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Application of Nanotechnology in Oral and Maxillofacial Surgery

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Abstract: *Nanotechnological developments have changed the perception of the world to the disease. Its potential has revolutionized the field of diagnostic imaging, medicine and surgery. With the use of nanomaterials drugs with narrow therapeutic index, resistant antibiotics or toxic at higher dose can easily and safely be administered. It also enables to perform surgeries at cellular level and can be integrated with various materials to impart antibacterial, as a scaffold or osteointegration properties.*

***Key Word**: **N**anotechnology; Orofacial pain management; Drug delivery system; Nanodiagnostics; oral cancer.*

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I. Introduction

As the fundamental building blocks of life fall within this size range of 10-9m, such as double strand DNA (diameter 2 nm), cell membranes (thickness of 10 nm) and eukaryotic cells (diameter 10 µm) nano-materials can bridge between both living systems and artificial devices.

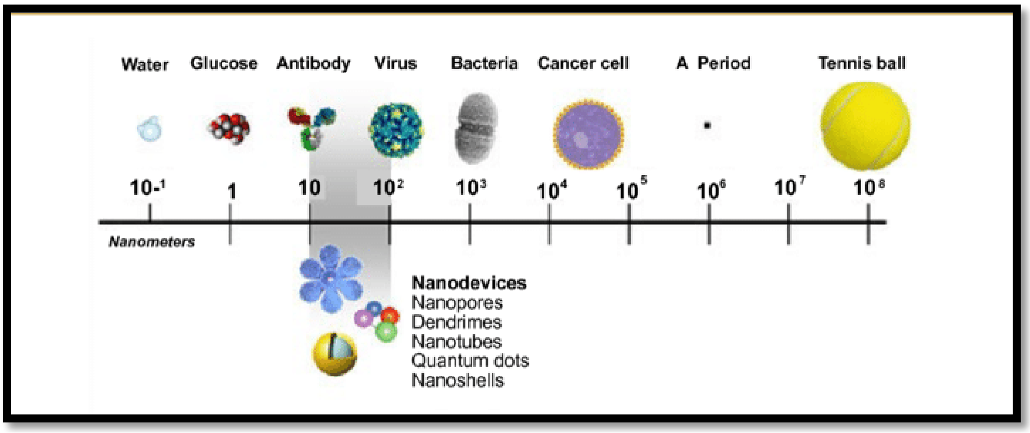
Nanotechnology can be defined as the science and engineering involved in the design, synthesis, characterization and application of materials and devices whose smallest functional organization in at least one dimension is on the nanometer scale (one-billionth of a meter).

According to the National Nanotechnology Initiative "nanotechnology is the direct manipulation of materials at the nanoscale."[1].

Due to their geometric arrangement they have an “extremely large surface area to the volume ratio” and because of small dimensions, electrons are spatially placed resulting in exceptional electrical, chemical, magnetic and optical properties. Nanotechnology gives us the ability to arrange atoms for achieving desired effectiveness and complete control on the structure of matter.

In this dissertation we will discuss recent developments in the field of nanotechnology and their application as diagnostic and therapeutic agents in oral and maxillofacial surgery.

II. NANOSCALE AND NANOSTRUCTURES



On the basis of phase composition nano materials can be classified [2] as-
1. Single phase solids- Crystalline and amorphous layers.
2. Matrix composites- coated particles.
3. Multi- phase systems- colloids aero gels and ferro-fluids.

On the basis of dimension nanomaterials can be classified as-
1. Nano rods, nano wires
2. Tubes, fibers, platelets
3. Particles, quantum dots, hollow spheres.

In 1958, the first nano-device 'Bucky ball' was designed.
It had the ability to alter the immune response by binding itself with anti-oxidants which stopped the mast cells to release histamine thus prevented allergic response [1].
Its invention provided researchers with a new field in which they can manipulate different elements to easily pass cellular barriers and its action can be controlled.
Examples,
1. Vibro-tactile devices,
2. Computer controlled local anesthetic system and
3. Jet injections

Various drugs with a narrow therapeutic index can be guided to the targeted area by conjugating them with nanomaterials. This allows optimum concentration of the drug at the desired site and prevents dose related side effects and toxicity.
Examples,
1. Trans-dermal patches:
2. Vaccines in which contain viral fragments which are the cause immune reactions. The viral fragment is replaced with nanoparticles attached macrophages and human dendritic cells. This selectively activates the T- cells and provides passive immunity without any allergic reactions [3].
3. Liposome's with nanoparticles containing anti- proliferative gene p53 DNA for the prevention of head and neck cancer
4. Nano bone replacement materials such as hydroxyl apatite tri-calcium phosphate etc. are available in market and is frequently used for osseous defects and cleft patients.

