REVIEW ARTICLE

# NANOPARTICLES: AN OVERVIEW

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**ABSTRACT**

Nanoparticles are the preparations having size in nanometers. Particulate systems like nanoparticles have been used as a physical approach to alter and improve the pharmacokinetic and pharmacodymanic properties of various types of drug molecules.They have been used in vivo to protect the drug entity in the systemic circulation, restrict access of the drug to the choosen sites and to deliver the drug at a controlled and sustained rate to the site of action. Various polymers have been used in the formulation of nanoparticles for the drug delivery research to increase therapeutic benefit, while minimizing side effects.Here we review various aspects of nanoparticle formulation, characterization, effect of their characteristics and their applications in delivery of drug molecules and therapeutic genes.

**Keywords:** Nanoparticles, controlled and sustained rate, polymers, characterization, evaluation

## INTRODUCTION

Nanoparticles are sub-nanosized colloidal structures ranging from 10 nm to 1000 nm and are compared of synthetic or semi synthetic polymers[1]. The first reported nanoparticles were based on non-polymeric systems (polymethyl methacrylate, poly acrylide, polystyrene etc.). Because of the possibility of chronic toxicity due to tissue and immunological response towards non-degradable polymeric burden, these were not used systematically. Natural polymers i.e., proteins and polysaccharides are refused to be used in this area since they vary in purity and often require cross-linking that could denature the embedded drug. Soon the biodegradable polymers were taken up and nanoparticles based on poly (cyano acrylate) are extensively used systematically.

Nanoparticles have been actively explored at delivery system for small drug molecules as well as macromolecules such as nucleic acids, peptides, proteins and hormones. Because macromolecules, such as peptides and proteins have stability problems, their encapsulation provides protection against gastrointestinal enzymes and pH effects, when administered by oral route. Further it was realized that the nanoparticles loaded bioactive could not deliver drugs at specific organs within the body but delivery in addition could also be controlled[2]. Now a days, nanoparticles are widely utilized as a delivery system for drug molecules posing problems of solubility, poor bioavailability on oral administration and have been known to be an efficient approach to achieve better pharmacokinetics profiles, reduced toxicity and to increase the oral bioavailability of several drugs through specialized uptake mechanisms from gastrointestinal tract (GIT) through payer's patches via M cells of lymphatic system[3]. In addition, nanoparticles have also been used *in vivo* to protect the drug entity in the systematic circulation, restrict access of the drug to the chosen sites and to deliver the drug at a controlled and sustained rate to the site of action. Various polymers have been used in the formulation of nanoparticles for drug delivery research to increase therapeutic benefit, while minimizing side effects[4]. Nanoparticles offer better advantages over other carrier systems. A major advantage of nanoparticles which makes them an efficient delivery system is their submicron size which makes extravasations possible and occlusion of terminal blood vessels[5]. In addition, high density of therapeutic agent can often be encapsulated, dispersed or dissolved in these nanoparticles, which in turn depends on the preparation process to yield different properties and release characteristics of the entrapped agent. Though liposomes have been used as potential carriers with properties including protecting drugs from degradation, targeting to site of action and reduction in toxicity or side effect. Despite of this versatility, some technical limitations including poor reproducibility and stability have been reported[6]. Moreover drug delivery systems designed as liposomes cannot be used for controlled release of drug because of leakage of drug entrapped inside liposomes. On the other hand, polymeric nanoparticles offer some specific advantages of increasing the stability of drugs/proteins and possess useful controlled release properties[7]. Other features of nanoparticles include low number of excipients used in their formulations, simple procedure for preparation, high physical stability, and the possibility of sustained drug release that may be suitable in the treatment of chronic diseases. By varying the polymer composition of the particle and morphology, one can effectively tune in a variety of controlled release characteristics, allowing moderate constant doses over prolonged periods of time. Liversidge and Cundy reported that availability of drug molecule entrapped in nanoparticle was 77% higher than a similar formulation consisting of microspheres[8]. Further, the nanoparticle system was used for various routes for administration including oral, nasal, parenteral, ophthalmic application[9]. Oral delivery of small drugs molecules can also be achieved which otherwise would not be available as injectable such as anticancer agents[10]. Also, the nanoparticles are good candidates to be shown as adjuvant for vaccines and advantageous features of nanoparticles include increased interaction of drug molecules with epithelial cells can be achieved leading to maximal absorption of the drug molecule[11].

