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A Review on Microspheres as a Novel Drug Delivery System

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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. The range of Techniques for the preparation of microspheres offers a Variety of opportunities to control aspects of drug administration and enhance the therapeutic efficacy of a given drug. Microspheres are the newly developed system for controlled release of the drug. Microspheres are also called as micro-particles. It is designed to overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. To get the desired effect the drug should deliver at the target tissue in an optimal amount in the right period of time with maximum therapeutic effect and minimum side effect. There are many methods used for the preparation of microspheres as Spray drying and spray congealing, Polymerization techniques, Phase separation coacervation technique, Single emulsion technique, Double emulsion technique, Solvent Evaporation etc. Microspheres are evaluated by methods like Physicochemical Evaluation Characterization, Particle size, and shape, Electron spectroscopy for chemical analysis, In vitro methods, In vitro-In vivo correlations, Swelling Index etc. microspheres are applied in Ophthalmic Drug Delivery, Gene delivery, Gastrointestinal drug delivery, multiplex immunoassay, chemotherapy, Per oral drug delivery etc.

INTRODUCTION: [1, 2,3,4,5]

Microspheres are used as carriers of drug and used to the controlled release of drug, vaccines, antibiotics, and hormones. Microspheres are defined as "therapeutic agent distributed throughout the matrix either as a molecular dispersion of particle. There is small spherical free flowing particle with a diameter in a range of 1 μm to 1000 μm. Microspheres are manufactured by using natural and synthetic materials polymer and waxes. Stability, solubility, and drug release depend upon the type of polymer used for the preparation of microspheres. Glass microspheres, polymer microspheres and ceramic microspheres are available. Glass microspheres are used as fillers and volumizer for weight reduction, retro-reflector for high safety, additives for cosmetics and adhesives in medical technology. Polyethylene, polystyrene and expandable microspheres are the most common types of polymeric microspheres. Ceramic microspheres are used primarily as grinding media. Microspheres are manufactured in solid and hollow form. Hollow microspheres are used as additives to lower the density of a material. Microsphere-based topical formulations have gained wider importance in the treatment of psoriasis due to their ability for controlled drug delivery and enhanced therapeutic effectiveness for prolonged periods of time. Microparticulate drug delivery systems have recent trends that are especially suitable for achieving controlled or delayed release oral formulations with low risk of dose dumping, a flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. The stability and biological activity of drug should not affect during the microencapsulation process, yield and drug encapsulation efficiency should be high, microspheres quality and drug release profile should be reproducible within specified limits. Many methods are used for the preparation of microspheres. Spray drying and milling can thermally denature some compounds. Polymer phase separation, spray drying, and emulsification processes often lead to an amount of residual solvent that is higher than authorized values. Near critical or supercritical fluid techniques are promising and fulfill some of the new requirement.

Ideal properties of microsphere:

Preparation of an ideal microsphere should satisfy certain criteria:

- Sterilizability
- Control of content release.

- Biocompatibility with a controlled biodegradability.
- Controlled particle size and dispersibility in aqueous vehicles for injection.
- Stability of the preparation after synthesis with a clinically acceptable shelf life.
- The ability to incorporate reasonably high concentration of the drug.
- Increase therapeutic efficiency.
- Susceptibility to chemical modification.
- Reduction of toxicity.
- Bioreabsorbability.

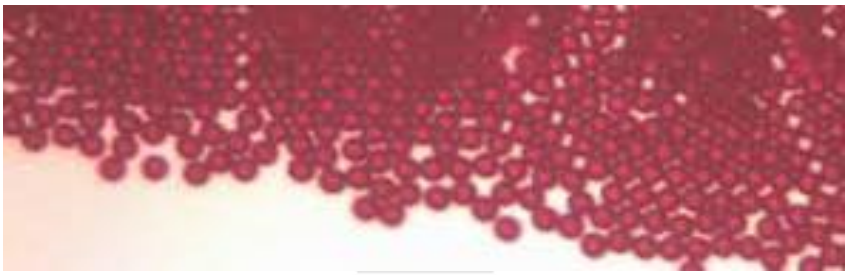

Figure 1: Images of microsphere

Objectives for preparation of microspheres:

- Best formulation for incompatible materials
- Provide protection to drug against the environment
- Masking of taste and odor.
- Safe in case of toxic substances.
- A flow of powder is improved.
- Sustained-release, controlled-release, targeted medication can produce
- Reduced dose dumping

Advantages

1. Microspheres provide constant and prolonged therapeutic effect.

2. Reduces the dosing frequency and thereby improve the patient compliance.

3. They could be injected into the body due to the spherical shape and smaller size.

4. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.

