IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

RECENT ADVANCES OF NANOTECHNOLOGY IN PHARMACEUTICAL FIELD

Shital Bhosale, Jaydeep Pawar*, Nikita Shinde.

Department Of Pharmaceutics, HSBPVT's GOI College of Pharmacy (Affiliated to Savitribai Phule Pune University), Kashti, Dist. Ahmednagar, 414701, Maharashtra, India.

Abstract: Reduction in size is one of the most important unit operation that is of great importance in the field of pharmacy. This helps to enhance stability and bioavailability, reduce toxicity, increase release and provide better product formulation opportunities.

Now a days, Nanotechnology is gaining importance rapidly as a powerful technology. Recent developments in nanotechnology have permitted the development of elaborate Nano sized particles for different biomedical applications. The rapid development of nanotechnology has increased the possibility of using engineered nanoparticles that interact for disease treatment within biological environments. Nanoparticles change the kinetics, drug delivery, and subsequent drug release. Some effects include tissue or cell specific drug targeting, and a controlled release prevents unintended side effects. The present paper aims to review various applications of nanotechnology in the field of pharmaceuticals.

Key Words: Stability, Bioavailability, Nanotechnology, Nanoparticles, Drug Delivery.

INRTODUCTION

Nanotechnology is a fast-growing science of developing and using nano-sized particles, which is measured in nanometer. In other words, nanotechnology is the practice of systemically characterizing, manipulating and arranging matter on a nanometer scale, creating a revolution in science, engineering, technology, drug delivery and therapeutics.[1]

Nanoparticles are defined in the 10-1000 nm range as particulate dispersions or solid particles. The drug has been dissolved, trapped, encapsulated, or attached to a matrix of nanoparticles. Nanoparticles, nanospheres, or nanocapsules may be obtained, depending on the preparation method. Nanocapsules are structures in which the drug is confined to a space surrounded by a distinctive polymer membrane, whereas nanospheres are systems of matrix in which the drug is distributed uniformly and evenly. Biodegradable polymeric

nanoparticles, especially those covered with hydrophilic polymer such as poly (ethylene glycol) (PEG) known as long-circulating particles, have been used as potential drug delivery devices in recent decades, due to their ability to circulate over a longer period of time, target a specific organ, as a carrier of DNA in gene therapy, and their ability to deliver protein, peptides and genes.[2]

Nanotechnology is the study of controlling the matter on an atomic and molecular scale. Nanotechnology is sometimes proposed as a general-purpose technology, because it will have a significant impact in its advanced version on almost all areas of society and all industries.[3]

HISTORY OF NANOTECHNOLOGY

James Clerk Maxwell proposed a novel idea of nanotechnology as early as 1867. Prof. Kerie E. Drexler invented the term nanotechnology. Richard Zsigmondy brought about the idea of nanomaterials in the early 20th century. In 1959, Nobel laureate Richard P. Feynman said his colleague, Albert R. Hibbshad, proposed an interesting possibility for absolutely tiny machines. In the year of 2000, R.A. Freitas Jr., coined the term "nanodentistry". He created visions for orthodontics, dentition reconstruction, nanomaterials, and robotics utilising nanorobots in dentifrices-dentifrobots. While most of his ideas were and remain science fiction, these ideas are being slowly put into practice. Today several nanoscale technologies are recognized and used in the field of dentistry. [4]

Today, there are many procedures that take a lot of time and are very costly as well. Faster and much cheaper therapies can be produced using nanotechnology in the pharmaceutical sector. Another aspect of using pharmaceutical nanotechnology is available. Drugs usually work through the entire body until they enter the region affected by the disease. The medication can be targeted to the specific region with this pharmaceutical nanotechnology, which will make the drug even more successful and decreases the chances of potential side effects. Pharmaceutical nanotechnology, through early diagnosis, prediction, prevention, personalised treatment and medication, offers a novel approach and advanced technology against cancer. The main research areas in which nanotechnology will play a crucial role are target-specific drug therapy and methods for early detection of diseases.[1]

Mainly there are two widely related principles in nanotechnology:

• Positional assembly

• Massive parallelism

Positional assembly aims to get the right molecular parts in the right areas and massive parallelism helps to keep the costs down.[5]

Types of nanotechnologies

1)Nano devices: They are used in delivery of diagnostic and therapeutic agents.

It can be categories into three potent molecular technologies:

• Nanoscale materials and tools to be used in advanced diagnostics and biosensors, controlled drug delivery and smart medicines.

• Molecular machines and medical nanorobots assist in the rapid diagnosis and treatment of microbials and in the development of physiological function.

• Molecular medicine by genomics, proteomics, artificial biobotics (microbial robots)

2) Nano pharmaceuticals: Applications of the nanopharmaceuticals include lung disease, antiviral agents, cancer, arteriosclerosis, tissue cell repair, gene therapy, tissue engineering and diabetes.[6]

ADVANTAGES OF NANOPARTICLES

1. Targeted drug delivery.

2. Very good control over size and size distribution.

3. Protection of encapsulated drug.

4. Retention of drug at the active site.

5. Increased surface area.

6. Solubility enhancement.

7. Increased dissolution rate.

8. Increased oral bioavailability.

9. Clearance time is longer.

10. Rapid onset of therapeutic action.

11. Small amount of dose is required.

12. Less toxicity.

13. Reduction in fed/fasted variability.

14. Due to the small size of nanoparticles, they penetrate small capillary and are taken up by the cell which allows for efficient drug accumulation at the target sites in the body. [7,8]

DISADVANTAGES OF NANOPARTICLES:

1. Cytotoxicity.

2. Inflammation of alveoli.

3. Pulmonary carcinogenicity and pulmonary inflammation.

4. Toxicity issues are seen if polyvinyl alcohol is used in excessive amount as a detergent.

5. Targeting abilities are limited.

6. The disturbance of autonomic imbalance by nanoparticle which is having direct effect on heart and vascular function.[7]

VARIOUS APPROACHES USED IN SYNTHESIS OF NANOSTRUCTURES

In the production of nanoparticles, following methods are adopted, namely, Bottom up approach, Top down approach and functional approach.

