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Dental Medicine Nanosystems: Nanoparticles and their use in Dentistry and Oral Health Care

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Abstract

The major goal in dentistry and oral health care is maintaining the health of oral tissues. Thus, to achieve this goal, the advances in nanosciences and nanotechnology have paved the way to approach this goal. The application of these nanotechnologies to dental medicine have given rise to nanodentistry, whitch is an innovative branch of science. Many studies indicate extensive application of the medical nanosystems in numerous fields of nanodentistry such as prevention, diagnosis, therapeutic, restoration and tissue regeneration. The lattery, cover all dentistry specialties such as restorative dentistry, periodontics, endodontic, orthodontics, prosthodontics, oral implantology and regenerative dental Medicine. These dental Medicine nanosystems as nanostructred materials constitute new innovative nanoproducts that make possible the maintenance of oral health care in a very precise, safe and effective way. The objective of this review is to expose briefly, the recent advances in these dental Medicine nanosystems, especially in nanoparticles and nanoparticles-based nanomaterials. In addition, the article sets out to describe the various potential applications of this type of nanostructured materials and the challenges they present in clinical, cosmetic and esthetic dental and oral health care.

Keywords: Dental Medicine Nanosystems; Nanodentistry; Nanoparticles; Nanomaterials; Oral Health Care

Introduction

Nanotechnology is the engineering of functional systems by controlling atoms and molecules to achieve effective, complete control of the structure of matter with new functions. The nanotechnology tools and ideas allow to create a new nanosystem with novel, physico-chemicals, mechanicals, and biological properties. However, the applications of these nanotechnologies has rapidly expanded into all areas of health care science including that of odonatological science [1]. Nanotechnology aided in processing a variety Dental Medecine Nanosystems (DMN) with innovative applications. Nanosystems means the assembly of nanoscale components for the purpose of performing a function. In the literature, nanosystems are described as manufactured nanostructured particles (nanoparticles) and nanostructured materials (nanomaterials) or their combination.The nanomaterials may have intrinsic properties related to their structures and their components or develop new properties related to the simple structuring caused by the incorporation of the nanoparticles. In the recent years, various advances in engineering of nanoparticles and nanomaterials or their combination, have allowed the development of a new innovative DMN. The advances in the applications of these DMN cover all dentistry specialities namely restorative dentistry [2], periodontics [3], endodontic [4], orthodontics [5-6], prosthodontics [7], oral implantology [8-9], regenerative dentistry [10]. They also cover dental fields such as prevention, diagnosis, therapeutic, restoration and tissue regeneration [11]. DMN are numerous, varied and have greatly extended. This field has been the subject of potential in a wide spectrum of dental industry and oral health care. The present review, focuses on the following DMN: nanoparticles [12-13-14], nanoparticles-based nanomaterials [15-16-17-18]. Nanoparticles are divided into, organic nanoparticles [19], inorganic [20] and hybrids [21]. In this regard, they are often used in dentistry and oral health care in free or incorporated form. Dental materials (metals, composites / resin-composites and polymers) are used as restorative systems, adhesives and bonding systems, cement and sealant systems and tissue regenerative systems. The incorporation of nanoparticles in dental materials proves to be very promising as it makes it possible to obtain new DMN systems. Hence, it will improve the functional and structural properties of dental materials, while optimize clinical, cosmetic and esthetic dental and oral health care performances [22]. On the other hand, recently, the nanosafty of the inorganic nanoparticles for use in diverse biomedical applications including dentistry was investigated. The results of which are encouraging and emphasise the need for more precise and more detailed studies [23].

The aim of this review is to demonstrate and to describe the recent advances in the nanoparticles and their incorporation into dental nanomaterials. In addition, view their potential applications for prevention, therapeutic, restoration, tissues regeneration and diagnosis.

Dental Prevention and Prophylaxis Applications

Tooth wear is a dental disease and includes tooth erosion and toothloss. The comprehension of the main oral problems and the challenges related to DMN in the oral environment and this constitutes the basis for developing innovative and new nanoproduct that can provide an improved oral tissue protection. This could be beneficial especially for improving the effectiveness of preventive therapy for dental pathologies and oral diseases. Currently, established prevention of dental plaque relies heavily on tooth-brushing and the strengthening of tooth enamel by fluoride. Therefore, the development of enhanced dental medicine nanosystems for oral hygiene is of paramount importance in increasing the protection of the teeth and of the oral cavity from detrimental processes [24]. These developments concern nanoparticles and nanoparticles-based materials, in particular, aspects related to preventing the formation of dental plaque, biofilm and primary, secondary infections. However, the organic and inorganic nanoparticles were used in free or incorporated forms, and several strategies are used to design these dental prevention nanostructured materials such as dental medicine nanosystems as show as in **Figure 1**. On the other hand, the prevention of the biofilm development concernes dental equipment and this is the case in dental unit water lines (DUWL) [25]. It was reported that the problem of the susceptibility of biofilm development and bacterial growth in DUWL, leads to water contamination, which causes health and ecological effects. Overall, recent advances in the design and use of these DMN for dental prevention and prophylaxis are described in **Table 1 and 2**.

