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Nanotechnology in dentistry- A comprehensive review

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Abstract

Nanotechnology refers to research and development of materials and techniques at a nanoscale i.e, $1x10^{-9}$m. The applications of nanotechnology were primarily in the medical sciences, however over the last decade or so, there have been many advancements in the applications of nanotechnology in dental sciences. Commonly referred to as Nanodentistry, the applications in this field aim to provide alternative approaches to diagnosing and treating various oral ailments with a higher degree of accuracy and specificity. Achieving maximum therapeutic efficacy with minimal side effects is the goal of developing techniques and materials using nanotechnology. Various applications of nanotechnology could be the use of nanocomposites,use of dentifrobots, use of nanoparticles for targeted drug delivery,etc. Electronic databases like GoogleScholar, PubMed, and ScienceDirect were used to search articles that aimed at studying the scope of nanotechnology in dentistry. This article aims to provide a comprehensive review of the literature pertaining to various applications of nanotechnology in various fields of dentistry.

Keywords: Nanotechnology in dentistry, Nanodentistry, Nanomaterials, Nanoparticles.

Introduction

National Nanotechnology Initiative defines "Nanotechnology as the research and technology development at the atomic, molecular, or macromolecular scale, leading to controlled creation and use of structures, devices, systems with a length scale of 1-100 nanometers"[1] The idea of the concept of Nanotechnology was given by Nobel winning physicist Dr Richard Feynman in the year 1959. Almost fifteen years later, Norio Taniguchi used nanotechnology to describe semiconductor processes that occurred on the scales of a nanometer(10^{-9}) [2]. Nanotechnology is also defined as "the art of manipulating materials on an atomic or molecular scale especially to build microscopic devices."[3] The US government defines it as "Nanotechnology is research and technology development at the atomic, molecular, or mac-romolecular level in the length scale of approximately 1–100 nm range, to provide a fundamental understanding of phenomena and materials at the nanoscale and to create and use structures, devices, and systems that have novel properties and functions because of their small and/or intermediate size.”[3]

Regardless of what definition one chooses, the essence of Nanotechnology is developing the ability to control material properties by assembling such materials at the nanoscale.[4]The work in nanotechnology is on the verge of creating extraordinary advances in every field including the medical and dental sciences. This work would be both associated with providing an improved understanding of the structures/systems at the nanoscale and coming up with technologies to analyse and replicate those systems.[4]

The ongoing research in the domain of nanotechnology is due to the unique properties of nanoparticles. Biomolecules interact more efficiently with nanoparticles than with macro or microparticles. This is due to the high surface-to-core ratio of nanoparticles, a unique property of nanoparticles, which means that there are more atoms at the surface of a nanoparticle than within its core. This is particularly useful since surface atoms have unbound surfaces in comparison to the core atom, with the potential of creating new and strong bonds, thus rendering nanoparticles more reactive than micro and macroparticles.[5]

Approaches to Nanotechnology-

To go about the synthesis of nano-engineered materials two approaches have been postulated, namely:

- The Top-down technique- Top down technique involves the breakdown of bulk material into nanosized structures. Here small/nano features are created by starting with larger-sized materials and patterning them down to make precise nanoscaled structures.[6] It is relatively easy to implement a top-down approach because it requires either division of bulk material or miniaturisation of bulk fabrication to produce nanomaterials with desired properties. As the size of the matter reduces the ratio of surface area to volume increases.[6] The applications of the Top-down approach in dentistry include[7] -

  - Nanocomposites.
  - Nano glass-ionomer cement.
  - Nano impression materials.
  - Nano-coating for dental implants.
  - Nano-based bone regenerative materials.
  - Nanoencapsulation.
  - Nanoneedles.

