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REVIEW ON MICROSPHERES: METHODS OF PREPARATION AND EVALUATION

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ABSTRACT

Microspheres are typically free flow powders consisting of proteins or synthetic polymers which are biodegradable in nature. And ideally having a particle size less than 200µm. Microsphere after ball bearing effects because of their spherical shape. The therapeutic efficacy of microspheres contain drug depends upon their characteristics that can be altered in required terms by altering materials, methods, polymers or techniques used. A Microspheres has its drug dispersed throughout the particle i.e. the internal structure is a matrix of drug and polymeric excipients. 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 tumor. 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, Drug delivery, target site, preparation, evaluation, application.

INTRODUCTION

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. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion.[4] One such approach is using microspheress as

carriers for drugs. Microspheress can be described as small particles (in 1-1000 micrometer size range) for use as carriers of drugs and other therapeutic agents consisting of proteins or synthetic polymers which are biodegradable in nature. The term microspheress describes a monolithic spherical structure with the drug or therapeutic agent distributed throughout the matrix either as a molecular dispersion or as a dispersion of particles.[20] 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.

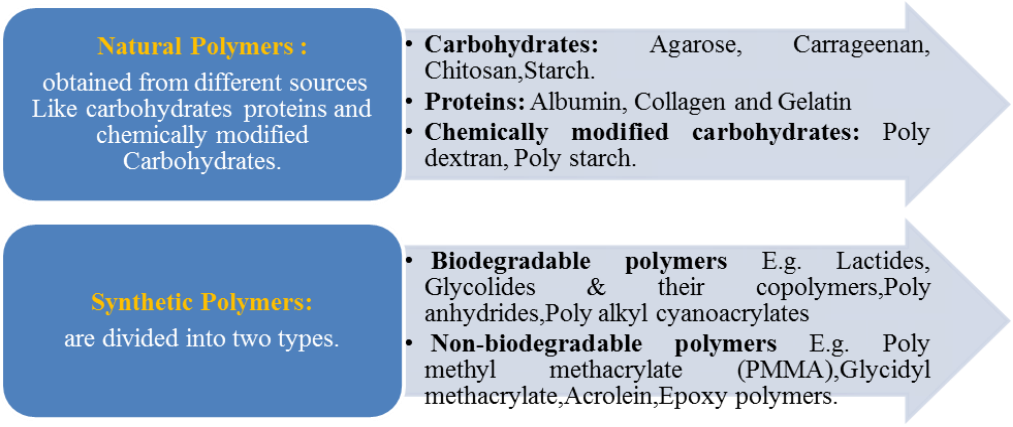
Materials used in the preparation of Microsphere

A number of different substances both biodegradable as well as non-biodegradable have been investigated for the preparation of microspheress. These materials include the polymers of natural and synthetic origin and also modified natural substances. Synthetic polymers employed as carrier materials are methyl methacrylate, acrolein,lactide, glycolide and their copolymers, ethylene vinyl acetate copolymer, polyanhydrides, etc. The natural polymers used for the purpose are albumin, gelatin, starch, collagen and carrageenan.

Classification of polymer[5]

They are classified into two types:

1. Natural polymers
2. Synthetic Polymers



Ideal micro particulate carriers[21]

The material utilized for the preparation of micro particulates should have the following properties.

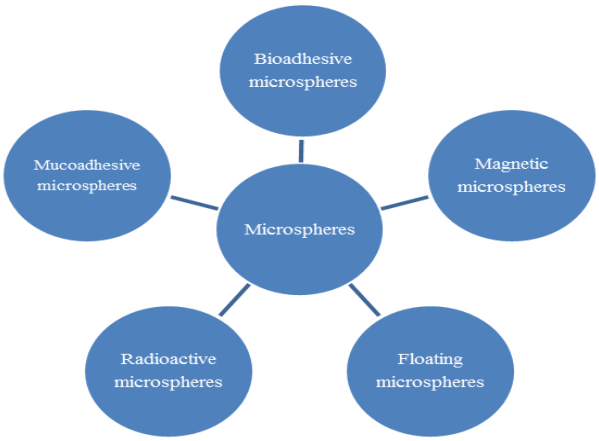
- Longer duration of action
- Control of content release
- Increase of therapeutic efficiency
- Protection of drug
- Reduction of toxicity
- Biocompatibility
- Sterilizability
- Relative stability
- Water solubility or dispersability
- Bioresorbability
- Target ability
- Polyvalent

The microsphere in pharmaceutical industry for their following applications

- Masking of taste and odor.
- Delay of volatilization
- Safe in case of toxic substances.
- Flow of powder is improve
- Sustained-release, controlled-release, targeted medication can produce
- Reduced dose dumping, etc.

