A Conceptual Review on Microspheres

[1]Vanshaj Sharma, [2]Shilpi Arora

[2]Associate Professor
Himachal Institute of Pharmacy
Paonta Sahib Distt. Sirmaur, H.P.India

***Abstract*- The concept of targeted drug delivery is designed for attempting to concentrate the drug in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues. As a result, drug is localized on the targeted site. Hence, surrounding tissues are not affected by the drug. So, carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanoparticles, liposomes, niosomes etc which modulates the release and absorption characteristics of the drug. Microsphere or Microparticles are defined as a free-flowing spherical particle consisting for polymer matrix and drug they consist of protein or synthetic polymer which are biodegradable in nature having a particle size less than 200µm. Microsphere improves bioavailability, reduce the side effects, improves stability, decrease dose frequency and the targets the drug to specific site at predetermined rate. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body.**

***Keywords*: Microspheres, controlled release, Types of microspheres, Methods of preparation, characterisation of microspheres, applications.**

Introduction

A novel drug delivery method uses a controlled and long-term model to deliver a therapeutic ingredient to the target location. [1] A microsphere, also known as a microparticle, is a spherical particle made up of a polymer matrix and medication that flows freely. They are made of artificial polymers or proteins. which, in nature, biodegrade with particles smaller than 200 µA microsphere is a tiny, spherical particle having a diameter in the range of µ, usually between 1 and 1000 m. [2] Microsphere can also be called as a microparticle.

- For microspheres, beads and microbeads are utilized interchangeably.
- A microsphere should ideally be perfectly round and uniformly sized.

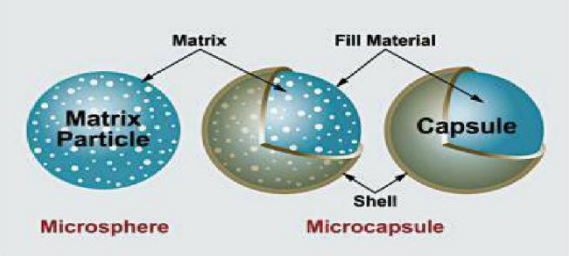

Fig1. Microsphere and Microcapsule

Advantages of Microsphere [3-4]

- They enhance the surface area of the microsphere by decreasing its size, which boosts the efficacy of the poorly soluble substance.
- Dose frequency and adverse effects can be reduced.
- Enhances bioavailability.
- First pass metabolism can be reduced.
- Biological half-life can be enhanced.
- Provide constant and prolonged therapeutic effect.
- Provide constant drug concentration in blood.
- Decrease dose and toxicity.
- Improve patient compliance.

Disadvantages of Microsphere [4]

- The cost is more.
- Reproducibility is less.
- Process condition like change in temperature, pH solvent addition, and evaporation agitation may influence the stability of core particles.
- Degradation of product due to heat hydrolysis, oxidation, solar radiation or biological agents.

