IJPSR (2011), Vol. 2, Issue 2 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 06 October, 2010; received in revised form 16 November, 2010; accepted 14 January, 2011

NANO DRUG DELIVERY SYSTEMS - A REVIEW

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Keywords:

Nano carriers,
Nanoparticles,
Nanocrystals,
Nanotubes,
Controlled manner

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ABBREVIATIONS:

µm- Micrometer, nm- Nanometer, PMMA - Poly (methylmethacrylate), PACA - Poly (alkylcyanoacrylate), PMM - Poly (methylidenemalonate), SME - Sub-micron emulsion, PAMAM - Polyamido amines, 5-ASA - 5-Aminosalicylic acid, Mc- Molar mass of the core, Mm- Molar mass of the branched monomer, Mt- Molar mass of the terminal groups, nc- Core multiplicity, nm- Branch-juncture multiplicity, G- Generation number, CMC- Critical micelle concentration, PEO - Poly (ethylene oxide) DNA- Di-ribo nucleic acid MWNTs- Multi-walled nanotubes, SWNTs- Single-walled nanotubes, EAD- Electric arc discharge, CVD- Chemical vapor deposition, LA- Laser ablation, CNTs- Carbon nanotubes, MD- Molecular dynamics, MEMS- Microelectro mechanical systems, PHSNP- Porous hollow silica nanoparticles

ABSTRACT

Drug delivery is an interdisciplinary area of research that aims at making the administration of complex new drugs feasible, as well as adding critical value to the drug that are currently in the market. At present, one of the most attractive areas of research in drug delivery is the design of 'Nano drug delivery systems' that are able to deliver drugs to the right place, at appropriate time. In the present review article different nano carriers are explained (Nanoparticles, nanocapsules, nanocrystals, nanoemulsion, dendrimers, polymeric micelles and nanotubes). Nanostructured drug carriers allow for the delivery of drugs not only small-molecule drugs but also the delivery of nucleic acids and proteins. Delivery of these molecules to specific areas within the body can be achieved, which will reduce systemic side effects and allow for more efficient use of the drug. These nano carriers are able to protect associated drug against degradation and facilitate its transport across critical and specific barriers. Some of them are further able to release the drug to the target in a controlled manner. The use of nanomaterials including peptide-based nanotubes to target the vascular endothelial growth factor receptor and cell adhesion molecules like integrins, cadherins and selectins is a new approach to control disease progression.

INTRODUCTION: The predominant methods to deliver drugs are oral and injection, which has limited the progress of drug development. Most drugs have been formulated to accommodate the oral or injection delivery routes, which are not always the most efficient routes for a particular therapy. New biologic drugs such as proteins and nucleic acids require novel delivery technologies that will minimize side effects and lead to better patient compliance. Market forces are also driving the need for new, effective drug delivery methods[1]. Drug particles in the nanometer size range have unique characteristics that can lead to enhanced performance in a variety of dosage forms. Particles in this size range are resistant to settling and can have higher saturation solubility, rapid dissolution, and enhanced adhesion to biological surfaces, thereby providing a rapid onset of therapeutic action and improved bioavailability. Scientists use nanotechnology to approach classical and novel drug delivery applications [2].

Nanotechnology is expected to have a dramatic impact on medicine. The application of nanotechnology for treatment, diagnosis, monitoring, and control of biological systems is now often referred to as nanomedicine. Among many possible applications of nanotechnology in medicine, the use of various nanomaterials as pharmaceutical delivery systems for drugs, DNA, and imaging agents has gained increasing attention. Many varieties of nanoparticles are available, such as different polymeric and metal nanoparticles, liposomes, niosomes, solid lipid particles, micelles, quantum dots, dendrimers, microcapsules, cells, cell ghosts, lipoproteins, and different nanoassemblies[3]. In recent years, tremendous efforts have been devoted in order to develop modern nanoparticulate drug delivery systems. However, for newly developed powerful drug molecules with moderate biopharmaceutical profiles, adequate drug carriers are still missing. The entrapment of such compounds would protect them from the biological environment and facilitate their transport through biological barriers [4]. In order to properly describe the impact of nanotechnology on the delivery of drugs some definitions are necessary. For the purposes of this discussion, nanotechnology can be defined as structures that:

- Have at least one length dimension less than or equal to 500 nm.
- Exhibit novel and unique chemical, physical, or biological behavior because of their small size.

Drug delivery alternatives: In addition to the commonly used oral and injection routes, drugs can also be administered through other means, including transdermal, transmucosal, ocular, pulmonary, and implantation. The mechanisms used to achieve alternative drug delivery typically incorporate one or more of the following materials: biologics, polymers, silicon based materials, carbon-based materials, or metals. These materials are structured in microscale and more recently nanoscale formats. **Table 1** summarizes the materials and structures [1].

Nanoparticles and Nanocapsules: Polymeric particles used for drug delivery are defined as colloidal systems made of solid polymers that may be classified according to their size and preparation processes. The term nanoparticles designate systems smaller than 1 µm (submicronic particles). *Nanocapsules* are composed of a polymeric wall containing a liquid inner core where the drug is entrapped while *nanospheres* are made of a solid polymeric matrix in which the drug can be dispersed (**Fig. 1**). Active substances may be either adsorbed at the surface of the polymer or encapsulated within the particle. Particles may be produced by polymerization of synthetic monomers, or dispersion of synthetic polymers or natural macromolecules [5].

