



## Review Article

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# MICROSPHERE: A PROMISING APPROACH FOR DRUG DELIVERY

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### ABSTRACT

The recent evolution in new drug delivery systems plays a important role in pharmaceutical industries. There are various controlled release products, Microsphere is one among all due to the sustained release and controlled release properties. Microsphere are small spherical shape characteristically free flowing powders, with diameters typically ranging from 1  $\mu\text{m}$  to 1000  $\mu\text{m}$  (1 mm). Microspheres can be produced using several natural and synthetic polymeric materials. Depending on the method, solid or porous microspheres can be obtained for specific intended applications. The variety of methods for the production of microspheres offers numerous opportunities to control the aspects of administration of the API. It provides the prolonged therapeutic action and reduce the dosing frequency, which improve the patient compliance. To get the desired effect the drug should deliver at the target tissue in an ideal amount in the right period of time with maximum therapeutic effect and minimum side effect. Now a day's microspheres have been used to deliver drugs, vaccines etc. The article is mainly focus on the various aspect of microspheres drug delivery system along with their method of preparation, technique to evaluate its efficiency and pharmaceutical application of microspheres.

### INTRODUCTION

To procure maximum therapeutic efficacy, it is important to deliver API to the target tissue in the optimal amount with in right period of time which reduce the toxicity and side effects. Several approaches are available which can deliver drugs to the target site. One such approach is microspheres as carriers for drugs [1]. Microspheres are small spherical shape particles range from 1  $\mu\text{m}$  to 1000  $\mu\text{m}$  in size [2]. Microsphere, as carrier for drug delivery gain popularity in recent era. Various

natural and synthetic polymers are successfully used to design microspheres. Most common types of polymer microspheres includes Polyethylene and polystyrene microspheres are popular among other. Polyethylene microspheres are most commonly used as permanent or temporary filler where as polystyrene microspheres are used in biomedical applications [3]. Floating microspheres, mucoadhesive microspheres, protein-loaded microspheres (like as triptorelin (Trelstar<sup>TM</sup>

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Depot) are other well-known established concept of recent trends in this section. In pharmaceutical research one of the most challenging part is development of novel delivery systems that deliver the drug at the targeted site and also minimize the side effects. Microspheres most efficiently serve the purpose and also enhance the therapeutic efficacy of drugs [4].

#### Advantages of microspheres- [5, 6, 7]

1. Proteins, enzymes can be deliver through this system.
2. Drug targeting is possible
3. It provides constant and prolonged therapeutic benefit.
4. It provides constant drug concentration in blood thereby increasing patient compliance.
5. It improves the bioavailability and decrease the toxicity.
6. It reduces dosing frequency & improve patient compliance and stability.
7. It can easily mask the unpleasant taste and defend GIT irritation.

#### Limitation- [2,3,5]

1. Poor reproducibility and poor entrapment efficiency is reported
2. The process conditions like temperature change, pH, solvent addition, and evaporation/agitation may influence the stability of core particles to be encapsulated.
3. Difference in the release rate from one dose to another.
4. Premature drug release is also reported.

#### Types of microsphere-

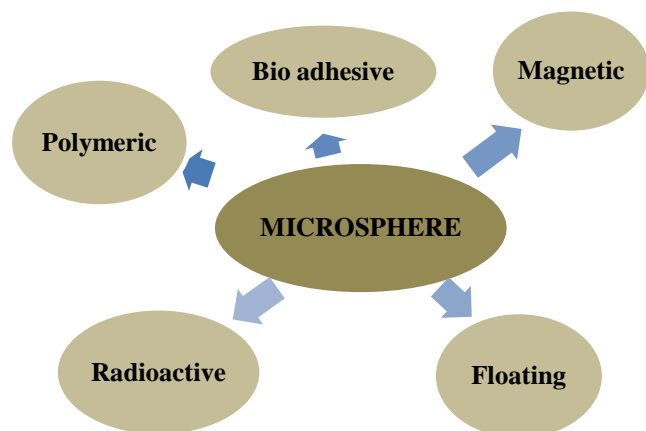


Figure1: Type of microsphere

#### Materials used in the preparation of microsphere-

Polymers are mainly use for the preparation of microsphere [8, 9]. They are classified into two types:

1. Natural polymers
2. Synthetic Polymers

1. Natural polymers are obtained from different sources like
  - a) Carbohydrates
  - b) Proteins
  - c) Chemically modified Carbohydrates

Carbohydrates: Agarose, Carrageenan, Chitosan, Starch

Proteins: Albumin, Collagen and Gelatin

Chemically modified carbohydrates: Poly dextran, Poly starch.

