Available online on www.ijcpr.com
International Journal of Current Pharmaceutical Review and Research; 7(5); 258-266

ISSN: 0976 822X

Research Article

Advancement of Nanopharmaceutics in Drug Delivery

Dinesh S R*, Umashankar M S, Rini R, Aditi D, Kanchan K

SRM College of Pharmacy, SRM University, Kattankulathur, Tamil Nadu.

Available Online: 1st October, 2016

ABSTRACT

In the current era, the development in nanoparticles drug delivery is widely expected to change the outlook of pharmaceutical industries for the upcoming prospects. Nanotechnology has become a significant priority worldwide. A variety of manufactured nanoparticles - particles with one dimension less than 100 nm – are rampantly used in consumer products. In the range of nanosize, the properties of materials differ significantly from bulk materials having the same composition, mostly because of the increased specific surface area and reactivity, which might result into increased bioavailability and toxicity. A nanoparticle has incepted as a promising strategy for the efficient delivery of drugs used for the treatment of some diseases by specific targeting. These Carriers are designed in such a way that they are self-standing in the environments and selective at the pharmacological site. The delivery of drug has its substantial physicochemical parameters like ionic strength, surface charge, particle size, molecular weight, pH and monomer concentration in the formation of nanoparticles. The major problem in chemotherapy which is the multi drug resistance can be overcome by these nanoparticles where it has the capability to reverse these conditions. Immunotherapy, cancer therapy and radiotherapy are the most common and well known therapies which are used in this technology. This mini-review is summarizing the information on different methods of manufacturing nanoparticles, focusing on its properties and biological transport.

Keywords: Nanopharmaceutics, Drug delivery, Bioavailability

INTRODUCTION

Nanotechnology is extensively recognized as one of the key technologies of this century. Nanotechnology and Nanoscience subsume the study and implementation of extremely small things and can be employed across various other scientific fields, like biology, chemistry physics, materials science and engineering. Nanotechnology and Nanoscience involves the ability to perceive and to control individual molecules and atoms. This technology has the potential to make a substantial impact on healthcare by inculcating step-changes in diagnosis of disease and its monitoring, implants and regenerative medicine, delivery of drug as well as research tools for discovery of drug and biomedical science. The qualities that make nanomaterials so intriguing are the increase in reactivity and the ability of drug molecule to cross cell membranes with improved health and safety impacts[1]. Drug delivery is the process of administration of a pharmaceutical product to produce a therapeutic effect in humans and/or animals. A Pharmaceutical product or compound maybe defined as the substance which is manufactured as a drug intended for medicinal and therapeutic use. Nanotechnology under delivery of drugs includes “engineered particles”, which act by a distinct mechanism; first these particles are attracted to diseased cells, allowing the direct treatment of those particular cells. This technique is lucrative owing to its reduced tendency to damage the healthy cells in body[2]. Nanopharmaceutical is certainly one of the most promising fields under Nanotechnology. This is because nanomaterials enter our body through dermal exposure, ocular contact, inhalation or ingestion; they devote themselves to futuristic novel drug delivery systems. Pharmaceutical research, formulation, toxicology studies and manufacture of pharmaceutical products require characterization of materials to ensure persistent safety and efficacy of the drug. Nanopharmaceuticals have innumerable advantages not only for the treatment of the disease and delivery of therapeutic agents, but also in unleashing their innate sub cellular or intracellular behaviour, enabling profound information regarding diagnosis and prognosis, quantifying efficacy of the treatment and designing better therapeutics. Nanopharmaceutics has emerged as a discipline having enormous potential as carrier for spatial and temporal delivery of bioactives which provides smart materials for tissue engineering. It is now well-established as specialized area for drug delivery and treatment of diseases through its nanoengineered tools. Few nanotechnologies based products and delivery systems are already in market. Nanopharmaceutics also provides opportunities to improve materials, medical devices and help to develop new technologies where existing and more conventional technologies may be reaching their limits. Besides, nanopharmaceutics also raises new hope to pharmaceutical industries by providing new cutting age patentable technologies in view of revenue loss caused due to off-patent drugs. Scientific societies, industries and governments all over world are looking with great anticipation and contributing their best to clutch the potential of this technology. This technology of

*Author for Correspondence: dinesh060991@gmail.com

nanopharmaceutics has the potential to make significant contributions to disease detection, diagnosis, therapy, and prevention. Pharmaceutical nanotechnology could have a profound influence on disease prevention efforts because it offers innovative tools for understanding the cell as well as the differences between normal and abnormal cells. It could provide insights into the molecular basis of disease. However, going towards bottom size increases the unknown health risk. However, some suggested initiative must be taken in order to exploit the advantage of this very fascinating and ever growing potential technology. Some of these are (i) identifying, defining and characterizing model nanomaterials, (ii) developing toxicity testing protocol, (iii) detecting and monitoring exposure level, (iv) assessing the impact of environment, and (v) developing the biocompatible hybrid system[3.]

Classification of nanomaterials[4]

Evaluation parameters[5]

Mean particle size and size distribution

The mean particle size and the width of particle size distribution (called Polydispersity Index) are determined by Photon Correlation Spectroscopy (PCS). PCS measures the particle size in the range of 3nm- 3 μm only. polydispersity index (PI) governs the physical stability of nanosuspensions and should be as low as possible for long-term stability. (Should be close to zero). PCS is a versatile technique but has low measuring range. In addition to PCS analysis nanosuspensions are analysed by Lase Diffractometry (LD).