## ADVANTAGES OF NANOPARTICLES

- Nanoparticles have dimensions below the critical wavelength of light renders them transparent, a

 

property which makes them very useful for applications in packagings, cosmetics and coatings.
- Particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both active and passive targeting.
- Release of the drug can be controlled or sustained so as to achieve increase in therapeutic efficacy of drug and reduction in side-effects.
- They are capable of being stored for a period of upto 1 year and hence have longer shelf stability.
- They have the ability to incorporate both hydrophilic and hydrophobic drug molecules.
- They have higher carrier capacity and drugs can be incorporated without any chemical reaction and hence preserving the drug activity.
- The system can be administered via different routes including oral, nasal, parenteral etc.
- These have the potential to increase the bioavailability of drugs.
- They have longer clearance time.
- Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or by using magnetic guidance.

## DISADVANTAGES OF NANOPARTICLES

- It involves higher manufacturing costs which may in turn lead to increase in the cost of formulation.
- These have low encapsulation efficiency.
- Water-soluble drugs can be rapidly leaked out in the presence of blood components.
- Their small size and large surface area can lead to particle-particle aggregation, making physical handling of nanoparticles difficult in dry and liquid forms.
- They may trigger immune response and allergic reaction.
- It may involves use of harsh toxic solvents in the preparation process.

## IDEAL PROPERTIES OF NANO PARTICLES

Nanoparticles can be considered as a realizable method for drug delivery, following ideal properties of the system are required:

- Stable in blood
- Non toxic
- Non thrombogenic
- Non immunogenic
- Non inflammatory
- No activation of neutrophils
- Biodegradable
- Avoidance of the reticulo-endothelial system
- Applicable to various molecules, such as small molecules, proteins, peptides or nucleic acids (platform technology)
- Scalable and inexpensive manufacturing process

Because poly (butyl-cyano-acrylate) nanoparticles above properties and were reported to be useful tools to deliver the drugs in several experiments. In addition, they exhibit very low toxicity and are considered to be ideal.

## STRUCTURE OF NANOPARTICLES

Drug nanoparticles consist of the drug and biocompatible polymer, either biodegradable or non biodegradable. Nanoparticles can be further classified into nanocapsules and nanospheres based on their structure. A nanocapsule consists of central oily core containing the lipophillic drug surrounded by a shell composed of polymer. Nanospheres are solid core spherical particulates having a matrix consisting of a homogeneous distribution of the drug and polymer. The drug is either solubilized in the polymer matrix to form an amorphous particle or embedded in the polymer matrix as crystallites[12].

- A matrix –type nanoparticles, where the drug molecules are dispersed in the polymer matrix.
- A core shell nanoparticles, where e core containing the drug is covered with a polymer shell.
- A matrix-type nanoparticle, where drug crystals are embedded in a polymer matrix.

## SURFACE PROPERTIES OF NANOPARTICLES

When nanoparticles are administered intravenously, they are easily recognized by the body immune systems and are then cleared by phagocytes from the circulation[13]. Apart from the size of nanoparticles; their surface hydrophobicity determines the amount of adsorbed blood components, mainly proteins (opsonins). This in turn influences the *in vivo* fate of nanoparticles[14]. Binding of these opsonins onto the surface of nanoparticles called opsonization acts as a bridge between nanoparticles and phagocytes. The association of drug to conventional carriers leads to modification of drug biodistribution profile, as it is mainly delivered to mononuclear phagocytes system (MPS) such as liver, spleen, lungs and bone marrow. Indeed, once in the blood stream, surface non modified nanoparticles (conventional nanoparticles) are rapidly opsonized and massively cleared by the macrophages of MPS rich organs[15]. Usually, C3 components of IgG are used for recognition of foreign macromolecules. Hence to increase the likelihood of the success in drug targeting by nanoparticles, it is necessary to minimize the opsonization and to prolong the circulation of nanoparticles in vivo. This can be achieved by (a) surface coating of nanoparticles with hydrophilic polymers/surfactants; (b) formulation of nanoparticles with biodegradable copolymers with hydrophilic segments such as polyethylene glycol (PEG), polyethylene oxide, poloxamer, poloxamine and polysorbate 80[16]. The zeta (ζ) potential of nanoparticles is commonly used to characterize the surface charge property of nanoparticles. Nanoparticles with a ζ potential above (+/-) 30 mV are stable in suspension as the surface charge prevents the aggregation of the particles. The ζ potential can also be used to determine whether a charged active material is encapsulated within the center of the nanoparticles or adsorbed onto the surface[17].

