MICROENCAPSULATION

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- Definition
- Advantages and disadvantages
- Microspheres/ microcapsules
- Microparticles
- Methods of Encapsulation
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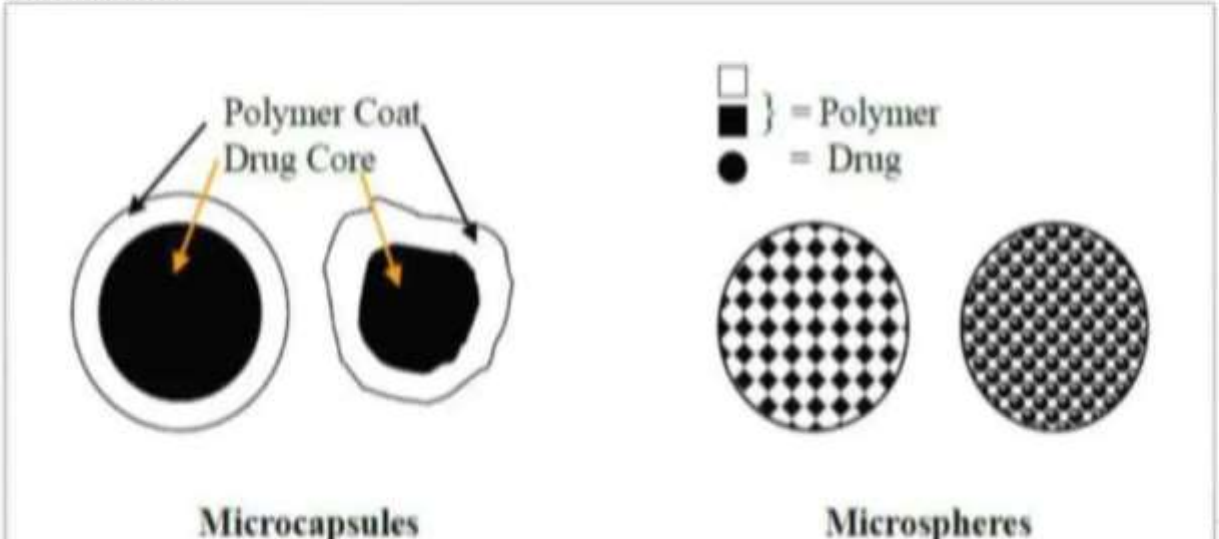
Introduction

- Microencapsulation is defined as a process of **enclosing** or **enveloping solids, liquids** within **second material with a continuous coating of polymeric materials yielding microscopic particles** (ranging from less than 1 micron to several hundred microns in size).
- In this process, **small discrete solid particles** or small **liquid droplets** and dispersions are surrounded and enclosed by applying **thin coating** for the purposes of providing environmental protection and controlling the release characteristics or availability of coated active ingredients

- Microencapsulation process is widely employed to **modify** and delayed drug release form different pharmaceutical dosage forms.
- The materials enclosed or enveloped within the **microcapsules** are known as **core materials or pay-load materials or nucleus**, and the **enclosing materials** are known as **coating materials or wall material or shell or membrane**



Advantages

- To Increase of **bioavailability**.
- To produce a **targeted** drug delivery
- To provide **environmental protection** of the core material from moisture, light, and oxygen.
- It enhances the **solubility of poorly soluble drugs** and the safe handling of toxic medications.
- It Masks the **taste of bitter drugs** to make them more palatable and improving patient compliance.
- To **decrease evaporation rate** of the core material.(Reduction of volatility)

Disadvantages

- The **cost** of the materials used and the formulation process might be **higher** than standard formulations.
- **Reproducibility** is less
- The effect of the polymer matrix, polymer additives, and their degradation products on the environment in response to heat, hydrolysis, or biological agents vary significantly.
- The core particle's stability is affected by the change in the process conditions like change in temperature, pH, solvent addition, or evaporation of the solvent

- ***Microparticles:***

"Microparticles" refers to the particles having the diameter range of **1-1000 µm**, irrespective of the precise exterior and/or interior structures.

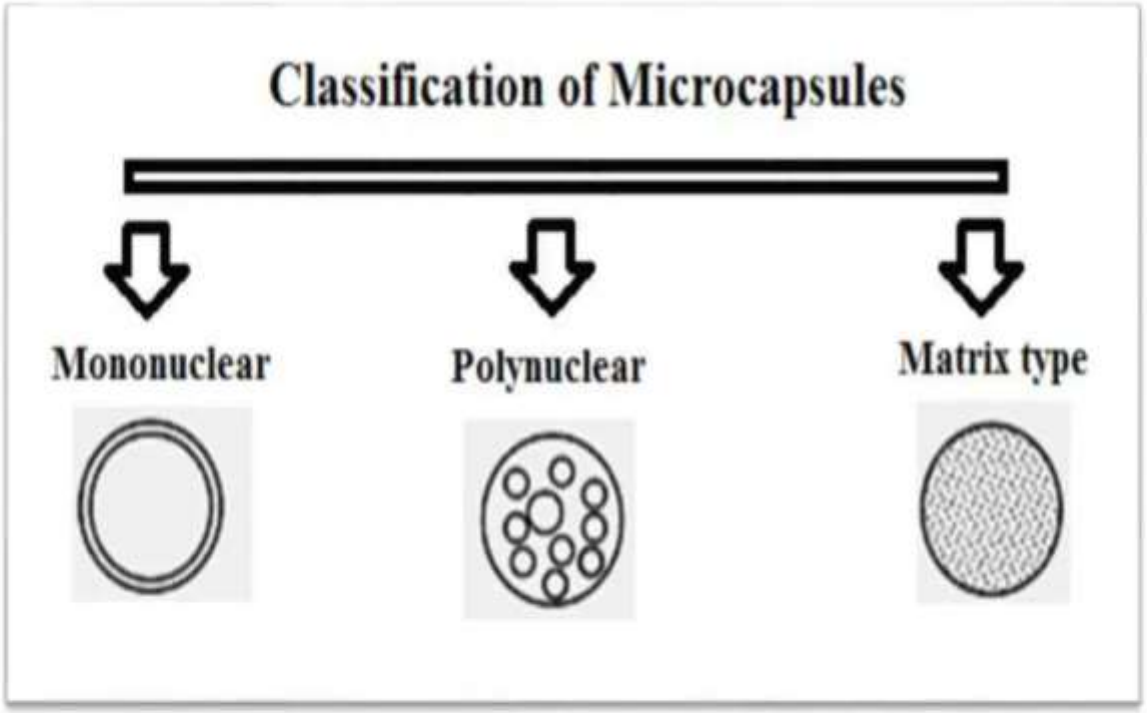
- ***Microspheres:***

"Microspheres" particularly refers to the **spherically shaped** microparticles within the broad category of microparticles.