5. Microsphere morphology allows a controllable variability in degradation and drug release.

6. Avoid first pass metabolism.

7. Improved protein & peptide drug delivery system.

8. Ability to bind & release a high concentration of a drug.

9. Method of preparation is simple,

10. Masking of taste.

11. Enhance biological half-life.

12. Improve physical stability and gastric enzymatic stability.

Disadvantages

Some of the disadvantages were found to be as follows

1. The modified release from the formulations.

2. The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit through the gut.

3. Differences in the release rate from one dose to another.

4. 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.

5. Dosage forms of this kind should not be crushed or chewed.

Materials Used [2, 3, 6]

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

1. Synthetic Polymers

2. Natural polymers

1. Synthetic polymers

Synthetic polymers are divided into two types.

a. Non-biodegradable polymers

E.g. Polymethylmethacrylate (PMMA), Acrolein, Glycidyl methacrylate, Epoxy polymers

b. Biodegradable polymers

E.g. Lactides, Glycolides & their copolymers, Poly alkyl cyanoacrylates, Poly anhydrides

2. Natural polymers

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

Proteins: Albumin, Gelatin, and Collagen

Carbohydrates: Agarose, Carrageenan, Chitosan, Starch

Chemically modified carbohydrates: Poly dextran, Poly search.

Types of microspheres

Types of microspheres depending upon its composition

1. Glass microspheres

- Hollow glass microspheres.
- Solid glass microspheres.

2. Polymer microspheres.

- Polyethylene microspheres.
- Polystyrene microspheres.
- Fluorescent microspheres.

3. Starch microspheres.

- Cross-linked Starch microspheres.

4. Gelatin microspheres.
5. Ceramic Microspheres.
6. Dextran microspheres.
7. Albumin microspheres.
8. Chitosan microspheres.
9. Alginate microspheres.
10. Poly anhydride microspheres.
11. Polyphosphate microspheres.'
12. Poly acrolein microspheres

Types of microspheres depending upon its properties [7, 8, 9,10, 15]

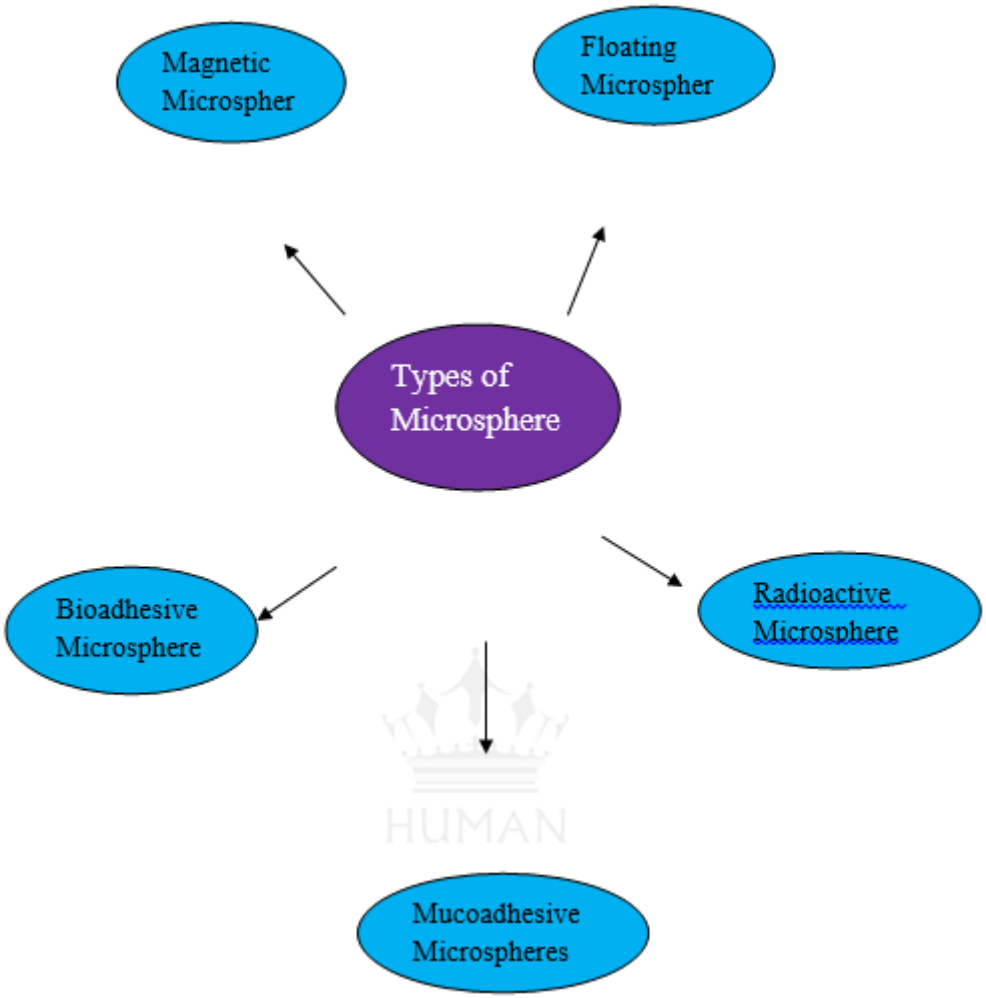

Figure 2: Types of microsphere

Bioadhesive microspheres:

Adhesion can be defined as sticking of the 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, urinary, colon and gastrointestinal tract, etc, can be termed as bioadhesion. Bioadhesive drug delivery devices to the mucosal tissue offer the possibility of creating an intimate and prolonged contact at the site of administration. This prolonged residence time can result in enhanced absorption and in combination with a controlled release of the drug also improved patient compliance by reducing the frequency of administration.

Magnetic microspheres

Magnetic microspheres localize the drug to the disease site. In magnetic targeting, a drug or therapeutic radioisotope is bound to a magnetic compound, injected into a patient's bloodstream and then stopped with a powerful magnetic field in the target. In this larger amount of freely circulating drug can be replaced by the smaller amount of magnetically targeted drug to locally diseased sites, reaching effectively up to several folds increased localized drug levels. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, Dextrans etc. Depending on the type of drug, it is then slowly released from the magnetic microspheres. The different types of magnetic microspheres are:

• **Therapeutic magnetic microspheres:** It used to deliver therapeutic radioisotopes and a chemotherapeutic agent to liver tumors. The advantage of this method over external beam therapy is that the dose can be increased, resulting in improved tumors cell eradication, without harm to nearby normal tissues.

• **Diagnostic microspheres:** It acts as contrast agents for magnetic resonance imaging. Smaller supra magnetic iron oxides have been developed into unimodular manometer sizes and used for the imaging of liver metastases or to distinguish loops of the bowel from other abdominal structures.

Floating microspheres:

Floating microscopes are the microspheres whose bulk density is less than the gastric fluid and so remains buoyant in the stomach without affecting the gastric emptying rate. The drug is released slowly at the desired rate if the system is floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration. Moreover, it also reduces the chances of striking and dose dumping. One another way, it produces the prolonged therapeutic effect and therefore reduces dosing frequencies.

Effervescent type: stated that swellable polymers e.g., methylcellulose, chitosan and various effervescent compound e.g., sodium bicarbonate, citric acid, and tartaric acid are used for the preparation of effervescent dosage.

Non-effervescent type: Highly swellable cellulose type hydrocolloids, polysaccharide, and matrix forming polymer such as polycarbonate, polyacrylate are used to form an effervescent system.

Radioactive microspheres:

They are injected into the arteries that lead to the tumor of interest. So, all these conditions radioactive microspheres deliver the high radiation dose to the targeted areas without damaging the normal surrounding tissues. It differs from the drug delivery system, as radioactivity is not released from microspheres but acts from a radioisotope within a typical distance and the different kinds of radioactive microspheres are α, β and γ emitters. It offers new solutions for patients, who need drugs delivered directly to tumors, diabetic ulcers, and other disease sites. Diagnostic uses of radioactive microspheres are lungs scintigraphic, bone marrow imaging, tumor imaging, gastrointestinal transit study, blood flow measurement, infection localization & diagnostic radio immobilization.

Mucoadhesive microspheres:

It consisting either entirely of a mucoadhesive polymer or having an outer coating of it and having 1-1000 mm in diameter. These mucoadhesive microspheres having some advantages like efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer, specific targeting of a drug to the absorption site achieved by anchoring plant lectins, bacterial adhesions, and antibodies on the surface of the microspheres. Mucoadhesive microspheres are used for designing of nasal product. It provides more prolonged contact with nasal mucosa and enhances the rate and extent of drug absorption. It is used by using biocompatible materials like dextran, albumin, gelatin, and starch.

Methods of Preparation [10, 11,12, 13]

Factors considered during the manufacturing of microspheres

- The problem associated with stability.
- It should have a longer duration of action.
- Particle size.

- Concentration and molecular weight of the polymer.
- Drug and polymer concentration or ratio.
- Dispersibility in an aqueous vehicle for injection.

Methods used for the preparation of microspheres are:

- Single emulsion techniques.
- Double emulsion techniques.
- Polymerization.

a. Normal polymerization

b. Inter-facial polymerization

- Phase separation coacervation technique.
- Spray drying.
- Solvent extraction.
- Solution-enhancement dispersion method.
- Wax coating Hot-melt method.

1. Single emulsion technique.

Single emulsion involves o/w or w/o type of emulsion. Single emulsion technique involves the use of chemical cross-linkers for cross-linking. The crosslinkers used are diacid chloride glutaraldehyde, formaldehyde etc. Some crosslinkers show some disadvantage.

