Chapter 12
Recent Advances in Nanodentistry

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1 Introduction

To have general health and well-being, oral health is of great importance. A lot of genius drug delivery systems were developed for local treatment to prevent various diseases in the oral cavity. However, there are a few optimized systems and many therapeutic challenges that remain unsolved, including weak drug effectiveness and maintenance at targeted centers [1, 2].

Oral drug delivery is the most favored and helpful way of drug administration due to high patient compliance, cost-effectiveness, lowest amount of sterility limitations, adaptability in the designing of dosage form, and facility of generation [3]. In any case, the challenges confronted in oral drug delivery include low bioavailability of drug; this limitation is identified by three important factors—dissolution, permeability, and solubility [4–6].

The oral cavity (mouth) is discussed as the first section of the digestive tract, which includes various anatomical sectors: teeth, gingiva (gum) and their escort tissues, hard and soft palate, tongue, lips, and a mucosal membrane which lines the interior surface of the cheek [7]. The most known oral disorders among the world are dental caries, periodontal diseases, oral malignancies, and oral infections. In these cases, local therapy proposes numerous advantages over systemic drug administration, such as directly targeting the affected area while minimizing systemic side effects [8].

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One of the most routine factors influencing human lifestyle is inevitable caries formation and other tooth-related diseases, as they often lead to loss of teeth. A large ratio of research has been devoted to introduce control and preventive approaches [9]. It seems that a current challenge in the endodontic therapy field may be the elimination of the microbial infection, specifically the multispecies infections induced by aerobic and anaerobic bacteria [10–12]. It appears to be a suitable approach to treat and control dental infections by antibiotics or other active agents (such as nanoparticles to load in specific drug vehicle systems), even if the used delivery systems are less established when compared with other tissues. Based on the importance of biomedical delivery compartments, this study aims to provide a clear review on the amendments in drug delivery systems for dental applications [13, 14].

One can use the oral cavity as a limited drug delivery route in such cases like periodontitis and dental caries or for oral mucosal drug delivery—such as alveolar osteitis, analgesia, transmucosal systemic effect, or delivery of new biotechnological products like proteins and peptides. The present chapter provides an overview of dental physiology, prevalent dental diseases, and some nano-/bio dental materials and drug delivery systems corresponding to the oral cavity [15].

Different diseases affecting the orodental region, along with conventional as well as new and emerging drug delivery and technologies that improve local drug therapy, are presented in this chapter. Various types of drug delivery, along with their important clinical views, will be discussed. This chapter will offer the reader with a general and inspiring landscape on recent and promising aspects of innovation in oral drug delivery.

Nanotechnology is a field that studies the matter at the levels of molecule and atom, which has evolved the territory of dentistry as “nanodentistry” [16, 17].

Nanodentistry, as a term and a field, was coined in the twentieth century. Parallel to advancement of nanomedicine, dentistry commenced evolving in the field of nanotechnology, too. It seems that the nanotechnology field will influence the fields of diagnosis, surgery, and restorative dentistry. These promising new tools—like nanorobotics, nanodiagnosis, nanomaterials, nanosurgery, and nanodrugs—will highly impact clinical dentistry in the future [16–19].

The field of nanotechnology provides the diagnosis and treatment of oral cancer. Nanotechnology identifies the biomarkers of tumor cells and thus discovers them earlier, increasing the sensitivity of the test [20]. Many nanomaterials exist that can be utilized for restoration and/or prevention of decayed, carious, missing, or fractured teeth. Current progress in nanomaterials has introduced nanocomposites, nanoimpression, and nanoceramic in the area of clinical dentistry [17, 19, 21].

Although many ideas have been proposed for nanodentistry, most of them are not applicable because of various difficulties like designing challenges, medical challenges, social challenges, and so on. It is difficult to place and assemble the molecular scale part in a precise manner [21]. Manipulating the functions of some nanorobots simultaneously is also challenging. Nanomaterials can also be pyrogenic, so it is also an obstacle to produce biocapable nanomaterials. Social concerns, such as ethics and public acceptance, can be obstacles as well [16, 18].

Nanodentistry is an interdisciplinary research area that discusses the new nanomaterials and device applications in all the areas of human functionality [22]. Taking into account the advances in nanotechnology, nanomaterials and nanorobots show great attraction [23]. Though there is long-term research activity for this promising field, the clinical results have a strong tendency to highly promote the diagnosis and treatment approach planning for improving esthetics in the dental field. However, more research and trials are needed for the application of nanotechnology in oral tract and dental care. Nanodentistry will maintain comprehensive oral health by linking nanomaterials and biotechnology, including tissue engineering and dental nanorobotics. Although it is at an early stage, it has made a sufficient clinical and commercial effect [24].

2 Nanodentistry

Nanotechnology is an interesting branch in which all disciplines of natural sciences meet at nanoscale; for instance, physical forces merge with biologic sciences, engineering, organic/inorganic chemistry, materials science, and computational means, which are all highly linked. This inherent interdisciplinary nature devotes wide potency for multidisciplinary functions [5, 14, 20].

