Journal of Advances in Medicine and Medical Research

26(6): 1-17, 2018; Article no.JAMMR.40828
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Nanotechnology Controlled Local Drug Delivery System for the Treatment of Periodontitis

Vishal Garg[1*], Kirti Chawla[2] and Simran Kaur Pawar[3]

[1]Maulana Azad Institute of Dental Sciences, New Delhi, India.
[2]Department of Periodontology, Faculty of Dentistry, Jamia Milia Islamia, New Delhi, India.
[3]Healthy Smile Dental Care and Cure Clinic, Mohali, Punjab, India.

Authors' contributions

This work was carried out in collaboration between all authors. Author VG did the literature search and review and contributed to manuscript writing. Author KC contributed for literature search, manuscript writing and editing. Author SKP edited the manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2018/40828
Editor(s):
(1) Muhammad Torequl Islam, Nuclear of Pharmaceutical Technology (NTF), Federal University of Piaui, Brazil.
Reviewers:
(1) Kauss Tina, University of Bordeaux, France.
(2) Mirazul Islam, University of Malaya, Malaysia.
(3) David K. Mills, Louisiana Tech University, USA.
Complete Peer review History: http://www.sciencedomain.org/review-history/24597

Review Article

Received 19th February 2018
Accepted 7th May 2018
Published 12th May 2018

ABSTRACT

Nanotechnology is one of the most promising technologies of the 21st century. The remarkable application of nanotechnology for targeted site-specific drug delivery has created significant improvements in the bioavailability and bio-distribution of the drugs. There have been various efforts in designing different drug delivery systems for periodontal diseases based on the functionalized nanoparticles.

The aim of this article is to review the recent information regarding the experimental progress on nanotechnology in the treatment of various periodontal diseases comprehensively. Novel applications of different types of nanomaterials (nanoparticles to 3D nanostructured scaffolds) for treating periodontal diseases are summarized. Moreover, this paper also focuses on basic principles of utilizing the nanomaterials to create better drug delivery systems for treatment of periodontal diseases.

We addressed some queries to electronic databases including, Google Scholar, Google Books, and

**Corresponding author: E-mail: vishalgarg0055@gmail.com;*

MEDLINE using the keywords nanotechnology in periodontics, Nano drug delivery in periodontics and we have taken into consideration the articles and monographs in the field of nanomedicine and nanotechnology issued in English until the February 2018. From the collected materials, we have conceived a summary of the data about the design and architecture of nanomaterials, as well as their applications in dental nanomedicine.

By the improvement in the periodontal drug delivery systems, it can be emphasized that the nanoparticles technology which is antibiotic free, mucoadhesive, biodegradable has a huge opportunity for designing a novel, low dose, and effective treatment. It will make possible for Nano dentistry to maintain the comprehensive oral health by employing nanomaterials, biotechnology which includes the tissue engineering and dental nanorobotics. Even though this technology is at a primary stage, it has already made a profound clinical and commercial impact in the field of dentistry.

Keywords: Local drug delivery; nanotechnology; periodontitis; periodontal diseases.

1. INTRODUCTION

The definition of nanotechnology has evolved over the past few years. The Merriam dictionary [1] definition states that nanotechnology is "the art of manipulating materials on an atomic or molecular scale specially to build microscopic devices." Other definitions include the US government [2] which state that "Nanotechnology is research and technology development at the atomic, molecular or macromolecular level in the length scale of approximately 1 nm-100 nm range, to provide a fundamental understanding of phenomena and materials at the nanoscale and to create and use structures, devices, and systems that have novel properties and functions because of their small and/or intermediate size." The earliest definition concerned only the size of materials (1 nm-100 nm). Currently, nanotechnology is being exploited to promote and control biological interactions because nanoscale (1 nm ~100 nm) materials are ubiquitous. For instance, all human tissues consist of hierarchical structures which are principally based on the nanoscale. The traditional disciplines of sciences are being revolutionized by the interdisciplinary fields of nanobiotechnology, including nanomedicine. For example, the emergence of nanotechnology brought tremendous progress in the research area of controlled drug delivery. These systems are approachable to multitasking 'smart' entities with the capability to sense, diagnose, image and cure numerous diseases [3,4,5]. Acknowledging these advancements has also evoked an interest in nanotoxicity because it is widely unknown how the body reacts to particulate drug-delivering materials of this size range.

Oral cavity inhabits millions of micro-organisms. These microbes are commensals as well as pathogenic. The pathogenic bacteria cause various types of infective diseases. Periodontal diseases are one of the most active areas of the oral infectious diseases. Therefore, most of the nanotechnology-based drug delivery applications are focused towards treating it. Periodontal problems are considered to be one of the dental problems globally. It is one of the primary cause of tooth loss and other oral health problems throughout the world [6].

Periodontal disease is defined as the inflammation of the gingiva and adjacent deeper periodontal tissues, leading to gingival swelling, hemorrhaging, and bad breath. The end stage of the disease results in the degeneration of the supporting structures along with alveolar bone breakdown and formation of periodontal pocket due to gingival epithelium migration [7,8,9]. The objective of periodontal treatment is to eradicate the bacterial deposits or dental plaque (biofilm) from the surface of the tooth by a combination of mechanical treatment and adequate oral hygiene to prevent the reoccurrence of infection in the subgingival area by periodontopathic microorganisms and consequently to preserve the tooth [10,11,12].

In the treatment of periodontal diseases, the primary hindrance is delivering therapeutic agents to the periodontal pocket (target site). Local drug delivery consists of using lower dosage which is a benefit of achieving higher concentrations of the drug to the target site associated with a reduction in side effect and toxic effects. For instance, irrigation devices dentifrices, mouth rinses, dental gels, and syringes.

The inefficiency of mouth rinses and dentifrices is due to a limited period of contact of the drug

within the tissues with lack of selectivity and inadequate penetration into the periodontal pocket. Dental irrigation assists in lowering the subgingival microflora and dental plaque. Small improvements in clinical and microbiological parameters seen by using gel such as metronidazole (MET), tetracycline (TET), minocycline (MIN) which also allow inaccurate dosage [13,14].

Systemic antibiotics are now rarely used for the periodontal treatment disease because of side effects such as the rapid decline of antibiotic concentration in the plasma to subtherapeutic levels, gastrointestinal intolerance, the inadequate amount of antibiotic concentration at the site of the target site, development of microbial resistance, and hypersensitivity. These side effects have gained researchers' interest in the emergence of new effective local drug delivery systems for the periodontal disease treatment.

Drug delivery systems are the approaches, formulations, technologies, and methods for carrying pharmaceutical compound in the body to establish a therapeutic effect safely. An ideal drug delivery system should be capable of transporting active compound(s) to the intended site of action safely. It should be able to make optimal contact with the mucosal surfaces in the periodontium and should enhance the residence time at the targeted site (i.e., in the periodontal pocket). Also, delivery system should strengthen contact with the junctional epithelium to improve the epithelial transport of inefficiently absorbable drugs. This method is a preferable approach to enhance the regeneration ability of deteriorated tissues and to treat periodontal disease efficiently.

