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A Brief Review on Nano-Pharmaceutical Technology

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ABSTRACT:

Nanotechnology is vast term used for processes, products and theirs properties at the nanometer /micrometre scale which results into change in chemical, physical and life sciences. Micronization of materials is imparted by novel optical, mechanical and/or electrical properties. Nano size is ranging from 1-1000nm. Nano pharmaceutical's is branch of nanotechnology. The current Review describe about various Nanopharmaceuticals, Their types, their Method of Preparation, Evaluation Test, and their Applications.

KEYWORDS: Nanotechnology, Micronization, Nano-Pharmaceutical Technology

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INTRODUCTION:

"Nanotechnology is widely anticipated as one of the key technologies of the 21st century." "Nano" means dwarf in Greek, a nanometer is one billionth of a meter i.e 10^{-9} meter.Specifically, as a particle's size decreases, a greater proportion of its atoms are located on its surface relative to its core, often as the particle size decreases,its total surface area increases exponentially. rendering the particle more reactive (over their conventional 'bulk' counterparts) in addition.[1]

What are nanopharmaceuticals? Nanopharmaceuticals are particles having size of 10 to 1,000 nm. They can be used in drug delivery. Nanopharmaceuticals are different both in their shape and composition and give an advantage as compared to their bulk molecules. Due to this, the properties of nanoparticles are basically different from their macroscopic/ bulk forms because of an increased surface area.

There are two types of nanopharmaceuticals:

Those where the therapeutic molecules are themselves the drug (i.e.,the therapeutic compound itself also functions as its own carrier); and Those where the therapeutic molecules are directly coupled (functionalized, entrapped, or coated) to a nanoparticle carrier. Because there is no universal convention or nomenclature that classifies nanopharmaceuticals, various nanoscale structures of different shapes are sometimes classified as nanopharmaceuticals. In fact, some of the common shapes include spheres (hollow or solid), tubules, particles (solid or porous), and tree-like branched macromolecules. Although there are only a few nano-pharmaceuticals on the market that have been approved by the FDA , these formulations are already having an effect on medicine and promise to alter the health care landscape. And pharmaceuticals have enormous potential in addressing the failures of

traditional drugs that could not be formulated effectively because of factors such as poor water solubility, toxicity issues, low bioavailability, or lack of target specificity (e.g., delivering the drug to a specific tissue site).[2]

Classification of NanoPharmaceuticals:

1.Nano Engineered Drugs : e.g: nanocrystals ,nanoprecipitates, nanosupensions, nanoparticles.

Development of different dosage forms (Ex. Nano-suspensions for parentrals) Exploring different routes of administrations (Ex. Nasal and ophthalmic delivery provides a patient-friendly alternative).

2. Nanocarriers: First product which saw the day of light based on Nanocarriers strategy is Doxil® PEGylated liposomal formulation for doxorubicin. Theses liposomes are called as "Stealth" liposomes with size <200nm which are long circulation.

Theses nanocarriers can also be attached with ligands for active targeting. Hence nanotechnology is a "holy grill" for fundamental problems of drug targeting.[3]

Some nanopharmaceutical product:

NANOSUSPENSION: Pharmaceutical nanosuspensions can be defined as sub-micron colloidal dispersions of discrete drug particles, ranging from 100 to 1,000 nm, stabilized with polymers or surfactants or a mixture of both These have unique properties of high surface area and small size that allows for such desirable qualities as increased bioavailability, altered disposition as well as drug targeting. The dispersion medium for nanosuspensions is generally aqueous but it can also be hydro-alcoholic or non-aqueous.

METHOD OF MANUFACTURING.

Nanosuspensions can be manufactured by different processes:

TOP DOWN PROCESSES- The top down approach consists of breaking down bigger particles into smaller particles by various milling techniques. Particle size reduction can be achieved by different methods namely: media milling, high pressure homogenization and microfluidization. No harsh solvents are used in these processes and high drug loading can be achieved. However, these are high energy processes in which a lot of heat is generated, and therefore, unless cooling accessories are employed thermolabile materials are difficult to process by these methods.

