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# Microspheres - A Novel Drug Delivery System

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**ABSTRACT:** Oral modified-release multiple-unit dosage forms have always been more effective therapeutic alternative to conventional or immediate release single-unit dosage forms. With regards to the final dosage form, the multiparticulates are usually formulated into microspheres and filling them into hard gelatin capsules. Microspheres are spherical & free flowing particles ranging in average particle size from 1 to 1000 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. Microspheres received much attention not only for prolonged release, but also for targeting of drugs. In future microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, genetic materials, targeted and effective drug delivery.

**KEY WORDS:** Microspheres, target site, controlled release, novel drug delivery, therapeutic efficacy, novel drug delivery.

## 1. INTRODUCTION: [1,2]

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 effects1. 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 µm2. **Microsphere**s are small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm). Microspheres are sometimes referred to as microparticles.

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Microspheres can be manufactured from various natural and synthetic materials. Glass microspheres, polymer microspheres and ceramic microspheres are commercially available. Solid and hollow microspheres vary widely in density and, therefore, are used for different applications. Hollow microspheres are typically used as additives to lower the density of a material. Solid microspheres have numerous applications depending on what material they are constructed of and what size they are. Polyethylene and polystyrene microspheres are two most common types of polymer microspheres.

## 2. MATERIALS USED IN THE PREPARATION OF MICROSPHERE [5,6,12,13,16]

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

1. Natural polymers
2. Synthetic Polymers

**A. Natural polymers:** These are obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.

**Proteins:** Albumin, Gelatin, and Collagen

**Carbohydrates:** Agarose, Carrageenan, Chitosan, Starch

**Chemically modified carbohydrates:** Poly dextran, Poly starch

In case of non-biodegradable drug carriers, when administered parenterally, the carrier remaining in the body after the drug is completely released poses possibility of carrier toxicity over a long period of time. Biodegradable carriers which degrade in the body to non-toxic degradation products donot pose the problem of carrier toxicity and are more suited for parenteral applications1.

**B. Synthetic polymers:** These are divided into two types.

a) Biodegradable polymers

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

b) Non-biodegradable polymers

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

**2.1 Natural polymers[13]**

Albumin is a widely distributed natural protein .It is considered as a potential carrier of drug or protiens (for either their site specific localization or their local application into anatomical discrete sites). It is being widely used for the targeted drug for the targeted drug delivery to the tumour cells. Gelatin microspheres can be used as efficient carrier system capable of delivering the drug or biological response modifiers such as interferon to phagocytes. Starch belongs to carbohydrate class. It consists of principle glucopyranose unit, which on hydrolysis yields D-glucose. It being a poly saccharide consists of a large number of free OH groups. By means of these free OH groups a large number of active ingredients can be incorporated within as well as active on surface of microspheres. Chitosan is a deacylated product of chitin. The effect of chitosan has been considered because of its charge. It is insoluble at neutral and alkaline Ph values, but forms salts with inorganic and organic salts. Upon dissolution, the amino groups of chitosan get protonated, and the resultant polymer becomes positively charged.

**2.2 Synthetic polymers[10]**

Poly alkyl cyano acrylates is a potential drug carrier for parenteral as well as other ophthalmic, oral preparations. Poly lactic acid is a suitable carrier for sustained release of narcotic antagonist, anti cancer agents such as cisplatin, cyclo phosphamide, and doxorubicin. Sustained release preparations for anti malarial drug as well as for many other drugs have been formulated by using of co-polymer of poly lactic acid and poly glycolic acid. Poly anhydride microspheres (40µm) have been investigated to extend the precorneal residence time for ocular delivery. Poly adipic anhydride is used to encapsulate timolol maleate for ocular delivery. Poly acrolein microspheres are functional type of microspheres. They do not require any activation step since the surficial free CHO groups over the poly acrolein can react with NH2 group of protein to form Schiff's base.

