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+ Normal Polymerization

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INTERFACIAL POLYMERIZATION:

Definition-) reaction of various polymers at the interface of 2 immiscible liquid to form polymer film that encapsulate dispersed phase.

DEFINITION:

"Interfacial polymerization is a technique in which polymerization of two monomers, one oil soluble and other water soluble, takes place and a polymer is formed at the interface of two immiscible substances".

- This technique is mostly used for the encapsulation of liquids rather than solids because penetration of monomer in to polymerization zone is much easy from the liquid-state rather than the solid state.

GENERAL METHOD OF PREPARATION:

- The process consists of bringing two reactants together at the interface of the dispersed phase and the continuous phases in emulsion system.
- This is usually accomplished by emulsifying the liquid containing first reactant (dispersed phase) into continuous phase, which is initially devoid of second reactant.
- Additional continuous phase containing the second reactant is then added. The interfacial polymerization reaction produces a continuous film of the polymer around the drug.
- The recovery of microcapsules from the continuous phase can be accomplished by:
  - Spray drying
  - Flash evaporation OR
  - Filtration etc.

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Steroidal drug ⇒ oil in nature.

oil + polymer (internal phase)

water + monomer 2.

eg PLA, PGA

Solvent interfacial polymerization technique

FLOW CHART OF INTERFACIAL POLYMERIZATION PROCESS

Liquid to be encapsulated
Containing the 1st monomers
(Dispersed phase) OR
Liquid core + monomer

Continuous phase with
emulsifying agent

↓

Prepare emulsion

↓

Add additional continuous phase containing
2nd monomer with constant mixing

↓

Polymer encapsulated
Liquid particles

↓

Separate encapsulated
liquid particle and dry

PROBLEMS:

Associated with this technique includes:

"Reaction of active drug with the reagents (monomer) used to form the wall."

LIMITATIONS:

1. Toxicity which occur due to unreacted monomers.
2. Degradation of drug caused by monomer reaction
3. High permeability of coating (because of increase permeability whole drug may be released immediately and whole system get failed)
4. Friability of microcapsules.

PROPERTIES OF MICROCAPSULES PREPARED BY INTERFACIAL POLYMERIZATION:

A. SURFACE MORPHOLOGY:

Microcapsules prepared by interfacial polymerization method have spherical geometry. The interior surface of these microcapsules is generally irregular and exterior surface is uniform and smooth.

B. SIZE AND SIZE DISTRIBUTION

Mostly by interfacial polymerization, large microcapsules are produced.

Various factors which effect size of microcapsules are:

- Presence of salt in aqueous phase ⟶ increases microcapsule size (Because salts have ability to facilitate the coalescence of droplets.)
- decrease in temperature and monomer concentration ⟶ increases microcapsule size
- Addition of thickening agent ⟶ increases microcapsule size (Because thickening agent increases viscosity of system, decreases stirring speed)
- Increase agitation speed ⟶ decrease particle size

C. MEMBRANE PROPERTIES

It includes:

i) Membrane thickness
ii) Membrane permeability
iii) Membrane stability

i) Membrane thickness:

The membrane thickness of microcapsules depends on the method of preparation. Microcapsules prepared by interfacial polymerization possess a thickness in the nanometer range because the membrane thickness is restricted by limited solubility of the reactants in the phase to be encapsulated.

ii) Membrane permeability:

Membrane permeability defines the rate of mass transfer from the surrounding solution in to microcapsules & it depends upon:

- Membrane thickness
- Pore size AND
- Chemical composition of the polymer .

The permeability characteristics of microcapsules give us information about the sustained/controlled release properties of the encapsulated drugs.

- When membrane thickness is increased, permeability is decreased and vice versa.
- When pore size is increased, permeability is increased.
- Different chemical composition produces different membrane thickness and ultimately different membrane permeability.

iii)Membrane Stability:

Membrane stability of microcapsules membranes depends upon:

- Total polymer ratio
- Ratio of amines to acid chlorides And

It was found that stable capsule membrane was obtained by increasing the ratio of amines to acid chlorides and with low concentration of total polymer.