Media Milling/Nanocrystals: Media milling or Nanocrystals® is the patented technology of Elan Drug Delivery Systems. It was first developed by Liversidge et al. in 1991. The process includes filling the milling chamber with water, milling medium, drug to be milled and stabilizer for stabilization and rotating the milling shaft with high speed. In milling chamber, high shear forces are generated because of impact of the milling media, and attrition between the particles which causes breakdown of particles along fracture points. The milling medium is genrally prepared by of glass, non-corrosive metal. One of the main disadvantages of this technique is contamination of the product with undesirable particles from the milling material. The mill can be used in a batch.

High Pressure Homogenization- It includes passing of a macro suspension of the drug through a small hole under high pressure. Pressure is dropped due to high velocity which results into formation of bubbles as per Bernoulli's law. When the suspension emerges out from the small aperture there is a decrease in velocity and an increase in pressure to the atmospheric pressure. This causes bubbles to explode and that generate high energy shock waves which gives particle size reduction.

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

BOTTOM UP PROCESS- This process involves building up of the nano-sized material from their solutions, and is commonly called as precipitation. This method is generally useful when the active pharmaceutical ingredient can be dissolved in a non-aqueous water miscible solvent.

These processes can be carried out at various temperatures, and therefore thermo labile materials can be size reduced efficiently. There are different methods of this approach, such as

Solvent anti-solvent: In this technique, the drug is dissolved in a water miscible organic solvent such as ethanol. The organic solution is then poured slowly 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 present in the aqueous phase. Water constitutes the bulk of the dispersion, almost 95% of the formulation. These dispersions are highly susceptible to particle growth and are stable only for short periods of time. Freeze drying or spray drying is usually employed immediately after precipitation to maintain the particle size. Nanoparticles can also be produced by controlled addition of the antisolvent into the solution of a drug in an organic solvent in the presence of a stabilizer. In such procedures, the rate of addition of the anti-solvent, mixing speed, ratio of the solvent to anti solvent, concentration of the stabilizer, and solubility of the drug itself play an important role in the successful formation of nano-sized particles.

Supercritical Fluid Process: As described above, nano-sized particles can be produced by addition of anti-solvent, evaporation of solvent, or changes in temperature and pH etc. However, the above methods are based only on mixing, highly efficient mixers and controlled conditions are required to propagate the changes efficiently throughout the bulk to produce reproducible batches of nanoparticles. Therefore, there is a need for a solvent or anti-solvent that has liquid properties yet can diffuse or mix rapidly like a gas, so that the change can be affected instantaneously. This makes supercritical fluids, which have high diffusivities and unique solvent properties, ideal candidates for the preparation of nanoparticles. Carbon dioxide is the most extensively used supercritical fluid (SCF). Advantage of supercritical process is the smooth surface morphology and low surface energy of the nanoparticles prepared as compared to other techniques such as micronization.

Emulsion-solvent evaporation:

Due to these advantages, emulsions are being used as templates for the preparation of drug nanosuspensions. Two types of emulsions can be used for the preparation of the drug nanosuspensions. The first type of emulsion consists of the drug solubilized in a volatile organic solvent, such as methylene chloride, which is then emulsified with the help of suitable stabilizers to produce stable nanoemulsions. Removal of the solvent from the nanodroplets under reduced pressure produces drug nanosuspensions. The second type involves the use of solvents such as butyl lactate, ethyl acetate and benzyl alcohol that are partially miscible with water. In this method, solvent containing the dissolved drug is emulsified in water to produce an O/W water emulsion. This emulsion is then diluted with excess water which leads to the formation of drug nanoparticles.

Spray Drying:

Spray drying is used for number of application in pharmaceutical industry for example to covert crystals into amorphous, preparation of high solubility solid dispersions and for coating and drying of solids etc. Generally the particle size achieved by spray drying is in the micrometre range. In spray drying drug is dissolved in suitable organic solvent and sprayed via a small nozzle under the surface of liquid nitrogen, which results into immediate freezing and micro size droplets are formed.[4]

EVALUATION PARAMETERS-

1) 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).

