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Chapter No. 3

MICROENCAPSULATION

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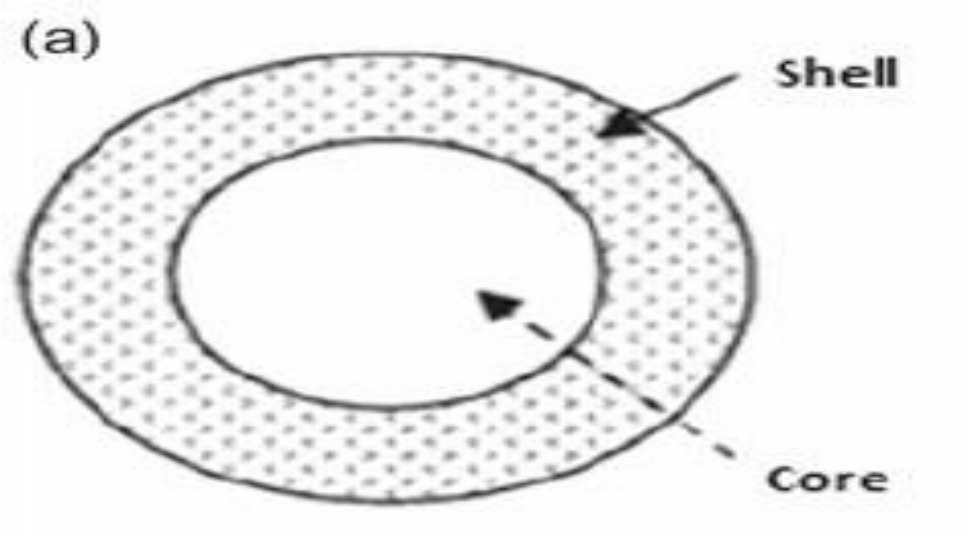
Definition

"The process by which tiny solid particles or droplets of liquid are surrounded or coated with a continuous film of polymeric material to produce a capsule in the micrometer to millimeter range."

i. MICROPARTICLES

Definition

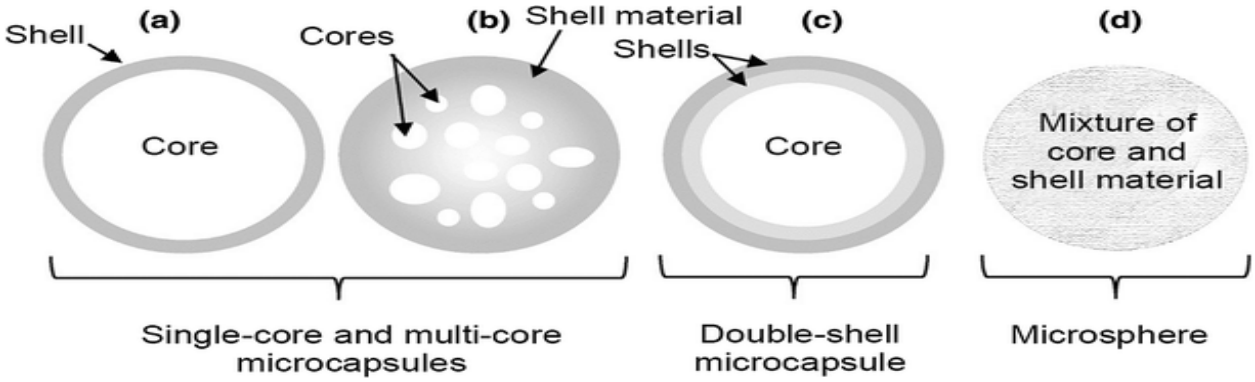
Hollow microparticle composed of a solid shell surrounded a core forming space available to permanently or temporarily entrapped substances. Particulate dispersions or solids particles with a size in the range of 1-1000 micrometer (μm)



ii. MICROSPHERE

Definition:

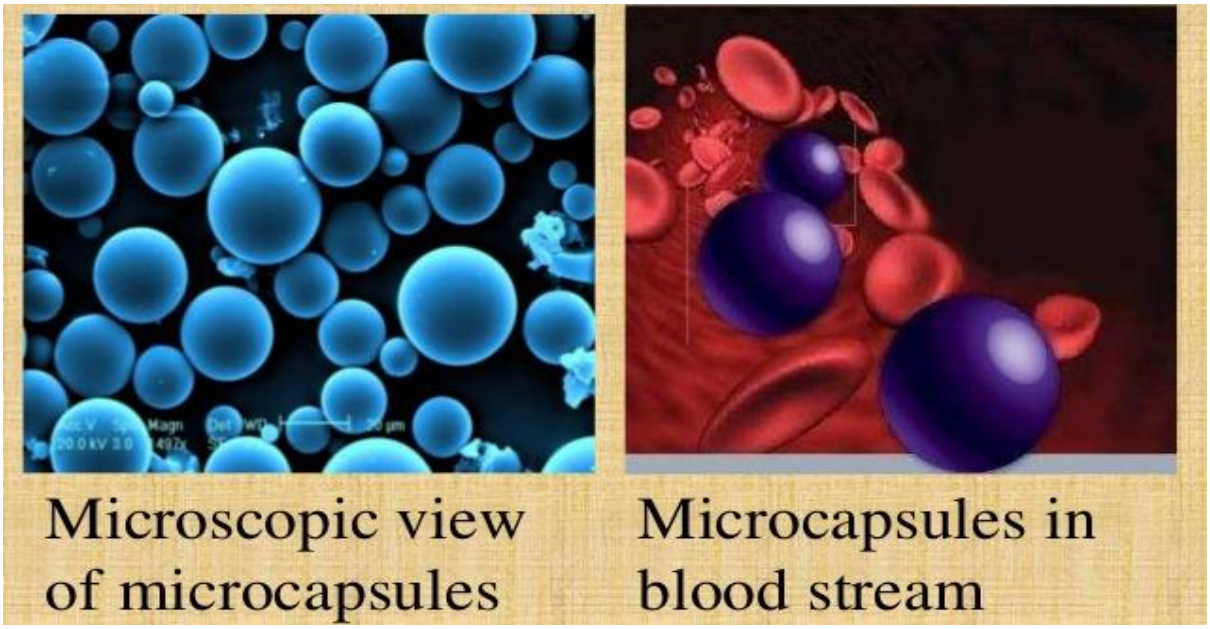
"Microcapsules are tiny capsule containing materials as adhesive or medicine which release when the capsules are broken, melted or dissolved."



iii. MICROCAPSULES

Definition:

"Microcapsules are tiny capsules containing materials as adhesive or medicine which release when the capsules are broken, melted, or dissolved."



iv. MICROSPONGES

Definition:

"Microsponges are Polymeric delivery system composed of porous microspheres. They are tiny sponge like spherical particles with large surface"

Diameter:

Its diameter ranges from 5-25 µm (Micrometer)

MATERIALS INVOLVED IN MICROENCAPSULATION

1. Core Material:

The material to be coated

- May be liquid or solid
- Liquid core may be dissolved or dispersed material
- Composition of coating material
  - Drug or active constituent
  - Additive like diluents
  - Stabilizers
  - Release rate enhancers

2. Coating Material:

Inert substance which coats on core with desired thickness

- Compatible with the core material
- Stabilization of core material
- Inert toward active ingredients
- Controlled release under specific conditions
- The coating can be flexible, brittle, hard, thin etc.
- Abundantly and cheaply available
- Composition of coating
  - Inert polymer
  - Plasticizer
  - Colouring agent

EXAMPLES OF COATING MATERIALS

1. Gums:

- Gum Arabic
- Sodium alginate
- Carragenan

2. Carbohydrates:

- Starch
- Dextran
- Sucrose

3. Celluloses:

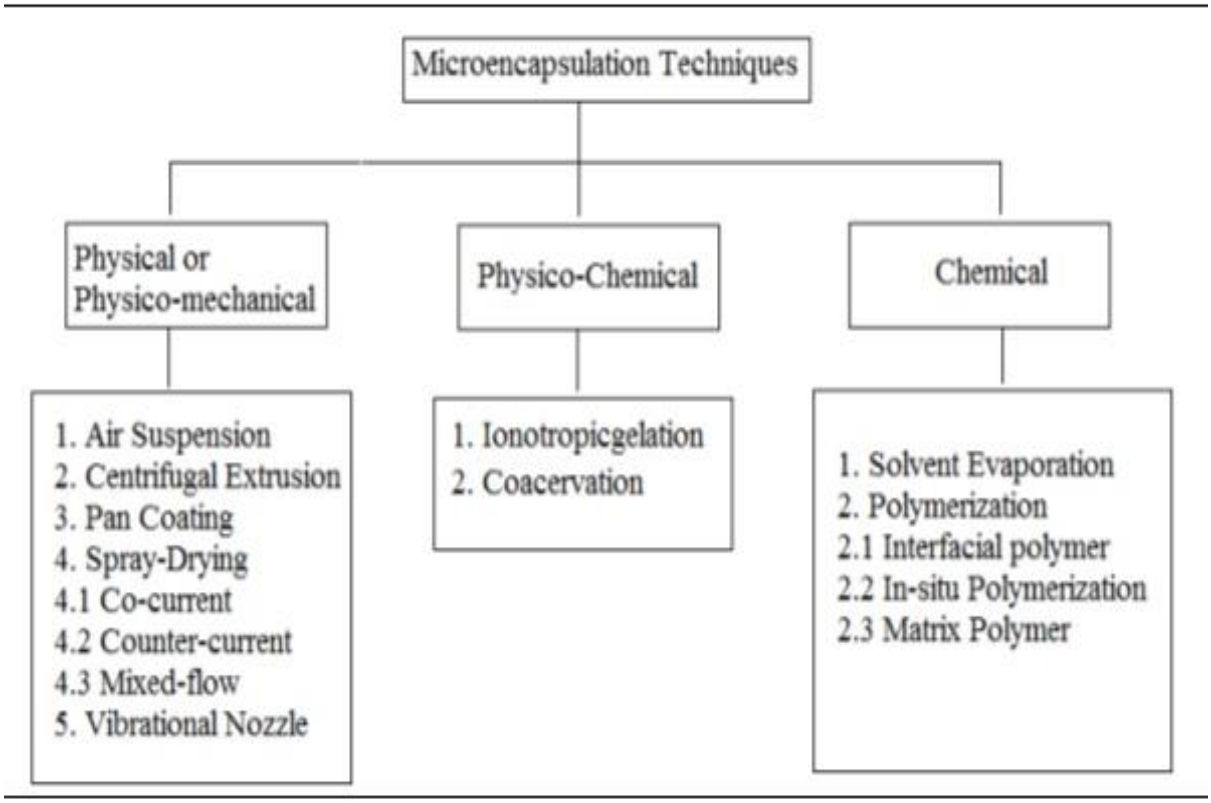
- Methylcellulose
- Carboxymethylcellulose

