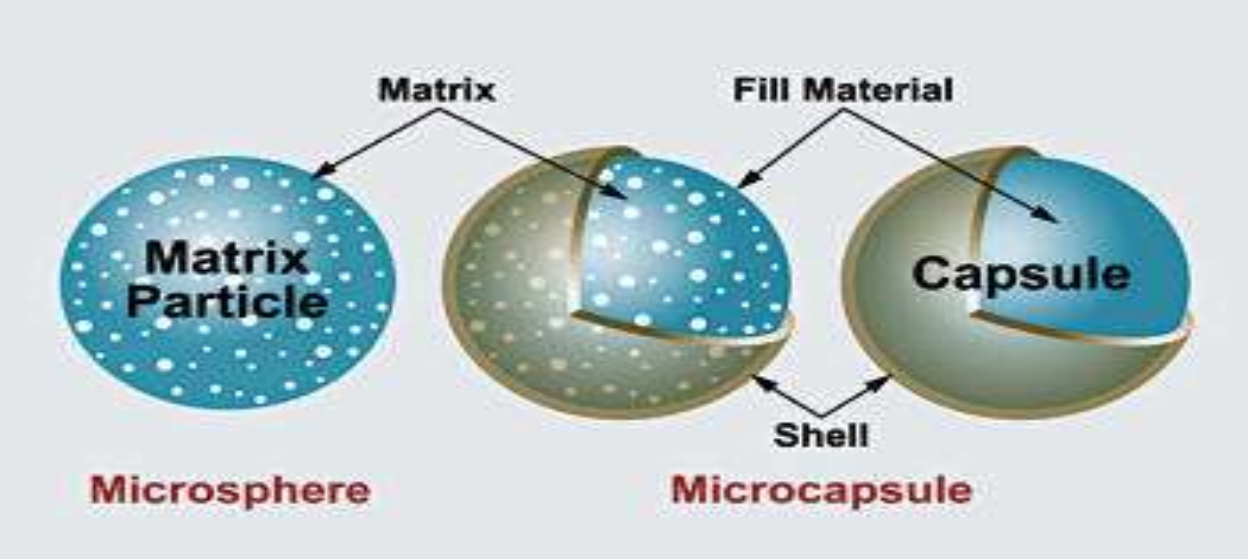
MICROENCAPSULATION



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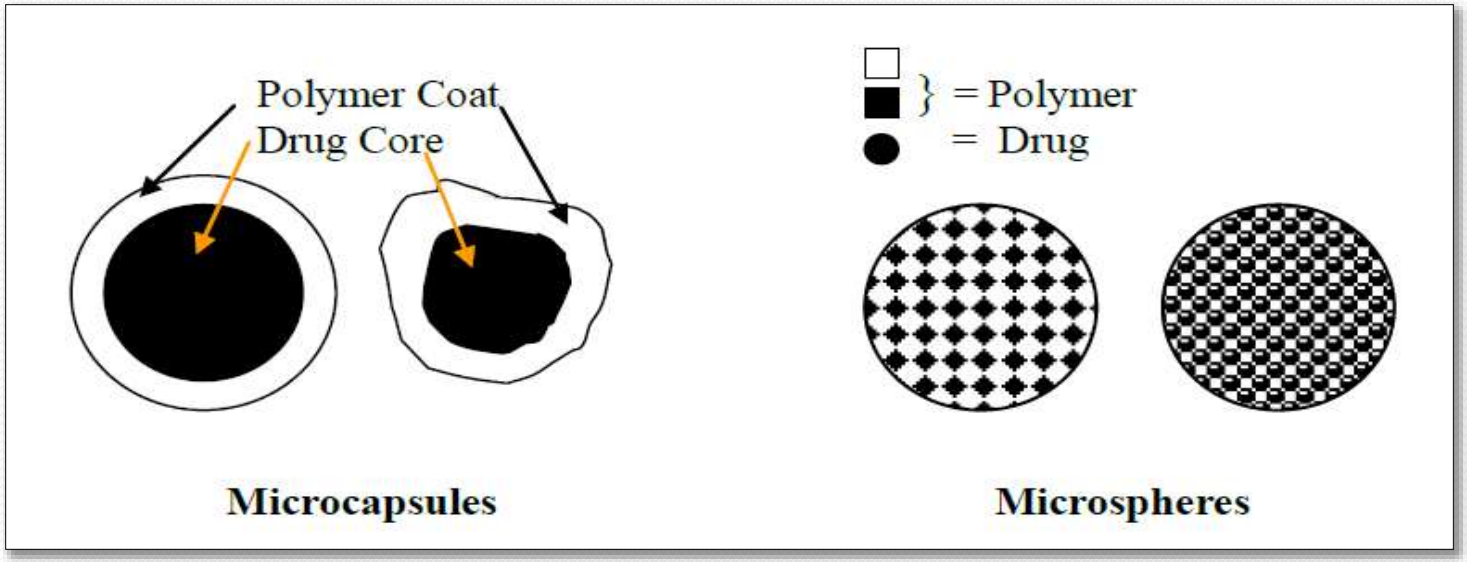
INTRODUCTION

- ✓ Microencapsulation is a process in which very tiny droplets or particles of liquid or solid material are surrounded or coated with polymeric, waxy or protective material.
- ✓ The product obtained by this process is called as micro particles, microcapsules.
- ✓ Particles having diameter between 3 - 800µm are known as micro particles or microcapsules or microspheres.
- ✓ Particles larger than 1000µm are known as Macroparticles .

Generally Micro particles consist of two components

a) Core material

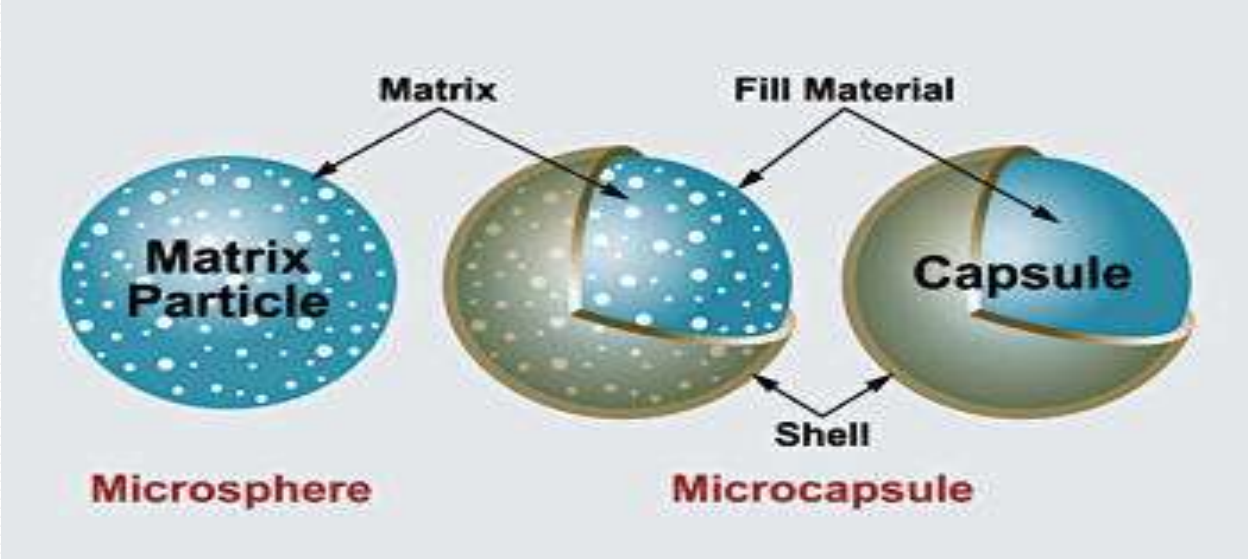
b) Coat or wall or shell material.



Microcapsules: micrometric **reservoir** systems

Microspheres: micrometric **matrix** systems

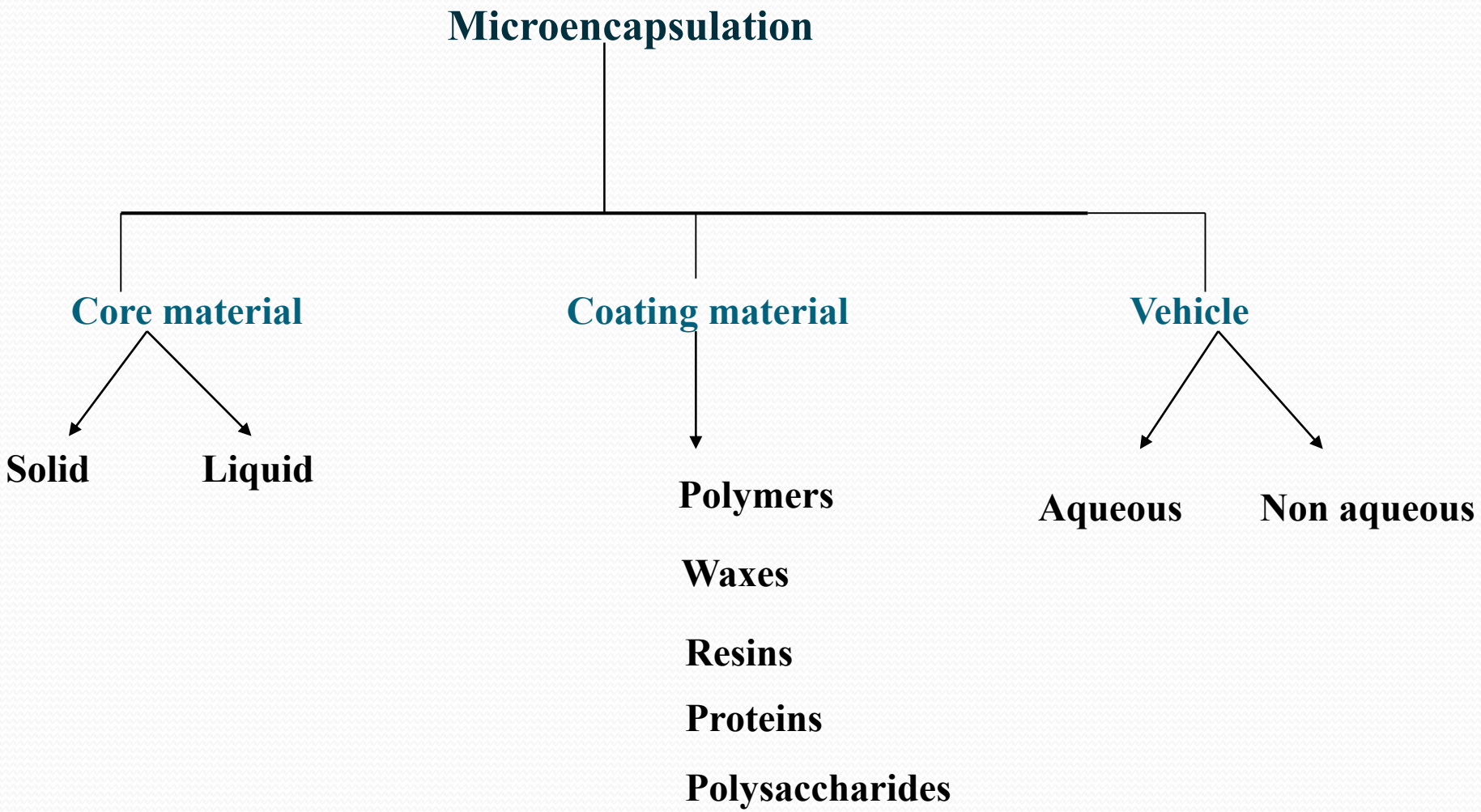
Difference Microcapsule and Capsule



ADVANTAGES:

- ✓ To Increase of bioavailability.
- ✓ To alter the drug release.
- ✓ To improve the patient's compliance.
- ✓ To produce a targeted drug delivery.
- ✓ To reduce the reactivity of the core in relation to the outside environment.
- ✓ To decrease evaporation rate of the core material.(Reduction of volatility)
- ✓ To convert liquid to solid form & To mask the core taste.