Particle charge (Zeta Potential)

Particle charge determines the stability of nanosuspensions. For electrostatically stabilized nanosuspensions a minimum zeta potential of ±30mV and for combined steric and electrostatic stabilization it should be a minimum of ±20mV.

Crystalline state and particle morphology

Differential Scanning Calorimetry (DSC) determines the crystalline structure. When nanosuspensions are prepared drug particles get converted to amorphous form hence it is essential to measure the extent of amorphous drug generated during the production of nanosuspensions. The X-Ray Diffraction (XRD) is also used for determining change in physical state and extent of amorphous drug.

Saturation solubility and dissolution velocity

The nanosuspensions increase the saturation solubility as well as dissolution velocity. Saturation solubility is compound specific constant depending upon temperature and the properties of dissolution medium. Kelvin equation and the Ostwald-Freundlich equations can explain increase in saturation solubility**.**

Applications

Formulations in nanopharmaceutics

Nanosuspension[5,6]

Pharmaceutical nanosuspensions are sub-micron colloidal dispersions of discrete drug particles, their range is from 100 to 1,000 nm, and are stabilized with polymers or surfactants or a mixture of both They have peculiar properties of small size and high surface area that allows attainment of some desirable qualities as increased bioavailability, drug targeting and altered disposition. For nanosuspensions, the dispersion medium is generally aqueous but it can also be non-aqueous or hydro-alcoholic.

Methods of Manufacturing

The different manufacturing processes for Nanosuspensions are Top down processes, this process involves breaking of larger particles into smaller particles by different milling techniques. Reduction of particle size can be achieved by various methods, they are: high pressure homogenization, media milling and microfluidization. Use of harsh solvents is avoided in these processes and high drug loading is feasible. However, these are high energy processes in which cause generation of high amount of heat, and therefore, dealing with thermolabile materials is difficult in these processes unless cooling accessories are employed.

High Pressure Homogenization

In this method, a macro suspension of the drug is passed through a small hole under high pressure. Due to high velocity, the pressure is dropped which results in the formation of bubbles according to "Bernoulli's law". There is a decrease in velocity and an increase in pressure to the atmospheric pressure when the suspension emerges out from the small aperture. This causes bubbles to explode generating high energy shock waves which induce particle size reduction.

Media Milling/Nanocrystals

This technology was first developed by Liversidge et al. in 1991. Media milling or Nanocrystals® is the patented technology of Elan Drug Delivery Systems. This process involves filling of water in the milling chamber, milling medium, and drug to be milled, addition of stabilizer and high speed rotation of the milling shaft. High shear forces are generated in milling chamber because of impact of the milling media and attrition between the particles which causes breakdown of particles along fracture points. The milling medium is mostly made of glass, non-corrosive metal. Contamination of the product with undesirable particles from the milling material is one of the main disadvantages of this technique. The mill can be used in a batch.

Microfluidization

This technique includes the passage of suspension via special chambers under high pressure. The suspension is passed forcefully at high velocities through the narrow openings of these chambers. The shape of chamber divides the suspension in the two different jets and these jets are then made to impact on each other. During this impact, the particle size is reduced.

Bottom up process

In this process the nano-sized materials are made to build up from their solutions and the phenomenon is commonly known as "precipitation". This method is generally useful when the active pharmaceutical ingredient (API) is soluble in a non-aqueous water miscible solvent.

These processes can be carried out at different temperature ranges, and therefore the size of thermo labile materials can be reduced efficiently. There are different methods included in it, such as:

Solvent anti-solvent

In this technique, the drug is made to dissolve in a water miscible organic solvent for example, ethanol. The organic solution is then slowly poured into a vessel containing a large amount of water. The stabilizers can be either added to the organic solution of the drug or they can be mixed in the aqueous phase. Bulk of this dispersion is constituted by water, which is almost 95% of the formulation. These dispersions have a predisposition towards particle growth and are stable only for short interval of time. To maintain the particle size, freeze drying or spray drying is generally employed immediately after precipitation. Nanoparticles can also be manufactured by controlled addition of the antisolvent into the solution of a drug in an organic solvent, along with a stabilizer. In such processes, the rate of addition of the anti-solvent, ratio of the solvent to anti solvent, concentration of the stabilizer, mixing speed and solubility of the drug play a crucial role in the formation of nano-sized particles.

Supercritical Fluid Process

As explained above, production of nano-sized particles can be achieved by addition of anti-solvent, evaporation of solvent, or changes in temperature and pH etc. However, the above methods are based primarily on mixing, efficiency of mixers, also controlled conditions are required to bring about the changes efficiently throughout the bulk to produce considerable batches of nanoparticles. Therefore, there is a need for a solvent or anti-solvent that has liquid properties which must be able to diffuse or mix rapidly like a gas so that the change can be affected promptly. This brings into account "supercritical fluids", which have unique solvent properties and high diffusivities, making them the ideal solvent for the production of nanoparticles. The most widely and commonly used supercritical fluid (SCF) is Carbon Dioxide. An important merit of supercritical process is the smooth surface morphology and low surface energy of the nanoparticles produced as compared to other techniques like micronization.

Spray Drying

Spray drying has numerous applications in pharmaceutical industry such as for coating and drying of solids, for converting crystals into amorphous forms, preparation of high solubility solid dispersions etc. Usually, particle size in micrometre range is achieved by spray drying method. In this technique, the drug is dissolved in a suitable organic solvent and sprayed through a small nozzle under the surface of liquid nitrogen, this result into immediate freezing and formation of micro size droplets.

