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# APPROACHES OF MICROSPHERES- A REVIEW

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## ABSTRACT

Microspheres are the colloidal drug delivery system. Microspheres are characteristically free-flowing powders consisting of proteins/synthetic polymers that are biodegradable in nature and ideally having a particle size less than 200mm. Biodegradable microspheres can be utilized to direct drugs to certain organs through capillary blockade. Its success depends on the size of the microspheres used and on the mode of administration (intravenous/intra-arterial). The microspheres can also be used for targeting anticancer drugs to the tumor. This review represents the various dimensions and prospective for different areas where microspheres can be used to function as a great drug delivery system. The major categories and types of micro particulate system that can be utilized ranging from radioactive microspheres to floating microspheres for site targeted or sustained release, are being discussed in this review.

**KEYWORDS:** Microspheres, Methods of Preparation of microspheres, mechanism of microspheres, Evaluation of microspheres.

## INTRODUCTION[1-2]

Recently micro particles or microspheres have gained great attention due to their free flowing powder characteristics and biodegradable nature generally made up of proteins or synthetic polymeric materials having particle size in the range of 1–200µm. Depending upon the encapsulation of active drug moieties there are two types of microspheres (microcapsules and micro matrices). Microcapsules are multiple unit dosage forms in which active drug molecule is encapsulated and surrounded by separate polymeric wall but in case of micro matrices drug is uniformly dispersed throughout the polymeric matrix.1–3 Microspheres have number of advantages over conventional drug delivery systems including an important or effective for

administration of therapeutic active molecules in controlled and sustained manner to the target site with improved therapeutic effects4, To increase the gastric emptying time and control over the release of the drug from the devices, the increasing sophistication of delivery technology will ensure the development of increasing number of gastro retentive drug delivery systems to optimize the delivery of molecules that exhibit low bioavailability and extensive first pass metabolism. A gastric floating drug delivery system can overcome at least some of these problems and is particularly useful for drugs that are primarily absorbed in the duodenum and upper jejunum segments, and it can prolong retention times of dosage forms in the GIT, and thereby improve their oral bioavailability. Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach.

**Advantages of microspheres[3]**

- These systems provide prolonged and constant therapeutic effect
- Reduces the dosing frequency and therefore improvement in patient compliance.
- Microspheres produce more reproducible drug absorption.
- Drug discharge in stomach is hindered and that's why local unwanted effects are reduced.
- In case of microspheres, better therapeutic effect for short half-life of drugs can be achieved.
- Dose dumping effect can be reduced by microspheres.
- Microspheres also reduce the chances of G.I. irritation.
- Microspheres provide freedom from drug and recipients incompatibilities especially with buffer.
- Better protection of drugs against environment conditions.
- Taste and odour of unpleasant drugs can be effectively masked.
- Microspheres reduce the first pass metabolism.
- Microspheres can be easily injected in body because of their small and spherical size.

**Disadvantages[4]**

1. They are not suitable candidates for drugs with stability or solubility problem in stomach.
2. FDDS require sufficiently high level of fluid in stomach so that the system can float and thus sufficient amount of water (200-250 ml) of water to be taken together with FDDS.
3. Drugs having irritant effect on gastric mucosa are not suitable candidates for FDDS.
4. Drugs which are absorbed along the entire GIT and which undergo first pass metabolism may not be desirable e.g. nifedipine.

## MATERIALS USED[5]

### 1. Natural Polymers

Depending upon the source from which these materials are obtained these are further classified as:

**a. Proteins:** Collagen, Albumin and Gelatin.

**b. Carbohydrates:** Starch, Agarose, Chitosan and Carrageenan.

**c. Chemically modified carbohydrates:** Poly dextran, Poly Starch.

### 2. Synthetic Polymers

- These polymeric materials are synthesized by using different chemical substances given below
- Biodegradable polymers include Lactides, Glycolides & their copolymers, Polyanhydrides.

## METHODS OF PREPARATION

**The most important physical chemical factors that may be controlled in microsphere manufacture are**

- The particle size requirement
- Molecular weight of polymer
- Polymer to drug ratio
- No stability problem
- Final product should be non-toxic.
- Total mass of drug and polymer
- Reproducibility
- Controlled particle size and dispersability in aqueous vehicles for injection
- Release of active reagent with a good control over a wide time scale

### Techniques for Microsphere Preparation[6-7]

1. Single emulsion techniques
2. Double emulsion techniques
3. Polymerization

a. Normal polymerization

- Bulk
- Suspension

- Emulsion

b. Inter-facial polymerization

4. Phase separation coacervation technique

5. Spray dryingSolvent extraction

6. Solution-enhancement dispersion method

7. Wax coating Hot-melt method

**1. Single Emulsion Technique**

There are several Proteins and carbohydrates, which are prepared by this technique. In which the natural polymers are dissolved in aqueous medium and the followed by dispersion in oil phase i.e. non-aqueous medium. That is the first step in Next step cross linking is carried out by two methods

**(1) Cross linking by heat:** by adding the dispersion into heated oil, but it is unsuitable for the thermolabile drugs.