TABLE NO. 1. NANOSCALE DRUG DELIVERY TECHNOLOGIES

DRUG DELIVERY TECHNOLOGY	MATERIALS	NANOSTRUCTURE FORMS
BIOLOGIC	PEPTIDES, LIPIDS, VESICLES, NANOTUBE, RINGS	NUCLEIC ACIDS, NANOPARTICLES
POLYMERIC	POLY (LACTIC ACID), POLY(GLYCOLIC ACID), POLY(ALKYLCYANOACRYLATE), POLY(3-HYDROXYBUTANOIC ACID), POLY(ORGANOPHOSPHAZENE), POLY(ETHYLENE GLYCOL), POLY(CAPROLACTONE), POLY(ETHYLENE OXIDE), POLY(AMIDOAMINE), POLY(L-GLUTAMIC ACID), POLY(ETHYLENEIMINE), POLY(PROPYLENE IMINE	VESICLES, SPHERES, NANOPARTICLES, MICELLES, DENDRIMERS
SILICON BASED	SILICON, SILICON DIOXIDE	POROUS, NANOPARTICLES NANONEEDLES
CARBON BASED METALLIC	CARBON, GOLD, SILVER, PALLADIUM, PLATINUM	NANOTUBES, FULLERNESS NANOPARTICLES, NANOSHELLS

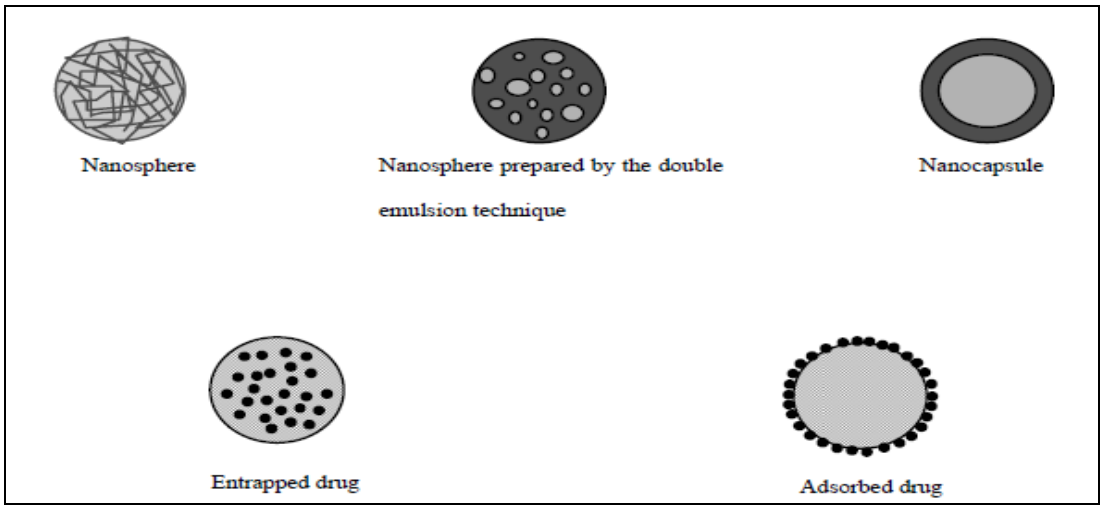

FIG. 1: DIFFERENT TYPES OF POLYMERIC PARTICLES

The physicochemical properties of particles play a critical role in the rate of absorption by the intestinal tract. Since those properties are greatly influenced by the preparation method, it is useful to have a brief presentation of these techniques. The polymers used to make particles for oral administration are rather diverse. The choice of a preparation method depends greatly on both the nature of the drug and the polymer [5].

Nanoparticles and Nanocapsules both are prepared by the following methods: There are number of ways to make Nanoparticles as described in **Fig. 2**. Particle formation by polymerization reactions (emulsion polymerization) has been primarily developed for polymers such as poly (methylmethacrylate) (PMMA), poly (alkylcyanoacrylate) (PACA), and poly (methylidenemalonate) (PMM). Briefly, the water insoluble monomer is dispersed in an aqueous phase and the polymerization is induced and

controlled by addition of a chemical initiator or by variations in physical parameters such as pH or γ-radiation in the presence or the absence of surfactants to stabilize the emulsion. Drugs are entrapped in the polymeric wall when added to the polymerization medium or adsorbed on preformed particles afterwards. The preparation of particles from preformed polymers is based on polymer precipitation (**Fig. 3**). Basically, an organic solution of the polymer is emulsified in an aqueous solution with or without a surfactant.

In a second step, the organic solvent is removed by different methods such as evaporation, diffusion or salting out under stirring to allow particle formation. With these techniques, the drug has to be at least partially soluble in an organic solvent to be encapsulated. This is a major limitation to the encapsulation of hydrophilic compounds such as peptides, proteins or nucleic acids. Therefore, alternative methods have been developed to increase the encapsulation rate of hydrophilic molecules. It is possible, for example, to derivatize a hydrophilic compound to form a hydrophobic complex. A more common way is to use a double emulsion technique in which an aqueous solution of the hydrophilic compound is first emulsified in an organic solution of the polymer (Fig. 3). The primary emulsion is then poured into large volume of water with or without surfactant. The double emulsion technique has fairly good encapsulation efficiency for hydrophilic compounds; however, particle size is usually larger than with single emulsion technique. Another way of preparing particles from a preformed polymer is the spray-drying method where the drug is solubilized or dispersed in an organic solution of the polymer to be nebulized in a hot air flow. The solvent is almost instantly evaporated and dried nanoparticles are readily recovered. This technique, easily applicable at the industrial scale, is used for hydrophilic, as well as lipophilic molecules. Nanocapsule technology offers several advantages for improving the entrapment efficiency of lipophilic compounds, or for providing a controlled release system. It has also been used with hydrophilic drugs especially with oily suspensions of insulin.

