

MICROSPHERES: A NOVEL DRUG DELIVERY SYSTEM AN OVERVIEW

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SUMMARY

Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature. Microspheres are particles between 0.1 and 200µm in size. A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. A Microsphere 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 tumour. Microspheres are spherical microparticles, and are used where consistent and predictable particle surface area is important. . A microsphere 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.

KEYWORDS: Microspheres, target site, specificity, novel drug delivery, controlled release.

INTRODUCTION

A 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 effects. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion ¹. 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. ²

MATERIALS USED

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 ³

A) **Synthetic Polymers:** divided into two types;

- 1) Non-biodegradable ^{4,5}- Acrolein,
Glycidyl methacrylate,
Epoxy polymers, etc.

2) Biodegradable (6)-Polyanhydrides,

Polyalkyl cyano acrylates

Lactides and glycolides and their copolymers.

B) Natural materials: obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates. ^{7,8}

i) Proteins (albumin, gelatin, collagen)

ii) Carbohydrate (starch, agarose, carrageenan)

iii) Chemically modified carbohydrates [poly (acryl dextran), Poly (acryl starch)]

Pre-requisites for ideal micro particulate carriers ³

The material utilized for the preparation of micro particulates should ideally fulfill the following prerequisites.

- 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

Polymeric microsphere ³

The various types of polymers are used for preparation of microspheress e.g.

- Albumin microspheress
- Gelatin microspheress
- Starch microspheress
- Dextran microspheress

- Poly lactide and poly glycolide microspheress
- Polyanhydride microspheress and polyphosphazene microspheress
- Chitosan microspheress
- Polysaccharides or lipid cross linked chitosan microspheress
- Carrageenan microspheress
- Alginate microspheress
- Poly (alkyl cyanoacrylate) microspheress.
-

ADVANTAGES OF MICROSPHERESS OVER SINGLE UNIT DOSAGE FORMS ⁹

- 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 tumour ¹⁰

DRUG LOADING AND DRUG RELEASE KINETICS

The active components are loaded over the microspheress principally using two methods, i.e. during the preparation of the microspheress or after the formation of the microspheress 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 microspheress.The release profile from the microspheress 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 microspheress is influenced by structure or micro-morphology of the carrier and the properties of the polymer itself.

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.

In order to study the exact mechanism of drug release from the microspheres, drug release data was analyzed according to Zero-order, First-order, Higuchi square root, Hixson Crowell and Peppas equation. The criterion for selecting the most appropriate model was chosen on the basis of goodness of fit test. ¹¹The zero-order kinetic (equation1) describes the systems in which the drug release rate is independent of its concentration. The first order kinetic describes the systems in which the drug release rate is concentration dependent. ¹²Higuchi described the release of drug from an insoluble matrix as a square root of the time-dependent process on the basis of Fickian diffusion. ¹³The Hixson Crowell cube root law describes the drug release from systems in which there is a change in the surface area and the diameter of particles present in the tablet. Peppas equation describes the release when more than one type of release phenomena could be involved or when the release mechanism is not well known. ¹⁴

$$R = k_0t \quad \dots\dots\dots(1)$$

$$\text{Log UR} = k_1 t^{2.303} \quad \dots\dots\dots(2)$$

$$R = k_2 t^{1/2} \quad \dots\dots\dots(3)$$

$$(\text{UR})^{1/3} = k_3t \quad \dots\dots\dots(4)$$

$$\log R = \log k_4 + n \log t \quad \dots\dots\dots(5)$$

Where R and UR are the released and unreleased percentages, respectively, at time t. And K₀, K₁, K₂, K₃ and K₄ are release rate constants for Zero order, First order, Higuchi, Hixson-Crowell and Peppas-Korsmeyer rate equations, respectively

METHODS OF PREPARATION

The choice of the technique mainly depends on the nature of the polymer used, the drug, the intended use, and the duration of therapy. Moreover, the method of preparation and its choice are equivocally determined by some formulation and technology related factors as mentioned below:

- The particle size requirement.
- The drug or the protein should not be adversely affected by the process.
- Reproducibility of the release profile and the method.
- No stability problem.
- There should be no toxic product(s) associated with the final product³

Different types of techniques are employed for the preparation of the microspheres using hydrophobic and hydrophilic polymers as matrix materials are,

1. **Single emulsion technique**

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.

