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# A Review on Microsphere Drug Delivery System and its Applications

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**ABSTRACT**

**Microspheres are small spherical particles, which are prepared to obtain prolonged or controlled drug delivery. Microspheres consisting of proteins or synthetic polymers having a particle size ranging from 1-1000µm. microspheres characteristically free flowing powders, which is use to improve stability, bioavailability of conventional drug and minimizing side effects. The present review highlights various types of microspheres, different methods of preparation includes emulsification technique with single emulsion technique, double emulsification technique, phase separation co-acervation technique, spray drying and spray congealing, solvent extraction. Microspheres have wide range of applications particularly in diseased cell sorting, diagnostics, gene and genetic material, safe, targeted, supplements as miniature versions of diseased organ and tissues in the body and effective in vivo delivery.**

**Keywords: Microspheres, Bioavailability, Conventional drugs, Novel drugs, etc;**

## INTRODUCTION

Microspheres are multi- particulate drug delivery systems and they are made from polymeric waxy or other protective materials such as natural, semi-synthetic polymers. Microspheres are free-flowing powders and particle sizes ranging from 1-1000µm. microspheres are also known as macroparticles. There are 2 types of microspheres:

1) Microcapsules
2) Micro matrices.

Microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall and micro matrices in which entrapped substance is dispersing throughout the microsphere's matrix. microspheres are various types like bio adhesive microspheres, biodegradable polymeric microspheres, magnetic microspheres, floating microspheres, radioactive microspheres, synthetic polymeric microspheres, etc; the microspheres incorporating a drug dispersed or dissolved through particle-matrix have the potential for the controlled release of a drug. Microspheres are well designed modified release systems for the compound that can overcome some of the problems of conventional.[1,2]

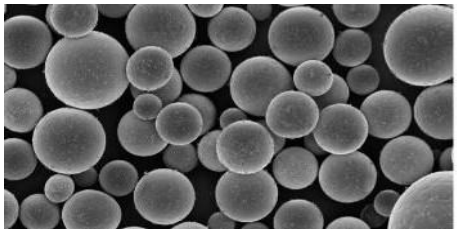

**Fig no: 1 microsphere.**

**Advantages:**[2,3]

1. Particle size reduction which enhances the solubility of the poorly soluble drug.
2. Less dosing frequency leads to better patient compliance.
3. Microspheres reduce dose dumping.
4. Microspheres avoid, the first-pass metabolism. Microspheres also reduce the chances of
5. G.I irritation.
6. Microspheres provide controlled, sustained, and targeted delivery of the drug.
7. Microspheres show better therapeutic effects for the short half-life of drugs can be achieved.
8. Microspheres are used to control drug release rates thereby decreasing toxic side effects and eliminating the inconvenience of repeated injections.
9. Microspheres protect the drug from enzymatic and photolytic cleavage and also from the environment.
10. Microspheres can be easily injected into the body because of their small and spherical size.

**Disadvantages:**[2,4,5]

1. The cost of the materials and processing of the controlled release preparations.
2. Reproducibility is less.
3. Process conditions like change in temperature, pH, solvent addition, and evaporation\ agitation may influence the stability of core particles to be encapsulated.
4. Dosage forms of this kind should be crushed or chewed.
5. Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristic of the dosage form may lead to potential toxicity.
6. Low drug loading is done in the case of parental microspheres.

**Types of Microspheres:**

1.**Bioadhesive Microspheres**: The drug delivery system involving sticking of the drug to the membrane by using polymers for adhesion to mucosal membranes are categorized as Bioadhesive spheres. Adhesion of drug is majorly observed at mucosal membrane such as buccal, ocular, rectal, nasal, etc; This type of microsphere delivery exhibits a prolonged residence time at the site of application.[6]

2.**Magnetic Microspheres:** This kind of delivery system is gaining prominence in localizing the drug to the target site. The different types are therapeutic magnetic microspheres and diagnostic microspheres.

