A REVIEW ON NANOPARTICLES: BACKROUND, TRENDS & FUTURE PERSPECTIVES

Venkata Durga Seshu Priya Punagani*, Ruby S, Venketeswarlu B.S

Department of Pharmaceutical Sciences, Vinayaka Mission's Research Foundation – Deemed University, Salem - 636 308, Tamil Nadu, India.

Corresponding Author

Mrs. Punagani Venkata Durga Seshu Priya

Department of Pharmaceutical Sciences, Vinayaka Mission's Research Foundation – Deemed University, Salem - 636 308, Tamil Nadu, India.

Corresponding Email: seshupriyaphd@gmail.com

Mobile No. : 9959523469

Abstract

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 deliver drugs at specific site within the body but delivery in addition could also be controlled. 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). Nanoparticles are sub-nanosized colloidal structures ranging from 10 nm to 1000 nm and are composed of synthetic or semi synthetic polymers.

Keywords: *Encapsulation Efficiency, Nano-Carriers, Emulsification Process, Solvent Evaporation Process, Surfactants.*

INTRODUCTION

Nanotechnology is a rapidly developing field and interdisciplinary approach. Traditional procedures have produced nanoparticles in several ancient activities, although they have not been identified as nanosystems or nanoparticles[1]. Ayurveda, the old traditional system of medicine in India has identified many "Bhasmas" which include particles with diameters in nano range and have been utilized traditionally. Because nanoparticles have a larger surface area than their volume, friction and clumping of the nanoparticles into a bigger structure is unavoidable, which could compromise their effectiveness as a drug delivery mechanism. Furthermore, due to the small particle size and vast surface area, drug loading and burst release are easily achieved[2]. Once nanoparticles have been injected into the human body, they should be monitored by an external control system to ensure that they do not cause harm. Bypassing first-pass metabolism and increasing desired bioavailability while administering the medicine with the fewest adverse effects possible. 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[3].

In addition, high density of therapeutic agent can often be encapsulated, dispersed 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[4]. Despite of this versatility, some technical limitations including poor reproducibility and stability have been reported.

Moreover, drug delivery systems designed as nanoparticles cannot be used for controlled release of drug because of leakage of drug entrapment. On the other hand, polymeric nanoparticles offer some specific advantages of increasing the stability of drugs/proteins and possess useful controlled release properties[5]. 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[5]. But, varying the polymer composition of the particle and morphology, one can effectively tune in a variety of controlled release characteristics in allowing moderate constant doses over prolonged period of time[6].

LIMITATIONS OF NANOPARTICLES

Solubility

The solubility of NPS may differ in certain conditions such as varying temperatures. The changes in temperature can influence the interaction between NPS and drug[7]. This can cause certain patients to encounter different therapeutic impacts which are undesirable for medical treatments.

Bioavailability

The administration route of NPS may affect the bioavailability of the drug that is delivered to the body. Nasal route is the most practical and admissible as it is one of the most noninvasive methods.

Blood Brain Barrier

The blood brain barrier (BBB) plays an important function in neuronal circuits and synaptic transmission. However, it remains to be an impenetrable obstacle for a larger number of exogenous substances. Drug delivery using NPS is one of the possibilities to transport active molecules efficiently across the BBB. This is due to ligands that are functionalized onto NPS to improve the targeted drug delivery to overcome BBB. However, the efficiency of these ligand-modified NPS needs to be evaluated as it still requires a long blood-residency time to be able to pass through the BBB and hit their target system[8-9].

Toxicity

Consuming high amount of nanocarriers containing surfactants and cosurfactants due to low encapsulation efficacy and loading capacity of NPS can cause serious adverse effects. Certain NPS that have been administered into the body cannot be easily removed by various clearance systems. This may cause the NPS to accumulate within the brain system causing to cytotoxicity. Long-term accumulation of NPS in the brain may lead to brain injuries[10].