2. **Double emulsion technique (Multiple emulsion)**

Double emulsion method of microsphere preparation involves the formation of the multiple emulsions or the double emulsion of type w/o/w (Fig.1.3) and is best suited to the water-soluble drugs, peptides, proteins and the vaccines. This method can be used with both the natural as well as the synthetic polymers. A number of hydrophilic drugs like leutinizing hormone releasing hormone (LH-RH) agonist, vaccines, protein/peptides and conventional molecules are successfully incorporated in to the microspheres using the method of double emulsion solvent evaporation/extraction.

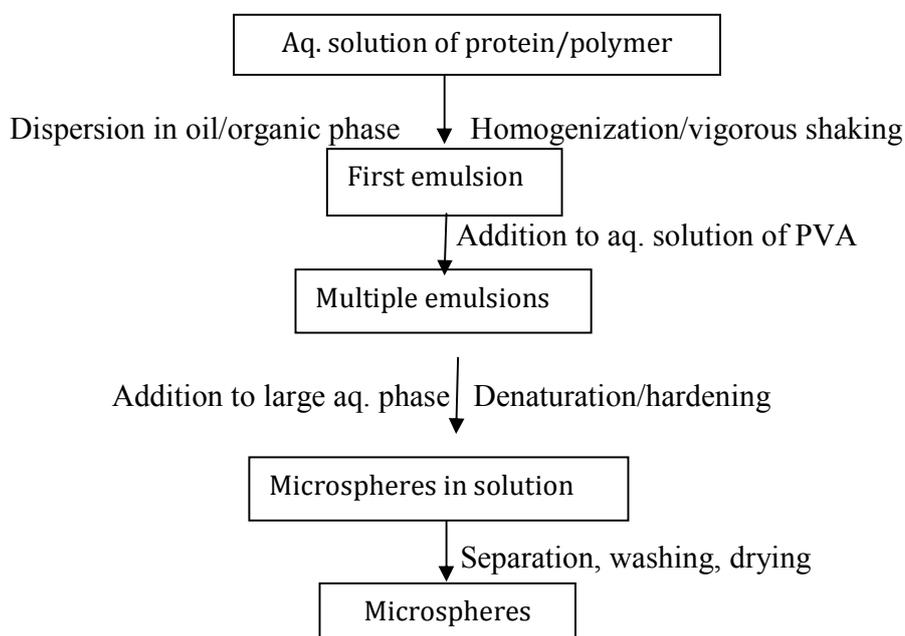


Figure 7: Schematic representation of double emulsion method of microsphere preparation.

3. Polymerization techniques

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.

3.1. 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.

