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AN OVERVIEW ON NANOSPHERE DRUG DELIVERY

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ABSTRACT

Delivering of a therapeutic agent to the desired site is a major challenge in treating many diseases. With the emergence of Nanotechnology, it offers drugs in the nano meter size range which has the advantage of enhancing the performance of a wide variety of drugs. Nanosphere is the division of polymeric nanoparticle having size range 10-200nm. They have got many advantages including targeted drug delivery. It can enclose variety of drugs, enzymes, genes and is characterised by a long circulation time. This review briefly explains about formulation aspects including the polymers used for its preparation, different techniques for formulating nanospheres. Also about the characterisation parameters used for the nanospheres. It also gives an idea about the various applications of nanospheres for tumour targeting, brain targeting, gene delivery etc.

KEYWORDS: Nanotechnology, Nanosphere, Targeted drug delivery.

INTRODUCTION

Nanotechnology is the field of science that deals with the treatment of individual atoms, molecules or compounds into structures to produce materials having special properties. It involve the study of extremely small structures whose dimensions in the nanometer scale length (1-100nm).[1] The advancement in the nanotechnology and its application to pharmaceuticals and medicine has revolutionized the twentieth century. The polymeric nanoparticle are those where the drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix.[2] This can be divided into Nanosphere and nanocapsule (figure 1). Nanospheres are matrix particles whose entire mass is solid.[3] These spherical particulate systems are characterised by a size between 10-200nm in diameter. These exhibit some new enhanced size dependent properties when compared to larger spheres of same material. Basically in nanospheres, the drug is being dissolved, entrapped, encapsulated or attached to the matrix of polymer. Here the drug is uniformly dispersed to form homogeneous structure. Nanospheres can be biodegradable or non-biodegradable. Some of the biodegradable Nanosphere includes modified starch nanospheres, gelatin Nanosphere, polypropylene dextran Nanosphere, albumin Nanospheres and polylactic acid nanospheres. They can also be crystalline and amorphous. The administration of medication via these systems offers high advantageous since they can be ingested or injected. Also site specific delivery of drugs can be used for organ targeted release of drugs.[4]

Thus the Nanosphere offers high potential to formulate diverse range systems that can give new patent life to known effective pharmacophores.[5]

The main objective for designing the nanospheres as a targeted drug delivery system is to:

- ✓ Control the particle size.
- ✓ Release of therapeutically active agents to achieve the site specific action at the therapeutically optimal rate and dose regimen.[6]

ADVANTAGES OF NANOSPHERES

- ➢ Due to their ultra tiny volume the nanospheres can easily pass through the smallest capillary vessels.
- ➢ Nanospheres can be used to target the organs like liver, spleen, lungs, spinal cord as they easily penetrate the cells and tissue gap.[7]
- ➢ The duration in the bloodstream can be prolonged since they avoid rapid clearance by phagocytes.
- ➢ Nanospheres can be formulated for controlled release action.
- ➢ Reduction of toxicity.
- ➢ They can be administered via oral, nasal, parenteral route.
- ➢ Site specific targeting by attaching the ligands to the surface of the spheres.[8]

DISADVANTAGES OF NANOSPHERES

- ➢ It is difficult to handle nanospheres in liquid and dry form.
- ➢ They are prone to particle aggregation due to smaller size and larger surface area.

- Due to smaller size and larger surface area drug loading and subsequent burst release of drug is limited.[9]

POLYMERS USED TO DESIGN NANOSPHERES

Various kinds of polymers are used to prepare the polymeric nanoparticle including nanospheres (table 1).[10] Both biodegradable polymers and their co-polymers such as Di-block, Tri-block, and multi-block or radial block copolymer structures have been used to prepare them and to encapsulate the active ingredients. Also the polymer must be compatible with our body i.e.; they should be non-toxic and non-allergent. The polymer of natural origin used for the preparation of nanospheres include albumin, gelatin, sodium alginate, chitosan.[10] Also synthetic polymers can be used such as poly(lactide co-glycolide) (PLGA), poly (methyl methacrylate), polyethylene glycol etc.