4. Lipids:

- Bees wax
- Stearic acid
- Phospholipids

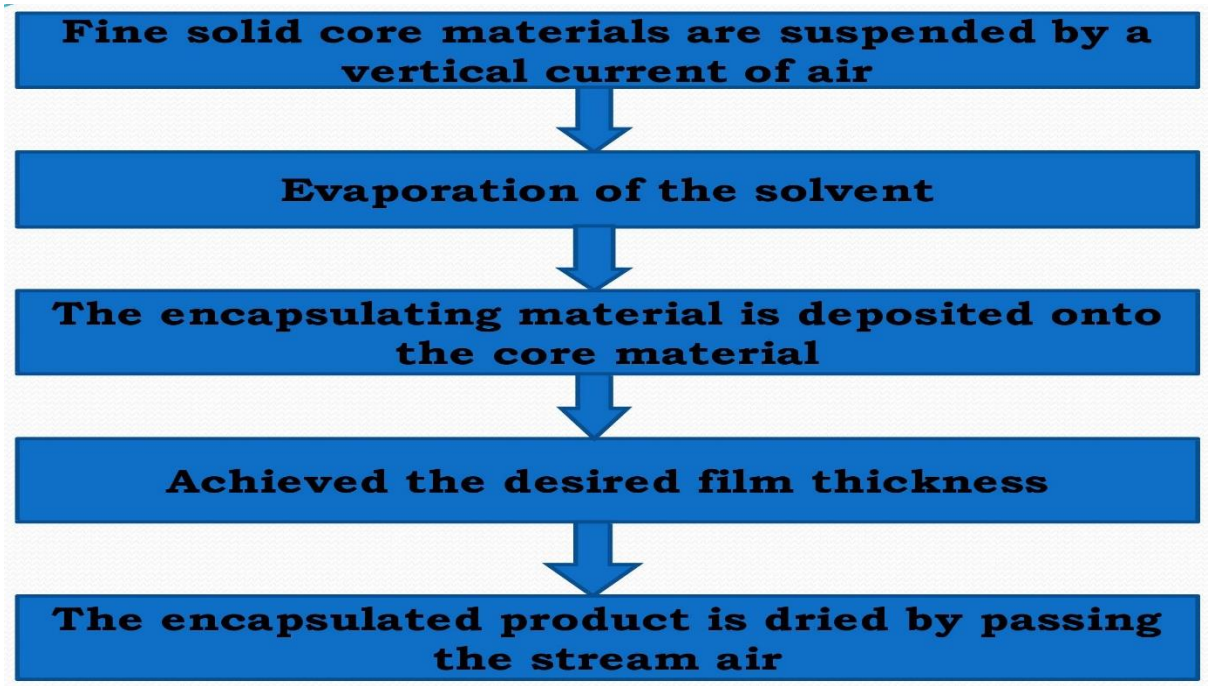
5. Proteins:

- Gelatin
- Albumin

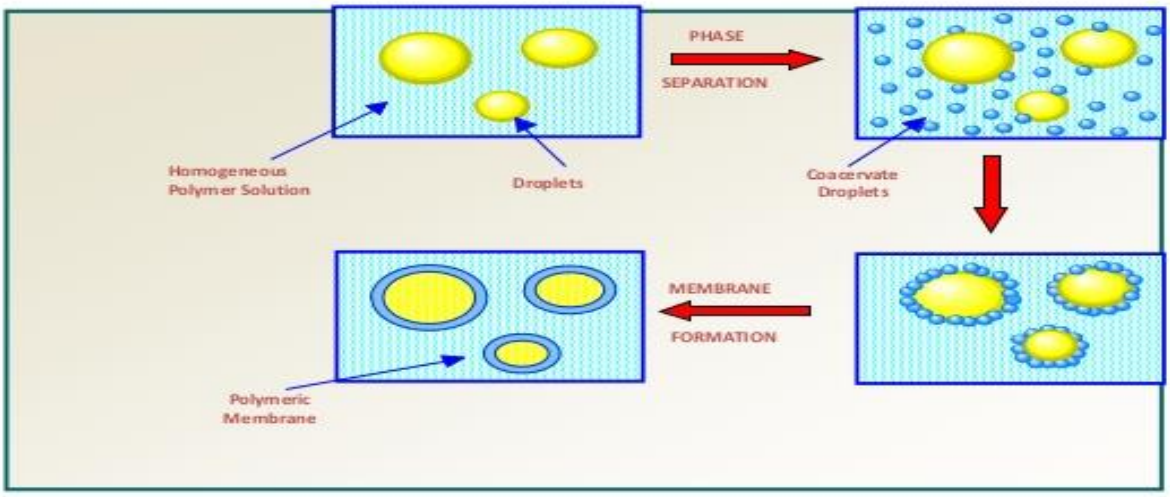


I. PHYSICO-CHEMICAL TECHNIQUE

A. Coacervation phase separation:

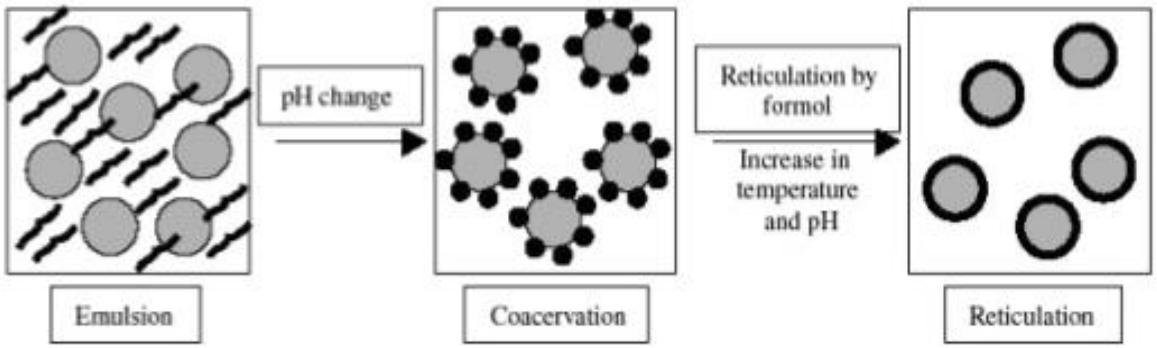


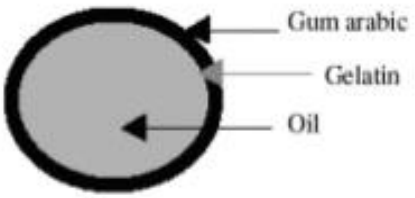
COACERVATION / PHASE SEPARATION



1. Formation of three immiscible phase
2. Deposition of coating
3. Rigidization of coating.

COECERVATION FORMATION





METHODS

Two methods

a) Simple coacervation

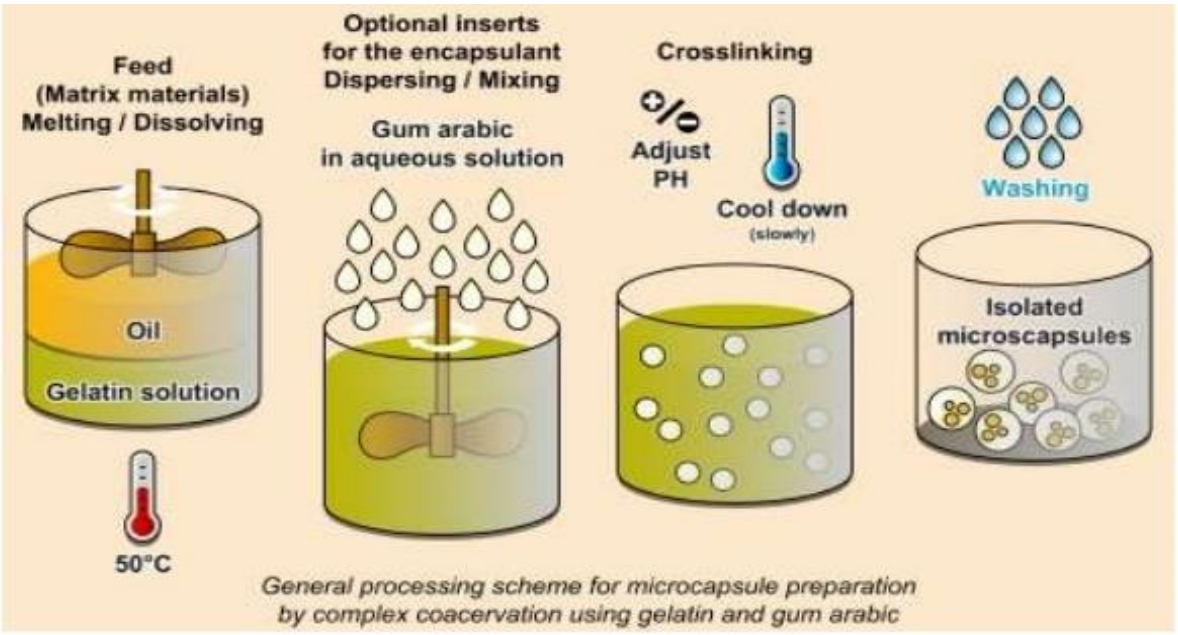
b) Complex coacervation

a) Simple coacervation

A desolvation agent is added for phase separation

b) Complex coacervation

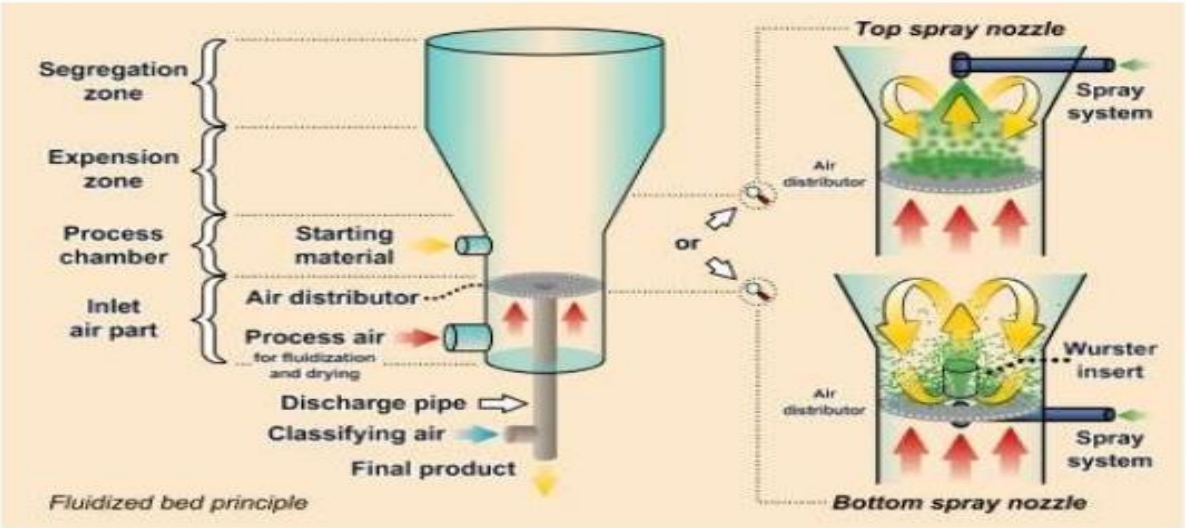
Involves complexation between two oppositely charged polymers.

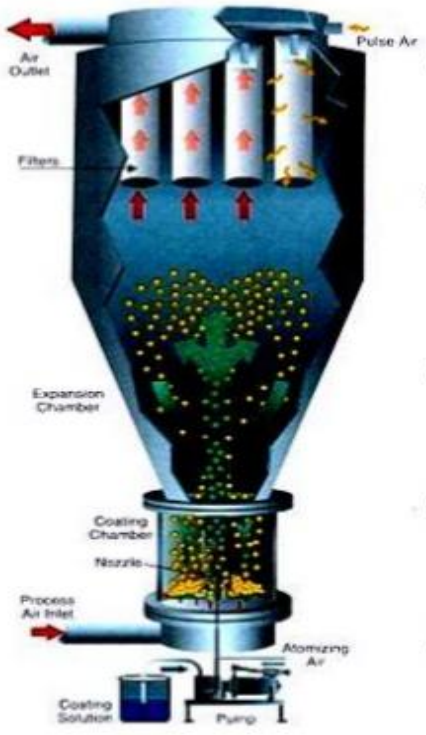


General processing scheme for microcapsule preparation by complex coacervation using gelatin and gum arabic

II. PHYSICO-MECHANICAL TECHNIQUE

A. Air suspension Techniques





The Wruster Process

- This technology is characterized by the location of a spray nozzle at the bottom of a fluidized bed of solid particles.
- The particles are suspended in the fluidizing air stream that is designed to induce a cyclic flow of the particles past the spray nozzle.
- The nozzle sprays an atomized flow of coating solution, suspension, or other coating vehicle.
- The technology can be used to encapsulate solid materials with diameters ranging from near 50μm to several centimeters.
- Wruster Process can be used to encapsulate vitamins, minerals, and functional food ingredients.

B. PAN COATING

Solid particles are mixed with a dry coating material

↓

Temperature is raised

↓

The coating material melts and encloses the core particles

↓

Then is solidified by cooling

↓

Microcapsule

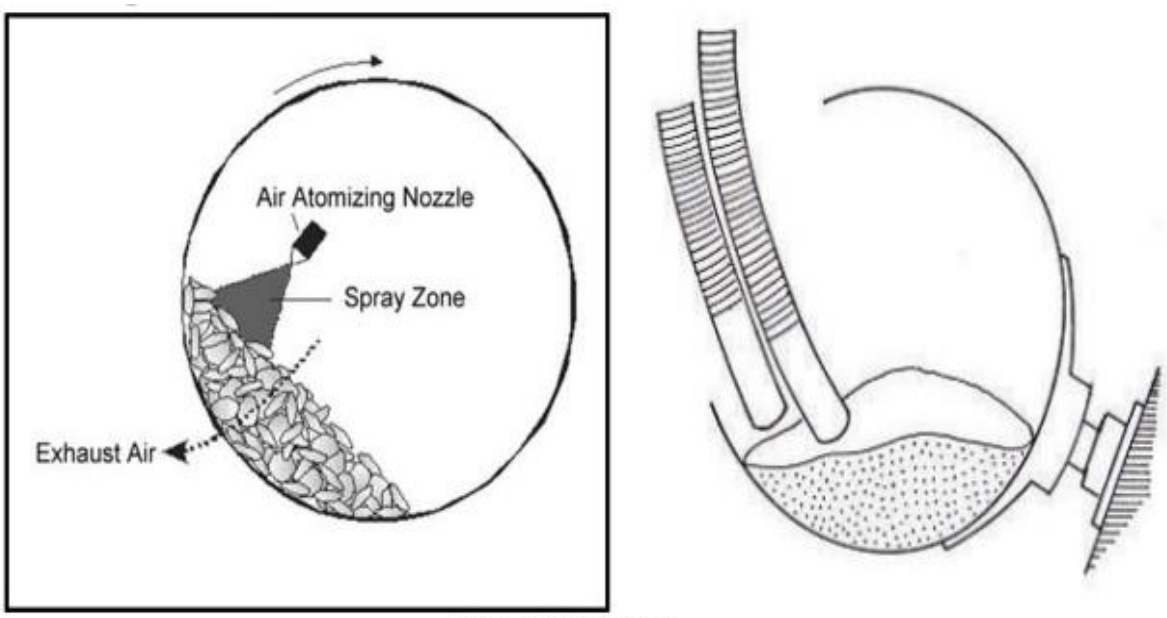
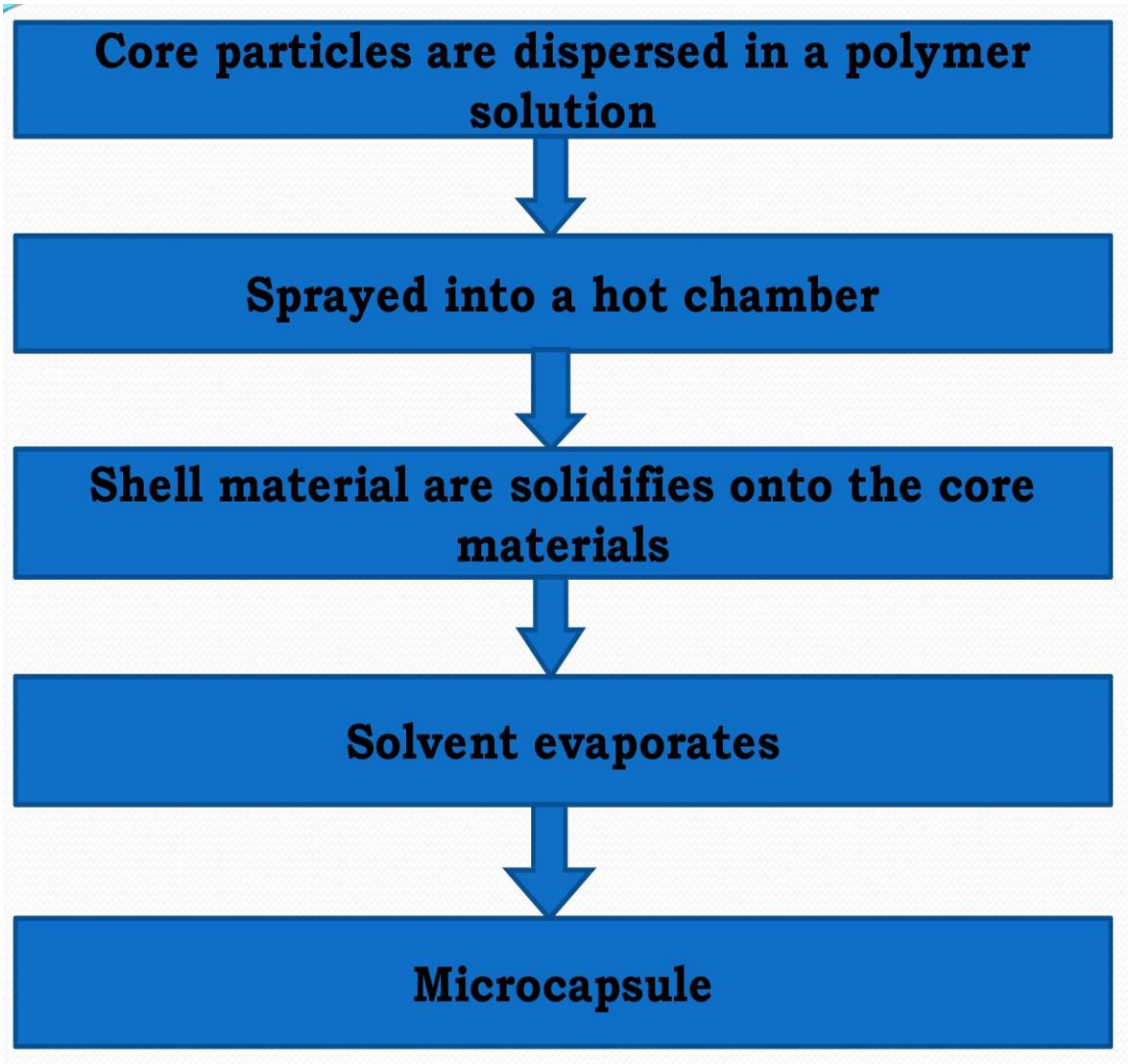
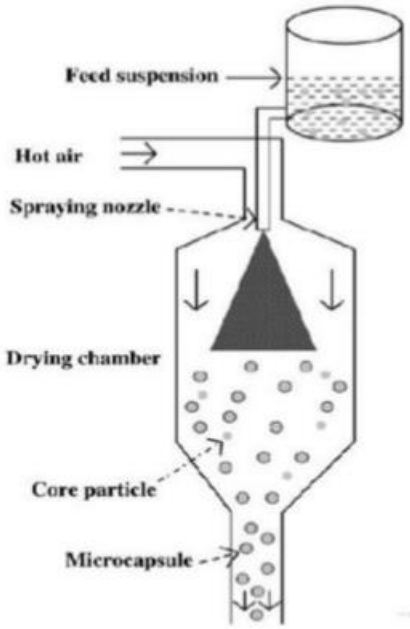