The Bottom-Up approach- Bottom-Up refers to the build up of material from the bottom, atom by atom, molecule by molecule or cluster by cluster. Bottom-up technique aims to arrange smaller components into more complex assembly.[6] This begins by designing and synthesising custom made molecules that possess the ability to self-assemble, or self-organise into higher order structures.[6] The bottom-up approach has the potential to create less waste and hence be more economical. The applications of Bottom-up approach in dentistry include[7]-

- Nanodiagnostics.
- Local anaesthesia.
- Hypersensitivity cure.
- Oral Tissue biomimetics.
- Endodontic regeneration.
- Nano Diagnosis.
- Nanorobotics.

Nano dentistry- A novel concept

Robert A. Freitas Jr. in 1993 put forward the concept of nanomedicine, as observing, controlling, and treating biological systems of the human body at the molecular level using nanostructures and nanodevices.[8] Using nanostructured materials and nanotechnological concepts various oral ailments can be diagnosed and treated with a higher degree of specificity, helping in the maintenance of near-perfect oral health.

Application of Nanotechnology in Dentistry-

Nanotechnology in Oral Diagnostics

Potential applications of nanotechnology in diagnostics is the use of nanorobotics for early detection and diagnosis of various diseases like various oral cancers. To identify cancer cells using polymeric nanoparticles and to detect cancer with minimally invasive techniques at early stages to improve the prognosis is one of the aims of nanodiagnosis.[9] Various applications of nanodiagnostic are NEMS[9](Nanoelectro mechanical systems), OFNASET[9](Oral Fluid Nanosensor Test), Optical Nanobiosensors[9], Nanocantilevers[10], Nanopores[10], Nanowire senors[10].

NEMS are used to transform biochemical signals and cantilever array sensors into sensitive technology that can help detect various bacteria, viruses and DNA at the molecular level[9].

OFNASET are electromechanical systems that use sensor array chips for the detection of electrochemical sensors of cancers like salivary proteins and RNA biomarkers.[9] A combination of two salivary proteomic biomarkers(thioredoxin and IL-8) and four salivary mRNA biomarkers(IL-8, IL-1β, SAT, OZD) have high specificity and sensitivity for the detection of oral cancers using nanosensors.[9]

Optical Nanobiosensors- use the principles of optics for the transduction of biochemical interactions, and for analysis of intracellular components such as cytochrome C, into suitable output signals.[9]

Nanopores- Nanopore technology refers to nanosized pores that can be placed into thin membrane structures to detect potential change when charged biomolecules pass through the pores, thus making it easy to sense and analyse single-molecule amino acids, DNA, and RNA.[11] This technology can help assess DNA sequence or genetic defects with potential risks for cancer development.

Nanotechnology in Preventative Dentistry

The main goal of preventative dentistry is to prevent the progression of biofilm-related oral diseases like dental caries, periodontal disease, and endodontic disease.

One approach to achieving prevention against biofilm-related diseases is reversing an incipient carious lesion,i.e Biomimetic remineralisation.[12] Calcium carbonate nanoparticles showed good retention on oral surfaces when added to the experimental dentifrice.[12] It was seen that Calcium carbonate nanoparticles could act as vehicles for the slow but continuous release of high concentrations of calcium ions into surrounding oral fluids and dental plaque.[12] Continuous presence of calcium ions also increases the pH of surrounding fluid that helps in the remineralization of the incipient carious lesions.[12] Nanohydroxyapatite toothpaste delivers a nanocrystalline form of hydroxyapatite particles in the size range of 20-50 nm which is an optimal size for initiating the natural repair.[9] Some studies reported that the use of nanohydroxyapatite toothpaste results in the inhibition of caries development and exhibits a higher potential for remineralization of incipient lesions in comparison with toothpaste containing amine fluorides.[9]

Another approach could be the use of mouth rinse containing nanosized Calcium fluoride. Nanosized Calcium fluoride(CaF_2), is highly soluble and reactive with dicalcium phosphate dihydrate, owing to which a high level of fluoride can be incorporated into a stable refraction product.[12] A mouthrinse containing nanosized CaF_2 could potentially be used as an anticaries agent and could even enhance tooth remineralization by increasing the fluoride ion concentration in oral fluids.[12]