Types of Microspheres

There are following types of microspheres.



- **Bioadhesive Microspheres**

Adhesion can be define 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 term as bioadhesion. The term "bioadhesion" describes materials that bind to biological substrates', such as mucosal members. Adhesion of Bioadhesive drug delivery devices to the mucosal tissue offers the possibility of creating an intimate and prolonged contact at the site of administration. This prolonged residence time can result in enhanced absorption and in combination with a controlled release of drug also improved patient compliance by reducing the frequency of administration. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanospheres, liposome's, nanoparticles, etc., which modulates the release and absorption of the drug. Microspheres constitute an important part of these particulate drug delivery systems by virtue of their small size and efficient carrier capacity.[3]

- **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.[22] The different type are Therapeutic magnetic microspheres are used to deliver chemotherapeutic agent to liver tumor. Drugs like proteins and peptides can also be targeted through this system.

Diagnostic microspheres[23]

Magnetic drug transport technique is based on the fact that the drug can be either encapsulated into a magnetic microsphere or conjugated on the surface of the microsphere. The accumulation of the carrier at the target site allow them to deliver the drug locally.[24]

- **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, increases gastric residence and fluctuation in plasma concentration. It also reduces chances of striking and dose dumping and produces prolonged therapeutic effect. Drug (ketoprofen) given through this form.[25]

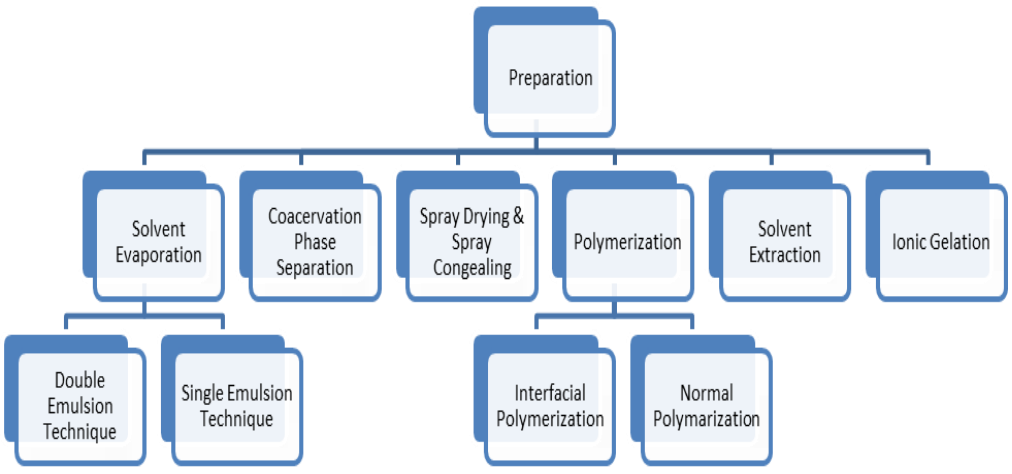
- **Radioactive microspheres**

Radio immobilization therapy microspheres sized 10-30 nm are of larger than capillaries and gets tapped in first capillary bed when they come across. They are injected to the arteries that lead to tumor of interest. So these 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 and the different kinds of radioactive microspheres are α emitters, β emitters, γ emitters.[3]

- **Mucoadhesive microspheres**

Mucoadhesive microspheres which are of 1-1000mm in diameter and consisting either entirely of a mucoadhesive polymer or having an outer coating of it and coupling of mucoadhesive properties to microspheres has additional advantages, *e.g.* efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer, specific targeting of drug to the absorption site achieved by anchoring plant lectins, bacterial adhesions and antibodies, etc. on the surface of the microspheres. Mucoadhesive microspheres can be tailored to adhere to any mucosal tissue including those found in eye, nasal cavity, urinary and gastrointestinal tract, thus offering the possibilities of localized as well as systemic controlled release of drugs.[26]

