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Review on Microsphere

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ABSTRACT

Microspheres are free-flowing powders made of proteins or synthetic polymers with particle sizes ranging from 1-1000 m. The variety of techniques for preparing microspheres provides a variety of options to regulate elements of medication delivery. administration and improve a specific drug's therapeutic effectiveness There are several methods to delivering a medicinal material to the target location in a regulated and continuous manner fashion should be released. It is a dependable method for delivering the medication to the target location with specificity if adjusted and maintaining the appropriate concentration at the place of interest without causing side effects. Microspheres have gotten a lot of interest recently, not just for their long-term release, but also for their ability to direct anticancer medicines to the tumour. Microspheres will play a central role in novel drug delivery in the future, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted, and effective in vivo delivery, and supplements as miniature versions of diseased organs and tissues in the body, thanks to the combination of various other strategies.

INTRODUCTION

Drug delivery systems (DDS) can accurately regulate the rate of drug release or deliver medicines to a specific location.

The healthcare system has been greatly impacted by certain bodily sites. The perfect medication throughout the delivery system, the medication is delivered at a pace determined by the body's needs.

Therapy and only delivers the active ingredient to the action location. As a result, carrier technology by attaching the medication to a carrier particle such as a nanoparticle, offers an innovative method to drug delivery.

Microspheres, nanoparticles, liposomes, and other particles influence the release and absorption of substances, drug characteristics.1 Drug delivery systems come in a variety of shapes and sizes.

LIPOSOME is a kind of liposome.

• NIOSOME (National Institute of Health)

• NANOPARTICAL SYSTEM

MICROSPHERE

Natural and manmade materials can be used to create microspheres. Commercially accessible microspheres include glass, polymer, and ceramic microspheres. Solid and hollow microspheres have varying densities and are utilized for different purposes. Hollow microspheres are commonly utilized as additions to reduce a material's density. Solid microspheres may be used for a variety of things depending on the substance they're made of and the size they're made of. Microspheres made of polyethylene and polystyrene are the two most prevalent kinds of polymer microspheres. Polystyrene microspheres are commonly utilized in biomedical applications because they can make operations easier. Polystyrene microspheres are ideal for medical research and biological laboratory studies because proteins and ligands adsorb quickly and persistently on the material. Microspheres made of polyethylene are widely employed as permanent or temporary fillers. Lower melting temperature enables polyethylene microspheres to create porous structures in ceramics and other materials. The high sphericity of polyethylene microspheres, as well as the availability

of colored and fluorescent microspheres, makes them highly desirable for flow visualization and fluid flow analysis, microscopy techniques, health sciences, process troubleshooting, and numerous research applications.

Charged polyethylene microspheres are also used in electronic paper. digital displays. Glass microspheres are primarily used as filler for weight reduction, retro-reflector for highway safety, additive for cosmetics and adhesives, with limited applications in medical technology.

Ceramic microspheres are used primarily as grinding media. Microspheres vary widely in quality, sphericity, uniformity of particles, and particle size distribution. The appropriate microsphere needs to be chosen for each unique application. (2)

