Chapter 3
Insights into Nanotools for Dental Interventions

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Contents

Abstract Orodental afflictions although not life-threatening have recently been found to be clinically associated with a large variety of life style related diseases, adding to the disease burden and leading to poor health outcomes. The disease ramifications might lead to poor quality of life and often go unnoticed till exhibits severe symptoms and evidence of disease associations. Despite being a locoregional affliction, they do not remain restricted to the mouth cavity; rather they have negative effects on distant organs too. Henceforth the disease requires a thorough understanding, and the treatment modalities are devised in a manner to cater mild to severe status of orodental afflictions. Successful treatment of orodental afflictions requires the customized therapeutic approaches which can be borrowed from the nanotechnology. The advancement in nanotechnology and its ramification into

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medicinal and allied fields has brought remarkable changes in the field of dentistry. Additionally, the forays into nanomaterial sciences, biotechnology, and maneuvering through dental nanorobotics have further added impetus to contemporary dental practices. Often the dental infections are progressive in nature and need an umbrella approach for treatment to deliver comprehensive oral hygiene and health. Nanotechnology tools with their aesthetic approach have recently emerged as a favored tool for both practitioners and patients. The treatment protocols could include controlled oral analgesia, dentin replacement therapy, as well as cure for dental hypersensitivity. Interesting development of mechanical dentifrobots for tooth repairing via covalently bonded diamondized enamel ensures robust orodontal environment. Succinctly put, nanotools have opened up avenues in the diagnosis, treatment, and prevention of dental diseases. The development of nanotools allows perfect therapeutic approach which has led to nearly seamless oral health, possibly due to the use of nanomaterials, tissue engineering, nanocomposites, and nanorobots. Nanotools have elicited great impact on restorative dentistry, pharmacotherapeutics, and diagnostic techniques and offers better ways toward maintaining perfect oral health. This chapter focuses on a review of various approaches of nanotechnology which has contributed to the advancements in dentistry. It also focuses on advent of other nanotools which will cater to a variety of dental ailments associated with bony as well as soft tissue defects. It is realized that the nanotechnology offers a perfect tool to treat a multitude of orodental infections.

Keywords Bone grafts · Laser therapy · Nanoanesthesia: Nanofibers · Nanocomposites · Nanodentistry · Nanotechnology · Orodental infections · Orthodontics · Periodontics

3.1 Introduction

The global prevalence of orodental infections has risen enormously in the last few decades leading to reported cases of about 3.5 billion, majorly affecting the population of lower social strata (Dye 2017). Although it is rarely associated with fatal disease outcomes, recent clinical findings have established its foray into systemic complications (Bošnjak et al. 2001). These findings are reasons enough to attract the attention of current researchers who are focusing on oral diseases, customizing their treatment modalities, and progressively designing the advanced drug delivery systems.

Orodental afflictions broadly include the various diseases which attack the gingival and subgingival tissue as well as the dental adnexa. The various dental infections and their progressions can be summarized with the help of Fig. 3.1.

Amelioration of such diseases requires customized treatment which has recently borrowed from the discoveries of nanotechnology armamentarium. The treatment premise primarily depends on the disease stage and types of dental affliction and the

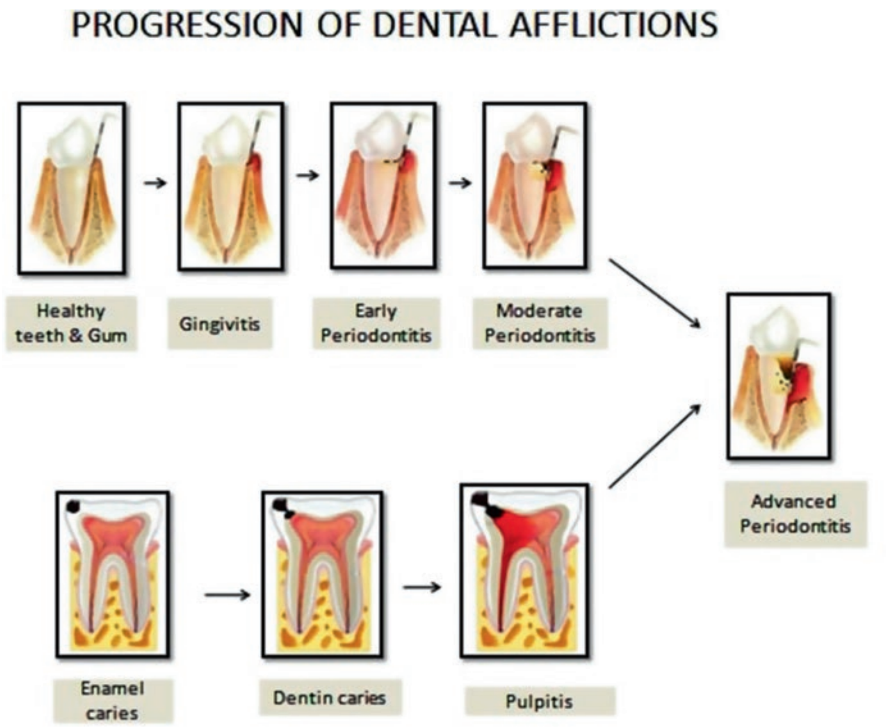

Fig. 3.1 Progression of dental afflictions
The dental afflictions progresses in two ways: In one way, it starts from gingivitis, early periodontitis, then moderate periodontitis, and ultimately severe periodontitis. In another way, it begins with enamel caries, dental caries, then pulpitis, and ultimately advanced stage periodontitis

intervention required. Intrapocket infections like periodontitis with its specific stages and treatment challenges constitute the largest umbrella of diseases in this area. Up till now dental treatments are challenging as people are psychophobic toward dentistry. On account of this fear, they avoid the dental treatment as they are scared for injection and drills that are used in dental clinics. Also it is a fact that conventional methods of root planning, scaling, and plaque removal have limited success and poor patient compliance because of length of procedure and high treatment costs. To ease the discomfort in recent times, dentistry offers period of dynamic changes and growth with the use of ozone in dental treatment. Through ozone therapy, the pain is eradicated significantly. Ozone also stimulates remineralization in case of caries-affected teeth providing potentiality for an atraumatic, biologically based treatment for conditions encountered in dental practice (Gupta and Mansi 2012; Moezizadeh 2013).

The integration of nanotechnology in "dental interventions" ever since its existence has immensely contributed to the advancements in diagnosis, prevention, and treatment of various dental ailments (Uysal et al. 2009). The potential applications of nanotools include an umbrella of dental techniques focused at dentition renaturalization, local anesthesia, orthodontic realignments, permanent hypersensitivity cure, covalently bonded diamondized enamel, oral health maintenance with the help of mechanical dentifrobots, and artificial bone and teeth creation (Rybachuk et al. 2009). There is an increase in opinion that if nanotools are applied to dentistry, it will bring significant advances in the diagnosis, prevention, and treatment of dental disease in numerous ways.