A) Bottom up technique: -

Smaller components are organised into more complex assemblies in this method. This starts by designing and synthesising custom-made molecules capable of self-assembling or self-organizing into mesoscale or macroscale structures of a higher order. Modern synthetic chemistry has reached the point where the small molecules can be prepared for almost any structure. Currently, these techniques are used to produce a wide range of important chemicals, such as pharmaceuticals or commercial polymers. Such bottom up techniques are much cheaper than top-down methods.[6]

By templating and non-templating, the self-assembling of atoms or molecules can be achieved. Under the influence of a particular sequence, pattern, structure, external force or spatial constraint, templating involves the interaction of biomacromolecules. In the formation of nanostructures, for example non-ionic surfactants and block co-polymers are used as templates. Two dimensional hexagonal nanostructures formed by cylindrical polymeric amphiphilic micelles were used as templates for the production of semiconductor cadmium sulphide nanotubes. Non-templating is the production of nanostructures from externally influenced atoms or molecules. Self-assembly lithography is reliable and cost-effective and produces nanostructures smaller than 100 nm in size. 'Bottom-Up' is thought to be an optimal nanotechnology technique.[9]

B) ‘Top-Down’ approach

Smaller devices are produced in this process by using larger ones to direct their assembly. Small features are then created by beginning with the patterning and carving of larger materials to create nanoscale structures in specific patterns. It is possible to produce complex structures containing hundreds of millions of precisely located nanostructures. Materials are reduced to the nanoscale and can suddenly exhibit very distinct properties, allowing specific applications. As the device size decreases, the ratio of surface area to volume increases and the number of physical phenomena becomes noticeably pronounced. This approach aims to create smaller devices by using larger ones to direct their assembly. Pit & fissure sealants, nanocarriers for bone targeting, and other products are included in this. [6]

By certain processes, bulk materials are reduced to form nanostructures. ‘Top-down’ is accomplished by breaking, cutting or etching techniques which is achieved by bulk or film machining, surface machining and mould machining employing lithography. Bulk machining employs photolithography, which applies the etching method, whereas soft lithography is used for mould machining. Electron beam lithography, x-ray lithography and lithography of micro-electro-mechanical devices are other techniques. [9]

C) Functional approach: Components of a desired functionality are developed in this approach, regardless of how they might be assembled. Different approaches followed at Rice University are as follows:

D) Wet nanotechnology

Analysis of the biological system, which primarily occurs in the water environment which includes genetic material, proteins, enzymes, and cellular components of nano scale.

E) Dry nanotechnology

This derives from surface science and physical chemistry focuses on structure fabrication in carbon, silicon and other organic materials.

F) Computational nanotechnology

This allows for the modelling and stimulation of complex nanometer-scale structure, and the predictive and analytical ability of computation is key to nanotechnology success.

The objectives created by nanotechnology can be accomplished when the scientist is able to manipulate individual atoms, construct nanoscopic machines, called assemblers that can be programmed to manipulate atoms and molecules at will, and are programmed to build new assemblies in order to create enough assemblers to manufacture consumer goods, some nanomachines called replicators, will programmed to build new assemblies. [6]

TYPES OF PHARMACEUTICAL NANOSYSTEMS

1. **Liposomes**

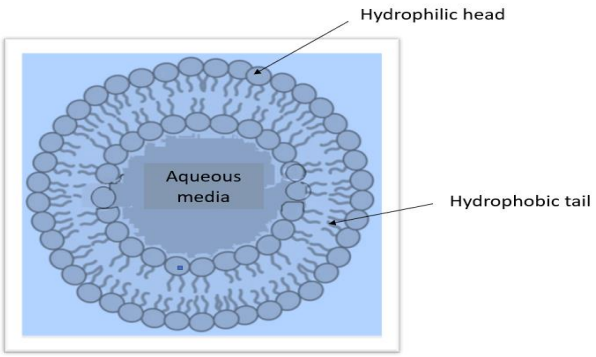

Fig. 1. Structure of Liposome

Liposomes are self-assembled, spherical, closed colloidal structures composed of lipid bilayers surrounding a central aqueous area and 400 nm in size. Liposomal preparations have demonstrated an ability to enhance related drug pharmacokinetics and pharmacodynamics. For the treatment of metastatic breast cancer and Kaposi's sarcoma, liposome-based formulations of several anticancer agents were approved. [10]

Nanoscale systems of drug delivery using liposomes and nanoparticles are new technologies for the appropriate delivery of chemotherapeutic drugs in cancer treatment. Its use offers improved pharmacokinetic properties, regulated and sustained drug release, and, more significantly, reduced systemic toxicity. Liposomal formulations of anticancer drugs for human use have already been approved. Doxil® is a liposomal

formulation of the anthracycline drug doxorubicin, which is used to treat cancer of Kaposi sarcoma and multiple myeloma associated with AIDS. Higher efficacy and less cardiotoxicity are its benefits over free doxorubicin. These benefits are related to passive tumour targeting due to leaky tumour vasculature and EPR (enhanced permeation and retention) effects, as well as to lower free doxorubicin concentrations at healthy tissue sites. In addition, Doxil® is currently being clinically studied for the treatment of breast cancer. [11,12]

2.Dendrimers

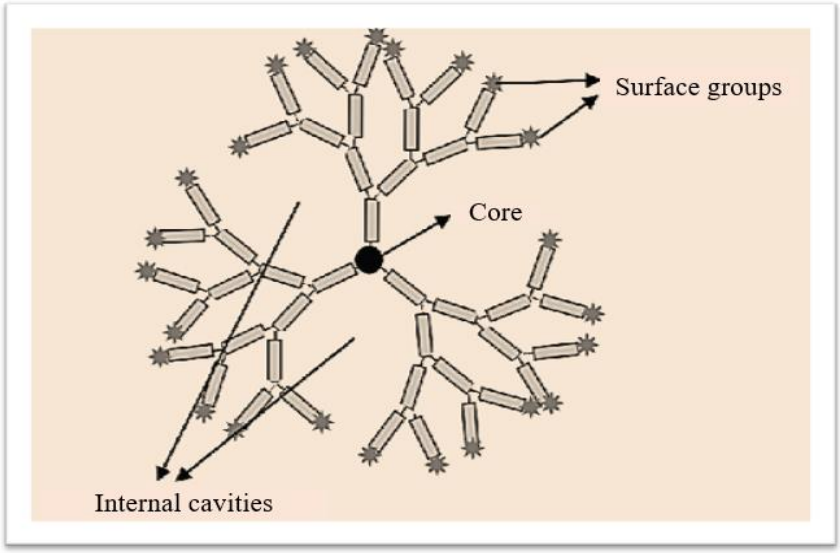

Fig. 2. Structure of Dendrimers.

