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Najam ul Hassan [a] Maria Naz Bakhtiari [b] Dur E Nayab [c] Anam Arshad [d] Gul Shahnaz [e]

Pharmaceutical Nanotechnology: Nanomaterial Based Implants

Abstract

Implants are sterile and small cylinders of active drug utilized for slow absorption and prolong action should be administered below skin, muscle or tissue. Implants are based on the principle that many drugs and hormones are insoluble in aqueous solvents which enables them to provide slower dissolution for required therapeutic effects. Implants should be biocompatible with tissues of the human body. Its surface properties should be compliant depending on surface tension and roughness. Materials treated by multiple techniques for the nanoscale modified surface. These techniques include physical, chemical and mechanical modifications. Materials are selected on the basis of inertness, tolerance and activity in the body. Metals, ceramics, carbon materials and polymers are utilized for this. Carbon nanotubes, graphene, hydroxyapatite, zirconia, titanium alloys, silver, silica and polymers are used as implants. Applications of nanotechnology in implants are discussed.

Key Words: Nanomaterials, Implants, Nano Scaling

Introduction

Materials that are synthesized by man that are biocompatible to be inserted and grafted into the body and used for replacing tissues are implant biomaterials (Stephen JDG et al., 2017). It includes orthopaedic implants that are used in replacing joints, stabilising fractures, replacing ligaments and maintaining the spinal in the body (Kropf & Antunes AMDS, 2017). Dental implants replace teeth, for filling and coating purposes (Priyadasrini S et al., 2018). Brain implants are used for treating Parkinson's disease, epilepsy and depression. With advancements in nanotechnology, nanomaterials like metals, polymers, ceramics etc. are being deposited on implant surfaces like dental, brain implants, eye implants, and breast implants that are enhancing their adhesive properties on biological surfaces of the body and thus improving the performances of implants clinically.

History

The concept of implants was started in the Egyptian era and South American cultures. Recently treatment with implant materials has improved with the enhancement of the quality and quantity of implant materials. There have been reports of dental implants made of ivory and stone from China and Egypt. Ivory and gold implants from the 16th and 17th centuries have also been documented. Gold was used as a tooth root by Maglio in 1809. In the early 20th century, implants made of gold, lead, iridium, stainless steel, tantalum and cobalt alloy were reported. In the modern era, materials like synthetic polymers, metal alloys and ceramics have started replacing natural materials because of their better and more understandable results. Lambotte invented plants in the 1900s using materials such as aluminium, brass, red copper, gold, magnesium, and silver soft steel that had been plated in gold and nickel. Strock was the first scientist to achieve a 15-year implant survival rate by mounting a vitllium screw inside the bone and covering it with a porcelain crown (Saini M et al., 2015).

[a] M.phil Scholar, Department of Pharmacy, Faculty of Biological Sciences, Quaid-i-Azam University, Islamabad, Pakistan.
[b] M.phil, Department of Pharmacy, The Islamia University of Bahawalpur, Punjab, Pakistan.
(Email: Khan.mahi221@gmail.com)
[c] M.phil, Department of Pharmacy, The Islamia University of Bahawalpur, Punjab, Pakistan.
[d] Pharm-D, Department of Pharmacy, Lahore College for Women University, Lahore, Punjab, Pakistan.
[e] Associate Professor, Department of Pharmacy, Faculty of Biological Sciences,
Quaid-i-Azam University, Islamabad, Pakistan.

Characteristics of implant materials

For better performance, bio-implants should have specific characteristic properties. All properties of compatibility, manufacturing, and mechanical properties criteria should be fulfilled. The implant should have the following properties (Stephen JDG et al., 2017; Saini et al., 2015):

- To avoid severe tissue adverse reactions, it should be biocompatible to tissues.
- It must be compatible with the human body
- It must show resistance to degradation
- Must have acceptable strength so that it can easily load.
- Wear resistant
- Ductility of 8% for dental implants
- Modulus of elasticity (18 GPa) to reduce bone resorption
- It should have high yield strength, and tensile strength to avoid fractures.

