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A REVIEW ON NANOSPHERES

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ABSTRACT

Nanosphers is the division of polymeric nanoparticle having size range 10-200nm. The tiny capsule of drug store house is called vesicles and the solid skeleton structure is called Nanospheres. Nanospheres are biodegradable or non-degradable. It can enclose variety of drugs enzymes, genes and is characterized by a long circulation time. The review briefly explains about formulation aspects including the polymers used for its preparation, different techniques for formulating nanospheres. Also about characterization parameters used for the nanospheres.

Keywords: Nanotechnology, Nanospheres.

I. INTRODUCTION

Nano drug delivery system is one of the field of science, the explosive growth of nanotechnology has brought rapid development in drug delivery is called Nano drug delivery system (NDDS).[1,2] It's the study to individual molecules, atoms or compounds into structures to produces materials having special properties. It's the study of small structures whose dimensions in the nanometers scale length (1-100).[3,4] Nano DDS can cause the drug to remain in blood circulation for a long time, thereby leading to lesser fluctuations in plasma levels and therefore, minimal side effects. In these Nano DDS includes large range of Nano carriers such as nanoparticles, micelles, nanogels, Dendrimer, solid lipid nanoparticles, polymersomes, liposomes, carbon nanotubes, nanocrystals, silica nanoparticles, nanocapsules and nanospheres (show in figure1)[1,5,6].

Nanospheres are the division of polymeric nanoparticles. Nanospheres are matrix type structure, which the spherical particulate systems are characterized by a size range between 10-200nm-are widely used as carriers in drug delivery systems in clinical application.[7] Basically the drug dissolved, encapsulated, entrapped and attached to the matrix of polymer. The drug uniformly dispersed to form homogeneous structure. Nanospheres can be amorphous or crystalline in nature, and also they have protected the drug from enzymatic and chemical degradation.[8,9]. Nanospheres can be biodegradable or non- degradable. Some of biodegradable nanospheres include modified starch nanospheres, albumin nanospheres, gelatin nanospheres, polypropylene dextran nanospheres and polylactic acid nanospheres. Administration of medication via systems offers high advantageous, they can be ingested or injected. Nanospheres can be used for the organ targeted release of drug. Nanospheres offer high potential to formulate diverse range systems that can be given by new patent life to known effective pharmacophores.[3,10].

The main objectives of formulation of Nanospheres:

- Control the particle size
- Dose regimen
- Therapeutically release the active agents to achieve the site specific action at the therapeutically optimal rate.[11]

Advantages of Nanospheres

- Nanospheres can easily pass through the smallest capillary vessels.
- It can be used target the organs like liver, spleen, lungs, spinal cord.[12]
- Nanospheres reduce the toxicity and reduction in the frequency of the dosages.
- Nanospheres can be administered via various routes (oral, nasal, parenteral route).
- Rapid clearance & Site specific targeting[13]

Disadvantages of Nanospheres

- Nanospheres are difficult to handle in liquid and dry form.

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- Requires skills to manufacture.
- They are prone to particle aggregation due to size and larger surface area.[14]

