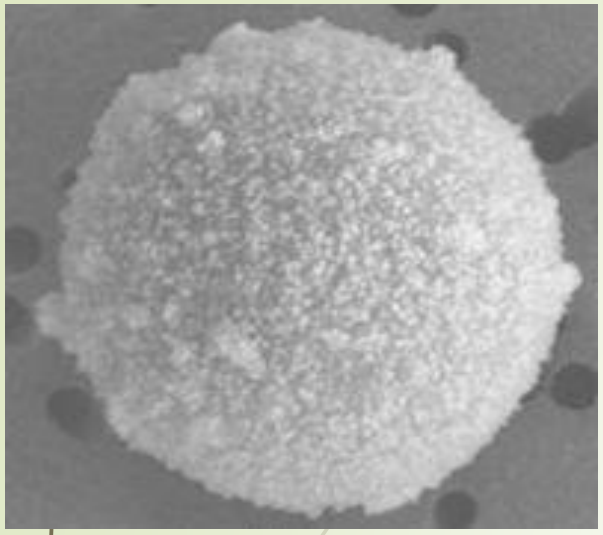

# Microencapsulation

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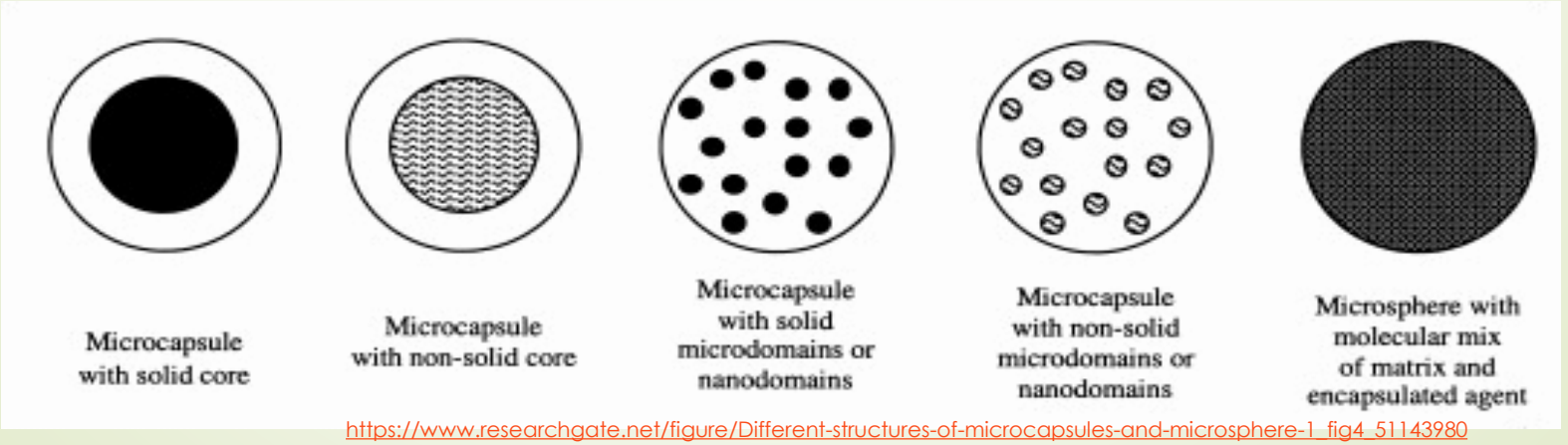
# Contents

- Definition
- Advantages and Disadvantages,
- Microspheres & Microcapsules, Microparticles,
- Methods of Microencapsulation,
- Applications

# Microencapsulation : Definition

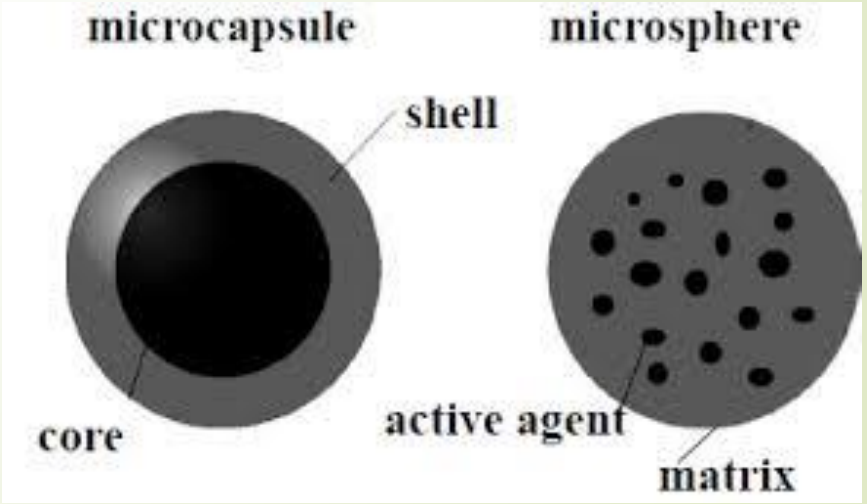
- Microencapsulation is a technique by which microscopic particles of solids, liquids or gases are enclosed within uniform thin coatings.
- It is the process by which individual particles or droplets of solid or liquid material (the core) are surrounded or coated with a continuous polymeric film material (the shell) to produce capsules in the micrometer to millimetre range, known as microcapsules.
- The product obtained by microencapsulation process is called as microparticles
- Particles size between 3 - 800µm are known as **microparticles** (microcapsules or microspheres).
- Particles larger than 1000µm are known as **macroparticles**