Surface Properties of Implants

Surface tension and surface energy of implants affect the adsorption of proteins or other materials on the surface. The wettability of the surface is also determined by it.

Surface Roughness

The surface area of the implant should be enhanced, by altering surface roughness, thus improving response toward cells and increasing its adhesion property. Implant surfaces are divided on the basis of different criteria.

According to the roughness of the surface:

- Slightly rough (0.5-1m)
- Intermediate roughness (1-2m)
- Rough (2-3m)

Based on texture:

- Concave texture (additive treatment with HPa coating or spraying plasma)
- Convex texture (etching or blasting)

Based on the orientation of surface irregularities:

- Isotropic surfaces (same topography)
- Anisotropic surfaces (clear directions and differ in roughness) (Saini M et al., 2015).

Techniques used for nanoscale surface modification

Biomaterials structures are synthesized using a top-down approach and a bottom-up approach. Different methods were used for modifying the surfaces of biomaterials. The only issue in some of the techniques is the prolonged existence of surface modification and its robustness during the purification of implants while being used clinically. By surface modification contact of an implant to a bio surface enhances and thus improves clinical performance. The techniques of surface modification are divided into mechanical, and chemical surface modification.

Mechanical Techniques

Mechanical removal or erosion processes are used to get superficial surfaces.

As a result, surface topography with enhanced surface area improves the adhesive property of implant surfaces. This mechanical method is limited to the microscale. SMAT (surface modification attrition treatment) has now been developed to modify surfaces on the nanoscale. The particle size in SMAT is less than 100nm. Nanoscale roughening of surfaces yields a high percentage of particle boundaries that have great adhesion to osteoblast cells. The grain sizes in human bone are 20-80nm and 2-3 nm for bone implants. Because of the resulting improved adhesive property, it shows excellent cellular reactions. However, SMAT is limited in controlling intracellular responses.

Chemical techniques

In this technique, proteins or peptides are grafted on implant surfaces making covalent bonds. Three major techniques for treating metal surfaces include physicochemical adsorption, molecular covalent binding and inclusion of peptides onto carrier molecules.

Anodic Oxidation:

It is electrochemical in which oxide film is formed on the surface by electrode reactions through oxygen and metal ion diffusion. Electrolytes like acids (H_2SO_4, acetic acid, H_3PO_4) are used to enhance adhesion. The benefit of anodic oxidation is the control that can be altered like electrode potential, temperature, electrolyte and current. It controls the diameter of nanotubes <100nm. Carbon nanotubes, pillar-like structures or nanocrystalline hydroxyapatite coatings have been fabricated as surface modifications

Chemical Vapor Deposition:

It uses chemical reactions in the gas phase in the presence of a sample surface that results in the deposition of nonreactive compounds on the surface of the substrate. To achieve mechanical and biological improvements, diamond films have been deposited on titanium surfaces.

Acid/Alkali Treatment:

It is the most popular method for achieving Nano surface properties on implant surfaces. A thin oxide surface layer of diameter <10nm is obtained through acid etching. The antibacterial effects have been improved using hydrofluoric acid that attaches fluorine to surfaces. This oxidative process generates Nano pits on metal alloys. By controlling temperature and acid/alkali exposure length, surface properties like wettability and roughness can be transformed. This treatment increases apatite formation, and pore size and improves bioactivity and resistance to corrosion of implant materials.

Sol-Gel Transition reactions:

It is used for changing metal surface characteristics that deposit a coating of <100μm.The reaction interface is within the solution. This process was utilized in investigating the function of TiO2 nanoparticles, in which nanoparticles are inserted on the surface of metals.

Oxidative Nano pattering:

This technique is used to deposit oxides or Nano chemical moieties of diameter 20-100nmc on the surfaces. It enhances the bioactivity of implants.