**(2) Chemical cross linking agents:** By using agents i.e. formaldehyde, diacid chloride, glutaraldehyde etc. but it is having a disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing and separation. Chitosan solution (in acetic acid) by adding to Liquid paraffin containing a surfactant resulting formation of w/o emulsion.

**2. Double Emulsion Technique**

It is formation of multiple emulsions i.e. W/O/W is preparing by pouring the primary w/o emulsion into aqueous solution of poly vinyl alcohol. This w/o/w emulsion put a t constant stirring for 30 min. Slowly add some water to the emulsion over a period of 30 min. collect Microcapsules by filtration and dry under vacuum. It is best suited to water soluble drugs, peptides, proteins and the vaccines. Natural as well as synthetic polymer can use for this method. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. Disperse in oil/organic phase homogenization/vigorous i.e. formation of first emulsion then addition to aqueous solution of PVA (Poly Vinyl Alcohol) emulsion.

**3. Polymerization Techniques**

Mainly two techniques are using for the preparation of microsphere are classified as:

**(A) Normal Polymerization**

In bulk polymerization, a monomer or a mixture of number of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres. Drug loading may be done by adding the drug during the process of polymerization. It is a pure polymer formation technique but it is very difficult to dissipate the heat of reaction which affects the thermo labile active ingredients. Suspension polymerization is carried out of lower temperature and also refer to as pearl polymerization in which heating the monomer mixture with active drug as droplets dispersion in continuous aqueous phase. Microsphere size obtained by suspension techniques is less the 100 μm.

**(B) Interfacial Polymerization**

It involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase. In this technique two reacting monomers are employed; one is dissolve in continuous phase while other is disperse in continuous phase (aqueous in nature) throughout which the second monomer is emulsified. Two conditions arise because of solubility of formed polymer in the emulsion droplet. That is formation is monolithic type of carrier if the polymer is soluble in droplet. Capsular type formed if the polymer is insoluble in droplet

**4. Spray Drying and Spray Congealing**

Concept of spray drying technique depending upon the removal of solvent or the cooling of solution the two processes are spray drying & spray congealing. Evaporation is the basic mechanism in spray drying, whereas in spray congealing it is that of a phase inversion from a liquid to a solid. Both processes are similar, except for energy flow1. Spray drying is the most widely used industrial process involving particle formation and drying. Therefore, spray drying is an ideal process where the end product must comply with precise quality standards regarding particle size distribution, residual moisture content, bulk density, and particle shape.

**Principle[8]**

Three steps involved in spray drying

a.) Atomization: of a liquid feed change into fine droplets.

b.) Mixing: it involves the passing of hot gas stream through spray droplets which result in evaporation of liquids and leaving behind dried particles.

c.) Dry: Dried powder is separated from the gas stream and collected.

In this technique polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high-speed homogenization. This dispersion is then atomized in a stream of hot air, this form small droplets or the fine mist, from which the solvent evaporates instantaneously leading the formation of the microspheres. The size range is 1-100 μm. By using hot air separate of Microparticle by means of the cyclone separator while the traces of solvent are removed by vacuum drying. Advantages of the process are feasibility of operation. This technique is very useful to encapsulate various penicillin's. Thiamine mononitrate10 and sulpha ethylthiadizole11 are encapsulated in a mixture of mono- and diglycerides of stearic acid and palmitic acid using spray congealing. Very rapid solvent evaporation, however leads to the formation of porous microparticles.

1. The sprays are produces by either rotary (wheel) or nozzle atomizers. Evaporation of moisture from the droplets and formation of dry particles proceed under controlled temperature and airflow conditions. The quality of product is improved by addition plasticizer spray flow rate should kept constant around 6ml/min.
2. Formaldehyde as a cross linking and also reported a novel method in which cimetidine and famotidine were entrapped in microsphers.

Spray drying used for the preparation of PCL microspheres of ketoprofen spray drying of multiple emulsion (o/w/o or w/o/w).

**Advantages and Disadvantages**

Spray drying is very useful for pulmonary drug delivery as well as for oral dosages form and it is remarkable versatility of the technology, and a wide range of product can be obtained by this technique. Powder quality remains constant during the dryer. The overall thermal efficiency is low, as the large volumes of heated air pass through the chamber without contacting a particle.

**5. Wax Coating and Hot MELT**

In this technique polymer is disperse in suitable dispersion medium and slowly cooled to form the microspheres. The wax suspension is dispersed by high speed mixing into cold solution for example liquid paraffin. Agitate the mixture for one hour. Then decanted the external phase and suspended microspheres collect from solvent. And allow drying it in air. It is inexpensive method as comparison to others and drug release is more rapid.