- ***Microcapsules:***

"Microcapsules" refers to microparticles having a **core surrounded by the coat or wall material**(s) distinctly different from that of the core or pay-load or nucleus, which may be solid, liquid, or even gas.

- Microcapsules can be classified on three types
- i). **Mononuclear**: Containing the shell around the core.
- ii). **Polynuclear**: Having many cores enclosed with in shell.
- iii). **Matrix** type: Distributed homogeneously into the shell material.



Microspheres

- Microspheres are small spherical particles, with diameters **1 µm to 1000 µm.**
- They are **spherical free** flowing particles consisting of **proteins or synthetic polymers which are biodegradable in nature.**
- There are two types of microspheres

1. **Microcapsules** are those in which entrapped substance is distinctly surrounded by distinct capsule wall
2. **Micromatrices** in which entrapped substance is dispersed throughout the matrix

- Microspheres are sometimes referred to as microparticles.

Ideal characteristics of microspheres:

- The ability to **incorporate reasonably high concentrations** of the drug.
- **Stability** of the preparation after synthesis with a clinically acceptable **shelf life**.
- Controlled **particle size and dispersability** in aqueous vehicles for injection.
- Release of active reagent with a **good control over a wide time scale.**
- **Biocompatibility**

Advantages of microspheres:

1. **Particle size reduction** for enhancing solubility of the poorly soluble drug.

2. provide **constant and prolonged** therapeutic effect.

3. provide constant drug concentration in blood there by increasing patent compliance,

4. Decrease **dose** and **toxicity**.

5. Protect the drug from **enzymatic and photolytic** cleavage hence found to be best for drug delivery of protein.

6. Reduce the **dosing frequency** and thereby improve the **patient compliance**

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

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

9. Convert liquid to solid form & to **mask** the **bitter** taste.

10. Protects the GIT from irritant effects of the drug.

11. Biodegradable microspheres have the advantage over large polymer implants in that they do not require **surgical procedures for implantation and removal**.

12. Controlled release delivery biodegradable microspheres are used to control drug release rates thereby **decreasing toxic side effects**, and eliminating the

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

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. Quassi emulsion solvent diffusion

MATERIALS USED IN THE PREPARATION OF MICROSPHERE:

- 1. **Natural polymers-** Natural polymers obtained from different sources like carbohydrates proteins and chemically modified **Carbohydrates** Carbohydrates: Agarose, Carrageenan, Chitosan, Starch
- **Proteins**: Albumin, Collagen and Gelatin Chemically modified carbohydrates: Poly dextran, Poly starch.
- 2. **Synthetic Polymers** Synthetic polymers are divided into two types.

Biodegradable polymers

- E.g. Lactides, Glycolides & their co-polymers,Poly anhydrides,Poly alkyl cyano acrylates

Non-biodegradable polymers

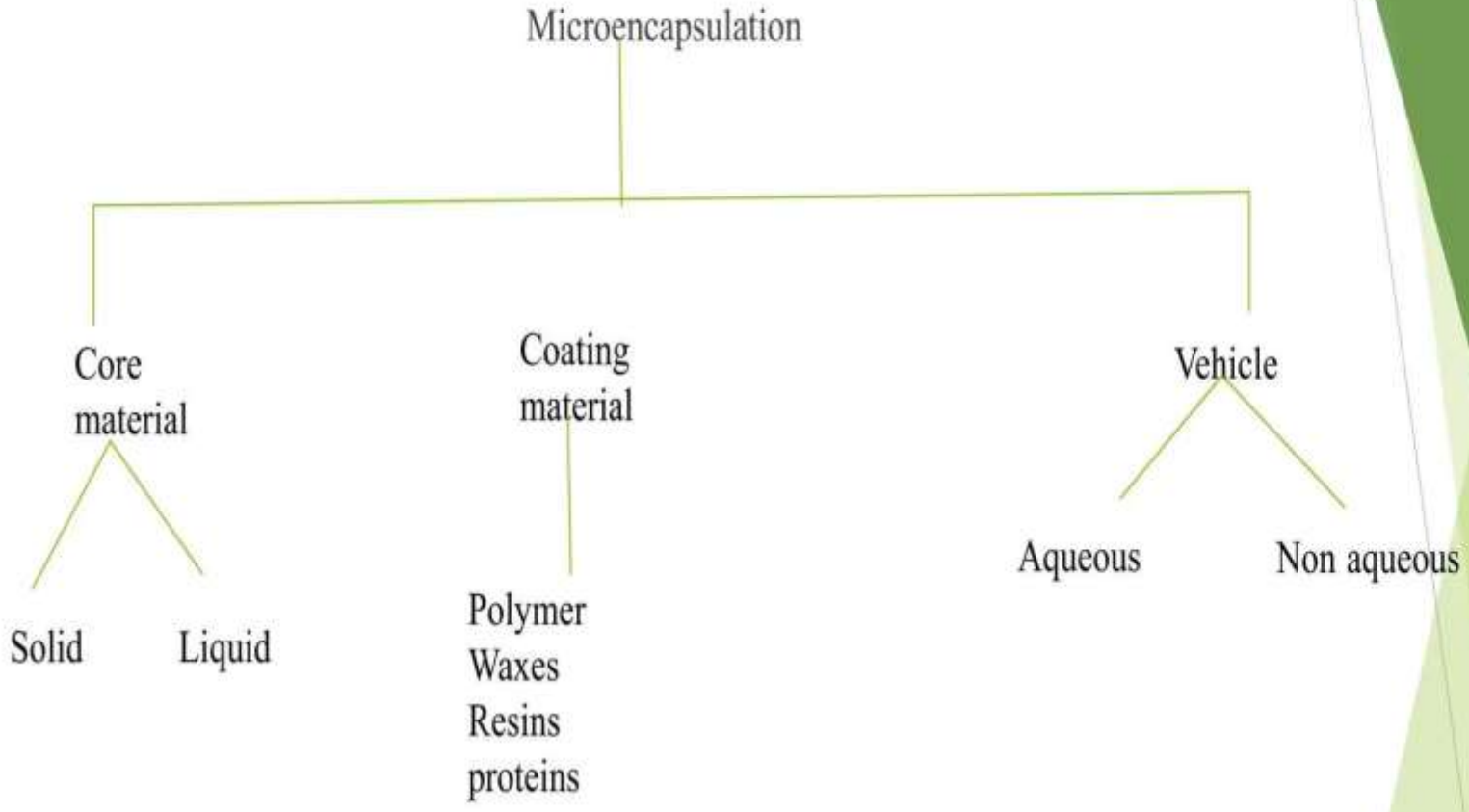
EVALUATION OF MICROSPHERES:

- Particle size and shape
- Electron spectroscopy for chemical analysis:
- Density determination
- Angle of contact:
- In vitro methods:
- Drug entrapment efficiency
- Swelling index

APPLICATION OF MICROSPHERES IN PHARMACEUTICAL INDUSTRY:

1. Ophthalmic Drug Delivery
2. Oral drug delivery
3. Gene delivery
4. Nasal drug delivery
5. Intratumoral and local drug delivery
6. Buccal drug delivery
7. Gastrointestinal drug delivery
8. Transdermal drug delivery
9. Colonic drug delivery
10. Vaginal drug delivery

FUNDAMENTAL CONSIDERATION



MICROENCAPSULATION TECHNIQUES:

- Physical Methods:
- Air suspension techniques (Wurster)
- Coacervation Process
- Pan Coating
- Spray Drying & Congealing
- Fluidized bed technology
- Solvent Evaporation
- Polymerization
- Single & Double Emulsion Techniques
- Supercritical fluid Anti Solvent method (SAS)
- Nozzle Vibration Technology
- Interfacial cross linking
- Multiorific-centrifugation

- Chemical Methods:

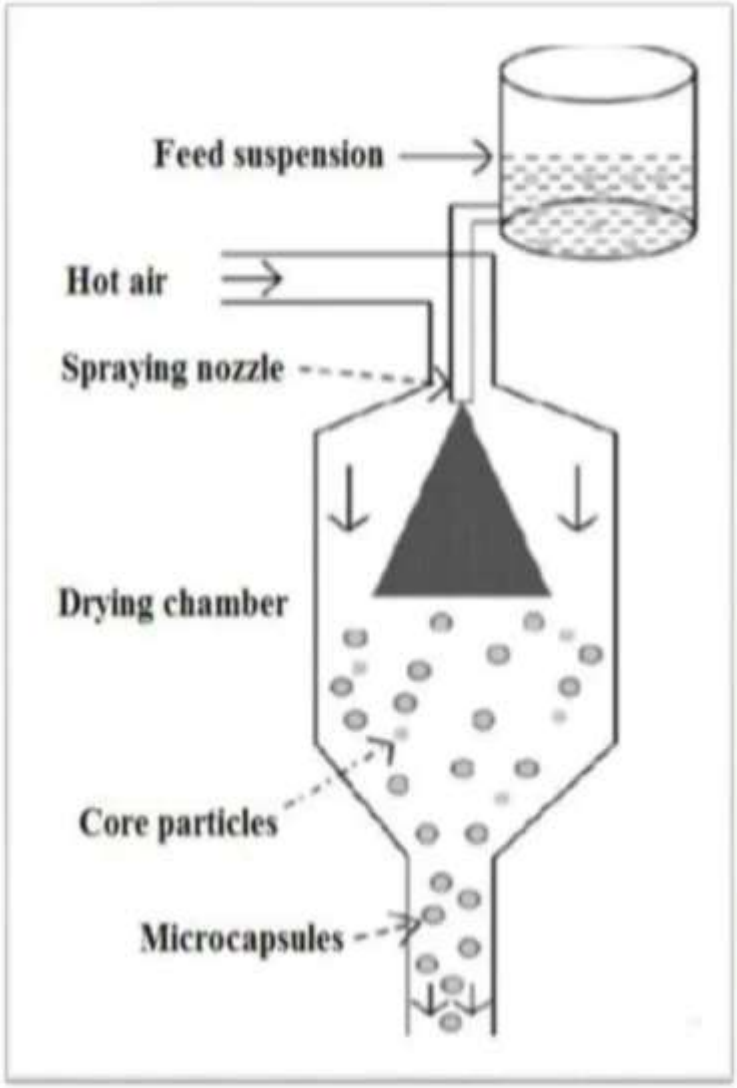
- Interfacial polymerization
- In-situ polymerization
- Matrix polymerization

Physical Methods

- **Air suspension**

- This process is also known as Wurster Air Suspension and is based on Fluidized Bed coating process.
- Microencapsulation by air suspension method **consists** of the **dispersing of solids, particulate core materials in a supporting air stream** and the **spray coating** on the air suspended particles.
- Solutions and suspensions of coating materials in both water and volatile organic solvents are employed.
- Within the coating chamber, **particulate core** materials are **suspended** on an upward moving air stream.

- The chamber design and its operating parameters influence a re-circulating flow of the particles through the coating-zone portion of the coating-chamber, where a **coating material** is **sprayed** to the moving particles.
- During **each pass** through the coating-zone, the **core material** receives a coat and this cyclic process is repeated depending on the purpose of microencapsulation.
- The supporting air stream also serves to dry the product while it is being encapsulated.
- The drying of the coated particles is accomplished at either room or elevated temperatures, depending on the solvent used.
- The **drying rate** is **directly** related to the **temperature of the supporting air stream used.**