ADVANTAGES OF MICROSPHERES 3,4

1. They provide protection before after administration for the unstable drug.

2. They reduced the concentration of drugs at a site other than the tissue or the target organ.

3. Decrease dose and toxicity.

4. Particle size reduction for enhancing solubility of poorly soluble drugs.

5. Provide constant and prolonged therapeutic effects.

Materials Used

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

1. Synthetic Polymers

2. Natural polymers

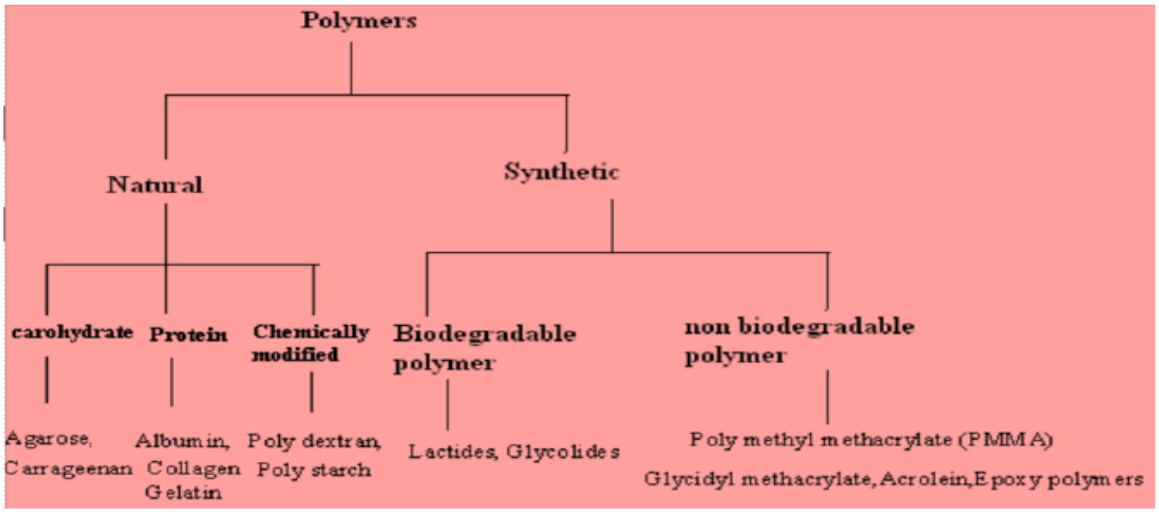

Figure No. 1: Polymers used in Microspheres Development

Synthetic polymers are divided into two types.

i. Non-biodegradable polymers

- Polymethyl methacrylate (PMMA)
- Acrolein
- Glycidyl methacrylate
- Epoxy polymers

ii. Biodegradable polymers**5, 6**

- Lactides, Glycolides & their copolymers
- Poly alkyl cyano Acrylates
- Poly anhydrides

Natural polymers are obtained from different sources like proteins, carbohydrates, and chemically modified carbohydrates.

A] Proteins:

- Albumin
- Gelatin9
- Collagen

B] Carbohydrates:

- Agarose
- Carrageenan
- Chitosan10
- Starch

C] Chemically modified carbohydrates:

- Poly dextran11
- Poly starch.

TYPES OF MICROSPHERES

1. Bioadhesive microspheres

2. Magnetic microspheres

3. Floating microspheres

4. Radioactive microspheres

5. Polymeric microspheres

I) Biodegradable polymeric microspheres

II) Synthetic polymeric microspheres

1. Bioadhesive microspheres (3,4,5)

The sticking of the drug to the membrane by using the sticking property can be defined as the Adhesion of water-soluble polymers. These types of microspheres exhibit a prolonged residence time at the site of application. Adhesion of the drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal, etc.

2. Magnetic microspheres (6,7)

This type of delivery system is very much important for localizing the drug to the disease site. site. In which a larger amount of freely circulating drug can be replaced by a small amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field.

3. Floating microspheres (6,8)

In floating microspheres the bulk density is less than the gastric fluid, therefore, it remains buoyant in the stomach without affecting the gastric emptying rate. The drug is released slowly at the desired rate of the site. it also reduces chances of striking and dose dumping Produces.

4. Radioactive microspheres (7)

Radio mobilization therapy microspheres having sizes 10-30 nm are larger than capillaries. They are injected into arteries which lead to the tumor of interest. These radioactive microspheres deliver a high radiation dose to targeted areas without damaging the normal tissues. Different types of radioactive microspheres are α emitters, β emitters, γ emitters.9

5. Polymeric microspheres

The different types of polymeric microspheres classified as

I) Biodegradable polymeric microspheres (6,7)

Natural polymers such as starch are used as the concept that they are biodegradable, biocompatible, and also Bioadhesive in nature. This polymer prolongs the residence time when contact with mucous membrane due to its high degree of swelling property with an aqueous medium, resulting in getting gel formation.

II) Synthetic polymeric microspheres (8,9,10,11)

Synthetic polymeric microspheres are widely used in clinical applications, that are also used as bulking agents, fillers, embolic particles, and drug delivery vehicles, etc. and proved to be safe and biocompatible but the disadvantage of this kind of microspheres, are tend to migrate away from the injection site and lead to potential risk, embolism, further organ damage.

