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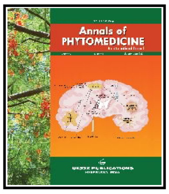

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Applications of nanomaterials in biomedical science

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Abstract

Nanotechnology is an emergent and evolving field of science. Nanotechnology simply means the development of engineered materials that have at least one of their dimensions less than 100 nanometers. Nanomaterials are of various types, and can be composed and analyzed by different methods. Nanotechnology has the capacity to improve the quality and durability of products which are synthesized by existing technologies in different fields such as electronics, textiles, aviation, optics and biomedical sciences. Focusing more on the application of nanomaterials in biomedical sciences, nanomaterials can help in various purposes such as diagnosis, delivering drugs, therapy, gene editing, vaccines, artificial implants, hyperthermia, photoablation, coating medical equipment, wound dressings and medicinal robotics. Some of the properties of nanomaterials which makes their use possible for above mentioned applications are their huge surface to volume ratio, ease of functionalizing by capping them with biocompatible materials, and their unique optical and magnetic properties. Though nanomaterials can be used for a variety of biomedical applications (as mentioned above), most of them are at the preclinical research stage and have not yet been tested directly on humans due to various hypothesized risk factors such as nanotoxicology and proposed environmental concerns. If, all these challenges are taken into consideration and due precautions are taken to overcome them, nanotechnology will scale great heights and advance the branch of biomedical sciences in near future.

1. Introduction

The idea of nanomaterials and its possible applications was first given by Richard Feynman, for which he was honored with the Nobel prize in 1959. Nanomaterials are present in nature and can also be artificially synthesized in the laboratory by various substances such as metal ions, metal oxides and lipids. The textbook definition of nanomaterials is, "an object which has at least one of its dimensions less than 100 nanometers". Materials which are synthesized artificially to such a small scale are known as the engineered nanomaterials. When a bulk substance is divided, the particles synthesized have an enormously huge surface to volume ratio in comparison to the materials from which they are synthesized. This gives them unique electrical, magnetic, and optical properties, which are used for electronic, medicinal and many other such applications. Moreover, nanotechnology utilizes particle sizes that are slightly larger than the molecule and smaller than a cell, hence these nanomaterials can move freely in and out of cells (Ramos *et al.,* 2017).

1.1 Classification of nanomaterials

Nanomaterials are classified on the basis of numerous characteristics, such as from the materials they are synthesized, their morphology, size, structure and phase of matter contained.

On the basis of materials from which nanomaterials are synthesized, they are differentiated into various types; namely, metallic nanomaterials (gold nanoparticles), non-metallic nanomaterials (carbon nanotubes), metal oxide nanomaterials (titanium oxide nanomaterials), semiconductor nanomaterials (silicon-based nanomaterials) and organic nanomaterials (liposomes) (Khan *et. al.,* 2017).

Size, structure and morphology are also important attributes of nanomaterial classification, depending on this the nanomaterials whose all three dimensions fall in the nanoscale range are known as zero-dimensional nanomaterials for example, nanospheres; the ones whose only two dimensions fall in the nanoscale are called as one-dimensional nanomaterials or 'nanofibers' (hollow fibers are called nanotubes whereas solid fibers are called as nanorods); the nanomaterials of which only one dimension is in the nanoscale range are called as two-dimensional nanomaterials or 'nanoplates'. Three-dimensional nanomaterials are the ones which are not limited to the nanoscale range in any of the three dimensions. These have all three dimensions above 100 nm, for example, nanolayers (polycrystals) (Joudeh and Linke, 2022). The general classification of nanomaterials is represented in Figure 1.

Based on the phase of the matter contained, nanomaterials are divided into completely solid materials called 'nanocomposites', solid or liquid matrix containing a gas called as 'nanofoams', solid materials having pores known as 'nanoporous' materials and nanomaterials composed of crystalline granules called as 'nanocrystalline' materials (Joudeh and Linke, 2022).

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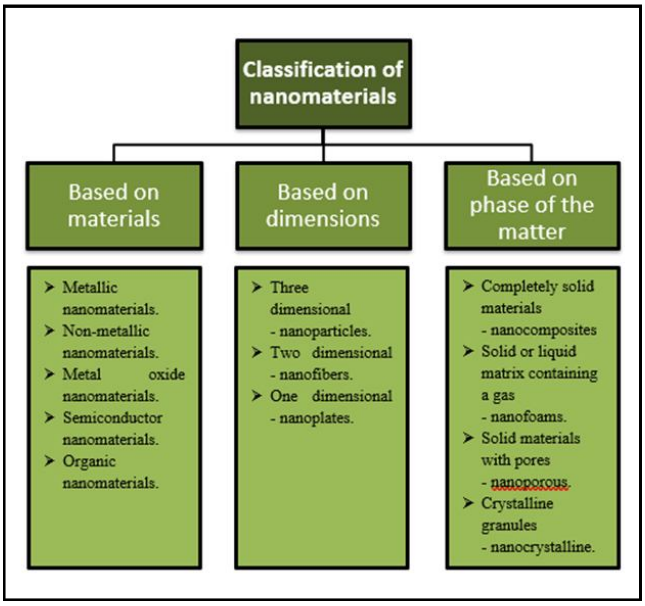

Figure 1: Classification of nanomaterials.