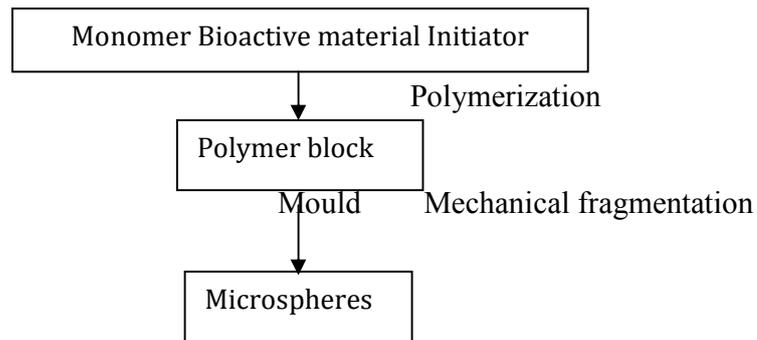


Figure 8: Schematic representation of bulk polymerization

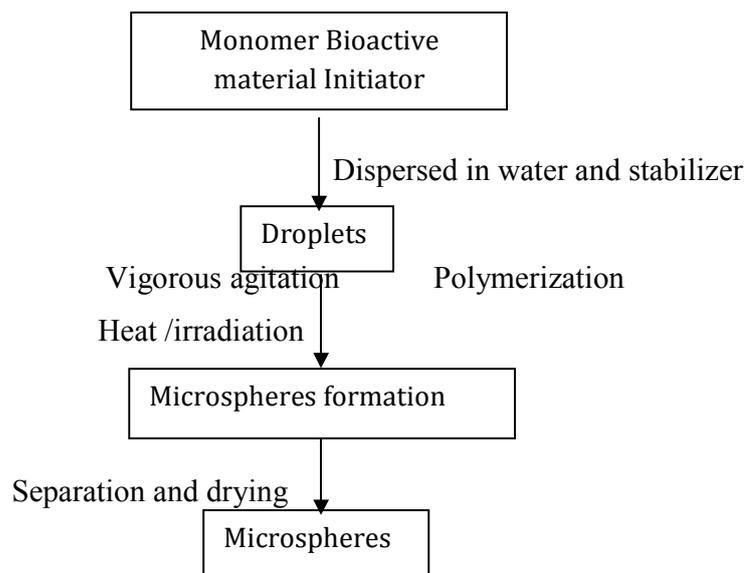


Figure 9: Schematic representation of suspension polymerization for microspheres formation.

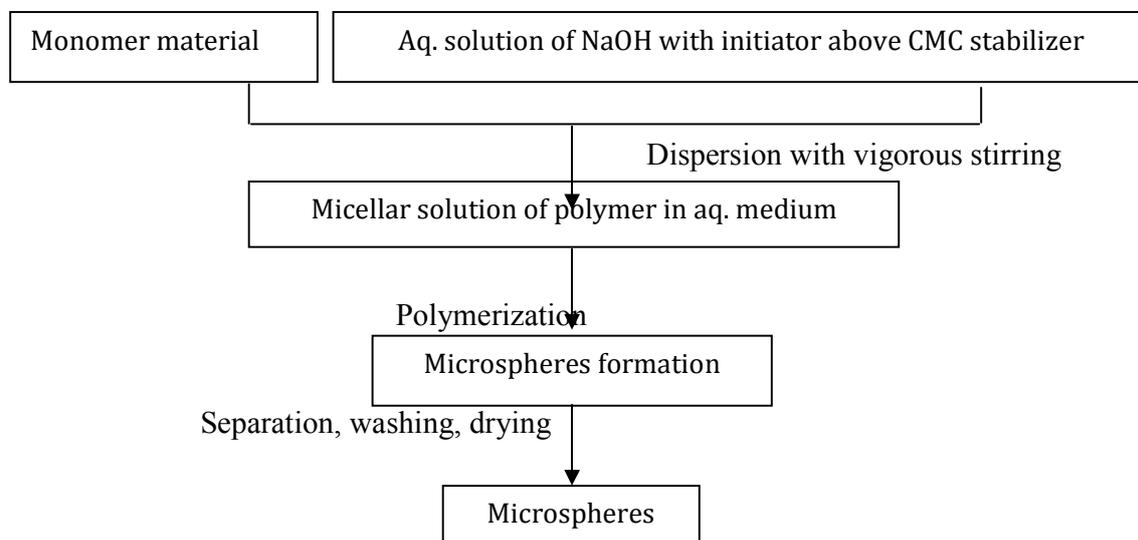


Figure 10: Schematic representation of emulsion polymerization

The bulk polymerization has an advantage of the formation of pure polymer, but it is very difficult to dissipate the heat of reaction, which can adversely affect the thermo labile active ingredients. On the other hand the suspension and emulsion polymerization can be carried out at lower temperature.