Recent developments in dental field research have made treatment routes fast, precise, safe, and less painful in recent years. Newborn techniques—such as nanotechnology, dental implants, cosmetic surgery, laser application, and digital dentistry—have had remarkable influence on dental treatment and restoration time [25, 26]. In the medicine research area, nanotechnology has been integrated to diagnose, prevent, and treat diseases. The following sections of the chapter address the recent developments in this integrative field that bridges nanotechnology and dentistry, nano-/biomaterials in oral health research, and some usages of nano-/biomaterials in this field [22, 27]. Oral medicine is an evolving field of dentistry, in which its multidisciplinary approaches have led to advancement of other areas in prevention, diagnostics, and therapeutics [28, 29].

Nanotechnology concerns the study of materials at molecular and atomic scale, which has evolved the field of dentistry, namely nanodentistry. This newly born scope is established on four approaches (biomimetics, functional, top-down, and bottom-up) and can be defined as a promising discipline that provides nanotechnology based on next-generation devices and tools for use in oral health care [16, 17, 19].

2.1 The Bottom-Up Approach

The bottom-up approach includes producing nanostructures and devices by arranging atom by atom. This approach involves self-assembly, using chemical or physical forces functioning at nanoscale to assemble smaller blocks to form larger structures.

Some instances of bottom-up path include synthesis of chemical materials, self-assembly, and molecular production. In other words, this approach is similar to building—taking many blocks and lining them together to fabricate the ultimate structure. Another tangible example from nature is that of body cells, which utilize enzymes to generate DNA by various components and assemble them to produce the final superstructure. Bottom-up approach fields in nanodentistry confine polymerization, precipitation, and micellar compartments [30, 31].

2.2 *The Top-Down Approach*

The top-down approach (that in some cases is recognized as the term decompose and also used as a synonym to stepwise design) refers to the breaking down of a collection to understand its components in a reverse engineering mode. In this approach, an original view of the system is figured out and characterized, but not in detail. Then, each subsystem component is studied in greater detail, sometimes in many additional sublevels, until the full specification is reached to elementary blocks. In this approach, synthesis of the particles is occurring in a routine manner and then made smaller by grinding or milling. Among all, the most successful industry that uses the top-down approach is the electronics industry [31]. Some applications of top-down and bottom-up approaches are summarized in Table 12.1.

2.3 *In the Functional Approach*

In the functional approach, the final goal is to create favored functionality components, regardless of the routine process. These desired properties might be electronic in the case of molecular scale electronics or materials with mechanical properties, like synthesized molecular motors.

Table 12.1 Some applications based on top-down and bottom-up approaches [18, 30, 32–34]

Top-down approach	Bottom-up approach
Nanomaterials for anesthesia	Nanocomposites
Major particles for tooth repair	Nanolight treatment glasses as ionomer restorative
Particles for repositioning tooth	Impression materials
Hypersensitive cure	Nanocomposite denture teeth
Dental sturdiness and apparent features	Nanosolution
Dental robots	Nanoencapsulation
Cancer diagnostic tools	Applying the laser plasma for periodontia
Therapeutic aid in oral disorders	Prosthetic implant
	Nanoneedles
	Materials for bone replacement

2.4 The Biomimetic Approach

The biomimetic approach is also called bionics. This name comes from the properties, which mimic the biological systems to form nanoscale devices. This approach refers to the inspiration and application of concepts from nature for generating new compositions, tools, and systems. The technology is still at its beginning stages and has not yet reached commercialization [35].

3 Nano-/Bio Dental Materials

Medical application of nano-/biomaterials in dentistry has been the focus of research laboratories worldwide [36]. Nowadays, nanotechnology is conducting dental materials industry to important growth areas. It seems that the prevalence of nanotechnology in dentistry answers the mysteries or challenges concerning routine materials, because they have the potential to mimic surface and interface properties of biological tissues [16, 18, 19]. Similar to nanomedicine, nanotechnology used in dentistry is expected to possible nearly perfect oral health by using nanomaterials and biotechnologies, such as tissue engineering and different technologies [37].

Nanotechnology, as a drastic field, has the power to control the individual particles in the nanometer scale. Some of these results are to a large extent relevant and remain impactful to human life. Although over the last few decades the fields of regenerative medicine and tissue engineering have gained a lot, still a large amount of research is required to innovate new materials in order to overcome the defects of existing biomaterials [5, 14, 20].

Orthodontic nanomaterials have come into practice widely, due to the industrialization process of nanotechnology and the patients having the opportunity to come into contact with them. These materials have resulted in remarkable improvements in medical treatments and have driven the creation of multiple routine dental materials. Some principal applications of nanomaterials in the field of dentistry are discussed in this section, and a summary of these functions is illustrated in Table 12.2.

4 Nano-/Biomaterials as Dental Drug Carriers

Drug carrier considerations include approaches, formulations, techniques, and systems for transporting pharmaceutical compounds in the human body as needed to safely reach therapeutic effect. This concept has been merged with dosage form and method of administration. The term “target drug delivery system” was coined by Ehrlich, who proposed the term “magic bullet” in 1906. The main difficulty in target drug delivery carriers was based on three important factors: finding the target of the disease, identifying the drug that will sufficiently cure the disease, and selecting

Table 12.2 Summary of some common nanomaterials in dentistry field and their characteristics