APPLICATIONS OF NANOPARTICLES

- ✓ Targeting of nanoparticles to epithelial cells in GI tract using ligands.
- ✓ Brain targeting
- ✓ Tumor targeting
- ✓ Reversion of multidrug resistance in tumor cells[11-12]

Biodegradable polymer in drug nanoparticles

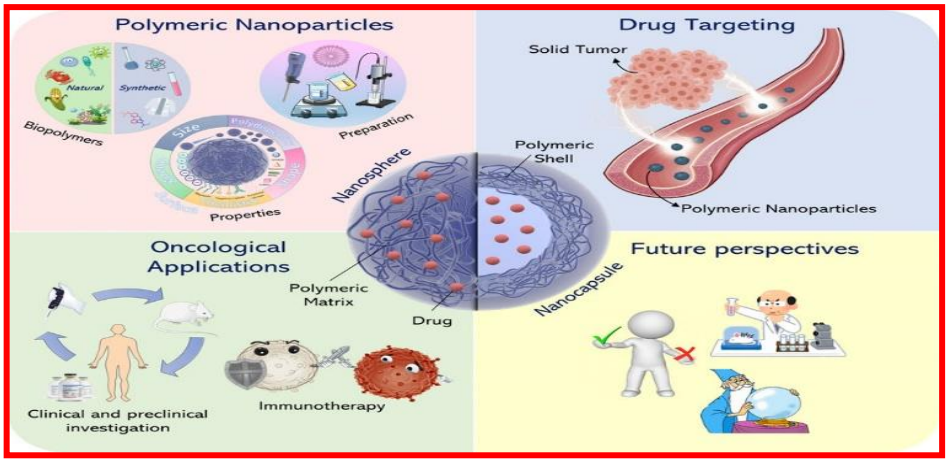

Figure 1. Biodegradable or non-biodegradable polymeric Nanoparticles

Nanoparticles can be further classified into nanocaspules and nanospheres based on their structure. Drug nanoparticles consists of the drug and biocompatible polymer, either biodegradable or non-biodegradable as represented Fig 1. A nanocapsule consists of central oily core containing the lipophilic drug surrounded by a shell composed of polymer.

Nanospheres are solid core spherical particles having a matrix consisting of a homogeneous distribution of the drug and polymer[13]. The drug is either solubilized in the polymer matrix to form an amorphous particle in the polymer matrix as crystals. A matrix type nanoparticle, where the drug molecules are dispersed in the polymer matrix. A matrix type nanoparticle, where drug crystals are embedded in a polymer matrix.

TARGETING THROUGH NANOCARRIERS

Nanoparticles have been extensively studied as targeted delivery systems in last three decades. The word "nanoparticle" is commonly used for the depiction of nearly all pharmaceutical carriers, hence, added differentiation is required for clarity. A cluster of nanocarriers, polymer drug conjugates and colloidal carriers of polymers developed using techniques such as emulsion polymerization, colloidal gold, crosslinked nanogel matrices, dendrimers, quantum dots and carbon nanotubes.

Nanoliposomes

Nanoliposomes are composed of lipid bilayers made up of phospholipid having enclosed aqueous compartment as represented Fig.3 which can be used for the delivery of smaller molecular weight therapeutics, imaging agents, peptides, proteins and nucleic acids. The particle size can range from 25nm to several micrometres depending on the number of bilayers as well as method of preparation[14-15]. Liposomes are proved to possess adaptable properties in terms of particle size, bilayer composition and their encapsulation ability, makes these carriers useful for drug delivery. Smaller nano size liposomes can sustain the release of an encapsulated agents, resulting in prolonged exposure at the target site and enhanced efficacy. Nevertheless, nanoliposome does prone to faster degradation and taken up by liver macrophages and could be used for active targeting.

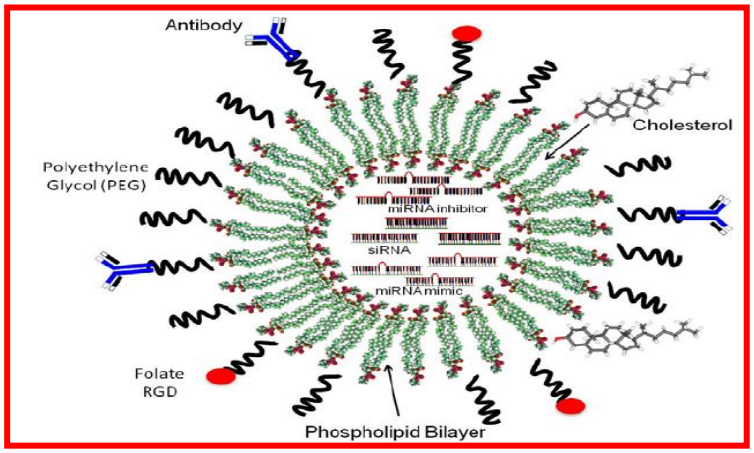

Figure 2. Nano liposomes

Unilamellar Hydrophobic Nanosomes

Niosomes are unilamellar and having aqueous compartment capable for encapsulation of hydrophilic drugs while hydrophobic drugs are entered into the hydrophobic bilayer as represented Fig.3.

