# Nanotechnology in medicines- Recent Developments and Future Prospects

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**Abstract :**

Nowadays, lot of research is being focused on Nanotechnology. This branch of science and technology usually deals with studying matter at atomic and molecular levels. The use of nanotechnology in the field of modern medicine is overwhelming. Due to site-specific, and target-oriented delivery of precise nano-medicines, now it is possible to treat long standing chronic human diseases. The synthesized nanoparticles can be used as a diagnostic tool for imaging, capturing and recognizing the biomolecules. The use of nanoparticle as nanodrugs helps in carrying the drug to the specific target tissue known as targeted drug delivery. Nanomedicines can also be useful as an adjunct for regenerating tissues. The present chapter summarizes the recent updates about nanotechnology in the field of medicines and how nanotechnology and nanomaterials can be effective as drug delivery system for treatment of various diseases. It also discusses about the future scope of nanotechnology when nanorobots will play a major role in delivering the health care. Also, the demerits of relying on an artificial system to take care of inside the human body are discussed.

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## Introduction

The term “nano” is derived from a Greek word meaning “dwarf. When we consider one nanometer it means that one meter length divided by one billion, that is $10^{-9}$ m. Nanotechnology deals with studying and controlling the matter on an atomic or molecular level. The material is changed to a size between 1-100 nanometers so that it gets smaller, stronger and more durable.

Nanotechnology deals with understanding, manipulating and controlling the matter at the level of individual atoms and molecules The use of nanotechnology for medical purposes has been termed nanomedicine and is defined as the use of nanomaterials for diagnosis, monitoring, control, prevention and treatment of diseases. The first guidelines for nanotechnology were published by K Eric Drexler. In his book Engines of Creation. The United States National Human Genome Research Institute adopted a new eco-friendly socially acceptable approach for nanotechnology, This was accomplished by addressing the ethical, legal, and social implications before entry of nano-products into the market.

## History

- In early 2003, the European Science Foundation initiated its “Forward look on nanomedicine”. This first foresight study highlighted the medical applications of nanosciences and nanotechnology.100 leading European experts participated in the Forward Look and they tried to determine the current status of the field.

- On 23 February 2005, a policy briefing document was published which summarized the recommendations of the Forward Look.

- In June 2003, UK Government commissioned the Royal Academy of Engineering and the UK National Academy of Science to carry out an independent study to evaluate whether nanotechnology can raise new ethical, health and safety or social issues not covered by current regulation.

- In July 2004, Final report with 21 recommendations for a sure, safe and responsible development of nanotechnology was published. Also,The Commission of the European Communities released its guidelines on the European strategy for nanotechnology.

- In September 2005, Release of Vision Paper and Basis for a Strategic Research Agenda for Nanomedicine.

- In 2007, establishment of the European Foundation for Clinical Nanomedicine in Basel (Switzerland).

- In 2004 National Institutes of Health (NIH) Atlantic Ocean, released their first roadmap on nanomedicine.

- In 2005 and 2006 a national network of eight Nanomedicine Development Centres, NIH Nanomedicine Roadmap Initiative was developed.

- In 2004, the National Cancer Institute (NCI), as part of NIH, launched the Cancer Nanotechnology Plan, a strategic initiative to transform clinical oncology and basic research through the directed application of nanotechnology.

**Branches of Nanotechnology**

**There are three main branches of nanotechnology –**

**I) Nanomaterials**

Includes nano-scale products which have been widely accepted as biocompatible materials and analytic methods. They are also used in surgical and dental practice, studying nerve cells and performing biomolecular research.

**II) Molecular nanotechnology**

Includes mechanical systems, designed and fabricated at a molecular level that can play a major role in medicine.

**III) Biotechnology**

The basic concept of using biological systems in technological and industrial processes, also involving genetic engineering and creating artificial representations of organic life.

## NANOTECHNOLOGY IN MEDICINES - NANOMEDICINES

Nanomedicine, is actually nanotechnology in medicine. Even if the word "nanomedicine" is been widely used, it is more proper to refer to "nanotechnology enabled medicine" in different sub-areas of medicine such as diagnostics,therapy or monitoring.

### Definition Nanomedicine controversy

The definition of nanomedicine slightly varies on both sides of the Atlantic Ocean.The US National Nanotech Initiative refers it to a nanoscale whereas the European Science Foundation and the European Technology Platform on Nanomedicine do not agree with it.

### Different definitions

• **The US National Nanotech Initiative**

Nanotechnology is the understanding and control of matter at dimensions between approximately 1 and 100 nanometres, where unique phenomena enable novel applications. Nanotechnology involves imaging, measuring, modelling, and manipulating matter at this length scale. Nanomedicine is the application of nanotechnology to medicine.

• **The European Science Foundation**

The field of nanomedicine is the science and technology of diagnosing, treating and preventing disease and traumatic injury of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body.