## METHODS OF PREPARATION OF NANOPARTICLES

Current methods used in preparation of drug nanoparticles can be divided into two groups, namely, those based on polymerization and those taking advantage of preformed polymers. The choice of the method for the preparation of nanoparticulate formulation depends upon various factors including (a) size of nanoparticles required; (b) inherent properties of drug, e.g., aqueous solubility and stability;(c) surface characteristics such as charge and permeability (d) degree of biodegradability, biocompatibility and toxicity

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(e) drug release profile desired (f) Antigenicity of the final product[18].

**Emulsion/ Evaporation[19]:** This method can be used for preparation of particles with sizes varying from a few nanometers to micrometers by controlling the stirring rates and conditions, showing high efficiency in incorporation of lipophillic drugs. Organic solution of polymer and drug is emulsified in an aqueous solution containing stabilizer. Droplet size is reduced by using a high energy source followed by evaporation of organic phase under reduced pressure or vacuum to produce fine aqueous dispersion of nanoparticles and freeze dried for storage.

**Double Emulsion[20]:** This method referred to as variant of the Emulsion/Evaporation method as this method suffers from poor entrapment efficiency of hydrophilic drugs. Therefore, this method is used for incorporating hydrophilic drugs. Nanoparticles are recovered by ultracentrifugation and lyophilized. High encapsulation efficiency can be achieved by this method and considered as one of the appropriate methods for proteinateous substances due to high solubility of protein in water. Poly (lactide-co-glycolide) (PLGA) nanoparticles loaded with bovine serum albumin (BSA) were prepared by double emulsification method. Typically BSA and PLGA were dissolved separately in aqueous and organic phases respectively and subjected to ultrasonication to yield water in oil emulsion (W1/O). This water in oil was further added to a poly vinyl alcohol (PVA) aqueous solution to yield was evaporated during stirring first at atmospheric pressure and then at reduced pressure (from 100mmHg to 30mm Hg) to yield nanoparticles.

**Salting Out[21]:** This technique is suitable for drugs and polymers that are soluble in polar solvents, such as acetone or ethanol. Solution of polymer and drug in a slightly water miscible solvent is added to aqueous solution containing a salting out agent and stabilizer under stirring. A small amount of water is added to o/w emulsion for dilution which forces diffusion of organic solvent into a aqueous phase producing particles in nano size range. This process differs from Nano precipitation technique. In it, the organic phase is completely miscible in external aqueous phase but in case of salting out technique, the miscibility of bith the phases is prevented by saturation of external aqueous phase with PVA.

**Emulsification – Diffusion[22]:** It is a modified version of solvent evaporation method. In this method, the water miscible solvent along with a small amount of water immiscible organic solvent is used as an oil phase. Due to the spontaneous diffusion of solvents an interfacial turbulence is created between the two phases leading to formation of small particles. As the conc. of water miscible solvent increases, a decrease in size of particle can be achieved.

Both solvent evaporation and diffusion method can be used for hydrophobic and hydrophilic drugs. In case of hydrophilic drug, a multiple w/o/w emulsion needs to be formed with the drug dissolved in internal aqueous phase. Although this method is a modification of salting out procedure, it provides an advantage of avoiding the use of salts, thus eliminates for intensive purification steps. Limitation of this method is that it suffers from low entrapment efficiency of hydrophilic drug in nanoparticles, which can be overcome by incorporation of medium chain glycerides into aqueous solution which has been found to increase the efficiency of water soluble drugs into nano spheres offering the advantage of simplicity, narrow particle size distribution and ready dispersibility of resultant particles.

**Solvent Displacement/ Nanoprecipitation[23]:** This method incorporates the solution of polymer, drug and lipophillic surfactant in a semi polar water miscible solvent and then poured into solution containing stabilizer under stirring. Rapid diffusion of solvent results in nanoparticles formation. Hydrophilic drugs possess low drug loading efficiency than hydrophobic drugs because of their poor interaction with polymer leading to diffusion of drug from polymer in organic phase to the external aqueous environment. Barichello et al demonstrated improved bioavailability of proteins and peptides using PLGA nanoparticles by the nano precipitation method. Jaing et al established precipitation method for formation of ibuprofen (IBU) nanoparticles stabilized by DEAE dextran (Ddex). The process fabricated core shell particles by which poor water soluble drugs can be dispersed effectively with rather good stability during storage. The method includes precipitation of IBU in a super saturated solution and deposition of Ddex onto the precipitated IBU particles through electrostatic interaction. The difficulty faced in this preparation method is the choice of drug/polymer/solvent/non solvent system in which the nanoparticles would be formed and the drug efficiently entrapped.