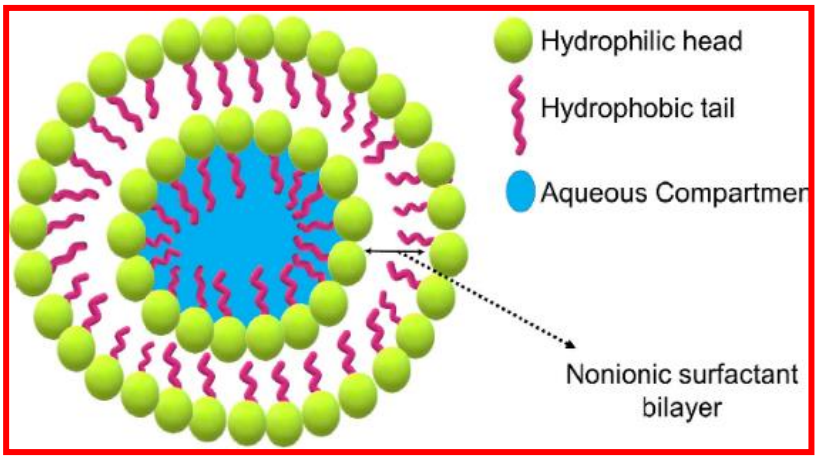

Figure 3. Niosomes

Since, niosomes are composed of surfactants, hence, having greater stability as compared to liposomes. The surface-active agents used for the preparation of niosomes should be biodegradable, biocompatible and nonimmunogenic. Niosomes are lamellar structures created by combining cholesterol and non-ionic surfactant of the alkyl or dialkylpolyglycerol ether class and followed by their hydration in order to form closed bilayer vesicle by means of providing some energy such as physical agitation[16-17]. The size, charge, lamellarity and tapped volume of the niosomes could be altered by changing the surfactant composition.

Polymeric Nanoparticles

Nanoparticles are submicron sized (10–1000nm) made up of solid polymeric carriers. Polymeric nanoparticles hold noteworthy assurance for the effective treatment of disorders as they have striking physicochemical properties, that is size, surface charge, hydrophilicity and hydrophobicity as represented Fig.4 hence, they have been considered as prospective carriers for drugs and pharmaceuticals[18]. Actually, nanoparticles offer several advantages over free drugs, such as protection from unwanted interaction with biological moieties and degradation, improving the absorption into the desired organ (tumours), and escalating the pharmacokinetics of the therapeutics.

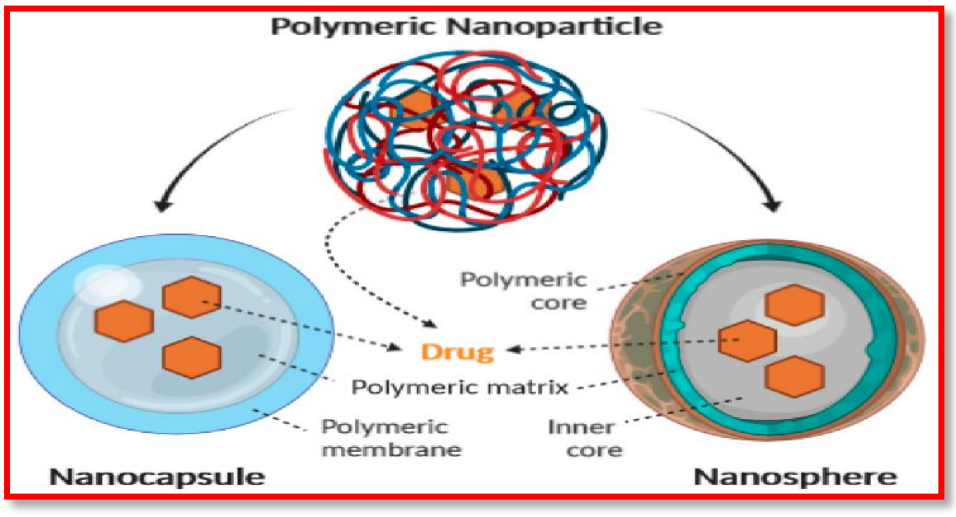

Figure 4. Polymeric Nanoparticles

Solid Lipid Nanoparticles (SLNs)