Physical Techniques

Ion implantation: It utilizes physical spraying of coating or rearrangement of ions such as fluorine, and sodium. The depth and concentration of ions can be controlled.

Plasma deposition

By depositing plasma under vacuum conditions, plasma gas excitation occurs by radiofrequency, electrons or microwaves endures surface reactions.

Vapour deposition: Under vacuum conditions, a thin metal is deposited to be coated on the surface. In electron beam vapour deposition, a material is heated on which electrons are deposited before it is condensed from vapour form and coated on the surface. It enhances Nano nodules or Nano rough layers.

Thermal oxidation

The crystalline structure of metals like titanium can be altered through heating and then cooling of surfaces that yield stress and modify surfaces, thus enhancing adhesion property. (Staruch RMT et al., 2016)

Nanostructured implants:

Nanostructures are structures having dimensions within the range of nanoscale (between 0.1 nm and 100nm). Increased development of nanostructures-based implant materials has been shown. By integrating the nanostructures in implant biomaterials, we can get exceptional structural and mechanical properties.

Types of implant materials

On the basis of bioactivity implant material:

Bio inert: Titanium, titanium alloys, Al oxide, Zirconium oxide

Bio tolerant: Gold, stainless steel, niobium. Tantalum, polymethylmethacrylate

Bioactive: tricalcium phosphate, carbon-silicon, bio-glass, and hydroxyapatite.

On the basis of materials:

Table 1. Types of implant **materials** (Dutta AC. et al., 2017, Velmurugan D 2017).

Metals:	Titanium, titanium alloys, stainless steel. tantalum, silver, cobalt-chromium alloys
Ceramics	Metallic oxides (Alumina, Zirconia), hydroxyapatite, bioglass (SiO_2/CaO)
Carbon materials	Carbon nanotubes, Graphene, Diamond.
Polymers	Natural polymers (chitosan, collagen, hyaluronic acid) Synthetic polymers (Poly Lactic acid (PLA), polyethene, poly lactic-co-glycolic acid (PLGA), polymethylmethacrylate, poly(3,4-ethylene dioxythiophene) (PEDOT)

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Nanoparticles used in Implants:

Table 2. Nanomaterial implants, their uses, benefits and side effects. (Munhoz AM, 2017, Priyadasrini S et al., 2018, Mazaheri, et al., 2015).

Nanomaterials	Use	Advantages	Side effects
Carbon nanotubes	Teeth filling and coating Bone implant	It provides Greater surface area and brings active moieties to live cells. Can easily attach to biological Membranes. Have good mechanical strength.	Nanotubes when crossed by cell membranes, can produce inflammatory responses and fibrotic reactions
Graphene	Dental implant, bone implant	High tensile strength and thermal and mechanical conductivity. fracture-resistant, low-density, treated bacterial biofilm	Depending on the size, shape, and oxidation state of graphene, metallic impurities may be incorporated during processing and cause harmful reactions.
hydroxyapatite	As a cavity filler, reduces dental hypersensitivity, and repairs enamel surfaces. Provides bone structural support and bone bonding. By coating on magnesium used for bone cancer hyperthermia	Nano-sized Hap can easily be incorporated into dental tubules. It is biocompatible with teeth and bone, protects the teeth by making a film and is adsorbed to enamel. Slow biodegradation rate. Excellent osteointegration	It makes a protein-particle complex by binding to proteins, which are phagocytosed by macrophages. It is distributed through blood in different organs. The toxicity of nanoparticles affects inflammatory reactions and signalling pathways.
Zirconia	Reduces bacterial adhesion, and provides protection and polishing.	Low cytotoxicity. Biocompatible and resistant to fractures.	May cause damage to DNA in T-cells and cell death occurs. On exposure to zirconium, cell proliferation is inhibited. It induces oxidative stress that causes cell mortality. As it can cross cell barriers, it incorporates into cells and stops the cell cycling process.
Titanium alloys	Dental implants. Bone implants	Long-term effect. By surface modification properties like less bacterial attachment and hardness improved. Osteoconductive Anticorrosive	More toxic to the human body. It can enter the body through inhalation. Produces cancer. It can cross BBB and enter brain regions. Exposure to TiO_2 results in microglia production, ROS production activation of signaling pathways resulting in cell death.
Silver	Antimicrobial agent	Decrease bacterial colonization by penetrating bacterial membranes. It has good biocompatibility and	Silver-based nanoparticles produce toxicity due to ROS revelation. It is also involved in the production of oxidative