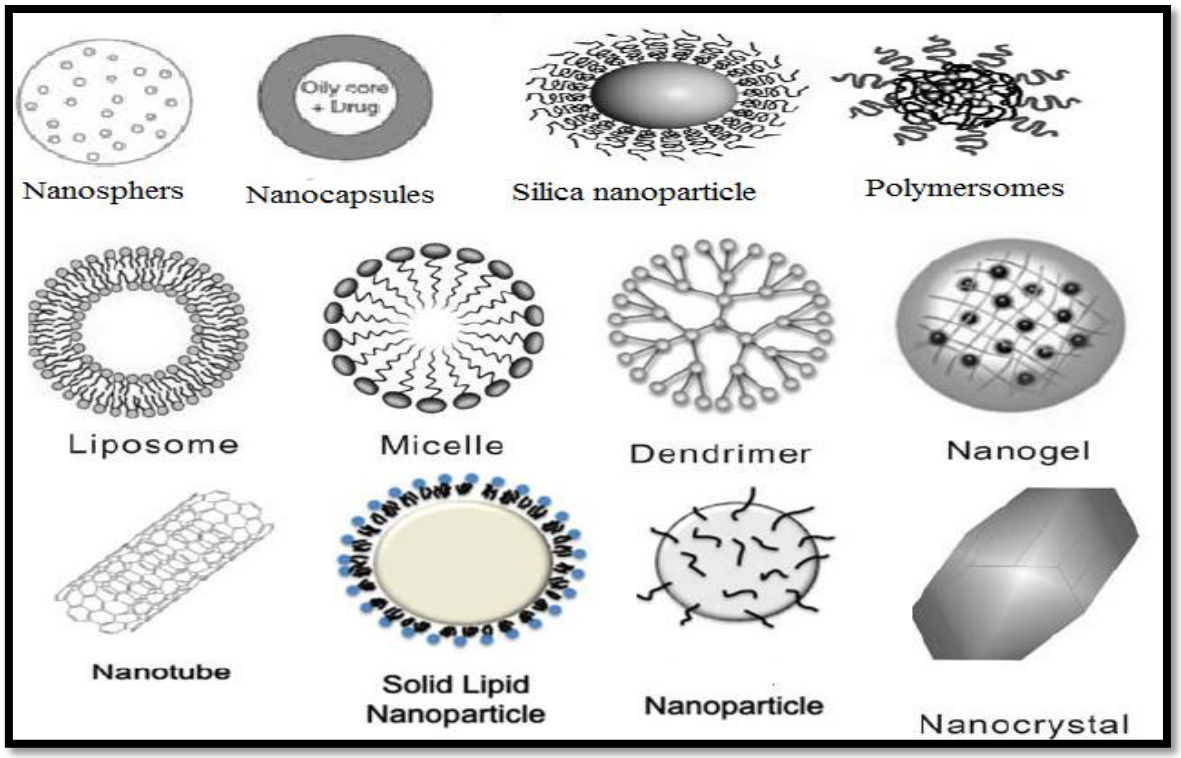

Fig 1: Nano drug delivery systems (nanoparticles, micelles, nanogels, Dendrimer, solid lipid nanoparticles, polymersomes, liposomes, carbon nanotubes, nanocrystals, silica nanoparticles, nanocapsules and nanospheres)

Polymers used in design of the nanospheres

Different type of polymers are used for the preparation of nanospheres.[15] Natural, biodegradable, synthetic, homo and copolymers are used for the preparation of nanospheres. The polymer are compatible with our body (i.e., non-toxic & non-allergent).The natural polymers used for drug delivery system have focused on proteins (gelatin& albumin) and polysaccharides (chitosan, starch). Also biodegradable synthetic polymers including homopolymers and co polymers have been widely used for pharmaceutical application.[1,3,16]

S.No	Type of polymer	Example	Abbreviation
1	Natural polymers	Chitosan Starch Alginate Gelatin Albumin	
2	Synthetic Homopolymers	PLA PLGA PCL	Poly(lactide) Poly(lactide-co-glycolide) Poly(ε-caprolactone)}
3	Copolymers	PLA-PEG PLGA-PEG	Poly(lactide)-poly(ethylene glycol) Poly(lactide-co-glycolide)-

		PCL-PEG PLGA –PEG-PLGA	poly(ethylene glycol) poly(ε-caprolactone)-poly(ethylene glycol) Poly(lactide-co-glycolide)-poly(ethylene glycol) – poly(lactide- co-glycolide)
4	Colloid stabilizer	Dextran Pluronic F68 PVA Tween80	 F68 Polyvinyl alcohol

II. METHOD OF PREPARATION OF NANOSPHERES

Various types of methods are used for the preparation of nanospheres. Different methods should include

- Polymerization method
- Solvent evaporation
- Solvent displacement technique
- Double emulsion method[8,9]
- Controlled gellification method
- Desolvation technique
- Ionic gelation method
- Salting out method[3]

