e-ISSN: 2249-7625
Print ISSN: 2249-7633

International Journal of
Pharmacy Practice & Drug Research
www.ijppdr.com

Review Article

MICROSPHERE- AN EFFECTIVE FORM OF DRUG DELIVERY

Rina Parveen H*, Siva P, Reshma Fathima K

Grace College of Pharmacy, Kodunthirapully, Palakkad – 678 004, Kerala, India.

ABSTRACT

Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 µm. A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs. It is the reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumour. 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, Target site, Specificity, Novel drug delivery, Controlled release.

INTRODUCTION

A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effect. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs. Microspheres are characteristically free flowing powders consisting of protiens or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 µm [1-3].

Access this article online

Home page: http://ijppdr.com//

DOI: http://dx.doi.org/10.21276/ijppdr.2017.7.1.8

Quick Response code

Received:02.03.17 **Revised**:12.03.17 **Accepted**:30.03.17

Corresponding Author

Rina Parveen H
Grace College of Pharmacy, Palakkad – 678 004, Kerala, India.

Email : rinaparveenh003@gmail.com

CHARACTERISTICS

1. Microsphere size may be critical to the proper function of an assay, or it may be secondary to other characteristics. Considering traditional diagnostic methods, the test or assay format commonly dictates particle size, such as the use of very small spheres (~0.1- 0.4µm) to ensure satisfactory wicking in lateral flow tests, or the use of larger, cell-sized spheres (~4-10µm) for bead based flow cytometric assays [4-6].
2. Common microsphere compositions include polystyrene (PS), poly(methyl methacrylate) (PMMA), and silica.

These materials possess different physical and optical properties, which may present advantages or limitations for different applications. Polymer beads are generally hydrophobic, and as such, have high protein binding abilities. However, they often require the use of some surfactant (e.g. 0.01-0.1% Tween® 20 or SDS) in the storage buffer to ensure ease of handling. During synthesis, functional monomers may be co-polymerized with styrene or methyl methacrylate to develop beads with surface

reactive groups. Functional groups may be used in covalent binding reactions, and also aid in stabilizing the suspension. Silica microspheres are inherently hydrophilic and negatively charged. Consequently, aqueous silica suspensions rarely require use of surfactants or other stabilizers. Carboxyl- and amine functionalized silica spheres are available for use in common covalent coating protocols, and plain silica microspheres may be modified using a variety of silanes to generate functional groups or alter surface properties [7-9].

3. Microspheres may be coated with capture molecules, such as antibodies, oligo nucleotides, peptides, etc. for use in diagnostic or separation applications. Microsphere coatings are typically optimized to achieve desired specific activity, while minimizing nonspecific interactions. Consideration should also be given to the required stability, development time frame and budget, and the specific bio molecule to be coated. These factors will aid in determining the most fitting coating strategy for both short- and long-term objectives. Standard microsphere products support three basic coating strategies: adsorption, covalent coupling, and affinity binding.

4. Many applications in the life sciences demand added properties, such as fluorescence or a visible color, or iron oxide inclusions for magnetic separations. Polymer spheres (and polymer based magnetic spheres) are often internally dyed via organic solvent swelling, and many standard products are available. Dye concentrations can be adjusted to produce beads with different intensities to meet special needs, such as Quantum Plex™ for multiplexed flow cytometric assays, or our Dragon Green or Flash Red Intensity Standards, which support imaging applications and associated instrument QC. Many surface- or internally labelled fluorescent beads are also available as specialized flow cytometry standards.

ADVANTAGES

1. Microspheres provide constant and prolonged therapeutic effect.
2. Reduces the dosing frequency and thereby improve the patient compliance.
3. They could be injected into the body due to the spherical shape and smaller size.
4. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
5. Microsphere morphology allows a controllable variability in degradation and drug release.

LIMITATION

Some of the disadvantages were found to be as follows

1. The modified release from the formulations.
2. The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit though gut.
3. Differences in the release rate from one dose to another.
4. Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
5. Dosage forms of this kind should not be crushed or chewed

TYPES OF MICROSPHERES

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 [10-12].

2. Magnetic microspheres

This kind of delivery system is very much important which localizes 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. The different types of

A. Therapeutic magnetic microspheres used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system.

B .Diagnostic microspheres, used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nano size particles supra magnetic iron oxides.

