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NANOPARTICLES AND CURRENT TECHNOLOGY IN PHARMACY AND MEDICINE: AN OVER VIEW

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ABSTRACT

Nanoparticles are of great interest for a wide variety of applications in the field of information, energy, environmental, industrial, medical and pharmaceutical technologies due to their unique or improved properties determined primarily by size, composition and structure along with their self organized film structures, the most emerging branch in Nanotechnology is medicinal or pharmaceutical sciences known as "*Pharmaceutical nanotechnology"* presents new tools, opportunities and scope, which are expected to have significant applications in disease diagnostics and therapeutics. Recently nanopharamceuticals reveal enormous potential in drug delivery as carrier for spatial and temporal delivery of bioactive and diagnostics. Additionally it also provides smart materials for tissue engineering. This discipline is now well established for drug delivery, diagnostics, prognostic and treatment of diseases through its nanoengineered tools. Drugs that are transformed into nano range offers some unique features which can lead to prolonged circulation, improved drug localization, enhanced drug efficacy etc. Various pharmaceutical nanotechnology based systems which can be termed as nanopharmaceuticals like polymeric nanoparticles, magnetic nanoparticles, liposomes, carbon nanotubes, quantum dots, dendrimers, metallic nanoparticles, polymeric nanoparticles, etc. have brought about revolutionary changes in drug delivery as well as the total medical service system. However some recently found health risk evidences limits their utilization in pharmaceutical industry. Some concerning issues like safety, bioethical issues, toxicity hazards, physiological and pharmaceutical challenges get to be resolved by the scientists. Current researchers are still lacking sufficient data and guidelines regarding safe use of these nanotechnology based devices and materials. Therefore pharmaceutical nanotechnology is still in developmental stage. This article summarizes the types of nanopharmaceuticals with the most important applications and nanoparticles associated health risk related information available till date.

KEYWORDS: Nanotechnology, Pharmaceutical nanotechnology, Nanoshells, Nanobulba, Nanobiotechnology.

INTRODUCTION

Nanotechnology is the science that deals with matter at the scale of 1 billionth of a meter (i.e., 10^{-9} m = 1 nm), and is also the study of manipulating matter at the atomic and molecular scale.[1] A nanoparticle is the most fundamental component in the fabrication of a nanostructure, and is far smaller than the world of everyday objects that are described by Newton's laws of motion, but bigger than an atom or a simple molecule that are governed by quantum mechanics.[2] In general, the size of a nanoparticle spans the range between 1 and 100 nm. Metallic nanoparticles have different physical and chemical properties from bulk metals (e.g., lower melting points, higher specific surface areas, specific optical properties, mechanical strengths, and specific magnetizations), properties that might prove attractive in various industrial applications.[3] However, how a nanoparticle is viewed and is defined depends very much on the specific application. Not surprisingly, the optical characteristics of nanoparticles have been used from time immemorial in sculptures and paintings even before the 4th century AD. The most famous example is the Lycurgus cup (fourth century AD).

Nanoparticles are of current interest because of an emerging understanding of their possible effects on human health and environmental sustainability, and owing to the increasing output of manmade nanoparticles into the environment. Nanoparticles are used in many different applications and created by many different processes. Their measurement and characterization pose interesting analytical challenges.[1] Particles having diameter in range between 10-100 nm are known as Nanoparticles. They are used as targeted delivery system for delivery of small and large molecules by changing their pharmacodynamics and pharmacokinetic properties.[2] They can be defined as system which contain active ingredient dissolved, encapsulated or

adsorbed in matrix material which are used as target delivery system.[3] To see the effect of drug in target tissue, to increase stability against degradation through enzymes and for solubilization at intravascular route nanoparticles have been used.[4] During the designing of nanoparticle some control has to take in care such as their release pattern, their size and surface properties which determine site specific action at optimal rate with right dose regimen.[5] Nanoparticles are sub nano sized colloidal structure of synthetic or semi synthetic polymer. The first reported nanoparticles were based on non biodegradable polymeric system[6] (polyacrylamide, polymethylmethaacrylate, polystyrene). The polymeric nanoparticles can carry drugs or proteineous substances, i.e. antigens. These bioactives are entrapped in polymer matrix as particulates or solid solution or may bound to particle surface by physical adsorption or chemically. The drugs may be added during preparation of nanoparticle or to the previously prepared nanoparticles. Nano medicine is an emerging field of medicine with novel applications for future.[7]

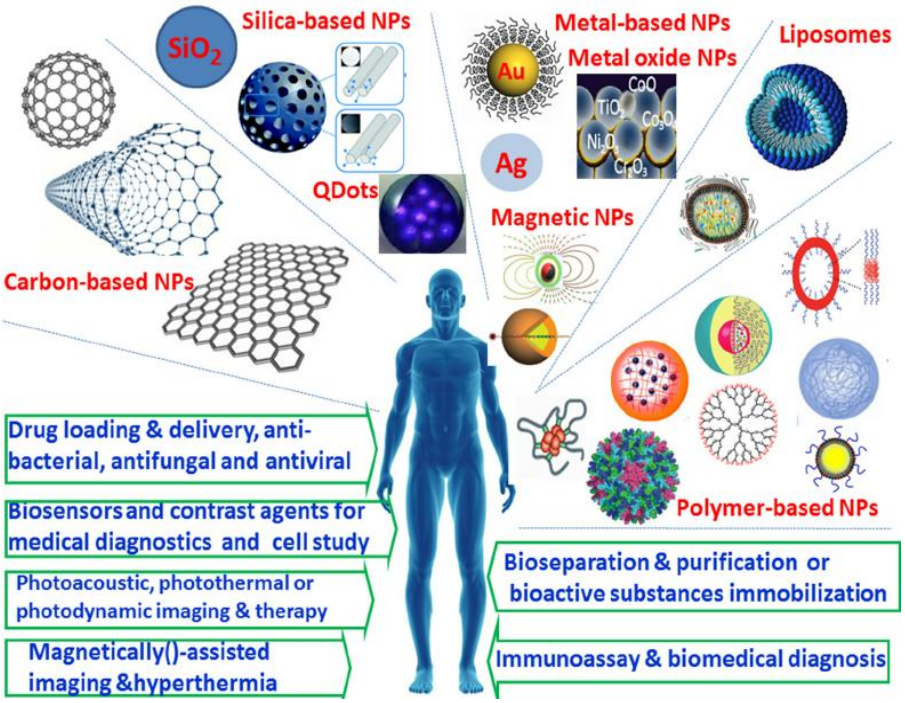


Fig: 1.