Dendrimers are a new class of macromolecules that have a symmetrical centre and form the 3-D spherical structure. These have a branching structure that gives them vast amounts of surface area that can be connected to therapeutic agents or other biologically active molecules. A single dendrimer may hold a molecule recognizing cancer cells, a therapeutic agent destroying certain cells, and a molecule recognizing the cell death signals. Dendrimers are said to be engineered to release their contents only in the presence of certain cancer-related trigger molecules. [10] Applications of dendrimers include drug delivery, gene delivery and transfection, sensors, blood substitution, nanoparticles, crop protection and agrochemicals. [13]

3. Carbon Nanotubes

Carbon nanotubes in a hexagonal network of carbon atoms are a new form of carbon molecule around them, these hollow cylinders can be as small as 0.7 nm in diameter and exceed several millimeters in length. Each end of a fullerene half molecule can be opened or closed. Together with their extraordinary physical, mechanical and electrical properties, the small dimensions of nanotubes make them special materials. The carbon nanotubes ' mechanical strength is more than sixty-fold greater than that of the best steels, although they weigh six times less. These often cover a very large specific area of the earth, are excellent heat conductors and exhibit unique electronic properties, providing three dimensional configurations. They have greater capacity to absorb molecules. [7] The main applications of Carbon Nanotubes in pharmacy and

medicine include drug, biomolecule, gene delivery to cells or organs, tissue regeneration, and biosensor diagnostics and analysis. [14]

4. Quantum dots

Quantum dots are tiny crystals that glow when stimulated by ultraviolet light. When stimulated by light, the latex beads filled with these crystals emit the colour that illuminates the interest series. Through combining different quantity dots within a single bead, it is possible to create samples that emit a distinct spectrum of different colours and lights intensities, acting as spectral bar code. Crystal-filled Latex beads can be designed to bind to specific DNA sequences. As light activates the crystals, the colours they emit act as colours and illuminate the sequences of interest. [10]

Quantum dots could make medicine revolutionary. Sadly, these are mostly harmful. Interestingly, the presence of heavy metals in QDs such as cadmium, a well-established human toxicant and carcinogen, presents potential hazards especially for future medical usage, where quantum dots are intentionally inserted into the body. [15]

5. Nanosuspension

Nano-suspension is a suspension of drug nanoparticles in a liquid. A size of nanoparticles lies between 200 and 500 nm and the excellent characteristic of nanosuspension is increased saturation, solubility, increased compound dissolution. Solubility and saturation rise below 1 mcm of particle size. Nanosuspension can cause changes in the crystalline structure to increase the amorphous particle fraction or even to produce entirely amorphous particles is an additional feature of nanosuspension. Nanoparticles and nanosuspensions have improved tissue adhesivity. It has been stated that oral drug administration in the form of nanosuspension increases the rate of absorption and bioavailability.

Examples of Nanosuspension: ibuprofen nanosuspension is prepared by emulsion solvent diffusion technique to increase the ocular availability, while Danazole nanosuspension is prepared by nanocrystal technology to enhance bioavailability. [16,17]

6. Solid lipid Nanoparticles (SLN)

The solid lipid nanoparticles are colloidal sub-micron carriers (50-1,000 nm) consisting of physiological lipid, distributed in water, or in aqueous surfactant. To address the drawbacks of liquid oil droplets, liquid lipid was replaced by a solid lipid, which gradually became solid lipid nanoparticles. [7]

7. Polymeric nanoparticles

The drug is dissolved, absorbed, attached or encapsulated in the matrix of nanoparticles. Nanoparticles, nanospheres or nanocapsules may be obtained with various properties and release characteristics for encapsulated therapeutic agent, depending on the preparation method. Nanoparticles are vesicular structures in which the drug is confined to a cavity surrounded by special polymer membranes, in which the drug is mechanically and uniformly distributed as nanospheres. The benefits of drug delivery using nanoparticles are

the result of their two main basic properties. Firstly because of their small size, first nanoparticles can pass into smaller capillaries and are taken up by cells, enabling efficient accumulation of drugs at the target sites. Secondly, the use of biodegradable materials for the preparation of nanoparticles permits the continued release of drugs within the target site for days or even weeks. [7]

8. Polymeric micelles

Polymeric micelles have been extensively studied as drug carrier. In physiological solution, polymeric micelles have improved thermodynamic stability, as shown by their low critical micellar concentration, which makes polymeric micelles stable and prevents their rapid in vivo dissociation. Micelles have a fairly narrow nanometer range size distribution and are distinguished by their unique core-shell construction, in which hydrophobic parts are isolated from the aqueous exterior.

For systemic delivery of water-insoluble drugs, micellar systems are beneficial. Drugs can be partitioned in the hydrophobic cores of micelles and the outer hydrophilic layer from stable dispersion in aqueous media which can then be given intravenously. Due to their smaller size and hydrophilic shell, the distribution of drug-loaded polymer micelles (less than 100 nm in diameter) after intravenous administration has been shown to have extended systemic circulation time, which significantly reduces their uptake by the reticuloendothelial system. Drugs incorporated into polymeric micelle can accumulate in tumours to a greater degree than free drugs and show decreased distribution in non-targeted areas. [7]

9. Magnetic Nanoparticles

Magnetic nanoparticles are efficient and powerful medical diagnostic devices. Techniques for magnetic immunoassay were established in which the main field is produced by the magnetically labelled target that was detected directly with a sensitive magnetometer. Magnetic resonance imaging uses superparamagnetic nanoparticles as contrast agents. Polymer such as dextran is used for coating the magnetic nanoparticle. Magnetic indomethacin nanoparticles showed selective targeting under the magnetic field of 8000 Oe-strength, after normal administration, the concentration of drug was higher in the liver and spleen where endocytosis and phagocytosis may occur. [7, 18]

10. Ceramic nanoparticles

The newly emerging field of using inorganic (ceramic) particles with trapped biomolecule has potential applications at many frontiers of modern materials science like drug delivery system. Ceramic nanoparticles have the advantages of easy preparation with desired size, shape and porosity, and no effect on swelling or porosity without pH change. [7]

11. Nanopores

Materials with defined pore-sizes in the nanometer range are of special interest for a broad range of industrial application because of their outstanding properties with regard to thermal insulation, controllable material separation and release and their applicability as templates or fillers for chemistry and catalysis. One example of nanopores material is aerogel, which is produced by sol-gel chemistry. [7]

12. Nanowires

Nanowires are conductive or semi-conductive particles with a few dozen nm crystalline structure and a high ratio of length / diameter. Nanowires based on silicone, cobalt, gold or copper have already been developed. For nanoelectronics, they are used to transport electrons that could be made of various metals, oxides, sulphides and nitrites. [7]

