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Nanoparticles: An Overview

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ABSTRACT

From the last few decades, there has been a considerable research interest in the area of drug delivery using particulate delivery systems as the carriers for smaller and larger molecules. The particulate systems like nanoparticles have been used as a physical approach to alter and improve the properties of various types of drug molecules like pharmacokinetic and pharmacodynamic. The nanoparticles are defined as particulate dispersions or solid particles with the size in the range between 10-1000nm. The drugs are dissolved, entrapped, encapsulated or attached to the nanoparticle matrix. Nanoparticles, nanospheres or nanocapsules can be obtained which depends upon the method of preparation, This review article covers the different methods of preparation of Nanoparticles, different types of Nanoparticles, their evaluation and applications of Nanoparticles

Keywords: Nanoparticles, particulate delivery systems, solid particles.

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INTRODUCTION

The liberation of the drug agents at a right time in a reproducible manner and safe manner, usually to the target site which is specific. The conventional dosage form such as the orally administered pills and subcutaneous or IV injection, are the predominant routes for the drug administration. But pills and injections are offered limited control over the rate of release of drug into the body; they are usually associated with the immediate release of a drug. The initial concentration of the drug in the body must be high to achieve the therapeutic levels that extend over time, causing peaks [to stay just below known levels of toxicity for a drug they are often adjusted] that gradually diminish over the time to a level which is ineffective. The duration of the therapeutic effect depends upon the half- life of the drug and the frequency of dose administration in these mode of delivery. In certain cases this peak and valley delivery is known to cause toxicity, most famously with chemotherapy drugs for the treatment of cancer. The pharmaceutical and biotech industries have developed more sophisticated and potent drugs in recent years. Many of these agents are DNA or proteins, the therapeutic window [that is, concentration of ranges that brackets the effective and toxic regimes for a drug] for these drugs are often narrow the toxicity is observed for concentration spikes, which renders traditional methods of drug delivery ineffective. In addition, the conventional oral doses of these agents are useless frequently, because the drugs are poorly absorbed and destroyed during intestinal transit. The interest in the new types of drug agents has catalyzed innovation in the controlled-release of drug delivery systems. The number of mechanisms can provide controlled release of drugs- which includes the implants, transdermal patches, bioadhesive systems, inhalation systems and the microencapsulation-and now there are, commercially available products and pioneering products in all of these categories. The one of the major advances in the recent years has been the further size reduction of these systems. It is now possible to make the polymer delivery systems that are nanometer in scale that can be easily inhaled or injected and are much smaller than-and are capable of being internalized by the many types of human cells. Although, there are many ways of achieving nanoscale delivery systems which includes the self assembling systems based on the micelles or liposomes the most stable and versatile systems are miniaturized versions of a synthetic materials that have been used already in drug delivery applications. Usually this is accomplished with degradable polymers such as poly [lactide-co-glycolide]. For circulation or used to release drugs locally these particles can be injected. If appropriate methods of fabrication are used to assemble the nanoparticle the encapsulated drugs can be complex. The nanoparticle is defined as the particulate dispersions or

the solid particles with a size in the range in between 10 to1000nm. The drugs are dissolved, entrapped, encapsulated or attached to the nanoparticle matrix. The nanoparticles, nanospheres or nanocapsules can be obtained depending upon the method of preparation. The nanocapsules are the systems in which the drug is confined to the cavity surrounded by the unique polymer membrane, while the nanospheres are matrix systems in which the drug is uniformly and physically dispersed. A polymeric nanoparticle which is biodegradable, those particularly coated with hydrophilic polymer such as poly (ethylene glycol) [PEG] also known as the long circulating particles that have been used as potential drug delivery devices in recent years, because of their ability to circulate for the prolonged period time to target the particular organ, as carriers of the DNA in the gene therapy and their ability to deliver proteins, genes and peptides. To control particle size, surface properties and release of the pharmacologically active agents in order to achieve the site-specific action of a drug at the therapeutically optimal rate and dose regimen is a major goal in designing the nanoparticles as the delivery system. Although the liposomes have been used as the potential carriers with unique advantages which includes protecting the drugs from the degradation, reduction toxicity or side effects and targeting to site of action, their applications are limited due to various inherent problems such as rapid leakage of water soluble drug in the presence of blood components and poor storage stability and the low encapsulation efficiency. The polymeric nanoparticles offer some specific advantages over the liposomes on the other hand. They help to increase the stability of drugs/proteins and possess useful controlled release properties [1-9].

Need for development of Nanoparticles

The major goal in designing the Nanoparticles as a delivery system are to control particle size, surface properties, and release of pharmacologically active agents so a to achieve the site specific action of the drug at the rationale rate and the nanoparticles that are dose polymeric offers some of the specific advantages over liposomes. They also help to increase the stability of the drugs or proteins and possess useful controlled release properties [8,9].

Advantages of Nanoparticles

By using the nanoparticles as the drug delivery system include the following advantages;

a) The surface characteristics and the particle size of the nanoparticles can be manipulated easily to achieve the both active and passive targeting of drug after the parenteral administration.

b) They sustain and control the release of the drug during the transportation and at the site of the localization by altering organ distribution of the drug and subsequent clearance of the drug so as to achieve the increase in the therapeutic efficacy of the drug and the reduction in the side effects.

c) By attaching targeting ligands to surface of particles or by the use of magnetic guidance, the site-specific targeting can be achieved.

d) The controlled release and the degradation characteristics of the particle can be modulated readily by the matrix constituents choice. The drug loading is relatively high and the drugs can be incorporated into the systems without any chemical reaction, which is an important factor for preserving the activity of drug.

e) This system can be used for the various routes of administration which includes the nasal, oral, intra-ocular and parenteral etc[4].

Disadvantages of Nanoparticles

a) The small size and the large surface area can lead to the particle aggregation, which makes the physical handling of the nanoparticles difficult in the liquid and the dry forms.

b) The particles which are small in size and large surface area readily result in the limited loading of drug and burst release. This practical problem has to be overcome before nanoparticles can be clinically used or been made available commercially[4,5].

Preparation of Nanoparticles [10,11]

The nanoparticles can be prepared from the variety of materials such as polysaccharides, proteins and the synthetic polymers. The matrix materials selection is dependent on many factors which include;

[1]The size of nanoparticles required

[2]The inherent properties of the drug, for e.g., the aqueous solubility and stability

[3] The surface characteristics such as the charge and permeability

[4] The degree of biocompatibility, biodegradability and toxicity

[5]The desired drug release profile

[6] The final product Antigenicity.