Method of Preparation



Double Emulsion Technique

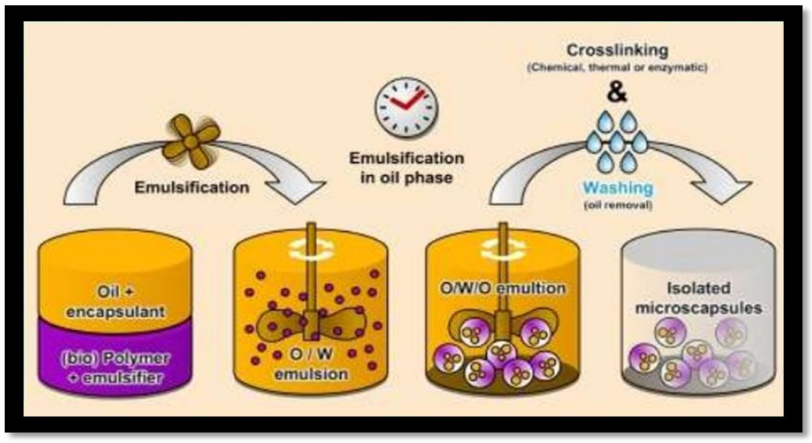


Fig no 1: Double Emulsion Technique.

It is formation of multiple emulsions i.e. W/O/W is preparing by pouring the primary w/o emulsion into aqueous solution of poly vinyl alcohol. This w/o/w emulsion put at constant stirring for 30 min. Slowly add some water to the emulsion over a period of 30 min. collect Microcapsules by filtration and dry under vacuum.[14] It is best suited to water soluble drugs, peptides, proteins and the vaccines. Natural as well as synthetic polymer can use for this method. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. Disperse in oil/organic phase homogenization/vigorous i.e. formation of first emulsion then addition to aqueous solution of PVA (Poly Vinyl Alcohol) i.e. multiple emulsion formed now by addition to large aqueous phase denaturation/hardening after this separation, washings' and drying and collection of microspheres1 genistein chitosan microsphere were prepared by the o/w/o multiple emulsion method by Wu and Li (2002).[15]

Single Emulsion Technique

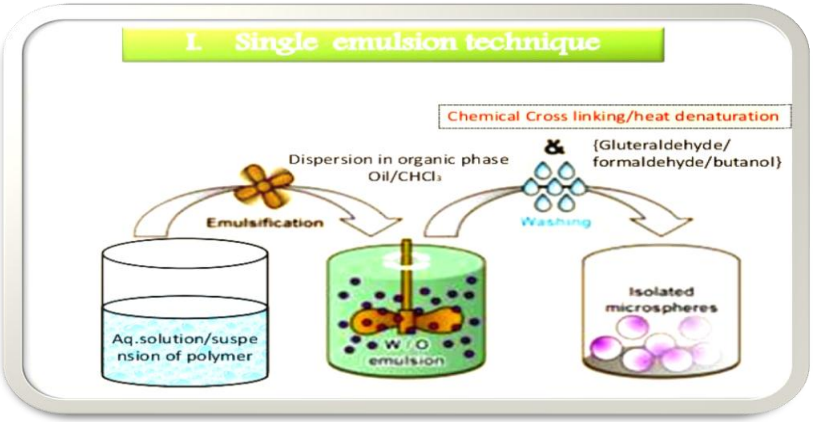


Fig no 2: Single emulsion Technique.

There are several Proteins and carbohydrates, which are prepared by this technique. The single emulsion method is primarily used for encapsulating hydrophobic drugs through an oil-in-water (o/w) emulsification process.[2] In which the natural polymers are dissolved in aqueous medium and the followed by dispersion in oil phase i.e. non-aqueous medium. That is the first step in Next step cross linking is carried out by two methods.[1]

(1) Cross linking by heat: by adding the dispersion into heated oil, but it is unsuitable for the Thermo labile drugs.

(2) Chemical cross linking agents: - by using agents i.e. formaldehyde, di acid chloride, glutaraldehyde etc. but it is having a disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing and separation. Chitosan solution (in acetic acid) by adding to Liquid paraffin containing a surfactant resulting formation of w/o emulsion. Metformin hydrochloride microsphere are prepare by using gluteraldehyde 25% solution as a cross linking agent.

Coacervation Phase Separation Technique

It is the simple separation of a micro molecular solution into two immiscible liquid phase. In this process, the polymer is solubilized to for a solution. Specially designed for preparing the reservoir type of the system, i.e., to soluble drugs e.g. peptides, proteins, matrix type particularly[10], when the drug is hydrophobic in nature e.g., steroids. In matrix type device, the drug or the protein is soluble in the polymer phase. The principle of coacervation is decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervates.[1] The coacervation can be brought about by addition of the third component to the system which results in the formation of the two phases, one i.e. supernatant, depleted of the polymer. In this technique, the polymer is first dissolved in a suitable solvent & then drug is dispersed by making its aqueous solution, if hydrophilic or dissolved in the polymer solution itself, if hydrophobic. Phase separation is then accomplished by changing the solution conditions.