**Emulsion-Difussion-Evaporation:** This method incorporates both evaporation and diffusion process in nanoparticles formation. Solution of polymer in solvent is added to aqueous phase under stirring .To this emulsion, water is added which results in nano precipitation. The basic methodology involves dispersion of organic phase as globules in equilibrium with external aqueous phase due to continuous stirring. The emulsion is stabilized by adsorption of stabilizer at the interface. The globule size is further lowered by homogenization. Addition of water destabilizes the equilibrium and diffusion of organic solvent to aqueous phase causes local super-saturation near the interface resulting in nanoparticles formation. The organic phase is removed from the preparation by evaporation at $40^0$C.

**Coacervation or Ionic Gelation Method[24]:** Much research is now focused on the nanoparticles using biodegradable hydrophilic polymers such as chitosan, gelatin and sodium alginate. Calvo and co-workers proposed a method for preparation hydrophilic chitosan nanoparticles by ionic gelation. The method involves a mixture of two aqueous phases; of which is the polymer chitosan, a di-block co-polymer ethylene oxide or propylene oxide (PEO-PPO) and the other is a poly anion sodium tri-polyphosphate. In this method, positively charged amino group of chitosan interacts with negative charged Tripolyphosphate to form coacervates with a size in the range on nanometer. Coacervates are due to the result of electrostatic interaction two aqueous phases, whereas, ionic gelation involves the material undergoing from lipid to gel due to ionic interaction conditions at temperature room.

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**Spray Drying[25]:** Spray-drying has been widely used for the production of micron-sized particles. Spray-dry involves the conversion of a solution droplet into a dry particle by evaporation of the solvent in a one-step process. Temperature –liable compounds such as proteins and enzymes have been successfully spray-dried. It has been shown that particles consisting of various polymers and drugs, both water –soluble and water-insoluble, can be prepared without problem of drug leakage to another phase and thus, the recovery of drug in the particles is almost the particle properties, especially morphology, can be controlled by the solvent properties and the spray-drying variables.

## NANO PARTICLE CHARACTERIZAION TECHNIQUES

**Particle Size Determination[26]:** Particle size and size distribution are the most important characteristics of nanoparticle systems. They determine the *in vivo* distribution, biological fate, toxicity and the targeting ability of nanoparticle systems. In addition, they can also influence the drug loading, drug release and stability of nanoparticles. Many studies have demonstrated that nanoparticles of sub-micron size have a number of advantages over microparticles as a drug delivery system.

**Static Light Scattering[27]:** Dynamic light scattering (DLS) is the name that covers different techniques for measurement of particle size from the dynamic changes of the scattered light intensity. Photon correlation spectroscopy (PCS) is at present the most widely used name. It relates to the correlation technique that is most frequently applied in instruments. Quasi-elastic light scattering (QELS) was used as a name often in the past. This term relates to the type of interaction between particles and light. It is a rapid method for determining the mean size, the size distribution and the polydispersity index (PdI) of a sample. In the DLS technique, the intensity of the scattered light by an ensemble of particles is measured at a given angle (90º) as a function of time. The Brownian motion of the dispersed particles determines the rate of change of the scattered light intensity. The temporal intensity changes are converted to a mean translational diffusion coefficient. Fast intensity changes are related to a rapid decay of the correlation function and a large diffusion coefficient. The diffusion coefficient is then converted into particle size by means of the Stokes–Einstein equation. DLS measurement range is about 0.005–1 and time required for measurement is typically about 0.5–10 min. For measurement of large particles (larger than about 0.5 μm), three problems are generally encountered are:

- Particles may settle out of the measurement zone to the bottom of the cell and thus will gradually become out of reach for measurement.
- Few particles suffice to reach the maximum allowable concentration in view of multiple scattering and thus changes of their number concentration will bias the sizing result.
- Brownian motion is very slow, especially in liquids of increased viscosity. Thus, long measurement times have to be applied, during which both instrument and suspension should remain stable. Typically, the particulate concentration during measurement is around $10^{-2}$ –$10^{-3}$ % (v/v).