Major applications	Nanomaterial type	Particle size	Significant characteristics	References
Composite resins	Nano-ZnO	125 nm	Better antibacterial and mechanical properties	[25]
	Nanosilica	7 nm 70 nm	Better mechanical properties	[38, 39]
	Nano-Ca3$(PO_4)_2$ and CaF_2	112 nm 53 nm	Better stress-bearing capabilities and the inhibition of caries	[40]
	Nano-TiO_2	<20 nm	Improved microhardness and flexural strength	[41]
Dental adhesives	Nano-HAp	20–70 nm	Better bonding strength to dentin	[42]
	Nanosilver and calcium phosphate	<10 nm 112 nm	Improved antibacterial properties	[43]
	Nanosilica	7 nm	High mechanical strength and good thermostability	[44, 45]
Root canal fillings	Nano-HAp	–	Better osteogenesis and improved bacteriostatic and antibacterial effects	[46, 47]
Bone repair materials	Nano-HAp	100 nm 20 nm 3 nm	Guiding the regeneration of periodontal and bone tissue	[48–50]
Bioceramics	Nano-ZrO_2/HAp composite	70–90 nm/ 500–1000 nm	Guiding bone reconstruction	[51]
	Nano-ZrO_2/Al_2O_3	–	Better resistance to crack propagation	[52]
	Nanosilver	10 nm	Increased fracture toughness and Vickers hardness	[53]
Silicone elastomer material	Nano-Ti-, Zn-, Ceoxide	30–40 nm 20 nm 50 nm	Improved mechanical properties	[54]
Denture base materials	Nanosilver	10–20 nm	Better antifungal properties and biocompatibility	[55]
Coating materials for dental implants	Nanoporous alumina	20–200 nm	Good cell adhesion and no adverse effect on cell activity	[56]
	Nano-zirconia/ calcium phosphate	360 nm/151 nm	High bioactivity potential and good mechanical stability	[57]
	Nano-ZnO	10–100 nm	Better antimicrobial and biocompatible properties	[58]
	Nano-HAp	–	Achieving rapid osseointegration	[59]

(continued)

Table 12.2 (continued)

Major applications	Nanomaterial type	Particle size	Significant characteristics	References
Drug delivery	Nanosilica	150 nm	Sustained and controlled release of anticancer drugs (as drug carriers)	[60]
	Polymeric NPs (vitamin e TPGS)	300–1000 nm	Controlled release of anticancer drugs (as drug carriers)	[27]
Tumor imaging	Superparamagnetic iron oxide NPs	82 ± 4.4 nm	Good superparamagnetic and optical properties	[61]

suitable target mediums transport the drug in a stable shape while preventing other interactions and harm to the healthy tissues.

The delivery of targeted particles has the potential to transport high-density drug molecules while expressing ligands on the surface of the particle at the same time. Nanomedicine is the field of development and use of nanotechnology in the area of medicine to block, detect, and treat diseases at the cellular and molecular level. Nanoproducts delivered through target drug delivery carriers use the pathophysiological and anatomical variances within the defected tissue to differentiate it from healthy tissues to get site-specific targeted drug delivery. Thus, the goal of this section is to show a brief landscape of the targeted drug delivery system using nanoparticles and nanovectors for different treatment purposes in dentistry.

4.1 Various Delivery Vehicles

Nanoparticles are used as potent carriers along with targeting ligands for the target drug. These materials have multiple advantages over larger systems because of their submicron size. The principal characteristics of these systems are that they should be biodegradable, biocompatible, toxic-free, and physicochemically durable. Drug release should be even, scheduled, predictable, and without any side effect to the main drug [62, 63]. The main advantages of nanoparticle drug delivery carriers are their small size, which makes them a suitable candidate to be extravasated through blood vessels and tissues, especially in tumors. Targeted drugs can be designed to avoid first-pass metabolism. Moreover, they may also show properties like optical and electrical characteristics. These features make it possible to chase and localize the drug intracellularly. However, it has its disadvantages, such as toxicity, requiring skill to administer, and limited drug durability. A variety of submicron colloidal nanosystems of size <1 μm are included. They may have various structures and compositions like inorganic, liposome, or polymer-based colloidal systems, which have acted as effective drug carriers for several decades [63, 64].

4.1.1 Liposomes

Liposomes are structures composed of two components—amphiphilic phospholipids and cholesterol in bilayers that confine an aqueous interior. Liposomes as a reservoir for target drug delivery were first introduced by Gregoriadis [65]. These bodies have provided promising results in improving therapeutic benefits, diminishing side effects, and increasing patient relief, as they mimic the biologic membrane. They can also be designed as bio-adhesives that are retained by the enamel, increasing the exposure time and residence in the oral cavity [28, 29]. They break down into smaller structures that can surround hydrophilic drugs in the aqueous interior or hydrophobic drugs in the bilayer. There are two methods for encapsulation, namely, by the pH gradient and ammonium sulfate method. Adding polyethylene glycol (PEG) to the lipid surface enhances its surface properties via functioning as an obstacle to avoid interaction with the plasma proteins, thereby retarding detection by the reticuloendothelial system (RES). This results in an increased circulation time of the liposomes. Phosphatidylcholine-based liposomes are used to target bacterial biofilms, whereas succinylated concanvalin A (conA) liposomes are targeted for delivery of triclosan to the biofilm of *Staphylococcus epidermidis* and *Proteus vulgaris*. However, application of liposomes in target drug delivery displays the following disadvantages: low control over drug release, poor encapsulation yield, and poor stability during encapsulation [66].

