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Special Focus on Materials

Review

Advances in Dental Materials through Nanotechnology: Facts, Perspectives and Toxicological Aspects

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Nanotechnology is currently driving the dental materials industry to substantial growth, thus reflecting on improvements in materials available for oral prevention and treatment. The present review discusses new developments in nanotechnology applied to dentistry, focusing on the use of nanomaterials for improving the quality of oral care, the perspectives of research in this arena, and discussions on safety concerns regarding the use of dental nanomaterials. Details are provided on the cutting-edge properties (morphological, antibacterial, mechanical, fluorescence, antitumoral, and remineralization and regeneration potential) of polymeric, metallic and inorganic nano-based materials, as well as their use as nanocluster fillers, in nanocomposites, mouthwashes, medicines, and biomimetic dental materials. Nanotoxicological aspects, clinical applications, and perspectives for these nanomaterials are also discussed.

'Nanodentistry'

Nanotechnology (see Glossary) has induced the generation of innovative and cost-effective dental materials and devices, enabled the understanding of biomechanical properties of enamel (e.g., fracture behavior and crack propagation), and contributed to the improvement of bone-tissue regeneration as well as the diagnosis and prevention of pathologies [1,2]. A useful definition of nanotechnology with no arbitrary size limitation is: 'the design, characterization, production/application of structures, devices, and systems by controlled manipulation of size and shape at the nanometer scale (atomic, molecular, scale) that produce structures, devices, and systems with at least one novel/superior characteristic or property' [3]. Nevertheless, national and international institutions are looking for an appropriate size-range definition to generate guidelines for the nanotechnology field – at least one of the dimensions of the material lie between 1 and 100 nm. The European Commission defines nanomaterials as those with 'natural, incidental or manufactured materials containing particles in non-binding states, agglomerates or aggregates in which 50% or more of the total particles size distribution by number lie in a range between 1 and 100 nm' [4]. The US FDA excludes in its definition any naturally-existing substances at small scales, such as microorganisms or proteins [5].

Trends

Nanotechnology is improving dental materials and overall oral treatment.

Nanomaterials used in dentistry may provide mechanical reinforcement, improve aesthetic aspects, and induce antimicrobial and therapeutic effects.

Striking recent advances in organic nanotechnology for dentistry have come from polymer-based nanomaterials including modified chitosan, polymeric nanogels, and dendrimers.

Emerging nanocomposites for dentistry comprise fillers based mainly on carbon nanomaterials, nano-silica, nano-titania, and nano-zirconia.

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Dental materials have evolved with the advent of nanotechnological research focusing on the production and application of nanoparticles with high-quality structural characteristics. The incorporation of a myriad of nanoparticles into dental materials (e.g., quartz, colloidal silica, zirconia, zinc oxide) represents an innovation by manufacturers to improve the chemical and physical properties of these materials [6]. This area of research has been coined 'nanodentistry', defined as the 'science and technology of diagnosing, treating and preventing oral and dental diseases, relieving pain, preserving and improving dental health using nanostructured materials' [7]. The propensity of research activity in this area is reflected by the number of patent applications (151) over the past decade [8]. Although an overall perspective of nanotechnology has been presented in recent reviews [7,9–16], little discussion has been provided on the characteristics, properties, and mechanisms through which nanomaterials act when they are utilized in dental materials. This review provides a discussion on the state-of the-art in nanodentistry together with the most recent advances in this field, as well as toxicological aspects of the use of nanomaterials in dentistry. Nanodentistry is reviewed here from the scientific and technological perspectives by following a property–function–application basis that addresses most of the recent advances on the use of (i) **polymeric** (e.g., polyethylene glycol, solid lipids, nanogels, dendrimers, chitosan); (ii) **metallic** (e.g., silver, gold, copper); and (iii) **inorganic nano-based materials** (e.g., zirconia, silica, titanium dioxide, hydroxyapatite, quantum dots, nanocarbons). Because of growing concerns about environmental and human exposure to nanomaterials, this review also provides discussion of the toxicological aspects of the use of nanomaterials in dentistry.

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Antimicrobial Dental Nanomaterials

Silver Nanoparticles (AgNPs)

Silver-based nanomaterials are effective against biofilms [17–19] because they can attack multiple sites within the cell at a very low concentration (0.5–1.0%) to prevent bacterial growth (Box 1). A comparative study evaluated the antibacterial effects of chlorhexidine, silver, titanium dioxide (TiO_2), and silicon dioxide (SiO_2) nanoparticles (AgNPs, ~60 nm; TiO_2 NPs, ~23 nm; SiO_2 NPs, 14 nm) on *Streptococcus mutans* [20], and demonstrated that $AgNO_3$ had the most efficient bactericidal effect, followed by AgNPs.

On the antibacterial mechanism of silver nanoparticles, proteoglycans present inside the bacteria cells and on the membrane appear to act as binding sites for AgNPs and silver ions [21]. Furthermore, silver ions can interact with sulfuryl groups during protein synthesis, thereby interfering with the replication of bacterial DNA (Figure 1) [22].

In dentistry, fundamental aspects must be considered during the preparation of AgNPs, such as: (i) diffusion of nanoparticles into a plaque biofilm exhibits an inverse relationship between size and effectiveness, such that nanoparticles larger than 50 nm cannot penetrate the biofilm [23]; and (ii) negatively charged nanoparticles have difficulty in diffusing through the biofilm, possibly due to the presence of carboxyl and phosphoryl groups on the bacteria surface that render the cell surface electronegative [24]. The toxicity of AgNPs was found to be directly related to the activity of free Ag ions released into the medium [25,26]. A further concern exists regarding the capacity of AgNPs to cross the blood–brain barrier through trans-synaptic transport, with consequent accumulation in the brain [27]. *In vitro* studies showed that AgNPs decrease mitochondrial function in murine neuroblastoma cells [28], hepatic cells [29], human skin carcinoma [30] and human epidermal keratinocytes [31]. Other *in vivo* studies demonstrated the influence of these nanoparticles on oxidative stress processes, myocardial infarction, thrombosis, and inflammation [25,32].

Zinc Oxide-Based Nanoparticles (ZnONPs)

Zinc has been also used in dentistry for many years as the major filler component of dental cements. Zinc ions exhibit effective antibacterial activity and this effect is higher when zinc oxide