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 [13].

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 andthe 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 microspheres [14].

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 [15].

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 microspheres is complex and is difficult to control the drug release. However they provide wide range of application in microsphere based treatment.

ii) Synthetic polymeric microspheres

Synthetic polymeric microspheres are widely used in 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 [16].

METHOD OF PREPARATION

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

1. Spray Drying

In Spray Drying technique, the polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution with 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 the formation of the microspheres in a size range 1-100μm. Micro particles are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying. One of the major advantages of this process is feasibility of operation under aseptic conditions [14].

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. 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 for the polymer of the core material is 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 in soluble materials. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous [14, 17].

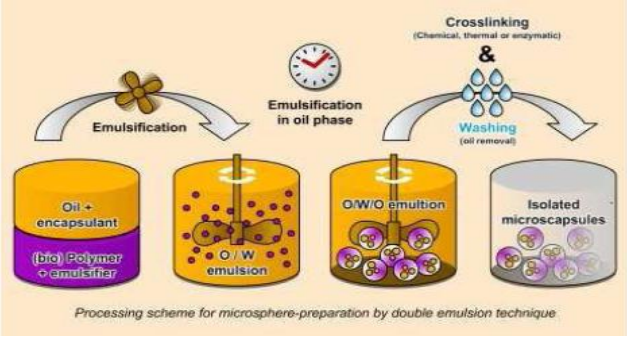
3. Single emulsion technique

The micro particulate carriers of natural polymers i.e. those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium like oil. In the next step, the cross linking of the dispersed globules carried out. The cross linking can be achieved either by means of heat or by using the 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 ingredient 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 [2].

4. Double emulsion technique

Double emulsion method of microspheres preparation involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited for water soluble drugs, peptides, proteins and the vaccines. This method can be used with both the natural as well as synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase. The primary emulsion is subjected then to the homogenization or the sonication before addition to the aqueous solution of the poly vinyl alcohol (PVA). This results in the formation of a double emulsion. The emulsion 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 [20-21].

Fig 1. Double emulsion technique



Processing scheme for microsphere-preparation by double emulsion technique

5. Phase separation coacervation technique

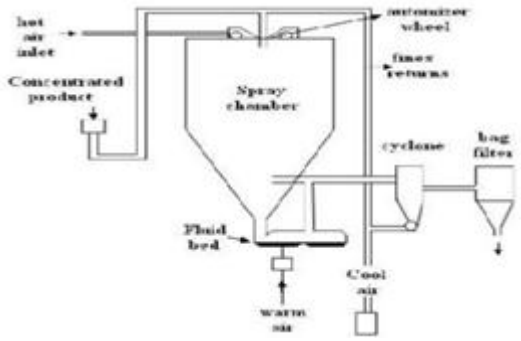
This process is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervates. In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of polymer. Poly lactic acid (PLA) microspheres have been prepared by this method by using butadiene as incompatible polymer. The process variables are very important since the rate of achieving the coacervates determines the distribution of the polymer film, the particle size and agglomeration of the formed particles.

The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer since as the process of microspheres formation begins the formed polymerize globules start to stick and formthe agglomerates. Therefore the process variables are critical as they control the kinetic of the formed particles since there is no defined state of equilibrium attainment.

6. Spray drying and spray congealing

These methods are based on the drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively. The polymer is first dissolved in a suitable volatile organic solvent such as 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 the formation of the microspheres in a size range 1-100 µm. Micro particles are separated from the hot air by means of the cyclone separator while the traces of solvent are removed by vacuum drying. One of the major advantages of the process is feasibility of operation under aseptic conditions. The spray drying process is used to encapsulate various Penicillins. Thiamine mono nitrate and sulphaethyl thiadizole are encapsulated in a mixture of mono- and diglycerides of stearic acid and palmitic acid using spray congealing. Very rapid solvent evaporation, however leads to the formation of porous micro particles.