13. Nanoshells

Nanoshells (NS) are miniscule beads with gold coating. The light wavelength that the beads absorb is related to the coatings ' thickness. Therefore, the beads can be constructed by adjusting the thickness of the layers that make up the NS that absorb different wavelength of light. The most effective NS are those which absorb near-infrared light which can easily penetrate several centimetres of human tissues. Light absorption by NS produces an intense heat which is lethal to the cells. Metal NS which are powerful near-infrared absorbers on human breast carcinoma cells are effective both in-vivo and in-vitro. [7]

APPLICATIONS OF NANOTECHNOLOGY IN PHARMACEUTICAL FIELD

Recent nanotechnology advances have led to the rise of nanomedicine, a new field that involves various diagnostic and therapeutic applications involving nanomaterials and nanodevices. The main objective of any new therapeutic procedure is to reduce the toxicity or any harmful effect of the agents by allowing them more sensitive to the target and, therefore, to minimize their dosage. Nanotechnology has a useful application in stem research that involves monitoring stem cell surface molecules, non-invasive tracking of in vivo transplanted stem cells and progenitor cells, tracking system of stem cell delivery, and intracellular delivery of DNA, Ribonucleic acid interference (RNAi), proteins, peptides, and small stem cell differentiation drugs. Nanotechnology finds its way also in the identification of bacteria and toxins. The following paragraphs discuss in brief about the applications of nanotechnology in pharmaceutical field.

1. **Inhibition of neointimal hyperplasia**

Neointimal hyperplasia refers mainly to the proliferation and migration of vascular smooth muscle cells in the tunica intima, resulting in arterial wall thickening and reduced space of arterial lumen. Neointimal hyperplasia is the main cause of restenosis following percutaneous coronary procedures such as stenting or angioplasty. [19,20]

Atherosclerosis affects many of whom need arterial intervention, treatment frequently fails due to the occurrence of neointimal hyperplasia, requiring reintervention. The fact that Nitric Oxide (NO) prevents neointimal hyperplasia is well known. Diazeniumdiolates are a class of NO donors which, when placed in an aqueous condition, release NO spontaneously. The nanofiber gels were used to formulate these diazeniumdiolates. [10]

2. Management of tuberculosis

TB control is either preventive (i.e. vaccination) or medical (i.e., chemotherapy) treatment. Liposomes and lipid nanoparticles are widely used to deliver the anti-TB drugs for long-term therapy with sustained release profiles and also to enhance the agent's pharmacokinetic profile. [10]

Treatment of TB needed a constant and regular supply of drugs to the cells. The NP was attached to drugs such as rifampin (RMP), isoniazid (INH)/Pyrazinamide (PZA), and coated with PEG to provide TB cells with drugs in sustainable way. In TB therapy, researchers are seeking to enhance bioavailability, minimise dosing frequency and drug administration methods [21]

3. Nanotechnology in pharmaceutical aerosols

Some drugs are very poor candidates for the production of aerosols, but with nanotechnological principles applied to prepare nanosuspensions for drugs that are insoluble in both aqueous and oily media, improved pharmacokinetics has resulted in improved bioavailability of aerosol-administered drugs. In addition, the production of bioadhesive nanoparticles helped to increase the drug's mucosal residence time with increased drug absorption and subsequently increased bioavailability. [22,23,24]

4. Cancer detection and targeting

The identification and targeting of cancer tissues or cells has always been a challenge for the formulator. Cancerous tissues or cells that are themselves becomes very difficult to target specific cells or organs; as a result, many normal cells are killed in the process. Several nanotechnology-based devices have come to the rescue of the formulators, whereby the anticancer agents can only be targeted to specific cells or organs using biomarkers. One such method of cancer detection is the use of Photodynamic Therapy (PDT) using 5-aminolaevulinic acid which is a photosensitizer in body metabolized to protoporphyrin IX. Quanum dots (QD) are also well established in the literature in the mapping of lymph nodes, which is an important technique for mapping cancer during surgery, and in vivo cancer imaging using semiconductor.[10]

The regular tumor cell drug delivery produces side effects in normal tissues such as nephrotoxicity, neurotoxicity, cardiotoxicity, and multiple drug resistance (MDR) decreases concentration of the drug at the target place, low accumulation. MDR is primarily due to the rise in cell membrane efflux pumps such as P-glycoprotein. Paclitaxel loaded NP can transfer drugs without causing MDR disruption. NP dependent drug delivery system is used to solve these problems. The tumor sites are developing new blood vessels to rapidly provide oxygen and nutrients. These newly developed vesicles are defective and have leaky vasculature which allows diffusion of NP. The demand for energy is increasing, and glycolysis occurs. Ultimately generated acidic environment and the benefit of pH uses for drug release.

Cetureimab, fluorouracils are medications that are bound to liposomes, hydrogels, crystals to treat oral cancers, and to tackle low solubility, permeability and poor bio-availability. [21]

5. **Nucleic acid delivery**

The cell membrane lipid bilayer represents the major obstacle to nucleic acid delivery, such as small interfering RNA or plasmid DNA. A variety of viral and polymeric nanocapsules, cationic liposomes and non-viral vectors (lipoplexes, polyplexes and inorganic nanoparticles) have been developed that are able to effectively cross the lipid membrane and deliver nucleic acids in vitro with ease and low cytotoxicity. [25,26]

6. **Biochemical sensors**

A biosensor is commonly defined as a measuring device consisting of a sample with a sensitive biological recognition feature, or a bioreceptor, a part of a physicochemical detector, and a transducer between to amplify and transmit these signals in a measurable form. [8]

These devices are used to assess the specific pathological proteins and physiological-biochemical markers associated with disease or impaired body metabolism. A nanobiosensor or nanosensor is a biosensor with dimensions on the order of a nanometer. Biosensors are used

Catalysis is one of the most important functions of nanoparticles, especially with noble metal nanoparticles that have a high catalytic activity for many chemical reactions. Since nanomaterials also have excellent biocompatibility, they are used to immobilise biomolecules for biosensor manufacturing. Glucose nanosensors are used in diabetics to measure the glucose levels. Triglyceride nanosensors are of great use in the detection of hyperlipidaemia. Free optical biosensors based on gold colloids are essential for qualitative and quantitative determination of biomolecular interactions and recent advances in the development of gold colloid-based localized surface plasmon resonance (LSPR) biosensors and their applications in immunosensing, nucleic acid detection and toxin quantification have added great value to this technology. For polynucleotide or protein detection, oligonucleotide-capped gold nanoparticles have also been documented using various methods of detection / characterization such as atomic force microscopy, gel electrophoresis, Raman spectroscopy, and surface plasmon resonance imaging. [10]

