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Nano-Biomaterials and Their Biocompatibility in Restorative Dentistry: A Review

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Abstract: *Human healthcare is facing a major uprising in the wake of ongoing technological expansions in the field of nanotechnology. Incorporation of nanotechnology into dentistry will make possible the maintenance of near perfect oral environment by using nanomaterials, including tissue engineering, and ultimately, dental nanorobots. New potential treatment prospects in dentistry may include: dentition renaturalization and permanent hypersensitivity cure, local anaesthesia, complete orthodontic realignments during a single office visit, covalently bonded diamondised enamel, and oral health maintenance using mechanical dentifrobots, to destroy bacteria in the mouth that cause dental caries or even repair spots on the teeth where decay has set in, by use of computer to direct these tiny workers in their tasks. Nanodentistry still faces many significant challenges in realizing its tremendous potential. There are larger social issues of public acceptance, regulations, ethics and human safety that must be taken into consideration before molecular nano-technology can enter the modern medical armamentarium. However, there is equally powerful motivation to surmount these various challenges such as the possibility of providing high quality dental care to 80% of the population that at present receives no noteworthy dental care. Time, financial and scientific resources, specific advances and human needs will conclude which of the applications to be realized first!*

Keywords: *Nanotechnology, Biocompatibility, Nanorobots, Nanodentistry, Restorative dentistry, Nanobiomaterials*

I. Introduction

Science is undergoing yet another revolution, in helping mankind enter a new era, the era of “Nanotechnology”. The term “Nanotechnology” was introduced by Prof. Kerie E. Drexler, a lecturer and researcher of nanotechnology. Nanotechnology is the science of manipulating matter measured in the nanometer, approximately the size of 2 or 3 atoms [1]. The basic idea of this technology is to employ individual atoms and molecules to construct functional structures. Researchers are looking for methods to use microscopic devices to perform tasks that are now done by hand or with equipment. Diagnosis and treatment will be personalized to match the preferences and genetics of individual patient. Technology should be able to target specific cells in an individual, suffering from life-threating conditions. Toxic drugs used to fight these illness would become much more specific and subsequently less harmful to the body.

Last decade witnessed an unparalleled growth in all the fields of research in medicine. Nanotechnology has revolutionized many aspects of health care into a new paradigm of state-of-the-art patient care beyond traditional and dentistry is no exception. Nanotechnology has come a long way to find its application in supramolecular chemistry - self-assembling drug carriers and gene delivery systems, nanoparticles and nanocapsules, polymer-drug conjugates, antibody technologies, polymer-protein and antibody conjugates, nano-precipitation, nanocrystals, liposome technology, in situ polymerization, dendrimer technologies, tissue engineering and repair, molecular imprinting including recent innovations in dental diagnostics, material and therapeutics.

II. History Of Nanotechnology

The history of nanotechnology is dotted with a certain amount of skepticism. Some people believe that this is a brand new form of scientific evolution that did not develop until the late 1980s or early 1990s. Others have confirmed that the history of nanotechnology can be traced back to the year 1959. The history of nanotechnology, in some sense dates back to prehistoric eras when early humans/hominoids made use of naturally-occurring, nanoscale elements. In 1959, Dr. Richard Phillips Feynman described molecular machines building with atomic precision using nanotechnology. In 1974, Norio Taniguchi used the term "Nano-technology" in paper named ‘On the basic concept of Nanotechnology’. Later on Dr. K. Eric Drexler introduced molecular nanotechnology concepts at MIT (Masuchettes Institute of Technology) in 1974 and he published a first nanotechnology book, named ‘Engines of Creation: The coming era of Nanotechnology’ in 1986. The field of nanotechnology has evolved in the 21st century to largely embrace research in chemistry and materials science as well as molecular engineering. Nanotechnology possesses incredible potential, but social issues of public acceptance, regulation, ethics and human safety must be addressed before nanotechnology can be seen as the option of providing high quality dental care. Because nanotechnology carries a significant potential for misuse and abuse on a scale and scope never seen before. It has been suggested that nanodentistry will make it possible to maintain near-perfect oral health through the use of nanomaterials [2, 3], biotechnology [4-7] and nanorobotics.

III. Approaches To Nanotechnology

Various approaches have been utilized successfully in nanotechnology and as the technology progresses further, approaches may emerge. The approaches employed thus far have been dictated by the technology available and the background experience of the researchers involved.

***Top-down approach*:** Involves fabrication of device structures via monolithic processing on the nanoscale. It has been used with spectacular success in the semiconductor devices used in consumer electronics.

