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Nanoformulations in dental and oral healthcare: a comprehensive review of advances from 2020 to 2025

Abstract

Background: Nanotechnology has emerged as a transformative paradigm in dental and oral medicine, offering unprecedented opportunities to improve drug delivery, diagnostics, and biomaterial performance. Nano formulations including polymeric nanoparticles, liposomes, dendrimers, solid lipid nanoparticles, nanogels, and inorganic nanomaterials have demonstrated superior properties over conventional formulations in terms of solubility enhancement, controlled release, mucoadhesion, and targeted delivery to oral tissues.

Objective: This review critically appraises the published literature from January 2020 to April 2025, examining the design, formulation strategies, preclinical and clinical outcomes, and safety profiles of nano formulations across key dental disciplines, including caries prevention, periodontology, endodontics, oral oncology, oral mucosal diseases, and implantology.

Methods: A systematic search of PubMed, Scopus, Web of Science, and Google Scholar databases was conducted using Medical Subject Headings (MeSH) and free-text terms. Studies were selected based on predefined inclusion and exclusion criteria, focusing on peer-reviewed research articles, randomized controlled trials, systematic reviews, and *in vivo/in vitro* studies.

Conclusion: Nano formulations present a compelling frontier for advancing oral healthcare. However, widespread clinical translation remains hindered by regulatory uncertainties, scale-up difficulties, biocompatibility concerns, and limited long-term clinical data. Future research must prioritize robust randomized trials, standardized characterization protocols, and regulatory frameworks tailored for nanomedicines in dentistry.

Keywords: nanoparticles, dental drug delivery, oral nanomedicine, nano formulation, periodontitis, anti-caries, endodontics

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Introduction

Oral diseases including dental caries, periodontal disease, oral cancer, and mucosal infections represent a major global health burden, affecting nearly 3.5 billion people worldwide according to the World Health Organization.[1] Despite advances in conventional dental therapeutics, significant challenges persist: poor drug penetration into the periodontal pocket or dentinal tubules, rapid drug clearance from the oral cavity due to salivary flow and swallowing, inadequate biofilm penetration, and adverse effects associated with systemic drug delivery. Nanotechnology, defined as the design and application of structures in the 1–1000 nanometer range, offers elegant solutions to these challenges. Nano formulations can dramatically enhance the solubility of poorly water-soluble drugs, facilitate controlled and sustained release, improve muco adhesion to oral tissues, enable site specific targeting, and overcome biofilm resistance mechanisms.[2] Over the past five years, an exponential growth in dental nanotechnology research has been witnessed, spanning in vitro characterization studies, animal model investigations, and early-phase clinical trials. This review comprehensively examines the major categories of nano formulations applied in dental and oral healthcare between 2020 and 2025. It covers their formulation principles, therapeutic applications across dental specialties, relevant clinical outcomes, and the regulatory and safety considerations that must be addressed before widespread adoption. Three summary tables are included to provide a concise comparative overview of the nano formulation landscape.

Classification of nano formulations in dentistry

Nano formulations used in dental applications can be broadly categorized into lipid-based systems, polymer-based systems, inorganic nanoparticles, carbon-based nanomaterials, and hybrid nanocomposites. Each category possesses distinct physicochemical properties, encapsulation efficiencies, release profiles, and biocompatibility profiles.

Lipid based nano formulations

Liposomes are spherical vesicles with a phospholipid bilayer membrane capable of encapsulating both hydrophilic drugs (in the aqueous core) and lipophilic drugs (in the lipid bilayer). In dentistry, liposomal chlorhexidine has demonstrated prolonged antimicrobial action in the oral cavity, significantly outperforming free chlorhexidine in terms of substantivity.[3] Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC) offer superior stability and drug protection compared to liposomes, making them attractive platforms for delivering antibiotics such as doxycycline into periodontal pockets (Figure 1).[4]