Applications of nanoparticles in different fields

Nanoparticles are used in many different applications and created by many different processes. Nanotechnology is also being applied to or developed for application to a variety of industrial and purification processes. Purification and environmental cleanup applications include the desalination of water, water filtration, wastewater treatment, groundwater treatment, and other nanoremediation. In industry, applications may include construction materials, military goods, and nano machining of nano wires, nano rods, few layers of graphene, etc. Also, recently a new field arisen from the root of Nanotechnology is called Nanobiotechnology. Nanobiotechnology is the biology based, application oriented frontier area of research in the hybrid discipline of Nanoscience and biotechnology with an equivalent contribution.[4] Some of the important areas where nanotechnology is being applied successfully and continuing to develop through Medicine, Diagnostics, Drug delivery, Tissue engineering, Environment, Filtration, Energy Reduction of energy consumption, Increasing the efficiency of energy production, Information and communication, Memory Storage, Novel semiconductor devices, Novel optoelectronic devices, Displays, Quantum computers, Heavy Industry, Aerospace, Catalysis, Construction, Nanotechnology and constructions, Nanoparticles and steel, Nanoparticles in glass, Nanoparticles in coatings, Nanoparticles in fire protection and detection, Risks of using nanoparticles in construction, Vehicle manufacturers, Consumer goods, Nanofoods, Household, Optics, Textiles, Cosmetics, Agriculture, Sports etc.

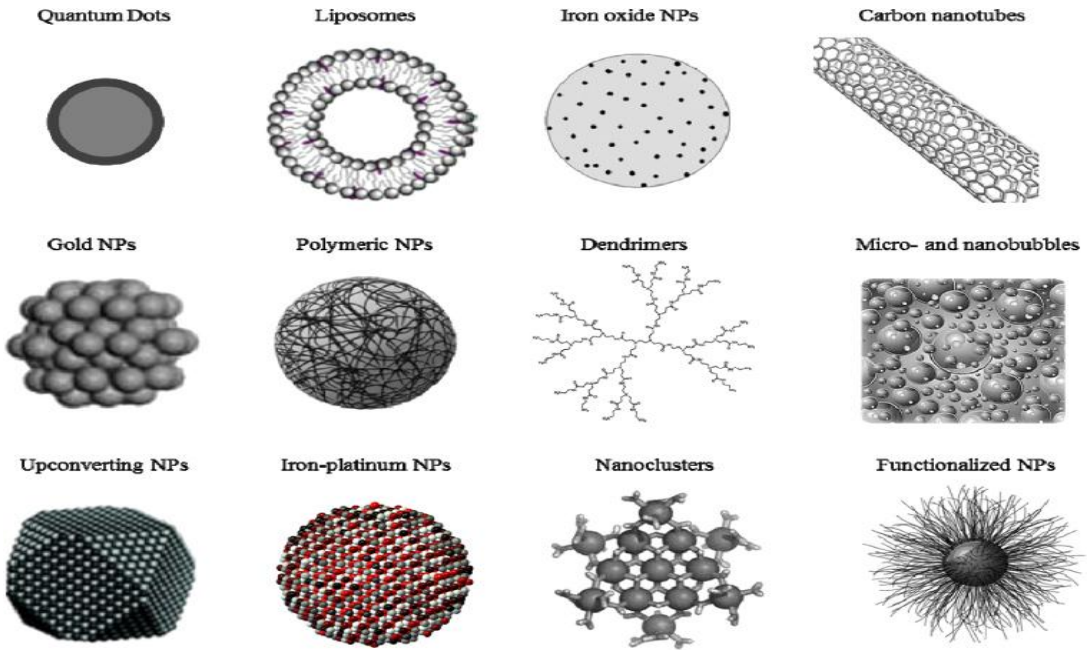


Fig: 2.

Medicinal and Pharmaceutical applications of Nanosystems

1. Carbon Based Structures

Carbon nano tubes are carbon based tubular structures that are discovered in 1991.[9] These structures are arranged in fashion like a graphite sheet rolled up into a cylinder and capped at one or both ends by a buckyball. These are hexagonal networks of carbon atoms having diameter of one nanometer and length from 1 to 100 nm. These carbon networks are arranged layer of graphite rolled up into a cylinder. There are two carbon based configuration that have received much attention recently: single walled nanotubes (SWNTs) and multiwalled nanotubes (MWNTs). In addition to these types C 60 fullerenes is also a part of common configurations. These are hollow, carbon based, cage like architectures (nanotubes and fullerenes), also known as bucky balls, which are different in the arrangement of their graphite cylinders.

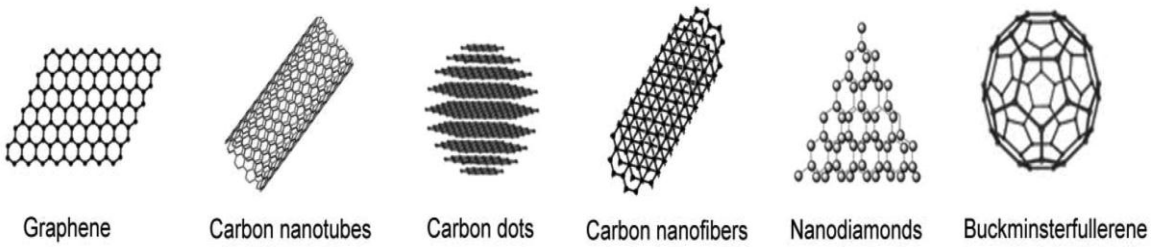


Fig: 3.

