ISSN: 0976-7126

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES

Microsphere as a novel drug delivery

Nirav R. Patel*, Dhagash A. Patel, Praful D. Bharadia, Vikram Pandya and Darshan Modi
Department of Pharmaceutics, B.S.Patel Pharmacy College,
Linch, Mehsana - India

Abstract

Microspheres are spherical & free flowing particles ranging in average particle size from 1 to 50 microns which consist of proteins or synthetic polymers. Some of the problems of overcome by producing control drug delivery system which enhances the therapeutic efficacy of a given drug. One such approach is using microspheres as carriers for drugs. The target site drug deliver with Specificity & maintain the the concentration at site of interest without untoward effects. It will find the central place in novel drug delivery. 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 body (for example in lungs), to a particular group of cells (for example, kupffer cells) and even to the intracellular structures (as lyzosomes or cell nucleus). The rate of drug release from the microspheres dictates their therapeutic action. Release is governed by the molecular structure of the drug and the 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, diffusion of the entrapped drug through the pores in the polymeric microspheres.

Key-Words: Microspheres, target site, controlled release, novel drug delivery,therapeutic efficacy, novel drug delivery.

Introduction[1-2]

Some of the problems of overcome by producing control drug delivery system which enhance the therapeutic efficacy of a given drug For obtain maximum therapeutic efficacy and minimum side effects it necessary to deliver the agent to the target tissue in the optimal amount. In a sustained controlled release fashion, there are various approaches in delivering a therapeutic substance to the target site. Microsphere, as carrier for drug is one such approach which can be used in a sustained controlled release fashion.The range of techniques for the preparation of microspheres offers a variety of opportunities to control drug administration issue. This approach allows the accurate delivery of small quantity of the potent drugs, reduced drug concentration at the site other than the target site and the protection of the labile compound before and after the administration and prior to the site of action.

*** Corresponding Author:**
E-mail: nirav_neer_4u@yahoo.co.in

The behaviour of the drugs in vivo can be manipulated by combining the drug to a carrier particle. The clearance kinetics, tissue distribution, metabolism i.e. kinetics and cellular interaction of the drug are strongly influenced by the behaviour of the carrier. The exploitation of these changes in pharmaco dynamics behaviour may lead to enhanced therapeutic efficiency. However, an intelligent approach to therapeutics employing drug carriers phenomenon requires a detailed understanding of the carrier interaction with cellular and organ systems and of the limitations of the systems with respect to the formulation procedures and stability issues. A variety of substances have been used as drug carrier, including immunoglobulins serum proteins, liposomes, microspheres, microcapsules, nanoparticles and even cells such as erythrocytes. [1- 3]

Materials used in the preparation of Microsphere[4-9]

Microspheres used usually are polymers. They are classified into two types:

1. Natural polymers
2. Synthetic Polymers

ISSN: 0976-7126

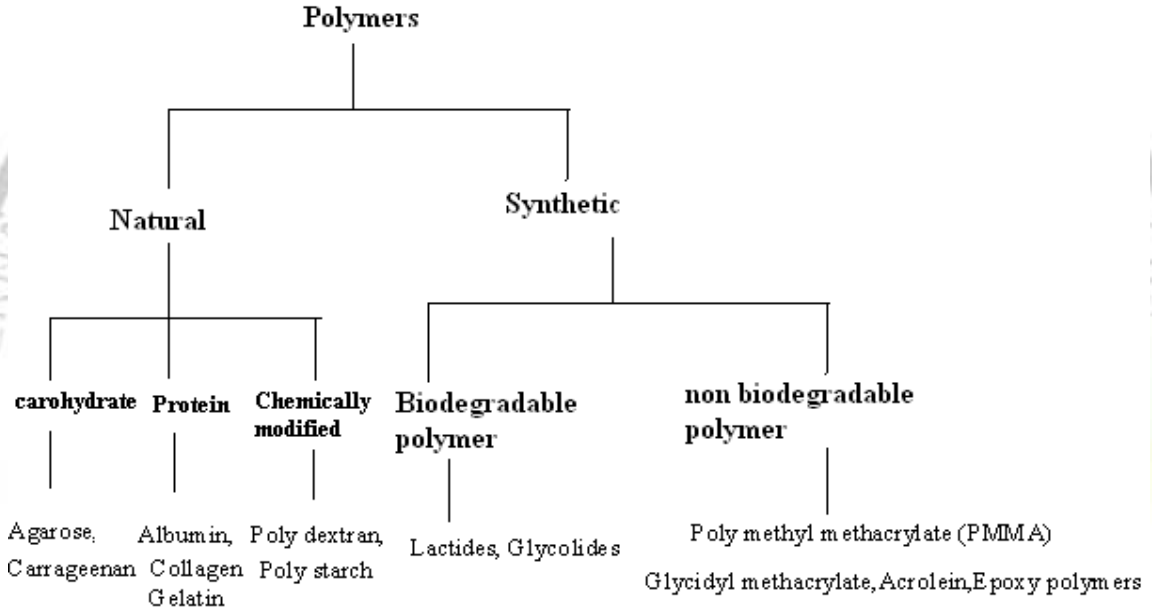
1. Natural polymers obtained from different sources Like carbohydrates proteins and chemically modified Carbohydrates.
Carbohydrates**:** Agarose, Carrageenan, Chitosan, Starch
Proteins**:** Albumin, Collagen and Gelatin
Chemically modified carbohydrates: Poly dextran, Poly starch.
2. Synthetic polymers are divided into two types.

