

Nanodrug Delivery Systems in Periodontics

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ABSTRACT

Nanotechnology is of intense interest to researchers due to the basic fact that the properties of the material can be effectively manipulated when the size is transformed to nanoscopic. New opportunities arise out of the unique features which have been effectually utilized in the development of nano pharmaceuticals. This has revolutionized the health care system extensively by its diverse applications in modern medicine and dental science. Material science and periodontics have jointly adopted this technology to produce nanoparticles for targeted drug delivery, which find considerable significance in the management of periodontal diseases. Periodontitis is principally polymicrobial in nature, affecting the supporting structures of the tooth. In addition to the conventional mechanical debridement, adjunctive chemical therapy is, at most times, required to resolve the chronic inflammation. Hence, targeted drug delivery using nanoparticles with improved pharmacological and therapeutic

properties may form better treatment strategies for managing this chronic inflammation. As nanoscale technology finds a scope in varied applications in periodontics, this current review highlights the various nanoscale drug delivery systems for managing periodontal diseases.

Key words: Dendrimers, Liposomes, Nanocarriers, Nanofibers, Nanogels, Periodontal disease.

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DOI: 10.5530/ijpi.2021.1.2

INTRODUCTION

Nanotechnology has evolved over the decades and revolutionized the developments in material science, biotechnology and medicine. Nanomaterials exhibit a size less than 100nm, at least in one dimension, including particles less than 100nm in size, films measuring <100nm in thickness and fibers measuring <100nm in diameter and composites having a combination of the components as mentioned earlier. Nanomaterials exhibit better performance than the conventional materials in terms of enhanced stiffness, toughness, transparency, resistance to heat, solvent and abrasion. Additionally, their optical, electro-optical, chemical and magnetic properties pave the way to meet the captivating demand in the field of health care.¹ An additional fascinating feature of nanomaterials is the ability of self-assembly, in which the autonomous arrangement of nanoparticles emerges into structures even without external intervention.² These unique characteristics make nanotechnology emerge with tremendous progress in the field of drug delivery. In particular, the development of refined means of delivering therapeutic dosage of a drug to target sites is crucial in clinical science. Such applications will be a breakthrough in providing therapeutic strategies for periodontal diseases.

Periodontitis is a chronic inflammatory disease affecting the supporting structures of the tooth, namely, the gingiva, periodontal ligament, cementum and alveolar bone.³ The relationship between bacterial plaque and the development of periodontal disease is well established. Antibacterial agents have been used effectively as adjuvants to conventional mechanical debridement due to limited access to the periodontopathic organisms in the deep periodontal pocket and those that are invasive in nature.^{4,5} However, the systemic administration of antimicrobials is not routinely warranted in the treatment of periodontal diseases due to the development of microbial resistance, gastric intolerance, inadequate drug concentration reaching the target site, etc.

with additional side effects.⁶ Hence, local delivery of antimicrobials has been considered for overcoming the limitations of systemic antimicrobial therapy and has gained tremendous interest.⁷ Nanotechnological drug delivery approaches provide an appropriate path through which therapeutic molecules incorporated into nanocarriers are used for targeted drug delivery at the inflamed periodontal site.⁸

Additionally, the nanocarriers provide significant improvements in the biodistribution and bioavailability of drugs. Currently, nanotechnological advances are of immense attention to significantly upgrading the properties of existing drug delivery systems. Continued clinical research in this direction will undoubtedly render a near-ideal drug delivery strategy for managing periodontal diseases. This review highlights the various nano-drug delivery systems for the management of periodontal diseases.

