INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Review Article

# A REVIEW ON MICROSPHERE FOR NOVEL DRUG DELIVERY SYSTEM

**KVM. Krishna[1]*, CH. Srinivas Reddy[1] and S. Srikanth[2]**

[1]Department of Pharmaceutics, Teegala Ram Reddy College of Pharmacy, Hyderabad, Andhra Pradesh, India.

[2]Department of Pharmaceutical Chemistry, Teegala Ram Reddy College of Pharmacy, Hyderabad, Andhra Pradesh, India.

**ABSTRACT**

The Non ideal pharmaceutical, pharmacokinetic, and therapeutic properties often combine to reduce the effectiveness of certain compounds. For the vectoring of such compounds to target areas, liposomes, nanoparticles, and microspheres have been suggested. The range of techniques for the preparation of microspheres offers a variety of opportunities to control aspects of drug administration. This approach facilitates accurate delivery of small quantities of potent drugs, reduced drug concentrations at the sites other than the target site and protection of the labile compounds before and after administration, prior to appearance at the site of action. Physicochemical properties of the drug and excipient such as permeability of one in the other, identity of the polymer, degree of crystallinity, inclusion of plasticizers and fillers and thickness of the polymer influences the drug release rate.

**Keywords**: Microspheres, target site, diffusion, biodegradable, carriers, sustain release.

## INTRODUCTION

The development of new delivery systems for the controlled release of drugs is one of the most interesting fields of research in pharmaceutical sciences. Micro particles can be used for the controlled release of drugs, vaccines, antibiotics, and hormones. For example, by taking advantage of the characteristics of microspheres, beyond the basic benefits, the microspheres could provide a larger surface area and possess an easier estimation of diffusion and mass transfer behaviour also the encapsulated small molecules could diffuse out of the barrier with precise kinetics modelling and control-release of drugs to the body fluid. Among the polymer systems employed, the chitosan, a weak cationic polysaccharide, has many advantages for developing micro-particles in drug release applications. Chitosan is a derivative of chitin, the second most abundant polymer in nature, which is a supporting material of crustaceans, insects, and fungal mycelia. Among the ifferent species of crustaceans, shrimp and crab shells have been widely used for the isolation of chitin. Another important application of chitosan's in industry is the development of drug delivery systems. The use of controlled release systems has certain advantages compared with conventional dosage forms, as they can minimize side effects, and prolong the efficacy of the drug. These release forms regulate the drug release rate and can reduce the frequency of administration of the drug, thus assuring better patient compliance[1]. The clearance kinetics, tissue distribution, metabolism and cellular interaction of the drug are strongly influenced by the behaviour of the carrier. The exploitation of these changes in pharmacodynamics behaviour may lead to enhanced therapeutic effect. However, an intelligent approach to therapeutics employing drug carrier's technology requires a detailed understanding of the carrier interaction with critical cellular and organ systems and of the limitations of the systems with respect to the formulation procedures and stability.

## TYPES OF MICROSPHERES

### A. 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 resi- dence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action.

### B. 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 are therapeutic magnetic microspheres and diagnostic microspheres[10-11].

#### 1. Therapeutic magnetic microspheres

It is used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system.

#### 2. Diagnostic microspheres

It can be used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nano size particles supramagnetic iron oxides.

### C. 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, if the system is floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration. Moreover it also reduces chances of striking and dose dumping. One another way it produces prolonged therapeutic effect and therefore reduces dosing frequencies[12].

### D. Radioactive microspheres

Radio immobilization therapy microspheres sized 10-30 nm is of larger than capillaries and gets tapped in first capillary bed when they come across. They are injected to the arteries that lead 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 sys-tem, as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microspheres.

### E. Polymeric microspheres

The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and synthetic polymeric microspheres.

#### 1. Biodegradable polymeric microspheres

Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also bioadhesive in nature. Biodegradable polymers prolongs the residence time when contact with mucous membrane due to it's high degree of swelling property with aqueous medium, results gel formation. 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[15].