Emulsion Solvent Evaporation

Emulsions are being used as templates for the production of nanosuspensions of drugs. Two types of emulsions can be employed for the preparation of the drug nanosuspensions, first type consists of the drug solubilized in a volatile organic solvent, like methylene chloride, and with the help of suitable stabilizers it is emulsified to produce stable nanoemulsions. Drug nanosuspensions are produced by removal of the solvent from the nanodroplets under reduced pressure. In the second type, solvents such as butyl lactate, ethyl acetate and benzyl alcohol that are partially miscible with water are used. In this method, drug dissolved in the solvent is emulsified in water to produce an O/W water emulsion. This emulsion is then diluted with excess of water which contributes to the formation of drug nanoparticles[4].

Nanogels[6,7]

These are crosslinked particles of sub-micrometer size which are made of hydrophilic polymers. They are soluble in water, and have properties which are different from linear macromolecules of similar molecular weight. Such structures and their larger analogues - microgels – have numerous practical applications, chiefly in medicine, for example in stomatology and in pharmacy, such as stimuli-sensitive drug delivery systems. Nanogels may be defines as gel macromolecules which are in the size range of tens to hundreds in nanometer. These are created either through covalent bonds for stable and insoluble 3D networks or unstable (physical) gels via hydrogen bonds, van der Waals forces, and chain entanglements or through form action of crystalline regions. The properties of these nanogel particles depends on the nature of monomeric units present in the polymeric chains of gel networks, functional group present with monomer, which affects drug carrying and drug releasing properties. On the other hand, some functional groups have the potential to conjugate with drugs/antibodies for targeting applications.

Techniques for preparing nanogel are

Micromolding methods

In this process, cells are suspended in a hydrogel precursor solution consisting of methacrylated hyaluronic acid (MeHA) or poly (ethylene glycol diacr ylate) and a photoinitiator in water. The resulting mixture is to be deposited onto plasma-cleaned hydrophilic PDMS patterns and then photocrosslinked via exposure to UV light. The resulting cell-laden microgels are then removed, hydrated, and harvested. They are also molded into different shapes such as square prisms, disks, and strings.

Microfluidic preparation

This method requires fabrication of microfluidic devices by soft lithography using elastomeric materials, particularly PDMS or polyurethane elastomers as building blocks. The devices usually consist of inlets for monomers (or oligomers) and continuous liquids, and microchannels with a tapered junction where two immiscible phases merge. Emulsification of monomers is achieved by breaking up liquid threads to droplets and in-situ crosslinking of the droplets by photopolymerization or polycondensation, these are the two general steps involved in the continuous microfluidic preparation of microgels. There are several techniques of microfluidic preparation of micron-sized microgels of both biological as well as synthetic polymers which are based on gelation methods in microchannels; chemical gelation, physical gelation by temperature change, reversible shear thinning, and ionic crosslinking, and coalescence-induced gelation.

Dispersion Polymerisation

This technique allows for the preparation of micron-sized particles with narrow size distribution. In the process, most ingredients such as monomers, polymeric stabilizers, and initiators are soluble in an organic solvent, as a continuous phase. Initially, in a homogeneous reaction mixture

Table

S.NO.	Categories	Types	Description	Examples
1.	According to Origin	Natural nanomaterial Artificial Nanomaterials	Obtained from natural resources Obtained from well defined, mechanical and fabrication process	Protein Molecules (antibody), Minerals- Clays, Nanocolloids, Milk and Blood. Carbon Nanotubes, Semiconductor Nanoparticles (Quantum Dots)
2.	According to Dimensions	Zero Dimensional (0-D) One Dimensional (1-D) Two Dimensional (2-D) Three Dimensional (3-D)	Possess nano dimensions in all 3 directions One dimension outside the nanometer range Two dimensions outside the nanometre range All dimensions outside the nanometre range	Metals (Gold, Silver) Nanowires and nanotubes of metal oxides Coatings, Thin film multilayers of nanosheets and nanowalls Bulk materials composed of individual blocks
3.	According to Structural Configuration	Carbon-based nanomaterials Metal-Based Nanomaterials Dendrimers Composites	Ellipsoidal configured carbon nanomaterial Mainly composed of metals Highly branched macromolecules in nanometre scale Multiphase solid material where at least one of the phase is 1,2 or 3 dimensional in nanoscale	Spherical and Ellipsoidal tubes Nanogold, Nanosilver, Metal oxides like Titanium dioxide PAMAM dendrimers and Fractal dendrimers Nanosuspension, Colloids, Gels and Copolymers

polymerization occurs; however, the formed polymers become insoluble in the continuous medium, eventually resulting in the formation of stable dispersion of polymeric particles with an aid of colloidal stabilizers. This method has been primarily employed in the preparation of uniform microspheres of hydrophobic polymers including polystyrene (PS) and poly (methyl methacrylate) (PMMA).

Precipitation polymerization

It is similar to dispersion polymerization; this approach involves the formation of homogeneous mixture in the initial stage and the occurrence of initiation and polymerization in the homogeneous solution. The use of cross linker is necessary to crosslink polymer chains for the isolation of particles as the formed polymers are not swellable but are soluble in the medium. Consequently, the resulting crosslinked particles sometimes have an irregular shape with high polydispersity (PDI).

