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Review Article

MICROSHERES – A REVIEW

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ABSTRACT

Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers having a particle size ranging from 1-1000 µm. 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 also known as microparticles. 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. The nasal mucosa has also received attention as a viable means of systemic administration of analgesics, sedatives, hormones, cardiovascular drugs, and vaccines.

Keyword: Microspheres, Microparticles, Matrix, Novel drug delivery.

INTRODUCTION

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm). Microspheres are sometimes referred to as microparticles. Microspheres can be manufactured from various natural and synthetic materials. The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration [1]. The most convenient and commonly employed route of drug delivery has historically been by oral ingestion. Microspheres are defined as "monolithic spheres or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles" or can be defined as structure made up of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level. It has a particle size less than 200 µm. 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 pharmacodynamics behaviour may lead to enhanced therapeutic efficiency. However, an intelligent approach to therapeutics employing drug carriers phenomenon requires a detailed understanding of the carrier interaction with cellular and organ systems and of the limitations of the systems with respect to the formulation procedures and stability issues. A variety of substances have been used as drug carrier, including immunoglobulins serum proteins, liposomes, microspheres, microcapsules, nanoparticles and even cells such as erythrocytes. **[1][3]**Polyethylene and polystyrene microspheres are two most common types of polymer microspheres. Polystyrene microspheres are typically used in biomedical applications due to their ability to facilitate procedures such as cell sorting and immuno precipitation. Proteins and ligands adsorb onto polystyrene readily and permanently, which makes polystyrene microspheres suitable for medical research and biological laboratory experiments. Polyethylene microspheres are commonly used as permanent or temporary filler. Lower melting temperature enables polyethylene microspheres to create porous structures in ceramics and other materials. High sphericity of polyethylene microspheres, as well as availability of colored and fluorescent microspheres, makes them highly desirable for flow visualization and fluid flow analysis, microscopy techniques, health sciences. 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 effects. 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 proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 µm.[1-3]

Table 1: Properties of microspheres

Properties	Consideration[4,5]
Size	Diameter
	Uniformity/distribution
Composition	Density
	Refractive index
	Hydrophobicity/hydrophilicity
	Nonspecific binding
	Autofluorescence
Surface chemistry	Reactive groups
	Level of functionalization
	Charge
Special properties	Visible dye/fluorophore
	Super-paramagnetic

ADVANTAGES

- Microspheres provide constant and prolonged therapeutic effect.
- Reduces the dosing frequency and thereby improve the patient compliance.
- They could be injected into the body due to the spherical shape and smaller size.
- Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
- Microsphere morphology allows a controllable variability in degradation and drug release.[6,7]

LIMITATIONS

Some of the disadvantages were found to be as follows:

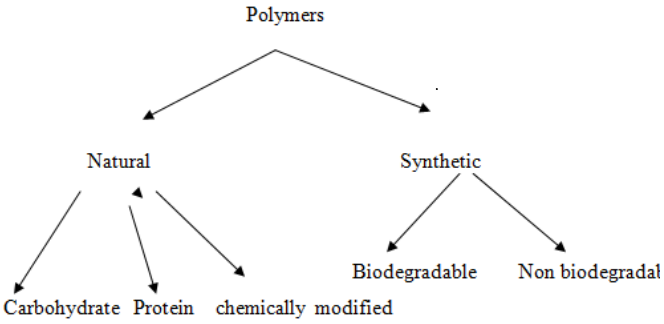
- The modified release from the formulations.
- The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit though gut.
- Differences in the release rate from one dose to another.
- Controlled release formulations generally contain a higher 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 cannot be crushed or chewed[8,9]

Materials used in the preparation of Microsphere

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

1. Natural polymers

2. Synthetic Polymers



- Natural polymers obtained from different sources
- Carbohydrates**:** Agarose, Carrageenan, Chitosan,[10-12]

Starch

- Proteins**:** Albumin, Collagen and Gelatin
- Chemically modified carbohydrates: Poly dextran, Poly starch.
- Synthetic polymers are divided into two types.
- Biodegradable polymers
- E.g. Lactides, Glycolides & their co polymers,Poly anhydrides,Poly alkyl cyano acrylates

Non-biodegradable polymers

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

Synthetic polymers [13]