SLNs are made of solid lipids and stabilized with emulsifying agents in an aqueous dispersion. They resemble with nanoemulsion only replacing liquid lipid with a solid lipid. Controlled drug release can be attained in an outstanding manner by replacing solid lipids with oils, since solid lipid lower mobility of drug significantly, as compared to oil phase. SLNs are associated to possess some advantages and circumvent few disadvantages of many other carrier systems such as polymeric nanoparticle, liposome and lipid emulsion[19]. Recently major challenges, applications and safety aspects of lipid-based nanocarriers have been reviewed in an excellent manner.

Dendrimers

These are novel category of controlled-structure polymers having nanoscale dimension with structural surface functionality. These have demonstrated site-specific programmed of therapeutics along with usefulness in imaging studies[20]. Usually, dendrimers have hyper branched structures with a core in which therapeutics and imaging agents have been trapped as represented Fig.5.

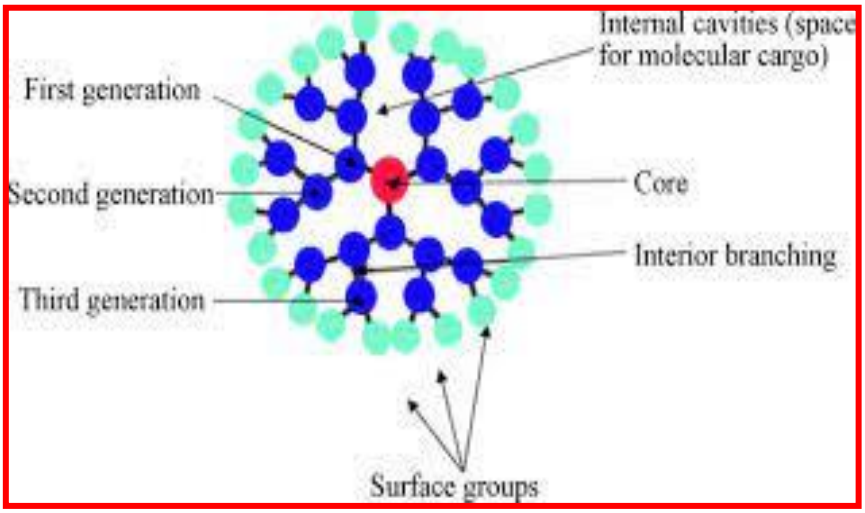

Figure 5. Dendrimer

Inorganic Nanocarriers

Current progression in nanotechnology has led to the application of various inorganic nanoparticles such as calcium phosphate, carbon nanotubes, graphene oxide nanoparticles, mesoporous silica nanoparticles (MSNs) and gold nanoparticle in drug delivery. Day by day inorganic nanoparticles are gaining importance among them, carbon nanotubes, gold nanoparticles and nanospheres have been widely investigated as drug carrier, as their nanometre size enables them to move easily inside the body. The major advantages of inorganic nanoparticles attributed due to their hydrophilic nature, low toxicity profile, biocompatibility and resistant to microbial growth and higher stability.

Carbon Nanotubes

Carbon nanotubes are hexagonal network of carbon atoms, 1 nm in diameter and 100 nm in length, as a layer of graphite rolled up into cylinder as represented Fig.6. CNTs are of two types, single walled carbon nanotubes (SWCNTs) and multiwalled carbon nanotubes (MWCNTs). The small dimensions of carbon nanotubes, combined with their remarkable physical, mechanical and electrical properties, make them unique materials. They display metallic or semi conductive properties, depending on how the carbon leaf is wound on itself. The mechanical strength of carbon nanotubes is sixty times greater than the best steels. Carbon nanotubes have a great capacity for molecular absorption and offering a three-dimensional configuration. Moreover, they are chemically very stable[21].