Polymerization method

This method also called as interfacial polymerization and emulsification polymerization. In this method polymer (poly methyl methacrylate and poly cyano crylate) are emulsified i.e. emulsification polymerizations. Monomers are polymerized to form the nanospheres in an aqueous solution. After the completion of the polymerization, the drug can be incorporated by dissolving in the polymerization medium or via adsorption onto the nanospheres (Figure2). The obtained nanospheres are purified, centrifuged and finally freeze dried.[17]

Desolvation technique

In these technique used for the preparation nanospheres, and then natural polymers (albumin) are used in this technique. Here polymeric solution was prepared by using poly ethylene glycol, and after drug dissolve in the organic solvent (ethanol). Then above solution (organic phase) was added drop wise in to the polymeric solution under magnetic stirring. After then added cross linking agent and continue the cross linking process for 12hours. Finally nanospheres suspension was obtained, centrifuged and lyophilized.[18,19] (Figure3)

Solvent evaporation method

In this method polymer dissolved in a suitable organic solvent, thus mixture sonicated for 2min, and then the drug dispersed into the previous solution and again sonicated for 2min. this above mixture is then emulsified using the suitable emulsifying agent (e.g. poly vinyl alcohol, gelatin) to form O/W emulsion. To formed emulsion is subjected to solvent evaporation via continuous mixing or increasing temperature or by reducing pressure. After then process completed nanospheres are formed.[3,20](Figure4)

Salting out method

The polymer dissolved in suitable organic solvent. Then organic phase dissolved in aqueous phase (that contains suitable emulsifier and high concentration of salts) under mechanical shear to induce emulsification and formed O/W emulsion (Examples of high concentrate salts magnesium chloride hexa hydrate or magnesium acetate tetra hydrate). Pure water added to the above emulsion under mild

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stirring to enhance diffusion of organic solvent into the aqueous phase to form nanospheres. Finally nanospheres purified by centrifugation and remove the salting out agent. [20](figure5)

Solvent displacement method

This method also called as nanoprecipitation. In these method polymer dissolve in the organic solvent (water miscible solvent). Above solution dispersed into the aqueous phase in the presence or absence of a surfactant which can be induced precipitation of polymer and thus formation of nanospheres can occur.[20,21](Figure6)

Controlled gellification method

In this method preparation of nanospheres by using natural polymers (sodium alginate), suitable amount of calcium chloride is added to sodium alginate solution to induce gellification. Poly –l-lysine added to above solution in order to form a polyelectrolyte complex. The obtained nanospheres suspension was then stirred for 2hrs. Finally nanospheres are obtained are separated via centrifugation.[22,23](Figure7)

Ionic gelation method

This method also called as coacervation method. In this method nanospheres prepare by using natural polymers like sodium alginate, gelatin, and chitosan. In this method aqueous solution of polymer and drug is taken. Crosslinking agent added to another aqueous phase. Due to the electrostatic interaction of the two phases, they form a coacervate having the particle size in nanometer range.[24,25](Figure8)

D**ouble emulsion method**

Double emulsion method of nanospheres preparation involves the formation of the multiple emulsions or the double emulsion is best suited to water soluble drugs. Drug and polymer transfer into the internal aqueous phase. In this aqueous solution dispersed into the organic polymer solution with continuous stirring to get single emulsion. This solution was added drop wise into the external aqueous solution (containing surfactant) with continuous stirring by homogenization or sonication to get double emulsion to assist the removal of residual solvents. The nanospheres thus obtained were washed, dried and lyophilized.[26](Figure9)