Nanomaterials	Use	Advantages	Side effects
		provides an antibacterial effect for a long time.	stress and gene toxicity, distortion of actin, stimulation of hemocyte phagocytosis and inhibits Na-K ATPase.
Silica	Dental filling, as a polishing agent, prevents bacterial contamination and promotes bone regeneration, in breast implants	Good biocompatibility, low density, can easily adsorb. cost-effectiveness, have reduced roughness	Severe inflammatory response, bleeding when silica released on rupturing. It can cause lung cancer and silicosis. Can cause apoptotic cell death. It also damages genes
Polymers	Used in Nano coating and 2D/3D scaffolds	Natural polymers provide a better substrate for all binding because of little immune response. Synthetic polymers are biodegradable, biocompatible, stable, inert and have low ductility.	

Applications of Nanomaterial Implants:

Following are the main applications of Nanomaterial implants

1. Nanotechnology Brain implants
2. Nanotechnology Eye implants
3. Nanotechnology Breast implants
4. Nanotechnology Dental implants
5. Nanotechnology Orthopedic implants
6. Nanotechnology Bone implants
7. Drug Delivery System

Nanotechnology Bone implants

Advancements in nanotechnology play a role in the development of bone implants that incorporate surrounding bone tissues which prevent inflammation, bacterial growth and the relapse of bone cancer. (Foresight Institute, 2009)

With age, bones become very brittle which increases the risk of bone fracture. The acute bone fracture can be filled with bone content, but, if it's chronic then there is a need for more everlasting metal implants i.e. titanium and its alloys. Implant is not only to fill the fracture gap with a strong material but it is also used to increase bone growth and to maintain bone function. (Foresight Institute, 2009)

Previously bone implants were composed of inert materials which consist of thick, impervious tissue layers formed outside an implant. However, these designs make the implant distort with time and lose its strength around 10-15 years, which leads to severe pain (Foresight Institute, 2009).

After insertion of implants proteins absorb instantaneously to the implant when cells interact with the protein layer. Numerous materials have been improved which include titanium and its alloys, porous polymers, bone cement and hydroxyapatite. Changes occur on the surface while bulk material properties remain unchanged which enhances the interaction with proteins. This results in the adherence of osteoblasts to the implant and triggers them to grow more bone.

The 'Smarter implants' are developing that are able to sense the type of tissue that is growing and release the drugs that improve tissue growth. This advancement avoids complications such as infection, inflammation, implant loosening and the relapse of cancer. Investigations are being made to develop implants that are built to protect the body from infection or inhibit cancer growth e.g. selenium (Foresight Institute, 2009).

Biomechanical analysis reveals that the push-in forces for implants that were sandblasted, alkali- and heat-treated were greater than those of implants that were merely sand-blasted. These findings are further supported by a histomorphometric examination that, upon implantation, demonstrates increased bone-to-implant contact on the surface of the removed, nanomodified implants. (Foresight Institute, 2009)

Breast implant technology

Breast implants use elastomer interface modification to improve their surface roughness. The "micro/macro texturization", multiple interfacial changes had been done to raise roughness. Materials like Biocell surface, an aggressive open-pore textured surface treated with a lost salt technique in which the entire elastomer shell is embedded on a bed of finely graded salt with low pressure, and Siltex texturing, a patterned surface created as a negative contact imprint off of a texturing foam, can be used for this (Munhoz AM, Pompeo FSD & Mezerville RD 2017).