MECHANISM OF DRUG RELEASE[11]

The delivery of the drug at the tissue site from these drug carriers can be achieved by:

- Rupture or degradation of polymer at the site of delivery due to enzymatic degradation which result in release of drug from the entrapped inner core.
- Swelling of polymer by hydration resulting in release of drug (figure 2)[11]
- Dissociation of drug from the polymer causing subsequent release of drug from the swelled polymeric nanoparticle.

PREPARATION METHODS FOR NANOSPHERES

Various preparation methods can be adopted for the preparation of nanospheres. The different methods include:

- Polymerisation(Emulsification polymerisation)
- Solvent displacement method (nanoprecipitation method)
- Solvent evaporation method
- Salting out
- Controlled gellification method
- Desolvation technique
- Ionic gelation method

Polymerisation method[12]

Generally it includes interfacial polymerisation and emulsification polymerisation. In this method polymer like polymethylmethacrylate and polycyanocrylate are emulsified i.e. emulsification polymerisation and interfacial polymerisation of polyalkylcyanoacrylate. Monomers are polymerized to form the nanospheres in an aqueous solution. After the completion of the polymerisation, the drug can be incorporated by dissolving in the polymerization medium or via adsorption onto the nanospheres (Figure 3). The obtained nanospheres are purified, centrifuged and finally freeze dried.

Solvent displacement method

The solvent displacement method is also known as nanoprecipitation method. This method is based on displacement of the semi polar solvent followed by the interfacial deposition of a polymer. (Figure 4). The technique involves dissolving polymer in a water miscible solvent(organic). This solution is then added to an aqueous phase in the presence or absence of a surfactant which can induce precipitation of polymer and thus formation of nanospheres can occur.[13]

Solvent evaporation method

The polymer is dissolved in a suitable organic solvent and then the drug is dispersed into the previous solution. This mixture is then emulsified using suitable emulsifying agent (e.g. gelatin, PVA) to form o/w emulsion. The formed emulsion is then subjected to solvent evaporation via continuous mixing or increasing temperature or by reducing pressure. (Figure 5).[13]

Salting out

The polymer is dissolved in a suitable organic solvent. This is then added to an aqueous phase (that contains suitable emulsifier and high concentration of salts) under mechanical shear stress to induce emulsification. The salts used include magnesium chloride hexa hydrate (60%w/w) or magnesium acetate tetra hydrate (1:3 polymer ratios). Pure water is then added to the formed o/w emulsion under mild stirring to enhance diffusion of organic solvent into aqueous phase to form nanospheres. Finally purified by centrifugation or cross flow filtration to remove salting out reagent. [13]

Controlled gellification method

This method is used to prepare sodium alginate nanospheres. Suitable amount of calcium chloride is added to sodium alginate solution to induce gellification. Then to this add poly-l-lysine in order to form a polyelectrolyte complex. The obtained nanospheres suspension was then stirred for 2hr. Finally the nanospheres are separated via centrifugation.[14]

Desolvation technique

The desolvation technique can be used to prepare nanospheres from natural polymer like albumin. Here the polymeric solution was prepared with polyethylene glycol solution (PEG). The drug after mixing dissolving with ethanol was added drop wise to prepared polymeric solution under magnetic stirring. After that suitable cross linking agent is added and cross linking process is continued for about 12hr. Finally the obtained suspension was centrifuged and lyophilised.[15]

Ionic gelation method

Ionic gelation or coacervation method can be used to prepare nanospheres from natural polymers like gelatin, sodium alginate, chitosan. In this method the aqueous solution of polymer and drug is taken. Due to the electrostatic interaction of the two aqueous phases, they

form a coacervate having the particle size in nanometer range.[16]

CHARACTERISATION OF NANOSPHERES

1. Particle size and distribution

The particle size and distribution are one of the most important characteristics of nanoparticle systems. It determines the in vivo distribution, biological fate, toxicity and targeting ability. It is done by various methods including Scanning electron microscopy (SEM), Transmission electron microscopy (TEM) and Photon correlation spectroscopy. The shape and surface morphology of dried nanospheres done using SEM (Figure 6). The results obtained by photon-correlation spectroscopy are usually verified by SEM or TEM.[17]