Applications

Cell specifi city

Enhancement of cell specificity by conjugating antibodies to carbon nanotubes with fluorescent or radiolabelling.[12]

Internalization

Internalization within mammalian cells can be achieved by surface functionalized carbon nanotubes.

Vaccine delivery

Conjugation with peptides may be used as vaccine delivery structures.

Gene delivery

The ability of nanotubes to transport DNA across cell membrane is used in studies involving gene therapy. During this therapy DNA can be attached to the tips of nanotubes or can be incorporated within the tubes. It has been found that gene therapy with β galactosidase marker gene nanotubes showed greater expression compared to transfer of naked DNA. This assures the advantage of non immunogenicity in contrast to viral vectors used for gene transfer.

Transport of peptides, nucleic acids and other drug molecules

Incorporation of carboxylic or ammonium groups to carbon nanotubes enhances their solubility which makes

them more suitable for the transport of peptides, nucleic acids and other drug molecules.

Reduced toxicity and increases the efficacy

Carbon nanotubes enhance drug delivery, efficacy and reduces the toxicity as found in the case of Amphotericin B nanotubes. It has been found that Amphotericin B nanotubes has shown enhanced drug delivery to the interior of cells, increased antifungal efficacy and reduced toxicity to mammalian cells when compared to amphotericin B administration without nanotubes.[69] The efficacy of amphotericin B nanotubes was also effective on strains of fungi which are usually resistant to amphotericin B alone.[13]

Gene silencing

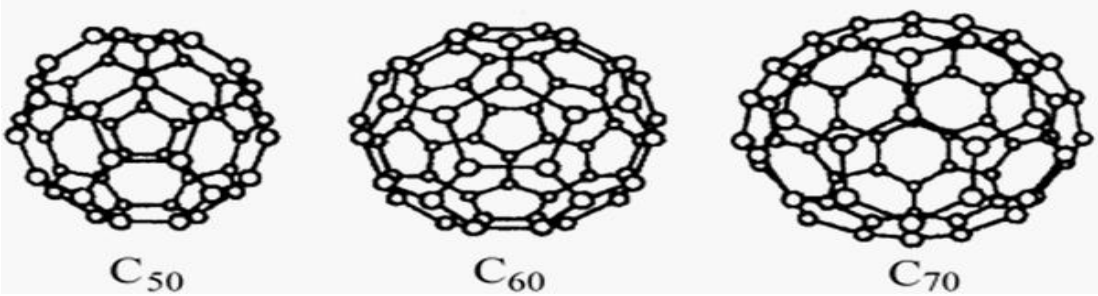
Highly selective therapy is required for cancer therapy where tumor cells will be selectively modulated. In this case gene silencing has been done with small interfering RNA. This can be achieved by targeting functionalized single walled carbon nanotubes with siRNA to silence targeted gene expression in the targeted cell.[14]

In diagnostics

It was reported that compounds that are bound to nanotubes enhance the efficiency of diagnostic methods. This property of functionalization and high length to diameter aspect ratio (which provides a high surface to volume ratio), assists in designing the highly efficient biosensors.[15] Thus carbon nanotubes offer diverse advantages over other drug delivery and diagnostic systems due to very interesting physicochemical properties such as ordered structure with high aspect ratio, high electrical conductivity, high mechanical strength, ultra-light weight, high thermal conductivity, metallic or semimetallic behavior and high surface area.[15]

2. Fullerenes

They are also known as bucky balls, that are the carbon allotrope discovered in 1985[16] having dimensions near around 7 Å in diameter and composed of 60 carbon atoms that are arranged in a shape known as truncated icosahedrons.[17] Its shape is quite similar to soccer ball with 20 hexagons and 12 pentagons and is highly symmetrical.[18] There are various types of fullerenes such as Alkali doped fullerenes, endohedral fullerenes, endohedral metallofullerenes, exohedral fullerenes and heterofullerenes.



Applications

Diagnostics

Endohedral metallofullerenes can be used for diagnostic purposes as radio contrast media in magnetic resonance imaging and other imaging procedures. Since the radioactive metal is enclosed within the buckyball, these are less toxic and safer. This method can also be employed for imaging organs as radioactive tracers.[21] Animal studies with C 60 fullerene conjugated with thyroglobulin have produced a C 60 specific immunological response which can be detected by ELISA with IgG specific antibodies. This can be used to design methods of estimation of fullerene levels in the body when used for therapeutic or diagnostic purposes.[22]

Drug transport

Fullerenes are being investigated for drug transport of antiviral drugs, antibiotics and anticancer agents.[23 – 26]

Free radical scavengers

Due to presence of high number of conjugated double bonds in the core structure fullerenes can also be used as free radical scavengers. They also provide protection to the mitochondria against injury induced by free radicals[27], owing to this property they can be used in cancer therapy.[28]

Photosensitizers

Fullerenes especially exohedral fullerenes can be used as photosensitizers in photodynamic therapy against various types of malignancies. These fullerenes potentially generate reactive oxygen species when stimulated by light and kills the target cells. This method is now also being investigated for antimicrobial property as these cause cell membrane disruption especially in Gram positive bacteria and mycobacterium.[23–26]

Stimulate host immune response and production of antibodies

Fullerenes are efficient in stimulating host immune response and production of fullerene specific antibodies.

3. Quantum Dots

Quantumdots (QDs) are nanocrystals of semiconducting materials measuring around 2–10 nm, consisting of a semiconductor inorganic core (CdSe), an aqueous organic coated shell (e.g., ZnS) to improve optical

properties, and can be made to fluorescence when stimulated by light. Quantumdots bear a cap which enables them in improving their solubility in aqueous buffers.[29] They are neither atomic nor bulk semiconductors. Core of the quantumdots determines the color emitted and outer aqueous shell is available for conjugation with biomolecules. Biomolecular conjugation of the quantum dots can be modified according to target various biomarkers.[29] Their properties originate from their physical size, which ranges from 2 to 10 nm in radius. Owing to their narrow emission, bright fluorescence, high photostability and broad UV excitation QDs have been adopted for tracking of intracellular process for longer time, for in vitro bioimaging and for real time monitoring.