Nanotechnology in Periodontics

Local drug delivery- Local drug delivery systems effectively treat periodontal diseases. Nanotechnology has helped the local drug delivery system in effectively administering drugs for accurate results. Nanosized local drug delivery systems like films, chips, nanofibers, strips, etc., show excellent mucoadhesive properties owing to which they have strong on-site retention, and are also proven to be highly biocompatible and biodegradable.[13]Pinon-Segundo et al have developed Triclosan-loaded nanoparticles as a new drug delivery system for treating periodontitis.[14] Drugs can be incorporated into nanospheres composed of a biodegradable polymer.[14] A preliminary in vivo study was conducted on dogs using Triclosan-loaded nanoparticles that concluded a successful reduction in inflammation of the experimental sites.[14] Drugs incorporated into nanospheres help in the sustained and timely release of drugs at the site. For example, Restininin where tetracycline is incorporated into microspheres for local drug delivery in periodontal pockets.[13,14]

Bone regeneration

The aim of initiating periodontal treatment is to help regenerate the tooth-supporting structures lost due to long-standing periodontal infections. Autogenous bone grafts are considered the gold standard for treating bone defects caused by periodontal infections. Alternatively, allografts and xenografts are also used for bone regeneration purposes. To imitate the natural nanostructure of natural bone is the aim.[15] Nanobone® Synthetic Bone Graft is a nanocrystalline hydroxyapatite embedded in a silica gel matrix. The nanocrystallites show loose microstructure, with nanopores embedded between crystallites[15] This helps form a rough surface between the boundary of biomaterial and cells, which is important to induce cell growth.[15] The blood cells are bigger than the nanopores, thus all the blood plasma containing the important proteins are retained at the site.[15]

Tissue Engineering

Currently the tissue engineering concepts for periodontal regeneration are focused on the development and use of scaffold systems for the purposes of cell delivery.[16] Scaffold materials play a vital role in the success of tissue engineering procedures, for they provide an environment that is suitable for cell adhesion, proliferation and differentiation.[17] Natural bone itself is composed of a highly organised extracellular matrix at the nanoscale, thus designing and using nano scaffolds can provide an intrinsic advantage.[17]Nanoscaffolds can be produced with exact similarities with the tissue-specific extracellular matrix.[17] Nanoscaffolds may also be used for local and systemic drug delivery or delivery of genetic materials, biological factors.[17]They also help stabilise bioactive agents by encapsulation or surface attachment.[17] They help control and provide sustained release of drugs or biological factors owing to their size and high surface area, making them stimulus-sensitive delivery vehicles which can release, loaded drugs or biological factors, in response to external stimulus.[17]

Nanotechnology in Restorative Dentistry

Nanocomposites: With the advent of nanotechnology, the limitations of traditional resin-based composites have been overcome. This is achieved by introducing nanofillers, namely Nanomers and Nanoclusters, in resin-based composites.[18] Nanomers are nanostructures that are synthesised from aqueous colloidal silica sols by drying the powder of silica(20-75nm) treated with 3-methacryloxypropyltrimethoxysilane.[18] Nanoclusters are loosely bound agglomerates of nanoparticles that are synthesised in two forms, first form is silica particles of size 75 nm agglomerate to form a nanocluster which has a size of 0.6µm; the second form is developed from a colloidal solution of silica and zirconyl salt, producing zirconia-silica particles ranging from size 20-20nm.[18] Both forms of nanoclusters are then treated with a silane coupling agent to improve bonding between filers and resin matrix.[18] Resin-based composites produced with nanofillers can be called Nanocomposites.