NANO- DRUG DELIVERY SYSTEM

A nanoparticle is a submicroscopic solid material with the size ranging from 1-100nm.⁹ Various non-toxic, biodegradable polymers have been utilized efficiently to prepare nanoparticle drug carriers.¹⁰ The nanoparticle size's inherent properties provide potential advantages in nano-drug delivery compared to emulsion-based carriers and microparticles. The advantages are; 1. Controlled release characteristics, enhanced stability and dissolution in aqueous medium;¹¹ 2. Increased transportation across the cell membrane which reduces clearance and enhances bioavailability; 3. Improved drug loading ability due to increased surface area per unit mass and higher surface reactivity;^{12,13} 4. Size simulating and biomimicking natural tissue and thus better tissue tolerance.

Several chemical and physical adsorption methods are used to modify the surface properties, altering their geometry and architecture. This

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results in enhanced drug loading, drug transportation, drug release, degradability and biocompatibility. Additionally, the property of hydrophilicity is crucial in the assemblage of nanoparticles *in situ*, thus influencing the adsorption and degradability of the drug, tissue response and clearance from the body.¹⁴

The various nanoparticles that are being employed for drug delivery in the management of periodontal diseases include nanospheres, nanocapsules, nanofibers, nanogels, nanocomposites, dendrimers and

liposomes. Table 1 highlights the various nano-formulations that can be used for the management of periodontal disease.

Nanospheres and nanocapsules

They are considered as components of nanoparticles differing in their morphology. Nanospheres are composed of a dense polymeric matrix and nanocapsules are formed of an oil core enclosed by a polymeric membrane.³³ These two forms make up the polyerosomes and contribute to the most significant class of nanoparticles for drug

Table 1: Nano-formulations for the management of periodontal disease.