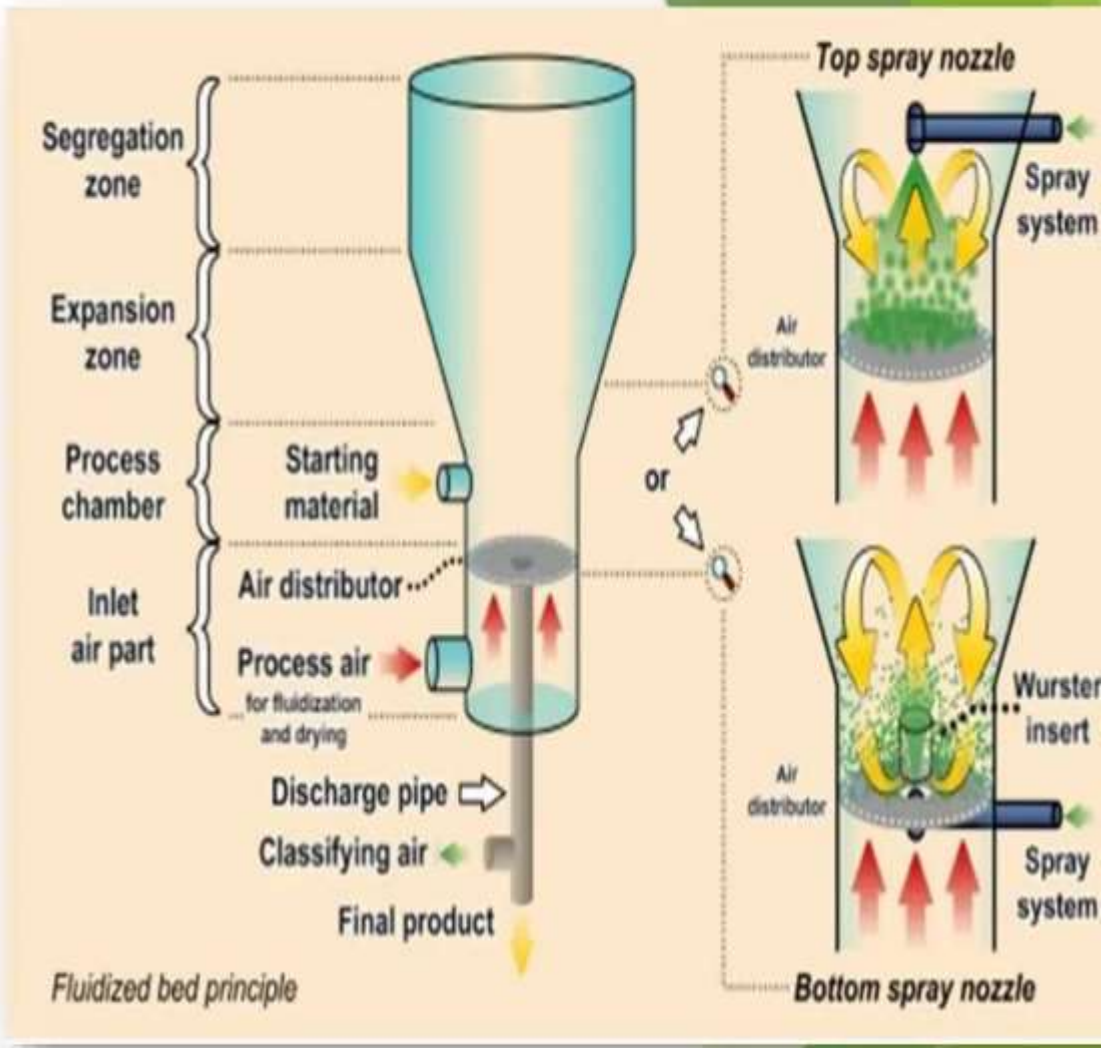
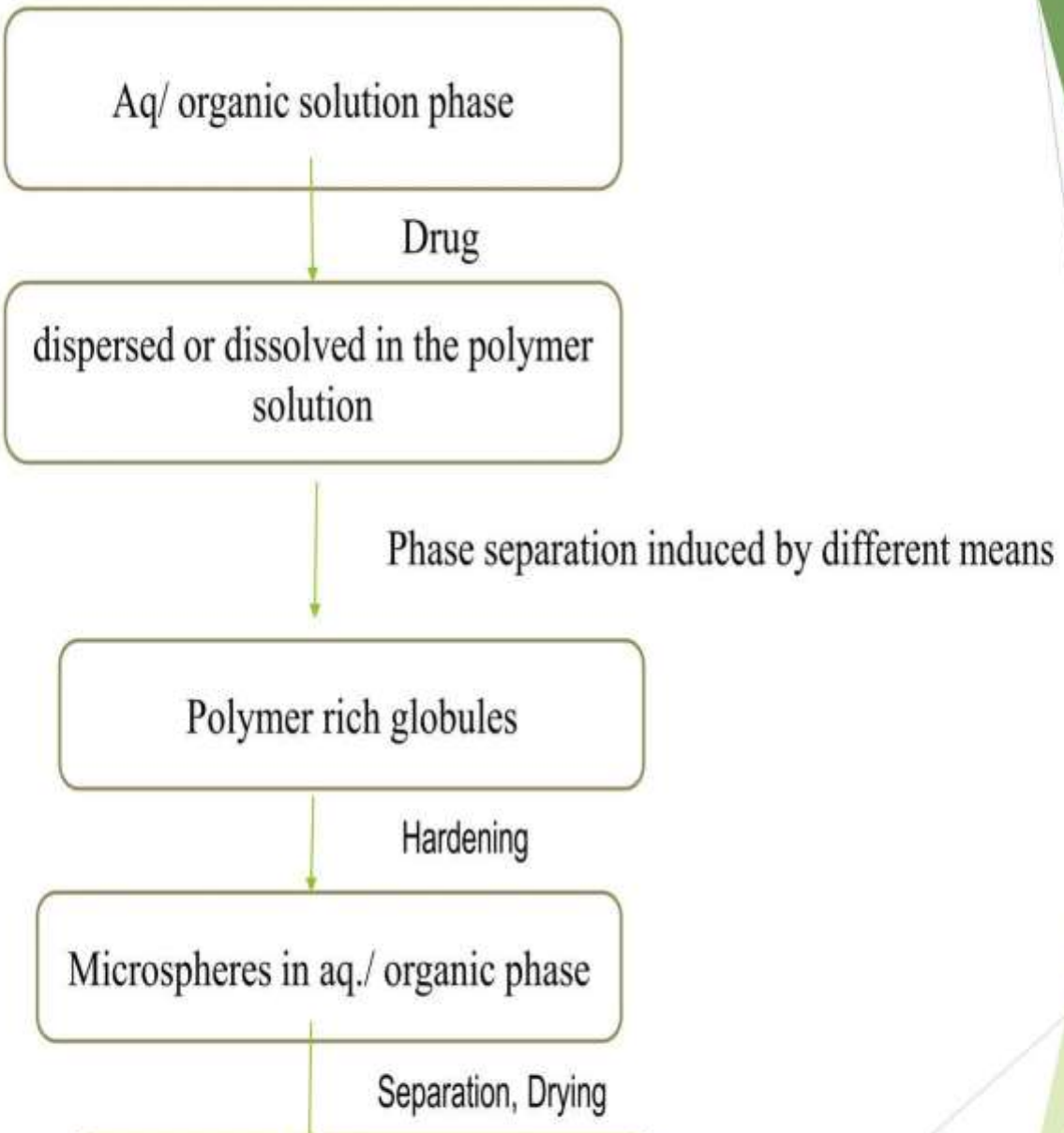