• **The European Technology Platform on Nanomedicine**

Nanomedicine is defined as the application of nanotechnology to health. It exploits the improved and often novel physical, chemical, and biological properties of materials at the nanometric scale.

**Principles and Properties of nanomedicines/nanomaterials**

The properties of nanomedicine should be understood in order to study its behavior in the human body. The following characteristics of nanomedicine can be defined in terms of its particle size, shape and size distribution, aggregation and agglomeration state, crystal structure, specific surface area, porosity, chemical composition, surface chemistry, charge, photocatalytic activity, zeta potential, water solubility, dissolution rate/kinetics, and dustiness.

Depending upon its chemical composition, nanomaterials can be classified as organic, inorganic, crystalline or amorphous particles. They can be organized as single particles, aggregates, agglomerate powders or can be dispersed in a matrix which give rise to suspensions, emulsions, nanolayers, or films. An important property in the design of drug delivery systems is its biocompatibility. A biocompatible surface is such that it cannot trigger an undesired' response from the organism. Biocompatibility can be defined as "the ability of a material to perform with an appropriate response in a specific application".

**Nanoparticles in medicines**

**Definition**

Nanoparticles are also referred to as "zero-dimensional" nanomaterials. This definition is due to the fact that all of their dimensions are in the nanoscale, as compared to one-dimensional nanomaterials, which have one dimension larger than the nanoscale and two-dimensional nanomaterials, which have two dimensions larger than the nanoscale.

Nanoparticles are organic or inorganic structures (sizes 1–100 nm) similar to antibodies and DNA plasmids. These materials have overall dimensions in the nanoscale, ie, under 100 nm. Nanoparticles plays an important role in modern medicine, with applications varying from contrast agents in medical imaging to carriers for gene delivery.

According to FDA guidelines, there are three basic aspects to identify the presence of a nanomaterial. This includes surface area, particle size distribution (PSD) and size. The most important aspect to take into consideration is size, because it is applicable to a huge range of materials. The conventional size varies from 1 to 100 nm. The Particle size distribution is a parameter which is widely used to identify the type of nanomaterial. It gives an idea about the range of variation of sizes. Since the nanomaterial is usually polydisperse, it is important to set the PSD, which means, it is composed of particles with different sizes. The determination of the surface area by volume is a relational parameter, which is important due to additional legislation. if the surface area by volume is larger than 60 m2/cm3, then the material can be considered under the definition.

**Types of nanoparticles**

Nanoparticles can be divided into I) organic and II) inorganic III) Nanocrystals IV) Protein and polysaccharides

| **Organic Nanoparticles** | **Inorganic Nanoparticles** | **Nanocrystals** | **Protein and polysaccharides** |
|---|---|---|---|
| Chitosan,Alginate, Cellulose, Dendrimers, Micelles, Liposomes, | Silver, Gold, Iron oxide and Silica nanoparticles | Pure solid drug particles within 1000 nm range. | Natural biopolymers extracted from biological sources such as plants, animals, microorganisms and marine sources |

| | | | |
|---|---|---|---|
| | Metal nanoparticles like silver and gold have SPR (surface plasmon resonance) property that liposomes, dendrimers, micelles lack. | These are 100% drug without any carrier molecule attached to it and are usually stabilized by using a polymeric steric stabilizers or surfactants. | Decomposable and Metabolizable |

**Chitosan** Chitosan shows muco-adhesive properties and hence it makes it suitable to act in the tight epithelial junctions. Chitosan-based nanomaterials are widely used for continued and sustained drug release systems for various types of epithelia, including buccal, intestinal, nasal ,eye and pulmonary.

**Alginate** It is a mucoadhesive biopolymeric material with abilities to be used as a drug delivery agent in medical field. Due to presence of final carboxyl groups, it has been classified as anionic mucoadhesive polymer which has greater mucoadhesive strength as compared to cationic and neutral polymers.

**Cellulose** Different forms of cellulose can be used a**s** cellulose nanocrystals (CNC), cellulose nanofibrils (CNF) and bacterial cellulose (BC), All of them have been investigated as drug delivery vehicles and it was found that CNC and CNF bind and release some water-soluble drugs via ionic interactions whereas BC releases drugs from flexible membranes. The rationale for using nanocellulose is that the high surface area-to-volume ratio of the material increases its drug binding capacity at the surface.

**Dendrimers**. These are functional groups in the form of anionic, cationic or neutral ions, that can be used to modify the entire molecular structure, resulting in improved properties Dendrimers are macromolecules with exterior functional groups alongwith branched repeating units expanding from a central core. The interior space of dendrimers can be used to load therapeutic agents or attached to the surface groups, which makes it highly bioavailable and biodegradable. On conjugation with with saccharides or peptides example Polyamidoamine dendrimer-DNA complexes (called dendriplexes), it showed marked improvement in the properties. Dendriplexes were evaluated as gene delivery vectors and showed enhancement of successive gene expression, targeted drug delivery and drug efficacy properties.

