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MICROSPHERES-A REVIEW ARTICLE

K. Malleswari*, D. Rama Brahma Reddy, U. Sravani and K. Sonia Chowdary

Department of Pharmaceutics, Nalanda institute of Pharmaceutical sciences, Kantepudi, Guntur.

***Corresponding Author: K. Malleswari**

Department of Pharmaceutics, Nalanda institute of Pharmaceutical sciences, Kantepudi, Guntur.

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ABSTRACT

Microspheres are characteristically free flowing powders consisting of proteins or synthetic/natural polymers having a particle size ranging from 1-1000µm micrometers. Oral modified-release multiple-unit dosage forms have always been more effective therapeutic alternative to conventional or immediate release single-unit dosage forms. With regards to the final dosage form, the multi particulates are usually formulated into microspheres and filling them into hard gelatin capsules. Microspheres received much attention not only for prolonged release, but also for targeting of drugs. Microspheres are various types like Bio adhesive microspheres, Magnetic microspheres, Floating microspheres, Radioactive microspheres, Polymeric microspheres, Biodegradable polymer- i.e microspheres, Synthetic polymeric microspheres. The current aim of this review is to study various aspects of the microparticles including types and evaluation tests.

KEYWORDS: Microspheres, types of microspheres, evaluation of microspheres.

INTRODUCTION[1-4]

A spherical shell that is usually made of a biodegradable or resorbable plastic polymer , that has a very small diameter usually in the micron or nanometer range and i.e often filled with a substance(as drug or antibody)for release as the shell is degraded.

Microspheres can encapsulate many types of drugs including small molecules, proteins, and nucleic acids and are easily administered through a syringe needle. Microspheres are multi particulate drug delivery systems which are prepared to obtain prolonged or controlled drug delivery to improve bioavailability, stability and to target the drug to specific site at a predetermined rate. They are generally biocompatible, can provide high bioavailability, and are capable of sustained release for long periods of time. Several commercial products are based on polymer microspheres. There are two types of microspheres; microcapsules and micromatrices, which are described as, Microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall. And micromatrices in which entrapped substance is dispersed throughout the matrix. Microspheres are sometimes referred to as microparticles. Microspheres play an important role to improve bioavailability of conventional drugs and minimizing side effects.

Ideal Characteristics of Microspheres

- The ability to incorporate reasonably high concentrations of the drug.
- Stability of the preparation after synthesis with a clinically acceptable shelf life.
- Controlled particle size and dispersability in aqueous vehicles for injection.
- Release of active reagent with a good control over a wide time scale.
- Biocompatibility with a controllable biodegradability.
- Susceptibility to chemical modification.

Advantages of Microspheres[5]

1. Particle size reduction for enhancing solubility of the poorly soluble drug.
2. Provide constant and prolonged therapeutic effect.
3. Provide constant drug concentration in blood there by increasing patent compliance.
4. Decrease dose and toxicity.
5. Increases duration of action.
6. Method of preparations are simple.
7. Patient compliance is good.
8. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumour47. 8. The size, surface charge and surface hydrophilicity of microspheres have been found to be important in determining the fate of particles in vivo.
9. Studies on the macrophage uptake of microspheres have demonstrated their potential in targeting drugs to pathogens residing intracellularly. 10. Protects the GIT from irritant effects of the drug.

Disadvantages of microspheres[6]

1. Removal once injected is difficult.
2. Sometimes non uniformity of drug content may result while preparation.
3. Unknown toxicity of beads.
4. Difficulty of large scale manufacturing.
5. Maintaining drug stability and poor control of drug release rates.
6. Reproducibility is less.

Types of Microspheres[7-8]

Microspheres are various types like

1. Bio adhesive microspheres
2. Magnetic microspheres
3. Floating microspheres
4. Radioactive microspheres
5. Polymeric microspheres

I. Biodegradable polymeric microspheres
II. Synthetic polymeric microspheres

1. Bio Adhesive Microspheres

Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc. can be termed as bio adhesion. These kinds 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 localises the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc.4 The different type are Therapeutic magnetic microspheres are used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system. Diagnostic microspheres. Magnetic drug transport technique is based on the fact that the drug can be either encapsulated into a magnetic microsphere or conjugated on the surface of the microsphere. The accumulation of the carrier at the target site allow them to deliver the drug locally.

3. Floating Microspheres

In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, and the system is found to be floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration. Moreover it also reduces chances of dose dumping. It produces prolonged therapeutic effect and therefore reduces dosing frequencies. Drug (ketoprofen) is given in the form of floating microspheres.

4. Radioactive Microspheres

Radio embolization therapy microspheres sized 10-30 nm are of larger than the diameter of the capillaries and gets tapped in first capillary bed when they come across. They are injected in the arteries that leads them to tumour of interest so all these conditions radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. It differs from drug delivery system, as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microspheres are α emitters, β emitters, γ emitters.