Nano-delivery system	Study inference	Reference
Nanoparticles	Triclosan loaded nano-particles prepared using poly(D,L-lactide-co-glycolide), poly(D,L-lactide) and cellulose acetate phthalate, produced and characterized by the emulsification- diffusion process were able to reduce gingival inflammation. Thus, could be a promising novel nano-delivery system	Pinon-Segundo <i>et al.</i> 2005 ¹⁵
	Poly (D,L-lactide-co-glycolide) nanoparticles incorporated with <i>Harungana madagascariensis</i> leaf extract showed better antibacterial activity against the important oral pathogens causing dental caries and gingivitis	Moulari B <i>et al.</i> 2006 ¹⁶
	PEGylated PLGA nanoparticles containing minocycline, prepared by ion pairing, showed the highest drug loading and greater antibacterial activity than the free drug	Kashi TS <i>et al.</i> 2012. ¹⁷
	Poly(ethylene glycol)-poly(lactic acid) nanoparticles loaded with minocycline were locally administered to treat periodontitis in dogs	Yao <i>et al.</i> 2014 ¹⁸
	Minocycline concentration in the gingival crevicular fluid (GCF) showed a gradual decrease while retaining an effective concentration of the drug over a longer period of time	
	Tetracycline nanoparticles prepared by ionic gelation process showed sustained drug release, antibacterial activity against <i>Staphylococcus aureus</i> and <i>Escherichia coli</i> , unaltered cytocompatibility and enhanced alkaline phosphatase activity. Thus, could be useful in periodontal management	Reddy NS <i>et al.</i> 2014 ¹⁹
PolymP- <i>n</i> Active nanoparticles loaded with calcium and zinc, resulted in the precipitation of calcium phosphate and showed non-toxicity. Thus, could provide useful strategy for periodontal treatment	Osorio R <i>et al.</i> 2016 ²⁰	
Nanofibers	Poly ϵ -caprolactone electrospun nanofibers incorporated with metronidazole benzoate showed a sustained drug release suitable for managing periodontal disease	Zamani M <i>et al.</i> 2010 ²¹
	A sustained release drug system of Poly ϵ -caprolactone electrospun nanofibers containing metronidazole was clinically evaluated for the management of periodontal disease. The retentive nanofibers resulted in controlled delivery of the drug	Chaturvedi TP <i>et al.</i> 2012 ²²
	Doxycycline incorporated Poly ϵ -caprolactone electrospun nanofibers were clinically evaluated in chronic periodontitis patients and showed better drug retention and a controlled delivery	Chaturvedi TP <i>et al.</i> 2013 ²³
	The electrospun collagen chitosan membrane showed excellent biocompatibility, physiochemical properties and a highly positive effect on guided bone regeneration. Hence the membrane showed a good prospect in tissue regeneration	Guo S <i>et al.</i> 2019 ²⁴
	The electrospun poly ϵ -caprolactone polymer membranes incorporated with <i>Pterodon pubescens</i> Benth and <i>Arrabidaea chica</i> Verlot showed a controlled release of the active compounds and induced fibroblast formation. Thus, proved to be suitable for applications in GTR	Salles TH <i>et al.</i> 2020 ²⁵
Nanogels and nanocomposites	A novel bioactive composite containing 3% of 2-methacryloyloxyethyl phosphorylcholine and 3% of dimethylaminohexadecyl methacrylate for class V restorations in sub-gingival areas, significantly inhibited bacterial growth of four aggressive periodontal pathogens, thus prevented periodontitis in those restored teeth	Wang L <i>et al.</i> 2016 ²⁶
	Chitosan based nanogel system of dual action with triclosan and flurbiprofen showed anti-bacterial and anti-inflammatory activity, showed excellent therapeutic outcomes on experimental periodontitis in rats	Aminu N <i>et al.</i> 2019 ²⁷
Dendrimers	Triclosan, an effective antimicrobial agent encapsulated into the PAMAM dendrimer resulted in the solubilization of TCN, thus slow release of the drug and improved efficacy	Gardiner K <i>et al.</i> 2008 ²⁸
	PAMAM dendrimer loaded with different metronidazole concentrations showed prolonged release of the drug, thus proved to be a suitable vehicle for the delivery of antimicrobial drugs at the target site. Hence, it has a relevant application in periodontal therapy	Dung Th <i>et al.</i> 2013 ²⁹
Liposomes	liposome-encapsulated superoxide dismutase showed a suppression in periodontal inflammation in artificially induced periodontitis in beagle dogs	Petelin M <i>et al.</i> 2001 ³⁰
	Doxycycline incorporated nano-liposome slow drug- release gel showed a reduction in MMP-8 levels and an improvement in rat periodontitis	Jin HL <i>et al.</i> 2010 ³¹
	The pH activated quaternary ammonium chitosan-liposome nanoparticles exhibited excellent cytocompatibility, inhibited biofilm formation and thus proved a promising system for the treatment of periodontal diseases	Hu F <i>et al.</i> 2019 ³²

delivery.^{34,35} The term polymer therapeutics constitutes the nanosized therapeutic agents consisting of a water-soluble polymer covalently linked to the active component, a drug molecule, gene, protein, or peptide.³⁶ They are rigid particulate material with size ranging from 1nm- 1000nm. Their surface hydrophilicity and presence of free functional groups allow adequate modification leading to fine-tuning of the drug loading and drug release ability as well as their biodegradability. They also become extremely dispersible in an aqueous medium, attain high stability and provide a controlled release of the drug.³⁷ Additionally, a polymer-protein conjugate results in improved biological and clinical efficacy due to the extended plasma circulation period by altering the proteolytic degradation.³⁸

The use of these biodegradable polymers has gained considerable attention in periodontal therapy.^{39,40} The antibacterial agent is incorporated into nanospheres made of biopolymers. The gradual disintegration of the nanospheres results in the controlled release of the drug and site-specific drug delivery. Nanocapsules made of poly(lactic-co-glycolic acid), PLGA, have shown to cause photo destruction of plaque biofilm and enhanced drug delivery.⁴¹ An intrapocket drug delivery system consisting of polymeric nanoparticles loaded with triclosan has been used effectively to treat periodontitis.¹⁵ It is also shown that PLGA nanoparticles combined with polyethylene glycol nanoparticles incorporating minocycline have shown to exhibit better antibacterial action than the free drug.¹⁷ This is due to the better penetration and delivery of the drug facilitated by the nanoparticles. The enhanced antibacterial activity of the active drug is due to the biopolymers' bio-adhesive nature, which binds to the bacterial cell wall and thus prolongs the drug action.