**a. Therapeutic Magnetic Microspheres**: widely used to deliver the chemotherapeutic agent to the liver tumor. Drugs like proteins and peptides can also be targeted through this system.

**b. Diagnostic Microspheres:** widely used in imaging liver metastases and to distinguish bowel loops from other abdominal structures by forming Nano size particles named supramagnetic iron oxides.[2]

**3.Floating Microspheres:** In floating microspheres the bulk density of granules is less than the density of the gastric fluid and so remains buoyant in the stomach without affecting gastric emptying rate. The drug is released slowly at the targeted site with desired release rate. It also reduces the chances of striking and dose dumping..[2,6]

4.**Polymeric Microspheres**: Different types of polymeric microspheres are classified as follows:

**a. Biodegradable Polymeric Microspheres**: Natural polymers such as starch is used as biodegradable, biocompatible material with bioadhesive property in addition. These polymers prolong the residence time in contact with mucous membrane due to its high degree of swelling property in the aqueous medium, resulting in getting gel form.

**b. Synthetic Polymeric Microspheres:** synthetic polymeric microspheres are widely used in formulations as bulking agent, fillers, embolic particles and drug delivery vehicles, etc; they are proved to be safe and biocompatible but the disadvantage of these kinds of microspheres, are they tend to migrate away from the administered site and lead to potential risk, embolism and further organ damage.[6]

**5. Radioactive Microspheres:** Radio immobilization therapy utilizes microspheres having sizes ranging 10-30nm that are larger than capillaries. They are injected into the arteries that lead to tumors of interest. These radioactive microspheres deliver a high radiation dose to targeted areas without damaging the normal tissue. Different types of radioactive microspheres are α emitter, β emitters, γ emitters.[6]

**6. Mucoadhesive Microspheres:** Mucoadhesive microspheres are in the range of 1-1000nm in diameter and consist either entirely of a mucoadhesive polymer or having an outer coating of it and coupling of mucoadhesive properties to microspheres possessing additional advantages e.g; efficient absorption and enhanced bioavailability of the drugs due to

a high surface to volume ratio, with more intimate contact with the mucus layer, specific targeting of drug to the absorption site achieved by anchoring plant lectins, bacterial adhesions and anti-bodies etc; on the surface of the microspheres. Mucoadhesive microspheres can be tailored to adhere to any mucosal tissue including those found in the eye, nasal cavity, urinary and gastrointestinal tract, thus offering the possibilities of localized as well as systemic controlled release of drugs.[2]

**Methods of Preparation:**

**1. Spray Drying Technique:**

In spray drying technique, the polymer is first dissolved in a suitable volatile organic solvent such as Dichloromethane, acetone etc; 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 within the size range of 1-1000µm. microparticles are separated from the hot air by means of cyclone separator while the trace of solvent is removed by vacuum drying. One of the major advantages of the process is the feasibility of operation under aseptic conditions rapidly and leads to the formation of porous microparticles.[7]