5. Polymeric Microspheres

The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and Synthetic polymeric micro-spheres.

I) Biodegradable Polymeric Microspheres

Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also bio adhesive in nature. 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. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner. The main drawback is, in clinical use drug loading efficiency of biodegradable micro- spheres is complex and is difficult to control the drug release. However they provide wide range of application in microsphere based Synthetic polymeric microspheres are widely used in treatment.

II) Synthetic Polymeric Microspheres

Clinical application, moreover that also used as bulking agent, fillers, embolic particles, drug delivery vehicles etc. and proved to be safe and biocompatible but the main disadvantage of these kind of microspheres, are tend to migrate away from injection site and lead to potential risk, embolism and further organ damage.

Mechanism of Action Microspheres[9]

Most of the drug delivery through microparticles inhibits a matrix type internal solid dispersion morphology structure. The drug may be insoluble in the polymeric matrix and the drugs are released by erosion initially water diffuses into the matrix dissolving the resulting adjacent to the surface of the device. The resulting osmotic pressure is relieved by forming a channel to the surface releasing a defined amount of drug in the initial drug burst.

EVALUATION OF MICROSPHERES[9-10]

1. 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 microparticles. LM provides a control over coating parameters in case of double walled microspheres. The microspheres structures can be visualized before and after coating and the change can be measured microscopically. SEM provides higher resolution in contrast to the LM. SEM allows investigations of the microspheres surfaces and after particles are cross-sectioned.

Test
Microspheres (50mg) are suspended in distilled water (5ml) containing 2% w/v of tween80, to prevent microsphere aggregation, the above suspension is sonicated in water bath and the particle size is expressed as volume mean diameter in micrometer.

2. Electron Spectroscopy
The surface chemistry, atomic composition of surface and surface degradation of biodegradable microspheres can be determined using the electron spectroscopy for chemical analysis (ESCA).

Test
Surface morphology is determined by the method SEM. In this microcapsule are mounted directly on the SEM sample. Slab with the help of double sided sticking tape and coated with gold film under reduced pressure and analysed.

3. Density Determination
The density of the microspheres can be measured by using a multi volume pychnometer. Accurately weighed sample in a cup is placed into the multi volume pychnometer. Helium is introduced at a constant pressure in the chamber and allowed to expand. This expansion results in a decrease in pressure within the chamber. Two consecutive readings of reduction in pressure at different initial pressure are noted. From two pressure readings the volume and hence the density of the microsphere carrier is determined

4. Isoelectric Point
The micro electrophoresis is an apparatus used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined. The electrophoretic mobility can be related to surface contained charge, ionisable behaviour or ion absorption nature of the microspheres.

5. Angle of Contact
The angle of contact is measured to determine the wetting property of a micro particulate carrier. It determines the nature of microspheres in terms of hydrophilicity or hydrophobicity. The angle of contact is measured at the solid/air/water interface.

6. In Vitro Methods
In vitro drug release studies have been employed as a quality control procedure in pharmaceutical production, in product development etc. Sensitive and reproducible release data derived from physic-chemically and hydro dynamically defined conditions are necessary, however no standard in vitro method has yet been developed. Different workers have used apparatus of varying designs and under varying conditions, depending on the shape and application of the dosage form developed.

7. Drug entrapment efficiency
Test
Microspheres containing of a drug (5mg) are crushed and then dissolved in distilled water with the help of ultrasonic stirrer for 3 hours, filtered then assayed by UV-Visible spectroscopy. Entrapment efficiency is equal to ratio of actual drug content to theoretical drug content.

8. Swelling Index
This technique is used for characterization of sodium alginate microspheres. Different solution (100ml) are taken such as [distilled water, buffer solution of pH (1.2,4.5,7.4)] and alginate microspheres (100mg) are placed in a wire basket and kept on the above solution and swelling is allowed at 37 degrees centigrade. Thus, changes in weight variation between initial weight of microspheres and weight due to swelling is measured by taking weight periodically and soaking with filter paper.
Swelling index= (mass of swollen microspheres -mass of drug microspheres/mass of dried microspheres)100.

9. Stability Studies
Stability studies are done by place in the microspheres in screw capped glass container and storing them at following conditions:

- Ambient humid condition
- Room temperature (27+/- 2^0 C).
- Oven temperature (40+/-2^0C).
- Refrigerator (50+/-8^0C).

It was carried out of for 60 days and the drug content of the microsphere is analysed.

10. X-Ray Diffraction
Change in crystalinity of drug can be determined by this technique. Microparticles and its individual components are analysed by the help of XRD instrument. Scanning range angle between 80^0 C-70^0C.

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 version of diseased organ and tissues in the body.

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