**Liposomes.** Liposomes are lipid bilayers which consists of spherical vesicles with particle sizes of 30 nm to several microns. Hydrophilic therapeutic agents can be included inside the aqueous phase whereas the liposomal membrane layer can incorporate hydrophobic agents. The surface characteristics can be modified using antibodies, proteins and polymers that enables the macromolecular drugs like nucleic acids and crystalline metals, to be integrated into liposomes Poly(ethylene glycol) (PEG)ylated liposomal doxorubicin (Doxil®) is the first FDA-approved nanomedicine, for treatment of breast cancer..

**Micelles.** The diameter of micelles ranges from 10-100 nm. These are surfactant which consist of lipids and amphiphilic molecules. Under aqueous conditions the micelles molecules spontaneously aggregate and self-assemble into spherical vesicles. Due to the hydrophilic nature of outer monolayer and a hydrophobic core, these molecules can be used to incorporate hydrophobic therapeutic agents. The solubility of hydrophobic drugs thus increases and the bioavailability is improved. Micelles can be used as a therapeutic agents, drug delivery agents, imaging agents and contrast agents.

**Carbon nanotubes**. Carbon nanotubes consists of cylindrical molecules with rolled-up sheets of a single-layer of carbon atoms (graphene). Classified as single-walled, multi-walled, or made of several concentrically interlinked nanotubes. Because of its high external surface area, carbon nanotubes exhibits high drug loading capacity. Also, their unique optical, mechanical and electronic properties makes it suitable for imaging contrast agents and biological sensors.

**Metallic nanoparticles**. Research in metallic nanoparticles has been growing in different medical and dental applications, which includes bioimaging, biosensors, target/ sustained drug delivery, hyperthermia and photoablation therapy. The ability to modify and functionalize these nanoparticles with specific functional groups helps them to bind to antibodies, drugs and other ligands, The most extensively studied, metallic nanoparticles are gold, silver, iron and copper.

**Quantum dots.** Quantum dots (QDs) are fluorescent semiconductor nanocrystals (1-100 nm) and have shown promising use for several biomedical applications, such as target drug delivery and cellular imaging Quantum dots consists of a shell-core structure, in which the core structure is composed of II-VI or III-V group elements of the periodic table.

**Applications of nanoparticles in medicines**

Nanoparticles plays a major role in nanomedicine because of its application in three different areas:

I) Diagnosis (nanodiagnosis)

II) Controlled drug delivery (nanotherapy) and

III) Rregenerative medicine.

A new field known as Theranostics is emerging which combines diagnostics and therapeutics and is a promising approach which holds in the same system both the diagnosis/imaging agent and the medicine.

**I) Diagnosis (nanodiagnosis)**

Diagnosis is one of the most critical steps in medical field. All diagnoses should be quick, accurate and specific to prevent 'false negative' cases. Nowadys, Molecular imaging and image guided therapy acts as a basic tool for monitoring disease and in developing almost all the applications of in vivo nanomedicine

Biological markers serves as a basic tool to detect illnesses or symptoms. The use of nanotechnology has helped us to design high precision molecular imaging agents. In addition to diagnosis, imaging is also an important part for detecting potential toxic reactions, in controlled drug release profile, evaluating drug distribution within the body and closely monitoring the progress of a treatment. The most widely used techniques in medical field includes X-rays, ultra-sound, computed tomography, nuclear medicine and magnetic resonance imaging. Use of contrast and targeting agents based on nanotechnologies have improved the resolution and specificity, by indicating the diseased site at the tissue level. Presently, used medical contrast agents exhibit fast metabolism and a non-specific distribution, which results in undesirable toxic side effects. Since, nanomaterials exhibit lower toxicity, enhanced permeability and retention effects in tissues, use of nanotechnologies helped in developing more powerful contrast agents for almost all imaging techniques.

### II) Controlled drug delivery (nanotherapy)

An ideal drug delivery system consists of two parts: a) Control over drug release and b) the targeting ability, Specifically targeting and killing of harmful or cancerous cells results in reducing the side effects significantly and ensuring increase drug efficiency. Also, controlled drug release decreases the side effects of drugs. Due to their small size, intravenous and other delivery routes becomes more easier which results in less irritant and improved penetration into tissues. Specificity of nanoparticle drug delivery systems is enhanced when nano-scaled radioactive antibodies are attached which are complementary to antigens on the cancer cells producing desirable results, showing improved i) drug bioavailability, ii) delivery of drugs specifically to the target site, and iii) uptake of low solubility drugs

### III) Rregenerative medicine.

Regenerative medicine is the process of creating living, functional tissues, to repair or replace tissue or organ function lost due to age, disease, damage, or congenital defects. Regeneration of tissues can be achieved by the combination of living cells and bioactive compounds to its target location for treatment of various diseases. Various drug delivery systems have been tried, but still certain challenges need to be addressed which includes development of an advanced technology for successful delivery of drugs to its target sites. Nano based drug delivery systems are currently been investigated widely that will facilitate the advanced system of drug delivery.