Figure 1: Illustration of Dental Medicine Nanosystems design and the strategies of their use for preventive, therapeutic, restoration, tissues regeneration and theirs combination

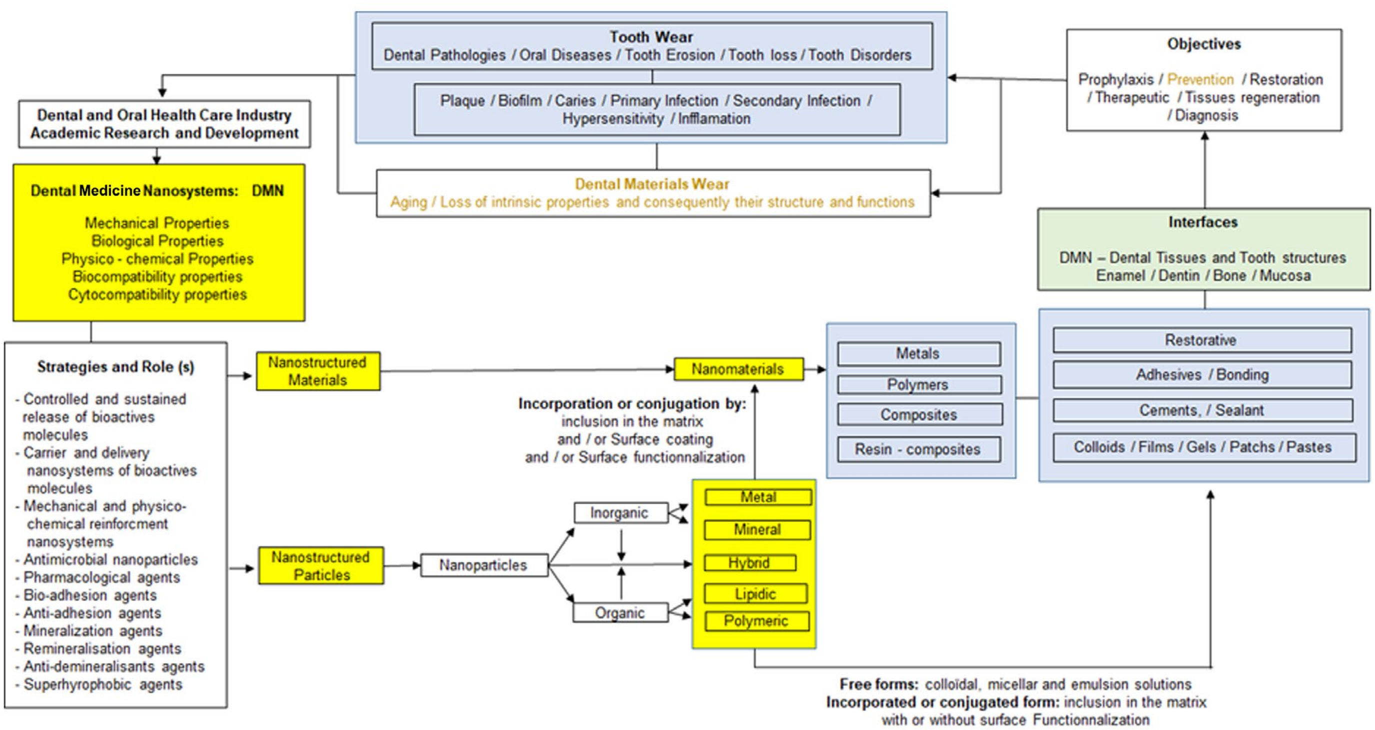

Table 1: Use of nanoparticles (NPs) for dental prevention treatments / Prophylactic prevention.

	Type and Composition		Form		Aim (s) and Strategy	Reference (s)
	Polymer	Lipid	Free	Incorporated		
Organic nanoparticles	Chitosane: BA-NPs			Varnich (Sodium Fluoride: MA) (Miswak, Propolis): PA	- Incorporation of NPs by inclusion in matrix - Bioadhesiion into dental tissues - Antibacterial effect - Mineralisation effet - Sustained and release of bioactives molecules delivery nanosystem - Caries prevention by demineralisation inhibition	Wassel et al., 2017 [42]
			Colloidal Solution (Sodium Fluoride: MA)		- Bioadhesion into dental tissues - Sustained and release of bioactives molecules delivery nanosystem - Low and continuous release of fluoride at pH5 - Protection against caries development by miniralisation	Nguyen et al., 2017 [43]
		Solid Lipid Nanoparticles (SLN)		Transmucosal patch (TP) (Diclofenac diethylamine / DDEA): PA	- Incorporation of NPs by inclusion in matrix - TP loaded with DDEA-SLN applied at the gingival site immediately after dental surgery has the potential to produce therapeutic relief locally which is prolonged 24h - Sustained and release of bioactives molecules delivery nanosystem	Malviya et al., 2015 [44]
		Phosphatidylcholin (PC) Cholesterol (CHOL): PC-CH-liposomes	Colloidal Solution		- Bioadhesion into dental tissues - PC/CHOL liposomal formulations can be used for prophylactic or therapeutic treatments in the oral cavity - Sustained and release of bioactives molecules delivery nanosystem	Cadinoiu et al., 2014 [33]

__Legend:__ **NPs:** Nanoparticles; **MA:** Memineralisant agents; **PA:** Pharmacological agents; **ADA:** Anti-demineralisant agents; **BA:** Bioadhesive agents; **RA:** Remineralisant agents; **AAA:** Anti-adhesion agents.