Nanomaterials
The ability to control nanoparticles surface chemistry by conjugating it with various ligands allows its manipulation at the molecular level. Using property various devices have been fabricated like,
Nanoscale Cantilevers:
These are flexible beams resembling a row of dividing board that can be engineered to bind to molecules associated with cancer.
• Nanopores:
These are tiny holes that allow DNA to pass through one strand at a time. They make DNA sequencing more efficient.
• Nanotubes:
These are carbon rods about half the diameter of a molecule of DNA that not only detect the presence of altered genes but also pinpoint the exact location of those changes.
• Quantum dots:
It helps in optical detection of gene proteins and cell assays in tumor and lymph node samples.
These nano-materials glow very brightly when illuminated with Ultra-violet light. Quantum dots can binds themselves to protein unique to cancer cells, literally bringing tumors to light.
• Dendimers:
They are highly branched macromolecules with a controlled three dimensional architecture. It has branches which makes it possible to attach other molecules like drugs, contrast agents etc. to the cancer cell surface.
Nanoshell:
These are microscopic beads having core of silica and a metallic outer layer which is usually gold. By manipulating the thickness of the layers making up the nanoshells scientists can design these beads to absorb near infra-red light, creating an intense heat which is lethal to cancer cells.
Digital dental imaging:
Nano-phosphor scintillations provide high quality images with low radiation dosages.

III. Synthesis of Nanoparticles

There are two main approaches
1. Top-down technique:
It begins with taking a microscopic material and incorporating smaller scale details into it. These molecules are rearranged to get the desired property.

2. Bottom- Up technique:
It begins by designing and synthesizing custom made molecule that has the ability to self replicate. These molecules are then organized into higher macro-scale structures [4].

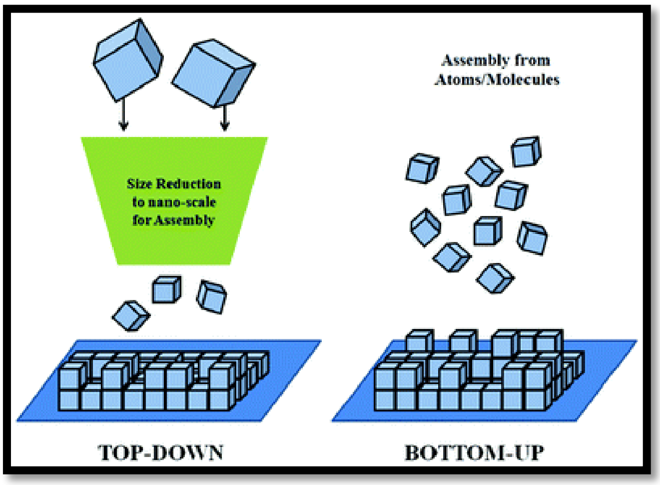


FIGURE 1 FABRICATION OF NANOMATERIALS

IV. Nanotechnology in the field of oral and maxillofacial surgery

Orofacial pain management:
Vibrotactile devices (battery operated vibrators VibraJact, DentalVibe, Accupal) use the concept of gate control theory through simultaneous activation of nerve fibers via vibrations.
Computer controlled local anesthesia system (CCLAD) (WandTM/ CompuDent^{TM} system) - control the flow rate of local anesthetic solution through light weight hand piece and foot control. ***Jet injection technology*** uses mechanical force creating sufficient pressure to push LA via small orifice. It creates a thin column of fluid which can penetrate soft tissues without needle.
Safety dental syringes reduce the risk of accidental needle prick injury by covering the needle with a sheath after it is removed from patient's tissue. Eg.Ultra Safety Plus XL syringe, UltraSafe Syringe, HypoSafety syringe with translucent plastic syringe barrel with retractable needle sheath, SafetyWandTM and RevVacTM Safety syringe.