***Bottom-up approach*:** Involves fabrication of device structures via systematic assembly of atoms, molecules or other basic units of matter. This approach nature uses to repair cells, tissues and organ systems in living things and for life processes such as protein synthesis.

Some other approaches include:

Functional approach: It develops components of the desired functionality without much importance to their assembly or structure.

Speculative approach: In this approach more emphasis is given on its societal implications than the details of how such inventions could actually be generated.

Biomimetic approach: It seeks to apply biomolecules for applications in nanotechnology.

IV. Nanobiomaterials In Dentistry

Nanotechnologies are on the verge of originating extraordinary advances in biological and biomedical sciences. These would be related with both providing the tools for improved understanding of essential building blocks of materials and tissues at the nanoscale and designing technologies for analysing and reconstructing them.

Nanoscale Materials:

The nanomaterial field takes a science-based approach to study materials with morphological features on the nanoscale, mainly those that have exceptional properties stemming from their nanoscale dimensions. **Nanoscale** is defined as smaller than one-tenth of a micrometer in at least one dimension. An important aspect of nanotechnology is the vastly increased ratio of surface area to volume available in many nanoscale materials, which makes promising new quantum mechanical effects.

Nanoparticles:

These are nanometer-sized particles that are nanoscale in three dimensions. The different applications of nanoparticles include drug delivery systems, cancer targeting and dentistry. Nanoparticles are of great scientific importance as they are effectively a bridge between bulk materials and atomic or molecular structures.

Siegel has categorized nanomaterials as zero-dimensional, one-dimensional, two-dimensional and three-dimensional nanostructures. Various nanostructures include the following:

1. Nanopores
2. Nanotubes
3. Nanorods
4. Quantum dots
5. Nanoshells
6. Dendrimers & dendritic copolymers
7. Liposomes
8. Fullerenes
9. Nanospheres
10. Nanowires
11. Nanobelts
12. Nanorings
13. Nanocapsules
14. Nanofibers

Inorganic nanoparticles either currently in use or under development include:

1. Semiconductor nanoparticles
2. Metal nanoparticles

3. Metal oxide nanoparticles
4. Silica nanoparticles
5. Polyoxometalates
6. Gold nanocrystals

Nanobiomaterials in Preventive Dentistry:

The aim of modern dentistry is the early prevention of tooth decay rather than invasive restorative therapy. However, despite remarkable efforts in promoting oral hygiene and fluoridation, the prevention and treatment of early caries lesions are still challenges for dental research and public health, particularly for individuals with a high risk for developing caries. Recent studies indicate that nanotechnology might offer novel strategies in preventive dentistry, specifically in the control and management of bacterial biofilms or remineralization of submicromelcular-sized tooth decay [8-10].

To inhibit the pathogenic consequences of tenacious intraoral biofilm formation over a longer interval, wear-resistant ***nanocomposite*** surface coatings have been established for the alteration of the tooth surface *in vivo*. Easy-to-clean surface properties are accomplished by integrating nanometer-sized inorganic particles into a fluoro-polymer matrix. These biocompatible surface coatings have a surface free energy of 20-25 known as theta surfaces [11] and therefore can enable the detachment of adherent bacteria and adsorbed salivary proteins under the influence of physiological shearing forces in the mouth. Other nano-assisted approaches for biofilm management are oral health care products which contain bioinspired apatite nanoparticles, either alone or in combination with proteinaceous additives such as casein phosphopeptides (CPP) [11-13]. CPP-stabilized amorphous calcium phosphate (ACP) nano-complexes with a diameter of 2.12 nm [14, 15] seem to play a definite role in biomimetic strategies for biofilm management.

Nanobiomaterials in Restorative Dentistry:
Dental Nanocomposites:

During the past decade, more efforts have been concentrated on dental nanocomposite, with a hope that contemporary nanocomposites with ceramic nanofillers should offer increased strength, esthetics and durability. Variety of calcium phosphates, such as hydroxyapatite, ACP, tetracalcium phosphate and dicalcium phosphate anhydrous have been studied as fillers to create mineral releasing dental composites. Nanotechnology or molecular manufacturing may provide resin with filler particle size that is smaller in size, can be dissolved in higher concentrations and polymerized into a resin system with molecules that can be fabricated to be compatible when coupled with a polymer and provide unique characteristics. Nanoproducts Corporation has successfully synthesized nonagglomerated discrete nanoparticles that have homogeneous distribution in resins to produce nanocomposites. The nanofiller used comprises an aluminosilicate powder having a mean particle size of 80 nm and a 1:4 M ratio of alumina to silica with a refractive index of 1.508. Advantages include superior flexural strength, superior hardness, modulus of elasticity and translucency, 50% reduction in filling shrinkage and Excellent handling properties. *Trade name*: Filtek^{TM} Supreme Universal Restorative.