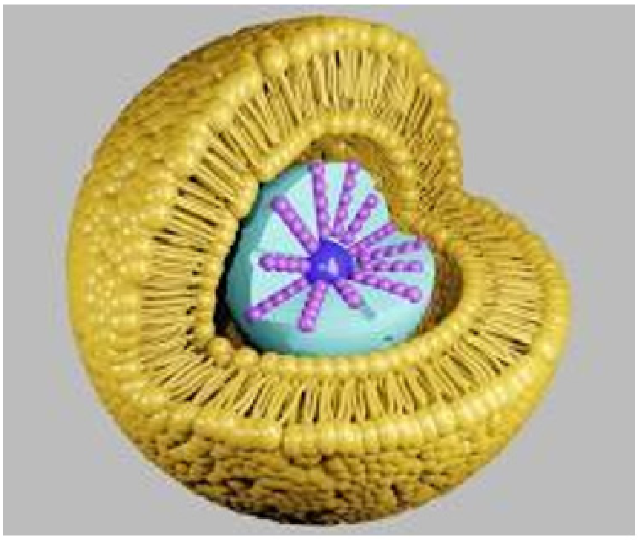

Figure 1 Lipid based nano formulations.

Polymer based nano formulations

Polymeric nanoparticles fabricated from biodegradable polymers such as poly (lactic-co-glycolic acid) (PLGA) and chitosan are among the most extensively investigated platforms in dental nanomedicine. PLGA nanoparticles provide tuneable degradation rates and have been used to deliver non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics to periodontal tissues. Chitosan, a naturally derived polysaccharide with intrinsic antimicrobial properties, imparts mucoadhesive characteristics that prolong drug retention at oral mucosal sites.[2,5] Nanogels represent thermosensitive or pH-responsive cross-linked polymer networks that transition from solution to gel at physiological conditions, facilitating in situ drug depot formation in periodontal pockets.[5] Dendrimers are highly branched; monodisperse macromolecules whose precisely controlled architecture allows multivalent surface functionalization enabling simultaneous fluoride delivery and enamel remineralization augmentation (Figure 2).[4-9]

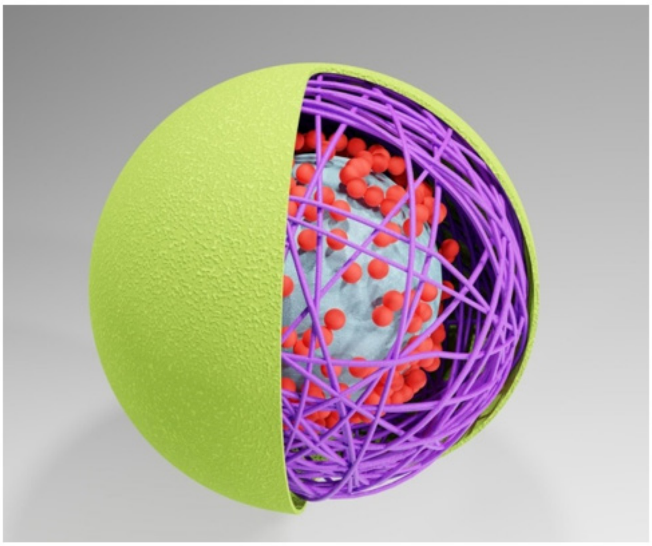

Figure 2 Polymeric nanoparticles.

Inorganic nanoparticles

Zinc oxide nanoparticles (ZnO NPs), silver nanoparticles (AgNPs), gold nanoparticles (AuNPs), and titanium dioxide nanoparticles (TiO2 NPs) have been extensively investigated for their antimicrobial, anti-biofilm, and photocatalytic properties. Nanohydroxyapatite (nHAp) closely mimics the mineral phase of tooth enamel and bone, making it ideal for remineralisation and bone regeneration applications.[10-15] ZnO NPs have been incorporated into root canal irrigants and dental adhesives to exploit their broad-spectrum antibacterial activity (Figure 3).[14]