FUNDAMENTAL CONSIDERATION:



List of coating material:-

Water soluble resin	Water insoluble resin	Wax & lipid	Enteric resin
Gelatin, Gum arabic, PVP, CMC, Methyl cellulose, Arabinogalactan, Polyvinyl acrylate, Polyacrylic acid.	Ethyl cellulose, Polyethylene, Polymethacrylate Cellulose nitrate, Silicones.	Paraffin, Carnauba wax, Bees wax, Stearic acid, Stearyl alcohol.	Shellac, Zein, Cellulose acetate phthalate.

ROLE OF POLYMERS :

- ✓ Polymers are substances of high molecular weight made up by repeating monomer units.

- ✓Polymer molecules may be linear or branched, and separate linear or branched chains may be joined by crosslinks.

- ✓Polymers are used widely in pharmaceutical systems as coating materials and, a components of controlled, site-specific drug delivery systems, reduction of toxicity, increase therapeutic efficiency.

Polymers Used For Preparation

- **Synthetic Polymers**

  Non-biodegradable:

  PMMA

  Acrolein

  Glycidyl methacrylate

  Epoxy polymers

- **Natural Polymers**

  Proteins

  Carbohydrates

  Chemically modified carbohydrates

Biodegradable:

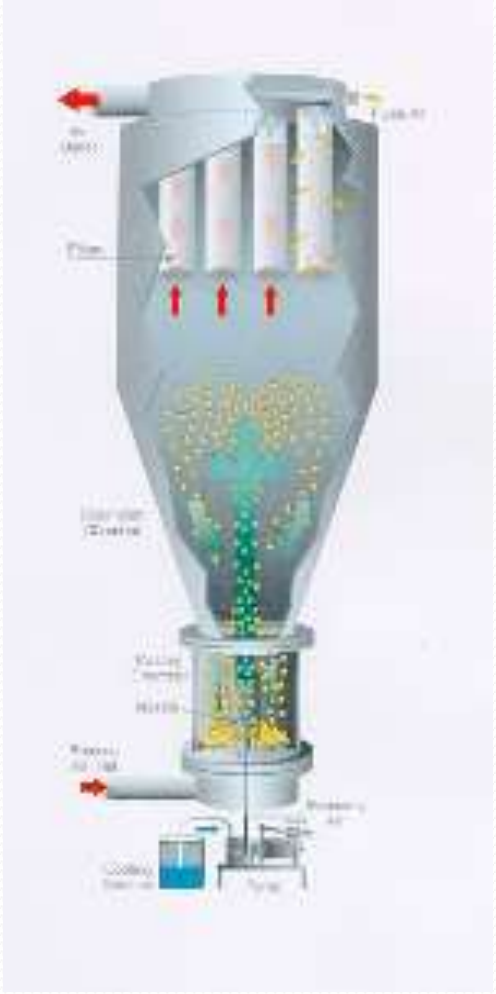
Lactides & Glycolides & their copolymers

Polyalkyl cyano acrylates

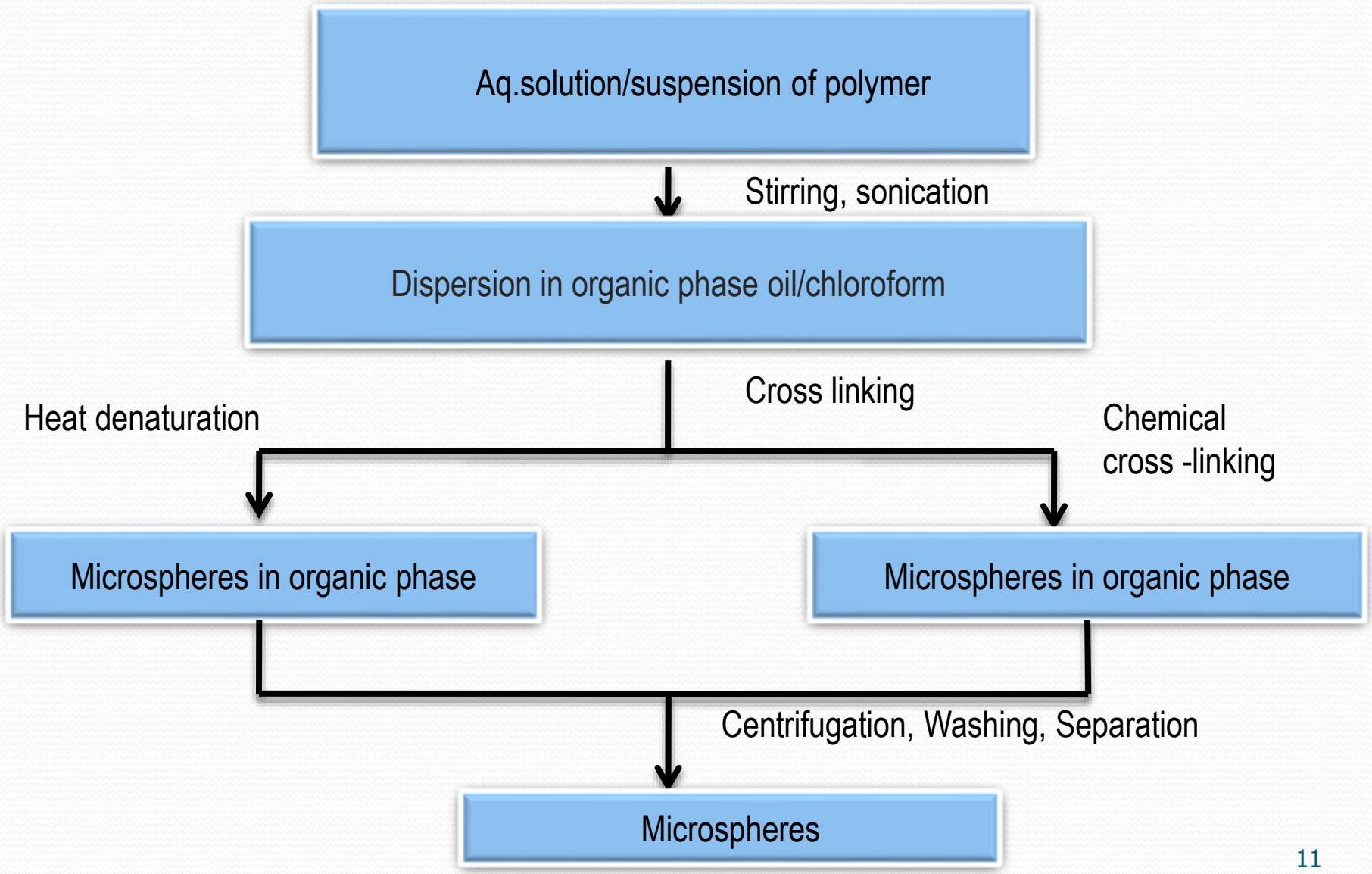
Polyanhydrides

MICROENCAPSULATION TECHNIQUES:

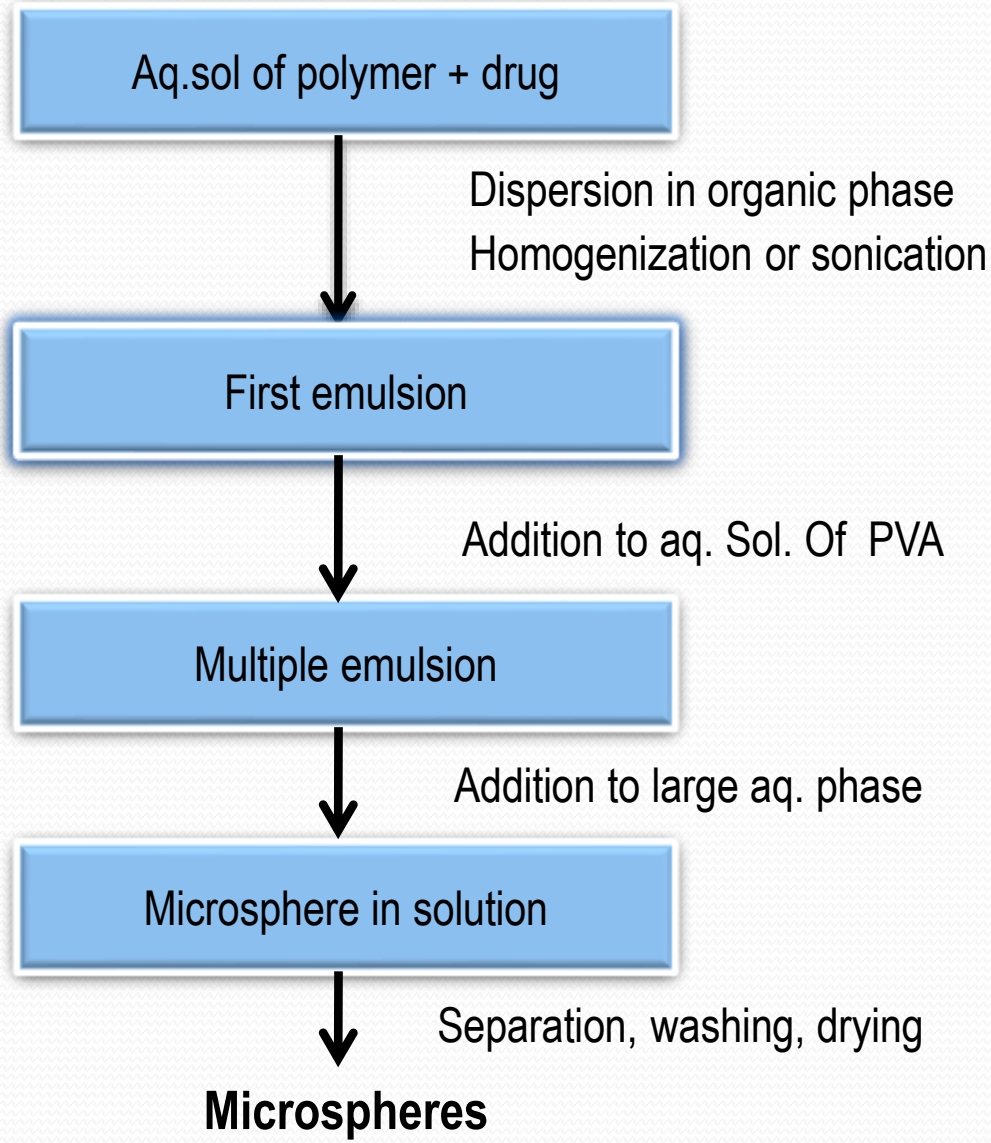
- **General Methods:**
  - Single Emulsion Techniques
  - Double Emulsion Techniques
- **Physical Methods:**
  - Phase separation coacervation technique
- **Mechanical Methods:**
  - Spray drying & congealing
  - Fluidized Bed Technology
  - Solvent evaporation
  - Pan Coating
  - Rotational Suspension Separation
  - Extrusion
  - Nozzle Vibration Technology
  - Multiorifice Centrifugal Process