The advantages of using nanocomposites are:

- Reduced polymerization shrinkage due to increased filler loading.[19]
- Enhanced compressive, tensile, and flexural strength.[19]
- Excellent aesthetic properties, good polish retention.[19]
- Good wear resistance.[19]
- Higher modulus of elasticity.[19]
- Increased shade-matching ability and colour stability.[19]
- Improved hardness and fracture toughness.[19]
- Even stress distribution throughout the composite restoration.[19]
- Better marginal seal, reduced tendency of microcracks.[19]
- Decreased water sorption and solubility.[19]
- The decreased disparity of coefficient of thermal expansion.[19]

One example of a recently developed nanohybrid reason composite is the Ormocer-based resin composite system. When evaluated using USPHS criteria, its performance was found satisfactory after 4 years of evaluation in a ClassII cavity.[9]

Nano Light-curing Glass Ionomer cement- Combining nanotechnology and fluoralumino-silicate technology is proven to improve the wear resistance, aesthetics, and polishability of traditional glass-ionomer cement.[9] The logic behind the addition of nanoparticles to GIC is to increase the particle size distribution and thereby increase the mechanical properties of GIC.[20] Forsterite nanoparticles when added to GIC can increase the fluoride release of GIC[20] Use of nano-agglomerated glass is shown to increase the compressive strength of GIC.[20] Various antibacterial nanoparticles like silver and zinc could also be incorporated in GIC to impart anticaries activity.[20]

Dental Hypersensitivity: Dental Hypersensitivity- Dental Hypersensitivity is one of the most painful, chronic, and least successfully treated ailments that a dentist encounters. Hypersensitivity has been treated symptomatically with many options like desensitising toothpastes and mouthwashes or varnishes, restorative materials, liners, etc.[13] Nanoparticles of silica, bioactive glass, functionalized nano-hydroxyapatite have been recently used to treat the issue of dentinal hypersensitivity.[21] The main advantage of using nanoparticles is the size which allows them to reach dentinal tubules and occlude then providing relief from hypersensitivity.[21]

Nanosolutions / Bonding Agents: Nanosolutions provide dispersible nanoparticles that can be used in bonding agents.[22] Advantages of using nanosolutions or nanoparticles in bonding agents include high stress absorption, high bond strength, durable marginal seal, fluoride release, longer shelf life, and no requirement for acid etching.[9] A new flowable composite called Dentiflow has an acceptable shear bond strength for orthodontic bracket bonding[22]

Nanotechnology in Prosthodontics

Removable dentures, fixed crowns and bridges can be fabricated based on impressions taken from the mouth to perform oral rehabilitation.

Impression materials- Nanofillers added to vinyl polysiloxane produce an impression material that has shown to have better flow, improved hydrophilic properties and enhanced precision detail.[22] Nanotech elite H-D plus(Zhermack Italy) is a commercially available impression material that shows these properties.[9]

Nano Composite Denture teeth: Nanocomposite denture teeth contain uniformly dispersed nanosized fillers and polymethylmethacrylate which have superior surface texture, high polishability, improved surface hardness, and improved wear resistance.[9]

The acrylic resins containing heat-cured Polymethylmethacrylate (PMMA) show acceptable aesthetics and biocompatibility, but they suffer from some polymerisation shrinkage, face fatigue failure, microbial adhesion, and possible irritations to the oral mucosa..[7] Addition of carbon nanotubes to PMMA can help reduce the degree of polymerization shrinkage and improve the mechanical properties of denture material.[7] Addition of TiO_2 or Al_3O_2 to PMMA reduces denture porosity and hence reduce the bacterial adhesion.[7]

In fixed prosthodontics: Nanofillers can be added to ceramics to enhance polish ability and enhances wear resistance.[6] Nanopigments can be added to adjust the shade of restoration to the surrounding teeth.[6]

Nanotechnology in Oral Surgery

Local Anesthesia- Nanorobots could be used to administer local anaesthetics using nanotechnology. A colloidal suspension containing millions of active analgesic nanosized robots, that can be instilled in the gingiva and that can be controlled by input from the dentist. After reaching the crown of the tooth or the mucosa, these nanorobots can reach the pulp via the gingival sulcus, lamina propria, and dentinal tubules guided by chemical gradient and temperature difference controlled by inputs from a computer. After reaching the pulp they can shut down all sensations by establishing control over the nerve-impulse traffic. After completion of procedure, all sensation is restored.[22] Nanorobotic analgesics could be used in similar manner and offer greater patient comfort, less side effects, precise analgesic effect, minimal patient anxiety, greater control and complete reversability.[9]