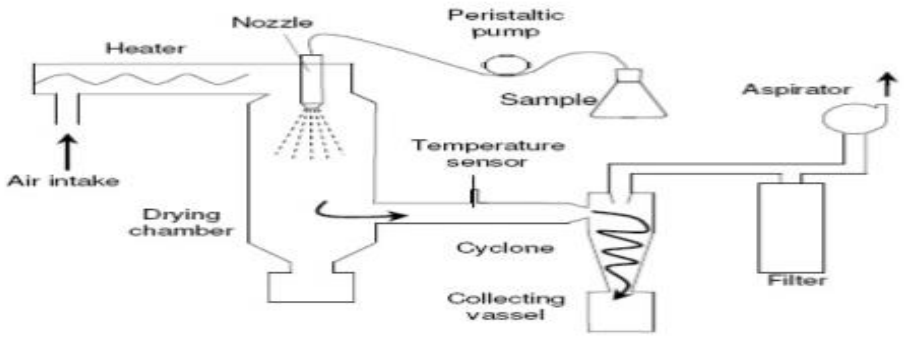
Figure Pan coater

C. SPRAY DRYING AND CONGEALING





SPRAY DRYING & CONGEALING (COOLING)



Spray drying : spray = aqueous solution / Hot air

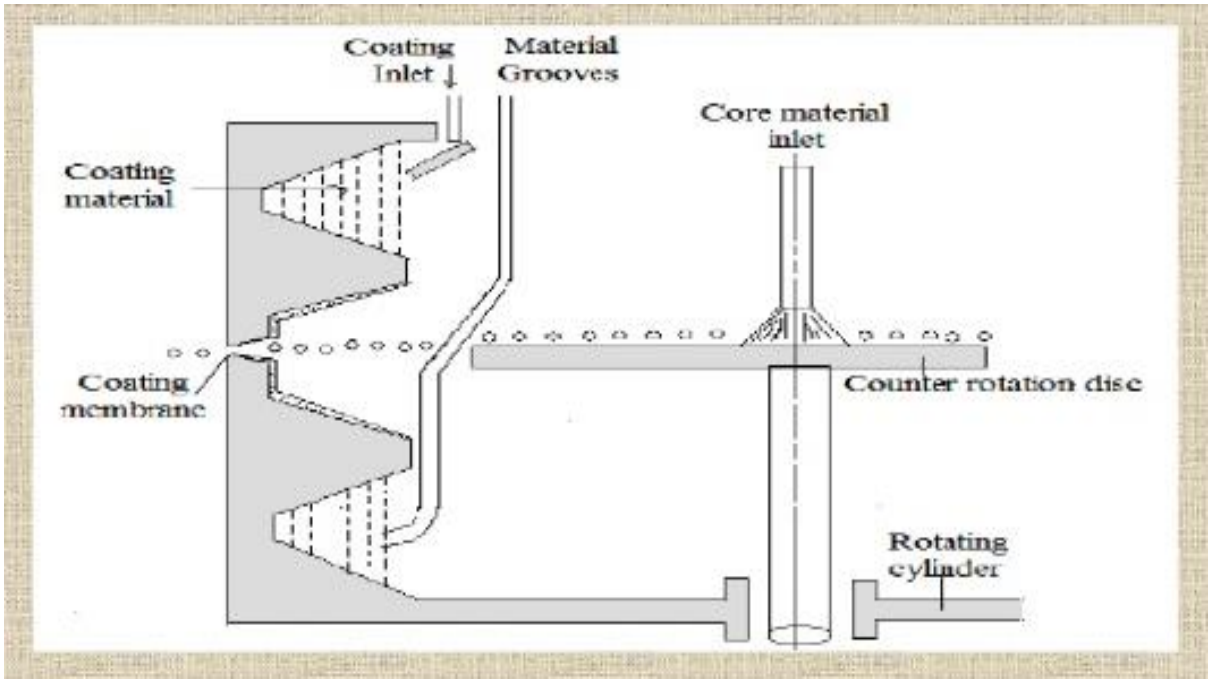
Spray congealing : spray = hot melt/cold air

D. SPRAY COOLING / CHILLING

- Spray cooling/chilling is the least expensive encapsulation technology.
- It is used for the encapsulation of organic and inorganic salts, textural ingredients, enzymes, flavors and other functional ingredients.
- It improves heat stability, delay release in wet environments, and/or convert liquid hydrophilic ingredient into free flowing powders.
- Spray cooling/chilling is typically referred to as 'matrix' encapsulation because the particles are more adequately described as aggregates of active ingredient particles buried in the fat matrix.