Nanocapsules may be prepared by interfacial polymerization from alkylcyanoacrylate monomers. The drug and the monomer are then dissolved or dispersed in a mixture of ethanol and oil under magnetic stirring into an aqueous phase. Capsules may also be obtained from preformed polymer, based on a desolvation process. Recently, a new method based on the emulsification-diffusion process has been described.

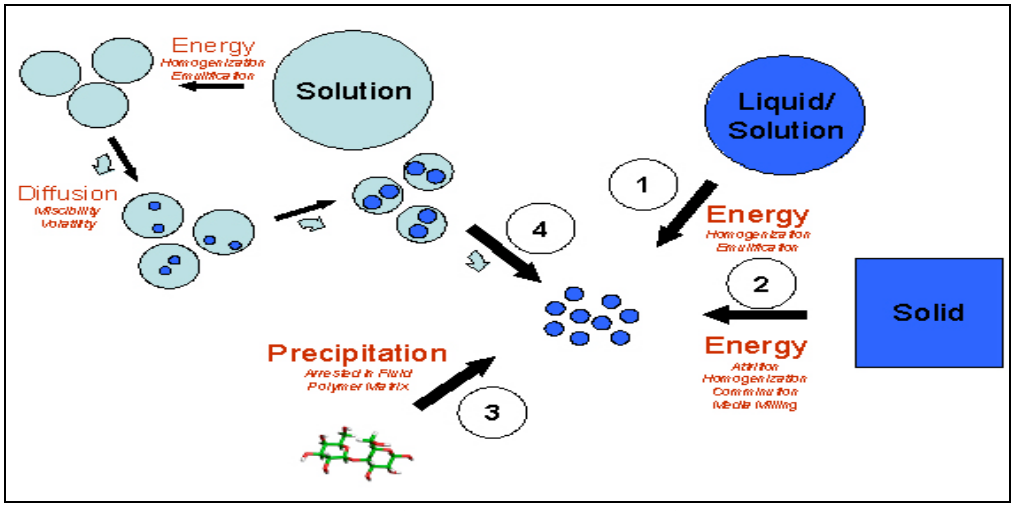

FIG. 2: NUMBER OF WAYS TO MAKE NANOPARTICLES

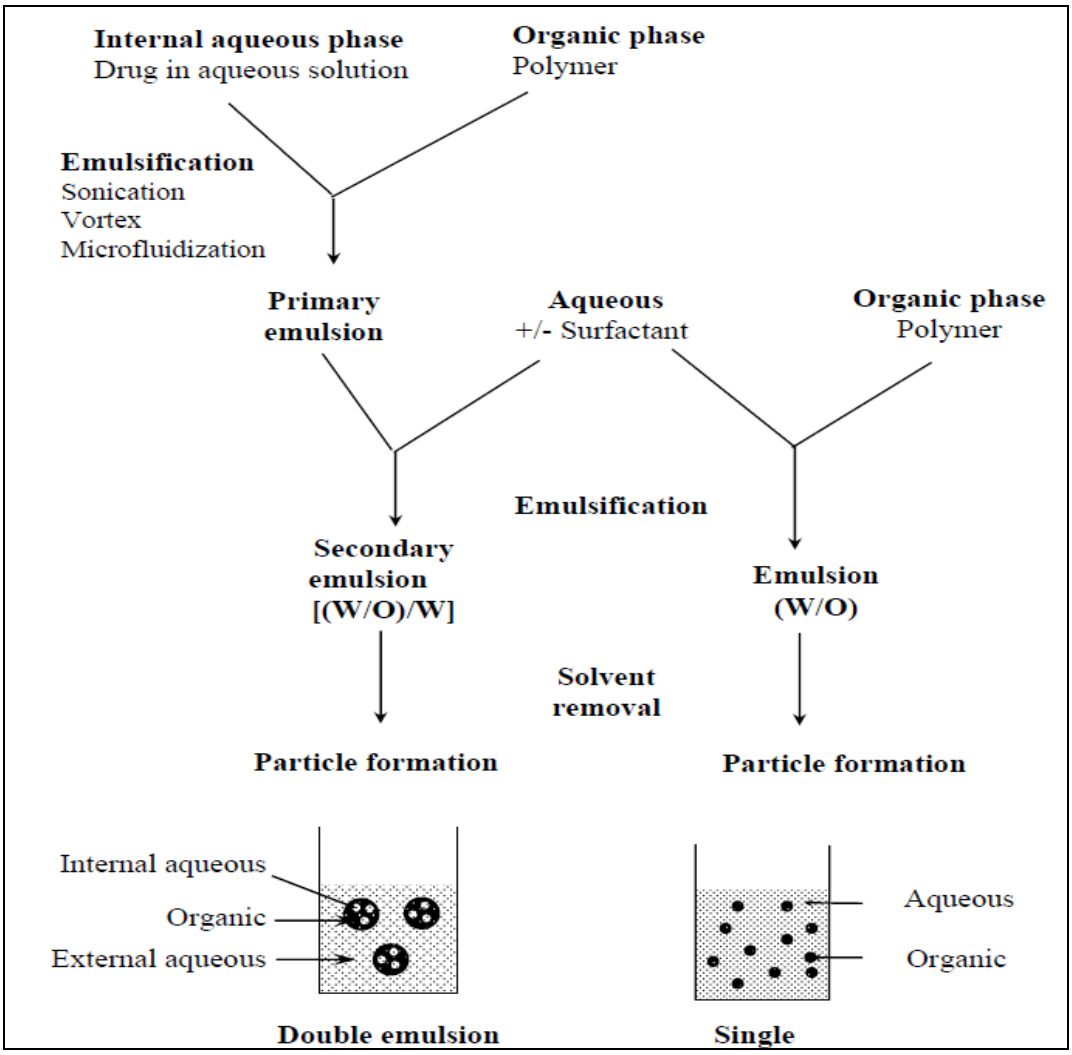

FIG. 3: NANOPARTICLES PREPARATION BY EMULSIFICATION METHOD

Lambert *et al*. also used this technique to encapsulate oligonucleotides where the nanocapsules were suspended in an aqueous medium more suitable for intravenous administration. Once the particles are formed as spheres or capsules, a purification step is needed to remove the potentially toxic additives necessary for the manufacturing or to separate unincorporated drug. It is used as a concentration technique as well. This may be achieved by centrifugation or ultracentrifugation depending on the size of the particles, by filtration (centrifugal filtration or cross flow filtration), gel permeation or dialysis [5].