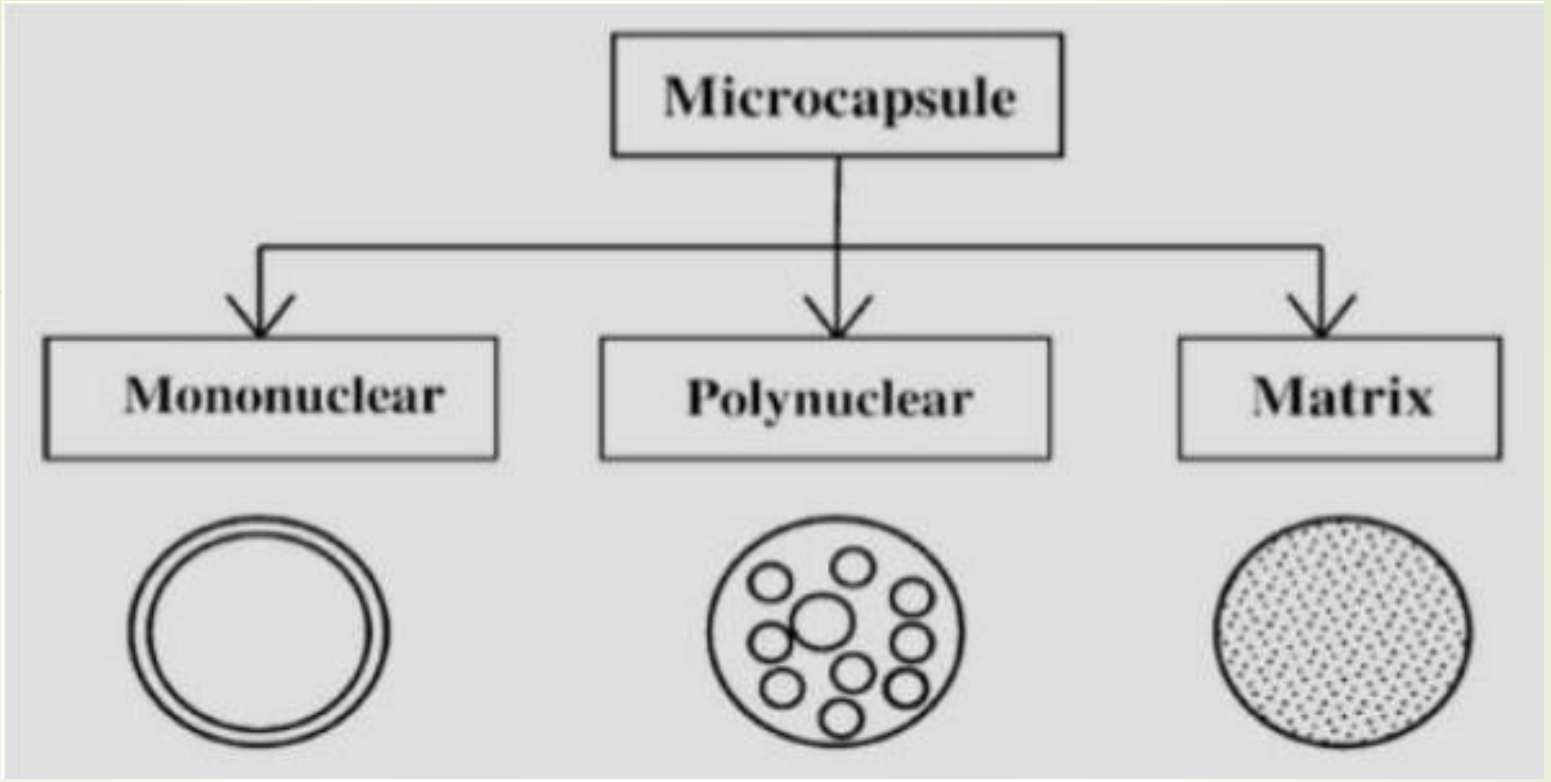



https://www.researchgate.net/figure/Different-structures-of-microcapsules-and-microsphere-1_fig4_51143980

# Microparticles: Microcapsules& Microspheres

- Microparticles are particulate drug delivery systems of size range of 1-1000 μm.
- Microparticles consist of two components
  - a) Core material (Drug solid/liquid)
  - b) Coat or wall or shell material (polymer)
- Depending upon whether drug has been entrapped or dispersed, they have been classified as
  - Microcapsules: reservoir type systems
  - Microspheres: matrix type systems



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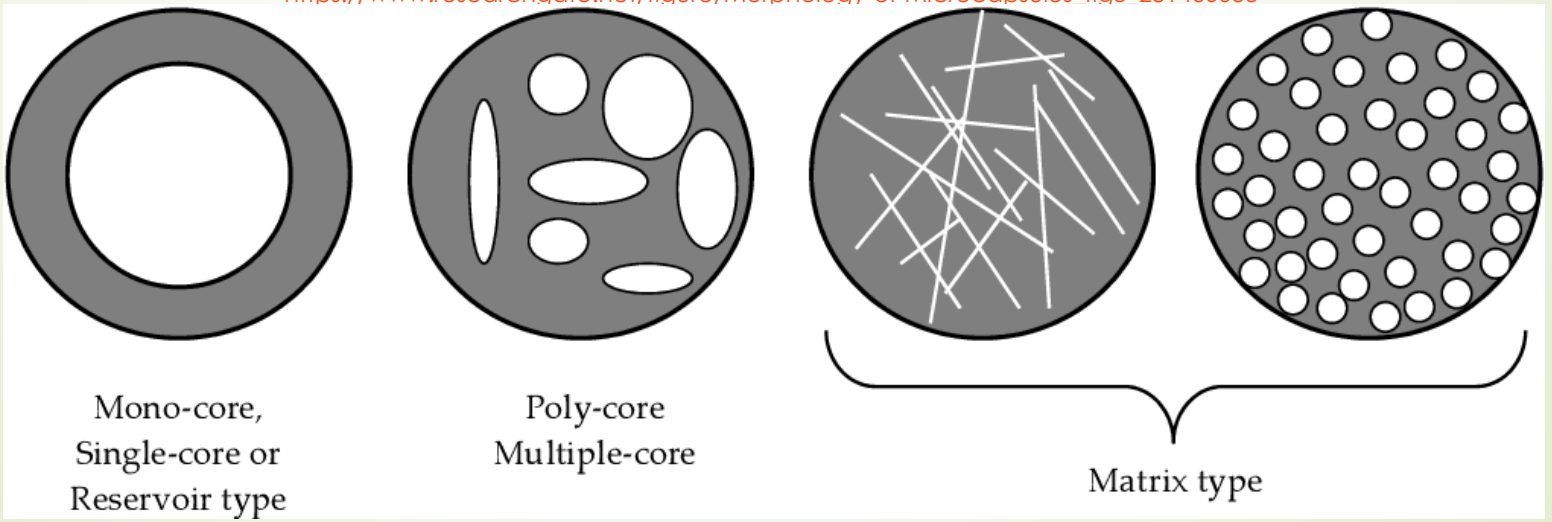



https://www.semanticscholar.org/paper/Polysaccharides-as-Carriers-and-Protectors-of-and-Raybaudi-Massilia-Mosqueda-Melgar/4322927737d74d12fb059cff187f625ebe62ef8b

# Advantages

- Provide Protection to unstable, sensitive materials from their environments prior to use
- Improve the solubility, dispersibility, flow ability and bioavailability of drug
- Improve the shelf life of drug by preventing reactions (oxidation, dehydration)
- Provide Controlled, sustained, or timed release
- Provide safe and convenient handling of toxic materials
- Mask the odour and bitter taste of drug
- The surface of microcapsule can be modified by attaching ligands such as antibodies which would enable them to target specific organs and sites in the body
- Conversion of liquid to pseudo solid and handle liquids as solids Eg: Eprazinone
- Reduction of vaporization of volatile drugs. Eg: Methyl salicylate.
- Prevention of incompatibilities among drugs. Eg: Aspirin and Chlorpheniramine maleate .
- Reduction of hygroscopicity .Eg: NaCl.

# Disadvantages of Microencapsulation

- Possible cross reaction between core and shell material.
- Difficult to achieve continuous and uniform film.
- Shelf life of hygroscopic drugs is reduced.
- More production costs.
- More skill and knowledge is required

# Release Mechanisms

the release mechanisms for microcapsules can be

- by pressure or shear stress.
- by melting the wall
- by dissolving it under particular conditions, as in the case of an enteric drug coating.
- by solvent action
- by enzyme attack
- by chemical reaction
- by hydrolysis or slow disintegration.