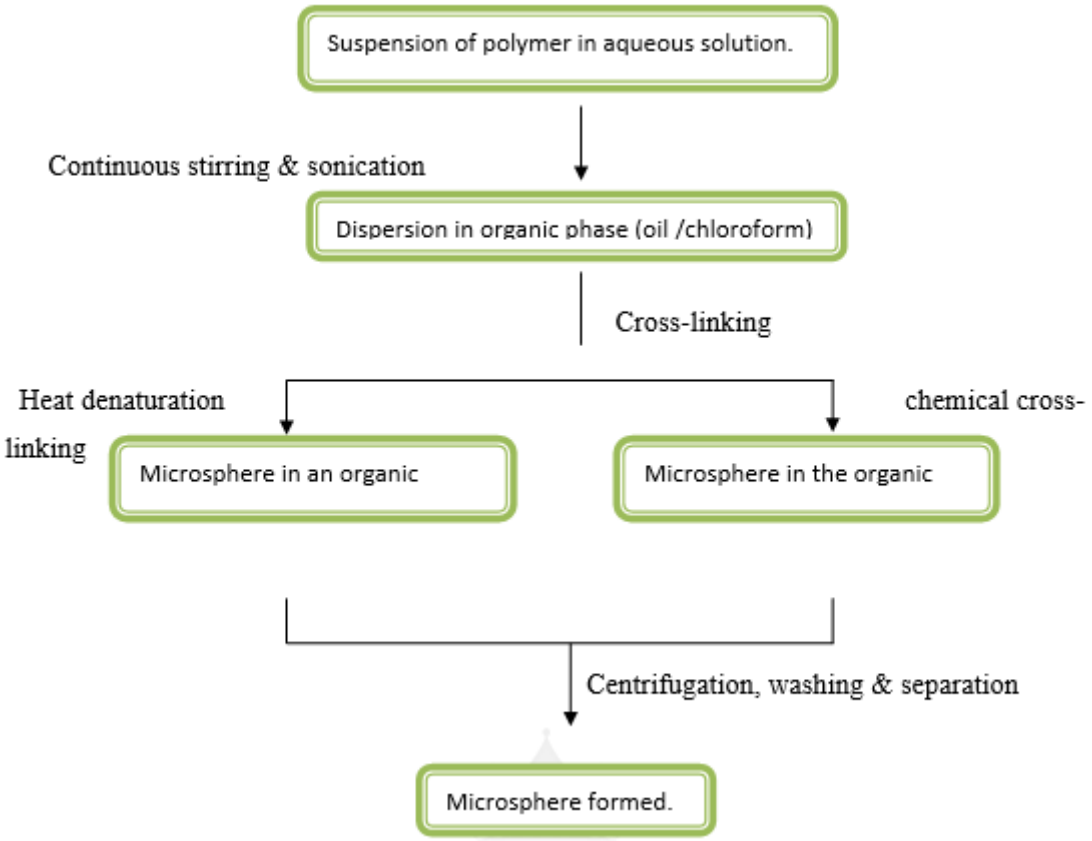

Figure 3: Diagrammatic representation of single emulsion techniques.

2. Double emulsion techniques.

In double emulsion techniques, both the natural as well as synthetic polymers are used for the synthesis of microspheres. This involves the formation of the multiple emulsions or the double emulsion of type w/o/w. This technique is suitable for protein, peptides, vaccines as well as water-soluble drugs.