Inverse (mini) emulsion polymerization

It is a W/O polymerization process that subsumes aqueous droplets (including water-soluble monomers) stably dispersed with the help of oil-soluble surfactants in a continuous organic medium. Stable dispersions are formed by mechanical stirring for inverse emulsion process and by sonification for inverse miniemulsion polymerization. Polymerization occurs within the aqueous droplets on addition of radical initiators, leading to the production of colloidal particles. Various reports have demonstrated the synthesis of hydrophilic or water-soluble particles of Poly 2-hydroxyethyl methacrylate, Poly Acrylic Acid, and polyacrylamide, temperature sensitive hollow microspheres of poly (N-isopropyl acrylamide), core shell nanocapsules with hydrophobic shell and hydrophilic interior and polyaniline nanoparticles. Furthermore, this method is also implemented for the preparation of stable organic inorganic hybrid particles containing magnetic iron oxide nanoparticles and clays in cyclohexane based inverse miniemulsions.

Nanocarrier System[8]

The particulate drug carriers are cleared from the circulation by spleen and liver after their i.v. administration depending upon the size of the particles administered. Reports suggest that particles less than 200 nm can escape this physical screening and hence nanoparticulate carriers may prove to be of great importance.

The different types of nanocarriers introduced now a days are:

Polymer micelle, Dendrimers, Liposomes, Quantum dots

Polymer Micelle

These are nano-sized particles which are made up of polymer chains and are generally formed by self-assembly in a liquid spontaneously, as a result of hydrophobic or ion pair interactions between polymer segments. Micelles typically have a so-called core-shell structure. The core of the micelles, which is either the hydrophobic part or the ionic part of the nanoparticles, may contain small (or big) molecules like therapeutic drugs, whereas the shell provides interactions with the solvent and makes the nanoparticles stable in the liquid. They consist of an inner core of assembled hydrophobic segments that are capable of solubilizing lipophilic substances and an outer hydrophilic corona which serves as a stabilizing interface

between the hydrophobic core and the external aqueous environment. Depending on the delivery purpose, the size, charge, and surface properties of these carriers can be selected simply by adding new ingredients to the mixture of amphiphilic substances before micelle preparation and/or by alteration of the preparation method.

Method of Formulation

In general, there are three major methods for loading drugs into polymer micelle cores:

Chemical conjugation

Physical entrapment or solubilization

Polyionic Complexation (e.g. ionic binding).

Chemical conjugation

Ringsdorf's group58 first proposed drug incorporation into polymer micelles via chemical conjugation, in 1984. As per this technique, a drug is chemically conjugated to the core-forming block of the copolymer through a carefully designed pH- or enzyme-sensitive linker, which can be cleaved for the release of the drug in its active form within a cell. The polymer-drug conjugate then acts as a polymer prodrug which self assembles into a core-shell structure. The most suitable choice of conjugating bond depends on specific applications.

Physical entrapment

The physical incorporation or solublization of drugs within block copolymer micelles is mostly preferred over micelle-forming polymer-drug conjugates especially for hydrophobic drug molecules. Many polymers and drug molecules, indeed, do not contain reactive functional groups for chemical conjugation, and therefore, specific block copolymers need to be designed for a specific type of drug. On contrary, by engineering the structure of the core-forming segment, a variety of drugs can be physically incorporated into the core of the micelles. In addition, molecular characteristics such as molecular weight, composition, presence of functional groups for active targeting within a homologous copolymer series can be designed to optimize the performance of a drug for a given drug delivery situation.

Polyionic complexation

It was proposed independently by Kabanov and Kataoka in 1995, that the charged therapeutic agents can be introduced into block copolymer micelles, through electrostatic interactions with an oppositely charged ionic segment of block copolymer.This approach is now extensively employed for the incorporation of various polynucleic acids into block ionomer complexes, for the development of non- viral gene delivery systems. The formation of stable block ionomer complexes is affected by ionic block lengths, charge density, and ionic strength of the solution, and in turn, control the amount of drug that can be incorporated within the micelles.

Dendrimers

Dendrimer is a highly branched polymer and consists of a core where a monomer unit is attached. Dendrimers are large complex molecules with well-defined chemical structures. Dendrimers are nearly ideal monodisperse (meaning of a consistent size and form) macromolecules with a regular and highly branched 3-D architecture. They consist of three major architectural components: 1.) Core 2.) Branching unit 3.) End groups. Dendrimers are built from a starting atom, like nitrogen, and after a repeating series of chemical reactions, carbon and other elements are added into it to produce a spherical branching structure. As the process is repeated, it leads to the formation of a spherical macromolecular structure.

Type of dendrimers

Radially layered poly (amidoamine-organosilicon) dendrimers (PAMAMOS)

Poly (amidoamine) dendrimers (PAMAM)

Poly (Propylene Imine) dendrimers (PPI)

Chiral dendrimers

Liquid crystalline dendrimers

Tecto dendrimer

Hybrid Dendrimers

Multilingual Dendrimers

MicellarDendrimers

Method of Formulation

Divergent growth method

This method was introduced by Tomalia in which growth of dendrimers originates from a core site. The core is reacted with two or more moles of reagent containing at least two protecting branching sites, followed by removal of the protecting groups, leading to the first generation dendrimers. This process is continued until the dendrimer of desired size is produced. By this technique, the first synthesized dendrimers i.e. polyamidoamines (PAMAMs), also known as starbust dendrimers were produced.

Convergent Dendrimer Growth

Convergent dendrimer growth incepts at what is the surface of the dendrimer, and works inwards by gradually linking surface units together with more. When the growing wedges are large enough, several are attached to a suitable core to form a complete dendrimer. This method has several advantages like relatively easier purificiation of the desired product; minimization of the occurrence of defects in the final structure, this method precludes the formation of high generation dendrimer because stearic problems occur in the reactions of the dendrons and the core molecule.

Double Exponential and Mixed Growth

In this approach two products, monomers for both convergent and divergent growth are reacted together to yield an orthogonally protected trimer, which may be employed to repeat the growth process again. Strength of double exponential growth is subtler than the ability to build large dendrimers in relatively lesser steps.

