**Title: Scope and Future of Nanotechnology in Dentistry.**

**Running Title: Nanotechnology in Dentistry.**

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INTRODUCTION

Science is currently going through a major development that will usher mankind into a new age known as the era of nanotechnology. (1) The term "Nano" is derived from Greek, meaning "dwarf." Nanotechnology is the study of manipulating matter that is smaller than a nanometer, or billionth of a meter, or about the size of two or three atoms. (2) Its application in oral health looks promising, based on evaluation of its advantages and efficacy in the field of dentistry. (3,4,5) This is mainly because of the inherent characteristics of nanomaterials that makes it similar to the nanostructure of the components of the tooth and the biological components in the oral cavity that are nanoscale in size, as well as. (6) The procedures of conventional dental technology have been improved by the revolutionary concepts of nanotechnology, which has provided a fresh viewpoint on conventional materials and methods. (7) With the help of nanomaterials, bioengineering and nanorobotics, the goal is to achieve optimal oral health by regenerating dental tissues. (8,9) However, the development of these biocompatible nanoproducts necessitates a keen understanding of the anatomy and physiology of the target site with which it comes in close contact, hence determining the fate of the nanomaterial inside the body. (10) An updated list of new nanomaterials for dental treatments across several fields is included in this review. A future outlook on nanodentistry is also presented, along with the difficulties of using nanoparticles in dental therapies.

NANOTECHNOLOGY

Nanotechnology, which is also known as nanoscience or molecular engineering, is that branch of technology which functions in the dimension of < 100 nano-meters or the study of components at the levels molecules and atoms. (11,12) Examples of which include objects such as glucose molecules which measure 1 nm in size up to viruses of 100 nm. (13) The direct manipulation of materials directly at the nanoscale which confers overall control over the structure of matter at nanoscale dimensions is considered nanotechnology according to National Nanotechnology Initiative. This will give the ability to arrange atoms as desired and subsequently to achieve effective, complete control of the structure of matter. (14) The materials which are used are measured on the nanometre scale and are called as nanomaterials. (15) It is used commercially most commonly in cosmetics and food packaging and recently in the field of medicine it has been used for prevention, diagnosis and treatment. (16) It often requires a multidisciplinary collaboration and has grown rapidly in almost all fields of science and is posed majorly to change and innovate dentistry. (17)

NANODENTISTRY

It is the science and technology of maintaining near-perfect oral health through the use of nanomaterials such as tissue engineering and nanorobotics. This technology has aided drastically the advances made in the field of biomaterials and has broadened its holistic usage in dentistry. It has numerous applications in dentistry and has evolved as a new science for improving dental health, by its use in local anaesthesia, field of periodontology, movement of teeth orthodontically and even diagnosis of oral conditions. (15) Nanotechnology has been used in dentistry extensively from its incorporation in ceramics to composites. It’s use in dentistry has been credited with increase in aesthetics and efficiency thereby enhancing patient satisfaction (18)

HISTORY

This dimension of discovery was made in 1959 by Nobel Prize–winning physicist Richard P. Feynman in his *Plenty of Room at the Bottom* lecture to the American Physical Society. In 1974, Norio Taniguchi gave the phrase "nanotechnology" to explain a "production technique to get extra high accuracy and ultra-fine dimensions." K. Eric Drexler introduced the idea of molecular nanotechnology later in 1986 in his book *Engines Of Creation: The Future Era of Nanotechnology*, which helped to advance the field. (17)

APPROACHES IN NANOTECHNOLOGY

Referred to as nanomaterials or nanosized materials, atomic clusters, grains, fibres, films, nanoholes and composites made of these components are a few examples. When present in one dimension, nanomaterials are referred to as sheets, while when it is present in two dimensions as nanowires and nanotubes, and those in three dimensions as quantum dots. (19) They can be produced using two distinct methods.