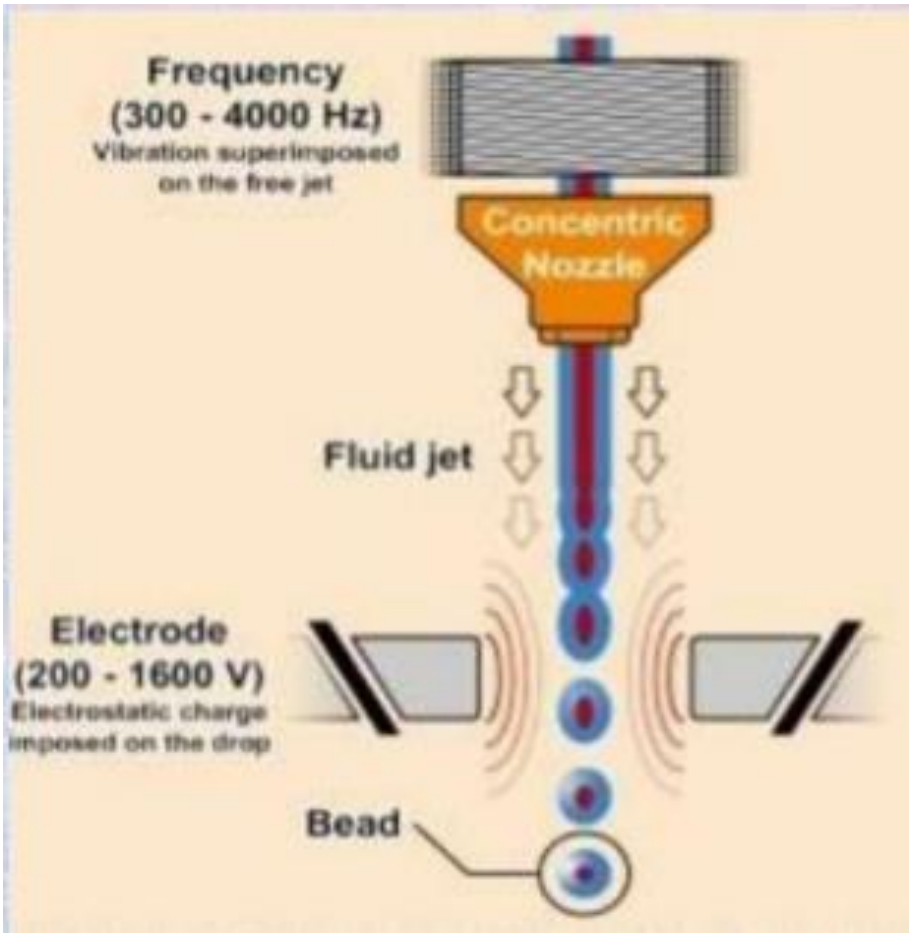
E. MULTIORIFICE- CENTRIFUGAL PROCESS

- centrifugal forces to hurl a core material particle trough an enveloping microencapsulation membrane thereby effecting mechanical microencapsulation.
- Processing variables include the rotational speed of the cylinder, the flow rate of the core and coating materials, the concentration and viscosity and surface tension of the core material.
- The multiorifice-centrifugal process is capable for microencapsulating liquids and solids of varied size ranges, with diverse coating materials. The encapsulated product can be supplied as slurry in the hardening media or as a dry powder. Production rates of 50 to 75 pounds per our have been achieved with the process.



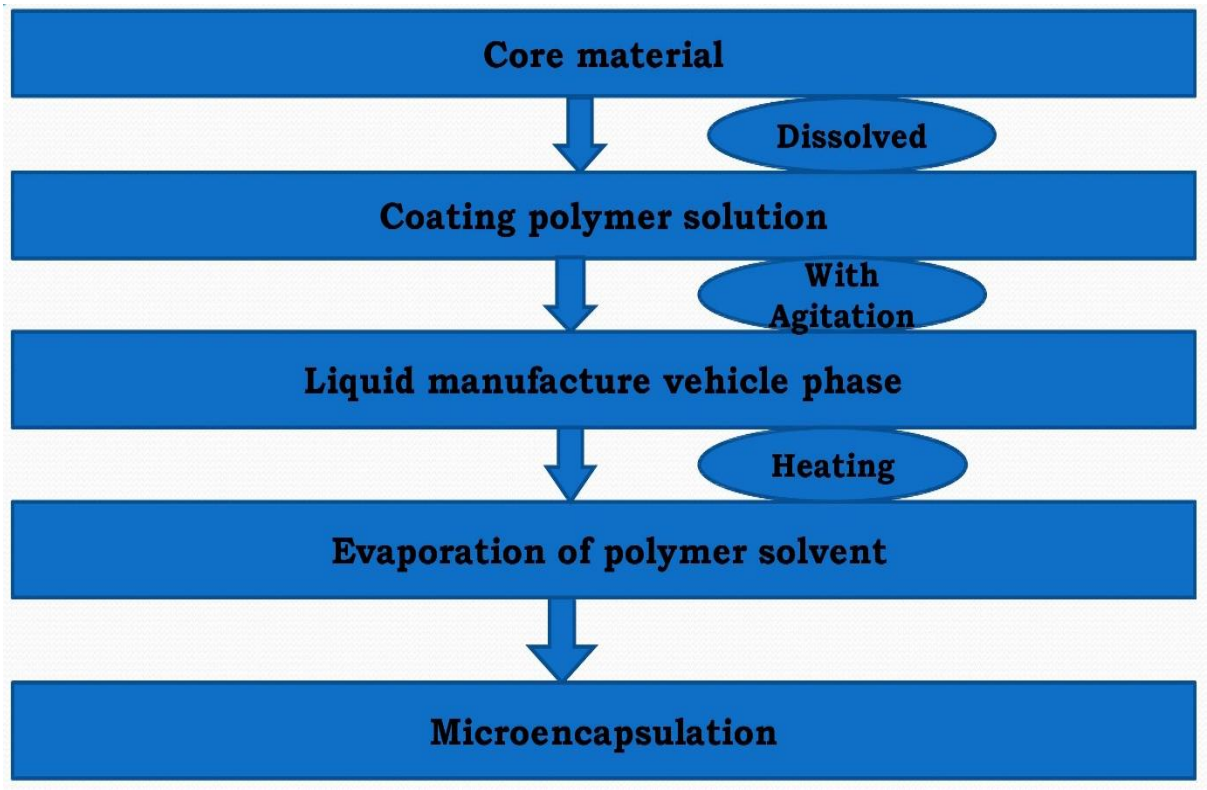
F. VIBRATIONAL TECHNOLOGY

A Fluid of liquid core and shell materials is pumped through concentric tubes and form droplets under the influence of vibration.

