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MICROSPHERE: A REVIEW

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Abstract: Microspheres are defined as “Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles” (or) can be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level. Microspheres are characteristically small free flowing particles that consisting of proteins or synthetic polymers which are biodegradable in nature. A microsphere is a homogeneous structure made of a continuous phase of one or more miscible polymers in which particulate drug is dispersed throughout the matrix, at either the macroscopic (particulates) or molecular (dissolution) level. Microspheres are particles between 0.1 and 200 μ m in size. Microspheres are used for both oral and parenteral controlled release of drugs. It is the reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the required concentration at the site of interest. This review reflects various types of microspheres, different methods to preparations and characterizations.

Keywords: Microspheres, novel drug delivery, controlled release, target site, specificity, therapeutic efficacy.



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INTRODUCTION

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm). Microspheres can be defined as microparticles sometimes. Microspheres can be prepared by various natural and synthetic materials¹. Glass microspheres, polymer microspheres and ceramic microspheres are commercially available². Alternatively, a microsphere is a homogeneous structure made of a continuous phase of one or more miscible polymers in which particulate drug is dispersed throughout the matrix, at either the macroscopic (particulates) or molecular (dissolution) level³. Further, currently available slow release oral dosage forms, such as enteric coated/ double layer tablets which release the drug for 12-24 hours still result in inefficient systemic delivery of the drug and potential gastrointestinal irritation⁴. Microspheres can be used for both oral and parenteral controlled release of drugs. In mucoadhesive microspheres, physical entrapment of drugs in microsphere pores occurs or it may be by chemical conjugation to polymer matrix⁵. Microspheres received much attention not only for prolonged release, but also to targeting of anticancer drugs⁶.

ADVANTAGES⁷

1. Microspheres provide constant and prolonged therapeutic effect.
2. Reduces the dosing frequency and hence improve the patient compliance.
3. Microspheres could be injected into the body due to the spherical shape and smaller size.
4. Better drug utilization can improve the bioavailability and reduce the incidence or intensity of adverse effects.
5. Microsphere morphology allows a controllable variability in degradation, drug release.

DISADVANTAGE⁷

1. The release from the formulations may get modified.
2. The release rate may vary from a variety of factors like food and the rate of transit through gut, mucin turnover rate etc.
3. Differences in the release rate can be found from one dose to another.
4. Any loss of integrity in release pattern of the dosage form may lead to potential toxicity.
5. These kinds of dosage forms cannot be crushed or chewed.

TYPES OF MICROSPHERES^{8,9}

- 1) Bio adhesive microspheres
- 2) Magnetic microspheres
- 3) Floating microspheres
- 4) Radioactive microspheres
- 5) Biodegradable polymeric microspheres
- 6) Synthetic polymeric microspheres

1. Bioadhesive microspheres

Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water soluble polymers. Adhesion of microspheres to the mucosal membrane such as buccal, ocular, rectal, nasal etc can be named as bioadhesion. These types of microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action.

2. Magnetic microspheres

This kind of delivery system is very much important which localizes the drug to the disease site. In the larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug.

A. Therapeutic magnetic microspheres

It is used to deliver chemotherapeutic agent to liver tumor. Drugs like proteins and peptides may also be targeted through this system.

B. Diagnostic microspheres

It may be used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nano size particles supramagnetic iron oxides.

3. Floating microspheres

In this type of microspheres the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate.

4. Radioactive microspheres

Radio immobilization therapy microspheres sized 10-30 nm is of larger than capillaries and gets trapped in first capillary bed when they come across. They injected to the arteries that lead to tumour of interest.

5. Biodegradable polymeric microspheres

Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also bioadhesive. Biodegradable polymers prolongs the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium, results gel formation.

6. Synthetic polymeric microspheres

The synthetic polymeric microspheres are used in clinical application widely, moreover that also used as bulking agent, fillers, embolic particles, drug delivery vehicles etc and proved to be safe and biocompatible.

METHOD OF PREPARATION^{7,10,11,13}

1. Single emulsion techniques
2. Double emulsion techniques
3. Phase separation coacervation technique
4. Spray drying
5. Solvent removal
6. Wax coating Hot-melt method

1. Single emulsion technique

The micro particulate carriers of natural polymers those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dispersed in aqueous medium followed by dispersion in non aqueous medium like oil. Cross linking of the dispersed globule is carried out. The cross linking may be achieved either by means of heat or by using the chemical cross linkers. The chemical cross linking agents which used are glutaraldehyde, formaldehyde, di acid chloride etc. Heat denaturation is not suitable to thermolabile substances. Chemical cross linking suffers with the disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, separation.

2. Double emulsion technique

This process consumes formation of the multiple emulsions or the double emulsion of type w/o/w & is best suited to the water soluble drugs, peptides, proteins & the vaccines. Aqueous protein solution is dispersed in a lipophilic organic continuous phase which is generally consisted of polymer solution that eventually encapsulates protein contained in dispersed aqueous phase. The primary emulsion is subjected to the homogenization before addition to aqueous solution of PVA. This results in formation of double emulsion which is then subjected to solvent removal by solvent evaporation maintaining the emulsion at reduced pressure or by stirring so that organic phase evaporates out.