1) Top-down/Mechanical-Physical production processes: This method uses external mechanical forces to break down the substance into nanoparticles while producing nano-things from larger entities without molecular level control. (20)

2) The bottom-up/ Chemo-physical production processes: This method employs materials and devices made up of atomic and molecular fillers that creates more specific and complex structures by regulating the molecular forms, sizes and ranges. It consists of sol gel processes, aerosol processes, and precipitation reactions. (20)

Figure 1: Two strategies used in nanodentistry (20)

**CLASSFICATION OF NANO MATERIALS USED IN DENTISTRY**

Figure 2: Classification of dental nanomaterials on the based-on composition and shape

These nanomaterials based on their shape and composition are grouped as Nanoparticles, Nanotubes and Nanoplatelets into three categories (21)

**1) Nanoparticles (NP):**

Conventional nanoparticles are usually made of metals and metal oxides. Their utilisation has been the focus of research for many years. The newest fillers for cutting-edge biomaterials used in dentistry include unconventional nanoparticles (nanoshells, nanodiamonds and quantum dots), which can be manipulated easily for the application. (21) The commonly used NPs in dentistry are; (figure 2)

* Silver nanoparticles (AgNPs)- Silver has long been known to have antibacterial characteristics, and it can also be employed in dental products. It also demonstrates to have antifungal and antiviral effects. The silver ions act by inactivating enzymes, which prevents replication of DNA that eventually results in death of the microbial cell. (22,23)
* Gold nanoparticles (AuNPs)- Gold has been utilised extensively in dentistry for the treatment and diagnosis of cancer, because of its inert, biocompatible behaviour and antibacterial qualities. Initially AuNPs have been used for nano drug delivery. Compared to other metal nanoparticles, AuNPs are less hazardous and can be synthesised by a variety of methods, including chemical functionalization. (24)
* Copper nanoparticles (CuNPs)- Microorganism's cell membranes become unbalanced as a result of copper, which results in leakage and cell death. Without affecting the formulation's mechanical qualities, the addition of CuNPs to dental adhesives gives them adequate antibacterial activity against S. mutans and avoids the deterioration of the adhesive interface. (25)
* Zinc oxide nanoparticles (ZnO NPs)- Zinc at nanoscale, is antibacterial. Composite resins used in dentistry with ZnO NPs along with AgNPs have demonstrated notable antimicrobial effect against Lactobacillus and S. mutans. (26)
* Titanium dioxide-based nanoparticles (TiO2 NPs)- Human gingival fibroblasts exhibit inflammatory behaviour at higher concentrations of TiO2 nanoparticles. The colony counts of S. sanguinis and S. mutans have decreased as a result of the incorporation of TiO2 nanoparticles into composite resins, which has demonstrated strong antibacterial action. (27,28)
* Zirconium dioxide nanoparticles (ZrO2 NPs)- It is the perfect choice for the production of dental implants and used to coat dental prosthetics due to its biocompatibility, osseo-conductivity and propensity to decrease plaque collection. To enhance the mechanical properties of the PolyMethyl MethaAcrylate PMMA matrix, ZrO2NP can be utilised as a filler. (29) When used with ceramics it performed better than alumina-based ceramics with respect to resistance to bending and strength. (30)
* Aluminium oxide nanoparticles (Al2O3 NPs)- Alumina when used in ceramics, has exhibited better aesthetics, wear resistance, hardness, and good biocompatibility to oral tissues as it presents a polished surface. The orthodontic brackets are usually made of polysulfone and alumina nanoparticles. (31)
* Silicon dioxide nano particles (SiO2 NPs)- It is incorporated as a filler to enhance the mechanical qualities of restorative materials in dentistry. In order to polish the rough surface of the tooth and avoid food buildup or plaque formation, fine powdered silica is used in general dentistry. Because of its size, biocompatibility, and surface area, SiO2 NPs play a vital role in dentistry. (32)
* Nano diamonds- They are extremely small diamonds measuring less than 100 nanometers it serves as a filler in the creation of dental nanocomposite materials. (33) Amoxicillin-loaded nano diamond Guttapercha composite (NDGP-AMC) has been manufactured recently and evaluated for its use in root canal procedures, and the results are found to be encouraging. (34)
* Quantum dots- Depending on the quantity and wavelength of the irridiation, quantum dots, which are semi-conductive nanoparticles made of lead sulphide, zinc sulphide and indium sulphide, can emit light. They are mainly used in treatment of cancer of head and neck or oral cancer. (35)
* NanoShells- They have a variety of therapeutic uses in dentistry. By activating the metal covering of NanoShells under infrared light, can cause cell death, hence oral cancer causing cells can also be destroyed. This approach can be employed for vascular ligation to enhance wound healing, limit internal bleeding and reduce angiogenesis. (36)

