Review Article

JRAD Journal of Research and Advancement in Dentistry

J Res Adv Dent 2018;9:1:281-289.

Evolution of Nanotechnology in Dentistry

Khwairakpam Chaoton Singh[1*] Sagar Gopalakrishna[2] Albert Ashem[3] Ishani Ningthoujam[4] Rajan Rajput[5] Bandana Waikhom[6]

[1]Consultant Oral and Maxillofacial Surgeon, Imphal, Manipur, India.
[2]Consultant Oral and Maxillofacial Surgeon, Mysuru, Karnataka, India.
[3]Senior Lecturer, Department of Oral Medicine and Radiology, Maharaja Ganga Singh Dental College and Research Center, Sri Ganganagar, India.
[4]Consultant Prosthodontist, Imphal. Manipur, India.
[5]Reader, Department of Oral Medicine & Radiology, Narsinhbhai Patel Dental College & Hospital, Faculty of Dental Sciences, Sankalchand Patel University, Visnagar. Gujrat, India.
[6]Clinical Practioner, Dental Unit, Maipakpi Maternity and Child Hospital, Imphal, Manipur, India.

ABSTRACT

Background: Nanotechnology is at the forefront of medical research, and translational medicine is a challenge to both scientists and clinicians. Nanotechnology is manipulation of matter on the molecular and atomic levels. Various avenues in the field of dentistry are being aided with nanotechnology and the future holds great promise. The purpose of this article is to look into the present aspects of Nanotechnology, its current use in various field dentistry, and implications and challenges for the future.

Keywords: Nanodentistry, Nanomaterials, Nanomedicine, Quantum dots, Nanotoxicology.

INTRODUCTION

Small ideas create big wonders, small things makes the world bigger. "Nano" is derived from the Greek word which stands for "dwarf"[1]. Nanotechnology is the science of manipulating matter, measured in the billionths of meters or manometer, roughly the size of two or three atoms. Nanotechnology is artistic engineering on a scale of less than 100 nm to accomplish desired design, functions and performance of end products.

It engages the characterization and control of materials at the atomic or molecular level [2]. At nanoscale, physical, chemical and biological properties are different from the properties at an individual atomic/molecular level and bulk matter [3]. Nanotechnology is one of the most popular areas of current research and has developed in multiple disciplines

History

The term nanotechnology was defined by Japanese scientist *Dr. Nori Taniguchi* in 1974 and was defined as "the processing of separation, consolidation, and deformation of materials by one atom or one molecule" [4]. Long time before the introduction of the term "nanotechnology", the concept was set up by physicist *Richard Feynman* in 1959. The idea was entitled as "There's Plenty of Room at the Bottom" and presented at an American Physical Society meeting at the California Institute of Technology in 1959. Richard Feynman proposed the direct manipulation of individual atoms as a more powerful form of synthetic chemistry [5]. Although Feynman did not apply the term "Nanotechnology or Nanosciences" however described the novel process in which scientist can manipulate materials at atomic or molecular levels. The field started to develop in 1980s with the birth of cluster science and the development of Scanning Tunneling Microscope. *Eric Drexler* popularized nanotechnology in 1986 in his book "Engines of

Received: July. 17, 2018: **Accepted**: Sept. 5, 2018
*Correspondence **Dr. Khwairakpam Chaoton Singh.**
Consultant Oral and Maxillofacial Surgeon, Imphal, Manipur, India.
Email: Not Disclosed

pISSN 2278-0076
eISSN 2321-9270

Creation: The coming era of Nanotechnology." around late 1980s. In 1991, the publication by Sumio Lijima "Helical microtubules of graphitic carbon" introduced the concept of nanotubes and boosted nanomaterials research . Nanotubes, Nanowires and Nanoparticles have been developed and are under investigation for possible uses in everyday areas, including medicine.[6] The idea of nanotechnology was further probed in depth and promoted by Dr. Drexler and published a book titled "Engines of Creation-The Coming Era of Nanotechnology".