These goals can be achieved using nanotechnological drug delivery approaches. They provide a path by which therapeutic molecules such as nanoparticles or scaffolds could be capsulated/loaded in carriers, to allow targeted, sustained and controlled release to the intended site of action [15].

A considerable number of nanoparticulate drug delivery systems have emerged during the last two decades, and many of them have shown favorable results [16]. Among the main benefits of this approach is that drug concentration in the periodontal tissue is enhanced by including the drug into controlled release delivery systems that can be deposited locally in the periodontal pockets [17,18]. Hence, minimizes the exposure of the drug in the overall body [19,20]. This local drug delivery system can be used even in areas with which are difficult to access due to anatomical complexity or depth, as in furcation defects [21]. Many reports have revealed that associating the active moiety with a carrier system is an efficacious approach to optimize targeting or to enhance the action of drugs [22].

Many studies have been carried out in the past to assess the efficacy of nanoparticles as local drug delivery systems [23,24,25]. A compilation of the recent research data on the use of nanotechnology for local drug delivery systems in periodontology is not available. Therefore, in this review, the current developments and novel application of periodontal-related nano-drug delivery are summarized, and the trends of existing studies to acquaint the researchers, formulation scientists, and health-care providers.

2. METHODS

A literature search with no restrictions regarding status or language of publication was done both electronically and manually. We addressed some queries to electronic databases including, Google Scholar, Google Books, and MEDLINE using keywords nanotechnology, local drug delivery, periodontology, periodontics, periodontitis and periodontal diseases. The articles and monographs in the field of nanomedicine and nanotechnology issued in English until February 2018 were taken into consideration. From the collected data, we have conceived a summary of the research findings about the design and architecture of nanomaterials, as well as their applications and advantages in periodontal local drug delivery systems.

3. NANOPARTICLE SIZE MATERIALS APPLICATION AS DRUG DELIVERY SYSTEMS

3.1 Fundamental and Principles

The inherent properties of nanoscale materials (physical, chemical, mechanical, electrical, magnetic and optical properties) can be utilized to strengthen the performance of drug delivery systems. The nanometer particle size of a drug carrier provides various benefits for drug delivery purposes, which include

i. Increased transport across cell membranes, hence, lowering clearance from the body and enhancing targeted drug delivery. [3,26]
ii. More surface area-to-volume ratios and consequently greater surface reactivity, as a result, improving drug loading ability, providing controlled dissolution rates and drug bioavailability; [27]
iii. Dispersibility for homogeneous drug loading also increased with the release of drug molecules;
iv. Size simulating to natural tissue components, therefore enable better tissue acceptance by biomimicking tissue structure.

Many reports have shown that the differences among the size of drug carriers in the nanoscale range strongly influence the drug bioavailability and blood circulation times [3,28,29].

A variety of geometries and architecture of drug carriers also influence the drug release. Nanoscale hollow structures (specifically, tubes, cages, shell, and so forth) have revealed precise handling over drug loading amounts and time of release. By controlling tube length, diameter, and wall thickness, one can control many aspects of drug delivery (such as loading amount and time of release) [30]. Nanomaterials consist of different magnetic, electrical and optical properties which is advantageous for controlled drug delivery processes by helping in the external handling of drug transportation, targeting, and even sensing, diagnosing and treating the disease at the same time [31,32,33].

The modification done on surface properties of nanomaterials through physical or chemical adsorption methods build superior drug delivery systems through nanotechnology. The physical or chemical adsorption of drugs to nanoparticles is governed by the natural chemistry or physical properties of the materials, which also affects drug loading, particle transportation, drug release, biocompatibility and degradability properties. A critical surface property of the drug carriers is surface hydrophilicity. This property can determine the construction and assembly of nanomaterials in situ, affecting the adsorption/desorption of drug and proteins, cell and tissue responses as well as clearance from the body [34]. Intended delivery of drug has been improved by the application of nanoswitches, nanosensors, and other nanodelivery systems.

The primary objective of nanoparticulate drug delivery system is the entry of drug on nanoparticles as carriers into the cell by the process of endocytosis and delivery of the drug to the desired tissue or cell to reduce the drawbacks. Various nanoscale delivery vehicles are now under research such as nanoshells, polymeric particles, dendrimers, magnetic nanoparticles liposomes, gold nanoparticles, etc.

4. NANOPARTICULATE MATERIAL FOR DRUG DELIVERY SYSTEMS

A nanoparticle is a small rigid material with the size varying from 1 nm -100 nm [2]. Materials utilized for the production of a nanoparticle can be biodegradable such as albumin, ethyl cellulose, gelatin polyesters, or non-biodegradable. These materials are serializable and non-toxic [35,36]. Nanoparticulate drug delivery systems can be endocytosed directly as compared to the larger size drug-delivery particles which release high local drug concentrations [37,38]. Hence, it can release drugs either on the exterior or interior side of the target cells which allow for smaller amounts of drug delivery to attain the desired effect. Because of their small size, nanoparticles can access sites unreachable for other devices, like the periodontal pocket regions below the gum line. Various nanoparticulate systems available for local drug delivery used for periodontal diseases include polymeric nanoparticles, nanofibres, liposomes, quantum dots, and nanocomposites/nanogels. Dendrimers are the emerging polymeric constructs which are known for their defined structures, versatility in drug delivery and high functionality are the properties which resembles with biomolecules. These nanostructured macromolecules have shown their potential abilities in entrapping and/or conjugating the high molecular weight hydrophilic/hydrophobic entities by host-guest interactions and covalent bonding (prodrug approach) respectively [105,106].

4.1 Polymeric Nanoparticles

The most significant class of nanoparticles used in drug delivery are the polymeric nanoparticles (PNPs) owing to their easily customized biodegradability properties [39]. These PNPs are available in two forms- nanospheres and nanocapsules (polymerosomes) [40]. Drug loading and release ability of PNPs can easily be tuned by changing the surface hydrophilicity

/charge, molecular mass (MM), and free functional groups. They are particulate dissemination or rigid particles having a size varying from 1 nm–1000 nm. The drug is dispersed, trapped, enveloped, or coupled to a nanoparticle matrix. They are highly dispersible in aqueous medium, offer controlled release rate and enhanced stability [41]. A uniform drug distribution for the prolonged period is obtained thus decreasing the dosage frequency. Various studies showing PNPs loaded with the drug used for the treatment of periodontitis have been listed in Table 1.