D. ZETA POTENTIAL:

Microcapsules prepared by interfacial polymerization technique have a microcapsule membrane that does not bear any electric charge. However wher. suspended in an aqueous medium, they migrate either to anode or cathode, depending on the sign of electric charge on the encapsulated polyelectrolyte.
Following factors will affect the zeta potential of microcapsule:

- Ionic strength of medium
- pH of medium
- Concentration of polyelectrolyte

- Ionic strength of medium.....Decrease in mobility of microcapsules when ionic strength is increased.
- pH of medium.....Movement of microcapsules occur either towards anode or cathode depending upon the pH of the medium

E. Flow Properties: Microcapsules which are spherical in shape have free flow properties. However microcapsules which are irregular in shape

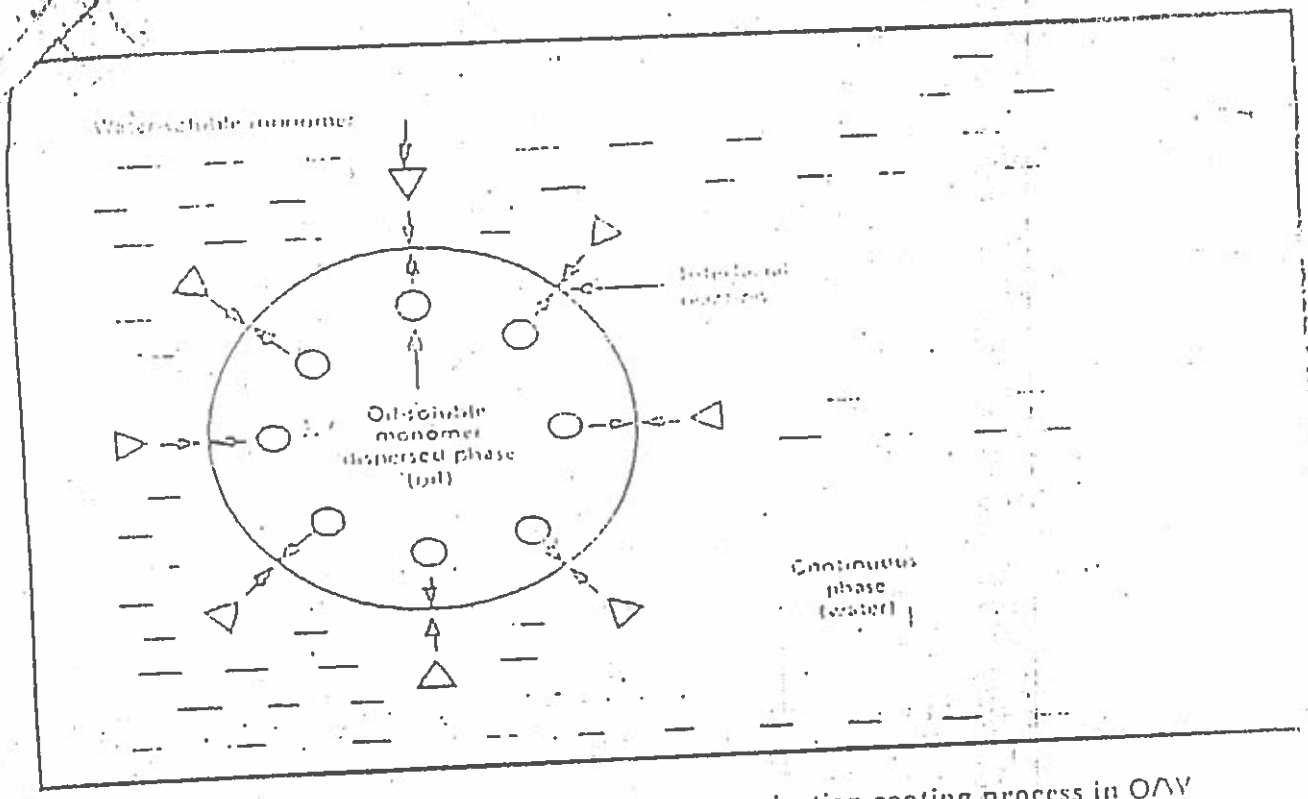


Figure: Schematic diagram of interfacial polymerization coating process in O/W Emulsion system.

Depending upon the nature of drugs to be encapsulated, three procedures can be adopted under the heading of interfacial polymerization technique.

