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Microsphere: A Novel Drug Delivery System

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ABSTRACT

Microspheres are powder which are free flowing and contain of proteins or synthetic polymers which are biodegradable and its size ranges between 1 – 1000 nm. It is a well-developed controlled drug delivery system that can overcome some issues of conventional drug delivery system and increase the therapeutic efficacy of a given drug. There are many approaches for delivering a therapeutic substance to the target site in a sustained and controlled release form. Among them microspheric drug delivery system has obtained vast attention because of its broad spectrum applications which also covers targeting the drug to a particular site to imaging and helping the diagnostic features. Microspheres has received much attention for prolonged release and also for anticancer drugs. Microspheres are micro particles which are spherical in shape. Microspheres have the drug located centrally inside the particle and encapsulated in a unique polymeric membrane. The purpose of this review article is to put together the different types of microspheres, the different methods of preparation of microspheres, the evaluation methods and its applications.

Keywords- (Microsphere, Introduction, advantages, Material used, method of prepration, Application)

INTRODUCTION:

Microspheres are small and spherical particles and it has diameters of 10 um to 1000 um. Microsphere plays a crucial role to increase the bioavailability of conventional drugs and reduces any side effects. The principal advantage of applying microspheres as a drug delivery system is the controlled release of the drug content. To increase the patient compliance, microencapsulation is used to retard the drug release from the dosage forms and lessen any side effects. In this method, to obtain a sustain release drug delivery system an

aqueous insoluble core (drugs) is coated with an aqueous insoluble coat (polymer) by emulsion solvent diffusion evaporation technique. Microspheres can be prepared by many ways such as, emulsification technique with single or double solvent evaporation system, spray-dry technique or phase separation technique. Microspheres are made by dissolving the starting materials in volatile solvents and then dispersing them into another solvent which is not miscible with the previous solvent. Later on the complete evaporation of the former solvent will make a fine powder which is called as microspheres and it is soluble in water. There are two types of microspheres;

• Microcapsules.

• Micrometrics.

In microcapsules the entrapped substance is distinctly surrounded by a discrete capsule wall and in micrometrics the entrapped substance is dispersed all over the microspheres matrix. Microspheres which are solid biodegradable that incorporates a drug dispersed or dissolved through particle matrix has the capability for the control release of drug. They are prepared of polymeric, waxy, or other protective materials, which are biodegradable synthetic polymers and are modified natural products [1-3].

ADVANTAGES:

1. Microspheres give persistent and prolonged therapeutic effect.
2. They reduce the dosing frequency and thus enhance the patient compliance.
3. Microspheres can be given through IV due to their spherical shape and smaller size.
4. It reduces the intensity of side effects and also enhances the bioavailability due to improvised drug utilization
5. Microsphere morphology has a controllable variability in degradation and also drug release [4].

LIMITATIONS:

The limitations are found to be as follows:

1. The modified release from the formulations.
2. The release rate of the controlled release dosage form may differ from many factors such as food and the rate of transit though gut.
3. The difference in the release rate from one dose to another dose.
4. Controlled release formulations mainly consists of a higher drug load and as a consequence any loss of integrity of the release characteristics of the dosage form can steer potential toxicity.
5. This type of dosage forms shouldn't be crushed or chewed [4].

CHARACTERISTICS OF MICROSPHERES:

1. The size of the microsphere can be critical to the proper function of an assay, or it might be secondary to other characteristics. When we consider traditional diagnostic methods, the test or assay format often speak about the particle size, for example, to make sure about the adequate wicking in lateral flow tests, very small

spheres (-0.1- 0.4 um) are used, or for the bead based flow cytometric assays, larger, cell-sized spheres (-4 - 10 um) are used

Sr. No.	Property	Consideration
1	Size diameter	Uniformity/ distribution
2	Composition	Density, Refractive index, Hydrophobicity/ hydrophilicity Nonspecific binding Autofluorescence
3	Surface Chemistry	Reactive groups Level of functionalization Charge
4	Special Properties	Visible dye/ fluorophore Superparamagnetic

Table: Microsphere property

2. Polystyrene (PS), poly (methyl methacrylate) (PMMA) and silica are common microsphere compositions. These materials have various physical and optical properties, which can present advantages or disadvantages for various applications. Polymer beads are mostly hydrophobic in nature, thus having more protein binding abilities. Although, they frequently need some surfactants (e.g. 0.01-0.1% Tween® 20 or SDS) in the storage buffer to provide ease of handling. At the time of synthesis, functional monomers can be co-polymerized with styrene or methyl methacrylate to make beads with surface reactive groups. In covalent binding reactions, functional groups can be used and can also assist in stabilizing the suspension. The silica microspheres are mostly hydrophilic and negatively charged. As a result, aqueous silica suspensions barely need the use of surfactants or other stabilizers. In common covalent coating protocols, carboxyl- and amine functionalized silica spheres are ready for use, and plain silica microspheres can be altered using various silanes to make functional groups or to change surface properties.

