WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

A Review on Microspheres: Methods of Preparation of Microspheres.

Badde Anusha, K. Anie Vijetha

Department of Pharmaceutics, Centre for Pharmaceutical Sciences, JNTUH UCEST, JNTUH, Hyderabad, Telangana-500085.
anushabadde1998@gmail.com

ABSTRACT:

The article concentrates on methods of preparation of microspheres based on recent literature . Microspheres are tiny spherical particles that have a diameter, They are widely used in various fields such as pharmacy, cosmetics and biotechnology for controlled drug delivery. Microsphere manufacturing processes can be divided into physical and chemical processes. Physical methods include solvent evaporation, solvent diffusion, and spray drying. Chemical processes include ionic gelation, emulsion solvent evaporation, and Coacervation. Each method has its own advantages and disadvantages, . The choice of method depends on the properties of the polymer and drug to be encapsulated. Manufacturing conditions such as temperature, pH, and agitation speed also play important roles in forming microspheres of desired size, shape, and drug release profile.

Key words : Microspheres, manufacturing processes, polymer, spherical particles , Physical methods, Chemical processes .

INTRODUCTION:

Microspheres are free-flowing powders composed of proteins or synthetic polymers that are naturally biodegradable. They are used for drug delivery and measurement. They are composed of a hydrophilic core that contains an active compound (e.g., drugs, enzymes) surrounded by hydrophobic material that protects the core from harmful reactive compounds that may be present in the body. The microspheres can be either porous or non-porous. If porous, they are typically formed by crosslinking of biodegradable polymers; if non-porous, they may be produced by polymerization. There are two types of microspheres;

- **Microcapsules.**
- **Micromatrices.**

- Microcapsules are those in which the trapped substance is clearly surrounded by a separate capsule wall.
- Micromatrices in which the remaining substance diffuses into the microsphere matrix.

Microspheres are being investigated in controlled release systems as carriers to deliver a therapeutic agent to local sites. They consist of proteins or synthetic polymers that are naturally biodegradable. A well-designed controlled drug delivery system can overcome some of the problems of conventional therapy and improve the therapeutic efficacy of a given drug. Materials and Methods Microspheres are usually made of polymers. They are classified into two types:

• Synthetic polymers

• Natural polymers

- **Synthetic polymers :-**

Synthetic polymers in turn are divided into two types,

a) **Non-biodegradable polymers: -**

polymethyl methacrylate (PMMA), acrolein, glycidyl methacrylate, epoxy polymers, HPMC.

b) Biodegradable polymers: :-

Lactides, glycosides and their copolymers, polyalkyl cyanoacrylates, polyanhydrides

- **Natural polymers: -**

These are obtained from various sources such as proteins, carbohydrates and chemically modified carbohydrates.

- **Proteins:** Albumin, Gelatin, Collagen .
- **Carbohydrates:** Agarose, Carrageenan, Chitosan, Starch .
- **Chemically modified carbohydrates:** Polydextran, Polyamyl and Eudragit.

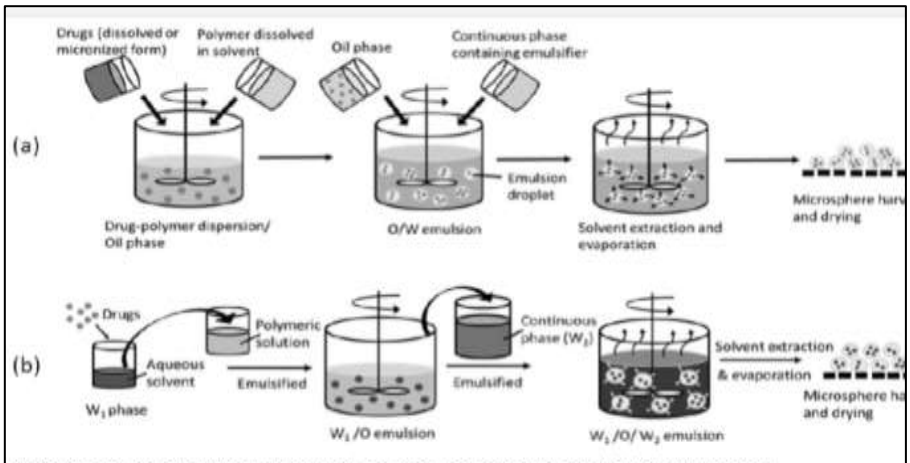
Criteria for choosing a production method :