Table 1. Polymeric Nanoparticles as Intrapocket drug delivery system for the treatment of Periodontitis

Year	Aim	Result/inference	Polymer	Drug	Ref.
2018	To develop pH-responsive polylactide-glycolic acid co-polymer and chitosan (PLGA/chitosan) nanosphere as an inflammation-responsive vehicle and evaluate the potential of the nanosphere encapsulating metronidazole, an antibiotic, and N-phenacylthiazolium bromide (PTB), a host modulator, for treating periodontitis.	PLGA/chitosan nanospheres encapsulating MET or PTB showed potential for modulating periodontitis progression.	PLGA	MET	[42]
2016	To design calcium(Ca) and zinc(Zn)-loaded bioactive and cytocompatible NPs for the treatment of periodontal disease.	Ca-loaded NPs promote precipitation of calcium phosphate deposits, together with their observed non-toxicity property offered new strategies for treating periodontal disease.	PolymP-n Active NPs	Ca & Zn	[43]
2016	To investigate the effect of antimicrobial photodynamic therapy on human dental plaque bacteria in suspensions and biofilms in vitro using methylene blue (MB)-loaded poly(lactic-co-glycolic) (PLGA-NPs and red light at 660 nm.	Utilization of PLGA nanoparticles encapsulated with MB may be a promising adjunct in antimicrobial periodontal treatment.	PLGA	MB	[44]
2016	To prepare atorvastatin calcium (ATR) loaded PCL nanoparticles (ALPNs) to assess the enhancement of oral bioavailability, efficacy and safety profile of drug.	The study showed that ALPNs as a promising novel drug delivery system for sustained release with enhanced bioavailability, efficacy and safety profile of ATR.	PCL	ATR	[45]
2015	The aim of this study was to alleviate shortcomings in periodontal treatment by	The G-PNP were prepared, characterized and	G-PNP	SZ	[46]

Year	Aim	Result/inference	Polymer	Drug	Ref.
	utilizing a mucoadhesive gel containing immunotherapeutic ganglioside coated polymeric nanoparticles (G-PNPs) bearing Satranidazole (SZ).	incorporated successfully in sodium carboxy methyl cellulose (SCMC) based gel. the formulation was highly user friendly with high degree of retention accorded by mucoadhesive nature which ensured prolonged drug exposure.			
2015	To develop and study the novel periodontitis epithelial cell-targeting nanoparticulate drug delivery system by conjugating MIN-loaded PEG–PLA NPs with RGD peptide.	RGD-NP-MIN epithelial cell-targeting NPs offered a novel and effective local delivery system for the treatment of periodontitis.	PEG-PLA	MIN	[47]
2015	To develop PGE-loaded poly-ethylenimine-dextran sulfate nanoparticles (PDNPs) and to explore the possibility of this system as a mucoadhesive buccal drug delivery system.	The drug delivery system was developed successfully with dextran sulfate played a significant role in controlling particle size and entrapment efficacy.	PDNPs	Chlor-hexidine (CHX)	[48]
2014	To prolong the residence time of the dosage form of Curcumin-loaded chitosan-coated PCL in the oral cavity and to increase drug absorption through the buccal mucosa.	Mucoadhesive films containing NPs offered a promising approach for buccal delivery of curcumin, which may be particularly useful in the treatment of periodontal diseases that require a sustained drug delivery	chitosan and plasticizer glycerol	Curcumin	[49]
2014	To prepare the MIN-loaded PEG-PLA NPs and administered locally to investigate for long drug retention and enhanced treatment of periodontitis in dogs	In-vitro release of MIN from MIN-NPs showed a remarkably sustained releasing characteristic which significantly decrease symptoms of periodontitis compared with pericline and MIN solution	PEG-PLA	MIN	[50]
2014	To fabricate, characterize and evaluate in vitro, an injectable $CaSO_4$ bone	Cytocompatible $CaSO_4$ -TET-NPs composite beads	2-hydroxyethyl methacrylate (HEMA)	TET-NPs in $CaSO_4$ beads	[51]

Year	Aim	Result/inference	Polymer	Drug	Ref.
	cement beads loaded with an antibiotic nanoformulation, capable of delivering antibiotic locally for the treatment of periodontal disease.	could be valuable in declining bacterial count at the infection site.			
2013	To assess the Ag NPs for apparent antibacterial effects against the anaerobic oral pathogenic bacteria and aerobic bacteria.	Ag NPs are more effective against aerobic bacteria than the anaerobic oral pathogenic bacteria.	Poly (D, L-lactide-coglycolide) PDLGA	Ag	[52]
2013	To assess polymersomes as vehicles to deliver antibiotics in an attempt to kill intracellular p. Gingivalis within monolayers of keratinocytes and organotypic oral mucosal models.	Polymersomes are useful delivery systems for antibiotics into host cells decreasing the count of p. Gingivalis significantly.	Polymersomes	MET, DOX	[53]
2013	To develop Triclosan-loaded PCL-NPs for the treatment of periodontal infections.	Triclosan-loaded PCL- NPs served as a novel colloidal drug delivery system against periodontal infections.	PCL	Triclosan	[54]
2012	To investigate different methods of producing PLGA NPs containing MIN, a drug suitable for periodontal infections.	MIN-PEGylated PLGA NPs prepared by the ion pairing method had the best drug loading and entrapment efficiency compared with other prepared NPs. They also showed higher antibacterial activity than the free drug.	PLGA	MIN	[55]
2012	To test a nanotechnological formulation as a carrier for 15d-pgj2, and to investigate the immunomodulatory effects of this formulation in a mouse periodontitis model.	Bone resorption and inflammatory reactions diminished in periodontitis mouse model using this formulation.	PDLGA	15-deoxy-(d12,14)-pg j (2) (15dpgj (2))	[56]
2011	To develop a local, oral mucoadhesive MET benzoate delivery system that can be applied and removed by the patient for the treatment of periodontal diseases.	The system provides targeted, sustained delivery with improved oral availability	Thiolated chitosan - poly (methacrylic acid)	MET benzoate	[57]
2007	To test the release of the oligonucleotide from chitosan-tripolyphosphate(TPP)/ oligonucleotide NPs.	Sustained release of the oligonucleotide from chitosan NPs may be suitable for the local therapeutic	Chitosan	Antisense oligonucleot ide	[58]

Year	Aim	Result/inference	Polymer	Drug	Ref.
		application in periodontal diseases.			
2006	To investigate the in vitro bactericidal activity of the ethyl acetate *H. Madagascariensis* leaf extract(HLE) on the main oral bacterial strains largely implicated in dental caries and gingivitis infections, and the possibility of potentialization of HLE antibacterial effects using the poly (d, l-lactide-coglycolide) NPs (PLG-NPs).	PLG-NPs enhanced the bactericidal effect of the extract.	PLGA	HLE	[59]
2005	To produce and characterize triclosan-loaded NPs by the emulsification–diffusion process to obtain a novel delivery system adequate for the treatment of periodontal disease.	Triclosan-loaded NPs penetrate through the junctional epithelium in in-vivo induced periodontal defects	PLGA, PLA	Triclosan	[60]

PNPs have a better stability in biological fluids. They have a god solubilization capacity, transparency, high stability and are simple to manufacture [61]. These biodegradable PNPs can penetrate into the junctional epithelium [62]. The above studies showed that these nanoparticles have no cytotoxicity and sufficient shelf life. They show improved clinical results in terms of probing depth reduction and clinical attachment gain. These advantages infer that PNPs can be used as a potential intrapocket drug delivery systems in future.