Nanocrystals and Nanosuspensions: More than 40 percent of the drugs coming from High-through output screening are poorly soluble in water. Obviously poorly water-soluble drugs show many problems in formulating them in conventional dosage forms. One of the critical problems associated with poorly soluble drugs is too low bioavailability and erratic absorption. There are number of formulation approaches to resolve the problems of low solubility and low bioavailability. The approaches include micronization, solublization using co-solvents, use of permeation enhancers, oily solutions, surfactant dispersions, salt formation and precipitation techniques.

Other techniques like liposomes, emulsions, microemulsions, solid-dispersions and inclusion complexes using cyclodextrins show reasonable success but they lack in universal applicability to all drugs. These techniques are not applicable to the drugs, which are not soluble in both aqueous and organic medias. Hence there is need of some different and simple approach to tackle the formulation problems to improve their efficacy and to optimize the therapy with respect to pharmacoeconomics. Nanotechnology can be used to resolve the problems associated with these conventional approaches for solubility and bioavailability enhancement.

The drug microparticles/micronized drug powder is transferred to drug nanoparticles by techniques like Bottom Up Technology (precipitation) and Top Down Technology or disintegration methods[5]. Nanocrystals are aggregates of a few hundred to tens of thousands of atoms that combine into a crystalline form of matter known as a "cluster." Typically around ten nanometers in diameter, nanocrystals are larger than molecules but smaller than bulk solids and therefore frequently exhibit physical and chemical properties somewhere in between. Given that a nanocrystal is virtually all surface and no interior, its properties can vary considerably as the crystal grow in size [6].

Nanosuspensions consist of the pure poorly water-soluble drug without any matrix material suspended in dispersion. It is sub-micron colloidal dispersion of pure particles of drug stabilized by surfactants. By formulating nanosuspensions problems associated with delivery of poorly water-soluble drugs and lipid-soluble drugs can be solved. Nanosuspensions differ from nanoparticles, which are polymeric colloidal carriers of drugs (Nanospheres and nanocapsules), and from solid-lipid nanoparticles (SLN), which are lipidic carriers of drug [5].

Common preparation methods for Nanocrystals and Nanosuspensions:

a) **Milling:** Nanoscale particles can be produced by wet-milling process. In ball mills, particle size reduction is achieved by using both impact and attrition forces. The most common models are a tumbling ball mill and a stirred media mill. One problem of this method is the degradation of mill surfaces and subsequent suspension contamination [7].

b) **High pressure homogenization:** In high pressure homogenization, an aqueous dispersion of the crystalline/suspensions drug particles is passed with high pressure through a narrow homogenization gap with a very high velocity. Homogenization can be performed in water (DissoCubes) or alternatively in non-aqueous media or water-reduced media (Nanopure). The particles are disintegrated by cavitation and shear forces.

The static pressure exerted on the liquid causes the liquid to boil forming gas bubbles. When exiting from the gap, gas bubbles collapse under normal air pressure. This produces shock waves which make the crystals/suspensions collide, leading to particle disintegration. A heat exchanger should be used when operating on temperature sensitive materials because high pressure homogenization causes increase in the sample temperature. The particle size obtained during the homogenization process depends primarily on the nature of the drug, the pressure applied and the number of homogenization cycles [7].

c) **Combined Precipitation and Homogenization (Nanoedege):** The precipitated drug nanoparticles have tendency to continue crystal/particles growth to the size of

microcrystals/particles. They need to be processed with high-energy forces (Homogenization). They are amorphous, partially amorphous or completely crystalline which create problems in long term stability and bioavailability. The precipitated particle suspension is subsequently homogenized which preserve the particle size obtained after the precipitation step [5].

Nanoemulsions: Nanoemulsions can be defined as oil-in-water (o/w) emulsions with mean droplet diameters ranging from 50 to 1000 nm. Usually, the average droplet size is between 100 and 500 nm. The particles can exist as water-in-oil and oil-in water forms, where the core of the particle is either water or oil, respectively. The terms sub-micron emulsion (SME) and mini-emulsion are used synonyms. Usually, SMEs contain 10 to 20 per cent oil stabilized with 0.5 to 2 per cent egg or soybean lecithin [8].

The droplets are stabilized by surfactants. They are not formed spontaneously; their properties depend not only on thermodynamic conditions but on preparation methods and the order of addition of the components. On the other hand, nanoemulsions are equilibrium structures distinctly different from emulsions Nano-emulsions may possess high kinetic stability and optical transparency resembling microemulsions. Nanoemulsions can be used as micro reactors of controlled size for the preparation of monodisperse particles [9].