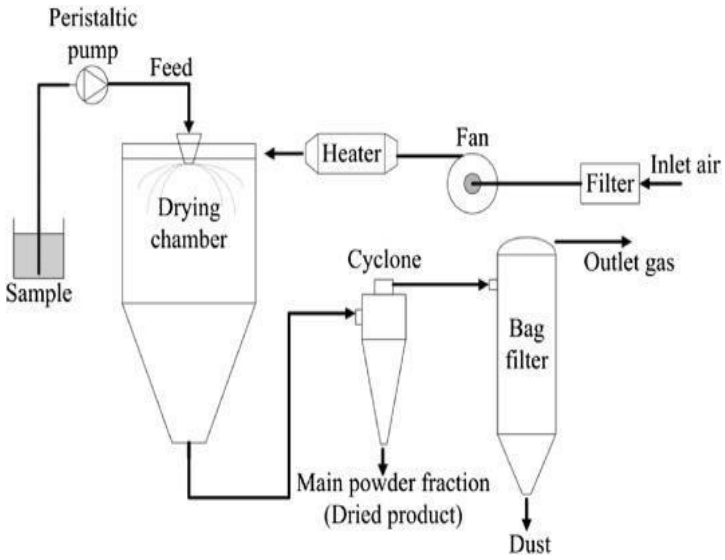


**Fig.no:2 Spray drying technique.**

**2. Solvent Evaporation**:

This process is carried out in a liquid manufacturing vehicle phase. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. The core material to be microencapsulated is dissolved or dispersed in the coating polymer solution with agitation. The core particle 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 for the polymer to disperse in the polymer solution, polymer shrinks around the core. If the core material is dissolved in the coating polymer solution, matrix-type microcapsules are formed. The core materials may be either water-soluble or water insoluble materials. [8,9]

**3. Co- acervation Method:**

Co-acervation thermal change: Desired amount of ethyl cellulose was dissolved in cyclohexane with vigorous stirring at 800º c by heating. The drug was finely pulverized and added with vigorous stirring on the above solution and phase separation was done by reducing temperature and ice- bath. Then above product was washed twice with cyclohexane and air-dried then passed through a sieve [sieve no 40] to obtain individual microcapsules.

Co- coacervation non-solvent addition: developed by the weighed amount of ethyl cellulose and dissolved in toluene containing propyl isobutylene in a closed beaker with magnetic stirring for 6hr at 500 rpm and the drug is dispersed in it and stirring is continued for 15 mins. Then phase separation is done by petroleum benzoin's times with continuous stirring. After that, the microcapsules were washed with n-hexane and air-dried for 2hr and then in the oven at 50ºc for 4hrs.[11]

**4. Single Emulsion Method:**

The microparticulate carriers of natural polymers i.e; those of proteins and carbohydrates are prepared by a single emulsion technique. The natural polymers are dissolved or dispersed in an aqueous medium followed by dispersion in non –aqueous medium like oil. Next cross-linking of the dispersed globule is carried out. The cross-linking can be achieved either by means of heat or by using chemical cross-linkers. The chemical cross-linking agents used are glutaraldehyde, formaldehyde, acid chloride, etc; heat denaturation is not suitable for thermolabile substances. Chemical cross-linking suffers the disadvantage of excessive exposure of active ingredients to chemicals if added at the time of preparation and then subjected to centrifugation, washing, 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. [10]