3.1.1 Dental Tissues or Tooth Anatomy

The human teeth are composed of four types of tissues, namely, enamel, dentin, cementum, and pulp. Out of the four, pulp is the only soft, noncalcified connective tissue and contains nerves and blood vessels. And the other three are the hard tissues (Berkovitz et al. 1978).

Enamel is the hard substance or the calcified tissue and covers the dentin in the crown. It is the hardest substance/tissue of human body and composed of 96% inorganic minerals, 1% organic materials, and 3% water. Calcium and phosphorus (as hydroxyapatite) are the two main inorganic constituents. It is devoid of living cells and blood supply and thereby lacks the potential of autoregeneration (Türp and Alt 1998).

Dentin is present in between the enamel and cementum. Dentin is porous in nature and constitutes to the largest portion of tooth. Dentin also consists of 70% inorganic matter and 30% organic matter and water. It is a living tissue and is perforated with microscopic tubules that run between the cement–enamel junction and the pulp. If the enamel gets degraded from the surface, then these tubules start stimulating the sensations of heat and cold thereby generating the sensitivity (Black 1897).

Cementum is the hard bone-like connective tissues, covers the root of tooth, and provides the attachment to periodontal ligament. It is composed of approximately 55% organic material and 45% inorganic material. The major components of inorganic material are the calcium salts. The area where the cementum joins the enamel is called as the cement–enamel junction, and such areas are very sensitive to the external stimuli such as heat and cold (Türp and Alt 1998).

Dental pulp is the soft tissue that develops from the connective tissues of dental papilla and contains nerves and blood vessels. Beneath the crown, the chamber containing pulp is called the pulp chamber and the pulp is called as coronal pulp, whereas inside the root, the pulp is called as radicular pulp. The main function of the pulp is the formation and nourishment of the dentin. It also provides sensation to the tooth and shows irritation response in terms of inflammation. The nerves and blood vessels pass through the end of radicular pulp to reach the interior of the tooth (Black 1897).

3.1.2 Types of Nanotechnological Approaches

The main approaches which could help in tangible use of nanotools in practice are as follows:

(i) Bottom-up approach; where it involves arrangement of smaller components into complex structures. It focuses on the use of micron-sized nanorobots which could be manipulated for a variety of hands on jobs like instilling local anesthesia, polishing the enamel surface with diamondized covalent bonding, curing of teeth hypersensitivity, dental durability and cosmetic appearance, and use of photosensitizers like quantum dots for hitting the specific targets (Kumar and Vijayalakshmi 2006).
(ii) Top-down approach: where it embraces development of nanostructures of smaller dimensions using larger parts. It primarily involves the use of nanosolutions, nanoneedles, nanofillers, nanocomposites, and bone replacement materials (Sasalawad et al. 2014).

Adper™ single bond plus is the example of dentin adhesive nanosolution with single step application procedure (Perdigao 2007). Suture needles such as Sandvik Bioline RK 91™ needles are developed to a carry nanosized stainless steel crystals to minimize the tissue damage (Suresh et al. 2014). The top-down approach of nanotechnology has application in salivary diagnostics as well, where the saliva can be analyzed by the biochemical sensors. Oral fluid nanosensor test (OFNASET) is the one such automated and integrated system to detect the targeted protein and nucleic acid in saliva (Terry 2004; Wong 2006).

Although it is a futuristic and promising tool in dental practice, patient acceptability and desired success is still elusive to nanotools in dentistry. However, it is marred with a set of unique tasks which encompass engineering, biological, as well as ethical and social issues. The manufacturing and engineering challenge lies in the lack of mass production, precise positioning and assembly of molecular scaling part, manipulating, and coordinating activities of large numbers of independent microscale robots. Simultaneously biological challenges are there for the development of biofriendly nanomaterial that would ensure compatibility with all intricacies of the human body. Although nanotechnology would possess tremendous potential, the social issues of ethics, public acceptance, regulation, and human safety needs to be addressed as it carries a significant potential for misuse and abuse on such a scale that has never seen before. In this review, current status of nanotools in dentistry has been discussed that provides an insight into its future along with the ethical and safety concerns related to it.

3.2 Applications of Nanotechnology in Dentistry

As the nanotechnology includes bottom-up approach and top-down approach, depending upon these approaches, various applications of nanotechnology are explained in the individual sections and summarized in Fig. 3.2.

3.2.1 *Applications of Nanotechnology in Restorative Dentistry*

Emergence of nanodentistry and its various uses aid in the maintenance of affected oral health through the use of various nanomaterials, tissue engineering, nanotools, and nanorobotics that could lead to achieve a near to perfect oral health. In the following sections, using different nanodevices pertaining to the oral health has been discussed.

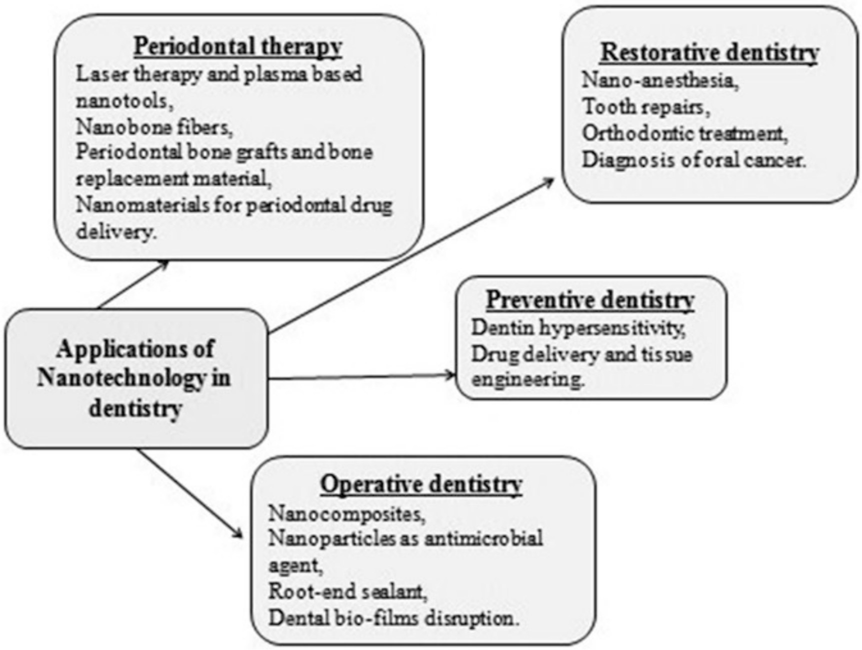

Fig. 3.2 Various applications of nanotechnology in dentistry
Various application of nanotechnology are categorized into restorative dentistry, operative dentistry, preventive dentistry, and periodontal therapy