- Biodegradable polymers

E.g. Lactides, Glycolides & their co polymers,Poly anhydrides,Poly alkyl cyano acrylates

- Non-biodegradable polymers

E.g. Poly methyl methacrylate (PMMA),Glycidyl methacrylate,Acrolein,Epoxy polymers



Synthetic polymers[10-13]

Poly alkyl cyano acrylates is a potential drug carrier for ophthalmic, oral and parenteral preparations. Poly lactic acid is a proper carrier for sustained release of anti neoplastic agents such as cisplatin, cyclo phosphamide, and doxorubicin and narcotic antagonist.co-polymer of poly lactic acid and poly glycolic acid are used for sustained release preparation for anti malarial drug. Poly adipic anhydride is used to encapsulate timolol maleate for opthalmic delivery. Poly acrolein microspheres are functional type of microspheres. They do not require any activation step since the surfacial free aldehyde groups over the poly acrolein can react with Ammonia group of protein to form Schiff's base.

Natural polymers [7,8,9,14]

Albumin is widely distributed natural protein .This is considered as a potential carrier of drugs or proteins (for their site specific localization). It is widely used for the targeted drug delivery to the tumour cells in cancer. Gelatin microspheres can be used as carrier system capable of delivering the drugs or biological response modifiers as interferon to phagocytes. Starch, polysaccharide belongs to carbohydrate class. It consists of glucopyranose as principle unit, which on hydrolysis yields D-glucose. Starch,being a poly saccharide consists of a large number of free hydroxyl groups. By means of these free hydroxyl groups a large number of active substances can be incorporated within as well as active on surface of microspheres. Chitosan is a deacylated product of chitin. The chitosan effect has been considered because of its Charge. It is insoluble at neutral and alkaline PH values, but it forms salts with inorganic and organic salts. Upon dissolution, the amino groups of chitosan get hydrogenated, and the resultant polymer gets positively charged.

Microspheres should satisfy certain criteria as following:

1. It should incorporate reasonably high concentrations of the drug.
2. Stability of the preparation after synthesis with acceptable shelf life.
3. Controlled particle size and solubility in aqueous vehicles for injection.
4. Release of active pharmaceutical reagent with a good control over a wide time scale.

5. Compatibility with a controllable biodegradability.
6. Susceptible to chemical modification.

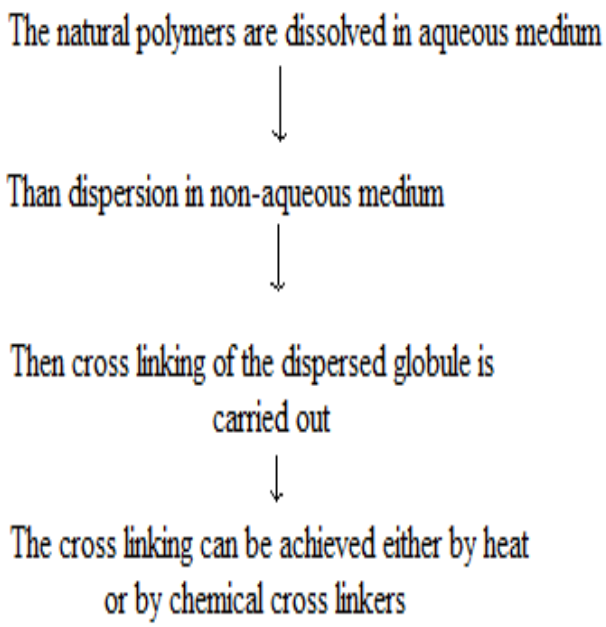
Methods of Preparation[15-16]