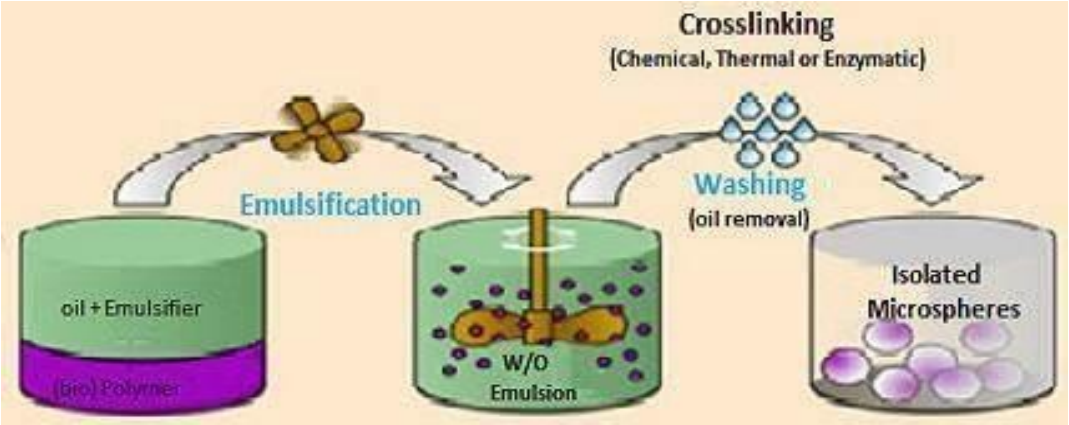


**Fig no 3: single emulsion technique.**

**5. Double Emulsion Technique:**

Double emulsion method of microspheres preparation involves the formation of multiple emulsions or the double emulsion of type *w|o|w* and is best suited for water-soluble drugs, peptides, proteins and vaccines. This method can be used with both natural as well as synthetic polymers. The aqueous portion solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain active constituents. The continuous phase generally consists of the polymer solution that eventually encapsulates the protein contained in the dispersed aqueous phase. The primary emulsion is subjected then to the homogenization or the sonication before addition to the aqueous solution of the polyvinyl alcohol [ PVA]. This results in the formation of a double emulsion. The emulsion result is then subjected to solvent removal either by solvent evaporation or by solvent extraction. A number of hydrophilic drugs like luteinizing hormone-releasing hormone [LH-RH] agonist, vaccines, proteins/peptides and conventional molecules are successfully incorporated into the microspheres using the method of double emulsion solvent evaporation/extraction. [10]

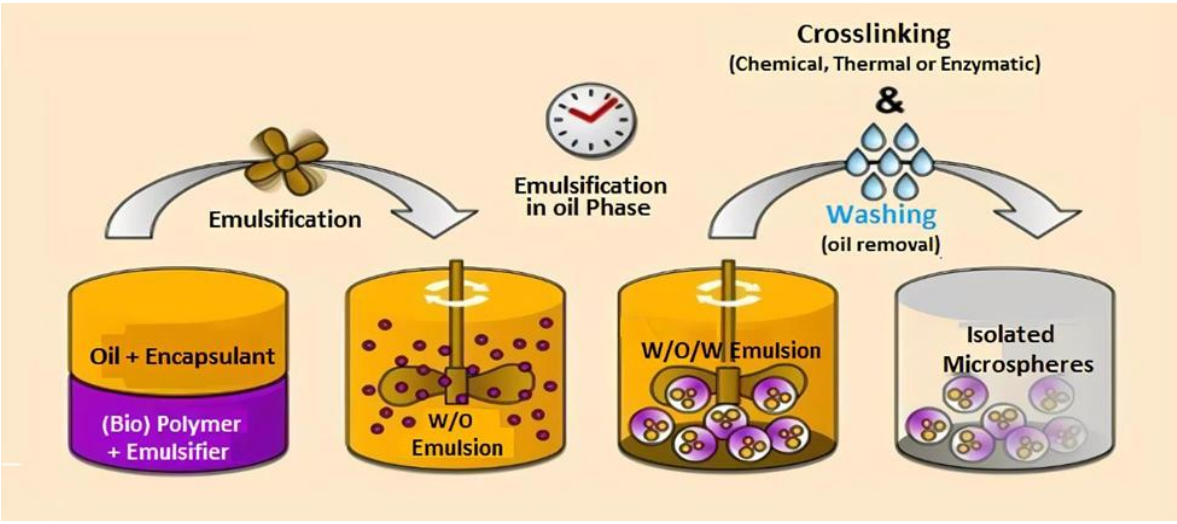


**Fig no 4: Double emulsion method.**

**6. Solvent Evaporation:**

Solvent evaporation method is used for manufacturing microparticles, involving removal of the organic phase by extraction of the aqueous or non-aqueous solvent. This method involves water-miscible organic solvents like isopropanol. The organic phase can be removed by extraction with the water. This process decreases the hardening time for the microspheres. One variation of the process involves direct incorporation of the drug or protein to the polymeric organic solution. Rate of solvent removal by extraction method depends on the temperature of the water, the ratio of emulsion volume to the water and the solubility profile of the polymer.[9,10]