# Film-forming Polymer used as coating material

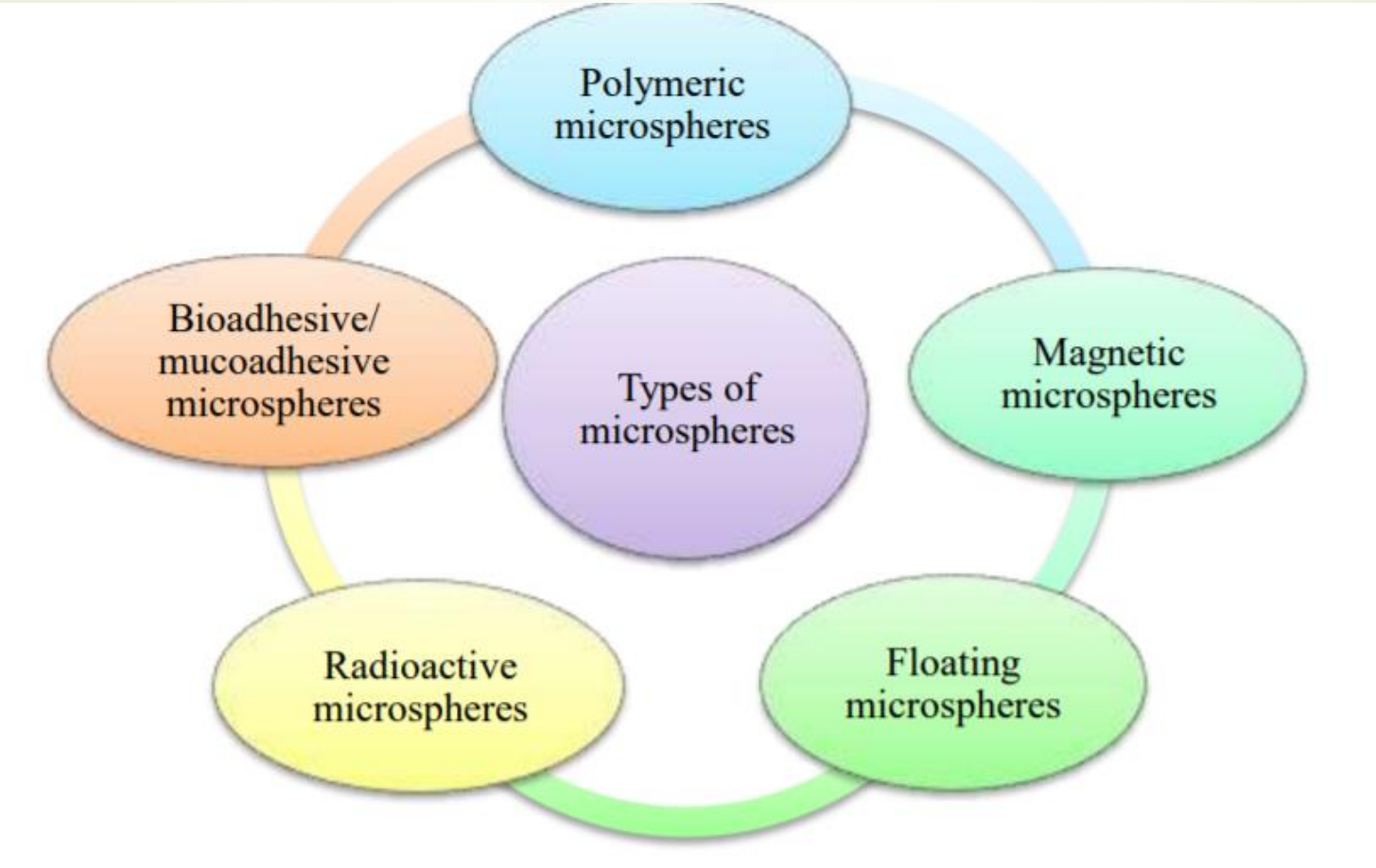
## Hydrophilic Polymers

- Alginates
- Carbopol
- Gelatin
- Hydroxypropylcellulose
- Methyl and ethyl cellulose
- Starches
- Cellulose acetate phthalate,.

## Hydrophobic Polymers

- Carnauba wax
- Cetyl alcohol
- Hydrogenated vegetable oils

# Types of Microparticles

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# Types of Microparticles

- **Bioadhesive/mucoadhesive microspheres-** This includes adhesive drug delivery system that adhere to mucosal membranes for producing close and extended residence time at site of administration which could result in superior absorption.
- **Radioactive microspheres** These are used for diagnostic purpose such as
  - diagnostic radioembolization (treatment of cancer wherein radioactive moieties are transported to tumor via bloodstream).
  - Thrombus imaging in deep vein thrombosis
  - Lung scintigraphy
  - Diagnostic radioembolization
  - Tumor imaging

# Types of Microparticles

- **Floating microspheres-** Gastro-retentive floating microspheres being low density device produce adequate buoyancy to drift above gastric fluid for expanded period with gradual release of drug at desired rate. Furthermore, this diminishes probability of dose dumping, extended therapeutic effect and reduces dosing frequencies.
- **Magnetic microspheres-** These microspheres are sufficiently minute to flow through capillaries and devoid of creating embolic occlusion (< 4 μm), however, these are adequately vulnerable (ferromagnetic) to be arrested in micro vessels. Magnetic microspheres can be used in
  - DNA analysis, protein purification, targeting drugs to tumor sites and cell isolation.

# Types of Microparticles

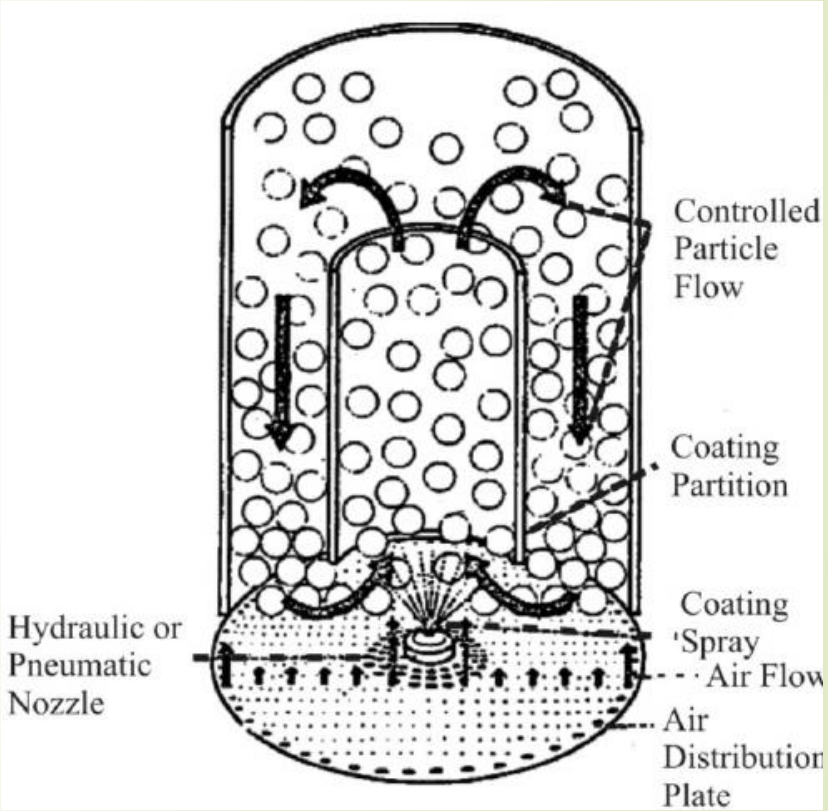
- **Polymeric microspheres** Polymeric microspheres can be potentially utilized for **sustained and controlled** delivery of medication. Polymeric microspheres can be classified on the basis of nature of origin of polymer.
- **Non-biodegradable polymeric microspheres** These microspheres are produced from non-biodegradable polymers for instance poly-methyl-(methacrylate), acrolein and glycidyl methacrylate.
- **Biodegradable polymeric microspheres**
  - Natural biodegradable polymeric microspheres Polymers such as starch, albumin, casein, gelatin, chitosan, dextran and cellulose lengthens residence period over mucous membrane attributable to excessive level of swelling characteristics. Majority of natural polymers are biodegradation and biocompatible having less toxicity problems. Moreover, existence of antigenic determinants over natural polymers deviate attention of researchers from natural biodegradable to synthetic biodegradable polymers.
  - Synthetic biodegradable polymeric microspheres Lactide, glycolide & their co-polymers, polycaprolactone, polyhydroxybutyrate, poly-alkyl cyanoacrylates, poly-anhydrides has been extensively utilized for controlled delivery of numerous proteins and drugs.

# Microencapsulation Techniques:

1. Air suspension techniques( Wurster)
2. Coacervation process
3. Spray drying & congealing
4. Pan coating
5. Solvent evaporation
6. Polymerization
7. Multiorific-centrifugal
8. Extrusion
9. Layer-by-Layer Technique
10. Double emulsion techniques