Initially, they were developed as carriers for vaccines and anticancer drugs. The nanometer size ranges can significantly enhance the drug delivery by modifyin the bio-distribution and toxicodynamics of drugs. Many types of toxic drugs can be delivered in vivo relatively easy with nano drug delivery. Target delivery of drugs by modifying or functionalizing nanoparticles facilitates crossing the blood brain barrier for treatment of brain tumors. For example, doxorubicin does not cross the blood–brain barrier, but its combination with polysorbate 80 modified polybutylcyanoacrylate nanoparticles can enhance its delivery to the brain to a significant extent. DNA delivery vectors can also be successfully created using nanoparticle system, because of their size, shape and functionality. They can penetrate deep into tissues provide biological functionality, and can serve as materials, which act as scaffolds to support cell proliferation. The future scope for nano-assisted regenerative medicine is the development of cost-effective disease-modifying therapies that will enacble in-situ tissue regeneration.

## NANO-BASED DRUG DELIVERY SYSTEM

Recently, there has been drastic developments in the field of drug delivery systems to provide therapeutic agents or drugs which can be absorbed by the cells efficiently.

One of the latest advance development in pharmacotherapy is the development of Nano-sized colloidal carriers of drugs. They serve as potential carriers for several types of drugs like anti-cancer, anti-hypertensives, hormones, etc.. Submicron colloidal particles have been used as nanoparticles and as a drug delivery agent and also for the diagnosis of diseases. Nanoparticles have broadened the scope of pharmacokinetics for insoluble drugs. For example, the trans-retinoic acid nanoparticle system coated with $CaCO3$ was developed as a new drug delivery system, which on spray dryingleads to formation of aggregates. The aggregates thus formed were then found to re-disperse in water, which stimulation of islet cells of pancreas to secrete insulin.

### Applications of Nanobased drug delivery systems

### I) Cancer

Sengupta and colleagues (2005) developed a nanoparticle based drug delivery system composed of two layers: a core of poly-(lactic-co-glycolic) acid (PLGA) conjugated with doxorubicin enclosed within a liposome composed of phospholipids conjugated with PEG and combretastatin, In this system, doxorubicin is the chemotherapeutic agent and combretastatin is the antiangiogenic agent. These multilayered nanoparticles dimensions were 80–120 nm. The underlying plan was to deliver the particles to the targeted tumor site and then release the drug slowly by degradation of the PLGA core. When administered intravenously to mice with tumors induced by carcinoma or melanoma cells, the particles were readily taken up by the tumor cells. The nanoparticles drug delivery resulted in significant inhibition of tumor growth and prolonged the lifespan of the animals.

**II) Neurodegenerative diseases**

Researchers have found that nanoparticles synthesized from poly(hexadecyl cyanoacrylate) and related compounds have been shown to facilitate drug transport across the Blood Brain Barrier (BBB). Kreuter and colleagues (2003) adsorbed dalargin (an analgesic) onto poly(butyl cyanoacrylate) (PBCA) nanoparticles and demonstrated penetration of nanoparticle loaded drug across the BBB in rats. Also, Siegemund and colleagues (2006) showed how PBCA nanoparticles loaded with thioflavins can target fibrillar amyloid β in a murine model of Alzheimer's disease. Calvo and colleagues (2002, 2001) synthesized a nanoparticle system composed of a copolymer of PEG and poly(hexadecyl cyanoacrylate) (PHDCA). Since PEG is hydrophilic and PHDCA is hydrophobic, an aqueous environment enables the copolymer molecules to arrange themselves as particles with an insoluble PHDCA core and a surface layer of PEG. because Since PEG is not recognized as a foreign material by macrophages in blood, the incorporation of PEG is common in many drug delivery systems which facilitates increase in the half life of drug carriers in blood (Harris and Chess 2003).

**III) HIV/AIDS**

De Jaeghere and colleagues (2000) synthesized pH-sensitive nanoparticles from a copolymer of methacrylic acid and ethyl acrylate. and studied the delivery of an HIV-1 protease inhibitor, CGP 70726. A major problem while delivering CGP 70726 is poor water solubility. De Jaeghere and his team emulsified a solution of the copolymer with a mixture of CGP 70726 and benzyl alcohol to synthesize the nanoparticle. The nanoparticles were administered orally to dogs and their blood samples analysis showed successful drug release.