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

Natural polymers

Albumin is widely distributed natural protein .This is considered as a potential carrier of drugs or proteins (for their site specific localization). It is widely used for the targeted drug delivery to the tumour cells in cancer. Gelatin microspheres can be used as carrier system capable of delivering the drugs or biological response modifiers as interferon to phagocytes. Starch, polysaccharide belongs to carbohydrate class. It consists of glucopyranose as principle unit, which on hydrolysis yields D-glucose. Starch,being a poly saccharide consists of a large number of free hydroxyl groups. By means of these free hydroxyl groups a large number of active substances can be incorporated within as well as active on surface of microspheres. Chitosan is a deacylated product of chitin. The chitosan effect has been considered because of its Charge. It is insoluble at neutral and alkaline pH values, but it forms salts with inorganic and organic salts. Upon dissolution, the amino groups of chitosan get hydrogenated, and the resultant polymer gets positively charged.[14]

Microspheres should satisfy certain criteria as follows:

- 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.[15,16]

TYPES OF MICROSPHERES

1. Bio-adhesive microspheres

Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc can be termed as bio adhesion. These kinds of microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action.[17]

2. Magnetic microspheres

This kind of delivery system is very much important which localises 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.[18]

3. Therapeutic magnetic microspheres

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

4. Diagnostic microspheres

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

5. 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 gasteric content and increases gastric residence and increases fluctuation in plasma concentration. Moreover it also reduces chances of striking and dose dumping. One another way it produces prolonged therapeutic effect and therefore reduces dosing frequencies. Drug (ketoprofen) given through this form.

6. Radioactive microspheres

Radio emobilisation 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 tumour of interest. So all these conditions radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues.[9]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 microsphers are α emitters, β emitters, γ emitters.

7. Polymeric microspheres

The diffenttypes of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and Synthetic polymeric microspheres.

8. Biodegradable polymeric microspheres

The natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also bio adhesive in nature. Biodegradable polymers prolongs the residence time when contact with mucous membrane due toit's high degree of swelling property with aqueous medium , results gel formation. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner. The main drawback is, in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release. However they provide wide range of application in microsphere based treatment[19,20]

9. Synthetic polymeric microspheres

The interest of synthetic polymeric microspheres are widely used in clinical application, moreover that also used as bulking agent, fillers, embolic particles, drug delivery vehicles etc and proved to be safe and biocompatible. But the main disadvantage of these kind of microspheres, are tend to migrate away from injection site and lead to potential risk,

embolism and further organ damage. Different kinds of polymers used for microspheres.[21]

Pharmaceutical applications of microspheres

- Gene therapy with DNA plasmids and also delivery of insulin
- Vaccine delivery for treatment of diseases like hepatitis, influenza, pertusis, ricin toxoid, diphtheria, birth control..
- Tumour targeting with doxorubicin and also treatments of leishmaniasis.
- Magnetic microspheres can be used for stem cell extraction and bone marrow purging.
- Used in isolation of antibodies, cell separation, and toxin extraction by affinity chromatography.

As Monoclonal antibodies are extremely specific molecules, this extreme specificity of monoclonal antibodies can be utilized to target these microspheres to selected site.

- Used for various diagnostic tests for infectious diseases like bacterial, viral, and fungal.
- Passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens, by intra arterial/ intravenous application.
- Release of proteins, hormones and peptides over extended period of time.[22,23]

Application of microspheres in pharmaceutical industry

- 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 condition
- 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