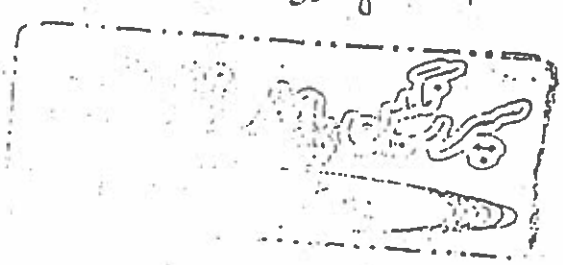
These include:

A. PROCEDURE FOR WATER IMMISCIBLE LIQUID CORE (hydrophobic)
B. PROCEDURE FOR WATER MISCIBLE LIQUID CORE (hydrophilic)
C. PROCEDURE FOR SOLID CORE

A. PROCEDURE FOR WATER IMMISCIBLE LIQUID CORE:

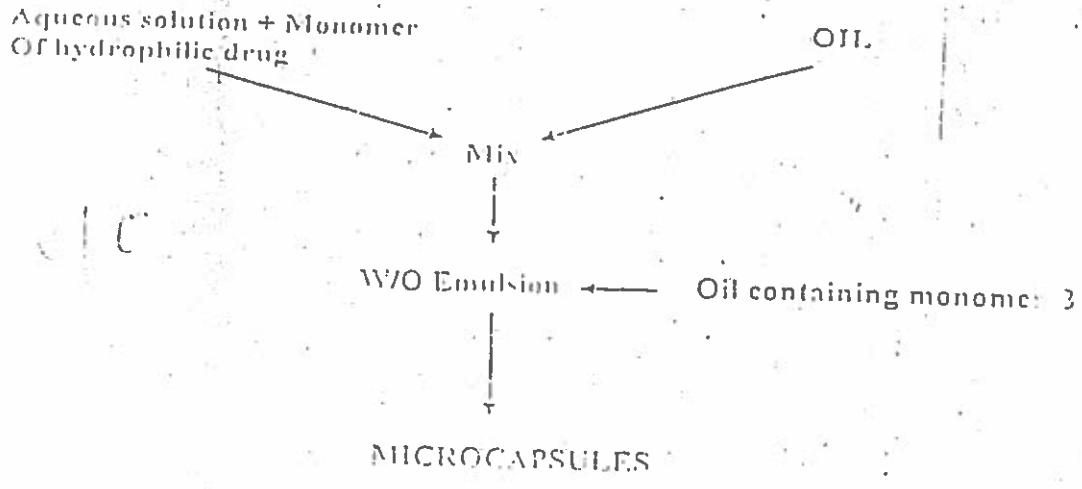
When the core material is lipophilic liquid, the monomer is dissolved in the liquid core. Usually isocyanate or acid chloride is used as monomer. Then this solution is dispersed in aqueous phase (containing 2nd monomer [illegible]). This produce polymerization of monomers at the interface and results in formation of the capsule wall.

Isocyanate / acid chloride



B.PROCEDURE FORWATER MISCIBLE LIQUID CORE:

Aqueous solution of water solubie drug (dispersed phase) containing monomer is disp sed in toan organic phase (continuous phase) which contain the emulsifier to form w/o emulsion. When additional oil containing 2nd monomer is added to w/o emulsion, poly er membrane is formed. Then microcapsules are separated by different techniques.



C.PROCEDURE FOR SOLID CORE:

Solid cores are encapsulated by vinyl monomers that polymerize by free radical reac on.

DIFFERENT SOLVENTS USED:

- CCL_4 (Carbon tetrachloride)
- Chloroform ($CHCl_3$)
- Methanol (CH_3OH)
- H_2O etc

DIFFERENT MONOMERS USED:

Water soluble monomer	Oil- soluble monomer	Polymer formed
1. Polyamine e.g. Hexamethylene diamine	Polybasic acid halide Sebacoyl chloride	Polyamide polyamide
2. Polyphenol e.g. Hydroxy phenyl propane	Polybasic acid halide Sebacoyl chloride	Polyphenyl ester Polyphenly ester

Concentration of polyelectrolyte..... Decrease zeta potential due to increase conc. of counter ions liberated from the encapsulated polyelectrolyte molecules.