By 3 methods the nanoparticles have been prepared most frequently;

[A] The dispersion of preformed polymers [B] The polymerization of the monomers and [C] ionic gelation or coacervation of the hydrophilic polymers. The other methods such as the supercritical fluid technology and PRINT [particle replication in non-wetting templates] have also been described in literature for the production of the nano particles. The latter was claimed to have absolute control of the particle shape, size and the composition which would set an example for the future production of mass in the nano particles in industry.

The Dispersion of preformed polymers: This is a common technique used to prepare the biodegradable nano particles from the poly [lactic acid] [PLA], poly [D, L-glycolide] PLG, poly

[D, L-lactide-co-glycolide] [PLGA] and poly [cyanoacrylate] [PCA]. In various ways this technique can be used as described below[12-14].

The Solvent evaporation method: The polymer is dissolved in an organic solvent such as chloroform, dichloromethane or ethyl acetate which is also used as a solvent for dissolving the hydrophobic drug. A mixture of polymer and drug solution is then emulsified in an aqueous solution which contains the surfactant or the emulsifying agent to form oil in water [o/w] emulsion. After the stable emulsion is formed, the organic solvent is evaporated either by continuous stirring or by reducing the pressure. The particle size was found to be influenced by the concentrations and type of stabilizer, homogenizer speed and the concentration of polymer. In order to produce smaller particle size, often the ultrasonication or the high-speed homogenization may be employed [15-16].

The Spontaneous emulsification or solvent diffusion method

It is a modified version of solvent evaporation method. The water miscible solvent along with a small amount of the water immiscible organic solvent is used as an oil phase in this method. An interfacial turbulence is created between the two phases due to the spontaneous diffusion of solvents which leads to the formation of small particles. A decrease in the size of particle can be achieved as the concentration of water miscible solvent increases. The both solvent evaporation and solvent diffusion methods can be used for the hydrophilic or hydrophobic drugs. The multiple w/o/w emulsion needs to be formed with the drug dissolved in the internal aqueous phase, in case of the hydrophilic drug[17].

The Polymerization method

The monomers are polymerized in an aqueous solution to form nano particles in this method. The drug is incorporated either by being dissolved in to the polymerization medium or by the adsorption onto the nano particles after completion of the polymerization. The nano particle suspension is then purified to remove the various surfactants and stabilizers employed for the polymerization by the ultra-centrifugation and re-suspending the particles in the surfactant-free medium which is isotonic. This technique has been reported for making polybutylcyanoacrylate or poly [alkyl cyanoacrylate] nanoparticles. The nanocapsule formation and their particle size depends on the concentration of the stabilizers and surfactants used [18-20].

Coacervation or ionic gelation method

Much research has been focused on the preparation of nanoparticles using the biodegradable hydrophilic polymers such as gelatin, chitosan and sodium alginate. Calvo and co-workers have developed a method for preparing the hydrophilic chitosan nano particles by ionic gelation. The

method involves a mixture of two aqueous phases in which one is the polymer chitosan[a di-block co-polymer ethylene oxide] or propylene oxide [PEO-PPO] and the other is a poly-anion sodium tripoly phosphate. In this method, the positively charged amino group of chitosan is interacts with negative charged tripoly phosphate to form coacervates which have size in the range of the nanometer. The coacervates are formed from electrostatic interaction between two aqueous phases, whereas, the ionic gelation involves the material undergoing transition at room temperature from the liquid to gel due to ionic interaction conditions [21-22].

Production of nanoparticles using supercritical fluid technology

The conventional methods such as solvent extraction-evaporation, solvent diffusion and the organic phase separation methods require the use of organic solvents which are hazardous to the environment as well as to physiological systems. Therefore, the supercritical fluid technology has been investigated as an alternative to prepare biodegradable micro and nanoparticles because supercritical fluids are environmentally safe. A supercritical fluid can be generally defined as a solvent at a temperature above its critical temperature, at which the fluid remains a single phase regardless of pressure. The supercritical CO2 [SC CO2] is the most widely used supercritical fluid because of its mild critical conditions [*T*c = 31.1 °C, *P*c = 73.8 bars], non-toxicity, non-flammability and low price. The most common processing techniques involving supercritical fluids are supercritical anti-solvent [SAS] and rapid expansion of critical solution [RESS]. The process of SAS employs a liquid solvent eg. methanol, which is completely miscible with the supercritical fluid [SC CO2] to dissolve the solute to be micronized, at the process conditions because of the solute is insoluble in the supercritical fluid the extract of the liquid solvent by supercritical fluid leads to the instantaneous precipitation of the solute resulting in the formation of nano particles. Thote and Gupta (2005) reported the use of a modified supercritical anti-solvent method for formation of a hydrophilic drug dexamethasone phosphate for microencapsulation purpose. Rapid expansion of critical solution differs from the SAS process in that its solute is dissolved in a supercritical fluid [such as supercritical methanol] and then the solution is rapidly expanded through a small nozzle into a region lower pressure. Thus the solvent power of supercritical fluids dramatically decreases and the solute gets precipitates. The precipitate is basically solvent free so this technique is clean. RESS and its modified process have been used for the product of polymeric nano particles. The supercritical fluid technology technique is environmentally friendly and suitable for the mass production and it requires specially designed equipment and is more expensive [23,10,24,25].

Evaluation of Nanoparticles

Nuclear Magnetic Resonance

The nuclear magnetic resonance (NMR) can be used to determine the size and the qualitative nature of nano particles. The selectivity afforded by chemical shift complements the sensitivity to molecular mobility to provide the information on the physico-chemical status of components within the nano particle. For eg, the mobility of Miglyol 812 within solid lipid nano particles confirmed the liquid-like nature of the interior so it was more limited than the same oil in an o/w emulsion. Pulsed field gradient methods are allow diffusivity of the entire particle to be quantified and compared to produce 2-D, diffusion ordered plots in which colloidal behavior and chemical speciation are leveraged . In one case, the diffusion coefficient is used as a surrogate for the size of the nano particles with results that compare well to separation and DLS so only nuclear magnetic resonance (NMR) could simultaneously detect the micellar precursors.

Electron Microscopy

The scanning electron microscopy [SEM] and transmission electron microscopy [TEM] are provide a direct way to observe nanoparticles with the former method being better for the morphological examination. The transmission electron microscopy has a smaller size limit of the detection and is a good validation for the other methods and it affords structural information via electron diffraction but staining is usually required. One must be cognizant of statistically small sample size and the effect that vacuum can have on the particles. Freeze-fracture approaches very detailed images data in which a cast is made of the original sample. The extensive sample preparation is results in the sample corruption so the lower vacuum (environmental- or E-SEM) instrumentation reduces this manipulation at the loss of some resolution.

