Application of Nanoparticles in Medicine

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Abstract

Nanomaterials due to their size (ranging from 0.1-100 nm, at least in one dimension) and higher ratio of surface area to volume display dominant quantum effects causing drastic changes in their chemical reactivity as well as optical, elastic, electrical and magnetic properties. The electrons due to their wave nature move very easily without scattering in nanomaterials and allow their use as biological sensors. Nano wires, semiconducting in nature, act as a versatile optoelectronic component in photodetectors sensitive to polarization and arrays with sub wavelength resolution. The wide applicability of nanomaterials in medicines emerge from the similarity in size of biomolecule moieties of metabolic processes occurring at nano levels.

Optical properties of quantum dots allow their use as biomarkers subsequent to coating with a material able to bind selectively with certain biological structures like cancer cells by fluorescent absorption followed by emission of electrons known as functionalised quantum dots. Nanomaterials on combining with biomolecules develop ability to recognize sensitive diagnostic and regulated drug delivery processes with appreciably better performances and may be used as tissue substitutes. The properties produced in organic solvents make them hydrophobic and incompatible to biological molecules. At the same time, they may be converted into water soluble form and made biocompatible through different techniques like ligand exchange, encapsulation, polymer coating (with functional groups attached to the surface) providing reactive site for bio conjugation through different processes keeping limitations of the processes in view.

Nanomaterials play prominent role in medicines as obviated by growing global market for them in the field expected to reach to USD 182.3 billion by 2027 at a compounded annual growth rate of 19.9% from 2021.

Keywords: Nanomaterials, Quantum effect, Drug delivery, Cancer, Characterization, Limitations

Introduction

Nanomaterials (NM), (size ranging from 0.1-100 nm, at least in one dimension)[1,2] have relatively appreciable fractions of large number of atoms on the surface making quantum effect dominant altering chemical reactivity as well as optical, elastic, electrical and magnetic properties drastically. Furthermore, wave nature of electrons in nanomaterials has far reaching consequences on electronic energy levels and electrical properties in zero, one- and two-dimensional nanostructures. Electrons in graphene move very easily without scattering and may be used as biological sensors. Semiconducting nano wires act as a versatile optoelectronic component in polarization sensitive photodetectors and arrays with sub wavelength resolution.

Optical properties of functionalised (coated) quantum dots allow their use as biomarkers subsequent to coating with a material able to bind selectively with certain biological structures like cancer cells. The coated dots have usually CdS, CdSe, and CdTe as core material with ZnS as fluorescent coat. Cancer cells are identified by fluorescent absorption followed by emission of electrons.

Biomolecules on combining with NM develop unique characteristics due to their properties of recognizing sensitive diagnostic and regulated drug delivery implements with appreciably better performances and may be used as novel tissue substitutes, NMs can be divided according to their geometry such as equiaxed (equal in all dimensions), one dimensional (fibrous or wire) and two-dimensional or lamellar. The physical, electronic, chemical and optical properties as well as unique quantum mechanical effects of NM, give rise to unexpected physicochemical properties. The properties produced in organic solvents make them hydrophobic and incompatible to biological molecules. At the same time, they may be converted into water soluble form to make them biocompatible through different techniques. The techniques include ligand exchange, encapsulation, polymer coating (with functional groups attached to the surface) and provide reactive site for bio conjugation or cross linking through direct attachment (hydrophobic or electrostatic interaction) and some time through biotin avidin systems. The molecules produced have to be checked for drawbacks like low yield and loss of functionality after conjugation.

The NM biosensors are highly sensitive, stable, assembled into barcodes and high-density arrays needing light emitting diodes as power source. Researches in Nanotechnology leads to miniaturized, speedier, automated, less error prone, disposable devices for the analysis of genetic structure; their effect on cellular functions changes focus from diagnosis and

treatment to identification and prevention. This leads to individually tailored patients' specific treatment and therapies.