**3. ADVANTAGES OF MICROSPHERESS OVER SINGLE UNIT DOSAGE FORMS[23]**

- Microspheress spread out more uniformly in the GIT, thus avoiding exposure of the mucosa locally to high concentration of drug.
- Microspheress ensure more reproducible drug absorption.
- The risk of dose dumping also seems to be considerably lower than with single unit dosage form.
- Microspheress allow the administration of much smaller doses than are normally required. This reduces local irritation when compared to single unit dosage forms.
- Drug discharge in the stomach may be hindered and local unwanted effects may be reduced or eliminated.
- Microspheress posses many other advantages such as high bioavailability, rapid kinetic of absorption and improvement of patient compliance.
- Microspheress received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumour10

**4. DISADVANTAGES OF MICROSPHERESS OVER SINGLE UNIT DOSAGE FORMS[23]**

- The modified release from the formulations.
- 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.
- Differences in the release rate from one dose to another.
- 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.
- Dosage forms of this kind should not be crushed or chewed.7 tissues in the body.

**5. MICROSPHERES SHOULD SATISFY CERTAIN CRITERIA AS FOLLOWING[27]**

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

- Compatibility with a controllable biodegradability.
- Susceptible to chemical modification.

**6. DRUG LOADING AND DRUG RELEASE KINETICS**

The active components are loaded over the microspheres principally using two methods, i.e. during the preparation of the microspheres or after the formation of the microspheres by incubating them with the drug/protein. The active component can be loaded by means of the physical entrapment, chemical linkage and surface adsorption. The entrapment largely depends on the method of preparation and nature of the drug or polymer (monomer if used). Maximum loading can be achieved by incorporating the drug during the time of preparation but it may get affected by many other process variables such as method of preparation, presence of additives (e.g. cross linking agent, surfactant stabilizers, etc.) heat of polymerization, agitation intensity, etc. Release of the active constituent is an important consideration in case of microspheres.The release profile from the microspheres depends on the nature of the polymer used in the preparation as well as on the nature of the active drug. The release of drug from both biodegradable as well as non-biodegradable microspheres is influenced by structure or micro-morphology of the carrier and the properties of the polymer itself. The drugs could be released through the microspheres by any of the three methods, first is the osmotically driven burst mechanism, second by pore diffusion mechanism, and third by erosion or the degradation of the polymer. In osmotically driven burst mechanism, water diffuse into the core through biodegradable or non-biodegradable coating, creating sufficient pressure that ruptures the membrane. The burst effect is mainly controlled by three factors the macromolecule/polymer ratio, particle size of the dispersed macromolecule and the particle size of the microspheres. The pore diffusion method is named so because as penetrating water front continue to diffuse towards the core. The polymer erosion, i.e. loss of polymer is accompanied by accumulation of the monomer in the release medium. The erosion of the polymer begins with the changes in the microstructure of the carrier as water penetrates within it leading to the
plasticization of the matrix. Drug release from the non-biodegradable type of polymers can be understood by considering the geometry of the carrier. The geometry of the carrier, i.e. whether it is reservoir type where the drug is present as core, or matrix type in which drug is dispersed throughout the carrier, governs overall release profile of the drug or active ingredients.

**7. METHODS OF PREPARATION**

**I. Single emulsion technique:[28]**

The micro particulate carriers of natural polymers 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. Next cross linking of the dispersed globule is 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, di 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.

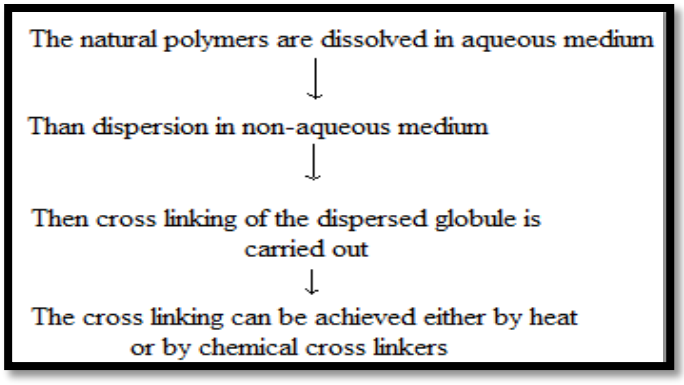


**Fig. 1: Schematic representation of Single emulsion method of microsphere preparation**

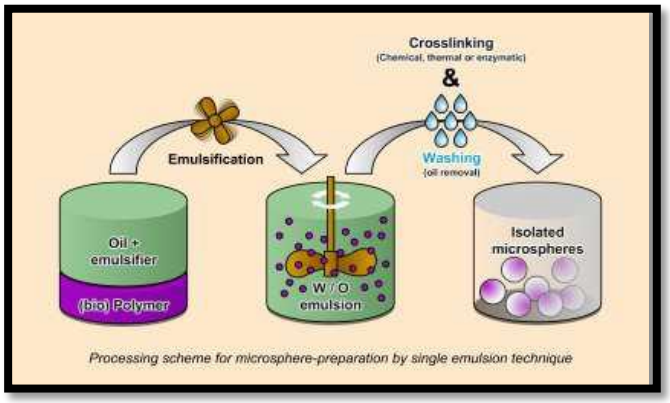


**Fig. 2: Process of Single emulsion technique**

**II. Double emulsion technique:[25]**

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 to 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 leutinizing 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.