Applications

Cancer therapy

In one report it was proven that quantum dots are accumulated in prostate cancer developed in nude mice by enhanced permeability and retention.[31]

Bioconjugation with polymer

It was reported that its conjugation with polyethylene glycol (PEG) and antibody and targeting to prostate specific membrane antigen enhances its accumulation and retention[31] in the tumor tissue.

Imaging

They can be utilized for imaging of sentinel node in cancer patients for tumor staging and planning of therapy. This application assists in detecting suitable therapy and stage for various malignancies like melanoma, breast, lung and gastrointestinal tumors.[31] In addition quantum dot probes provide real time imaging of the sentinel node with Near Infra Red (NIR) fluorescence system which is having the potential to produce reduced[32] background noise and deeper penetration of rays into the biological sample.

4. Nanoshells

Nanoshells are the new modified forms of targeted therapy, having core of silica and a metallic outer layer.[33] The properties of nanoshells can be altered by simply tuning the core to shell ratio. With the recent advancement in new techniques it is now possible to synthesize these nanostructures in desired shape, size and morphology. For obtaining desirable morphology core particles of different morphologies such as rods, wires, tubes, rings, cubes, etc. can be coated with thin shell in core shell structures. These shells are inexpensive as precious materials can be deposited on inexpensive cores. Therefore while synthesizing nanoshells expensive material is required in lesser amount than usual. Targeting of nanoshells can be achieved by using immunological methods. Nanoshells occupies variety of applications in diverse areas such as providing chemical stability to colloids, enhancing luminescence properties, engineering band structures, biosensors, drug delivery, etc. Synthesis of nanoshells can be useful for creating.

Applications

Cancer therapy

This technology is being evaluated for cancer therapy. Nanoshells are tuned to absorb infra red rays when exposed from a source outside the body and get heated and cause destruction of the tissue. This has been studied in both *in vitro* and *in vivo* experiments on various cell lines.[33]

Diagnostic purposes

They are useful for diagnostic purposes in whole blood immunoassays e.g. coupling of gold nanoshells to antibodies to detect immunoglobulins in plasma andwhole blood.

Hydrogel mediated delivery

Nanoshells can be easily embedded in hydrogel polymer containing the drug. Such type of delivery system can be used for targeting tumor cells. Mechanism is based on the targeting of gel to tumor tissue by immunological methods and exposed under infrared laser beam to heat the polymer which facilitates the release of the drug at the desirable site.

Micro metastasis and diabetes

Nanoshells are currently studied for micro metastasis of tumors and also for treatment of diabetes.[34]

5. Nanobubbles

Nanobubbles (NBs) are nanoscaled bubble like structures that are generated in the interface of hydrophobic surfaces in liquids. These nanobubbles remain stable at room temperature and when heated to physiological temperature within the body coalesce to form microbubbles. There are four types of nanobubbles: bulk, interfacial, plasmonic and oscillating nanobubbles.[35] Cancer therapeutic drugs can be incorporated into these nanoscaled bubbles like structures. Nanobubbles potentially exhibit advantages in targeting the tumor tissue and delivering the drug selectively under the influence of ultrasound exposure. This may enhance the intracellular uptake of the drug by the tumor cells. Additionally these nanobubbles can be easily visualized in tumor by means of various ultrasound methods.[35,36]

Applications

Delivery of drugs

NBs can be potentially utilized in delivery of drugs like doxorubicin *in vitro* and *in vivo*. These NBs reach the tumor and get accumulated which is followed by formation of microbubbles by coalescing of nanobubbles. Disruption of the microbubbles occurs when the site is focused with high intensity focused ultrasound, which ultimately causes release of the drug. This may results in accumulation of higher levels of drug in the target cells and reduced toxicity and increased efficacy.

Gene therapy
Liposomal nanobubbles and microbubbles are also being studied for effective non viral vectors for gene therapy. Nanobubbles combined with ultrasound exposure have shown improved transfer of gene in both *in vitro* and *in vivo* studies.[37,38]

Thrombolysis
Nanobubbles are also being investigated for removal of clot in vascular system in combination with ultrasound. This process is called as sonothrombolysis. This method is non invasive and causing less damage to endothelium.[39] Toxicity.

6. Paramagnetic Nanoparticles
Magnetic drug targeting is conceptualized with an objective to target magnetic drug carrier particles at a specific site in the body using an externally applied magnetic field. Magnetic nanoparticles are a class of particulate materials of less than 100 nm size that can be manipulated under the magnetic field.[41] These particles are composed of magnetic elements such as cobalt, nickel, iron and their respective oxides such as magnetite, maghemite, cobalt ferrite and chromium dioxide. The classification of these particles is based on their magnetic susceptibility which is defined as ratio of induced magnetization to the applied field. Paramagnetic nanoparticles have a greater magnetic susceptibility than conventional contrast agents. They are investigated for both diagnostic and therapeutic purposes. For diagnostic purpose paramagnetic iron oxide nanoparticles are used as contrast agents in magnetic resonance imaging. Targeting with paramagnetic nanoparticles enables identification of specific organs and tissues.[42]

Applications
Cancer therapy
Conjugation of paramagnetic nanoparticles with antibodies and their expression in breast cancer cells have been used with MRI to detect breast cancer cells *in vitro.*[41] More over conjugation of paramagnetic nanoparticles with luteinizing hormone (releasing hormone as breast cancer cells express LHRH receptors) studied for the detection of breast cancer cells in vivo.

Eliminate plasma opsonins and increase in circulation time
On intravenous administration of decoy of nanoparticle plasma opsonins can be eliminated and reduces uptake of the nanoparticles. Moreover alteration in surface charge of the nanoparticle to neutral by covalent coupling to chemicals leads to an increase in circulation time.