Fig 2. Spray drying and spray congealing



7. Solvent extraction

Solvent evaporation method is used for manufacturing of micro particles, involves removal of the organic phase by extraction of the non aqueous solvent. This method involves water miscible organic solvents as isopropanol. Organic phase can be removed by extraction with water. This process decreases the hardening time for the microspheres. One variation of the process involves direct incorporation of the drug or protein to polymer organic solution. Rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and solubility profile of polymer [20].

8. Quassi emulsion solvent diffusion

A novel quasi-emulsion solvent diffusion method to manufacture the controlled release microspheres of drugs with acrylic polymers has been reported in the literature. Micro sponges can be manufactured by a quasi emulsion solvent diffusion method using an external phase containing distilled water and polyvinyl alcohol. The internal phase consists of drug, ethanol and polymer .The concentration of polymer is in order to enhance plasticity. At first, the internal phase is manufactured at 60.C and then added to the external phase at room temperature. After emulsification process, the mixture is continuously stirred for 2 hours. Then the mixture can be filtered to separate the micro sponges. The product is then washed and dried by vacuum oven at 40.C for a day.

Polymerization techniques

The polymerization techniques conventionally used for preparing the microspheres are mainly classified as:

I. Normal polymerization

II. Interfacial polymerization.

Both are carried out in liquid phase.

I. Normal polymerization:

It is carried out by using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization methods. In bulk, a monomer or a combination of monomers along with the initiator or catalyst is usually heated to initiate polymerization.

Polymer so obtained may be moulded as microspheres

Drug loading may be done during the polymerization process. Suspension polymerization also referred as bead or pearl polymerization. It is carried out by heating the monomer or composition of monomers as droplets dispersion in a continuous aqueous phase. Droplets may also contain an initiator and other additives. Emulsion polymerization deviates from suspension polymerization as due to the presence initiator in the aqueous phase, which afterwards diffuses to the surface of micelles. Bulk polymerization has merits of formation of pure polymers.

II. Interfacial polymerization

This involves the reaction of various monomers at the interface between the two immiscible liquids to form a film of polymer that essentially envelops the dispersed phase [21].

Table 1. Microsphere property

S. No.	Property	Consideration
1	Size	Diameter Uniformity/distribution
2	Composition	Density Refractive index Hydrophobicity/hydrophilicity Nonspecific binding Autofluorescence
3	Surface chemistry	Reactive groups Level of functionalization Charge
4	Special properties	Visible dye/fluorophore Super-paramagnetic

ACKNOWLEDGEMENT

The authors are grateful to Management of Grace College of Pharmacy, Palakkad to provide facilities to publish this review article.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

1. Hardenia SS, Jain A, Patel R, Kaushal A. Formulation and evaluation of mucoadhesive microspheres of ciprofloxacin. *Journal of Advanced Pharmacy Education & Research*, 1(4), 2011, 214-224.
2. S. Kataria, A. Middha, P. Sandhu, A. Bilandi and B. Kapoor. Microsphere: A Review. *International Journal of Research Pharmaceutical Chemistry*, 1(4), 2011, 1185-1198.
3. Punitha S, Girish Y. Polymers in mucoadhesivebuccal drug delivery system. *International Journal of Research and Pharmaceutical Sciences*, 1(2), 2010, 170-186.
4. Sachan NK, Bhattacharya A. Basic and Therapeutic Potential of Oral Mucoadhesive Microparticulate Drug Delivery Systems. *International Journal of Pharmaceutical and Clinical Research*, 1, 2009, 10-14.
5. Asane GS, Nirmal SA, Rasal KB, Naik AA, Mahadik MS. Polymers for Mucoadhesive drug delivery system. *Drug Development and Industrial Pharmacy*, 34, 2011, 1246-1266.
6. Patel J. Bioadhesion is a topic of current interest in the design of controlled or targeted drug delivery system.
7. Boddupalli BM, Zulkar MNK, Nath RA, Banji D. Mucoadhesive drug delivery system: An overview. *J Adv Pharm Tech Res*, 1(4), 2010, 381–387.
8. Alagusundaram M, Chetty MS, Umashankari K, Badarinath AV, Lavanya C, Ramkanth S. Microspheres as a novel drug delivery system: A review. *Int J Chem Tech Res*, 1(3), 2009, 526-534.
9. Muthukumaran M, Dhachinamoorthi D, Chandra KBS, Sriram NA. Review On Polymers Used In Mucoadhesive Drug Delivery System. *In. J Pharm Ind Res* , 1(2), 2011,122-127