2. Zeta potential analysis

The zeta potential is used to characterise the electrical potential and surface charge property of nanospheres. These are influenced by the composition of the particle and the dispersed medium. The zeta potential measurement is also useful to know about charge stability and particle aggregation. It is determined by using zetasizer.[18]

3. Estimation of drug entrapment efficiency (EE %) and drug loading (DL %) percentages

Nanospheres suspension after centrifugation, washing, re-centrifugation and subsequent filtration, an aliquot from the supernatant is taken and diluted with methanol. The free drug can be estimated from the filtrate using uv-visible spectrophotometer. Amount of entrapped drug was calculated by subtracting the amount of free drug from the total amount of drug added in the formulation.[19]

$$\text{EE (W/W)\%} = \frac{\text{Amount of entrapped drug}}{\text{Total amount of the drug added}} \times 100$$

$$\text{DL (W/W)\%} = \frac{\text{Amount of entrapped drug}}{\text{(amount of polymer + entrapped drug)}} \times 100$$

4. Fourier transform infrared (FT-IR) spectroscopy analysis

The chemical integrity and possible chemical interaction between drug and polymer can be estimated by FT-IR analysis using FT-IR spectrophotometer.[19]

5. Differential scanning calorimetry (DSC) analysis

The physical state of the drug inside the nanospheres can be assessed by the DSC analysis after lyophilisation of the investigated nanospheres. About 5 mg of each sample is placed separately into a sealed aluminium pan and heated under nitrogen atmosphere from 25˚C to 300˚C with a heating rate of 10˚C/min. An empty aluminium pan can be used as the reference pan.[20]

6. *In vitro* drug release studies

In vitro release of drug from the selected nanospheres formulations as well as the free drug suspension can be evaluated by dialysis bag diffusion technique using a thermo-stated shaking water bath.[20]

7. Drug release kinetics

In vitro release data obtained are analyzed kinetically to find out the mechanism of drug release from nanospheres. The data thus obtained can be fitted for zero-order, first-order, Higuchi, Hixsoncrowell erosion equation, and Korsmeyer-Peppas equation.[21]

8. Stability study

The stability studies are done to evaluate the effect of storage conditions on various physicochemical parameters of Nanosphere formulations. These studies are helpful in determining the suitable storage conditions. The selected Nanosphere formulations are subjected to both room temperature and refrigerated temperature for about 6 months and they are assessed for changes in physicochemical parameters.[21]

PHARMACEUTICAL APPLICATIONS

Nanospheres have got wide range of applications in the field of medicine. Nanospheres can be used in controlled delivery of pharmacological agents to the target site thus reducing the dose, the frequency of drug administration and consequently the side effects. The targeting action of nanospheres can be applied for tumour targeting, brain targeting, gene targeting.

1. Nanospheres for targeting tumour

Nanospheres have gained much attention for their potential to deliver chemotherapies in cancer treatment. They can deliver a concentrate amount of drug at the tumour site by enhancing permeability or active targeting by ligands present on the Nanosphere surface. (Figure 7).[22]

As the drug distribution is limited to target organ, they reduce the drug exposure to healthy tissues thus reducing toxicity. Inside a tumour, nanospheres target receptors on the blood vessels and on the cancer cells themselves. When the nanospheres are bound it begins to release their drug, which is engulfed by the cancer cells as a result, the drug can attack the cancer cell from inside. Various anticancer drugs are available (figure 8). But one of the drawbacks is that nanospheres have a greater tendency to be captured by liver at the time of biotransformation thus reducing the amount of drug reaching the tumour.[22]

2. Nanospheres for oral drug delivery[23]

The delivery of bioactive molecules like proteins and peptides is very difficult due to their susceptibility to GI degradation by digestive enzymes. Polymeric nanoparticle like Nanosphere allows encapsulation of these bioactive molecules and protects them against enzymatic and hydrolytic degradation.