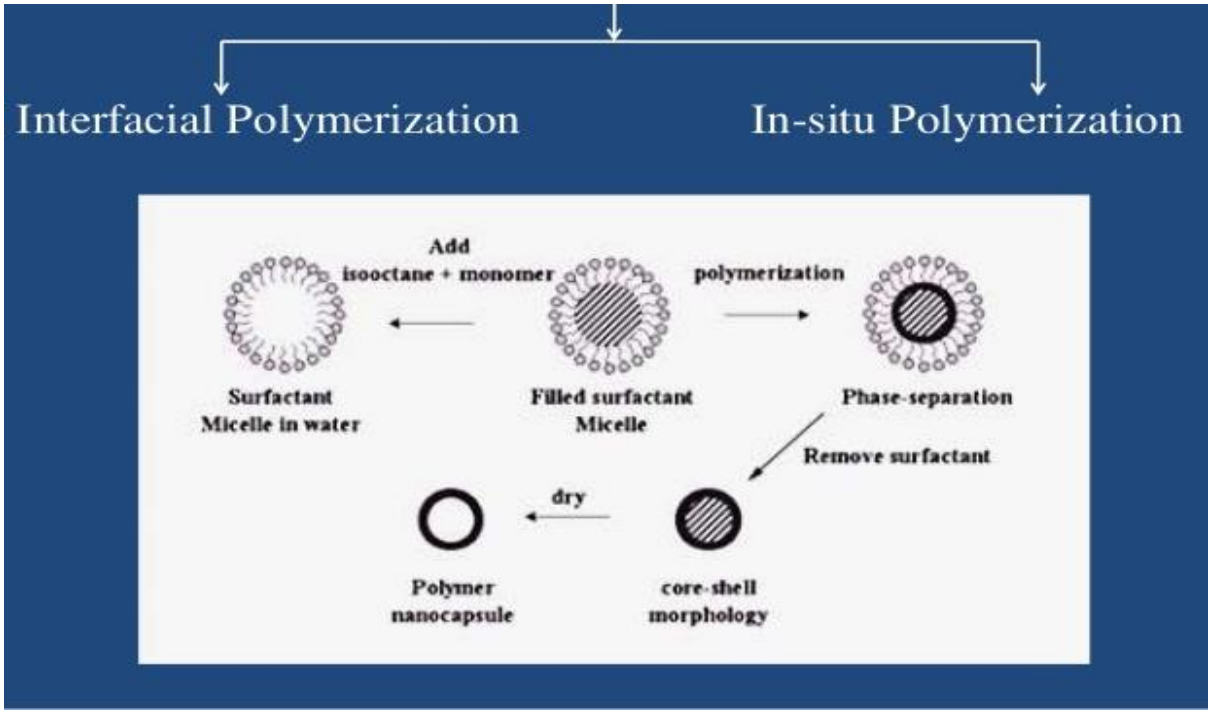


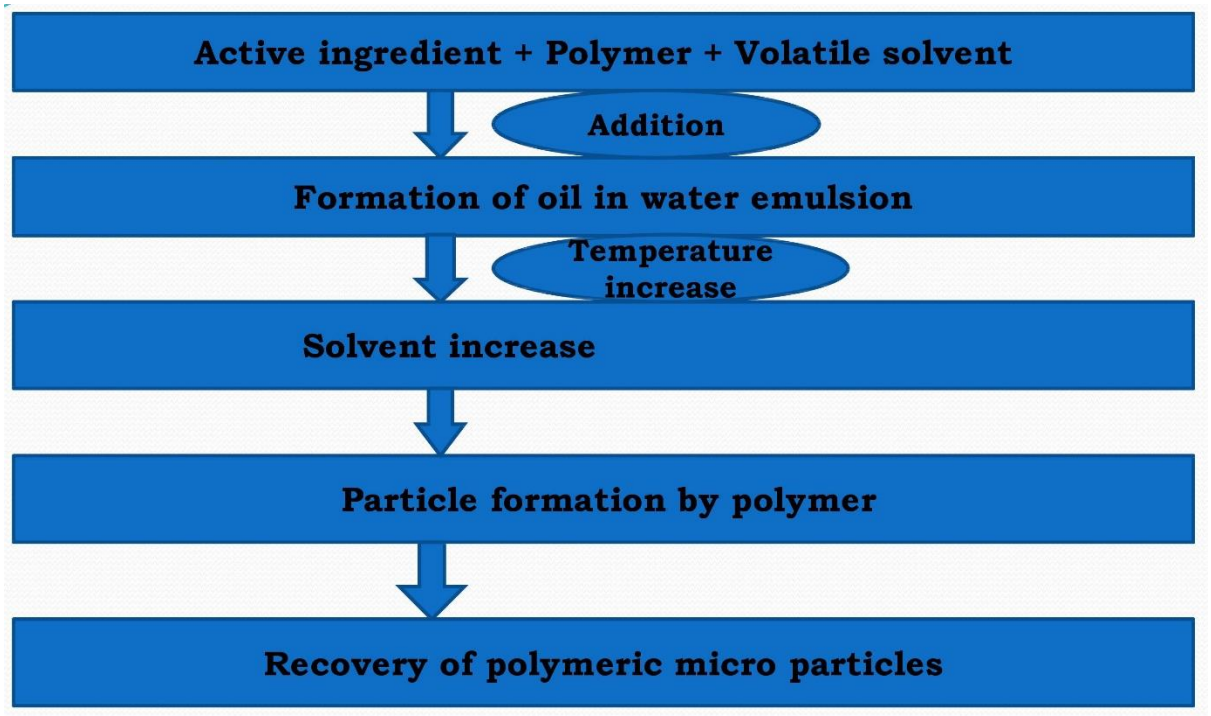
III. CHEMICAL TECHNQUE

a. Solvent Evaporation



b. POLYMERIZATION





EVALUATION OF MICROTUBULES

1. Percentage Yield

The total amount of microcapsules obtained was weight and the percentage yield calculated taking into consideration the weight of the drug and polymer.

%age yield=Amount of microcapsule obtained/Theoretical Amount X100

2. Scanning Electron Microscopy

Scanning electron photomicrographs of drug loaded ethyl cellulose microcapsules were taken. A small number of microcapsules was spread on gold stub and amount of scanning electron microscopy (SEM) chamber.

The SEM photomicrographs was taken at the acceleration voltage of 20 KV.

3. Particle size analysis

For size distribution analysis, different sizes in a batch were separated by sieving by using a set of standard sieves. The amounts retained on different sieves were weighted.

Encapsulation efficiency Encapsulation efficiency was calculated using the formula:

Encapsulation = Actual Drug Content / Theoretical Drug Content x 100

4. Estimation of Drug Content

Cefotaxime sodium drug content in the microcapsules was calculated by UV spectrophotometric method. The method was validated for linearity, accuracy and precision. A sample of microcapsules equivalent to 100mg was dissolved in 25ml ethanol and volume was adjusted upto 100ml using phosphate buffer of pH 7.4. The solution was filtered through Whatman filter paper. Then the filtrate was assayed for drug content by measuring the absorbance at 154nm after suitable dilution.

5. Invitro Drug release Studies

Drug release was studied by using USP type II dissolution test apparatus in Phosphate buffer of pH 7.4 (900ml). The paddle speed at 100rpm and bath temperature at 37°c were maintained throughout the experiment. A sample of microcapsules equivalent to 100mg of cefotaxime sodium was used in each test. Aliquot equal to 5ml of dissolution medium was withdrawn at specific time interval and replaced with fresh medium to maintain sink condition. Sample was filtered through Whatman No. 1 filter paper and after suitable dilatation with medium; the absorbance was determined by UV spectrophotometer at 254nm. All studied were conducted in triplicate. The release of drug from marketed sustained release tablet was also studied to compare with release from microcapsules

ADVANTAGES OF MICROENCAPSULATIONS

1) Microorganism and enzyme immobilization

- Enzymes have been encapsulated in cheeses to accelerate ripening and flavor development. The encapsulated enzymes are protected from low pH and high ionic strength in the cheese.
- The encapsulation of microorganisms has been used to improve stability of starter cultures.

2) **Protection against UV, heat, oxidation, acids, bases** (e.g. colorant sand vitamins).

   E.g. Vitamin A / monosodium glutamate

3) **Improved shelf life due to preventing degradative reactions**

   (dehydration, oxidation).

4) **Masking of taste or odours**

5) **Improved processing, texture and less wastage of ingredients**

   - Control of hygroscopy
   - enhance flowability and dispersibility
   - dust free powder
   - enhance solubility

6) **Handlings liquids as solids**

7) **There is a growing demand for nutritious** foods for children which provides them with much needed vitamins and minerals during the growing age. Microencapsulation could deliver much needed ingredients in children friendly and tasty way.

8) **Enhance visual aspect and marketing concept**

9) **Textile industry** makes use of microencapsulated materials to enhance the properties of finished goods. One application increasingly utilized is the incorporation of microencapsulated phase change materials (PCMs). Phase change materials absorb and release heat in response to changes in environmental temperatures. When temperatures rise, the phase change material melts, absorbing excess heat, and feels cool. Conversely, as temperatures fall, the PCM releases heat as it solidifies, and feels warm

10) **Pesticides are encapsulated to be released overtime** allowing farmers to apply the pesticides less amounts than requiring very highly concentrated and toxic initial applications followed by repeated applications to combat the loss of efficacy due to leaching, evaporation, and degradation.

11) **Ingredients in foods are encapsulated for several reasons**

- Most flavorings are volatile; therefore encapsulations of these components extend the shelf-life of these products.
- Some ingredients are encapsulated to mask taste, such as nutrients added to fortify a product without compromising the product's intended taste.
- Alternatively, flavors are sometimes encapsulated to last longer, as in chewing gum.

12) Controlled and targeted release of active ingredients

- Many varieties of both oral and injected pharmaceutical formulations are microencapsulated to release over longer periods of time or at certain locations in the body

13) Microencapsulation allows mixing of incompatible compounds

Microencapsulation processes are usually categorized into two groupings: chemical processes 5-10 and mechanical or physical processes. These labels can, however, be somewhat misleading, as some processes classified as mechanical might involve or even rely upon a chemical reaction, and some chemical techniques rely solely on physical events. A clearer indication as to which category an encapsulation method belongs is whether or not the capsules are produced in a tank or reactor containing liquid, as in chemical processes, as opposed to mechanical or physical processes, which employ a gas phase as part of the encapsulation and rely chiefly on commercially available devices and equipment to generate microcapsules.

DISADVANTAGES OF MICROENCAPSULATIONS

1. Possible cross reaction between core and shell material

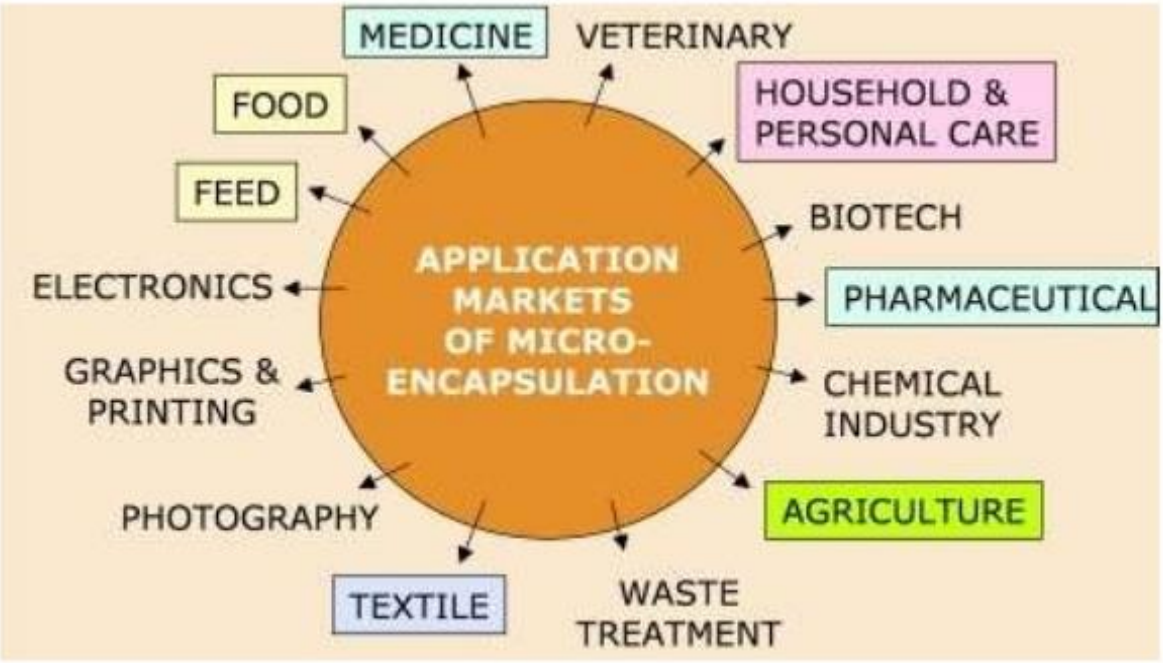
2. Difficult to achieve continuous and uniform film