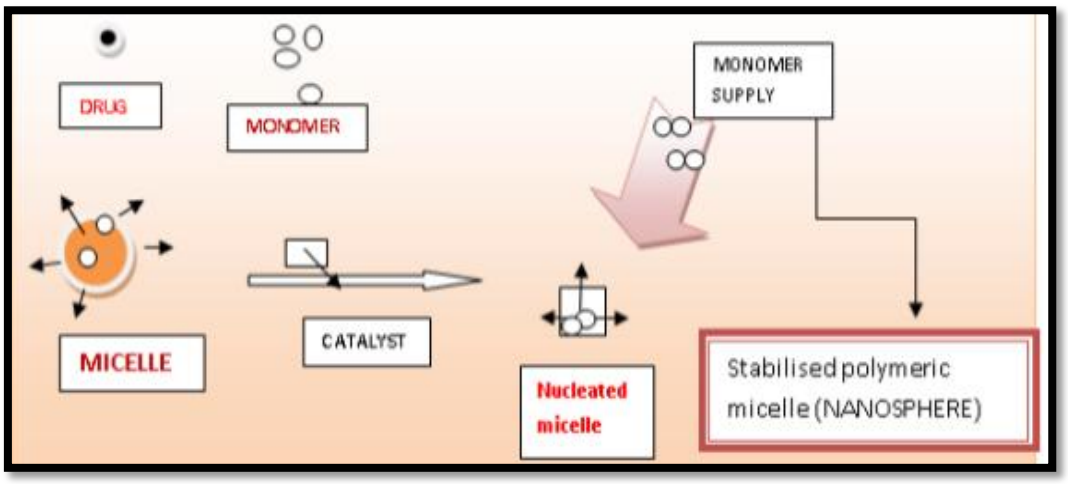

Fig-2: Polymerization

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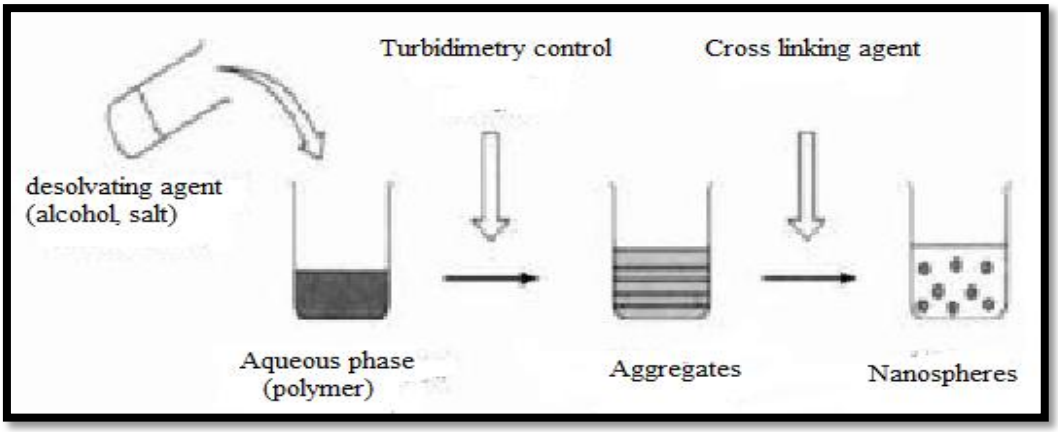