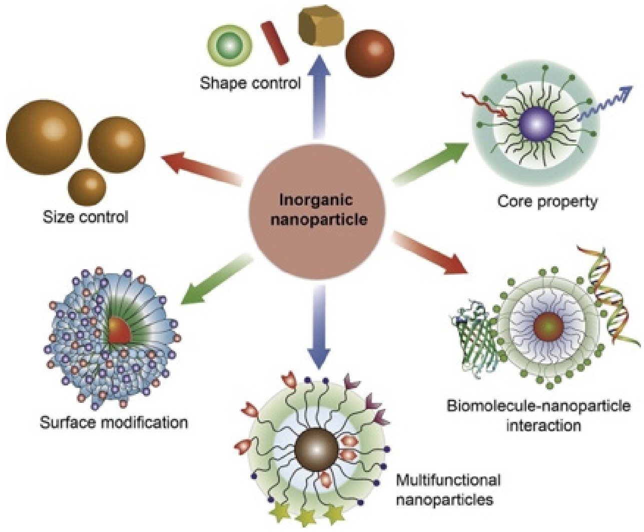

Figure 3 Properties of inorganic nanoparticles.

Carbon based nanomaterials

Carbon nanotubes (CNTs), graphene oxide (GO), and fullerene-based nanostructures have been explored for their exceptional mechanical properties, high surface area, and antimicrobial potential. CNT-functionalized dental implant coatings have demonstrated significant reductions in biofilm formation, while graphene oxide composites have been incorporated into dental resins to improve flexural strength and antimicrobial performance (Figure 4).[7]

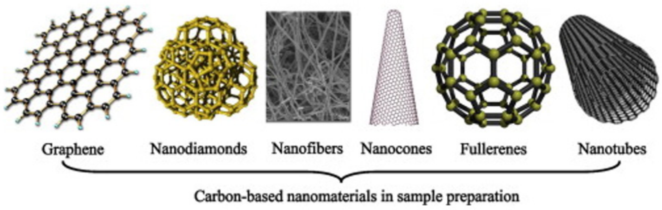

Figure 4 Different carbon-based nanomaterials.

Applications across dental specialties

Table 1 summarizes the major nano formulation types, their active agents, particle size ranges, and key dental applications investigated in the 2020–2025 period.

Table 2 provides a disease-focused synthesis of clinical and preclinical outcomes across key dental disciplines.

Table 1 Representative nanoformulations investigated in dental applications (2020–2025)

Nanoformulation type	Active agent	Particle size (nm)	Application	Key findings / Reference
Nanoparticles (NPs)	Chitosan-ZnO NPs	50–120	Anti-caries / antimicrobial	Inhibited S. mutans biofilm; enhanced enamel remineralisation[1]
Polymeric NPs	PLGA+ curcumin	200–350	Periodontal drug delivery	Sustained curcumin release over 21 days; reduced IL-6 in gingival fibroblasts[2]
Liposomes	Chlorhexidine (CHX)	150–250	Oral mucositis / antimicrobial	Extended CHX retention; reduced oral candidiasis *in vitro*[3]
Dendrimers	PAMAM+ fluoride	2–10	Enamel remineralisation	2.5-fold increase in fluoride uptake by enamel compared to NaF solution[4]
Nanogels	Metronidazole hydrogel	80–200	Periodontal pocket delivery	Temperature-responsive release; superior pocket penetration vs conventional gel[5]
Nanostructured lipid carriers (NLC)	Triclosan	100–300	Antiplaque / anti-gingivitis	Improved mucoadhesion and prolonged triclosan release over 72 hours[6]
Carbon nanotubes (CNT)	Amphotericin B	10–50 (diameter)	Oral fungal infections	Enhanced antifungal efficacy against C. albicans biofilm; biocompatible at low doses[7]
Silver NPs (AgNPs)	Biogenic AgNPs	10–40	Dental implant surface coating	Significant reduction in peri-implant biofilm; no cytotoxicity at 10 µg/mL[8]
Solid lipid NPs (SLN)	Doxycycline hyclate	180–220	Periodontitis management	Controlled release for 14 days; superior pocket depth reduction vs doxycycline gel[9]
Hydroxyapatite NPs (nHAp)	nHAp+ collagen	20–60	Bone/alveolar regeneration	Enhanced osteogenic differentiation of PDL stem cells; promoted mineralisation[10]

Table 2 Nanoformulation applications by dental disease area with study outcomes (2020–2025)