Nanoneedles- Nanosized stainless steel crystals can be used to manufacture suture needles. Research on nanotweezers is currently being carried out. Nanotweezers along with nanoneedles may help cell surgery with precision possible in the near future.[9]

Nanotechnology in Endodontics

Root canal Irrigants- Conventionally used root canal irrigants are Chlorhexidine, Sodium Hypochlorite, and Ethylenediaminetetraacetic acid. Chitosan, a polysaccharide derived from chitin, can be added to root canal irrigants as it possesses excellent antimicrobial, antiviral and antifungal properties.[23]Chitosan also shows chelating property that inhibits enzymatic activity which is necessary for bacterial survival.[23] Its antifungal property can be attributed to the fact that it can penetrate the nucleus of cells where it binds to the DNA and inhibits the formation of RNA.[23]

Intracanal medicament: Calcium Hydroxide is the most commonly used intracanal medicament, which works by initiating the release of hydroxyl ions that increase the pH of the canal disrupting the activity of various microorganisms in the canal.[24]Incorpoprating 0.2% silver nanoparticles in the intracanal medicament for a 7-day application can lead to a significant reduction of microbial count with the destruction of E. faecalis biofilm.[24]

Obturating Material: Gutta-percha(GP) is the single most widely used material for obturating prepared root canals. It shows a slight antimicrobial effect owing to the presence of zinc oxide.[24] But some studies have shown increased affinity of microbes towards gutta-percha. To combat this issue antimicrobial agents were introduced into gutta percha, like calcium hydroxide GP points, chlorhexidine GP, iodoform GP or tetracycline GP.[24] Another approach could be the introduction of Silver nanoparticle coating on the GP, which showed good antibacterial property against E. faecalis, S. mutans, E. coli, and antifungal property against C. albicans[24] Bioactive glass nanoparticles incorporated into polyisoprene based root canal fillers that don't require a root canal sealer show promising results.[24]

Root Canal Sealers: To enhance the antimicrobial effect of root canal sealers various nanoparticles like Zinc oxide nanoparticles, Chitosan nanoparticles, Bioactive glass nanoparticles, Calcium phosphate nanoparticles, Quaternary ammonium polyethyleneimine nanoparticles(QPEI), etc can be added.[24] Adding cationic nanoparticles like chitosan or zinc oxide nanoparticles to zinc oxide-based or resin-based sealer can enhance its antimicrobial effect.[24]

Vital Pulp Therapy: Pulp capping to induce the formation of tertiary dentin to maintain the vitality of the pulp after exposure is the goal of initiating Vital pulp therapy procedure.[24] Traditionally Mineral trioxide aggregate (MTA) and Dycal (Calcium hydroxide) are used for pulp capping procedures. Nanocrystalline Hydroxyapatite paste was found biocompatible and superior to formocresol as a pulp capping and pulpotomy agent.[24] Addition of 3% wt of nano-hydroxyapatite to calcium hydroxide, enhanced the release of calcium ions thus speeding up the process of remineralisation.[24]

Nanotechnology in Oral Implantology

Nanocoatings can be used for surface modifications of dental implants, as the chemistry and roughness play a significant role in achieving and maintaining osseointegration.[6] Implant surface can be modified be direct surface tailoring, like etching or sandblasting, or by functionalization like bioglass coating or peptide coating.[7] Nanotechnological approaches to implants could be etching the implant surface with solutions of alkaline sodium, alkaline potassium and hydrogen peroxide to form nanostructures like nanotubes, nanoneedles on the surface of implants.[7] These nanostructures increase the wettability and treatment with alkali solutions increase the hardness, which when taken together could lead to better protein adsorption, blood clot formation and neoangiogenesis at the implant interface.[7] Nano Topographies at the implant surface can also be achieved by sandblasting with nanopowders, laser melting, plasma spraying,etc.[7] Nanohydroxyapatite coating with silver nanoparticles on implants have found significant reduction of biofilm around implant surface.[10]

