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A REVIEW ON MICROSPHERES: FORMULATION TYPES AND ITS EVALUATION

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ABSTRACT

Conventional drug delivery gives the limitations of plasma drug concentration fluctuations in the blood which causes increased dosing. Controlled drug delivery has been approached to overcome the disadvantages by using nanocarrier which it coupled with drug molecule such as liposomes, niosomes, microspheres etc., which regulate the concentration. Microspheres are free flowing particle with particle size range 1-1000µm.The various synthetic and natural polymers are used for manufacturing. It improves efficacy, safety, reduced toxicity and increased patience compliance compared to conventional drug delivery. The article briefly shows the types of microspheres and various parameters to evaluate the efficiency and also its importance.

KEY WORDS: Microspheres, nanocarrier, controlled drug delivery

INTRODUCTION

There has been an enormous impact on the health care system from drug delivery systems (DDS) that are capable of precisely controlling the rate of release or targeting drugs to specific body sites.

A drug delivery system that meets the individual needs of the body throughout the course of treatment and delivers the active substance exclusively to the target site will provide the body with the maximum benefit.

In other words, carrier technology provides a powerful approach to the delivery of drugs by coupling the drug with a particle that modulates its release and absorption in an intelligent manner [1]. Liposomes, nanoparticles, microspheres, and nanoparticles are among the types of carriers available

Microspheres

Essentially, microspheres were small, free-flowing particles, having a diameter between 1 to 1000µm, made up of biodegradable proteins or synthetic polymers [2]. Generally, it has 2 types

Microcapsules:

In this type, the entrapped substances have been remained inside the matrices

Micromatrices

In this type, the entrapped substances have been remained throughout the matrices.

Various natural and synthetic materials were used for manufacturing microspheres. A number of conventional drugs have been improved and side effects reduced using this technique.

Microsphere's characteristics

- **Having ability of incorporation of high amount of substance**
- **High stability and likely acceptable shelf life**
- **Average particle size**
- **May have controlled dispersibility in aqueous vehicle for injection**
- **Sustained action on drug release**
- **Controlled degradability with more stable bioavailability**
- **Modifications by chemical means should be possible**

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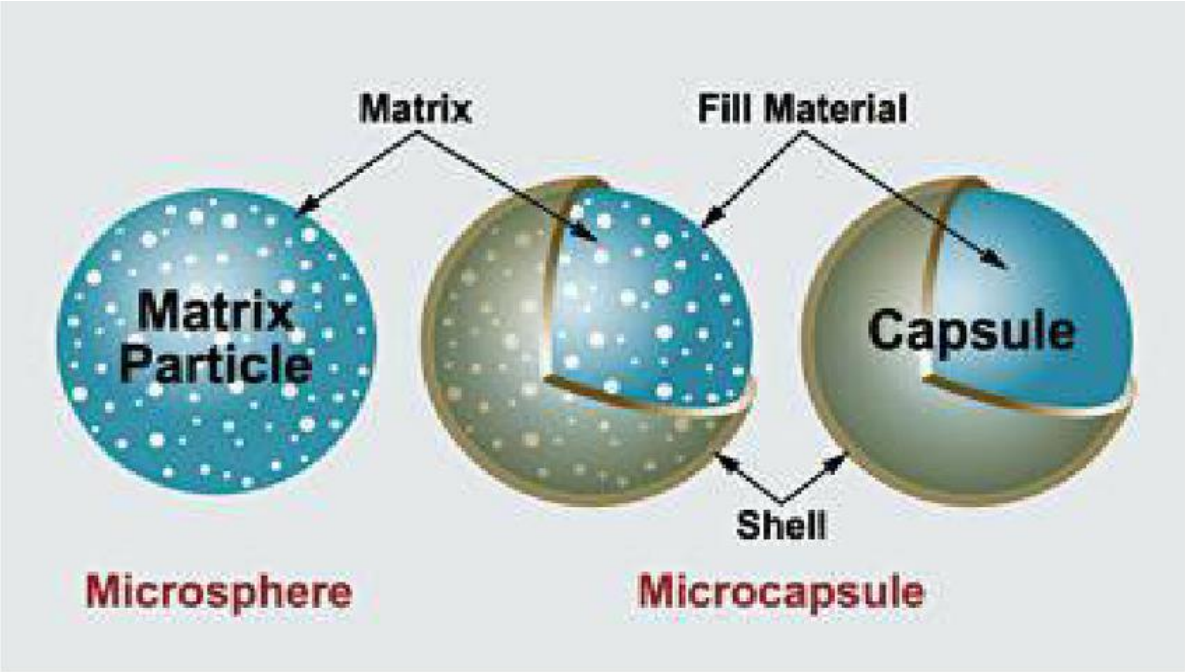