- ✓ Ability to add a sufficiently high concentration of drug substance.
- ✓ Stability of formulation after synthesis with clinically acceptable shelf life.
- ✓ Controlled particle size and dispersibility in aqueous solutions for injection.
- ✓ The release of the active reagent is well controlled on a wide time scale.
- ✓ Sensitivity to chemical modifications.

TECHNIQUES FOR MANUFACTURING MICROSPHERES:-

- **Solvent evaporation technique**
- **Cross linking method**
- **Coacervation method**
- **Ionic gelation**
- **Spray drying technique**
- **Polymerization techniques**
- **Spray Congealing**
- **Emulsification method**
- **Freeze drying technique**
- **Solvent Evaporation Technology:-**

This process is performed in a liquid manufacturing vehicle. The core material to be encapsulated is dissolved or dispersed in the coating polymer solution. With agitation, the core coating material mixture is dispersed into the liquid phase of the manufacturing vehicle to obtain the appropriate microcapsule size.



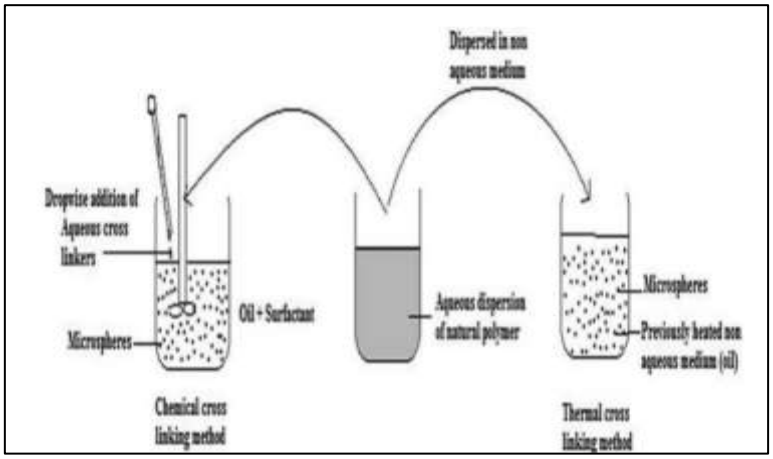
Schematic of the (a) O/W solvent extraction/evaporation technique and (b) W1/O/W2 solvent extraction/evaporation technique for microsphere preparation.

Schematic representation of Solvent evaporation technique

Microcapsules obtained can be used in the form of suspensions, applied to substrates, or isolated as powders. Schematic of the emulsification/solvent evaporation technique for preparing drug-loaded microparticles.

◆ **cross-linking method:-**

In this method, the drug was dissolved in a gelled aqueous solution that was heated for 1 hour. at 0°C. The mixture was stirred at 1500 rpm for 10 minutes at 35°C while the solution was added drop wise to liquid paraffin to obtain a w/o emulsion followed by further stirring at 15°C for 10 minutes. After the microspheres thus prepared were washed with acetone and isopropyl alcohol three times each, they were air-dried and dispersed in 5 ml of an aqueous toluene solution saturated with glutaraldehyde for 3 hours at room temperature. It was then treated with 100 ml of 10 ml glycine containing 0.1% w/v Tween 80 at 37°C for 10 min to block unreacted glutaraldehyde.



Schematic representation of Crosslinking Method

Coacervation Method:-

Coacervation encapsulation is one of the most widely studied methods. The process consists of three steps with continuous agitation.

Step 1: -

Disperse the core material into the coating polymer solution.