Preparation of microspheres should satisfy certain criteria:

1. The ability to incorporate reasonably high concentrations of the drug.

2. Stability of the preparation after synthesis with a clinically acceptable shelf life.

3. Controlled particle size and dispersibility in aqueous vehicles for injection.

4. Release of the active reagent with good control over a wide time scale.

5. Biocompatibility with a controllable biodegradability and

6. Susceptibility to chemical modification.

METHOD OF PREPARATION

1. Spray Drying

2. Solvent Evaporation

3. Single emulsion technique

4. Double emulsion technique

5. Phase separation coacervation technique

6. Spray drying and spray congealing

7. Solvent extraction

8. Quasi emulsion solvent diffusion:

1. Spray Drying (3)

In the Spray Drying technique, the polymer is first dissolved in a volatile organic solvent such as dichloromethane, acetone, etc. The drug in solid form is then dispersed in polymeric solution with high-speed homogenization. This dispersion is then atomized in the hot air stream. The atomization leads to the form the small droplets from which the solvent evaporates instantly lead the formation of the microspheres in the size range 1-100µm. Microparticles are separated from hot air by the cyclone separator while the trace of solvent is removed by vacuum drying. the major advantage of this process is the feasibility of operation under aseptic conditions.

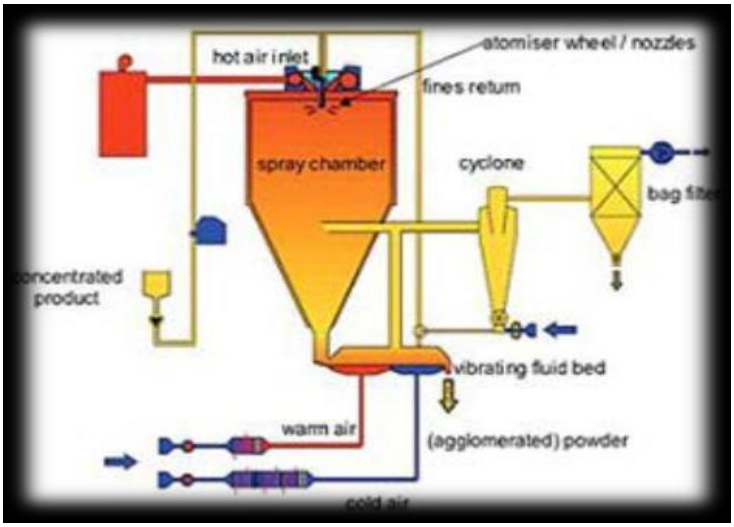

Figure No. 2: Spray Drying

2. Solvent Evaporation: (12,13,)

This process is carried out in the vehicle phase of liquid manufacturing. The microcapsule coating is dispersed in the volatile solvent which is immiscible with the vehicle phase of liquid manufacturing. A core material that is microencapsulated is dissolved in the coating polymer solution. Agitation With the core material mixture is dissolved in the liquid manufacturing vehicle phase to obtain appropriate size microcapsule. Then the mixture is heated if necessary to evaporate and the solvent for the polymer of the core material is dissolved in the polymer solution, around the core polymer shrinks. If core material is dissolved in the coating polymer solution, matrix-type microcapsules are formed. The core materials are either water-soluble or soluble.