**2) Nanotube based nanomaterials**

* Carbon nano tube (CNT)- They have commendable electronic and mechanical properties. They are commonly used to reinforce the strength of dental composites when incorporated as fillers. (37) CNT are also used for the delivery of anti-cancer drugs. (38)
* Halloysite nano tube (HNT)- These are clay based nano materials that serve as an effective substitute for dental fillings and nanodrug delivery systems. They are one of the best fillers for creating dental composites because they appear natural milky white and have excellent strength. HNTs can also be loaded with antibiotics. (39)

3) Nanoplatelets based nano materials: They are usually used as nanosheets or flakes. Graphene is a primarily used because of its physical properties and graphene oxide are used in dentistry for their unique properties. (21)

* Graphene oxide- It is a material exhibiting unique characteristics that is present as a hexagonal honeycomb lattice arranged as a single layer of carbon atoms. Graphene has created the new opportunity for the manufacturing of dental Nano-materials being incorporated in the form of nano-powder. (40,41) It’s an important anti-microbial agent in dental materials that has shown strong antibacterial activity against S. mutans. (42)

CLINICAL APPROACHES OF NANOTECHNOLOGY IN DENTISTRY

As a novel idea for the production of materials with improved characteristics and antimicrobial potential, nanotechnology has been used with dental materials. Nanomaterials hold considerable promise for reducing biofilm buildup, obstructing the demineralization process, remineralizing tooth structure and battling germs linked to caries. (4) Nanomaterials provide better bioavailability and efficacy and hence have the potential to provide better control over managing oral diseases. (21) The use of nanoparticles in dentistry has had a significant influence and has offered new opportunities with the development of novel procedures, making it feasible the to maintain comprehensive dental health through the use of nanomaterials, biotechnology, along with tissue engineering and ultimately, dental nanorobotics. (43)