Advantages of Nanoemulsions:

1. Nanoemulsions have a much higher surface area and free energy than macroemulsions that make them an effective transport system.
2. Nanoemulsions do not show the problems of inherent creaming, flocculation, coalescence and sedimentation, which are commonly associated with macroemulsions.
3. Nanoemulsions can be formulated in variety of formulations such as foams, creams, liquids and sprays.
4. Nanoemulsions are non-toxic; non-irritant hence can be easily applied to skin and mucous membranes.
5. Since nanoemulsions are formulated with surfactants, which are approved for human consumption, they can be taken by enteric route.
6. Since nanoemulsions do not damage healthy human and animal cells, suitable for human and veterinary therapeutic purposes.

Methods of Preparation of Nanoemulsions: Since nanoemulsions have very small particle size range, they can be most effectively produced using high-pressure equipment. The most commonly used methods for producing nanoemulsions are 'High-pressure homogenization' and 'Microfluidization' which can be used at both laboratory and industrial scale. Other methods like 'Ultrasonification' and 'In-situ emulsification' are also suitable but are mostly used at laboratory scale and not for commercial production.

1. **High-Pressure Homogenization:** This technique makes use of high-pressure homogenizer/ piston homogenizer to produce nanoemulsions of extremely low particle size (up to 1nm). In a high-pressure homogenizer, the dispersion of two liquids (oily phase and aqueous phase) is achieved by forcing the mixture through a small inlet orifice at very high pressure (500 to 5000 psi), which subjects the product to intense turbulence and hydraulic shear resulting in extremely fine particles of emulsion.

Homogenizers of varying design are available for laboratory scale and industrial scale production of nanoemulsions. This technique has great efficiency, the only disadvantage being high energy consumption and increase in temperature of emulsion during processing (**Fig. 4**) [8].

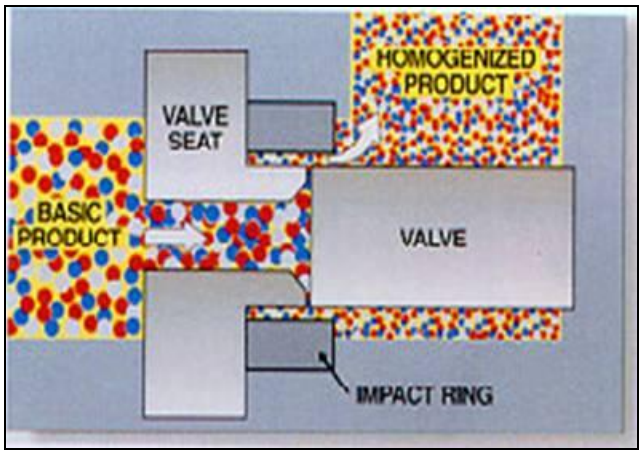

FIG. 4: HIGH PRESSURE HOMOGENIZATION

2. **Microfluidization:** Microfluidization is a patented mixing technology, which makes use of a device called microfluidizer. This device uses a high-pressure positive displacement pump (500 to 20000 psi), which forces the product through the interaction chamber consisting of small channels called 'microchannels'. The product flows through the microchannels on to an impingement area resulting in very fine particles of sub-micron range.

   Method: The two solutions (aqueous phase and oily phase) are combined together and processed in an inline homogenizer to yield a coarse emulsion. The coarse emulsion is further processed in a microfluidizer to obtain desired particle size for a stable nanoemulsion. The bulk emulsion is then filtered through a filter under nitrogen to remove large droplets resulting in a uniform nanoemulsion [8].

Dendrimers: Dendrimers are spheroid or globular nanostructures (**Fig. 5**) that are precisely engineered to carry molecules encapsulated in their interior void spaces or attached to the surface. Size, shape, and reactivity are determined by generation (shells) and chemical composition of the core, interior branching, and surface functionalities. Dendrimers are constructed through a set of repeated chemical synthesis procedures that build up from the molecular level to the nanoscale region under conditions that are easily performed in a standard organic chemistry laboratory. The dendrimer diameter increases linearly whereas the number of surface groups increases geometrically.

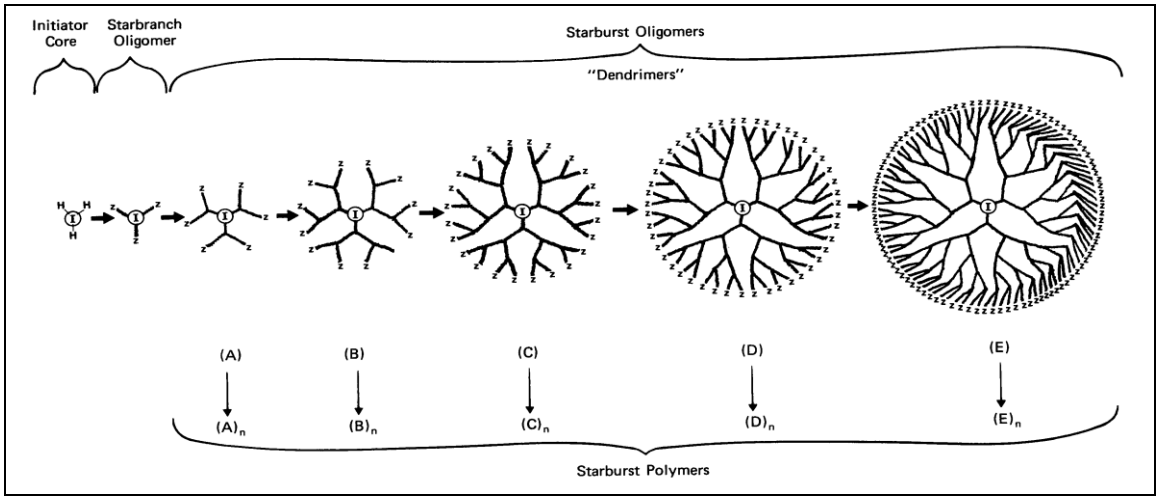

FIG. 5 GENERAL STRUCTURE OF DENDRIMERS

Dendrimers are very uniform with extremely low polydispersities, and are commonly created with dimensions incrementally grown in approximately nanometer steps from 1 to over 10 nm. The control over size, shape, and surface functionality makes dendrimers one of the "smartest" or customizable nanotechnologies commercially available[10]. The utilization of dendrimers as drug delivery carriers is of great interest due to their highly controllable structure and size. The terminal functional groups of dendrimers show higher chemical reactivity compared to that when present in other classes of polymers [11].