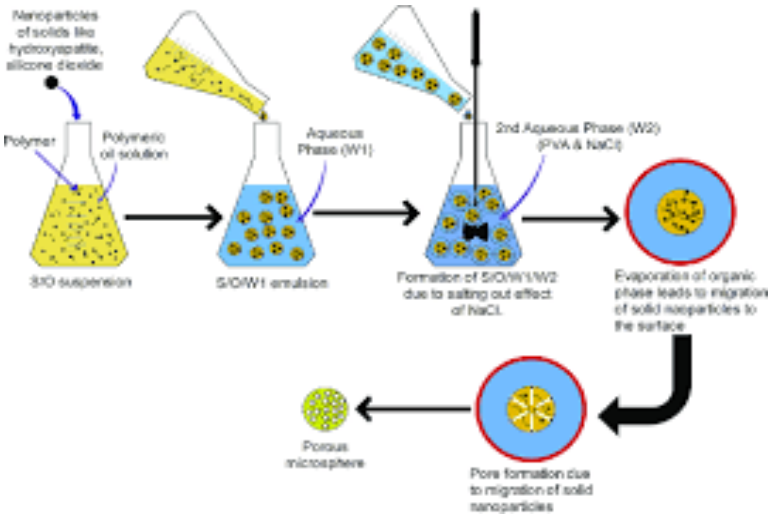

Figure No. 3: Solvent Evaporation

3. Single emulsion technique (3)

The microparticulate carriers of the natural polymers i.e. proteins and carbohydrates are prepared by the single emulsion technique. Natural polymers are dissolved in an aqueous medium which is followed by dispersion in a non-aqueous medium like oil. In the next step, the cross-linking of dispersed globules is carried out. The cross-linking can be achieved by heat or by using chemical cross-linkers. T chemical cross-linking agents used are glutaraldehyde, formaldehyde, acid chloride. Heat denaturation is not suitable for the thermolabile substance. Chemical cross-linking has the disadvantage of excessive exposure of active ingredients to chemicals if added at time of preparation and then subjected to centrifugation, washing, separation, nature of the surfactants used to stabilize the emulsion phases can be greatly influenced by the size, size distribution, surface morphology and loading drug release, and bio per-performance of the final multiparticulate product.

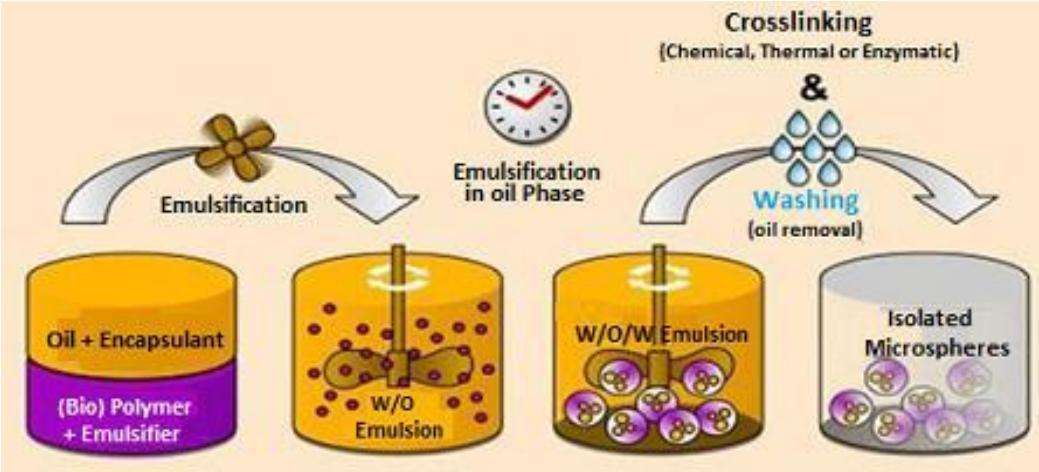

Figure No. 4: Single emulsion technique

4. Double emulsion technique:(14)

This method of microspheres preparation involves the formation of multiple emulsions or double emulsions of type w/o/w and is best suited to water-soluble drugs, peptides, proteins, and vaccines. This method can be used with both natural as well as synthetic polymers. The aqueous protein solution is dispersed in the lipophilic organic continuous phase. This protein solution may contain active constituents.

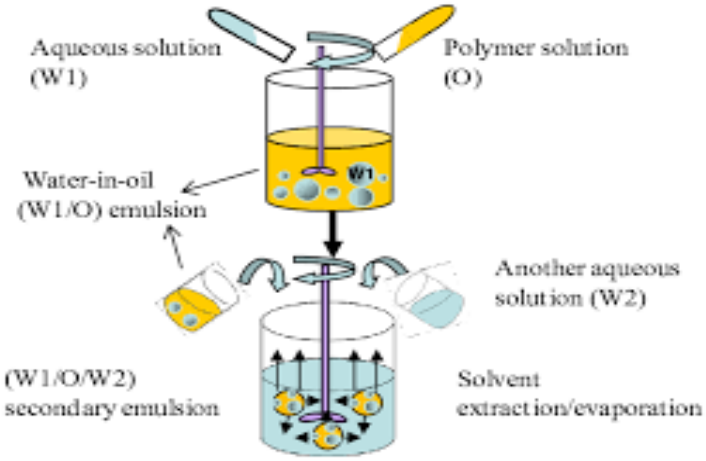

Figure No. 5: Double emulsion technique

5. Phase separation coacervation technique: (3)

This process is based on the principle of decreasing the solubility of the polymer in the organic phase which affects the formation of the polymer-rich phase called the coacervates. In this method, drug particles are dispersed in a solution of polymer and an incompatible polymer is added to the system which makes the first polymer for the phase separation.