Nanoanesthesia for Surgical Intervention

The major deterrent for a dental patient is the assumption of the ensuing pain which he/she will face on a visit to the dentist, and therefore in dental practice, the most common procedure is the administration of oral anesthesia. The colloidal suspension of oral nanoanesthesia is comprised of millions of active analgesic nanorobotic particles and administered to the patient's gingiva. After that it comes in contact with the crown or mucosa and the ambulating nanorobots reach the dentin by migrating painlessly through the thick layer of loose tissue at the cement–dentinal junction. These nanorobots then enter the dentinal tubules holes (~1 to 4 microns in diameter) and progress toward the pulp guided by a combination of chemical gradients, temperature difference, as well as positional navigation under the control of the onboard nanocomputer as directed by the dentist. The branching pattern of tubules sometimes gives a significant challenge to navigation. The robotic movements are successful due to the constant motion of natural cells around and inside the teeth. Once it is successfully installed and it has established control over the nerve impulse traffic, the analgesic dental nanorobots can be commanded by the dentist to shutdown the sensitivity for any particular tooth that needs treatment. After the hand held controller, the targeted tooth become numb and treatment procedure is followed. The nanorobot is aspired out after completion of the oral procedure, and the dentist restores all the sensation (Schleyer 2000).

These nanorobotic analgesics provide great patient comfort, reduced anxiety, specific selectivity, as well as controllability to avoid most side effects and complications. Also, it is envisioned that nanorobots will assist dentists in precisely operating the complex cases of microscopic level. And in the future, it will be a prime tool for dentists to practice conventional as well as four-handed dentistry.

Tooth Repairs

Most common dental problem is dental caries, which occurs in all age groups and adversely affects an individual's daily life seriously. The dental caries are slowly progressive and infectious disease that results in loss of dental hard tissue. In conventional treatment the caries are mechanically excavated and then filled up with resins or metals comprising inorganic-base cements as glues. Ideal filling materials are usually similar to the structure and composition of natural tooth (John 2007). The dental hard tissue is composed of inorganic hydroxyapatite (HA) crystal and organic matrix; by the process of biomineralization the hydroxyapatite crystal is orderly oriented. In routine clinical treatments, microleakage occurs with the secondary caries due to the discrepancy in physicochemical property between filled materials and tooth.

Various synthetic materials are available to restore the dental caries. Hydroxyapatite crystal, minerals like amorphous calcium phosphate (ACP), casein protein (CPP) compounds, nanobioactive glass; and the stimulated body fluid could reverse the early caries lesion in dentin or enamel surface (Yamagishi et al. 2005;

Andersson et al. 2007; Vollenweider et al. 2007). Guided tissue remineralization can also be imposed for partially demineralized human dentin where dentin collagen could guide the phase transition of nano-ACP into HA (Tay and Pashley 2008).

With the help of nanotechnology, molecular biomimetics materials were fabricated. These biomimetics materials are based on molecular recognition between genetically engineered peptides for inorganics (GEPIs) and inorganic crystal. Hybrid of GEPI and HA crystal can be used in the assembly of functional nanostructures using their recognition properties to repair dental hard tissue in the future (Zhou et al. 2008).

With the availability of tooth repair materials, dental caries is not a difficult problem to handle, and with the help of nanomaterials, partial to complete restoration is possible and this serves as boon for dental cosmetics industry.

Orthodontic Treatment

In orthodontic treatment sliding a tooth along the arch wire involves more frictional force for its movement. Applying excessive orthodontic force might cause loss of anchorage and root resorption. Redlich et al. (2008) reported the reduction of friction by coating inorganic fullerene like tungsten disulfide nanoparticles (IF-WS2) nanosolution. IF-WS2 is known for their excellent dry lubrication properties. The NP-coated wires offer better friction reduction opportunity up to 54% during the tooth movement. Polymer nanocomposites are used as orthodontic adhesives for increasing mechanical properties, tensile, comprehensive strength, and resistance to fracture. These nanocomposites illustrate excellent optical properties, superior polish ability, and easy handling. These nanofiller nanocomposites can decrease the surface roughness of the orthodontic adhesives. As, the oral cavity is an open growth system, where attachment and colonization of bacteria takes place and it gradually shifts towards disease. The rough surface promotes plaque formation and maturation and strong binding. Therefore decrease in roughness by nanocomposites can dramatically enable very less bacterial accumulation (Quirynen and Bollen 1995; Lee et al. 2004). Nanoinomers are based on resin-modified monomers of acrylic and itaconic acid copolymers which polymerizes via free radical addition and curing by light activation (Korkmaz et al. 2010). The nanocomposites, i.e., Filtek Supreme Plus Universal, and nanoionomers like Ketac ™ N100 Light Curing are suitable for bonding as they fulfill better clinical acceptability shear bond strength (SBS) in comparison to the conventional light-cured orthodontic bonding adhesive (Transbond XT, 3 M Unitek) (Uysal et al. 2009). In another study, Bishara et al. compared the shear bond strength between Grandio (Voco, Germany) and Transbond XT, 3 M Unitek, while testing the bonding of the orthodontic brackets. It was found that the nanofilled composites demonstrated better bonding ability, nice flowability, and ready attachability in orthodontic bracket base (Bishara et al. 2007). Over the past decade there has been an increased demand in manufacturing aesthetic orthodontic wires that would complement tooth colored brackets. Responsive polymer materials are those polymers that can adapt to surrounding environments, regulate transport of ions and molecules, change wettability and adhesion of different species on external stimuli, or convert chemical and biochemical signals into optical, electrical, thermal, and mechanical signals and vice versa (Stuart et al. 2010). The sharp memory polymers can memorize a macroscopic or equilibrium shape and then be manipulated and fixed to a temporary or dormant shape under specific conditions of temperature and stress. At later phase they can relax to original, stress-free condition under thermal, electrical, or environmental condition which is associated with elastic deformation stored during prior manipulation toward its equilibrium shape accompanied by an adequate and prescribed force. The sharp memory polymers have the ability to meet the unattainable needs of current orthodontic materials which will further comfort the procedure of orthodontist. Once placed inside the mouth, these polymers can be activated by body temperature or light and enable the tooth movement and provide lighter more constant forces giving less pain to patients. The sharp memory polymeric materials are colorless and stain resistant which give aesthetically appealing appliance during treatment. Moreover the high percent of elongation of sharp memory polymers provides continuous force for a long range of tooth movement hence less number of visits to patients (Redlich et al. 2008). Using these properties and better features, aesthetic nanocomposite wires can be formed for orthodontic purpose (Meng and Hu 2009; Leng et al. 2011).