Optical Microscope

More of the nano particles are below the resolution limit (ca. 0.5 μm) of the direct optical imaging so microscopy is still useful to get an estimate of the size and the crystalline nature of the starting materials and it might be desirable in the instance of the combination or homogenization process or other larger particles. The dark field techniques, in which the particles are observed indirectly as bright spots on a dark background because of their scattering under horizontal illumination is valuable in assessing the presence and the numbers of nano particles.

Atomic Force Microscopy (AFM)

In this a probe tip with atomic scale sharpness is restored across the sample to produce the topological map based on the forces which play between the tip and the surface. The probe can be dragged across the sample i.e. contact mode or allowed to hover just above i.e. noncontact mode

with the exact nature of the particular force employed serving to distinguish between the sub techniques. The ultra high resolution is obtained with this approach, which along with the ability to map the sample according to properties in addition to the size for e.g. the colloidal attraction or the resistance to deformation makes atomic force microscopy a valuable tool. So the size and the shape have been the most common applications. The need to raster the probe is renders the method very time-consuming and the size of the sample observed is small. The nanoparticles are typically presented as an evaporated suspension on the smooth silicon or mica surface which not without the possibility of deformation. The application of various forms of atomic force microscopy to the nanoparticle characterization represents an area of the active research.

Other Forms of Microscopy

The size resolution of the transmission electron microscopy [TEM] can be leveraged for morphological studies by placing the sample across a well-defined electron beam (STEM) and if X-rays are substituted for electrons (STXM) the high resolution and some chemical information can be extracted. While these methods have not been applied to the pharmaceutically relevant nanoparticles and the studies of related samples suggest that they may be worth investigating for this purpose. The optical analog of the atomic force microscopy is near-field microscopy which affords nanoscale resolution and use of light allows for simultaneous chemical imaging by Raman spectroscopy. The Confocal microscopy has proved a valuable and being used frequently in the study of the nanoparticle uptake in the biological tissues such as eye, brain and skin.

Differential Scanning Calorimetry (DSC)

Another method that is a little different from its implementation with bulk materials, differential scanning calorimetry can be used to determine the nature and speciation of the crystallinity within the nanoparticles through the measurement of glass and the melting point temperatures and their associated enthalpies. A complement to X-ray diffraction, this method is regularly used to determine the extent to which the multiple phases exist in the interior or to which the various constituents including the drug interaction.

X-Ray Diffraction (Power X-ray Diffraction, Small-Angle Neutron Scattering, Small-Angle X-ray Scattering, Electron)

The geometric scattering of the radiation from crystal planes within the solid allow the presence or absence of the former to be determined thus permitting the degree of crystallinity to be assessed. For e.g. the crystallization of interior lipids could be tracked. The application of the method is little different from that for the bulk powders, though broadening of the diffraction pattern's peaks is observed for the particles less than 100nm in diameter. For the nanoparticles, order on the smaller

scale can be investigated by reducing the wavelength and the angle of incident radiation. Using electron or neutron beams allows reduction of the former parameter due to the shorter DeBroglie wavelengths of such particles.

Electrophoresis

The body's response to the introduction of nanoparticles into circulation is such that within a short period of time their surface is festooned with lipoproteins and related species. This process will determine the clearance and bio distribution of the colloid, so evaluating the exact nature of the surface coverage is required to achieve a useful understanding. The small size of nanoparticles allows their electrophoretic behavior to be observed using bioanalytical tools such as isoelectric focusing and 2-D polyacrylamide gel electrophoresis. As with any *ex vivo* approach, the investigator needs to take into account the effect that sample preparation may have on the experimental observations. Similar information has been derived by electrophoresis of serum proteins desorbed from incubated nanoparticles.

Hydrodynamic Chromatography

In a sufficiently narrow channel of parabolic flow, particles of different size will on average experience different flow lines because of their differential ability to approach the channel wall. The particles will separate based on that property, with those that are smaller eluting later just as they would in flow-FFF. Indeed, hydrodynamic chromatography (HDC) can be thought of as flow-FFF with the narrowness of the channel substituting for the cross flow. Thin capillaries serve as the channels, which can also be created by the interstitial spaces within a packed column. The former approach is also known as capillary hydrodynamic fractionation and has been further miniaturized. The results are highly sensitive to the surfactants employed in the analysis. Size exclusion chromatography is little used for analytical size separation of colloids, though there are examples of its application.

Hydrophobic Interaction Chromatography

In this method the analyte is first adsorbed onto a chromatographic stationary phase using a high concentration of an antichaotropic salt. Elution occurs using a gradient in which the salt concentration is decreased, so that those materials eluting first are the least hydrophobic because the salt concentration did not need to be decreased much before the analyte desorbed. Originally developed for proteins, hydrophobic interaction chromatography has been pressed into service as a means of characterizing the hydrophobicity of nanoparticle surfaces, a property influenced by the choice of surfactant and/or polymer and also a key parameter in determining their *in vivo* fate.

Field-Flow Fractionation

Particles are driven toward either the top or the bottom of a thin channel within which eluent is continuously flowing in a direction perpendicular to the driving force. Liquid flow of the eluent is parabolic so that particles spending more time toward the center of the channel where the flow lines are faster emerge first. The nature of the perpendicular force defines the type of field-flow fractionation (FFF) and thus the particle property on which separation occurs: sedimentation (buoyancy, size), flow (hydrodynamic size), electrostatic (charge), or thermal (diffusion). FFF necessitates more complicated methodology and the data interpretation is less straightforward than chromatography, but it can provide a wider range of information and can also be used as a preparative method for nanoparticles.

Dissolution Concerns

In some cases nanoparticles are formed to increase the dissolution rate because of the high surface area they afford. This introduces the possibility that particles are dissolving during the analysis. This problem is general in nature and should be carefully considered in any measurement especially when dilution, sometimes significant in extent, is a requisite of the analysis. While an obvious concern when size is to be determined, such dissolution can lead to skewed results in any measurement because the analyte content is not stable. Extrapolating results to initial conditions or using media in which the particles are insoluble are ways of dealing with this problem.