Requisites of Nanomaterials

Quantum dots (QDs) fluorescence exhibits broad excitation profile, narrow and symmetric emission spectra, high photo stability, high quantum efficiency and excellent multiple detection capability in biosensing[3] and imaging contrary to organic dyes. Near- field scanning optical microscope (NSOM) has helped in developing nano transducers which recognize the binding events and actively generate highly sensitive signals simultaneously. NM for drug delivery to tumours, must be small (<100 nm), nontoxic, should not aggregate, should be biodegradable and biocompatible. They should avoid the reticulo-endothelial system (RES) uptake[4], should not aggregate, escape opsonization, be non-inflammatory besides prolonged circulation time to make the drug more effective for therapy and should be economic cost wise, with minimum side effect. Effects of size, charge, shape, surface modification, loading and other chemical properties of NM on the drug delivery system while employing it as carrier need to be examined. Besides, Interaction of NM with their hosts in bio distribution, organ accumulation/ degradation, toxicity, genetic or cellular structure damage or inflammatory foreign body effect, toxicity of nanocarriers and various other parameters need to be investigated.

Benefits of Nanomaterials

Nanoparticles, their nano-range size at least in one dimension, with a small diameter of 0.1-1000 nm in general, in medicine 5-250 nm[5] and a very high surface area to volume ratio render their high reliability and reproducibility[6] in drug delivery. An industrial revolution is in offing in nanoscience, to convert negative nanostructures into its positive and productive aspect. Nanotechnology is predicted to play a great role in the developing world, contributing to advances in medicine and pharmacy besides transport, energy storage etc[7]. Their shape, surface properties and size on modification give rise to several nano systems which may be utilized in imaging, diagnosis and treatment of serious diseases. Besides, they may also be utilised in dentistry, sunscreens, cosmetics, environmental clean-up, gene inactivation and biological sensors[8,9,10].

The nano materials with characteristic functional groups at the nano scale, prepared by physical and chemical methods, send drugs to particular sites or tissues[11]. Tissue and cell interactions are function of several parameters such as charge, size, shape and structure of

drug molecules[12] which may be optimized by studying and regulating them. Nanotechnology products find extensive use in healthcare. Several nano systems have been developed for prevention, identification, deciphering and cure of several diseases such as cancer, cardiovascular, ocular and central nervous system related diseases[13,14,15.] Several nano systems have been revealed to be more efficient in comparison to conventional ones for theragnostic (therapeutic and diagnostic both) purposes. The radioactive drugs are used to diagnose and drug delivers therapy to treat the main and any metastatic tumours.

Nano materials gel with biomedical devices due to their almost similar sizes[9]. In the field of drug delivery, nano systems render the drug supply with high degree of precision to the target at a regulated rate increasing delivery time in comparison to usual processes.

Nano particles are highly effective in drug delivery to the specific target locations utilizing biodegradable materials in the majority of the cases[16,17]. The drug delivery is further facilitated due to their ability to cross blood brain barrier entering pulmonary system, endothelium of tumours coupled with absorption through tight junctions of skin endothelial cells. The effective absorption by different types of cells as well as selective drug delivery in the target locations[18,19] make the nano particles of immense use in drug delivery system. Their small particle size and large surface area[20] cause greater solubility and superior bioavailability. The active pharmaceutical ingredients (API) are dissolved, entrapped, encapsulated or linked to nanoparticle matrix[21]. Nanoparticles may be utilized to transport proteins, nucleic acid, antibiotics, vaccines besides their use as drug delivery systems in different type of therapies such as gene therapy, cancer therapy, aids therapy etc.

Nanoparticles may also be used more efficiently for intravenous administration than conventional micro-particles. Due to their relatively smaller size than that of the smallest body capillaries (diameter 5-6 μm) they are free from causing obstruction in an artery, by a clot of blood or an air bubble i.e., embolism. Natural and synthetic biodegradable polymer may be used for preparation of Nanoparticles with improved bioavailability and controlled release behaviour of medicines in a particular dose at a focal point for an elongated duration by adapting the system in a way to prevent endogenous system to destroy the drug[22]. Moreover, Nanoparticles act as creative carrier systems for proteins or nucleic acids present in medicines (even without proper formulation) to avoid their decomposition and improve their efficiency[23].