These findings suggest that in the future, orthodontic nanorobot-based treatment could directly manipulate the periodontal tissues, allowing rapid and painless tooth straightening, rotating, and vertical repositioning within minutes to hours. With this method, the need for the cumbersome and dreaded braces could be eliminated.

Diagnosis of Oral Cancer

The noticeable contribution from nanotechnology in the field of dentistry is mostly observed in the diagnosis of oral cancer. Obtaining the image plays a critical role in designing of treatment plan and overall cancer management. For getting basic information regarding tumor location, size, and spread, standard structural imaging techniques such as computer tomography (CT), molecular resonance imaging (MRI), and ultrasound are used. However, these imaging techniques become less reliable to distinguish between benign and metastatic tumor where the tumor size is smaller than 5 mm (Popovtzer et al. 2008; Reuveni et al. 2011). Recently gold nanoparticle (AuNP)-based CT imaging have been shown progress. For specificity these gold nanoparticles can be functionalized with ligands to target the receptors of overexpressed tumors (Hainfeld et al. 2004; Marega et al. 2012).

One of the most common types of cancer in oral oncology is the oral squamous cell carcinoma, representing ~6% of all cases of cancers. Selective targeting of oral squamous cell carcinoma is an enduring problem because of the lack of specificity of current drugs. Popovtzer et al. (2008) studied the molecular CT imaging of oral cancer with the targeted gold nanoparticles. They reported that the attenuation coefficient is five times higher than the untargeted cells of oral squamous cell carcinoma.

Yang et al. (2011) conjugated cell-penetrating peptides to near-infrared quantum dots for cancer diagnostics. In their pioneering approach, the group labeled oral squamous cell carcinoma cells with quantum dots and conjugates by endocytosis for visual in vivo imaging on a mouse model.

In another study, Bhirde et al. (2009) demonstrate superior efficacy of single wall carbon nanotube bioconjugate, over nontargeted bioconjugates. The three colors, two-photon intravital video imaging demonstrated administration of epidermal growth factor (EGF) targeted single wall carbon nanotube quantum dot in live mice which was selectively taken up by head and neck squamous carcinoma cell (HNSCC) tumors, whereas the nontargeted single wall carbon nanotube quantum was cleared from the tumor region in less than 20 min. Regression in tumor growth was fast in mice treated with single wall carbon nanotube–cisplatin–EGF compared to nontargeted single wall carbon nanotube–cisplatin.

The above studies suggest that the nanotechnology is not only restricted to the tooth restoration, rather it has the potential in the imaging of oral cancer as well. Also imaging with the nanotechnology can help to diagnose and combat the oral cancers during initial stages.

3.2.2 Application of Nanotools in Preventive Dentistry

The aim of modern dentistry is prevent the disease progression before it enters in the noncontrollable state. The prevention of tooth decay and treatment of lesions and cavities are the prime concerns; thereby treating dental diseases with the help of nanotools has been of great interest (Hannig and Hannig 2010). Application of nanotools for preventive dentistry can be stretched from dentin hypersensitivity to drug delivery and tissue engineering.

Dentin Hypersensitivity

Dentin is a yellow-hued calcified tissue and the major components of teeth usually covered by enamel on the crown and cementum on the root that surrounds the entire pulp. It has elastic-like properties and serves as the support for enamel. Due to its soft nature, it decays rapidly and form cavities when not treated properly. The dentin hypersensitivity occurs when the protective layers are removed causing pain (Addy and Urquhart 1992). The protective layer gets lost due to the response to chemical, thermal, or osmotic stimuli or any other form of dental defect or pathology. Apart from that, improper tooth brushing, gingival recession, and periodontal also expose the root surfaces, and the thin covering cementum layer (approximately 20–50 μm) is easily lost. In all these situations, the sensitive dentin tissues are exposed which has numerous tubules that in turn changes the fluid pressure hydrodynamics of the fluid inside the dentinal tubules and is subjected to many external sources of irritation. Liu et al. (2007) explored the possibility of nanoscale gold particle in the occlusion of dentinal tubules that would reduce movement of dentinal fluid or dentin permeability should decrease sensitivity. The gold nanoparticles (GNPs) possess smaller dimension than dentinal tubules, so they can easily enter the tubules without much resistance. Also the GNPs have large absorption coefficients (Taton et al. 2000; Liu et al. 2007). The dentinal tubules were occluded with GNPs by adsorbing onto the inner dentinal tubule walls, followed by a silver staining to reduce the dentin sensitivity. In another process, highly concentrated GNPs are brushed into the opened ends of the dentinal tubules and after laser irradiation induced photofusion of GNPs via photothermal conversion (Liu et al. 2007). Using biological materials' induction of dental nanorobots offers a speedy cure to dentin hypersensitivity by precisely occluding the tubules in minutes (Schleyer 2000).Based on the above discussion, it can be concluded that owing to the small size, the nanoparticles have the capacity to enter the dentinal tubules and treat the dentin hypersensitivity. Although nanoformulation-based products are not yet available in the market for dentin hypersensitivity, in the near future, this potential can be commercialized.

Drug Delivery and Tissue Engineering

Tissue engineering has become one of the promising approaches for delivering of therapeutically relevant molecules to treat the damaged tissues. These molecules can be effectively loaded in large quantities in scaffolds or nanoparticles for sustained and controlled release. The nanochemistry of the scaffold can carry signaling molecule for homing and the therapeutic molecule for sustained release to the surrounding tissues for regulation of cellular function (Treuel et al. 2013; Kettler et al. 2014). Various polymeric materials or inorganics and their hybrids have been developed for the delivery of molecules. In case of treatment of periodontal disease, two methods are used: antibacterial process to avoid progression of the disease and the regenerative therapy which can be able to regenerate the damaged tissue (Pragati et al. 2009). For the regenerative treatment, bone morphogenic proteins (BMPs) are used as they are involved in osteogenic differentiation of stem cells are for the regeneration of periodontal ligament (PDL), cementum and alveolar bone (Giannobile et al. 1998; Ripamonti et al. 2001; Wikesjö et al. 2004). Similarly in case of dental pulp infection, successful regeneration of odontoblasts, endothelial cells, fibroblasts, and even neurons is greatly needed to restore pulp tissue. In the regeneration process, different growth factors such as transforming growth factor (TGF-β1), bone morphogenic protein (BMP), and platelet-derived growth factor can be either used alone or in combination. For periodontal regeneration, PLGA nanoparticles were developed which can encapsulate minocycline for periodontal infections in a sustained manner for several weeks impacting significant antibacterial effect compared to native (Kashi et al. 2012).