Fig-3: Desolvation

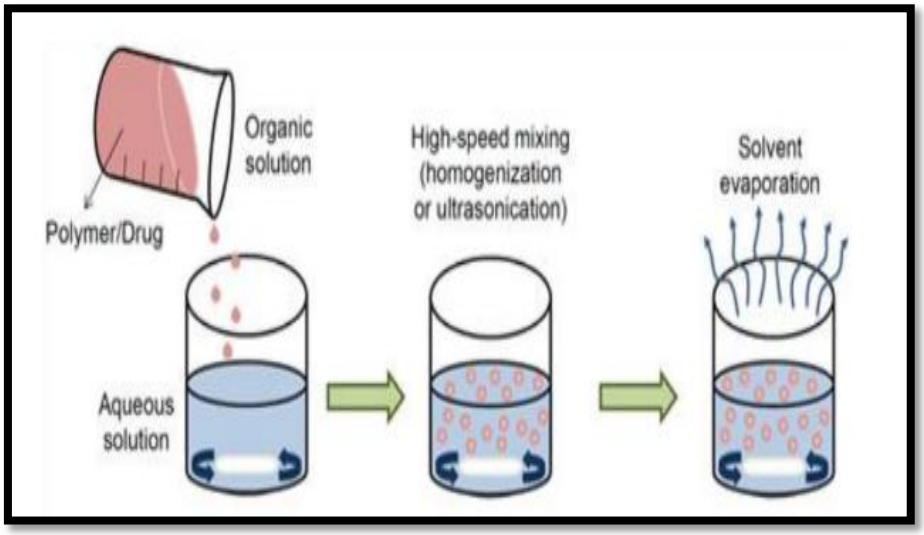

Fig-4: Solvent evaporation

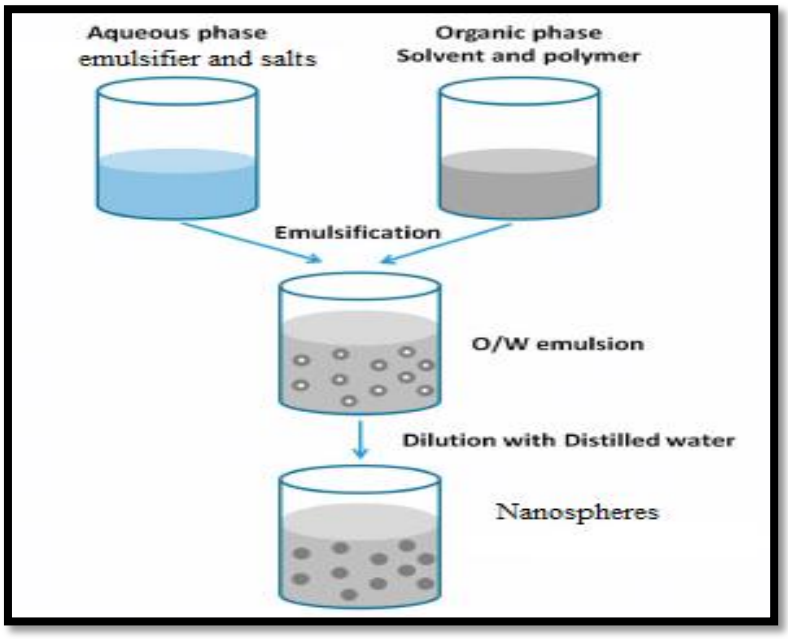

Fig-5: Salting out

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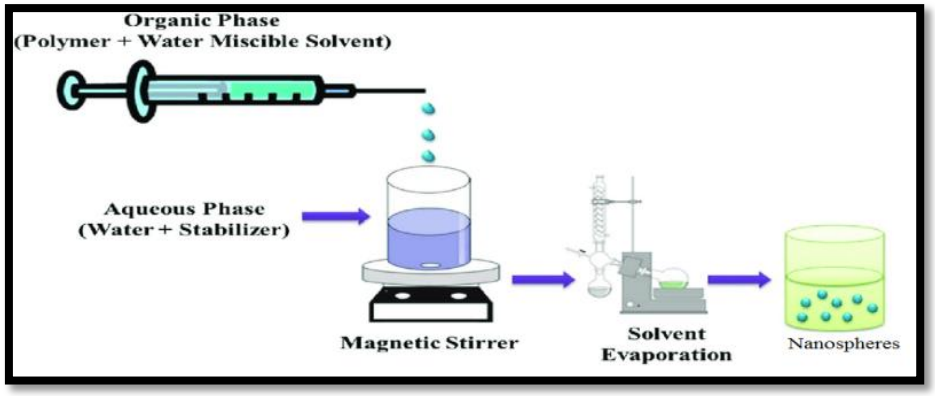