Nano-encapsulation:
These includes Hollow spheres, core–shell, nanotubes and nano-composite are widely explored to provide a novel method for controlled drug delivery. E.g., *arestin* and minocycline are incorporated into microspheres for drug delivery by local means into the periodontal pocket.

Surface modified vertical silicone nanowires - delivers bio-molecule in mammalian cells without modifying its chemical structures thus allowing assessment of phenotypic sequences DNA, RNA, peptides, proteins and small molecules.

Trans-dermal drug delivery system - Bypasses the first pass metabolism and goes into systemic circulation with more targeted effect thus resulting in least toxicity.

Suture needles:
Which incorporates nano sized stainless steel crystals RK91 needle developed Sandvik Bioline, Sweden. Nano-tweezers are also under development, which will make cell surgery possible in near future.
For treatment of the malignant cells, photo-sensitive Quantum dots can be used.

Bone replacement materials:
Bone is a natural nanostructured composite (<100nm) composed of organic compound primarily collagen and reinforced with inorganic ones. It is this natural nanostructure that nanotechnology aims to match for its orthopedic and dental applications. E.g. Otim (hydroxyl apatite), VITOSSO (hydroxyl apatite and tricalcium phosphate) and NanOSS are nanoparticles used in cleft patients and osseous defects in the field of oral surgery and periodontics.

Ideal properties for bone graft material
1. Osteoinductive
2. Fully synthetic
3. Non sintered
4. Highly porous
5. Nanostructured
6. Absorbs intrinsic proteins into the nanopores
7. Degradation by osteoclasts cells
8. Very good processibility
9. No ionic solution products

Implants:

Use of Surface modifiers, such as application of thin ceramic layer of bioactive materials such as calcium phosphate (CP), hydroxyl apatite (HA), tri calcium phosphate (TCP) and bioactive glasses etc. were done to reduce the chances of implant failure. Upon implantation they form a carbonated apatite (HCA) layer on the implant surface, which is equivalent and structurally similar to the mineral phase of osseous tissue. It facilitates the osteo-integration between prosthesis and osseous tissue, thereby increasing long term integrity, faster healing time, enhanced bone formation and reduction of metallic ion release.

Popular coating methods are enameling, plasma spraying, RF sputtering, Sol-gel and pulse laser deposition.
Anodic oxidation Is being used to create micro and nano porosity at the surfaces of Ti- based implants and is considered a platform for drug delivery.
Alternative strategy for enhancing cellular adhesion, promotion of mineralization and production of matrix and marker proteins is done by molecular grafting and chemical treatment.
In molecular grafting proteins like fibronectin (FN), vitronectin (VN) laminin (LN) etc. are grafted in the extracellular matrix and on implant surface.
Recently the focus is shifted to the *signaling domain*, which composed of several amino acids (short peptides are preferred as it does not fold) present on extracellular matrix protein to interact with the cell membrane receptors.
Chemical treatment provides hydrophilic implant surface which promotes protein adhesion thus leading to accelerated integration of implant with wider bone-implant contact area.

V. Applications in the fields of oral cancer

Nanodiagnostics:
Nanodiagnostic is the use of nanodevices for the early identification of disease.

Direct intracellular imaging can be done using the optical confocal microscope and quantum dots attached with *Nanosensors.* These nano-sensors can be synthetic chromophores, fluorescent protein or fluorescent quantum dots linked DNA probes. This allows defective DNA imaging at molecular level.
On this basis *Lab-on-a–chip technology* is developed to completely analyze raw mixture. NanoChip uses nanoliter sample which can be quickly hybridized electrically, allowing its use in the field of biomedical research, genetic testing, medical diagnostic and drug discovery.
X- Shaped RNA nano particles have been created by University of Kentucky, which can carry four functional modules. They are thermodynamically and chemically stable and also resist degradation by RNAase in the blood stream for more than 6 hours in mice body. These designs enable precise binding with cancer cells thus regulating their genetic expression, cellular function and can effectively perform therapeutic and diagnostic functions.

