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PREPARATION METHODS FOR NANOPARTICLE: A SMART CARRIER SYSTEM FOR TREATMENT OF CANCER

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ABSTRACT

Novel approaches of drug delivery such as formulating the polymeric nanoparticles is revolutionizing the future of medicines. However there are several methods to prepare polymeric nanoformulation such as thin film hydration, Solid dispersion, Emulsion polymerization, Fessi method, emulsion-diffusion-evaporation method, interfacial polymerization method, Microemulsion, Fatty acid coacervation technique, High pressure emulsification-solvent evaporation technique. But the selection of a suitable method is a real concern, as the selection of inappropriate method may lead to loss of material resources, financial resources and time of research. Newly potent and target specific formulation led to enhance therapeutic utility. These challenges, coupled with the complexity and variety, are fueling the advancement of novel drug delivery systems that overcome bioavailability and delivery obstacles. In present scenario, nanoparticles have been acting as carriers for delivering a wide range of potential drugs. Due to their versatility and wide range of properties and they represent a promising drug delivery system of controlled and targeted release.

KEYWORDS: Polymeric nanoparticles, bioavailability, preparation methods for nanoparticles, therapeutic utility.

INTRODUCTION

The polymeric nanoparticles (PNPs) are prepared from biocompatible and biodegradable polymers in size between 10-1000 nm where the drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation for

nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed.[1] Polymers are very convenient materials for the manufacture of countless and varied molecular designs that can be integrated into unique nanoparticles constructs with many potential medical applications. Several methods have been developed during the last two decades for preparation of PNPs but the selection of an appropriate method is a real concern, as the selection of appropriate method reduces the loss of material resources, financial resources and time of research. Target specific formulation led to enhance therapeutic utility. So by considering these challenges, we have tried to summarize the different methods involved for the preparation of polymeric nanoparticles there by they will be target to specific sites and reduces the toxicity and maintain the drug concentration adequately within the therapeutic window and increases bioavailability.[2]

Classification of Nanoparticles

Nanoparticles are broadly classified in to three different classes as follows.

- One dimension nanoparticles for example biological sensors, magneto-optic and optical device, fiber-optic systems.
- Two dimension nanoparticles for example Carbon nanotubes.
- Three dimension nanoparticles for example Dendrimers, Quantum Dots etc.[3]

Preparation methods of nanoparticles

Targeting specific tissue or cells by the means of specifically designed carriers that are attached to drugs is a more reliable approach in drug delivery system. Such approach is known as targeting. Size reduction of targeted formulation and designing its pathways for suitable drug delivery system is a more fundamental and successful approach that forms the basis of nanotechnology. Several methods have been developed by different researchers to formulate polymeric nanoparticles and these techniques are classified based on whether the particle formation involves a polymerization reaction or nanoparticles form directly from a macromolecule or preformed polymer.[4] Here we have described the different techniques for preparation of polymeric nanoparticles as follows:

- ✓ Interfacial polymerization method
- ✓ Solid dispersions method
- ✓ Emulsion polymerization method

- ✓ High pressure emulsification-solvent evaporation technique
- ✓ Emulsion-diffusion evaporation method
- ✓ Microemulsion method
- ✓ High pressure emulsification-solvent evaporation technique

Interfacial polymerization method

It is one of the well-established methods used for the preparation of polymer nanoparticles[5,6] It involves step polymerization of two reactive monomers or agents, which are dissolved respectively in two phases (i.e., continuous- and dispersed-phase), and the reaction takes place at the interface of the two liquids. Nanometer-sized hollow polymer particles were synthesized by employing interfacial cross-linking reactions as polyaddition and polycondensation or radical polymerization. Oil-containing nanocapsules were obtained by the polymerization of monomers at the oil/water interface of a very fine oil-in-water micro-emulsion. The organic solvent, which was completely miscible with water, served as a monomer vehicle and the interfacial polymerization of the monomer was believed to occur at the surface of the oil droplets that formed during emulsification. To promote nanocapsule formation, the use of aprotic solvents, such as acetone and acetonitrile was recommended. Protic solvents, such as ethanol, n-butanol and isopropanol, were found to induce the formation of nanospheres in addition to nanocapsules. Alternatively, water-containing nanocapsules can be obtained by the interfacial polymerization of monomers in water-in-oil micro-emulsions. In these systems, the polymer formed locally at the water-oil interface and precipitated to produce the nanocapsule shell.