2) 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.

3) 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.

4) 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.[4]

APPLICATION:

1. Intravenous administration. One of the important applications of nanosuspensions technology is the formulation of intravenously adm inistered products. IV administration results in several advantages, such as adm inistration of poorly soluble drugs without using a higher concentration of toxic cosolvents, improving the therapeutic effect of the drug available as conventional oral formulations and targeting the drug to macrophages and the pathogenic microorganisms residing in the macrophages.

2. Bioavailability enhancement. Nanosuspensions resolve the problem of poor bioavailability by solving the twin problems of poor solubility and poor permeability across the membrane. Bioavailability of poorly soluble oleanolic acid, a hepatoprotective agent, was improved using a nanosuspension formulation.

The therapeutic effect was significantly enhanced, which indicated higher bioavailability. This was due to the faster dissolution (90% in 20 min) of the lyophilized nanosuspension powder when compared with the dissolution from a coarse powder (15% in 20 min).

3. Ocular administration. Ocular delivery of the drugs as nanosuspensions to provide a sustained release of drug. Pignatello et al. prepared Eudragit retard nanosuspensions of cloricromene for ocular delivery. They observed that the drug showed a higher availability in rabbit aqueous hum or and the formulation appeared to offer a promising means of improving the shelf-life and the bioavailability of this drug after ophthalmic application.

4. Drug targeting. Nanosuspensions can also be used for targeting as their surface properties and changing of the stabilizer can easily alter the in vivo behavior. The drug will be up taken by the mononuclear phagocytic system to allow regional- specific delivery. This can be used for targeting anti-mycobacterial, fungal or leishmanial drugs to the macrophages if the infectious pathogen is persisting intracellularly.

5. Mucoadhesion of the nanoparticles. Nanoparticles orally administered in the form of a suspension diffuse into the liquid media and rapidly encounter the mucosal surface. The particles are immobilized at the intestinal surface by an adhesion mechanism referred to as "bioadhesion." From this moment on, the concentrated suspension acts as a reservoir of particles and an adsorption process takes place very rapidly.The adhesiveness of the nanosuspensions not only helps to improve bioavailability but also improves targeting of the parasites persisting in the GIT.5

NANOGELS:

Nanogels are crosslinked particles of sub-micrometer size made of hydrophilic polymers. They are soluble in water, but have properties different from linear macromolecules of similar molecular weight. Such structures, along with their bigger analogues - microgels - have a number of practical applications, mostly in medicine (for example in stomatology) and pharmacy (stimuli-sensitive drug delivery systems). Up till now pharm aceutical field have witnessed developed of organogels and hydrogels, the recent addition to this are nanogels. Nanogels are defined as gel macromolecules in the size range of tens to hundreds in nanometer. These are formed either through covalent bonds for stable and insoluble three-dimensional networks or unstable (physical) gels via hydrogen bonds, van der Waals forces, and chain entanglements or through form action of crystalline regions.

Properties of Nanogel: The properties of nanogel particles depend on the nature of monomeric units present in the polymeric chains of gel networks. The functional group present with monomer 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. The drug carrying efficiency is also contributed by pendant functional group which contributes for establishing weak hydrogen bond or van der Walls forces.5

Techniques for preparing nanogel:

MICROMOLDING METHODS- In this process, cells were suspended in a hydrogel precursor solution consisting of either methacrylated hyaluronic acid (MeHA) or poly(ethylene glycol diacr ylate) and a photoinitiator in water. The resulting mixture was deposited onto plasma-cleaned hydrophilic PDMS patterns and then photocrosslinked via exposure to

UV light. The resulting cell-laden microgels were removed, hydrated, and then harvested. They were also moulded into various shapes including square prisms, disks, and strings.