Figure:1 General description of Microsphere and Microcapsule

Types

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

A. **Bio-adhesive type**

An adhesion occurs when a membrane sticks to a water-soluble polymer due to its sticking property. A bioadhesion is defined as the adhesion of drugs to mucosal membranes (such as buccal, oral, rectal, nasal etc.,). Due to their prolonged contact with the absorption site, these microspheres are most effective at treating certain conditions [3].

B. **Magnetic type**

These microspheres concentrate drugs in order to deliver them directly to diseased areas. With this delivery system, free-circulating drugs are replaced with magnetically targeted drugs. A magnetic field transmits magnetic response to magnetic carriers through the incorporated materials (e.g. chitosan, dextran) used for magnetic microspheres [4]. There are two types of magnetic microspheres.

- Diagnostic purpose
- Therapeutic purpose

a. Therapeutic microspheres

Chemotherapeutic agents were delivered to liver tumours using these. Proteins and peptides can also be targeted with them.

b. Diagnostic microspheres

Diagnostic purposes are served by these. By forming nano-sized supramagnetic iron oxide particles, for example, liver metastases can be scanned as well as bowel loops can be distinguished from other abdominal structures [5].

C. Floating microspheres

Since these microspheres are low in bulk density, they remain buoyant in the stomach and do not affect gastric emptying. In addition to increasing gastric residence time, the microsphere system also increases fluctuations in plasma concentration as the drug is released at the rate desired. Furthermore, these systems reduce the likelihood of dose dumping, result in a prolonged therapeutic effect, and reduce the frequency of dosing. For instance, ketoprofen can be delivered as floating microspheres [6].

D. Radio-active microspheres

Radio embolization therapy uses microspheres that are 10-30 nm in diameter (larger than capillary diameters). As soon as they discover a capillary bed, they get trapped in it. A high radiation dose is delivered to the targeted areas with radioactive microspheres injected into the arteries without damaging the surrounding tissues [7]. Drug delivery using this system differs from other systems in that the radioactive substance is not released from the microspheres, but rather is absorbed by a radioisotope. Microspheres that emit radiation are known as emitters. (α, β and γ emitters) [8].

E. Polymeric microspheres

It has 2 types namely, biodegradable and synthetic microspheres

1. Biodegradable polymeric microspheres

In these microspheres, natural polymers like starch were used that they are biodegradable; bio-compatable and bio-adhesive. When an aqueous medium is added to these polymers, they have a high swelling property. Consequently, they prolong their residence time on mucous membranes and form a gel like substance [9]. Release rates and extents depend on polymer concentrations and sustained release patterns

2. Synthetic polymeric microspheres

Clinical applications of the microspheres include bulking agents, filters, embolic particles, drug delivery vehicles etc., In spite of being safe and bio-compatable, synthetic polymeric microspheres move away from their injection site, which can cause embolism and organ damage [10].

Formulation

It is possible to prepare microparticles from various polymers, including biodegradable and non-biodegradable ones. In addition to natural as well as synthetic, a modified type of natural substances also be used. For the manufacture of microspheres, the following polymers were used,

Synthetic substances:

- Biodegradable examples- Lactides and glycosides, Polyalkyl cyanoacrylates, Polyanhydrides
- Non-biodegradable examples- Polymethyl methacrylate, acrolein, glycidyl methacrylate, epoxy polymers

Natural substances

- Proteins- albumins, gelatin and collagen
- Carbohydrates- Starch, agarose, carrageenan and chitosan