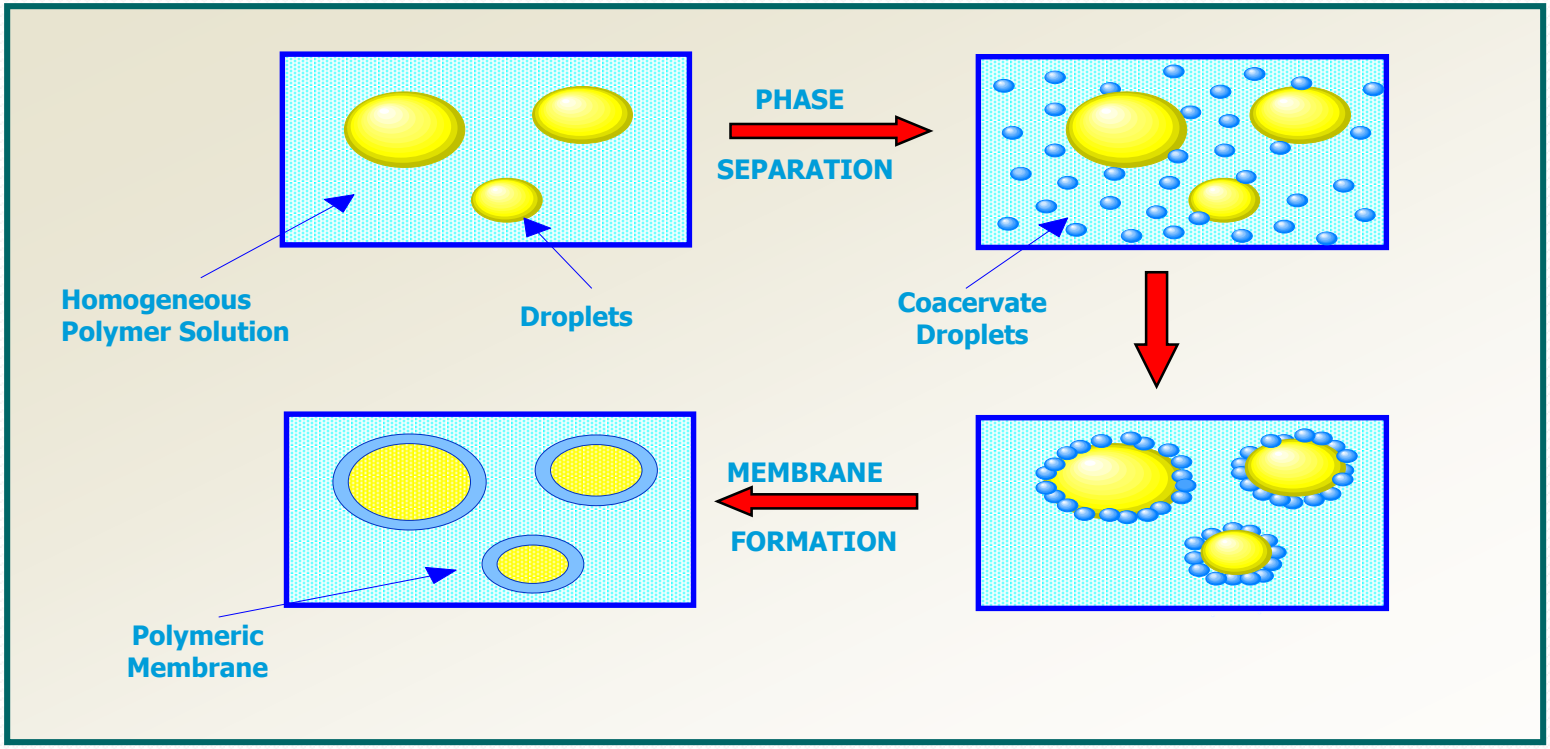
Single emulsion techniques



Double emulsion techniques



COACERVATION / PHASE SEPARATION:



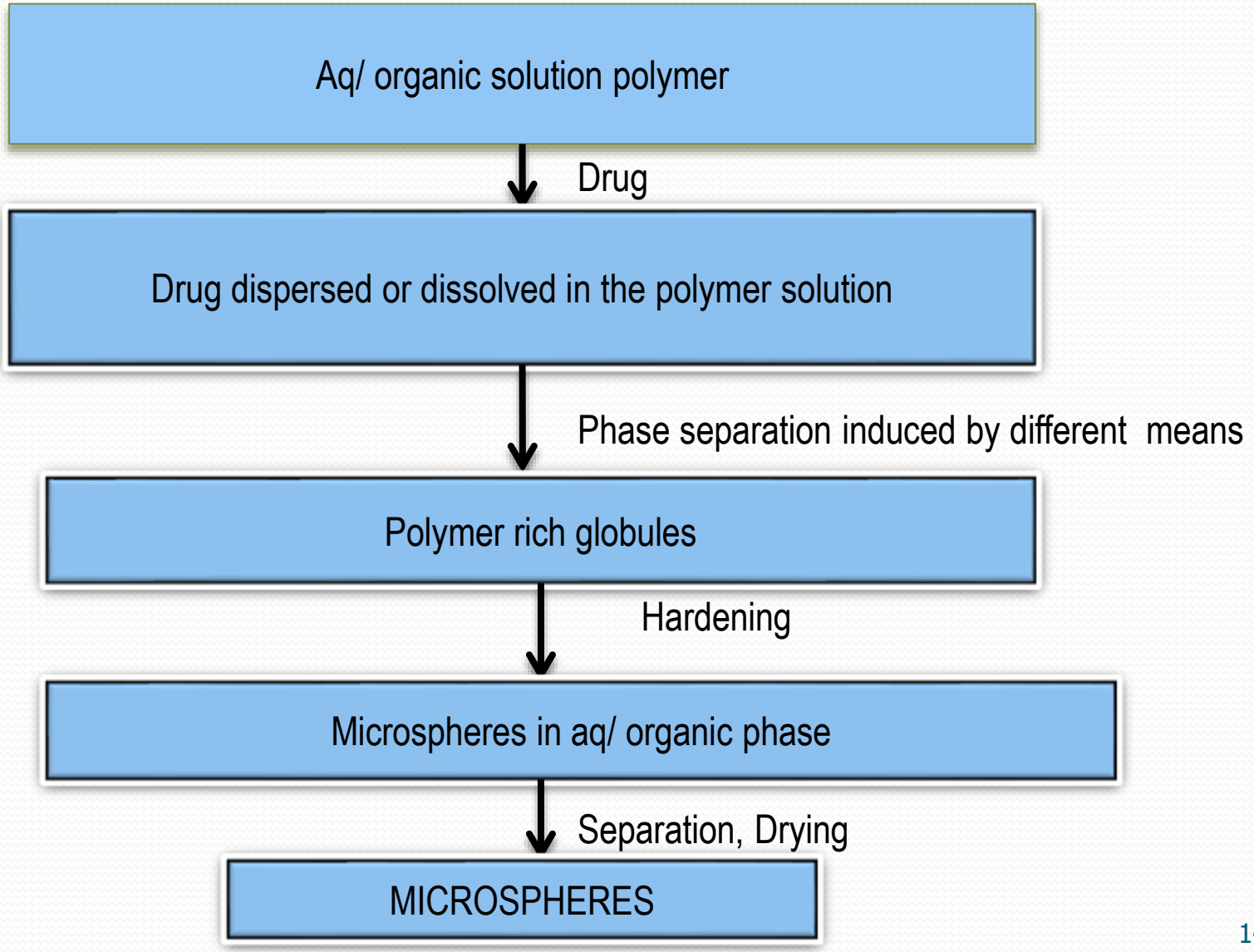
Process consist of 3 phases:

1.Formation of three immiscible phase

2.Deposition of coating

3.Rigidization of coating.

Phase Separation Coacervation Technique



Step: 1) Three immiscible phases are as:

a) LMVP

b) Core material phase

c) Coating material phase.

Coating material phase formed by utilizing following methods:

A) Temperature change.

B) By addition of incompatible polymer

C) By non-solvent addition

D) By salt addition

E) Polymer-polymer interaction.

A) Temperature change:-

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

EC + Cyclohexane → Polymer solution + N-acetyl p-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)

↓ 55^0C

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

↓ 55^0C

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 $\longrightarrow$ 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

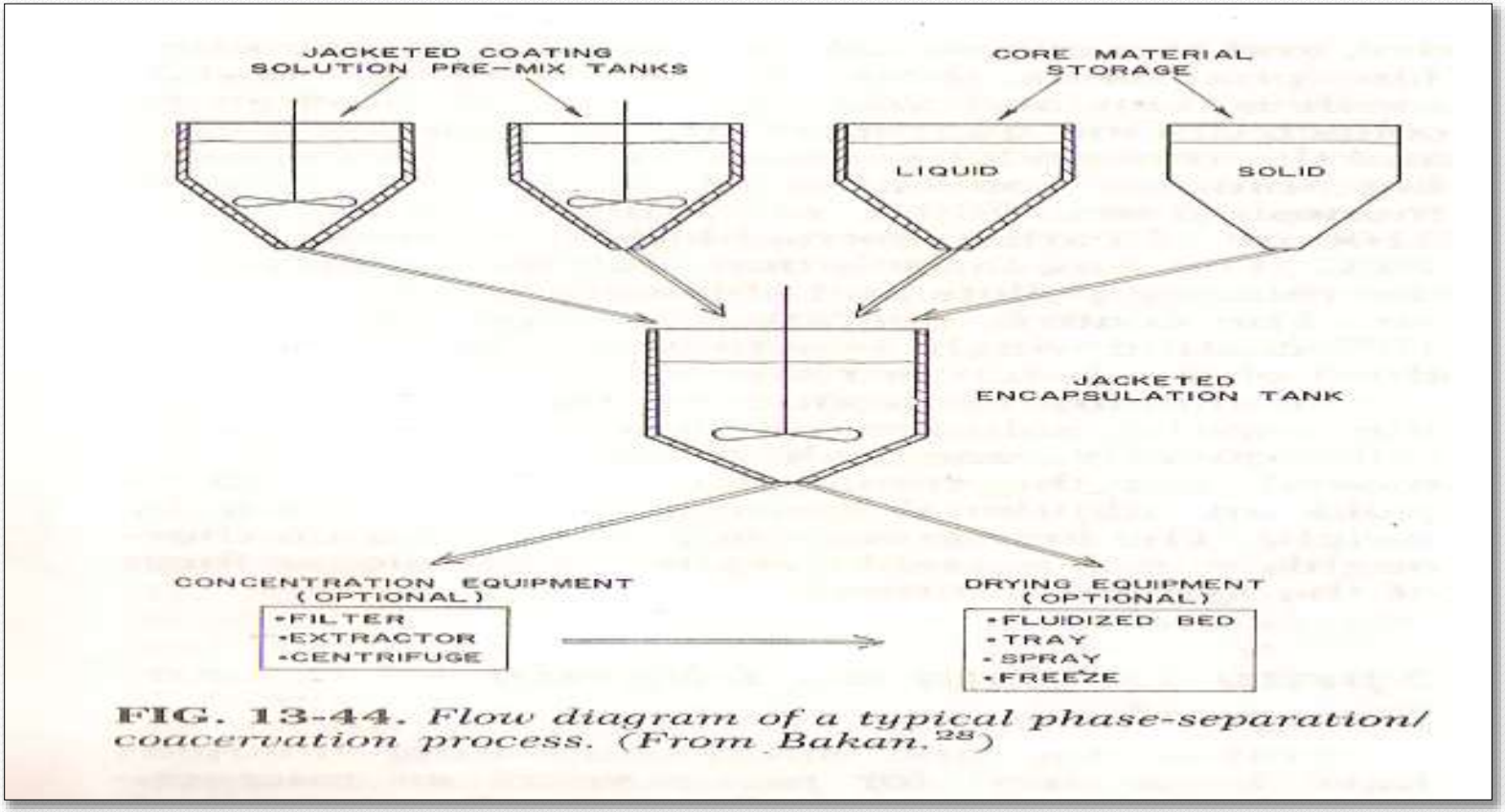


FIG. 13-44. *Flow diagram of a typical phase-separation/ coacervation process. (From Bakan.[28])*