4.1.2 Solid Biodegradable Nanoparticles

Solid biodegradable nanoparticles are another kind of carriers that are widely seen because they have different polymer compositions and morphologies than liposomes, which can sufficiently control release features over a long period of time. These families of materials include aliphatic polyesters, specifically hydrophobic polylactic acid, hydrophilic polyglycolic acid, and their copolymers, such as polylactide-co-glycolide. These materials have been utilized for various clinical applications for over three decades and are regarded as safe to use in human body [64].

4.1.3 Micelles

Micelles are another group of polymers, which are composed of lipids and have spherical structure, but lack a lipid bilayer or an inner hole. Their typical size is about 10–80 nm, and they can transport various drugs with better longevity, low circulation time, and stability. They have better penetration and flexibility to enter the target sites because of their size, which allows them to enhance the drug effect on the target site. These drug delivery elements target cancer cells and are presumed to have magnetic resource imaging (MRI) contrast characteristics [67].

4.1.4 Dendrimers

Dendrimers are molecules that possess three-dimensional, multi-branched structures. They are well-defined, unimolecular, monodisperse materials ranging from 1 to 10 nm in size. These structures, due to their branching pattern, offer a larger surface area for drug binding. Dendrimers are the best way to deliver both water-soluble and insoluble drugs [65, 68]. Multifunctional types of them are synthetically formulated in conjugation with fluorescein isothiocyanate used for imaging and folic acid for targeting cancer cells, which overexpress folate receptors and paclitaxel as a chemotherapeutic drug [69].

4.1.5 Polymers

Polymeric nanoparticles can deliver low-molecular-weight drugs, macromolecular proteins, and genes. Unlike liposomes, these nanoparticles show less toxicity, high durability, higher loading capacity for water-soluble drugs with sustained release of drugs, and many physicochemical properties [65, 70]. Due to their slow clearance by RES, their use as biodegradable nanoparticles is rapidly increased; the dosage of the drugs has been decreased due to enhanced plasma half-life. Polyketals are biocompatible, hydrophobic polymers and have been synthesized recently for use as biodegradable ketal linkages. This linkages aid in creating nanoparticles to encapsulate and enrich hydrophobic drugs or proteins [71]. PEG is a hydrophilic polymer used to form a stealth layer to minimize the nonspecific enrichment of the drug. This advantage leads to more stability of the nanoparticles and targeting of the site [70, 72].

4.1.6 Carbon Nanotubes

Carbon nanotubes are single or multiple sheets produced from graphene and rolled into a cylinder. They can pass into living cells without causing any cell death or defect to their size or shape. Although these nanoparticles show high potential in nanodrug delivery, their safety remains obscure because of needle-like fiber shape and toxicity [26, 65].

4.1.7 Gold Nanoparticles

Gold nanoparticles can be synthesized in a range of sizes. They are biocompatible, easy functionable, highly dispersed, and able to conjugate with other molecules. Their high surface area/volume index, inert entity, and small size allow their use extensively as delivery systems [73]. Studies have addressed that monodisperse spheres can be synthesized using reducing agents, like citrate, by acting on some given gold salts, such as tetrachloraurate [74].

4.1.8 Nanodiamonds

Nanodiamonds are allotropes of carbon with a size of about 2–8 nm. These type of nanoparticles possess functional groups, which can attach a wide spectrum of compounds, such as chemotherapy agents and other drugs [75]. They possess unique physical characteristics like small size, less corrosion, high mechanically stable, and biocompatibility and function as biomarkers and biosensors [76]. Recently, these materials have been widely used to collect proteins and deliver drugs to the target areas. For example, when they are bound to doxorubicin and encapsulated into polymeric microfilms, they can be used to sustain release of drugs [65, 75] [76]. They can be formulated into dental materials and used as a filling or veneer, and their hardness makes them a good candidate for implant and cutting tools formation. When dry, nanodiamonds provide favorable appearance, such as natural enamel, and it is believed to treat gum illness when utilized as toothpaste [30].

4.1.9 Nanogel

Nanogel is a novel biocompatible polymer with a core-shell formulation. Nanogel nanoparticles are of submicron range size and have a gel-like appearance that contains colloidal aggregates, which come from hydrophilic polymers. Nanogels have both nanoparticle and hydrogel advantages and show a high potential to deliver genes and proteins [32].

5 Nano-/Biomaterials as Dental Filling Agents

In dental applications, fillers are the additives in solid form with various polymer composition and structure. These additives are comprised frequently of inorganic materials and partly organic material [31]. In recent decades, with advent nanotechnology incorporated into the medical field—particularly dentistry, considerable endeavors have been demonstrated for design of innovative promising dental restorative structures, for instance, nanofillers [33]. Nanofillers are nanosized reinforcement particles blended with resins of various properties, rather than traditional fillers that necessitate a shift from a top-down to a bottom-up construction methodology, which are usually blended with resins to create nano-filled resin composites [34].

Considering the excellent features of nanomaterials, these structures are currently considered as novel fillers to improve the mechanical and esthetic properties of polymer composites in dentistry. Nanofillers that possess greater aspect ratio—the ratio of largest to smallest dimension—depict an appropriate reinforcement for nanocomposites fabrication. To date, diverse materials with organic and inorganic nature are utilized for the preparation of nanofillers; silica, titanium dioxide, calcium carbonate, and polyhedral oligomeric silsesquioxane are examples of inorganic materials [35]. Coir nanofiller, carbon black, and cellulosic nanofiller can also be utilized as inorganic fillers [77].