4.2 Nanofibers

Polymeric fibers having diameters in submicron or nanometer range (10^{-6}m– 10^{-9}m) are called nanofibers [63]. They allocate many outstanding features such as a greater surface area to volume ratio (this ratio can be as large as 10^3 times of that of microfiber), pliability in surface functionalities and better mechanical performance (e.g. stiffness and tensile strength) [64].

Several studies showing drug-loaded nanofibers used for the treatment of periodontitis have been listed in Table 2.

These studies show that electrospun nanofibers have advantages such as higher drug loading efficiency in comparison to encapsulation [71]. The drug release profile can be modified by a modulation on the morphology, porosity and composition of nanofibers [72]. The small diameter of nanofibers provides a short diffusion passage length and their high surface area is advantageous for mass transfer and efficient drug release [73].

4.3 Liposomes

A lipid bilayer surrounds liposome consisting of an aqueous core, which separates the inner aqueous core from the bulk outside [74]. Cholesterol and non-toxic, non-immunogenic phospholipids synthesize liposomes which make it biodegradable, biologically inert [75]. Drug distribution in liposomes is controlled primarily by properties of the liposomal carrier and no longer by physicochemical characteristics of the drug substance only [76]. Hence, the therapeutic index of drugs is improved because of reduced metabolism of drugs, extended biological half-life, and reduced toxicity. Moreover, they produce no antigenic reactions [77].

Liposomes are considered appealing and safe drug delivery carriers that can circulate in the bloodstream for a longer time because they are non-synthetic materials [78].

Table 2. Nanofibres as Intrapocket drug delivery system for the treatment of Periodontitis

Year	Aim	Result/Inference	Nanofibre	Drug	Ref.
2017	To prepare tinidazole (TNZ) functionalized biodegradable chitosan / (PCL) mucoadhesive hybrid nanofiber membrane (TNZ-PCHNF) to alleviate existing shortcomings in treatment of periodontitis	Biodegradable, TNZ loaded electrospun Chitosan/PCL hybrid nanofiber membrane was fabricated which was capable of efficiently delivering TNZ in a sustained manner up to 18 days with low burst release and able to inhibit bacterial growth.	PCHNF	TNZ	[65]
2016	The aim of this study was to alleviate shortcomings in the treatment of periodontitis by electrospinning of a novel biodegradable PCL based nanofiber membrane functionalized with TNZ.	*In vivo*-study by ligature-induced periodontitis in rats confirmed that TNZ loaded nanofiber membrane can significantly improve continuity of epithelium and trans-septal fiber of interdental papilla in comparison to tinidazole gel.	PCL	TNZ	[66]
2013	To develop a low-dose controlled-release delivery system for the treatment of periodontal infections.	Low-dose controlled released of DOX using PCL were found to be efficacious in the treatment of periodontal disease as demonstrated by improvement in probing depth (PD), plaque index (PI), and gingival index (GI) of the study subjects.	PCL	DOX	[67]
2012	To develop a low-dose controlled-release delivery system for the treatment of periodontal infections.	Low-dose controlled released of DOX using PCL were found to be efficacious in the treatment of periodontal disease with additional benefits observed when combined with Scaling and Root Planning	PCL	MET	[68]
2010	To study the sustained and controlled release of MET Benzoate from PCL electrospun nanofibers for periodontal diseases.	In vitro studies indicated low burst release and a sustained drug release of at least 19 days of MET drug.	PCL	MET-Benzoate	[69]
2009	To establish human periodontal ligament(HPDL) cell-containing structures on electrospun PLGA nanofiber membrane scaffolds, assess their viability and characteristics.	Multilayered hybrid structures were established acting as a support to cell adhesion, viability and osteogenic differentiation properties of cells	PLGA	HPDL cells seeded on PLGA nanofiber membrane scaffold	[70]

Various liposomes used for the periodontitis treatment have been listed in Table 3.

From the above studies it can be concluded that the liposomes have unique feature to compartmentalize and solubilize both hydrophilic and hydrophobic materials by nature. This unique feature, coupled with biocompatibility and biodegradability make liposomes very attractive as drug delivery vehicles [80].

4.4 Quantum Dots

QDs are submicroscopic semiconductor nanocrystals that glow brightly on stimulation by ultraviolet light, also are found to be stable and non-toxic. Their intense light absorbance property makes them eligible to be applied as fluorescent labels for biomolecules [81]. They play roles other than diagnostic purposes such as photosensitizer and carrier. QDs upon stimulation by UV light attaches an antibody to the target cell, and in turn, yield a reactive oxygen species that have the capability of killing the target cells [82]. QDs are used in periodontal therapy to improve the healing of inflamed periodontal tissues [83]. Various quantum dots used for the periodontitis treatment have been listed in Table 4.

From the study conducted on Quantum dots nanocarrier systems, it can be concluded that the drugs improve the stability of drugs [85]. This system also increases the circulation time of medicine in vivo and also improve the distribution and metabolism process of drugs [86]. Hence, increase the antimicrobial and antibiofilm activities in the oral cavity.

4.5 Nanocomposites/Nanogels

In the current data polymer, matrix-based nanocomposites have produced a significant amount of attention. The architecture of polymers or microparticle-based hydrogels influences the rate of release thereby, enabling them to be applied in periodontics. The nanocomposite hydrogels are combined as replica systems for in situ cured local drug delivery devices in the treatment of periodontal diseases. The nanocomposite consists of various components such as nanoparticles, a matrix gel, and the suitable antibacterial drug. By the process of free radical initiated copolymerization of monomers, 2-hydroxyethyl methacrylate (HEMA) and polyethylene glycol methacrylate in aqueous solution results in the formation of the nanoparticles. The same monomers are used to prepare crosslinked matrices by photopolymerization. Nanocomposite hydrogels synthesis take place by mixing the nanoparticles, monomers and the drug in an aqueous solution followed by crosslinking through the process of photopolymerization. These nanoparticles can be included in a hydrogel matrix and to design new drug delivery devices for applying the treatment of periodontal diseases. The following table outlined the application of nanocomposites for local drug delivery till date [87,88,89,90].