#### 2. Synthetic polymeric microspheres

The interest of 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 kinds of microspheres, are tend to migrate away from injection site and lead to potential risk, embolism and further organ damage[16]. as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microspheres' are a emitters, ß emitters, g emitters[13].

## METHOD OF PREPARATION

Production of sustained release, controlled release and targeted medications reduce the dose dumping potential compared to large implantable devices. Different methods of microspheres are as follow.

#### 1. Wax coating and hot melt

Wax may be used to coat the core particles, encapsulating the drug by dissolution or dispersion in molten wax. The waxy solution or suspension is dispersed by high speed mixing into cold solution, such as cold liquid paraffin. The mixture is agitated for at least one hour. The external phase (liquid paraffin) is then decanted and the microspheres are

suspended in a non- miscible solvent and allowed to air dry. Carnauba wax and beeswax can be used as the coating materials and these can be mixed in order to achieve desired characteristics.

**2. Spray coating and pan coating spray**

Coating and pan coating employ heat-jacketed coating pans in which the solid drug core particles are rotated and the coating material is sprayed. The core particles are in size range of micrometers upto few millimetres. The coating material is usually sprayed at angle from the side into the pan[18-19]. The process is continued until an even coating is completed. In addition, several batches of microspheres cab be prepared with different coating thickness and mixed to achieve specific controlled release pattern.

**3. Coacervation**

This process is a simple separation of macromolecular solution into two immiscible liquid phases, a dense coacervate phase, which is relatively concentrated in macromolecules and a dilute equilibrium phase. In presence of only one macromolecule, this process is referred to as simple coacervation. When two or more macromolecules of opposite charge are present, it is referred to as complex Coacervation. Former one is induced by various parameters like change in temperature, addition of non-solvent or micro ions, which results in dehydration of macromolecules because they promote polymer-polymer interactions over polymer-solvent interaction. These can be manipulated to produce microspheres with specific properties[20].

**4. Spray drying**

It is single step, closed- system process applicable to wide variety of materials, including heat-sensitive materials. The drug and polymer coating materials are dissolved in suitable solvent (aqueous or non-aqueous) or the drug may be present as a suspension in the polymer solution. Alternatively, it may be dissolved or suspended within an emulsion or coacervate system. For example, biodegradable polylactide microspheres can be prepared by dissolving the drug and the polymer in methylene chloride. The microsphere size is controlled by the rate of spraying, the feed rate of the polymer drug solution, the nozzle size, the temperature in drying and collecting chambers, and the size of the two chambers. The quality of the spray dried products are improved by the addition of plasticizers that promote the polymer coalescence and film formation and enhance the formation of smooth surfaced and spherical microspheres[21].

**5. Solvent evaporation**

In this method, the drug and the polymer must be soluble in organic solvent, frequently methylene chloride. The solution containing polymer and drug may be dispersed in an aqueous phase to form droplets. Continuous mixing and elevated temperatures may be employed to evaporate the more volatile organic solvents and leave the solid polymer-drug particles suspended in an aqueous medium. The particles are finally filtered from the suspension[22].

**6. Precipitation**

It is a variation on the evaporation method. The emulsion consists of polar droplets dispersed in a non-polar medium. Solvent may be removed from the droplets by the use of a co solvent. The resulting increase in the polymer concentration causes precipitation forming a suspension of microspheres.

**7. Freeze Drying**

This technique involves the freezing of the emulsion and the relative freezing points of the continuous and dispersed phases are important. The continuous phase solvent is usually organic and is removed by sublimation at low temperature and pressure. Finally the dispersed phase solvent of the droplets is removed by sublimation, leaving polymer- drug particles.

**8. Chemical and thermal cross - linking**

Microspheres made from natural polymers are prepared by a cross-linking process, polymer includes gelatin, albumin, starch and dextrin. A water-oil emulsion is prepared, where the water phase is a solution of polymer that contains drug to be incorporated. The oil phase is a suitable vegetable oil or oil - organic solvent mixture containing an oil soluble emulsifier. Once the desired water-oil emulsion is formed, the water soluble polymer is solidified by thermal treatment or addition of a chemical cross-linking agent such as gluteraldehyde to form a stable chemical cross link

**A. Therapeutic magnetic microspheres**

It is used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system.