1. NANOROBOTICS: Nanorobots have a diameter of 0.5–3 microns and size of 1–10 nanometers. Since they are so small, dentists can use electromagnetic and acoustic waves to guide them into body canals or into blood vessels. (44) The applications of nanorobotic in dentistry are many, few of them are listed below.
* Local anaesthesia: Anaesthetic dental robots are suspended in a colloidal solution. These when inserted beneath the gingival tissue, move through the dentin to the pulp and then eliminate all tooth sensation by migrating through the dentinal tubules. (43)
* Treatment for hypersensitivity: Hydrodynamic pressure changes that are communicated to the pulp may be the source of dentin hypersensitivity. Dental nanorobots use biological materials to precisely and quickly occlude the tubules, providing a rapid and long-lasting treatment for dentin hypersensitivity. (43)
* Dental biomimetics: The most fascinating area for debate on nano repair of tooth structures is where nanotechnology mimics natural processes, including the synthesis of dental enamel. (45)
* Dentifrobots: When used atleast once every day, dentifrobot-infused toothpastes or mouthwashes scan the entire gingival surface, metabolising trapped organic debris into flavourless, odourless vapours. It is used as a mouthwash and is packed with artificial nanomachines that can recognise and eliminate harmful bacteria, allowing the mouth's beneficial flora to flourish in a healthy ecosystem. (43)
* In orthodontics: Because robotic brackets are time and self-efficient, the positioning of bracket placement is significantly easier thereby increasing efficiency of orthodontic tooth movement. (18)
1. PREVENTIVE NANO DENTISTRY
	* Dental caries: Early enamel lesions could be remineralized with the help of toothpaste containing calcium carbonate in nanoscale form. A study that looked at how Streptococcus mutans, causing dental caries, was affected by the bacteriostatic effects of zinc oxide, gold and silver nanoparticles found that, in comparison, silver nanoparticles had lower toxicity accompanied by antimicrobial effect even at lower concentrations. (19)
	* Caries vaccine: It prevents bacterial accumulation by either blocking the surface protein antigen Pac or inhibiting the glucosyltransferase enzyme. Numerous trials are currently being undertaken to create a successful anti-caries vaccine. It was discovered that an efficient, secure, stable and affordable immunogenic method could be by use of DNA vaccine to induce an effective cellular and humoral immune response. Many animal or human trials are underway to identify potential DNA vaccines. These vaccines include the pcDNA3-Pac, pCIA-P, pGJGLU/VAX, and pGLUA-P, for instance. (19)
	* Varnish: Varnish is a combination of natural ingredients with clinically effective levels of ion release, re-mineralization potential, and fluoride in chitosan nanoparticles (CS-NPs) at optimal concentrations. The anti-bacterial properties of dental varnishes with miswak, CS-NPs and propolis with or without addition of sodium fluoride (NaF) have been assessed against S. mutans. The use of natural items containing fluoride in dental varnish is one of the most efficient ways to halt caries, especially with propolis and miswak in areas with limited economic resources. (46)
2. ENDODONTIC DENTISTRY
* Endodontic sealers: EndoSequence BC is a bio-ceramic sealant containing calcium silicate, hydroxide, phosphate, with zirconia, and a thickening agent. The use of nanoparticles increased its physical qualities and handling, as well as its adaptability to uneven dentin surfaces. A sealer containing silicon along with silver nanoparticles < 30 nm in size and gutta-percha powder has also been introduced. (47)
* Disinfectants: Endodontics has adopted disinfection using with chitosan, zinc oxide, and silver nanoparticles to give more effective microbial elimination. Chitosan because of the presence of amino groups, carboxyl and phosphate, alters membrane permeability by binding to negatively charged bacterial cell walls and limits replication by binding to bacterial DNA. (48)
1. RESTORATIVE DENTISTRY
* Nanocomposite: Recently composite resins with nano-particles as fillers added either as clusters or single particles have been introduced. As the size of the fillers used in these composites are smaller than the wavelength of light, it has higher translucency, leading to enhanced aesthetic of restorations that allows a wide range of colour possibilities. They also have good surface quality and contouring and therefore can repair or replace decayed/broken or missing tooth effectively. (19)
* Nanosolution (Nanoadhesives): They constitute nanoparticles which are dispersible and can be used as components in bonding agents. Nanoadhesives consistently provide a homogeneous and seamlessly blended adhesive. The benefits of nanosolution include: increased enamel and dentine bond strength, fluoride release, increased absorption of stress, prolonged storage, good and long-lasting seal at the margins of the restoration with no additional etching required. (19)
* Nano-glass ionomers: Nano ionomers are glass ionomers with nanoparticles. The use of nanoparticles increased the aesthetics, polish ability, and while effectively lowering setting time while stabilizing the glass ionomer cement. (19)
1. PROSTHODONTIC DENTISTRY
* Impression material: Nano fillers are incorporated into vinylpolysiloxanes to deliver a completely distinct substitute for siloxane based impression materials. This material ensures improved flow, precision in details and has hydrophilic characteristics. (19)
* Prosthetic implants: Surfaces with predefined topography and chemical composition can be created using nanotechnology that ensures better tissue-integration. Nanoparticles of TiO2, ZrO2 and silver are combined with PMMA to form a cover on the occlusal surface of implant. This would help to improve physical and antibacterial characteristics. (18)
1. PERIODONTICS DENTISTRY
* Dentifrices: Dentifrices can be formulated with specific compounds that aid in the prevention of dental caries, remineralization of early carious lesions and desensitisation of abraded teeth. They are composed of nanoscale hydroxyapatite molecules. They will form a protective shell on the tooth surface and cure any damage. (15)
* Nanoneedles: Stainless steel crystals are intended for the production of nanosized suture needles used in surgical interventions in periodontology. With technological innovation, it is now possible to create nano-pliers and conduct surgeries at cellular level in the oral cavity with the assistance of these nano-needles and nano-forceps. (15)
* Bone replacement materials: Bone is a natural nanocomposite made-up of organic materials that have been strengthened with inorganic compounds such as hydroxyapatite and can thus be used in dentistry. Furthermore, as particle size decreases, surface area increases drastically.