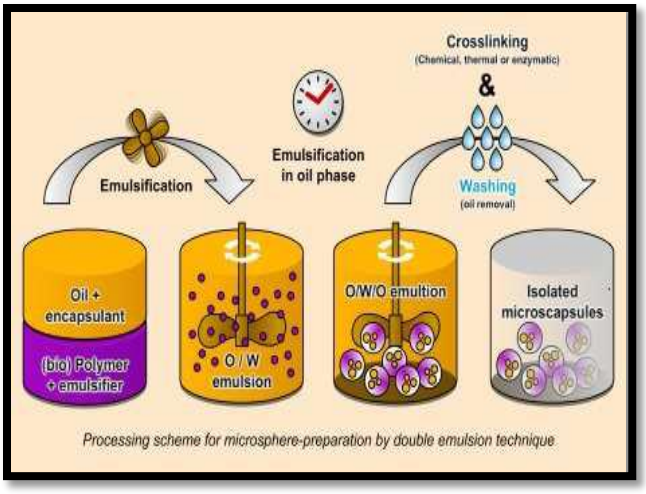


Fig. 3: Process of Double emulsion technique

**III. Polymerization techniques:**[27]

The polymerization techniques conventionally used for the preparation of 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 using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes.In bulk, a monomer or a mixture 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 process of polymerization. Suspension polymerization also referred as bead or pearl polymerization. Here it is carried out by heating the monomer or mixture of monomers as droplets dispersion in a continuous aqueous phase. The droplets may also contain an initiator and other additives. Emulsion polymerization differs from suspension polymerization as due to the presence initiator in the aqueous phase, which later on diffuses to the surface of micelles. Bulk polymerization has an advantage of formation of pure polymers.

**Interfacial polymerization**:

It involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase.

**IV. Phase separation coacervation technique:**[29]

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 form the 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.

**V. Spray drying and spray congealing:**[29]

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 highspeed 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. Microparticles 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 mononitrate14 and sulpha ethylthiadizole15 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 microparticles.