3. Microspheres can be coated with capture molecules, for example, antibodies, oligonucleotides, peptides, etc. for the utilization in diagnostic or separation applications. To accomplish desired specific activity, microsphere coatings are generally developed, at the same time decreases nonspecific interactions. The appropriate stability, development time frame and budget, and the particular biomolecule to be coated should also be considered. These factors will help to decide the most suitable coating strategy for both short- and long-term objectives. Standard microsphere products hold up to three fundamental coating strategies: adsorption, covalent coupling, and affinity binding.

4. Various applications in life sciences need added properties, for example, fluorescence or a visible color, or iron oxide inclusions for magnetic separations. Polymer spheres (and polymer based magnetic spheres) are mostly dyed internally by means of organic solvent swelling, and various standard products are available. To meet the requirements, dye concentrations can be altered to make beads with various intensities, for example, QuantumPlexTM for multiplexed flow cytometric assays, or Dragon Green or Flash Red Intensity Standards, that assists imaging applications and related instrument QC. As specialized flow cytometry standards, various surface or internally labelled fluorescent beads are also accessible [39].

MATERIALS USED:

Various substances both biodegradable and non-biodegradable were investigated for the preparation of microspheres. The polymers of natural and synthetic origin as well as modified natural substances are the included materials. Methyl methacrylate, acrolein, lactide, glycolide and their copolymers such as, ethylene vinyl acetate copolymer, polyanhydrides, etc. are the synthetic polymers which are employed as the carrier material. Albumin, gelatin, starch, collagen and carrageenan are the natural polymers used [5].

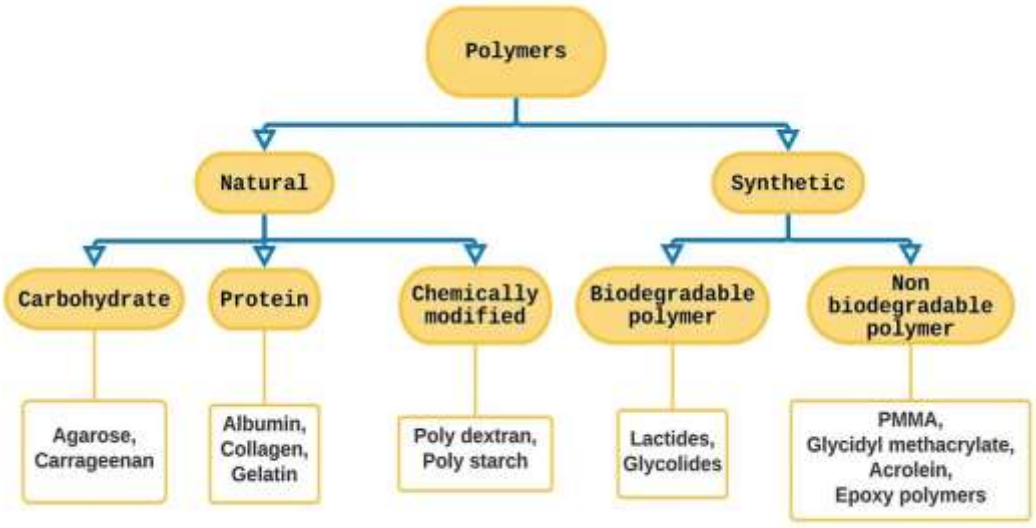

Fig. 1: Polymers used in microsphere development

CLASSIFICATION OF POLYMER: [6]

A) Synthetic Polymers: These are divided into two types;

1. Non-biodegradable:4,5- Acrolein, Glycidyl methacrylate, Epoxy polymers, etc. [7,8]

2. Biodegradable: (6)-Polyanhydrides, Polyalkylcyanoacryalates Lactides and glycolides and their copolymers.

B) Natural materials: These are obtained from various sources like: [9,10]

•Proteins (albumin, gelatin, collagen)

•Carbohydrate (starch, agarose, carrageenan)

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

Pre-requisites for ideal micro particulate carriers: [6]

The material that is used for the preparation of micro particulates should preferably attain 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

TYPES OF MICROSPHERES:

Bioadhesive microspheres:

Adhesion is defined as the sticking of drug to the membrane by using the sticking property of water soluble polymers. Bio adhesion is termed as the adhesion of the drug delivery device to the mucosal membrane i.e. buccal, rectal, ocular, nasal, etc. These types of microspheres show an extended residence time at the site of application and causes close contact with the absorption site and produces greater therapeutic action. [11]

Magnetic microspheres:

This type of delivery system is quite important which localizes the drug to the disease site. In this delivery system larger quantity of freely circulating drug can be replaced by smaller quantity of magnetically targeted drug. Magnetic carriers get magnetic feedback to a magnetic field from the included materials that are used for magnetic microspheres. These magnetic carriers are chitosan, dextran etc. [12] The various types are:

-Therapeutic magnetic microspheres: They are used to transport chemotherapeutic agent to the liver tumour. Drugs such as proteins and peptides can also be targeted through this system. [11]

-Diagnostic microspheres: These are used for the imaging of liver metastases and can also be used to differentiate between bowel loops from other abdominal structures by the formation of nano size particles supramagnetic iron oxides. [13]

Floating microspheres:

In this kind of microspheres the bulk density is lower than the gastric fluid and thus remains buoyant in the stomach without altering the gastric emptying rate. If the system is floating on the gastric content and hikes the gastric residence and increases variation in plasma concentration, the drug is released at a slow pace at the desired rate. It also decreases the possibility of striking and dose dumping. In another way it produces extended therapeutic effect and thus decrease dosing frequencies. The drug (ketoprofen) is given in this form. [14]

Radioactive microspheres:

In the radio emobilisation therapy the microspheres of 10-30 nm size are larger than the capillaries and thus gets trapped in the first capillary bed when they meet up. Then they are injected in the arteries that lead to the concerned tumor. Thus, in all of these situations radioactive microspheres gives high radiation dose to the targeted areas without injuring the normal neighboring tissues. [15] It is different from the drug delivery system, because the radio activity is not released from microspheres but in fact acts from inside a radioisotope typical distance and the various types of radioactive microspheres are alpha and beta emitters. [16]

Polymeric microspheres:

The different kinds of polymeric microspheres are classified as:

Biodegradable polymeric microspheres:

Polymers which are natural for example starch are used because they are biodegradable, biocompatible as well as bio adhesive in nature. When there is contact with the mucous membrane, the biodegradable polymers lengthens the residence time because of its high degree of swelling property with aqueous medium which results in the formation of gel. The rate and extent of drug release is regulated by the concentration of polymer and release pattern in sustained manner. The principal disadvantage is that in clinical application drug loading efficiency of the biodegradable microspheres is complicated and is hard to control the drug release. Nevertheless they give a broad range of applications in treatment based on microsphere. [17]

Synthetic polymeric microspheres:

Synthetic polymeric microspheres are extensively used in clinical applications, in addition they are also used as bulking agent as well as fillers, embolic particles, drug delivery vehicles, etc. and proved to be safe and biocompatible. But the principal drawback of these types of microspheres are, they tend to drift away from the injection site and lead to potential risk, embolism and further organ damage. [18]

METHOD OF PREPARATION OF MICROSPHERES:

Single emulsion technique:

Various Carbohydrates and Proteins are mostly prepared by this technique. In this technique, firstly the natural polymers are dissolved in an aqueous medium and then it is dispersed in a non-aqueous medium i.e. oil phase, which is then followed with the next step i.e. crosslinking of dispersed globule; which can be accomplished by 2 methods:

•**By Heat:** Addition of the dispersion in the heated oil, but this method is not fit for thermolabile drugs.

•**By Chemical Cross-linking Agent:** It uses glutaraldehyde, formaldehyde, acid chloride etc. as the cross-linking agent. Chemical cross-linking bears the drawback of extreme exposure.

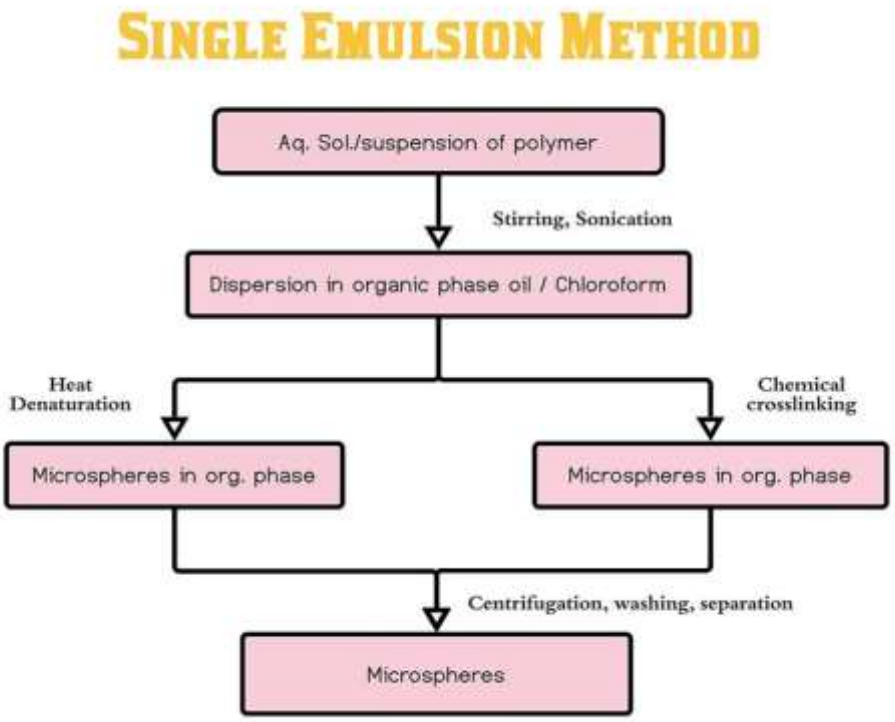

Fig. 2: Single emulsion technique

Double emulsion technique:

In the double emulsion method for the preparation of microspheres there is formation of the multiple emulsions or the double emulsion of type w/o/w and it is mostly suitable for the drugs that are water soluble, peptides, proteins and vaccines. In this method, both natural as well as synthetic polymers can be used. The protein solution that is aqueous, is dispersed in an organic continuous phase which is lipophilic in nature. The protein solution might consist of the active constituents. The continuous phase mostly consists of the polymer solution that in the end encapsulates of the protein contained in dispersed aqueous phase. Then the primary emulsion is exposed to the homogenization or the sonication prior to its addition to the aqueous solution of poly vinyl alcohol (PVA). This forms a double emulsion. The emulsion is then put through solvent removal by solvent evaporation technique or by solvent extraction technique. Various hydrophilic drugs such as luteinizing hormone releasing hormone (LH-RH) agonist, vaccines, proteins/peptides and conventional molecules are successfully included in the microspheres using the double

emulsion solvent evaporation/extraction method.

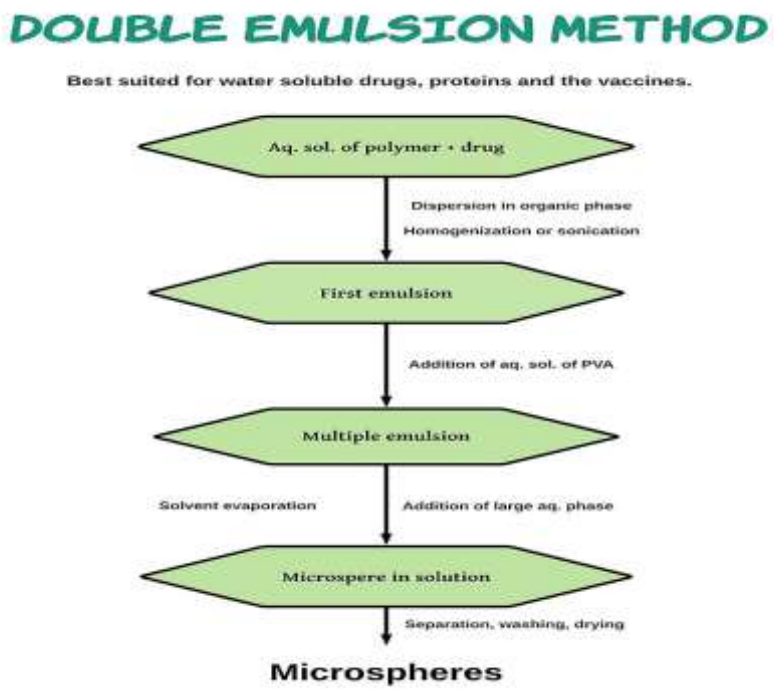

Fig. 3: Double emulsion technique

Polymerization techniques:

The polymerization techniques that are used for producing the microspheres are mostly classified as follows:

• Normal polymerization

• Interfacial polymerization

Both of these techniques are carried out in liquid phase.

• Normal polymerization:

It is carried out by using various techniques such as bulk, suspension, precipitation, emulsion as well as micellar polymerization methods. In bulk, a monomer or a combination of monomers together with the initiator or catalyst is mostly heated to start off the polymerization. Polymer that is obtained can be molded as microspheres. The drug loading can be done amidst the polymerization process. Suspension polymerization which is also referred as the bead or pearl polymerization. It is achieved by heating the monomer or composition of the monomers as droplets dispersion in a continuous aqueous phase. The droplets may also consist of an initiator and additional additives. The emulsion polymerization drifts away from suspension polymerization as a result of the presence initiator in the aqueous phase, which later on diffuses to the surface of micelles. Bulk polymerization has the benefit of formation of pure polymers.

• Interfacial polymerization:

Interfacial polymerization carries out the reaction of different types of monomers at the interface between the two immiscible liquids to make a film of polymer that basically envelops the dispersed phase.