3. Spray Drying

In Spray Drying the polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, Acetone, etc. Drug in the solid form is then dispersed in the polymer solution under high-speed homogenization. Then this dispersion is atomized in a stream of hot air. The atomization forms of the small droplets or the fine mist from which the solvent evaporate instantaneously leading the formation of the microspheres in a size range 1-100 μ m. Micro particles are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying. One major advantages of process is feasibility of operation under aseptic conditions this process is rapid and this leads to the formation of porous micro particles.

4. Phase separation coacervation technique

The method involves addition of drug into dilute polymeric solution, in methylene chloride; and resultant mixture is poured into an unstirred bath of strong non-solvent, petroleum ether, in a ratio of 1: 100. Microspheres produced are then clarified, washed with petroleum ether and air dried.

5. Wax coating Hot-melt method

Wax may be used to coat the core particles which encapsulate the drug by dissolution or dispersion in molten wax. The waxy solution is dispersed by high speed mixing into cold solution, i.e cold liquid paraffin. The mixture is agitated for at least one hour. The external phase (liquid paraffin) is then decanted and the microspheres are suspended in a non-miscible solvent and allowed to air dry. Carnauba wax and beeswax may be used as the coating materials and these can be mixed in order to achieve desired characteristics.

6. Solvent removal technique

It is a versatile non aqueous technique of preparation of microspheres. This technique comprises of drug is dissolved suitably in a polymeric solution and in volatile organic solvent. The resultant mixture is suspended in silicone oil containing span 85, Finally, petroleum ether was added till all the solvent was completely extracted in to the oil solution. The microspheres are dried by vacuum drying.

CHARACTERIZATION ENTRIC COATED MICROSPHERES^{14,15}

1. Micromeritic Properties

Angle of repose, density, hausner's ratio, compressibility index is determined by using proper equations.

2. Particle size and shape

The most widely used procedures to visualize microparticles are conventional light microscopy (LM) and scanning electron microscopy (SEM). Both can be used to determine the shape and outer structure of microspheres. LM provides a control over coating parameters in case of double walled microspheres. The microspheres structures may be visualized before and after coating and the change can be measured microscopically. SEM provides higher resolution in contrast to the LM. SEM permits investigations of the microspheres surfaces and after particles are cross-sectioned, it may also be used for the investigation of double walled systems. Confocal fluorescence microscopy can be used for the structure characterization of multiple walled microspheres.

3. Drug entrapment capacity¹⁶

Efficiency of drug entrapment for each batch may be calculated in terms of percentage drug entrapment (PDE) as per the following formula:

$$\text{PDE} = \text{Actual drug loaded} / \text{theoretical loading} \times 100$$

Theoretical drug content can be determined by calculation assuming that the entire drug present in the polymer solution used gets entrapped in microspheres and no loss occurs at any stage of preparation of microspheres.

4. Yield of Microspheres¹⁷

The prepared microspheres were collected and then weighed. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres.

% Yield = (Actual weight of product / Total weight of excipients and drug) x 100

5. Swelling index¹⁸

This technique was used for characterization of microspheres were performed with swelling index technique. Different solution (100mL) were taken such as (distilled water, buffer solution of pH (1.2, 4.5, 7.4) were taken and microspheres (100mg) were placed in a wire basket and kept on the above solution and swelling was allowed at 37°C and changes in weight variation between initial weight of microspheres and weight due to swelling was measured by taking weight periodically and soaking with filter paper.

6. In Vitro drug release¹⁸

To carry out In Vitro drug release, weighed 50 mg of loaded microspheres were dispersed in dissolution fluid in a beaker and maintained at 37±2 °C under continuous stirring at 100 rpm. At certain time intervals 5 mL samples were withdrawn through a hypodermic syringe fitted with a 0.4 µm millipore filter and replaced with the same volume of pre-warmed fresh buffer solution to maintain a constant volume of the receptor compartment. The samples analyzed spectrophotometrically. The drug release was determined from the standard calibration curve of given drug.

7. In vitro diffusion studies¹⁸

In Vitro diffusion studies were performed using in vitro nasal diffusion cell. The receptor compartment was filled with buffer maintained at 37 ± 2 °C. Accurately weighed microspheres equivalent to 10 mg were spread on sheep nasal mucosa. At selected time intervals 0.5 mL of diffusion samples were withdrawn through a hypodermic syringe and replaced with the same volume of pre warmed fresh buffer solution to maintain a constant volume of the receptor chamber. The samples were analyzed spectrophotometrically.

CONCLUSION:

The microspheres are better choice of drug delivery system than many conventional types of drug delivery system because of its target specificity and better patient compliance. So, in future microspheres will have an important role to in the development of new pharmaceuticals.

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