The presence of biofilms in the root canal has been proven by several studies [1, 2] and the bacteria are found to have invaded the depths of the dentinal tubules [3, 4]. The tissue remnants, biofilms, and infected dentin are physically eliminated by mechanical preparation [5]. A large portion of the root canal remains uninstrumented by mere mechanical preparation [6, 7]. The presence of isthmuses, accessory canals, and dentinal tubules, all of which can harbor bacteria and biofilms have made the complete root canal disinfection a challenge [8]. Although current chemical irrigants, such as chlorhexidine (CHX) and sodium hypochlorite (NaOCl), are effective antimicrobials, they have limited efficacy to penetrate the dentinal tubules to provide a complete root canal disinfection [9, 10]. Several studies have been done to devise an ideal solution as an adjuvant to root canal treatment as each product has different physical properties, antimicrobial effects and biocompatibility [11]. Till today, the data based evidence shows that for the past 4-5 decades there is no decrease in the rate of treatment failure beyond 18-26% despite the advancements in the treatment strategies[12-14]. The reason for this could be due to the inability or inefficiency of the current technologies to handle the disease sequel completely [15]. Besides this, several challenging factors are emerging and making the conservative management of infections by the use of topical and systemic antibiotics ineffective [16, 17]. Furthermore, the use of antibiotics is highly debatable, as ‘‘In the ongoing war against antibiotics, the bacteria seem to be winning, and the drug pipeline is verging on empty’’ [18].

The potential benefits of nanotechnology in the biomedical field have become widely accepted for the generation of promising strategies to treat various bacterial diseases. A wide range of nanoparticles (NPs) with antimicrobial activity have been developed [19,20]. They are responsible for the anti-bacterial effect by the electrostatic interaction between positively charged nanoparticles and negatively charged bacterial cells [21]. In addition, nanoparticles may change the chemical and physical properties of dentin and reduce the bacterial strength of adhesion to the dentin itself [22]. These nanoparticles by virtue of their size can be delivered into complex anatomies. Based on the composition, nanoparticles are generally classified as either naturally occurring or synthetic [Table 1]. They are further categorized as organic or inorganic in nature. Based on the shape, they are classified as particles, spheres, tubes, rods, plates, and so on. Functionalized nanoparticles are those that have a core of one material and additional molecules or proteins bonded on its surface or encapsulated within. Depending on the specific applications, nanoparticles can be functionalized with peptides, drugs, photosensitizers, and so on [23, 24]. The core nanoparticles can be used as a convenient surface for molecular assembly and may be composed of inorganic or organic materials. An additional layer of linker molecules is required to proceed with functionalization wherein the linker molecules have reactive groups at both ends that bind various moieties like biocompatibles (dextran), antibodies, fluorophores, and so on onto the core nanoparticle.

Advanced disinfection strategies are being devised and tested to overcome the shortcomings of the existing technologies in the elimination of biofilm from the root canals. Newer antibacterial nanoparticles that have been introduced at the laboratory levels with significant potential to eradicate biofilms when used in root canal irrigation have been reviewed here, aiming to provide comprehensive scientific knowledge for the use of nanoparticles in irrigation.

**Table 1:** Nanoparticles available based on the composition

| *Inorganic* | *Metallic* | *Polymeric* | *Quantum dots* | *Functionalised with* |
|---|---|---|---|---|
| Zinc oxide | Gold | Alginate | Cadmium sulphide | Drugs |
| Iron oxide | Silver | Chitosan | Cadmium selenide | Photosensitisers |
| Titanium dioxide | Iron | | | Antibodies |
| Cerium oxide | Copper | | | Proteins |
| Aluminium oxide | Magnesium | | | |
| Bioactive glass | | | | |

**Ideal requirements of an endodontic irrigant [25]**

1) Broad antimicrobial spectrum
2) High efficacy against anaerobic and facultative microorganisms organized in biofilms
3) Ability to dissolve necrotic pulp tissue remnants
4) Ability to inactivate endotoxin
5) Ability to prevent the formation of a smear layer during instrumentation or to dissolve the latter once it has formed.
6) Systemically nontoxic when they come in contact with vital tissues, non-caustic to periodontal tissues, and with little potential to cause an anaphylactic reaction.