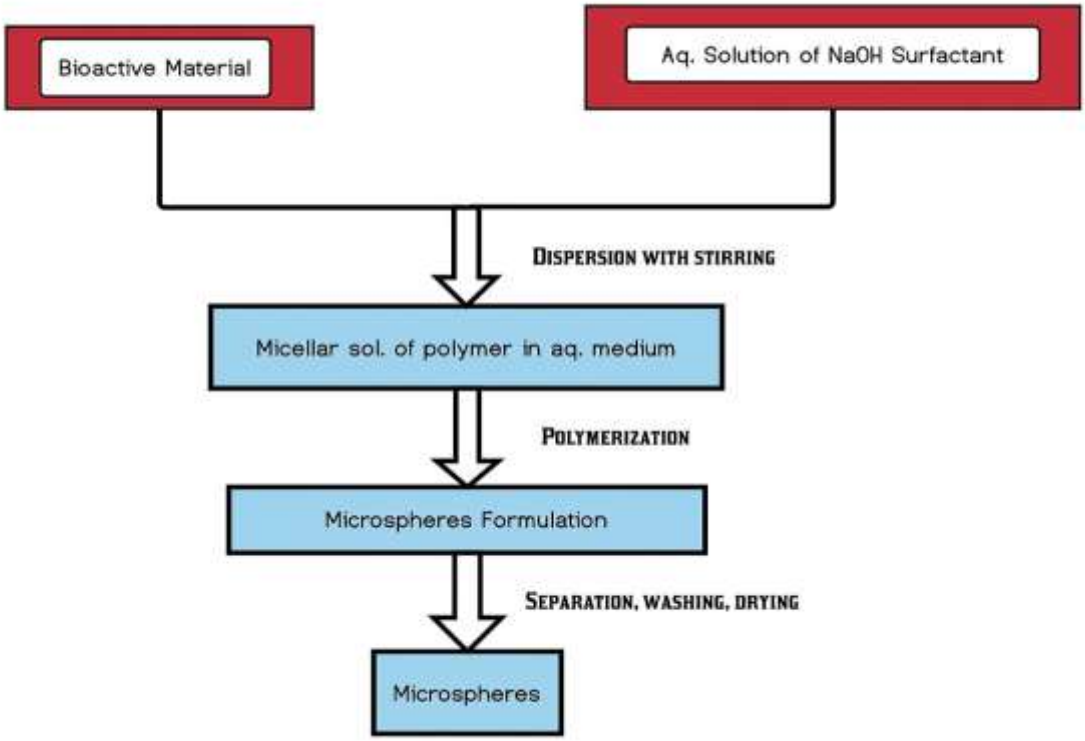

Fig. 4: Polymerization techniques

Spray drying technique:

In this technique, the polymer is dissolved in organic volatile solvent such as dichloromethane, acetone etc. and then solid form drug is dispersed in polymer solution which undergoes high speed homogenization. Then the dispersion gets atomized in the hot air stream, and atomization forms small droplets from which solvent evaporates immediately, that leads to the formation of microsphere in a size between 1-100 pm. Prepared micro particles are isolated by hot air with the help of cyclone separator and solvent traces is detached by vacuum drying. [19,20]

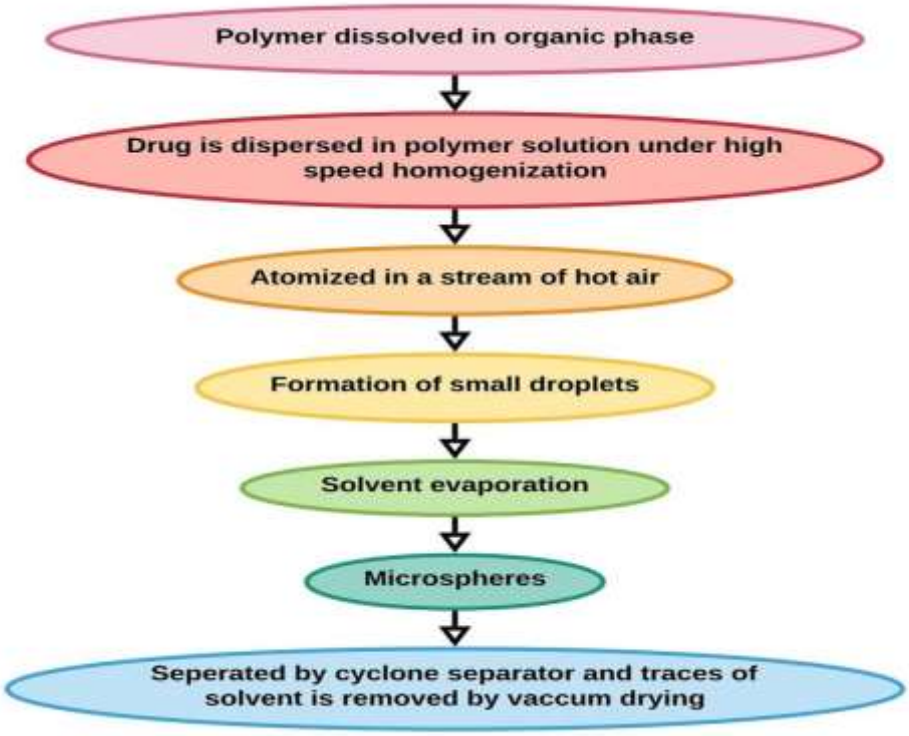

Fig. 5: Spray drying technique

Solvent extraction:

Solvent evaporation technique is used for production of micro particles, involves detachment of the organic phase by drawing out of the aqueous or non-aqueous solvent. This method includes water soluble organic solvents as isopropanol. Organic phase can be detached by extraction with water. This process reduces the hardening time for the microspheres. One variation of the process includes immediate incorporation of the drug or protein to polymer organic solution. Rate of solvent detachment by extraction method be contingent on the temperature of water, ratio of emulsion volume to the water and solubility profile of polymer. [21,22]

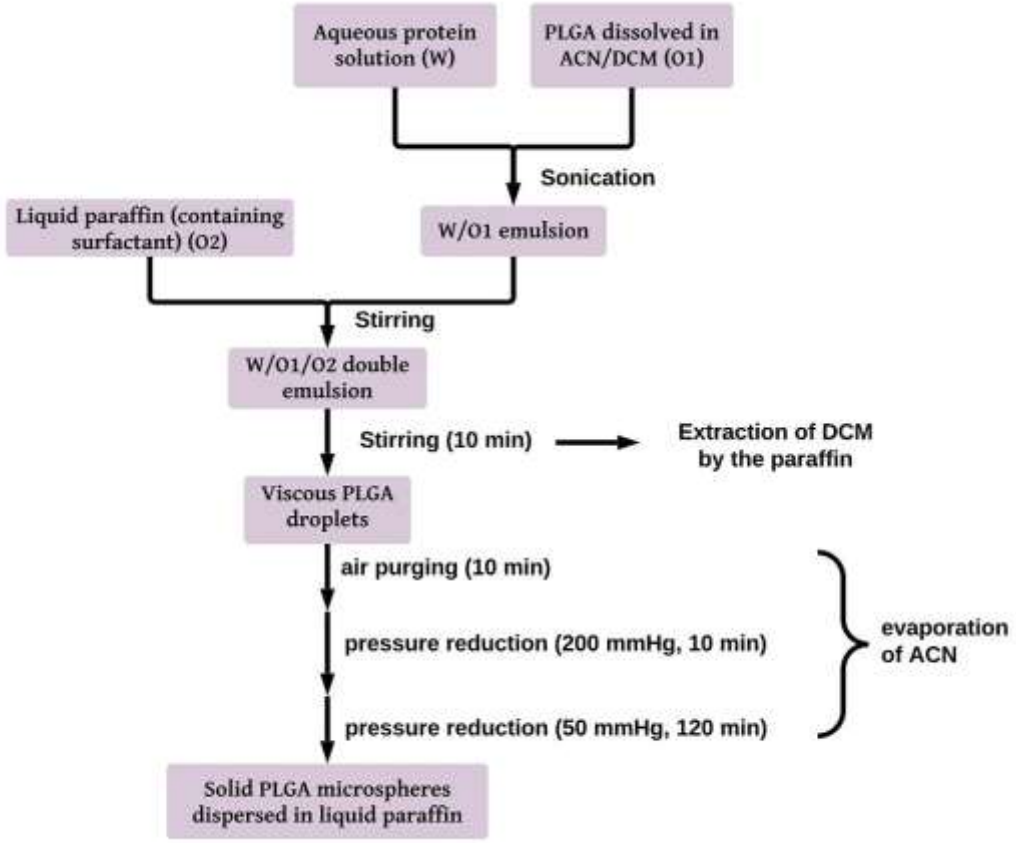

Fig. 6: Solvent extraction

Phase separation co-acervation technique:

Phase separation technique is mainly designed for preparing the reservoir type of the system. This method is used to encapsulate water miscible drugs e. g. peptides, proteins and some of preparations having matrix type particular, when the hydrophobic drug e. g. steroids. The technique is based on the principal of decreasing the solubility of the polymer in the organic phase to affect the evolution of the polymer rich phase called the coacervates. The coacervation can be brought about by the inclusion of the third component to the system which results in the formation of the two phases, one rich in polymer, while other not, i.e. supernant, exhaust of the polymer. There are many methods which are effectively employed for coacervates phase separation. The process are based on the salt addition, on-solvent addition, addition of the incompatible polymer. [23,24]