) FLOW PROPERTY:

Microcapsules which are spherical in shape have free flow properties; owever microcapsules which are irregular in shape do not have free flowing properties.

PPLICATIONS OF INTERFACIAL POLYMERIZATION:

Interfacial polymerization is a technique which is widely used in the field of griculture, medicine, pharmacy, and biotechnology.
ome of the important applications are as follows:

) ENZYMES:

- Microcapsules containing aqueous solutions of enzymes are artificial analogs of biological cells
- Microencapsulation can greatly increase the stability and duration of action of enzymes. For example, microcapsules containing ASPARAGINASE prepared by interfacial polymerization possess membrane that is resistant to mechanical shock or attack of CHYMOTRIPSIN.
- Enzyme like Catalases can be encapsulated to provide protection against leakage and immunological reaction.

) PROTEINS:

- Microcapsules of Human serum albumin and bovine fibrinogen and ovalbumin were prepared by interfacial polymerization. Then they are treated with alkaline hydroxylamines which result in attachment of hydroxamide group to the membrane, making the microcapsules capable of iron binding. Lower amounts of iron were found to be complexed by human serum albumin as compared with fibrinogen and ovalbumin microcapsules.
- Microcapsules containing hemoglobin solution can be used as substitute of RBCs or artificial RBCs.
- Bovine serum albumin can also be encapsulated by interfacial polymerization.

) ARTIFICIAL CELLS:

- Microcapsules prepared by interfacial polymerization are used as artificial cells because of their semi permeable properties.
- Membranes of artificial cells are impermeable to macromolecules or suspensions but they are extremely permeable to solutes present in biological fluids. Thus they are used in the treatment of chronic renal failure, liver failure & acute toxicity.

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4) PHARMACEUTICALS:

Examples of pharmaceuticals which are encapsulated by interfacial polymerization technique include:

1. Benzalkonium chloride
2. Sodium phenobarbital

5) ADSORBANTS:

Encapsulated Activated charcoal can be used for purification, decolorization and extraction.

6) HORMONES AND ANTIBODIES:

- Beta- Estradiol
- 17- Hydroxyprogesterone antibody and Antithyroxine antibody.

7) PIGMENTS, OILY LIQUIDS &POLYELECTROLYTES:

Pigments, oily liquids and polyelectrolyte can also be encapsulated by interfacial polymerization technique.

4. Solvent extraction can be done by adding the emulsion to a large quantity of water (with or without surfactant) into which the organic phase diffuses out.
5. The solid microspheres are then obtained by filtration and washing.