Nanomaterials

Nanomaterials are those materials with components less than 100 nm in at least one dimension, including clusters of atoms, grains, fibres, films, nanoholes, and composites. These nanomaterials if present in one dimension are called as sheets, if in two dimensions are nanowires and nanotubes, if present in three dimensions are called as quantum dots. The various nanostructures are Nanopores , Nanotubes , Quantum dots, Nanoshells, Dendrimers. [7]

Nanomaterial properties

Nanomaterials are of interest from a fundamental point of view because with new materials, come new properties, which result in new opportunities for technological and commercial development, and applications of nanoparticles have been proposed in areas as diverse as microelectronics, coatings and paints, and biotechnology. From these applications has come the development of nanopharmaceuticals, nanosensors, nanoswitches, and nanodelivery systems. Two principal factors cause the properties of nanomaterials to differ significantly from other materials: the increase in relative surface area and quantum effects. For example, a particle of 30 nm has 5% of its atoms on its surface, at 10 nm 20% of its atoms, and at 3 nm 50% of its atoms. Nanoparticles have a much greater surface area per unit mass compared with larger particles. In tandem with surface area effects, quantum effects can begin to dominate the properties of matter, as size is reduced to the nanoscale it can affect the optical, electrical, and magnetic behavior of materials, particularly as the structure or particle size approaches the smaller end of the nanoscale. For example, nanocrystalline nickel is as strong as hardened steel.[8]

Nanomedicine

"Nanomedicine" is the science of preventing, diagnosing, and treating disease and preserving and improving human health, using nanosized particles.[9] Advances in the medical implementations of nanotechnology have resulted in the formation of a new field called nanomedicine.[10]This concept was first put forward in 1993 by Robert A. Freitas Jr. and was defined as observing, controlling, and treating the biological systems of the human body at the molecular level using nano-structures and nano-devices.[11] Nanomedicine includes various applications ranging from drug release with nanospheres to tissue scaffolds based on nanotechnologic design that realize tissue formation, and even nanorobots for diagnostic and therapeutic purposes.[12] Drug molecules transported through the body by the circulatory system may cause undesirable adverse effects in untargeted regions. On the other hand, nanorobots can recognize unhealthy cells and can find and destroy them wherever they are located. Drug delivery to the exact target is of particular importance in cancer in order to destroy all of the cancer cells and at the same time avoid harming healthy cells.[13] Nanomedicine can overcome many important medical problems with basic nanodevices and nanomaterials, some of which can be manufactured today. The results of many studies performed today in the field of nanomedicine are very close to transformation into practice; therefore, it can be said that these successful developments are inevitable. Nanomedicine provides improvements in available techniques in addition to developing fully new techniques.[14]

Nanodentistry

Nanodentistry is defined as the science and technology of diagnosing, treating and preventing oral and dental diseases, relieving pain, preserving and improving dental health using nanostructured material. There are varieties of new dental products available, ranging from implants to oral hygiene products that rely on nanoscale properties. Nanotechnology has a wide range of applications ranging from its use in achieving pain control to bone regeneration, Major Tooth Repair, Hypersensitivity Cure-, Dental Durability and Cosmetics, Nanorobotic Dentifrice (dentifrobots), Tooth repositioning, Local drug delivery, Nanodiagnostics, Therapeutic aid in oral diseases. Many nanomaterials in dentistry has been developed which includes Nanocomposites, Nano Light-Curing Glass Ionomer Restorativ, Nano Impression Materials, Nano-Composite Denture Teeth, Nanosolutions, Nanoencapsulation , Plasma Laser application, Prosthetic Implants, Nanoneedles, Bone replacement materials. Nanoscaled drug delivery systems , liposomes and drug-conjugated nanoparticles are being used in clinical trials for the treatment of cancer.

APPROACHES IN NANOTECHNOLOGY

There are many different approaches followed for creation of nanoproducts; the most common approaches are bottom up, top down, and functional.