Nanofibers

Nanofibers are rigid or flexible in nature, with a size of around 100nm in diameter. They are fabricated by electrospinning, laser spinning, or phase separation utilizing the natural, synthetic or hybrid polymers.^{42,43} A combination of these polymers is also used to increase the resistance and stability. Poly(caprolactone), poly(p-dioxanone) and chitosan are the most used polymers for its fabrication. Nanofibers are currently being explored for drug delivery of various active molecules.⁴⁴ Several biomolecules, proteins and antimicrobial molecules such as tetracycline, ciprofloxacin, metronidazole are being incorporated into nanofibers. The nanofibers are considered a good option for antimicrobial drug delivery systems and guide the formation of periodontal tissues.⁴⁵ Poly (caprolactone) nanofibers incorporated with metronidazole, ciprofloxacin and a combination of both have shown to exhibit potent antimicrobial properties against micro-organisms associated with periodontal disease, namely *Porphyromonas gingivalis*, *Fusobacterium nucleatum* and *Aggregatibacter actinomycetemcomitans*.⁴⁶ However, the use of nanofibers for drug delivery in periodontal treatment resulted in the burst release of the antimicrobial agent and hence impaired its long term therapeutic efficacy. To overcome this drawback, multilayer constructs were designed to increase the drug retention ability in the nanofibers. In addition to delivering antimicrobial agents, it has the potential for bone tissue regeneration in periodontal therapy. The promising results shown by the nanofibers suggest that it has the propensity to be routinely included in periodontal treatment modalities.

Nanogels/ nanocomposites

Currently, the nanocomposite hydrogels have gained considerable attention for drug delivery. They are formed by a blend of various components such as nanoparticles, a matrix system gel and a suitable antimicrobial agent. The nanoparticles were obtained by free-radical initiated copolymerization of monomers, 2-hydroxyethyl methacrylate

(HEMA) and polyethylene glycol dimethacrylate in an aqueous medium.⁴⁷ Finally, the nanocomposite hydrogels are synthesized by the blending of the nanoparticles, the monomers and the drug in an aqueous medium followed by crosslinking by photopolymerization. The nanoparticles, thus incorporated in the hydrogel matrix, form a new drug delivery device for the management of periodontal disease. An antimicrobial release system of chitosan nanocomposites incorporating copper nanoparticles exhibited potent *in vitro* antimicrobial activity against *A. actinomycetemcomitans* and thus appeared a promising tool in periodontal therapies.⁴⁸ Additionally, chitosan and pectin hydrogel incorporating chlorhexidine (CHX) showed improved bioavailability of CHX and exhibited a good drug-releasing ability.⁴⁹ Due to its higher bio-adhesive property, nanogels facilitate better adhesion in the periodontal pocket. Due to the high-water content, it possesses good flow properties and is thus a promising drug delivery system in periodontal therapy.