7. **Drug discovery**

Pharmaceutical nanotechnology plays a key role in drug discovery, which depends on a greater understanding of the drug action process and biomarker recognition associated with clinical disease. Nanotechnology helps to find and verify the target by recognizing the protein that is present on the surface of the cell or target. [8]

Nanotechnology can improve the drug delivery process by miniaturizing, automating, and assay reliability. Single walled nanotubes are used effectively in the detection of pathogen surface protein. Quantum dots-monitor individual glycine receptors for duration ranging from milliseconds to minutes to study their dynamics in the neuronal membrane of living cells. Some widely used nanomaterials in diagnosis are gold nano particles, nanobodies (smallest, accessible, intact antigen-antibody fragments), developed by ablynx. The pharmaceutical nanotechnology is used to identify pathogens in humans, to isolate and purify molecules and cells and to detoxify chemicals. [27]

8. **Molecular Diagnostics**

Molecular imaging is the nanoscience in which subcellular biological processes in intact organisms are described, characterized and quantified. Such processes involve gene expression, association with protein proteins, signal transduction, cell metabolism, and intracellular and intercellular trafficking. They were widely used in various optical imaging, magnetic resonance imaging, nuclear imaging and ultrasonic imaging. [8]

The combining nanoparticles with other materials based on nanotechnology has the potential to tackle this growing challenge and provide technologies that allow single-cell and single-molecular diagnoses. Particles of cadmium selenide (CdSe), cadmium telluride (CdTe), indium phosphide (InP), and indium arsenide (InAs) act as contrast agents in bioimaging QDs, offering far greater resolution than actual fluorescent colours. [1]

Many other uses include precise cell and tissue labelling, useful for long-term imaging, multicolour multiplexing, complex visualization of subcellular structures and fluorescence resonance energy transfer (FRET) and magnetic resonance imaging (MRI). Nanomaterials such as dendrimer, quantum dots, carbon nanotubes, and magnetic nanoparticles are substituted with MRI agents. [27]

9. **Nanoparticle in cosmetics**

Nanoparticles are also used in various cosmetic products like Deodorant, Soap, Toothpaste, Shampoo, Hair conditioner, Anti-wrinkle cream, Moisturizer, Foundation, Face powder, Lipstick, Blush, Eye shadow, Nail polish, Perfume and After-shave lotion etc.

i. **Sunscreens:** - UV filters, such as titanium dioxide and zinc oxide, are used to make the sunscreen transparent rather than white in the form of nano rather than bulk form. It is also asserted that when used in nano form, they are more powerful.
ii. **Breast cream:** - St Herb Nano Breast Cream says that it is a mixture of "nanotechnology and the timeless Thai herb, Pereira Mirifica" and that noisome "expands the cell substructure and growth of the breast lobules and alveoli,"
iii. **Hair care:** - The Nanoceuticals Citrus Mint Shampoo and Conditioner from RBC Life Science was made with Nano Clusters TM. Nanoclusters gives shine to the hair.
iv. **Make-up:** - Nano Dispersion technology from Serge Lutens Blusher "creates an extremely fine and light powder with exceptional properties: outstanding elasticity, extreme softness and quick diffusion.
v. **Fullerenes:** - Nanotechnology can be used to produce new types of materials, such as carbon fullerenes. Those tiny carbon spheres are believed to have anti-aging properties. [20] 28

10. **Tissue Engineering**

Nanomaterials are used in tissue regeneration, implant coating, tissue repair and replacement, structural implant materials, Bio-resoursable materials, bone repair, Surgical aids, Implantable devices (sensory aids, retina implants), operating tools and also in smart instrument. [19] 27

Nanotechnology may help to replicate damaged tissue, or rebuild it. "Tissue engineering," using appropriate nanomaterial-based scaffolds and growth factors, allows use of artificially stimulated cell proliferation. Tissue

engineering may replace conventional treatments nowadays such as organ transplants or artificial implants. Nanotechnologies and microtechnologies can be combined with biomaterials to create tissue engineering scaffolds that can sustain and control the actions of cells. [1]

11. Gene therapy

Liposomes smaller than 100 nm can be used to transfer genetic material to cells. Liposomes effectively integrated by liver Kupffer cells with polyethylene glycol and galactose target liver cells, because of their rapid absorption. Thus, gene therapy for various liver diseases such as Wilson's disease and hereditary hemochromatosis can be attempted with liposomal nanoparticles. In addition, polymeric nanoparticles have been applied to breast cancer cells in gene therapy, resulting in antiproliferative effects. [1,29]

12. Artificial organs and implants

The development of artificial cells, tissues and organs is another area where the advances of nanotechnology can be actually implemented. The use of artificial cells to replace defective or incorrectly functioning cells and organs, particularly related to metabolic functions, is being actively investigated. [1]

13. Nanoparticles in ocular delivery systems

The use of nanoparticles for the extended release of drugs to the eye has been studied in several ways. The main problem of ophthalmologic formulation is the quick removal from the eye, which means clearance of the applied drug through the nose. For nanoparticles, it could be seen that improved adhesiveness is available at the target site of action, contributing to higher drug levels. However, the fundamental issue was that there was limited toxicological acceptance of the nanoparticles. Gasco has shown that SLN has a prolonged retention period in the eye. Using radiolabelled formulations and γ-scintigraphy, this has been verified. Lipids of SLN are easy to metabolise and open up a new route for the delivery of ophthalmologic drugs without impairing vision.[20] Polymeric NP, nanogels, liposomes, micelles, dendrimers, chitosan and protein NPs are examined for the treatment of various ophthalmic back diseases such as retinoblastoma, diabetic retinopathy, retinitis pigmentosa. For the treatment of posterior segment disorders such as choroid and retina, the drug and gene deliver to the target tissue, enhancing diagnosis and retinal prosthesis. [21]

Celecoxib-loaded drug nano particles have been produced using various biodegradable polymers such as poly(L-lactide) (PLA), poly-ε-caprolactone (PCL) and poly (D, L-lactide-co-glycolide) (PLGA) through impulsive solvent emulsification diffusion process. Drug release from these formulations was seen in a sustained manner without any bursting effect. Non-fickian diffusion with appropriate Higuchi model fitting has been observed. These products had an acceptable level of toxicity potential as assessed by cytotoxic analysis.[30]

14. Diabetes

NP containing matrix-attached insulin has been developed. The enzymes are attached to NP when blood glucose levels rise, enzymes induce the release of insulin and can eventually control the level of blood glucose for many days. [21]

Oral Insulin

Insulin is currently given by injection for type 1 diabetes, as insulin given orally has limited efficacy. It is denatured by the stomach's acidity and its large size means that it is slowly absorbed, which means that before it can be absorbed into the bloodstream, it can also partially digest enzymes in the intestine.