Hypercores and Branched Monomers growth

This method subsumes the pre-assembly of oligomeric species which can be linked together to give dendrimers in lesser steps along with better and higher yields.

Nanoliposomes

Nanomeric version of liposomes is called as “Nanoliposomes”and is one of the most widely employed encapsulation and controlled release systems. The word liposome is derived from two Greek words, lipos meaning fat and soma meaning body or structure, which together mean a structure in which a fatty envelope encapsulates internal aqueous compartment(s). Liposomes, which are also known as bilayer lipid vesicles are ideal models of

cells and biomembranes. These are nano sized artificial vesicles, spherical in shape which can be produced from natural phospholipids and cholesterol. Bangham discovered that phospholipids when combined with water immediately form a bi-layered sphere since one end of each molecule is water soluble, while the opposite end is water insoluble. Liposomes are broadly classified on the basis of their structure as follows

Multilamellar liposomes:

Spherically concentric multilamellar (many bilayers) structures

Unilamellar liposomes:

Spherical concentric unilamellar (one bilayer) structures.

Manufacturing methods

Sonication Technique

It is a simple method for reduction of size of liposomes and is implemented in the production of nanoliposomes. The commonly employed laboratory method involves treating hydrated vesicles with a titanium-tipped probe sonicator for several minutes in a temperature controlled environment.

Extrusion Method

Extrusion is a process by which micrometric liposomes (e.g. MLV) are modified structurally to form large unilamellar vesicles (LUV) or nanoliposomes depending on the pore-size of the filters used in the process. Vesicles are physically extruded under pressure through polycarbonate filters of defined pore sizes. A mini extruder device, such as from Avanti Polar Lipids, Inc., Alabaster, AL, USA; or Avestin Inc., Mannheim, Germany, with 0.5 mL or 1 mL gas-tight syringes can be used in this procedure. A small, hand-held, extruder is used for the production of nanoliposomes.

Microfluidization

Microfluidization is a technique of nanoliposome production without the involvement of potentially toxic solvents and is achieved using a microfluidizer which was traditionally used in the pharmaceutical industry to make liposomal products and pharmaceutical emulsions. Microfluidization is based on the principle of dividing a pressure stream into two parts; each part is passed through a fine orifice directing the flows at each other inside the chamber of microfluidizer. Within the interaction chamber, reduction in particle size of the liposomes occurs by cavitation along with shear and impact. Microfluidizer uses high pressures (up to l0,000 psi) to guide the flow stream through microchannels toward the impingement area. Advantages of microfluidization are that a large volume of liposomes can be produced in a continuous and reproducible manner; the average size of the liposomes can be adjusted; very high capture efficiencies (>75%) can be obtained and the solutes to be encapsulated need not be exposed to sonication, organic solvents or detergents.

Heating Method

In many techniques for the manufacture of nanoliposomes potentially toxic solvents, e.g. chloroform, methanol, diethyl ether and acetone or high shear force procedures are implemented. It has been speculated that residues of these toxic solvents may remain in the final liposome or nanoliposome preparation which contributes to potential toxicity and influence the stability of the lipid vesicles. These obstacles can be overcome by implementing alternative methods of preparation like the heating method by which liposomes and nanoliposomes (in addition to some other carrier systems) can be manufactured in the absence of potentially toxic solvents using a single apparatus.

Quantum Dots

The quantum dots are semiconductor nanocrystals and core-shell nanocrystals that contain interface between different semiconductor materials. The size of quantum dots can be continuously altered from 2 to 10 nm which after polymer encapsulation usually increases to 5–20 nm in diameter. Particles which are smaller than 5 nm are rapidly cleared by renal filtration. Semiconductor nanocrystals have peculiar and intriguing optical properties; therefore, have become an indispensable tool in biomedical research, especially for multiplexed, quantitative and long-term fluorescence imaging and detection. QD core serves as a structural scaffold, and the imaging contrast agent and small molecule hydrophobic drugs can be embedded between the amphiphilic polymer coating layer and the inorganic core. Hydrophilic therapeutic agents including antisense oligodeoxynucleotide (ODN), small interfering RNA (siRNA) and targeting biomolecules such as peptides, antibodies and aptamers can be immobilized onto the hydrophilic side of the amphiphilic polymer via covalent or non-covalent bonds. This fully integrated nanostructure behaves like magic bullets that not only identify, but also bind to diseased cells and assist in it treatment. It also emits detectable signals for real-time monitoring of its trajectory.

Nanofillers[9]

Carbohydrate polymers

The main objective of latest work and current research is development of a technique that can be used for the reinforcement of the tensile properties. Orodispersible films (ODFs) are related to the development of dosage forms with tensile properties that are well suited for packaging and patient's handling. One such research demonstrated the use of amorphous water insoluble Nanofiller – Polyvinylacetate (PVAc), for the improvement of tensile strength of maltodextrins (MDX) based ODFs. To investigate the probable interactions occurring between the components, ATR-FTIR spectroscopy and DSC were employed. These analyses revealed that MDX and PVAc were immiscible, even if the addition of plasticizers allowed the homogenous dispersion of PVAc in the film until the attainment of 10% w/w concentration. Consequently, PVAc nanoparticles were found to be an efficient reinforcing agent, at only 3% and 5% w/w concentrations. The tensile strength in this optimal range increased at least 1.5 fold and there was 4 times increase observed in the elastic modulus.