2. Again synthetic polymers are also divided into two types.

- a) Biodegradable polymers
- b) Non-biodegradable polymers

a) Biodegradable polymers: Lactides, glycolides & their co-polymers, Poly anhydrides, poly alkyl cyano acrylates

b) Non-biodegradable polymers:

Poly methyl methacrylate (PMMA), glycidyl methacrylate, acrolein, epoxy polymers.

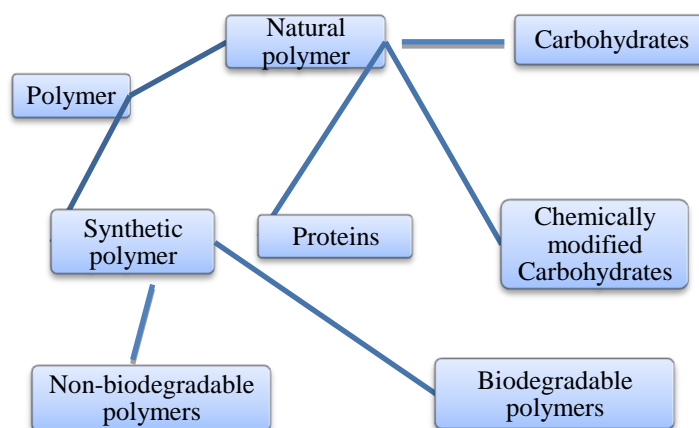


Figure 2: Types of polymer

#### Method of preparation:

The technique choice is mainly depends upon the nature of polymer, nature of drug and the duration therapy.

Techniques for microsphere preparation

1. Single emulsion techniques
2. Double emulsion techniques
3. Phase separation coacervation technique
4. Spray drying
5. Solvent extraction
6. Solvent evaporation
7. Polymerization
  - a. Normal polymerization
  - b. Inter-facial polymerization

### 1. Single emulsion technique:

Single emulsion technique is used for the preparation of micro particulate carriers for drug delivery. The natural polymers are dissolved in aqueous medium and it followed by dispersion in non-aqueous medium such as oil. In the next step cross linking can be carry out either heat or by using the chemical cross linkers. Cross linking by heat: by adding the dispersion into heated oil, but it is not suitable for the thermo labile drugs. The main disadvantage of chemical cross linking is to excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing, and separation [6,7, 10]

### 2. Double emulsion technique:

Both natural as well as synthetic polymer can be used in this method and it is more suitable for aqueous soluble drugs, peptides, proteins and vaccines. This method is involves in the preparation of double emulsions of w/o/w type. In this technique, the aqueous active constituent protein solution is dispersed in lipophilic organic continuous phase .Continuous phase is generally composed of polymer solution which encapsulates protein dispersed in water phase. After that, before addition to aqueous solution the primary emulsion is homogenized and the formation of double emulsion occurs and then solvent removal is occur either by solvent evaporation or solvent extraction method [6, 11].

### 3. Phase separation coacervation technique:

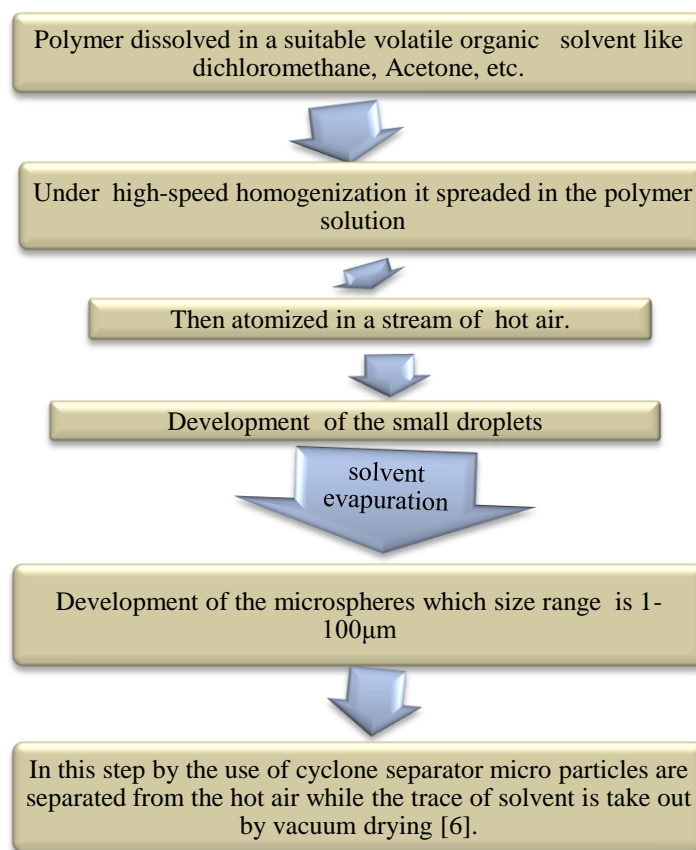
The coacervation term is come from latin word *acervus* which means ‘‘heap’’. This process was first reported to modify for the industrial production of microcapsule. In organic phase the solubility of polymer is decrease which affect the formation of the polymer rich phase called as coacervation .This process is utilize for the development of reservoir type system for example encapsulated water soluble drug like proteins, peptides. The matrix type preparations also can be developed in this process e.g. hydrophobic drug such as steroids [6, 11,12].