Nanorobots:
Nanorobotics is the manufacture of ‘smart’ nanodevices that can subsequently be exploited for diagnostic and therapeutic purposes.
Nanorobots may release inhibitors, antagonists or down regulators for the pyrogenic pathway in a targeted fashion to selectively absorb the endogenous pyrogens, chemically modify them and release them back into the body in a harmless inactivated form.

Imaging:
The tumor targeting and detection on the basis of pygelated gold nanoparticles and surface enhanced Raman scattering (SERS) is being used.
The tumor looks brighter in pegylated SERS than the quantum dots in infrared spectrum of light.

Management of oral cancer:
The key feature of nanoparticles such as *Size* (10-100nm) enables it to bypass kidney, leak out of vessels to accumulate inside tumors, 50-100nm slightly charged nano structure can penetrate into the large tumors.
S*urface charge*-slightly positive/ negative on the nanostructure minimizes macrophages scavenging.

N*anoparticles targeting legends* or moieties (small molecule, peptide or antibodies) enhance its uptake into cancer cells (via transferrin receptors).

The nanoparticles can carry a large payload of drug and prevent it from degradation. This load can be sufficiently large to contain multiple target ligand which can bind to different cell receptor and can carry multiple layers of drug molecule.

Doxil™ PEG-liposome containing cytotoxic drug doxorubicin which is an approved drug for AIDS related Kaposi's sarcoma, ovarian cancer and multiple myeloma has 100times longer half life than free doxorubicin without cardio toxicity. Their decreased clearance rate increases tumor uptake and shows enhanced efficacy in treatment with fewer side effects which makes it superior to the other treatment modalities.

Therefore fluorescent quantum dots produce a higher contrast image at a lower cost than organic dyes which is used as a contrast media. But they are not in use as they are prepared from toxic elements [5].

Furthermore, nanoparticle size of the 10-100 nm, preferentially accumulate at tumor sites as tumors lack an effective lymphatic drainage system. Multifunctional nano particles can be manufactured that would detect, image, and then treat a tumor in future cancer treatment. *Kanzius RF therapy*- attaches microscopic nanoparticles to cancer cells and then "cooks" tumors and adjacent cancerous cells inside the body with radio waves which heat only the nanoparticles.

Rice University used nano shells of 120 nm diameter, coated with gold to kill cancer cells in mice. These nano shells are targeted to bond cancerous cells by conjugating with antibodies or peptides to the nano shell surface. Area of the tumor can be irradiated with an infrared laser, heating the gold sufficiently enough to kill the cancer cells.

For superficial tumors, Cadmium selenide nano particles in the form of quantum dots are used in the detection of tumors cells which upon exposure to ultraviolet light glow.

The surgeon injects these quantum dots into cancer cells which can be seen as glowing tumor. This can be used to assess the tumor margins easily after removal.

Nano particles are used in the cancer treatment for photodynamic therapy: These particles were inserted within the tumor get illuminated with light from the outside and glow. The metal particle absorbing these lights gets heated. High energy oxygen molecules are produced due to light which chemically react with tumors cell and destroy it, without reacting with the other body cells. It has gained importance as a *noninvasive technique for dealing with tumors*.

VI. Conclusion

Nanotechnology has the potential to revolutionize the field of medicine, imaging and surgery. With the use of nano-encapsulation, drugs with narrow therapeutic range and resistant antibiotics can provide therapeutic effect for the longer duration than the conventional medicine.

There are always risks associated with radiation exposure during radiography. With the use of quantum dots fluorescence of different wavelength, clear demarcation of cancer cells against healthy cells can be made.

In the field of surgery biodegradable nanostructure graft possesses anti-thrombogenic effects to increase the graft survival. Nano-scaffold can allow external control over the healing tissue which can be helpful in nerve regeneration and implant osteo-integration. Currently, nano tweezers and nanoneedles are under development which can further help in performing cell surgeries. Newer anti bacterial cotton integrated with inorganic nano-structured materials having good antibacterial activity is developed [5].
Nanotechnology and its materials provided several benefits but it has issues and challenges which restrain its use and must be dealt with. For example, due to the small size of nano materials they easily cross the blood brain barrier which can cause oxidative changes and inflammation.

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