Aq. Gum arabic + Aq. Gelatin ⟶ mixture + water

↓ 4.5 pH, 40-50 ^{0}C

polymer interact to causes phase separation

↓ warm

mixture + methyl salicylate

↓

slowly cooled the mixture at 25 ^{0}C over 1 hr

↓

rigidization of coating is done by cooling microencapsule at 10 ^{0}C

Polymerization Techniques

1. Normal polymerization

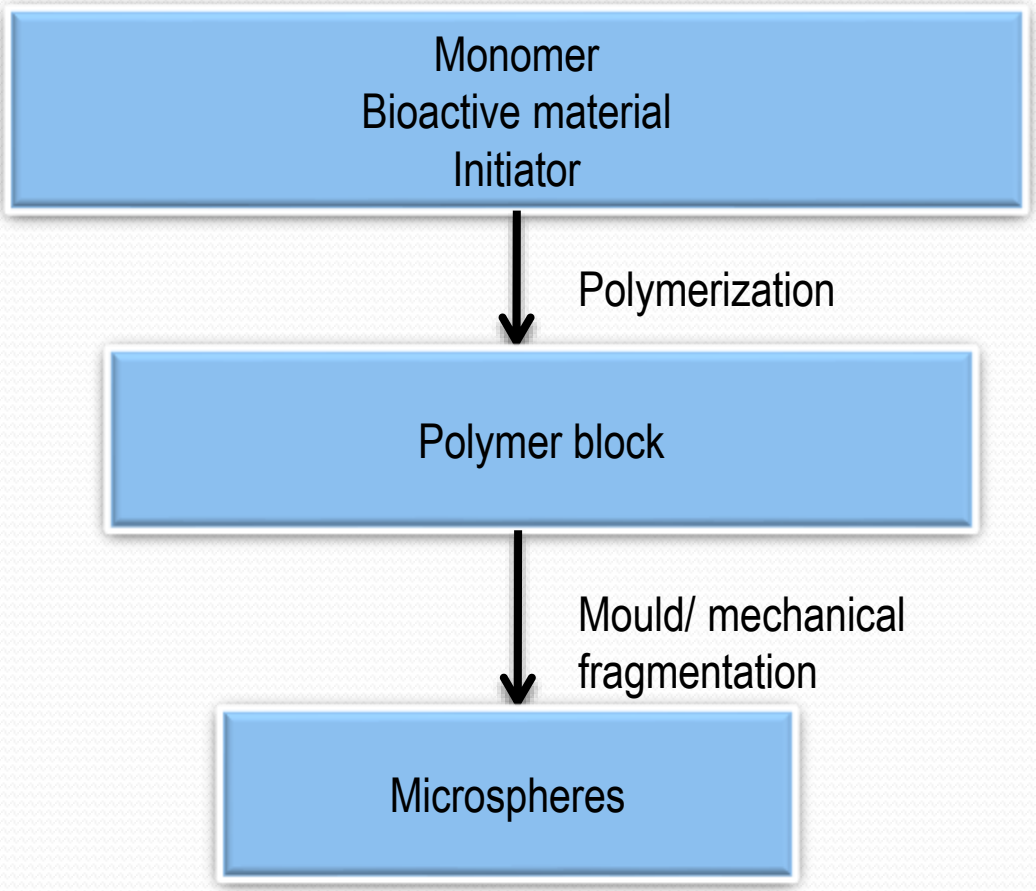
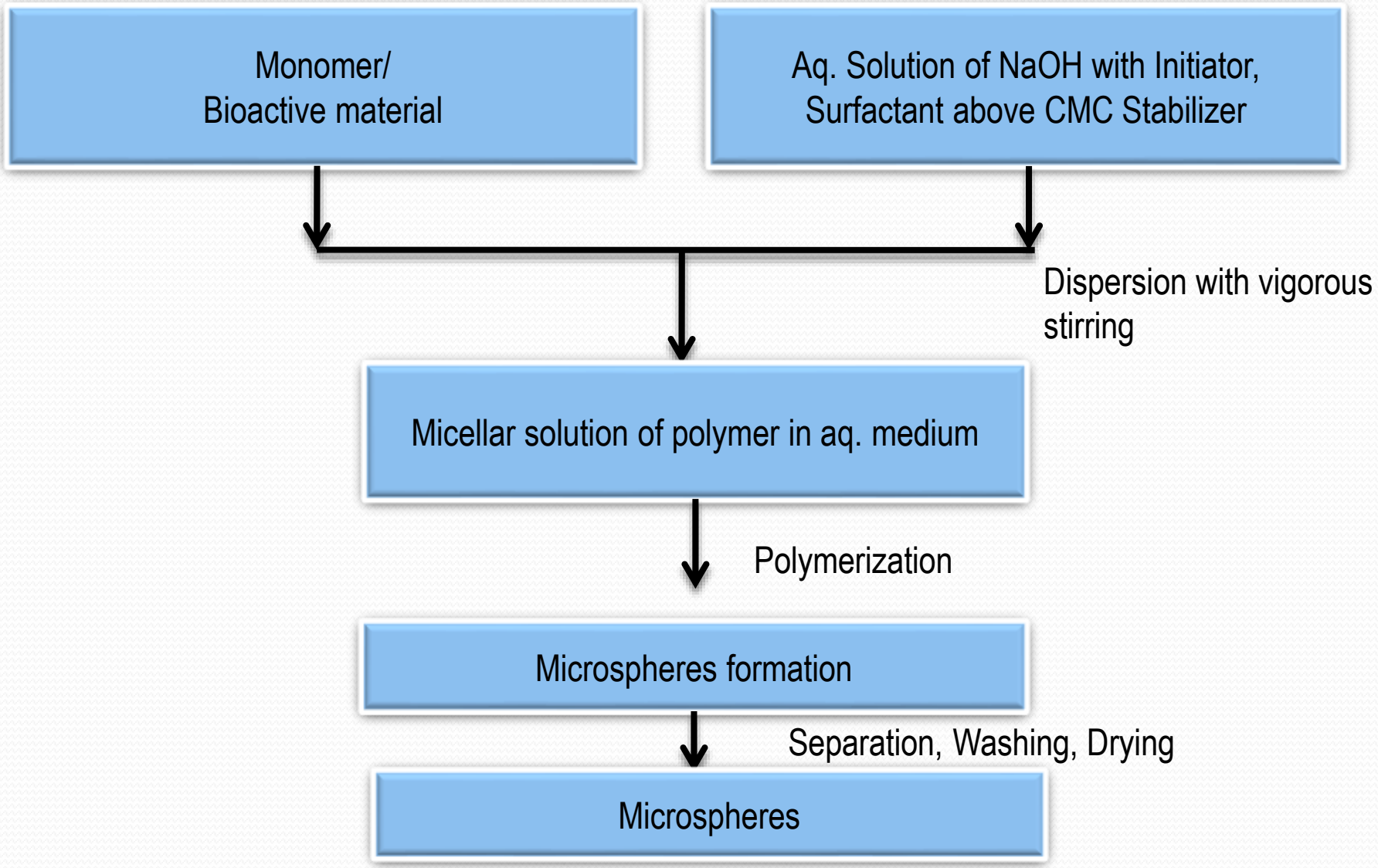
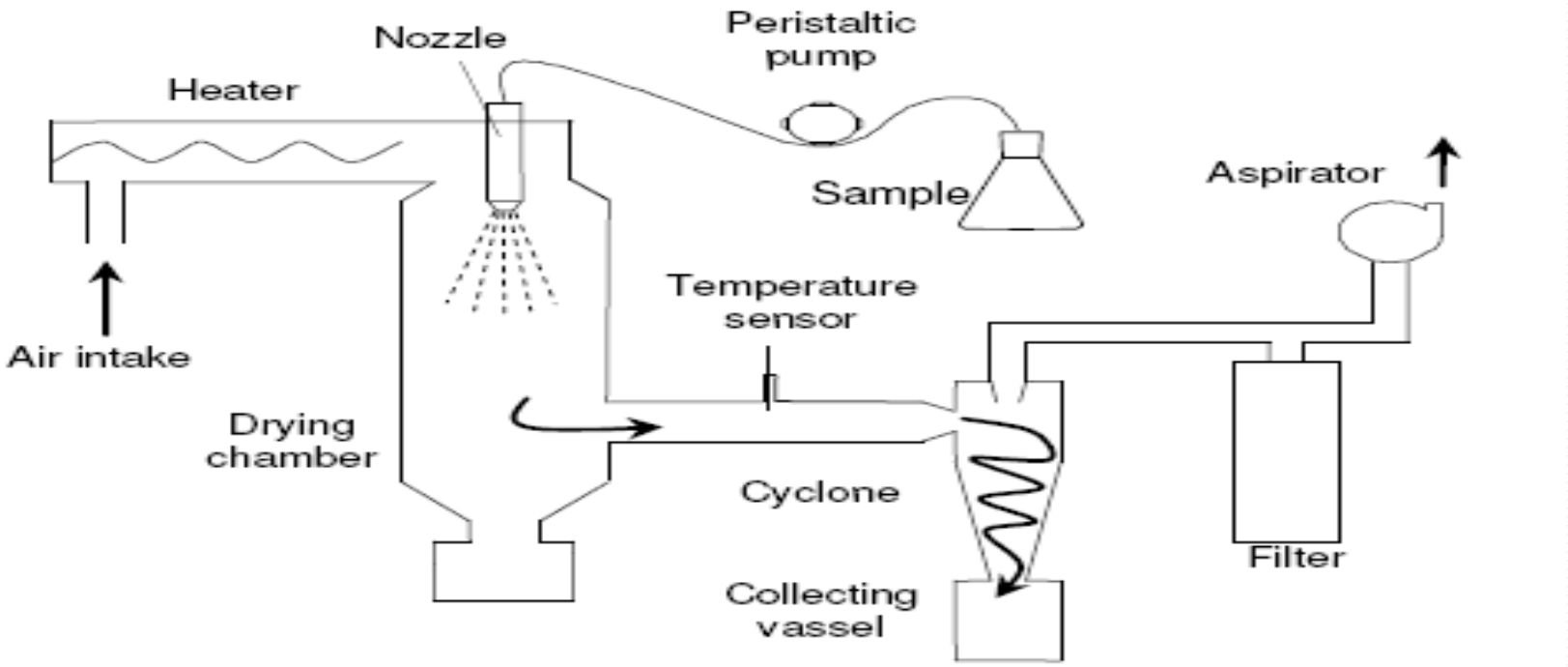


