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REVIEW ARTICLE

Nanoparticles: An Emerging Trend in Dentistry

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ABSTRACT

Introduction: A nanoparticle is a fundamental component in the fabrication of a nanostructure. Nanoparticles have the ability to interfere, translocate within, and damage/repair living organisms. They provide more effective and more convenient routes of administration, lower toxicity, extend the product life cycle, and are ultimately economical for health care. Hence, they provide useful diagnostic and treatment modalities in dentistry.

Objectives: To review the recent concepts of nanoparticles and nanotechnology in diagnostic and treatment aspects in different branches of dentistry.

Materials and methods: In this review, PubMed was searched for relevant English papers from 1981 to 2015. The key words in the search included were: "Nanoparticles," "dentistry," and "nanotechnology" in various combinations.

Results: There have been extensive applications of nanotechnology in different branches of dentistry. Application of nanostructures enables faster detection of oral cancers and assessment of the saliva for presence of viruses, proteins, or specific markers. Limitations in dental materials, instruments, procedures, and medications can be overcome with the use of nanoparticles

Keywords: Dentistry, Diagnosis, Drug delivery, Nanoparticles, Treatment.

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INTRODUCTION

"Nano" is derived from a Greek word meaning "dwarf." The late Nobel Prize winning physicist Richard P Feynman in 1959 speculated about the potential of nanosize devices as early as in 1959.[1,2] Modern science has learned to synthesize a bewildering array of artificial materials with structure, i.e., engineered at smaller scale. Nanotechnology is the branch of science that deals with nanoparticles. It is about studying manipulation of matter at the atomic and molecular scale. Nanoparticles have the ability to interfere, translocate within, and damage/ repair living organisms. This ability results primarily from their small size, which enables them to penetrate physiological barriers, and travel inside the circulatory systems of a host.

A nanoparticle is a fundamental component in the fabrication of a nanostructure. In general, the sizes of nanoparticles range between 1 and 100 nm.[3] They can be compared with the size of viruses, where the smallest have dimensions of tens of nanometers, which in nanotechnology might be called "nano-organisms."

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OBJECTIVES

The objective of the review is to convey the recent concepts of nanoparticles and nanotechnology in diagnostic and treatment modalities in different branches of dentistry.

MATERIALS AND METHODS

In this review study, PubMed was searched for relevant English papers from 1981 to 2015. The searched key words were: "Nanoparticles," "dentistry," and "nanotechnology" in various combinations. All the relevant articles are taken for the review.

RESULTS

Studies indicated extensive applications of nanotechnology in different branches of dentistry. The different approaches, indications, applications and treatment modalities are being described in detail.

APPROACHES

The following approaches are used in nanotechnology:[4,5]

- *Bottom-up approach*: Smaller components are arranged into complex assemblies. This method is used for production of nanoscale structures.
- *Top-down approach*: Creation of smaller devices using larger ones to direct their assembly. These methods are mostly extensions of methods, which are employed in small-scale assembly at the micron scale. By further miniaturization the nanodimension is entered.
- *Functional approach*: Development of components of a designed function without regard to how they might be assembled.

APPLICATION OF NANOPARTICLES IN MEDICAL TREATMENTS

Increase in the quantity of nanoparticles raises the scattering intensity. Due to this feature, the application to specific molecule recognition in a living body tissue is expected. For example, by covering the cancer cell surface it becomes possible to distinguish a healthy cell from a cancer cell by the presence of antibodies joined to the nanoparticle. Moreover, if a protein and a functional molecule were joined to the nanoparticle, it could also be used for imaging cells other than cancer cells.