1.2 Synthesis of nanomaterials

Nanomaterials are synthesized in two ways, top-down approach, in which parent substance is fragmented into smaller particles, for example, synthesis of metal nanoparticles, and bottom-up approach, wherein tiny components are aggregated into complex assemblies, for example, formation of carbon nanotubes. Nanomaterials can be synthesized by any of the above-mentioned phenomenon by physical, chemical or biological processes:

1.2.1 Physical processes

In physical processes, we have various techniques such as ball milling, melt mixing, sputtering deposition, chemical vapor deposition and others. In ball milling, bulk substance is grounded into a powered form with the help of a container having steel balls. In melt mixing, solid is converted into a gaseous phase, which gets deposited on a solid cold surface, and the final product is scrapped off. If, a laser is used for vaporization, then this technique is called ablation, whereas sputtering deposition and chemical vapor deposition is used to give a nanoparticle coating on various materials (Baig *et al.,* 2021).

1.2.2 Chemical processes

These techniques are simpler and energetically more feasible than the physical processes. The basic phenomenon in almost all of the chemical processes for synthesis of nanomaterials is "reduction" wherein metallic salts or acids are reduced to form nanoparticles. For example, gold particles can be generated through reduction of chloroauric acid ($HAuCl_4$) using tri-sodium citrate ($Na_3C_6H_5O_7$). Another important technique of chemical synthesis of nanomaterials is the Sol - Gel technique that is used for the synthesis of polymeric materials such as nanorods and nanotubes. Sols are basically solid particles in colloids which are converted into gels which are nothing but the liquid containing polymers by the process of polycondensation. Another important and widely used chemical process of nanomaterial synthesis is the synthesis of liposomes. In this technique, the lipid containing organic solvent is evaporated, which leaves behind dry film of lipids, which is further hydrated using an aqueous solution containing the hydrophilic drugs. Finally, vesicles are formed encapsulating the drug of interest, the vesicle entrapment efficiency can be increased by sonication (Baig *et al.,* 2021).

1.2.3 Biological processes

Biological processes are one of the safest and eco-friendly techniques in the production of nanomaterials, therefore this type of synthesis of nanomaterials is also known as "green synthesis". Microorganisms such as fungi and bacteria, are used in the production of nanomaterials, for example, fungi *Fusarium oxysporum* when challenged with gold or silver salts, is capable of producing the respective nanoparticles (Naimi-Shamel *et al.,* 2019), *Klebsiella pneumonia* is used to synthesize CdS (Cadmium sulfide) nanoparticles from cadmium nitrate (Rajeshkumar *et al.,* 2014). Plant extracts are also used for synthesizing nanoparticles, for example, brown seaweed (*S. myriocystom*) leaf extract contains a substance called 'Fucoidan' which helps in preparing zinc oxide nanoparticles. Similarly, *Murray koenigii* leaf extract has different metabolites like alkaloids and phenols, which are capable of synthesizing silver nanoparticles, from appropriate silver compounds (Kulkarni, 2014).

1.3 Confirmation and analysis of synthesized nanomaterials

After the nanomaterials are synthesized by various techniques mentioned above, the synthesis of nanomaterials should be confirmed by various techniques and along with that the morphology of the synthesized nanomaterials should also be studied. A few techniques studied for analysis and confirmation of synthesized nanomaterials are UV spectroscopy, transmission electron microscopy (TEM) and X-ray diffraction technique (Kulkarni, 2014).

1.3.1 Ultraviolet spectroscopy

In this technique, the percentage of incident ultraviolet rays absorbed by the analyte is quantified and on the basis of that the analyte under study is characterized. The nanomaterials have unique optical properties due to varying size, shape and refractive indices, making them one of the best samples for analysis by UV spectroscopy. Basically, the transition of color of the sample is observed as a signal for the beginning of synthesis of nanomaterials. Thus, there is a marked difference between the absorbance of the light by the sample before starting the synthesis of nanomaterials and after the complete synthesis of nanomaterials. For example, when we start the synthesis of gold nanoparticles, initially the sample solution is colorless but as the time passes and the concentration of nanoparticles in the sample increases, the sample color turns from colorless to purple to red. Similarly, during production of silver nanoparticles, the color of the analyte solutions changes from yellow to reddish brown and its wavelength maxima is around 430 nm (Kulkarni, 2014; George *et al.,* 2017).