Table 2: Use of nanoparticles (NPs) for dental prevention treatments / Prophylactic prevention.

	Type and Composition		Form		Aim (s) and Strategy	Reference (s)
	Metal	Mineral	Free	Incorporated		
Inorganic naoparticles	Copper Oxide (CuO-NPs): PA		Colloidal Solution		- Antimicrobial NPs - Potential bactericidal activity - Preventing dental caries or dental infections.	Amiri et al., 2017 [45]
	Zirconium (ZrO_2-NPs): PA			Bioactive resins	- Incorporation of NPs by inclusion in matrix - Antimicrobial NPs - Antibacterial effect - Anticaries	Fathima et al., 2017 [46]
	Silver (Ag-NPs)		Colloidal Solution		- Antimicrobial NPs - Antibacterial effect - Antibiofilm in dental unit water lines - Prevention of water contamination	Gitipour et al., 2017 [25]
		Calcium carbonate (CaCO3): RA-NPs		Toothpaste	- Incorporation of NPs by inclusion in matrix - Sustained and release of bioactives molecules delivery nanosystem - Reduce or prevent tooth erosion - Remineralize initial enamel lesions	Dizaj et al., 2015 [47]

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Dental Therapeutic Applications

Dental therapeutic treatments can have a triple purpose, preventive therapy, curative therapy and tissues regenerative therapy. The innovative therapeutic nanostructured materials, as nanoparticles or nanoparticles based nanomaterials was recently reviewed [22]. However, their use for dental applications have undergone extensive investigations due to their potential antimicrobial effect. In this regard, the exploitation of their toxic properties to bacteria, fungi and viruses as well as their incorporation into dental materials in order to control oral infections was reported [19-26-27-28-29-30-31-32-33]. Accordingly, all these studies, have reviewed the importance of this antimicrobial effect of these nanoparticles whether in free form or incorporated form. Thus, the therapeutic nanostructured materials are a real therapeutic alternative in dentistry. Several strategies are used to design and to formulate this nanostructured materials for the treatment of dental and oral diseases. Regardingly, **Figure 1** illustrates the design of the therapeutic dental nanostructured materials. In addition, the recent studies reflect recent advances in DMN for dental therapeutics applications (combination of preventive therapy and curative therapy) are described in **Table 3 & 4**. On the other hand, concerning tissue regenerative therapy, the understanding of the cell biological processes underlyies development and regeneration of oral tissues and leads to novel regenerative approaches and strategies. However, the recent advances in regenerative dentistry, by using stem cells, signaling molecules, growth factors molecules, nanomaterials and nanoparticles are reported [10-37-38-39]. Thus, the overall, recent advances in the use of nanoparticles for dental tissues regenerative applications are described in **Table 5.**

Table 3: Use of nanoparticles (NPs) for dental therapeutic treatments / Prevention therapy and Curative therapy

	Type and Composition		Form		Aim (s) and Strategy	Reference (s)
	Polymer (s)	Co-polymer (s)	Free	Incorporated		
Organic nanoparticles	Chitosan (C-NPs): BA Alginate (A-NPs): BA			Gel	- Incorporation of NPs by inclusion in matrix - Sustained and release of bioactives molecules delivery nanosystem - Bioadhesiion into dental tissues - C-NPs more cytocompatible - A-NPs more stable in salivary environnment	Pistone et al., 2017 [48]
Organic nanoparticles	Chitosan: BA-NPs			Film (Calcium hydroxide $Ca(OH)_2$) (Propolis): PA	-- Incorporation of NPs by inclusion in matrix - Sustained and release of bioactives molecules delivery nanosystem - Bioadhesiion into dental tissues - Antibacterial effect - Antibiofilm effect - Potential ability to kill bacteria in short and long term exposure	Del Carpio-Perochena et al., 2017 [49]
Organic nanoparticles	Poly(lactic-*co*-glycolic acid) (PLGA-NPs)		Colloidal solution (Chlorhexidine (CHX): PA)		- Sustained and release of bioactives molecules delivery nanosystem - Penetration inside dentinal-tubules of demineralized dentin-substrates and resin-dentin interface - Antimicrbial effect - CHX-PLGA-NPs show, low cytotoxicity, slow degradation and gradual CHX release profiles, delivered efficiently inside dentinal-tubules structure, even after bonding-resins infiltration and were attached / retained on collagen-fibrils - Bioadhesion effect	Priyadarshini et al., 2017 [50]
Organic nanoparticles		p(DMAEMA)-*b*-p(DMAEMA-*co*-BMA-*co*-PAA): BA-NPs	Micellar solution (Farnesol : PA)		- Sustained and release of bioactives molecules delivery nanosystem - Bioadhesion effect - Cationic and acidic pH-responsive NPs - Antibacterial effect - Enhanced topical pH-responsive drug release - High affinity for dental and biofilm surfaces - High binding capacity to hydroxyapatite and dental pellicle emulating surfaces - Greater antibiofilm efficacy *in situ*	Zhou et al., 2016 [51] and Horev et al., 2015 [52]