**IV) Ocular diseases**

The main reason for using nanoparticle-based drug delivery systems in ophthalmic applications is the ability to prolong release of drug molecules by trapping the drug in the ocular mucus layer.

Most of the ocular drugs are administered as eye drops. These are highly concentrated solutions and require frequent application but due to movement of mucus during blinking there is rapid precorneal loss. This problem can be effectively overcomed by using nanoparticles as drug carrier system..

Mixtures of polymer and drug were dissolved in ethanol and then emulsified (with the help of water and a surfactant) to form drug-embedded nanoparticles having100 nm size. These nanoparticles were then instilled in the conjunctive sac of the rabbit eyes. Nanoparticles loaded with Flurbiprofen and Ibuprofen effectively inhibited inflammatory responses due to surgical trauma. These results were comparable to conventional eye-drop controls. The significance of this study was that the nanoparticle system were used with lower drug concentration as compared to the eye-drop control. Also, the nanoparticle system was able to generate higher drug levels in the vitreous humor.

### V) Respiratory diseases

The applications of nanoparticle-based drug delivery system in respiratory diseases is somewhat limited. John and colleagues (2003) investigated the use of a liposome-based nanoparticle system to inhibit inflammation in a murine model caused by allergic asthma. The methodology used was to inhibit P-selectin receptors on activated endothelial cells in circulation. This,in turn, attenuates the development of peribronchial inflammation. The nanoparticles were designed to mimic the physiological P-selectin super ligand (PSGL-1). Lung inflammation and airway hyperreactivity were induced in mice by lipopolysaccharide LPS and cockroach antigen. In both cases, the liposomal nanoparticles were found to bind preferentially to selectins on activated endothelial cells. Histological examination showed significant reduction in peribronchial inflammation and airway hyperreactivity in mice treated with the nanoparticles compared with controls.

## NANOFIBERS

The world of nanomaterials encompasses a wide range of interesting materials with excellent physical and chemical properties and characteristics. These materials include zero-dimensional nanoparticles like the quantum dots or the one-dimensional nanowires, nanorods, nanofibers, and nanotubes or the two-dimensional nanosheets. Out of all these nanomaterials, nanofibers stand out among the rest of the nanomaterials. One of the most distinguishing features of nanofibers is their exceptionally high surface area-to-volume ratio and high porosity which makes it an ideal candidate for many advanced applications.

Nanofibers are one dimensional (1D) nanostructures, such that two of their dimensions are at the nanometric scale, rendering them optimized properties for biomedical, technological and environmental applications.

**Synthesis of Nanofibers**

There are different methods to fabricate nanofibers which includes melt spinning, air jet spinning, template synthesis, drawing, electrospinning, self-assembly, centrifugal spinning and phase separation. Amongst all these methods, electrospinning is a simple and inexpensive method and can produce a wide range of polymers in the form of nano and micrometer-scale fibers. The process of Electrospinning involves using an electric field which convert polymer solution or melt into a fiber form. Electrospun nanofibers have unique properties, which includes a) large surface to volume ratio b) increase pore density c) and excellent surface adhesion. The morphology of an electrospun nanofiber is affected by the material being used and processing parameters.

**Electrospinning technique**

Of all the present methods available for synthesizing one-dimensional nanofibers, electrospinning is one of the most established and widely used technique. The electrospinning machine consists of a syringe with a nozzle, an electric field source, a counter electrode or grounded target, and a pump.

Electrospinning involves use of electrostatic forces for producing continuous fibers having diameter in the range of several microns to few nanometers. In a typical electrospinning process, a syringe is filled with a polymer solution and then this solution is pushed to the tip of the syringe by external pumping with mechanical pistons. When the solution droplet is formed at the end of metallic needle, an electric voltage bias is applied between the metallic needle and a collector placed in front of it. When the applied voltage is gradually increased, the electric forces overcome surface tension which resulted in a jet formation, finally the droplet elongates Taylor cone, from which polymer nanofibers are produced and deposited onto the collector.

### Non-Electrospinning technique

Non-electrospinning method relies on centrifugal force or compressed gases rather than an electric field to generate nanofibers. These techniques reduces the use of a solvent, increase the output and lowers the production cost. The three most common non-electrospinning techniques for nanofiber production are blowing bubble spinning (gas-jet spinning), centrifugal spinning and fiber drawing. Quantity or production output of nanofibers is more with centrifugal spinning but quality performance is less.

## Application of nanofibers in medical field

Nanofibers have unique physical properties resembling the characteristics to the extracellular matrix (ECM). These properties include  surface area, diameter, and porosity. Different biomedical applications of nanofibres include medical implants, biomimetic actuators, dental materials, enzyme immobilization scaffolds, wound dressings, antimicrobial agents and drug delivery vehicles. The nanofiber scaffolds with seeded cells are used for tissue engineering purposes. The porous structure of the fiber facilitates the diffusion of drug particles out of the matrix. The rate of release of drug rate can be controlling by manipulating the thickness of the synthesized nanofibrous mat. For drug delivery systems, the nanofibrous membranes were loaded with the drug component to deliver the drug to the targeted site.