1. Double emulsion technique[18- 19]

This method of microspheres preparation involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited to aqueous soluble drugs, peptides, proteins and the vaccines. This method can be used with both the polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. The protein solution may contain the active substances. Continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein containing in dispersed aqueous phase. The primary emulsion is subjected to the homogenization or the sonication before addition to the aqueous solution of the poly vinyl alcohol. This results in the formation of a double emulsion. The emulsion is then subjected to removal either by solvent evaporation or by solvent extraction method. A number of hydrophilic drugs like leutinizing hormone releasing hormone (LH-RH) agonist, vaccines, proteins and conventional molecules can be successfully incorporated into the microspheres using the method of double emulsion solvent evaporation/ extraction method.

2. Single emulsion technique[17-18]

The microparticulate carriers of natural polymers i.e. those of carbohydrates and proteins carbohydrates are prepared by single emulsion technique.



The chemical cross linking agents used are as followings:

- glutaraldehyde,
- formaldehyde,
- di acid chloride etc.

Heat denaturation is not suitable for heat sensitive substances. Chemical cross linking have disadvantage of excessive exposure of active pharmaceutical ingredient to chemicals if added at the time of manufacturing and then subjected to centrifugation, washing, separation.

3. Polymerization techniques [19- 20]

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.

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 composition of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so

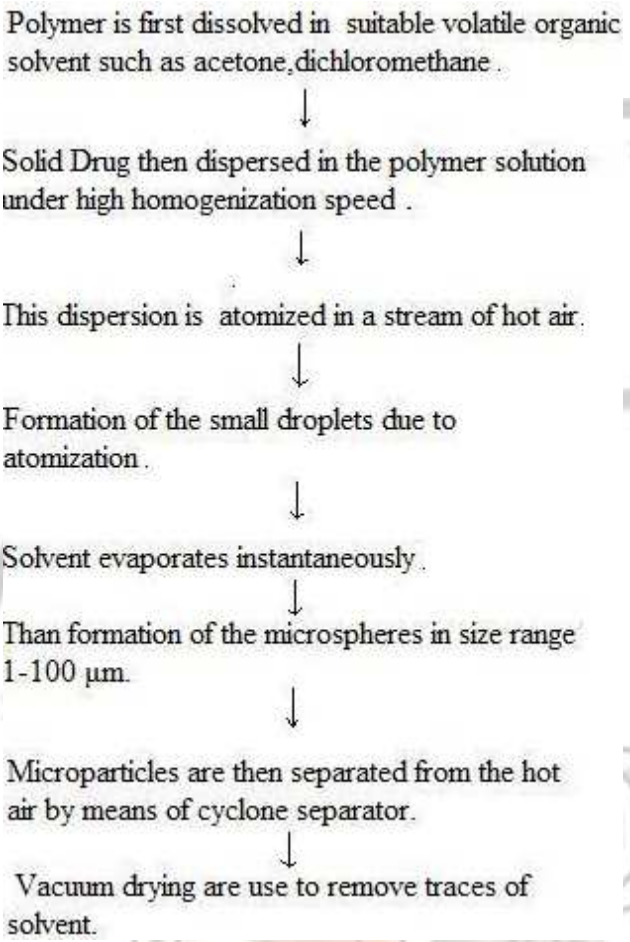
obtained may be moulded as microspheres. Drug loading may be done during the polymerization process. Suspension polymerization also referred as bead or pearl polymerization. It is carried out by heating the monomer or composition of monomers as droplets dispersion in a continuous aqueous phase. Droplets 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.

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.

4. Spray drying and spray congealing[18- 19]

These methods are based on drying of the mist of the polymer and drug in the air. Depending on the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing.



One of the major merits of the process is feasibility of process under aseptic conditions. Spray drying process is used to encapsulate various penicillins. Thiamine mononitrate and sulpha ethylthiadizole are encapsulated in a composition of mono- and di glycerides of palmitic acid and stearic acid using spray congealing. Very rapid solvent evaporation, however leads to the formation of porous microparticles.

5. Phase separation coacervation technique

This method based on the principle of decreasing the solubility of the polymer in nonaqueous phase to affect the formation of polymer rich phase called the coacervates. Here, the drug particles are dispersed in the solution of the polymer and an incompatible polymer is then added to the system which makes first polymer to separate and engulfment of the drug particles. Addition of organic results in the solidification of polymer. Poly lactic acid (PLA) microspheres have been manufactures by this method by using butadiene as incompatible polymer. The process variables are very useful because the rate of achieving the coacervates denotes the distribution of the polymer film, the size of particles and agglomeration of the formed particles. The agglomeration must be avoided by continuous stirring of the suspension using a optimum speed stirrer because as the process of microspheres formation starts the formed polymerize globules start to stick and form the agglomerates. So the process variables are critical as they control the kinetic of the particles because there is no defined state of equilibrium attainment.