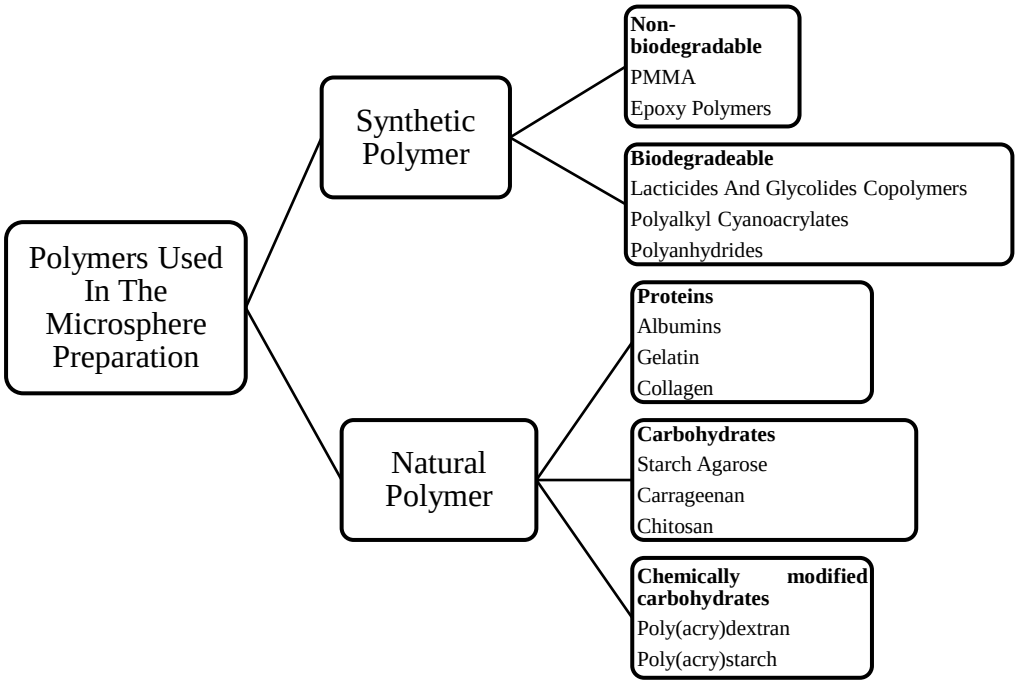

Fig 2. Polymers Used in the Microsphere Preparation [5]

Types of Microsphere

Microsphere are classified into different types as ;

1. Bio-adhesive microsphere.
2. Magnetic microsphere.
3. Floating microsphere.
4. Radioactive microsphere
5. Polymeric microsphere
6. Biodegradable Polymeric microsphere
7. Synthetic polymeric microsphere

1. Bio-adhesive Microsphere [6]

- Adhesion of drug deliveries device to the mucosal membranes such as buccal, ocular, rectal, nasal etc. can be termed as bio adhesion.
- This kind of microsphere exhibit prolonged residence time at the site of application at causes intimate contact with the absorption site and produce better therapeutic action.

2. Magnetic Microsphere [7]

- The kind of delivery system is very much important which localised the drug to the diseases site.
- In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug.
- Magnetic carries receive magnetic responses to a magnetic field from incorporated material that are used for magnetic microspheres are chitosan and dextran .

Therapeutic magnetic microsphere

Used to deliver chemotherapeutic agent to liver tumour.

Drugs like proteins and peptides can also be targeted through system.

Diagnostic microsphere

Used for imaging liver metastasis disease and also can be used to distinguish bowel loops from other abdominal structure by forming nano size particles supra magnetic iron oxides.

3. Floating Microsphere [8]

- Because the bulk density of floating kinds is lower than that of gastric fluid, the stomach stays buoyant without influencing the pace of gastric emptying.
- The drug is released gradually at the intended rate, and it is observed that the system is floating in the stomach content.

4. Radioactive Microsphere [9-10]

- Immobilization treatment When radio microspheres of size 10 to 30 nm are encountered, they are tapped into the first capillary bed because their diameter is greater than that of the capillaries.
- Under all these circumstances, radioactive microspheres give a high radiation dosage to the target locations without harming the normal surrounding tissues because they are injected into the arteries that flow to the tumour of interest.
- It is not the same as a medicine delivery system since radiation operates from within radioisotopes, usually at a distance, rather than being released from a microsphere. The different kinds of radioactive microsphere are a emitters beta emitters and Y emitters.

5. Polymeric Microsphere [11]

- Biodegradable and synthetic polymeric microspheres are two categories for polymeric microsphere.
- *Biodegradable polymeric microsphere: natural polymers, like starch, are utilized because they are biodegradable, biocompatible, and bio adhesive. Additionally, because natural polymers have a high degree of swelling property with aqueous medium that results in gel formation, they prolong the residence times when in contact with mucus membranes. The polymer concentration and the continuous release pattern regulate the drug's release's pace and extent. This kind of microsphere demonstrated an extended resistance period at the application location.
- Synthetic polymeric microspheres: these microspheres are safe and biocompatible, but they have a tendency to migrate away from the injection site, which increases the risk of embolism and additional organ damage. Despite this, synthetic polymeric microspheres are widely used in clinical applications as bulking agents, feelers, embolic particles, drug delivery vehicles, etc.