3.2. Interfacial polymerization

Interfacial polymerization essentially precedes involving 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. The monomers present in either phases diffuse rapidly and polymerize rapidly at the interface. Monomer droplet, the formed carrier is of capsular (reservoir) type. The interfacial polymerization is not widely used in the preparation of the microspheress because of toxicity associated with the unreacted monomer, high permeability of the film, high degradation of the drug during the polymerization, fragility of microcapsules, non-biodegradability of the microspheress.

4. Phase separation coacervation technique

The process is based on the principle of decreasing the solubility of the polymer in the organic phase to affect the formation of the polymer rich phase called coacervates. The coacervation can be brought about by addition of the third component to the system which results on the formation of the two phases, one rich in the polymer while the other one, i.e. supernatant, depleted of the polymer. The methods are based on salt addition, non-solvent addition, addition of the incompatible polymer or change in pH.

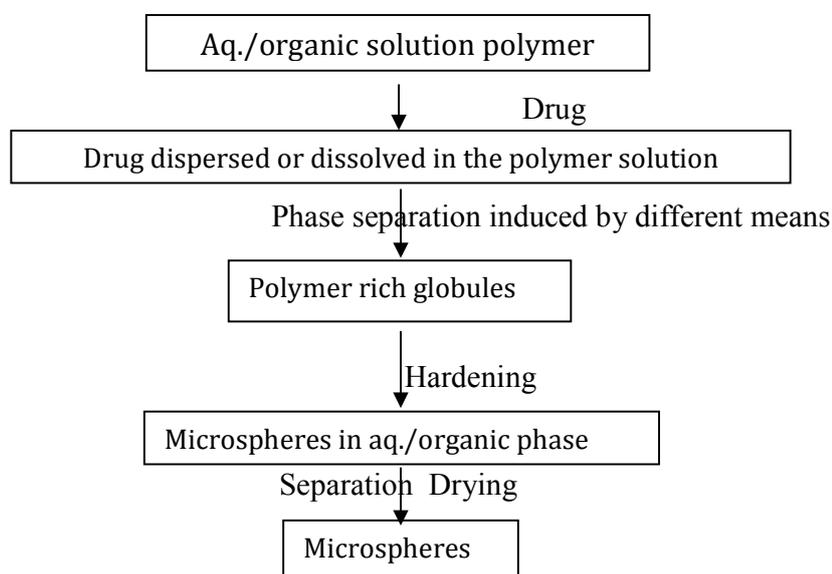


Figure 11: Schematic representation of microspheres formation by phase separation method.

5. Spray drying

These methods are based on the drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively. The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high-speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or