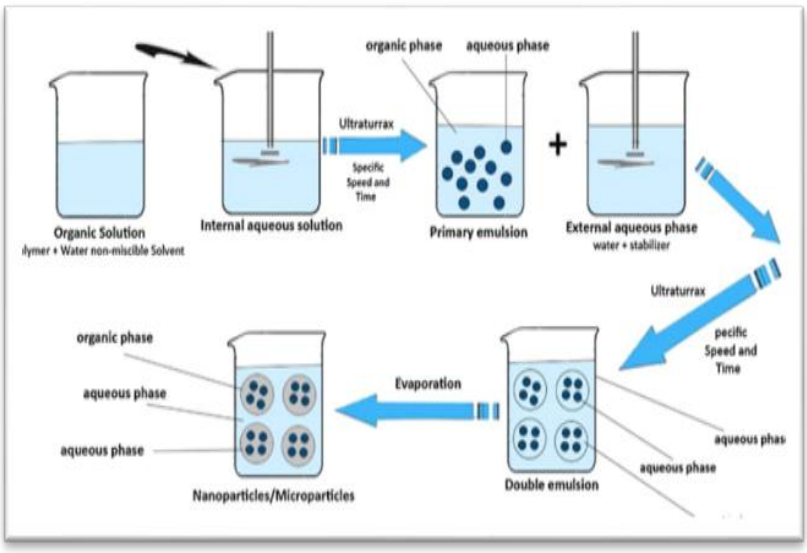

Fig.no.2: Prepartion of nanoparticles by Interfacial polymerization.

- **Solid dispersions method**

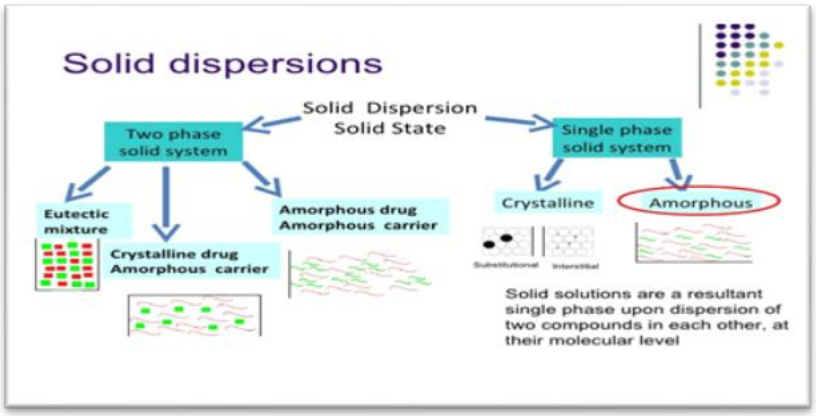

Fig.no.3: Prepartion of nano particles by Solid dispersions method.

- **Emulsion polymerization method:** Emulsion polymerization is one of the fastest methods for nanoparticle preparation and is readily scalable. The method is classified into two categories, based on the use of an organic or aqueous continuous phase. The continuous organic phase methodology involves the dispersion of monomer into an emulsion or inverse microemulsion, or into a material in which the monomer is not soluble (nonsolvent). Polyacrylamide nanospheres were produced by this method. As one of the first methods for production of nanoparticles, surfactants or protective soluble polymers were used to prevent aggregation in the early stages of polymerization. This procedure has become less important, because it requires toxic organic solvents, surfactants, monomers and initiator, which are subsequently eliminated from the formed particles. As a result of the non biodegradable nature of this polymer as well as the difficult procedure, alternative Approaches are of greater interest. Later, poly(methylmethacrylate) (PMMA), poly(ethylcyanoacrylate) (PECA), and poly(butylcyanoacrylate) nanoparticles were produced by dispersion via surfactants into solvents such as cyclohexane (ICH, class 2), n-pentane (ICH, class 3), and toluene (ICH, class 2) as the organic phase. In the aqueous continuous phase the monomer is dissolved in a continuous phase that is usually an aqueous solution, and the surfactants or emulsifiers are not needed. The polymerization process can be initiated by different mechanisms. Initiation occurs when a monomer molecule dissolved in the continuous phase collides with an initiator molecule that might be an ion or a free radical. Alternatively, the monomer molecule can be transformed into an initiating radical by high-energy radiation, including g-radiation, or ultraviolet or strong visible light. Chain growth starts when initiated monomer ions or monomer radicals collide with other

monomer molecules according to an anionic polymerization mechanism. Phase separation and formation of solid particles can take place before or after termination of the polymerization reaction.