For internalization
Paramagnetic nanoparticles internalization by macrophages can be overcome by treatment with drugs like lovastatin which reduce macrophage receptor expression for the nanoparticle.

Identification of proteins
Magnetic microparticle probes with nanoparticle probes have been used for identification of proteins like prostate specific antigen. Here magnetic microparticles coated with antibodies together with nanoprobes with similar coating and a unique hybridized DNA barcode are used.[43]

Imaging
Utilization of Iron oxide in MRI imaging faces limitations like specificity and internalization by macrophages. Monocrystalline iron oxide nanoparticles have been studied for magnetic resonance imaging of brain. These are rapidly taken up by the tumor cells.[44] Hence give long lasting contrast enhancement of tumor. The remaining nanoparticles are removed from the circulation by reticuloendothelial system.[44]

Targeted action
Conjugation of antibodies with paramagnetic nanoparticles to direct the nanoparticle to the target site helped to overcome problems with specificity of action.

7. Nanosomes
Nanosomes are currently being used for medical applications such as targeting, diagnosis and therapy.

Applications
Brain targeting
These nanosomes are being developed for treatment of various tumors (CNS tumors) e.g. silica coated iron oxide nanoparticles coated with polyethylene glycol used to access specific areas of brain involved with tumor.[45]

Tumor targeting
Nanosomal delivery with magnetic resonance imaging and laser assist in targeting the nanoparticle specifi cally to the tumor cells and destroy the cells loaded with these nanoparticles by the heat generated by iron oxide particles by absorbing the infra red light.

ROS production
Their stable integration with photocatalyst produces reactive oxygen species when stimulated by light and destroy the target tissue. These nano form exhibit advantages over conventional drugs in being much safer without the adverse effects of cancer chemotherapy drugs and also the absence of development of drug resistance.

8. Pharmacytes
Pharmacyte is an ideal nanotechnology based drug delivery system, which is a self powered, computer controlled medical nanorobot system capable of digitally precise transport, timing, and targeted delivery of pharmaceutical agents to specific cellular and intracellular destinations within the human body.[101] This may be constructed using future molecular manufacturing technologies such as diamond mechanosynthesis. Pharmacytes will have many

applications in nanomedicine such as initiation of apoptosis in cancer cells and direct control of cell signaling processes.[46]

9. Niosomes

Niosome is a class of molecular cluster formed by self association of non ionic surfactants in an aqueous phase. The unique structure of niosome presents an effective novel drug delivery system (NDDS) with ability of loading both hydrophilic and lipophilic drugs.[47] Niosomes are vesicles composed of non-ionic surfactants, which are biodegradable, relatively nontoxic, more stable and inexpensive, an alternative to liposomes. Niosomes behave in vivo like liposomes, prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability. As with liposomes, the properties of niosomes depend on the composition of the bilayer as well as method of their production. It is reported that the intercalation of cholesterol in the bilayers decreases the entrapment volume during formulation, and thus entrapment efficiency. However, differences in characteristics exist between liposomes and niosomes, especially since niosomes are prepared from uncharged single chain surfactant and cholesterol, whereas liposomes are prepared from double chain phospholipids (neutral or charged).[47] The concentration of cholesterol in liposomes is much more than that in niosomes. As a result, drug entrapment efficiency of liposomes becomes lesser than niosomes. Besides, liposomes are expensive, and its ingredients, such as phospholipids, are chemically unstable because of their predisposition to oxidative degradation; moreover, these require special storage and handling and purity of natural phospholipids is variable. Current opinions for the utilization of niosomes in the delivery of biomolecules can be unsubstantiated with a wide scope in encapsulating toxic drugs such as anti-AIDS drugs, anticancer drugs, and antiviral drugs.[47]

10. Dendrimers

Dendrimers are a unique class of polymers, they are hyper branched, tree like structures, whose size and shape can be precisely controlled and have compartmentalized chemical polymer. Dendrimers are fabricated from monomers using either convergent or divergent step growth polymerization. These nanostructures arise several branches from the core in shape of a spherical structure by means of polymerisation, resulting in formation of cavities within the dendrimer molecule which can be used for drug transport. Free ends of dendrimer can be utilized for conjugation or attachment to other molecule. These end groups that can be tailored according to requirements. Such interconnecting networks transport the attached molecules at desirable site and give dendrimers various functional applications.[47] These well defined nanostructures are equipped with surface functionalization capability, monodispersity of size, and stability properties that make them attractive drug carrier. Incorporation of drug molecule can be easily achieved via either complexation or encapsulation. As far as the construction is concerned it contains three different basic regions: core, branches, and surface. Branches or end groups can be tailored or modified into biocompatible compounds with low cytotoxicity and high biopermeability. Such branches or networks assist in delivery of bioactive ranging from vaccines, drugs, genes and metal to desired sites.[47]

Applications

Drug and gene delivery

Dendrimers are being investigated for both drug and gene delivery, as carriers for penicillin, and for use in anticancer therapy.

Imaging, targeting & diagnosis of disease

Complexes of dendrimers such as tectodendrimers with each dendrimer module of the complex performing different functions such as targeting, diagnosis of disease state, delivery of drug and imaging.

Chemotherapy

Tectodendrimers are the nano device that acquires potential applications in cancer chemotherapy as a mode of targeted drug therapy.[48]

Gene therapy

Dendrimers can be used for gene therapy where these can replace conventional viral vectors. They enter the cells by endocytosis and the DNA gets transported into nucleus for transcription of the applied gene.

Stimulation of immune reaction

The advantage of dendrimer based therapy is absence of stimulation of immune reaction.