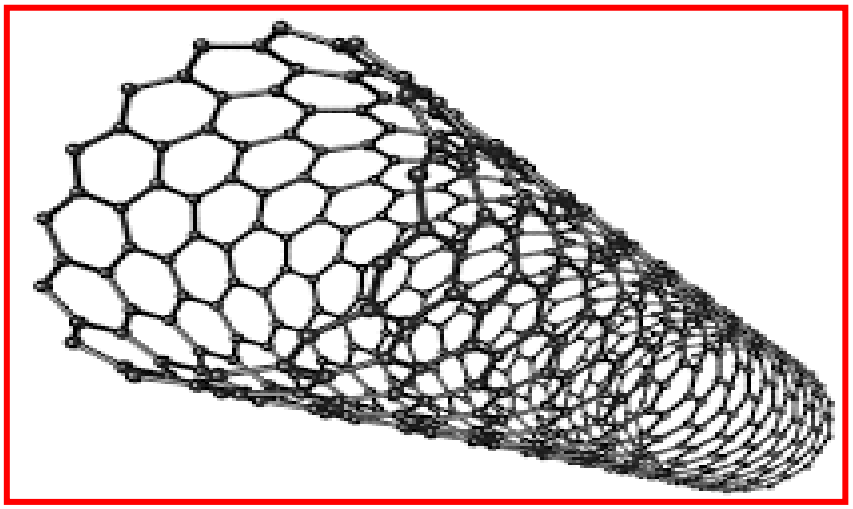

Figure 6. Carbon nanotubes

Silica Nanoparticles

Mesoporous silica is one of the widely employed inorganic material produces surface template nanoparticles via combination of surfactant along with silicates as represented Fig.7. MSNs are comparatively biocompatible, making them suitable for biological applications. However, they are not bioresorbable[21]. Pore size and pore structure could be easily controlled by selection of surfactant and co-assembly conditions.

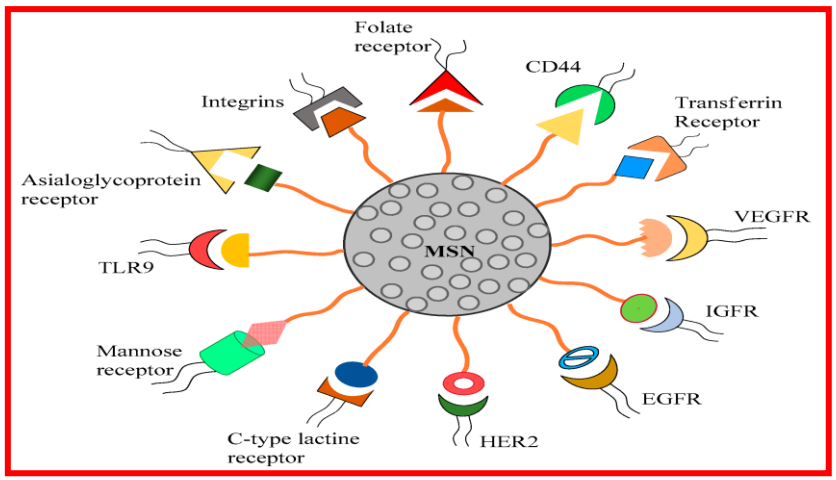

Figure 7. Silica Nanoparticles

Gold Nanoparticles

Gold nanoparticles have shown applications in biomedical use since they are bioinert, iocompatible, low toxicity, having flexibility of surface modifications and cellular imaging ability. Gold nanoparticles of 2.5nm size are explored as useful transporter for intracellular delivery of b-galactosidase into the various cell lines and found that galactosidase was effectively reached inside the cell membrane of HeLa cells as represented Fig 8.