**Scanning Electron Microscopy (SEM) [28]:** The scanning electron microscope (SEM) is a type of electron microscope that images the sample surface by scanning it with a high-energy beam of electrons in a raster scan pattern. The electrons interact with the atoms that make up the sample producing signals that contain information about the sample's surface topography, composition and other properties such as electrical conductivity. The types of signals produced by an SEM include secondary electrons, back-scattered electrons (BSE), characteristic X-rays, light (cathodoluminescence), specimen current and transmitted electrons. Secondary electron detectors are common in all SEMs, but it is rare that a single machine would have detectors for all possible signals. The signals result from interactions of the electron beam with atoms at or near the surface of the sample. In the most common or standard detection mode, secondary electron imaging or SEI, the SEM can produce very high-resolution images of a sample surface, revealing details about less than 1 to 5 nm in size. Due to the very narrow electron beam, SEM micrographs have a large depth of field yielding a characteristic three-dimensional appearance useful for understanding the surface structure of a sample. This is exemplified by the micrograph of pollen shown to the right. A wide range of magnifications is possible, from about 10 times (about equivalent to that of a powerful hand-lens) to more than 500,000 times, about 250 times the magnification limit of the best light microscopes. For the same reason, BSE imaging can image colloidal gold immuno-labels of 5 or 10 nm diameter which would otherwise be difficult or impossible to detect in secondary electron images in biological specimens. Characteristic X-rays are emitted when the electron beam removes an inner shell electron from the sample, causing a higher energy electron to fill the shell and release energy.

**Transmission Electron Microscopy (TEM) [29]:** A transmission electron microscope is analogous to a slide projector, with illumination from an electron beam rather than light. When an electron beam is impinged upon a sample, a black and white TEM image is formed from the passage of some electrons through the sample untouched, alongside the combination of interactions between other electrons and sample atoms (*e.g.*, inelastic/elastic scattering, diffraction). If the undiffracted beam is selected to form the image, it is referred to as *bright-field imaging*; in contrast, selection of strongly diffracting regions of the sample, which would appear brighter than the transmitted beam, is known as *dark-field imaging.* It should be noted that electrons may also be absorbed by molecules containing large atoms, or by surface contamination (*e.g.*, dust, grease). The absorption of a high density of electrons in a specific region will cause a buildup of heat, leading to sample destruction and poor image quality. Analogous to throwing a baseball of varying speeds through a wall, the relative degree of penetration through a particular sample is governed by the energy of the electron source. That is, higher energy electrons (*e.g.*, 200 keV *vs*. 100 keV) will be more penetrating, allowing for the characterization of thicker and/or less transparent samples. In general, increasing the thickness of a sample, or decreasing the energy (*i.e.*, accelerating voltage) of the electron beam,

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will induce more scattering events through more effective interactions between the electron beam and atoms of the sample. This effect will enhance image contrast, since there is a larger deviation between the path lengths of transmitted and scattered electrons that reach the viewing screen. However, this improvement of image quality is offset by plentiful inelastic collisions that yield a broadened wavelength distribution of the electron beam. Since individual electrons will have differing energies, they will be brought into focus at different points resulting in a blurry image (*i.e.*, decreased resolution).

**Atomic Force Microscopy[30]:** In this technique, a probe tip with atomic scale sharpness is raftered across a sample to produce a topological map based on the forces at play between the tip and the surface. The probe can be dragged across the sample (contact mode), or allowed to hover just above (noncontact mode), with the exact nature of the particular force employed serving to distinguish among the sub techniques. That ultrahigh resolution is obtainable with this approach, which along with the ability to map a sample according to properties in addition to size, e.g., colloidal attraction or resistance to deformation, makes AFM a valuable tool. However, size and shape has been the most common application to date. The need to raster the probe renders the method very time-consuming and the size of the sample actually observed is small. Nanoparticles are typically presented as an evaporated suspension on smooth silicon or mica surface, though not without the possibility of deformation. Application of various forms of AFM to nanoparticles characterization represents an area of active research.