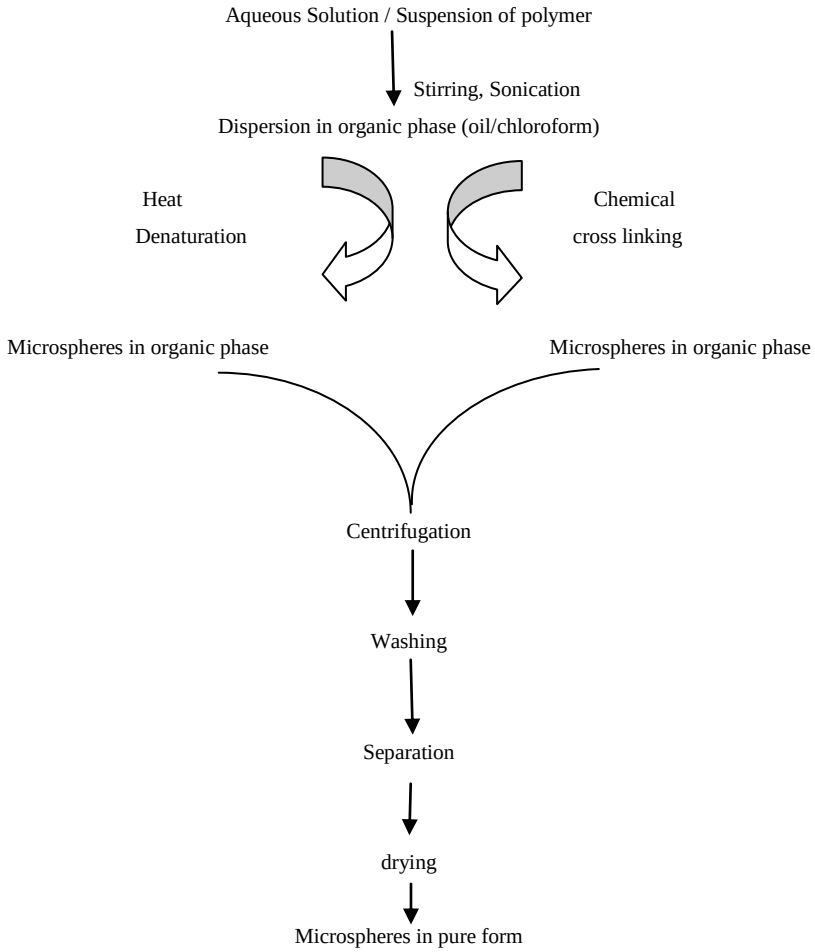
Methods of preparation

1. Single emulsion technique

The microparticulate carriers of natural polymers i.e. those of carbohydrates and proteins carbohydrates are prepared by single emulsion technique. The chemical cross linking agents used are as followings:

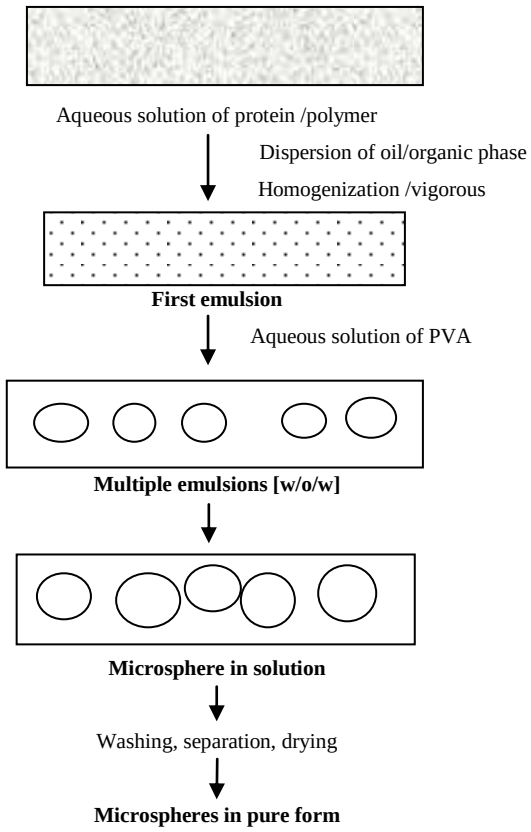
- glutaraldehyde,
- formaldehyde

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



Double emulsion technique

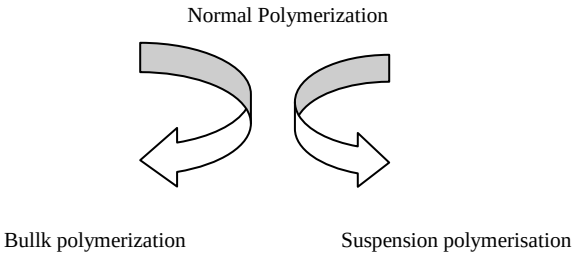
This method of microspheres preparation involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited to aqueous soluble drugs, peptides, proteins and the vaccines. This method can be used with both the polymers. The aqueous protein solution is dispersed in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