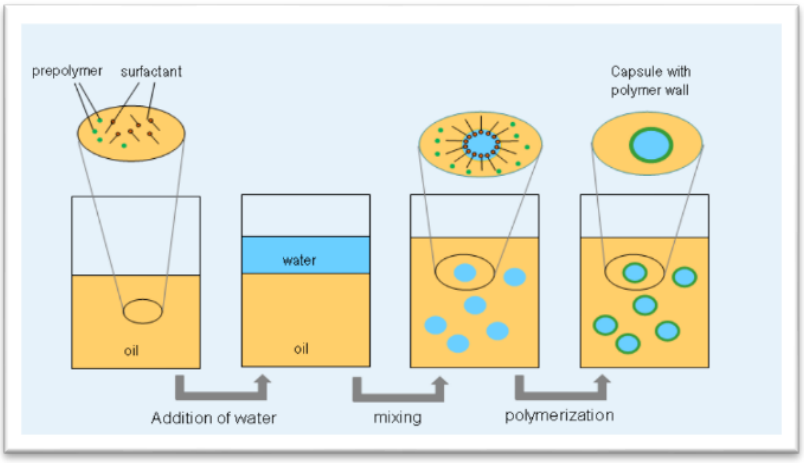

Fig.no.4: Prepartion of nanoparticles by emulsion poymarization method.

- **High pressure emulsification-solvent evaporation technique**

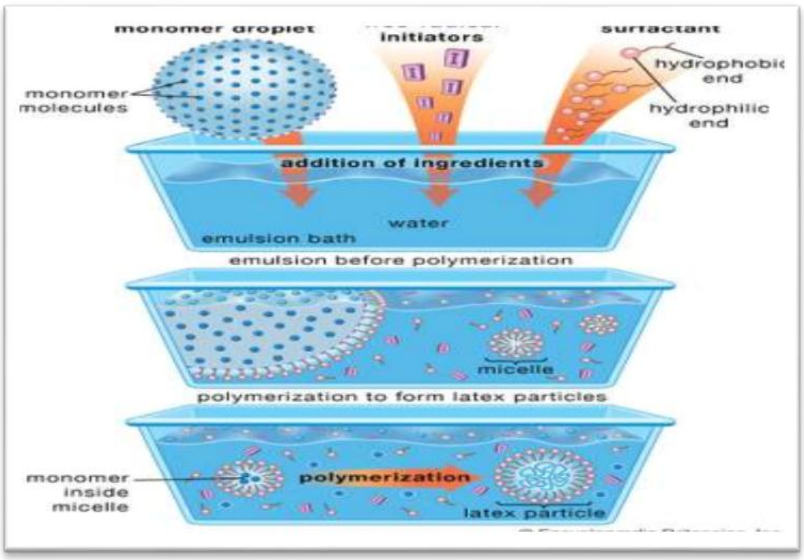

Fig.no.5: Prparation of nanoparticales by high pressure emulsification-solvent evaporation.

Emulsion-diffusion evaporation method

This is another widely used method to prepare nanoparticles. The encapsulating polymer is dissolved in a partially water-miscible solvent (such as propylene carbonate, benzyl alcohol), and saturated with water to ensure the initial thermodynamic equilibrium of both liquids. Subsequently, the polymer-water saturated solvent phase is emulsifi ed in an aqueous solution

containing stabilizer, leading to solvent diffusion to the external phase and the formation of nanospheres or nanocapsules, according to the oil-to-polymer ratio. Finally, the solvent is eliminated by evaporation or fi ltration, according to its boiling point. This technique presents several advantages, such as high encapsulation effi ciencies (generally 70 %), no need for homogenization, high batch-to-batch reproducibility, ease of scaleup, simplicity, and narrow size distribution.