Bottom up

These seek to arrange smaller components into more complex assembly. This begins by designing and synthesizing custom made molecules that have the ability to self-assemble or self-organize into higher order mesoscale or macroscale structures. Modern synthetic chemistry has reached the point where it is possible to prepare small molecules to almost any structure. These methods are used today to manufacture a wide variety of useful chemicals such as pharmaceuticals or commercial polymers. Such bottom-up approaches are much cheaper than top-down methods, but could potentially be overwhelmed as the size and complexity of the desired assembly increases. [15,16]. Methods used for producing nanoscale structure, through this method nanoparticles are produced directly.[17] Various nanoparticles produced through bottom up method and used in dentistry are nanopores, nanotubes, quantum dots, nanoshells, dendrimers liposomes, nanorods, fullerenes, nanospheres, nanowires, nanobelts, nanorings, nanocapsules.[18] Applications in dentistry includes Local anaesthesia, hypersensitivity cure, tooth regeneration, orthodontics treatment nanorobotics, nanodiagnosis, oral tissue biomimetic, endodontic reggenaration,impression materials. [19]

Top down

These seek to create smaller devices by using larger ones to direct their assembly. Here, small features are made by starting with larger materials patterning and carving down to make nanoscale structures in precise patterns. Complex structures containing hundreds of millions of precisely positioned nanostructures can be fabricated. Materials reduced to the nanoscale can suddenly show very different properties, enabling unique applications. As the size of system decreases there is increase in ratio of surface area to volume and number of physical phenomena becomes noticeably pronounced which include statistical as well as quantum mechanical effects. [15,16]. Top down is used to manufacture nanoscale structures. Mostly extension of method already employed in small scale (at micron size), this is further miniaturization.[18] Applications in dentistry includes Nanocomposites and nanocluster, nano liht curable glass ionomer cements,nano impression materials, nanoparticles coating in dental implants, nano based bone replacement cements, nanoencapsulations, nano needles. [19]

Functional approach

In this approach, components of a desired functionality are developed without regard to how they might be assembled.[18]

Applications of nanotechnology in dentistry

Dental diagnostics

In an attempt to improve upon medical diagnostics, the concept of nano-biosensing was introduced. A biosensor is "an analytical device which incorporates a biologically active element with an appropriate physical transducer to generate a measurable signal proportional to the concentration of chemical species in any type of sample" . Biosensors were introduced in 1962 by Clark and Lyons, followed by an ongoing extensive research and development of this promising technology by utilising various detection principles, leading to potential applications in public health, environmental monitoring, and food safety . In an effort to improve the biorecognition process and overall bioreceptor performance, nanobioreceptors were introduced, incorporating nanotubes, nanowires, and nano-dots in the sensing assembly [20].

The Oral Fluid Nano Sensor Test (OFNASET, The Wong Lab, University of California, Los Angeles) is a highly sensitive, specific, portable, and automated nanoelectromechanical system, which enables point-of-care detection of salivary proteomic biomarkers and nucleic acids specific for oral cancer, including 4 mRNA biomarkers (SAT, ODZ, IL-8, and IL-1β) and 2 proteomic biomarkers (thioredoxin and IL-8).[21]

Nanoparticles help in increasing the concentration, amplification and protection of a biomarker from degradation. For example, streptavidin-coated fluorescent polystyrene nanospheres fluospheres (green fluorescence) and transfluospheres (red fluorescence)are applied in single color flow cytometry to detect the epidermal growth factor receptor (EGFR) on A431 cells (human epidermoid carcinoma cells). The results have shown that the sensitivity of fluorescent nanospheres is 25 times more than that of the conjugate streptavidin-fluorescein. [18]

Diagnosis and treatment of oral cancer

Imaging

Current imaging techniques for the diagnosis and staging of cancer have their limitations. Fluorescent semiconductor nanocrystals (QD) have narrow and size-tuneable emission spectra that span from ultraviolet to near-infrared. This, together with their prolonged photostability, good photoluminescence, and high signal:noise ratio, make QD particularly suitable for non-invasive imaging, and they can be used for identification and long-term in vivo monitoring of disease in vivo.[22]