**6. Solvent Evaporation Method**

For the formation of the emulsion between polymer solution and an immiscible continuous phase in aqueous (o/w) as well as non-aqueous phase (w/o). The suspension of microspheres was filtered, washed and dried. Magnesium stearate was also added for preventing agglomeration as a Agglomeration preventing agent. And allow drying it in air. It is inexpensive method as comparison to others and drug release is more rapid. The results showed that average particle size decreased with increasing amount of magnesium stearate used for microsphere preparation17. Lim et al. (2000) investigated the comparison of mucoadhesive microspheres of hyaluronic acid, chitosan glutamate and a combination of the two prepared by solvent evaporation with microcapsules of hyaluronic acid and gelatin prepared by complex coacervation

**7. Phase Separation Coacervation Technique**

It is the simple separation of a micromolecular solution into two immiscible liquid phase. In this process, the polymer is solubilized to for a solution. Matrix types preparations can also be prepared by this process for hydrophilic drug e.g. steroids, Addition of non-solvent results in the solidification of polymers. Poly lactic acid (PLA) microspheres have been prepared by this method by using butadiene as incompatible polymer.

**8. Solvent Extraction**

In this method preparation of microparticles, involves removal of the organic phase by extraction of the organic solvent. The rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer**.**

**9. Emulsification Method**

Multiple emulsions may also be formed for example; a heated aqueous drug solution can be dispersed in molten wax to form a water-in-oil emulsion highly aqueous soluble drugs, a non aqueous phase can be used to prevent loss of drug to the external phase.

**EVALUATION PARAMETERS OF MICROSPHERE[9-10]**

**1. Yield of microsphers**

The prepared microspheres with a size range of 251-µm were collected and weighed. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microsphere.

%yield= (actual weight of the product/total weight of the product)*100

**2. Particle Size**

The particle size was measured by microscopic technique. In this method suspension of floating microspheres was prepared using castor oil. A drop of suspension was mounted on a slide and observed under optical microscope about 600 particles were measured with the help of the eye piece micrometer. All the microspheres in a field were counted.

**3. Bulk Density**

In this method floating microspheres are transferred to a measuring cylinder and is tapped manually till a constant volume is obtained. This volume is bulk volume and it includes true volume of the powder and the void space among the microspheres.

Bulk density=mass of microsphere/bulk volume

**4. Tapped Density**

In this method floating microspheres were transferred to a measuring cylinder & tapped for 100 times. After tapping volume of microspheres was visually examined. The ratio of mass of microspheres to volume of microspheres after tapping gives tapped density floating microspheres

Tapped density=mass of microsphere/volume of microsphere after tapping

**5. Carr's (Compressibility) Index**

This parameter was calculated from bulk density (the ratio of weighed quantity of microspheres to its volume), DP, and tapped density as follows

Compressibility index= (DT-DP)/DT*100

**6. Hausner's Ratio**

Hausner's ratio of microspheres was determined by comparing tapped density to bulk density using the equation.

Hausner's ratio=Bulk density/tapped density

Values less than 1.25 indicate good flow (= 20% Carr), whereas greater than 1.25 indicates poor flow (= 33% Carr).

**7. Angle of Repose**

Angle of repose of the microspheres, which measures the resistance to particle flow, was determined by a fixed funnel method4. The height of the funnel was adjusted in such a way

that the tip of the funnel just touches the heap of the blends. Accurately weighed microspheres were allowed to pass through the funnel freely on to the surface. The height and radius of the

$$\text{Angle of repose} = \tan^{-1} h/r$$

Where, - Angle of repose, h - Height of granules above the flat surface, r - radius of the circle formed by the granule heap.

**8. Scanning Electron Microscopy**

Dry microspheres are placed on an electron microscope brass stub a coated with gold in an ion sputter. Then picture of microsphere were taken by random scanning of the stub. The microspheres are viewed at an accelerating voltage of 20KV.

**9. Swelling Studies**

Swelling studies were performed to calculate molecular parameters of swollen polymers. Swelling studies may be determined by using dissolution apparatus, optical microscopy and other sophisticated techniques which include H1 NMR imaging, confocal laser scanning microscopy (CLSM), Cryogenic scanning electron microscopy (Cryo-SEM), Light scattering imaging LSI) etc. The swelling studies by using Dissolution apparatus was calculated as per the following formula.

Swelling ratio= weight of wet formulation/weight of formulation

**10. In-Vitro Buoyancy**

Microspheres (300mg) were spread over the surface of a USP XXIV dissolution apparatus type II filled with 900 ml of 0.1 N hydrochloric acid containing 0.02% tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 hrs. The floating and the settled portions of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres.

$$\text{Bouyancy (\%)} = [W_f / (W_{f+}W_S)]*100$$

**11. Drug Entrapment Efficiency[11]**

The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCl repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 0.1N HCl. The solution was filtered and the absorbance is measured by spectro random scanning of the stub. The microspheres are

viewed at an accelerating voltage of 20KV. photometer against appropriate blank. The amount of drug entrapped in the microspheres was calculated by the following formula

DEE= (Amount of drug actually present/theoritical drug load expected*100

## CONCLUSION

The present review article shows that microspheres are better choice of drug delivery system than many other types of drug delivery system. In future by combining various other strategies, microspheres will find the central and significant place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted, specific and effective *in vivo* delivery and supplements as miniature versions of diseased organ and tissues in the body.

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