**B. Diagnostic microspheres**

It can be used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming Nano size particles supramagnetic iron oxides. dence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action.

**MICROSPHERE EVALUATIONS**[28-32]

**% yield of microspheres**

Thoroughly dried microspheres were collected and weighed accurately. The percentage yield was then calculated using formula given below,

**% Yield = mass of microsphere obtained / total weight of drug & polymer X 100**

Particle size analysis, Particle size distribution and Particle size determination was done by sieving method. Size distribution plays an important role in determining the release characteristics of the microspheres.

**Shape and surface characterization**

The shape and surface characterization of microspheres were observed under a Scanning Electron Microscope (SEM). The instrument used for this study was ZEOL JSM – 5610 scanning electron microscope. The microspheres were mounted directly on the SEM sample stub, using double-sided sticking tape and coated with gold film (thickness 200 nm) under reduced pressure (0.001 torr) and photographed.

**Determination of drug content**

Accurately weighed 100 mg microspheres were crushed in glass mortar and pestle, powder microspheres were suspended in 100 ml of suitable solvent. After 12 hours the solution was filtered and the filtrate was analysed for the drug content using UV-Visible spectrophotometer.

**Encapsulation efficiency**

Encapsulation efficiency was calculated using the following formula;

**E = Qp / Qt X 100**

Where,

E = percentage of encapsulation of microspheres

Qp = quantity of drug encapsulated in microspheres

Qt = quantity of the drug added for encapsulation

**Swelling studies**

A known weight (50 mg) of microspheres was placed in a glass vial containing 10 ml of distilled water at 37 ± 0.50C in incubator with occasional shaking. The microspheres were periodically removed, blotted with filter paper and their changes in weights were measured during the swelling until equilibrium was attained. Finally, the weight of the swollen microspheres was recorded after a period of 3 hours, and the swelling ratio (SR) was then calculated from the following formula. The studies were carried out in triplicate.

**SR=We-Wo / Wo**

Where,

Wo = Initial weight of the dry microspheres,

We = Weight of the swollen microspheres at equilibrium swelling in the media.

**CONCLUSION**

Drugs can be targeted to specific sites in the body using microspheres. Degree of targeting can be achieved by localization of the drug to a specific area in the body (for example in lungs), to a particular group of cells (for example, kupffer cells) and even to the intracellular structures (such as lysosomes or cell nucleus). The rate of drug release is governed by the molecular structure of the drug and polymer, the resistance of the polymer to degradation, and the surface area along with the porosity of the microspheres. The internal structure of the microspheres can vary as a function of the microencapsulation process employed. Controlled drug release from microspheres occurs by diffusion of the drug through a polymeric excipient.

**REFERENCES**

1. Diane J Burgress. Dept of pharmaceutical sciences, University of Connecticut, Storrs, Connecticut, U.SA. Anthony J Hickey, Dept of Pharmaceutics, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina,U.S.A (Encyclopedia of Pharmaceutical Technology, 2328 - 2337).
2. Shirui Mao, Yi Shi, Luk Li, Jing Xu , Andreas Schaper and Thomas Kissel. Department of Pharmaceutics and Biopharmacy , Philipps - University of Marburg, Marburg ,Germany. EJBP 2008;68:214-223.
3. Jain RA. The manufacturing techniques of various drug loaded biodegradable poly (lactide-co-glycolide) (PLGA) devices. Biomateria ls. 2000;21:2475-2490.