Methods of Preparation of Microsphere

1. Solvent evaporation
2. Single emulsion technique
3. Double emulsion technique
4. Phase separation coacervation technique
5. Spray drying and spray congealing
6. Solvent extraction
7. Quassi-emulsion solvent diffusion

1. Solvent Evaporation [12]

The manufacturing vehicle phase is where the solvent evaporation process takes place. In the liquid production vehicle phase, the microcapsule coating is initially distributed in a volatile solution. The core material to be micro-encapsulated is dissolved or distributed in a coated polymer solution. In order to achieve a microcapsule of a suitable size, agitation is carried out to distribute the core material combination throughout the liquid production vehicle phase. In the event that the combination needs to be heated in order to operate the solvent, microcapsules of a polymer matrix type are created, containing either water soluble or water insoluble material at the core. The process of solvent evaporation entails the creation of an emulsion between an aqueous or non-aqueous polymer solution and an immiscible continuous phase.

2. Single Emulsion Technique [13]

It is possible to create the microparticulate carrying natural polymers, such as proteins and carbohydrates, using a single emulsion process. After being dissolved or dispersed in an aqueous media, the natural polymers are then disseminated in a non-aqueous medium, such oil. Cross connecting is the next step, and it can be accomplished using heat or chemical cross linkers. An acid chloride, glutaraldehyde, and formaldehyde were among the chemical cross-linking agents utilized. Heat denature cannot occur in a material that is thermolabile. If added during production, chemical cross linking has the drawback of exposing active components to excessive amounts of chemicals. Following centrifugation, washing, and separation, the final multi-particulate product's size, size distribution, surface morphology, drug loading, drug release, and bio performance can all be significantly impacted by the kind of surfactant employed to stabilize the emulsion phases.

3. Double Emulsion Technique [14]

The microsphere double emulsion technique, which works well with water-soluble medications, peptides, proteins, and vaccines, creates multiple emulsions or double emulsions of type (w\o\w). This technique works with both synthetic and natural polymers. The lipophilic organic continuous phase is used to distribute the aqueous protein solution. The active ingredients could be present in the protein solution. The polymer solution that finally encapsulates proteins that are scattered in the aqueous phase often makes up the continuous phase. Subsequently, the main emulsion is sonicated and added to the polyvinyl alcohol aqueous solution. A twofold emulsion forms as a result of this. Next, the emulsion undergoes a solvent removal process using either solvent extraction or solvent evaporation. Using the double emulsion solvent evaporation extraction approach, several hydrophilic medicines, including luteinizing hormone agonist, vaccination protein peptides, and conventional compounds, are effectively integrated into the microsphere.

4. Phase Evaporation Co-acervation Technique [15]

The idea behind this approach is to influence the creation of a polymer-rich phase known as coacervates by reducing the solubility of the polymer in the inorganic phase. The medication particles are spread throughout a polymer during this procedure. The polymer is dissolved in a volatile organic solvent, such acetone or dichloromethane, before being sprayed dried. Using high-speed homogenization, the solid medication is distributed throughout the polymer solution. After that, this dispersion is heated to atomization in a hot air stream. The process of atomization results in the production of tiny droplets or fine mists, from which the solvent instantly evaporates to create microspheres with a size range of 1-100µm. Cyclone separators are used to separate the microparticles from the heated air. While vacuum drying eliminates that solvent race. The ability of these procedures to function in an aseptic environment is one of their main benefits.

5. Solvent Extraction [16]

The process of solvent evaporation has been widely employed in the manufacturing of PLA and PLGA microspheres that are loaded with different medications. Numerous factors, including drug solubility, internal morphology, solvent type, diffusion rate,

temperature, polymer composition, viscosity, and drug loading, are shown to have a substantial impact on microsphere properties. Since the effectiveness of this approach depends on the active substance's successful entrapment into the particle, it works especially well with drugs that are either partially or completely soluble in a liquid media.

6. Quassi Emulsion Solvent Diffusion [17]

Acrylic polymers and quassi emulsions are employed in the solvent diffusion method of controlled release drug microsphere production. This approach allows for the production of micro sponge by employing an external phase that contains polyvinyl alcohol and distilled water. Internal phase comprises polymers, ethanol, and the medication. First, the external phase is applied to the heated internal face at 60º Celsius ambient temperature. For two hours, the mixture is continually stirred. After that, the mixture may be filtered to remove the tiny sponges.