Fig.-Schematic for Bulk Polymerization

2. Interfacial Polymerization1,4



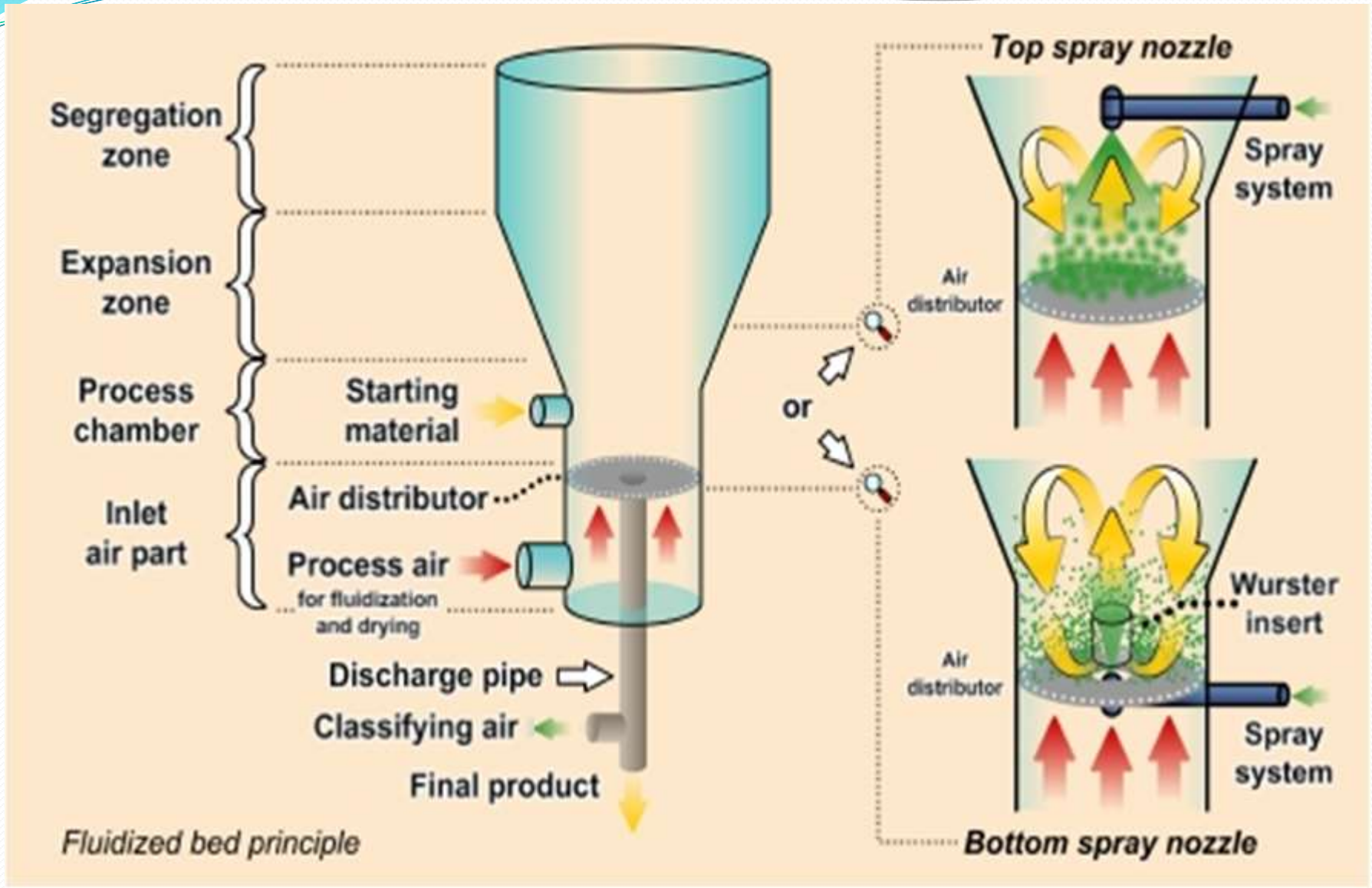
SPRAY DRYING & CONGEALING (COOLING):



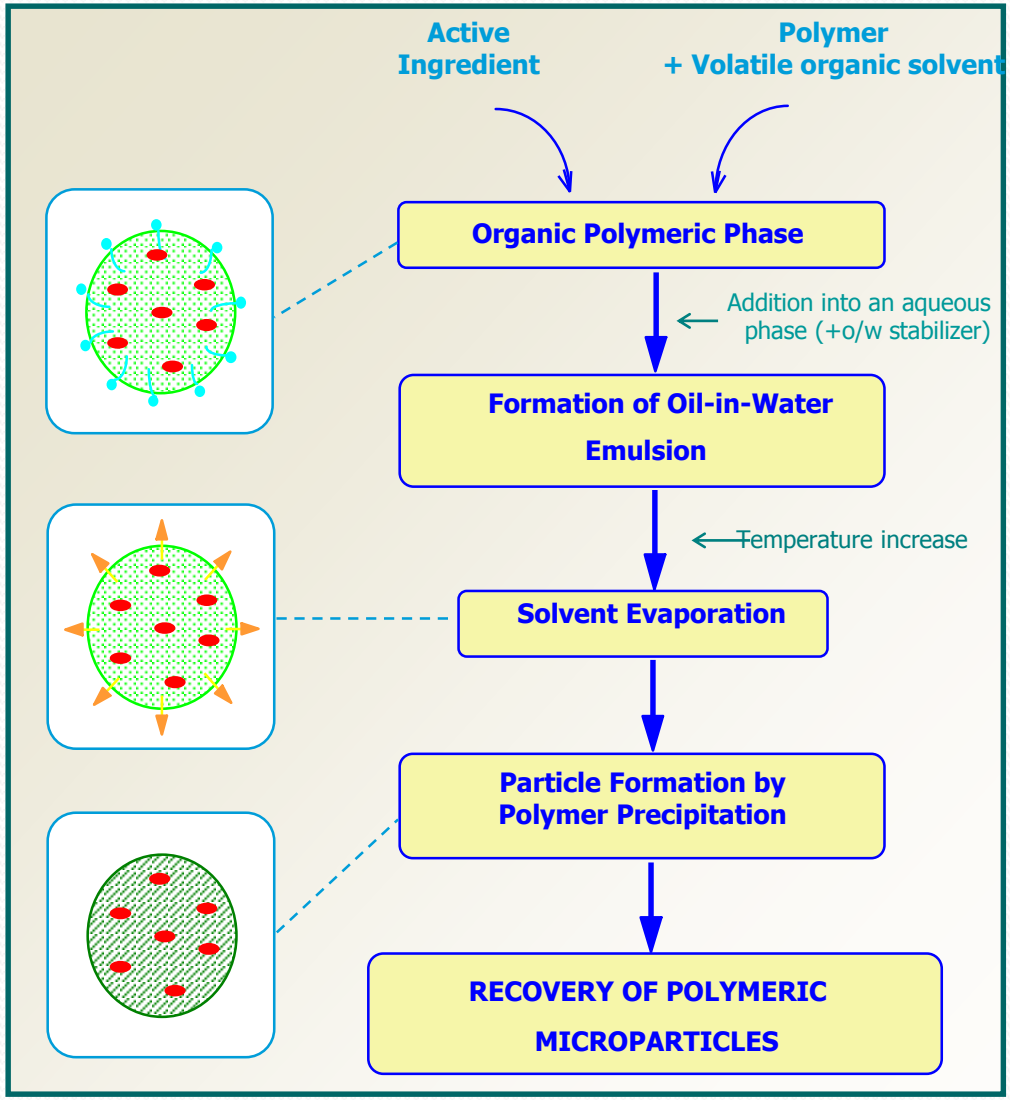
Spray drying : spray = aqueous solution / Hot air

Spray congealing : spray = hot melt/cold air

FLUIDIZED BED TECHNOLOGY:



SOLVENT EVAPORATIONS:



Step 1:

Formation of a solution/dispersion of the drug into an organic polymer phase.

Step 2:

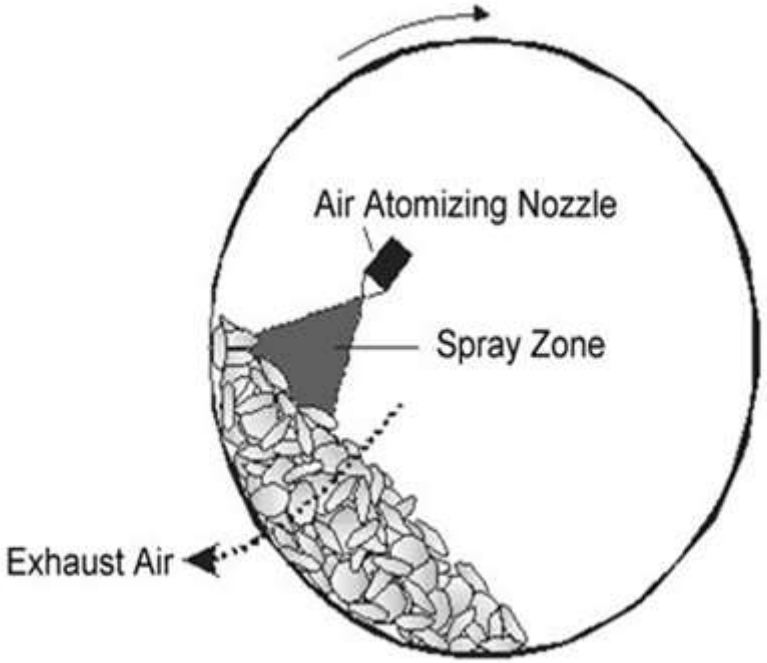
Emulsification of the polymer phase into an aqueous phase containing a suitable stabilizer, thus, forming a o/w emulsion.

Step 3:

Removal of the organic solvent from the dispersed phase by extraction or evaporation leading to polymer precipitation and formation of the microspheres.

Pan Coating:

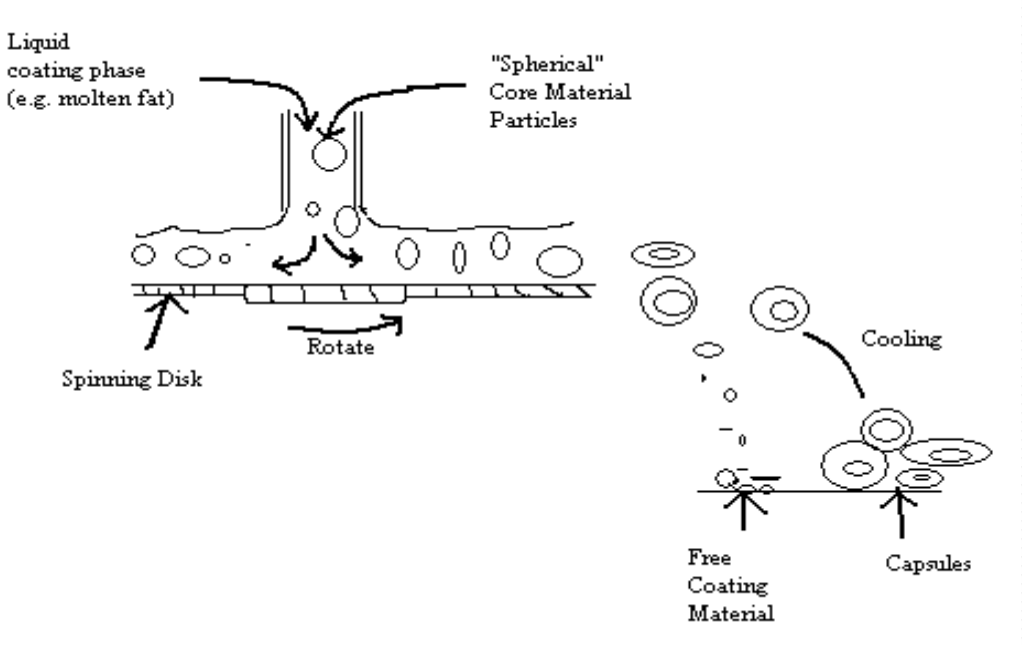
- The coating solution is applied as atomized spray to the solid core material in the coating pan.



- To remove the coating solvent warm air is passed over the coated material.

- By using this technique larger sized particles will be coated effectively.

Rotational Suspension Separation:



- In this process, core material dispersed in a liquid shell formation is fed onto a rotating disk.
- A flat disk is shown, but conical or bowl shaped disks can be used.
- Individual core particles coated with a film of shell formation are flung off the edge of the rotating disk along with droplets of pure coating material.
- When the shell formation is solidified,(e.g.. by cooling) microcapsules are produce.

EXTRUSION:

- This method was first patented in 1957.
- The process involves forcing a core material dispersed in a molten carbohydrate mass through a series of dies, into a bath of dehydrating liquid.
- When contact with the liquid is made, the carbohydrate case hardens to entrap the core material.
- The extruded filaments are separated from the liquid bath, dried using an anti-caking agent such as calcium tripolyphosphate .
- This process is particularly useful for heat labile substances such as flavors, vitamin C and colors.

Multi-orifice Centrifugal Process

- SWRI develop a mechanical process that utilizes centrifugal forces to hurl, a core material particle through an enveloping membrane.
- Production rate of 50 to 75 pound/hr have been achieved with this process.