10. Madhav S. Mule, Mr. Kshirsagar R.V. Gastroretentive mucoadhesive microsphere: a review. *Indo American Journal of Pharmaceutical Research*,1(6), 2011,483-505
11. Yassin AE, Alanazi FK, El-Badry M, Alsarra IA, Barakat NS, Alanazi FK. Preparation and characterization of spironolactone-loaded geluciremicroparticles using spray-drying technique. *Drug Dev Ind Pharm*, 35(3), 2009, 297-304.
12. Meena KP, Dangi JS, Samal PK, Namedo KP. Recent advances in microsphere manufacturing technology. *International Journal of Pharmacy and Technology*, 3(1), 2011, 854-855.
13. Moy AC, Mathew ST, Mathapan R, Prasanth VV. Microsphere-An Overview. *International Journal of Pharmaceutical and Biomedical Sciences*, 2(2), 2011, 332-338.
14. Rajput G, Majmudar F, Patel J, Thakor R, Rajgor NB. Stomach-specific mucoadhesive microsphere as a controlled drug delivery system. *Sys Rev Pharm*, 1(1), 2010, 70-78.
15. Parmar H, Bakliwal S, Guajarati N, Rane B, Pawar S. Different method of formulation and evaluation of mucoadhesive microsphere. *International Journal of Applied Biology and Pharmaceutical Technology*, 1(3), 2010, 1157-1167.
16. Chakraborty S, Dinda SC, Ch. Patra NC, Khandai M. Fabrication and Characterization of Algino-Carbopol Microparticulate System of Aceclofenac for Oral Sustained Drug Delivery. *Int J Pharm Sci Review Res*, 4(2), 2010, 192-199.
17. Poonam P, Daksha C, Milind W. A review on ionotropic gelation method: novel approach for controlled gastro retentive microspheres. *International Journal of Pharmacy and Pharmaceutical Sciences*, (34), 2014, 27-32
18. Zhang L, Liu Y, Wu Z and Chen H. Preparation and characterization of coacervate microcapsules for the delivery of antimicrobial oyster peptides. *Drug Dev Ind Pharm*, 35(3), 2009, 278-369.
19. Mathiowitz E, Kreitz MR and Peppas LB. Microencapsulation. In: Mathiowitz E, ed. Encyclopedia of Controlled Drug Delivery, New York: John Willey & Sons; 9, 1999a: 493-504.
20. SellappanVelmurugan ; Mohamed Ashraf Ali, *Int. J. Drug Dev.& Res*, 5, 2013, 229-233.
21. Chiman lal beri, Richa sood, Hemraj, Avneet gupta. Stomach specific mucoadhesive microspheres as controlled drug delivery system. *International Journal of Pharmacy and Pharmaceutical Sciences*, 5(2), 2013, 21-26.
22. Upendra C Galgatte, Pravin D Chaudhari. Preparation Evaluation of Bioadhesive Microspheres Prepared by Ion Gelatin Method and Effect of Variables on Quality of Microspheres. *Am. J. Pharm Tech Res*, 3(4), 2013,535-546.
23. Harshad P, Sunil B, Nayan G, Bhushan R, Sunil P. Different methods of formulation and evaluation of mucoadhesive microsphere. *International journal of applied biology and pharmaceutical technology*, 1(3), 2010, 1157-1167.
24. Shaikh R, Singh TRR, Garland MJ, Donnelly RF. Mucoadhesive Drug Delivery Systems. *Journal of Pharmacy and Bioallied Sciences*, 3(1), 2011, 89-100.
25. Alexander A, Tripathi DK, Verma T, Patel S. Mechanism responsible for mucoadhesion of mucoadhesive drug delivery system. *International Journal of Applied Biology and Pharmaceutical Technology*, 2(1), 2011, 434-445.

Cite this article:
Rina Parveen H, Siva P, Reshma Fathima K. Microsphere- An Effective Form of Drug Delivery. *International Journal of Pharmacy Practice and Drug Research*, 2017; 7(1): 37-42. **DOI:** http://dx.doi.org/10.21276/ijppdr.2017.7.1.8