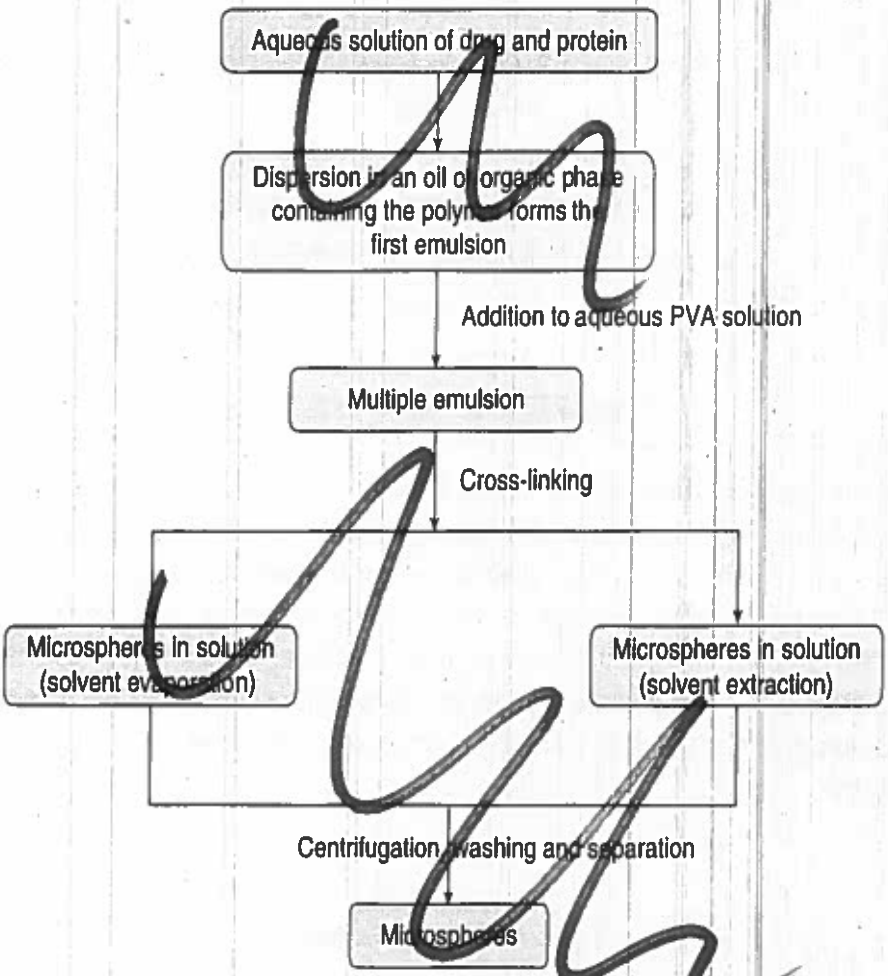

Figure 6.7.2 Preparation of Microspheres by Double Emulsion Technique

Polymerization Techniques

There are two polymerization techniques that can be used for the preparation of the microspheres. They are normal polymerization and interfacial polymerization.

Normal polymerization: It is carried out using different techniques such as bulk, suspension, precipitation, emulsion and micellar polymerization processes.

1. In bulk polymerization, a monomer or a mixture of monomers along with the initiator or catalyst is heated to initiate polymerization. The initiator or catalyst is added to accelerate the rate of the reaction. The polymer so obtained may be molded as microspheres. Drug entrapment may be done during the process of polymerization (refer Fig. 6.7.3).

   The advantage of this technique is the formation of pure polymers. The disadvantage is that it is very difficult to release the heat of the reaction, which can adversely affect the thermolabile active ingredients.

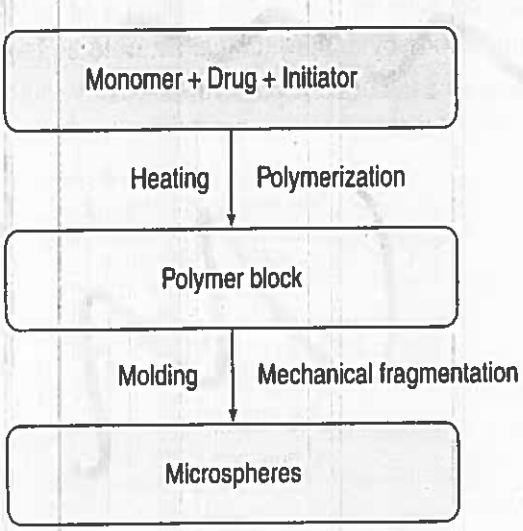

Figure 6.7.3 Bulk Polymerization Process

2. Suspension polymerization is also known as bead or pearl polymerization. It is carried out by heating the monomer or mixture of monomer with drug as a droplet dispersion in a continuous aqueous phase. Initiator and other additives may also be added (Fig. 6.7.4).

   The advantages of this method are that it can be carried out at a lower temperature, since the continuous external phase is water through which heat can easily be released. The process also results in the formation of high molecular weight polymers at a relatively fast rate. The disadvantage is that the polymers formed may react with the unreacted monomers and other additives.

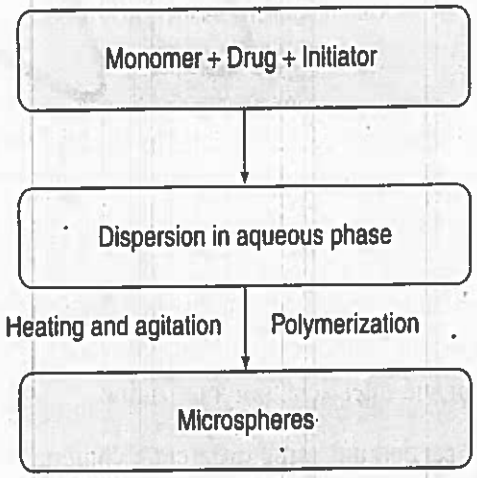

Figure 6.7.4 Suspension Polymerization Process

3. Emulsion polymerization is a method in which the initiator is present in the aqueous phase, which later on diffuses to the surface of micelles or the emulsion globules. This method can be carried out at a lower temperature, since the continuous external phase is water through which heat can easily be released (Fig. 6.7.5).