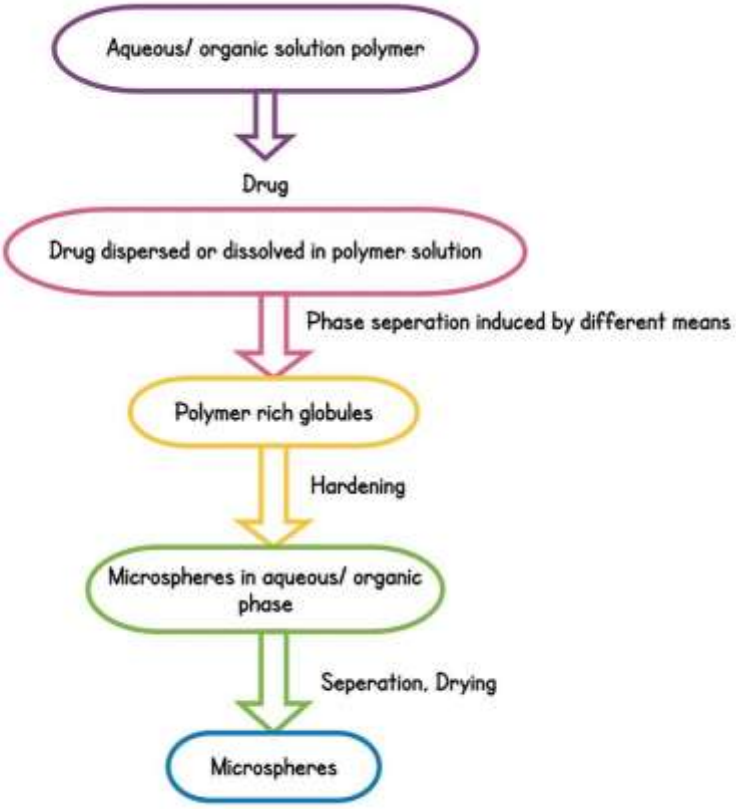

Fig. 7: Phase separation co- acervation technique

Solvent evaporation technique:

This is one of the advanced methods of microsphere manufacture. The polymer and drug must be mixed in an organic solvent, mostly methylene chloride. The solution having the polymer and the drug can be dispersed in an aqueous phase to form droplets. Constant mixing and raised temperatures can be employed to evaporate the more volatile organic solvent and let the solid polymer-drug particles remain suspended in an aqueous medium. The particles are ultimately filtered from the suspension. [25,26]

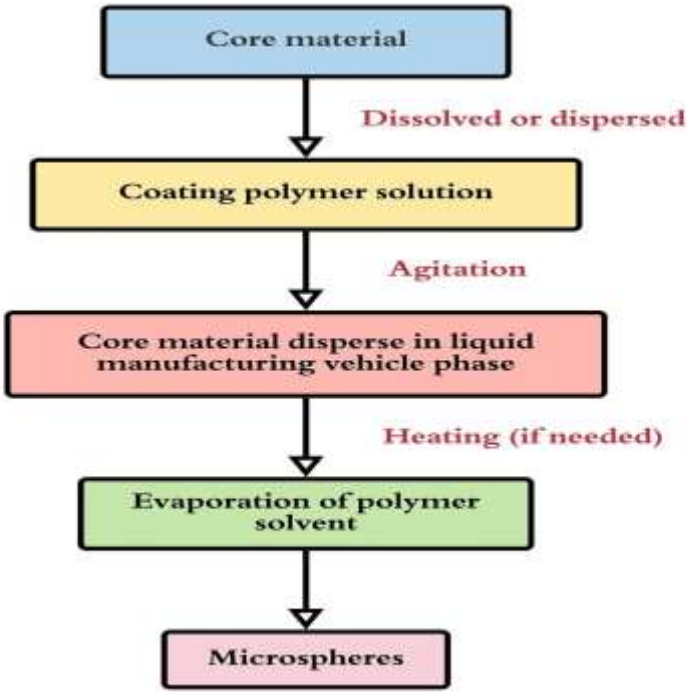

Fig. 8: Solvent evaporation technique

EVALUATION OF MICROSPHERES:

Particle size analyser:

Microsphere (50 mg) are suspended in distilled water (5mL) which contains 2% w/v of tween 80, to avert microsphere aggregation, the above suspension is sonicated in water bath and the particle size is indicated as volume mean diameter in micrometer. [27]

Optical microscopy:

This technique is used to find out the particle size by using optical microscope (Meizer OPTIK) The calculation is done under 450x (10x eye piece and 45x objective) and 100 particles are calculated. [28]

Scanning electron microscopy (SEM):

By the method SEM, surface morphology is determined. In this technique the microcapsule are mounted precisely on the SEM sample slab with the aid of double sided sticking tape and coated with gold film under reduced pressure and analyzed. [29]

Swelling index:

This method is used for the characterization of sodium alginate microspheres. Various solution (100mL) are taken for example [distilled water, buffer solution of pH (1.2, 4.5, and 7.4)] and alginate microspheres (100mg) are kept in a wire basket and is placed on the above solution and swelling is allowed at 37°C. Therefore, the shift in weight variation between initial weight of microspheres and weight due to swelling is calculated by taking weight periodically and soaking with filter paper. [30]

Entrapment efficiency:

Microspheres that contains 5 mg of drug are crushed and then it is dissolved in distilled water with the aid of an ultrasonic stirrer for 3 hr, it is then filtered and assayed by uv-vis spectroscopy. Entrapment efficiency is equal to the ratio of the actual drug content to the theoretical drug content. [30]

X-ray diffraction:

The change in the crystallinity of the drug can be determined through this method. The micro particles and its separate components can be analyzed by the help of XRD Instrument. [33] The scanning range angle is between 80°C - 70°C.