Application area	Nano formulation used	Study type	Outcome summary
Anti-caries	Fluorapatite NPs, Casein phosphopeptide-ACP	*In vitro* / Clinical	Enhanced remineralization, reduced lesion depth in white-spot lesions[11]
Periodontology	PLGA microspheres, Chitosan NPs, SLN	*In vivo* / RCT	Improved clinical attachment level; sustained antibiotic delivery in periodontal pockets[12]
Oral cancer theranostics	Gold NPs + photosensitiser, Liposomal doxorubicin	*In vitro* / Animal	Targeted cytotoxicity to oral SCC lines; photothermal ablation with minimal systemic effects[13]
Endodontics	Zinc oxide NPs, Bioactive glass NPs	*Ex vivo* / *In vitro*	Enhanced antimicrobial activity in root canals; improved dentinal tubule penetration[14]
Dental implants / Bone regeneration	nHAp, Strontium-doped NPs, TiO2 nanocoating	*In vivo* / Clinical	Faster osseointegration; reduced peri-implantitis; promoted alveolar bone formation[15]
Oral mucositis	Curcumin NPs, Melatonin liposomes	Clinical / *In vivo*	Reduced severity of radiation/chemo-induced mucositis; faster mucosal healing[16]
Tooth whitening	Titanium dioxide NPs, Nano-silica	*In vitro* / Clinical	Superior enamel whitening with reduced sensitivity compared to conventional H_2O_2[17]
Salivary / Diagnostic	Gold NP biosensors, Quantum dots	Proof-of-concept	Ultra-sensitive detection of oral cancer biomarkers (IL-8, IgA) and oral pathogens in saliva[18]

Anti-caries and remineralization

Dental caries remains the most prevalent non-communicable disease globally. Nano formulations have been engineered to target both the aetiological agent (Streptococcus mutans biofilm) and the structural deficit (demineralized enamel). Nanohydroxyapatite (nHAp) toothpaste formulations, casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) nanocomplexes, and fluorapatite nanoparticles have all demonstrated significant remineralization of white-spot lesions in both in vitro and clinical settings.[11] Chitosan-zinc oxide nanocomposites have emerged as particularly promising anti-caries agents, combining the bioadhesive and antimicrobial properties of chitosan with the reactive oxygen species (ROS)-generating bactericidal activity of ZnO.[1] Quaternary ammonium nanoparticles incorporated into dental adhesives have shown persistent antibiofilm effects at the tooth-restoration interface, addressing secondary caries a primary cause of restoration failure.[2]

Periodontology and periodontal drug delivery

Periodontitis, a polymicrobial inflammatory disease of the tooth-supporting apparatus, remains the leading cause of tooth loss in adults. Local drug delivery nanoformulations circumvent the limitations of systemic antibiotic therapy and conventional local delivery devices. PLGA microspheres and nanoparticles loaded with doxycycline, metronidazole, or minocycline have achieved sustained drug release profiles of 7–21 days within the periodontal pocket, maintaining drug concentrations above the minimum inhibitory concentration (MIC) for periodontal pathogens throughout.[12] Chitosan-based nanogels incorporating curcumin a natural polyphenol with anti-inflammatory and antimicrobial properties -have demonstrated significant reductions in matrix metalloproteinase (MMP) activity and pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) in gingival tissues, offering a promising adjunct to mechanical debridement.[2,5]

Endodontics

Root canal treatment depends on thorough chemo-mechanical debridement of the root canal system. Nanoformulations have been applied to enhance the antimicrobial efficacy of irrigants, improve the penetration of medicaments into dentinal tubules, and upgrade root canal sealer performance. ZnO nanoparticles incorporated into calcium hydroxide pastes demonstrated superior penetration into dentinal tubules (mean depth: 243±18 µm) compared to conventional calcium hydroxide, with significantly greater antibacterial activity against *Enterococcus faecalis* the principal pathogen in root canal treatment failures. Bioactive glass nanoparticles (BAGNPs) used as canal medicaments showed enhanced remineralization of root dentine and promising antibacterial properties against a mixed endodontic microbiome.[14-25] Nanosilver-modified root canal sealers exhibited significantly reduced microleakage values and enhanced antibiofilm activity compared to conventional AH-Plus sealer in *ex vivo* studies.