Table 3. Liposomes as Intrapocket drug delivery system for the treatment of Periodontitis

Year	Aim	Result/inference	Matrix	Drug	Ref.
2010	To evaluate the therapeutic effects of DOX nano-liposome slow-release gel on the periodontitis in an established rat model.	This study showed that DOX nano-liposome slow-release gel improves rat periodontitis by decreasing MMP-8 level.	Nanogel liposome	DOX	[79]

Table 4. Quantum dots as Intrapocket drug delivery system for the treatment of Periodontitis

Year	Title	Aim	Result/inference	Nanogel-nanocrystal	Drug	Ref.
2017	Curcumin Quantum Dots Mediated Degradation of Bacterial Biofilms.	To evaluate the antimicrobial and antibiofilm activities of curcumin QDs.	Curcumin quantum dots has enhanced antimicrobial as well as antibiofilm activities.	Quantum dot	curcumin	[84]

Table 5. Nanogels as Intrapocket drug delivery system for the treatment of Periodontitis

Year	Aim	Result/ Inference	Gelling agent	Drug	Ref.
2016	To design an antimicrobial release system for periodontal therapy based on chitosan and copper nanoparticles and assess it's *in- vitro* antibacterial activity against Aggregatibacter actinomycetemcomitans.	Copper nanoparticles/ chitosan nanocomposites effectively inhibit the growth of A. Actinomycete-mcomitans and appear as promissory systems for the development of localized periodontal therapies.	Chitosan hydrogel	copper	[94]
2014	To improve the bioavailability of CHX through the inclusion of the drug in the hydrogels	Hydrogels allowed the incorporation of an increased amount of chlorhexidine and presented a good drug release capacity	Chitosan and Pectin hydrogel	CHX	[95]
2013	To evaluate the drug release from the formulation of chitosan with drugs.	The chitosan gels proposed in this study have particular characteristics making them an adequate system for local, intra-pocket drug delivery.	Chitosan Gel	Tet-HCl and MET Benzo ate	[96]
2011	To Develop and optimize eugenol loaded nanostructured lipid carriers for periodontal delivery.	In the present study, a gel formulation of eugenol loaded NLC was developed for periodontal delivery such that it would effectively deliver the drug in a sustained manner.	Nanostru ctured Lipid	Eugen ol	[97]
2008	Synthesis of biocompatible nanocomposite hydrogels as a local drug delivery system	Synthesis of biocompatible nanocomposite hydrogels as a local drug delivery system with distinct advantages compared to simple hydrogels as drug delivery systems	HEMA& PEGDM A	CHX	[98]
2007	To synthesize biocompatible NPs by free radical initiated copolymerization of the monomers, 2-hydroxyethyl methacrylate (HEMA) and polyethylene glycoldimethacrylate (PEGDMA) in aqueous solution, which can support the formation of NPs that can be used as a drug delivery system for dental applications.	NPs are appropriate for introducing into a hydrogel matrix and providing a new drug delivery system	HEMA and PEG	Di-methac rylate, MET	[99]

The semisolid or gel forms can have some benefits of attaining local delivery into the periodontal pockets. Hydrogels mimic natural tissues, and because of their high-water content, they can transport these materials in a minimally invasive manner [91,92,93].

Several drug-loaded nanogels used for the treatment of periodontitis have been listed in Table 5.

Due to their higher biocompatibility and bio adhesive property, these Nanogels facilitate

adhesion to the dental pocket, and as a result, they can be rapidly terminated through normal catabolic pathways, lowering the risk of systemic anaphylactic reactions at the site of application. The therapeutic index of drugs such as efficiency, specificity, and tolerability, are also enhanced [100,101,102]. Nanogels have shown good flow properties and syringealibility capacity which are important characteristics for an intrapocket drug delivery system [103]. They have advantages of both emulsions and liposomes i.e. controlled drug release, avoid drug leakage, low toxicity, good biocompatibility and bioavailability [104].

5. CONCLUSION

Research in the recent decade has demonstrated that drug delivery systems for periodontal diseases can be enhanced using nanotechnology. Nanoparticulate used as drug delivery carriers have an exceptional potential towards treating periodontal diseases owing to their ability to modulate drug release kinetics, incorporate multifunctional molecules, target-specific and respond to various external signaling sources (whether biological, mechanical, electric or magnetic). Drug delivery using nanotechnology helps the drug to reaches the right site in the body, at the right time, at the right concentration without exerting side effects on its way to the target site or during the clearance process.

Though the application of nanotechnology to drug delivery has been dramatic and successful, several challenges still exist that needs attention to transform nanotechnology assisted drug delivery from basic research to clinical practice. The major challenges faced are understanding the underlying mechanism of controlling the intracellular uptake, and the fate of nanomaterials in complex biological networks to avoid some significant limitations such as rapid clearance by the immune system and difficulty in crossing biological barriers. Another challenge is the nature of preparation method and high cost of material employed.

Realizing such a goal requires harmonized efforts among scientists in various disciplines, including medicine, materials science, engineering, physics and biotechnology. Better cross training would produce better proposals with a greater likelihood of success. Experts from different disciplines need to work together to translate novel laboratory innovation into commercially viable medical products. In addition, continuous cooperation between federal agencies and the pharmaceutical industry is necessary. Although this technology is at an early stage, it has already made a significant clinical and commercial impact, and it will continuously revolutionize the local drug delivery area.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Merriam Webster Dictionary; 2010.
2. US Government. Available:http://www.nano.gov/ (Retrieved 20th April, 2018)
3. Anderson DG, Burdick JA, Langer R. Smart biomaterials. Science. 2004; 305(5692):1923-4.
4. Goldberg M, Langer R, Jia X. Nanostructured materials for applications in drug delivery and tissue engineering. Journal of Biomaterials Science, Polymer Edition. 2007;18(3):241-68.
5. Lavan DA, McGuire T, Langer R. Small-scale systems for *in vivo* drug delivery. Nature Biotechnology. 2003;21(10):1184.
6. Slots J. Subgingival microflora and periodontal disease. Journal of Clinical Periodontology. 1979;6(5):351-82.
7. Álvarez AL, Espinar FO, Méndez JB. The application of microencapsulation techniques in the treatment of endodontic and periodontal diseases. Pharmaceutics. 2011;3(3):538-71.
8. Jain N, Jain GK, Javed S, Iqbal Z, Talegaonkar S, Ahmad FJ, Khar RK. Recent approaches for the treatment of periodontitis. Drug Discovery Today. 2008;13(21-22):932-43.
9. Piñón-Segundo E, Mendoza-Muñoz N, Quintanar-Guerrero D. Nanoparticles as dental drug-delivery systems. In Nanobiomaterials in Clinical Dentistry. 2013;475-495.
10. Vyas SP, Sihorkar V, Mishra V. Controlled and targeted drug delivery strategies towards intraperiodontal pocket diseases.

Journal of Clinical Pharmacy and Therapeutics. 2000;25(1):21-42.