1.3.2 Transmission and scanning electron microscopy

Transmission electron microscopy is useful to determine size of synthesized nanomaterials. The principle remains the same as that of our classical microscope, the only difference here is that we use a beam of electrons in place of a source of light, and the image obtained cannot be seen by the naked eyes but instead is projected onto a screen. The synthesized nanomaterials are citrate stabilized and placed on the positively charged silicon grid plate, the electrons are bombarded onto the sample, and the image of the sample is obtained by various computer softwares, which is finally projected on a screen including the details of all the relevant measurements. Similarly, scanning electron microscopy can be used for characterization of nanostructures, the exposure of the electrons to the sample reveals details about the texture and chemical compositions of the sample (Kaiser, 2007).

1.3.3 X-ray diffraction

It is helpful to investigate and observe structural and overall surface morphology of the synthesized nanomaterials. The phenomenon is based on Bragg's law which links wavelength of incident light, diffraction angle and distance between two lattice planes. Diffracted X-rays are detected, calculations are done *via* computer software and finally the structural model of the nanomaterials is built (Dorofeev *et al.,* 2012).

2. Applications of nanomaterials in biomedical sciences

Nanotechnology is exploited in a number of applications, majorly in the domain of electronics, textiles, optics, aviation and medicines. In this section, we will be speculating on the applications of the nanomaterials in biomedical sciences.

The branch of nanotechnology which deals with biomedical applications is known as "Nanomedicine", which can be defined as a way to comprehensively detect, repair, control, monitor, construct, protect and enhance human physiological systems using engineered nanostructures and device. The properties of nanomaterials which support their use for such applications are their mechanical strength, thermal stability, catalytic activities, and enhanced electrical, magnetic and optical properties than the bulk substances from which they are synthesized (Ramos *et al.,* 2017). The nanomaterials in biomedicine are used for various applications such as delivery of drugs, diagnosis, therapy, photoablation, prosthetics and implants, vaccines, gene therapy, wound dressings and nanorobotics.

2.1 Applications of nanomaterials in diagnosis

Nanomaterials are used in the field of diagnosis; they play a pivotal role in detection of diseases like cancer at early levels of progression. Nanotechnology based diagnostic tools are more sensitive than conventional diagnostic tools. Nanomaterials are mainly used as contrasting agents in bioimaging, since their surfaces are designed with imaging agents due to having a larger surface area in comparison to their volume. Absorption in NIR has paved the way for use of metal nanomaterials in the domain of detection. Gold nanoparticle coating on suitable substrates or addition to appropriate substrates helps in increasing luminescence (Bhattacharya and Mukherjee, 2008). Gold, silver and bismuth are used as contrasting agents in computerized tomography as they have higher X-ray absorption along with prolonged blood circulation duration than other conventionally used contrasting agents. Magnetic resonance imaging (MRI) is another phenomenon which gives better contrast while analyzing the soft tissues. Traditionally, gadolinium-based contrast agents were used in this technique but compared to them nanoparticle-based contrast agents can give better contrast, higher retention time and lesser side effects. Iron oxide nanoparticles are majorly used for this purpose (Tong *et al.,* 2012). Zinc oxide-based nanomaterials, like the zinc oxide nanowires when functionalized and made biocompatible can be used for diagnosis of cancer due to its natural fluorescence properties (Hong *et al.,* 2011). Fe-Pt bimetallic nanoparticles can be exploited as contrasting agents in the MRI and CT detection techniques. Cytotoxicity of Fe-Pt has been tested against cervical cancer cell lines and vero cell lines and thus are proven to be nontoxic. They can also be conjugated to various antibodies like the anti-Her2 antibodies for target specificity. The Fe-Pt nanoparticles have also been coated by silica so as to incorporate fluorescent dye-fluorescein-isothiocyanate (FITC), such particles can be detected by both confocal laser microscopy and MRI (Lai *et al.,* 2012). Similarly, carbon nanotubes can be conjugated to semiconductor nanocrystals, conventional fluorophores and quantum dots either directly or indirectly through biotin-streptavidin linkages and these complexes can be used for the diagnostic purpose.

Quantum dots are another interesting tool in nanotechnology which are used to detect early DNA damages. These are tiny crystals which emit light on stimulation with the UV light. This phenomenon is used to detect cancerous cells by targeting latex beads packed with quantum dots specific for the DNA sequences related to cancer cells. In short, these quantum dots act as probes for the detection of cancerous cells.