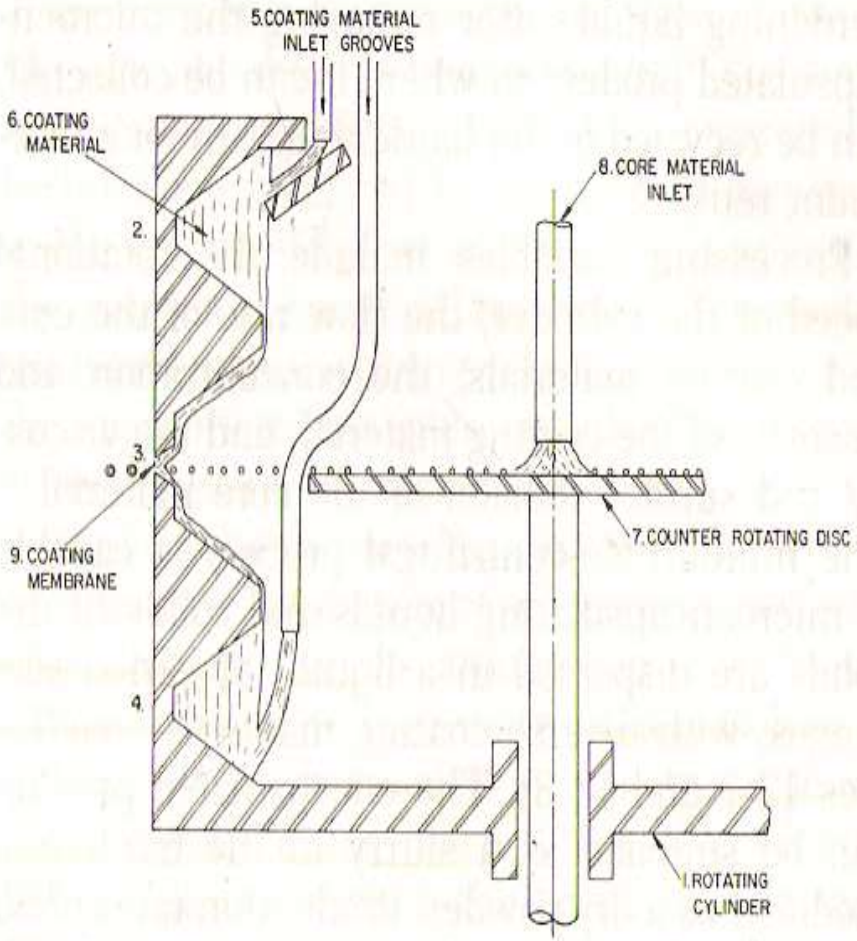
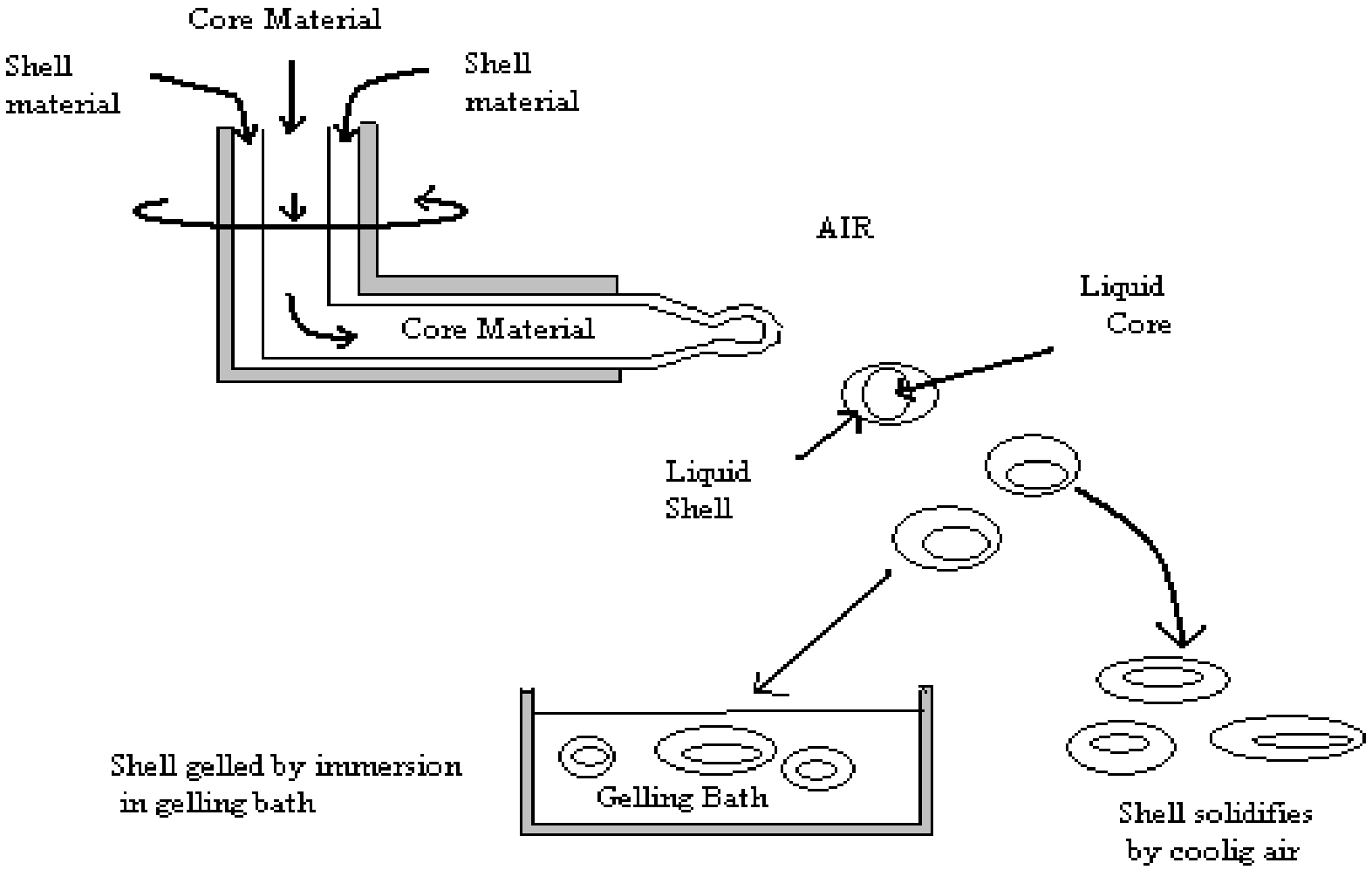
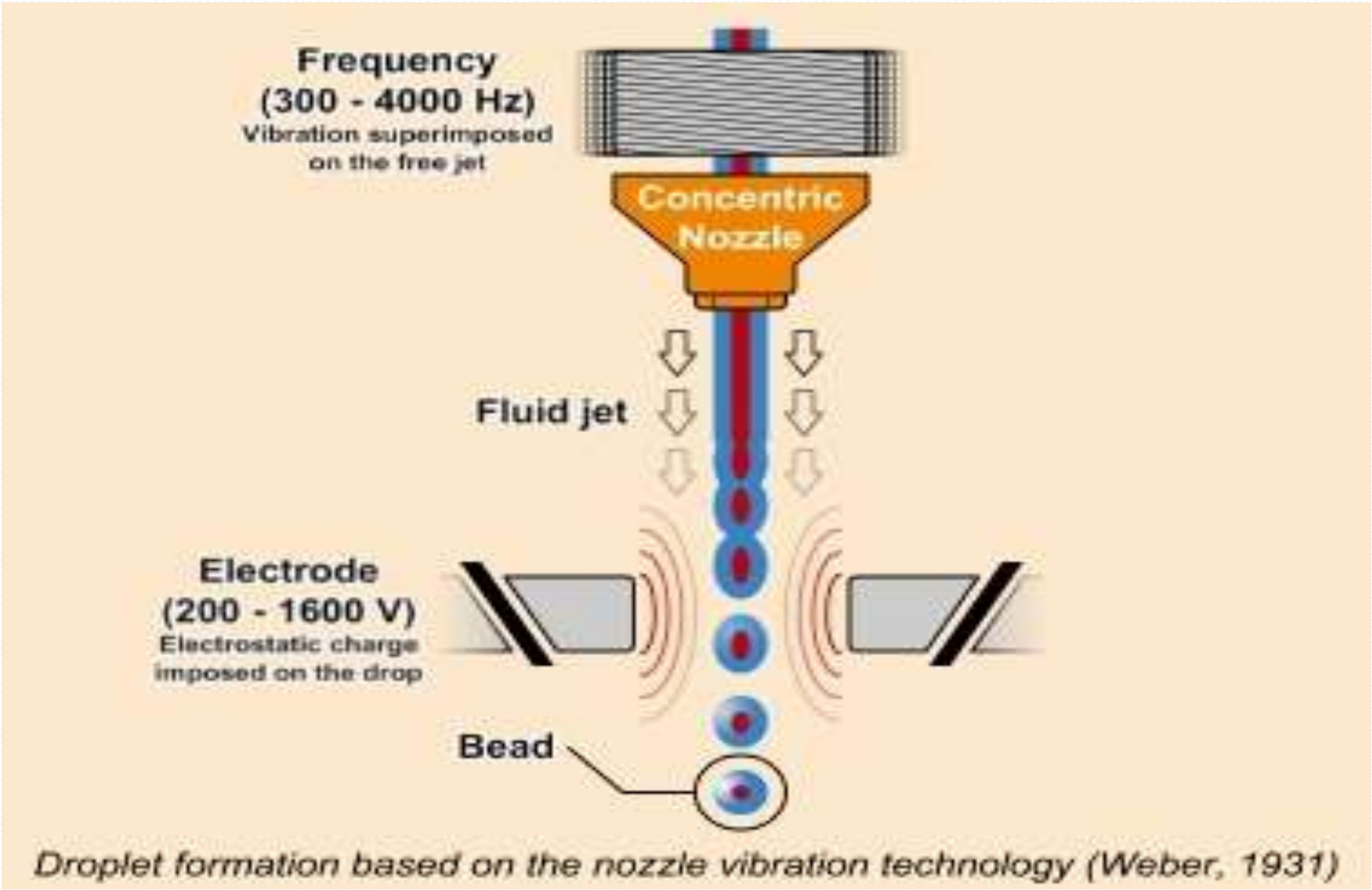


FIG. 13-45. *Sectional diagram of multiorifice-centrifugal microencapsulation apparatus. (From Mattson.[30] Courtesy Conover-Mast Publications, Inc.)*

Centrifugal extrusion:



NOZZLE VIBRATION TECHNOLOGY :



Droplet formation based on the nozzle vibration technology (Weber, 1931)

Microencapsulation processes & their applicabilities:-

process	Applicable core material	Approx. particle size (micron)
Air suspension	solid	35-5000
Coacervation phase separation	Solid & liquid	2-5000
Pan coating	solid	600-5000
Spray drying & spray congealing	Solid & liquid	600.

Evaluation of Microencapsulation:-

1) Morphology
2) Drug content
3) Bulk density
4) Angle of repose
5) Particle size determination
6) Determination of % drug entrapment
7) In vitro dissolution
8) Stability studies.

Partical Size and Shape:

- Conventional light microscopy-

  Used to determine the shape and outer structure of the microparticles.

- Scanning electron microscopy-

  It can be used for the investigation of double walled systems.

- Conflocal fluorescence microscopy-
  - used for the structure characterization of multiple walled microspheres.
  - It allows visualization and characterization of structures not only on the surface, but also inside the particals.

Electron spectroscopy for chemical analysis:

- Used to determine surface chemistry of the microspheres.
- ESCA provides a means for the determination of the atomic composition of the surface.
- The spectra obtained using ECSA can be used to determine the surface degradation of the biodegradable microspheres.

Attenuated total reflectance Fourier Transform- Infrared Spectroscopy

- FT-IR is used to determine the degradation of the polymeric matrix of the carrier system.
- The IR beam passing through the ATR cell reflected many times through the sample to provide IR spectra mainly of surface material.
- The ATR-FTIR provides information about the surface composition of the microspheres.