Microfluidic preparation: Microfluidic methods have been recently explored for the preparation of monodisperse micron-sized microgels. The methods require the fabrication of microfluidic devices by soft lithography using elastomeric materials, particularly PDMS or polyurethane elastomers as building blocks. The devices generally consist of inlets for monomers (or oligomers) and continuous liquids, and microchannels with a tapered junction where two immiscible phases are merged. Emulsification of monomers by breaking up liquid threads to droplets and in-situ crosslinking of the resulting droplets by photopolymerization or polycondensation are the two general steps involved in the continuous microfluidic preparation of microgels. Several approaches were examined for the microfluidic preparation of micron-sized microgels of both synthetic and biological polymers. They 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 polymerization- Dispersion polymerization is a technique that allows for the preparation of micron-sized particles with narrow size distribution. In the process, most ingredients including monomers, polymeric stabilizers, and initiators are soluble in an organic solvent. as a continuous phase. At the onset, polymerization occurs in a homogeneous reaction mixture; however, the formed polymers become insoluble in the continuous medium, ultimately leading to the formation of stable dispersion of polymeric particles with an aid of colloidal stabilizers. The method has been mainly applied to prepare uniform microspheres of hydrophobic polymers including polystyrene (PS) and poly(methyl methacrylate)(PMMA).

Precipitation polymerization- Similar to dispersion polymerization, precipitation polymerization involves the form action of homogeneous mixture at its initial stage and the occurrence of initiation and polymerization in the homogeneous solution. As the formed polymers are not swellable but soluble in the medium, the use of cross linker is necessary to crosslink polymer chains for the isolation of particles. As a consequence, the resulting crosslinked particles often have an irregular shape with high polydispersity (PDI).

Inverse (mini)emulsion polymerization- Inverse (mini)emulsion polymerization is a W/O polymerization process that contains aqueous droplets (including water-soluble monomers) stably dispersed with the aid 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. Upon addition of radical initiators, polymerization occurs within the aqueous droplets producing colloidal particles. Several 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. In addition, his method has also been utilized to prepare stable organic inorganic hybrid particles containing magnetic iron oxide nanoparticles and clays in cyclohexane based inverse miniemulsions.6

APPLICATION:

Many applications of microgels for drug delivery have been proposed and experimentally evaluated during the last few years.

Mucoadhesive microgels- Microgels composed of mucoadhesive polymers may be used to design new types of carriers for oral and non-oral drug delivery. Understanding of the surface interactions between hydrophilic polymer surfaces and mucins could lead to improved adhesion.

Metal-containing nanocarriers- Metal-containing microgels have been recently developed and tested in a wide range of therapeutic and diagnostic applications including magnetic, photoactive or quantum dot nanogels. The major approach employed polymer microgels as templates for the synthesis of metal nanoparticles impregnated into the polymer network. In the field of diagnosis, magnetic resonance imaging was one of the first and most developed applications of metal nanoparticles.

Polymeric nanogels- Microgels can be rendered sensitive to physiological conditions. A responsive drug release system is recognized as one of the most important technologies necessary for an intelligent drug delivery. Biocompatible PAA was commonly incorporated in hydrogels to introduce pH sensitivity.

The PAA- based microgels can protect protein or other sensitive drugs against digestion by proteolytic/nucleolytic enzymes in the stomach, due to their low swelling ratio at a low pH. However, when the hydrogels pass through the GI tract they swell due to ionization of carboxylic acid groups at higher pH and become able to release drug from the polymer network. A novel type of nanosized polymeric microgel (nanogels) consisting of a crosslinked polymer network of polyionic segments, such as polyethylenimine (P`EI) or PAA, and neutral segments, such as polyethylene glycol (PEG) or Pluronic®, was recently developed in our laboratory.6

NANOCARRIER SYSTEM

After i.v. administration of particulate drug carrier they will be cleared from the circulation by spleen and liver depend upon the size of the particles. It was reported that particles less than 200 nm can escape this physical screening, hence, nanoparticulate carriers might be of great interest.