4. Alexandra Giteau, Marie-Claire Venier-Julienne, Stephane Marchal, Jean-Luc Courthaudon, Michele Sergent, Claudia Montero-Menei, Jean- Michel Verdier and Jean– Pierre Benoit. EJBP. 2008;70:127-136.
5. Luginbuehl V, Meine L, Merkle HP and Gander B. Localized delivery of growth factors for bone repair. Eur J Pharm Biopharm. 2004;58(2):197 -208.
6. Sinha VR and Trehan A. Biodegradable microspheres for protein delivery. J controlled release. 2003;90(3):261 -280.
7. Elisabetta Gavini, Giovanna Rassu, Corrado Muzzarelli, Massimo Cossu and Paolo Giunchedi. Department of Drug Sciences, University of Sassari, Sassari, Italy, Institute of Biochemistry ,University of Ancona, Ancona. Italy. EJBP. 2008;68:245- 252.
8. Hamman JH, Stander M, Junginger HE and Kotze AF. Enhancement of paracellular drug transport across mucosal epithelia byN-trimethyl chitosan chloride. S.T.P Pharm Sci. 2000; 10:35-38.
9. Thanou M, Nihot MT, Jansen M, Coos Verhoef J and Junginger HE. MonoN-carboxymethyl chitosan (MCC), a polyampholytic chitosan derivative enhances the intestinal absorption of low molecular weight heparin across intestinal epithelia in vitro and in vivo. J Pharm Sci. 2001;90:38-46.
10. Francesca Maestrelli, Marzia Cirri, Giovanna Corti, Natascia Mennini and Paola Mura. Department of Pharmaceutical sciences, University of Florence. Italy. EJBP. 2008;69:508-518.
11. Chein YW. Oral Drug Delivery and Delivery systems. In Novel drug delivery systems. Vol. 50, Marcel Dekker, Inc, New York. 1992;139-177.
12. Lachman LA, Liberman HA and Kanig JL. The Theory and Practice of Industrial Pharmacy. 3rd edition 1991; Varghese Publishng House, Mumbai, India. 414-415.
13. Amsden BG and Goosen M. An examination of the factors affecting the size, distribution, and release characteristics of polymer microbeads made using electrostatics. J Control Rel.1997; 43:183–196.
14. Ando S, Putnam D, Pack DW and Langer R. PLGA Microspheres Containing Plasmid DNA: Preservation of Super coiled DNA via Cry preparation and Carbohydrate Stabilization. J Pharmaceut Sci.1998;88(1):126– 130.
15. Cleland JL, Duenas ET, Park A, Daugherty A, Kahn J, Kowalski J and Cuthbertson A. Development of poly-(D,L-lactide-co-glycolide) microsphere formulations containing recombinant human vascular endothelial growth factor to promote local angiogenesis. J Control Rel. 2001;72(1–3):13–24.
16. Jain NK. Controlled and Novel drug delivery, CBS Publishers New Delhi, India; 4th Edition, 236-237.
17. Deore BV, Mahajan HS and Deore UV, Development and characterization of sustained release microspheres by quasi emulsion solvent diffusion method. International Journal of ChemTech Research. 2009;634-642.
18. Hafeli UO. Magnetically modulated therapeutic systems. Int J Pharmaceutics. 2004;277:19–24.
19. Ramington GA. The Science and Practice of Pharmacy. BI publication, Delhi, India, 21st Edition, Volume I, P-924(2006).
20. Venkatesan PC, Manavalan R and Valliappan K. Selection of better method for the preparation of microspheres by applying Analytic Hierarchy Process. J Pharm Sci and Res. 2009;1(3):64-78.
21. Kumar ABM and Rao KP. Poly (palmitoyl-l-hydroproline ester) microspheres as potential oral controlled drug delivery system. Int J Pharm. 1997;149:107–114.
22. Gilles Ponchel. Formulation of oral mucosal drug delivery systems for the systemic delivery of bioactive materials. Advanced drug delivery review. 1994;13(1-2):75-87.
23. Scherer F, Anton M and Schillinger U. Magnetofection enhancing and targeting gene delivery by magneticforce in vitro and in vivo. Gene Therapy 2002;102–10.
24. Alagusundaram M, Madhu Sudana chetty, and Umashankar C. Microspheres as a Novel drug delivery system. International J of chem Tech. 2009;526-534.
25. Chan LW and Heng PWS. Effects of poly(vinylpyrrolidone) and ethylcellulose on alginate microspheres prepared by emulsification. J Microencaps. 1998;409.