There are also certain unique nano mechanical devices like silicon-based cantilevers which can be used for disease detection purposes, they are very sensitive towards their target, and can detect the diseased cells even if their population is very low, as a result helping in the early detection of the disease. Cantilevers are tiny bars which are anchored at one end specially designed to bind cancer associated molecules. When they bind their desired targets, they tend to bend, by monitoring the extent of this bending it is inferred whether cancer related molecules are present or not (Navalakhe and Nandedkar, 2007).

2.2 Applications of nanomaterials in drug delivery

Traditionally "only drugs" are taken orally or through intravenous administrations against a particular disease. However, this method of "only drug" administration has many disadvantages such as, the drugs sometimes not reaching the desired target, the possibility of them acting on non-target healthy cells and the quick degradation of drugs which have a low half-life. To counter these problems, nanomaterials can be used for drug delivery since they can ensure targeted delivery of drugs and controlled and slow release of drugs at desired sites. This minimizes the off-target effects of the drugs on healthy body cells, prolongs the degradation time of the drugs and minimizes toxicity (Veerendra *et al.,* 2021).

In most cases, the nanomaterials used for such delivery systems are coated with a biocompatible material. The drug is either adsorbed on the nanoparticle surface or encapsulated in the nanoparticle. A receptor for the target is attached on the outer surface, and then is administered to the sick person. Once the nanomaterials with the drug enters into the body, it is carried to the target site via the blood stream. The change in the pH, oxygen concentration and temperature, causes the release of the drug conjugated with the nanomaterial (McNamara and Tofail, 2016).

Drugs can be combined with gold nanoparticles, the gold nanoparticles are capable of delivering them to the desired locations, and the liberation of drug is mainly directed by biological stimuli (Patra *et al.,* 2018). Gold nano bioconjugates synthesized from onion peel extract which contain a metabolite 'quercetin' have been tested for their anti-inflammatory and antioxidant properties (Phukan *et* *al.,* 2021). Silver nanoparticles synthesized with the help of *Woodfordia floribunda* leaf extract can be used for anti-inflammatory therapy (Naikwadi *et al.,* 2022). Silver Nanoparticles are also used as potential drug carrier systems for the targeted liberation of drug ornidazole (Patra *et al.,* 2018). According to a study, Fe-Pt bimetallic nanoparticles can be exploited as drug delivery agents in treating lung and gastric cancers. Pore consisting Fe-Pt nanoparticles were packed with anticancer drug doxorubicin and magnetic field was used for their targeted delivery (Fuchigami *et al.,* 2012). Titanium oxide nanoparticles were shown to deliver daunorubicin (DNR), a potent drug for cancer therapy. The use of this drug is limited because of its toxicity and side effects, but conjugation of this drug to the TiO_2 nanoparticles makes their use possible due to targeted and controlled delivery thereby minimizing its toxicity by many folds. Similarly, TiO_2 nanoparticles functionalized by polyethylene glycol and folic acid can be used to deliver the drug paclitaxel (Chen *et al.,* 2012; Venkatasubbu *et al.,* 2013). Functionalized carbon nanotubes are one of few efficient nano drug delivery systems due to their shape and huge surface: volume ratio. The drug of interest can be either adsorbed on their surface or placed inside the tubes. The bioavailability of the drug methotrexate increases when it is conjugated with carbon nanotubes before administration (Pastorin *et al.,* 2006).

Liposomes are another commonly used drug delivery system. If, the drug is hydrophilic, it is added through an aqueous medium after the evaporation of the organic solvent containing the lipid. These drugs are therefore present in the polar center of the liposomes (Imad *et al.,* 2020). If, the drug is hydrophobic, it is mixed right at the beginning when the lipids are added to the organic solvent during liposome preparation. These drug molecules are found interspersed between the two bilayers of the liposomes. Liposomes are biocompatible and nontoxic under physiological conditions and therefore are the most suitable drug transporting systems for a whole lot of antimicrobials, anticancer drugs and anti-inflammatory substances (Ghalhandarlaki *et al.,* 2014).

Studies on use of nanomaterials in the delivery of contraceptives are under clinical trials. Oral and injectable contraceptives have a lot of side effects, therefore for the precise use of contraceptives and their targeted delivery, nanoparticles may play a major role by targeting the drug to the specific location. For example, anti-fertilization agent to the oviduct and anti-implantation drug to the uterus thus minimizing the side effects on other organs (Navalakhe and Nandedkar, 2007).

Recently, a study demonstrated the use of ranolazine, solid lipid nanoparticles in treating hypertension, which was successful due to improved therapeutic potential and increased bioavailability (Khan *et al.,* 2022). Both synthetic and natural nanoparticles, made up of polymers like chitosan and alginate, can be used to improve the oral delivery of drugs like clotrimazole and econazole. The drugs administered in this fashion showed high retention time in the body, *i.e.*, a retention time of 4-5 days was observed; whereas when the drugs were administered without the nanoparticles their retention time in the body was reduced to less than 12 hours (Pandey *et al.,* 2005).