Generally, nanofillers are able to improve/adjust the variable properties of the materials into which they are incorporated, like fire-retardant, optical or electrical, mechanical, as well as thermal properties, occasionally in synergy with conventional fillers. From the prevalent nanofillers in nanocomposites, nanoclays, nanooxides, and carbon nanotubes are some examples [78, 79].

6 Nano-/Biomaterials as Dental Adhesive Agents

Dental adhesives are systems that consist of monomers with hydrophilic and hydrophobic groups, creating the resin dental substrate interaction. Hydrophilic groups provide an appropriate wettability to dental hard tissues, whereas the presence of hydrophobic groups in adhesive systems leads to interaction and copolymerization with the restorative materials [80]. Curing initiators, inhibitors or stabilizers, solvents, and inorganic fillers are major chemical components of dental adhesives. Overall, considering the anatomy of the tooth is a pivotal issue in design of dental adhesives; particularly, composition and structure of enamel and dentin are requisite parameters for examination of their influence on adhesive bonds [81]. Indeed, enamel is composed of hydroxyapatite (HAp), as a hard solid crystalline structure, together with water and organic materials. In comparison with enamel, dentin has low intermolecular forces and low energy surfaces. This humid layer, which lies immediately underneath the enamel, is a component similar to enamel [82].

Resin composites, as esthetic components in dentistry, are being progressively employed as dental restorations owing to significant improvements in their properties and performance. Nevertheless, composites possess a tendency for accumulation of biofilm in vivo, which could lead to production of acids and subsequently cause dental caries. The principal reason for restoration fracture is recurrent caries and, therefore, for 50–70% of all operative work, it should be conducted for replacement of the failed restorations. To circumvent this drawback, several research groups designed antibacterial resins based on nanostructures. In recent research, to treat dental caries, antibacterial resins and silver (Ag) filler particles were used as an appropriate approach for management of caries [83]. It is well documented that nanoparticles of Ag are effective for antibacterial applications [84]. Another study introduced a new alternate method for inhibiting the caries, in which researchers applied center-filled calcium phosphate (CaP) composite particles that can release Ca and P ions and remineralize tooth lesions. Recently, calcium phosphate nanoparticles were fabricated using a spray-drying method. Some new nanocomposites were designed, which contain amorphous CaP. These nanoparticles can release calcium and phosphate ions in the same way as traditional calcium phosphate composites. Moreover, they possess higher mechanical properties for loading tooth restorations [85].

7 Nano-/Biomaterials as Dental Implants

When teeth are lost, endoosseus oral implants are—from the clinical point of view—“the last stand” of bite reconstruction. The idea of using Ti implants in dentistry began in the early 1980s and was based on Brennemark’s definition of osseointegration, which explained the direct contact of a living bone with functionally loaded oral implants [86]. From that moment, implant dentistry has evolved, and the conceptions of treatment protocols have changed. One thing that remained the same was the struggle to improve implant–bone interconnection quality. Along with views on surface modifications, the classic approach to implant surface treatment—“the rougher-the better”—was rejected in the early 2000s. This was based on clinical observations that showed that a micro-rough surface, despite better stability in the beginning, may initiate subsequent bone osteolysis and favor biofilm formation and infection development, which is commonly known as “periimplantitis” [87, 88].

Along with the evolution of nanodentistry, the views on implant surface modification followed the general rule of mimicking nature. It was proposed that the implant surface may imitate the bone-like structure and properties at the nanoscale level, as bone is nothing more like a biological nanocomposite. Dental implants usually consist of three independently manufactured parts: intraosseous screw, transmucosal abutment, and prosthetic crown [89].

Among all dental sciences, oral implantology represents the fastest developing area and applies to all implant components, as well as surgical instruments. An approach to oral implants, with regard to their intraosseous portion, is focused on osseointegration improvement. The process of implant connection with bone consists of two phases: primary interlock corresponds to the mechanical anchorage and mostly macro design of implants, such as the screw shape of threads geometry. The second anchorage relies on bone remodeling at the implant interface and the creation of biological bonding. This process is related to surface micro-nano topography, chemical composition, wettability, and roughness which, taken together, has an impact on the biochemistry and dynamics of bone formation de novo [90, 91].

Clinically, a decrease in implant stability can be observed between the primary mechanical and secondary biological anchorage as a natural consequence of biological remodeling of bone tissue following surgical injury (osteotomy preparation, implant insertion, inflammatory response). Good modification of the surface from macro to nanoscale may promote the process of implant healing [92]. There are a lot of ways for modifying the surface in order to roughen it, based on direct surface tailoring (e.g., etching, sandblasting) and/or making functions (bio-glass coatings or polymers, peptides, etc.), or combinations of these techniques to commercially available implants to achieve roughness at the micro level. However, this technique could decrease surface hardness and, moreover, cause a loss of superficial material layer that damages screw threads, possibly negatively affecting proper implant anchorage to bone. Other techniques that provide modifications at the microscale could result in coating delamination, surface contamination with hydrocarbons (re-hydrophobization of the surface), and many others, which are elucidated in the detail in the recent work of Durracio et al. [93, 94].

