Microsphere – A Review

[1]Guruprasad S, [2]Barnedo p, [3]Jeeva N R, [4]Poovarasan, [5]Jaganathan K

[1]Associate professor, [2] Student, [3] Student, [4] Student, [5]Professor

[1]Department of Pharmaceutics

[1]JKKMMRF Annai JKK Sampoorani Ammal College of Pharmacy, Namakkal, Tamilnadu, India.

[1]gurukpm95@gmail.com, [2]josnabarnedo1007@gmail.com, [3]nrjeeva15@gmail.com

ABSTRACT

Microspheres as a novel drug delivery system, defining them as spherical particles ranging from 1 to 1000 \bm{\mu}m that encapsulate drugs to provide sustained and controlled therapeutic action. The study categorizes various types of microspheres—including bio-adhesive, magnetic, floating, radioactive, and polymeric systems—and details their specific applications, such as targeting anticancer drugs to tumors or improving bioavailability by extending gastric residence time. While highlighting advantages like biocompatibility, reduced dosing frequency, and site-specific delivery, the report also addresses preparation methods like solvent evaporation and evaluation techniques essential for ensuring the stability and efficacy of these advanced carriers.

1.INTRODUCTION

- The concept of the advanced drug delivery systems, especially those offering a sustained and controlled action of the drug to the desired area of effect, has attained great appeal for nearly half a century.
- However, before the appeal of improved alternative methods, drug delivery systems were considered only as a means of getting the drug into the patient's body.[1]
- **Microspheres** can be characterized as solid, approximately spherical particles with a diameter between 1–1000µm, including dispersed drugs in a certain solution or micro crystalline shape. Both the terms **microcapsules** and **microspheres** are often used as synonyms. [2]
- Medication that is simply transmitted from the gastrointestinal tract (GIT) and also has a short half-life is immediately destroyed from the circulatory system in the blood. The oral sustained or controlled release (CR) has also been developed to avoid this problem, as that will slowly discharge the substance into the GIT and retain a steady medication intensity in the plasma for a prolonged time period.
- A suitable dosage formulation reaches the required plasma therapeutic Drug concentration and remains constant throughout the treatment period. This can be achieved by delivering a traditional dosage type in a fixed dose and at a specific frequency. [3]

The term **microsphere** is defined as a spherical particle with a size varying from 50nmto 2 mm, containing a core substance. Microspheres are, in a strict sense, spherical empty particles. However, the terms microcapsules and microspheres are often used synonymously.

The microspheres are characteristically free-flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature, and ideally have a particle size less than 200 µm.[1]

- the major advantage of Microspheres, injected in the form of suspension, do not require surgical implantation.
- Problems associated with vaginal rings, such as erosion of the vaginal wall, ring expulsion, interference with coitus, unpleasant ring odour, can be overcome by using microspheres.[4]
- But it is Less reproducibility and,
- These dosing types must not be broken or chewed.
- variations in the rate of discharge from one dosage to the next. [5]

2. TYPES OF MICROSPHERES

Different types of microspheres are categorized as

- 2.1Bio-adhesive microspheres
- 2.2Magnetic microspheres
- 2.3Floating microspheres
- 2.4Radioactive microspheres
- 2.5Polymeric microspheres

Biodegradable polymeric microspheres

Synthetic polymeric microspheres

2.1 BIOADHESIVEMICROSPHERES

"*Bio adhesion*" in simple terms can be described as the attachment of a synthetic or biological macromolecule to a biological tissue. An adhesive bond may form with either the epithelial cell layer, the continuous mucus layer or a combination of the two layer.

 The term "**mucoadhesion"** is used specifically when the interaction occurs with the mucus layer covering a tissue. Generally, bio adhesion is deeper than muco-adhesion. Bio-adhesive microspheres include micro particles and microcapsules (having a core of the drug) of 1–1000 µm in diameter and consisting either entirely of a bioadhesive polymer or having an outer coating of it, respectively.[6]

2.2 MAGNETIC MICROSPHERES

Magnetic microspheres are the supramolecular particles that are small enough to circulate through the capillaries but are sufficiently susceptible to be entraptured in micro vessels by applying magnetic fields of 0.4 T-0.8 T. [7] A drug or therapeutic radioisotope is encapsulated in a magnetic compound; injected into patient's blood stream & then stopped with a powerful magnetic field in the target area. Depending on the type of drug, it is then slowly released from magnetic carriers or confers a local effect, thus it reduces the loss of drug as freely circulating in body. Drug targeting is a specific form of drug delivery where the drug is

directed to its site action or absorption. This could be a particular organ structure, a cell, subset or even an intercellular region.[8]

2.3 FLOATING MICROSPHERES

Floating drug delivery systems or hydro dynamically balance systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time without affecting the gastric emptying rate. The drug is released slowly at a desired rate from the system and drug residual systems are emptied from the stomach. This results in increase in the gastric residence time and a better control of qualification in plasma drug concentration. [9]Gastric retention can be achieved by the mechanism of mucoadhesive or bio adhesion systems, expansion system, high density systems, magnetic systems, super porous hydrogels, raft forming systems, low density system and floating ion exchange resins. [10]

Types of Floating Drug Delivery System

Effervescent systems

Non-effervescent systems

2.4 RADIOACTIVE MICROSPHERES:

The subgroup of microspheres that is radioactive behaves and is generally used in a similar fashion to non-radioactive microspheres. But in addition to the matrix substance, which defines the microsphere and gives its targeting properties in a desired tissue or organ, the radioactive microsphere also contains one or more radionuclide(s) that are intimately bound to it.