Chitosan nanoparticles (a derivative of chitin, a natural structural polymer found in crustaceans and fungi) have been found to be used as a carrier for oral insulin. It protects insulin from digestive juices and helps insulin to be absorbed even more efficiently into the bloodstream.

Monitoring Glucose Levels

Present blood glucose monitoring techniques are invasive and sometimes painful. Because of this, the finger-prick test was associated with non-adherence by diabetic patients to treatment protocols, but it also has very limited precision. It cannot be conducted during certain tasks, such as driving or sleeping, and its irregular nature means that it can miss significant and potentially harmful spikes and fluctuations in blood glucose levels between tests.

In recent years several advanced approaches have been developed for non-invasive, continuous monitoring of blood glucose. Nanosensors should be able to selectively measure glucose concentrations using carbon nanotube electrodes. Functionalization or nanotubes will alter the current flowing down the conductive nanotubes by allowing glucose to be present. This data could then be fed into an embedded microchip, which could wirelessly transmit the data to a wearable device. This would allow blood glucose levels to be controlled accurately and continuously.[31]

Scientists have stated that in a mouse model of type I diabetes, microgels with enzyme nanocapsules facilitate insulin discharge and induce a drop in blood glucose levels. As a result of the enzymatic transformation of glucose into gluconic acid and the protonation of the chitosan network, the microgel system expanded when exposed to hyperglycaemic conditions that serve as a regulator and release insulin. [30]

15. **Bone diseases**

Work has shown that nanotechnology has wide potential in the fields of orthopedics and onthrodontology. Researchers optimizing dental implants by applying nano-tubes to the implant's surface. It improves the ability to load the nanotubes with anti-inflammatory drugs that can be applied directly to the implant region. Owing to their promising antimicrobial properties, silver nanoparticles have gained ever greater interest in orthopaedics. They are used as bone cement in tumor prostheses, wound implants and as well. For another research novel protective salivary peptides & chitosan-based nanoparticles were extensively studied in the orthodontic field as the delivery system. [30]

Calcium-phosphate dependent NP is used without toxicity to bone tissues in drug delivery for bone diseases. Drugs, such as biosphosphonates, are used to treat arthritis, osteoarthritis, osteosarcoma and metabolic bone cancer. Success in bone regeneration with Silica and magnetic NP. [21]

16. Central nerve system diseases

NP can cross blood brain barrier (BBB) and it can be used to administer medicine to brain tumors, Alzheimer's disease, inborn metabolic disorders such as lysosomal storage disease, infectious diseases and aging etc. Most therapeutic particles cannot move through BBB, BBB can only move through a small class of drugs or molecules with high lipid solubility and low molecular mass. NP has a high affinity and is able to distribute drugs directly via BBB. Many transport molecules, such as growth factors, insulin, and transferrin, will improve drug efficiency and kinetics across tissue spectrum. [21]

17. Transdermal drug delivery: -

SLN dispersions with low lipid content (up to 5 per cent) have the smallest particle sizes. In dermal administration, the higher concentration of the distributed lipid and poor viscosity are also disadvantageous. For most situations, it is important to add the SLN dispersion in an ointment or gel to obtain a consistency which can be applied to the skin. The stage of incorporation implies further reduction in the lipid material. The increase in the solid lipid content of SLN dispersion results in semi-solid, gel-like systems that may be suitable for direct skin application. Alternative dosage forms to transdermal therapeutic systems are typically difficult to develop due to a low permeation rate that also applies to LN. Introducing enhancers, iontophoresis, and micro needles which are all invasive are prospective strategies that are the focus of the study. [28]

18. **Topical application**

As far as the issues of regularity are concerned, topical application is generally unproblematic. The defensive properties of SLN for chemically labile drugs against degradation and the occlusion effect due to the formation of film on the skin are the key advantages of topical products. There are several compounds, such as retinol or vitamin C, particularly in the cosmetics industry, which cannot be introduced due to a lack of chemical stability. Retinol can only be introduced when certain safety measures are applied during manufacturing (e.g. noble gasing) and when specific packaging materials (e.g. aluminium) are used. [32,33]

19. Nanoparticles as per-oral drug delivery

Aqueous dispersions or SLN loaded conventional dosage forms, such as tablets, pellets or capsules, may be included in per oral SLN administration form. Due to its acidity and high ionic strength, the microclimate of the stomach favours particle aggregation. It is anticipated that food will have a major impact on the performance of the SLN. [123] Following administration of CA-SLN suspension versus a CA(Cyclosporin) solution (CA-SOL), plasma levels and body distribution have been determined. Two plasma peaks had been observed following CA – SLN administration. The presence of free drugs has been attributed to the first peak; the second peak can be attributed to regulated SLN release or possible intestinal uptake of SLN. In the total CA concentration-time profiles of all measured organs, these two peaks have also been found. It was also found that CA was shielded from hydrolysis by incorporation into SLN. The finding of this study was that SLN after oral administration is a promising sustained release mechanism for CA and other lipophilic

medicines. Enhanced bioavailability and sustained plasma levels have been documented following oral administration of lipid nano dispersive cyclosporine to animals. [28]

20. Implantable delivery systems

Because of its size, nanoparticles can serve as delivery mechanisms, operated by approximately zero order kinetics, otherwise they can cause toxicity compared to I.V. Liposomes, ethosomes and transferosomes are the carriers. These aid in lowering peak plasma levels and reduce the risk of adverse reactions, make the duration of action more predictable and prolonged, reduce the frequency of re-dose, and increase the acceptance and compliance of patients. SLN is given to animals intravenously. Pharmacokinetic trials of SLN-incorporated doxorubicin showed higher blood levels after i. v. injection in rat relative to commercial drug solution. A rat injection. As far as body distribution is concerned, SLN was found to cause higher concentrations of drugs in the lung, spleen and brain, while the solution led to a greater distribution in the liver and kidneys. For SLN, parenteral application is a very broad field. For commercial purposes, subcutaneous injection of a drug loaded with SLN can be used, e.g. erythropoietin (EPO), interferon-β. Intraperitoneal and also intra-articular are other routes. Because of the application region, intraperitoneal application of the drug-loaded SLN will prolong the release. Furthermore, compared to injecting drug micro particles, incorporation of the drug into SLN may decrease irritancy. [28]