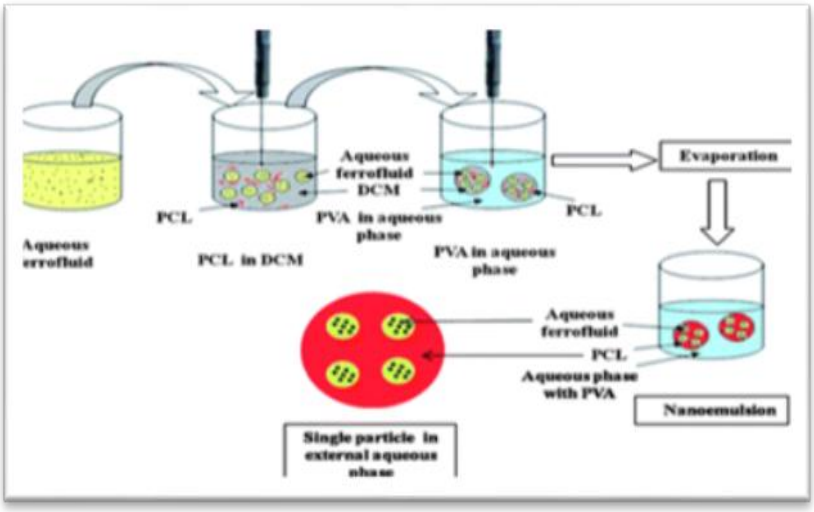

Fig.no.6: Preparation of nanoparticales by emulsion- diffusion evaporation method.

Microemulsion method

- Ultrafine metal nanoparticles of diameter between 5 nm and 50 nm can be prepared by water-in-oil microemulsions (the details of microemulsions are given in Lecture 4 of Module.
- The nanodroplets of water are dispersed in the oil phase. The size of the droplets can be varied in the range of 550 nm by changing the water/surfactant ratio. The surfactant molecules provide the sites for particle nucleation and stabilize the growing particles. Therefore, the microemulsion acts as a microreactor. The reactant metal salts and reducing agents are mostly soluble in water. Therefore, the nucleation of particles proceeds in the water pools of the microemulsion. One microemulsion contains the metal salt and the other microemulsion contains the reducing agent.

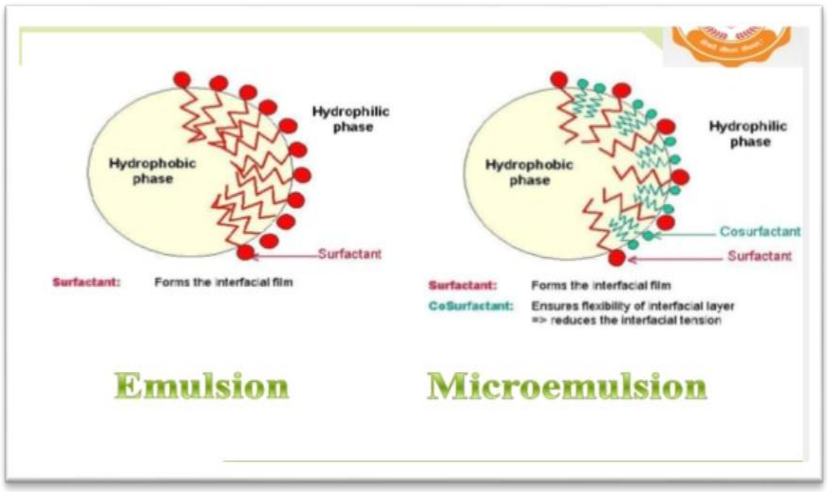

Fig.no.7: Prepartion of nanoparticles by emulsion method.

- **Solvent evaporation method**

Solvent evaporation method is one of the most frequently used methods for the preparation of nanoparticles. This method involves two steps (fi rst is emulsifi cation of the polymer solution into an aqueous phase and second is evaporation of polymer solvent, inducing polymer precipitation as nanospheres). This method is based on the solubility of polymer and hydrophobic drug since both polymer and hydrophobic drug are dissolved in an organic solvent (dichloromethane, chloroform or ethyl acetate) which is also used as the solvent for dissolving the. Mixture obtained from polymer and drug solution is then emulsifi ed in an aqueous solution. This aqueous solution contains surfactant or emulsifying agent to form oil in water (o/w) emulsion. Once the stable emulsion forms, the organic solvent is evaporated either by continuous stirring or by reducing the pressure. Size range of nanoparticles was found to be infl uenced by the concentrations and type of stabilizer, polymer concentration and homogenizer speed.[7] Ultrasonication or high-speed homogenization may be often employed in order to produce small particle size.[8] The nano particles are collected by ultracentrifugation and washed with distilled water to remove stabilizer residue or any free drug and lyophilized for storag]. Modifi cation of this method is known as solvent evaporation method and high pressure emulsifi cation This method involves preparation of a emulsion which is then subjected to homogenization under high pressure followed by overall stirring to remove organic solvent.