Radioembolization therapy utilizes microspheres, measuring 10-30 μm, which are too large to pass through the capillary bed, and are injected into the arteries that supply the tumor.

These microspheres accumulate and delivery concentrated dose of radiation, without sparing surrounding healthy tissue.

The microspheres retain their radioactivity, acting locally without releasing radiation. Three types of radioactive microspheres are: Alpha (α) emitters, Beta (β) emitters, Gamma (γ) emitters. [11]

2.5 POLYMERICMICROSPHERES

Polymeric microspheres are composed of natural or synthetic polymers., used to encapsulate drugs within a spherical polymer matrix or shell. This technique allows for controlled and sustained drug release, targeted delivery, and improved drug stability and bioavailability[12]

Polymeric microspheres are classified as.

- Biodegradable polymeric microspheres
- Synthetic polymeric microspheres

3.MATERIALS USED IN THE PREPARATION OF MICROSPHERES

3.1 Natural polymers

They are of three types

(a) Carbohydrate examples are chitosan, starch.

(b) Protein examples are albumin, gelatin.

(c) Chemically altered carbohydrate examples are polydextran

3.2 Synthetic polymers

They are classified into two categories

(a) Non-biodegradable polymer, examples are PMMA, epoxy polymers.

(b) Biodegradable polymer examples are polyanhydrides.

Chitosan

The partial deacetylation of chitin gives chitosan, which is a natural cationic biopolymer. The linear β-(1-4) glycoside connections of 2-acetamido-d-glucose and d-glucose units comprise the biopolymer.[13]

Alginates

Formulations of alginates, which are naturally occurring substances present in both algae and brown seaweed, have an attention in pharmaceutical dosage forms.[13]

Gellan

An anionic deacetylated exocellular polymer, Gellan is secreted by Pseudomonas elodea and contains a tetra saccharide repeating unit consisting of two β-D-glucose, one β-lrhamnose, and one β-D-glucuronic acid.[13]

Pectin

An anionic polymer found in cell wall pectin is mostly derived from apple or citrus fruits. A series of D-galacturonic acid-rhamnose makes up the majority of the structure.[13]

Carboxy methyl cellulose

Cellulose is the source of carboxy methyl cellulose (CMC), an anionic water-soluble derivative. The repeating units have β-1,4-glycosidic linkages between them.[13]

4.DIFFERENT METHODS OF MICROSPHERE PREPARATIONS

There are several ways to prepare microspheres. Single emulsion technique, Double emulsion technique, Solvent evaporation, Spray drying and spray congealing, Quasi-emulsion solvent diffusion, Phase separation coacervation technique, Solvent extraction, Ionotropic Gelation

4.1 Single emulsion technique

The micro particulate carriers of natural polymers, i.e., those of proteins and carbohydrates, are prepared by the single emulsion technique. The natural polymers are dissolved or dispersed in an aqueous medium,

followed by dispersion in a non-aqueous medium like oil. Next, crosslinking of the dispersed globule is carried out. The crosslinking can be achieved either by means of heat or by using chemical crosslinkers. The chemical crosslinking agents used are glutaraldehyde, formaldehyde, acid chloride, etc. Heat denaturation is not suitable for thermostable substances.

Chemical crosslinking suffers the disadvantage of excessive exposure of the active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing, and separation. The nature of the surfactants used to stabilize the emulsion phases can greatly influence the size, size distribution, surface morphology, loading, drug release, and bio-performance of the final multi-particulate product.[14]

4.2 Double emulsion technique

It is the best technique for water-soluble drugs such as proteins, peptides, and vaccines. Because it produces several emulsions or double emulsions of the w/o/w type. Both synthetic and natural polymers are used in this process. The drug is distributed in aqueous solution and exists in the organic phase. After the drug is dissolved in the aqueous phase and encapsulated in the organic phase, a primary emulsion is formed, which contains a coated polymer. A secondary emulsion is made by adding aqueous PVA solution after it has been homogenized. Then microspheres are produced, dried, and filtered. [14]

4.3 Solvent evaporation

The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent that is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation, the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated, if necessary, to evaporate the solvent.[14]

4.4 Spray drying and spray congealing

Depending upon the removal of the solvent or cooling of the solution, the two processes are named as spray drying and spray congealing. The polymer is first dissolved in a suitable volatile organic solvent such a 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. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously, leading to the formation of the microspheres [15]

4.5 Phase separation coacervation technique

This process is based on the principle of decreasing the solubility of the polymer inorganic phase to affect the formation of polymer-rich phase called the coacervates. In this method, the drug particles are dispersed in a solution of the polymer, and an incompatible polymer is added to the system, which causes the first polymer to phase separate and engulf the drug particles. The addition of a non-solvent results in the solidification of the polymer.