## Nanofibers as drug delivery system

Localized and targeted delivery of therapeutic drugs can be achieved with individual nanofibers or nanofibrous scaffolds that can act as effective vehicles. Active biomolecules including drugs and growth factors can be encapsulated or incorporated into different nanofibers to modify the cellular function. Large surface area and porous structure increases the effectiveness of nanofiber as a carrier for drug and therapeutic agent delivery  One of the significant examples in the application of nanofibers as drug carrier is the development of a drug loaded nanofiber for delivery of therapeutic peptides across the blood-brain barrier. The peptide nanofibers were synthesized in such a way that the active peptide epitope firmly surrounded the nanofiber core..

## APPLICATIONS OF NANOMEDICINES IN DIFFERENT DISEASES

### I) Treatment of Atherosclerosis using naoparticles with annexin

Atherosclerosis is one of the main causes of cardiovascular diseases. It is a slowly progressing pathology that reduces the lumen of arteries.that may lead to critically decreased blood flow to the vital organs, which results in their failure.

Three pathomechanisms that play a vital role in atherosclerosis includes arterial wall damage, non-resolving inflammatory response, and the release of clot-promoting material to the bloodstream. Normally, the resolution of the inflammatory response is mediated by Annexin A1 (AA1), a glucocorticoid-regulated protein, which is a natural anti-inflammatory. In order to influence the progression of atherosclerosis, Fredman et al. synthesized nanoparticles loaded with AA1 molecules and injected them into the mouse bloodstream. This experimental study proved that nanoparticles with resolution-mediating substances can activate receptors in myeloid cells to treat atherosclerotic lesions.

### II) Cancer therapy

The field of nanomedicine has made it possible to concentrate on alternative methods of delivering drugs and increasing their efficiency. The current approaches for treating cancer includes surgical intervention, radiotherapy and chemotherapy. These approaches are mostly effective but they often cause severe systemic damage and destroy a considerable amount of adjacent healthy tissues.

Various treatment options have been tried in recent times in order to preserve the surrounding healthy tissues during treatment. One of the technique known as Nanoshell approach is undergoing clinical trials. Nanoshells are extremely small nanoparticles covered with gold that can selectively target cancer cells by penetrating deep inside the tissues and can also be adjusted to be absorbed in the near-infrared region (NIR). These nanoshells can be implanted into the neoplastic tissue through injection and then if irradiated with NIR laser can cause ablation of the tumor cells. Irradiation with NIR laser can be done either through the skin or by using an optical fiber for example, the lungs. Nanoparticles bounded with antibodies via polyethylene glycol can also be used in breast cancer therapy.

Clinical trials of albumin-bound paclitaxel formulation have proved that it is better tolerated by patients as compared to the conventional placitaxel therapy. In metastatic lung cancer therapy, .cationic bovine serum albumin (CBSA) has been studied as an effective method of transporting siRNA. CBSA has the ability to form stable nanoparticles with siRNA, which protects it from degradation and increases the chances of its successful delivery to the lungs.

## III) Treatment of Inoperable neoplasms with nanoknife

In recent times, nano-knife has proved to be capable of efficiently destroying cancer cells. Nanoknife works on the principle of irreversible electroporation (IEP), means subjecting cancer cells to altering electrical fields with a voltage up to 3000 V for micro- or milliseconds. There is flow of electric current between the electrodes which are located at the edges which causes unique form of biological effect at the center of the tumor called as irreversible electroporation (IRE). IRE is a new, non-thermal type of ablation that depends on creating irreversible holes (pores) at the level of cellular membrane.

Advantages of nano-knife over the traditional types of ablation methods includes lesser time required for the surgical procedure and no negative thermal effect on the healthy tissues The most striking feature of nano-knife as compared to the other methods is that it preserves living structures containing collagen fibers like blood vessels, bile ducts or pancreatic ducts

## IV) Regeneration of damaged nerve through nanografts or carbon nanotubes

The unique properties of carbon nanotubes (CNT) have made it possible to use CNT as tissue repairing agent especially damaged tissues requiring electrical stimuli. Researchers have studied the effect of CNTs when interfaced with glass fiber (CNT-PGFs) on sciatic nerves in rats. It was found that CNTs has the ability to induce sciatic nerve regeneration. Thus CNT-PGFs scaffolds can be used at the interface between peripheral neural tissues and the nerve conduit. CNTs also has the ability to transport proteins through the cell membrane which helps in inducing their naturally mediated effect. Functionalizing CNTs with appropriate molecules represents can be one of the promising strategies for inducing selective nerve regeneration.