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Table 4: Use of nanoparticles (NPs) for dental therapeutic treatments / Prevention therapy and Curative therapy

	Type and Composition		Form		Aim (s) and Strategy	Reference (s)
	Metal	Mineral	Free	Incorporated		
Inorganic naoparticles		Mesoporous silica (SiO_2-NPs) (baicalin (BI): PA baicalein (BE): PA)	Colloidal solution		- Anti-inflamatory effect - Sustained and release of bioactives molecules delivery nanosystem - *In vitro* BE-NPS exhibits notable anti-inflammatory effects in gingival epithelial cells through effective release and cellular internalization approaches	Li et al., 2017 [53]
Inorganic naoparticles	Silver (Ag-NPs): PA			Dicarboxylic cellulose film	- Sustained and release of bioactives molecules delivery nanosystem - Antimicrobial NPs - Excellent antibacterial activity	Salama et al., 2017 [54]
Inorganic naoparticles	zinc oxide (ZnO-NPs): PA Cooper (Cu-NPs): PA		Colloidal solution With Chlorhexidine (CHX): PA		- Antimicrobial NPs - Synergistically antibacterial and anti-biofilm effects	Afra et al., 2017 [55]
Inorganic naoparticles		Silicon dioxid (SiO_2-NPs)		Nanofilm (Poly(ethylene terephthalate)-glycol and Silsesquioxane)	- Incorporation of NPs by inclusion in matrix - Bioadhesion effet - Antibacterial property related to the superhydrophilicity of the film	Lin et al., 2016 [56]
Inorganic naoparticles		Maghemite (M-NPs)	Colloidal solution		- Anti-hypersensitivity effect - Polyethylene-glycol (PEG): coating and functionnalisation of NPs surface - Superparamagnetic PEG-M-NPs navigated inside the dental tubules via an external magnetic field - Potential for reducing the permeability of dental tubules by occluding the open tubular area and they could deliver other therapeutic agents inside the tubules	Dabbagh et al., 2014 [57]

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Table 5: Use of nanoparticles for dental tissues regenerative / Tissues regenerative therapy

	Type and Composition		Form		Aim (s) and Strategy	Reference (s)
	Metal	Mineral	Free	Incorporated		
Inorganic naoparticles	Gold (Au-NPs)			calcium phosphate cement (CPC)	- Incorporation of Au-NPs improved cells behavior on CPC, including better cell adhesion and proliferation, and enhanced osteogenic differentiation - Au-NPs-CPC enhanced the osteogenic functions of cells (hDPSCs) and as bioactive additives thus enhance bone regeneration	Xia et al., 2017 [96]
		Calcium silicate (Ca_2SiO_4-NPs) (Gentamicin and FGF-2)	Colloidal Solution		- Sustained and release of bioactives molecules delivery nanosystem - Endodontic materials for biocompatible and osteogenic dental pulp tissue regenerative - Used as drug carriers to maintain sustained release gentamicin and FGF-2 - The Ca_2SiO_4-NPs stimulate more odontogenic-related protein than calcium silicate matrice because of the FGF-2 release	Huang et al., 2017 [97]
	Gold (Au-NPs)			Titanium implants	- Antimicrobial NPs - The Au-NPs were osteogenic agents due to their potential effects on the stimulation of osteoblast differentiation. - The Au-NPs were immobized on the titanium implants surface - The Au-NPs enhances the osteogenic differentiation in vitro - The Au-NPs have significant influence on the osseous interface formation in vivo - Au-NPs can be useful as osseo-integration inducing dental implants for formation of an osseous interface and maintenance of nascent bone formation.	Heo et al., 2016 [98]
		Bioactive Glass (BG-NPs)	Colloidal Solution		- BGs-NPS were non-toxic at a concentration of 20 mg/m - Increased proliferation cell with smaller BGs-NPS - Use in dental and bone treatments as fillers or bone-tissue bond forming materials	Ajita et al., 2015 [99]

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Dental Restoration Applications