As long as surface properties have a key role in long-term stability of bone tissues, dental implants are increasingly used as nanotechnology tools for surface modifications. To reach this purpose, it is necessary for implants to have direct contact with bone. This direct contact makes good biomechanical anchoring, rather than encapsulation via fibrous tissues [91]. The surface roughness of bone is approximately near 100 nm, and this nanoscale data is important to the surface of implants, as the proliferation of osteoblast is induced via production of nanosized particles on the surface of implants [95, 96]. Roughening the implant surface at the nanoscale level is important for the optimum cellular reaction that takes place in the tissue and stimulates merging of the implant into the bone [97, 98].

Using nanotechnology methods, some titanium implants were fabricated, then their surface was coated with calcium and inserted into rabbit tibias. Finally, their impact on osteogenesis was measured. As a result, the responsiveness of the bone around the implant was increased due to the insertion of the nanostructured calcium coat [99]. In vitro research on these materials illustrates that the most effective factor on osteogenic cells is the topography of the implant, and this nanosized surface enhances the surface area and the adhesion of osteoblastic cells. This enhanced surface provides an increased surface area that facilitates the reaction with biologic environment [99–101]. Recent nanostructured implant coatings are as follows:

1. *Nanostructured Diamond*: This coating type presents very high hardness, improved toughness over common microcrystalline diamond, low friction, and good adhesion to titanium alloys [102].
2. *Nanostructured Coatings of HA*: This type of coating material is applied to amend the favored mechanical characteristics and to enrich surface reactivity and has shown increment of osteoblast adhesion, proliferation, and mineralization [56, 90, 103].
3. *Metalloceramic-Based Nanostructured Coatings*: These coatings cover a vast range from nanocrystalline metallic bond at the interface to hard ceramic bond on the surface.

Nanostructured ceramics, carbon fibers, polymers, metals, and composites enhance osteoblast adhesion and calcium/phosphate mineral deposition.

Some researchers have shown that nanophase ZnO and TiO_2 may lower *Staphylococcus epidermidis* adhesion and intensify the osteoblast functions that are vital to elevate the effectiveness of orthopedic implants [91, 104, 105].

8 Nanodiagnosis in Dentistry

Nanodiagnosis technology uses nanodevices and nanosystems to detect disease in early stages at the cellular and molecular level. The development of nanoscale diagnostic methods on human fluids or tissue samples could increase efficiency of these methods. Nanodiagnosis devices will be able to detect and identify the early presence of diseases, such as tumor cells and toxic molecules, and quantify them inside the body. In cancer diagnosis, the advantages of this technology include being a less invasive and less uncomfortable method for identifying and measuring disease indicators, which will be applied in diagnosis as well as in monitoring recurrence or metastasis and types and behaviors of malignancies [106]. Here, some of the techniques used in nanodiagnosis are described briefly (Fig. 12.1).

Nanopores: Nanopores are a pore of tiny and nanometer size that allows DNA sequencing to pass more efficiently. Researchers can use this technology to decode coded information, including errors in a code known as cancer [107].

Nanotubes: hese are carbon rods that can help detect and pinpoint the presence of altered genes and their exact location. From this category, the quantum dots may help to identify DNA changes associated with cancer and designed quantum dots that match with altered genes in sequences of DNA responsible for disease [35]. The quantum dots are excited with light, then they emit their characteristic bar codes and visible cancer-associated DNA sequences [108].

Nanoscale Cantilevers: These flexible beams can be designed to bind to cancer-related molecules. They bind to altered DNA sequences or proteins in certain types of cancer and can provide rapid and sensitive detection of cancer-related molecules [109].

Nanoelectromechanical Systems (NEMS): NEMS-based biosensors based on nanotechnology that show a specific sensitivity to detect single-molecule levels are under development. These systems convert biochemical signals into electrical signals, monitoring the health status, disease progression, and result of treatment by noninvasive means [16, 110].

Laboratory-on-a-Chip (LOC): These are devices that integrate several laboratories on a single chip. This technology deals with a very low volume—less than

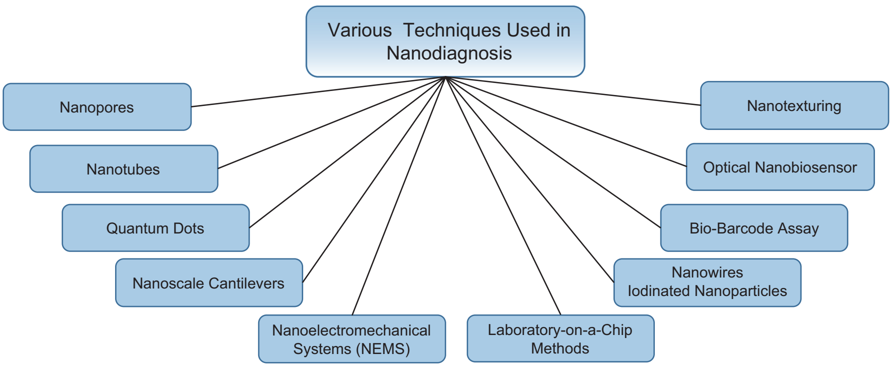

Fig. 12.1 Some of the techniques used in nanodiagnosis

picoliters—of fluid. The basis of these assays is the use of chemical sensitivities that are embedded in silicon sheets in fluids and are capable of optical detection. The special advantage of LOC devices is performing complex tests with small sample size, short-time analysis, and reduction in reactive costs [111, 112].

Oral Fluid Nanosensor Test (OFNASET): This technology is a combination of self-assembled monolayers (SAM), microfluidics, and enzymatic amplification to identify salivary biomarkers for oral cancer. The high specificity and sensitivity of *OFNASET* technology was demonstrated in the detection of salivary proteomic and mRNA biomarkers in oral cancer.