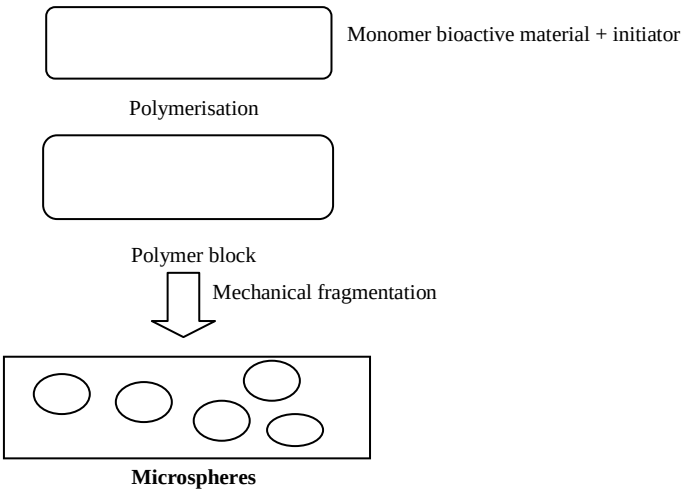
3. Polymerization techniques

The polymerization techniques conventionally used for preparing the microspheres are mainly classified as:

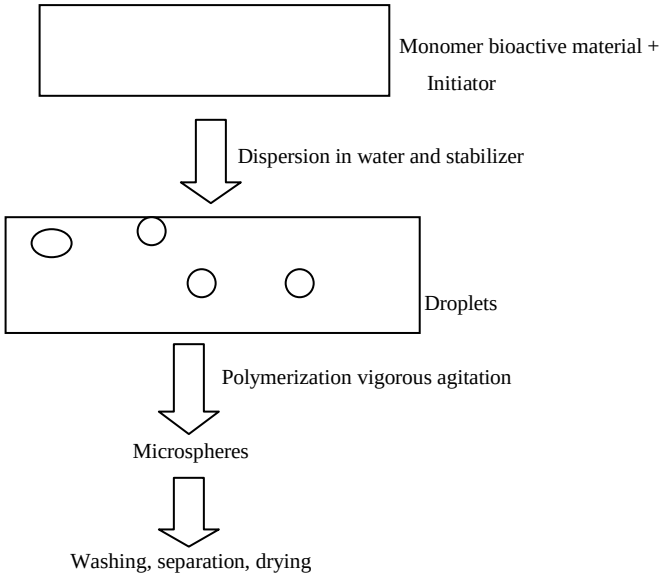
I. Normal polymerization



1.Bullk polymerization



2. Suspension polymers



II. Interfacial polymerization.

Both are carried out in liquid phase.

Normal polymerization

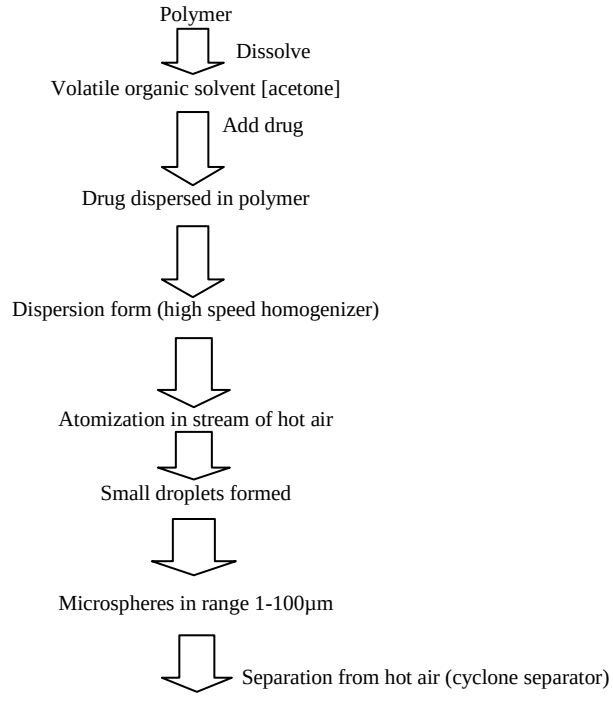
It is carried out by using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization methods. In bulk, a monomer or a composition of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres. Drug loading may be done during the polymerization process. Suspension polymerization also referred as bead or pearl polymerization. It is carried out by heating the monomer or composition of monomers as droplets dispersion in a continuous aqueous phase. Droplets may also contain an initiator and other additives. Emulsion polymerization deviates from suspension polymerization as due to the presence initiator in the aqueous phase, which afterwards diffuses to the surface of micelles. Bulk polymerization has merits of formation of pure polymers.