Therefore it can be concluded that nanotechnology can play a major role in the development of cost-effective therapies for drug delivery and in situ tissue regeneration.

3.2.3 Applications of Nanotools in Operative Dentistry

Operative dentistry can be defined as the branch of dentistry which deals with the diagnosis and treatment of tooth defects which do not require full restoration. Thereby operative dentistry is of prime importance for enhancing the dental health. Employment of nanotechnology for operative dentistry is the budding field wherein various nanotools can be explored. Also various commercial preparations of the dental materials are available and are summarized in Table 3.1. In general, up till now nanotools in the form of nanocomposites, antimicrobial agents, root-end sealants, and dental biofilm penetrators have been instigated.

Nanocomposites

Dental composites are the solid materials composed of synthetic matrix, inorganic fillers, initiators, activators, and coupling agents. The activator promotes the light-initiated polymerization of the organic matrix to generate cross-linked polymer structure, and coupling agents mainly with silane groups ensure the bonding of nanofillers to the polymer matrix.

The most commonly used organic matrix in the commercial dental composites is Bis-GMA monomer. As high viscosity-related problems are associated with the Bis-GMA, it must be diluted with other fluid monomers to attain the desired viscosity for dental composites. Other base monomers used in manufacturing of commercial composites are uretane dimethacrylate (UDMA), triethyleneglycol dimethacrylate (TEGDMA), ethoxylated bisphenol-A-dimethacrylate (Bis-EMA), urethane tetramethacrylate (UTMA), bis(methacryloyloxymethyl) tricyclodecane, and decanediol dimethacrylate (D3MA) (Ferracane 1995).

Table 3.1 Various marketed preparations of dental materials

Dental approach	Marketed preparations
Orthodontic materials	Ketac ™ N100 Light Curing, Filtek Supreme Plus Universal, Grandio (Voco, Germany), Transbond XT; 3 M Unitek, Adper™ single bond plus, Sandvik Bioline RK 91™
Nanocomposites	Filtek Supreme (3 M ESPE, St. Paul, MN, USA), Premise (Kerr/Sybron, Orange,CA, USA) Nano-DCPA whiskers, TTCP-whiskers, Polymer kaolinite
Root-end sealant	Endo Sequence BC sealer, Gutta-Flow Sealer
Plasma-based nanotools	MicroPlaSter
Periodontal bone grafts and bone replacement material	Ostim (Osartis GmdH, Germany), NanOSST(Angstrom, Medica, USA), Vitoss (Orthovita Inc., USA)

When the inorganic phase of dental composite is nanosized, it becomes nanocomposites. Nanofillers in the nanocomposites are added either in dispersed form or in cluster form. Due to their smaller size dimension, the nanofillers are invisible and are capable to improve the optical property (Mitra et al. 2003). Owing to their small particle size, nanofillers are capable to increase the overall filler levels. Also the physical properties of nanocomposites can be improved by increasing and decreasing the filler level and resin content, respectively.

In dental composites, good mechanical properties can be obtained by strong covalent interaction between the fillers and organic matrix. Coating of fillers with silane coupling agent assures the bonding between the two phases, i.e., matrix and fillers. 3-Methacryloxypropyltrimethoxysilane.

(MPTS) is a typical example of coupling agent. One end of this molecule can be bonded to the hydroxyl groups of silica particles and the other end copolymerize into the polymer matrix.

Various nanocomposites are available in the market. Filtek Supreme (3 M ESPE, St. Paul, MN, USA) is a dental nanocomposite based on nanomers and nanoclusters. Nanomers are the uniformly dispersed, nonaggregated, and nonaglomerated silica particles of 20–70 nm particle size. In the Filtek Supreme, filler content is about 58–60% by volume and 78.5% by weight (Mitra et al. 2003).

Premise (Kerr/Sybron, Orange, CA, USA) is another dental nanocomposite, composed of three different types of filler components such as nonagglomerated silica nanoparticles, prepolymerized fillers (PPF), and barium glass fillers. The combination allows the filler loading up to 69% by volume and 84% by weight (Bauer et al. 2000).

Dental nanocomposites can be mechanically strengthened by incorporation of reinforced fillers such as nanofibers (Tian et al. 2007), short E-glass fibers (Garoushi et al. 2008), and TiO2 nanoparticles (Xia et al. 2008). Dental nanocomposite of ion-releasing properties have been developed to increase the mineral content and to control the dental caries. Nanocomposites such as nano-DCPA whiskers (Xu et al. 2007) or TTCP-whiskers (Xu et al. 2009) and polymer kaolinite (Wang et al. 2007) release calcium, phosphorus, and fluorides, respectively, thereby increasing the mineralization of tooth and control the caries development. It has been proven that the significant improvement in the field of dental materials has been majorly contributed by the development of dental nanocomposites.

Potential of nanotechnology has been extended to the characterization of dental materials as well. Various techniques such as atomic force microscopy, scanning electron microscopy, X-ray photoelectron spectroscopy, and Piezoresponse force microscopy (PFM) have been successfully utilized to study the surface characteristics of dental nanocomposites (Sharma et al. 2010; Khanal et al. 2015; Salerno and Diaspro 2015). Figure 3.3 enlists the various techniques for the nanoscale characterization of the dental materials.

Nano-characterization of dental materials	
Atomic force microscopy (AFM)	Optical profilometry
Scanning electron microscopy (SEM)	X-ray diffraction spectroscopy
Scanning tunneling microscopy (STM)	Fourier-transformed infrared spectroscopy (FTIR)
X-ray photoelectron spectroscopy	Raman scattering
Dynamic mechanical analysis (DMA)	Energy dispersive spectroscopy (EDS)
Transmission electron microscopy (TEM)	Total internal reflection fluorescence (TIRF)
Optical microscope mapping	High speed-AFM
Lorentz contact resonance spectroscopy	Fluorescence resonance energy transfer (FRET)
Piezoresponse force microscopy (PFM)	Scanning ion conductance microscopy (SICM)
Scanning probe microscopy (SPM)	Live-cell interferometry (LCI)

Fig. 3.3 Nanocharacterization techniques of dental materials
Various techniques to characterize the surface morphology and to study the surface behavior of dental materials are enlisted