***In Vitro* Release**

The solubilization of active components from the individual nanoparticles is of obvious interest. This process can involve release of compound from a polymer or lipid matrix, or dissolution of the entire particle. In either case, separation of the ultra-small particles from the release media is critical so that the nanoparticles are not mistaken for solubilized drug. In the latter case, the high rate of dissolution is frequently an additional complicating factor. In typical experiments, it is the appearance of solubilized material that signifies that dissolution is taking place. Using conventional filtration to remove undissolved material for in situ experiments presents serious challenges. The nanoparticles can easily pass through most filter membranes typically used for this purpose, if not at the beginning of the experiment, then at the end, when the particle size may have dropped sufficiently. Small filter pore sizes as low as 0.02 μm are commercially available, but can be plugged easily. The separation issue can be avoided by using a method, such as polarography, where only solubilized material is detectable. In this way, the need for separation is obviated. Use of dialysis membranes and filtration is an option because they are less prone to blockage and the pore size is very small. The nanoparticles can be placed within a dialysis sac and samples taken

from the large receiving medium. Alternatively, the reverse approach can be used with the nanoparticles dispersed throughout the larger volume and the receiving media located within the sac. Diffusion cells have also been used. Separation of particles can also be effected by centrifugation, or avoided implicitly by using two immiscible phases with one containing the nanoparticles and the other serving as the receiving medium. When nanoparticles are used to increase the dissolution rate, a significant drawback to these approaches is the time it takes for the dissolved material to diffuse across a membrane or boundary. While this transfer function can be determined experimentally, the associated time constant can be on the scale of tens of minutes, if not hours. Such a long lag precludes the deconvolution of the drug release rate from the experimental data when the dissolution occurs within a few minutes or less. Rather than detecting drug as it appears in a solubilized form, dissolution information can also be derived by observing the disappearance of the undissolved form, i.e., loss of the nanoparticles themselves. Spectroscopic methods such as light scattering or turbidity are good means of making such observations, and are useful because the corresponding measurements are essentially instantaneous in time, thus eliminating the deconvolution problem. Indeed, the limitation on measurable dissolution rate then arises from issues such as mixing times. Deliberately using nonsink conditions is a way of slowing down the process to avoid these problems.

Turbidimetry

For nonabsorbing particles, turbidity is the complement to light scattering because it represents the amount of incident radiation not reaching a detector, that is, light lost to scattering. Hence the turbidity spectrum is also described by Mie theory and thus can be used to determine particle size as long as the data are normalized for concentration. This approach requires tiny amounts of sample and can be easily executed using a spectrophotometer. However, it suffers the ills common to all ensemble methods and the lack of commercial implementation requires the investigator to carry out the appropriate calculations on their own.

Filtration

A simple, yet effective, approach of determining particle size is filtration, in which the concentration of a suspension is determined before and after passage through filter membranes of various sizes. Subject to the caveats of nonspecific adsorption, aggregation, and particle shape effects, the results give a semi quantitative assessment of the particle size distribution that is not based on instrumentation and algorithms. The practitioner should make sure that if more than one pore size is used, all filters are made of the same material and the same protocol, i.e., the amount of material passed through the filter, is maintained throughout.

Single-Particle Optical Sensing (SPOS)

A particle counting method, SPOS, which is also known as optical particle counting, involves recording the obscuration or scattering of a beam of light that results from the passage of individual particles through a sensor. Signal magnitude is translated to the size of the particle via use of a previously determined calibration curve using standards approximating the sample in terms of shape and optical properties. The direct result is a number-based size distribution. SPOS cannot distinguish between a single primary particle and an aggregate (few methods can), and is subject to error at a number of concentrations above which there is a significant chance of multiple particles being present simultaneously in the light beam. Particles of diameter less than 1 μm are largely undetected, thus making SPOS very useful in the determination of the few large particles in a population that may represent a safety concern, indicate a problem in production, or be harbingers of instability. Count rates of 8000 particles/sec or more are typical, thus thousands to millions of particles are observed in an experiment. Hence, detecting the few large particles present in a distribution is more likely than is the case with microscopy. Drawbacks include the possible dissolution of analyte during analysis, the large dilution required, and the need for low backgrounds. Detecting an interruption in the flow of electrical current through a solution is an analogous method termed electrozone or Coulter counting. This technique sees little recent use because of its need for colloid destabilizing electrolytes and the more complicated instrumentation required, though a novel approach that also determines electrophoretic mobility has been recently reported. A great benefit afforded by SPOS is the ability to quantify the large particle population. The total volume detected during the experiment can be calculated from the number distribution by assuming a shape, e.g., spherical, and integrating under the resulting volume distribution curve. When compared to the concentration of the suspension, what results is a ratio that describes the fraction of material present as detectable, i.e., large, particles. Hence, a suspension in which all of the particles are larger than the size detection limit of the sensor would yield a recovery of 100%. A recovery of near 0% suggests that, subject to the statistical assurance associated with the number of particles counted, the mass of the distribution resides primarily as particles of less than that size. By comparison, ensemble methods do not measure the absolute amount of material present; only the relative contribution of sizes is determined. Hence, integrating under the corresponding size distribution always sums to 100% regardless of size.

Isopycnic Centrifugation

Another bioanalytical method applied to nanoparticles is centrifugation of analyte using a sucrose gradient as the suspending media. Under the influence of Stokes' laws, sedimenting particles will

settle until they reach a point where their density matches that of the gradient. This self-focusing separation allows nanoparticle density to be determined, which along with particle size and bulk substituent concentration can in turn be used to calculate a number concentration. Conventional analytical centrifugation has been employed as well. The results can also be used to extract size, rather than buoyancy, information directly from sedimentation FFF.

Zeta Potential

Zeta potential is used as a surrogate for surface change, and is often measured by observing the oscillations in signal that result from light scattered by particles located in an electric field, though there are other approaches. There are a number of instrumental configurations by which this is achieved, mostly using a Doppler shift, and the user should familiarize themselves with the particular approach implemented in their equipment. Instrumentation concerns aside, the need for dilution begs the question of what are appropriate diluents because its choice can profoundly influence the surface chemistry and thus the results. One approach is to use a particle-free supernatant to dilute the sample. This will not account for concentration effects, however, and obtaining such a diluent is nontrivial as the particle size drops. Electroacoustic methods should in principal eliminate or reduce the need for dilution and its inevitable consequences. Nonpolar media and the combination of low mobility with high ionic strength are also problematic; however, phase analysis light scattering, a newer method in which a phase delay shift rather than a frequency shift is observed, addresses these issues [26].