Nano electromechanical system (NEMS) converts biochemical to electrical signal and cantilever array sensor is an ultrasensitive mass detection technology that can be used for the detection of 10–12 bacteria, viruses and DNA. These are extremely useful in the diagnosis of oral cancer and diabetes mellitus and for the detection of bacteria, fungi and viruses. Nanomaterials for brachytherapy like "BrachySilTM" (Sivida, Boston & Perth, Australia) deliver 32P, are in the clinical trial. Drug delivery system that can cross the blood brain barrier is vision of the future with this technology. Parkinson disease, Alzheimer disease, brain tumors will be managed more efficiently. Nanovectors for gene therapy are in a developing stage to correct disease at molecular aspect.[23]

Sentinel node biopsy

Quantam Dots can be used in the biopsy of sentinel lymph nodes. Current methods of detection based on lymphoscintigraphy and vital dyes can be confounded by the autofluorescence of background tissue. QD that emit at the near-infrared region are associated with a reduction in the autofluorescence of tissue and can be used in deep tissue imaging, making localisation accurate and sensitive, and subsequent excision of foci of cancer possible. [22]

Targeted cellular destruction

Quantum dots can be used as photo-sensitizers which can mediate targeted cellular destruction. They can bind to antibody present on surface of target cell and when stimulated by UV light, will release reactive oxygen species and this will be lethal to target cell. This therapy can be used to fight with malignant cells [23]

Preventive dentistry

Researchers developed a nano-toothbrush, by incorporating nanogold or nanosilver colloidal particles between toothbrush bristles (Raval et al., 2016). In addition to its ability to improve upon mechanical plaque removal, researchers reported an antibacterial effect of the added gold or silver which could ultimately lead to a significant reduction in periodontal disease. Oral hygiene products such as toothpastes and mouthwash solutions were also nano-modified according to recent reports. Nano-calcium fluoride, for instance, was added to mouthwash products to reduce caries activity, reduce dentine permeability, and increase labile fluoride concentration in oral fluid (Sun and Chow, 2008). Toothpastes containing calcium carbonate nanoparticles and 3% nanosized sodium trimetaphosphate have been reported to promote remineralisation of early carious lesions in comparison to a conventional toothpaste with no nano-additives (Danelon et al., 2015). According to results from an in vitro study, toothpastes containing nano-hydroxyapatite crystals (nHA) significantly increased microhardness values in human enamel following an erosive challenge, in comparison to the same toothpaste without nHA (Ebadifar et al., 2017). The benefits of a nHA containing toothpaste was first reported in Japan in the 1980s (Kani et al., 1989). In 1983, three primary schools were enrolled in their 3-year clinical study. Schools were provided with toothbrushes and toothpastes. One school was given a 5% nHA based toothpaste, while the other two schools were provided with controls. [20]

Restorative dentistry

The incorporation of nanofiller particles in composite resins has given rise to a new class of materials with improved properties over micro- and macrofilled composites. Nanofillers reduce the polymerization shrinkage and thermal expansion, and enhance the polishing ability, hardness, and wear resistance of composites.The size of these particles range from 0.005-0.01 µm. At this size, the optical properties of the resin and the filler particles become a fraction of the wavelength of light. Consequently, these particles cease to reflect back light, resulting in a more physiologic color expression by the material. The bottoms-up approach is required for the production of nanofiller particles. Two different types of nanofillers, nanomers (5-75 nm) and nanoclusters (2-20 nm) have been synthesized. Their incorporation into an existing resin matrix system has been shown to improve the optical and polishing properties of microfill composites and the strength of hybrid composites.[24] An improvement has also been made to resin-modified glass ionomer cement (RMGIC) with the addition of nanosized fillers. This has been reported to improve the polishability and esthetic properties of the RMGIC.[25] The inclusion of nanofilled resins in posterior restorative GIC selfadhesive coatings has also demonstrated high hydrophilicity and protection against abrasive wear.The low viscosity of the coating provides an optimal seal and glaze to the GIC surface, which gives time for the restoration to mature and increases its esthetic properties.Thus, it could be stated that these improvements in filler technology can be used to develop new resin-based dental restoratives with enhanced mechanical properties.[26][27]