Nanoparticles as Antimicrobial Agent

The plethora of work in the field of design and development of nanoparticles has led to an enormous use of these systems for treatment of versatile kinds of diseases including dental infections and other dental afflictions. Such usage of nanoparticles is akin to the Paul Ehrlich's concept of "magic bullet" where the systems invariably engage with the target and yield positive therapeutic outcomes. Owing to the polycationic or anionic nature and large surface area with charge density, nanoparticles interact effectively with the bacterial cell and result in higher antibacterial activity (Allaker 2010). Chitosan nanoparticles being antimicrobial and biocompatible in nature have been exploited in the treatment of bacterial biofilm and wound healing (Raafat and Sahl 2009; Kong et al. 2010). Chitosan nanoparticles are less cytotoxic in nature and can be used as drug delivery carriers in various systemic diseases. They provide a remarkable improvement in root canal disinfection by selectively removing the residual adherent and nonadherent bacteria also increasing the flux of antimicrobial agent from the root canal sealant (Shrestha et al. 2009). The nanosize hydroxyapatite particles having remineralization capacity also have been shown to inhibit the formation of oral biofilm (Venegas et al. 2006). Various oral healthcare products such as toothpastes and mouth rinses containing nanohydroxyapatite have been developed. And it has been suggested that their efficacy is related to the size specific effects of nanohydroxyapatite (Reynolds et al. 2003; Rahiotis et al. 2008).

Also nanotechnology is gaining tremendous popularity in the present world due to its capability of modulating metals into nanosize, which enormously modulates the physicochemical and optical properties of metals. Silver nanoparticle which is the derived form of metallic silver is a good example of antimicrobial agent. Also, as the bacterial resistance toward the antibiotics is increasing day by day, then in such cases, the use of silver nanoparticle can be an alternative. Various medical applications of silver nanoparticles are available as silver-based dressings, silver nanogels and nanolotions, etc. The antimicrobial efficacy of silver, gold, and zinc nanoparticles against the bacterial strain of *S. mutans*, which is a major causation of dental caries, was compared. The studies revealed higher antimicrobial effects against *S. mutans* of silver nanoparticles at lower concentrations than gold or zinc (Hernández-Sierra et al. 2008). Also it is concluded that with size reduction, contact surface increases, which is important for the broad-spectrum antimicrobial effect of silver. The low concentration of silver can avoid the teeth staining. In this manner silver nanoparticles can be a powerful approach for treatment of dental caries.

Nanotools as Root-End Sealant

With the enhancement of nanotechnology, the quality of dental biomaterial has also improved. Nanotechnology manufactures materials with better properties or modulating the properties of existing materials. Root-end sealants play the important role as pulp filling material in a carious primary tooth. Also the nanomaterial enhanced retrofill polymers (NERPs) impart superior strength and adaptability to the tooth surface. In the study of extracted tooth model, the results showed that NERP materials reduce the microleakage and hence have the ability to seal effectively. Bioaggregate white nanoparticles are a novel type of ceramic cement primarily which consists of calcium silicate, calcium hydroxide, and hydroxyapatite (Yuan et al. 2010). Recently, Endo Sequence BC sealer which is a bioceramic-based nanomaterial has been developed. It mainly consists of calcium silicate, calcium hydroxide, calcium phosphate, zirconia, and a thickening agent. Handling and physical properties of the nanoparticles have been improved. During the root canal treatment, hydration reaction occurs with the formation of calcium silicate and hydroxyapatite. Availability of water is the key factor for hydration reaction and setting time in overly dried canals. Nanosized particles assure delivery of capillary needle of size from 0.012 to adopt into the irregular dentin surfaces. Within few hours, it sets hard and provides excellent seal with dimensional stability. This form of hydroxyapatite is bioactive and biocompatible. Its high alkaline pH, i.e., 12.8, provides additional antimicrobial properties as well. Similarly Gutta-Flow Sealer is an example of root-end sealant which consists of silicon, gutta-percha powder, and silver nanoparticles (Koch and Brave 2009). This nanosealer sets within half an hour and has good biocompatibility and dimensional stability. It is reported that this material can provide better bacterial penetration resistance and enhance the sealing capability. Also from the infection reference, antimicrobial activity of root-end sealants can be a synergistic effect. Recently antibacterial nanoparticle, i.e., quaternary ammonium polyethyleneimine (QPEI), was incorporated into already existing sealers like AH plus, Epiphany and Guttaflow. Results suggest prolonged antibacterial activity without compromising the mechanical properties. In order to obtain antibacterial effect in endodontic sealers, 0–2% nanoparticles of QPEI were incorporated into the marketed sealers. The obtained product was very stable and remains biocompatible; however the antibacterial effect was excellent (Abramovitz et al. 2012).

The above studies suggest that the nanosize-based root-end sealants are better in strength and durability than the other root-filled materials. Also with the nanobased root-end sealants, antibacterial effect can be obtained, and this will further aid to the root canal treatment.

Nanotools for Dental Biofilms

Nanotechnology tools help to study the interspecies interaction involved in the development of biofilm and can be used to understand the demineralization/remineralization process in development of dental caries. For example, atomic force microscope can be used to detect bacterial plaque-generated demineralization at an ultrasensitive level.$^{16}O/^{18}O$ reverse proteolytic labeling is another application of nanotechnology used to determine the influence of bacterial culture on the cell envelope proteome of *Porphyromonas gingivalis* which is responsible for periodontitis (Ang et al. 2008). Nanotechnology also makes it possible to detect both cultivable and non-cultivable bacteria and can selectively and preferentially remove cariogenic bacteria without disturbing the normal oral flora. Similarly plaque acidity, which is a good marker of tooth demineralization, can be monitored using a microscale planar pH sensor. New silver-based nanotechnology has been proven to be active against biofilms. The silver has high affinity for negatively charged side groups like sulphydryl, carboxyl and phosphate moieties of bacterial cell wall. Silver selectively binds to these moieties and arrests the bacterial cell wall synthesis, protein function, membrane transport, electron transport, and other physiological cell functions. It is effective against biofilm-associated pathogens including *E. coli, S. pneumoniae, S. aureous*, and *A.niger* (Bhardwaj et al. 2009). For preventing cell growth in certain bacteria, as little as one part per billion of silver may be effective (Gibbins 2003). The various aspects of nanotechnology in oral biofilm have led us to visualize the smart mouthwash comprises of nanomachines which will selectively allow the nonpathogenic flora of mouth to flourish in healthy environment and simultaneously inhibits the pathogenic ones, thereby increasing the oral health of human beings.