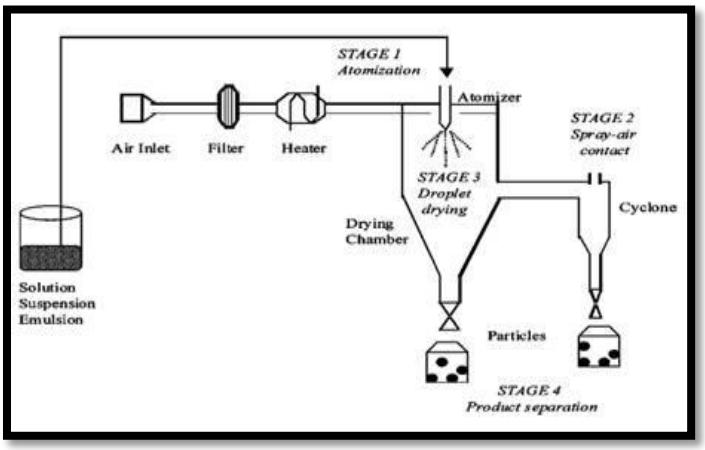


Fig - 4: Microspheres by Spray Drying Technique

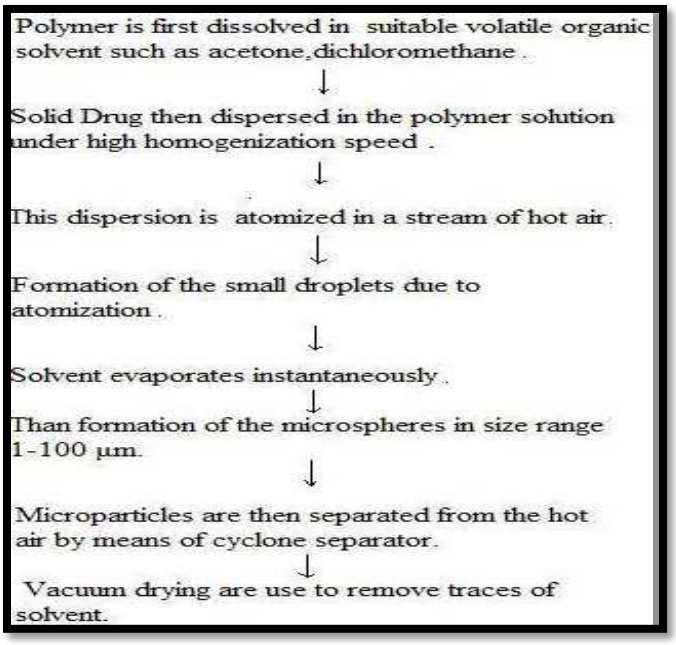


Fig. 5: Schematic representation of microsphere preparation by spray dried technique.

**VI. Solvent extraction:**[27]

Solvent evaporation method is used for the preparation of microparticles, involves removal of the
organic phase by extraction of the organic solvent. The method involves water miscible organic solvents such as isopro panol. Organic phase is removed by extraction with water. This process decreases the hardening time for the microspheres. One variation of the process involves
direct addition of the drug or protein to polymer organic solution. The rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer**.**

**8. PHYSICOCHEMICAL EVALUATION CHARACTERIZATION**

The characterization of the micro particulate carrier is an important phenomenon, which helps to design a suitable carrier for the proteins, drug or antigen delivery. These microspheres have different microstructures. These microstructures determine the release and the stability of the carrier16.

**8.1Particle size and shape**[32]

The most widely used procedures to visualize microparticles are conventional light microscopy (LM) and scanning electron microscopy (SEM). Both can be used to determine the shape and outer structure of microparticles. LM provides a control over coating parameters in case of double walled microspheres. The microspheres structures can be visualized before and after coating and the change can be measured microscopically. SEM provides higher resolution in contrast to the LM17. SEM allows investigations of the microspheres surfaces and after particles are cross-sectioned, it can also be used for the investigation of double walled systems. Conflocal fluorescence microscopy1 is used for the structure characterization of multiple walled microspheres. Laser light scattering and multi size coulter counter other than instrumental methods, which can be used for the characterization of size, shape and morphology of the microspheres.

**8.2 Electron spectroscopy for chemical analysis:**[33]

The surface chemistry of the microspheres can be determined using the electron spectroscopy for chemical analysis (ESCA). ESCA provides a means for the determination of the atomic composition of the surface. The spectra obtained using ECSA can be used to determine the surfacial degradation of the biodegradable microspheres.

**8.3 Attenuated total reflectance FourierTransfom-Infrared Spectroscopy:**

FT-IR is used to determine the degradation of the polymeric matrix of the carrier system. The surface of the microspheres is investigated measuring alternated total reflectance (ATR). The IR beam passing through the ATR cell reflected many times through the sample to provide IR spectra mainly of surface material. The ATRFTIR provides information about the surface composition of the microspheres depending upon manufacturing procedures and conditions.

**8.4 Density determination:**
The density of the microspheres can be measured by using a multi volume pychnometer. Accurately weighed sample in a cup is placed into the multi volume pychnometer. Helium is introduced at a constant pressure in the chamber and allowed to expand. This expansion
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 hence the density of the microsphere carrier is determined.

**8.5 Isoelectric point:**
The micro electrophoresis is an apparatus used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined. The mean velocity at different Ph values ranging from 3-10 is calculated by measuring the time of particle movement over a distance of 1 mm. By using this data the electrical mobility of the particle can be determined. The electrophoretic mobility can be related to surface contained charge, ionisable behaviour or ion absorption nature of the microspheres.

**8.6 Surface carboxylic acid residue:**
The surface carboxylic acid residue is measured by using radioactive glycine. The radioactive glycine conjugates is prepared by the reaction of c14-glycine ethyl ester hydro chloride with the microspheres. The glycine residue is linked using the water soluble condensing 1- ethyl-3 (3-dimethyl amino propyl) carbidiimide (EDAC). The radioactivity of the conjugate is then measured using liquid scintillation counter. Thus the carboxylic acid residue can be compared and correlated. The free carboxylic acid residue can be measured for hydrophobic or hydrophilic or any other derivatized type of the microspheres.