2.3 Applications of nanomaterials in cancer therapy

Nanotechnology can prove to be a huge aid against cancer. Nanotechnology can be used in each and every aspect of cancer therapy right from detection of tumors, to targeted delivery of drugs, and for destruction of tumors. Destruction of cancer cells by nanomaterials is better than chemotherapy or radiotherapy, as healthy cells do not get killed in this treatment. Dendrimers is an example of a multifunctional nanomaterial which can help in all these aspects.

Dendrimers are branched molecules which provides researchers with the scope of attaching many molecules to a single dendrimer molecule, therefore only a single dendrimers molecule can be attached with molecules which detect and bind to cancer cells (folic acid), molecules which destroy the tumors (drug paclitaxel) and FITC molecules which detect the cell death signals (Menjoge *et al.*, 2010).

Nanoshell is a product of nanotechnology. These are minute beads coated with gold which can penetrate to several centimeters in the human tissues, which absorb light of a specific wavelength. When the light is absorbed by the nanoshell, strong heat is created which is lethal to the cells. Antibodies can be linked to the nanoshells against the cancerous cells. Metal nanoshells which are infrared light absorbers have been shown to be potent both *in vivo* and *in vitro* on the human breast carcinoma cells (Hirsch *et al.,* 2003).

The cell toxic effect of silver nanoparticles on acute myeloid leukemia (AML), a kind of blood cancer, has been studied. The effect of polyvinylpyrrolidone (PVP)-coated silver nanoparticles on various cell lines was studied. The impact of nanoparticles on mitochondrial disruption, apoptosis, cell viability, generation of reactive oxygen species (ROS) and damage to the DNA were interpreted. The outcome of the study was that silver nanoparticles are impactful on AML cell lines with an anti-leukemia effect. It was observed that apoptosis increased with the generation of silver ions and ROS which caused damage to the DNA and ultimately cell death. This action was more effective towards AML cells than normal cells. Thus, in conclusion silver nanoparticles coated with PVP can play an important role in AML treatment (Guo *et al.*, 2013). Fe-Pt nanoparticles after being functionalized by adding folic acid were targeted on breast cancer cell lines. A near infrared femtosecond laser was helpful in activating functionalized Fe-Pt nanoparticles. Once the Fe-Pt nanoparticles are irradiated by the laser beam, the nanoparticles demonstrated the photothermal phenomenon which resulted in perforations and breakage of the cell membrane of the cancer cells. Therefore, this technique has important use in target cancer therapy (Chen *et al.*, 2013).

2.4 Applications of nanomaterials in vaccines and gene therapy

Liposomes are used as delivery agents for vaccines and gene therapy since the last two decades, this is because compounds with different solubility can be incorporated inside various regions of liposomes. Liposomes also act as adjuvants and therefore help to elicit a better immunologic response to the antigen present in the vaccine. There are many liposomes based therapeutic and prophylactic vaccines for HIV, dengue and malaria, in the clinical trial phase. Epaxal and Cervarix are currently available liposome-based vaccines against Hepatitis A and Human Papilloma Virus respectively (Nisini *et al.*, 2018).

Nanotechnology can also be used in the new field of personalized vaccines, mainly the cancer targeting ones. It is part of therapy for cancer patients after tumor removal. Chen *et al.* (2021) have developed a personalized cancer vaccine which consists of membranes of *E.coli* and autologous resected tumor cell membranes incorporated into nanoparticles. It was seen that these hybrid nanoparticles elicit a better immunity against cancer as opposed to low immunogenicity of only autologous tumor antigens. The *E.coli* membrane acts as an adjuvant to enhance the immune response. This experiment was done for breast tumor and melanoma mouse models, the vaccine induces efficient tumor regression in both the models for quite a long term.

Talking more about gene therapy and its relation to nanomaterials, we all know about the CRISPR/Cas9 and its capability of disease treatment by gene editing. But a major problem faced with the actual *in vivo* application of CRISPR/Cas9 is its efficiency in targeted and safe delivery. Nanotechnology can be used for this purpose, such that CRISPR/Cas9 is efficiently delivered towards cancer gene editing and immunotherapy. Use of nanotechnology based delivery ensures targeted delivery, cellular internalization and regulated release of CRISPR/Cas9 to the desired site. Liposomes, porous silicon, Dendrimers and gold nanoparticles, can be used for CRISPR/Cas9 targeted delivery. Both the cancer vaccines and gene therapy are of major importance and are way better than radiotherapy, chemotherapy or tumor surgery, as the cancerous tumors have very high recurrence frequency and the permanent treatment of cancer cannot be achieved by these methods (Xu *et al.,* 2021).