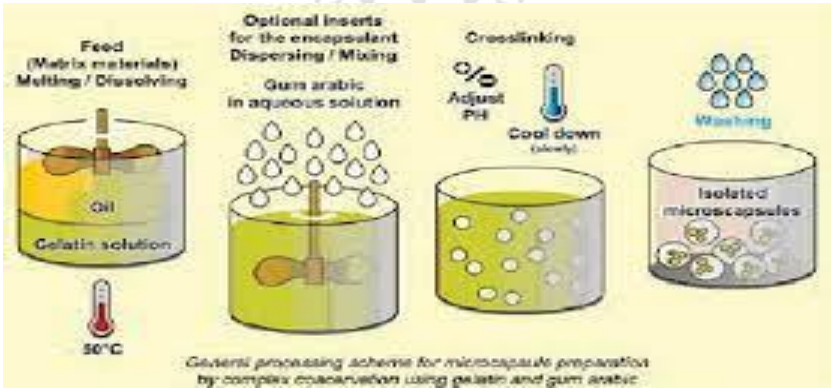

Figure No. 6: Phase separation coacervation technique

6. Spray drying and spray congealing: (15)

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

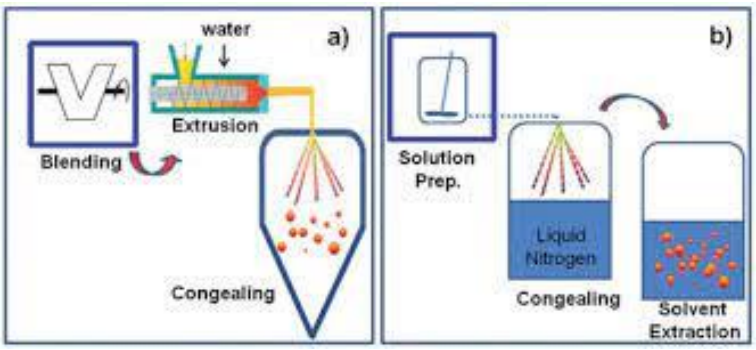

Figure No. 7: Spray drying and spray congealing

7 Solvent extraction: (3)

The solvent evaporation method is used for the manufacturing of microparticles and involves the removal of the organic phase by extraction of the non-aqueous solvent. This method involves the water-miscible organic solvent which is isopropanol.

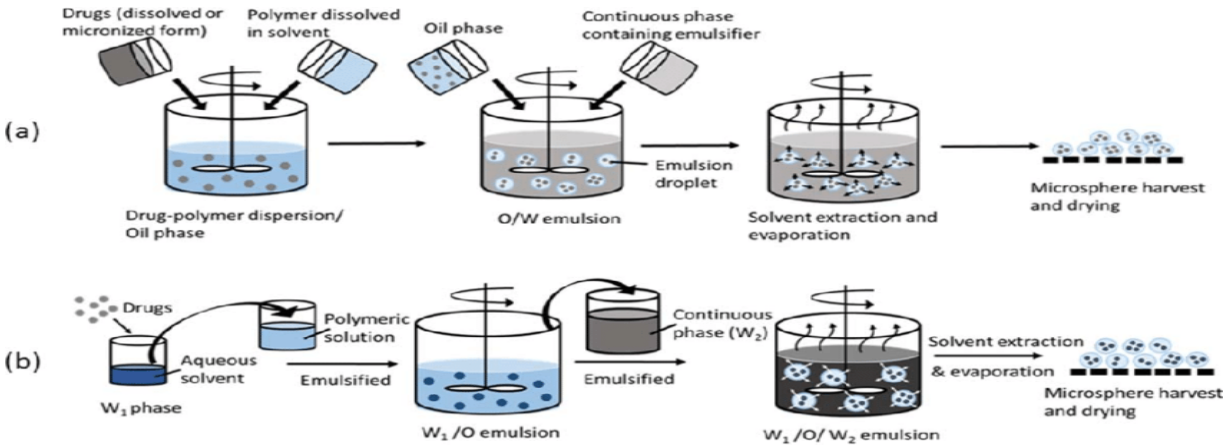

Figure No. 8: Solvent extraction

8 Quasi emulsion solvent diffusion: (15, 16)

A novel quasi-emulsion solvent diffusion method used for the manufacturing of the controlled release microspheres of drugs with acrylic polymers has been reported in the literature. Microsponges can be manufactured by the quasi emulsion solvent diffusion method by using an external phase that contains distilled water and polyvinyl alcohol. The internal phase consists of the drug, ethanol, and polymers. Firstly, the internal phase is manufactured at 60ºC and then added to the external phase at room temperature. Then emulsification the mixture is continuously stirred for 2 hours. Then the mixture can be filtered to separate the microsponges.