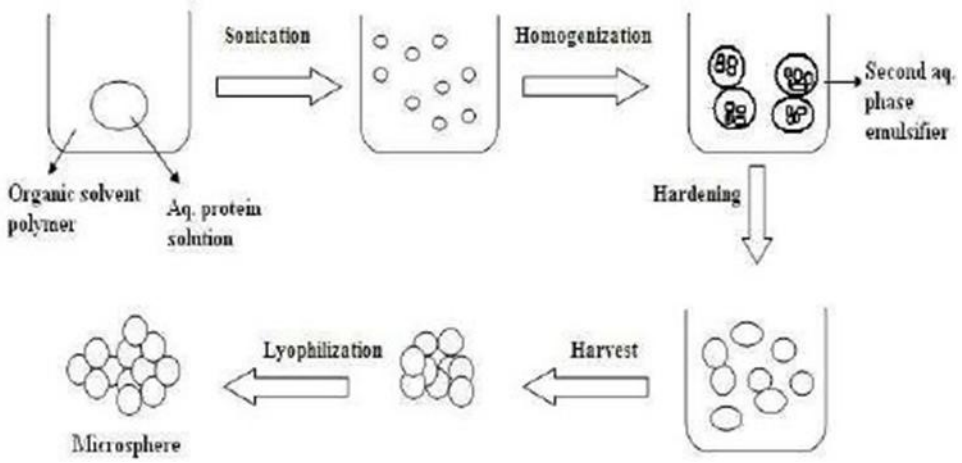


**Fig no 5: solvent evaporation method.**

**Evaluation of Microspheres**[1,2]

1.**Particle Size and Shape:** Particle size can be determined using optical microscopy by calibrated eyepiece micrometer. 100 microspheres size can be measured and the average particle size is calculated by using the formula.

Dmean =Ɛnd/Ɛn.

Where n= no. of microspheres checked; d= mean size.

**2. Scanning Electron Microscopy {SEM}:** surface morphology is determined using SEM. Microcapsules are mounted directly on the SEM sample slab with the help of double-sided sticking tape and coated with the gold film under reduced pressure and analyzed.

**3. Density Determination:** The density of microspheres can be measured by using a multi-volume pycnometer. Accurately sample is weighed in a cup that is placed into the multi-volume pycnometer. Helium is introduced at a constant pressure in the chamber and allowed to expand. This experiment 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 density of microsphere carriers are determined.

**4. Angle of Repose:** The angle of repose of microspheres measures the resistance to particle flow. It is calculated using 2h/d where h is height and d is the surface area of the free-standing height of microspheres heap formed after making microspheres flow from the glass funnel.

**5. Iso-electric Point:** The isoelectric point can be measured by using micro- electrophoresis apparatus by measuring electrophoretic mobility of microspheres. The mean velocity at different PH values from 3-10 is calculated by measuring the time of particle movement over a distance of 1nm.

**6. Angle of Contact:** The angle of contact is used to determine the wetting property of a microparticulate carrier. It determines the nature of microspheres in terms of hydrophilicity or hydrophobicity. This thermodynamic property is specific to solid and affected by the measured at the solid/air/ water interface. The advancing and receding angles of contact are measured by placing a droplet in a circular cell mounted above the objective of inverted microscope contact angle is measured at 200c within a minute deposition of the microsphere.

**7. In-vitro Method:** This method allows the determination of release characteristics and permeability of a drug through the membrane. In- vivo method is employed as a quality control procedure in pharmaceutical production and in product

development etc; sensible and reproducible release data derived from physically, chemically and hydrodynamically defined conditions are necessary.

**8. Drug Entrapment Efficiency:** Weighted amount of microspheres are taken and crushed. They are dissolved in buffer solution with the help of stirrer and filtered. The filtrate is assayed by UV- spectrophotometer at a particular wavelength by using calibration curve.
Drug entrapment efficiency= actual weight of microspheres/theoretical weight of drug and polymerχ 100.