2.5 Applications of nanomaterials in magnetic hyperthermia and photoablation

Hyperthermia simply means a technique in which heat is applied to destroy the diseased part of the body. This technique is generally coupled with the radiotherapy for the destruction of the carcinogenic cells without affecting the normal cells. Although, there are 3 varieties of hyperthermia namely regional, whole and local body hyperthermia, local is the one which is mostly preferred due to its safety. For local hyperthermia therapy magnetic nanomaterials are used which are functionalized by coating them with antibodies against the target cells and injecting them into the arteries supplying blood to the tumor. Once the nanoparticles reach their desired site, an alternating magnetic field is enforced. The applied magnetic field is useful in stabilization of the magnetic nanoparticles by relaxing their internal magnetic moments, an equilibrium state is reached which leads to dissipation of heat energy which is fatal for the target cells. Fe-Pt, Fe_2O_3, cobalt and manganese doped ferrite nanoparticles are few of the nanomaterials used for magnetic hyperthermia.

Nanomaterials can also be used in photoablation therapy. Photoablation therapy has two types *i.e.,* photodynamic therapy and photothermal therapy. In photodynamic therapy light sensitive substances are used which on exposure to a light of particular wavelength becomes toxic. Generally, TiO_2 nanoparticles are used due to their biocompatibility and photo-catalytic activity. On exposure to a light of a particular wavelength, they produce photo activated electrons and holes. The electrons transfer in the conduction band whereas the holes remain in the valence band. Both the holes and the electrons accumulate on the exterior of the nanoparticle; the water molecules react with holes to produce hydroxyl radicals and the oxygen molecules react with electrons to produce superoxide radical, both being reactive oxygen species that cause inevitable death of target diseased cells. On the other hand, photothermal therapy is more or less similar to hyperthermia, in which an infrared light source is used to irradiate the nanomaterials, which produce heat ultimately leading to diseased cell death by apoptosis, nanomaterials made up of gold and titanium oxide, are used for photothermal therapy (McNamara and Tofail, 2016).

2.6 Applications of nanomaterials in artificial implants

Nanotechnology also has a huge impact in the field of artificial implants, like dental and bone implants, cartilage implants, neural implants and stents. A major problem with these artificial implants is that they tend to get rejected by the host and therefore need replacement periodically. This is not only very expensive but the patient has to periodically undergo complicated procedures. In order to prevent this from happening the implants should be biocompatible as much as possible. The nanomaterials have the capacity to make an implant biocompatible and this is achieved either by layering the implant with nanomaterials or by making an entire implant with nanomaterials, doing so not only improves the biocompatibility of the implants but also protect it from various bacterial and fungal infections. Along with this the biomaterial coating also promotes the healthy cell and tissue growth at the location of the implants.

Starting with the bone and dental implants, nanotechnology can be used in the development of biocompatible extracellular matrices which help to enhance osteointegration. The nanomaterials provide a large porous surface area with high mechanical strength which is very optimal for cell-to-cell adhesion and cell migration. Coating both bone and dental implants with TiO_2/HA (hydroxyapatite) nano coating helps in stimulation of nerve regeneration, this also showed increased deposition of calcium and phosphorous as compared to conventional metal plates in the implanted area indicating enhanced osteoblast metabolic functions (Yang *et al.,* 2008). Titanium implants can also be incorporated or coated with certain growth factors like bone morphogenetic protein (BMP) which helps in good growth of the bone tissue at the point of implantation. Ceramic based composites in nanostructures have been produced which are biocompatible for dental implants as well as for knee and hip replacements, these have very high crack resistance. Zirconia nanocrystal-based nanocomposites which almost exactly shows mechanical strength and activity similar to natural bones helps in enhanced contact and proliferation of osteoblast cells along with optimal rates of angiogenesis when used as scaffolds. Hence, they are one of the most preferred materials for bone implants (Deville *et al.,* 2004). One of the major problems of cartilage is to repair itself naturally after damage. Hence, the only way to repair a damaged cartilage is to grow it outside the body on scaffolds and then to transplant it to the damaged location. PLGA/HA nanocomposites can be used for regeneration of cartilage, improved attachment of chondrocyte, proliferation and also increases the tensile strength (Lee *et al.,* 2008).

Carbon nanotubes and nanocomposites can also be used to grow chondrocytes (Khang *et al.,* 2008). One of the most common implants which are mainly used following an angioplasty to support the blood vessels are stents. Stents are usually composed of stainless steel and cobalt chromium alloys, as mentioned earlier stents are very useful in restoring the blood flow after an angioplasty but there can also be certain complications while using stents for example, there can be restenosis (narrowing of the arteries again after they were treated for the blockage) due to overgrowth of smooth muscles at the place of the implant and accumulation of proteins, on the stent surface. Restenosis can further lead to the clot formation which can be highly fatal. The formation of a coat of endothelium on the surface of the stents can be a solution to this problem. This coating can be given on the surface of stents with the help of endothelial cells coated with magnetic nanoparticles (Polyak *et al.,* 2008).