Fig-6: Solvent displacement

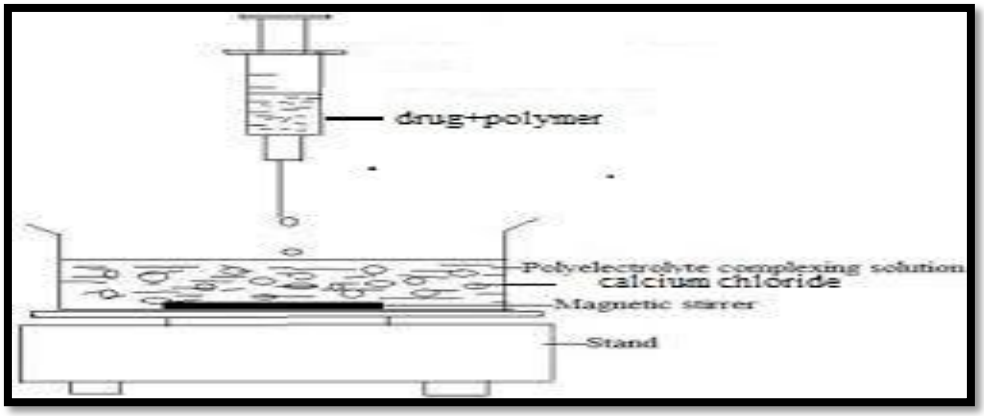

Fig-7: controlled gellification

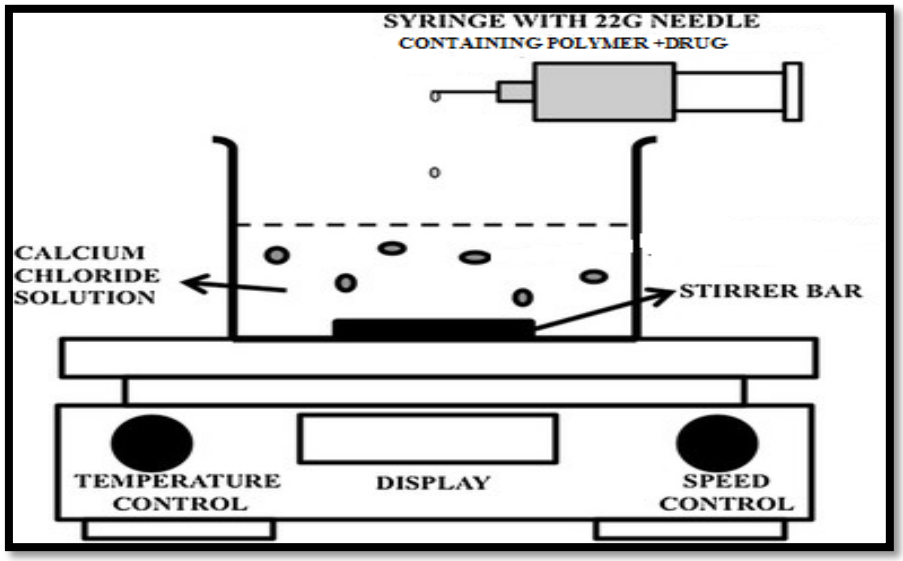

Fig-8: ionic gelation

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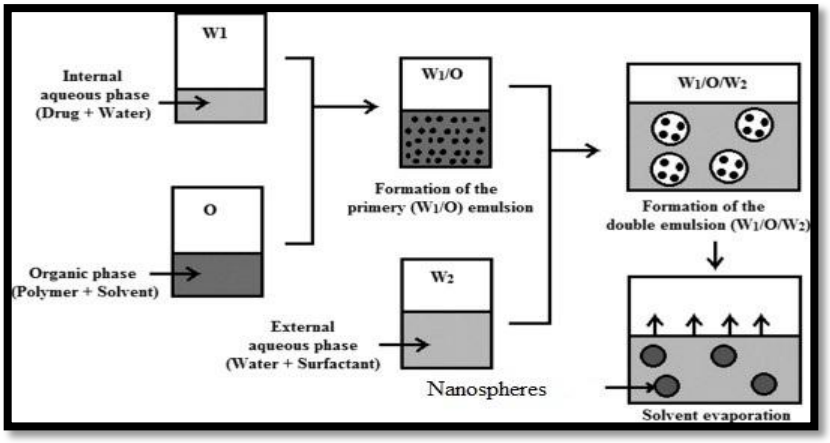