Gene transfer

It was studied that the potential use of transferring conjugated gene transfer for tumors of various tumors PEG modified polyamidoamine dendrimers and magnetic nanoparticle modified dendrimers for targeted gene delivery to the brain and in transfer of antisense surviving oligonucleotides in tumor cell lines. These methods provide an effective alternative to viral vectors of gene transfer for treatment of various tumors.[49]

Transfection

Various dendrimer based DNA transfection kits (NanojuiceTM Transfection Kit produced by EMD Chemicals Inc. and Superfect ® Transfection Reagent of Qiagen) are used for delivering DNA into the cell. These are claimed to have improved transfection efficacy and low toxicity to cells.[50]

Antiretroviral therapy

Dendrimer based drugs are being tried for antiretroviral therapy. Some of the dendrimer based drugs was found to successfully prevent simian HIV infection.

Treatment of cancer
Treatment of cancer by conjugating with anti cancer drugs like cisplatin, adriamycin or methotrexate.[51] PAMAM dendrimers can also be used in treatment of cancer.

Reduces the cytotoxicity
While antibacterial investigation it was observed that PEG coating of the dendrimer reduces the cytotoxicity of unmodified PAMAM dendrimers. Hover reduces the efficacy against Gram positive bacteria without change in efficacy against Gram negative bacteria like *Pseudomonas.*

Contrast agents for imaging
Dendrimers are also used as contrast agents for imaging. The 1, 4-diaminobutane core dendrimer and the PAMAM dendrimer are well studied commercially available dendrimers for imaging studies. Renal excretion is the main route of clearance and is dependent on the size of the particle and more than 60% of injected DAB or PAMAM dendrimer is cleared from circulation within 15 min.

Rapid clearance
Smaller sized dendrimers undergo rapid renal clearance whereas dendrimers with charged surface or hydrophobic surfaces are rapidly cleared by the liver. Those dendrimers with a hydrophilic surface escape renal clearance and have a greater circulation time.

11. Nanopores
Nanopores were designed in 1977, consist of wafers with highly dense pore of size 20 nm (diameter). Main advantage of these nanopores that they doesn't allow the entry of oxygen glucose and other products. They can be potentially utilized to protect transplanted tissues from the host immune system.

Application
DNA sequencing
Currently several researchers are working on modified nanopores that have the ability to differentiate DNA strands based on differences in base pair sequences. Nanopores are also being developed with ability to differentiate purines from pyrimidines.

Pharmacogenomics in drug development process
DNA sequencing via nanopores could possibly read a thousand bases per second per pore. These can be used for low cost high throughput genome sequencing which would be of great benefit for application of pharmacogenomics in drug development process.

Treatment for insulin dependent diabetes mellitus
β cells of pancreas can be enclosed within the nanopore device and implanted in the recipient's body.

12. Microbivores
Function of these nano based hypothetical forms is to trap circulating microbes just like the function of white blood cells in the blood stream. They are designed in such a way so that they acquire greater efficacy than cellular blood cells in phagocytosis. Their surface is arranged in such a fashion which can extend in length and secure the microbe which gets in contact with it. Entrapped microbe will be gradually transferred to the ingestion port and undergoes the process of morcellization and enzymatic degradation. Degraded products are ultimately released as amino acids, fatty acids, nucleotides and sugars.

Application
Clears blood circulation
Microbivores could theoretically clears blood stream in septicaemia at a much greater rate than the natural defense mechanism with antibiotics.[52]

13. Nanocrystals and Nanosuspension
These are aggregated structures that are formed by the combination of various particles of drug in crystalline form coated with surfactant or combination of surfactants. To achieve static and electrostatic surface stabilization a minimum quantity of surfactants needs to be added in nanocrystals. These aggregated forms reduce limitations of several drugs that are suffering from bioavailability and absorption problems. In addition problems of preparing the parenteral dosage form may be resolved by formulation as nanocrystals. Loading capacity especially in carrierbased nanoparticles is quite low however administration of high drug levels with depot release can be achieved if dissolution is sufficiently slow.

Applications
Drugs in pipeline
Nanocrystals such as Rapamune ®, containing sirolimus which is an immunosuppressant drug and Emend ®, which contains aprepitant, MK 869, are in pipeline.

Favorable drug delivery system
Serve as a favorable delivery system for drugs like amphotericin B, tacrolimus, etc.

Safe and effective passage
The size of nanocrystals allows for safe and effective passage through capillaries.

Targeting
Nanoparticles offer the potential for targeting the mucosa of the gastrointestinal tract after oral administration, and targeting the cells of the mononuclear phagocytic system (MPS) to treat infections of the MPS such as fungal mycobacterial infections and leishmaniasis.

14. Solid Lipid Nanoparticles
Solid lipid nanoparticles were developed as an alternative carrier system to liposomes, polymeric

nanoparticles and emulsions as a colloidal carrier system for controlled drug delivery. Solid lipid nanoparticles carry distinct advantages that mak them unique carriers systems than others like liposomes and polmeric nanoparticles. This type of nanoparticles constitute solid lipid matrix with an average diameter below 1µm. Drug is normally incorporated in this matrix. These nanoparticles can also be produced by high pressure homogenization. Different surfactants are used to avoid aggregation and to stabilize the dispersion. These surfactants have an accepted GRAS (Generally Recognized as Safe) status.

Applications

Can be used for diverse route system

SLN have been developed and investigated for parenteral, pulmonal and dermal application routes.

Non viral transfection

SLN have been considered as new transfection agents using cationic lipids for the matrix lipid composition. Cationic solid lipid nanoparticles for gene transfer can be formulated using the same cationic lipids as for liposomal transfection agents. Cationic lipid composition seems to be more dominant for *in vitro* transfection performance than the kind of colloidal structure it is arranged in. Hence, cationic SLN extend the range of highly potent non viral transfection agents by one with favorable and distinct technological properties.