Interfacial polymerization

This involves the reaction of various monomers at the interface between the two immiscible liquids to form a film of polymer that essentially envelops the dispersed phase [24]

Spray drying and spray congealing

These methods are based on drying of the mist of the polymer and drug in the air. Depending on the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing. One of the major merits of the process is feasibility of process under aseptic conditions. Spray drying process is used to encapsulate various penicillins. Thiamine mononitrate and sulpha **ethylthiadizole are encapsulated in a composition of mono- and di** glycerides of palmitic acid and stearic acid using spray congealing. Very rapid solvent evaporation, however leads to the formation of porous microparticles.



Phase separation coacervation technique

This method based on the principle of decreasing the solubility of the polymer in nonaqueous phase to affect the formation of polymer rich phase called the coacervates. Here, the drug particles are dispersed in the solution of the polymer and an incompatible polymer is then added to the system which makes first polymer to separate and engulfment of the drug particles. Addition of organic results in the solidification of polymer. Poly lactic acid (PLA) microspheres have been manufactures by this method by using butadiene as incompatible polymer. The process variables are very useful because the rate of achieving the coacervates denotes the distribution of the polymer film, the size of particles and agglomeration of the formed particles. [25]The agglomeration must be avoided by continuous stirring of the suspension using a optimum speed stirrer because as the process of microspheres formation starts the formed polymerize globules start to stick and form the agglomerates. So the process variables are critical as they control the kinetic of the particles because there is no defined state of equilibrium attainment.

Solvent extraction

Solvent evaporation method is used for manufacturing of microparticles, involves removal of the organic phase by extraction. This method involves water miscible organic solvents as isopropanol. Organic phase can be removed by extraction with water. This process decreases the\hardening time for the microspheres. One variation of the process involves direct incorporation of the drug or protein to polymer organic solution. Rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and solubility profile of polymer**.**

Quassi emulsion solvent diffusion [21]

A novel quasi-emulsion solvent diffusion method to manufacture the controlled release microspheres of drugs with acrylic polymers has been reported in the literature. Microsponges can be manufactured by a quasi-emulsion solvent diffusion method using an external phase containing distilled water and polyvinyl alcohol. The internal phase is consisting of drug, ethanol and polymer is added at an amount of 20% of the polymer in order to enhance plasticity. At first, the internal phase is manufactured at 60ºC and then added to the external phase at room temperature. After emulsification process, the mixture is continuously stirred for 2 hours. Then the mixture can be filtered to separate the microsponges. The product is then washed and dried by vacuum oven at 40ºC for concentration.[1][2]

EVALUATION PARAMETERS

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 microspheres have different microstructures. These microstructures determine the release and the stability of the carrier.

Particle size and shape

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 LM. 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.

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.

Attenuated total reflectance Fourier Transfom- 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 microspheres 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 microsphere carrier is determined.

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.

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. Contact angle is measured at 200C within a minute of deposition of microspheres.

***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 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 Volume of the medium used in the literature for the studies varies from 50-500 ml and the stirrer speed form 60-300 rpm. [26]

***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.

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 [27]

Swelling Index

Swelling index was determined by measuring the extent of swelling of microspheres in the given buffer. To ensure the complete equilibrium, exactly weighed amount of microspheres were allowed to swell in given buffer. The excess surface adhered liquid drops were removed by blotting and the swollen microspheres were weighed by using nmicrobalance. The hydrogel microspheres then dried in an oven at 60° for 5 h until there was no change in the dried mass of sample. The swelling index of the microsphere was calculated by using the formula

Swelling index= (mass of swollen microspheres – mass of dry microspheres/mass of dried microspheres) [28, 29]

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