Density determination:

- The density of the microspheres can be measured by using a multi volume pychnometer.
- The chamber containing the sample is first pressurized with a gas, preferably helium. Subsequent expansion of this gas into a precisely measured volume results in a pressure drop.
- The sample volume and density are then easily calculated from the two pressure readings as displayed on the digital indicator

Isoelectric point:

- The micro electrophoresis is an apparatus used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined.

- By using this data the electrical mobility of the particle can be determined.

Angle of contact

- The angle of contact is measured to determine the wetting property of a micro particulate carrier.
- It determines the nature of microspheres in terms of hydrophilicity or hydrophobicity.
- The angle of contact is measured at the solid/air/water interface.

Release Studies

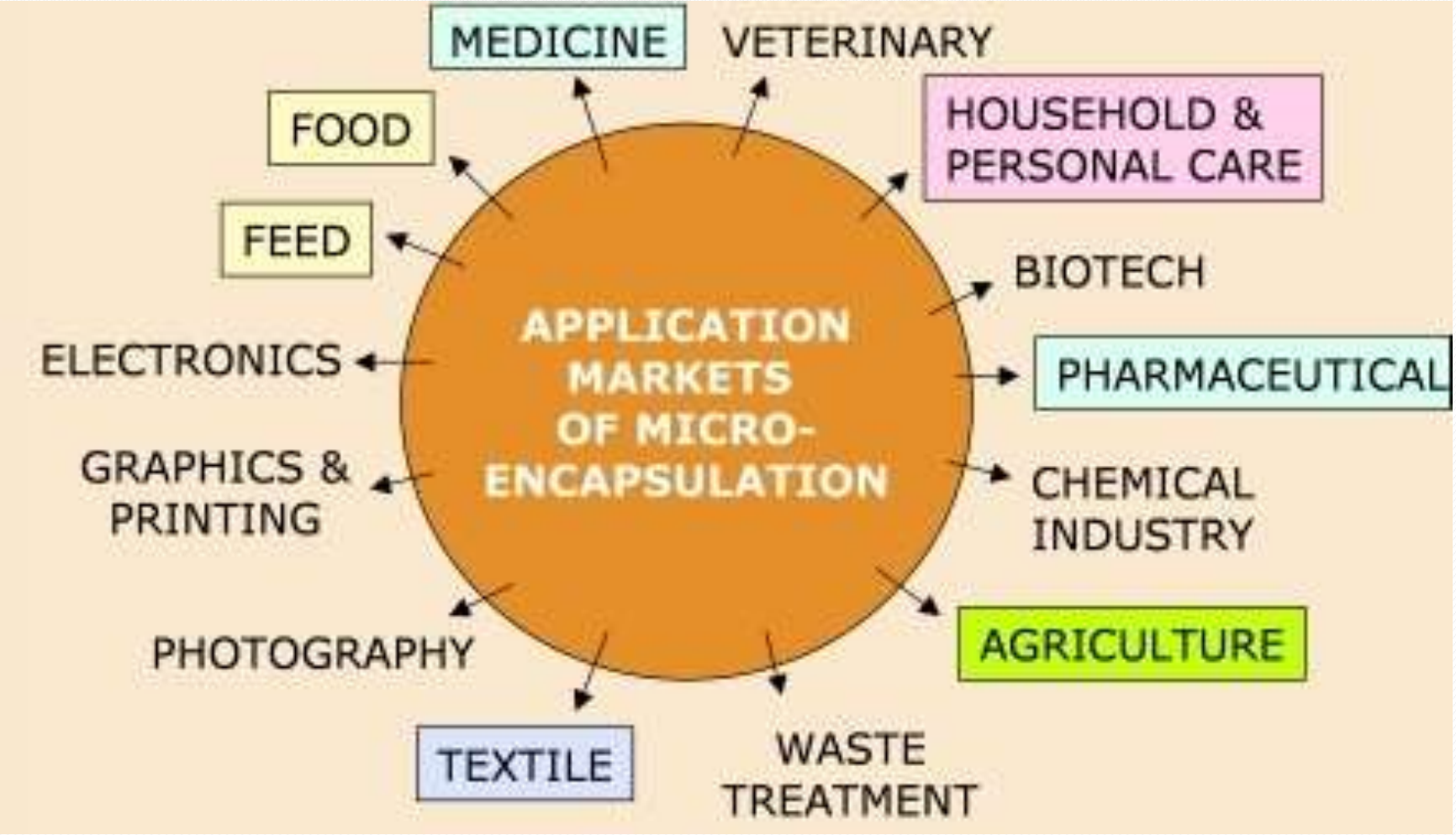
- The drugs could be released through the microspheres by any of the three methods.

- Osmotically driven burst mechanism
- Pore diffusion mechanism
- Erosion or degradation of the polymer

- Release studies for microspheres in phosphate saline buffer of Ph 7.4,are carried out using-

1. Rotating paddle apparatus
2. Dialysis method

APPLICATIONS :



Application:-

- Taste masking e.g. acetaminophen.
- Sustain release e.g. aspirin, isosorbide dinitrate.
- Conversion of liquid to solid e.g. clofibrate
- Odor masking e.g. castor oil, cysteine.
- Reducing gastric irritation e.g. phenylbutazone.
- Stabilization to oxidation e.g. vitamin

Applications of microencapsulation

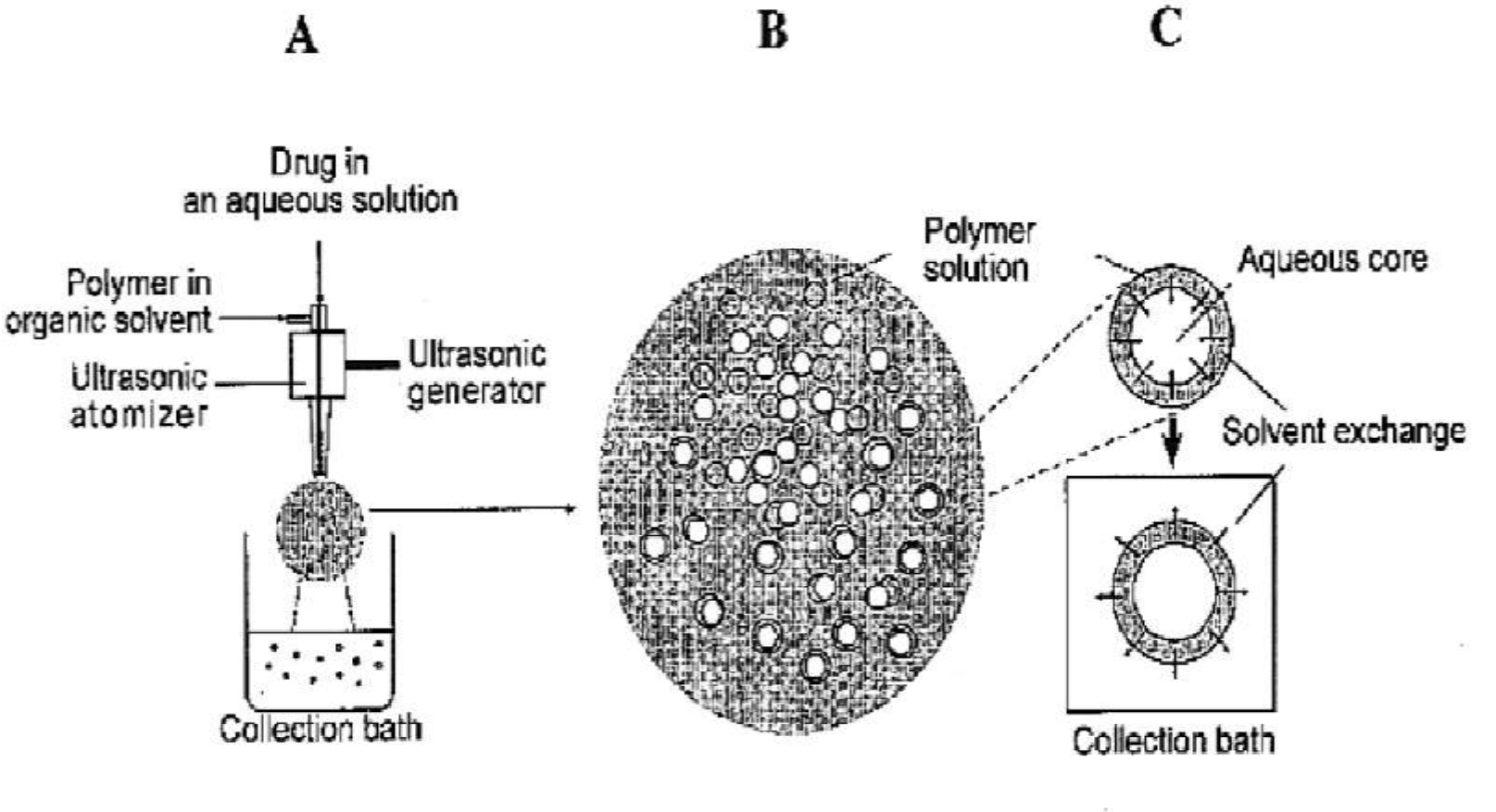
- **Protection of reactive material from environment**

a) hygroscopic properties
b) stability of vitamin A
c) reduce volatility

- **Taste masking of bitter Drugs** :
e.g. aspirin , acetaminophen , ampicilin , etc .

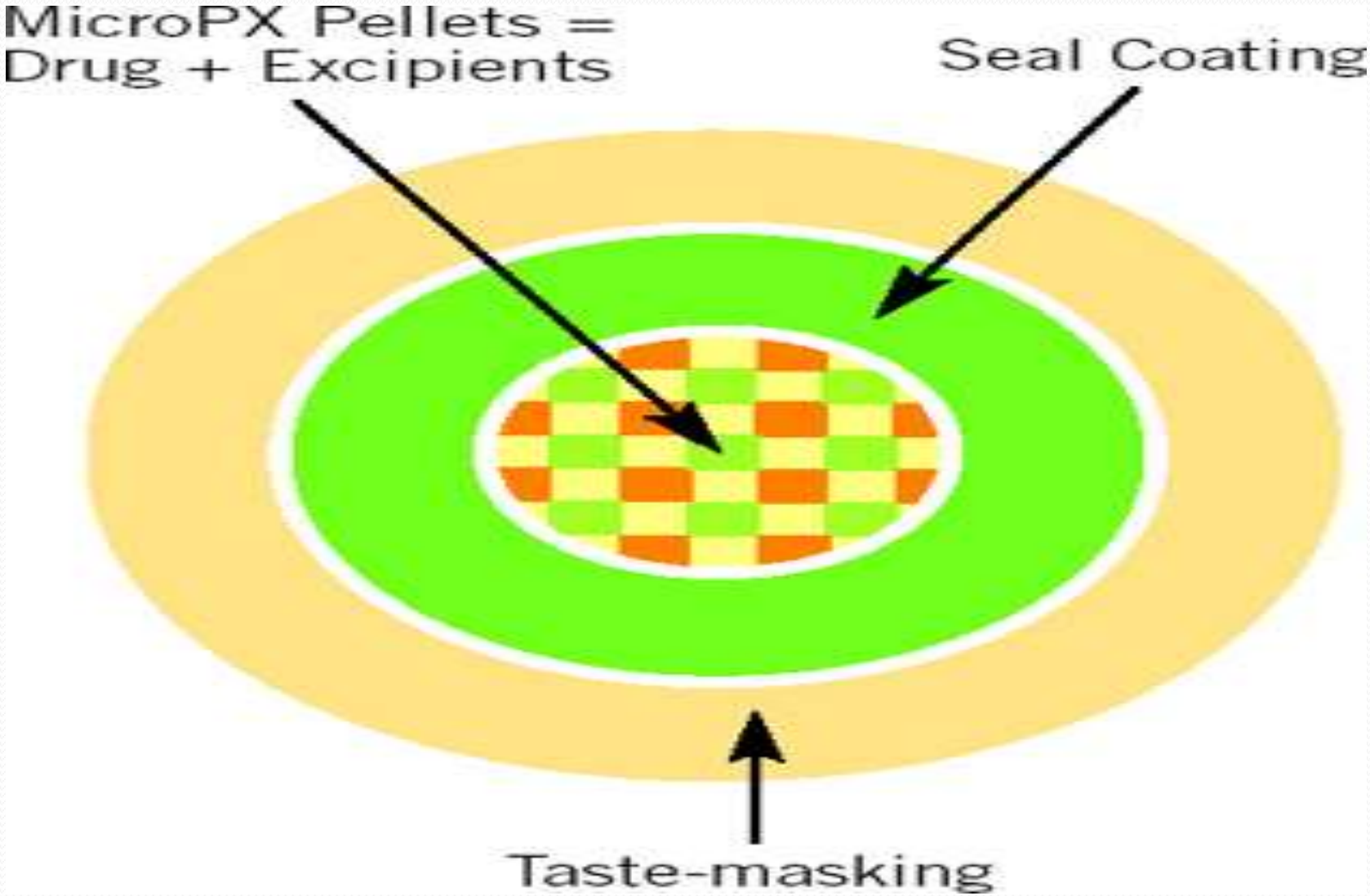
Means of handling liquid as solid[2]