Classification of Nanoparticles

Liposomes

The cancer chemotherapeutic drugs and other toxic drugs like hamycin and amphotericin when used as the liposomal drugs they produce much better safety and efficacy as compared to the conventional preparations. The liposomes can be loaded with drugs either in the lipid membrane or in the aqueous compartment. Lipid soluble drugs are incorporated in the liposomal membrane. The lipid soluble drugs are incorporated in the liposomal membrane and water soluble drugs are loaded in aqueous compartment [Gregoriadis G et al 1972] The major drawback of liposome is its degradation takes place rapidly and clearance by the liver macrophages [McCormack B et al 1984] hence reducing the duration of action of the drug it carries. This can be reduced to the certain extent with a advent of the stealth liposomes where the liposome is coated with the materials like polyoxyethylene [Illum L et al 1984] which prevents the opsonisation of the liposome and their uptake by the macrophages. [Senior J et al 1999]. The other ways of prolonging the time of circulation of liposomes are the incorporation of the substances like cholesterol [Kirby C et al

2003] and the high transition temperature phospholipids distearoyl phosphatidycholine [Forssen EA et al 2002] [27-32].

Fullerene

The fullerene [Carbon allotrope] it is also known as the bucky balls were discovered in the 1985. [Thakral S et al2006]. A buckminster fullerene is the most common form of fullerene which measures about 7 A in the diameter with 60 carbon atoms arranged in the shape known as the trauncated icosahedrons [Kratschmer W et al 1990]. It resembles the soccer ball with 20 hexagons and 12 pentagons and is highly symmetrical [Taylor R et al 1990] [33-35]

Dendrimers

The dendrimers are nanomolecules with the regular branching structures. The size of the dendrimer is determined by the number of branching that can be controlled. The branches arise from the core in shape of the spherical structure by the means of polymerization. This would result in the formation of the cavities within the dendrimer molecule which could be used for the drug transport. With other molecules the ends of the dendrimer molecule can be attached for the transport. Various functional applications are given by these molecules to the dendrimers. The tectodendrimers are the complexes of the dendrimers with each of the dendrimer module of the complex performing the different functions such as diagnosis of disease state, targeting, delivery of the drug and imaging. These extended Nano device have the potential applications in the cancer chemotherapy as the mode of the targeted drug therapy. The dendrimers can be used for the gene therapy where it can replace the conventional viral vectors. It enters the cells by the endocytosis and the DNA gets transported into the nucleus for the transcription of the applied gene. The absence of stimulation of immune reaction dendrimer based therapy is its advantage. The dendrimers have been tested in animal models and in mammalian cell types. The Huang *et al* have demonstrated a potential use of the transferring conjugated PEG modified polyamidoamine [PAMAM] dendrimers for the targeted gene delivery to the brain. The Pan *et al* have demonstrated the efficacy of the magnetic nanoparticle modified PAMAM. The dendrimers in transfer of the antisense *survivin* oligonucleotides in tumour cell lines. This method provides an effective alternative to the viral vectors of gene transfer for the treatment of the various tumours. The Nanojuice TM Transfection Kit produced by the EMD Chemicals Inc. and Superfect® The Transfection Reagent of Qiagen are the dendrimer based DNA transfection kits used for delivering the DNA into the cell. These are claimed to have the improved transfection efficacy and the low toxicity to the cells. The dendrimer based drugs are being tried for the antiretroviral therapy and it is in the stages of the clinical trials after getting clearance from the US-FDA on July 2003. This

molecule was found to be successfully prevent simian HIV infection19. The PAMAM dendrimers can also be used for the treatment of the cancer by conjugating with anti-cancer drugs like methotrexate, cisplatin or Adriamycin. The calabretta *et al* have demonstrated the antibacterial property of the amino-terminated polyamidoamine [PAMAM] dendrimers and their partially PEG [polyethylene glycol] coated derivatives. Against both Gram positive *Staphylococcus aureus and* Gram negative *Pseudomonas* and the antibacterial property was observed. Hence, the PEG coating of the dendrimer which reduces the cytotoxicity of the unmodified PAMAM dendrimers, it reduces the efficacy against the Gram positive bacteria without any change in the efficacy against the Gram negative bacteria like the pseudomonas. The dendrimers are also used as the contrast agents for the imaging. The 1,4-diaminobutane [DAB] core dendrimer and the PAMAM dendrimers are studied well commercially available dendrimers for the imaging studies. The main route of clearance is the renal excretion is and is dependent on the size of the particle and more than 60 per cent of injected PAMAM or DAB dendrimer is cleared from the circulation within the 15 min. The smaller sized dendrimers undergo the rapid renal clearance, whereas the dendrimers with charged surface or the hydrophobic surfaces are rapidly cleared by the liver. Those dendrimers with the hydrophilic surface escapes the renal clearance and have the greater circulation time. The cationic dendrimers have the greater potential to cause the cytotoxicity compared to the PAMAM dendrimers or the anionic dendrimer. It is proposed to cause cell membrane instability and the lysis of cell. The toxicity of the dendrimer is dependent on the size of the particle and increase with the size. Hence, it can be reduced by the means of the surface modification of a dendrimer with incorporation of the polyethylene glycol or fatty acids[36-47].

Carbon nanotubes

Carbon nanotubes discovered in 1991 are tubular structures like a sheet of graphite rolled into a cylinder capped at one or both ends by a buckyball. Nanotubes can be single walled carbon nanotube (SWCNT) or multi walled carbon nanotube (MWCNT) in concentric fashion. Single walled nanotube has an internal diameter of 1-2 nm and multi walled nanotube has a diameter of 2-25 nm with 0.36 nm distance between layers of MWCNT. These vary in their length ranging from 1 μm to a few micrometers. These are characterized by greater strength and stability hence can be used as stable drug carriers. Cell specificity can be achieved by conjugating antibodies to carbon nanotubes with fluorescent or radiolabelling. Entry of nanotubes into the cell may be mediated by endocytosis or by insertion through the cell membrane. Carbon nanotubes can be made more soluble by incorporation of carboxylic or ammonium groups to their structure and can be used for the transport of peptides, nucleic acids and other drug molecules. Indium-111 radionuclide labelled

carbon nanotubes are being investigated for killing cancer cells selectively. Amphotericin B nanotubes has shown increased drug delivery to the interior of cells compared to amphotericin B administration without nanotubes. The efficacy of amphotericin B nanotubes was greater as an antifungal agent compared to amphotericin B alone and it was effective on strains of fungi which are usually resistant to amphotericin B alone. Further, there was reduced toxicity to mammalian cells with amphotericin B nanotubes. The ability of nanotubes to transport DNA across cell membrane is used in studies involving gene therapy. DNA can be attached to the tips of nanotubes or can be incorporated within the tubes. Prato *et al* showed greater expression of the β galactosidase marker gene through nanotubes compared to transfer of naked DNA. This confers the advantage of non immunogenicity in contrast to viral vectors used for gene transfer. Gene silencing studies with small interfering RNA (siRNA) have been done as a modality of cancer therapy where tumour cells will be selectively modulated. Functionalized single walled carbon nanotubes can be used with siRNA to silence targeted gene expression. It was observed that carbon nanotubes, except acetylated ones, when bonded with a peptide produce a higher immunological response compared to free peptides. This property can be used in vaccine production to enhance the efficacy of vaccines. Further, it was also found that compounds bound to nanotubes increase the efficacy of diagnostic methods like ELISA. These can also be used for designing of biosensors owing to property of functionalization and high length to diameter aspect ratio which provides a high surface to volume ratio. Water insoluble forms of nanotubes like pristine carbon nanotubes have high *in vitro* toxicity compared to modified water dispersible forms of nanotubes. It was also seen that the toxic potential decreases with functionalization. Further, functionalization also affects the elimination of the nanotube. SWCNTs without conjugation to monoclonal antibody have a high renal uptake and modest liver uptake as compared to SWCNTs with conjugation to monoclonal antibody having higher liver uptake and lower renal uptake [48-54].