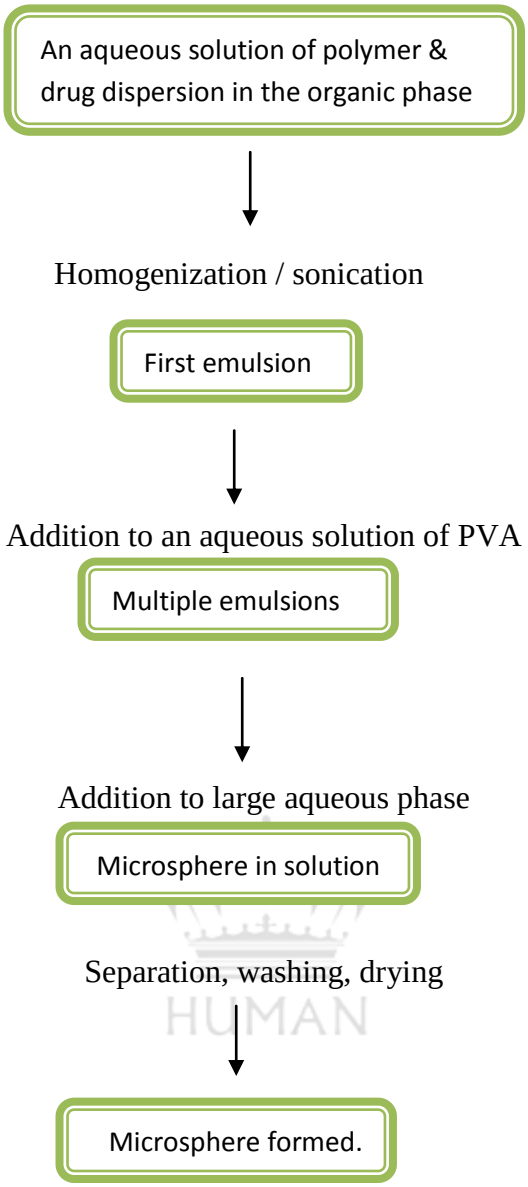

Figure 4: Diagrammatic representation of double emulsion techniques.

3. Polymerization techniques:

The polymerization techniques are used for the preparation of the microspheres are divided into two classes as follows,

I. Normal polymerization

II. Interfacial polymerization. Both are carried out in the liquid phase.

Normal polymerization:

In this method, there are many techniques used as bulk, suspension, precipitation, emulsion and micellar polymerization processes. Firstly the catalyst & monomers are heated to initiate the polymerization. Drug loading is done during the process of polymerization. Suspension polymerization also called as the bead or pearl polymerization. This process is carried out by heating the monomer or mixture of monomers as droplets dispersion in a continuous aqueous phase. The droplets may contain an initiator and other additives. Emulsion polymerization differs from suspension polymerization as only due to the presence of an initiator in the aqueous phase, which later on diffuses to the surface of micelles. Bulk polymerization has an advantage of formation of pure polymers.

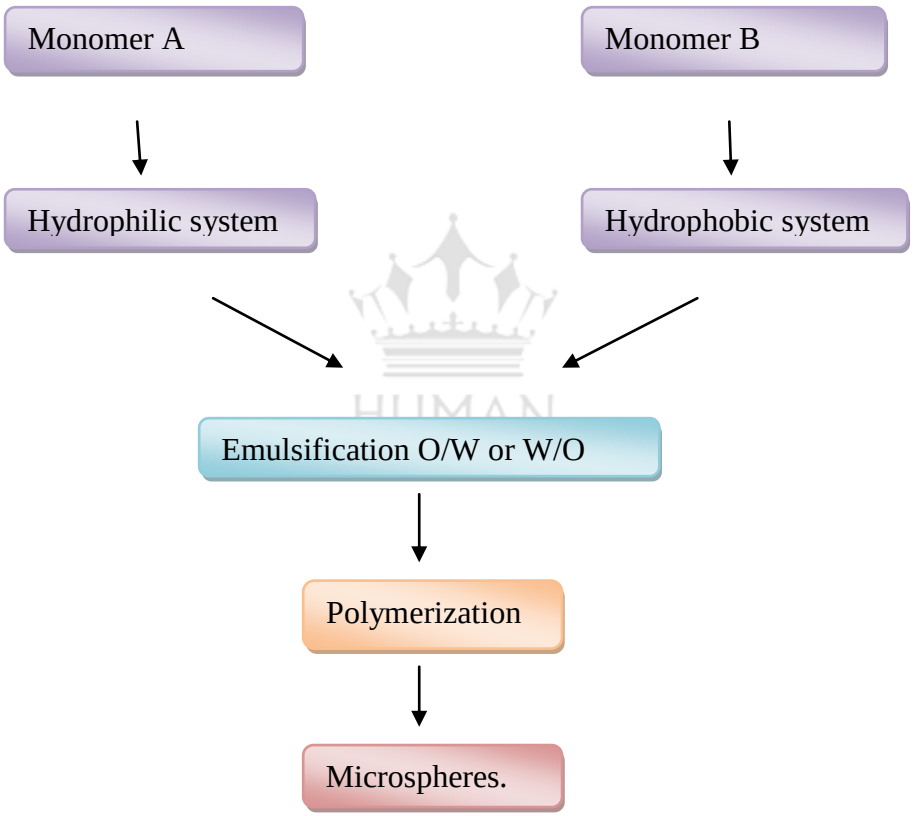

Figure 5: Diagrammatic representation of polymerization techniques.

Interfacial polymerization

This process involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase.

4. Phase separation Coacervation technique:

This process involves three phase

1. Formation of three immiscible phases.

2. Coating of polymer around the core.

When polymer gets coacervates from solution, it forms a coating around the core material which is the rigidised with physical or chemical means core particles are coated by

- Coalescence of many individual coacervates droplets and around the core.

- Single coacervates droplet may encompass one or more particles.

3. Regidization of coating material around the core.

Regidization of the polymer is essential for the stability and protection from drug leaching from microspheres. Methods used for regidization are

- By cross-linking agent.