Nanometer-sized particles are in the same dimensions as that of antibodies, membrane receptors, nucleic acids, and proteins. These features along with their high surface: Volume ratio and the possibility of modulating properties make them incredible and noteworthy for imaging, diagnosis, and treatment.[6,7]

Antimicrobial Agents

Metal nanoparticles, nano-chitosan, carbon nanotubes, nano-quaternary ammonium.[8]

APPLICATIONS FOR NANOPARTICLES IN THERAPEUTICS

Imaging

Optical imaging techniques are used extensively in clinical diagnosis. However, the organic fluorophores used currently are not photostable and have low intensity. Similarly, fluorescence proteins are limited because they cannot be utilized in multicolor assays. Nanoparticles might help to overcome certain limitations. For example, quantum dots which are resistant to photobleaching, photochemical and metabolic degradation. These exhibit high quanta yield and help in enabling the simultaneous identification of multiple markers.[9] Magnetic resonance imaging (MRI) applications are limited because they are insensitive to low concentrations of imaging agent. For these reasons, intensive research efforts aim in developing MRI contrast agents to enhance imaging. Hence, superparamagnetic iron oxide nanoparticles have been proved effective in enhancing contrast in magnetic imaging.[10]

Diagnosis

The accurate targeting of molecules indicative of disorders of the cell at the single-molecule level is a necessary task for current analysis systems. The combination of nanoparticles and other nanotechnology-based materials is beneficial in combating this emerging challenge that enables diagnoses at the level of single cells and single molecules.[11] There are several nanoparticle-based commercialized systems for medical diagnostics.[6] Nevertheless, the possibilities for nanoparticle applications in diagnostics are unlimited because nanoparticles enable the selective tagging of medically important targets, such as bacteria, biomarkers, such as proteins, and deoxyribonucleic acid (DNA).[3]

Drug Delivery

Nanoparticle-based drug delivery provides enhancing drug-therapeutic efficiency and pharmacological characteristics. They help in improving the solubility of deficiently water-soluble drugs, modifying pharmacokinetics, enhancing drug half-life by reducing immunogenicity and increasing specificity toward the target cell or tissue, improving bioavailability, diminishing drug metabolism and controllable release of therapeutic compounds, and the delivery of two or more drugs simultaneously for combination therapy.[12,13]

Nanoparticle-based Therapeutics Approved for Clinical Use

Liposomes are frequently used as pharmaceutical carriers because of their ability of

- Encapsulating hydrophilic and hydrophobic high-efficiency therapeutic agents
- Protecting the encapsulated drugs from undesired external conditions
- Functionalizing with specific ligands, which target specific cells, tissues, and organs
- Coating with inert and biocompatible polymers, such as polyethylene glycol
- Forming desired formulations with needed composition, size, and other properties.[14-16]

Polymer Drug Conjugates

Small-molecule therapeutic agents, anticancer chemotherapeutic agents, have two properties: Short circulation half-life, which leads to frequent administrations, and nonspecific targeting, resulting in systemic side effects which are undesired. The conjugation of molecule drugs to nanocarriers can reduce the undesirable adverse effects. Polymer drug conjugates prolong the *in vivo* circulation time from several minutes to several hours and also reduce cellular uptake to the endocytic route. This enhances the passive delivery of drugs to tissues in conditions, such as tumors and atherosclerotic plaques.[17]

Other macromolecule drug conjugate is Abraxane, an albumin-bound paclitaxel drug, which was approved by the Food and Drug Administration in 2005 as a second-line treatment for patients with breast cancer.[18] Abraxane concentrates in the tumor through the passive enhanced permeability and retention effect and partly through the transendothelial transport mechanisms via the albumin-binding protein gp60. Clinical studies showed that Abraxane increases the therapeutic response rate and also increases time to disease progression and overall survival in patients with breast cancer.[3]

In addition to the approved nanoparticles, numerous other nanoparticles are currently under various stages of development, including various liposomes, dendrimers, gold nanoparticles, quantum dots, and ceramic nanoparticles. With continued research and development efforts, this nanoparticle technology is expected to have a tremendous impact on medicine for decades to come.

NANOTECHNOLOGY IN DENTISTRY

Nanodentistry is a promising field in which oral health care could be developed to unprecedented heights. They have their applications in various components of nanotechnology, nanomaterials, dental nanorobots, and tissue engineering. Following are the applications of nanotechnology in dentistry. There are two types of approaches in which nanoparticles can be used in dentistry.