Types of Nanocomposites:

- Light-cured dental nanocomposites
- Self-cured / dual-cured dental nanocomposites

Resin–Modified Nano-Glass Ionomer Composites:

A nanofilled resin–modified GIC (RMGIC) or "nanoionomer" was developed lately by 3M ESPE-Ketac^{TM} N100 (KN). This light curing nanoionomer restorative is the first paste/paste, RMGIC material developed with nanotechnology. Because it adds benefits not usually related to glass ionomers, it has resulted in a new category of glass ionomer restorative material, known as, the nanoionomer. The technology of KN restorative represents a mixture of FAS technology and nanotechnology. Nanoparticle-filled RMGIC is manufactured by the addition of nanoparticles to RMGIC materials. This combination offers exceptional characteristics of wear and polish and filler particle size can influence abrasion resistance, strength and optical properties. The addition of nanoparticles to KN provide an improved finish and a smoother, more esthetic restoration without adversely affecting its other advantageous properties, including fluoride release, high early bond strength, adhesion to enamel and dentin and less susceptibility to moisture and dehydration. *In vitro* study reveals that the addition of nanofillers provides enhanced surface wear and polish relative to other commercially available dental materials [16, 17].

Silver Nanoparticles:

Silver has a long and fascinating history as an antibiotic in human health care [18]. It has been used in water purification, wound care, bone prostheses, cardiac devices, reconstructive orthopaedic surgery, catheters and surgical appliances. Advancing biotechnology has enabled the integration of ionizable silver into fabrics, for clinical use to reduce the risk of nosocomial infections and for personal hygiene [19].

The antimicrobial, antifungal, and antiviral action of silver is proportional to the amount of released bioactive silver ions (Ag~) and its availability to interact with fungal or bacterial cell membranes [20]. Bacterial sensitivity to silver is genetically determined and relates to the levels of intracellular silver acceptance and its ability to interact and irreversibly denature key enzyme systems. Resin composites containing silver ion implanted fillers that release silver ions have been found to have antibacterial effects on oral bacteria, e.g. Streptococcus mutans [21]. Most studies available on the antimicrobial effect of silver containing composites describe the effect of the silver particles on different species of cariogenic bacteria. Some of these studies tested the mechanical properties of the silver containing composite [22].

V. Biocompatibility Of Nanobiomaterials

Biocompatibility is defined as "the ability of a material to function in a specific application in the presence of a suitable host response" (Williams DF 1987). There are a vast number of cytotoxicity screening techniques available for measuring the biocompatibility of a dental restorative material. The application of various methods of cytotoxicity screening has been shown to produce a spectrum of biocompatibility assessments for the same material [23-26]. Evaluating the biocompatibility of a material using an in vitro cell culture assay, and from this, attempting to predict in vivo oral tissue responses is debateable [27]. It has been found that the biocompatibility assessments produced by cell culture assays have not been in agreement with animal *in vivo* biocompatibility implantation method [28-31]. These interpretational complications have provided the impetus for efforts to standardize the use of cytotoxicity assays, and regulate the context of their application at national and supranational levels.

Biocompatibility Testing Standards:

1. International standard ISO 7405: is entitled the Preclinical evaluation of biocompatibility of medical devices used in dentistry. This ISO document was prepared in combination with the World Dental Federation. It includes the preclinical testing of materials used in dentistry and supplements ISO 10993.
2. International standard ISO 10993: entitled the biological evaluation of medical devices is a combination of international and national standards and guidelines. The primary goal of it is protection of humans.

Guidelines ISO 7405 and ISO 1099 have mentioned certain standard practices for the biological evaluation of dental materials. They include:

1. It is incumbent upon the dental material manufacturer to select the suitable tests, based on the proposed use of the material, and known toxicity profile of the material.
2. A manufacturer may select one of the three cytotoxicity tests in preference to another due to cost, experience or other reasons.
3. Overall, there are four levels of analysis. New materials should be assessed using initial cytotoxicity and secondary tissue screening tests before extensive animal testing and clinical trials.
4. The test result should always be assessed and interpreted with respect to the manufacturers' stated use for the particular material.