- By thermal processes.

- By de-salvation.

- Salting out method.

- By using non- aqueous vehicle and an aqueous vehicle.

This process is based on the principle of decreasing the solubility of the polymer in the organic phase to affect the formation of a polymer rich phase called the coacervates. The drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes the first polymer to phase separate and engulf the drug particles. Non-solvent is added for the solidification of a polymer. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer since as the process of microspheres formation begins the formed polymerize globules start to stick and form the agglomerates. Therefore the process variables are critical as they control the kinetics of the formed particles since there is no defined state of equilibrium attainment.

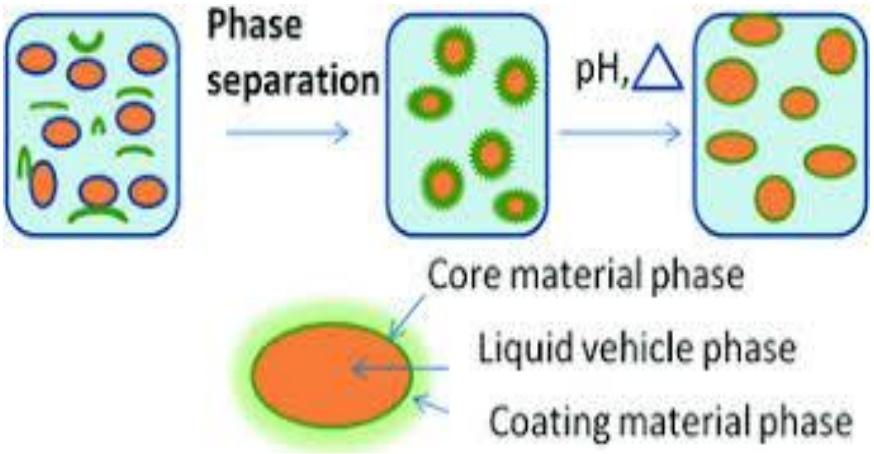

Figure 6: Phase separation Coacervation technique

5. Spray drying and spray congealing:

Depending upon the removal of the solvent or cooling of the solution, the two processes are named as spray drying and spray congealing. The polymer is first dissolved in a suitable volatile organic solvent such a 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 to the formation of the microspheres in a size range 1-100 μm. A cyclone separator is used for separation of microspheres and an excess of solvent is removed by vacuum drying. Hot air is used in spray drying, instead of hot air cool air blow in the process of spray congealing.

e.g. penicillin's microspheres are prepared by using spray drying.