21. Nanoparticles as Pulmonary drug delivery

The pulmonary administration of SLN tends to be a rather interesting application. Since the particle size is too small and they will be exhaled, SLN powders should not be administered to the lung. The aerosolization of aqueous SLN dispersions is a very simple technique. The significant point is that during aerosolization, the SLN should not accumulate. Aerosol droplets were collected by an aerosol collision with the beaker's glass wall. This essentially shows that SLN is perfect for pulmonary delivery. The substance can be released from the lipid particles in a controlled manner following localization into the bronchial tube and in the alveoli. [28]

22. Nanoparticles as carriers for nasal vaccine delivery

In the field of nanotechnology, there is currently significant enthusiasm about the possible use of nanosystems as carriers for the delivery of mucosal vaccines. Several diseases are associated with the entry of microorganisms into the respiratory mucosal surfaces, such as influenza, respiratory syncytial virus infection, measles and meningitis. It is therefore highly beneficial to obtain a local mucosal protection at the entry pathway of the corresponding pathogens, that is, the primary site of infection, upon vaccination against these diseases, since it reduces the risks of person-to-person and environmental infection. This can be achieved by nasal delivery of vaccines, as both mucosal and systemic immune responses (i.e. humoral and cell-mediated) can be induced, particularly if the vaccine is adjuvanted by an immune stimulator or delivery system. Furthermore, secretory mucosal immunoglobulin (Ig)A is caused by nasally administered vaccines. [28]

23. Cardiovascular diseases

There is the potential for a modern nano-therapeutic approach to enhance the safety and effectiveness of thrombolytic drugs. It requires the mechanical activation by high-fluid shear strains inside blood vessels to selectively target drugs to vascular hindrance locations. In vitro and in vivo readings have shown that this technique can be used competently to lyse clots by means of a substantially lesser thrombolytic drug quantity than its requirement when supplied in a soluble preparation. The prime example of this is seen in application of dendrimers. Dendrimers are circular nanoparticles developed for a number of diseases that have been used as a way of administering medicinal agents. A team of researchers created a technique for attaching dendrimers to tissue plasminogen activator (tPA) to create a drug delivery system that would require lower doses with reduced side effects. The results showed that during the course of a varying proportion of dilutions, this drug delivery system developed an advanced concentration of tPA dendrimer complex. [30]

NP is a translation-generated protein used to bind damaged areas of the arteries as well as to dissolve blood clots. In order to deliver proteins to the right position in arteries, NPs are tried to direct under the magnetic field. [21]

24. Nanoparticles in Asthma

As compared to conventional drug administration, the most advanced fields of nanotechnology research currently applicable to asthma are related to drug delivery, which provides better outcomes, increased patient compliance, and optimum therapeutic protection. Asthma-related anti-inflammatory and bronchodilator drugs (e.g., glucocorticoids and β2-agonists) are considered to be more beneficial for topical use in respiratory organs than systemic routes. Since the significance of local drug delivery for asthma is already known, nanotechnology has been used to improve the delivery of drugs. A previous study indicated that inhalation of nanoparticle dry powder improved the delivery of inhalation as well as deeper lung permeability. Matsuo et al. also demonstrated that in a murine model of asthma, a steroid encapsulated in biocompatible blended nanoparticles produced sustained and greater benefits at the site of inflammation of the airway relative to free steroids. By allowing the delivery of the medication to the target tissue, nanoparticles improve the therapeutic effect, thus enhancing the deposition of the drug in the lungs. [34]

RISKS OF NANOTECHNOLOGY

Although nanotechnology offers a great deal of promise in the field of medicine, we can't neglect safety issues and concerns. Regulation of nanotechnology is required in order to minimize risk involved. [35]

The safety of nanotechnology in humans, animals and plants and its effects on the environment are of concern, despite the great potential of nanotechnology. Owing to their increased surface area, some nanoparticles exhibit increased toxicity. Research have shown that carbon nanotubes in the lungs of laboratory animals are cytotoxic and cause granulomas. In addition, cells have inflammatory and harmful effects on metals and metallic oxide nanoparticles such as copper, cobalt, titanium oxide and silicon oxide. It can also contribute

to immune responses that are resistant to such technologies when it comes to drug delivery using nanotechnology. [9]

Researchers often claim that it is dangerous to inhale nanoparticles. They get trapped in the deepest portion of the lungs. This allows them to move through the lung cell linings to enter the blood vessels. There is no evidence regarding their toxic value in the bloodstream. [35]

However, research and discussions on the benefits and threats of nanotechnology are ongoing. Optimistically, the advantages of nanotechnology are immense, and studies that include economic, financial, ethical and safety concerns will demonstrate how to optimize benefits and minimize risk. Macro- and microtechnology had their risks, but they accepted the benefits. [9]

A balance must be established between the security of the nanomaterials and the treatment effectiveness. Nanomaterials must be checked extensively before they are used in the healthcare field. [35]

CONCLUSION

Many new techniques for treating different diseases have been developed in the last few years. The use of nanotechnology to build drug delivery nanocarriers brings plenty of optimism and excitement in the field of drug delivery science. Nanoscale drug delivery devices have several advantages that enhance stability and bioavailability, reduce toxicity, increase release and provide better product formulation opportunities and display a higher intracellular uptake than other traditional drug delivery systems.

The interdisciplinary design of nanotechnology allows for diversification and growth to enhance quality of life. Pharmaceutical nanotechnology has emerged as a field with immense potential as a carrier for the spatial and temporal delivery of bioactives and diagnostics and offers intelligent materials for tissue engineering purposes. It provides new technologies, possibilities and scope, which through its nano-engineered technologies are expected to have a great effect on many areas of illness, diagnostics, prognosis and illness care. Pharmaceutical nanotechnology offers opportunities for improving materials, medical devices and helping to develop new technologies where existing and more traditional technologies may meet their limits.

Pharmaceutical nanotechnology has a profound impact on efforts to prevent disease, as it provides novel methods to understand the cell as well as the distinction between normal and abnormal cells. It may provide insights into disease molecular basis.Therefore, drug delivery systems of nanoscale size could revolutionize the entire drug therapy strategy and in the near future bring it to a new height. Nevertheless, the nanosize formulations toxicity issues should not be neglected. To assess both the short- and long-term toxicity analysis of the nanosize drug delivery systems, full proof methods should be developed.