We all know that the regeneration of neurons is a very difficult task due the intricate microenvironments and control it requires. Carbon nanotubes and nanofibers have been proposed as ideal material for the replacement of injured neurons due to their electrochemical properties which mimic exactly similar to that of the axons. Carbon nanotube fibers helps in promotion of neuronal migration, cell growth and proliferation (Dubin *et al.,* 2008).

2.7 Applications of nanomaterials in coating medical equipment, wound dressings and dental adhesive materials

We all are aware about the antibacterial activity of silver. This characteristic of silver nanoparticles has been exploited in various applications. Moreover, nowadays different nanomaterials like zinc oxide nanoparticles are studied for their antibacterial activity. They can be used as a potential supplement that may substitute toxic antibacterial agents (Deshmukh *et al.,* 2022).

Medical devices or equipment used in clinical settings or hospitals are prone to contamination with bacteria responsible for most of the cases of nosocomial (hospital associated) infections. The medical equipment which are prone to get contaminated by different kinds of bacteria are urinary catheters, surgical sutures, intravenous catheters, endotracheal tubes and prosthetic heart valves. The major group of organisms which are related to these medical instrument related infections are *Staphylococci* (coagulase negative), usually considered as non-pathogenic or commensals of the human body, but it is found that these are opportunistic pathogens and they can cause device related infections. Coagulase negative *Staphylococci* have the potential to produce heterogeneous biofilms and are resistant to multiple antibiotics. Once they attach to a medical device, they secrete a slimy polysaccharide matrix which helps in firm attachment and therefore difficulty in their removal. To tackle this problem silver nanoparticles were studied for its effectiveness against the coagulase negative *Staphylococci*. Two species of *Staphylococci* (coagulase negative) were selected namely *Staphylococcus epidermidis* and *Staphylococcus haemolyticus* and antimicrobial functions of silver nanoparticles on them was studied. The outcome showed that silver nanoparticles have bactericidal action against both *Staphylococcus epidermidis* and *Staphylococcus haemolyticus* by disrupting their cell membranes. After confirming the antimicrobial potential of the silver nanoparticles against the coagulase negative *Staphylococci,* a model device (urinary catheter) was selected to test the antibiofilm potential of the silver nanoparticles. Two catheters were taken, one coated with the silver nanoparticles and the other one was an uncoated normal urinary catheter (control). Both the catheters were exposed to the above-mentioned groups of bacterias and incubated for a suitable period of time. The results showed that there was a thick biofilm formation on the surface of normal catheter and on the other hand there was not even a minute evidence of formation of bacterial biofilm on the catheters coated with silver nanoparticles. This experiment concluded that silver nanomaterial fabricated medical devices can limit bacterial implantation, growth and also retard biofilm formation and thus help in reducing severe opportunistic infections (Thomas *et al.*, 2015).

The antimicrobial effect of silver nanoparticles can also be exploited or made use of by incorporating them in wound dressing materials. Polycaprolactone was chosen as the base material to build the wound dressing material along with the incorporation of silver nanomaterials. It was noticed that due to the incorporation of silver nanoparticles the wound dressing material showed a substantial increase in the antibacterial activity, there was a decrease in the water contact angle (hydrophobicity of the material reduced) and even the tensile capacity of the material increased. Thus, its overall performance was seen to be improved as per the requirements for clinical applications (Thomas *et al.,* 2015).

Dental restorative composites such as polymethyl methacrylate resins are commonly susceptible to the biofilm formation on their surface. These biofilms are mainly of *Streptococcus mutans* who thrive well in the oral cavity due favorable environments such as presence of moisture and nutrients. Thus, there is a huge requirement to produce dental restorative material with antibacterial properties. Through several experiments conducted it is seen that silver nanoparticles incorporated polymethyl methacrylate resins inhibit the formation of Streptococcus *mutans* films and thus can be used in dental adhesive materials for microbial resistance (Thomas *et al.,* 2018).

2.8 Applications of nanomaterials in medical robotics

Another emerging branch of nanotechnology is nano robotics, which aims at creating robots as well as machines at nanometer scale. Very active research and development is going on in this field. Nanorobots can be used for wide number of applications in medicines like for drug delivery, in surgery and for the detection of toxic cells. They also have the ability to enter into the cells and correct the faulty DNA, in repair of cells tissues and organs, breaking down blood clots, breaking of kidney and gallstones and monitoring of glucose level in human blood. Few of the illustrated examples are as follows.