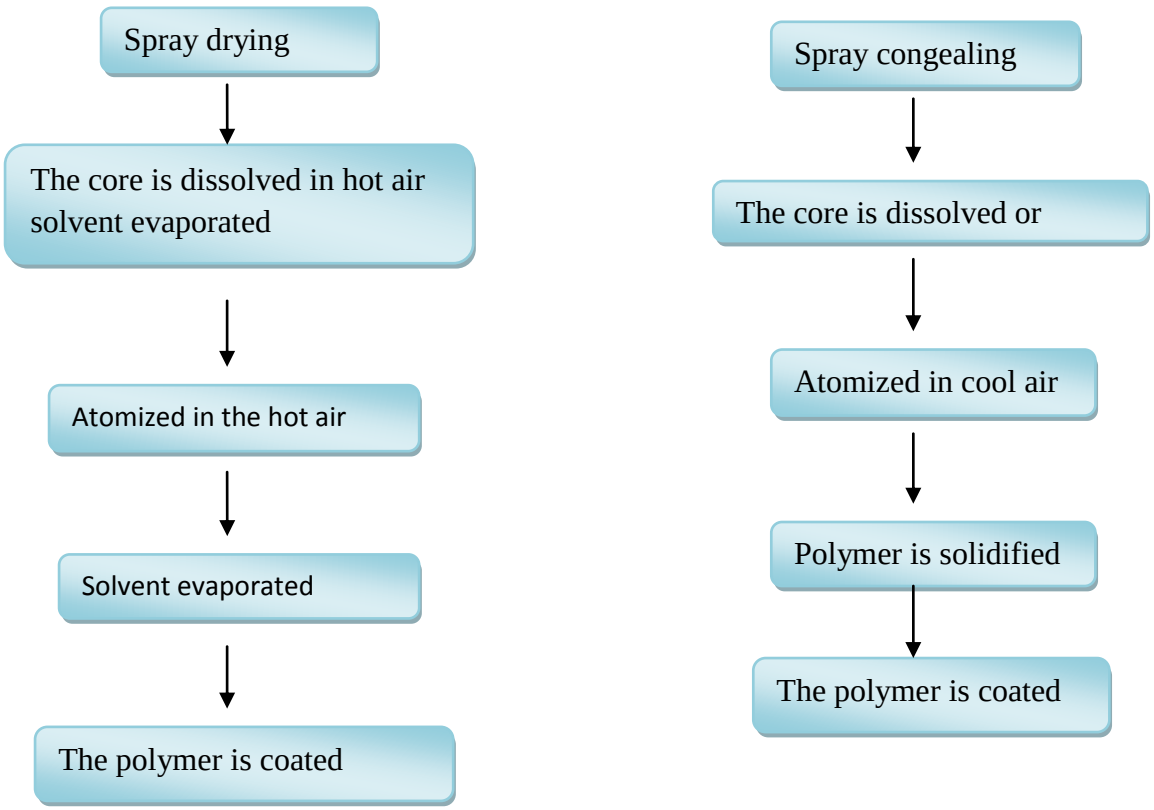

Figure 7: Diagrammatic representation of spray drying and spray congealing

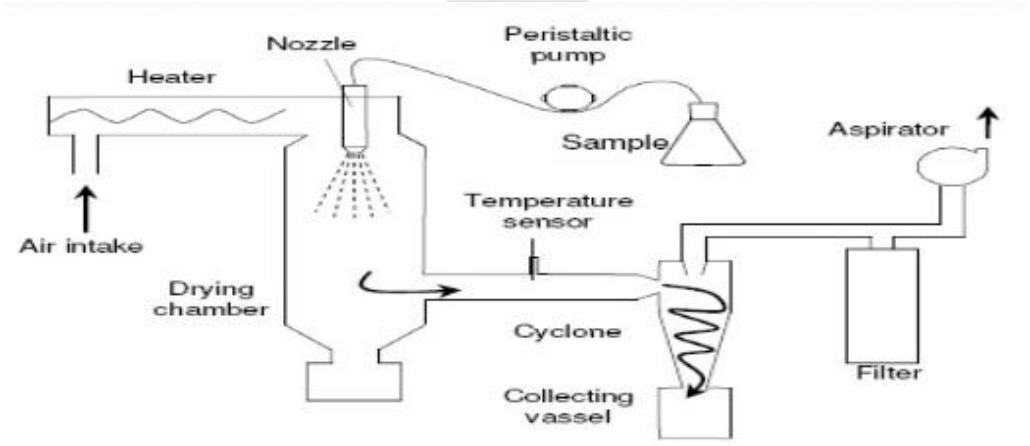

Figure 8: Image of spray drying and spray congealing

6. Solvent extraction

This method involves removal of the organic phase by extraction of the organic solvent. It involves water-miscible organic solvents like chloroform, isopropanol. The organic phase is removed by extraction with water. This process decreases the hardening time for the microspheres. The drug is directly added to a polymer organic solution. The rate of solvent

removal by extraction method depends on the temperature of water, a ratio of emulsion volume to the water and the solubility profile of the polymer**.**

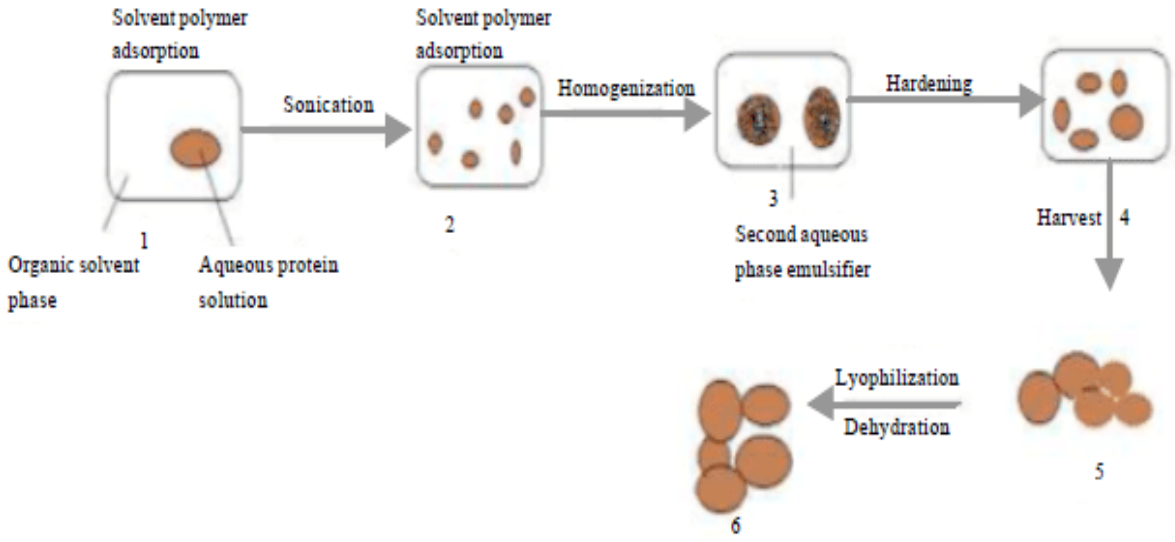

Figure 9: Solvent extraction method

Physicochemical Evaluation

Particle size and shape

The shape and outer structure of microparticles are determined by using conventional light microscopy (LM) and scanning electron microscopy (SEM). Laser light scattering and multi-size coulter counter other than instrumental methods, which can be used for the characterization of size, shape, and morphology of the microspheres. Confocal fluorescence microscopy1 is used for the structural characterization of multiple-walled microspheres. The surface chemistry of the microspheres can be determined using the electron spectroscopy for chemical analysis (ESCA)