# Air suspension techniques( Wurster)

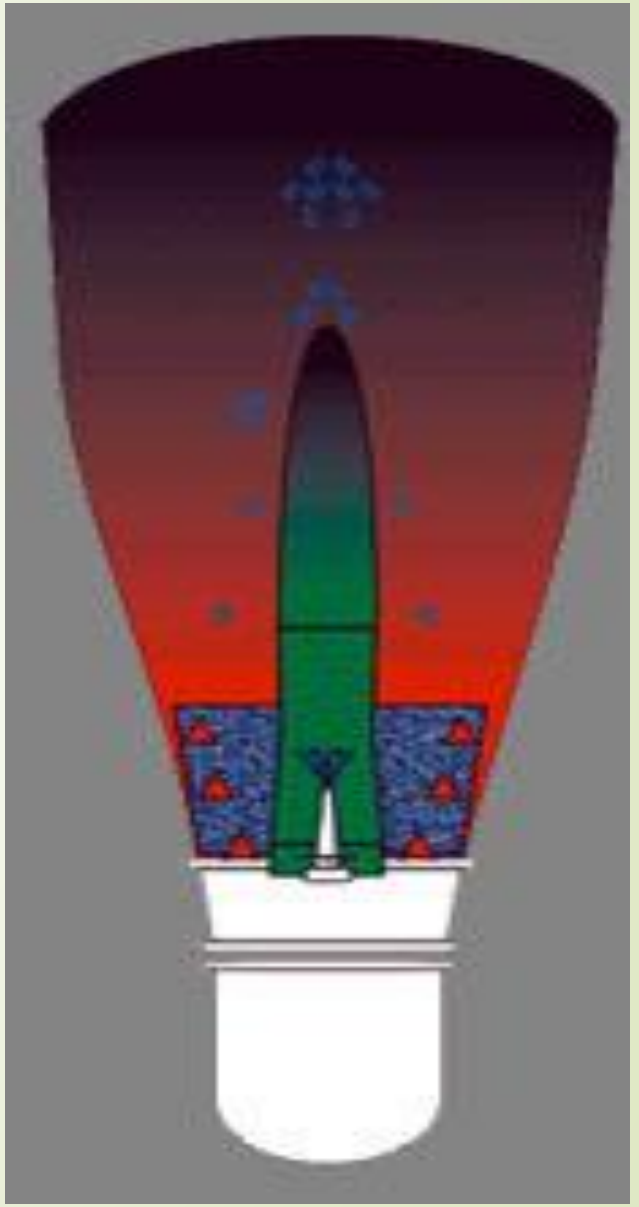
1. In Wurster process or Air Suspension technique solid particulate or core materials is dispersed in a supporting air stream and the spray-coating is done of the air suspended particles.
2. The particles are suspended within the coating chamber, on an upward moving air stream as indicated in the drawing.
3. The design of the chamber is such that, its operating parameters provide a recirculating flow of the particles through the coating zone of the chamber and coating material is sprayed to the moving particles.




https://www.researchgate.net/figure/The-Wurster-process-Hinkes-1977_fig3_279498086

# Air suspension techniques( Wurster)

- During each cycle of passing through the coating zone, the core material receives an increment of coating material.
- This process is repeated several times depending on the coating thickness desired.
- The hot air stream also serves to dry the product while it is being encapsulated.



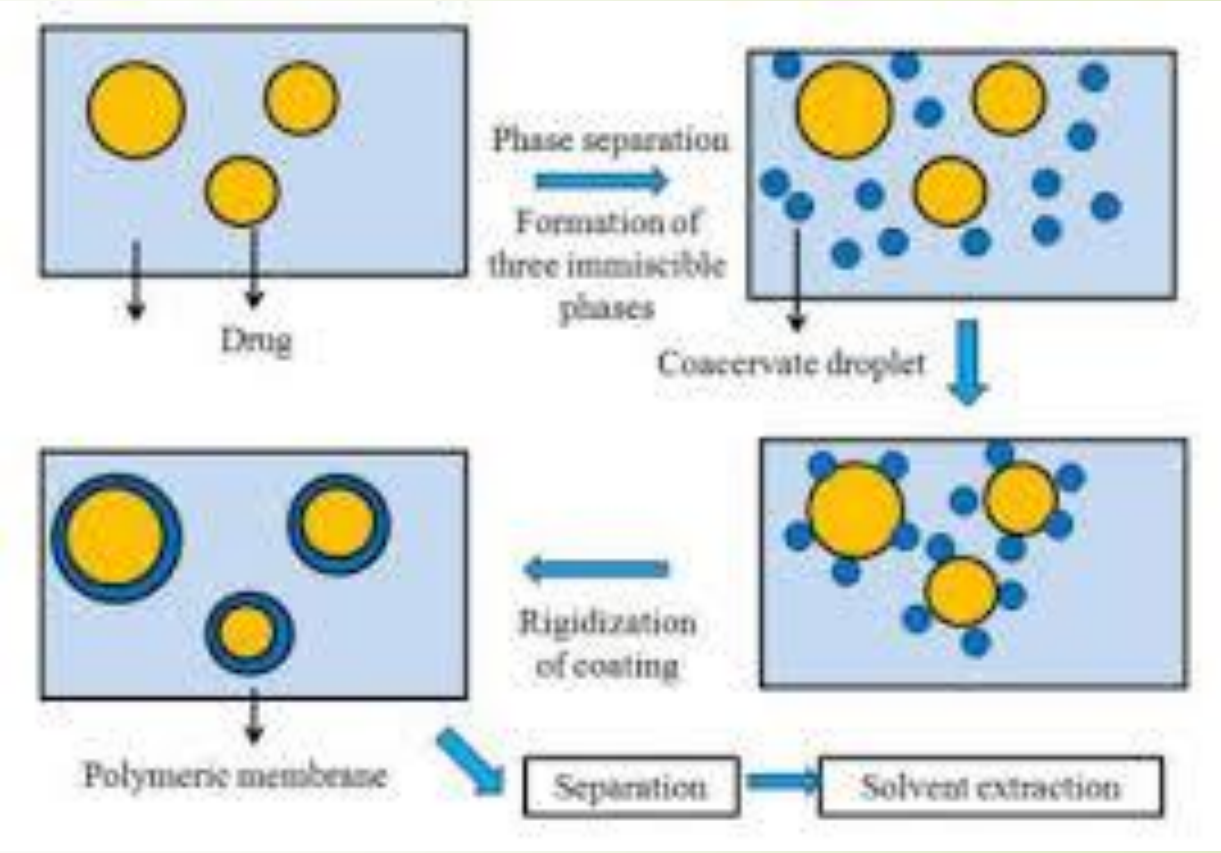
# Pan coating

- This method, is similar to coating of Tablet
- the coating is applied as an atomized spray to the desired ***solid*** core material in the coating pan.
- To remove the coating solvent, a warm air is used.
- Pan Coating process is used for solid particles greater than 600µm in size.
- The coating is applied as a solution, or as an atomized spray, to the desired solid core material in the coating pan.
- Warm air is passed over the coated materials as the coatings are being applied in the coating pans to remove the coating solvent.

# Coacervation Phase Separation

The process consists of three steps

- Formation of three immiscible phases;
  a liquid manufacturing phase,
  a core material phase and a
  coating material phase.
- Deposition of the liquid polymer coating on the core material.
- Rigidizing the coating usually by thermal, cross linking or desolvation techniques to form a microcapsule.
- Coacervation can be achieved through:
  - Temperature change
  - Addition of incompatible polymer
  - Polymer-polymer interaction
  - Non-solvent or salt addition

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# Coacervation Phase Separation

**Step 1**

To form the three phases, the coating polymer solution is mixed with **immiscible** solvent to form two immiscible liquids, then the core material is added to form the third phase.

**Step 2**

Deposition of the liquid polymer coating around the core material occurs if the coating polymer is adsorbed at the interface between the core material and the immiscible solvent phase, and this adsorption phenomenon is a prerequisite (essential) to effective coating

**Step 3**

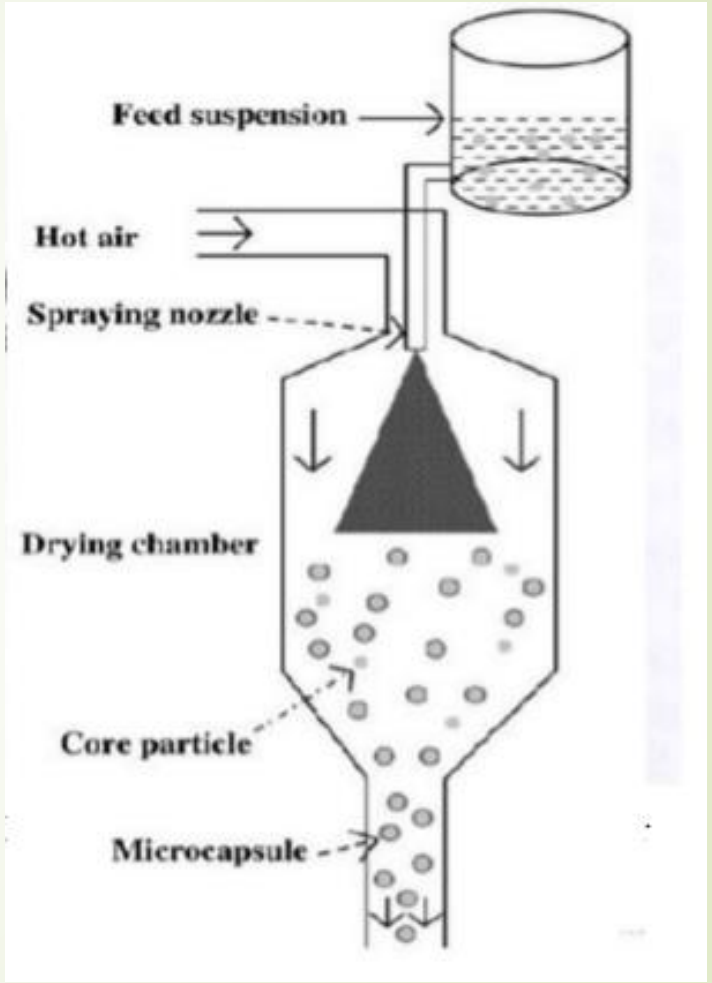
Rigidizing the coating, usually by thermal techniques, to form the microcapsules.