3.2.4 Applications of Nanotechnological Tools in Periodontal Therapy

Periodontal disease is a complex disease involving the destruction of tooth supporting materials and alveolar bone loss (Verma et al. 2010). Thus the ultimate goal of therapy is to restore the tissue destruction by repair and regeneration. Similar to the other branches of dentistry such as preventive, restorative, and operative, periodontics is also impacted by the advances of nanotechnology. Utilization of nanotechnology or nanotools for periodontal therapy has led to the development of better imaging and drug delivery alternatives and mainly includes the laser plasma-based nanotools, nanobone fibers, periodontal bone grafts, and nanomaterials for periodontal drug delivery.

Laser Therapy and Plasma-Based Nanotools

Lasers in the range of middle- and far-infrared regions allow their successful use in dentistry for hard and soft tissue procedures, because of its high sensitivity and the lack of the associated risks of ionizing radiation (Jha et al. 2017). For periodontal applications, lasers have been explored in various procedures such as soft tissue extraction, calculus removal, bacterial reduction, incision and ablation, biostimulation, decontamination of root and implant surface, and bone removal. Laser wavelength like Er:YAG, Er, and Cr:YSGG are greatly absorbed by hydroxyapatite and can be utilized for bone removal (Romanos 2015).

Laser therapy (diode and Nd:YAG lasers) can be of great help in treating noninvasive problems like gingival hyperpigmentation and also revealed that it could easily replace the need for analgesics (Shankar et al. 2013). Low-temperature plasma has a promising usage in the field of dentistry and can be effectively used to sanitize the gingival crevices and periodontal pockets (Chen Fa-Ming et al. 2009). This type of treatment alleviates the fear of dental visits which is called as odontophobia and can help in the treatment of dental infections in children and adults as well.

Plasma devices could be highly effective in inhibiting bacterial growth significantly in the root canal and consequently lead to complete sterilization during dental treatments (Liang et al. 2015). A significant advantage of plasma is amenability to both wet and dry environments, and henceforth, presence of blood, gingival crevicular fluid, and saliva does not compromise its efficacy (Jha et al. 2017). They can regenerate and differentiate periodontal stem cells and thus show potential as a future dental therapy, and they facilitate successful gingival treatments such as that for gummy smile, resulting in the more rapid generation of various dental-related cells (e.g., fibroblasts and collagen) with the least amount of postoperative pain to the patient (Miletić et al. 2013). Plasma is available in various types like dielectric barrier discharge, plasma jet, plasma torch, and barrier coronal discharge. Research is being done in the research centers and medical industry with advent of new devices for fast and easy treatment. In medical field, argon plasma torch, i.e., MicroPlaSter, has been introduced for a randomized controlled trial for patients with chronic infected wounds with well-tolerated healing results. Summarily, plasma-aided dental devices that are futuristic in its approach may replace exciting technologies and emerge as a future nonsurgical, noninvasive treatment modality, especially in periodontal dentistry.

Nanobone Fibers

Nanofibers are the preferred reinforced constituent of dental nanocomposites. In order to enhance the mechanical strength of nanocomposite, nanofibers are incorporated into them. Nanobone fibers have 100 times the strength to that of steel (polyphosphazene nanofibers). They have attained popularity in local drug delivery system due to their superior properties (Slavkin 1999). Studies suggest that incorporation of high-strength inorganic fibers in the dental composite led to the significant improvement in mechanical properties (Fong 2004; Callaghan et al. 2006) Recently, nanofibers have been employed to formulate HA- and fluoro-HA-containing ceramics (Kim and Kim 2006). Nanofibrillar silicate crystals have also been studied for the capacity of regenerating or supporting of dental structures. One such type of combination consists of 2,2′-bis-[4-(methacryloxypropoxy)-phenyl]-propane (Bis-GMA) and thinning agent as triethylene glycol dimethacrylate (TEGDMA) (Tian et al. 2007; Tian et al. 2008). After incorporation of relatively small amount of nylon 6 nanofibers into the resin, the three-point bending test of the modified dental composite suggests that flexural strength, work of fracture, and elastic modulus were considerably increased. But addition of more than 6% mass fraction of nylon 6 nanofibers into the resin did not enhance the mechanical properties of the dental composite significantly. If formulated in the correct proportions and with uniform distribution, nanofibers were reported to enhance the physical properties of the composites.

As the size of the nanofiber is less than the wavelength of visible light, it does not affect the transparency of the nanocomposite and offers an advantage of using nanofibers as reinforcement materials (Bergshoef and Vancso 1999). The aforementioned advantages of polymer nanofibers make them a promising candidate for future development of orthodontic composites that are of sufficient mechanical strength and of desired aesthetic properties.

Periodontal Bone Grafts and Bone Replacement Material

In dentistry, one of the biggest challenges is the predictable regeneration of alveolar bone destroyed by periodontitis. A great success in this field has been achieved by the periodontal bone grafts (Brunsvold and Mellonig 1993). The periodontal bone grafts are inserted with the objectives of reduction of probing depth; regain the clinical attachment, alveolar bone fill and regeneration of bone, cementum and periodontal ligament (Schallhorn 1977). Periodontal bone grafts allows ideal bone regeneration as they have greater surface area as compared to other synthetic bone grafting material, due to their microporosity and nanoporosity (Slavkin 1999). In bone therapy, from very recent time autogenous and allogenic bone grafts have been used, synthetic biomaterials have been developed, but none of them is similar to the natural bone in terms of structure and composition. Owing to the fact that hydroxyapatite/collagen systems are structure- and composition-wise similar to the natural bone, their nanocomposites are promising bone grafts. Their functional characteristics in the nanorange facilitate collagen growth and subsequent periodontal tissue formation (Whitesides and Love 2001). Smart material for periodontium, developed through nanotechnology, will aid in repair and regeneration of bone (Khosla 2009). Synthetic hydroxyapatites have been marketed in various forms such as resorbable, solid nonresorbable, and porous nonresorbable. Ostim (Osartis GmdH, Germany), NanOSST(Angstrom, Medica, USA), and Vitoss (Orthovita Inc., USA) are the hydroxyapatite nanoparticle used to repair bone defects (Sheikh et al. 2015). Other synthetic variant is the bioglass. Bioactive glass is mainly composed of sodium calcium salts, phosphates, and silicon dioxide (Anderegg et al. 1999). Bioactive glass possesses the ability to release mineral ions and promote natural bone regeneration. Once it reacts with blood, it attaches to the bone and slowly releases silica ions (Hoppe et al. 2011). There it initiates osteoblast differentiation and proliferation (Hench 2006; Jones 2015). In due course of time, it gets fully absorbed and replaced by the bone. When the bioactive glass is mixed with autogenous bone graft material, synergistic effect is produced, and natural bone regeneration process gets doubled (Oonishi et al. 2000). In summary the complex procedure of bone regeneration can be minimized with the various types of available bone grafts and bone replacement materials.