**8.7 Surface amino acid residue:**
Surface associated amino acid residue is determined by the radioactive c14-acetic acid conjugate.
The carboxylic acid residue is measured through the liquid scintillation counter and hence the amino acid residue can be determined indirectly. EDAC is used to condense the amino group and the c14 –acetic acid carboxylic acid residue. The method used for determiningthe free amino or the free carboxylic acid residues are based on indirect estimation, by measuring the radioactivity of the c14 having acetic acid or the glycine conjugate. The accuracy of the method however, depends on the time allowed for conjugation of the radioactive moiety and the reactivity of free functional group.

**8.8 Capture efficiency:**
The capture efficiency of the microspheres or the percent entrapment can be determined by allowing washed microspheres to lyse. The lysate is then subjected to the determination of active constituents as per monograph requirement. The percent encapsulation efficiency is calculated using following equation:
% Entrapment = Actual content/Theoretical content x 100

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

**8.10 *In vitro* methods[34]**
There is a need for experimental methods which allow the release characteristics and permeability of a drug through membrane to be determined. For this purpose, a number of *in vitro* and *in vivo* techniques have been reported. *In vitro* drug release studies have been employed as a quality control procedure in pharmaceutical production, in product development etc.
Sensitive and reproducible release data derived from physico chemically and hydro dynamically defined conditions are necessary. The influence of technologically defined conditions and difficulty in simulating *in vivo* conditions has led to development of a number of *in vitro* release methods for buccal formulations; however no standard *in vitro* method has yet been developed. Different workers have used apparatus of varying designs and under varying conditions, depending on the shape and application of the dosage form developed18.

**8.10.1 Beaker method[35,37,38]**
The dosage form in this method is made to adhere at the bottom of the beaker containing the medium and stirred uniformly using over head stirrer. Volume of the medium used in the literature for the studies varies from 50-500 ml and the stirrer speed form 60-300 rpm.

**8.10.2 Interface diffusion system**
This method is developed by Dearden & Tomlinson. It consists of four compartments. The
compartment A represents the oral cavity, and initially contained an appropriate concentration of drug in a buffer. The compartment B representing the buccal membrane, contained 1-octanol, and compartment C representing

body fluids, contained 0.2 M HCl. The compartment D representing protein binding also contained 1-octanol. Before use, the aqueous phase and 1-octanol were saturated with each other. Samples were withdrawn and returned to compartment A with a
syringe.

**8.10.3 Modified Keshary Chien Cell[39,40]**
A specialized apparatus was designed in the laboratory. It comprised of a Keshary Chien cell containing distilled water (50ml) at 37 C as dissolution medium. TMDDS (Trans Membrane Drug Delivery System) was placed in a glass tube fitted with a 10# sieve at the bottom which reciprocated in the medium at 30 strokes per min.

**8.10.4 Dissolution apparatus[44]**
Standard USP or BP dissolution apparatus havebeen used to study *in vitro* release profiles using both rotating elements, paddle and basket.Dissolution medium used for the study varied from 100-500 ml and speed of rotation from 50-100 rpm.

**8.11 Other methods:[46]**
Few other methods involving plexi glass sample blocks placed in flasks30, agar gel method, Valia-Chein cell USP n2 III dissolution apparatus etc have also been reported. Although a number of methods have been reported, the ideal method would be one where sink condition is maintained and dissolution time *in vitro* simulates dissolution time *in vivo.*

**8.12 *In vivo* methods**
Methods for studying the permeability of intact mucosa comprise of techniques that exploit the biological response of the organism locally or systemically and those that involve direct local measurement of uptake or accumulation of penetrants at the surface. Some of the earliest and simple studies of mucosal permeability utilized the systemic pharmacological effects produced
by drugs after application to the oral mucosa. However the most widely used methods include *in vivo* studies using animal models, buccal absorption tests, and perfusion chambers for studying drug permeability.

**8.12.1 Animal models**
Animal models are used mainly for the screening of the series of compounds, investigating the mechanisms and usefulness of permeation enhancers or evaluating a set of formulations. A number of animal models have been reported in the literature, however, very few *in vivo*
(animal). Animal models such as the dog, rats, rabbits, cat, hamster, pigs, and sheep have been reported. In general, the procedure involves anesthetizing the animal followed by administration of the dosage form. In case of rats, the oesophagus is ligated to prevent absorption pathways other than oral mucosa. At different time intervals, the blood is withdrawn and analysed.