There are various types of nanocarriers are introduced now days such as:

Polymer micelle, Dendrimers , Liposomes , Quantum dots.

PO LYMER MICELLE- Polymeric micelles are nano-sized particles that are made up of polymer chains and are usually spontaneously formed by self-assembly in a liquid, generally 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, can contain small (or bigger) molecules such as therapeutic drugs, while the shell provides interactions with the solvent and make the nanoparticles thereby stable in the liquid. They consist of an inner core of assembled hydrophobic segments capable of solubilizing lipophilic substances and an outer hydrophilic corona serving as a stabilizing interface between the hydrophobic core and the external aqueous environment. Depending on the delivery purpose, one can select the size, charge, and surface properties of these carriers simply by adding new ingredients to the mixture of amphiphilic substances before micelle preparation and/or by variation of the preparation method.

Method of Formulation: In general, there are three major methods for loading drugs into polymer micelle cores: (1) chemical conjugation, (2) physical entrapment or solubilization, and (3) polyionic complexation (e.g. ionic binding).

Chemical conjugation- Drug incorporation into polymer micelles via chemical conjugation was first proposed by Ringsdorf's group58 in 1984. According to this approach, a drug is chemically conjugated to the core-forming block of the copolymer via a carefully designed pH- or enzyme-sensitive linker, that can be cleaved to release a drug in its active form within a cell.59,60 The polymer-drug conjugate then acts as a polymer prodrug which self assembles into a core-shell structure. The appropriate choice of conjugating bond depends on specific applications.

Physical entrapment- The physical incorporation or solublization of drugs within block copolymer micelles is generally preferred over micelle-forming polymer-drug conjugates especially for hydrophobic drug molecules. Indeed, many polymers and drug molecules do not contain reactive functional groups for chemical conjugation, and therefore, specific block copolymers have to be designed for a given type of drug. In contrast, a variety of drugs can be physically incorporated into the core of the micelles, by engineering the structure of the core-forming segment. In addition, molecular characteristics (i.e. 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

Poly ionic complexation Charged therapeutic agents can be incorporated into block copolymer micelles, through electrostatic interactions with an oppositely charged ionic segment of block copolymer. Since it was being proposed independently by Kabanov and Kataoka in 1995.

This approach is now widely used for the incorporation of various polynucleic acids into block ionomer complexes, for developing non- viral gene delivery systems. Ionic block lengths, charge density, and ionic strength of the solution affect the formation of stable block ionomer complexes, and therefore, control the amount of drug that can be incorporated within the micelles.

Applications of polymer micelle- The studies on the application of polymer micelles in drug delivery have mostly focused on the following areas that are considered below: (1) delivery of anticancer agents to treat tumors (2) drug delivery to the brain to treat neurodegenerative diseases (3) delivery of antifungal

agents (4) delivery of imaging agents for diagnostic applications (5) delivery of polynucleotide therapeutics.

DENDRIMERS- Dendrimer is a highly branched polymer, as shown in the schematic below, and consists of a core where a monomer unit is attached. Dendrimers are large and complex molecules with very well-defined chemical structures. From a polymer chemistry point of view, dendrimers are nearly perfect monodisperse (basically meaning of a consistent size and form) macromolecules with a regular and highly branched 3 dimensional architecture. They consist of three major architectural components: 1. Core 2. Branching Unit 3. End groups Dendrimers are built from a starting atom, such as nitrogen, after a repeating series of chemical reactions, carbon and other elements was added into it; produce a spherical branching structure. As the process repeats, result is a spherical macromolecular structure. Dendrimers possess three distinguished architectural components, namely a central core which is either a single atom atomic group, Generation in which branches emanating from the core composed of repeating units, which is radially in position and many terminal functional group generally located in the exterior of the macromolecule. Structure of dendrimer. The Dendrimer Structure Four main components are present in the dendrimer structure like Generation number is the number of focal points when going from the core towards the dendrimer surface, if dendrimer when going from the centre to the periphery having five focal points, is denoted as the 5 generation dendrimer. Between the focal points and the generation space, the homo-structural spatial segment is present that is Shell. The space between the last outer branching point and the surface known as outer shell, consists of a varying number of Pincers created by the last focal point before reaching the dendrimer surface. End group is also known as terminal group or surface group of the dendrimer, if are termed am ino dendrimers having amine end-groups –terminated dendrimers.