The nanoparticles are promising for incorporation in dental materials-related restorative materials systems, adhesives-bonding systems, cements and sealants systems and prothesis bases systems. Therefore, these nanoparticles have potential to significantly improve the biological, mechanical, optical, thermal and the physico-chemical properties of dental medicine nanosystems (nanostructured materials). Thus, the production of nanostructured and functionnalized dental materials with more efficient biological properties must take into consideration the non-sacrifice of the other properties of these dental materials. Concerning restorative nanomaterials, in the dental implantology, infection is the most common factor that leads to dental implant failure. Antibacterial implant surfaces based on nano-scale modifications appear as an attractive strategy for control of peri-implantitis.The summary of the application of nanoparticles as dental implant coating nanomaterials that control and improve the implant success rate, with focus on enhanced osseointegration and antimicrobial effect was overviewed [34]. The investigation of the addition of an antibacterial agent to dental implants may provide the opportunity to decrease the percentage of implant. However, the use of nanoparticles to coat implants could provide osteoconductive and antimicrobial functionalities to prevent failure. But, the current research in dental adhesives and bonding naomaterials, aims at increasing the durability of resin–dentin bonds. Thus, the fundamental processes responsible for the aging mechanisms involved in the degradation of resin-bonded interfaces and the potential approaches to prevent and counteract this degradation by creating stable resin–dentin bonds that are able to resist the collagenolytic hydrolysis are also reviewed [35]. In the case of dental cements and sealants nanomaterials, glass ionomer cement (GICs) are usualy used as restorative materials have still lots of challenges due to their secondary caries and low mechanical properties. Therefore, many efforts have been proposed to modify the antibacterial and the mechanical features of GICs in order to prevent the secondary caries. Particularly, to achieve this goal, the nanoparticles were incorporated into GICs and their effectiveness has been proven [36]. Finaly, in the case of dental prothesis nanomaterials, the incorporation of nanoparticles was used in order to have a high biocompatibility with the oral tissues, excellent esthetics, superior mechanical properties. Clinical failures of complete or partial dental prothesis are most likely in the form of fracture either due to fatigue or impact forces of mastication. Several strategies are used to improve and to ameliorate the structure and the functions of these dental restoration materials as well as all the problems related to their contact with the various dental tissues and especially the interfaces. Thus, **Figure 1** illustrates the design of the restorate dental nanostructured materials. In addition, the latest studies and in DMN for dental restoration applications (combination of restoration, prevention and therapy) are described in **Table 6 (A, B, C, D, E, F)** and **7.**

Table 6 (A): Use of nanoparticles (NPs) in dental nanomaterials for restoration treatments

	Type and Composition		Form		Aim (s) and Strategy	Reference (s)
	Metal	Mineral	Free	Incorporated		
Inorganic naoparticles	Silver (Ag-NPs): PA			Titanium microimplant	- Antimicrobial NPs - Coating the microimplants with Ag-NPs (Ti-Ag-NPs) or with a Ag-NPs-coated biopolymer (Ti-BP-Ag-NPs) with bioadhesion effect - Ti-BP-Ag-NP exhibit excellent antibacterial properties	Venugopal et al., 2017 [58]
	Paladium (Pd-NPS) Silver (Ag-NPs): PA	Hydroxyapatite ($Ca_5(PO_4)_3(OH)$-NPS)		Implants	- Incorporation of NPs by Surface coating and functionnalisation - Antimicribial NPs - Improvement of osseointegration of dental implant - Using TiO2 nanotube oxide barrier layer with ultra-fine structure deposition of Pd-NPs, Ag-NPs, HA-NPs	JIang et al., 2017 [20]
	Silver (Ag-NPs): PA			Titanium implants	- Antimicrobial NPs - Fabricate porous titanium implants with interconnected pores and biofunctionalized by embedding (Ag-NPs) in an oxide surface layer grown - Porous implants released silver ions more than solid implants with strong antimicrobial activity and Any signs of cytotoxicity	Van Hengel et al., 2017 [59]
	Silver (Ag-NPs): PA			Titanium implants	- Antimicrobial NPs - Presence of Ag-NPs on the titanium surface provides an antibacterial activity - Osteoconductive Ag-NPs induce a chemical bond with bone to attain good biological fixation for implants - No changes in mechanical properties	Pokrowiecki et al., 2017 [60]
		Silica (SiO_2-NPs)		Dental stone	- Incorporation of NPs by inclusion in matrix - Addition of SiO_2-NPs affect the diametral tensile strength and compressive strength - Surface roughness was lower when SiO_2-NPs were added	De Cessero et al., 2017 [61]
	zinc oxide (ZnO-NPs): PA	Hydroxyapatite ($Ca_5(PO_4)_3(OH)$-NPS)		Titanium implants	- Antimicrobial NPs - Antibiofilm activity of mixture of ZnO-NPs and HA-NPS coated titanium surface discs	Abdulkareem et al., 2015 [62]
	Silver (Ag-NPs): PA			Titanium composite	- Antimicrobial NPs - Incorporation of NPs into nanoporous silica film - Long-term antibacterial activity - Nano-scale surface modification is a promissory strategy to control infections associated with dental implant rehabilitation - Strong antibacterial effect on titanium surface and reducing the extent of biofilm formation - Prevent microbial aggregation around dental implants can lead to loss/loosening of the implants.	Massa et al., 2014 [63]

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Table 6 (B): Use of nanoparticles (NPs) in dental nanomaterials for restoration treatments.