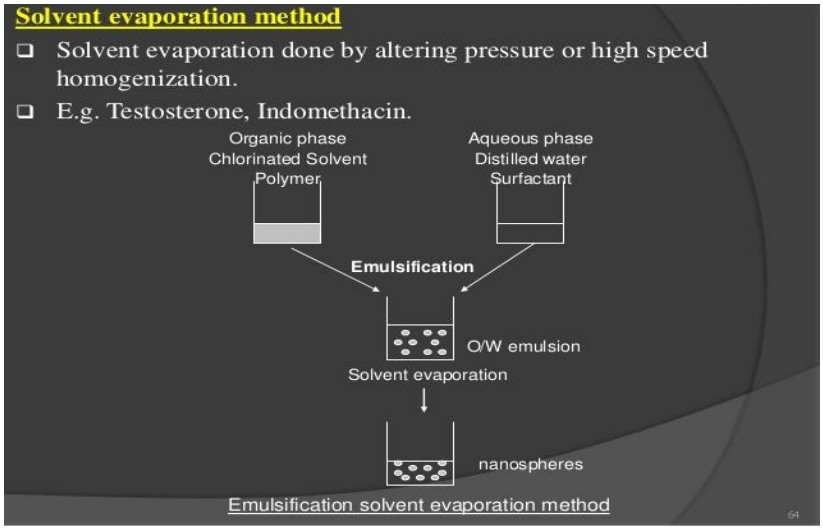

Fig.no.8: Prepartion of nanopaticles by solvent evaporation method.

Characterization of Nanoparticles

Characterization of nanoparticles is based on the size, morphology and surface charge, using such advanced microscopic techniques as atomic force microscopy (AFM), scanning electron microscopy (SEM) and transmission electron microscopy (TEM). Properties such as the size distribution, average particle diameter, charge affect the physical stability and the in vivo distribution of the nanoparticles. Properties like surface morphology, size and overall shape are determined by electron microscopy techniques. Features like physical stability and redispersibility of the polymer dispersion as well as their in vivo performance are affected by the surface charge of the nanoparticles.[9]

Advantages of polymeric nanoparticles

Increases the stability of any volatile pharmaceutical agents, easily and cheaply fabricated in large quantities by a multitude of methods-

- They offer a significant improvement over traditional oral and intravenous methods of administration in terms of efficiency and effectiveness.
- Delivers a higher concentration of pharmaceutical agent to a desired location.
- The choice of polymer and the ability to modify drug release from polymeric nanoparticles have made them ideal candidates for cancer therapy, delivery of vaccines, contraceptives and delivery of targeted antibiotics.
- Polymeric nanoparticles can be easily incorporated into other activities related to drug delivery, such as tissue engineering.[10,11]

Disadvantages

- Nanoparticles caneasily become, breathing in can potentially damage the lungs.
- They might be toxic to some types of cell, such as skin, bone, brain and liver cells.

APPLICATIONS OF NANOPARTICLES

- **Parenteral administration**

  Following intravenous injection, many nanoparticle systems including chitosan NP exhibi ted a marked tendency to accumulate in a number of tumors. One possible reason for the phenomenon may involve the leakiness of tumor vasculature.[12]

- **Delivery of drugs**: NBs can be potentially utilized in delivery of drugs like doxorubicin in vitro and in vivo. These NBs reach the tumor and get accumulated which is followed by formation of microbubbles by coalescing of nanobubbles.
- **Gene therapy:** Liposomal nanobubbles and microbubbles are also being studied for effective non viral vectors for gene therapy. Nanobubbles combined with ultrasound exposure have shown improved transfer of gene in both in vitro and in vivo studies.[13]
- **Thrombolysis:** Nanobubbles are also being investigated for removal of clot in vascular system in combination with ultrasound. This process is called as sonothrombolysis. This method is non invasive and causing less damage to endothelium.
- **Toxicity:** NBs are not that much toxic since the disruption of the microbubbles occurs only at the targeted site when it's being exposed to ultra sound waves. Therefore drug is released at a particular site.
- **Identification of proteins:** Magnetic microparticle probes with nanoparticle probes have been used for identifi cation of proteins like prostate specifi c antigen.[14]

CONCLUSIONS AND FUTURE WORK

A number of nanoparticles-related research projects are actively being conducted in several countries. To establish a good correlation between nanoparticles and particlebased nanostructures or devices, it is necessary to secure human resources with a systematical organization, e.g. a national project. To put the research results of the wide variety of nanoparticles to practical use it is very essential to establish technology for measuring and evaluating the characteristics and performance of nanoparticles and nanostructures. Research and development of high-rate synthesis technology for nanoparticles also depend on the evaluation of particle generation in the liquid and gasphases examined experimentally and on the design of the reactor made by the use of a numerical simulation.

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