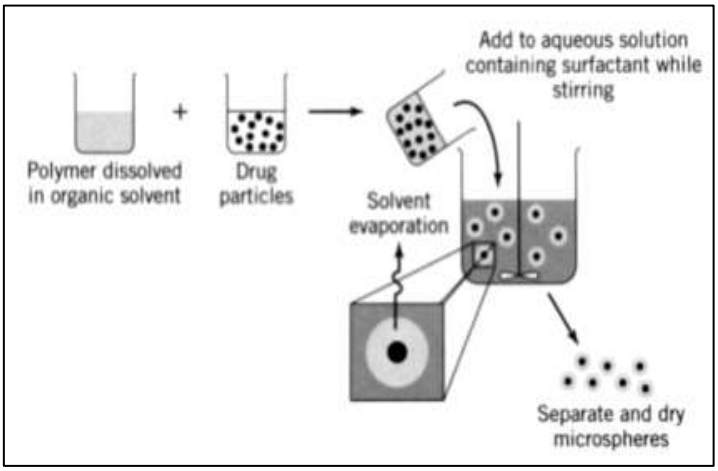
Step 2:-

Coating deposition. Accomplished through controlled physical mixing of the coating and core materials within the manufacturing vehicle.

Step 3:-

Solidification of the coating by heat, cross-linking, or desolventization techniques to form self-sustaining microcapsules. A subsequent drying operation is usually required as the core material is microencapsulated while dispersed in some liquid manufacturing medium.

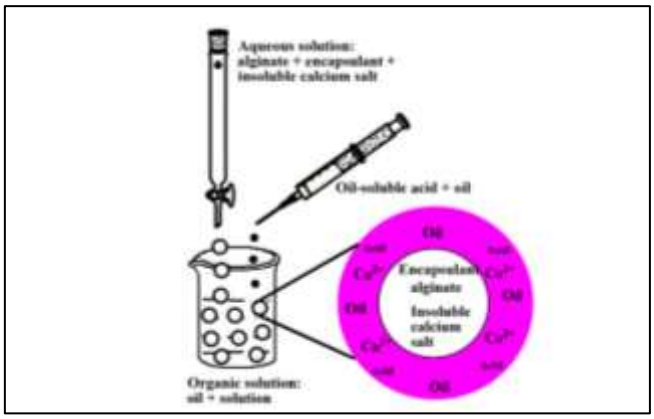
The coacervation method can be used to encapsulate a wide range of drugs, including hydrophilic, hydrophobic, and lipophilic drugs, and also the coacervation method can achieve high drug entrapment efficiencies, as the drug molecules are effectively trapped within the polymer matrix.



Schematic representation of Coacervation method

◆ **Ionic gelation:**

Ionic gelation is a physico-chemical process in which an aqueous polymer solution in which the active ingredient is dissolved or dispersed is extruded through an injection needle or nozzle. An alginate/chitosan particle system for releasing drug was prepared using this technique and the drug was added to 1.2% (w/v) sodium alginate aqueous solution. To obtain a complete solution, continue stirring and then add drop-wise to the solution containing the Ca_2/Al_3 and chitosan solution in acetic acid. The formed microspheres were kept in the original solution for 2 hours due to internal gelation and subsequently separated by filtration. Complete release was obtained at pH 6. -7.2, but no drug was released at acidic pH.



Schematic representation of Ionic gelation technique

◆ **Spray Drying Technology:-**

Spray drying is, by definition, the conversion of feed from a liquid state into a dry particulate form by spraying the feed onto a hot dry medium. The feed can be a solution, suspension or paste. Spray drying consists of four process steps:

I. Atomization of raw materials into spray

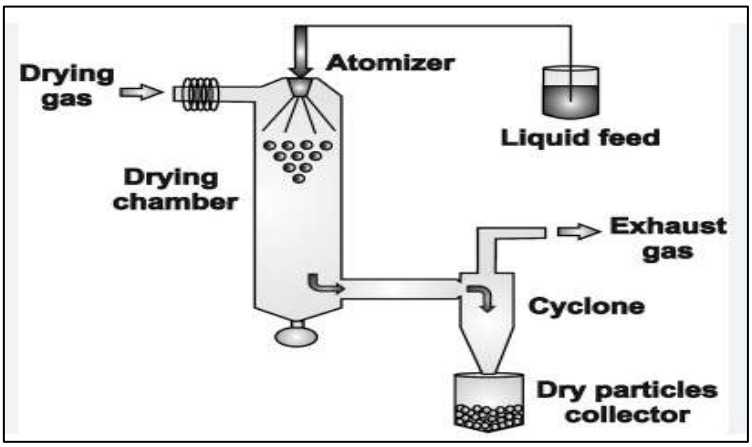
II. Spray-air contact (mixing and flow)