e.g. eprazonium



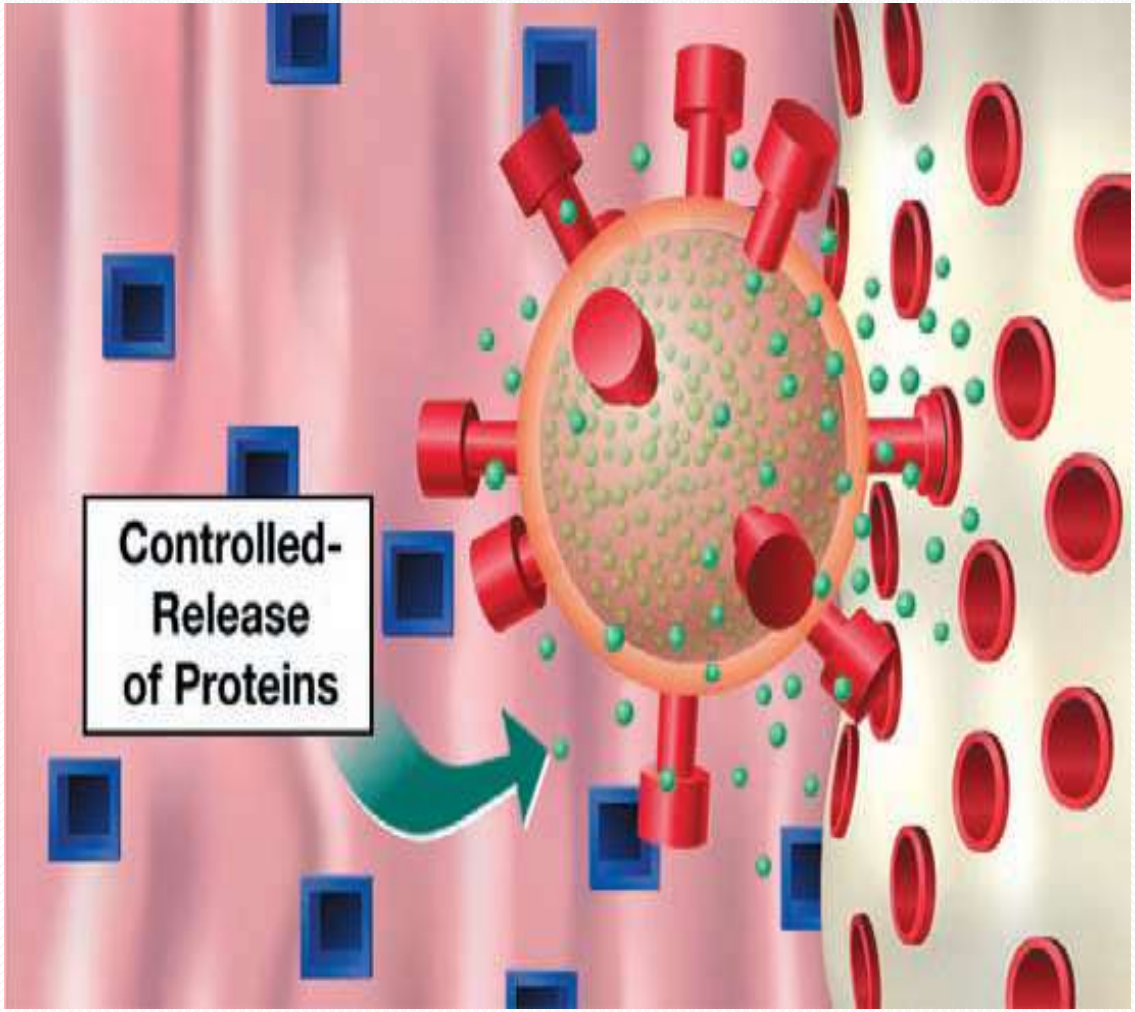
Taste masking of bitter Drugs[2,7] :

e.g. aspirin , acetaminophen , ampicilin , etc

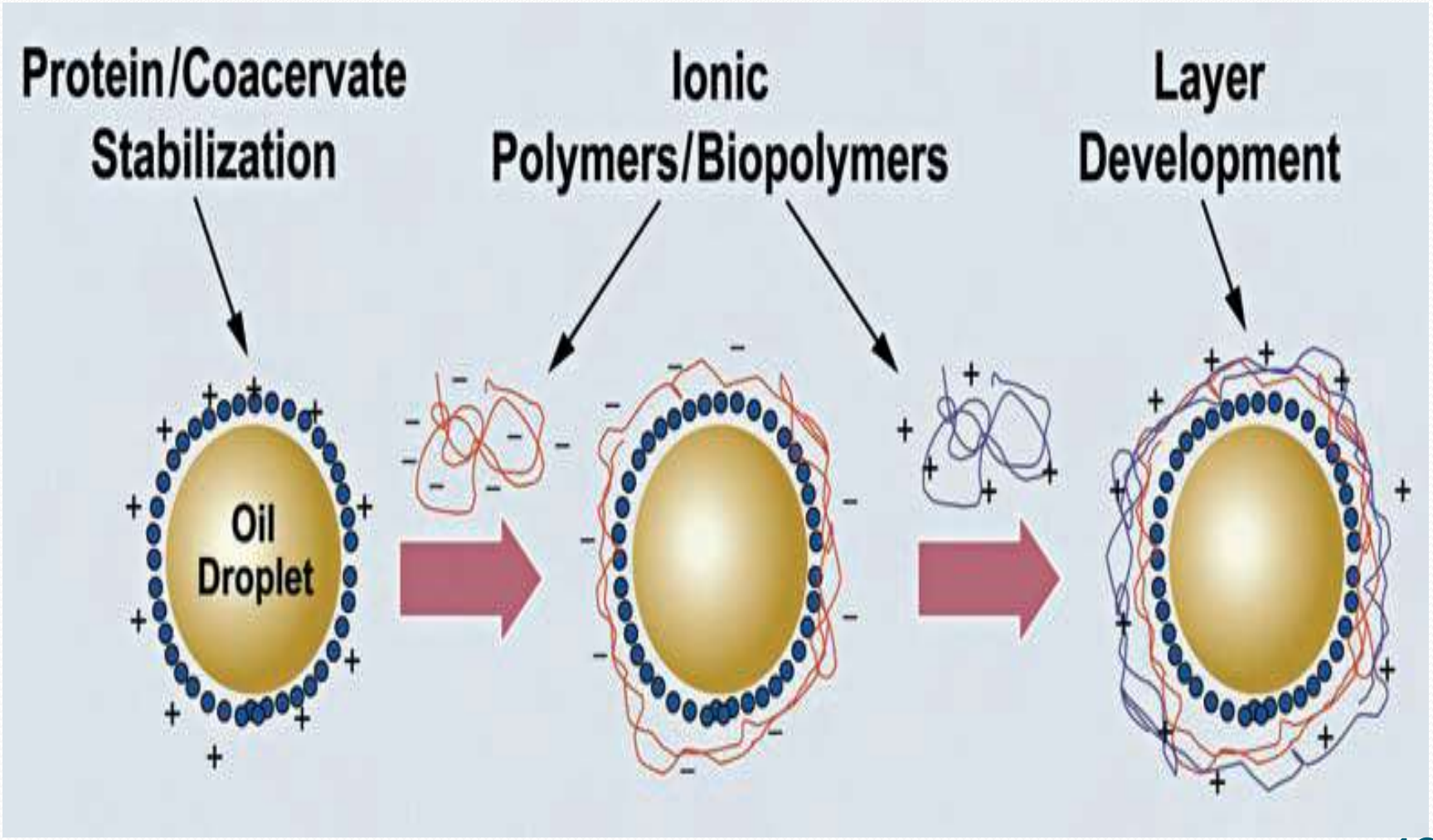


Targeted drug delivery[6]

Bone targeting nanocarriers that release their Payload following attachment to the target site.
Payload release may Occur by natural nanocarrier degradation application of external stimuli



Protein stability[6]



Drug delivery

- Microencapsulation as controlled release delivery systems.
- These systems allow controlling the rate, duration and distribution of the active drug. With these systems, micro particles sensitive to the biological environment are designed to deliver an active drug in a site-specific way (stomach, colon, specific organs).
- One of the main advantages of such systems is to protect sensitive drug from gastric environment. and to reduce the number of drug administrations for patient.

Agricultural and Industrial

- **Pesticides, fungicides and fumigants**
- **Animal feeds, seeds**
- **Veterinary formulations**
- **Paints and coatings**
- **Catalysts, resins, adhesives**
- **Pigments, dyes, colorants**
- **Lubricants and additives**
- **Inks**
- **Toys and novelty items**

CONCLUSION:

- The microencapsulation technique offers a variety of opportunities such as protection and masking, reduced dissolution rate, facilitation of handling, and spatial targeting of the active ingredient.

- This approach facilitates accurate delivery of small quantities of potent drugs, reduced drug concentrations at sites other than the target organ or tissue and protection of labile compounds before and after administration and prior to appearance at the site of action.

- In future by combining various other approaches, microencapsulation technique will find the vital place in novel drug delivery system.

References:

Books:

1. “The Theory & Practice of Industrial Pharmacy” by Lachman & liberman, Third edition 1991, Varghese publication house, Page no. 412
2. Encyclopedia of pharmaceutical Technology by Swarbrick & Boylan 1994, Page no. volume I:3, II:403, III.21,31,283, IX:423-439, VIII:206,210,213, X:3, XII:295.
3. Targeted & Controlled Drug Delivery (Novel Carrier System) by Vyas & Khar, CBS Publication, 2004,Page no.13, 325, 418.
4. The Design & Manufactures Of Medicines By Michal E. Aulton , Third edition , Page no.81.
5. Pharmaceutical Dosage Forms & Drug Delivery System by Ansel’s Hawards, Nicholas.
6. Physical Pharmacy by Martin , Fourth edition, Page no. 516,575.
7. Biopharmaceutics & Pharmacokinetics By Brahmankar & Jaiswal, First edition, Vallabh prakashan, Page no. 359.
8. Conrolled Drug Delivery by Robinson & Lee ,Second edition, Vol. 29, Page no.384,388,450.
9. Controlled & Novel Drug Delivery by N. K. Jain, First edition , 2004, CBS publication, Page no. 237

Web. Address:

10. www. microtecklabs.com/technical_overview.pdf
11. www.pharmainfo.in
12. www.books.google.in
13. www.sid.irlen/vewssid/J.pdf
14. www.globalresearchonline.nel
15. www.pharmatext.org
16. www.rmz.mg.com