Till date, there is no antimicrobial irrigant that could perform all these functions single-handedly. Therefore, combinations of two or more irrigants are used to achieve a bacteria-free root canal space prior to filling (25). The newer disinfection strategies should aim to circumvent these challenges by eliminating biofilm bacteria not only from the main canals but also from the uninstrumented portions and anatomical complexities of the root canal system without inducing untoward effects on dentin substrate and periradicular tissue. Development of novel antimicrobial delivery systems to improve the pharmacological characteristics of the applied antibacterial agents has been considered as a part of the solution for this problem [26].

**Advantages of nanoparticles over conventional irrigants**

Owing to their innovative functional properties, nanoparticles are the centre of attention in the past few decades as a novel strategy. These systems can greatly improve the therapeutic efficacy of pharmaceutical products by producing more favorable drug bioavailability, serum stability and pharmacokinetics. According to the literature, nano-based formulations provide better penetration and allow slow and controlled release of active ingredients at target sites [27–30]. When compared with their conventional counterparts the high surface areas of nanoparticles and consequently higher concentrations at target site are the most effective factors in antimicrobial behavior [31,32]. Nanoparticles have broad applications in infection control strategies, especially in the complex oral cavity environment by using their biocidal, anti-adhesive and delivery capabilities. Furthermore, the antibacterial potential of some nanoparticles, like those of metals, are of great importance in strategies used to eradicate chronic infections [26]. And now, this review is going to concentrate on the various nanoparticles studied to be used in endodontic irrigation.

**Metallic and Inorganic nanoparticles in irrigation**

Metallic nanoparticles of copper, gold, titanium, and zinc have attracted particular attention, with each of them having different physical properties and spectra of antimicrobial activity [33, 34 ]. It is known that magnesium oxide (MgO) and calcium oxide (CaO) slurries acted upon both gram-positive and gram-negative bacteria in a bactericidal manner [35], while zincoxide (ZnO - average 60-100 nm size) slurry acted in a bacteriostatic manner and exhibited stronger antibacterialactivity against gram-positive than gram-negative bacteria [35]. The antibacterial powders of magnesium oxide (MgO), calcium oxide (CaO), and ZnO generated active oxygen species, such as hydrogen peroxide and superoxide radical, which is responsible for their antimicrobial effect. These nanoparticles of metallic oxides with their high surface area and charge density exhibited greater interaction with bacteria and subsequently produced markedly high antibacterial efficacy [36, 39]. Furthermore, it is apparent that bacteria are far less likely to acquire resistance against metallic nanoparticles than other conventional antibiotics. Heavy metal ions are known to have different cytotoxic effects on bacterial cell functions [33,37]. Copper ions may induce oxidative stresses [33] and affect the redox cycling, resulting in cell membrane and DNA damages. Zinc ions applied above the essential threshold level inhibit bacterial enzymes including dehydrogenase [38], which in turn impede the metabolic activity [33]. Silver ions (average particle size of 40-60 nm) inactivate proteins and inhibit the ability of DNA to replicate [34]. However, few studies have shown that the antibiofilm efficacy of Ag nanoparticles was significant when applied as a medicament and not as anirrigant [40]. Irrigation solutions containing AgNP@SiO2 are highly promising for applications needing a long-term antimicrobial effect lasting upto 7 days due to sustainable availability of soluble silver [41]. Nanoparticles synthesized from the powders of Ag, CuO, and ZnO are currently used for their antimicrobial activities. The electrostatic interaction between the positively charged nanoparticles and negatively charged bacterial cells and the accumulation of large numbers of nanoparticles on the bacterial cell membrane have been associated with the loss of membrane permeability and cell death [37]. A newer concept of Nanocatalyst using $FeO/H_2O_2$ combination for disinfecting the root canal was studied by Bhukari et al and was found to have increased antimicrobial efficacy with greater depths of penetration into the dentinal tubules [42]. Bioactive glass (BAG - average size of 20-60 nm) consists of SiO2, Na2O, CaO2, and P2O5 at different concentrations and depends on the local physiological changes like high pH, osmotic effect and Ca-P precipitation for its antibacterial effects [41]. The micrometric counterpart of BAG was found to have a better antibacterial efficacy than its nanometric counterpart. Planktonic bacteria were killed significantly better compared with biofilm bacteria [42, 43].