# Coacervation Phase Separation

- Ex: Ethyl cellulose (a water insoluble polymer) is applied to aminophenol powder (core material) by utilizing the temperature characteristics of the polymer in the cyclohexane (solvent).
- The Ethyl cellulose is insoluble in cyclohexane at room temperature, but soluble at elevated temperature.
- The ethyl cellulose and cyclohexane mixture is heated to form a homogeneous (one phase) solution.
- The aminophenol is dispersed (as insoluble powder) in the solution with stirring.
- Allowing the mixture to cool with continuous stirring results in coacervation-phase separation of the ethyl cellulose from cyclohexane and microencapsulation of the core material. Allowing the mixture to cool further to room temperature causes gelation and solidification of the coating.
- The microencapsulated product is collected from by filtration.

# Spray drying & Spray Congealing

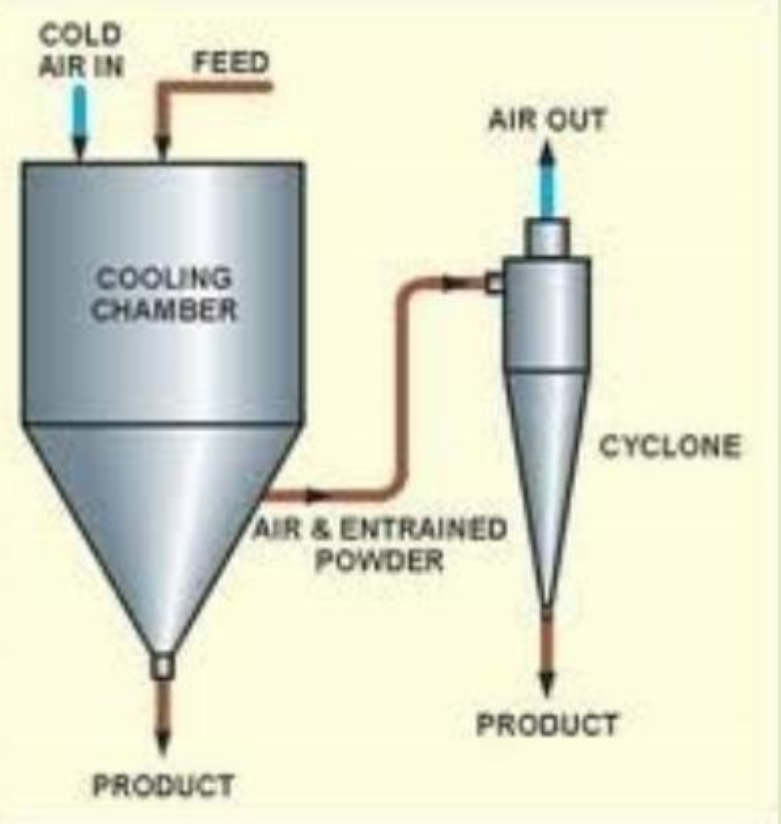
- Spray-drying and spray-congealing processes are similar in that both involve **dispersing the core material in a liquid coating material and spraying** the core-coating mixture into certain environmental condition, whereby rapid solidification of the coating is achieved.
- Microencapsulation by spray drying is done by dispersing a core material in a coating solution, in which the core material is insoluble and then atomizing the mixture into an air stream
- The hot air is used for vaporize or to remove the solvent from the coating material
- The equipment used for this purpose is the usual **spray dryer.**



# Spray drying & Spray Congealing

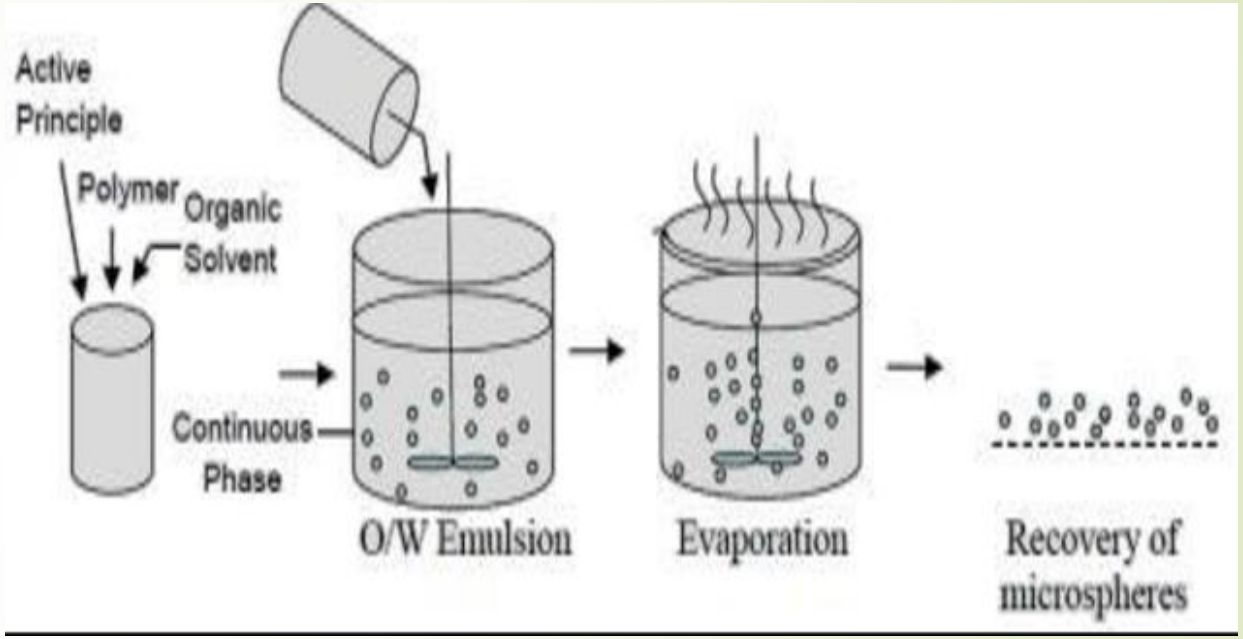
The principal difference between the two methods is the means by which the solidification is achieved.

- Coating solidification in the case of spray drying is achieved **by rapid evaporation** of a solvent in which the coating material is dissolved.
- Coating solidification in spray congealing methods is accomplished by **thermally congealing (cooling)**
- the core material is dispersed in a coating material **melt** rather than the usual coating solution. Coating solidification (and microencapsulation) is accomplished by spraying the hot mixture into a **cool** air.
- Ex: Waxes, fatty acids and certain polymers which are solids at room temperature but melt-able at high temperatures, are applicable to spray congealing technique.