Fig. : Air suspension method for microencapsulation

Coacervation phase separation

- Coacervation may be initiated in a number of different ways. Examples are changing the temperature, changing the pH or adding a second substance such as a concentrated aqueous ionic salt solution or a non-solvent.
- As the coacervate forms, it must **wet** the **suspended** core particles or core droplets and coalesce into a continuous coating for the process of microencapsulation to occur.


Aq/ organic solution phase
Drug
dispersed or dissolved in the polymer solution
Phase separation induced by different means
Polymer rich globules
Hardening
Microspheres in aq./ organic phase
Separation, Drying

- This process consists of three Steps-

- **Formation of three immiscible phases;**

1. a liquid manufacturing phase,
2. a core material phase and
3. a coating material phase.

- The core material is dispersed in a solution of the coating polymer, the solvent for the polymer being the liquid manufacturing vehicle phase.

- The **coating material phase,** an immiscible polymer in a liquid state, is formed by utilizing one of the methods of phase separation coacervation, that is,

- By changing the temperature of the polymer solution
- By adding a salt
- By adding a non-solvent
- By adding incompatible polymer to the polymer solution
- By inducing a polymer-polymer interaction.

A) Temperature change

- Core material: N-acetyl p-aminophenol
- Polymer:- ethyl cellulose
- Solvent: cyclohexane.

EC + Cyclohexane → Polymer solution + Nacetylp-aminophenol (1:2)

↓

Gelation & solidification of coating occur

↓

Collected by filteration, decantation & centrifugal technique.

B) Addition of incompatible polymer:

- Core material: Crystalline methylene blue HCl
- Coating material: Ethyl cellulose
- Solvent: Toluene
- Incompatible polymer: Polybutadiene

EC + Toluene mixture → methylene blue HCl (1:4)

55C

EC solidify by adding non-solvent hexane,

Collected by titration & drying technique.

C) By Non-solvent addition

- Core material: Methyl scopolamine HBr
- Coating polymer: Cellulose acetate butyrate
- Solvent: Methyl ethyl ketone
- Non-solvent: Isopropyl ether

CA butyrate + Methyl ethyl ketone mixture → methyl scopolamine

55C

mixture + isopropyl ether

(slowly cool at room temp.,

collected by centrifugation & drying)

D) By salt addition

- Core material: oil soluble vitamin
- Oil: corn oil
- Aq. phase: water
- Polymer: gelatin
- Salt: sodium sulphate

Salt : emulsion ratio is 4:10.

Oil soluble vitamin + corn oil

↓

mixture water +sodium sulphate

(oil droplet coated uniformly with gelation)

E) By polymer-polymer interaction:

- Core material: Methyl salicylate
- +ve charge polymer: Gelatin
- -ve charge polymer: Gum Arabic
- Aq. Gum arabic + Aq. Gelatin → mixture + water
- 4.5 pH, 40-50 0C
- polymer interact to causes phase separation
- warm
- mixture + methyl salicylate
- slowly cooled the mixture at 25 0C over 1 hr
- rigidization of coating is done by cooling
- microencapsule at 10 0C

- **Deposition of the liquid polymer coating on the core material**

- This is done by **controlled mixing** of **liquid** coating material and the core material in the manufacturing vehicle.

- Deposition of the liquid polymer coating around the core material occurs if the polymer is adsorbed at the interface formed between the core material and the liquid vehicle phase.

- **Rigidizing of the coating material by thermal, cross linking or dessolvation techniques to form microcapsules.**

- Important equipments necessary for microencapsulation by coacervation phase separation method are jacketed tanks with variable speed agitators