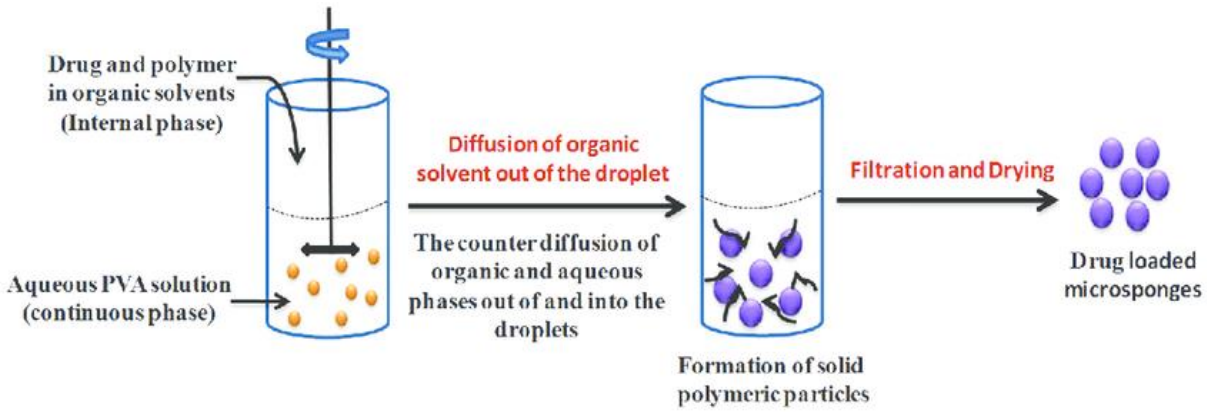

Figure No. 9: Quassi emulsion solvent diffusion

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 stability of the carrier. (17)

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 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 a higher resolution in contrast to the LM. SEM allows investigations of the microspheres surfaces and after particles are cross-sectioned. (18)

Electron spectroscopy for chemical analysis

The surface chemistry, atomic composition of surface and surface degradation of biodegradable microspheres can be determined using electron spectroscopy for chemical analysis (ESCA).

Attenuated total reflectance Fourier Transform 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 by measuring alternated total reflectance (ATR). The ATR-FTIR 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

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, ionizable behaviour, or ion absorption nature of the microspheres.

Surface carboxylic acid residue

The surface carboxylic acid residue is measured by using radioactive glycine. The radioactive glycine conjugates are prepared by the reaction of C14-glycine ethyl ester hydrochloride with the microspheres. The radioactivity of the conjugate is then measured using a liquid scintillation counter. Thus, the carboxylic acid residue can be compared and correlated.

Surface amino acid residue

The 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.

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 the monograph requirement. The percent encapsulation efficiency is calculated using the following equation:

% Entrapment = Actual content/Theoretical content x 100

Angle of contact

The angle of contact is measured to determine the wetting property of a microparticulate carrier. It determines the nature of microspheres in terms of hydrophilicity or hydrophobicity. The angle of contact is measured at the solid/air/water interface.

Drug release

 In vitro **methods**

In vitro, drug release studies have been employed as a quality control procedure in pharmaceutical production, product development, etc. Sensitive and reproducible release data derived from physic-chemically and hydrodynamically 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. (18)

 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 an overhead stirrer. The volume of the medium used in the literature for the studies varies from 50-500 ml and the stirrer speed from 60-300 rpm.

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. 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 was saturated with each other. Samples were withdrawn and returned to compartment A with a syringe. (19)

 Modified KesharyChien Cell

A specialized apparatus was designed in the laboratory. It comprised of a KesharyChien 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.(20)

 Dissolution apparatus

Standard USP or BP dissolution apparatus have been used to study *in vitro* release profiles using rotating elements, paddle, and basket. The dissolution medium used for the study varied from 100- 500 ml and the speed of rotation from 50-100 rpm. (21)

 ***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 penetrating 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.