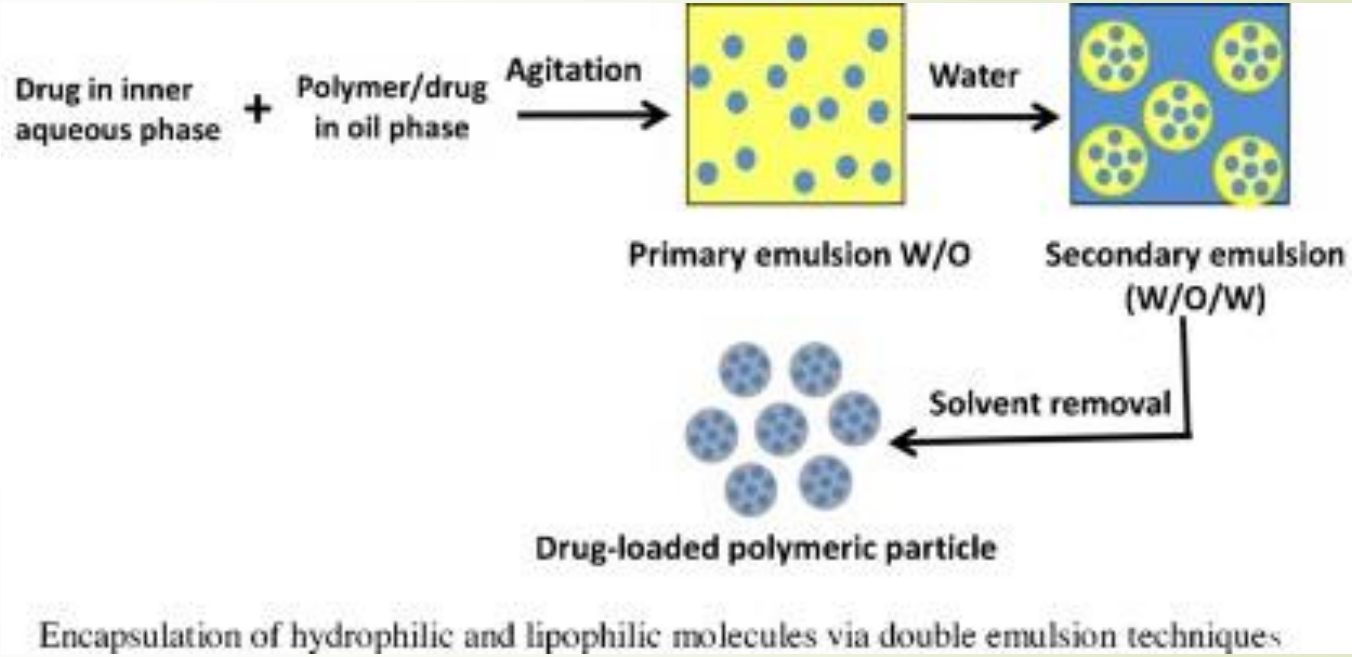
# Solvent evaporation/Single emulsion solvent evaporation method

- The polymer is dissolved in a water immiscible volatile organic solvent like dichloromethane or chloroform, into which the core material is also dissolved or dispersed.
- The resulting solution is added dropwise to a stirring aqueous solution having a suitable stabilizer like poly (vinyl alcohol) or polyvinylpyrrolidone, etc. to form small polymer droplets containing encapsulated material.



# Double emulsion techniques

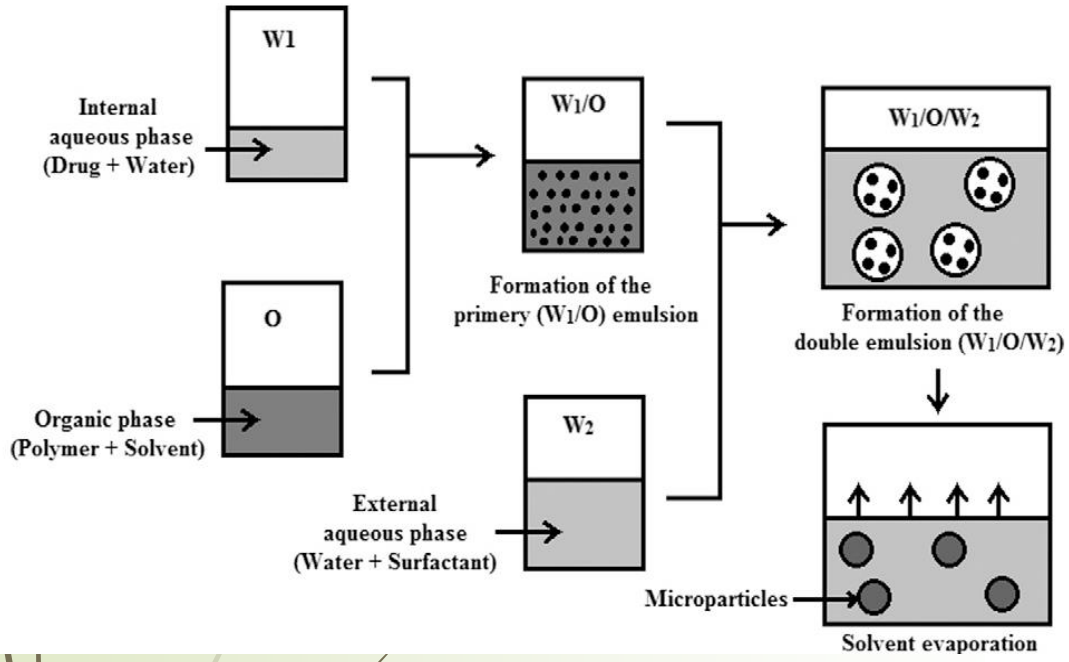
- also called “emulsions of emulsions
- encapsulation of both hydrophobic as well as hydrophilic drugs is possible
- This technique involves either w/o/w or o/w/o emulsification

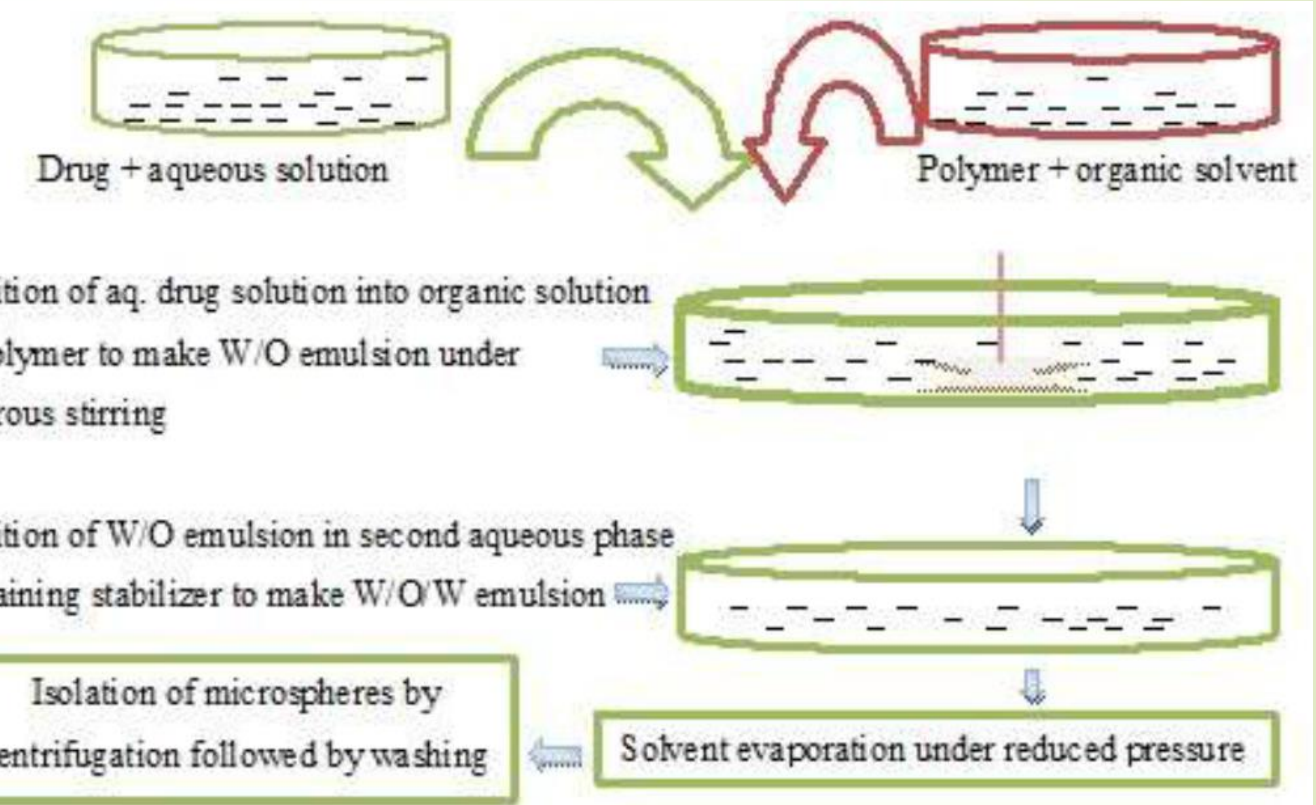



Encapsulation of hydrophilic and lipophilic molecules via double emulsion techniques