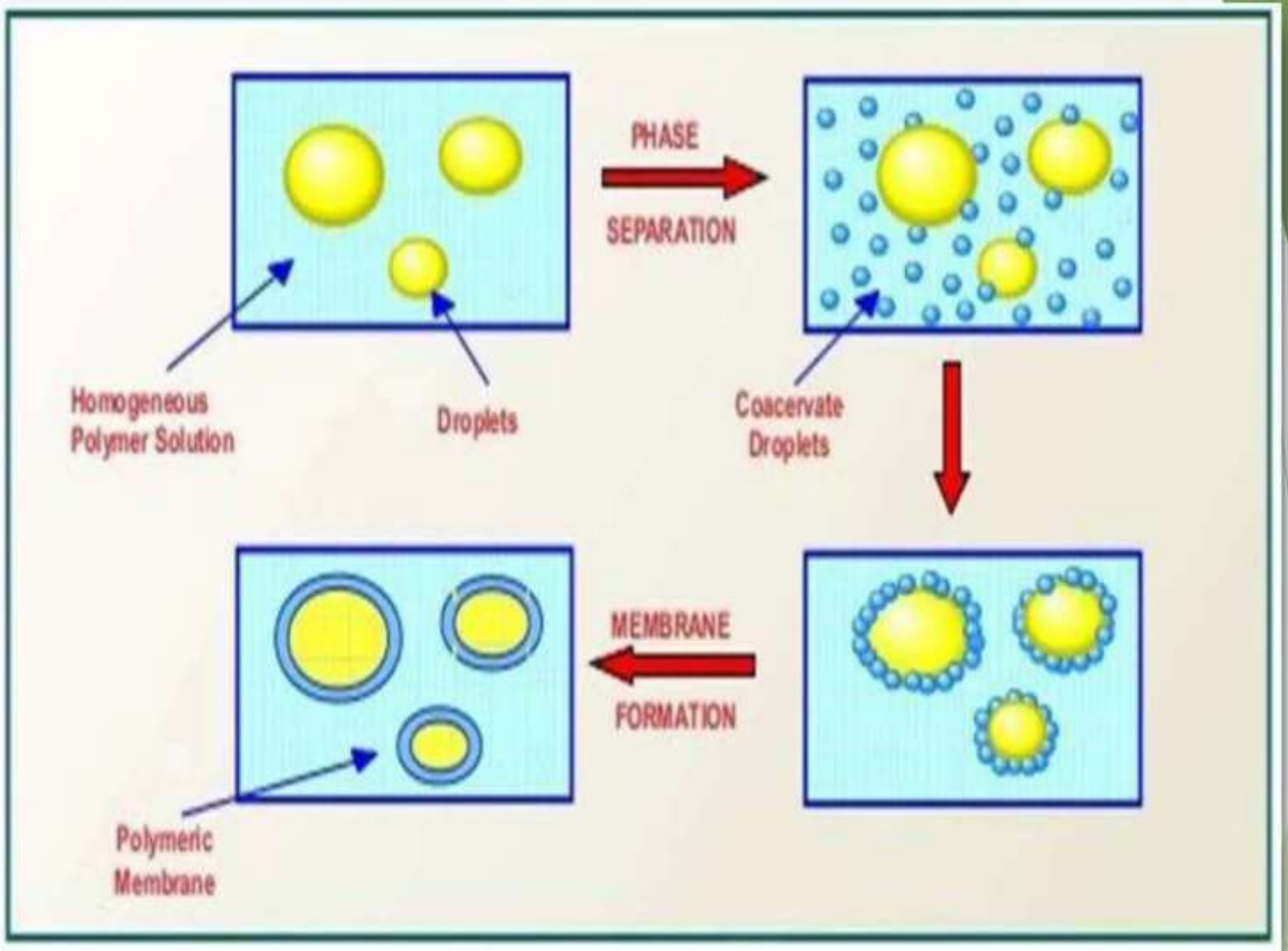
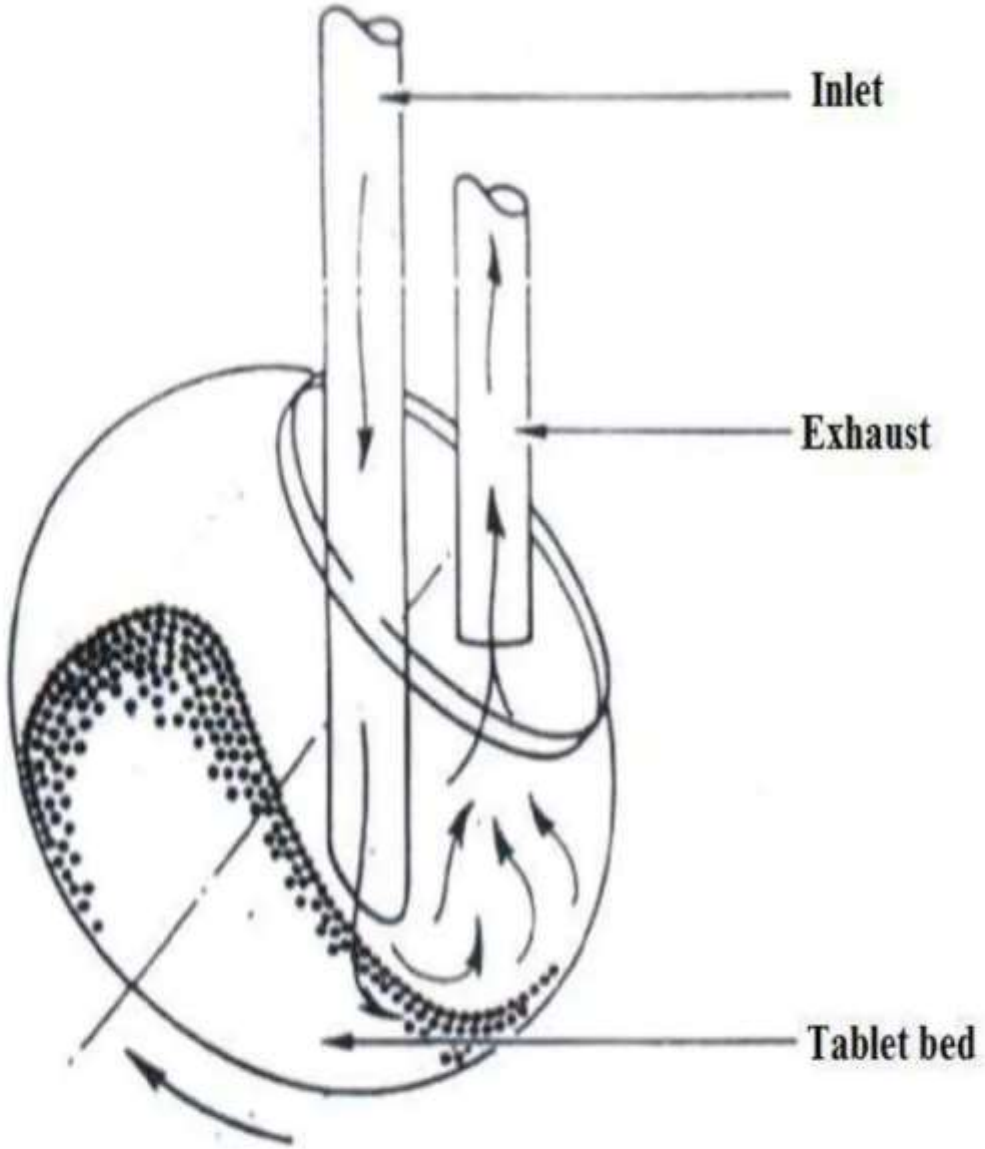