Spray Drying and Spray Congealing Technique

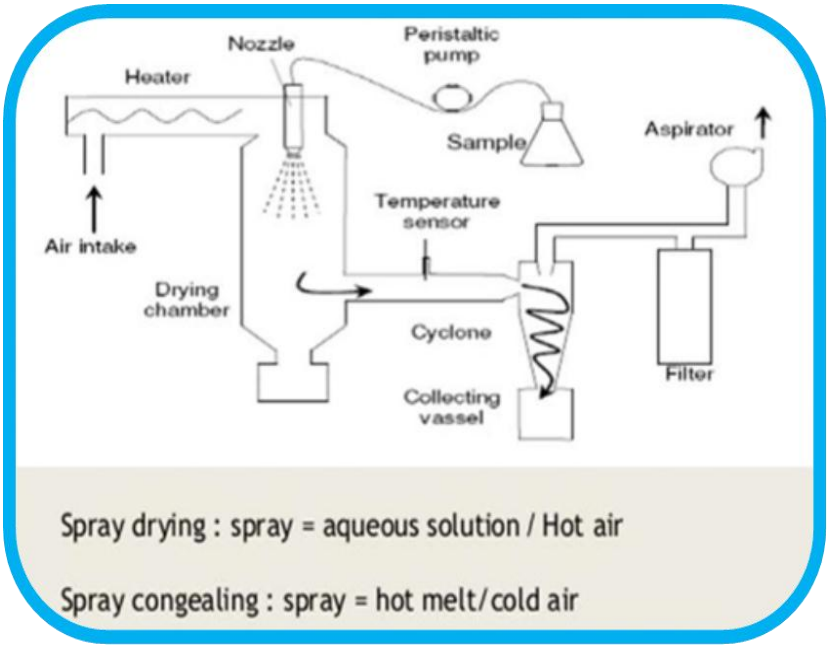


Fig no 3: Spray Drying and Spray congealing.

Concept of spray drying technique depending upon the removal of solvent or the cooling of solution the two processes are spray drying & 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- 100µm. 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 penicillin's. Thiamine mono nitrate and sulpha-ethyl-thi-dizole are encapsulated in a mixture of mono-and glycerides of stearic acid and palmitic acid using spray congealing[16] Very rapid solvent evaporation, however leads to the formation of porous micro particles.

Polymerization Technique

Interfacial Polymerization[10,17]

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. In this

technique two reacting monomers are employed; one is dissolve in continuous phase while other is disperse in continuous phase (aqueous in nature) throughout which the second monomer is emulsified. Two conditions arise because of solubility of formed polymer in the emulsion droplet. That is formation is monolithic type of carrier if the polymer is soluble in droplet. Capsular type formed if the polymer is insoluble in droplet.

Normal Polymerization[2]

Proceeds using techniques like bulk, suspension precipitation, emulsion & micellar polymerization processes. In bulk polymerization, a monomer along with initiator is heated to initiate polymerization. Initiator is added to accelerate the rate of reaction. Drug is added during process of polymerization. The polymer so obtained is fragmented to microspheres.

Suspension Polymerization

Suspension polymerization is also called as bead/pearl polymerization. Carried out by heating the monomer or mixture of monomers with active principles (drug) as droplets dispersion in a continuous phase. The droplets may also contain an initiator & other additives. The emulsion polymerization differs from the suspension polymerization as due to presence of initiator in the aqueous phase, which later on diffuses to the surface of the micelles or the emulsion globules. The suspension & emulsion polymerization can be carried out at lower temperature since continuous external phase is normally water through which heat can easily dissipate. The processes also lead to the formation of higher molecular weight polymer at relatively faster rate.