3. Nanospheres targeting to epithelial cells

Targeting the epithelial cells to to improve the interaction of nanospheres with adsorptive enterocytes and M-cells of Payer's patches in the GI tract can be achieved by either utilizing specific binding to ligands or receptors or those based on nonspecific adsorptive mechanism. The surface of enterocytes and M cells display cell-specific carbohydrates, which may serve as binding sites to colloidal drug carriers containing appropriate ligands.[24]

4. Treatment of autoimmune diseases

Nanospheres also show much promise to treat autoimmune diseases like lupus, multiple sclerosis and Type 1 diabetes.[25]

5. Nanospheres for brain targeting

The blood brain barrier (BBB) present in the central nervous system is made up of impermeable endothelial cells and tight junctions. The BBB only permits transport of selective molecules. With the advancement in nanotechnology an improved drug delivery to the brain can be achieved. Nanospheres can target drug to BBB, as they interact with the receptor transport system present in BBB. So the drugs which cannot easily cross the BBB can pass easily with the help of nanospheres. The drugs used for brain targeting include:

- Leu-enkephalin
- Valproic acid
- Dipeptide kytorphin
- Tubocurarine
- Doxorubicin
- Tacrine[26]

6. Nanospheres for gene targeting

Delivering genes to host cell will tends to initiate immune response. This can be achieved via vaccines based nano medicines. Such vaccines produce both cell mediated and humoral immunity. Nanospheres loaded with plasmid DNA could also serve as an efficient Sustained release gene delivery system due to their rapid escape from the degradative endolysosomal compartment to the cytoplasm compartment. This gene delivery strategy can be used to facilitate bone healing by incorporating therapeutic genes such as bone morphogenic protein.[27]

7. Nanospheres for cosmetics

Biodegradable polymer loaded nanospheres like PLGA nanospheres can be used for cosmetics formulations. Cosmetics are available for skin whitening, antiaging, sensitive skin protection and hair growth.[28]

8. Nanospheres for Nutraceuticals[29]

Many dietary supplements have low bio availabilities when taken orally due to several interacting reasons. Also when it is given orally, its bioavailability and, ultimately, its efficacy depend on the solubility and absorption in the gastrointestinal tract. Nanosphere delivery systems can now be used to deliver dietary supplements and nutraceuticals and thus providing improved bio stability, bioavailability, bioactivity and efficacy. So the advantages for developing such formulations include:

- Improvement of cellular transport
- Release of the active component inside the cell.
- Site-specific targeting
- Longer half-life in the body
- Minimal side effects and enhanced therapeutic value

Table 1: Polymer used for nanospheres preparation.

TYPE OF POLYMER	EXAMPLES	ABBREVIATION
Synthetic homopolymer	Poly(acrylate) and poly)methacrylate) Poly(lactide-co-glycolide) Poly(n- butylcyanoacrylate) Poly(lactide) Poly methyl methacrylate	Eudrajit PLGA PBCA PLA PMMA
Natural polymers	Chitosan Agar Albumin Gelatine Sodium alginate	
Colloid stabilizers	Dextran Pluronic F68 Poly(vinyl)alcohol Tween 80	 F68 PVA
Copolymers	Poly(lactide)-poly(ethylene glycol) Poly(lactide-co-glycolide)-poly(ethylene glycol)	PLA-PEG PLGA-PEG

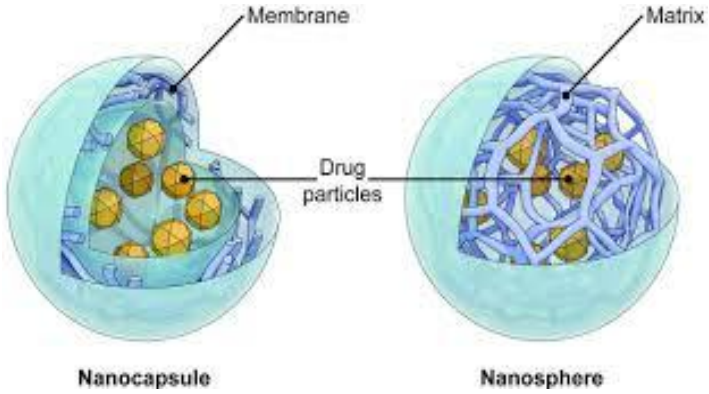

Figure 1: Polymeric nanoparticle.