**Polymeric nanoparticles in irrigation**

Chitosan is known as a versatile biopolymer that could be synthesized in various forms such as powder (micro- and nanoparticles), capsules, films, scaffolds, hydrogels, beads, and bandages[44]. Nanoparticles of chitosan (average particle size of 70 nm) have been developed mainly for drug/gene delivery applications. A more commonly proposed mechanism is contact-mediated killing that involves the electrostatic attraction of positively charged chitosan with the negatively charged bacterial cell membranes. This might lead to the altered cell wall permeability, eventually resulting in rupture of cells and leakage of the proteinaceous and other intracellular components [45]. Chitosan has excellent antibacterial, antiviral, and antifungal properties [46]. In case of bacteria, gram-positive bacteria were more susceptible than gram-negative ones [46, 47].

**Functionalized antimicrobial nanoparticles**

*Functionalization* is the process of modifying a nanoparticle by altering the surface composition, charge, and structure of the material wherein the original bulk material properties are left intact to perform a specialised task [48, 49]. Nanoparticle-based photosensitizers have been considered to potentiatephotodynamic therapy (PDT) efficacy [50, 51]. As mentioned in the review by Kishen [52], the combination of nanoparticles with photosensitizers could be achieved by

1. Photosensitizers supplemented with nanoparticles
2. Photosensitizers encapsulated within nanoparticles
3. Photosensitizers bound or loaded to nanoparticles
4. Nanoparticles themselves serving as photosensitizers [52]

The susceptibility to PDT was found to be influenced by the species of bacteria in the root canal system and their growth mode in a dose-dependent manner [53]. Furthermore, dentin, dentin matrix, pulp tissue, bacterial lipopolysaccharides, and bovine serum albumin were found to significantly decrease PDT antimicrobial efficacy [54]. An effort to enhance the photodynamic effect by encapsulating and delivering MB in polymeric nanoparticles appears promising [55]. Other strategies include the use of a photosensitizer solvent [56], efflux pump inhibitors [53], or photoactivated functionalized chitosan nanoparticles for disinfection and stabilization of the dentin matrix [57]. Methylene blue–loaded poly(lactic-co-glycolic) acid (MB-PLGA)

Nanoparticles (average particle size of 150-250 nm) have been tested in vitro on E. faecalis biofilm and human dental plaque bacteria in combination with PDT [55]. Similarly, photosensitizer-bound polystyrene beads with rose bengal(RB) as a photosensitizer were used by Bezman et al after activation with light, improving bacterial elimination with reactive oxygen species. Functionalization of various nanoparticles showed an overall increase in efficacy along with rapid action against bacteria [58]. The photosensitizer functionalized nanoparticles could be used as a final root canal disinfection strategy, whereas functionalized BAG and AG-NPs still need to be considered only as long-term root canal medicament. Optimization of the concentration and application method of these functionalized nanoparticles is under constant progress [19].