Fig.: Coacervation phase separation method for

Pan coating

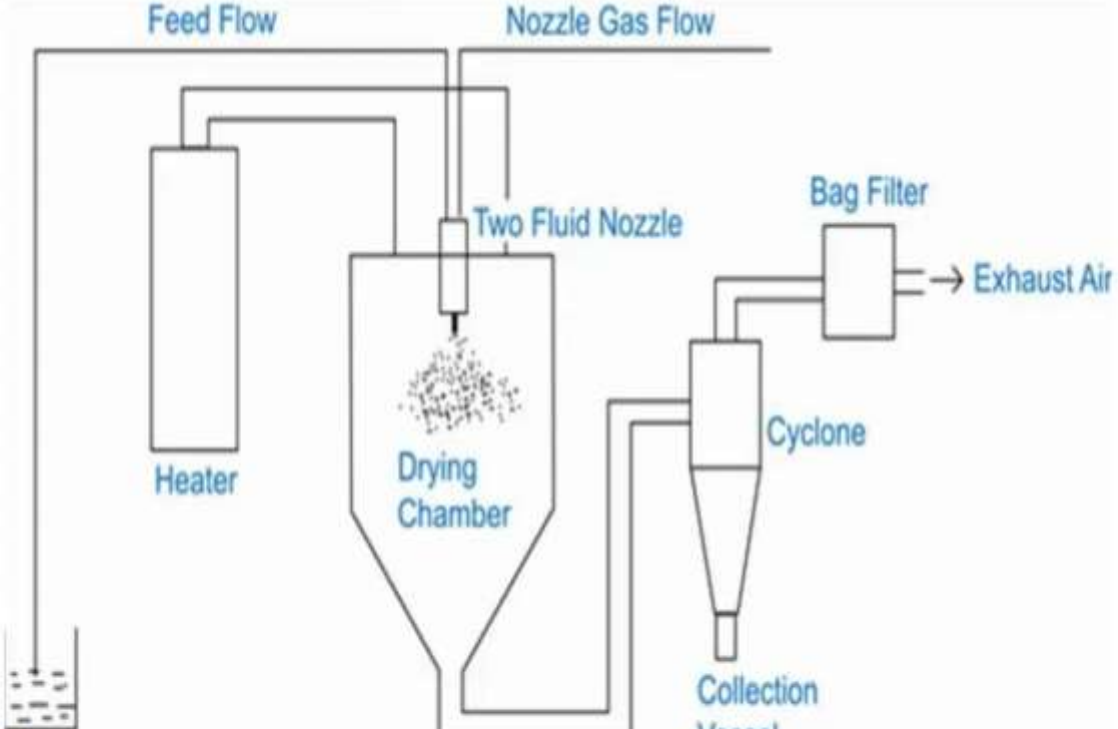
- For relatively large particles, which are greater than **600 µ in size, microencapsulation can be done by pan coating method,**
- In this method, various spherical core materials, such as **nonpareil sugar seeds are coated with a variety of polymers**
- In practice, the coating is applied as a solution or as an **atomized** spray to the desired solid core material in the coating pan.
- To remove the coating solvent warm air is passed over the coated material.
- By using this technique larger sized particles will be coated effectively


Inlet
Exhaust
Tablet bed

Spray Drying And Congealing

- methods of microencapsulation are almost similar
- both the methods entail the **dispersion of core material in a liquefied coating agent and spraying or introducing the core coating mixture into some environmental condition.**
- The main **difference** in-between these two microencapsulation methods are the **means** by **which** the **coating solidification** is **carried** out.
- In **spray drying method**, the coating solidification is influenced by the **quick evaporation** of a solvent, in which the coating material is dissolved

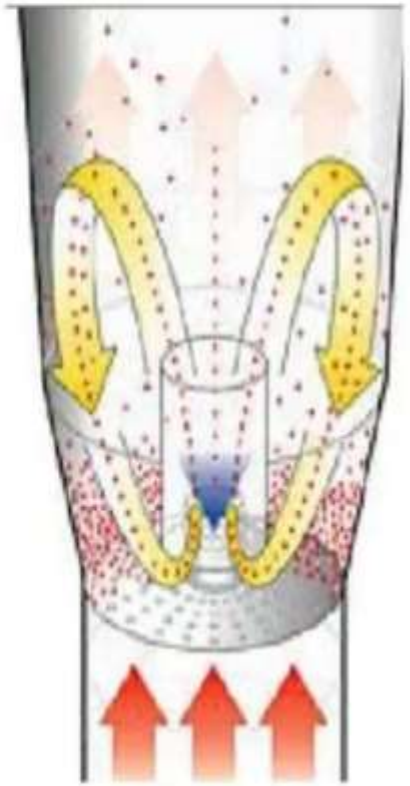
- In **spray congealing** method, the **coating solidification** is accomplished by the **thermal congealing** of **molten** coating material or solidifying a dissolved coating by introducing the coating core material mixture into a non-solvent.
- Removal of **non-solvent** or solvent from the coated product is often done by sorption **extraction** or **evaporation.**



Fluidized-bed technology

- used for the encapsulation of solid core materials, including liquids absorbed into porous solids .
- Solid particles to be encapsulated are **suspended** on a **jet** of **air** and afterward, are covered by a **spray** of **liquid** coating material.
- The capsules are traveled to an area where their **shells** are **solidified** by **cooling** or **solvent vaporization** .
- The processes of **suspending**, **spraying**, and **cooling** are repeated until the attainment of the desired thickness of the capsule-wall.
- This is known as **Wurster** process when the **spray nozzle** is located at the