TYPE OF DENDRIMERS- (1) Radially layered poly (amidoamine-organosilicon) dendrimers (PAMAMOS) (2) Poly (amidoamine) dendrimers (PAMAM) (3) Poly (Propylene Imine) dendrimers (PPI) (4) Chiral dendrimers (5) Liquid crystalline dendrimers (6) Tecto dendrimer (7) Hybrid Dendrimers (8) Multilingual Dendrimers (9)MicellarDendrimers

Method Of Formulation:

(1) Divergent growth method- This method was introduced by Tomalia. In this method 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, lead to the first generation dendrimers. This process is repeated until the dendrimer of the described size is obtained. By this approach the first synthesized dendrimers were polyamidoamines (PAMAMs), also known as starbust dendrimers. **(2) Convergent Dendrimer Growth-** Convergent dendrimer growth begins at what will end up being 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 give a complete dendrimer. convergent growth method has several advantages like relatively easy to purify the desired product, occurrence of defects in the final structure is minimised, does not allow the formation of high generation dendrimer because stearic problems occur in the reactions of the dendrons and the core molecule. **(3) Double Exponential and Mixed Growth-** In this approach two products (monomers for both convergent and divergent growth) are reacted together to give an orthogonally protected trimer, which may be used to repeat the growth process again. Strength of double exponential growth is more subtle than the ability to build large dendrimers in relatively few steps.

(4) Hypercores and Branched Monomers growth- This method involved the pre-assembly of oligomeric species which can be linked together to give dendrimers in fewer steps or higher yields.

APPLICATION OF DENDRIMER-

(1) Dendrimer in ocular drug delivery- PAMAM dendrimers with carboxylic or hydroxyl surface groups, improving residence time and enhance bioavailability of pilocarpine in the eye. **(2) Dendrimers in pulmonary drug delivery-** Positively charged PAMAM dendrimers (G2 and G3 generation) increased the relative bioavailability of pulmonary drug delivery of Enoxaparin.

(3) Dendrimers as Nano-Drugs- Dendrimers as Nano-Drugs, useful as antiviral drugs against the herpes simplex virus can potentially prevent/reduce

transmission of HIV and other sexually transmitted diseases (STDs) when Poly(lysine) dendrimers modified with sulfonated naphthyl groups.

(4) Dendrimers as biomimetic artificial proteins- "artificial proteins" Dendrimers are often referred to as due to their dimensional length scaling, narrow size distribution, and other bio mimetic properties. For examples PAMAM family, they closely match the sizes and contours of many important proteins and bio assemblies like insulin (3 nm), cytochrome C (4 nm), and haemoglobin (5.5 nm) are approximately the same size and shape as ammonia-core PAMAM dendrimers generations 3, 4 and 5 respectively. Generation 2 dendrimer matches the width (2.4 nm) of DNA duplexes (form stable complexes with histone clusters to condense and store DNA within the nucleosome of cells.) and generations 5 and 6 PAMAM dendrimers have diameters approximately equivalent to the thickness of lipid bilayer membranes (~5.5 nm) of biological cells.

(5) Dendrimers as nano-scaffolds- Reducing the interaction with macromolecules from the body defence system, and imaging tags due to an excellent platform provided for the attachment of cell specific ligands, solubility modifiers, and stealth molecules by dendrimer surface. For examples folate PAMAM dendrimers have been successfully used as carriers of boron isotopes in boron neutron -capture treatment of cancer tumors.