### 4. Spray drying:

The two processes spray drying and spray congealing are mainly depending on the removal of the solvent or cooling of the solution. The polymer which dissolved in a suitable volatile organic solvent. Under high-speed homogenization it dispersed in the polymer solution. Then it atomized in a stream of hot air which leads to the formation of small droplets and solvent

evaporation was done which developed the formation of microspheres. By the use of cyclone separator micro particles are separated from the hot air while the trace of solvent is take out by vacuum drying [13].

In this process one of the major advantage is feasibility of operation under aseptic conditions. However this process is used to encapsulate various penicillin's. Sulphaethylthiadizole and thiamine mononitrate are encapsulated in a mixture of monoglyceride and diglycerides of stearic acid and palmitic acid by using spray congealing [7,10]. Example- For the vaginal delivery of econazole much adhesive microsphere can be prepared by spray congealing technique [12]



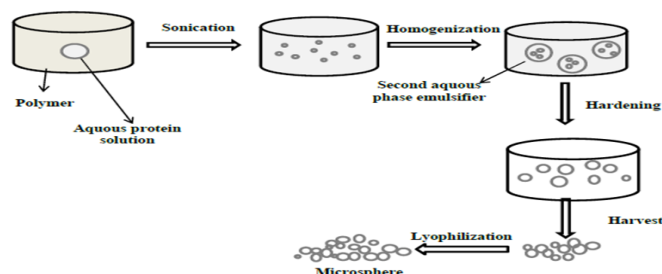
**Fig 3: Schematic representation of spray drying**

### 5. Solvent evaporation:

Solvent evaporation method is one the most important method for the preparation of microsphere. These process are mostly use in the liquid manufacturing vehicle. In this phase organic solvent like polymer and the aqueous protein solution is added. Then sonication is done for mixing the material. After that homogenization is done for making the solution uniform. Then second aquous phase emulsifier is added. After that hardening

is occur and then harvest it. After harvesting freeze drying technique is use. This is also called as lyophilization. It preserve the material by freezing it very quickly and then subjecting it to a vacuum which removes ice. And then microsphere is getting [10,14].

This technique is used for the preparation of microsphere of 5-Flurouracil by using dichloromethane and acetonitrile, however the polyvinyl alcohol is used as processing medium to solidify the microsphere [15].



**Fig 4: Solvent evaporation technique**

**6. Solvent extraction:** This method is used for the development of the micro particles, which involves in the removal of the organic phase by extraction of the organic solvent. The organic phase is eliminated by extraction with water. The hardening time of microspheres decrease in this method. The rate of solvent eliminate by extraction method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer [1,16].

**7. Polymerization technique:** Preparation of Microspheres by polymerization technique can be classified as:

- a. Normal polymerization
- b. Interfacial polymerization

**a. Normal polymerization:**

The normal polymerization is done by using different techniques as bulk, suspension, precipitation, emulsion etc. In case of bulk polymerization, a monomer along with catalyst is warmed up to set up polymerization. Then the polymer is obtained and form as microspheres, as well as drug loading may be done during the process of Polymerization. Bulk polymerization is a pure polymer development procedure but it is very difficult to evaporate the heat of reaction that affects the thermo labile active ingredients. Suspension polymerization is also called as Pearl/Bead Polymerization which is done at low temperature. In this process heating of monomers or a mixture of monomers with active drug as droplet dispersion in continuous aqueous phase [6, 10,17]

**b. Interfacial polymerization:**

Interfacial polymerization involves the reaction of various monomers at the interface between two immiscible liquid phases to form a film of polymer. It broadly cover the dispersed phase [6].

**Evaluation of microspheres**

**Particle size and shape**

The conventional scanning electron microscopy (SEM) and light microscopy (LM) are widely used for determine the shape and outer structure of micro particle. The laser light scattering and multi size coulter counter other than instrumental methods, which can be used for the identification of size, shape and morphology of the microspheres. Light microscopies produce a control over coating parameters in case of double walled microspheres. The microspheres structures can be identified before and after coating and also change can be estimated microscopically whereas the scanning electron microscopy provides higher resolution in variation to the LM [17, 18].