3. Shelf life of hygroscopic drugs is reduced

4. More production cost

5. More skills and knowledge is required

APPLICATIONS



PHARMACEUTICAL APPLICATIONS

1. **Masking of taste or odours**

   e.g. Ofloxacin

2. **Handling liquids as solids**

   e.g. Eprazinone

3. **Environmental protection**

   e.g. Vitamin A Palmitate

4. **Reduction of hygroscopicity**

   e.g. NaCl

5. **Reduction of vaporization of volatile Drugs**

   e.g. Methyl Salicylate

6. **Prevention of incompatibilities among drugs**

   e.g. Aspirin and Chlorpheniramine maleate

7. **Flow properties**

   e.g. thiamine

8. **Enhance stability**

   e.g. Vitamins

9. **Reduce volatility of materials**

e.g. Methyl Salicylate

10. **Mask unpleasant odour and taste**

    e.g. Castor Oil

11. **Convert liquid into Solid**

    e.g. Castor Oil

12. **Reduce gastric irritation**

    e.g. Indomethacin

i. MICROPARTICLES

Advantages:

1) Taste and odour masking

E.g. Fish oils, Sulfa Drugs

2) Protection of drugs

3) Particle size reduction for enhancing solubility of the poorly soluble drugs

4) Sustained or controlled drug delivery

E.g. KCl, Ibuprofen

5) Targeted releases of encapsulated material

6) Live cell encapsulation

E.g. Resealed erythrocytes

7) Aid in dispersion of water insoluble substance in aqueous media

Disadvantages:

1. The cost of materials and processing of the controlled release preparation, which may be substantially higher than those of standard formulations.
2. Reproducibility is less
3. Process condition like change in temperature, pH, solvent addition, and evaporation /agitation may influence the stability of core particles to be encapsulated.
4. The environmental impact of the degradation products of the polymer matrix produced in response to heat, hydrolysis, oxidation, solar radiations or biological agents

APPICATIONS OF MICROPARTICLES

1) Sustained drug delivery

2) Controlled drug delivery

3) Local drug delivery

4) Pulsatile drug delivery

5) Targeted drug delivery

ii. APPLICATIONS OF MICROSPHERE

1. Vaccine delivery

- Ag release
- Stabilization of Ag

2. Drug targeting

- **Ocular**: gelation with increased residence time
- **Intranasal**: proteins and peptide delivery

3. Magnetic Microspheres

4. Immunomicrosphere

5. Chemoembolization

6. Imaging

7. Microsponges

8. Surface modified micropshere

iii. MORPHOLOGY OF MICROCAPSULES:

The morphology of microcapsules depends mainly on the core material and the deposition process of the shell.

1. **Mononuclear:**

   Microcapsules contain the shell around the core

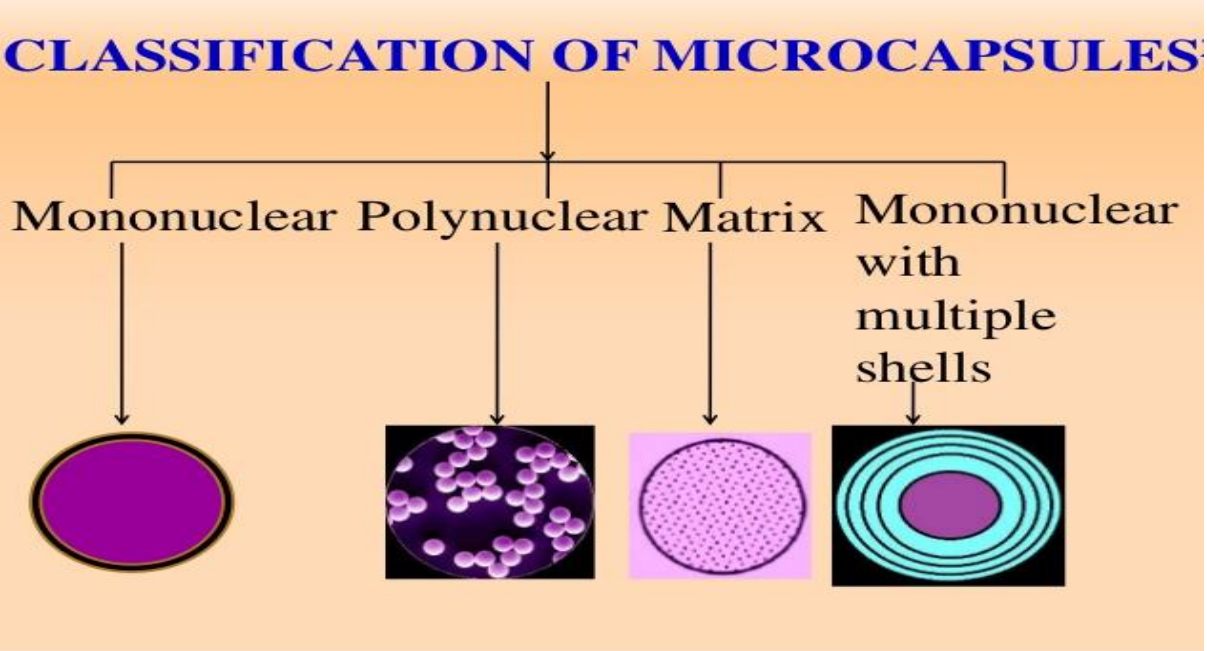
2. **Polynuclear:**

   Capsules have many cores enclosed within the shell

2. **Matrix Encapsulation:**

   In which the core material is distributed homogeneously into the shell material

- In addition to these three basic morphologies, microcapsules can also be mononuclear with multiple shells, or they may form clusters of microcapsules.



Reasons for Microencapsulation and Release Mechanism:

The reasons for microencapsulation are countless.

In some cases, the core must be isolated from its surroundings, as in isolating vitamins from the deteriorating effects of oxygen, retarding evaporation of a volatile core, improving the handling properties of a sticky material, or isolating a reactive core from chemical attack.

In other cases, the objective is not to isolate the core completely but to control the rate at which it leaves the microcapsule, as in the controlled release of drugs or pesticides.

The problem may be as simple as masking the taste or odor of the core, or as complex as increasing the selectivity of an adsorption or extraction process.

Microencapsulation is like the work of a clothing designer.

He selects the pattern, cuts the cloth, and sews the garment in due consideration of the desires and age of his customer, plus the locale and climate where the garment is to be worn.

By analogy, in microencapsulation, capsules are designed and prepared to meet all the requirements in due consideration of the properties of the core material, intended use of the product, and the environment of storage.

Different purposes of microcapsule-based final products require different characteristics of microcapsules.

The size and shape of microcapsules, chemical properties of microcapsule walls, and their degradability, biocompatibility and permeability have to be considered in the selection of raw materials and microencapsulation processes.

The purpose of microencapsulation is usually defined by the permeability.

Microcapsules with impermeable walls are used in products where isolation of active substances is needed, followed by a quick release under defined conditions.

The effects achieved with impermeable microcapsules include: separation of reactive components, protection of sensitive substances against environmental effects, reduced volatility of highly volatile substances, conversion of liquid ingredients into a solid state, taste and odor masking, and toxicity reduction.

On the other hand, microcapsules with permeable walls enable prolonged release of active components into the environment, such as in the case of prolonged release drugs, perfumes, deodorants, repellents, etc., or immobilization with locally limited activity of microencapsulated substances.

Examples of later include microencapsulated fertilizers and pesticides with locally limited release to reduce leaching into the ground water, or microencapsulated catalysts and enzymes for chemical and biotechnological processes.

The mechanisms of releasing encapsulated materials are planned in advance and depend on the purpose of microencapsulation.

An analysis of several hundred patent documents revealed that the first developed and still often used is the mechanism of external pressure which breaks the microcapsule wall and releases the liquid from the core.

This principle is applied in pressure sensitive copying papers (pressure of the penball or typewriter head), multi-component adhesives (activation in a press), deodorants and fungicides for shoes (mechanical pressure caused by walking), polishing pastes (rubbing) and aromas and sweeteners in chewing gums (chewing).

In some applications, the microcapsule wall breaks because of inner pressure, e.g. for blowing agents in the production of light plastic materials and synthetic leather.

In instant drinks, microcapsules dissolve in water.

Dissolution at the selected pH value is useful for microencapsulated catalysts and pharmaceuticals.

Drugs, vitamins, minerals, essential amino acids, fatty acids, or even whole diets, can be released into the gastro-intestinal tract by enzymatic degradation of digestible microcapsules.

The core substance can be released by abrasion of the microcapsule wall, e.g. in antistatic and fragrances for textiles (abrasion in washing machines and dryers), or for grinding and cutting additives.

In many applications, core materials are released by heat. Heat-sensitive recording papers (e.g. telefax paper), temperature indicators for frozen food, heat-sensitive adhesives, textile softeners and fragrances in formulations for dryers, cosmetic components to be released at body temperature and aromas for tea and baking, are based on the effect of melting of the microcapsule wall.

Microencapsulated fire retardants or extinguishers, based on release caused by burning of microcapsule walls, are used in fireproof materials. These types of microcapsules are used for wall paper, carpets, curtains, fire protecting clothes, and added to plastics and coatings for electric devices and wires.

Microcapsules in special photographic emulsions, light-sensitive papers and toners for photocopiers are decomposed (or hardened) by light. If the wall is permeable, it slowly releases the content of the core.