Nanoshells

West and Hales[west JL et al2000] developed the nanoshells at the Rice university as the new modality of the targeted therapy. The nanoshells consists of the nanoparticles with a core of silica and a coating of thin metallic shell. To desired tissue these can be targeted by using immunological method which is being evaluated for therapy of cancer. [Hirsch et al] Hirsch et al used the nanoshells which are tuned to absorb infrared rays [IR] when exposed from the source outside the body to demonstrate the nanoshells thermo ablative property. A nanoshell when exposed to NIR region of the electromagnetic spectrum gets heated and causes destruction of the tissue. This has been studied in both in-vivo and in-vitro experiments with HER 2 expressing SK-BR-3 human

breast carcinoma cells. The control cells do not loose their viability even after the treatment with nanoshells with non specific anti IgG or PEG and NIR ablation [Lowery AR et al 2006] [55-57]

Solid Lipid Nanoparticles [SLNs]

SLNs hold significant promise in the treatment of cancer. They are particles of the submicron size (50-1000nm) made from lipids that remain in the solid state at body temperature as well as room temperature. Different anti-cancer agents like daunorubicin, doxorubicin, paclitaxel etc have been encapsulated by using this nanotechnological approach. The several obstacles frequently encountered with the anti-cancer agents such as the high incidence of drug resistant tumor cells can be partially overcome by delivering them by using the solid lipid nanoparticles[Wong HL et al 2007][58]

Nanowires

Nanowires are glowing silica wires in the nanoscale wrapped around the single strand of human hairs. They are about 5 times smaller than the virus and several times stronger than spider silk. The nanowire based arrays have significant impact for the early diagnosis of cancer and the treatment of cancer. The nano-wire based delivery enables the simultaneous detection of the multiple analytes such as the cancer biomarkers in the single chip, also the fundamental kinetic studies for the biomolecular reactions.[Zheng G et al 2006]The protein coated nanowires have potential applications in the cancer imaging like the Ovarian malignancies, prostate cancer, breast cancer[59].

Gold Nanoparticles

The colloidal gold nanoparticles are another attractive platform for the diagnosis of cancer therapy. [Paciotti GF et al 2004]. The gold nanoparticles have been used as the contrast agent in the in-vitro based on their ability to scatter the visible light. The Sokolov et al successfully used gold nanoparticles conjugated to EGFR antibodies to label the cervical biopsies for identification of precancerous lesions [Sokolov K et al 2003] The Photoacoustic tomography has been used to image gold nanoparticles to the depth of 6 cm in experiments by using gelatin phantoms[Copland JA et al 2004]. In the subcutaneous model of colon cancer, it was demonstrated that the systemically delivered gold nanoparticles [size approx 33nm] conjugated to the tumor necrosis factor [TNF] accumulated in the tumors [Paciotti GF et al 2004] [60-62]

Quantum dots

The Quantum dots are the nanocrystals measuring around 2-10 nm which can be made to fluorescence when stimulated by the light. Its structure consists of an inorganic core, the size of which determines the colour emitted an inorganic shell and an aqueous organic coating to which the biomolecules are conjugated. To target various biomarkers the biomolecule conjugation of the

quantum dots can be modulated. The Quantum dots can be used for the biomedical purposes as the diagnostic as well as the therapeutic tool. This can be tagged with the biomolecules and used as the highly sensitive probes. The study done on the prostate cancer developed in nude mice has shown accumulation of quantum dots probe by the enhanced permeability and the retention as well as by the antibody directed targeting. A quantum dot conjugated with polyethylene glycol [PEG] and antibody to PSMA [prostate specific membrane antigen] were accumulated and retained in the grafted tumour tissue in the mouse. The Quantum dots can also be used for the imaging of the sentinel node in the cancer patients for the tumour staging and planning of the therapy. This method can be adopted for the various malignancies like, breast, gastrointestinal, melanoma, lung tumours. The Quantum dot probes provides the real time imaging of the sentinel node with NIR [Near Infra Red]fluorescence system. The NIR region of the electromagnetic spectrum produces the reduced background noise and deeper penetration of the rays, of up to 2 to 5 cm into the biological sample. The traditional fluorescence dyes yield low signal intensity when used in the NIR region. This limitation is overcomed, by using the NIR fluorescence system with the quantum dot probes. The fluorescence produced by the quantum dots is much brighter than those produced by the conventional dyes when used with the NIR fluorescence system. However, the application of quantum dots in the clinical setting has the limitations owing to its elimination factors. The Functionalization of the quantum dots which protects from the toxic core leads to increase in size of the Nanoparticle and is greater than the pore size of endothelium and renal capillaries, thus reducing its elimination and resulting in the toxicity. Also the *in vivo* studies are lacking on the metabolism and excretion of the quantum dots [63-64].

Paramagnetic Nanoparticles

The paramagnetic nanoparticles are being tried for both the diagnostic and therapeutic purposes. Diagnostically, the paramagnetic iron oxide nanoparticles are used as the contrast agents in magnetic resonance imaging. These have the greater magnetic susceptibility than the conventional contrast agents. The targeting of these nanoparticles enables the identification of the specific organs and tissues. The use of iron oxide in the MRI imaging faces the limitations like internalization and specificity by macrophages. The paramagnetic nanoparticles conjugated with antibodies to HER-2/*neu* which are expressed on the breast cancer cells have been used with the MRI to detect breast cancer cells *in vitro*. The study done by the Leuschner *et al* has demonstrated the *in vivo* detection of the breast cancer cells using the paramagnetic nanoparticles conjugated with the luteinizing hormone releasing the hormone as breast cancer cells express LHRH receptors. Thus, the use of antibodies to direct a nanoparticle to a target site helped to overcome