https://www.sciencedirect.com/science/article/pii/S0378517315303264

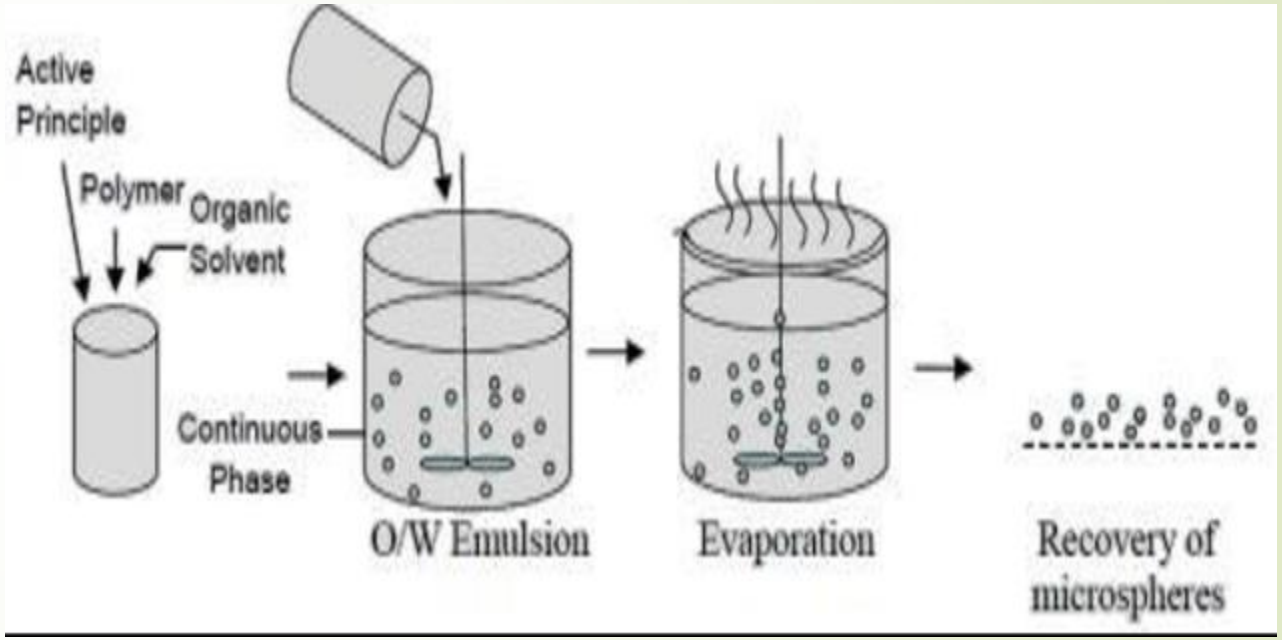
# Double emulsion techniques



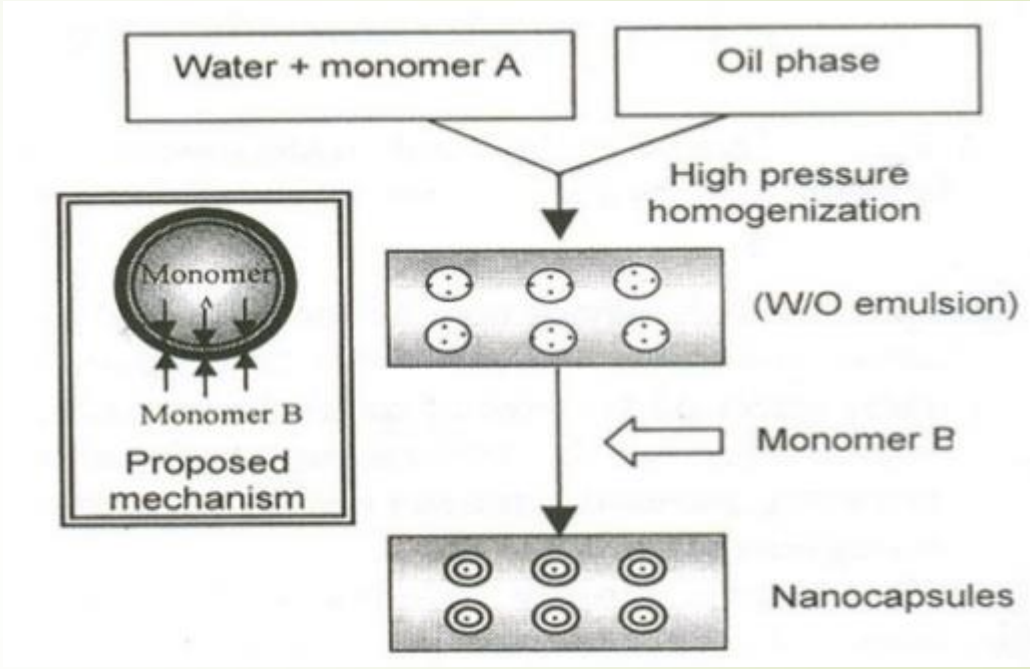
# Solvent evaporation/Single emulsion solvent evaporation method

- With time, the droplets are hardened to produce the polymeric microcapsules.
- This hardening process is accomplished by the removal of the solvent from the polymer droplets by solvent evaporation (by heat or reduced pressure).
- Stirring is done for several hours to allow solvent to evaporate.
- Further particles are removed by filtration, rinsing and drying.



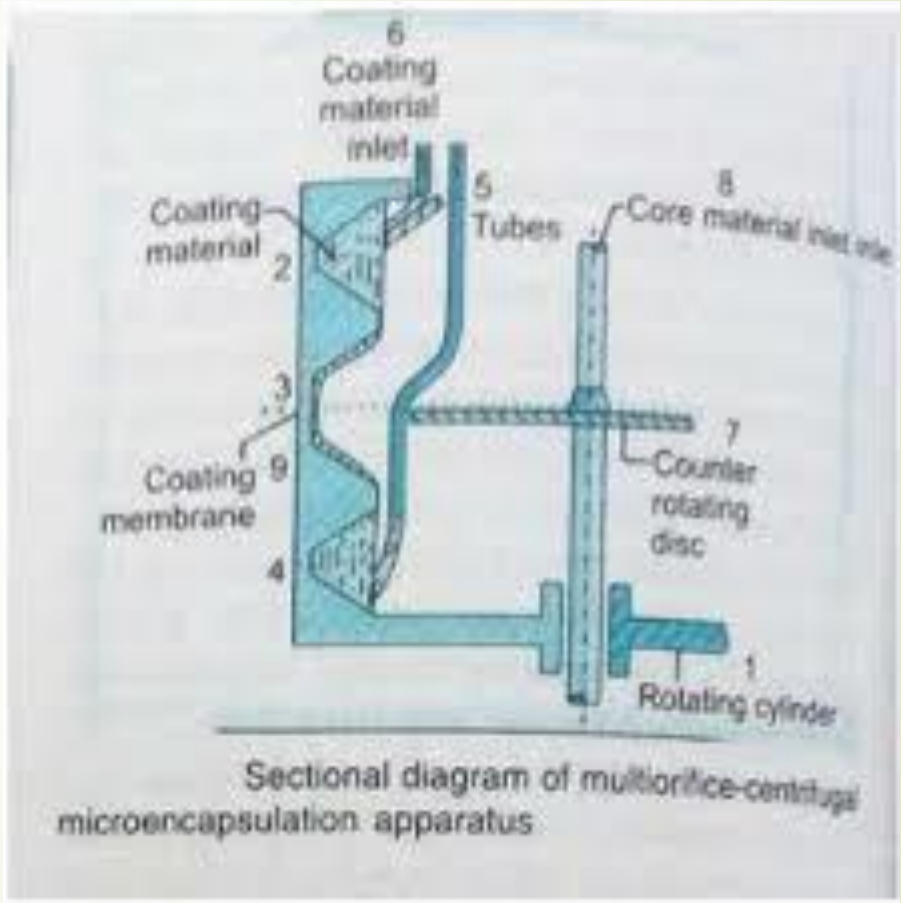
# POLYMERIZATION

- A relatively new methods involve the reaction of monomeric units located at the interface existing between a core material and a continuous phase in which the core material is dispersed.
- The continuous or core material supporting phase is usually a liquid or gas, and therefore the polymerization reaction occurs at a liquid-liquid, liquid-gas, solid-liquid, or solid-gas interface.