Dendrimers

Dendrimers are hyperbranched nanoparticulate structures made up of unimolecular micelles having a unique architecture. It possesses an outer hydrophilic and inner hydrophobic structure, making it a novel drug delivery vehicle.⁵⁰ They are also described as cascade polymers or arboroles. A dendrimer is composed of three layers: the core, building blocks and numerous functional groups at its periphery. The central core encapsulates the active chemical ingredient. The building blocks with its repeating units in the internal layers are arranged in a geometrical fashion, forming concentric layers called generations.⁵¹ Dendrimers are the most extensively explored polymer-based nanocarriers.⁵² The polypropylene imine⁵³ and the polyamidoamine dendrimers⁵⁴ are widely studied in the field of medicine. The active molecules can either get conjugated onto the surface or get encapsulated into the dendrimer architecture.⁵⁵ The PAMAM, which is cationic in nature, binds well to the anionic mucin creating an electrostatic attraction between them, thus, exhibiting mucoadhesive activity for its use in periodontal management. The gelatin-coated PAMAM dendrimer loaded with different metronidazole concentrations showed prolonged release of the drug, thus proving to be a suitable vehicle for the delivery of antimicrobial drugs at the target site. Hence, it has a relevant application in periodontal therapy.²⁹ Due to its hyperbranched structure and enhanced mucoadhesivity, it can thus as a superior drug delivery vehicle for the management of periodontal disease. An antimicrobial agent like triclosan (TCN) encapsulated into the dendrimer results in the solubilization of TCN, resulting in slow release of the drug and improved efficacy.²⁸ Thus the use of dendrimers as carriers of hydrophobic drug components is a potential strategy for delivering certain active pharmaceutical agents that otherwise may result in deranged pharmacokinetics due to its limited aqueous solubility.

Liposomes

Liposomes, the self-assembled nanoparticles composed of lipid bilayers, are extensively employed for biomedical applications.⁵⁶ Liposomes are spherical vesicles composed of an inner aqueous core and outer chemically active one to several concentric lipid bilayers. The lipid bilayers possess hydrophilic heads facing the surface and hydrophobic hydrocarbon tails encapsulating the aqueous spaces.⁵⁷ This feature makes them versatile drug carrier systems as they acquire the ability to stabilize and encapsulate hydrophilic molecules in its aqueous core and hydrophobic molecules in the lipid bilayers.⁵⁸ They are composed of either natural phospholipids or non-ionic surfactant components. Due to their lipid nature, they fuse with the bacterial cell membrane and destroys them.⁵⁹

The nanoscale version of liposomes is called nanoliposomes ranging with a diameter of 50-150nm. Apart from the physicochemical similarities with conventional liposomes, nanoliposomes additionally carry all the benefits of nanocarrier systems. The unilamellar or oligolamellar liposomes with an average size of 80 nm are used widely for drug delivery in cancer therapy.⁶⁰ The drug distribution in liposomes is mainly controlled by the characteristics of the liposomal carrier rather than the properties of the drug molecules alone. Hence there is improved therapeutic efficacy of the drug due to its extended half-life and absence of antigenic reactions.⁶¹ The doxycycline incorporated nano-liposome slow-release gel evaluated for the treatment of rat periodontitis showed an improvement in the condition by decreasing matrix metalloproteinase- 8.³¹ The unique, versatile feature of liposomes, their ability to encapsulate the hydrophobic and hydrophilic drugs even in nanoscale range, their similarity to biological membranes as well as their biodegradable and biocompatible nature makes them an attractive drug delivery system, which could thus be further explored for the management of periodontal diseases.

CONCLUSION

The nanocarriers encompass a specific, efficient and controllable drug delivery method, whose unique characteristics are beneficial for managing periodontal disease. They possess the exceptional potential to control periodontal disease due to their versatile nature and ability to modulate the drug release kinetics. They can effectively overcome the limitations of conventional local drug delivery systems while heading towards an integrated direction of therapy. The nanocarriers' application in the field of periodontics is at its infancy. Hence, several challenges need to be addressed by specialists from various disciplines whose harmonious collaboration can ultimately transform nanotechnology-controlled drug delivery from research to therapy.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

GTR: Guided Tissue Regeneration; **PAMAM:** Polyamidoamine.

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Article History: Submission Date : 18-07-2020; Revised Date : 22-11-2020; Acceptance Date : 19-12-2020

Cite this article: Yadalam PK, Arumuganainar D, Kasipandian R, Varatharajan K. Nanodrug Delivery Systems in Periodontics. *Int. J. Pharm. Investigation.* 2021;11(1):5-9.