Periodontal diseases

Nanotechnology has been used to prevent bone loss in an experimental periodontal disease model by local application of nanostructured doxycycline gel. Nanorobots (dentifrobots) mouthwash or toothpaste left on the occlusal surfaces of teeth with their continuous and fast movement (1–10 µm/ second) across the supra and subgingival surfaces continuously removes the organic residues and prevents the calculus accumulation. These nanorobots can be safely deactivated when they are swallowed.[28]

Nanocomposites

The particle size of conventional composites are so dissimilar to the structural sizes of the HA crystal, dentinal tubule, and enamel rods that there is a potential for compromise in adhesion between the macroscopic (40 nm–0.7 nm) restorative material and the nanoscopic (1 nm–10 nm in size) tooth structure. Nanocomposite systems have the potential to improve this continuity between the tooth structure and the nanosized filler particle and provide a more stable and natural interface between the mineralized hard tissues of the tooth and these advanced restorative

biomaterials. Nanotechnology or molecular manufacturing may provide composite resin with filler particles that are dramatically smaller, can be dissolved in higher concentrations, and are polymerized into the resin system with molecules designed to be compatible when coupled with a polymer, and provide unique physical, mechanical, and optical characteristics.The mineral component of the composite, which is a filler, is termed "the dispersed phase" and has been noticeably improved with the addition of small particles or fillers.In dental composites, fillers provide strength and reinforcement to the matrix One such nanocomposite system (Premise, Kerr/Sybron, Orange, CA) is composed of three different types of filler components: nonagglomerated "discrete" silica nanoparticles, barium glass, and prepolymerized filler. Nanoproducts Corporation has successfully manufactured nonagglomerated coatings to produce nanocomposites. The nanofiller used includes an aluminosilicate powder with a mean particle size of 80 nm and a 1:4 M ratio of alumina to silica and a refractive index of 1.508.[29]

Advantages include:

• Superior hardness

• Superior flexural strength, modulus of elasticity, and

translucency

• 50% reduction in filling shrinkage

• Excellent handling properties.

Nanoanesthesia

When nanotechnology or nanorobots are used to induce anes- thesia, the gingiva of the patient is instilled with a colloidal sus- pension containing millions of active, analgesic, micron-sized dental robots that respond to input supplied by the dentist. Nanorobots in contact with the surface of the crown or muco- sa can reach the pulp via the gingival sulcus, lamina propria, or dentinal tubules. Once in the pulp, they shut down all sensa- tions by establishing control over nerve-impulse traffic in any tooth that requires treatment. After completion of treatment, they restore this sensation, thereby providing the patient with anxiety-free and needleless comfort. The anesthesia is fast-act- ing and reversible, with no side effects or complications asso- ciated with its use.[10]

Bio-nano surface technology and dental implants

The natural bone surface has a roughness of approximately 100 nm, and such nano details are therefore important on the surfaces of implants. Osteoblast proliferation has been induced through the creation of nano-size particles on the implant surface. Roughing the implant surface at the nanoscale level is important for the cellular response that occurs in the tissue.[30][31]

Titanium implants treated with a nanostructured calcium surface coat were inserted into rabbit tibias, and their effect on osteogenesis was investigated; the nanostructured calcium coat increased the responsiveness of the bone around the implant. Many in-vitro studies have shown that the nanotopography of the implant surface considerably affects osteogenic cells and that the nanoscale surface morphology enhances osteoblast adhesion. Moreover, the nanoscale surface morphology augments the surface area and thus provides an increased implant surface area that can react to the biologic environment.[32]

Nanorobotic dentifrices

Nanorobotic dentifrices, when delivered either by mouthwash or tooth paste, can cover all subgingival surfaces, thereby metabolizing trapped organic matter into harmless and odor- less vapors. Properly configured dentifrobots can identify and destroy pathogenic bacteria that exist in the plaque and elsewhere. These invisibly small dentifrobots are purely mechanical devices that safely deactivate themselves when swallowed.