11. Jain N, Jain GK, Javed S, Iqbal Z, Talegaonkar S, Ahmad FJ, Khar RK. Recent approaches for the treatment of periodontitis. Drug Discovery Today. 2008;13(21-22):932-43.
12. Álvarez AL, Espinar FO, Méndez JB. The application of microencapsulation techniques in the treatment of endodontic and periodontal diseases. Pharmaceutics. 2011;3(3):538-71.
13. Pragati S, Ashok S, Kuldeep S. Recent advances in periodontal drug delivery systems. International Journal of Drug Delivery. 2009;1(1).
14. Unsal E, Akkaya M, Walsh TF. Influence of a single application of subgingival chlorhexidine gel or tetracycline paste on the clinical parameters of adult periodontitis patients. Journal of Clinical Periodontology. 1994;21(5):351-5.
15. Goodson JM. Antimicrobial strategies for treatment of periodontal diseases. Periodontology 2000. 1994;5(1):142-68.
16. Neel EA, Bozec L, Perez RA, Kim HW, Knowles JC. Nanotechnology in dentistry: Prevention, diagnosis, and therapy. International Journal of Nanomedicine. 2015;10:6371.
17. Chen X, Wu G, Feng Z, Dong Y, Zhou W, Li B, Bai S, Zhao Y. Advanced biomaterials and their potential applications in the treatment of periodontal disease. Critical Reviews in Biotechnology. 2016;36(4):760-75.
18. Pinon-Segundo E, Ganem-Quintanar A, Alonso-Pérez V, Quintanar-Guerrero D. Preparation and characterization of triclosan nanoparticles for periodontal treatment. International Journal of Pharmaceutics. 2005;294(1-2):217-32.
19. Schwach-Abdellaoui K, Vivien-Castioni N, Gurny R. Local delivery of antimicrobial agents for the treatment of periodontal diseases. European Journal of Pharmaceutics and Biopharmaceutics. 2000;50(1):83-99.
20. Hau H, Rohanizadeh R, Ghadiri M, Chrzanowski W. A mini-review on novel intraperiodontal pocket drug delivery materials for the treatment of periodontal diseases. Drug Delivery and Translational Research. 2014;4(3):295-301.
21. Pragati S, Ashok S, Kuldeep S. Recent advances in periodontal drug delivery systems. International Journal of Drug Delivery. 2009;1(1).
22. Kornman KS. Controlled-release local delivery antimicrobials in periodontics: Prospects for the future. Journal of Periodontology. 1993;64(8s):782-91.
23. Zupancic S, Kocbek P, Baumgartner S, Kristl J. Contribution of nanotechnology to improved treatment of periodontal disease. Current Pharmaceutical Design. 2015; 21(22):3257-71.
24. Iadiz MA, Bamedi M, Fakour SR. Periodontal diseases and recently applied nano-technology: A review article. Health. 2017;9(02):345.
25. Aminu N, Chan SY, Toh SM. Roles of nanotechnological approaches in periodontal disease therapy. Journal of Applied Pharmaceutical Science. 2017; 7(07):234-42.
26. Pramod K, Aminu N, Ali J. Targeted drug delivery systems for the treatment of periodontal infections. In: Singh B, Katare OP, Govil JN, Eds. Biotechnology, Novel Drug Delivery. U.S.A.: Studium Press LLC. 2014;8:97–128.
27. Qiu LY, Bae YH. Polymer architecture and drug delivery. Pharmaceutical Research. 2006;23(1):1-30.
28. Rabinow BE. Nanosuspensions in drug delivery. Nature Reviews Drug Discovery. 2004;3(9):785.
29. Ishida O, Maruyama K, Sasaki K, Iwatsuru M. Size-dependent extravasation and interstitial localization of polyethyleneglycol liposomes in solid tumor-bearing mice. International Journal of Pharmaceutics. 1999;190(1):49-56.
30. Kim K, Fisher JP. Nanoparticle technology in bone tissue engineering. Journal of Drug Targeting. 2007;15(4):241-52.
31. Skrabalak SE, Chen J, Au L, Lu X, Li X, Xia Y. Gold nanocages for biomedical applications. Advanced Materials. 2007; 19(20):3177-84.
32. Liu TY, Hu SH, Liu DM, Chen SY, Chen IW. Biomedical nanoparticle carriers with combined thermal and magnetic responses. Nano Today. 2009;4(1):52-65.
33. Huang X, El-Sayed IH, Qian W, El-Sayed MA. Cancer cell imaging and photothermal therapy in the near-infrared region by using gold nanorods. Journal of the American Chemical Society. 2006;128(6):2115-20.
34. Sirivisoot S, Webster TJ. Multiwalled carbon nanotubes enhance electro-chemical properties of titanium to

determine in situ bone formation. Nanotechnology. 2008;19(29):295101.
35. Marin E, Briceño MI, Caballero-George C. Critical evaluation of biodegradable polymers used in nanodrugs. International Journal of Nanomedicine. 2013;8:3071.
36. Wurm FR, Weiss CK. Nanoparticles from renewable polymers. Frontiers in Chemistry. 2014;2:49.
37. De Jong WH, Borm PJ. Drug delivery and nanoparticles: Applications and hazards. International Journal of Nanomedicine. 2008;3(2):133.
38. Singh R, Lillard Jr JW. Nanoparticle-based targeted drug delivery. Experimental and Molecular Pathology. 2009;86(3):215-23.
39. Muhamad12 II, Selvakumaran S, Lazim NA. Designing polymeric nanoparticles for targeted drug delivery system. Nanomed. 2014;287:287.
40. Muhamad12 II, Selvakumaran S, Lazim NA. Designing polymeric nanoparticles for targeted drug delivery system. Nanomed. 2014;287:287.
41. Xin Y, Yin M, Zhao L, Meng F, Luo L. Recent progress on nanoparticle-based drug delivery systems for cancer therapy. Cancer Biology & Medicine. 2017;14(3): 228.
42. Lin JH, Feng F, Yu MC, Wang CH, Chang PC. Modulation of periodontitis progression using pH-responsive nanosphere encapsulating metronidazole or N-phenacylthialzolium bromide. Journal of periodontal research. 2018;53(1):22-8.
43. Osorio R, Alfonso-Rodríguez CA, Medina-Castillo AL, Alaminos M, Toledano M. Bioactive polymeric nanoparticles for periodontal therapy. PloS One. 2016; 11(11):e0166217.
44. de Freitas LM, Calixto GM, Chorilli M, Giusti JS, Bagnato VS, Soukos NS, Amiji MM, Fontana CR. Polymeric nanoparticle-based photodynamic therapy for chronic periodontitis *in vivo*. International Journal of Molecular Sciences. 2016;17(5):769.
45. Kumar N, Chaurasia S, Patel RR, Khan G, Kumar V, Mishra B. Atorvastatin calcium loaded PCL nanoparticles: Development, optimization, *in vitro* and *in vivo* assessments. RSC Advances. 2016;6(20): 16520-32.
46. Singh Y, Vuddanda PR, Jain A, Parihar S, Chaturvedi TP, Singh S. Mucoadhesive gel containing immunotherapeutic nanoparticulate satranidazole for treatment of periodontitis: Development and its clinical implications. RSC Advances. 2015;5(59):47659-70.
47. Yao W, Xu P, Zhao J, Ling L, Li X, Zhang B, Cheng N, Pang Z. RGD functionalized polymeric nanoparticles targeting periodontitis epithelial cells for the enhanced treatment of periodontitis in dogs. Journal of Colloid and Interface Science. 2015;458:14-21.
48. Tiyaboonchai W, Rodleang I, Ounaroon A. Mucoadhesive polyethyleneimine–dextran sulfate nanoparticles containing *Punica granatum* peel extract as a novel sustained-release antimicrobial. Pharmaceutical Development and Technology. 2015;20(4):426-32.
49. Mazzarino L, Borsali R, Lemos-Senna E. Mucoadhesive films containing chitosan-coated nanoparticles: A new strategy for buccal curcumin release. Journal of pharmaceutical sciences. 2014;103(11):3764-71.
50. Yao W, Xu P, Pang Z, Zhao J, Chai Z, Li X, Li H, Jiang M, Cheng H, Zhang B, Cheng N. Local delivery of minocycline-loaded PEG-PLA nanoparticles for the enhanced treatment of periodontitis in dogs. International Journal of Nano-Medicine. 2014;9:3963.
51. Reddy NS, Sowmya S, Bumgardner JD, Chennazhi KP, Biswas R, Jayakumar R. Tetracycline nanoparticles loaded calcium sulfate composite beads for periodontal management. Biochimica et Biophysica Acta (BBA)-General Subjects. 2014; 1840(6):2080-90.
52. Lu Z, Rong K, Li J, Yang H, Chen R. Size-dependent antibacterial activities of silver nanoparticles against oral anaerobic pathogenic bacteria. Journal of Materials Science: Materials in Medicine. 2013;24(6):1465-71.
53. Wayakanon K, Thornhill MH, Douglas CI, Lewis AL, Warren NJ, Pinnock A, Armes SP, Battaglia G, Murdoch C. Polymersome-mediated intracellular delivery of antibiotics to treat Porphyromonas gingivalis-infected oral epithelial cells. The FASEB Journal. 2013; 27(11):4455-65.
54. Aminu N, Baboota S, Pramod K, Singh M, Dang S, Ansari SH, Sahni JK, Ali J. Development and evaluation of triclosan loaded poly-ε-caprolactone nanoparticulate system for the treatment of periodontal infections. Journal of Nanoparticle Research. 2013;15(11):2075.