**8.12.2 Buccal absorption test**
The buccal absorption test was developed by Beckett & Triggs in 1967. It is a simple and reliable method for measuring the extent of drug loss of the human oral cavity for single and multi-component mixtures of drugs. The test has been successfully used to investigate the relative importance of drug structure, contact time, initial drug concentration and Ph of the solution while
the drug is held in the oral cavity.

**8.13 in vitro-in vivo correlations**
Correlations between in vitro dissolution rates and the rate and extent of availability as determined by blood concentration and or urinary excretion of drug or metabolites are referred to as "in vitro-in vivo correlations" 36. Such correlations allow one to develop product specifications with bioavailability.

**9. APPLICATIONS**

**1. Microspheres in vaccine delivery[21]**
The prerequisite of a vaccine is protection against the micro organism or its toxic product. An
ideal vaccine must fulfill the requirement of efficacy, safety, convenience in application and cost. The aspect of safety and minimization of adverse reaction is a complex issue48. The aspect of safety and the degree of the production of antibody responses are closely related to mode of application. Biodegradable delivery systems for vaccines that are given by parenteral route may overcome the shortcoming of the conventional vaccines49. The interest in parenteral (subcutaneous, intramuscular, intradermal) carrier lies since they offer specific advantages
including:
1. Improved antigenicity by adjuvant action
2. Modulation of antigen release
3. Stabilization of antigen.

**2. Targeting using micro particulate carriers [34]**
The concept of targeting, i.e. site specific drug delivery is a well-established dogma, which is gaining full attention. The therapeutic efficacy of the drug relies on its access and specific interaction with its candidate receptors. The ability to leave the pool in reproducible, efficient and specific manner is center to drug action mediated by use of a carrier system. Placement of the particles indiscrete anatomical compartment leads to their retention either because of the physical properties of the environment or

biophysical interaction of the particles with the cellular content of the target tissue.

**3. Monoclonal antibodies mediated microspheres targeting[34]**

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

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

**4. Chemoembolization**

Chemoembolisation is an endovascular therapy, which involves the selective arterial embolisation of a tumour together with simultaneous or subsequent local delivery the chemotherapeutic agent. The theoretical advantage is that such embolisations will not only provide vascular occlusion but will bring about sustained therapeutic levels of chemotherapeutics in the areas of the tumour. Chemoembolisation is an extension of traditional percutaneous embolisation techniques.

**5. Imaging**

The microspheres have been extensively studied and used for the targeting purposes. Various cells, cell lines, tissues and organs can be imaged usingradio labelled microspheres. The particle size range of microspheres is an important factor in determining the imaging of particular sites. The particles injected intravenously apart from the portal vein will become entrapped in the capillary bed of the lungs. This phenomenon is exploited for the scintiographic imaging of the tumour masses in lungs using labelled human serum albumin microspheres.

**6. Topical porous microspheres[29]**

Microsponges are porous microspheres having myriad of interconnected voids of particle size range 5-300 µm. These microsponges having capacity to entrap wide range of active ingredients such as emollients, fragrances, essential oils etc., are used as the topical carries system further, these porous microspheres with active ingredients can be incorporated into formulations such as creams, lotions and powders. Microsponges consist of non collapsible structures with porous surface through which active ingredients are released in a controlled manner50.

**7. Surface modified microspheres**

Different approaches have been utilized to change the surface properties of carriers to protect
them against phagocytic clearance and to alter their body distribution patterns .The adsorption of the poloxamer on the surface of the polystyrene, polyester or poly methyl methacrylate microspheres renders them more hydrophilic and hence decrease their MPS uptake. Protein microspheres covalently modified by PEG derivatives show decreased immunogenicity and clearance. The most studied surface modifiers are:

1. Antibodies and their fragments
2. Proteins
3. Mono-, oligo- and polysaccharides
4 . Chelating compounds (EDTA, DTPA or Desferroxamine)
5. Synthetic soluble polymers Such modifications are provided surface of microspheres inorder to achieve the targeting to the discrete organs and to avoid rapid clearance from the body.

**9. 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

**10. CONCLUSION**

Microparticles are spherical microspheres, and are used 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. A microspheres has a drug located centrally within the particle, where it is encased within a unique polymeric membrane. 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.

**11. ACKNOLEDGEMENT:**
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