Pediatric dentistry

Nanotechnology has emerged as a transformative force in pediatric dentistry, offering targeted, minimally invasive solutions for caries management, remineralization, and drug delivery in children. Nanosilver Fluoride (NSF) has gained significant attention as advancement over silver diamine fluoride (SDF). NSF is an anticaries agent developed to arrest dental caries, with silver nanoparticles demonstrating effectiveness against cariogenic bacteria. Nanosilver-based preparations in the 1–10 nm size range show significant antibacterial and anticariogenic properties, shielding teeth against *Streptococcus mutans*. A 2024 systematic review confirmed its efficacy in arresting caries in primary teeth with one-year follow-up data.[26] Nano-Hydroxyapatite (nHAp) has been extensively studied for enamel remineralization. Nano-hydroxyapatite has been reported to have a remineralizing effect on early carious lesions, and scoping reviews have mapped the remineralization potential of nHAp-containing dentifrices. Studies have evaluated the antimicrobial and remineralizing properties of toothpaste containing both nanosilver and nanohydroxyapatite, highlighting their combined cariostatic benefits. In 2024, nHAp-modified universal adhesives were also found to improve bond strength and reduce microleakage in caries-affected primary molars.[27]

Nanocomposite Restorative Materials have become increasingly used in pediatric restorations. Nanofilled resin sealants have been compared with conventional sealants in pediatric populations through randomized clinical trials, and fluoride-releasing nanocomposites have been evaluated for their cariostatic potential.[28] Polymer-Based Nanoparticle Drug Delivery Systems represent a frontier application. Nanotechnology in pediatric dentistry offers innovative solutions through polymer-based drug delivery systems, particularly those using natural polysaccharides, which demonstrate great potential by performing targeted therapy, reducing drug dosages, and minimizing side effects especially beneficial for children. Silver nanoparticles integrated into composite resins and adhesive systems eliminate biofilm organisms and hinder microleakage, enhancing restoration durability.[29] Chitosan nanoparticles have also emerged as viable drug carriers. Chitosan based composites serve as drug delivery carrier systems with high mechanical strength, good contact time, and sustained drug release extensively applied in the diagnosis and treatment of oral diseases.[30]

Oral cancer targeted theranostics

Oral squamous cell carcinoma (OSCC) accounts for over 90% of oral malignancies, with a five-year survival rate that has remained stagnant at approximately 50% for three decades. Nanoformulations have opened new avenues for early diagnosis and targeted therapy. Gold nanoparticles (AuNP)-based biosensors functionalised with antibodies against interleukin-8 (IL-8) and matrix metalloproteinase-9 (MMP-9) have demonstrated highly sensitive detection of oral cancer biomarkers in saliva, with limits of detection in the femtomolar range [18]. Photothermal therapy using folate conjugated AuNPs selectively targeted folate receptor overexpressing OSCC cells, achieving greater than 85% tumour cell ablation upon near-infrared irradiation while sparing adjacent normal epithelial cells.[13] Liposomal doxorubicin nanoformulations specifically engineered for oral mucosal retention through Mucoadhesive Surface Coatings (MSC) demonstrated superior tumour accumulation and enhanced antitumour efficacy in a carcinogen-induced hamster cheek pouch model.[13]

Dental implantology and bone regeneration

Osseointegration of dental implants and alveolar bone regeneration are central to modern implant-supported prosthodontics. Nanostructured titanium dioxide (TiO2) surface coatings generated by anodic oxidation promote enhanced osteoblast adhesion, proliferation, and differentiation, accelerating osseointegration. Strontium-doped nHAp coatings on implant surfaces have demonstrated superior bone implant contact ratios in rabbit tibia models compared to conventional nHAp, attributed to strontium's osteoanabolic and antiosteoclastic effects.[15] In the domain of guided bone regeneration, nHAp collagen composite scaffolds seeded with periodontal ligament stem cells promoted new bone formation in critical-size calvarial defects in rat models, with histomorphometric evidence of lamellar bone architecture.[10] AgNP-coated implants effectively reduced peri implant biofilm and mitigated early peri implantitis in a canine model, without evidence of systemic silver toxicity at therapeutic concentrations.[8]