15. Silicon Based nanostructures

These silicon-based structures can be fabricated by techniques such as etching, photolithography, and deposition commonly used in the manufacture of microelectromechanical systems and semiconductors. Among various silicon based materials, porous silicon and silica, or silicon dioxide are the most materials that are architecture in form of calcified nanopores, platinum materials containing nanopores, porous nanoparticles, and nanoneedles. Nanopores size (diameter) and density can be accurately controlled to achieve a constant drug delivery rate through the pores. There are various forms (porous hollow silica nanoparticles) that are fabricated in a suspension containing sacrificial nanoscale templates. This followed by the addition of silica precursors, such as sodium silicate, into the suspension, which is then dried and calcinated. Template material is then dissolved further leaving behind the porous silica shell. These nanoparticles mixed with the drug molecule and subsequently drying the mixture to coalesce the drug molecules to the surface of the silica nanoparticles.

Applications

Various examples of therapies being studied for use with silicon-based delivery systems include.

For delivery of antitumor agent

Porous silicon embedded with platinum is reported.

Act as an artificial growth factor

Calcified porous silicon designed is reported.

For antibody delivery

Silicon nanopores are reported.

For antibiotics, enzymes, and DNA delivery

Porous silica nanoparticles are reported.

16. Metallic Nanoparticles

Currently these nanoparticles are emerging as good delivery carrier for drug and biosensor. For the synthesis of metallic nanoparticles diverse metals have been explored, though silver and gold nanoparticles are of prime importance for biomedical use. Surface functionalization on these nanonarticles can easily been done and various ligands have been decorated onto the surface. Variety of ligands such as sugars, peptide, protein and DNA has been linked to nanoparticles.

Applications

Metallic nanoparticles have been used for active delivery of bioactive, drug discovery, bioassays, detection, imaging and many other applications due to surface functionalization ability, as an alternative to quantum dots.

17. Liposomes

Liposomes are lipid based vesicles that are extensively explored and most developed nanocarriers for novel and targeted drug delivery. These vesicles are synthesized by hydration of dry phospholipids. Depending upon on their size and number of bilayers they are classified into three basic types:

a. Multilamellar vesicles.
b. Small unilamellar vesicles.
c. Large unilamellar vesicles.

Applications

They have been successfully exploited in cancer therapy, carrier for antigens, pulmonary delivery, leishmaniasis, ophthalmic drug delivery etc. Some of liposomebased formulations are already in market.

18. Polymeric Micelles

Polymeric micelles contains amphiphilic block copolymers assemble to form nanoscopic supramolecular core shell structures called as 'polymeric micelles'. These micelles are formed in solution as aggregates in which the component molecules are generally arranged in a spheroidal structure with hydrophobic cores shielded from water by a mantle of hydrophilic groups. There are several examples of component molecule such as Amphiphilic AB-type or ABA-type block copolymers, where A and B are hydrophobic and Hydrophilic components, respectively. These polymeric micelles are usually <100 nm and are used for the systemic delivery of waterinsoluble drugs. Their hydrophilic surface of these dynamic systems protects their nonspecific uptake by reticuloendothelial system. Polymeric micelle

Liposomes and their respective model drugs[67] Therapeutics Type of liposome Indications Amiloride hydrochloride Small molecular liposome Cystic fibrosis Budesonide Small molecular liposome Asthma carries advantage in trapping drugs or contrast agents physically within the hydrophobic cores or can be linked covalently to component molecules of the micelle. Additionally they are proved as an excellent novel drug delivery system due to their high stability in physiological conditions, high and versatile loading capacity, high accumulation of drug at target site, possibility of functionalization of end group for conjugation of targeting ligands and slower rate of dissolution.

19. Polymer Drug Conjugate

Polymer drug conjugate formed by the conjugation of low molecular weight drugs with polymer. This interaction/conjugation causes drastic change in pharmacokinetic disposition of drug in whole body and at cellular level. They are designed to increase the overall molecular weight, which facilitates their retention in cancer cells through enhanced permeation and retention effect using passive delivery approach.

20. Polyplexes/Lipopolyplexes

Polyplexes/Lipopolyplexes are the assemblies which are used in transfection protocols. These assembies are formed by spontaneous interaction between nucleic acids and polycations or cationic liposomes (or polycations conjugated to targeting ligands or hydrophilic polymers). Usually composition and charge ratio of nucleic acid to that of cationic lipid/polymer determines the shape, size distribution, and transfection potential of these complexes. Current research offers various types of polycations that have been used in gene transfer/therapy protocols:

- Cationic cyclodextrin.
- Linear- and branched-poly (ethyleneimine).
- Poly (amidoamine).
- Poly-amino esters.
- Poly- L –lysine.

21. Respirocytes

These are hypothetical nanodevices or called as artificial red blood cells and function as red blood cells but with greater efficacy. Respirocytes are having higher capacity to deliver oxygen to tissues. Their oxygen supplying capacity is 236 times more oxygen per unit volume than natural red blood cells. Respirocytes equipped with sensors on their surface which can detect changes in the environment. There is also a provision to regulate the intake and output of the oxygen and carbon dioxide molecules. According to past investigation an infusion of 1 L dose of 50% respirocytes saline suspension in a human can theoretically keep the patient oxygenated up to four hours following cardiac arrest.[52] According to FDA these devices are regulated under the provisions of the Medical Device Amendments of 1976, Safe Medical Devices Act of 1990, and the Medical Device Amendments of 1992.[53]

22. Polymeric Nanoparticles (Natural product based nanoparticles)

Natural polymer based nanoparticles are synthesized from biological systems and are usually biocompatible and non toxic, although often suffer from stability problems when delivered across the various biological membranes. Polymeric nanoparticles consist of biodegradable polymers which is biocompatible and non toxic. Features such as biocompatibility is required for potential application in tissue engineering, drug and gene delivery and new vaccination strategies. Recent research explore some advance modification of natural polymers which consists of synthetic polyesters like poly(D, L-lactide) or polycyanoacrylate and related polymers like poly(lactide-co-glycolide) PLA or poly(lactid acid). Among natural polymers the most widely used polymer which is used now days is chitosan. In addition to chitosan many others such as gelatin, and sodium alginate overcome some toxicological problems with the synthetic polymers. Natural polymer based nanoparticles offers a significant improvement over traditional oral and intravenous methods of drug delivery systems in terms of efficiency and effectiveness. The various natural polymers like gelatin, albumin and alginate are used to prepare the nanoparticles. However they have some inherent disadvantages like poor batch to batch reproducibility, prone to degradation and potential antigenicity. Synthetic polymers used for nanoparticles preparation may be in the form of preformed polymer e.g. polyesters like polycaprolactone (PCL), poly lactic acid (PLA) or monomers that can be polymerized in situ e.g. polyalkyl cyanoacrylate. There are many advantages of using polymeric nanoparticles in drug delivery:

- Biocompatable and biodregerable.
- Increase the stability of any volatile pharmaceutical agents.
- Less toxic.
- They are easily cheaply fabricated in large quantities by a multitude of methods.
- Have engineered specificity, allowing them to deliver a higher concentration of pharmaceutical.
- agent to a desired location.
- Nonimmunogenicity and nontoxicity.

Polymeric nanoparticles are a broad class comprised of both vesicular systems (nanocapsules) and matrix systems (nanospheres). Nanocapsules are systems in which the drug is confined to a cavity surrounded by unique polymeric membrane whereas nanospheres are systems in which the drug is dispersed throughout the polymer matrix. Polymeric nanoparticles are considered as a matrix system in which the matrix in uniformly dispersed. It should be mentioned, that besides of these spherical vesicular systems nanocapsules are also known, where a polymeric membrane surrounds the drug in a matrix core. The drug is dissolved, entrapped, attached or encapsulated throughout or within the polymeric shell/matrix. The choice of polymer and the ability to modify drug release from polymeric nanoparticles have made them ideal candidates for cancer therapy, delivery

of vaccines, contraceptives and delivery of targeted antibiotics.

Table 1: Nanoparticals are synthesized by biological methods and their applications.

S.No	Nanoparticals	Synthesis	Applications
1	Silver nanoparticals	Stem extract of Cissusquadranyularis	Antimicrobial and Antitumor activities
2	Platinum nanoparticals	Diopyros kaki leaf extract	Antitumor activities
3	Fluoresent carbon nanoparticals	Pomolo Peal	Used as probes for sensitive and selective detection of Mercury (II) ions
4	Silver nanoparticals	Papaya fruit extract	Antimicrobial
5	Cadmium Telluride (CdTe)quantum dots	Escherichia Coli	Imaging
6	Gold nanoparticals	Tamarind leaf extract	Chemical sensors
7	Gold nanoparticals	Onion (Allium Cepa) extract	As probes in imaging
8	Iron nanoparticals	Green tea, Oolong tea and black tea extract	Catalyst
9	Magnetite/Gold (Fe_2O_4/Au hybride nanoparticals	Grape seed proanthocyanidin	Contrast agents for MRI,CT and imaging

Health hazards of Nanomaterials

Nanotoxicology is the field which studies potential health risks of nanomaterials. The extremely small size of nanomaterials means that they are much more readily taken up by the human body than larger sized particles. How these nanoparticles behave inside the organism is one of the significant issues that need to be resolved. The behavior of nanoparticles is a function of their size, shape and surface reactivity with the surrounding tissue. Apart from what happens if non-degradable or slowly degradable nanoparticles accumulate in organs, another concern is their potential interaction with biological processes inside the body because of their large surface, nanoparticles on exposure to tissue and fluids immediately adsorb some of the macromolecules they encounter. The large number of variables influencing toxicity means that it is difficult to generalise about health risks associated with exposure to nanomaterials each new nanomaterial must be assessed individually and all material properties must be taken into account. Health and environmental issues combine in the workplace of companies engaged in producing or using nanomaterials and in the laboratories engaged in nanoscience and nanotechnology research. It is safe to say that current workplace exposure standards for dusts cannot be applied directly to nanoparticle dusts.

The National Institute for Occupational Safety and Health has conducted initial research on how nanoparticles interact with the body's systems and how workers might be exposed to nano sized particles in the manufacturing or industrial use of nanomaterials. NIOSH currently offers interim guidelines for working with nanomaterials consistent with the best scientific knowledge. At The National Personal Protective Technology Laboratory of NIOSH, studies investigating the filter penetration of nanoparticles on NIOSH certified and EU marked respirators, as well as non-certified dust masks have been conducted. These studies found that the most penetrating particle size range was between 30 and 100 nanometers, and leak size was the largest factor in the number of nanoparticles found inside the respirators of the test dummies. Other properties of nanomaterials that influence toxicity include: chemical composition, shape, surface structure, surface charge, aggregation and solubility, and the presence or absence of functional groups of other chemicals. The large number of variables influencing toxicity means that it is difficult to generalise about health risks associated with exposure to nanomaterials each new nanomaterial must be assessed individually and all material properties must be taken into account.

CONCLUSION

Nanoparticles can be made to reach a target site by virtue of their size and surface modification with a specific recognition ligand. Their surface can be easily modified and functionalized. This discipline is now well established for drug delivery, diagnostics, prognostic and treatment of diseases through its nanoengineered tools. Drugs that are transformed into nano range offers some unique features which can lead to prolonged circulation, improved drug localization, enhanced drug efficacy etc. Various pharmaceutical nanotechnology based systems which can be termed as nanopharmaceuticals like polymeric nanoparticles, magnetic nanoparticles, liposomes, carbon nanotubes, quantum dots, dendrimers, metallic nanoparticles, polymeric nanoparticles, etc. have brought about revolutionary changes in drug delivery as well as the total medical service system. However some recently found health risk evidences limits their utilization in pharmaceutical industry. Some concerning issues like safety, bioethical issues, toxicity hazards, physiological and pharmaceutical challenges get to be resolved by the scientists. Current researchers are still lacking sufficient data and guidelines regarding safe use of these nanotechnology based devices and materials. Therefore pharmaceutical nanotechnology is still in developmental stage. This review is written to get an insight about nanoparticles in the field of medicine and

pharmacy, their synthesis methods and their possible applications.

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