Nanotechnology in Orthodontics

Orthodontic nanorobots can directly be used to manipulate periodontal tissues, including gingivae, periodontal ligament, cementum and alveolar bone, which allows rapid and painless tooth straightening, rotating and vertical repositioning in a relatively short time.[6] Fixed orthodontic appliances currently use metals and their alloys for the fabrication of archwires, and brackets. The biggest disadvantage of which is the resultant production of friction, which can interfere with the teeth alignment and is responsible for white spot lesions and caries around the bracket.[7] To reduce friction, composite nanocoatings made up of nickelphosphorous and fullerene-like nanoparticles of tungsten disulfide.[7] Along with the reduction of friction they also increase the corrosion resistance of the archwire.[7] A study conducted by Cao *et al*. demonstrated that brackets coated with a thin film of nitrogen-doped titanium dioxide showed high antimicrobial and bacterial adhesion properties against normal oral pathogenic bacteria through visible light, which is effective in prevention of enamel demineralization and gingivitis in orthodontic patients.[22]

Concerns regarding toxicity

The physico-chemical properties of nanoparticles that make nanomaterials efficient for industrial use may prove harmful to living organisms. Due to their size, most nanoparticles can cross almost all biological barriers, including the blood-brain barrier.[7] The potential of the release of nanoparticles from nanocomposites into the oral cavity or lungs, during preparation, filling or replacement of old restoration is a cause for concern.[7] osteotomy preparation , implant placement, abutment preparation and subsequent mechanical loading, friction and shear forces may dislodge the nanoparticles into surrounding tissues leading to cellular uptake of these nanoparticles which may show diversified effects.[7]

Park *et al.* while studying the side effects of silver nanoparticles on mouse peritoneal macrophage cells observed a potential mechanism of nanoparticle toxicity where nanoparticles enter the cell via endocytosis and then release ions after ionisation from within the cell. This effect is termed as Trojan Horse effect.[7] Besides this the released ions can lead to the activation of reactive oxygen species, which inturn proves harmful for the cell.[7] Nanoparticles when enter the cell could also be internalised into different cell organelles like the nucleus where they can induce DNA damage.[7]

Nanoparticles released into body fluids can react with proteins, forming protein complex which attaches to surface of nanoparticles which may show altered biodistribution, clearance and toxicity.[7]

Challenges for Nano dentistry-

One of the significant challenges nano dentistry faces is from the engineering perspective, where mass production of nanomaterials is not very feasible.[25]

It is also difficult to manipulate and coordinate many activities of independent nano/micro scale robots simultaneously.[25]

Precise positioning and assembly of nano scale parts is also very difficult to achieve.[25]

Developing biocompatible nanomaterials is another significant challenge that needs to be overcome.[25]

The possible long-term effects of nanomaterials in environment need to be studied.[26]

The fabrication of nanomaterials is very expensive and the funding for research and fabrication of nanomaterials is suboptimal.[7]

Social issues of public acceptance, acceptance by the dental fraternity, ethical considerations and human safety are some issues that need to be addressed before nano dentistry becomes a norm.[26]

Conclusion

Nanotechnology has tremendous potential for revolutionising healthcare domains, especially dentistry. Although the applications of Nanotechnology in dentistry seem limited today, it has the potential to bring about significant improvements in the way we deliver oral care. Nanotechnology can help enhance procedures and materials that will help dentists deliver oral care in a more efficient way. But the challenges nanotechnology faces today from engineering, social, financial, and ethical perspectives are significant and more experiments need to be carried out in order to overcome them before nanodentistry becomes the new normal. With great potential for noble use, comes greater potential for misuse too. Further studies need to be done to overcome the challenges faced by nanotechnology before we move forward with it.

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