Chemically modified carbohydrates

- Cellulose (DEAE)
- Dextran (poly acryl)
- Starch (poly acryl)

Criteria's for preparation

- Incorporating the drug in a reasonably high concentration
- An acceptable shelf life for the preparation after synthesis
- For injection in aqueous solutions, controlled particle size and dispersibility are essential
- An active agent that can be controlled over a wide period of time
- Biocompatibility and biodegradability under control

Solvent evaporation

Microencapsulation is commonly carried out by solvent evaporation in the pharmaceutical industry. An encapsulation material used in this technique is polylactic co glycolic acid, a biodegradable polymer, which facilitates controlled release of the drug. Some examples of hydrophobic drugs like cisplatin, naltrexone, lidocaine and progesterone. The hydrophilic drugs like insulin, proteins, and vaccines has been encapsulated by solvent evaporation.

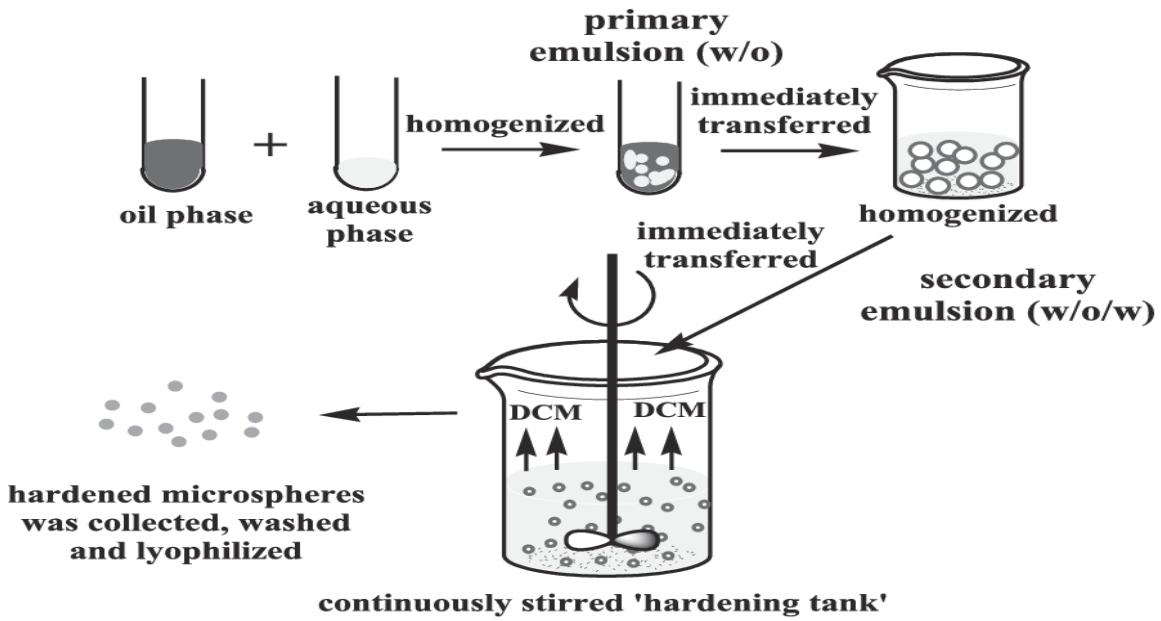

Figure: 2 SOLVENT EVAPORATION METHOD

As a result, an aqueous solution that contains viscosity enhancers or stabilisers is prepared and vigorously stirred into a polymer solution in a solvent such as DCM or CHCl3. Using the primary water in oil emulsion, a excess quantity of water, surfactant or emulsifier (such as PVA or PVP) are added to make a multiple emulsion. In order to obtain solid microspheres, the obtained double emulsion is stirred until most of the organic solvent evaporates.

Evaluation

1. Microsphere recovery [2]

As a result, it determines the number of microspheres obtained after preparation, as well as the amount of polymer and drug used. Calculate the microsphere recovery / yield as follows:

$$\% \text{ yield} = \frac{Practical\ yield}{\text{theoritical yield}}\ X\ 100$$

$$\text{Yield of microspheres in practical} = \frac{amount\ of\ encapsulated\ drug}{\text{amount of drug added}}$$

2. Entrapment efficiency

Drug entrapment in the microsphere and drug absorption on its surface or interior are determined in this method. In order to measure the efficacy of the microsphere in terms of its active ingredients, the amount of free, adsorbed, and entrapped drug should be measured separately.