III. Spray drying (evaporation of moisture)

IV. Separation of dry product from air

In this spray drying technology , the polymer was first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in solid form was then dispersed into the polymer solution by high speed homogenization. A fine mist that is atomized in the air and the small droplets or solvent evaporate quickly leading to the formation of microspheres. The size range is from 1 to 100 μm. A trace amount of solvent is removed by vacuum drying. The advantage of this method is the feasibility of the operation. This technique is very useful for encapsulating various penicillins. Thiamine mononitrate and sulfaethyl thiadiazole are encapsulated in a mixture of stearic and palmitic mono- and diglycerides using spray congealing. However, very rapid solvent evaporation leads to the formation of porous microparticles.

The spray drying technique can achieve high yields, with a large amount of microspheres produced in a single batch, also Spray drying can improve the stability of labile drugs, as the drying process is carried out at relatively low temperatures and the drying time is short and the particle size of microspheres can be controlled by adjusting the spray drying parameters, such as the flow rate of the polymer solution and the inlet air temperature.



Schematic representation of of spray drying technique

◆ **Polymerization Techniques:-**

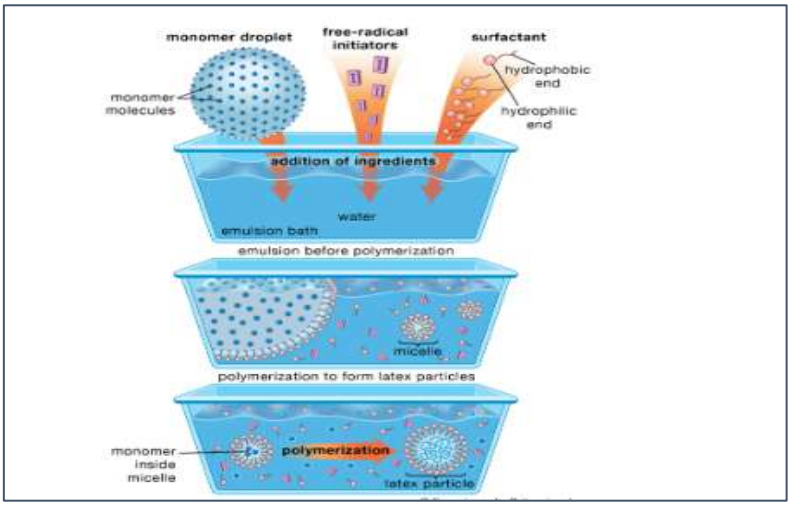
Two main techniques are used to produce microspheres which are classified as follows:

(a) Normal polymerization :

The polymers thus obtained can be molded into microspheres. Drug loading can be done by adding drugs during the polymerization process. Although this is a pure polymer formation technique, it is very difficult to dissipate the reaction heat acting on the thermolabile active ingredient. Suspension polymerization takes place at low temperatures, also called bead polymerization, where the active drug-containing monomer mixture is heated as a droplet dispersion in a continuous aqueous phase. The size of the micro-particles obtained by the suspension technique is less than 100 µm. Emulsion polymerization differs from suspension in that the initiator is present in the aqueous phase, but in the latter two techniques it is carried out at low temperatures as the external phase of the suspension, which is usually water, thus allowing heat to dissipate. becomes easier. Although these techniques allow for faster polymer formation, association of the polymer with unreacted monomers and other additives can occur.