**X-Ray Diffraction (Power X-ray Diffraction) [31]:** The geometric scattering of radiation from crystal planes within a solid allow the presence or absence of the former to be determined thus permitting the degree of crys` tallinity to be assessed. In one example; the crystallization of interior lipids could be tracked. Application of the method is little different from that for bulk powders, though broadening of the diffraction pattern's peaks is observed for particles less than 100nm in diameter. For nanoparticles, order on the smaller scale can be investigated by reducing the wavelength and angle of incident radiation. Using electron or neutron beams allows reduction of the former parameter due to the shorter De-Broglie wavelengths of such particles.

**Nuclear Magnetic Resonance Spectroscopy[32]:** Nuclear magnetic resonance (NMR) can be used to determine both the size and the qualitative nature of nanoparticles. The selectivity afforded by chemical shift complements the sensitivity to molecular mobility to provide information on the physicochemical status of components within the nanoparticle. For example; the mobility of Miglyol 812 within solid lipid nanoparticles confirmed the liquid-like nature of the interior, though it was more limited than the same oil in an o/w emulsion. Pulsed field gradient methods 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 simultaneously .In one case, the diffusion coefficient is used as a surrogate for size of the nanoparticle with results that compare well to separation and DLS, though only NMR could simultaneously detect micellar precursors.

**Fourier Transform Infrared Spectroscopy[33]:** Fourier transform spectroscopy is a measurement technique whereby spectra are collected based on measurements of the coherence of a radiative source, using time-domain or space-domain measurements of the electromagnetic radiation or other type of radiation. It can be applied to a variety of types of spectroscopy including optical spectroscopy, infrared spectroscopy (FT-IR, FT-NIRS), Fourier transform (FT) nuclear magnetic resonance, mass spectrometry and electron spin resonance spectroscopy. There are several methods for measuring the temporal coherence of the light, including the continuous wave Michelson or Fourier transform spectrometer and the pulsed Fourier transform spectrograph (which is more sensitive and has a much shorter sampling time than conventional spectroscopic techniques, but is only applicable in a laboratory environment).

**Differential Scanning Calorimetry (DSC) [34]:** Another method that is a little different from its implementation with bulk materials, DSC can be used to determine the nature and speciation of crystallinity within nanoparticles through the measurement of glass and melting point temperatures and their associated enthalpies. A complement to X-ray diffraction, this method is regularly used to determine the extent to which multiple phases exist in the interior or to which the various constituents, including the drug, interact.

**Surface Charge/ Surface Properties of Nanoparticles[35]:** When nanoparticles are administered intravenously, they are easily recognized by the body immune systems, and are then cleared by phagocytes from the circulation. Apart from the size of nanoparticles, their surface hydrophobicity determines the amount of adsorbed blood components, mainly proteins (opsonins). This in turn influences the *in vivo* fate of nanoparticles. Binding of these opsonins onto the surface of nanoparticles called opsonization acts as a bridge between nanoparticles and phagocytes. The association of a drug to conventional carriers leads to modification of the drug biodistribution profile, as it is mainly delivered to the mononuclear phagocytes system (MPS) such as liver, spleen, lungs and bone marrow. Indeed, once in the blood stream, surface non-modified nanoparticles (conventional nanoparticles) are rapidly opsonized and massively cleared by the macrophages of MPS rich organs. Generally, it is IgG, compliment C3 components that are used for recognition of foreign substances, especially foreign macromolecules. Hence, to increase the likelihood of the success in drug targeting by nanoparticles, it is necessary to minimize the opsonization and to prolong the circulation of nanoparticles *in vivo*. This can be achieved by (a) surface coating of nanoparticles with hydrophilic polymers/surfactants; (b) formulation of nanoparticles with biodegradable copolymers with hydrophilic segments such as polyethylene glycol (PEG), polyethylene oxide, poloxamer, poloxamine and polysorbate 80 (Tween 80). Studies show that PEG conformation at the nanoparticles surface is of utmost importance for the opsonins repelling function of the PEG layer. PEG surfaces in brush-like and intermediate configurations reduced phagocytosis and complement activation whereas PEG surfaces in mushroom-like configuration were potent complement activators and favored phagocytosis.

 

**Zeta Potential[36]:** 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 them with the particular approach implemented in their equipment. Instrumentation concerns aside, the need for dilution begs the question of what is an appropriate diluent, 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. Electro acoustic 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.

**Electrophoresis[37]:** 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 biodistribution 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 bio-analytical tools such as iso-electric focusing and 2-D poly acryl-amide 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.