Nanoparticles as mucoadhesive dosage forms[10]

A novel form of mucoadhesive nanoparticles (NPs) showing a prolonged residence time on mucosal tissues is developed. A new thiomer was synthesized by the covalent attachment of the amino acid l-cysteine ethyl ester to poly (acrylic acid) (100 kDa). The free thiol groups were

preactivated with the aromatic thiol bearing ligand 2-mercaptonicotinic acid (2-MNA) and the amount of coupled l-cysteine ethyl ester as well as the amount of attached 2-MNA was determined. Based upon the above determination, the preparation of preactivated thiomer NPs was done by ionic gelation using polyethylenimine (PEI) and resulting NPs were characterized as per size and zeta potential. Further, investigation of their mucoadhesive properties was carried out via rheological measurements with porcine intestinal mucus and by determination of the mucosal residence time of the particles. Accoding to the results, 1666.74 µmol l-cysteine ethyl ester and 603.07 µmol 2-MNA could be attached per gram of the polymer. Nanoparticles in the size range of 112.67-252.84 nm exhibited a zeta potential of -29 mV. There was a 2-fold increase in mucus viscosity due to thiolated NPs whereas preactivated NPs showed a 6-fold higher mucus viscosity in comparison to the unmodified particles. The mucosal residence time of thiolated NPs was prolonged by 1.6-fold and that of preactivated NPs was 4.4-fold higher to that of the unmodified particles. Concluding that, preactivated thiolated NPs provided a prolonged residence time on mucosal membranes which may prove to be a promising dosage form for a variety of applications.

Theranostic nanoformulation as an aid of oil core nanocarriers[11]

For the transport of both chemotherapeutic and imaging agents for successful extermination of cancer cells, a new theranostic Nanoformulation has emerged. This strategy involves the encapsulation of cytostatic drug and coumarin-6 (fluorescent biomarker) in oil-core nanocarriers stabilized by surfactants of diamidequat-type. The study indicates that for the stabilization of theranostic nanodispersions soft cationic diamidequat-type surfactants are most appropriate and they constitute a whole new functional class of stabilizers for nanoparticles. They will have a progressive impact on the development of formulations. The results demonstrated phenomenal biocompatibility of the long-sustained monodisperse oil-core nanocapsules under study.

Pegylated nanoformulation[12]

The poor bioavailability of chemotherapeutic drugs, such as methotrexate (MTX), hinders their success. Solid lipid nanoparticles (SLNs) have emerged as imperative therapeutic carriers pertaining to the biocompatible nature of their constituent materials. In this study, a nanoparticulate system consisting of a pegylated lipid core of stearic acid is designed to evaluate its potential for encapsulation and delivery of the chemotherapeutic drug MTX, which many a times suffers from poor bioavailability. Stable pegylated SLN formulations of MTX were prepared, having a mean particle size ~130 nm (zeta potential −34 mV) and low polydispersity. They were completely characterized using DSC, TEM and AFM and were found to show an almost spherical morphology. These drug-loaded formulations were assessed to have appreciable haemocompatibility, as quantified by haemolysis analysis. *In vitro* drug release studies at acidic pH (5.5) and physiological pH (7.4) demonstrated a power-law mechanism of release of MTX from the SLNs. Biological evaluation of these MTX-loaded formulations has been carried out with the help of radiolabeling techniques (with ^{99m}Tc radionuclide). Also, the blood kinetics profile of the ^{99m}Tc radiolabeled pegylated MTX formulations carried out in New Zealand Albino rabbits revealed higher blood circulation time, while tumour models used for biodistribution studies (balb/c mice) revealed their efficient tumour uptake, as evidenced by SPECT imaging. These studies convey the potential use of these pegylated SLNs based on stearic acid for the improvement of bioavailability of MTX and they are anticipated to be a valuable addition to the array of nanoparticles with wide therapeutic applications

Applications of nanomaterials in disease treatment

Autoimmune disorders

Cancer Treatment[13,14]

Nano particles have a unique property of high surface area to volume ratio, which allows various functional groups to get attached to a nano particle and thus enabling it to bind too certain tumour cells. Moreover, the 10 to 100 nm small size of nanoparticles, allows them to conversely accumulate at tumour sites because tumours lack an effective lymphatic drainage system. Nano particles with many functional groups can be manufactured that would detect, image, and then treat a tumour in future cancer treatment. Nano wires are used to prepare sensor test chips, which can detect proteins and other biomarkers left behind by cancer cells and aid in diagnosis of cancer even at the early stages from a single drop of a patient's blood. Nano particles are used in cancer photodynamic therapy, where the particle is inserted within the tumour in the body and is illuminated with photo light from the outside. The particle absorbs light and if it is of metal, it will get heated due to energy from the light as metals are good absorbers of heat energy. High energy oxygen molecules are produced due to light which chemically react and destroy tumour cells without reacting with other body cells. Photodynamic therapy has earned interest as non-meddling technique for dealing with tumours.

Neurodegenerative disorders

Alzheimer's disease[15]

About 35 million people around the globe are affected by Alzheimer's disease (AD), which is due to dementia. Nano technology finds its uses in neurology. These approaches successful on the early AD diagnosis and treatment and is made possible by designing and engineering of a glut of nanoparticulate bodies with high selectivity for brain capillary endothelial cells. Nano particles (NPs) have high rapport for the circulating amyloid-β (Aβ) forms and therefore may bring about “sink effect” and reform the AD condition. In vitro diagnostics for AD had improved due to ultrasensitive NP-based bio-barcodes and immune sensors, as well as scanning tunneling microscopy procedures which are able to detect Aβ1−40 and Aβ1−42.