   Similar to suspension polymerization, this method can be carried out at a lower temperature, since the continuous external phase is water through which heat can easily be lost. The process also results in the formation of high molecular weight polymers at a fast rate. The disadvantage is that the polymers formed may react with the unreacted monomers and other additives.

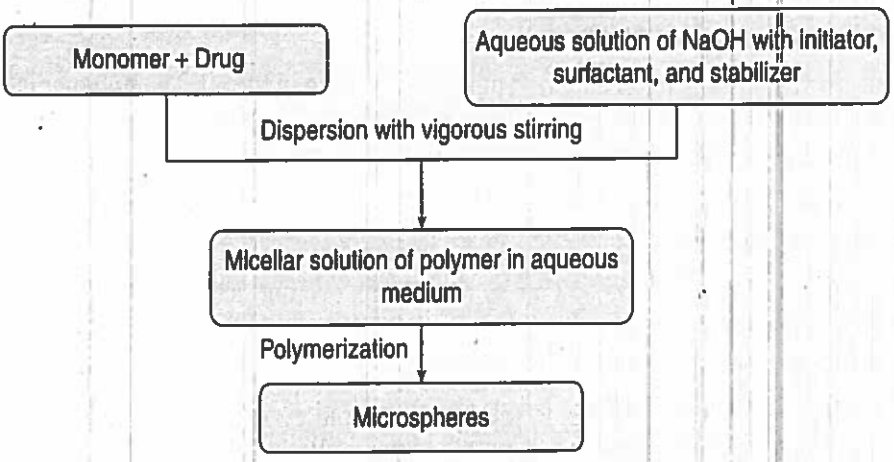

Figure 6.7.5 Emulsion Polymerization Process

Interfacial polymerization: It involves the reaction of various monomers at the interface of two immiscible liquid phases to form a polymer film that encapsulates the dispersed phase. Two immiscible solvents are used, with the monomer in one solvent reacting with the monomer in the other solvent. The continuous phase is aqueous in nature throughout which the second monomer is emulsified. The monomers present in both the phases diffuse rapidly and polymerize at the interface.

Phase Separation Coacervation Technique

The method is designed for preparing reservoir-type systems such as encapsulation of water-soluble drugs. The solubility of the polymer in organic phase is decreased to effect the formation of polymer-rich phase called the coacervates.

The drug particles are dispersed in a polymer solution and an incompatible polymer is added to the system, which makes the first polymer to separate out and engulf the drug particles. Addition of nonsolvent results in the solidification of the polymer (refer Fig. 6.7.6). Polylactic acid (PLA) microspheres have been prepared by this method by using butadiene as the incompatible polymer.

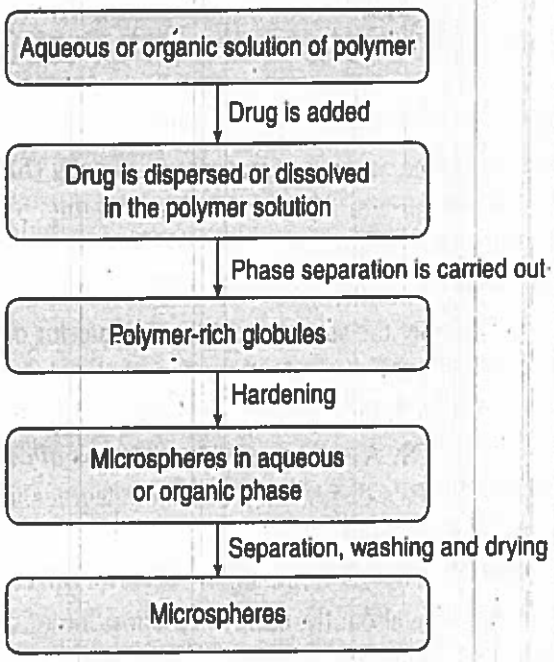

Figure 6.7.6 Phase Separation Coacervation Method

Spray Drying and Spray Congealing

These methods involve the drying of a mist of polymer and drug in the air. The polymer is dissolved in a volatile organic solvent such as dichloromethane and acetone. The solid drug is then dispersed in the polymer solution under high-speed homogenization. This dispersion is then atomized into 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. Microparticles are separated from the hot air by means of a cyclone separator while the traces of solvent are removed by vacuum drying.