Solvent Extraction Technique[10,18]

In this method preparation of micro particles, involves removal of the organic phase by extraction of the organic solvent. Isopropanol can be use as water miscible organic solvents. By extraction with water, Organic phase is removed. Hardening time of microsphere can be decrease by this method. 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**.**

Ionic Gelation Technique[19]

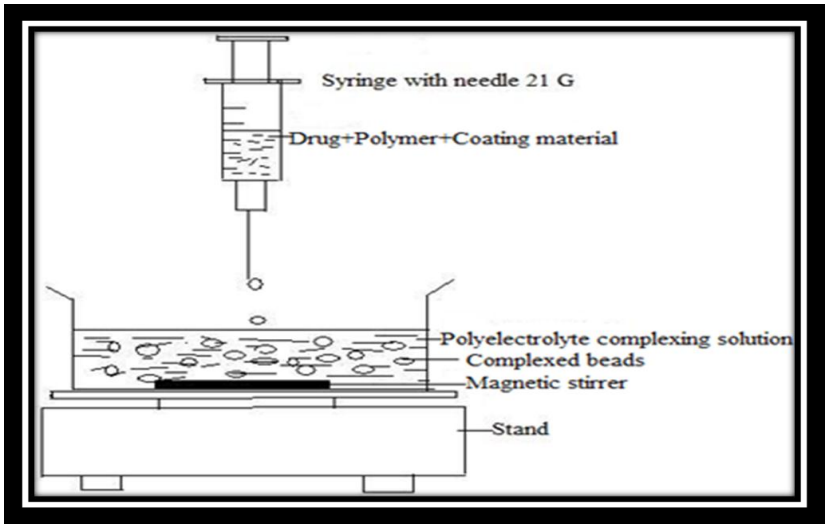


Fig no 4: Ionic Gelation Technique.

Microspheres were prepared by ionotropic gelation method. Initially, required quantity of sodium alginate was accurately weighed and dissolved in distilled water using mechanical stirrer. After some time, to this solution drug and polymer were added. The above solution was mixed thoroughly by means of mechanical stirrer. Then the solution was sonicated for about 30 min so as to remove air bubbles. After sonication, the solution was kept aside for 30 min. The resultant solution was dropped via a 23-gauge syringe needle (0.65 mm internal diameter) into 80 ml of 2% w/v calcium chloride (CaCl2) solution containing 5ml of acetaldehyde/formaldehyde as a hardning agent. Microspheres formed were washed with distilled water for 3 times. Then placed in aqueous solution of 1 % Formaldehyde for about 1 h. formaldehyde was used as a hardening agent. Finally, Microspheres were filtered and dried at room temperature.

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 carrier.[2]

Particle Size and Shape

The most widely used procedures to visualize micro particles are conventional light microscopy (LM) and scanning electron microscopy (SEM). Both can be used to determine

the shape and outer structure of micro particles. 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 LM.[6] SEM allows investigations of the microspheres surfaces and after particles are cross sectioned Confocal fluorescence microscopy is used for the structure characterization of multiple walled microspheres.[7] 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.

Electron Spectroscopy For Chemical Analysis

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 surface degradation of the biodegradable microspheres.[8]

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.

Density Determination

The density of the microspheress 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 microspheres carrier is determined.[9]

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 electrophoretic mobility can be related to surface contained charge, ionisable behaviour or ion absorption nature of the microspheres.

Angle of Contact

The angle of contact is measured to determine the wetting property of a micro particulate carrier. It determines the nature of microspheress 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.[4]

Entrapment Efficiency

The capture efficiency of the microspheres or the percent entrapment can be determined by allowing washed microspheress to lysate. 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

Drug Release

1) In Vitro Methods

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 physic-chemically and hydro dynamically defined conditions are necessary, 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 developed.[10]

2) Beaker Method

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 60-300rpm.

3) **Interface Diffusion System**

This method is developed by Dearden & Tomlinson. It consists of four compartments. 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.[3]

4) **Modified Keshary Chien Cell**

A specialized apparatus was designed in the laboratory. It comprised of a Keshary Chien cell containing distilled water (50ml) at 370 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.[11]

5) **Dissolution Studies**

Standard USP or BP dissolution apparatus have been used to study *in vitro* release profiles using rotating elements, paddle and basket. Dissolution medium used for the study varied from 100- 500 ml and speed of rotation from 50-100 rpm.[2]

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 penetrate at the surface. The most widely used methods include *in vivo* studies using animal models, buccal absorption tests, and perfusion chambers for studying drug permeability.

a) 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. 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 analyzed.[12]

b) 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.[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". Such correlations allow one to develop product specifications with bioavailability.

Pharmaceutical Application of Microspheres

a. Vaccine delivery

b. Monoclonal antibodies

c. Imaging

d. Topical porous microsphere

e. Nasal drug delivery

f. Oral drug delivery

g. Targeting drug delivery

h. Gastroretentive controlled delivery system

i. Bio-medical application

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