Parkinson's disease[16,17]

Nano materials can provide an improved therapy for Parkinson's disease (PD). Parkinson's disease (PD) is the second most common neurodegenerative disease next to Alzheimer's disease and affects one in every 100 persons who are above the age of 65 years. This is a disease of the

central nervous system where neuro inflammatory responses are affected and pose severe difficulties in body movements. The aim of the present day treatment is to improve the functional capacity of the patient for as long as possible but cannot alter the advancement of the neurodegenerative process. The aim of applied nanotechnology is regeneration and neuro protection of the central nervous system (CNS) and will significantly benefit from basic nanotechnology research conducted in parallel with advances in neurophysiology, neuropathology and cell biology. The efforts are taken to develop novel technologies that directly or indirectly help in providing neuro protection and or a tolerant environment and active signaling clues for axon growth. In order to reduce the peripheral side-effects of conventional forms of Parkinson's disease therapy, research is focused on the design, biometric simulation and optimization of an intracranial nano-enabled scaffold device (NESD) for the site-specific delivery of dopamine to the brain, as a strategy. Peptides and peptidic nano particles are newer tools for various CNS diseases. Nanotechnology will play a key role in developing new diagnostic and therapeutic tools. Nanotechnology could provide devices to limit and reverse neuro pathological disease states, to support and promote functional reclamation of damaged neurons, to provide neuro protection and to facilitate the perfusion of drugs and small molecules across the blood–brain barrier. For the delivery of CNS drugs, various nanocarriers such as dendrimers, nano gels, nano emulsions, liposomes, polymeric nano particles, solid lipid nano particles, and nano suspensions have been studied. Delivery of these nanomedicines has been effected across various in vivo and in vitro BBB models by endocytosis and/or transcytosis. Alzheimer's disease, brain tumors, HIV encephalopathy and acute ischemic stroke has become possible for early preclinical success for the management of CNS conditions.

Tuberculosis treatment

Tuberculosis (TB) is a deadly infectious disease. The long duration of the treatment and polypharmacy can retard patient lifestyle and result in the development of multi-drug resistant (MDR) strains. Tuberculosis creates a major problem in children. The first-line drugs in pediatric form is commercially available. Newly designed antibiotics can be designed to conquer drug resistance, reduce the duration of the treatment course and to bring down the drug interactions with antiretroviral therapies. A nanotechnology is one of the most assuring approaches for the development of more efficient and flexible medicines. The amelioration in nanobased drug delivery systems which are enclosed within a shell and release of anti-TB drugs can lead to evolution of a more effective and economical TB pharmacotherapy.

Antibiotic resistance[19]

Antibiotic resistance which is the resistance of the microbes towards antibiotics can be decreased by using nano particles as a combination therapy. For example, the nano particles of zinc oxide decreases the antibiotic resistance and augments the antibacterial activity of Ciprofloxacin against microbes, by impeding with several proteins that are interacting in the antibiotic resistance or pharmacological actions of drugs.

Immune response[20]

The nano device bucky balls have been used to alter the allergy/immune response. They inhibit release of histamine from mast cells into the blood and tissues, as these bind to free radicals much better than any anti-oxidant available, such as vitamin E and vitamin C.

Lung diseases[21]

Targeted delivery of drug molecules to organs or specific sites is one of the most threatening research areas in pharmaceutical sciences. By developing colloidal delivery systems such as liposomes, micelles and nanoparticles a new borderline was opened for enhancing the delivery of the drug. Nano particles with their special features like small particle size, large surface area and the ability of nano particles in changing the surface properties have enormous advantages as compared to other drug delivery systems. Targeted nano particle delivery to the lungs is an arising area of interest.

Infectious diseases[22]

The ability in delivering nano particles directly into the targeted cells is an important criterion in the therapeutic utilization for infectious diseases. The prospect of therapeutic agent being attached to the nanoparticles by modification in the chemical entity has contributed a novel drug delivery option. The introduction of carbon nanotubes and graphene has given a magnificent imaging and therapeutic agent for the biomedical applications. Despite of continuous advancement in pharmaceutical drug delivery which includes micelles, vesicles, liquid crystals, etc. In the past decades, their use has been limited which restrict their production. The properties of nanomaterials which are equal biodistribution, mass production, biodegradation, and longtime storage make them attractive alternatives for future biomedical applications. Nanoparticles surface functionalized with specific biomolecules based drug delivery has driven new direction for modulating the pharmacokinetics, pharmacodynamics, biorecognition, and increasing the efficacy of targeted drugs. All these new designs are anticipated to minimize loss and the degradation of drug, developing the availability of the drug, and opens up advanced glimpse for drug delivery.

Renal disease[23]

Nanoparticles have loomed in the medical field as a technology well-adopted for the diagnosis and treatment of renal disease states. Various nanomaterials have been developed which can be combined with targeting groups, and with the delivery of drug and ability of imaging or merging of both as theranostic agent. Nanoparticles for biological applications must be constructed in a way that they possess favorable characteristics when applied to cells, tissue, or serum. They inherently have a high surface area to volume ratio due to their small size. This results in a natural tendency to aggregate and interact with plasma proteins upon intravenous injection, leading to rapid clearance by the reticuloendothelial system (RES). Thus, NPs are often coated with hydrophilic and biocompatible polymers, such as polyethylene glycol (PEG) or pluronics,

which protect against opsonization and endocytosis, and afford an extended plasma half-life. The manipulation of these coating materials and size of the NP intern alters the drug release profile and drug concentration delivered.