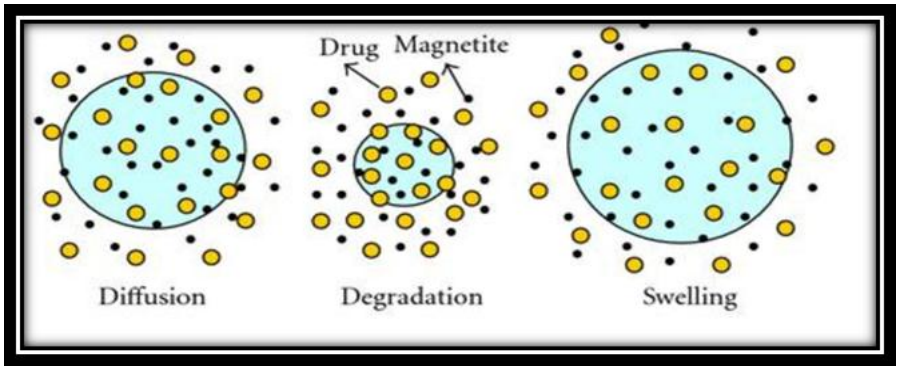

Figure 2: Mechanism of drug release.

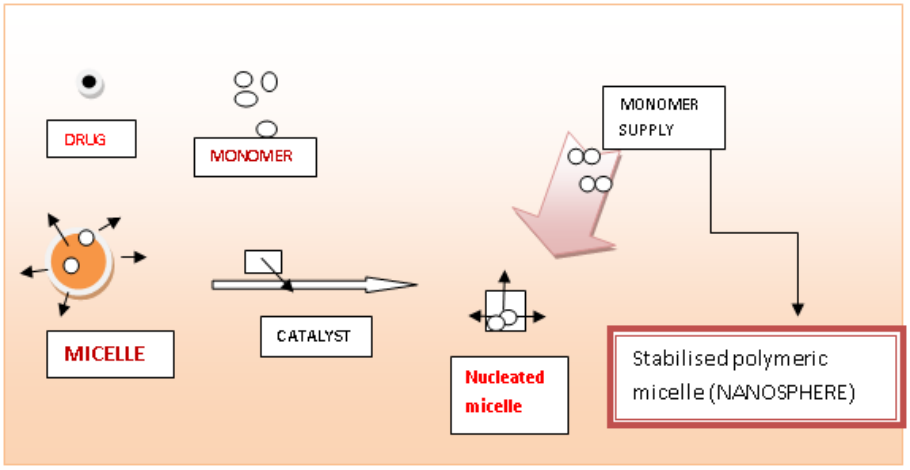

Figure 3: Polymerisation.

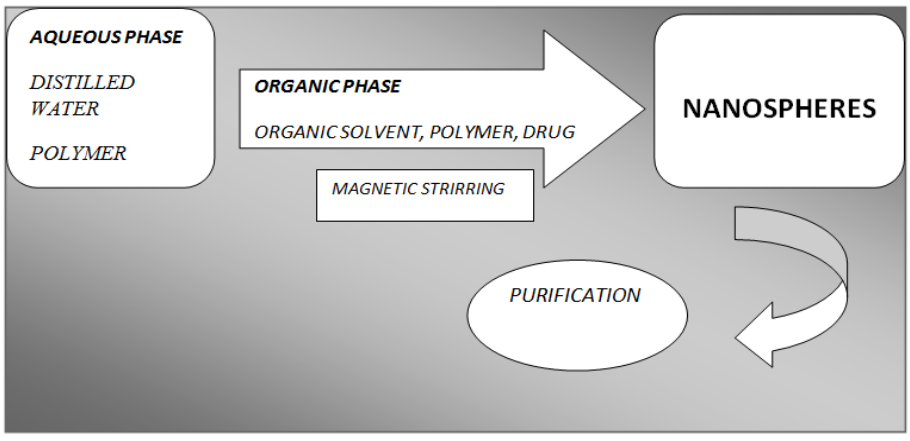

Figure 4: Solvent displacement.