Root canal disinfection

Several nanoparticles, such as zinc oxide and chitosan alone or in combination, have been incorporated into root canal sealers in an attempt to disinfect root canals. They had no effect on the flow characteristic of the sealers, but they enhanced the antibacterial action, observed by a significant reduction in Enterococcus faecalis adherent to treated dentin.[33] Prior surface treatment of root canal dentin with phosphorylated chitosan was effective in maintaining the inhibitory effect of a chitosan-modified root canal sealer on biofilm formation at the sealer–dentin interface.[34] Metal oxides such as magnesium oxide nanoparticles could be used as a potential root canal irrigant with promising antibacterial activity in both in vitro and ex vivo studies. Compared to the conventional NaOCl solution (5.25%), magnesium oxide nanoparticles (5mg/L) showed statistically significant long-term effect in the elimination of E. faecalis adherent to root canal dentin.[35]

Guided tissue regeneration

The concept of guided tissue regeneration (GTR) is being researched to replace earlier functional graded membranes with novel 3-layered membranes. The former system included bilayered GTR membranes with a porous surface on one side (for cellular ingrowth), and a smooth surface on the opposite side (for cellular occlusion). A novel system has come up with a 3-layered

GTR membrane composed of an innermost layer made of 8% nanocarbonated hydroxyapatite/collagen/polylactic-coglycolic acid (nCHAC/PLGA) porous membrane, a middle layer of 4% nCHAC/ PLGA, and an outer layer of PLGA nonporous membrane. These 3 layers combine to form a highly flexible, biocompatible, osteoconductive, and biodegradable composite membrane. When osteoblastic cells were cultured on this membrane, they showed a more positive response compared to a pure PLGA membrane.[36]

Pulp regeneration

Nanotechnology has potential in the region of dental pulp regeneration. The development of tissues to replace diseased or damaged dental pulp can provide a revolutionary alternative to pulp removal. The α-melanocyte-stimulating hormone (α-MSH) is known to possess anti-inflammatory properties. It has been suggested that nanofilms containing α-MSH could help revitalize damaged teeth. Further research is needed to evaluate these proposed therapeutic and regenerative approaches.[37]

Bone substitute

Biologically inspired rosette nanotubes and nanocrystalline hydroapatite hydrogel nanocomposites can be used as improved bone. HRN–helical rosette nanotubes are formed by chemically immobilizing 2 DNA base pairs, creating a novel type of soft nanomaterial that biomimics natural nanostructural component of bone. They are 3.5nm in diameter and are self assembled. Nanocrystalline hydroxyl apatite of 2 and 10%wt was well dispersed into helical rosette nanotubes. It demonstrated improved mechanical properties, increased osteoblast adhesion up to 236% compared to hydroxyapatite, Stimulated hydroxyapatite showed nucleation and mineralization along their main axis in a way similar to hydroxyapatite/collagen assembly pattern in natural bone.[38]

Hydroxyapatite nanoparticles used to treat bone defects which can be used in maxillofacial injuries requiring bone graft, cleft patient and osseous defect in periodontal surgeries are

- Ostim® (Osartis GmbH& Co. KG, Obernburg-Germany) HA
- VITOSSO (Orthovita, Inc., Great Valley Parkway Malvern, PA 19355 USA) HA + TCP
- NanOSSTM (Angstrom Medica, USA) HA

Orthodontic treatment

Sliding a tooth along an archwire involves a frictional type of force that resists this movement. Use of excessive orthodontic force might cause loss of anchorage and root resorption. In a study published by Katz, a reduction in friction has been reported by coating the orthodontic wire with inorganic fullerene-like tungsten disulfide nanoparticles (IF-WS2), which are known for their excellent dry lubrication properties. In future, orthodontic nanorobots could directly manipulate the periodontal tissues, allowing rapid and painless tooth straightening, rotating and vertical repositioning within minutes to hours.