Types of Nanoparticles used in Medicine

Carbon nanotubes (CNT)

Carbon nanotubes are nanosized, seamless carbon-based tubular structures constituted of graphite cylindrical sheets, sealed at one or both ends by bucky balls of varying length from 1 to 100 nm. They may be single or multiwalled nanotubes (SWNT or MWNT) suitable for detection of DNA mutation as diameter of DNA helix is half the size of SWNT. On the contrary, diameter of MWNT varies according to the number of walls in their structure and extend from a few nm to tens of nanometers[24]. Nanotubes possess the unique feature of entering living cell without causing its death or any other damage. It appears they behave like miniaturized needles and enter cells spontaneously with unrecognised mechanism. As revealed by computer simulation, the CNT are absorbed and accommodated onto the membrane surface with their axis parallel to plane of membrane. Cells don't recognize them as harmful intruder due to their smaller size (diameter 2-50 nm about 10,000 to 50, 000 smaller than human hair). The use of CNTs in drug delivery requires attachment of different functional groups on the external surface of nanotubes. The modified CNTs are used for delivery of antibiotics to different types of cells by selective transport through the membrane. CNT were used in administration of amphotericin -B a very powerful antibiotic considered to be most effective in chronic fungal diseases[25]. CNT finds use as a vector in gene delivery. Hollow core of CNT permits encapsulation of molecules.

CNT and fullerenes ($C_{60,}$ C_{70}, C_{76} etc., found in variety of graphite cylinder with hollow cage like configurations suitable for drug encapsulation) used as drug transporters are generally, produced by chemical vapour deposition, combustion procedures and electric arc discharge. Their capability is characterised by the strength and stability of the structures of nanotubes and fullerenes, CNTs being one of the strongest materials in terms of tensile strength and modulus of elasticity (almost 100 times of steel) due to covalent sp^2 bond existing between individual C atoms. They were also shown to exhibit antioxidant and antimicrobial activity[26]. The structure of fullerenes was capable of targeting tissues and intracellular mitochondria. CNT with their capability to cross partially permeable cell membrane very easily have potential to overcome obstructions, impossible to remove at an early stage, and therefore, find wide application in modern healthcare systems. Their capability to carry small molecules such as organic drugs, proteins, peptides, nucleic acids, antibiotics, etc., enhances further their utility. The molecules may be carried to precise location forming covalent bonds, adsorption or encapsulation in the CNT. Covalent or non -covalent bonding of smaller proteins (less than 80 KDa) with CNT help them in getting absorbed by smaller cells

covalently or non-covalently and are engulfed within the cell membrane via endocytosis[27]. X-rays produced from CNT (cold X-rays) allow imaging of superior quality due to its properties. The cells containing CNT solution on exposure to a laser infrared beam doesn't get destroyed despite getting heated up to 158° F up to two minutes due to CNT absorbing near infrared waves. Cancer cells, other than the normal cells, absorb wavelengths, and may be killed effectively by laser (with appropriate wavelength) due to their high intensity and near monochromaticity.

CNT are extensively used in treatment of osteoporosis, broken bones, blood compatible heparin CNT as artificial kidney[28], as heparin composite membrane with nano-pores could work efficiently as an artificial kidney (dialyzer) by filtering the blood and maintaining its flow. However, dispersion of CNT with tendency to aggregate in large bundles and ropes (due to their higher molecular weight and strong intertubular force (Vander Walls and electrostatics) specially in saline media or serum commonly used in toxicology, dictating entry into cell significantly, poses a big limitation. Sonification, use of surfactant in aqueous solution or highly polar organic solvents such as N, N dimethylformamide along with ultrasonic baths or probes gives stable dispersion in individual pristine CNT[27]. Many toxicological findings still consist of CNT aggregate. Chemical functionalisation i.e., covalently attaching appropriate molecules like peptides, acids, amines, polymers and poly-L- lysine to the side walls of CNT, most commonly achieved by amidation or esterification of the COOH group present after CNT purification or adsorption of bio molecules (most promising dispersion technique).

Quantum dots

Quantum dots (QD) nano crystals of size between 1.5- 10 nm are made up of semi-conducting structures. Their inorganic semiconductor nature allows electrons to transport enabling QD to fluoresce, emit different colours of light[29] according to their size (due to scattering). The phenomenon enables their use as labels in biosensing and imaging making them highly advantageous over the conventional organic dyes, due to their ability to emit several wavelengths on excitation with a single source as against organic dyes which need several excitation sources to emit different wavelengths. QD could therefore, be efficiently exploited to identify multiple targets as fluorescent probe other than the normal cells simultaneously, leading to replacement of organic dyes. Furthermore, they show high quantum efficiency, high stability to excitation and exceptional multiplexed detection capability[30, 31].