The main difference between spray drying and spray congealing is the process of solidification of the coating. In spray drying, the coating is solidified by rapid evaporation of a solvent in which the coating material is dissolved, whereas in spray congealing method, the coating is solidified by heat or by introducing the coated core mixture into a nonsolvent. The nonsolvent can be removed from the coated product by sorption, evaporation or extraction techniques.

Advantages: One of the major advantages of the spray drying process is that the operation can be carried out under aseptic conditions. The spray drying process is used to encapsulate various penicillins. Porous microparticles are formed due to rapid solvent evaporation.

Solvent Extraction

In this process, the coating polymer is dissolved in a volatile solvent that is immiscible with the vehicle. The core material to be microencapsulated is dispersed in the coating polymer solution. The core and coating material mixture is dispersed in the vehicle phase with stirring to obtain microcapsules of appropriate size. Stirring is continued until the solvent partitions into the aqueous phase and the solvent is removed by extraction with water. This process decreases the time required for hardening of the microspheres.

CHARACTERIZATION OF MICROSPHERES

Learning Objective

- Evaluation of microspheres

1. **Particle size and shape:** The most widely used methods to visualize microparticles are conventional light microscopy (LM) and scanning electron microscopy (SEM). LM provides a means of visualizing the microsphere structure before and after coating. SEM provides a higher resolution than LM. SEM allows investigations of microsphere surfaces. Confocal laser scanning microscopy (CLSM) can also be used as a nondestructive technique for studying microparticles. It allows investigation of not only the surface but also the interior of the particles, provided the material is sufficiently transparent and can be fluorescently labeled.
2. **Electron Spectroscopy for Chemical Analysis (ESCA):** The surface chemistry of the microspheres can be determined by ESCA, which provides a means of determining the atomic composition of the surface. The surface degradation of the biodegradable microspheres can then be determined from the spectra obtained.
3. **Attenuated Total Reflectance Fourier Transform-Infrared Spectroscopy (ATR-FTIR):** The ATR-FTIR provides information about the surface composition of the microspheres.
4. **Density determination:** The density of the microspheres can be measured with a multivolume pychnometer. Weighed amount of the sample is taken into the cup and loaded into the chamber. Helium is introduced at a constant pressure in the chamber and allowed to expand. There will

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be a decrease in pressure within the chamber due to the expansion of helium. Two consecutive readings of reduction in pressure at different initial pressures are noted. From the pressure readings, the volume and the density of the microspheres can be determined.

5. **Isoelectric point:** Microelectrophoresis is used to measure the electrophoretic mobility of the microspheres from which isoelectric point can be determined. The time of particle movement over a distance of 1 mm is measured and the mean velocity at different pH values ranging from 3 to 10 is calculated. Using this data electrophoretic mobility can be obtained.
6. **Surface carboxylic acid residue:** It is measured by using radioactive glycine, which is prepared by reaction of ^{14}C-glycine ethyl ester hydrochloride with the microspheres. The glycine residue is linked using a water-soluble condensing agent 1-ethyl-3(3-dimethylcamino propyl) carbidiimide (EDAC). The radioactivity of the conjugate is then measured in a liquid scintillation counter. Thus, the carboxylic acid residue can be compared and correlated.
7. **Surface amino acid residue:** It is determined by using radioactive ^{14}C-acetic acid conjugate. EDAC is used to condense the amino group and ^{14}C-acetic acid carboxylic acid residue. The free amino acid residues can be determined by indirect estimation of radioactivity of the ^{14}C having the glycine conjugate. The accuracy of the method depends on the time allowed for conjugation of the radioactive moiety and the reactivity of the free functional group.
8. **Drug entrapment efficiency:** The drug entrapment efficiency of the microspheres can be determined by lysing the washed microspheres. The lysate is then analyzed for its drug content. The equation is given by

$$\text{Percentage entrapment} = \frac{\text{Actual content}}{\text{Theoretical content}} \times 100$$

9. ***In Vitro* Release Studies:** The release of drug from microspheres can be carried out in phosphate saline buffer of pH 7.4 by using rotating paddle apparatus or dialysis method.