Parasitic diseases[24]

A parasitic disease like Lymphatic filariasis (LF) is a leading health problem in many countries due to lack of conducive filariasis elimination programs. The beneficial aspect of adopting nanomaterials in filariasis is that it improves the solubility, plasma half-life, overall pharmacokinetics and bioavailability of antifilarial agents. They also produce lymphatic targeted drug delivery system (TDDS) to target the adult worm and Wolbachia endosymbionts. Besides reduced dosage and dose frequency, it provides a precise treatment convenant which promotes patient compliance to current treatment approaches. It provides a wide design of multifunctional nanoparticles to conquer the billion-fold uneasiness of resistance towards the drug which reduces the toxicity levels of antifilarial agents.

REFERENCES

1. Jain, K.K. The role of nanobiotechnology in drug discovery. Drug Discovery Today (2005)10(21).1435-1442.
2. Sagar. Or et.al., Nanoparticles: Emerging carriers for drug delivery, Saudi Pharmaceutical Journal Volume 19, Issue 3, July 2011, Pages 129–141
3. Md. Zubayer Hossain Saad et al.: Nanopharmaceuticals: A New Perspective of Drug Delivery System, Asian Journal of Biomedical and Pharmaceutical Sciences 2(14) 2012, 11-20
4. Vicki stone et.al., Nanomaterials for environmental studies: Classification, reference material issues, and strategies for physico-chemical characterisation, Science of The Total Environment, Volume 408, Issue 7, 1 March 2010, Pages 1745–1754
5. Kulshreshtra, AK, singh, ON and Wall, GM. "Pharmaceutical suspension: From Formulation development to manufacturing." SpringerAAPS press, 2010, 285-288.
6. Kamble, VA et al. "Nanosuspension: A novel drug delivery system." International journal of pharma and biosciences, 2010, 1(4): 352-360.
7. Jung, KEh. "The development of microgel/ nanogels for drug delivery applications". Programme Polymer Science, 2008, 33(8):448-477.
8. Torchiline, VP. "Nanopaticulates as a drug carrier". Imperial college press, 2006:29-38.
9. Illaria.F et. al., Nanofiller for the mechanical reinforcement of maltodextrins orodispersible film, Carbohydrate Polymers 136 · September 2015, DOI: 10.1016
10. Menzel. C et.al., Preactivated thiolated nanoparticles: A novel mucoadhesive dosage form. Int J Pharm. 2016 Jan 30;497(1-2):123-8
11. Bazylińska U et.al. New diamidequat-type surfactants in fabrication of long-sustained theranostic nanocapsules: Colloidal stability, drug delivery and bioimaging, Colloids and Surfaces. B, Biointerfaces [2016, 137:121-132]
12. Kaminskas LM et.al., Pharmacokinetics and tumor disposition of PEGylated, methotrexate conjugated poly-l-lysine dendrimers, Mol Pharm. 2009 Jul-Aug;6(4):1190-204
13. Miller Stephen, Getts D, Martin A, McCarthy D, Terry R, et al. (2012) Micro particles bearing encephalitogenic peptides induce T-cell tolerance and ameliorate experimental autoimmune encephalomyelitis. Nature Biotechnology 30: 1217-1224.
14. Loo C, Lin A, Hirsch L, Lee MH, Barton J, et al. (2004) Nanoshell-enabled photonics-based imaging and therapy of cancer. Technol Cancer Res Treat 3: 33-40.
15. Davide B, Benjamin LD, Nicolas J, Hossein S, Lin-Ping Wu, et al. (2011) Nanotechnologies for Alzheimer's disease: diagnosis, therapy and safety issues. Nano medicine: Nanotechnology, Biology and Medicine 7: 521-540.
16. Nahar M, Dutta T, Murugesan S, Asthana A, Mishra D, et al. (2006) Functional polymeric nanoparticles: an efficient and promising tool for active delivery of bioactives. Crit Rev Ther Drug Carrier Syst 23: 259-318.
17. Wong HL, Wu XY, Bendayan R (2012) Nanotechnological advances for the delivery of CNS therapeutics. Adv Drug Deliv Rev 64: 686-700.
18. Xin Xia, Encapsulation of Anti-Tuberculosis Drugs within Mesoporous Silica and Intracellular Antibacterial Activities, *Nanomaterials* 2014, *4*(3), 813-826
19. Banoee M, Seif S, Nazari ZE, Jafari FP, Shahverdi HR, et al. (2010) ZnO nanoparticles enhanced Antibacterial activity of ciprofloxacin against Staphylococcus aureus and Escherichia coli. J Biomed Mater Res B Appl Biomater 93: 557-561.
20. Abraham SA (2010) Researchers Develop Bucky balls to Fight Allergy. Virginia Commonwealth University Communications and Public Relations.
21. Shizad azarmi et al., Targeted delivery of nanoparticles for the treatment of lung diseases, Advanced Drug Delivery Reviews, Volume 60, Issue 8, 22 May 2008, Pages 863–875
22. Sundar S 1, Prajapati VK., Drug targeting to infectious diseases by nanoparticles surface functionalized with special biomolecules. Curr Med Chem. 2012;19(19):3196-202
23. Brede C, Labhasetwar V. Applications of Nanoparticles in the Detection and Treatment of Kidney Diseases. Advances in chronic kidney disease. 2013;20(6): 10.1053/j.ackd.2013.07.006. doi: 10.1053/j.ackd.2013.07.006.
24. Said Soflaei, In Vitro Antiparasitic and Apoptotic Effects of Antimony Sulfide Nanoparticles on Leishmania infantum, Journal of Parasitology Research Volume 2012 (2012), Article ID 756568 (1-7)