6. Solvent extraction

Solvent evaporation method is used for manufacturing of microparticles, involves removal of the organic phase by extraction of the or 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**.**

7. Quassi emulsion solvent diffusion[21]

A novel quasi-emulsion solvent diffusion method to manufacture the controlled release microspheres of drugs with acrylic polymers has been reported in the literature. Microsponges can be manufactured by a quasi-emulsion solvent diffusion method using an external phase containing distilled water and polyvinyl alcohol. The internal phase is consisting of drug, ethanol and polymer is added at an amount of 20% of the polymer in order to enhance plasticity. At first, the internal phase is manufactured at 60ºC 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 microsponges. The product is then washed and dried by vacuum oven at 40ºC for a day.

Application of microspheres in pharmaceutical industry[1]

- For Taste and odour masking
- To delay the volatilisation
- For Separation of incompatible substances
- For Improvement of flow properties of powders
- To Increase the stability of the drug against the external conditions
- For Safe handling of toxic substances
- To Improve the solubility of water insoluble substances by incorporating dispersion of such material in aqueous media

- To reduce the dose dumping potential compared to large implantable devices.
- For conversion of oils and other liquids to solids for ease of handling

Novel Applications of Microsphere

Monoclonal antibodies mediated microspheres targeting

Monoclonal antibodies(Mabs) targeting microspheres are immunomicrospheres. This targeting is a method used to achieve selective targeting at specific sites. Monoclonal antibodies are extremely specific molecules. This extreme specificity of monoclonal antibodies (Mabs) can be used to target microspheres loaded bioactive molecules to selected sites by means of covalent coupling. The free amino groups, aldehyde groups, or hydroxyl groups on the external surface of the microspheres can be linked to the antibodies. Attachment of microspheres to Mabs by any of the following methods

1. Non specific adsorption
2. Specific adsorption
3. Direct coupling
4. Coupling with reagents

Targeting by using microparticulate carriers

The concept of targeing, i.e. site specific drug delivery is a well established dogma, which is gaining full attention. The therapeutic efficacy of the drug depends on its access and specific interaction with its candidate receptors. Placement of the particles indiscrete anatomical compartment leads to their retention either due to the physical properties of the environment or biophysical interaction of the particles with the cellular content of the target tissue.

Microspheres in vaccine deliver[22-23]

The prerequisite of a vaccine is protection against micro organism or its toxic product. An ideal vaccine must fulfil the requirement of efficacy, convenience in application and cost. The aspect of safety and minimization of side effect is a complex issue. Biodegradable delivery systems for vaccines that are given by i.v. route may overcome the shortcoming of the conventional vaccines. The interest in parenteral (subcutaneous, intramuscular, intradermal) carrier lies because they offer specific advantages including:

1. Modulation of antigen release
2. Improved antigenicity
3. Stabilization of antigen.

Topical porous microspheres

These microsponges are having capacity to entrap wide range of active ingredients such as emollients, fragrances, volatile oils etc., are used as the topical carries system furthermore, these porous microspheres with active medicaments can be incorporated into formulations such as creams, lotions and powders. .

Surface modified microspheres

Different approaches have been used to change the surface properties of carriers to protect them against phagocytic clearance and to modify their body distribution patterns. The adsorption of poloxamer on surface of the polystyrene, polyester or poly methyl methacrylate microspheres deviate them more hydrophilic and hence they decrease their MPS uptake. Protein microspheres can be covalently modified by PEG derivatives show decreased immunogenicity and clearance.