55. Kashi TS, Eskandarion S, Esfandyari-Manesh M, Marashi SM, Samadi N, Fatemi SM, Atyabi F, Eshraghi S, Dinarvand R. Improved drug loading and antibacterial activity of minocycline-loaded PLGA nanoparticles prepared by solid/oil/water ion pairing method. International Journal of Nanomedicine. 2012; 7:221.
56. Napimoga MH, da Silva CA, Carregaro V, Farnesi-de-Assuncao TS, Duarte PM, de Melo NF, Fraceto LF. Exogenous administration of 15d-PGJ2–loaded nanocapsules inhibits bone resorption in a mouse periodontitis model. The Journal of Immunology. 2012;189(2):1043-52.
57. Saboktakin MR, Tabatabaie RM, Maharramov A, Ramazanov MA. Development and in vitro evaluation of thiolated chitosan—Poly (methacrylic acid) nanoparticles as a local mucoadhesive delivery system. International Journal of Biological Macromolecules. 2011; 48(3):403-7.
58. Dung TH, Lee SR, Han SD, Kim SJ, Ju YM, Kim MS, Yoo H. Chitosan-TPP nanoparticle as a release system of the antisense oligonucleotide in the oral environment. Journal of Nanoscience and Nanotechnology. 2007;7(11):3695-9.
59. Moulari B, Lboutounne H, Chaumont JP, Guillaume Y, Millet J, Pellequer Y. Potentiation of the bactericidal activity of Harungana madagascariensis Lam. ex Poir. (Hypericaceae) leaf extract against oral bacteria using poly (D, L-lactide-co-glycolide) nanoparticles: in vitro study. Acta Odontologica Scandinavica. 2006; 64(3):153-8.
60. Pinon-Segundo E, Ganem-Quintanar A, Alonso-Pérez V, Quintanar-Guerrero D. Preparation and characterization of triclosan nanoparticles for periodontal treatment. International Journal of Pharmaceutics. 2005;294(1):217-32.
61. Kreuter, J., 1994. Nanoparticles. In: Kreuter, J. (Ed.), Colloidal Drug Delivery Systems. Marcel Dekker, New York, pp. 219–220.
62. Ganem-Quintanar AF. Etude de la perméabilité de la muqueuse orale: Évaluation de différentes approches pour augmenter le passage des principes Actifs (Doctoral dissertation).
63. Garg T, Malik B, Rath G, Goyal AK. Development and characterization of the nano-fiber patch for the treatment of glaucoma. European Journal of Pharmaceutical Sciences. 2014;53:10-6.
64. A Chou SF, Woodrow KA. Relationships between mechanical properties and drug release from electrospun fibers of PCL and PLGA blends. Journal of the Mechanical Behavior of Biomedical Materials. 2017; 65:724-33.
65. Khan G, Yadav SK, Patel RR, Kumar N, Bansal M, Mishra B. Tinidazole functionalized homogeneous electrospun chitosan/poly (ε-caprolactone) hybrid nanofiber membrane: Development, optimization and its clinical implications. International Journal of Biological Macromolecules. 2017;103:1311-26.
66. Khan G, Patel RR, Yadav SK, Kumar N, Chaurasia S, Ajmal G, Mishra PK, Mishra B. Development, optimization and evaluation of tinidazole functionalized electrospun poly (ε-caprolactone) nanofiber membranes for the treatment of periodontitis. RSC Advances. 2016; 6(102):100214-29.
67. Chaturvedi TP, Srivastava R, Srivastava AK, Gupta V, Verma PK. Doxycycline poly e-caprolactone nanofibers in patients with chronic periodontitis–a clinical evaluation. Journal of Clinical and Diagnostic Research: JCDR. 2013;7(10):2339.
68. Chaturvedi TP, Srivastava R, Srivastava AK, Gupta V, Verma PK. Evaluation of metronidazole nanofibers in patients with chronic periodontitis: A clinical study. International Journal of Pharmaceutical Investigation. 2012;2(4):213.
69. Zamani M, Morshed M, Varshosaz J, Jannesari M. Controlled release of metronidazole benzoate from poly ε-caprolactone electrospun nanofibers for periodontal diseases. European Journal of Pharmaceutics and Biopharmaceutics. 2010;75(2):179-85.
70. Inanç B, Arslan YE, Seker S, Elçin AE, Elçin YM. Periodontal ligament cellular structures engineered with electrospun poly (DL-lactide-co-glycolide) nanofibrous membrane scaffolds. Journal of Biomedical Materials Research Part A. 2009; 90(1):186-95.
71. Dastjani-Farahani F, Keshvari H, Gholipour-Kanani A, Bonakdar S, Shokrgozar MA. Mechanical reinforcement of chitosan-gelatin sponge with polycaprolactone electrospun nanofibrous sheets. J. Biomater. Tissue Eng. 2013;3: 320-29.