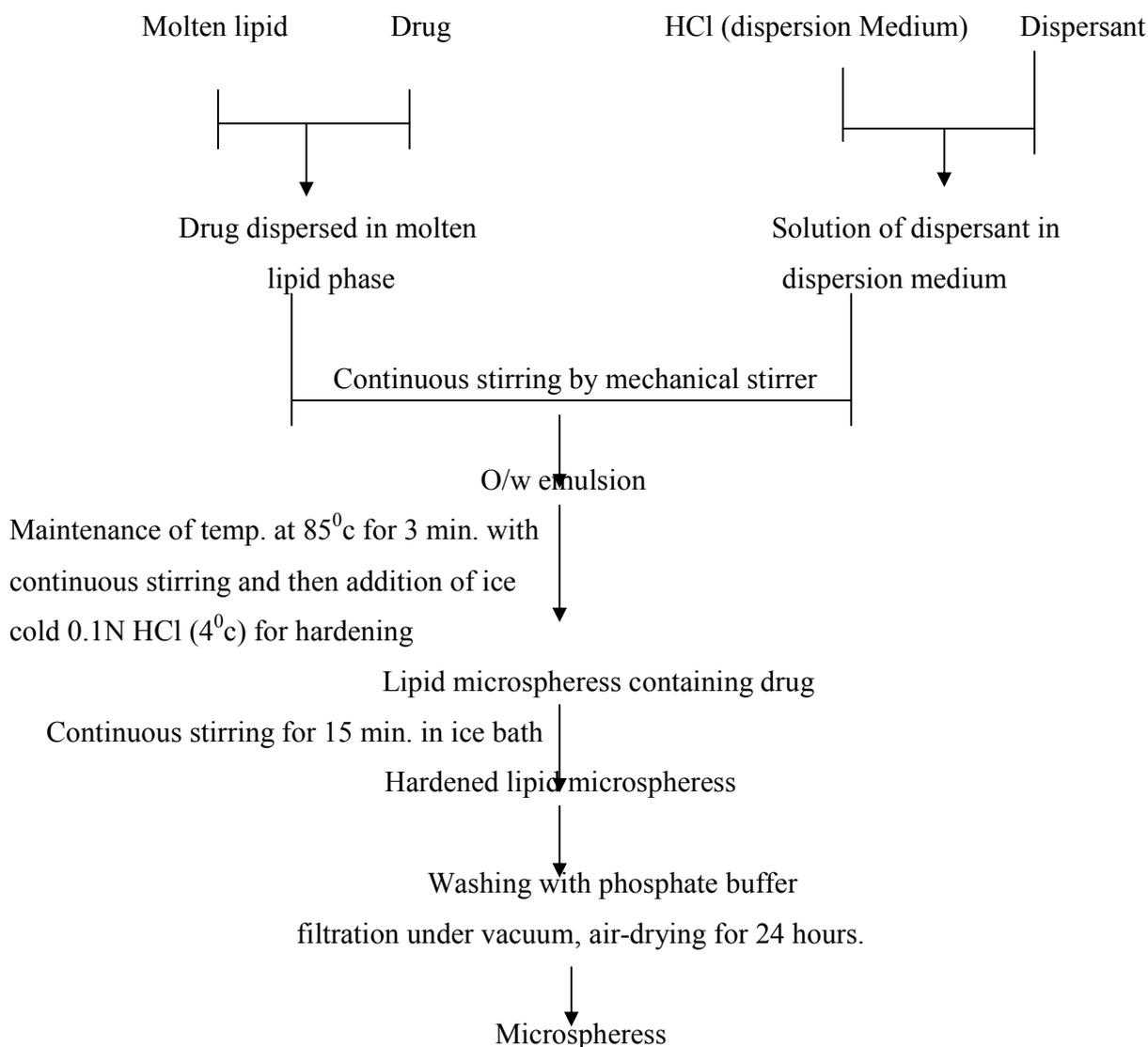
the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheres in a size range 1-100 μm . Microspheres are separated from the hot air by means of the cyclone separator while the traces of solvent are removed by vacuum drying. One of the major advantages of the process is feasibility of operation under aseptic conditions. The spray drying process is used to encapsulate various penicillins. Thiamine mononitrate and sulphathiazole 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 microspheres.

6. Non-aqueous solvent evaporation method

In these methods the polymer is dissolved in an organic solvent such as dichloromethane, chloroform, alcohol or ethyl acetate, either alone or in combination. The drug is either dissolved or dispersed into the polymer solution and this solution containing the drug is emulsified into an aqueous phase to make oil in water emulsion by using a surfactant or an emulsifying agent. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature or by continuous stirring. Solvent evaporation for preparation of embryonic microspheres under pressure or by continuous stirring, determines the size and morphology of the microspheres. It had been reported that the rapid removal of the solvent from the embryonic microspheres leads to the precipitation at the o/w interface. This leads to the formulation of cavity in the microspheres, making them hollow ¹⁵

7. Melt dispersion technique (Congealable dispersed phase encapsulation procedures)

In this technique, the drug is dissolved/ dispersed in the molten lipid/wax like beeswax, spermaceti wax, castor wax, carnauba wax under continuous stirring to form a homogeneous blend. During the emulsion step of microsphere preparation, the temperature is maintained at about 10 $^{\circ}\text{C}$ above the melting point of lipid/wax. A dispersant solution, previously heated to 5 $^{\circ}\text{C}$ above the lipid/wax melting point, is added to the melt with constant stirring to form an o/w emulsion. Hardening of the oily internal phase (containing lipid/wax and drug) and formation of microspheres is accomplished by pouring twice the emulsion volume of ice-cold water into the emulsion.