Thermal analysis:

Thermal analysis of a microcapsule and its component can be achieved by utilizing

Differential scanning calorimetry (DSC)

Thermo gravimetric analysis (TGA)

Differential thermometric analysis (DTA)

The sample is accurately weighed and is heated on an alumina pan at a continuous rate of 10°c/min under the nitrogen flow of 40 ml/min. [33]

FTIR:

The interaction of the drug and polymer as well as the degradation of drug during the processing for microencapsulation can be determined by FTIR. [31]

Stability studies:

Stability Studies are achieved by keeping the microspheres in screw capped glass container and storing them at the following conditions:

Ambient humid condition

Room temperature (27+/-2 °C)

Oven temperature (40+/-2 °C)

Refrigerator (5 0+/-8 °C).

It was executed for 60 days and the drug content of the microsphere is analyzed. [34]

Zeta potential:

The polyelectrolyte shell is made by incorporating chitosan of various molecular weight in the W2 phase and the consecutive particles are determined by zeta potential measurement. [32]

APPLICATIONS:

1. Microspheres in Vaccine Delivery:

The requirement of a vaccine is to protect against the microorganism or its toxic product. An ideal vaccine should satisfy the conditions of efficacy, safety, convenience in application and cost. The characteristic of safety and reduction of side effects is a complex issue [35]. The characteristic of safety and the level of the production of antibody responses are closely associated to the means of application. The biodegradable delivery systems for vaccines which are given by parenteral route can conquer any limitations of the conventional vaccines [36]. There is importance of parenteral (subcutaneous, intramuscular, intradermal) carrier because they offer certain advantages which includes:

1. Improvement in antigenicity by adjuvant action

2. Modulation of the antigen release

3. Antigen stabilization.

2. Targeting using Micro particulate Carriers:

The idea of targeting, which is also known as site specific drug delivery is a deep-rooted dogma, which is achieving full attention. The therapeutic efficacy of a drug depends on its approach and specific interaction with its candidate receptors. The potential to leave the pool in reproducible, systematic and in a specific way is center to the drug action mediated by the use of a carrier system. When the indiscrete anatomical compartment of the particles are placed, it leads to their retention either due to the physical properties of the environment or due to the biophysical interaction of the particles with the cellular content of the target tissue.

3. Monoclonal Antibodies Mediated Microspheres Targeting:

The monoclonal antibodies that target microspheres are immune microspheres. This targeting is a method which is used to attain selective targeting to the specific sites. The monoclonal antibodies are highly specific molecules. This high specificity of monoclonal antibodies (Mabs) can be used to target the bioactive molecules which are loaded with microspheres to the selected sites. By the means of covalent coupling the monoclonal antibodies can be attached directly to the microspheres. The free aldehyde groups, i.e. amino groups or hydroxyl groups on the surface of the microspheres can be joined to the antibodies. The monoclonal antibodies can be joined to microspheres by any of these methods mentioned below

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

4. Chemoembolization:

Chemoembolization is an endovascular therapy that includes the selective arterial embolization of a tumor together with concurrent or subsequent local delivery of the chemotherapeutic agent. The theoretical benefit is that these embolizations will not only provide vascular occlusion but will also bring about the sustained therapeutic levels of chemotherapeutics in the areas of the tumor. Chemoembolization is an add-on to the traditional percutaneous embolization methods.

5. Imaging:

The microspheres have been broadly studied and are used for targeting purposes. Different types of cells, cell lines, tissues and organs can be imaged by the use of radio labelled microspheres. The particle size range of microspheres is a key component for the determination of the imaging of specific sites. The particles that are injected through IV other than the portal vein will get entrapped in the capillary bed of the lungs. This phenomenon is utilized for the scintiographic imaging of the tumor masses in lungs by the use of labelled human serum albumin microspheres.

6. Topical Porous Microspheres:

The micro sponges are microspheres that are porous, which has myriad of interconnected voids of a particle size range 5300 um. These micro sponges have the capacity to entrap a broad-spectrum of active ingredients for example emollients, fragrances, essential oils etc., are used as the topical carries system additionally,

these porous microspheres with active ingredients can be included into formulations like creams, lotions and powders. Micro sponges contains non-collapsible structures with porous surface through which the active ingredients are delivered in a controlled release manner [37].

7. Surface Modified Microspheres:

Various perspectives are used to alter the surface properties of carriers to protect them against phagocytic clearance and to change their body distribution patterns. The adsorption of the poloxamer on the surface of polystyrene, polyester or poly methyl methacrylate microspheres makes them more hydrophilic in nature and therefore reduces their MPS uptake. Protein microspheres that are covalently modified by PEG derivatives exhibit lower immunogenicity and clearance. The surface modifiers that are often studied are:

1. Antibodies and their fragments
2. Proteins
3. Mono-, oligo- and polysaccharides
4. Chelating compounds (EDTA, DTPA or Desferroxamine)
5. Synthetic soluble polymers: These modifications are provided surface of microspheres for the sake of attaining the targeting to the discrete organs and to evade rapid clearance from the body [38].

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