72. Huang ZM, et al. Encapsulating drugs in biodegradable ultrafine fibers through co-axial electrospinning. J Biomed Mater Res. 2006;Part A 77A1:169–79.
73. Verreck G, et al. Incorporation of drugs in an amorphous state into electrospun nanofibers composed of a water-insoluble, nonbiodegradable polymer. J Controlled Release. 2003;92:349–60.
74. Gregoriadis G, Florence AT. Liposomes in drug delivery. Drugs. 1993;45(1):15-28.
75. Van Rooijen N, van Nieuwmegen R. Liposomes in immunology: Multilamellar phosphatidylcholine liposomes as a simple, biodegradable and harmless adjuvant without any immunogenic activity of its own. Immunological Communications. 1980;9(3):243-56.
76. Campbell PI. Toxicity of some charged lipids used in liposome preparations. Cytobios. 1983;37(145):21-6.
77. Grislain L, Couvreur P, Lenaerts V, Roland M, Deprez-Decampeneere D, Speiser P. Pharmacokinetics and distribution of a biodegradable drug-carrier. International Journal of Pharmaceutics. 1983;15(3):335-45.
78. Illum L, Jones PD, Kreuter J, Baldwin RW, Davis SS. Adsorption of monoclonal antibodies to polyhexylcyanoacrylate nanoparticles and subsequent immunospecific binding to tumour cells in vitro. International Journal of Pharmaceutics. 1983;17(1):65-76.
79. Jin HL, Wu W, Shu R. Doxycycline nano-liposome slow-release gel improves rat periodontitis. Shanghai Kouqiangyi xue= Shanghai Journal of Stomatology. 2010; 19(5):508-11.
80. Harini G, Kaarthikeyan G. Advanced drug delivery systems in treating periodontal diseases-a review. Journal of Dental and Medical Sciences. 2014;13(1):27-32.
81. Alharbi KK, Al-sheikh YA. Role and implications of nanodiagnostics in the changing trends of clinical diagnosis. Saudi J Biol Sci. 2014;21:109–117.
82. Bhardwaj A, Bhardwaj A, Misuriya A, Maroli S, Manjula S, Singh AK. Nanotechnology in dentistry: Present and future. J Int Oral Heal. 2014;6:121–126.
83. Harini G, Kaarthikeyan G. Advanced drug delivery systems in treating periodontal diseases-a review. IOSR J Dent Med Sci. 2014;13:27–32.
84. Singh AK, Prakash P, Singh R, et al. Curcumin quantum dots mediated degradation of bacterial biofilms. Frontiers in Microbiology. 2017;8:1517.
85. Zhao MX, Zhu BJ. The research and applications of quantum dots as nano-carriers for targeted drug delivery and cancer therapy. Nanoscale Research Letters. 2016;11(1):207.
86. De Jong WH, Borm PJ. Drug delivery and nanoparticles: Applications and hazards. International Journal of Nanomedicine. 2008;3(2):133.
87. Brigger I., C. Dubernet, P. Couvreur. Nanoparticles in cancer therapy and diagnosis. Advanced Drug Delivery Reviews. 2002;54(5):631-651.
88. Cui Z, Mumper RJ. Plasmid DNA entrapped nanoparticles engineered from microemulsion precursors: In vitro and in vivo evaluation. Bioconjugate Chemistry. 2002;13(6):1319-1327.
89. Levy BM. Is periodontitis a disease of the aged? Gerodontology. 1986;5:101-107.
90. Page RC. Periodontal disease in the elderly: A critical evaluation of current information. Gerodontology. 1984;3:63-70.
91. Buwalda SJ, Boere KWM, Dijkstra PJ, Feijen J, Vermonden T, Hennink WE. Hydrogels in a historical perspective: From simple networks to smart materials. Journal of Controlled Release. 2014;190: 254–273.
92. Censi R, Di Martino P, Vermonden T, Hennink WE. Hydrogels for protein delivery in tissue engineering. Journal of Controlled Release. 2012;161(2):680–692.
93. Wang X, Hao T, Qu J, Wang C, Chen H. Synthesis of thermal polymerizable alginate-GMA hydrogel for cell encapsulation. Journal of Nanomaterials. 2015;2015:Article ID970619:8.
94. González JP, Covarrubias C, Cádiz M, Corral C, Cuadra F, Fuentevilla I. Design of antimicrobial release systems based on chitosan and copper nanoparticles for localized periodontal therapy. J Dent & Oral Disord. 2016;2(7):1035.
95. Rata DM, Daraba O, Merlusca P, Dârtu LE, Mihalache C, Chirap AM, Buburuzan A. Hydrogels based on natural polymers with possible application in the treatment of periodontitis. International Journal of Medical Dentistry. 2014;4(4):265.
96. Popa LĂ, Ghica MV, Dinu-Pirvu CR. Periodontal chitosan-gels designed for improved local intra-pocket drug delivery. Farmacia. 2013;61(2):240-9.

97. Pokharkar VB, Shekhawat PB, Dhapte VV, Mandpe LP. Dvelopment and optimization of eugenol loaded nanostructured lipid carriers for periodontal delivery. Int J Pharm Pharm Sci. 2011;3(4):138-43.
98. Bako J, Szepesi M, Veres AJ, Cserhati C, Borbely ZM, Hegedus C, Borbely J. Synthesis of biocompatible nanocomposite hydrogels as a local drug delivery system. Colloid and Polymer Science. 2008; 286(3):357-63.
99. Bakó J, Szepesi M, Márton I, Borbély J, Hegedûs C. Synthesis of nanoparticles for dental drug delivery systems. Fogorvosi Szemle. 2007;100(3):109-13.
100. Alexis F, Pridgen E, Molnar LK, Farokhzad OC. Factors affecting the clearance and biodistribution of polymeric nanoparticles. Molecular Pharmaceutics. 2008;5(4):505–515.
101. Siyawamwaya M, Choonara YE, Bijukumar D, Kumar P, Du Toit LC, Pillay V. A review: overview of novel polyelectrolyte complexes as prospective drug bioavailability enhancers. International Journal of Polymeric Materials and Polymeric Biomaterials. 2015;64(18):955–968.
102. Hwang SR, Kim K. Nano-enabled delivery systems across the blood-brain barrier. Archives of Pharmacal Research. 2014; 37(1):24–30.
103. Jones DS, Lawlor MS, Woolfson AD. Formulation and characterisation of tetracycline-containing bioadhesive polymer networks designed for the treatment of periodontal disease. Curr. Drug Deliver. 2004;1:17-25.
104. Pokharkar VB, Shekhawat PB, Dhapte VV, Mandpe LP. Development and optimization of eugenol loaded nanostructured lipid carriers for periodontal delivery. Int J Pharm Pharm Sci. 2013;3(4):138-143.
105. Kanika Madaan, Sandeep Kumar, Neelam Poonia, Viney Lather, Deepti Pandita. Dendrimers in drug delivery and targeting: Drug-dendrimer interactions and toxicity issues. 2014;6(3):139–150.
106. Lin-ping Wu, Mario Ficker, Jørn B. Christensen, Panagiotis N. Trohopoulos, Seyed Moein Moghimi. Dendrimers in medicine: Therapeutic concepts and pharmaceutical challenges. Bioconjugate Chem. 2015;26(7):1198–1211.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history/24597