Bottom-up Approach Application in Nanodentistry

Local Anesthesia

It was Freitas who described how medical nanorobots might use specific motility mechanisms to crawl or swim through human tissues with navigational recession: Cytopenetration (e.g., pass through plasma membranes, such as the odontoblastic process without disrupting the cell, while maintaining clinical biocompatibility) and use of any of a multitude of techniques to monitor, interrupt, or alter nerve impulse traffic in individual nerve cells.[19] Colloidal suspension consisting of myriad of analgesic micron-sized dental robots will be infused on patient's gingiva. These wandering nanorobots reach the pulp through the gingival sulcus, lamina propria, and dentinal tubules. After reaching the pulp, the analgesic dental robots remove sensitivity in tooth requiring treatment. When treatment of a particular tooth would be done, nanorobots will retract the control of nerve signals after receiving commands from dentist and will exit from same path used for entry.[2,20]

Hypersensitivity Cure

Hydrodynamic pressure alterations transmitted to the pulp are most likely to be a cause of dentin hypersensitivity. This can be treated in future by dental nanorobots, which would selectively occlude tubules, utilizing native biological materials.[20]

Table 1: Diagnosis of oral cancer

Diagnosis of Cancer	
Nanoelectromechanical systems (NEMS)	Nanotechnology-based NEMS biosensors that exhibit sensitivity and specificity for a single molecule are being developed. They convert biochemical signal to electrical signal[2,20]
Multiplexing modality	Helps to sense large numbers of different biomolecules at a time[20]
Oral fluid nanosensor test	Used for detection of salivary biomarkers for early diagnosis of oral cancer
Optical nano biosensor	Minimally invasive analysis of intracellular components, such as cytochrome c for accessing levels of apoptosis[25]
Cantilevers	Flexible, small rods with endings that attach to cancer-related molecules, changed DNA sequences[8]
Nanopores	Small pores that enable the passage of one strand of DNA to study shape and electrical properties of each base on a DNA strand and genetic defects with potential risk of carcinogenesis[8]
Nanotubes	Nanocarbon tubes which have a diameter half that of a DNA to detect change in DNA sequence and the exact location of defect[8]

After reaching the dentin, the nanorobots enter dentinal tubular holes that are 1 to 4 μm in diameter and move toward the pulp, guided by chemical gradients, temperature differential, and position of navigation, controlled by nanocomputer, which is operated by the dentist. Nanorobots can complete the journey to the pulp chamber in roughly 100 seconds at a speed of 100 μm/sec, since the distance is supposed to be 10 mm.[20,21]

Diagnosis and Treatment of Oral Cancer

The diagnosis of oral cancer is given in Table 1 and the treatment of oral cancer is given in Table 2.

Dental Durability, Cosmetics, and Dentifrobots

Tooth durability and cosmetics may be enhanced by replacing upper enamel layers with pure sapphire and diamond, which can be made fracture resistant as nanostructured

Table 2: Treatment of oral cancer

Treatment of Cancer	
Nanomaterials for brachytherapy	BrachySil™ (Sivida, Australia) delivers ^{32}P (radioactive isotope of phosphorous), clinical trial[26]
Drug delivery across the blood–brain barrier	More effective treatment of Alzheimer's, brain tumors, Parkinson's in development
Nanovectors for gene therapy	Nonviral gene delivery systems[26]
Photodynamic therapy	Hydrophobic porphyrins are molecules used for the photodynamic therapy of solid cancers or ocular vascularization diseases

composites, probably including entrenched carbon nanotube.[20] Toothpaste or mouthwash could be used to transfer nanorobotic dentifrice, which would rest subocclusally, as they would be designed to avert occlusal region. They function like conventional dentifrices but the approach would be entirely different, as they would be micromechanical devices, working at a speed of 1–10 μm/sec, functioning by metabolizing trapped organic matter into harmless and odorless vapors and debriding calculus incessantly. From the safety point of view, if they were swallowed accidently, they would deactivate themselves. Dentifrobots would be programmed to identify and destroy pathogenic bacteria residing in the plaque and oral cavity, while sparing around 500 species of harmless indigenous oral microflora. Thus, they provide a blockade against halitosis, since bacterial putrefaction is the central metabolic process involved in oral malodor.[22] Conventional tooth decay and gingival disease can be prevented in this approach.