REFERENCES

1. Zahid Hosen S.M., Dash R, Junaid M, Khanam UH, Pharmaceutical Nanotechnology- A Short Review.
2. Kaur P, Kaur L, Khan MU, Nanoparticles as A Novel Drug Delivery System, International Journal of Research in Pharmacy and Chemistry, 2012, 2(3), 2231-2781.
3. Singh G, Khanna K, Kaur N. Nanotechnology: A Review.
4. Sharma VK, Trivedi H, Bey A, Gupta N. Nanotechnology: rise of a new era in periodontics. Univ. J. Dental Sci. 2016.
5. Purohit K, Khitoliya P, Purohit R. Recent advances in nanotechnology. Int. J. Sci. Eng. Res. 2012;3.
6. Gupta R, Tomer A, Dubey D, Recent Advances in the Field of Nanotechnology: A Review, IOSR Journal of Dental and Medical Science, January. 2017; 16(1); 14-18.
7. Shinde NC, Keskar NJ, Argade PD, Nanoparticles: Advances in Drug Delivery Systems, Research Journal of Pharmaceutical, Biological and Chemical, January – March 2012; 3(1); 922-929.
8. Varshney M, Mohan S. Nanotechnology" current status in pharmaceutical science. International Journal of Therapeutic Applications. 2012; 6; 14-24.
9. Ochekpe NA, Olorunfemi PO, Ngwuluka NC. Nanotechnology and drug delivery part 1: background and applications. Tropical journal of pharmaceutical research. 2009;8(3).
10. Martis EA, Badve RR, Degwekar MD. Nanotechnology based devices and applications in medicine: An overview. Chronicles of young Scientists. 2012 Jan 1;3(1).
11. Malam Y, Loizidou M, Seifalian AM. Liposomes and nanoparticles: nanosized vehicles for drug delivery in cancer. Trends in pharmacological sciences. 2009 Nov 1;30(11):592-9.
12. Ogawara KI, Un K, Minato K, Tanaka KI, Higaki K, Kimura T. Determinants for in vivo anti-tumor effects of PEG liposomal doxorubicin: importance of vascular permeability within tumors. International Journal of Pharmaceutics. 2008 Jul 9;359(1-2):234-40.
13. https://en.wikipedia.org/wiki/Dendrimer
14. He H, Pham-Huy LA, Dramou P, Xiao D, Zuo P, Pham-Huy C. Carbon nanotubes: applications in pharmacy and medicine. BioMed research international. 2013 Jan 1;2013.
15. https://www.nanowerk.com/what_are_quantum_dots.php
16. Muller RH, Bohm BH, Grau J, Wise DL. Nanosuspensions: a formulation approach for poorly soluble and poorly bioavailable drugs. Handbook of pharmaceutical controlled release technology. 2000 Aug 24:345-57.
17. Duchene D, Ponchel G. Bioadhesion of solid oral dosage forms, why and how?. European Journal of Pharmaceutics and Biopharmaceutics. 1997 Jul 1;44(1):15-23.
18. Was SP, Malaiya A. In vivo characterization of indomethacin magnetic polymethyl methacrylate nanoparticles. Journal of microencapsulation. 1989 Jan 1;6(4):493-9.
19. Kleinedler JJ, Foley JD, Orchard EA, Dugas TR. Novel nanocomposite stent coating releasing resveratrol and quercetin reduces neointimal hyperplasia and promotes re-endothelialization. Journal of controlled release. 2012 Apr 10;159(1):27-33.

20. Purcell C, Tennant M, McGeachie J. Neo-intimal hyperplasia in vascular grafts and its implications for autologous arterial grafting. Annals of the Royal College of Surgeons of England. 1997 May;79(3):164.
21. Wanigasekara J, Witharana C. Applications of nanotechnology in drug delivery and design-an insight. Current Trends in Biotechnology & Pharmacy. 2016 Jan 1;10(1):78-91.
22. Fadi E, Hartwig S, Muller BW. In vitro evaluation of cyclosporin A (CsA) inhalation nanosuspension. Respiratory Drug Delivery IX. 2004;2:433.
23. Takeuchi H, Yamamoto H, Kawashima Y. Mucoadhesive nanoparticulate systems for peptide drug delivery. Advanced drug delivery reviews. 2001 Mar 23;47(1):39-54.
24. Patel AR, Vavia PR. Nanotechnology and pharmaceutical inhalation aerosols. Indian J Exp Biol 2007;45:166-74.
25. Hart SL. Multifunctional nanocomplexes for gene transfer and gene therapy. Cell biology and toxicology. 2010 Feb 1;26(1):69-81.
26. Patel S, Bhirde AA, Rusling JF, Chen X, Gutkind JS, Patel V. Nano delivers big: designing molecular missiles for cancer therapeutics. Pharmaceutics. 2011 Mar;3(1):34-52.
27. Rangasamy M. Nano technology: a review. Journal of Applied Pharmaceutical Science. 2011 Apr;1(2):8-16.
28. Kumar P, Kulkarni P, Srivastava A, Pharmaceutical application of nanoparticles in drug delivery system, Journal of Chemical and Pharmaceutical Research, 2015, 7(8):703-712.
29. Faraji AH, Wipf P. Nanoparticles in cellular drug delivery. Bioorganic & medicinal chemistry. 2009 Apr 15;17(8):2950-62.
30. Maroof K, Zafar F, Ali H, Naveed S, Tanwir S, Scope of Nanotechnology in Drug Delivery, Journal of Bioequivalence & Bioavailability, Volume 8(1): 001-005 (2016)1 – 5.
31. Nanotechnology for Diabetes Treatment, By Will Soutter Jun 27 2012.
32. Lippacher A, Müller RH, Mäder K. Preparation of semisolid drug carriers for topical application based on solid lipid nanoparticles. International journal of pharmaceutics. 2001 Feb 19;214(1-2):9-12.
33. Yadav N, Khatak S, Sara US. Solid lipid nanoparticles-a review. Int. J. Appl. Pharm. 2013;5(2):8-18.
34. Yang B, Choi H, Kim SH, Yoon HJ, Lee H. How will nanotechnology lead to better control of asthma?. Annals of translational medicine. 2019 Oct;7(20).
35. http://www.justscience.in/articles/risks-development-nanotechnology-medicine/2017/12/13