Characterization of Microspheres [18]

1. Particle Size

The most widely used procedures to visualized microparticles are conventional light microscopy and scanning electron microscopy.

2. Degradation Behaviour

The surface chemistry of the microspheres can be determined using the electron spectroscopy for chemical analysis**.**

3. Angle of Repose

The powder Mass was allowed to flow through the funnel orifice kept vertically to a plane paper kept on the horizontal surface, giving a heap angle of powder on paper. The angle of repose was calculated by the following equation**.**

tanɵ = h/r where h and r are the height band radius of the powder cone

4. Bulk Density

Bulk density was obtained by dividing the mass of powder by the bulk volume in centimetre cube; it was calculated by using equation.

Bulk density=mass of microsphere/bulk volume

5. Tapped Density

It is the issue of total mass of the powder to the tab volume of the powder. It is expressed in gram/ml and is given by:

Tapped density=mass of microsphere/tapped volume.

6. Drug Entrapment Efficiency

It is the percentage of drug that is successfully in trapped with microsphere. Drug entrapment efficiency can be calculated by using following equation.

% Entrapment = Actual content /Theoretical content×100.

7. *In-Vitro* Methods

Release studies for different type of microsphere are carried out by using phosphate buffer pH 7.4, mostly by rotating paddle apparatus. Agitated with 100 rpm sample work collected at specific time interval and replaced by same amount and analysed.

Applications of Microspheres

1. Delivery of vaccines A vaccine's safety against microorganisms and their hazardous components is a need. Effectiveness, protection, cost-effectiveness, and ease of application are all requirements that a perfect vaccination should meet. It's difficult to avoid negative consequences and maintain safety. The way of administration has a direct bearing on both the safety factor and the degree of antibody response. The shortcomings of the same traditional vaccinations may be addressed by a biodegradable delivery mechanism for parent rally administered vaccines. Parenteral (subcutaneous, intramuscular, and intradermal) carriers are used despite the fact that they have certain notable benefits, such as:

1. Modulation of antigen release
2. Improved antigenicity
3. Anti stabilization

2.Oral Drug Delivery

Rabbits have been used to assess the possibility of polymer matrix containing diazepam for oral medication administration. A drug-polymer combination with a ratio of 1:0.5 may have been a useful dosage form that was on par with commercial tablet formulations **[19].**

3.Transdermal Drug Delivery

Polymers exhibit favourable film-forming properties. Both a film's cross linking and membrane thickness affect the release profile from the system. Beads and microspheres with chitosan-alginate polyelectrolyte structure have been created in-situ for possible use in surgical tools, controlled release systems, and packaging. Polymer gel beads have a delayed release action that improves treatment efficiency and are a highly biocompatible carrier for the chemotherapy of inflammatory cytokines for drugs such as prednisolone . It was discovered that the qualities of the cell wall being employed determined how much medication was released. For regulated drug release and release kinetics, a combination of chitosan membrane and chitosan hydrogel containing the local anesthetic lidocaine hydrochloride is a fantastic comprehensive procedure **[20].**

4. Microsphere in Gene Delivery

Viral vectors, non-ionic liposomes, polycation complexes, and microcapsule technology are examples of genotype drug delivery methods. Even while viral vectors may achieve a wide range of cell objectives and are incredibly effective, they are nonetheless essential for genotype delivery. Nevertheless, when applied in vivo, they activate the immune system and have harmful consequences. For gene therapy, non-viral delivery techniques have been developed as a solution to the issues with viral vectors.

The simplicity of preparation, ability to target specific cells or tissues, weakened immune system, unlimited plasmid size, and large-scale repeatable manufacturing are the benefits of non-viral delivery systems. In applications involving the transfer of genes, polymers are employed as DNA carriers**.**

6. Targeting By Using Micro Particulate Carriers

The concept of targeting is a well-established concept, which is gaining huge attention in present days. The efficiency of drug depends on availability and ability to interact with binding site. Generally, pellets technique is established that can be formulated by utilising extrusion / spheronization technique e.g. microcrystalline cellulose (MCC) and chitosan.