3. Surface morphology

A microsphere's porosity and microstructure can be determined by its porosity. Scanning electron microscopy (SEM) is the most commonly used technique for studying surface morphology. SEM requires a vacuum field to generate images, so the prepared sample is dehydrated for the purpose. Electron dense coating materials (gold, palladium, or a combination of them) are used to coat the samples (by sputter coating or thermal vacuum evaporation method), before loading them into a photomicrograph.

4. Particle size analysis

In order to make sure that the particle size of the formulation lies within the optimal range, particle size analysis is important. Particle size is determined using the following methods using different physical principles:

By manual method

- Optical microscopy
- Electron microscopy

By automatic methods

- Particle counters
- Scattering lights
- Flow cytometry
- Field flow fractionation

5. Chemical analysis by electronic spectroscopy [11]

A biodegradable microsphere's surface chemistry, atomic composition, and surface degradation can be studied using electron spectroscopy for chemical analysis (ESCA).

6. FT-IR by ATR method

By using FT-IR, it is possible to measure the degradation of the polymeric matrix of the carrier system. An attenuated total reflectance (ATR) measurement is performed on the surface of the microspheres. Microsphere surface composition can be determined using ATR FTIR depending on manufacturing procedures and conditions.

7. *In vitro* release studies

Studying the behaviour of these systems is intended to determine their efficacy and their release of drugs. As a heterogeneous system, microspheres release drugs from polymers via diffusion in an in vitro environment. This results in a biphasic system composed of a drug and its polymer matrix. The extent to which a polymeric microsphere is degraded determines the extent of drug release. We used a dialysis method for conducting the invitro release experiment, which involves placing weighed microspheres in a large volume of continuous phase acceptor fluid and stirring the compartment. There is a periodic sampling and analysis of the drug which diffuses from the microspheres into continuous phase.

8. *In vivo* tissue distribution study

Studying microspheres in vivo provides tangible evidence of their efficacy. Microsphere properties are also crucial to understanding how formulations function in biological systems. Adult albino mice/wistar rats/rabbits, etc of specified weight are used for in vivo analysis of formulation properties. Animals are given a measured dose of the drug as dispersion in saline with 1% tween 80. A microsphere is then injected to the animals through the tail route vein at scheduled intervals, and then they are sacrificed for targeted action studies by cervical dislocation. Lungs, liver, kidneys, heart, and spleen are removed, and HPLC analysis is used to determine the drug concentration in each organ. To prove the hypothesis that microspheres/formulations are targeted to organs and compare them with conventional dosage forms of a drug, in vivo tissue distribution studies are conducted using animal models.

Merits [12]

1. Ensures that drug is delivered with specificity and maintained at the target site with no untoward effect, if modified.
2. Controlled drug release is possible through solid biodegradable microspheres.

3. As well as long-term release, microspheres are important for targeting anticancer drugs
4. Several factors are associated with the fate of microspheres in vivo, including size, surface charge, and hydrophilicity.
5. Drugs can be targeted to intracellular pathogens through macrophage uptake of microspheres.

Demerits [13]

1. As a result of the formulation, a modified release occurs
2. As a result of many factors, such as food consumption and the speed of transit through the GI tract, it is possible to determine the release rate of a controlled release dosage form
3. Different release rates between doses
4. There may be potential toxicity associated with controlled release formulations because of their higher drug loads.
5. Crushed or chewed dosage forms are not recommended

DISCUSSION

The present review article demonstrates that microspheres are a better choice of delivery system for drug delivery than many other types of drug delivery systems that have been investigated in the past. Through the combination of various other strategies in the future, microspheres will play a fundamental role in novel drug delivery in the future, especially in diseased cell sorting, diagnostics, genes, & genetic materials, safe, targeted, specific, and effective in vivo delivery and supplementation as miniature versions of the diseased organs and tissues within the body, enabling the delivery of novel drugs.

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