LIPOSOMES- Nanoliposomes are nanometric version of liposomes, which are one of the most applied encapsulation and controlled release systems. The word liposome derives from two Greek words, lipos (fat) and soma (body or structure), meaning a structure in which a fatty envelope encapsulates internal aqueous compartment(s). Liposomes (also known as bilayer lipid vesicles) are ideal models of cells and biomembranes. Liposomes are nano size artificial vesicles of spherical shape that can be produced from natural phospholipids and cholesterol. Bangham discovered that phospholipids combined with water immediately form s a bi-layered sphere because one end of each molecule is water soluble, while the opposite end is water insoluble. Liposomes are broadly classified by their structure: **Multilamellar liposomes:** Spherically concentric multilamellar (many bilayers) structures

Unilamellar liposomes: Spherical concentric unilamellar (one bilayer) structures.

MANUFACTURING METHODS:

Sonication Technique- Sonication is a simple method for reducing the size of liposomes and manufacture of nanoliposomes. The common laboratory method involves treating hydrated vesicles for several minutes with a titanium -tipped probe sonicator in a temperature controlled environment.

Extrusion Method- Extrusion is a process by which micrometric liposomes (e.g. MLV) are structurally modified to large unilamellar vesicles (LUV) or nanoliposomes depending on the pore-size of the filters used. Vesicles are physically extruded under pressure through polycarbonate filters of defined pore sizes. A mini extruder device (e.g. 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 employed in this procedure. A small, hand-held, extruder used in the manufacture of nanoliposomes.

Microfluidization- A method of nanoliposome production without using potentially toxic solvents is the microfluidization technique using a microfluidizer. This apparatus has been 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, passing each part through a fine orifice, and directing the flows at each other inside the chamber of microfluidizer. Within the interaction chamber, cavitation, along with shear and impact, reduces particle sizes of the liposomes. Microfluidizer uses high pressures (up to l0,000 psi) to guide the flow stream through microchannels toward the impingement area. The advantages of microfluidization are that: a large volume of liposomes can be formed 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 are not exposed to sonication, detergents or organic solvents.

Heating Method- Majority of nanoliposome manufacture techniques either involve utilisation of potentially toxic solvents (e.g. chloroform, methanol, diethyl ether and acetone) or high shear force procedures. It has been postulated that residues of

these toxic solvents may remain in the final liposome or nanoliposome preparation and contribute to potential toxicity and influence the stability of the lipid vesicles. These hurdles can be overcome by employing alternative preparation methods such as the heating method by which liposomes and nanoliposomes (in addition to some other carrier systems) can be prepared using a single apparatus in the absence of potentially toxic solvents.

QUANTUM DOTS

QDs are colloidal semiconductor nanocrystals ranging from 2 to 10 nm in diameter. QDs can be synthesized from various types of semiconductor materials via colloidal synthesis or electrochemistry. The most commonly used QDs are cadmium selenide (CdSe), cadmium telluride (CdTe), indium phosphide (InP), and indium arsenide (InAs). In bio imaging these particles serve as contrast agents, providing much greater resolution than existing fluorescent dyes. These particles can absorb white light and re-emit it within nanoseconds with different bulk band gap energies corresponding to different combinations of particles. Thus, different QDs can end it different fluorescent light (in wavelength from 400 to 1350 nm). For example, 2-nm QDs will emit green light, whereas 5-nm particles will emit red light. QD libraries can be assembled to include particles of various size and composition to support derivation of multicolored images for bimolecular studies, gene expression, cell labeling and tracking, Fluorescence resonance energy transfer (FRET), in vivo imaging, and related applications. Similar to other nanoparticles, QDs can be modified via conjugation of various surface molecules for targeted delivery. QDs also provide enough surface area to attach therapeutic agents for simultaneous drug delivery and in vivo imaging, as well as for tissue engineering. In vivo cancer targeting and imaging in living animals by QDs was first demonstrated by Gao et al., wherein both subcutaneous injection of QD tagged cancer cells (prostate cancer) and systemic injection of multifunctional QD probes were used to achieve sensitive and multicolor fluorescence imaging of cancer cells. [7]

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