The functional groups of dendrimers have been conjugated to various biologically active molecules such as drugs, antibodies[12], sugar moieties[13], and lipids[14]. In dendrimer- drug conjugates (prodrugs) the drug is combined through a covalent bond either directly or via a linker/spacer to the dendrimer. The release of drug from a prodrug occurs *via* chemical or enzymatic cleavage of a hydrolytically labile bond. Several reports have investigated the conjugation of drugs to Polyamido amines (PAMAM) dendrimers as drug delivery systems. For example, 5-fluorouracil (5FU)-PAMAM dendrimer conjugates (G4 and G5) gave a slow release of 5FU [15].

5-Aminosalicylic acid (5-ASA) was conjugated using two different spacers, both containing an azo-bond, to G3 PAMAM dendrimer for use as a carrier for colonic delivery. Colon specificity and prolonged release of 5-ASA from the conjugates were reported suggesting that PAMAM dendrimers have potential for use as colon-specific drug carriers [16]. Propranolol, an insoluble drug and a substrate for the P-glycoprotein (P-gp) efflux transporter, was conjugated to surface modified G3 PAMAM dendrimer. The conjugate was shown to bypass the efflux of P-gp transporters in Caco-2 cells, thus dendrimer nanocarriers may enhance the bioavailability of drugs that are poorly soluble and/or substrates of efflux transporters [17].

Synthesis: Dendrimers are generally prepared using either a divergent method or a convergent one. There is a fundamental difference between these two construction concepts. In the divergent methods, dendrimer grows outward from a multifunctional core molecule. The core molecule reacts with monomer molecules containing one reactive and two dominant groups giving the first generation dendrimer. Then the new periphery of the molecule is activated for reactions with more monomers. The process is repeated for several generations and a dendrimer is built layer after layer (**Fig. 6A**).

The 'starburst' is a trademark of the Dow Chemicals Company. Ammonia is used as the core molecule. Divergent approach is successful for the production of large quantities of dendrimers. Problems occur from side reactions and incomplete reactions of the end groups that lead to structure defects. To prevent side reactions and to force reactions to completion large excess of reagents is required. It causes some difficulties in the purification of the final product. The convergent methods were developed as a response to the weaknesses of the divergent synthesis.

In the convergent approach, the dendrimer is constructed stepwise, starting from the end groups and progressing inwards. When the growing branched polymeric arms, called dendrons, are large enough they are attached to a multifunctional core molecule (**Fig. 6B**). The convergent growth method has several advantages. It is relatively easy to purify the desired product and the occurrence of defects in the final structure is minimized.

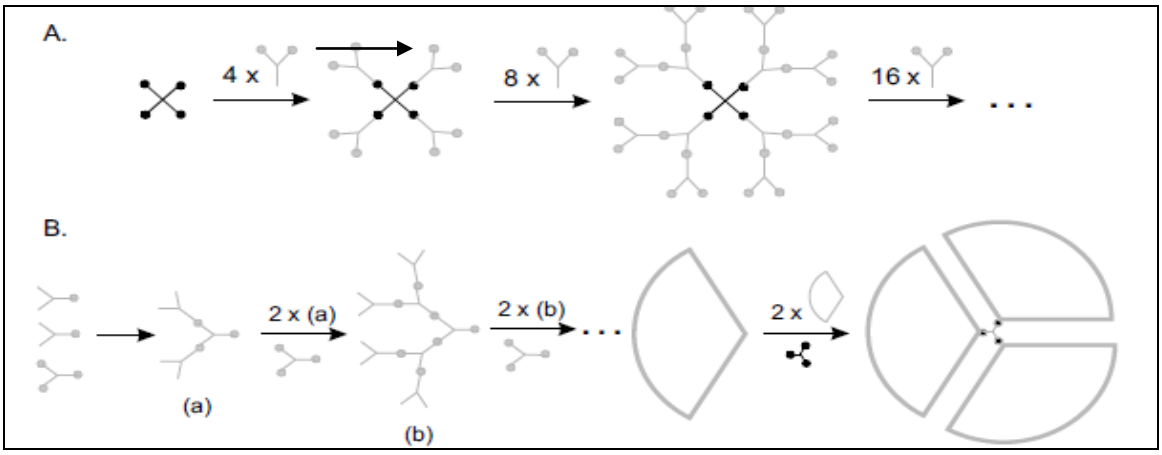

FIG. 6A: THE DIVERGENT GROWTH METHOD; B: THE CONVERGENT GROWTH METHOD

It becomes possible to introduce subtle engineering into the dendritic structure by precise placement of functional groups at the periphery of the macromolecule. The convergent approach does not allow the formation of high generations because steric problems occur in the reactions of the dendrons and the core molecule. The first synthesized dendrimers were polyamidoamines (**PAMAM**s). They are also known as starburst dendrimers. The term In the presence of methanol it reacts with methyl acrylate and then ethylenediamine is added:

$$NH_3 + 3CH_2CHCOOCH_3 \longrightarrow N(CH_2CH_2COOCH_3)_3 \quad (1)$$

$$N(CH_2CH_2COOCH_3)_3 + 3NH_2CH_2CH_2NH_2 \longrightarrow N(CH_2CH_2CONHCH_2CH_2NH_2)_3 + 3CH_3OH \quad (2)$$