 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 dogs, rats, rabbits, cats, hamsters, pigs, and sheep have been reported. In general, the procedure involves anesthetizing the animal followed by administration of the dosage form. In the case of rats, the esophagus is ligated to prevent absorption pathways other than oral mucosa. At different time intervals, the blood is withdrawn analyzed. (22)

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. (23)

***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.

Percent of Drug Dissolved *In-vitro* Vs Peak Plasma Concentration

One of the ways of checking the in vitro and in vivo correlation is to measure the percent of the drug released from different dosage forms and also to estimate the peak plasma concentrations achieved by them and then to check the correlation between them.

Percent of Drug Dissolved Vs Percent of Drug Absorbed

If the dissolution rate is the limiting step in the absorption of the drug and is absorbed completely after dissolution, a linear correlation may be obtained by comparing the percent of the drug absorbed to the percent of the drug dissolved. If the rate-limiting step in the bioavailability of the drug is the rate of absorption of the drug, a change in the dissolution rate may not be reflected in a change in the rate and the extent of drug absorption from the dosage form.

Dissolution Rate Vs Absorption Rate

The absorption rate is usually more difficult to determine than the absorption time. Since the absorption rate and absorption time of a drug are inversely correlated, the absorption time may be used in correlating the dissolution data to the absorption data. In the analysis of in vitro and in vivo drug correlation, rapid drug absorption may be distinguished from the slower drug absorption by observation of the absorption time for the dosage form. The quicker the absorption of the drug the less is the absorption time required for the absorption of a certain amount of the drug. The time required for the absorption of the same amount of drug from the dosage form is correlated.

Percent of Drug Dissolved Vs Serum Drug Concentration

For drugs whose absorption from GIT is dissolution rate limited, a linear correlation maybe established between the percent of drug dissolved at specified times and the serum drug concentrations at corresponding times.

Percent of Drug Dissolved Vs Percent of the Dose Excreted in urine

The percent of a drug dissolved and the percent of drug absorbed are linearly correlated. There exists a correlation between the amount of drug in the body and the amount of drug excreted in the urine. Therefore, a linear relationship may be established between the percent of the drug dissolved and the percent of the dose excreted in the urine. (24)

APPLICATIONS

1. Microspheres in vaccine delivery

An ideal vaccine must fulfill the requirement of efficacy, safety, convenience in the application and cost. Biodegradable delivery systems for vaccines that are given by parenteral route may overcome the shortcoming of conventional vaccines. 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 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 a reproducible, efficient and specific manner is center to drug action mediated by use of a carrier system.

3. Monoclonal antibodies mediated microspheres targeting

Monoclonal antibodies targeting microspheres are immune microspheres. This targeting is the method used to achieve selective targeting to the specific sites. Monoclonal antibodies are

extremely specific molecules. Mabs can be directly attached to the microspheres utilizing covalent coupling. The Mabs can be attached to microspheres by any of the following methods.

1. Nonspecific adsorption and Specific adsorption

2. Direct coupling

3. Coupling via reagents

4. Chemoembolisation

Chemoembolisation is an endovascular therapy, which involves the selective arterial embolization of a tumour together with simultaneous or subsequent local delivery the chemotherapeutic agent.

5. Imaging

The particle size range of microspheres is an important factor in determining the imaging of particular sites using radio labeled microspheres. 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 labeled human serum albumin microspheres.

6. Topical porous microspheres

Microsponges are porous microspheres having a myriad of interconnected voids of particle size range 5-300µm. These microsponges can entrap a wide range of active ingredients such as emollients, fragrances, essential oils, etc., are used as the topical carries system.

7. Medical application.

 Release of proteins, hormones, and peptides over an extended period.

 Gene therapy with DNA plasmids and also delivery of insulin.

 Vaccine delivery for treatment of diseases like hepatitis, influenza, pertussis, ricin toxoid, diphtheria, birth control.27

8. Radioactive microsphere's application.4

 Can be used for radioembolization of liver and spleen tumors.

 Used for radio synovectomy of arthritis joint, local radiotherapy, interactivity treatment.

CONCLUSION

The present review article shows that microspheres are the better choice of drug delivery system then many other types of drug delivery systems. In the future by combining various other strategies, microspheres will find the central and significant place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted, specific and effective *in vivo* delivery and supplements as miniature versions of diseased organ and tissues in the body.

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