QD are inorganic semiconductor nano crystals. The core is constituted of CdSe, CdTe and CdS with an organic shell covered with a layer of ZnS to make them luminescent on exposure to light. Solubility of QD improves in aqueous buffer by adding a cap to QD[32]. QD prepared from heavy metals like Cd are highly toxic and carcinogenic and therefore, avoided in health care. On the contrary, graphene and carbon QD have wide scope in health sector[33] as they are stable and safe. Some of the uses of QD in diagnostic and therapeutic applications include cell labelling, DNA hybridisation, creation of non- viral vectors for gene therapy, biomolecule detection and biological performance and act as carrier for drugs utilised for cancer cure. They also convey biological and non- biological agents[34] and act as carriers for cancer treatment. Semiconducting nano-materials ZnO, CuO and TiO_2 are mostly used in drug delivery.

Nanoshells

Nanoshells comprising of economic dielectric silica core with an outer metallic thin layer (usually gold) are used to target drugs after adequate alterations. The alterations cause varying characteristics with variations in ratio between the core and the shell. The Nanoshells are used to cover particles of specific shape to achieve desired morphology.

They are inexpensive as precious metals can be added to the dielectric economic cores and thus amount of precious metals is required in smaller quantities during synthesising nanoshells[35] for example gold nanoshells. The targeting efficacy of nanoshells is enhanced towards cancer cell due to antibodies occupying their outer gold surface[36].

Nanobubbles

Nanobubbles or ultrafine bubbles are cavities of gases with diameter less than 200 nm[37]. They are formed at the interface of lipophilic surfaces in liquids by cavitation process, mix at body temperature and form larger microbubbles by rapid dissolution of the supersaturated liquid. Microbubbles are stable at room temperature and rise up in supersaturated solution due to gas nucleation at the hydrophobic surface and cause air gas trapping. The nanobubbles may be classified as plasmonic, bulk, oscillating and interfacial Nanobubbles and on loading with drugs effectively target tumour tissues and thus have high utility for cancer treatment. The uptake of tumour cells by Nanobubbles is appreciably enhanced when exposed to ultrasound[38, 39].

Basically, microbubbles (sort of gas-liquid emulsions) have core of an inert gas surrounded by a protective biocompatible shell (of lipids, albumin, protein or polymer). The shell protects leakage of gas and particle fusion[40]. Diameter of the shell ranges between 1-10 μm

with varying shell compositions. Elasticity of the material depends on the shell composition. Higher the elasticity of the material greater the acoustic energy microbubble may withstand. Microbubbles loaded with an active drug being lipophilic can easily penetrate through brain, blood barrier (BBB) and deliver the drug into brain tissue through a focused ultrasound which ruptures tight junctions in a particular localized area and increases permeability[41] of BBB.

Microbubble combined with ultrasound helps in diagnostic applications as well as therapeutics to different lesions. Tumours due to leaky vasculature have large gaps of about 700 nm between the endothelial cells, provide access to nanoparticles of size less than 700 nm[42]. Nanobubbles similar to micro bubbles act as a promising agent for imaging and/ or therapeutic use.

MRI coupled with ultrasound therapy is utilised in a non-invasive thermal ablation method for the cure of uterine fibroids. The method has approval of FDA. The method is also used as a treatment for liver, bone prostrate and brain related diseases[43, 44].

Paramagnetic Nanoparticles

Paramagnetic Nanoparticles (PN) are small particles with diameter slightly less than 100 nm. They could be prepared by applying strong magnetic fields to paramagnetic substances i.e., atoms with unpaired electrons (gadolinium, magnesium, lithium, tantalum etc.). PN are classified on the basis of their magnetic sensitivity. PN have higher magnetic susceptibility. Under the influence of a magnetic field, PN act as effective targets for identification of specific organs[45,46]. They mainly comprise of rare earth metal oxides and hydroxides. The most commonly used rare earth is Gd^{3+} due to maximum number of unpaired electrons present in it (or Mn^{2+}) and is used as a positive contrast agent for MRI to improve the quality and hence accuracy of diagnosis of MRI scan