7. Other Applications

In the biotechnology industry micro encapsulated microbial cells are being used for the production of recombinant protein and peptides. Encapsulation of microbial cells can also increase the cell loading capacity and the rate of production in bioreactors. A feline breast tumour line which was difficult to grow in conventional culture has been successfully grown in microcapsule. Micro encapsulated activated charcoal has been used for hemoperfusion. Biodegradable synthetic polymers are modified natural products **[21]**.

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 .

REFERENCES:

1. Rajput S, Agrawal P, Pathak A, Shrivastava N, Baghel SS, Baghel RS. A review on microspheres: methods of preparation and evaluation. World journal of pharmacy and Pharmaceutical Sciences, 2012;1(1):422-438.
2. Saini S, Kumar S, Choudhary M, Nitesh, Budhwar V. Microspheres as controlled drug delivery system: an updated review. International journal of pharmaceutical sciences and research. 2018;9(5):1760-8.
3. Kadam N. R. and Suvarna V, Microspheres: A Brief Review, Asian Journal of Biomedical and Pharmaceutical Sciences, 2015;3(4):13-15.
4. Virmani Tarun and Gupta Jyoti, Pharmaceutical Application of Microspheres: An Approach for the Treatment of Various Diseases; International Journal of Pharmaceutical Sciences and Research, 2017; 8(1): 3257- 3259. DOI: 10.13040/IJPSR.0975-8232
5. Gurung BD, Kakar S. An overview on microspheres. Int J Health Clin Res. 2020;3(1):11-24.
6. Chaware P, Sharma S, Bhandari A, Garud A, Garud N. Bioadhesive Microspheres: A Review on Preparation and In-Vitro Characterization. World Journal of Pharmaceutical Research. 2014;4(2):423-36.
7. Farah Hamad Farah, Magnetic Microspheres: A Novel Drug Delivery System, Analytical and Pharmaceutical Research.2016;3(5):1-10. DOI: 10.20959/wjpps20179-10054.
8. Jagtap Yogesh Mukund , Floating microspheres: a Review, Brazilian Journal of Pharmaceutical Sciences, 2012;48(1):17-30.
9. Ur's Hafeli, Review: Radioactive Microspheres for Medical Applications, Cleveland Clinic Foundation, Radiation Oncology Department T28, 1-29.
10. Lachman LA, Liberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. Varghese Publishng House, Mumbai, India: 1991, (3);414-415.
11. Ketie Saralidze, Polymeric Microspheres for Medical Applications, Materials, 2010, 3,3537- 3564
12. E Veena Rani , Preparation and evaluation of aspirin loaded Microsphere by solvent evaporation Technique , Journal of Medicine and biology , 2019 ;1(1);27-32
13. Suvarna V, microspheres: a brief review, Asian Journal of Biomedical and Pharmaceutical Sciences, 2015; 5(47):13-19.
14. Prasanth VV, Moy A C, Mathew S ., Mathapan R, Microspheres An overview, Int. J. Res. Pharm. Biomed. Sci., 2011; 2:332 8. DOI https://doi.org/10.22270/jddt.v9i3-s.2826
15. Saravana Kumar K, A Review on Microsphere for Novel drug delivery System, Journal of Pharmacy Research, 2012;5(1):420-424. Doi: 10.52711/2231- 5713.2021.00025
16. Yadav R, Bhowmick M, Rathi V, Rathi J, Design and characterization of floating microspheres for rheumatoid arthritis, Journal of Drug Delivery and Therapeutics 2019; 9(2-s):76-81.
17. Abbaraju S, Biomedical applications of microspheres, Journal of Modern Drug Discovery and Drug Delivery Research, 2015;4(2):1-5.
18. Kazi M, Zakir H, Development of microspheres for biomedical applications: a review, Prog Biomater, 2014;8(4):1-19.
19. Kataria S, Microsphere: A Review, International Journal of Research in Pharmacy and Chemistry, 2011;1(4):1184-1198.
20. Reza A, Microspheres for biomedical applications: preparation of reactive and labeled microsphere, biomaterials, 1993;14 (1):5-15.
21. Tarun V, Pharmaceutical Application Of Microspheres: An Approach For The Treatment Of Various Diseases, International Journal of Pharmaceutical Science and Reaserch, 2017;8(8): 3252-3260. 10.13040/IJPSR.0975-8232.