(b) Interfacial polymerization:

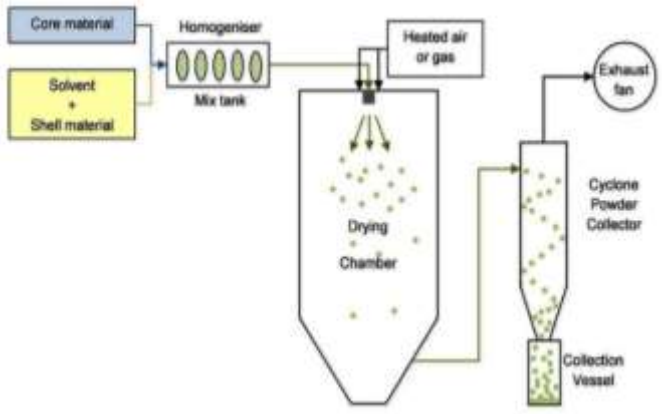
It involves the reaction of different monomers at the interface between two immiscible liquid phases, forming a polymer film that essentially encapsulates the dispersed phase. This technique uses two reactive monomers. One dissolves in the continuous phase and the other disperses in the continuous phase (which is aqueous in nature), where the second monomer is emulsified. Two conditions arise due to the solubility of the formed polymer in the emulsion droplets. That is, if the polymer is soluble in the droplets, the formation is of the monolithic carrier type. A capsule type that forms when the polymer does not dissolve in the droplet.



Schematic representation of polymerization technique

♦ **Spray congealing:**

The Spray congealing is similar to spray drying in that the core material is dispersed in a liquefied coating substance. Coating solidification occurs by solidification of molten coating material or by solidification of dissolved coating material by introducing the coating core material mixture into a non-solvent. Removal of non-solvent is then accomplished by sorption, extraction, or evaporation techniques. Waxes, fatty acids, alcohols, and polymers and sugars that are solid at room temperature but melt at elevated temperatures are amenable to the spray freezing process.

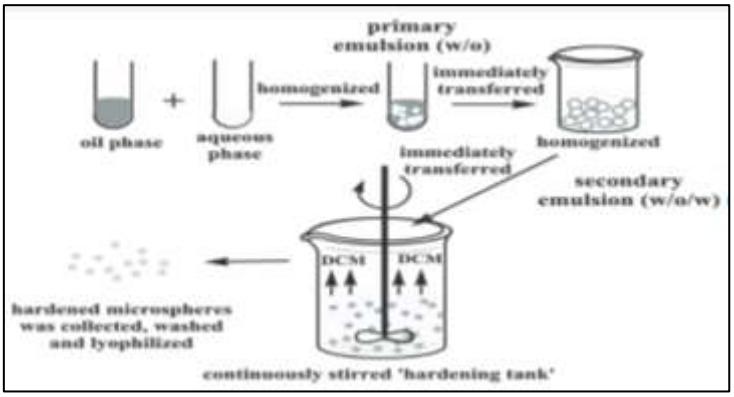


Schematic representation of spray congealing technique.

- **Emulsification process:**

For example, multiple emulsions can be formed. A heated aqueous drug solution can be dispersed in molten wax to form a water-in-oil emulsion, which can be emulsified with a heated external aqueous phase to form a water-in-oil-in-water emulsion. Cool the system and collect the microcapsules. For highly water-soluble drugs, a non-aqueous phase can be used to prevent the drug from being lost to the external phase. Another alternative is to rapidly lower the temperature as the primary emulsion is introduced into the external aqueous phase.