Liposomes

Liposomes are spherical double layered vesicles surrounding an aqueous core domain of the size varying from 50 nm to several micrometers. Liposome, synthetic particles, self-assembled amphiphilic phospholipids are in general, biocompatible as well as biodegradable with reduced toxicity and systemic effects[47]. Modified nanoscale liposomes are employed for transfer of proteins, DNA, small interferant (si) RNA, and cancer treatment but suffer from limitations of incapability to penetrate cells[48] causing discharge of drugs into extra cellular fluid besides rapid and inability to regulate[49] drug release and low loading capacity. However, drugs may be trapped persistently in aqueous phase of liposome with minimum drug loss during circulation[50] by using ammonium sulphate and may be coupled with antibodies to deliver drug to specific target[51].

Niosomes

Niosomes, with unique characteristics of containing lipophilic and lipophobic both agents[52] can be utilized as a new delivery system of drugs. They are self-assembled cluster of non-ionic surfactant molecules in aqueous phase. Their entrapment volume is decreased during formulation due to intercalation of cholesterol in their bilayers reducing their entrapment efficiency[53]. However, currently they are adopted for delivery of potent drugs[54] due to their entrapment capability to a broad extent for treatment of cancer[55] and viral diseases[54]. In vivo niosomes behave similar to liposome in extending entrapped drug circulation and may replace liposome as they are highly stable as well as nontoxic.

Dendrimers

Dendrimers with a small size in the range of 1-10 nm, 3D globules with branched layers giving rise to spherical shape create voids useful to entrap drugs and consequent delivery. They are biodegradable nanopolymers. Due to their lipophilic nature and small size, they can penetrate through cell membrane and are used for delivery of genes, drugs and vaccination. They are special category of polymers characterized by their core, made of an atom or multifunctional molecule, repeated branching bonded to the core usually covalently with functional groups at free ends to be conjugated to other molecules[56] and surface. Dendrimers interact chemically either through ionizable functional groups or through covalent bonding subsequent to mixing of their surface with active functional groups such as p- aminobenzoic acid, poly ethylene glycol (PEG) etc., formation of covalent bonds with the functional groups allows conjugation of dyes with dendrimers. Highly selective nature of dendrimers to target the desired tissue holds promises for future treatment of several diseases. Their nontoxic, biocompatible and safe nature are the key feature to make them site specific as well as long duration drug delivery carriers[57]. Their metal chelates are highly appropriate to use as magnetic resonance imaging contrast reagents[58].

Polymeric micelles

Polymeric micelles are nanoscopic copolymer micelle formed by lipophilic centre and the lipophobic block. The stability is achieved by corona of a lipophilic polymer chains. Polyethylene glycol (PEG) blocks form corona. Length of lipophilic centre forming block and that of hydrophilic block is similar[59]. Micelles forming surfactants improve solubility of a medicine with poor solubility in water besides increasing permeability of the medicine across physiological barriers and their bioavailability. Due to their smaller size and lipophilicity, polymeric micelles are retained for elongated duration in blood after intravenous delivery causing their reduced uptake by reticule- endothelial system. A target component when

attached to their surface is highly target specific. The medication is efficiently shielded from biological surroundings from possible deterioration due to their micellar nature[60]. Centre of lipophilic block of a polymeric micelle is stabilized by a corona of lipophilic polymeric chain. Due to micellar form, polymeric micelles find their path to the target organ or tissue.

Polymeric nanoparticles

Polymeric nanoparticles (PNP) although highly efficient and effective as intracellular delivery, site targeting systems and drug delivery as compared to conventional system, suffer from degradation, potential antigenicity and poor reproducibility. They may be in the form of nanocapsules (vesicular systems)[46] or nanospheres (matrix systems). The encapsulated drug release behaviour is controlled by manufacturing techniques. The drug may be dissolved, entrapped or encapsulated across or inside polymeric matrix. The drug is contained in the core enclosed by polymeric membrane while it is dispersed through the polymeric matrix. PNP have capability of customizing delivery of medicines and can be used as an excellent alternative in treatment of cancer[61]. Several efforts have been made to minimize the harmful effects of drugs during the delivery process to cure cancer and to prevent side effect on the nearby cells and tissues.

PNP can target the blood vessels which support tumour growth by supplying nutrients, oxygen etc., to cancer cells. They also target immune cells to develop anti-cancer immunotherapy[62].