The following are the characteristics of bone transplant materials:

• It is osteoinductive.

• Completely artificial

• It should be unsintered

• Highly porous

• It is nanostructured.

• Osteoclast degeneration

• High processability (15)

* Periodontal drug delivery: Periodontal drug delivery can be accomplished by utilising triclosan-impregnated nanoparticles. Reduction of inflammation was observed at the site of injection of triclosan particles, which implies other treatments could also use targeted drug delivery using nanoparticles. This could be used in the future for surgeries with Arestin, in which tetracycline containing microspheres can be used in periodontal pockets that ensures delivery of tetracycline locally. (49)
* Guided Tissue Regeneration: Previously, bilayered guided tissue regeneration (GTR) membranes with smooth surface on one side that encourages cellular occlusion and the opposing side with a porous surface that supports cellular ingrowth were used. GTR is being replaced by novel 3-layered membranes composed of 8% nanocarbonated hydroxyapatite/collagen/polylactic-coglycolic acid (nCHAC/PLGA) porous membrane, 4% nCHAC/PLGA, and PLGA nonporous membrane. This being a highly flexible, biocompatible, osteoconductive and biodegradable composite membrane enhances adhesion. (50)
1. ORTHODONTICS
* Orthodontic wires: Sandirk Nanoflex, is a unique stainless steel material, that is used to create wires. This has the benefit of having a very high strength as well as great deformability, corrosion resistance, and a nice surface polish. (19)
* Orthodontic devices: Orthodontic brackets pose as plaque retainers and in the most complex orthodontic treatments, cause in formation of biofilm, encourage colonization of bacteria, fall in pH, and the demineralization of tooth surface. Copper and zinc nanoparticles present in orthodontic brackets prevent biofilm formation and can prevent dental caries. (18)
1. ORAL MEDICINE AND DIAGNOSIS
* Diagnosis and treatment of cancer: Nanotechnology is helpful in terms of providing devices that are precise and sensitive, such as biologic, molecular and anatomic imaging; tumour selective therapy that is low on toxicity, that is superior to available standard care. (19) Liposomes, polymeric Nanoparticles and inorganic Nanoparticles are chosen for gene probing of DNA and drug delivery. Dendritic polymeric nanodevices can detect cancer cells and deliver anti-cancer therapies in a targeted manner. Carbon nanotubes search for single nucleotide polymorphism in DNA. Nanowires are selective and specific that makes them unique and can be used to detect markers at molecular level of cancerous cells. Contrasting agents with nanoparticles are in the process of innovation to aid in tumour detection. (19)
* Digital dental imaging: Recent advances in this field related to nanotechnology have resulted in major innovations in MRI and CT imaging. Eg, nanoparticles are used to improve spatial, resolution, soft tissue contrast, and differential and advanced metabolic structure options in MRI. When contrast chemicals are included, nanoparticles employed in CT can improve resolution, improve depth of penetration, and contrast of soft tissues. Use of nanophosphor scintillators in digital radiographies aids in reduction of radiation dose and images that are acquired are of high-quality. (19)
* Oral fluid nanosensor test (OFNASET): This method aids in the detection of salivary biomarkers for oral malignancies. Detection of salivary biomarkers can be done with the aid of microfluidics, Cyclic enzymatic amplification, bio-nano-technology and self-assembled monolayers (SAM). A combination of four salivary mRNA biomarkers (SAT, ODZ, IL-8, and IL-1b) with two salivary proteomic biomarkers (thioredoxin and IL-8) has shown to have increase specificity and sensitivity in detection of oral cancer. (19)
* Optical Nano-biosensor- Cytochrome C, a critical protein that plays a significant role in programmed cell death or apoptosis can be detected with minimal invasion using fiber optics based device. (17)
1. TISSUE ENGINERRING (TE) AND DENTISTRY: Tissue engineering and stem cell research in dentistry could be used for augmentation of facial bones, regeneration of temporomandibular joint cartilage and periodontal ligament, repair of pulp tissues, treatment of orofacial fractures and implant osseointegration. TE allows enhancement of implantation that shortens recovery period, ensure biologic and physiologic stability that supports early load bearing. The nanoscale fibres are arranged similar to arrangement of hydroxyapatite crystals and collagen fibrils in bone. However, despite their osteoconductive and biocompatible qualities, biodegradable polymers or ceramic materials have been found to have reduced mechanical durability that needs to be improved in further endeavours. (19)