### V) Tissue regeneration using Bioactive nano molecules

Use of Bioactive nano molecules will serve the following purposes :

1. In identifying signalling systems that can influence the self-healing potential of endogenous adult stem cells.
2. Formulate efficient targeting systems for adult stem cell therapies.

The future regenerative medicine strategies will be focused on biomaterials loaded with essential signaling molecules targeting adult progenitor stem cells in the implant site. The intention of cell-based therapies should be to effectively harvest adult stem cells, for immediate intra-operative administration using a standard biomaterial and bio-interactive delivery vehicle. Also, the ability to implant cell-free intelligent, bioactive materials that can effectively deliver signalling to modify the self-healing potential of the patient’s own stem cells will determine the future outcome of regeneration strategies.

### Clinically approved nanomedicines formulations

In 2017, FDA has approved Vyxeos for the treatment of acute myeloid leukemia. This nano-combination delivers two drugs cytarabine and daunorubicin simultaneously, at a synergic fixed ratio of 5:1 .This results in increase treatment efficacy and lower cumulated dose.

In 2018 Onpattro, the first lipid-based nanoformulation encapsulating siRNA, was approved for the treatment of transthyretin amyloidosis, a rare disease. This latest development in nanodrug technology is more significant as it addressed the needs of nucleic acid delivery and finally making it available for patients. Although, nucleotide-based drugs possesses a great therapeutic potential but have specific delivery challenges.

Following is the list of clinically approved nanodrugs approved by FDA –

| Trade name | Active ingredient | Indication | Nanotechnology |
|---|---|---|---|
| AmBisome | Amphotericin B | Fungal infections | Liposome |
| DepoCyte | Cytarabine | Lymphomatous meningitis | Liposome |
| Abraxane | Paclitaxel | Metastatic breast cancer | Albumin bound nanoparticles |
| Rapamune | Rapamycin | Immunosuppressant | Nanocrystal Elan |
| Taxotere | | Anti-neoplastic | Micelle |

## NANODENTISTRY

The maintenance of comprehensive oral health care can be done effectively by employing nanomaterials, biotechnology, including tissue engineering, and ultimately, dental nanorobotics. The applications of nanosciences in the field of dentistry has potential to revolutionize it in many areas which includes, local anesthesia, dentition renaturalization, permanent hypersensitivity cure, complete orthodontic realignments during a single office visit, covalently bonded diamondised enamel, and continuous oral health maintenance with mechanical dentifrobots.

### Applications of nanosciences in Dentistry

### Prosthodontics

In 2017, a 3D printed poly-methylmethacrylate (PMMA) denture base was studied in which 0.4% Titanium oxide ($TiO_2$) nanoparticles were added, inorder to improve its antibacterial characteristics and mechanical properties. The results of Fourier Transform Infrared Spectroscopy (FTIR), Scanning Electron Microscopy, and antimicrobial efficacy test against Candida species, showed improvements in the chemical, antimicrobial and structural properties of denture base.

### Nano in immunoprophylaxis

The ability of nanomaterials to provide sustained and controlled release profiles suggests that they can be an efficient antigen delivery systems. Also, nanomaterials have immunomodulatory effects that can be used to enhance and shape the humoral immune response. Nnanotechnological adjuvants can significantly improve the outcomes of vaccination..

Nanostructures that can potentially be used as adjutants are: polymeric nanoparticles, liposomes, particles resembling a virus, immune stimulating complexes (ISCOMs) and nanoemulsions. The most important property of nanoparticles is that some of them are capable of entering antigen-presenting cells and thus can regulate the immune response. This induces a Th1-type response against intracellular pathogens, which make them a viable option for delivery, on the surface of oral mucosa and through intradermal application

**FUTURISTIC NANOROBOTS**

The present status of nanotechnology in medicine is overwhelming and if the pace of advancements continues like this then a definite change in the notion of healthcare can be anticipated in the future. Nanotechnology is composed of two main strands. The first one is the Drexlerian molecule-sized machine, which has the ability to build and manipulate its environment at the atomic level. The second one is "biological" nanotech, which involves DNA and the machinery of life to create unique structures composed of proteins and DNA

1) **DNA-based origami robots**

DNA–based nanorobots are considered as one of the most advance experimentation in nanorobots. These nanorobots were inserted into a living cockroach which can perform a given task such as release of molecules stored within it after giving commands. Such nanorobots are also known as origami robots because of their ability to unfold and deliver drugs. These nanorobots could also be able to carry out complex programs like diagnoses or treatments.

## 2) Scallop-like microbots and nanoswimmers

These are exceptionally micro-sized, scalloped like smaller than a millimeter, robots that literally swim through our bodily fluids. They can be used to deliver drugs or other medical assistance in a highly-targeted way.