According to the scanning electron microscopy assessment, the latter depressions have irregular sizes because they have been treated with salt in several dimensions. The diameter and depth of the depressions range from 600 to 800 µm (0.6–0.8 mm) and 150 to 200 µm (0.15–0.2 mm), respectively. Each of these depressions has a raised edge that increases to a total depth of 70 to 90 µm. The surface properties can be changed by different techniques, they support the mechanism of bio integration more than that of a smooth surface (Munhoz AM, Pompeo FSD & Mezerville RD, 2017).

Implantable nanomaterials for orthopedics

The alloys made of stainless steel, cobalt-chrome, titanium, magnesium, HA, alumina, zirconia, polymethylmethacrylate (PMMA), poly (lactic acid) (PLA), carbon fibre/polyether ether-ketone, and carbon fibre/ultra-high molecular weight polyethene are the most often used alternatives to bon (Mazaheri *et al*., 2015).

Occasionally, mechanical properties and biocompatibility can be increased by Nanostructuring of metallic implantable devices. Titanium (Ti) and its alloys are among the bulk nanocrystalline (NC; <100 nm) and ultrafine-grained (UFG; ~100–500 nm) metals that have shown tremendous promise because of their exceptional strength, profound ductility, fair exhaustion life, good damage resistance, and safe ion release.

The use of selenium has a potential anticancer property. It's a trace bio-element in the human body. Bio ceramics are increasingly used materials for orthopaedic purposes, but their brittleness limits their usage. Nanostructuring of different bioceramics, such as zirconia, titania, alumina, calcium phosphates, bioactive glass (BG), and HA, is one area of advancement (Mazaheri *et al*., 2015).

Cancer therapy

Bone cancer results in skeletal complications which pose a great threat to health. Osteosarcoma is a rapidly growing tumour of bone in adults and neonates. Bone is particularly the target site for cancer growth along with multiplication and specifically has a role in prostate and breast cancer because they have a high chance of occurrence of bone tumour. Bone metastases are being cured by surgery, radiotherapy, systemic chemotherapy, bisphosphonates, and radioisotopes. Advancements have been made in the production of multitasking bio nanomaterials which directly target tumours in bone and release drugs over there. Magnetite can be modified to cause hyperthermia. In order to treat bone cancer, researchers have created a collagen/HA composite biomaterial that is enhanced with magnetite and can be used as a grafting material or to produce hyperthermia. They have created a 3D Nano magnetite/CS rod that causes bone cancers to become locally hyperthermic. The dimensions of this composite were roughly 400 µm, with pores that were roughly 0.2 µm in size. It has been shown that at concentrations of 30 mass per cent or less, magnetite masses were closely encircled within the cages of rod-shaped HA particles (Mazaheri *et al*., 2015).

Eye

The retinal implant uses nanotechnology blended with wireless electronics that have the property to respond to light in the retina. It works by interacting with cortical neurons in a retina prosthesis through an array of optoelectronic nanowires. (Business Research, 2017)

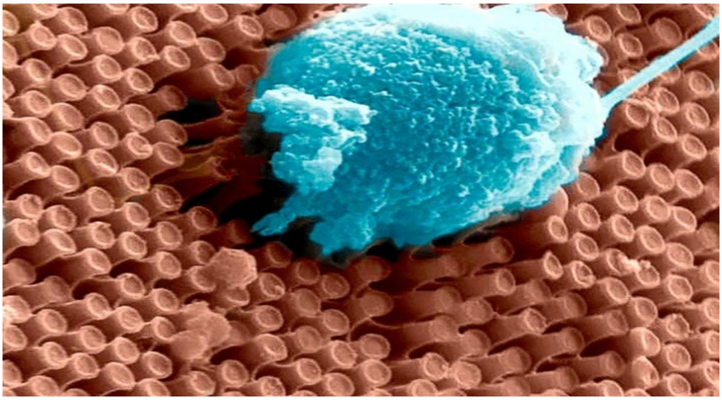

Figure 1. Primary cortical neurons are cultured on the surface of an array of optoelectronic nanowires. Here a neuron is pulling the nanowires, indicating the cell is doing well on this material.