**Determination of Density**

Multi-volume pycnometer mostly using for measured the density of the microsphere. Specifically weighed sample in a cup is placed into the multi-volume pycnometer. Helium is initiated at a constant pressure in the chamber and allowed to enlarge. This development results in a decrease in pressure within the chamber. Two continuous readings of reduction in pressure at different initial pressure are noted. From two pressure readings the volume as well as the density of the microsphere carrier is determined [18].

**Dissolution studies**

The standard USP or BP dissolution apparatus have been mostly used to evaluation *in vitro* release profiles using rotating elements, paddle and basket. Dissolution medium used for the study which ranging from 100- 500 ml and speed of rotation from 50-100 rpm [1].

**Stability studies**

In this study placing the microspheres in screw capped glass container which is stored at following conditions:

1. Ambient humid condition
2. Room temperature (27+/-2 ° C)
3. Oven temperature (40+/-2 ° C)
4. Refrigerator (5° C – 8 ° C).

It was carried out of 60 days and analyzed the drug content of the microsphere [13].

**Fourier Transform Infrared Spectroscopy**

The drug polymer interaction and degradation of microspheres can be evaluated by FTIR [7, 13]

**Drug Entrapment Efficiency**

Weigh amount of microsphere are taken and crushed. Then in buffer solution it is dissolved with the help of stirrer. After stirring filtered it [6]. The filtrate is analysed by UV spectrophotometer at particular wavelength by using calibration curve.

Drug Entrapment efficiency is analysed by actual weight of microspheres / the theoretical weight of drug and polymer  $\times$  100

**Percentage Yield**

The percentage yield is calculated by the weight of microspheres derived from each batch divided by total weight of drug and polymer used to prepare that batch multiplied by 100

**Optical microscopy**

The optical microscopy method is mostly used to evaluate particle size by using optical microscope. The measurement of particle size is done under 450x (10x eye piece and 45x objective) and 100 particles are measure [7].

**Swelling Index**

Swelling index is determined by measuring the extent of swelling of microspheres in a particular solvent. The equilibrium swelling degree of microspheres is determined by swelling in 5ml of buffer solution; 5mg of dried microspheres are poured in a measuring cylinder and keep it for overnight. The swelling index is calculated by given formula.

Swelling index =  $\frac{\text{The Mass of swollen microsphere} - \text{The mass of Dried Microspheres}}{\text{the mass of dried microspheres}} \times 100$  [6].

**Electron Spectroscopy for Chemical Analysis**

The surface chemistry of the microspheres can be determined by using the electron spectroscopy for chemical analysis. It provides a means for the confirmation of the atomic composition of the surface [15].

**Application of microsphere**

**Targeting drug delivery-** The concept of targeting i.e. site specific drug is a well-established conviction. It is gaining full attention. The therapeutic efficacy of drug relies on its approach and specific reaction with its receptor.

**In vaccine delivery-** vaccine is the important delivery system for protection against the microorganism. Most of the

parenteral vaccines have been compacted in biodegradable polymeric microspheres, including the diphtheria vaccine and tetanus [6].

**Buccal and sublingual drug delivery-** Buccal mucosa may have inherent for delivering peptide drugs low molecular weight, high potency and long biological half-life. mucoadhesive microspheres of venlafaxine using linseed mucilage as a muco-adhesive agent by using spray-drying technique for buccal delivery with a target to avoid hepatic first-pass metabolism, by increasing residence time in the buccal cavity [5,19].

**Microspheres in Cancer therapy [20]**

**Nasal Drug Delivery-** Polymer based drug delivery systems, like micro-spheres, liposomes and gels have been demonstrated to have good bio adhesive characteristics. It swells easily when in contact with the nasal mucosa increasing the bioavailability and residence time of the drugs to the nasal route. e.g. starch, dextran, albumin

**Other application-** Some other applications are there. The fluorescent microspheres can be applied for membrane based technology for flow cytometer, microbiology, cell biology [6]. Natural excipients are finding a wide application in microspheres [21]. Many recent studies reveal that natural excipients are being incorporated in novel drug delivery systems [22 – 24]

**CONCLUSION**

The present study shows that microspheres drug delivery system is a suitable choice of delivery system. It also reduce the dose frequency, and improved the stability, bioavailability and dissolution rate. It also help to deliver the drug to the specific sites in the body. In future prospect by combining various other strategies, microspheres will find the significant place in novel drug delivery, especially in the area of diagnosis, delivery of gene & genetic materials, proteins most effectively and safely

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**CONFLICT OF INTEREST**

The authors declare no conflict of interest

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