	Type and Composition		Form		Aim (s) and Strategy	Reference (s)
	Metal	Mineral	Free	Incorporated		
Inorganic naoparticles		Fluoro-Silica (F-SiO_2-NPs)		Resin-composite	- Photo-crosslinked polyurethane polymer (PU) - Superhydrophobic coating for preventing microleakage in a dental composite restoration - Superhydrophobic coatings with low PU/F-SiO_2 ratio (1:3) possessed excellent structure, high contact angle, low sliding angle, good transparency, the prominent cell viability and biocompatibility for clinical application - Superhydrophobic coatings effectively prevented water permeation in resin composite restoration	Cao et al., 2017 [9]
	Silver (Ag-NPs): PA			Resin-composite	- Incorporation of NPs by inclusion in matrix - Antimicribial NPs - Composite resin reinforced with Ag-NPs-laden HA nanowires provide both efficient reinforcement and high antimicrobial activity	Ai et al., 2017 [21]
	Silver (Ag-NPs): PA			Graphite oxide resin	- Antimicrobial NPs - High antimicrobial activity at very low concentration - Use as additive for endodontic fillings	Gerasymchuk et al., 2016 [64]
		zirconia (ZrO_2-NPs) Spinel ($MgAl_2O_4$-NPs)		Alumina Ceramics (Al_2O_3)	- Incorporation of NPs by inclusion in matrix - High optical properties - Achievement of high transparency of polycristalline alumina ceramics	Trunec et al., 2015 [65]
	Silver (Ag-NPs): PA Gold (Au-NPs): PA			Flowable Resin-composite	- Incorporation of NPs by inclusion in matrix - Significant Ag ion release in the presence of Au. - Resine composite modified with mixture of Ag-NPs and Au-NPs have lower light transmission and have opaque appearance - Higher microhardness	Sokolowski et al., 2014 [66]
	Silver (Ag-NPs): PA			Glass fibers filaments	- Antimicrobial NPs - Nanosystem for root dental fillings for endodontic therapy - Glass fibers filaments covered on the surface with Ag-NPs who formed thin films - Potential mechanical and antibacterial properties.	Nevarez-Rascon et al., 2014 [67]

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Table 6 (C): Use of nanoparticles (NPs) in dental nanomaterials for restoration treatments.

	Type and Composition		Form		Aim (s) and Strategy	Reference (s)
	Metal	Mineral	Free	Incorporated		
Inorganic naoparticles	Cooper (Cu-NPs): PA			Etch-and-rinse adhesive	- Incorporation of NPs by inclusion in matrix - Antimicrobial NPs - NPs did not affect mechanical properties, - At higher concentrations they produce more mechanical resistance - Prevent the degradation of adhesive-dentin interfaces,	Gutiérrez et al., 2017 [68]
	zirconia (ZrO_2-NPs) Titanium dioxide (TiO_2-NPs)			Orthodontic adhesive	- Incorporation of NPs by inclusion in matrix - Antimicrobial NPs - Antibacterial activity - Adding ZrO_2-NPs and TiO_2-NPs to orthodontic adhesive increased compressive strength, tensile strength, and shear bond strength *in vitro*	Felemban et al., 2017 [69]
		Sepiolite ($Mg_4Si_6O_{15}(OH)_2$-NPs)		Methacrylate dentin bonding	- $Mg_4Si_6O_{15}(OH)_2$-NPs can be considered as novel fillers to improve the mechanical properties of dentin bonding agents - Incorporation of the $Mg_4Si_6O_{15}(OH)_2$-NPs improved the bond strength to dentin with the highest values obtained at 1 w%	Fallahzadeh et al., 2017 [70]
	Titanium dioxide (TiO_2-NPs			Adhesives resin-composite	- Antimicrobial NPs - Photocatalytic NPs - Incorporate carboxylic acid-functionalized TiO_2-NPs into adhesive resin - Reactive oxygen species generated by functionalized TiO_2-NPs through visible-light irradiation enhanced shear-bond strength to human teeth with low cytotoxicity	Sun et al., 2017 [71]
	Zinc oxide (ZnO-NPs): PA			Adhesive resin-composite	- Incorporation of NPs by inclusion in matrix - Antimcrobial NPs - Use of single bond of adhesive with 10% of ZnO-NPs - Increases of anti-microbial properties without affecting bond strength	Saffarpour et al., 2016 [72]
	Silver (Ag-NPs): PA	Calcium phosphate ($Ca_3(PO_4)_2$-NPs): RA		Adhesive resin-composite	- Antimicrobial NPs - Quaternary ammonium methacrylates matrix (QAMs) - Ag-NPs antibacterial effect - $Ca_3(PO_4)_2$-NPs released calcium/phosphate ions and remineralized tooth-lesions and neutralized acids - Combining Ag-NPs/ $Ca_3(PO_4)_2$-NPs/QAM, a new class of composites and adhesives with antibacterial and remineralization double benefits	Cheng et al., 2015 [73]

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Table 6 (D): Use of nanoparticles (NPs) in dental nanomaterials for restoration treatments.

	Type and Composition		Form		Aim (s) and Strategy	Reference (s)
	Metal	Mineral	Free	Incorporated		
Inorganic naoparticles	Zinc oxide (ZnO-NPs): PA			Glass ionomer cements (GICs)	- Incorporation of NPs by inclusion in matrix - Antimicrobial NPs - Inclusion of ZnO-NPs at concentration 1% and 2% did not promote their antimicrobial activity against *S. mutans*. - Most important advantages of the GICs are associated with their ability to release long-term antimicrobial agents	Garcia et al., 2017 [74]
		Hydroxyapatite ($Ca_5(PO_4)_3(OH)$-NPS) Fluoropatite ($Ca_5(PO_4)_3F$-NPs)		Glass ionomer cements (GICs)	- Incorporation of NPs by inclusion in matrix - bioceramics HA-NPS and F-NPs improved mechanical properties of GICs	Barandehfard et al., 2016 [75]
		Forsterite (Mg_2SiO_4-NPs)		Glass ionomer cements (GICs)	- Highest compressive strength, flexural strength, and diametral tensile strength - Addition of 1 wt% Mg_2SiO_4-NPs to the ceramic component of GIC is desired for dental restorations applications	Sayyedan et al., 2014 [76]
		Hydroxyapatite ($Ca_5(PO_4)_3(OH)$-NPS) Calcite ($CaCO_3$-NPs)		Tricalcium-Dicalcium-Silicate Cement (TDS)	- The analyze of hydration reactions and physicochemical properties - Physicochemical properties were improved - Good properties, including sealing ability, biocompatibilty and the capacity to induce tissue regeneration.	Moreno-Vargas et al., 2017 [77]
	Titanium dioxide (TiO_2-NPs	Hydroxyapatite ($Ca_5(PO_4)_3(OH)$-NPS) Calcite ($CaCO_3$-NPs)		Tricalcium-Dicalcium-Silicate cement (TDS)	- Incorporation of TiO2-NPs with weight ratio of 1% increased the setting time, compressive strenght and push aout bond strenght of modified cement	Samiei et al., 2017 [78]
		Bioactive glass (BG-NPs)		Glass ionomer cements (GICs)	- BG-NPs-incorporated GIC enhanced mechanical properties and biomineralization properties without cytotoxicity	Kim et al., 2017 [79]