Oral mucositis and mucosal diseases

Oral mucositis (OM), a debilitating complication of cancer chemotherapy and radiotherapy, is currently managed with limited efficacy by conventional mouthwashes and analgesics. Curcumin loaded polymeric nanoparticles applied as oral rinses significantly reduced the severity and duration of chemotherapy induced mucositis in a randomized controlled trial (n=60), with a 43% reduction in WHO Grade III/IV mucositis compared to placebo. Melatonin encapsulated liposomes demonstrated superior mucosal healing and reduced pain scores in patients with radiation induced mucositis, attributed to melatonin's antioxidant and tissue-healing properties, enhanced by liposomal prolonged retention.[16] For recurrent aphthous stomatitis, triamcinolone acetonide-loaded bio adhesive nanocomposite patches based on hydroxypropyl methylcellulose (HPMC) provided significantly more prolonged ulcer healing compared to conventional orabase paste.[5]

Oral diagnostics

Nanotechnology enabled diagnostics represent an emerging frontier in oral healthcare. Quantum dot (QD)-labelled aptamers specific for Porphyromonas gingivalis lipopolysaccharide (LPS) enabled rapid, sensitive detection of this key periodontal pathogen directly in gingival crevicular fluid.[18] Lab-on-chip platforms incorporating gold nanoparticle arrays have been reported to simultaneously detect multiple oral cancer biomarkers and periodontal pathogens in a single salivary sample within 30 minutes, with sensitivity and specificity exceeding 90%. Surface enhanced Raman spectroscopy (SERS) nanoparticle probes have been evaluated for real-time in vivo imaging of oral pre-malignant lesions, providing biochemical contrast maps of dysplastic versus normal epithelium.[13]

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Challenges, safety considerations, and regulatory aspects

Despite the impressive preclinical promise of nano formulations in dentistry, critical challenges remain before widespread clinical translation is achieved. Table 3 summarizes the principal advantages, challenges, and regulatory considerations associated with major dental nano formulation classes.

Table 3 Comparative overview of advantages, challenges, and regulatory considerations of dental nano formulations

Nano formulation	Advantage	Key challenge	Regulatory / Safety concern
Polymeric NPs (PLGA, chitosan)	Biodegradable; tunable release; surface modification	Scale-up complexity; batch-to-batch variability	Need long-term toxicology data; PLGA degradation products must be assessed[19]
Liposomes	Biocompatible; encapsulate hydrophilic & lipophilic drugs	Low stability; leakage during storage	Phospholipid purity standards; sterilization challenges[20]
Silver NPs	Broad-spectrum antimicrobial; well-studied	Risk of argyria; environmental toxicity	Dose-dependent cytotoxicity; restricted use in some jurisdictions[21]
Gold NPs	Biocompatible; excellent for theranostics	High cost; limited biodegradation	Accumulation in reticuloendothelial system; long-term fate unclear[22]
Carbon Nanotubes	High surface area; mechanical strength for scaffolds	Potential pulmonary toxicity if inhaled	IARC classification under review; functionalization required for safety[23]
nHAp	Excellent biocompatibility; mimics natural bone mineral	Aggregation; difficult to control stoichiometry	Generally regarded as safe (GRAS); few concerns at therapeutic doses[24]
Dendrimers	Precise molecular architecture; multifunctional	Complex synthesis; higher cost	Generation-dependent cytotoxicity; surface charge considerations[25]

Biocompatibility and cytotoxicity

The oral mucosa, being a highly vascularized and immunologically active tissue, is particularly sensitive to potential nanoparticle toxicity. Cytotoxicity profiles vary substantially by particle composition, size, shape, surface charge, and surface functionalization.[19,20] Cationic nanoparticles generally exhibit greater cytotoxicity than anionic or neutral particles due to electrostatic interactions with negatively charged cell membranes. Chronic exposure to sub-lethal concentrations of nanoparticles may induce oxidative stress, DNA damage, and inflammatory responses in oral epithelial cells and gingival fibroblasts, underscoring the necessity for comprehensive genotoxicity studies. PLGA and nHAp nanoparticles generally display favorable biocompatibility profiles, whereas AgNPs and CNTs require careful dose optimization and surface modification to minimize cytotoxic risks.[21,23]