Solid lipid nanoparticles (SLN)

SLN prepared from solid lipids stabilized by surfactants are used as a colloidal drug delivery system as a substitute to emulsions, liposomes and PNP. SLN show various advantages as drug delivery agent over other particle carriers besides targeted impact on brain[63,64,] such as better tolerance, biodegradability and high bioavailability and administration through eyes (ocular route). Small size SLN may be injected intravenously and could be used for site targeting of drugs[25].

Nanoemulsions

Nanoemulsions are made up of immiscible liquids, either oil in water type (o/w) into aqueous phase or vice versa. The oral bioavailability of isotropic mixture formed by mild mixing of oil, surfactant, co- surfactant and drug[65,66] (weakly water-soluble medicines) is improved by several processes. The small size of the droplets reduces the surface tension between the oil

droplets and aqueous medium of gastrointestinal tract permitting uniform drug distribution spread widely in the gut[67].

Role of Nanotechnology in health care

NP with positive charge, small size and high surface to volume ratio can enter deep into the membranes and thus act as ideal vectors for gene delivery[68,69,70]. Some of the important nanoparticles utilised in gene therapy are liposomes, super paramagnetic iron oxide with fluorescent, quantum dot molecules

NP are relatively much better than viral vectors due to relative ease of preparation, almost nil risk of recombination and ability to load any size of gene.

Diseases like autoimmune disorders, viral infections and cancers may be treated by making the gene expression silent using small interferant RNA (siRNA). siRNA induces gene silencing through sequence specific cleavage of complementary messenger RNA molecule[71,72].

Gene could efficiently be delivered by conjugating gene materials such as RNA, DNA, siRNA with NP liposomes, polymeric and other nanomaterials. Genes are attached with NP by forming DNA-NP complex.

Cardiovascular Diseases through NP

The treatment is carried out by introducing anti- apoptotic and pro-angiogenic genes into stem cells to improve rate of survival and their paracrine secretion[73,74]. Liposomes are one of the best NP for gene delivery as they do not permit non-specific binding of genes and avoid their degradation[75,76]. NP used should be highly target specific[77] and capable to track and monitor stem cells. Super paramagnetic iron oxide nano particles (SPION) are attached to cell surfaces and subjected to enter the cells. QD are also used for monitoring the living cells for long period. Growth factors have been delivered to placental cells using chitosan alginates NP to improve the functioning of cardiac tissues at the site of myocardial infarction[78].

Treatment of brain diseases

Blood brain barrier (BBB), boundary between circulating blood and neural tissues of brain is the main obstacle in treatment of diseases related with brain as it prevents entry of the drug into central nervous system (CNS)[1]. Any sort of change in BBB causes neurodegeneration and neuro-inflammation and related diseases like Alzheimer (most common form of dementia) and Parkinson diseases (second most common form of brain disease) but the drugs are not allowed entry even after damage of BBB. However, due to their small size, high capacity of loading drugs and effective imaging performance (in case of inorganic NP) and

ability to conjugate with ligands, NP can cross BBB layer through several path ways and thus are capable of treating neurodegenerative diseases.

Some NP show therapeutic properties such as antioxidant, preventing beta-amyloid (Ab) peptide aggregation, decreasing reactive oxygen species (ROS) levels[79]. NP on conjugation with ligands interact to the optimum level with BBC receptors at low density through one of multiple pathways[69] so that it may cross BBB level and provide treatment of the related diseases such as Alzheimer's, Parkinson's etc. Circulation time of Zwitterion and neutral NP is greater in comparison to the charged NP[70,80].

Application of nanotechnology for diagnosis and treatment of cancer

Biocompatibility and time-consuming drug release characteristics of Nanoparticles made from PLGA polymer are utilised to load drug for cancer therapy. Anticancer drugs like doxorubicin, paclitaxel, 5- fluorouracil and dexamethasone prepared by utilising PLGA are highly effective for cancer treatment. Micro sphere version of Somatropin- PLGA Nanoparticle, Nutropin Depot, was authorized by food and drug administration (FDA) as anticancer drug, long back in 1999. The drug was approved as once per month to be administered as an alternative of human growth hormone (HGH) injection required daily to be taken[71]. Nanoparticles used in nano - oncology is highly effective to treat cancer due to its improved cancer cell targeting and overcomes cancer tissue multidrug resistance[72]. Doxorubicin primarily used to treat several types of cancer is highly toxic which effects heart and kidney also, besides tumour tissue but the same drug in liposomes is used as FDA approved nanomedical drug delivery system[81]. The liposomes formulation reduced doxorubicin passage to heart and kidney but enhanced doxorubicin accumulation[82].