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Table 6 (E): Use of nanoparticles (NPs) in dental nanomaterials for restoration treatments.

	Type and Composition		Form		Aim (s) and Strategy	Reference (s)
	Metal	Mineral	Free	Incorporated		
Inorganic naoparticles	Titanium dioxide (TiO_2-NPs			Acrylic resin prothesis (PMMA)	- Antimicrobial NPs - Incorporation of TiO_2-NPs in PMMA polymer matrix was proved to have antibacterial effects while modified viscosity characteristics and expected lower mechanical parameters - The newly obtained 0.4% nanocomposite was successfully used with stereolitographic technique for complete denture manufacturing	Totu et al., 2017 [80]
	Titanium dioxide (TiO_2-NPs)			Acrylic resin denture (PMMA)	- Incorporation of TiO_2-NPs in PMMA polymer matrix - TiO_2-NPs are the best candidate for improving the properties of PMMA composite	Rashahmadi et al., 2017 [81]
		Silicon dioxid ($Si0_2$), trietoxyvinylsilane (TEVES) (TEVS- SiO2-NPs)		Acrylic resin denture (PMMA)	- Increase the fracture toughness, the elastic modulus and the Glass Transition Temperature of PMMA resins used in fixed provisional restorations - TEVS- SiO2-NPs at low concentrations, may enhance the overall performance of fixed interim prostheses	Toupouzi et al., 2017 [82]
	Silver (Ag-NPs): PA	Calcium phosphate (CaP-NPs): MA		Dimethacrylate resin	- Antimicrobial NPs - Incorporation of NPs by inclusion in matrix - NPs formation *in situ* by a photoreduction process - Mixed CaP-NPs/Ag-NPs as ion-releasing fillers for remineralization and antibacterial activity - Optical properties were compromised by the presence of silver - Higher fracture strength and elastic modulus	Natale et al., 2017 [83]
	zirconia (ZrO_2-NPs)			Acrylic resin denture (PMMA)	- Incorporation of ZrO_2-NPs into the repair resin improved the flexural strength of repaired denture bases, whereas it decreased impact strength, especially with high (ZrO_2-NPs) concentrations as 7.5%.	Gad et al., 2016 [84]
	Silver vanadate (β-$AgVO_3$-NPS):			Poly (methyl methacrylate) resin	- Incorporation of NPs by inclusion in matrix - Antimicrobial NPs - Inhibition of biofilm of main microorganisms associated with dental prosthesis - No change of the mechanical properties	De Castro et al., 2016 [85]
	Silver (Ag-NPs): PA			Acrylic resin denture (PMMA)	- Antimicrobial NPs - Effect Ag-NPs incorporation on viscoelastic properties - Ag-NPs incorporation within the acrylic denture base material can improve its viscoelastic properties	Mahross et al., 2015 [86]

Legend: NPs: Nanoparticles; **MA:** Memineralisant agents; **PA:** Pharmacological agents; **ADA:** Anti-demineralisant agents; **BA:** Bioadhesive agents; **RA:** Remineralisant agents; **AAA:** Anti-adhesion agents.

Table 6 (F): Use of nanoparticles (NPs) in dental nanomaterials for restoration treatments.