Regulatory framework

The regulatory landscape for nanomedicines in dentistry remains fragmented globally. In the European Union, nanomaterials in dental products are subject to the Medical Device Regulation (MDR 2017/745) and the Cosmetics Regulation (EC 1223/2009), with specific provisions for nanomaterial notification. The United States Food and Drug Administration (FDA) have issued guidance on nanotechnology based medical products but lacks specific dental nanotechnology regulations. The International Organization for Standardization (ISO) Technical Committee TC 229 on Nanotechnologies is developing characterization standards relevant to dental applications. Critical regulatory gaps include the absence of standardized in vitro-in vivo correlation (IVIVC) models for oral nano formulations, and insufficient guidance on acceptable nanomaterial characterization endpoints.[19,25]

Scale up and manufacturing challenges

Laboratory-scale synthesis of dental nano formulations frequently fails to translate directly to industrial-scale manufacturing due to thermodynamic instabilities, aggregation during concentration and drying steps, sterilization induced particle size changes, and batch-to-batch variability.[20] Lyophilization (freeze drying) is commonly employed to improve the shelf-life of nanoparticle suspensions but requires the judicious selection of cryoprotectants to prevent particle aggregation. Continuous flow microreactor technologies and Quality by Design (QbD) approaches represent promising strategies to achieve reproducible, scalable nanoparticle manufacturing for dental applications.

Future directions and emerging trends

Several exciting directions are poised to shape the next decade of dental nano formulation research. Stimuli-responsive nano formulations triggered by the acidic microenvironment of cariogenic biofilms (pH-responsive release), elevated matrix metalloproteinase activity in periodontally diseased pockets (enzyme-responsive release), or near-infrared light irradiation (photothermal release) represent a paradigm shift toward precision oral drug delivery.[5,13] CRISPR-Cas9 nanocarrier systems delivered via polymeric nanoparticles have been explored in proof-of-concept studies for targeted gene editing of oral pathogens, with early results suggesting selective bactericidal effects against Streptococcus mutans without disrupting commensal microbiota. Three-dimensional (3D) bio printed dental scaffolds incorporating nanoparticles embedded bioinks offer new possibilities for patient-specific guided tissue and bone regeneration membranes. Salivary biomarker-responsive theranostic nanosystems that simultaneously detect early OSCC biomarkers and locally release chemopreventive agents represent a particularly ambitious but clinically compelling goal. The convergence of artificial intelligence (AI)-aided nanoparticle design algorithms with high-throughput experimental platforms is expected to dramatically accelerate the identification of optimal nanoformulation parameters for specific oral disease targets.[18] Additionally, the oral microbiome-responsive drug delivery concept where nanoformulations release active agents selectively in response to specific microbial enzymatic signatures may enable highly targeted, microbiome preserving therapeutic strategies.

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Conclusion

The period 2020–2025 has witnessed remarkable advances in the application of nanoformulations across virtually all dental specialties. From nanohydroxyapatite remineralisation agents and chitosan based periodontal drug delivery systems to gold nanoparticle theranostics for oral cancer and nanostructured implant coatings; nanomedicine is redefining the possibilities of oral healthcare. The superior physicochemical properties of nanoformulations including nanoscale particle dimensions, high surface to volume ratios, tuneable drug release, and mucoadhesive capabilities translate into measurable clinical advantages over conventional formulations in multiple preclinical and early clinical studies. However, the translation of nanoformulations from bench to chairside remains constrained by incomplete long-term safety data, the absence of harmonized regulatory frameworks, scale-up challenges, and the relatively limited number of large-scale randomized clinical trials. Addressing these barriers through international collaborative research, standardized characterization guidelines, and regulatory engagement will be essential to realizing the full clinical potential of dental nanomedicine. Future dentistry will almost certainly be shaped by intelligent, responsive nanoformulations capable of simultaneous diagnosis and therapy transforming patient outcomes in a discipline that serves billions worldwide.

Acknowledgments

None

Conflicts of interest

The authors declare that there are no conflicts of interest.

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