At the end of each branch there is a free amino group that can react with two methyl acrylate monomers and two ethylenediamine molecules. Each complete reaction sequence results in a new dendrimer generation. The half- generation PAMAM dendrimers (e.g., 0.5, 1.5, 2.5) possess anionic surfaces of carboxylate groups. The number of reactive surface sites is doubled with every generation [18]. The mass increases more than twice. The molar mass of the dendrimer can be predicted mathematically:

$$M = M_c + n_c \cdot \left[M_m \cdot \left(\frac{n_m^G - 1}{n_m - 1} \right) + M_t \cdot n_m^G \right],$$

Where: *M*c- is the molar mass of the core, *M*m- the molar mass of the branched monomer, *M*t- the molar mass of the terminal groups, nc- the core multiplicity, nm- the branch-juncture multiplicity, G- the generation number.

Polymeric micelles: Polymeric micelles are particulate self-assemblies in aqueous media that are composed of linear amphiphilic macromolecules possessing both hydrophilic and hydrophobic 'blocks' (AB-type) on a single strand (each copolymer strand is amphiphilic). At the appropriate ratio of block lengths, these copolymers spontaneously form spherical particles in water: the hydrophobic blocks form the 'core', while the hydrophilic blocks form the surrounding "corona" (**Fig. 7**).

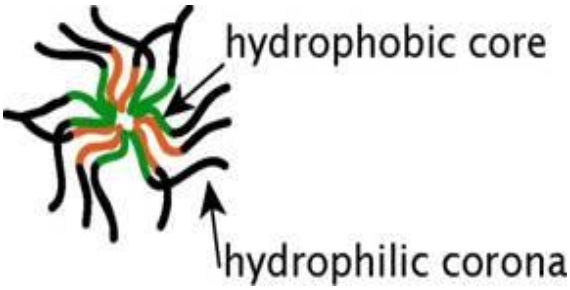

FIG. 7: GENERAL STRUCTURE OF POLYMERIC MICELLES

The particle sizes range between 10-100 nm, making them considerably smaller than phospholipid vesicles (liposomes). Another distinction of polymeric micelles is the absence of internal aqueous space. Like other micelle-forming amphiphiles, AB-type copolymers will dissociate upon dilution below their critical micelle concentration (CMC). However, due to the polymeric nature of the hydrophobic blocks, polymeric micelles possess very low CMC values and are thermodynamically and kinetically quite stable. Typical CMCs for polymeric micelles lie in the low micromolar range, whereas the CMCs for many commonly used low-molecular weight surfactants are in the millimolar or high micromolar range. Such low CMCs indicate that polymeric micelles require an energy input to dissociate and incorporate other materials, like membrane components [19].

Polymeric micelles have many potential uses in biomedicine. For example, polymeric micelles have been proposed for use in intraparenteral drug delivery applications, especially for delivery of drugs with low aqueous solubility or as carriers for protein/peptide therapeutics. Researchers have developed numerous varied formulations of amphiphilic polymeric preparations for stabilizing membrane proteins. Micelles as drug carriers provide a set of advantages- they physically entrap sparingly soluble pharmaceuticals and deliver them to the desired site of action at concentrations that can exceed their intrinsic water solubility and thus increase their bioavailability. The stability of the drug is also increased through micelle incorporation.

Furthermore, undesirable side effects are lessened in comparison with free drug as contact of the drug with inactivating species such as enzymes present in biological fluids are minimized. They can be prepared in large quantities easily and reproducibly. By far the most important feature of micellar delivery systems, which distinguish them from other particulate drug carriers, lies in their small size (~10 to 30 nm) and the narrow size distribution. Polymeric micelles have been studied extensively as delivery medium for injectable drug formulations of poorly water-soluble drugs such as paclitaxel, indomethacin, amphotericin B, adriamycin, and dihydrotestosterone. Overall, they proved to be highly effective drug delivery vehicles. To date, most contributions in the area of polymeric micelles for oral formulations have been made by the group of Kabanov. Their work focused mostly on micelles formed from commercially available Pluronic® triblock copolymers [also termed Poloxamer; poly (ethylene oxide) *x*-*b*-poly (propylene oxide) *y*-*b*-poly (ethylene oxide) *x*; PEO*x*-*b*-PPO*y* *b*-PEO*x*] and more recently, on block ionomer complexes as carriers for DNA [20].

Nanotubes: Nanotubes are two-dimensional crystalline sheets of atoms that have been rolled up and connected at the seam to form a closed cylinder (**Fig. 8**).

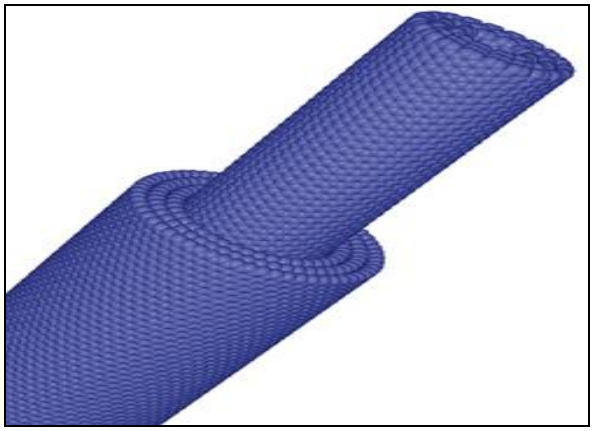

FIG. 8: THE CONTROLLED AND REVERSIBLE TELESCOPIC EXTENSION OF MULTI-WALLED NANOTUBES, AS SHOWN [ABOVE RIGHT] IN BOTH THE TRANSMISSION ELECTRON MICROSCOPE IMAGE AND THE COMPUTER GRAPHIC [ABOVE], COULD LEAD TO VIRTUALLY FRICTIONLESS NANOSCALE LINEAR BEARINGS AND CONSTANT-FORCE NANOSPRINGS