Adverse effects of nanotechnology - Nanotoxicology

Nanotoxicology is defined as a science that deals with the adverse effects of engineered nanodevices and nanostructures inliving organisms.[40] Techniques promising major breakthroughs in medical and dental sectors might also have a downside, and hence, must undergo stringent testing before human application. Some areas of concern include the unplanned entry of nanoparticles through the skin (via hair follicles), or through the respiratory tract, with the potential to penetrate vital organs. Safety protocols should be formulated and practiced during the early innovative stages of engineered nanomaterials to proactively curtail the development of counterproductive devices. Before commencing large-scale production of nanodevices, potential environmental hazards created due to waste generation should be considered. Further research is required to determine the mobility, reactivity, ecotoxicity, and persistence of nanoparticles in the environment.[41]

CONCLUSION

Nanotechnology is a relatively novel field, which involves manipulation of matter at the molecular level, including individual molecules and the interactions among them. Nanodentistry still faces many significant challenges in realizing its full potential. There are larger social issues of public acceptance,ethics,regulations and human safety that must be addressed before molecular nanotechnology can enter the modern medical armamentarium.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Verma SK, Prabhat KC, Goyal L, Rani M, Jain A. A Critical Review Of The Implication Of Nanotechnoloy In Modern Dental Practice. Natl J Maxillofac Surg 2010;1:41-4

2. Mnyusiwalla, A.; Daar, A.S.; Singer, P.A. "Mind the gap": Science and ethics in nanotechnology. Nanotechnology 2003, 14, R9–R13.

3. Roco, M.C. Nanotechnology: Convergence with modern biology and medicine. Curr. Opin. Biotechnol. 2003, 14, 337–346.

4. Yao C, Storey D, Webster TJ. Nanostructured metal coatings on polymer increase osteoblast attachment. Int J Nanomedicine 2007;2:487-92.

5. Feynman R. "Six Easy Pieces'. Mento Park, CA: Addison Wesley Pub. Co; 1963. p. 11

6. Aston D. Nanotechnology: The stuff of science fiction on science fact? School Sci Rev 2011;92:71-75.

7. Fruites RA Jr. Nanomedicine, Basic Capabilitise, Gergetown,TX;Londes Bioscience, 1999;1:345-354.

8. Drexler KE. Nanosystems: Molecular Machinery Manufacturing and Computation. New York: John Wiley and Sons; 2006.

9. Drexler KE, Peterson C. Unbounding the Future: The Nanotechnology Revolution. New York: William Morrow/Onill Books; 1991.

10. Freitas JR RA. Nanodentistry. J Am Dent Assoc 2000;131:1559-1565.

11. Freitas JR RA. Nanomedicine: Basic Capabilities. Volume 1. Landes Biosciences. Retrieved online January 3, 2008 from: www.nanomedicine.com

12. Freitas JR RA. What is nanomedicine? Nanomedicine 2005;1:2-9.

13. Freitas JR RA. Nanotechnology, nanomedicine and nanosurgery. Int J Surg 2005;3:243-246.

14. Caruthers SD, Wickline SA, Lanza GM. Nanotechnological applications in medicine. Current Opin Biotechnol 2007;18:26-30.

15. Bhardwaj A et al ; Nanotechnology in Dentistry Journal of International Oral Health 2014; 6(1):121-126

16. Lakshmi sree,Balasubramanian, Deepa; Nanotechnology in Dentistry – A Review; International Journal of Dental Science and Research, 2013, Vol. 1, No. 2, 40-44

17. Rybachunk AV, Chelkman IS. Nanotechnology and nanoparticles in dentistry. Pharmacol Pharm 2009;1:18-21.

18. T. S. V. Satyanarayana, Rathika Rai ; Nanotechnology: The future Journal of Interdisciplinary Dentistry / Jul-Dec 2011 / Vol-1 / Issue-2

19. Zohaib Khurshid , Muhammad Zafar , Saad Qasim , Sana Shahab , Mustafa Naseem , Ammar Abu Reqaiba ; Advances in Nanotechnology for Restorative Dentistry ; Materials 2015, 8, 717-731

20. Rawan N. AlKahtani ;The implications and applications of nanotechnology in dentistry: A review ;Saudi Dental Journal (2018) 30, 107–116

21. Gau V, Wong D. Oral fluid nanosensor test (OFNASET) with advanced electrochemical based molecular analysis platform. Ann N Y Acad Sci. 2007;1098:401-410.