The silicon nanowires are incorporated throughout the prototype prosthesis that is able to sense light and then accordingly stimulate the retina electrically. Silicon Nanowires increase the resolution meanwhile a wireless device transfers power and data to the nanowires. Retinal cells are stimulated by rods and cons cells which are imitated by these nanowires. By use of a telemetry system with inductive powering. The prosthesis is powered by power that is wirelessly transferred to the implant from outside the body. This apparatus keeps energy losses from occurring and recycles electrostatic energy inside the inductive resonant tank throughout the stimulation operation. Testing of the gadget on animals is being done to prove its clinical use in restoring vision in humans with retinal degeneration (Business Research, 2017).

Through The NR600 Implant, Nano Retina device the damaged photoreceptor cells are replaced and the remaining retinal cells are activated by electrical stimulation.

Dental implant surgery

In dental implant surgery, damaged or missing teeth are replaced with artificial teeth that look and feel just like real ones, with the tooth roots replaced with metal. It is a substitute for dentures, which have problems with fastening and support. It involves several procedures which depend on the condition of the tooth jaw (Mayo Care Clinic, 2018).

Figure 2.

Advantages

- It provides solid support for your new teeth
- It improves the tooth healing process around the implant.
- The materials cannot be damaged or destroyed
- It doesn't slip
- Patient compliance

In the following conditions dental implants are used:

- Jawbone failed to develop fully
- Not able to wear dentures
- To Enhance speech function

The following should be considered while having implants:

- Bone mass should be enough to hold the implants
- Must have healthy oral tissues
- Individuals must be healthy and committed to the process
- No smoking

Implants in Drug Delivery

Mostly drugs were given by enteric route, as liquids or in solid forms. These problems related to oral dosage forms can be modified using new dosage forms. (Dash & Cudworth, 1998). As time passes by, One new delivery system is required that can give a Constant rate of drug release to the required site. Due to this reason, new drug delivery Formulations were formulated to Standardize the therapeutic properties of new drug products and Increase their safety, effectiveness and reliability (Dash & Cudworth, 1998). An example of these types of systems is Implantable drug delivery systems (IDDS). Implantable systems can be classified into three main classes.

1-Biodegradable or non-biodegradable implants:

They exist as reservoir systems or as monolithic systems. The solubility and diffusion coefficient of the drug in the polymer, the drug concentration, and the polymer's in vivo dissolution kinetics—all play a role in the release rate of pharmaceuticals in these systems, just like in biodegradable systems (Dash & Cudworth, 1998).

2-Implantable pump systems:

An implantable pump modifies the remote-controlled flow rate and microtechnology of electronic devices to enable regulated drug delivery by maintaining a steady pressure differential (Dash & Cudworth, 1998).

3-Atypical implants.

It is made up of recently created materials such as transurethral implants for impotence, intraocular implants for glaucoma, and ceramic hydroxyapatite antibacterial systems beneficial in treating bone infections (Dash & Cudworth, 1998).

The main uses of these Implants include target delivery of drugs at a controlled rate, minimum drug needed for this disease Condition, fewer side effects, and Increased efficacy of treatment. Implants like systems have the capability of protecting drugs which are not stable inside the body and there might be a need for less frequent dosing times. (Dash & Cudworth, 1998).

Conclusion

For safe and effective delivery of drugs along with prolonged action, Implants can be utilized by combining the material with a nano process. Implant manufacturing increases the use of benefits of various biomaterials.

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