Test Program for the Biological Testing of Dental Material:

The selection and assessment of any material or device intended for use in humans necessitates a structured evaluation. The test program for the biological testing of dental materials is divided into four stages which are described in Table 1. Phases I and II include initial tests, which are of a short duration, cost effective and simple. Only after completing these tests adequately does a material progress through the testing hierarchy to become assessed in preclinical animal usage studies (Phase III) prior to clinical testing with a limited number of patients (Phase IV).

Cytotoxicity Screening Methods:

General regulation for *in vitro* cytotoxicity testing is presented in ISO 10993-5. For *in vitro* cytotoxicity screening, the suggested testing methods include;

1. Direct cell culture and culture extract testing or barrier screening assays
2. Agar diffusion testing
3. Filter diffusion testing
4. Dentin barrier testing

VI. Nanorobots: The Futuristic Approach

Nanorobotics is the technology of constructing machines or robots at or close to the microscopic scale of nanometers. According to nanorobotic theory, nanorobots are microscopic in dimension, it would probably be essential for very large numbers of them to work together to perform microscopic and macroscopic tasks [32].

Nanorobots in medicine are used for the purpose of maintaining and guarding the human body against pathogens. They are 0.5-3 µ in diameter and are fabricated of parts with dimensions in the range of 1 to 100 nm. The main component used is carbon, which is in the form of diamond or fullerene nanocomposite due to its improved strength and chemical inertness. Other light elements such as nitrogen, oxygen can be used for special purposes. The peripheral passive diamond coating provides a smooth, flawless coating and evokes less response from the body's immune system.

The powering of nanorobots can be done by metabolising local glucose, oxygen and externally supplied acoustic energy. Their controlling can be done by on-board computers capable of performing around 1000 or more computations per second. A navigational network installed in the body provide extraordinary positional accuracy to all passing nanorobots and keep track of the numerous devices in the body. Nanorobots are able to distinguish between different cell types by testing their surface antigens. Building nanorobots involves sensors, power, actuators, control, communications and interfacial signals across spatial scales and between organic or inorganic as well as biotic or abiotic systems [33, 34]. When the task of the nanorobot is completed, they can be rescued by allowing them to excuse themselves via the usual human excretory channels. They can also be removed by active scavenger structures.

Dental applications of nanorobots:

1. Maintenance of oral hygiene
2. Cavity preparation and restoration
3. Tooth repair
4. Dentin hypersensitivity
5. Esthetic dentistry
6. Tooth repositioning
7. Inducing anaesthesia

All these current expansions in technology leads clinicians a step closer to nanorobots, as simple operating tools in the near future. Nanodentistry has strong potential to revolutionize dentistry to diagnose and treat diseases. Nanorobots will alter dentistry, health care and human life more intensely than other developments. Although investigation into nanorobots is still in its primary stages, the aptitude of such technology is endless!

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Table 1: The test program for the biological testing of dental materials

Test phase	1	Assays under evaluation, not yet recommended by guidelines			2	3	4
Test evaluations	General toxicity	Assays under evaluation, not yet recommended			Local tissue irritation	Preclinical	Clinical
Assay type	Monolayer cell culture	Monolayer cell culture	Embryonic organ culture	Tooth culture	Animal implantation	Animal usage assay	Patient trials
Tissue source	Permanent cell lines	Primary cell lines	Human or animal	Human or animal	Small animals; guinea-pig	Primates; Monkey	Human
Test type	*In vitro*	*In vitro*	*In vitro*	*In vitro*	*In vivo*	*In vivo*	*In vivo*
Test element	3T3 cell lines	Odontoblast cell lines	Papilla	Tooth slice	Subcutaneous implant	In situ teeth	In situ teeth
Experimental time (days)	$\geq$ 1 day	$\geq$ 1 day	21-35 days	$\geq$ 14 days	$\geq$ 365 days	70 -/+ 5 days	$\leq$ 365 days
Test suitability							
Tissue inflammation and irritation	No	No	No	No	Yes	Yes	Yes
Hypersensitivity	No	No	No	No	No	No	Yes
Carcinogenic or mutagenic	No	No	No	No	Yes	Yes	Yes
Cytotoxicity and dentinal injury	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bacterial leakage	No	No	No	No	No	Yes	Yes
Genetic engineering	No	No	No	Yes	No	Yes	Yes
Growth factor therapy	No	No	No	Yes	No	Yes	Yes
Stem cell therapy	No	No	No	Yes	No	Yes	Yes