The earliest nanotubes were made from pure carbon. Formed naturally in the sooty residue of vaporized carbon rods, they were an elongated form of fullerene or "buckyball" molecules, clusters of 60 and 70 carbon atoms joined in a graphite-like mesh of hexagonal rings. The first generations were "multi-walled nanotubes" (MWNTs): about five to 40 single-walled nanotubes (SWNTs)-meaning the tube's surface consists of only a single layer of carbon atoms-each tube nesting inside the other like Russian dolls. Later, when scientists began to directly make SWNTs, it was discovered that they could be drawn out to exceedingly long lengths of nanowire without losing any strength or durability.

a) Carbon structures: Two nanostructures, carbon-based, cage-like architectures: nanotubes and fullerenes, also known as buckyballs because of their spherical structure resembling the geodesic domes of Buckminster Fuller. Single-wall nanotubes (SWNTs), multiwall nanotubes (MWNTs), and C60 fullerenes are common configurations. The size, geometry, and surface characteristics of these structures make them appealing for drug carrier usage. SWNTs and C60 fullerenes have diameters on the order of 1 nm, about half the diameter of the average DNA helix. MWNTs have diameters ranging from several nanometers to tens of nanometers depending on the number of walls in the structure. Fullerenes and carbon nanotubes are typically fabricated using electric arc discharge (EAD), laser ablation (LA), chemical vapor deposition (CVD), or combustion processes. Surface-functionalized carbon nanotubes (CNTs) can be internalized within mammalian cells, and when linked to peptides may be used as vaccine delivery structures. With use of molecular dynamics (MD) simulations, the flow of water molecules through CNTs has been modeled and implies their potential use as small molecule transporters. Other simulations have involved the transport of DNA through CNTs, indicating potential use as a gene delivery tool. Much work with CNTs has involved composite materials. For example, temperature stabilized hydrogels for drug delivery applications incorporate CNTs. Fullerenes have also shown drug targeting capability. Tissue-selective targeting and intracellular targeting of mitochondria have been shown with use of fullerene structures. Furthermore, experiments with fullerenes have also shown that they exhibit antioxidant and antimicrobial behavior [1].

b) Silicon-based structures: Silicon-based structures can be fabricated by photolithography, etching, and deposition techniques commonly used in the manufacture of semiconductors and microelectro mechanical systems (MEMS). The most commonly investigated silicon based materials for drug delivery are porous silicon and silica, or silicon dioxide. Architectures include calcified nanopores, platinum- containing nanopores, porous nanoparticles, and nanoneedles [21, 22, 23]. The density and diameter of the nanopores can be accurately controlled to achieve a constant drug delivery rate through the pores.

Porous hollow silica nanoparticles (PHSNP) are fabricated in a suspension containing sacrificial nanoscale templates such as calcium carbonate. Silica precursors, such as sodium silicate, are added into the suspension, which is then dried and calcinated creating a core of the template material coated with a porous silica shell. The template material is then dissolved in a wet etch bath, leaving behind the porous silica shell. Creation of drug carriers involves the mixing of the PHSNPs with the drug molecule and subsequently drying the mixture to coalesce the drug molecules to the surface of the silica nanoparticles [1, 24, 25]. Examples of therapies being investigated for use with silicon-based delivery systems include porous silicon embedded with platinum as an antitumor agent [26].

c) Metal structures: Hollow metal nanoshells are being investigated for drug delivery applications [27]. Typical fabrication methods involve templating of the thin metal shell around a core material such as a silica nanoparticle. Typical metals include gold, silver, platinum, and palladium. When linked to or embedded within polymeric drug carriers, metal nanoparticles can be used as thermal release triggers when irradiated with infrared light or excited by an alternating magnetic field[28]. Biomolecular conjugation methods of metals include bifunctional linkages, lipophilic interaction, silanization, electrostatic attraction, and nanobead interactions[29]. **Fig. 9** shows examples of silanization and electrostatic attraction methods of metal nanoparticles conjugation.

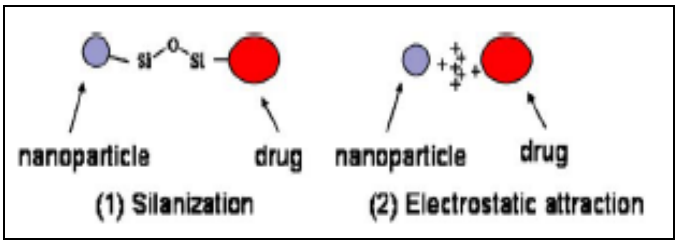

FIG. 9: NANOPARTICLE BIOCONJUGATION METHODS: (1) SILANIZATION, AND (2) ELECTROSTATIC ATTRACTION

CONCLUSION: Nano drug delivery systems are increasingly providing the pharmaceutical industry with solutions to formulation and opportunities for line extensions for existing drug through improved therapeutic outcomes or alternative routes of administration. As nanotechnology increasingly attracts research funding, the range of colloidal structures that can be employed in these tasks will be better characterized and efficient and reliable methods of manufacture will be developed. Consequently nano drug deliver systems will occupy growing presence in pharmaceutical products in the future, providing improved therapeutic outcomes for society and satisfying industry's need to make the most of their drug delivery programmes through maximizing available formulation alternatives.

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