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 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 pychnometer. An accurately weighed sample in a cup is placed into the multi-volume pycnometer.

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

% Entrapment = Actual content/Theoretical content x 100

In vitro-methods

There is a need for experimental methods which allow the release characteristics and permeability of a drug through the membrane to be determined. Standard USP or BP dissolution apparatus have been used to study in vitro release profiles using both rotating elements, paddle and basket type. Dissolution medium used for the study varied from 100 - 500 ml and speed of rotation from 50-100 rpm. The percentage drug release study is carried out by using the U.V spectrophotometer.

Stability studies

By placing the microspheres in a screw-capped glass container and stored them under the following conditions:

Table 1: Temperature condition for stability studies

Sr. No.	Ambient	humid condition
1	Room	(27 ± 2^0C)
2	Oven	(40 ± 2^0C)
3	Refrigerator	($5\ ^0C$ -8^0C)

Applications [13,14,15]

Chemo-embolisation

It is an endovascular therapy which involves the selective arterial embolization of tumors together with simultaneous/local delivery of the chemotherapeutic agent. It provides sustained therapeutic levels of chemotherapeutics in the areas of the tumor.

Microspheres as a Nasal Drug Delivery System

All types of microspheres that have been used as nasal drug delivery systems are water-insoluble but absorb water into the sphere's matrix, resulting in swelling of the spheres and the formation of a gel. The excellent absorption enhancing properties of bioadhesive microspheres are now being used extensively for both low molecular weight as well as macromolecular drugs like proteins.

Buccal drug delivery:

The polymer is an excellent polymer to be used for buccal delivery because it has muco/bioadhesive properties and can act as an absorption enhancer. Chitosan, Sodium Alginate.

Microspheres as carrier

Microspheres are used as a carrier in the targeted drug delivery i.e. site-specific drug delivery system and it improves the therapeutic efficacy of the drug. Placement of the particles indiscrete anatomical compartment leads to their retention because of the physical properties of the environment or biophysical interaction of the particles with the cellular content of the target tissue.

Transdermal drug delivery:

The polymer has good film-forming properties. The drug release from the devices is affected by the membrane thickness and cross-linking of the film. Eg. Chitosan, Alginate, PLGA

Microspheres in vaccine delivery

The vaccine gives protection against the microorganism and its toxic product. The aspect of safety and minimization of an adverse reaction is a complex issue. The interest in parenteral

like 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.

Imaging

Radiolabelled microspheres are used for various cells, cell lines, tissues, and organs imaging. The particle size range of microspheres is an important factor in determining the imaging of particular sites. Microspheres are used for lungs scintigraphic imaging of the tumor masses in lungs using labeled human serum albumin microspheres.

Monoclonal antibodies loaded microspheres

Monoclonal antibodies are extremely specific molecules. This extreme specificity of monoclonal antibodies (Mabs) can be utilized to target microspheres loaded bioactive molecules to selected sites. The Mabs can be attached to microspheres by the covalent bond the methods used for attachment are Non-specific adsorption, Specific adsorption, Direct coupling, Coupling via reagents.

Cosmetics industry

Microspheres are used in cosmetics for skin, hair etc. The chitosan derivatives have a good substantial, particularly to hair keratin, and prove to have hair strengthening and hair conditioning characteristics. e.g.; Hair setting lotion, Oxidation Hair-coloring Composition, Hair toning Composition, Skin Cream, Hair treatment Composition, Gel-form.

Gene delivery:

Microspheres could be a useful oral gene carrier because of its adhesive and transport properties in the GI tract. Eg. Chitosan, Gelatin, viral vectors, cationic liposomes, polycation complexes.

Ophthalmic Drug Delivery:

Microspheres developed using polymer exhibits favorable biological behavior such as bioadhesion, permeability-enhancing properties, and interesting physicochemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles. Eg. Chitosan, Alginate, Gelatin.

Vaginal drug delivery:

Polymer, modified by the introduction of thioglycolic acid to the primary amino groups of the polymer is widely used for the treatment of mycotic infections of the genitourinary tract. Eg. Chitosan, Gelatin, PLGA.

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