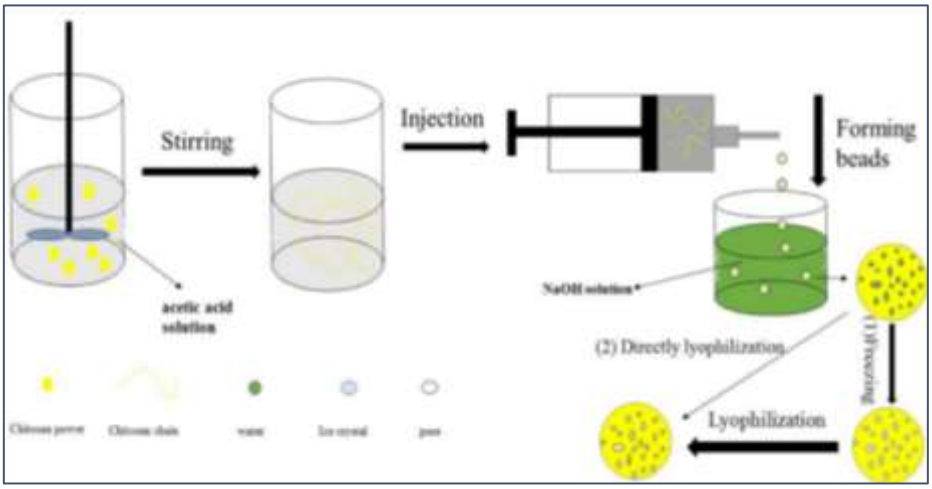
The emulsification process can achieve high drug encapsulation efficiencies, as the drug molecules are effectively trapped within the droplets of the emulsion , it can be used to encapsulate a wide range of drugs, including hydrophilic, hydrophobic, and lipophilic drugs.



Schematic representation of emulsification process

- **Freeze-Drying Technology:**

Freeze-Drying is a dehydration process commonly used to preserve perishable materials for extended shelf life or for shipment. Freeze-drying is to freeze the material and then reduce the pressure and apply heat to convert (sublimate) the frozen water in the material directly to vapor.It is a process in which water is removed from a product after it is frozen and placed under a vacuum, allowing the ice to change directly from solid to vapor without passing through a liquid phase.



Schematic representation of freeze drying

REFERENCES:

1. Microspheres: A Review of Materials, Methods of Preparation, and Applications, by Rajiv R. Soni, Anil K. Jana, and J. P. Shukla.
2. Preparation and Characterization of Polymer Microspheres: A Review, by S.C. Tjong and Y. Zhang.
3. Microspheres in Drug Delivery: An Overview ,by Divya Jain and Ruchi Varshney.
4. Fabrication and Characterization of Polymer Microspheres for Drug Delivery Applications" by D. Jain and A. K. Jana.
5. Microspheres for Biomedical Applications: Materials, Methods, and Applications, by Elena Arion and Wolfgang H. Binder.
6. Novel Microspheres for Biomedical Applications, by Juan E. Hernandez-Montes, Maria E. Caballero-Briones, and Edgar Martinez-Santiago.
7. Development of Microspheres for Drug Delivery, by M. Ali Raza and M. Al-Fayoumi.

8. Microspheres for Drug Delivery: Preparation, Characterization, and Applications, by S. Ali and A. S. Bawa.
9. Polymeric Microspheres for Controlled Drug Delivery: Preparation, Characterization, and Applications, by M. K. Jain and V. K. Gupta.
10. Chitosan Microspheres: Preparation, Characterization, and Applications in Drug Delivery, by Y. Zhang and H. Li.
11. PLGA Microspheres for Controlled Drug Delivery: Preparation, Characterization, and Applications. by X. Wang and L. Liu.
12. Alginate Microspheres: Preparation, Characterization, and Applications in Drug Delivery, by X. Liu and Y. Liu.
13. Gelatin Microspheres for Controlled Drug Delivery: Preparation, Characterization, and Applications, by K. S. Kim and S. H. Kim.
14. Polyethylene Glycol Microspheres: Preparation, Characterization, and Applications, by J. Kim and H. K. Kim.
15. PCL Microspheres for Controlled Drug Release: Preparation, Characterization, and Applications, by H. Yang and X. Li.
16. PEGylated PLGA Microspheres for Protein Delivery: Preparation, Characterization, and Applications, by X. Li and L. Zhang.
17. Polyvinyl Alcohol Microspheres for Controlled Drug Release: Preparation, Characterization, and Applications, by Y. J. Kim and H. J. Lee.
18. Chitosan-Alginate Microspheres for Drug Delivery: Preparation, Characterization, and Applications, by Y. Zhou and X. Zhang.