Fig-9: Double emulsion

III. CHARACTERIZATION OF NANOSPHERES

A. **Particle size and distribution:** It's the most important characterization. It determines particle size, in vivo distribution & toxicity of nanospheres. In these characterization done by various methods including scanning electron microscopy (SEM), Transmission electron microscopy (TEM) & photon correlation spectroscopy.[27]

- Scanning electron microscopy (SEM): Scanning electron microscopy was used to determine the shape and surface characteristics of the prepared nanospheres. The nanospheres are diluted with water, in these sample spread over glass slide and dried at room temperature (25°C), to form a thin film on glass slide. The shape and size determine by using scanning electron microscopy (SEM) & result obtained.[28]
- Transmission electron microscopy (TEM): A TEM instrument was used to examine the morphology of the optimized nanospheres. A drug loaded nanospheres was placed on the copper grids to form a film, followed by negative staining with drop of 2% (W/V) (ex: Phosphotungstic acid). The air dried sample was then viewed by TEM.[29]

B. **Zeta potential analysis**: It is used for the determination of electrical potential and surface charge property of nanospheres. These are influenced by the composition of the particle and the dispersed medium. It also used to measure the charge stability and particle aggregation. it is determined by the using zetasizer.[30]

C. **Fourier transform infrared (FT-IR) spectroscopy analysis**: In order to check the chemical integrity and possible chemical interaction between drug and polymer can be estimated by FT-IR analysis using FT-IR spectrophotometer.[31]

D. **Differential scanning colorimetry (DSC) analysis**: Thermal properties of nanospheres were determined by thermogravimetry (TG) by using DSC analyzer. The sample (10mg) placed on sealed aluminium pan and heated form 50oc-350oc at heating rate of 10-25oC/min under nitrogen atmosphere.[32]

E. **Swelling index:** An accurately weighed amount of nanospheres were placed in simulated gastric fluid like pH 1.2 and allowed to swell to a constant weight. The nanospheres were removed, blotted with filter paper and the changes in their weight were measured at an interval period and recorded. The degree of swelling was then calculated from the formula:[33]

$$\text{Swelling index} = \frac{\text{weight after swelling (Wf)} - \text{Initial weight (WO)} \times 100}{\text{Initial weight (WO)}}$$

F. **Drug entrapment efficiency (EE%) and Drug loading (DL%)** : Nanospheres are centrifugation, washing, re-centrifugation and subsequent filtration, an aliquot from the supernatant is taken and diluted. The free drug can be estimated from the filtrate using UV-Visible spectrophotometer. Amount

of entrapped drug was calculated by subtracting the amount free drug from the total amount of drug added in the formulation.[34]

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

$$\text{Drug loading (W/W)\%} = \frac{\text{Amount of entrapped drug} \times 100}{\text{Amount polymer} - \text{entrapped drug}}$$

G. **In-vitro drug release**: In-vitro drug release of drug loaded nanospheres can be evaluated by dialysis bag diffusion technique using a thermo –stated shaking water bath.in these technique dialysis membrane tube containing phosphate buffer solution and maintained temperature 37oC at the shaking rate of 120rpm.[35]

H. Drug release kinetics: In this characterization in-vitro release data obtained are analyzed kinetically to find the mechanism of drug release of nanospheres. The obtained data fitted into for zero-order, first order, Higuchi, Hixson Crowell erosion equation, and Korsmeyer-peppas equation.[36]

I. Stability studies: As per ICH guidelines the stability studies are done to evaluate the effect of storage conditions and various physicochemical parameters of nanospheres formulations. These studies are helpful in determining the suitable storage conditions. The selected nanospheres formulations are subjected to both room temperature and refrigerated temperature for about 6 months and they are assessed for changes in physicochemical parameters.[36]

IV. CONCLUSION

The combination of nanotechnology and polymers are extremely useful to development of polymeric nanoparticle like Nanospheres. Nanospheres can be prepared by various methods. Of the several methods solvent displacement method is the best one. Nanospheres have the ability to convert poorly soluble, poorly absorbed drugs into better deliverable drugs.

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