## DRUG LOADING AND IN-VITRO RELEASE PROFILE OF NANOPARTICLES

Lipophilic or poorly soluble drugs are often incorporated in a nanocapsule or nanoparticles using hydrophobic polymers. The selection of organic solvent which is to used in reservoir of system depends on the solubility of the drug. Depending on the drug hydrophobicity, it may require highly non-polar solvents like chloroform andmethylene chloride. The release of incorporated drug depends on partitioning behaviour between capsularreservoir and dispersion phase sink.

In hydrophilic drugs, the aqueous phase contains the drug molecules which are embedded in the polymeric cross-linked matrix. Drug-polymer affinity and interaction may be the critical factors that determine and regulate drug payload or percent drug incorporation and drug release. The encapsulation of drug in hydrophilic polymers requires some appropriate organic solvent depending on the procedural and formulation factors.

***In-vitro* release profile of lipophilic drugs:** Inner structure of polymeric colloidal system largely affects the in-vitro release behaviour of lipophilic compounds. Drug release from nanocapsules mainly occurs by the drug partition from the colloidal suspension to the external sink solution and thus in turn depends on the solubility of the drug in the oily core and external receptor medium. On the other hand, the in-vitro release characteristics of the lipophilic compounds from the nanoparticles are dominated by the polymer erosion and in most of the cases a biphasic release pattern results. The first phase (burst release) is due to the release of the drug adsorbed on the particles surface and the second phase is due to drug diffusion out of the polymer matrix.

***In-vitro* release profile of hydrophilic drugs:** A hydrophilic compound can be adsorbed on to preformed nanospheres or entrapped within a polymer matrix composed of natural macromolecules or synthetic polymers. Generally, in the first case, the release of hydrophilic drugs from polymeric nanoparticles occurs relatively fast (1-2 days) and the release rate reflects the affinity of the drug for the polymer. In the second case however, the polymer degradation rate and inner structure of nanoparticle in combination may influence the drug release profile.

## THERAPEUTIC APPLICATIONS OF NANOPARTICLES

Nanoparticles have been widely employed for different therapeutic applications, some of which are listed below:

- For intracellular targeting of anti-effective drugs to combat the difficult to treat' intracellular infections of the human body.
- For targeting of cytostatic drugs to reduce toxicity and increase therapeutic activity.
- For specific targeting of anti-inflammatory drugs to areas of inflammation, by which the side-effects of these drugs can be minimized.
- For ocular delivery systems, to deliver pilocarpine and other miotic drugs.
- As carriers for radionucleotides for diagnostic purposes in nuclear medicines.
- To improve the solubility and bioavailability of poorly soluble drugs and protects from gastrointestinal enzymes and hence, helps in peroral absorption.
- For skin and hair care in the form of solid nanoparticles, wherein the oily core contains a wide variety of different cosmetic oils and lipophilic agents.
- To deliver drugs across the blood brain barrier (BBB).
- To formulate sustained release preparations.
- For the controlled delivery of disinfectants or algicide into large bodies of water such as insect pest feed .
- For targeted delivery of proteins and peptides.
- As adjuvants to render antigens potent enough to be useful for vaccines.
- Have prolonged systemic drug effect due to prolonged systemic circulation and hence, uptake by reticuloendothelial system can be avoided.

## CONCLUSION

Nanoparticles are the colloidal particles whose size ranges in the nanometric size which are mainly employed through parenteral route, hence, requiring careful development of test methods and acceptance criteria for the specifications. The foregoing shows that nanoparticulate systems have great potentials, being able to convert poorly soluble, poorly absorbed and labile biologically active substance into promising deliverable drugs.To optimize this drug

 

delivery system, greater understanding of the different mechanisms of biological interactions, and particle engineering, is still required. Further advances are needed in order to turn the concept of nanoparticletechnology into a realistic practical application as the next generation of drug delivery system. In particular, the in vitro release test method and acceptance criteria require rigorous scientific consideration and should be developed with an eye toward understanding the mechanisms of drug release. The final specifications need to ensure the safety, identity, strength, performance, and quality of the drug product at release and during storage through the end of its shelf-life. The objective of nanoparticulate system is to achieve a desired pharmacological response in a sustained manner at a selected site without undesirable interactions at the other sites. This is especially important in cancer chemotherapy, enzyme replacement therapy etc.

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