Nanoparticles in vaccination against Covid-19

The recorded genome structure of SARS CoV-2 (corona virus) and knowledge of order of proteins laying the virus surface formed the basis for preparation of COVID-19 Nanoparticles based vaccines. The presence of spike proteins on the outer surface of the virus with a high connectivity towards nano-formulations and a high tendency to bind to host cell receptors was utilised as main point to develop CNPBV[83]. The FDA approved vaccine was highly effective in prophylaxis against COVID-19 to fight and restrict the spread of the Pandemic around the world. Pfizer-BioNTech and Moderna Vaccine were two vaccines relying on mRNA to encode the virus's spike glycoprotein (S) and incorporated the encapsulated modified mRNA into lipid base Nanoparticles[84] to aid transport of the protein antigen (spike protein) to immune cells and thus stimulating T cell activity induced antibody immunological response within the human body[85].

Toxicity of NP

Due to multiple applications of NP in medicines and other fields such as industrial etc., it becomes pertinent to have basic knowledge of toxic effects of NP to safeguard ourselves especially due to the fact that NP enters into the environment unnoticed due to its nanoscale size through air, water and soil by various activities of mankind.

Toxic effects of the NP being utilised for medical applications (CNT, QD, Iron oxide magnetic nanoparticles (IOMNP), liposomes and many others such as gold, silver, metal oxides, polymer NP) have been evaluated to a limited extent. In spite of toxicological effects being critical, there exists a wide gap between research on medical applications of NM and nano-toxicology[86]. Many of the NM useful in medicines show mild to almost nil toxicity.

However, studies reveal that even at very low aqueous concentration they effect environment in a significant way, for example, use of CdSe QD must be limited as they contain Cd which is reported to be toxic to cells at concentrations as low as 10 μgmL^{-1} [87].

CNT can enter into human cells and cause death of a cell by accumulating in cytoplasm[88]. The tubes have been observed to cause inflammation, fibrosis and toxicological effects in lungs[89] and may be easily inhaled due to its fibrous nature on dispersion in air and reach lungs. Among several studies made, AuNP of different shapes and sizes revealed almost negligible toxicity[90,91].

High reactivity, great capacity and small size of Magnetic NP making it advantageous could cause lethal effects by inducing adverse cellular toxic and harmful effects which is generally uncommon in micron sized counter parts. NP may translocate to different organs and tissues subsequent to entry into the body during ingestion or inhalation and cause toxicological effect. NP may aggregate in hard water or sea water and may be affected by some particular type of organic matter or colloids present in fresh water. Influence of Many abiotic factors for example pH, salinity, organic matter, state of dispersion of NP still remain to be ascertained responsible for NP to cause eco-toxicity[92]. AgNP is used as bandages, house hold items and even textiles due to its antimicrobial properties. Persistent exposure to silver may cause argyria and/ or argyrosis toxicity in human beings. High ratio of their surface area to volume in metal NP enhances release of Ag ions into solution but it's not confirmed that released silver from AgNP causes toxicity. Ag into solution causes toxic effects on aquatic species besides bacteria, algae, fish, and daphnia[92]. Interaction between Antigen and antibody labelled with fluorescent dyes, enzymes, radioactive materials or colloidal Au can help in detection of analytes in tissues which may help in assessment of toxicity[92].