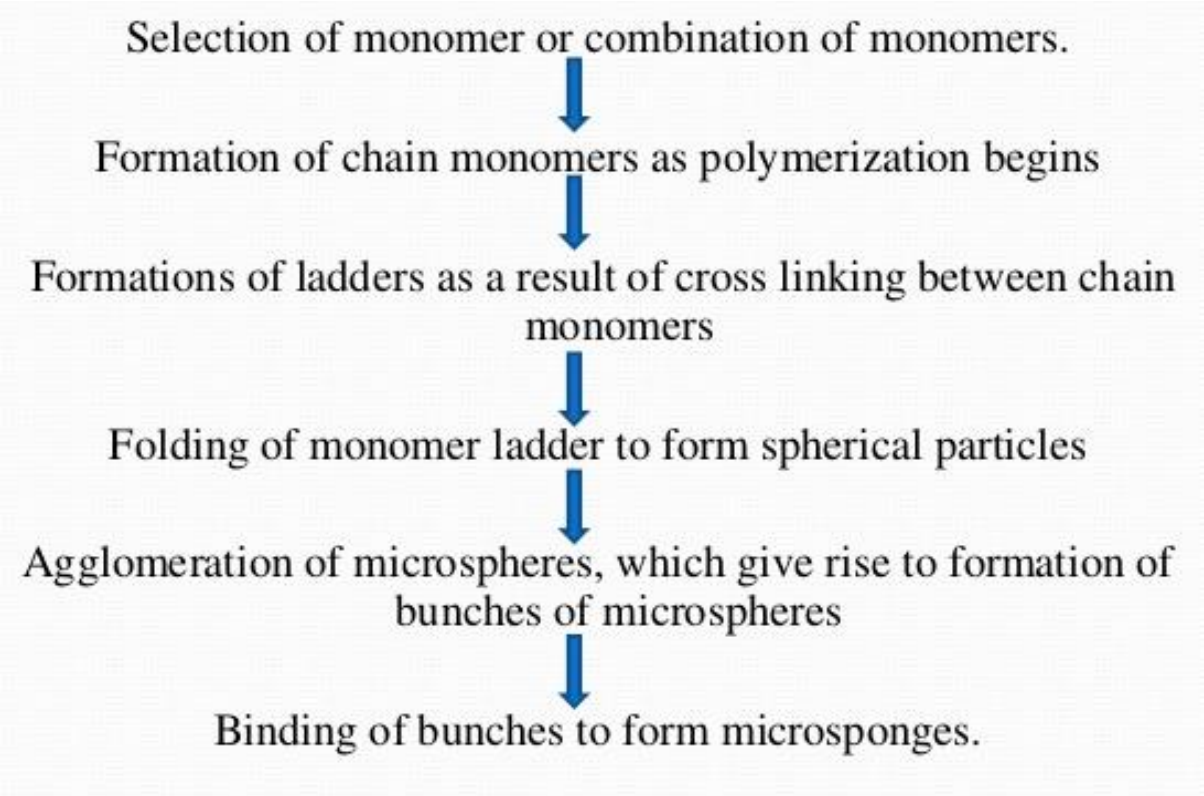
This mechanism can be applied in controlled drug release products, aromas, fragrances, insecticides and fertilizers.

In the case of microencapsulated cells and enzymes in biotechnology, high-molecular weight components can be retained in microcapsules, while low-molecular by-products and substrate residues are extracted through semi-permeable microcapsule walls.

A special example is that of microencapsulated phase change materials for active accumulation and release of heat in textiles, shoes and building insulation materials.

To remain functional over numerous phase transition cycles, they have to remain encapsulated within the impermeable and mechanically resistant microcapsule wall for the whole product life.

iv. PREPARATION OF MICROSPONGES



TECHNIQUES OF MICROSPONGES

1. Liquid-liquid suspension polymerization
2. Quasi Emulsion solvent diffusion

1. LIQUID-LIQUID SUSPENSION POLYMERIZATION

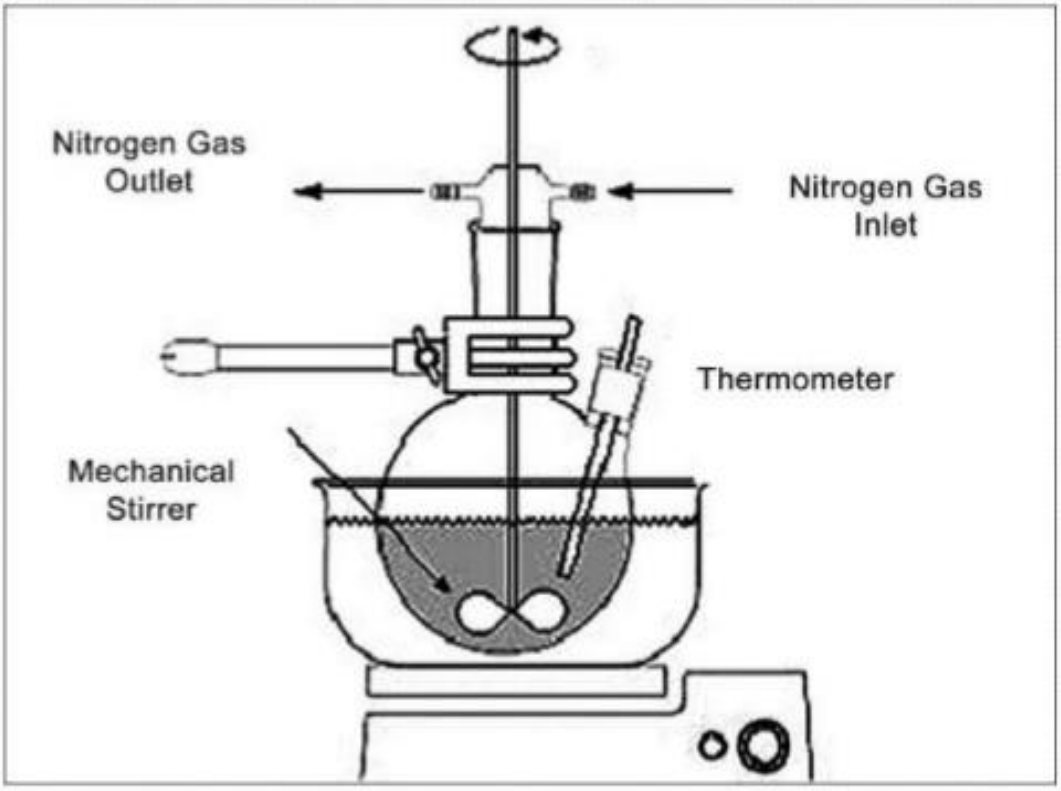
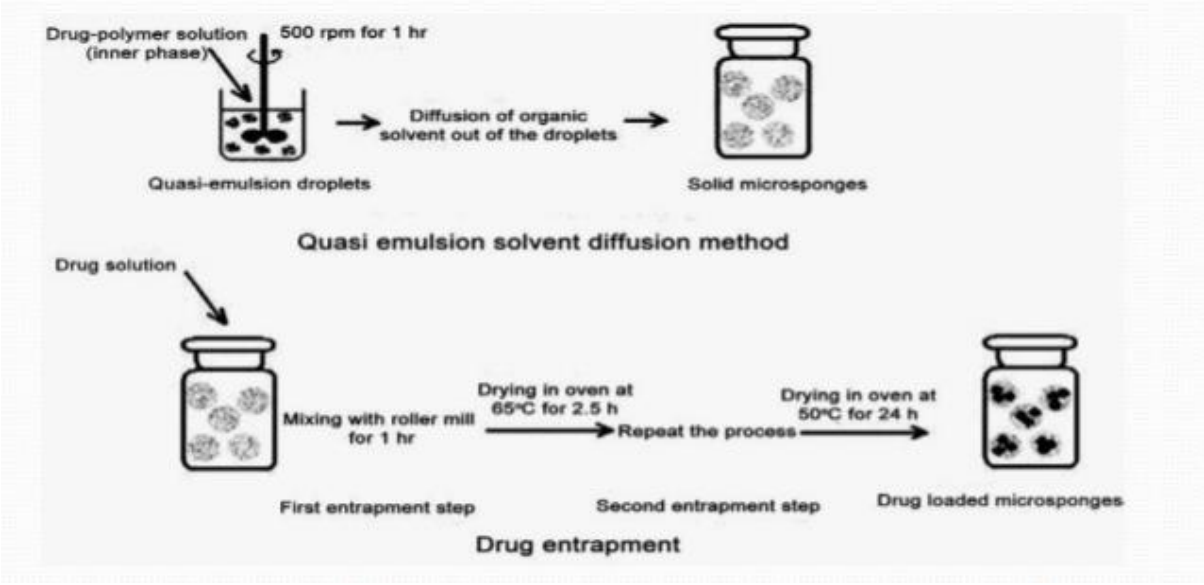


Fig.:- Reaction vessel for microsponge preparation by liquid-liquid Suspension Polymerization

2. QUASI-EMULSION SOLVENT DIFFUSION



ADVANTAGES OF MICROSPONGES

1. Non-irritating, Non mutagenic, Non allergenic

2. Improved formulation flexibility

3. Extended release of drug continuous upto 12 hours
4. Reduce irritation and improve patient compliance
5. Microsponges drug delivery can improve bioavailability of drug
6. They have better thermal, physical and chemical stability
7. Allow incorporation of immiscible products
8. Advanced oil control

DISADVANTAGES OF MICROSPONGES

1. The preparation methods usually use organic solvents as porogens, which pose an environmental hazard as some may be highly inflammable, posing a safety hazard.
2. In some cases, the traces of residual monomers have been observed, which may be toxic and hazardous to health.

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