**Delivery Of Nano- Particles In The Tubules:**

*Research To Generate High Intensity Focused Ultrasound [HIFU]*

In this experiment conducted by Shrestha A et al high-speed jetting of collapsing cavitation bubbles produced by HIFU has been tested for the delivery of antibacterial nanoparticles into the dentinal tubules.The basic principle behind the application ofultrasound is the formation of cavitation bubbles. These bubbles are in a non-equilibrium state and will oscillate and collapse. The violent bubble collapsewith high-speed jetting could be used beneficially (for example, for the removal of biofilm), or could cause undesirable collateral damage (for instance,vascular damage or hard and soft tissue damage in ultrasonic therapy. One way of generating an oscillating bubble is via the ultrasonic system used in root canal treatment known as endosonics (coined by Martin and Cunningham). In an endosonic system, a frequency of between 25 and 40 kHz is employed. The activated endosonic file is expected to produce cavitation, acoustic streaming, and heat within the irrigating solution. The rapid movement of fluid in a circular or vortex-like motion around a vibrating instrument such as the endosonic file is described as acoustic micro-streaming. The acoustic microstreaming leads to energy dispersal which causes radiating pressure and subsequently leads to shear stresses imposed along the root canal wall, therebydislodging the debris and adherent bacterial cells. HIFU may act as a supplementary method to reach the bacteria persisting within the anatomical complexities and dentinal tubules, thus to improve the success of root canal disinfection. Thenanoparticles used in the study possessedantimicrobial properties and biocompatibilitywhich have also been investigated in drug delivery and cancer therapies, and for the treatment of bacterial infections. These chitosan nanoparticles are small enough (<100 nm) to be delivered into the root canal complexities and dentinal tubules.This study was conducted in order to understand the basic mechanism of HIFU. The experiments were conducted in two stages. Characterization experiments were carried out using a spark bubble experiment to test the bubble's efficiency to propel particles through channels. These experiments were designed to help in the understanding of the mechanism involved in the delivery of nanoparticles into dentinal tubules. High speed photography is used to capture the transient bubble dynamics. Experiments were conducted to further reconfirm the bubble dynamics observed in the characterization experiments using human dentine specimens to deliver antibacterial nanoparticles into the dentinal tubules by using the HIFU system [59].

**Clinical Use in the Delivery of Nanoparticles High Intensity Focused Ultrasound**

To apply HIFU in endodontics, focused ultrasound should be generated inside the canal. This can be achieved by using piezo ceramic crystal on the tip of a non-vibrating file or extracorporeal use of HIFU with HIFU device touching only the tooth surface [59].

**Photodynamic Therapy Methylene blue loaded polylactico glycolic acid nanoparticles**

The irradiation source was a diode laser ( BWTEKInc, Newark, DE) with an output of 1 W and a wavelength of 665 nm. Due to the production of singlet oxygen when the sensitizer is activated with the laser there is photodestruction of root canal bioflims [55].

**Shortcomings**

Field emission scanning electron microscopic (FESEM) showing nanoparticles as clumps which formed a coating along the tubule walls. Antibacterial nanoparticles are found to be non uniform along the lumen of dentinal tubules and nanoparticles showed tendency to form aggregates. To help prevent aggregation of nanoparticles, stabilizing agents that bind to the entire nanoparticles surface can be used; these include oligo and polysaccharides, sodium dodecyl sulphate, polyethylene gycol and glycolipids [60].

## 2. Conclusion

The antibiofilm efficacy of endodontics can be increased by the utilisation of nanoparticles in irrigation. Optimization of the physical, chemical and biological characteristics of nanoparticles have to be done when their therapeutic efficacy is considered with additional concern on the tissue-specific factors at the site of infection and the method to deliver the nanoparticles effectively in the target tissue. Functionalized nanoparticles via surface modifications would provide the opportunity to deliver drugs/chemicals to the site of infection in order to selectively interact with biofilm and bacteria. Newer multifunctional nanoparticles are being developed based on the clinical requirements in collaboration with engineers, clinicians, and biologists. As only the positive effects of these antibacterial nanoparticles are known and the hazards and shortcomings are slowly exposed, this new technology in endodontics should be enthusiastically welcomed with caution.It is important todevelop the safety usage guidelines to deal with the toxicity especially when dealing with newer antimicrobial nanoparticles.

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