## Ant–like robots

These nanorobots are very fast that can locate, and use tools and are controlled by magnet. They have the ability to construct three–dimensional structures at a rapid pace.

## Sperm-inspired microrobots

Scientists at the University of Twente (Netherlands) and German University in Cairo has developed microrobot known as MagnetoSperm which can be controlled by weak oscillating magnetic fields. An external source of magnetic field is used to control its motion. Research is going on to develop a magnetic nanofiber that can be used as a flagellum.

## Bacteria-powered robots

These bacteria powered robots depend on electric fields and has the ability to navigate. They can be programmed to follow a particular path or to change its route.. These robots will play an important role in delivering medication exactly to the point where it is required, manipulation of stem cells to direct their growth, or building a microstructure.

## Clottocyte nanorobots

These nanorobots functions similarly to platelets in that they stick together to form a blood clot that stops bleeding and hence are also known as artificial mechanical platelets. They will have the ability to store fibers and on encountering a wound, will lay down fibers to help clot formation instantaneously.

**Respirocyte nanorobots**

These are nano creatures that can act as red blood cells, however, they would have the potential to carry greater amount of oxygen than natural red blood cells. This will be helpful in patients suffering from anemia.

**Nanoindustries and Commercialisation**

Nanomedicine market is markedly widespread and has presence of several important members. Following is the list of manufacturers who are most active in nanomedicine:

- Nanosphere Inc.,
- Par Pharmaceutical Companies Inc.,
- AMAG Pharmaceutical Inc.,
- Elan Corporation PLC,
- Life Technologies Corporation,
- Abraxis BioScience Inc. (now CelGene),
- Flamel Technologies S.A.,
- Oxonica Plc,
- Wyeth Pharmaceuticals Inc.,
- MagForce GmbH,
- NanoBioTix,
- Arrowhead Research Corporation

**FUTURE PROSPECTS**

Numerous clinical trials and patents have been done in the field of nanotechnology and nanosciences in the last two decades.. The best area where nanomedicines have made tremendous progress is cancer therapy. The application of nanomedicine and nano-drug delivery system would be one of the promising research areas for decades to come.The application of metal based nanoparticles including gold and silver both in diagnosis and therapy is an area of research that could potentially lead to wider application of nanomedicines in the future. Use of gold-nanoparticles for treating soft tissue tumors due to susceptibility of tumor cells to radiation based heat therapy is also one of the area to be focused in future.

Inspite of the broad understanding of future prospect of nanomedicine and nano-drug delivery system, its actual impact in healthcare system, and in cancer therapy/diagnosis, is very limited. This is attributed to the fact that the field of nanoscience has only two decades of actual research on the subject and lot of important fundamental attributes are still being unknown.

There has been a lot of keenness in development of nanorobots (and nanodevices) which can aid in tissue diagnosis and repair with full external control mechanism. This has not yet been a reality and remains a future challenge that might be attained by mankind in the very near future.

**Issues and Controversies with nanomedicines**

Apart from their benefits, the potential risk of nanomedicines both to humans and the environment requires long term study too. Hence, analysis of all new bimaterials for any acute or chronic toxicity effects on humans and environment must be analyzed

Biocompatibility is another important property in the design of drug delivery systems. Pre-clinical assessment of nanomaterials requires a thorough biocompatibility testing program, which involves in vivo studies. If the biocompatibility of nanomaterials cannot be warranted, different types of nanosystems may give rise to toxicological concerns. Appropriate and precise guidelines for risk assessment of nanomaterials is required. This could be accomplished with various regulatory agencies, pharmaceutical industry, government, and academicians. Inspite of all the measures taken for safety evaluation of nanoscale materials, most of them are still treated as conventional chemicals, thus lacking clear specific guidelines for safety.

The definition of nanomaterial has been controversial among the various scientific and international regulatory corporations. However, efforts have been made in order to find a consensual definition. The nano scale properties vastly increase a set of opportunities in the drug development; however, the physicochemical properties of the nanoformulation can results in the alteration of the pharmacokinetics, namely the absorption, distribution, elimination, and metabolism. Also, the potential for more easily cross biological barriers, toxic properties and their persistence in the environment and human body are some of the concerns over the application of the nanomaterials.

## Conclusion

Increase research in nanomedicine has helped in reformulation of pre-existing medicines or the development of newer ones. Alteration in toxicity, solubility and bioavailability profile are some of the modifications that nanotechnology induces in medicines. In the last decades, we have witnessed the translation of various applications of nanomedicine in the clinical practice, ranging from medical devices to nanopharmaceuticals. However, there is still a long way to bring about complete regulation of nanomedicines, from creating a uniform definitions to the development of protocols for the characterization, evaluation and process control of nanomedicines.

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