22. K. Shakib et al. / British Journal of Oral and Maxillofacial Surgery 52 (2014) 884–893

23. Sanjeev Kumar Verma, Prabhat K. C., Lata Goyal1, Manita Rani, Amit Jain;A critical review of the implication of nanotechnology in modern dental practice; Natl J Maxillofac Surg;Vol 1;Issue 1; Jan-Jun 2010

24. Mitra SB, Wu D, Holmes BN. An application of nanotechnology in advanced dental materials. J Am Dent Assoc. 2003;134(10):1382-1390.

25. Vaikuntam J. Resin-modified glass ionomer cements implications for use in pediatric dentistry. J Dent Child. 1997;64(2):131-134.

26. Furmann BR, Nicolella D, Wellinghof ST, et al. A radiopaque zirconia microfiller for translucent composite restoratives. J Dent Res. 2000;79:246.

27. Youngblood TA, Nicolella DP, Lankford J, et al. Wear and select mechanical properties of a zirconia nanofilled resin composite. J Dent Res. 2000;79:365.

28. Botelho MA, Martins JG, Ruela RS, Queiroz DB, Ruela WS. Nanotechnology in ligature-induced periodontitis: protective effect of a doxycycline gel with nanoparticules. J Appl Oral Sci. 2010;18(4):335–342.

29. Rosaiah Kanaparthy, Aruna Kanaparthy;The changing face of dentistry; International Journal of Nanomedicine 2011:6

30. Braceras I, De Maeztu MA, Alava JI, Gay-Escoda C. In vivo low-density bone apposition on different implant surface materials. Int J Oral Maxillofac Surg 2009;38:274-278

31. Ellingsen JE, Thomsen P, Lyngstadaas P. Advances in dental implant materials and tissue regeneration. Periodontol 2000 2006;41:136-156.

32. Suh JY, Jeung OC, Choi BJ, Park JW Effects of a novel calcium titanate coating on the osseointegration of blasted endosseous implants in rabbit tibiae. Clin Oral Impl Res 2007;18:362-369.

33. Kishen A, Shi Z, Shrestha A, Neoh KG. An investigation on the antibacterial and antibiofilm efficacy of cationic nanoparticulates for root canal disinfection. *J Endod*. 2008;34(12):1515–1520.

34. 188. Monzavi A, Eshraghi S, Hashemian R, Momen-Heravi F. In vitro and ex vivo antimicrobial efficacy of nano-MgO in the elimination of endodontic pathogens. Clin Oral Investig. 2015;19(2):349–356.

35. Lu Z, Rong K, Li J, Yang H, Chen R. Size-dependent antibacterial activities of silver nanoparticles against oral anaerobic pathogenic bacteria. *J Mater Sci Mater Med*. 2013;24(6):1465–1471.

36. Liao S, Wang W, Uo M, Ohkawa S, Akasaka T, Tamura K, Cui F, Watari F. A three-layered nano-carbonated hydroxyapatite/collagen/PLGA composite membrane for guided tissue regeneration. Biomaterials. 2007;26(36):7564-7571.

37. Fioretti F, Palomares CM, Helms M, et al. Nanostructured assemblies for dental application. ACS Nano. 2010;4(6):3277-3287.

38. Zhang L, Ramsaywack S, Fenniri H, Webster TJ. Enhanced osteoblast adhesion on self-assembled nanostructured hydrogel scaffolds.Tissue Eng Part A 2008;14:1353-64.

39. Katzs A, Redlich M, Rapoport, Wagner, Tenne R. A novel friction reduced orthodontic archwire coated with fulleren-like nanoparticles. Hebrew University, Dental School of Medicine, Jerusalem, Israel.

40. Oberdorster G, Oberdorster E, Oberdorster J Nanotoxicology:an emerging discipline evolving from studies of ultrafine particles. Env Health Perspect. 2005;113(7):823-839.

41. Som C, Nowack B, Krug HF, Wick P. Toward the development of decision supporting tools that can be used for safe production and use of nanomaterials. Acc Chem Res. 2013;46(3):863-872.