CHALLENGES FACED BY NANOTECHNOLOGY

The field of nanotechnology has made significant advancements in the recent times but is still undermined by certain challenges that prevents it from attaining its full potential. Following areas require consideration before it replaces current practices;

* Concern regarding biocompatibility
* Manufacture and precise positioning of nanoscale parts
* Mass manufacturing methods of nanorobots that are cost-effective
* Synchronized functioning of numerous independent nanorobots
* Tactical and financial concerns
* Ethical issues regarding public acceptance,
* Human safety and its regulation
* Proper and efficient assimilation of all clinical research conducted (51)

FUTURE PROSPECTS:

Nanotechnology may be considered a boon to change healthcare in a fundamental way, while it is a challenge with regard to its applicability in clinical practice especially with reference to replacing time tested older technologies such as dental composites or antimicrobial materials. Also minimizing the harm to the environment that is done during the synthesis nanomaterials raises a concern. Secondly, newly developed nanomaterials need to be tested in real clinical situations to prove their applicability. (52) Tooth-colored aesthetic shape-memory polymers that move teeth efficiently would be a game changer in the field of orthodontics, whereas in cosmetic dentistry, nanoscale diamond and sapphires used to replace enamel would be more durable and fracture resistant. But perphaps the most promising application of nanotechnology in dentistry would be its use in drug delivery systems in treatment of oral cancer. (53)

CONCLUSION:

Although the availability materials limit the applicability of nanotechnology in dentistry, rapid advances are paving the future of healthcare management. Nano dentistry focuses on primarily on preventing oral diseases and aims to ensure availability of comprehensive oral healthcare. With the availability of advanced and accurate diagnostic methods, a number of oral diseases can be prevented or treated at early stages when accurate and advanced methods of diagnosis are available. The future holds a strong promise of benefit of mankind by utilizing and maximizing the use of nanotechnology though it may appear largely theoretical at present. (19) Nanotechnology holds the ability to change healthcare and dentistry, becoming the core of dental and medical science and impacting human life profoundly. Only concerns preventing nanotechnology from becoming main stream medicine are questions regarding of public safety, acceptance and ethics, overcoming which it holds the golden key to unlocking a promising innovation. (53)

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