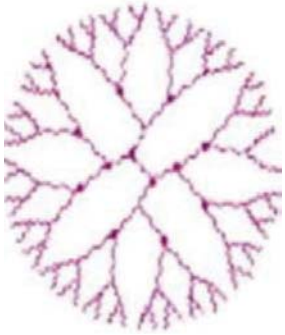
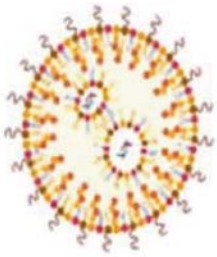
Conclusion

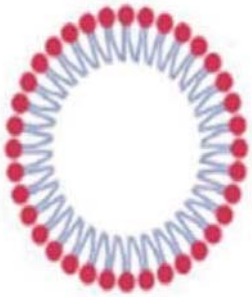
Nanotechnology is of immense use in drug related areas such as manufacturing and delivery of drugs besides their wide application in diagnostics. Nanoparticles have vital applications in medical field. Cancer diagnosis and treatment, gene therapy and genetic diseases like Alzheimer's, Parkinson's, Huntington's disease, amyotrophic lateral sclerosis, cystic fibrosis; nervous system disease, treatment of osteoporosis, broken bones, blood compatible heparin CNT as artificial kidney[28], vaccination against Covid-19; in implants, dentistry, MRI, DNA mutation[93] etc., are the various fields where nano particles play important roles. Table 1 lists detail of nanosystems (nanoparticles) and their applications. The prominent role of nanosystems (nanoparticles) in medicines is obviated by growing global market for them in the field expected to reach by 2027 to USD 182.3 billion at a compounded annual growth rate of 19.9% from 2021.

Table:

Table 1. Nanosystems/Nanoparticles utilised in Medicines

Types of Nanosystems	Figures	Application	Problems and Solutions
Nanoparticles		Applied in therapeutics for treatment of cancer, stem cell diseases, implants and prosthetic orthopaedic diagnosis, in treatment of infectious and non-infectious diseases, production of vaccine, diagnosis of cancer employing bio imaging and immunisation, gene therapy, genetic disorders, brain and CNS (central nervous system) disorders, cardiovascular diseases, ocular diseases, delivery of drugs etc.	

Quantum Dots[31,32,33,34]		In diagnosis, in vivo bio imaging in real time, in controlling several diseases, in delivery of small interferent RNA for RNA interference, intracellular tracking and therapeutic drug delivery	
Dendrimers[56,57,58]		In diagnosis, gene delivery, as anticancer drugs, as antibacterial agent, in treatment of ocular diseases and as antigen carriers to modify vaccine formulations.	
Liposomes[46,48,49,50,51]		In hydrophobic and hydrophilic drug delivery, drugs protection from degradation by chemicals and enzymes, in capsulation of anti-tumour drugs such as dox, anthracyclines such epirubicin and daunorubicin etc.	
CNT (carbon nano tubes)[25,26,27,28, 93]		Drug delivery in delivering small organic drug molecules, peptides, proteins, nucleic acids into cells and controlled delivery of anticancer drugs, in treatment of broken bones Vaccine delivery, as vectors in gene delivery, heparin CNT as artificial kidney, biosensors, osteoporosis, early breast cancer detection, CNT x-ray for in-vivo imaging, in tumour therapy, DNA	Hurdles Tendency to aggregate in large bundles and ropes especially in the media used commonly, (saline or serum) in toxicology. Overcome by sonification, attaching of suitable functional group covalently

		mutation [93] and disease protein biomarker detection	or making them stable by surfactant
Polymeric micelles[60]		In improving solubility of a medicine, permeability of the medicine across physiological barrier and their bioavailability, find their path to the target organ or tissue	
Polymeric nanoparticles (PNP)[61,62]		In intracellular delivery, site targeting system, in treatment of cancer, as target to immune cells to develop anticancer immunotherapy.	Drawbacks Suffers from degradation, potential antigenicity, poor reproducibility
Niosomes[54, 55]	.	In delivery of potent drugs for treatment of cancer and viral diseases.	
Nanoemulsions[67]		In uniform drug distribution in the gut	

Nanobubbles[38,39,41,43,44]		To increase uptake of tumour cells on exposure to ultrasound, micro bubbles easily penetrate through brain blood barriers with a focused ultrasound, micro and Nanobubbles used for imaging and/or therapeutic use, MRI (magnetic resonance imaging with ultrasound therapy used in non-invasive thermal ablation method for cure of uterine fibroids, liver, bone prostrate and brain related diseases.	
Nanoshells[36]		Used to cover specific shape particles to achieve desired morphology, gold nanoshells in enhancing targeting efficiency towards cancer cells.	
Paramagnetic Nanoparticles[45, 46]		As effective target for specific organs under the effect of external magnet, super paramagnetic iron oxide with fluorescent in gene therapy, as contrast agents for MRI	

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