Poly lactic acid (PLA) microspheres have been prepared by this method using butadiene as an incompatible polymer. The process variables are very important since the threat of achieving the coacervates determines the distribution of the polymer film, the particle size and the agglomeration of the formed particles. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer, since as the process of microsphere formation begins, the formed polymerized globules start to stick and form the agglomerates.t.[15]

4.6 Solvent extraction

This method involves the removal of the organic phase by the extraction of the organic solvent. It involves water-miscible organic solvents like chloroform, isopropanol. The organic phase is removed by extraction with water. This process decreases the hardening time for the microspheres. The drug is directly added to an organic polymer solution. The rate of solvent removal by the extraction method depends on the temperature of water, the ratio of emulsion volume to water, and the solubility profile of the polymer

4.7 Ionotropic gelation

The ionotropic gelation is the capacity of polyelectrolytes to cross-connect in the presence of counter ions to form hydrogel beads, also known as gel spheres. The following formulations can release gel spheres: spherical, cross-linked polymeric hydrophilic entities that can significantly gel and swell synthetic biological fluids and polymer relaxation regulates the drug release through it, drug-loaded polymer solution is dropped into an aqueous solution of polyvalent cations to create the hydrogel beads. A three-dimensional lattice of ionically crosslinked moiety is formed when the cation diffuses into the drug-loaded polymeric droplets[16]

5. FUTURE PROSPECTS

Gastro-Retentive Systems: Floating microspheres are highlighted as a superior formulation. Their ability to float and release drugs slowly makes them highly effective for drugs absorbed in the upper gastrointestinal tract, promising better patient compliance and reduced dosing frequency in future therapies .

Magnetic Targeting: The development of magnetic microspheres allows for precise drug localization using external magnetic fields. This technology holds future potential for treating localized diseases with minimal systemic side effects, provided the challenges of high manufacturing costs and technical complexity can be overcome.

6. CONCLUSION

Among the different types of microspheres—bio adhesive, magnetic, polymeric, and floating—the **floating microspheres are considered the best formulation** because they provide prolonged gastric residence time, controlled and sustained drug release, reduced dosing frequency, and improved patient compliance. Unlike bio adhesive microspheres, they do not rely on mucosal contact; Unlike magnetic ones, they do not require external devices; and compared to conventional polymeric microspheres, they offer better drug absorption in the upper GIT. Thus, floating microspheres combine efficiency, safety, and convenience, making them a superior choice in drug delivery systems.

7. REFERENCE

1.Vyas SP, Khar RK. Targeted & controlled drug delivery: Novel carrier systems [page-417].

2.Venkateswara Reddy B, et al. Formulation and evaluation of efavirenz micro spheres. Der Pharmacia Lettre. 2015;7(6):1-9.

3.Sarode SM, et al. Formulation and evaluation of floating microspheres of J Chem Pharm Res. 2011:3(3):775-83.

4. Sree Giri Prasad B, et al. Microspheres as Drug Delivery System A Review. J Glob Trends Pharm Sci. 2014;5(3):1961-72.

5.Sree Giri PB, Gupta VRM, Devanna N, Jagasuryga K. Microspheres as drug delivery system A review. JGTPS. 2014;5(3):1961-72.

6. Liu G, Yang H. Zhou J. Preparation of magnetic microsphere from waterin-oil emulsion stabilized by block copolymer dispersant. Biomacromolecules. 2005;6:12808.

7..Mahanur V, Sureka Y, Atole V. A Review on Magnetic Microspheres - A Novel Drug Delivery System.

8..Aggarwal A, Chhajer P, Maheshwari S. Magnetic drug delivery in

therapeutics. Int J Pharm Sci Res. 2012;3(2):4670-80.

9.28.Kataria S, Middha A, Sandhu P, Bilandi A, Kapoor B. Microsphere: A review. Int J Res Pharm Chem. 2011;1(4).

10.27.Arora S, Ali J. Floating drug delivery systems: A review. AAPS Pharm Sci Tech. 2005:6:372-90.

11..Mojaverian P, Vlasses PH, Kellner PE, Rocci ML. Effects of gender,

posture, and age on gastric residence time of indigestible solid: pharmaceutical considerations. Pharm Res. 1988;10:639–64.

12..Sinha VR, Goyal V, Trehan A. Radioactive microspheres in therapeutics.

13. Jain NK. Progress in controlled and novel drug delivery systems. 1st ed. New Delhi: CBS Publishers and Distributors; 2004. p. 84–85.

14. Jain NK. Introduction to novel drug delivery systems. New Delhi: CBS Publishers and Distributors; p. 177–78.

15.Chandrawanshi M. A review on microspheres as a novel drug delivery system. J Pharm Res Rev. 2018;12(2).

16.Kawashima Y, Niwa T, Takeuchi H, Hino T, Itoh Y. Characterization of poly morphs of tranilast anhydrate and tranilast monohydrates when crystallized by two solvent change spherical crystallization techniques. J Pharm Sci. 1991;80(5):472–8. doi:10.1002/jps.2600800515.