In case of the paddle apparatus, the sample is agitated at 100 rpm. Samples are withdrawn at predetermined time intervals. The drug content in the sample withdrawn is analyzed and release profile is determined by plotting the amount of drug released versus time.

Dialysis is the other method, in which the microspheres are kept in a dialysis bag or tube with a membrane. The dialyzing media is continuously stirred and samples of dialysate are taken at predetermined time intervals. The withdrawn sample is replaced each time with fresh buffer solution. The samples are estimated for drug content (refer Fig. 6.7.7).

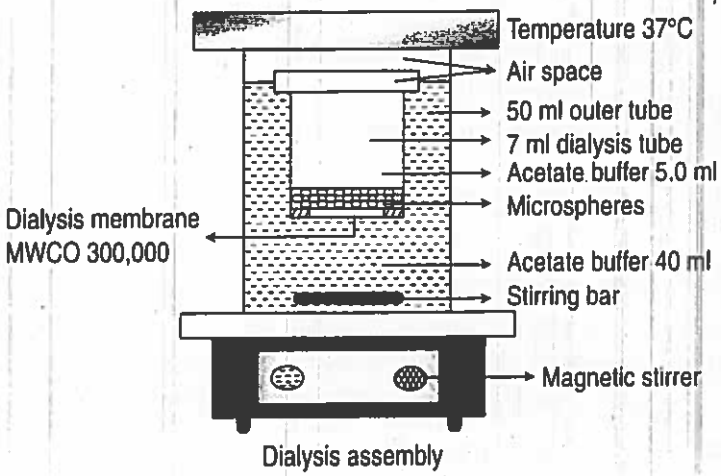

Figure 6.7.7 Dialysis Membrane Method

APPLICATIONS

1. **Microspheres in vaccine delivery:** Antigens such as staphylococcus enterotoxin B, diphtheria toxoid, hepatitis surface antigen and tetanus toxoid are formulated into microspheres by using thermoplastic polyesters of PLA and (glycolic acid) and their copolymers poly(lactides coglycolides).
2. **Microspheres in ocular drug delivery:** The eye and the cornea are easily accessible targets. However, the retention of microparticulate drug carriers in the corneal sac is difficult due to the washout effect. However, novel *in situ* drug delivery systems have been formulated, which can increase the retention of the microparticulate system by changing them to the gel form in the cul-de-sac of the eye.
3. **Microspheres in intranasal drug delivery:** The intranasal route is exploited for the delivery of peptides and proteins. The conventional dosage forms are rapidly cleared from the nasal mucosa. Bioadhesive microspheres are used as alternative dosage formulations having greater control over the surface character and release pattern.
4. **Microspheres in oral drug delivery:** Many drug substances are characterized by poor solubility in aqueous media and thus such drugs encounter pore problems. The incorporation of anti-infective agents of poor aqueous solubility into pH-sensitive microparticulates provides an efficient means for oral drug delivery.
5. **Magnetic microspheres:** Magnetic monitoring has the advantage of being efficient in allowing high local concentration of therapeutic agents. For example, amphotericin B magnetic microspheres are used in the treatment of pulmonary aspergillosis. Interleukin-2 magnetic microspheres are used to target the antiulcer tumor response of the macrophages.
6. **Imaging:** Various cells, cell lines, tissues and organs can be imaged using radiolabeled microspheres. Labeled human serum albumin microspheres can be used for the scintographic imaging of the tumor masses in lungs.
7. **Topical porous microspheres:** The microsponges act as topical carriers for a variety of functional substances such as antiacne, anti-inflammatory, antipyretic, antifungal and rubefacients.

REVIEW QUESTIONS

Answer in Detail

1. Discuss the various methods of manufacture of microspheres.
2. Write a note on the different types of microspheres.
3. Write in detail about characterization of microspheres.

Answer in Brief

1. Write a note on phase separation coacervation technique.
2. Discuss the therapeutic applications of microspheres.
3. Describe double emulsion technique of preparation of microspheres.
4. Discuss the formulation consideration in the synthesis of microspheres.
5. Write a note on the polymeric microspheres.

Answer in One

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