Nanomaterials for Periodontal Drug Delivery

Modern delivery systems are designed with the purpose of targeted and controlled drug release. Up to now polymeric or microparticulate delivery systems are utilized in dentistry which controlled the drug release due to their structure, but the intensive research in the nanotechnology leads to development of nanomaterials for effective periodontal drug delivery. When compared with the microparticulate systems, the nanomaterials offer several advantages such as high dispersibility in aqueous medium, controlled drug release, and better stability. Also owing to the small size, nanomaterials can penetrate deep inside the periodontal pockets and are suitable candidate for periodontal drug delivery (Jain et al. 2008). Nanomaterials particularly nanospheres, core-shell structure, nanotubes, and nanocomposites have been widely employed for controlled drug delivery system (Jain et al. 2019). Nanospheres can be fabricated with biodegradable polymer and drug for the controlled drug delivery. Biodegradable nanoparticles formulated with polyethyleneglycol dimethacrylate (PEGDMA) and 2-hydroxyethyl methacrylate (HEMA) can be used as drug delivery carrier for periodontal applications. Further these nanoparticles can be suitably incorporated into hydrogel matrix for ease of application (Bakó et al. 2007).

Recently, Pinon-Segundo et al. (2005) formulated and characterized triclosan-loaded nanoparticles through the process of emulsification-diffusion so as to obtain a novel delivery system directed toward periodontitis. These nanoparticles were formulated using poly(D,L-lactide-coglycolide), poly(D,L-lactide), cellulose acetate phthalate, and polyvinyl alcohol which were taken as stabilizer. These nanoparticles act as a homogeneous polymer matrix-type delivery system in which triclosan was dispersed. Results indicate that triclosan nanoparticles were capable to reduce inflammation at the experimental sites (Pinon-Segundo et al. 2005). The ongoing research in nanotechnology suggests that the suitably developed and optimized nanoformulations or nanomaterials could be effective drug delivery carriers for the periodontotherapy.

But before the submission of the formulation for patient use, it is imminent that these are subjected to animal studies for which number of authors has devised various experimental models, and the summary of the work is enlisted in Table 3.2.

3.3 Barriers of Nanotechnology

Continuous improvements of traditional approaches, development of novel restorative materials, advanced medications, and pharmacological strategies will continue to improve dental care. Derivatives of nanotechnological tools like nanoparticles and nanotubes have significant role in operative dentistry, periodontal management, endodontics, and restorative dentistry. Nanotechnology is set to revolutionize clinical dental practice. In no distant future, oral healthcare services will become less stressful for the dental surgeons, more acceptable to patients, and the outcome will significantly become more favorable. Optimal utilization of the advantages and opportunities offered by nanotechnology in clinical dental practice will facilitate improvements in oral health. The misuse and abuse of any technology continues to be a human issue, which could not be easily discerned by even intelligent systems**.** Nanotechnological tools if not properly controlled and directed carry a significant potential for misuse and abuse. The rapid progress and proper investigation will ensure that the development which seems unbelievable today is possible in the near future. However, in nanorobot mass production technique, precise positioning and assembly of molecular-scale part require simultaneous coordination of activities of large numbers of independent micron-scale robots. If the precision fails to some extent, then it will be havoc for the patients; hence it needs to be taken care of. Apart from that, the biocompatibility issue of the materials used till now or that will be engineered in the near future should possess no toxic effect to the health. Last but not the least, the funding and strategic issues because of inadequate venture capital, excessive bureaucracy and lack of medical input, insufficient integration of clinical research, and inefficient translation of concept to product would raise social issues of public acceptance, ethics, and regulation required for human safety.

Table 3.2 Animal models of periodontitis to assess the in vivo behavior of dosage forms

Animal model	Dosage forms	Aim of study	References
Mouse	Local delivery system	To study the effect of locally delivered antimicrobial agent on the inflammatory response	Vanderkerckhove et al. (1998)
Rat	Topical	To assess the potential effectiveness of the developed formulation in treating periodontitis	Luan et al. (2008), Jain et al. (2020)
	Gel foam pellet	To evaluate the combined efficacy of locally delivery of alandronate and tetracyclines in reducing alveolar bone loss	Yaffe et al. (2003)
	Isosorbide gel	To evaluate the role of nitric oxide (NO) on bone metabolism and effect of isosorbide on periodontal disease	Leitao et al. (2004)
	Bioerodible polymer insert	To evaluate a new class of bioerodible polymers as periodontal inserts for controlled release of metronidazole	Gates et al. (1994)
Beagle dogs	Nanoparticles	To evaluate in vivo efficacy of the developed dosage form of triclosan	Pinon-Segundo et al. (2005)
	Gel	To evaluate the potential of locally injected simvastatin in human sized periodontal defects	Morris et al. (2008)
	Collagen gel	To examine the effects of bFGF on the regeneration of cementum and periodontal ligament in experimentally induced partial defects	Sato et al. (2004)
	Ointment	To evaluate clinical, enzymatic and microbiological effects of controlled release localized administration of minocycline on dogs with periodontitis	Hirasawa et al. (2000)
	Biodegradable membrane	To evaluate the regenerative effect of a 25% doxycycline loaded biodegradable GTR membrane	Chang and Yamada (2000)
	Film-forming solutions	To evaluate the in vivo efficacy of the developed formulation	Kozlovsky et al. (1992)
	Dental paste	To study the effect of topical metronidazole therapy on ligature-induced periodontitis	Klinge et al. (1992)

3.4 Conclusion

The advancements in nanosciences/nanotechnology have led to an unprecedented growth in niche areas like medicine and its allied fields. Of these, an insurmountable effect has been on the contemporary dental practice and has led to the emergence of a newer discipline of dentistry. The bottom-up and top-down approaches of nanotools in dentistry aims at circumvention of all diseases of bony origin, dental adnexa, and associated soft tissues. One of the major challenges of dentistry is to address afflictions located at difficult to reach sites in the oral cavity. These often demand precise and controlled handling and require scrupulous sterilization so as to reduce bacterial deposition. Henceforth, the advents of laser, plasma, dentrifobots, and nanoassemblers have added robustness to dental cleaning and better oral hygiene. Likewise, the nanoencapsulation of antibiotics and their delivery into periodontal pockets ensure drug availability above MIC's over a prolonged period of times and do not require large doses of oral antibiotics. dentin hypersensitivity, tooth repairs, caries filling, and diagnosis of oral cavity cancer are other areas wherein the nanotools are highly commendable. Optimal utilization of the available nanotools in modern dental practice will definitely promise better oral health with a markedly reduced odontophobia.

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