Orthodontic Treatment

Orthodontic nanorobots could directly influence the periodontal tissues, allowing fast and painless tooth positioning in minutes to hours. This is in contrast to current molar uprighting techniques, which require a long time to complete.[20]

Tooth Repair

Nanodental techniques for tooth repair may develop through several stages of technological progress, first taking small steps of genetic engineering, tissue engineering, and regeneration and then development of whole new teeth *in vitro* and their installation.[23]

Top-down Approach Application in Nanodentistry

Nanocomposites

Nanoparticles are used to produce nanocomposites with homogeneously distributed nanoparticles in resins. Advantages are superior hardness, superior flexure strength, modulus of elasticity and translucency, 50% reduction in filling shrinkage, and excellent handling properties.[22]

Nanosolution

Nanosolutions produce unique and dispersible nanoparticles and can be used in bonding agents to ensure homogeneity and ensure that the adhesive is perfectly mixed everytime.[21,22]

Impression Materials

Nanofillers are integrated in vinylpolysiloxanes, producing a unique addition of siloxane impression materials. The material has improved flow, hydrophilic properties, and enhanced detail precision.[20,22]

NANOENCAPSULATION

Latest development in the field of targeted release systems is credited to South West Research Institute (SWRI), which had developed nanocapsules including novel vaccines, antibiotics, and drug delivery with minimal side effects. In this series of development, Osaka University in Japan holds the privilege of developing targeted delivery of genes and drugs to human liver in 2003. In their research project, engineered hepatitis B virus envelope L particles were allowed to form hollow nanoparticles displaying a peptide, i.e., imperative for liver-specific entry by the virus in humans. Likewise, in future nanoparticles could be used to target oral tissues, along with cells derived from the periodontium (Yamada et al 2003).[20,22]

OTHER PRODUCTS OF SWRI

Nanoneedles

Suture needles with nano-sized stainless steel crystals have been developed. Nanotweezers are also under development, which will make cell surgery possible in future (Table 3).

Materials used for Bone Replacement

Hydroxyapatite (HA) nanoparticles used to treat bone defects are:

- VITOSSO (Orthovita, Inc, USA) HA + tricalcium phosphate
- NanOSS™ (Angstrom Medica, USA) HA
- Ostim® (Osartis GmbH, Germany) HA

Table 3: Products of SWRI

Products	*Features*
Medical appendages for hastened healing	• Biodegradable nanofibers serve as delivery platform for hemostatic • Role of silk nanofibers in wound dressing is under development • Nanocrystalline silver particles having antimicrobial properties that can be used for wound dressing
Protective clothing and filtration masks	Utilizing antipathogenic nanoemulsions and nanoparticles
Bone targeting nanocarriers	Calcium phosphate-based biomaterial is developed. This is an easily flowable, moldable paste that conforms to and interdigitates with host bone. It helps in supporting growth of cartilage and bone cells[20,22]

CONCLUSION

Nanobiotechnology improves public health, but there is concern that technical developments may cause adverse effects. Humans are being exposed to nanoparticles throughout their evolution, but this exposure has been increased in the past century because of the industrial revolution. Epidemiological studies have shown that urban population with airborne particulate matter containing nanoparticles deriving from combustion sources, such as industrial emissions and motor vehicles, cause respiratory and cardiovascular morbidity and mortality. Similarly, nanoparticles may also contribute to the toxicological effects of nanoparticles in biological systems. The smaller particles have more surface area per unit mass, and this property makes nanoparticles very reactive in the cellular environment. The respiratory system, blood, central nervous system, gastrointestinal tract, and skin have been shown to be targeted by nanoparticles.[4,24] While coming to therapeutics, the main problems of nanotechnology include deficient funding, slow decision-making in application, retention of trained manpower, and lacking private enterprises engagement.[20]

FUTURE SCOPE

Research has to be done in the field of nanoparticles for its application in various aspects, which were previously thought to be impossible:

- In medicine and therapeutics
- In drug delivery and gene therapy
- In the development of nanotweezers for cell surgery
- In detection and modification of molecular signaling
- For patient-specific treatment

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