Optical Nanobiosensor: An important feature of nanobiosensor is a unique fiberoptics-based tool that provides the analysis of intracellular components with the least invasion. For example, cytochrome C, an important protein involved in the production of cellular energy and in apoptosis, can be analyzed through optical nanobiosensor [113].

Nanotexturing: Physicochemical-modified surfaces under nanoscale allow the analysis of low-molecular-weight proteins from body fluids and other biologic samples. This will result in separation based on size, selective adsorption of proteins, and lead enhancement of specific regions of the proteins [110].

Bio-Barcode Assay (BCA): This technique was developed by a magnetic probe for specific detection of a target molecule using a monoclonal antibody or complementary oligonucleotide. Target-specific gold nanoparticles can be used to capture the target, distinguishing it and amplifying the signal and, thus, be detected using the scanometric method [110].

9 Clinical Applications of Nano-/Bio Dental Materials

Nanodentistry has been recognized as a very promising field, through which oral health care could be pulled to an unprecedented height via the utilization of various components of nanotechnology, nanomaterials, tissue engineering, and dental nanorobots. Applications of nanotechnology in dentistry are as follows.

9.1 Local Anesthesia

In virtue of nanodentistry, a colloidal suspension composed of a myriad of active analgesic micron-sized dental robots is infused into the patient's gingiva. Next, these wandering nanorobots gain access to the pulp through the gingival sulcus, lamina propria, and dentinal tubules. Afterward, the dentist may control the analgesic dental robots to suppress all sensitivity in the tooth requiring treatment. When treatment of a specific tooth is completed, all sensations can be promptly recovered because nanorobots deny the control of nerve signals, having received the orders from the dentist, and leave from same path applied for entry [114].

9.2 Hypersensitivity Cure

Any change in the hydrodynamic pressure transmitted to the pulp is most liable to bring about dentin hypersensitivity. This hypothesis is due to the fact that dentinal tubules and tubules with diameter twice as big as non-sensitive teeth are eight times more numerous on the surface than non-sensitive teeth. In the foreseeable future, this complaint of patients will be curbed by dental nanorobots, which can selectively occlude tubules by native biological materials [114].

9.3 Diagnosis of Oral Cancer

- *Cantilever Array Sensors*: Based on ultrasensitive mass detection technology: picogram, bacterium; femtogram, virus; and attogram, DNA.
- *Nanoelectromechanical Systems (NEMS)*: Nanotechnology-based NEMS biosensors showing excellent sensitivity and specificity for analyte detection down to single-molecule levels are being developed. They can transform (bio)chemical to electrical signals.
- *Multiplexing Modality*: Sensing good numbers of diverse biomolecules at a time [114].
- *Oral Fluid NanoSensor Test (OFNASET)*: OFNASET technology is applied for multiplex detection of salivary biomarkers for early oral cancer diagnosis. It has been confirmed that the combination of two salivary proteomic biomarkers (thioredoxin and IL-8) and four salivary mRNA biomarkers (SAT, ODZ, IL-8, and IL-1b) can diagnose oral cancer with noticeable selectivity and sensitivity [18].
- *Optical Nanobiosensor*: Low invasive analysis of intracellular components, such as cytochrome c, a momentous protein in the process of producing cellular energy and the protein engaged in apoptosis, has become possible by the utilization of nanobiosensor, a sole fiber optics-based tool [110].

9.4 Treatment of Oral Cancer

- *Nanomaterials for Brachytherapy*: BrachySilTM (Sivida, Australia) delivers 32P, clinical trial. Drug delivery across the blood-brain barrier. More effective therapy of brain tumors, Alzheimer's and Parkinson's are in development.

- *Nanovectors for Gene Therapy*: Non-viral gene delivery systems.
- *Photodynamic Therapy*: Hydrophobic porphyrins are molecules that inherently attract the photodynamic therapy (PDT) of solid tumors or ocular vascularization disorders [115].

9.5 Dental Durability, Appearance, and Dentifrobots

The appearance and strength of the tooth may be intensified by substituting upper enamel layers with pure sapphire and diamond. This approach makes them more break safe as nanostructured materials. This could include entrenched carbon nanotube toothpaste or mouthwash that can be applied to deliver nanorobotic dentifrice. This would possess an inbuilt programmer to avoid the occlusal region. Their function would be similar to common dentifrices, yet the approach would be thoroughly diverse, as they would be infinitesimal [1–10 micron] mechanical devices, creeping at a speed of 1–10 microns/sec, performing by metabolizing trapped organic matter into safe and scentless vapors, and debriding calculus incessantly. Regarding the safety, if swallowed accidentally, they would be inactivated. Dentifrobots are programmed to recognize and demolish pathogenic bacteria dwelling in the plaque and the oral cavity while sparing around 500 species of safe oral microflora. Hence, by killing bacteria, dentifrobots would provide a blockade against halitosis on the grounds that bacterial putrefaction is the central metabolic process engaged in oral malodor [116]. With the assistance of this type of daily dental care available from an early age, common tooth decay and gingival disease will be eradicated.

9.6 Orthodontic Treatment

Orthodontic nanorobots could directly impact the periodontal tissues, providing the chance for quick and painless tooth straightening, revolving, and vertical repositioning within minutes to hours. This is in contrast with the commonly used molar uprighting methods, which require weeks or even months to be completed [114].