Bio hybrid nanorobots consisting of magnetotactic bacteria (produce iron oxide nanoparticles) coupled with liposomes containing the therapeutic material have been used to deliver the drug to the mouse tumors with the supplementation of an external magnetic field (Felfoul *et al.*, 2016).

Nanotechnology shall have a vital impact in the domain of biopsies or surgeries, as with the help of nano robotics improved precision and accuracy can be achieved in this field. Even the diseased parts of the body which are difficult to access by conventional technology can be easily accessed with the help of nanorobotics. Nano star shaped grippers have successfully been used to collect histological specimens from pig's bile duct, breakage of blood clots in the brain of mouse has been successfully done by nanotechnology, nowadays there are various devices like nano knifes operated by external electric fields capable of manipulating individual axons, this technology can prove to be very helpful for neurosurgical applications in near future (Saadeh and Vyas, 2014; Soto *et al.,* 2018).

Micro-machined devices synthesized from silicon wafers have been incorporated in the brain and their impacts on stimulation of brain were examined. A regulated response due to the device-tissue interaction was seen in animal models used to test the device. All animals survived the experimentation period without any side effects. The device was made use in deep-brain stimulation in the sub thalamic nucleus barring manipulation of the neighboring cells or tissues. Such stimulations with nano-devices have a great scope in the therapy of degenerative disorders like Alzheimer's, Parkinson's and spinal injuries (Szarowski *et al.,* 2003; Vidu *et al.,* 2014). An overview of the applications of nanoparticles in the various fields of biomedical science is depicted in Figure 2.

Figure 2: Applications of nanoparticles in biomedical sciences.

3. Challenges and future prospects

Nanotechnology is on the similar level like the IT sector was back in the 1970s and the field of biotechnology during the 1990s. Thus, it can be speculated by reading this review that nanotechnology has the capacity to gain new heights and new prospects similar to the above-mentioned sectors. It is clear that nanomaterials have a wide range of applications with extensive use in various domains such as textiles, electronics, heavy industries and medical sciences.

However, the direct use of nanotechnology in the domain of biomedical sciences is challenging, due to the risk of adverse effects on human life. There is an emergence of a new field termed nanotoxicology which has made us aware about the potential risk factors of nanomaterials. Thus, before applying the direct use of nanomaterials in medicines, we should examine the biosafety of nanotechnology by preclinical studies.

Nanoparticle toxicity is routinely accessed in cultured cell lines, with further examination of animal experiments. Few examples studied of nanotoxicology suggest that certain concentrations of carbon nanotubes have been seen to be harmful for humans. Similarly, large nanoparticles may accumulate in the vital organs of the body such as lungs and heart and may affect their working. Therefore, scientists need to consider all these possibilities about the behavior of these nanostructures after they enter the human body. Not only nanomaterials are harmful to humans but if accidently escaped into the environment can lead to the destruction of natural beneficial micro biota in soil as well as in water bodies. It may also inhibit or affect the growth of the plants and can cause adverse effects on fish growth, along with bio magnification (Wu and Li, 2003).

If all the above challenges are properly taken into consideration and due precautions are taken to overcome them, nanotechnology will scale great heights, advancing the field of biomedical sciences in near future.

4. Conclusion

Nanotechnology has the capacity to build a wide array of products that are incredibly powerful. Nanotechnology is a complicated field which consists of biotechnology, information technology and physical phenomenon, which makes its scope even more wide. After studying this review, it is evident that nanomaterials can be used for a variety of applications in biomedical sciences.

A few noted applications are in drug delivery systems, diagnosis, therapy, photoablation, prosthetics/implants, vaccines, gene therapy, wound dressings, nanorobotics. However, most of these applications are under clinical trial phase and not being practically used, as there are still many advances needed to improve nanomedicine. It can be inferred that as the size decreases, materials will become stronger and the medicines composed from them will cure many diseases. Hence, this technology working at the nano scale of atoms and molecules will be a large part of our futures.

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Abbreviations

AML, Acute Myeloid Leukemia; $AuCl_4$, Gold Chloride; BMP, Bone Morphogenetic protein; CdS, Cadmium Sulfide; CRISPR/CAS, Clustered regularly interspaced short palindromic repeats / CRISPR-associated proteins; CT, Computed Tomography; DNR, Daunorubicin; Fe - Pt, Iron - Platinum; Fe_2O_3, Iron Oxide; FITC, Fluorescein-isothiocyanate; HA, Hydroxyapatite; HER2, Human Epidermal Growth Factor Receptor 2; IT, Information Technology; MRI, Magnetic Resonance Imaging; $Na_3C_6H_5O_7$, Tri sodium citrate; NIR, Near Infrared; pH, Potential of hydrogen; PLGA, Polylactide Glycolic Acid; PVP, Polyvinylpyrrolidone; TiO_2, Titanium Oxide.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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