	Type and Composition		Form		Aim (s) and Strategy	Reference (s)
	Metal	Mineral	Free	Incorporated		
Inorganic naoparticles	Cooper (Cu-NPs): PA Zinc (Zn-NPs): PA		Colloidal solution		- Antimicrobial NPs - Antibaterial effect - *In-situ* generated NPs by ultrasonic dental surgical instruments - Disinfection during some types of dental surgery	Stubbing et al., 2017 [87]
	Silver (Ag-NPs): PA			Resin-composie	- Antimicrobial NPs - Antibacterial activity - Incorporation of NPs by Surface coating of resin-composite - Immobilized of NPs on yttria-stabilized zirconia polymer - Low cytotoxicity and total silver leaching level	Yamada et al., 2017 [88]
	Silver (Ag-NPs): PA			Orthodontic resin-composite	- Incorporation of NPs by inclusion in matrix - Antimicrobial NPs - Prevent oral pathogen growth during orthodontic treatment - *In vitro* potent antimicrobial activities	Lee et al., 2017 [6]
	Silver (Ag-NPs): PA Iron oxide (Fe_2O_3-NPs): PA		Colloidal solution		- Antimicrobial NPs - Antibacterial effect - Highly prolonged bactericidal activity against dentobacterial plaque - Used as dental filling of composite materials	Karasenkov et al., 2015 [89]
	Bimetallic Copper–Nickel (Cu-Ni-NPs): PA		Colloidal solution		- Antimicrobial NPs - Antibacterial activity against dental pathogens	Argueta-Figueroa et al., 2014 [90]
	Bimetallic Silver-titanium dioxide (Ag-TiO_2-NPs): PA			Epoxy resin	- Incorporation of NPs by inclusion in matrix - Antimicrobial NPs - Antimicrobial additive with photocatalytic properties	Chambers et al., 2017 [91]
	Zinc oxide (ZnO-NPs): PA			flowable resin-composite	- Incorporation of NPs by inclusion in matrix - Antimicrobial NPs and Antibacterial activity - Higher bond strength	Hojati et al., 2013 [92]

Legend: **NPs:** Nanoparticles; **MA:** Memineralisant agents; **PA:** Pharmacological agents; **ADA:** Anti-demineralisant agents; **BA:** Bioadhesive agents; **RA:** Remineralisant agents; **AAA:** Anti-adhesion agents.

Table 7: Use of nanoparticles (NPs) in dental nanomaterials for restoration treatments

	Type and Composition			Form		Aim (s) and Strategy	Reference (s)
	Metal	Polymer	Mineral	Free	Incorporated		
Organic nanoparticles		Quaternised PolyEthyleneI mine (QPEI-NPs): PA-NPS			Resin - composite	- Incorporation of NPs by inclusion in matrix - Antimicrobial NPs - Antibacterial effect by direct contact - Preventing bacterial recontamination during restoring teeth	Shvero et al., 2015 [93]
Hybrid nanoparticles	Polystyrene-acrylic acid (PSA), Zinc oxide(ZnO), Silica (SiO_2), Dimethylhydantation (DMH), Hypochlorite de sodium (NaClO): (PSA-ZnO-SiO_2-DMH-Cl-NPs): PA				Titanium implants	- Antimicrobial NPs - PSA-ZnO-SiO_2-DMH-Cl-NPs were immobilized on the surface of titanium plates - Modified surface exhibited excellent antibacterial activity - No obvious cytotoxicity - Novel surface system provides a promising self-antibacterial bioplatform for metallic implants without using antibiotics	Li et al., 2017 [94]
	Zinc oxide (ZnO-NPs): PA	Chitosan (C-NPs): BA			orthodontic resin - composite	- Incorporation of NPs by inclusion in matrix - Antimicrobial NPS - Bioadhesion effect - 10% of NPs mixture (ZnO-NPs and C-NPs) has induced an antibacterial activity in resin composite	Mirhashemi et al., 2013 [95]

Legend: **NPs:** Nanoparticles; **MA:** Memineralisant agents; **PA:** Pharmacological agents; **ADA:** Anti-demineralisant agents; **BA:** Bioadhesive agents; **RA:** Remineralisant agents; **AAA:** Anti-adhesion agents.

Dental Diagnosis Applications

The cancer diagnosis which involves the design, characterization, production, and application of dental nanosystems was reviewed [40]. Recently, an increased amount of efforts have been made to develop less invasive early diagnostic modalities for oral cancer, of which the in vivo high resolution imaging of oral epithelial tissues using novel optical systems and the chemical analysis of saliva show great promise as valuable tools. The metalic nanoparticles as iron nanoparticles (Fe-NPs) single or conjugated with polysaccarides, and gold nanoparticles (Au-NPs) single or conjugated with antibodies or peptides for specific cellular biomarkers were used in dental diagnostic. They have recently been investigated as optical or magnetical contrasting agents in medical imaging techniques for early detection of oral cancer, and for identifying and differentiating infectious pathogens [41].

Conclusion

The applications of nanostructured materials (nanoparticles and nanomaterials or their combination) such as dental medicine nanosystems (DMN) generally imply products that may bring prevention, diagnosis and therapy diseases and / or restoration of disorders and / or tissues regenerative of oral cavity benefits. The advances in surface and interface processing and engineering of nanoparticles, nanomaterials and their combination, allowed the design of a new nanostructured materials with innovative properties which can be a real support for the improvement of dental treatments. Currently, there is a wide range of this DMN developments and applications in different fields and specialties of dentistry and made dental procedures fast, reliable, effective, safe and less painful. The development of the DMN have raised substantial interest thanks to their use nowdays either in pre-clinical investigation they have already been approved and are in clinical practice of dentistry and oral health care. Currently, the challenge is to detail the cytotoxicity studies in vitro and especially in vivo, with the aim of taking numerous research outcomes and convert them into strategies for the development of clinical, cosmetical, esthetic dental practice and oral health care marketable nanoproducts. In addition, the development of new functional nanostructured materials and their design in the form of nanosystems, including “nanomachines” or “nanorobots” more effective and more suitable for dental treatment and oral health are in full evolution.

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