9.7 Tooth Repair

Nanodental methods for major tooth repair may thrive via several steps of technological progress: at first, taking modest steps of genetic engineering, tissue engineering, and regeneration and then making a great leap of development of whole new teeth in vitro and their installation [117].

9.8 Dentition Renaturalization

Esthetic dentistry would go into a fully novel era with the addition of dentition renaturalization procedures to the common dental practice armamentarium. Demand would observe an abrupt outburst for full coronal renaturalization procedures, in which all of the fillings, crowns, and other twentieth-century treatment methods will be substituted with the affected teeth remanufactured to become exactly similar to original teeth [118].

9.9 Nanocomposites

Corporation of nanoproducts has successfully produced non-agglomerated discrete NPs, which are homogeneously dispersed in resins or coatings to form nanocomposites. The nanofiller applied encompasses an aluminosilicate powder possessing a mean size for the particles about 80 nm and a 1:4 M proportion of alumina to silica and an index of refraction near 1.508. Merits have higher hardness, higher flexural strength, higher modulus of elasticity and translucency, 50% abatement in filling shrinkage, and adequate handling features [119].

Trade Name: Filtek O Supreme Universal Restorative Pure Nano O

9.10 Nanosolution

Nanosolutions generate special and distributable NPs, which are able to be utilized in bonding agents. This guarantees both the homogeneousness and adhesive sticking well mixed [119].

Trade Name: Adper O Single Bond Plus Adhesive Single Bond

9.11 Impression Materials

Nanomaterials that are used as fillers are incorporated in vinylpolysiloxanes, shaping a special expansion of siloxane impression materials. The material has more stream, improved hydrophilic virtues, and intensified detail accuracy [114].

Business Name: Nanotech Elite H-D

9.12 Nanoencapsulation

Latest evolution in the field of targeted release systems is attributed to SWRI [South West Research Institute], which has developed nanocapsules—such as novel vaccines, antibiotics, and drug delivery—with curtailed side effects. Among these series of evolutions, the most recent has come from Osaka University (Japan), which has improved targeted delivery of genes and drugs to the human liver in 2003. In this research, designed Hepatitis B virus encapsulated particles used to produce NPs showing a peptide momentous for liver-selective entry by the virus in humans. In the future, specialized NPs may be designed to reach oral texture corresponding to the cells originated from the periodontium [119].

9.13 Other Products of SWRI

(a) Medical supplements for fast healing:

- Biodegradable nanofibers will act as delivery platform for hemostasis.
- Function of silk nanofibers in wound dressings is still under investigation.
- Nanocrystalline silver particles with antimicrobial virtues on wound dressings [ActicoatTM, UK].

(b) Protective clothing and filtration masks using antipathogenic nanoemulsions and NPs.
(c) Bone targeting nanocarriers: Calcium phosphate-based biomaterial has been developed. It is a readily flowable, moldable paste that adapts to and interdigitates with host bone, providing support for the growth of cartilage and bone cells [114, 119].

9.14 Nanoneedles

Suture needles including nanosized stainless-steel crystals have been developed.

Trade Name: Sandvik Bioline, RK 91TM needles [AB Sandvik, Sweden]

Nanotweezers are under development. These materials possess the potential to make cell surgery possible in a foreseeable future [114, 119].

9.15 Materials Applied for Bone Replacement

Hydroxyapatite NPs are utilized to heal bone defects are [8, 15]: VITOSSO (Orthovita, Inc., USA) HA + TCP; NanOSSTM (Angstrom Medica, USA) HA; Ostim® (Osartis GmbH, Germany) HA.

10 Possible Hazards Resulting from NPs

Nanobiotechnology could strikingly ameliorate public health, but there are concerns that technical improvements could breed unexpected adverse effects. Human beings have been exposed to NPs during their developing phases; nevertheless, this exposure has increased in the past century due to the industrial revolution. Nanotechnology is also being utilized in medical sciences with the effort to develop a more personalized medicine. Epidemiological investigations have revealed that the urban population—with airborne particulate matter along with NPs—created combustion sources, such as motor vehicle and industrial emissions. These emissions play a vital role in respiratory and cardiovascular morbidity and mortality. Likewise, NPs may also be involved in the toxicological profile of NPs in biological systems. These smaller particles possess larger surface area per unit mass, and this feature makes NPs very reactive in the cellular media. The respiratory system, blood, central nervous system, gastrointestinal tract, and skin have been demonstrated to be affected by NPs [120, 121].

11 Summary

Nanotechnology has made bright progress in science, especially in the field of dentistry with an extrapolation of current resources, and offers a clear vision with the possibility of great advances under resources available. Although this technology is still very young, many applications of it will be introduced. In this chapter, we discussed a few applications that have already been developed and used to help patients. More research related to dental health care should focus on drug delivery systems and toxicity by the emergence of more biocompatible materials. There is a need for extensive research on this technology in various fields, including public and dental care, biomedicine, food, and agriculture. In the future, many diseases that do not have a cure today may be cured by nanotechnology. We also discussed some concerns in this area, however, with proper care these problems can be avoided. Still, the arrival of nanotechnology in the dentistry field has grown increasingly during recent years, but it is noteworthy that biosafety assessment of nanostructures should be considered prior to apply them in dental applications in order to avoid many pathological conditions.

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