the problems with the specificity of action. The internalization of the nanoparticles by macrophages can be reduced by the treatment with drugs like the lovastatin which reduce the macrophage receptor expression for the nanoparticle by reducing the recycling of receptors. The injection of decoys of nanoparticle can be used to eliminate the plasma opsonins and reduce the uptake of the nanoparticles. Also the change of surface charge of the nanoparticle to neutral by the covalent coupling to the chemicals leads to an increase in the circulation time. The MIONs [monocrystalline iron oxide Nanoparticles] have been studied by the Knauth *et al* in magnetic resonance imaging of brain. The MIONs helps in overcoming the disadvantage of the surgically induced contrast enhancement with the traditional contrast agents resulting in misinterpretation during the intra-operative MR imaging of the brain. The surgically induced contrast enhancement occurs in the brain due to the leak of contrast material from the cut end and oozing blood vessels in the brain when MR imaging is done post-operatively. This is avoided when MIONs are used pre-operatively. These are taken up rapidly by the tumour cells producing long lasting contrast enhancement of the tumour and the remaining nanoparticles are removed from the circulation by the reticuloendothelial system. The magnetic microparticle probes with nanoparticle probes have been used for the identification of proteins like the prostate specific antigen. Here the magnetic microparticles coated with the antibodies together with the nanoprobes with similar coating and the unique hybridized DNA barcode is used. A microparticle coated with antibody directed against the prostate specific antigen combines with it to form the complex and can be separated by using the magnetic separation. The presence of these separated complexes is determined by the dehybridization of the complexed DNA barcode sequence and polymerase chain reaction for the oligonucleotides. This allows prostate specific antigen detection at 30 attomolar concentration. This sensitivity is much greater than the conventional assays for the prostate specific antigen. The magnetic nanoprobes are used for the cancer therapy. The iron nanoparticles coated with the monoclonal antibodies directed to the tumour cells can be made to generate the high levels of heat after these accumulate in their targeted site by means of the alternating magnetic field applied externally. The cancer cells are killed by this heat selectively. This method is designed by Triton Biosystems, is about to enter the clinical trials for solid tumours in 2009[65-68].

Application of Nanoparticulate Delivery System

Tumor targeting using nanoparticulate delivery systems

The rationale of using the nanoparticles for tumor targeting is based on:

A] The nanoparticles will be able to deliver the concentrate dose of the drug in the vicinity of the tumor targets via the enhanced permeability and retention effect or active targeting by the ligands on the surface of the nanoparticles

b] The nanoparticles will reduce the drug exposure of health tissues by limiting the drug distribution to the target organ. The polymeric composition of the nanoparticles such as the type, hydrophobicity and biodegradation profile of the polymer along with the associated drug's molecular weight its localization in the nanospheres and mode of the incorporation technique, adsorption or incorporation, have the great influence on the drug distribution pattern *in vivo*[6].

Long circulating Nanoparticles

As a drug delivery system to be successful, nanoparticles must be able to target the tumors which are localized outside the mononuclear phagocytic system -rich organs. In past decade; the great deal of work has been devoted to the developing so-called "stealth" particles or the PEGylated nanoparticles, which are invisible to the phagocytes or macrophages. The major breakthrough in the field came when the use of hydrophilic polymers [such as the PEG, poloxamines, poloxamers, and polysaccharides] to efficiently coat the conventional nanoparticle surface produced an opposing effect to the uptake by the MPS. This coating provide the dynamic "cloud" of the hydrophilic and neutral chains at the particle surface which repel the plasma proteins. As the result, those coated nanoparticles become invisible to MPS hence, remained in the circulation for the longer period of time. The hydrophilic polymers can be introduced at the surface in 2 ways, either by adsorption of surfactants or by the use of block or branched copolymers for the production of nanoparticles. The studies shows that nanoparticles containing a coat of PEG not only have the prolonged half-life in the blood compartment but also be able to selectively extravasate in the pathological sites such as the tumors or inflamed regions with the leaky vasculature. As the result, such long-circulating nanoparticles have increased the potential to directly target the tumors located outside MPS-rich regions. A size of the colloidal carriers as well as their surface characteristics are the critical to the biological fate of the nanoparticles. The size less than 100 nm and the hydrophilic surface are essential in achieving the reduction of opsonisation reactions and subsequent clearance by the macrophages. The coating conventional nanoparticles with surfactants or the PEG to obtain the long circulating carrier has now been used as the standard strategy for drug targeting *in vivo*. The extensive efforts have been devoted to achieving "active targeting" of the nanoparticles in order to deliver the drugs to the right targets, based on the molecular recognition processes such as the antigen-antibody interaction or ligand-receptor. While considering that fact that folate receptors are over expressed on the surface of some human

malignant cells and the cell adhesion molecules such as the selectins and integrins are involved in the metastatic events, the nanoparticles bearing specific ligands such as folate may be used to target the ovarian carcinoma while specific peptides or carbohydrates may be used to target the integrins and selectins. The Oyewumi et al demonstrated that the benefit of folate ligand coating was to facilitate the tumor cell internalization and retention of Gd-nanoparticles in the tumor tissue. The targeting with small ligands appears more likely to the succeed since they are easier to manufacture and handle. It could be advantageous when the active targeting ligands are used in the combination with the long circulating nanoparticles to maximize the likelihood of the success in active targeting of nanoparticles [69-73].

Reversion of multidrug resistance in tumour cells

The anticancer drugs, even if they are located in a tumour interstitium it can turn out to be of limited efficacy against the numerous solid tumour types, because the cancer cells are able to develop mechanisms of resistance. This mechanism allow tumours to evade the chemotherapy. The multidrug resistance [MDR] is one of the most serious problems in the chemotherapy. The MDR occurs mainly due to the over expression of the Pgp [plasma membrane p-glycoprotein] which is capable of extruding the various positively charged xenobiotics, including some of the anticancer drugs, out of the cells. In order to restore the tumoral cells sensitivity to anticancer drugs by circumventing Pgp mediated MDR, the several strategies including the use of colloidal carriers have been applied. The association of drugs with colloidal carriers, such as nanoparticles, against drug resistance derives from the fact that the Pgp probably recognizes the drug to be effluxed out of the tumoral cells only when this drug is present in the plasma membrane and not when it is located in the lysosomes or cytoplasm after endocytosis [74-77].