PHYSICOCHEMICAL EVALUATION

Characterization

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

Particle size and shape

The most widely used procedures to visualize microspheress are conventional light microscopy (LM) and scanning electron microscopy (SEM). Both can be used to determine the shape and outer structure of microspheress.

LM provides a control over coating parameters in case of double walled microspheress. The microspheress structures can be visualized before and after coating and the change can be measured microscopically.

SEM provides higher resolution in contrast to the LM ¹⁷. SEM allows investigations of the microspheress surfaces and after particles are cross-sectioned, it can also be used for the investigation of double walled systems.

Confocal fluorescence microscopy is used for the structure characterization of multiple walled microspheress¹⁸

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 microspheress.

Density determination:

The density of the microspheress can be measured by using a multi volume pycnometer. Accurately weighed sample in a cup is placed into the multi volume pycnometer. 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. ¹⁹

Isoelectric point:

The micro electrophoresis is an apparatus used to measure the electrophoretic mobility of microspheress 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 microspheress.

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 microspheress²⁰

Electron spectroscopy for chemical analysis:

The surface chemistry of the microspheress 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 microspheress.

Fourier Transform-Infrared Spectroscopy:

FT-IR is used to determine the degradation of the polymeric matrix of the carrier system. The surface of the microspheress 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 ATR- FTIR provides information about the surface composition of the microspheress depending upon manufacturing procedures and conditions²¹

Entrapment efficiency:

The capture efficiency of the microspheress 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:

$$\% \text{ Entrapment} = \text{Actual content} / \text{Theoretical content} \times 100$$

IN VITRO METHODS

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 physicochemically 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

Beaker method²²⁻²⁴

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.

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 with drawn and returned to compartment A with a syringe.

Modified Keshary Chien Cell²⁵

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.

Dissolution apparatus

Standard USP or BP dissolution apparatus have been used to study in vitro release profiles using rotating elements, paddle ²⁶ and basket ²⁷ Dissolution medium used for the study varied from 100-500 ml and speed of rotation from 50-100 rpm.

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.

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. A number of animal models have been reported in the literature, however, very few in vivo (animal). Animal models such as the dog ²⁸, rats ²⁹, rabbits ³⁰, cat ³¹, hamster ³², pigs ³³, and sheep³⁴ 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 analyzed.

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 ³⁵

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.

APPLICATIONS

1. Microspheress in vaccine delivery

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 issue³⁷. 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 vaccines³⁸. 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.
4. Targeting using microparticulate carriers

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.

2. Chemoembolisation

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.

3. Surface modified microspheress

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 microspheress renders them more hydrophilic and hence decrease their MPS uptake. Protein microspheress 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 microspheress in order to achieve the targeting to the discrete organs and to avoid rapid clearance from the body.

4. Monoclonal antibodies mediated microspheress targeting

Monoclonal antibodies targeting microspheress are immunomicrospheress. 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 microspheress loaded bioactive molecules to selected sites. Mabs can be directly attached to the microspheress by means of covalent coupling. The free aldehyde groups, amino groups or hydroxyl groups on the surface of the microspheress can be linked to the antibodies. The Mabs can be attached to microspheress by any of the following methods

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

5. Imaging

The microspheres have been extensively studied and used for the targeting purposes. Various cells, cell lines, tissues and organs can be imaged using radio 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 scintigraphic imaging of the tumour masses in lungs using labeled human serum albumin microspheres.

6. Topical porous microspheres

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 carriers 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 manner³⁹.

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 microsphere 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.

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