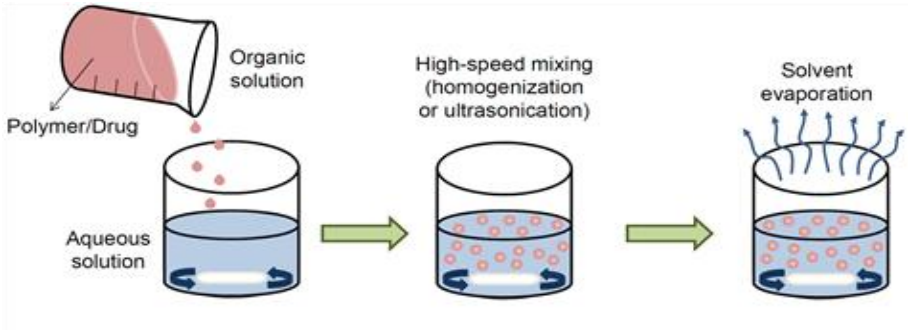

Figure 5: solvent evaporation.

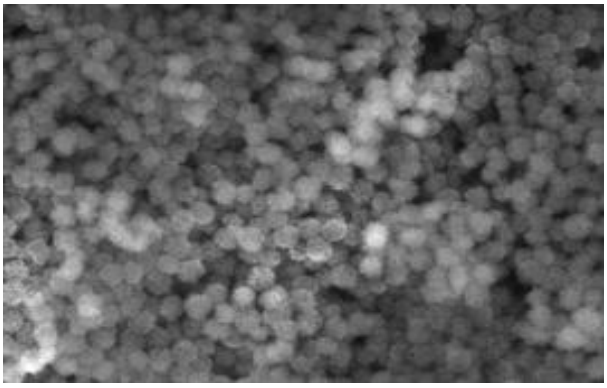

Figure 6: Microscopic image of nanospheres by SEM.

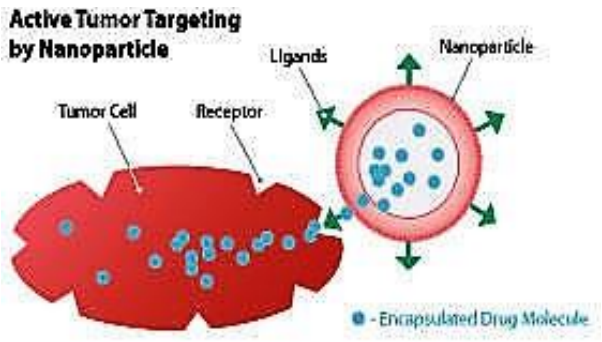

Figure 7: Tumour targeting mechanism.

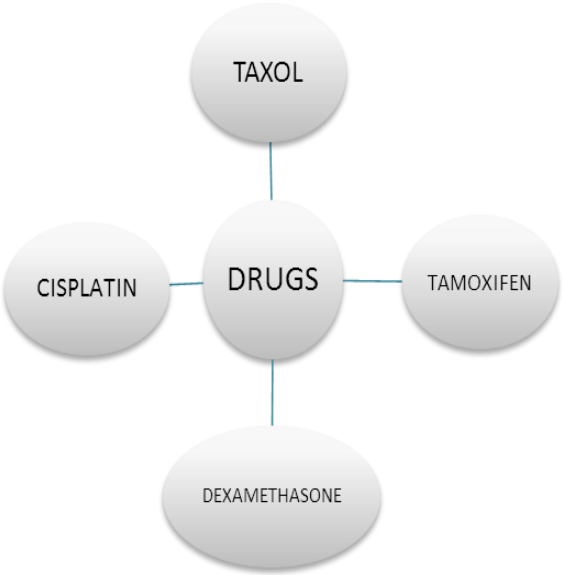

Figure 8: Anticancer drugs.

CONCLUSION

The combination of nanotechnology and polymers are extremely useful in various applications which led to development of polymeric nanoparticle like Nanospheres. Nanospheres can be prepared by various methods. Of these several methods solvent displacement method is the best one. They have been widely used as a targeted drug delivery system. So they can target tumour cells, brain cells etc. Therefore nanospheres have the ability to convert poorly soluble, poorly absorbed drugs into better deliverable drugs.

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