Nanoparticles for oral delivery of peptides and proteins

The significant advances in the biotechnology and the biochemistry have led to the discovery of the large number of bioactive molecules and the vaccines that is based on peptides and proteins. The development of suitable carriers remains the challenge due to the fact that bioavailability of this molecule is limited by the epithelial barriers of the GIT and their susceptibility to the gastrointestinal degradation by the digestive enzymes. The polymeric nanoparticles allow encapsulation of the bioactive molecules and protect them against the enzymatic and hydrolytic degradation. It has been found that the insulin-loaded nanoparticles have preserved the insulin activity and produced the blood glucose reduction in the diabetic rats for up to 14 days following the oral administration. A surface area of the human mucosa extends to two hundred times that of

the skin. The GIT provides the variety of the physiological and the morphological barriers against the protein or the peptide delivery,

e.g.

[1] The proteolytic enzymes in the gut lumen like pepsin, Trypsin and chymotrypsin

[2] The proteolytic enzymes at the brush border membrane (endopeptidases)

[3] The bacterial gut flora

[4] The mucus layer and epithelial cell lining itself.

A histological architecture of the mucosa is designed to efficiently prevent the uptake of the particulate matter from the environment. One of the important strategy to overcome the gastrointestinal barrier is to deliver the drug in the colloidal carrier system such as the nanoparticles, which are capable of enhancing the interaction mechanisms of the drug delivery system and the epithelia cells in the GI tract [78-80].

Targeting of nanoparticles to epithelial cells in the GI tract using ligands

The targeting strategies to improve the interaction of the nanoparticles with the adsorptive enterocytes and M-cells of Peyer's patches in the gastrointestinal tract can be classified into those utilizing specific binding to ligands or the receptors and those based on the nonspecific adsorptive mechanism. The surface of the enterocytes and the M cells display the cell-specific carbohydrates, which may serve as the binding sites to the colloidal drug carriers containing the appropriate ligands. There are certain glycoproteins and lectins that binds selectively to this type of surface structure by the specific receptor-mediated mechanism. The different lectins, such as the bean lectin and the tomato lectin, have been studied to enhance the oral peptide adsorption. The Vitamin B-12 absorption from the gut under the physiological conditions occurs via the receptor mediated endocytosis. A ability to increase the oral bioavailability of the different peptides [For e.g., granulocyte colony stimulating factor, erythropoietin] and the particles by covalent coupling to vitamin B-12 has been studied. For this intrinsic process, the mucoprotein is required which is prepared by the mucus membrane in the stomach and binds specifically to the cobalamin. The mucoprotein completely reaches the ileum where by the specific receptors the resorption is mediated [81-84].

Absorption enhancement using non-specific interactions

Generally, the GI absorption of macromolecules and the particulate materials involves either paracellular route or the endocytotic pathway. The paracellular route of the absorption of nanoparticles utilises less than the 1% of mucosal surface area. By using polymers such as chitosan 68, starch or the poly [acrylates] can increase the paracellular permeability of the macromolecules.

The endocytotic pathway for the absorption of the nanoparticles is either by receptor-mediated endocytosis, that is active targeting or adsorptive endocytosis which do not need any ligand. This process is initiated by the unspecific physical adsorption of the material to the cell surface by the electrostatic forces such as the hydrophobic interactions or hydrogen bonding. The adsorptive endocytosis primarily depends on the size and surface properties of the material. If a surface charge of the nanoparticles is positive or uncharged, it will provide an affinity to the adsorptive enterocytes though hydrophobic whereas if the surface charge is negatively charged and hydrophilic, it shows the greater affinity to the adsorptive enterocytes and M cells. This shows that the combination of the size, surface charge and hydrophilicity play the major role in the affinity. This is demonstrated with the poly [styrene] nanoparticles and when it is carboxylated [85-88].

Nanoparticles for gene delivery

The polynucleotide vaccines work by delivering the genes encoding relevant antigens to the host cells where they are expressed, by producing the antigenic protein within the vicinity of professional antigen presenting cells to initiate immune response. Such vaccines produce both the humoral and the cell mediated immunity because the intracellular production of the protein, as opposed to the extracellular deposition stimulates both the arms of the immune system. The key ingredient of the polynucleotide vaccines, DNA, can be produced cheaply and has much better storage and handling the properties than the ingredients of the majority of the protein-based vaccines. The polynucleotide vaccines are set to supersede many conventional vaccines particularly for the immunotherapy. There are several issues related to the delivery of the polynucleotides which limits their application. This issue includes efficient delivery of the polynucleotide to the target cell population and its localization to the nucleus of these cells and ensuring that the integrity of the polynucleotide is maintained during the delivery to the target site. The nanoparticles loaded with the plasmid DNA could also serve as the efficient sustained release gene delivery system due to their rapid escape from the degradative endo-lysosomal compartment to the cytoplasmic compartment [89-90].

Nanoparticles for drug delivery into the brain

The BBB [blood-brain barrier] is a most important factor limiting the development of the new drugs for the CNS. The BBB is characterized by the relatively impermeable endothelial cells with tight junctions, enzymatic activity and active efflux transport systems. It effectively prevents the passage of the water-soluble molecules from the blood circulation into the CNS and can also reduce the brain concentration of the lipid-soluble molecules by the function of the enzymes or the efflux pumps. Consequently, the BBB only permits the selective transport of molecules that are

essential for the brain function. The strategies for the nanoparticle targeting to the brain rely on the presence of and nanoparticle interaction with the specific receptor-mediated transport systems in the BBB. For example the polysorbate 80/LDL, the transferrin receptor binding antibody [such as OX26], cell penetrating peptides , lactoferrin and melanotransferrin have been shown capable of delivery of the self non transportable drug into the brain via the chimeric construct that can undergo the receptor-mediated transcytosis. It has been reported that poly [butylcyanoacrylate] nanoparticles was able to deliver hexapeptide dalargin, doxorubicin and the other agents into the brain which is significant due to of the great difficulty for the drugs to cross the BBB. Inspite of the some reported success with the polysorbate 80 coated NPs this system does have many other shortcomings which includes desorption of the polysorbate coating, rapid NP degradation and the toxicity caused by the presence of the high concentration of the polysorbate 80. The OX26 MAbs [anti-transferrin receptor MAbs], the most studied BBB targeting antibody, has been used to enhance the blood brain barrier penetration of the lipsosomes [91-97].

CONCLUSION

The foregoing show that nanoparticulate systems have great potentials, are capable to convert poorly soluble, poorly absorbed and labile biologically active substance into the promising deliverable drugs. In the next few years nanotechnology is expected to bring a fundamental change in manufacturing and it will have an enormous impact on life sciences, including diagnostics, drug delivery, production of biomaterials and nutraceuticals. A greater understanding of the different mechanisms of biological interactions and particle engineering, is still required to optimize this drug delivery system. In order to turn the concept of nanoparticle technology into a realistic practical application further advances are needed as the next generation of drug delivery system.

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