References

1. Diane J. Burgress and Anthony J. Hickey , The University of North Carolina at Chapel Hill, Carolina, U.S.A, *Encyclopedia of Pharmaceutical Technology*, 2328 -2337)
2. Jain N.K. (2001). *Controlled and Novel drug delivery*, 4 Edition, 236-237, 21.
3. Vyas S.P. and Khar R.K. (1999). *Targeted and Controlled drug delivery*, 7 Edition, 418.
4. Kreuter J., Nefzger M., Liehl E., CzokR. and Voges R. (1983). *J. Pharm Sci*., **72**: 1146.
5. Margel S. and Wiesel E. (1984) *J. Polym.. Sci*., **22**:145.
6. Wakiyama N., Juni K. and Nakano M. (1981). *Chem. Pharm.Bull*., **29**: 3363.
7. Sugibayashi K., Akimoto M., Moromoto Y., Nadai T. and Kato Y. (1979), *Pharmacobiodyn*., **23**:50.
8. Yoshioka T., Hashida M., Muranishi S. and Sezaki H. (1981). *Int. J. Pharm*., **8**: 131.
9. Russel G.F. (1983). *Pharma.Int*., **4**: 260.
10. Woodland J.H.R., Yolles S., Blake D.A., Hetrich M. and Meyer F.J. (1973) J. *Med.Chem*., **16**: 897.
11. Rojas J., Pinto. Alphandary H., Leo E., Pecqests., couvreur P., Gulik A. and Fattal. E. (1999). *Pharm Res*., **16**: 255.
12. Albertson AC., Carlfors J. and Sturess on C. (1993). *J. Appl .Polym.Sci*., **62**, 695.
13. Renbaum A. (1983) US patent 4,413,070.
14. Vyas S.P. and Khar R.K. (2007). *Targeted & Controlled drug delivery*. Edition, 435.
15. Koff US patent (March21963) 3,080,292.
16. John P.M and Becker. C.H. (1968). *J. Pharm. Sci.*, **57**: 584.
17. *Encyclopedia of pharmaceutical technology* volume-10, J.C Sworbrik and J.C.Boylen (Ed), Marcel Dekker,New York (Basel), 1988, No.1-29.

18. J.H Ratcliff, I.M Hunnyball, A. Smith and C.G Wilson (1984). *J.Pharmacol*., 431-436.
19. Fujimoto S. and Miyazaki M. (1985). Biodegradable motomycin C microspheres. Given intra-arterially for hepatic cancer, 2404-2410.
20. Improved patient compliance and comfort compared with intravenous administration .Rapid absorption, higher bioavailability.
21. Davis S.S. and Illum L. (1989). Microspheres as drug carrier in drug carrier system, F.H Roerdink and A.M.Kron (Eds), John Wiley and sons Ltd., 1.
22. Funden Berg H.H., Stites D.P., Caldwel J.L. and Wells J.V. (1978) In: *Basic and clinical immunology*, 2 ed., Lange Medical, Los Altosca.
23. Capron A.C., Locht C. and Fracchia G.N (1994). Vaccine, 12, 66
24. Nachts S. and Martin K. (1990) In: *The microsponges a novel topical programmable delivery formulation*, Marcel Dekker Inc.,Newyork., 299.
25. http://www.gate2tech.com/IMG/jpg/double_emulsion.jpg.
26. http://www.gate2tech.com/IMG/jpg/single_emulsion.jpg

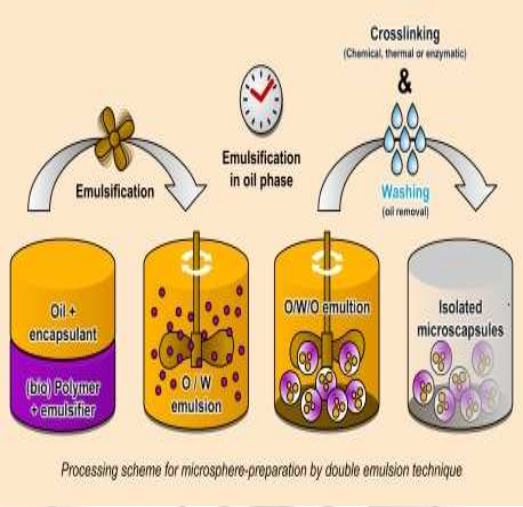


Fig. 1: Process of Double emulsion technique [25]

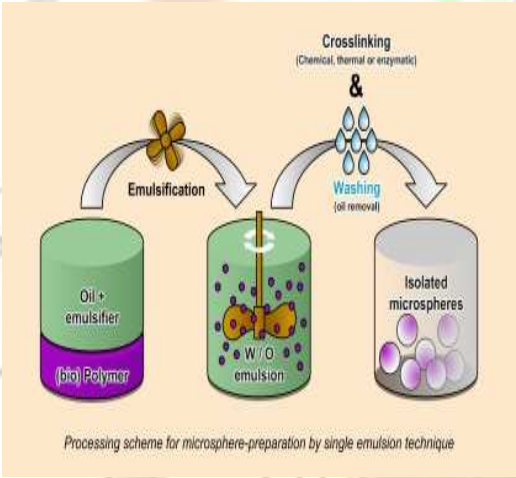


Fig. 2: Process of Single emulsion technique [26]