**9. Swelling Index:** It is determined by measuring the extent of swelling property of microspheres in a particular solvent. The equilibrium swelling degree of microspheres is determined by using 5mg of dried microspheres. the quantity weighed is transferred into 5ml of buffer solution and left overnight in a measuring cylinder. swelling Index is calculated by the formula mentioned below:

Swelling index=mass of swollen microsphere-mass of dried microspheres/mass of dried microspheres χ 100

**Applications:**[1]

1. Microspheres are used in vaccine delivery.
2. Microspheres are used in gene therapy.
3. Used in ophthalmic drug delivery.
4. Microspheres are used for oral and nasal drug delivery.
5. Gastrointestinal drug delivery.
6. Microspheres are used in perioral drug delivery.
7. Colonic, vaginal and also in transdermal drug delivery.
8. Multi particulate delivery system.

## CONCLUSION

Microspheres are the better choice of drug delivery system compared with other types of drug delivery systems. Microspheres act as effective carriers for the novel drug delivery system particularly in diseased cell sorting, diagnostics, gene and genetic material. They are safe, targeted, specific and effective in vitro delivery and supplements as a miniature version of diseased organs and tissues in the body. Most important are the targeted drug delivery [bio adhesive microspheres nasal, ocular, buccal, rectal etc.; magnetic microspheres and radioactive microspheres- for tumors]. Controlled and sustained drug delivery [polymeric microspheres, floating microspheres]. The microsphere is short-term, but it is having wide applications in drug delivery systems to get desired biological activity.

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## REFERENCES

[1]. Gavali, K. V., Kengar, M. D., Chavan, K. V., Anekar, V. P., & Khan, N. I. (2019). A Review on Microsphere and it's Application. Asian Journal of Pharmaceutical Research, 9(2), 123-129.
[2]. Das, M. K., Ahmed, A. B., & Saha, D. (2019). Microsphere a drug delivery system: A review. Int J Curr Pharm Res, 11(4), 34-41.
[3]. Prasad, B. S., Gupta, V. R. M., Devanna, N., & Jayasurya, K. (2014). Microspheres as drug delivery system-a review. Journal of global trends in pharmaceutical sciences, 5(3), 1961-1972.
[4]. Prasad, B. S., Gupta, V. R. M., Devanna, N., & Jayasurya, K. (2014). Microspheres as drug delivery system-a review. Journal of global trends in pharmaceutical sciences, 5(3), 1961-1972.
[5]. Kavita, K., Ashvini, V. R., & Ganesh, N. S. (2010). Albumin microspheres. Unique system as drug delivery carriers for non steroidal anti inflammatory drugs. Int J Pharm Sci Rev Res, 5(2), 10.
[6]. Sinha, V. R., Goyal, V., Bhinge, J. R., Mittal, B. R., & Trehan, A. (2003). Diagnostic microspheres: an overview. Critical Reviews™ in Therapeutic Drug Carrier Systems, 20(6).
[7]. Mukund, J. Y., Kantilal, B. R., & Sudhakar, R. N. (2012). Floating microspheres: a review. Brazilian Journal of Pharmaceutical Sciences, 48(1), 17-30.
[8]. Ramteke, K. H., Jadhav, V. B., & Dhole, S. N. (2012). Microspheres: As carrieres used for novel drug delivery system. Iosrphr, 2(4), 44-48.

[9]. Mahale, M. M., & Saudagar, R. B. (2019). Microsphere: a review. Journal of drug delivery and therapeutics, 9(3-s), 854-856.
[10]. Tewes, F., Corrigan, O. I., & Healy, A. M. (2013). Surfactants in Pharmaceutical Products and Systems. In Encyclopedia of Pharmaceutical Science and Technology, Fourth Edition (pp. 3464-3476). CRC Press.
[11]. Ghulam, M., Mahmood, A., Naveed, A., & Fatima, R. (2009). < A> comparative study of various microencapsulation techniques: effect of polymer viscosity on microcapsule characteristics.