a) Top-spray

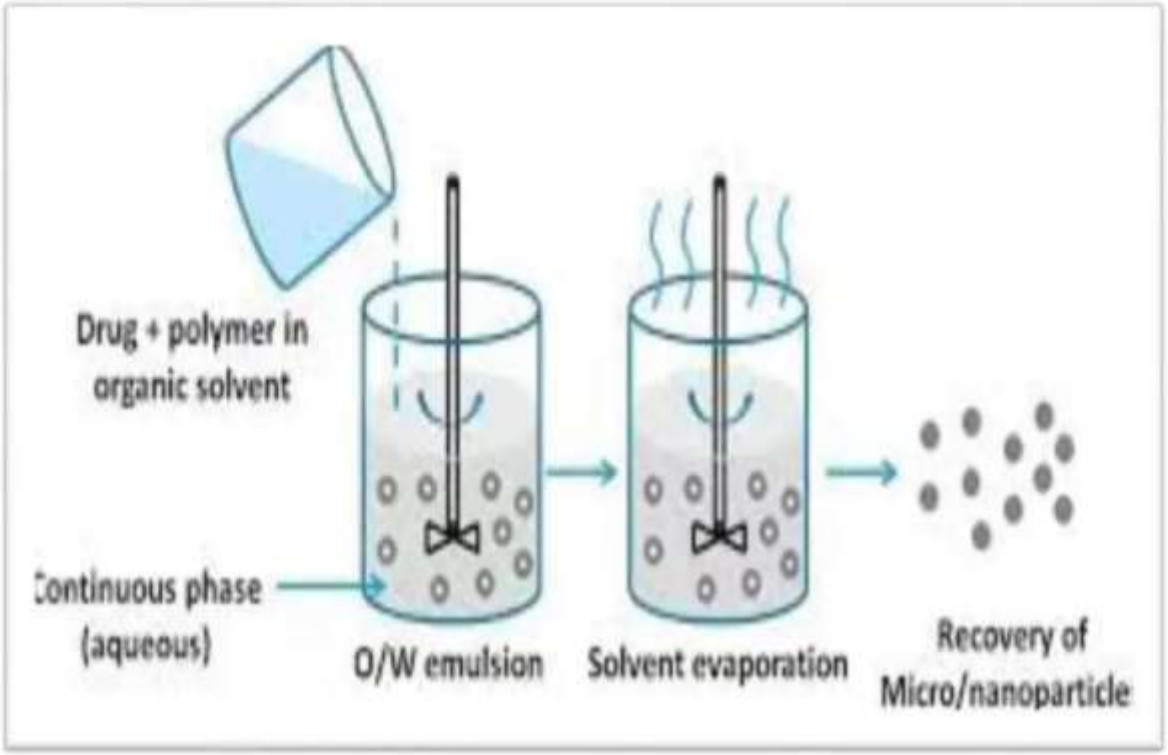


b) Bottom-spray

c) Tangential-spray

Solvent Evaporation

- appropriate for liquid manufacturing vehicle (O/W emulsion), which is prepared by agitation of two immiscible liquids.



- The solvent evaporation method involves **dissolving** microcapsule **coating** (polymer) in a volatile solvent, which is immiscible with the liquid manufacturing vehicle phase.
- A core material (**drug**) to be microencapsulated is dissolved or dispersed in the coating polymer solution.
- With **agitation**, the **core–coating** material mixture is **dispersed** in the liquid manufacturing vehicle phase to obtain the appropriate sized microcapsules.
- **Agitation** of system is continued until the solvent **partitions** into the aqueous **phase** and is removed by evaporation. This process results in hardened microcapsules.
- The most common method is the use of a **propeller style** blade attached to a

Process variables for solvent Evaporation

- rate of solvent evaporation for the coating polymer(s)
- temperature cycles
- agitation rates
- The most important factors that should be considered for the preparation of microcapsules by solvent evaporation method include **choice** of **vehicle** phase and **solvent** for the polymer coating, and **solvent** recovery systems.

Multiorific-centrifugation

- utilizes the centrifugal forces to hurl a core particle trough an enveloping membrane
- Various processing variables of multiorific-centrifugation method include
- (i) rotational speed of the cylinder,
- (ii) flow rate of the core and coating materials, and
- (iii) concentration, viscosity and surface tension of the core material

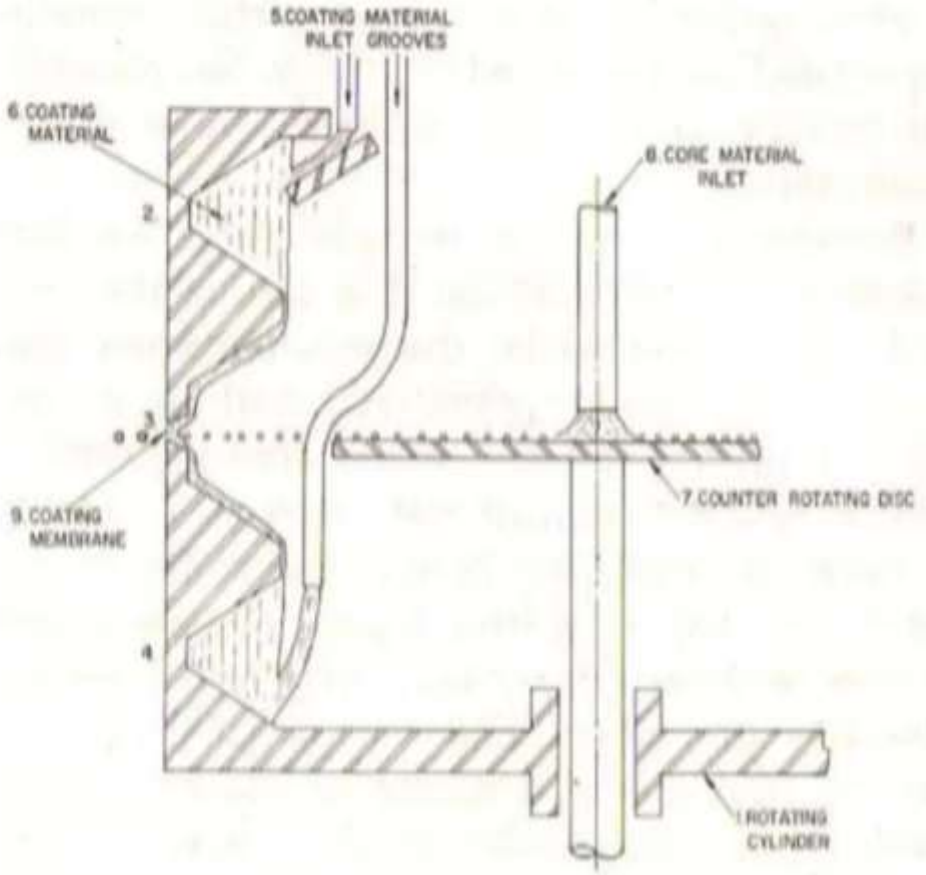


FIG. 13-45. *Sectional diagram of multiorifice-centrifugal microencapsulation apparatus. (From Mattson.[30] Courtesy Conover-Mast Publications, Inc.)*

Applications of Microencapsulation

- can be used to formulate various **sustained controlled** release dosage forms by modifying or delaying release of encapsulated active agents or core materials
- employed to formulate **enteric-coated** dosage forms,
- **Gastric irritant** drugs are being microencapsulated to reduce the chances of gastric irritation.
- The **taste** of bitter drug candidates can be masked
- **liquids** and **gases** can be changed into solid particles in the form of microcapsules.
- provides environmental protection to the encapsulated active agents from various environmental issues, such as light, heat, humidity, oxidation,

THANK YOU