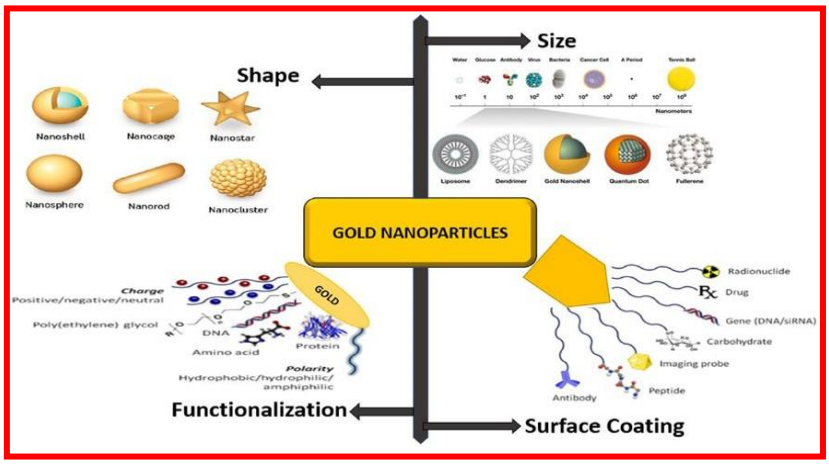

Figure 8. Gold nanoparticle

Magnetic Nanoparticles

Super para magnetic nanoparticles molecules are those that are attracted to a magnetic field but do not retain residual magnetism after the field is removed. Nanoparticles of iron oxide with diameters in the 5-100 nm range have been used for selective magnetic bio separations. Typical techniques involve coating the particles with antibodies to cell-specific antigens, for separation from the surrounding matrix. These characteristics make them attractive for many applications, ranging from various separation techniques and contrast enhancing agents for MRI to drug delivery systems, magnetic hyperthermia and magnetically assisted transfection of cells[22-23].

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[24-25] for the preparation of nanoparticulate formulation depends upon various factors including

- Size of nanoparticles required.
- Inherent properties of drug, e.g., aqueous solubility and stability.
- Surface characteristics such as charge and permeability.
- Degree of biodegradability, biocompatibility and toxicity.
- Drug release profile desired.
- Antigenicity of the final product.

Solvent Evaporation Method

This method can be used for preparation of particles with sizes varying from a few nanometres to micrometres by controlling the stirring rates and conditions, showing high efficiency in incorporation of lipophilic 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[26].

Double Emulsion Method

This method referred to as variant of the Emulsion 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. Typically, BSA and PLGA were dissolved separately in aqueous and organic phases respectively and subjected to ultrasonication to yield water in oil emulsion (W/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 (from100mm Hg to 30mm Hg) to yield nanoparticles.

Salting out Method

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[27-28]. A small amount of water is added to o/w emulsion for dilution which forces diffusion of organic solvent into an 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 both the phases is prevented by saturation of external aqueous phase with PVA30.

Emulsification Diffusion Method

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[29]. 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 15 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.

Nanoprecipitation Method

This method incorporates the solution of polymer, drug and lipophilic 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. The process fabricated core shell particles by which poor water-soluble drugs can be dispersed effectively with rather good stability during storage[30]. 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.

Ionic Gelation Method

Much research is now focused on the nanoparticles using biodegradable hydrophilic polymers such as chitosan, gelatine and sodium alginate. The method involves a mixture of two aqueous phases; of which is the polymer chitosan, a di-block copolymer ethylene oxide or propylene oxide (PEO-PPO) and the other is a poly anion sodium tri-polyphosphate. In this method[32], positively charged amino group of chitosan interacts with negative charged Tripolyphosphate to form coacervates with a size in the range on nanometre. 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 room temperature.

Spray Drying Method

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.

EVALUATION OF NANOPARTICLES

Particle size and Zeta Potential

Particle size and Zeta potential was determined by using a Malvern Zeta sizer. The most widely-used theory for calculating zeta potential was developed.

Transmission Electron Microscopy

Transmission Electron Microscope is a type of microscopy technique which operates on the same basic principle as the light microscope except TEM uses a beam of electrons, instead of

light. The image is formed by the interaction of the sample specimen when electron beams are transmitted through it. Due to the small de Broglie wavelength of electrons, it is possible to get significantly higher resolution down to 0.1 nm in TEM over light microscopy.

Entrapment efficiency

The ratio between mass of nanoparticles recovered and mass of polymer and drug used in synthesis. Centrifuge suspended nanoparticles and filter the unbound and its concentration of free drug in the supernatant was determined by UV – Spectrophotomety.

Measurement of Drug Release

The dialysis technique is generally preferred. Various researchers have proposed different methods with one common strategy of using synthetic membrane bag with specified porosity to hold the sample[33]. The bag containing the sample is immersed in the recipient fluid, which is stirred at a specified rpm. The collected samples are estimated for the drug content.

CONCLUSIONS

Nanoparticles have remarkable features that have made them important in a variety of industries recently, including energy, health care, the environment, agriculture, etc. Nanotechnology applications are capable of transforming unstable, poorly soluble, and poorly absorbed physiologically active compounds into promising deliverable chemicals, which shows their considerable promise. With outstanding applications, the use of nanomaterials for targeted medication delivery has advanced significantly, reducing the drawbacks of traditional drug delivery systems. For the targeted administration of pharmaceuticals, many nanomaterial types (such as spherical nanoparticles, core-shell, nanorods, nanowires, hollow, nanofibers, and mesoporous) are being investigated.

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