# Multiorific-centrifugal

- This is a mechanical process for producing microcapsules.
- It utilizes centrifugal forces to launch a core material particle trough an enveloping microencapsulation membrane thereby effecting mechanical microencapsulation.
- Factors that effect the process are
  - the rotational speed of the cylinder,
  - the flow rate of the core and coating materials,
  - The concentration of core material.
  - viscosity and surface tension of the coating materials
- Microencapsulation of liquids and solids both with varied size ranges and diverse coating materials can be done.



Sectional diagram of multiorifice-centrifugal microencapsulation apparatus

https://www.ejpmr.com/admin/assets/downloads/1519801331.pdf

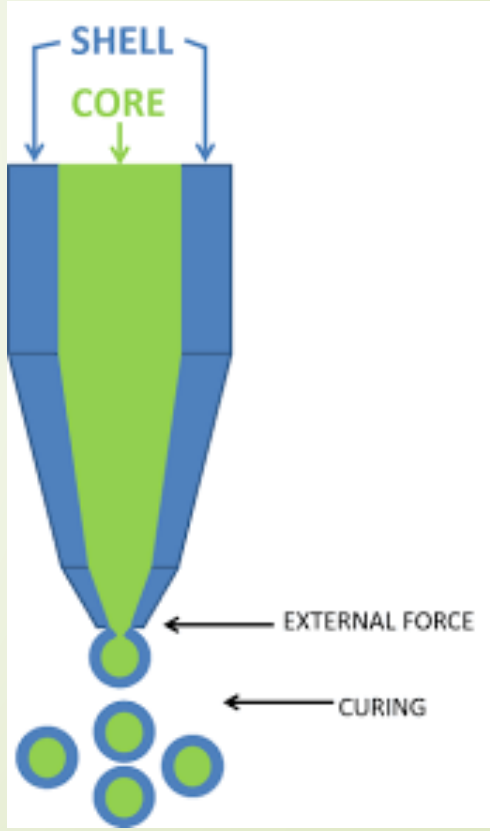
# choice of the microencapsulation method

**Selection appropriate technique for fabrication of microspheres depends on**

- **required particle size,**
- **period of drug release,**
- **physicochemical property of drug and**
- **nature of polymer to be loaded**

# Co-Extrusion Method

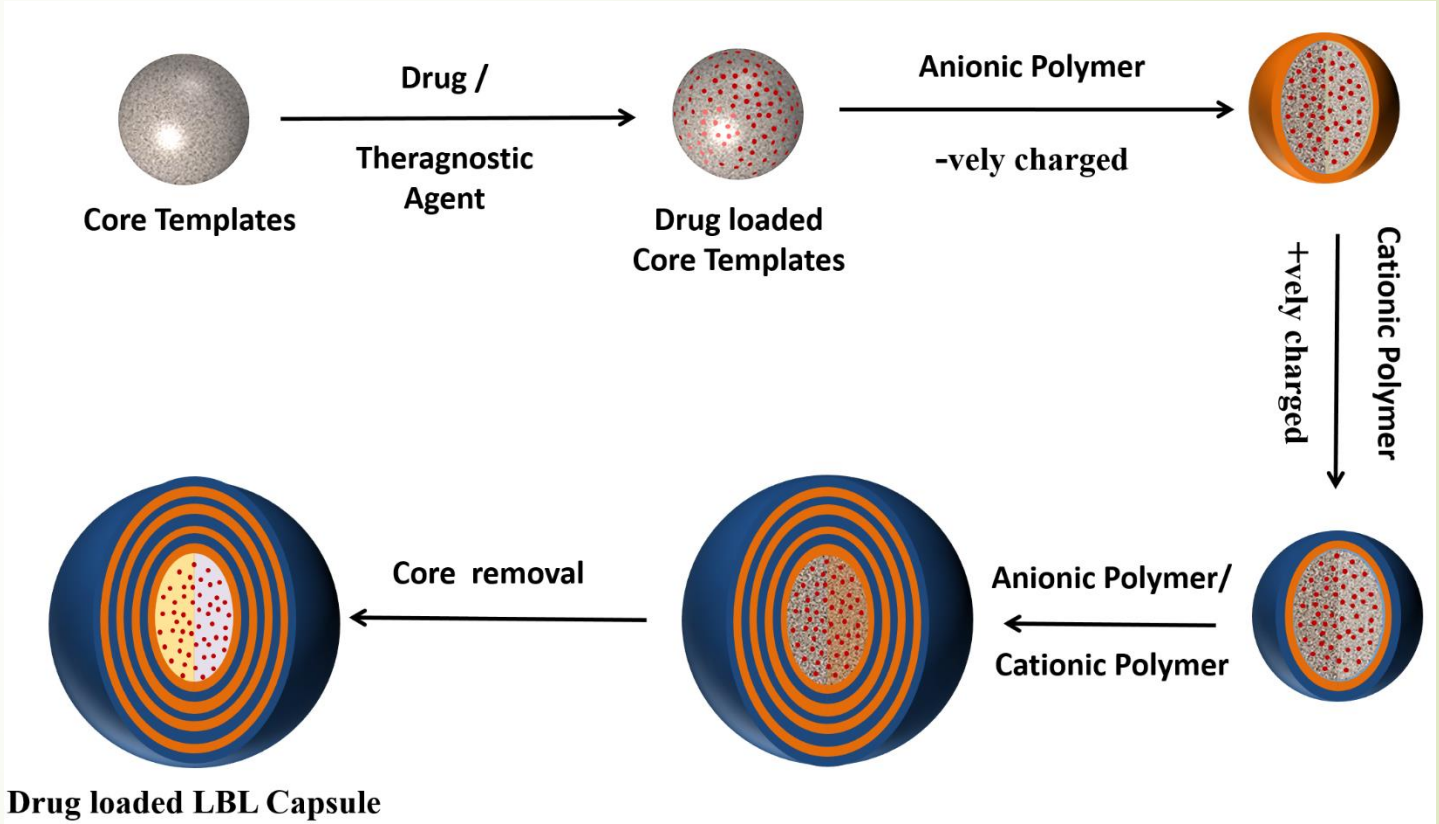
- In this process dual fluid stream is pumped through the nozzle
- One of the liquids contains core material and the other wall material.
- Droplets are formed by the vibrations applied at the exit of the concentric tubes.
- the droplets undergo solidification by chemical crosslinking, cooling or solvent evaporation




http://www.msrjournal.com/article_23652_95ae321b29dc78deae5c0bd3d69a0afa.pdf

# Layer-by-layer Technique

- This technique involves sequential adsorption of oppositely charged materials on a template to form polyelectrolyte shells.
- It is a simple and inexpensive method to control the shell thickness of the microcapsules and the release of encapsulated materials.



# Applications of Microencapsulation

- To formulate prolonged release dosage forms.
- To prepare enteric-coated dosage forms selectively absorbed in the intestine rather than the stomach.
- It can be used to mask the taste of bitter drugs.
- To reduce gastric irritation.
- useful in the immobilization of drugs, biopharmaceutics molecules, live mammalian and bacterial cell, as it can provide protection of the enclosed product, and controlled release of the encapsulated contents,
- ensure efficient and safe therapeutic effects of variety of drugs
- Microcapsules may also serve the role of protecting the encapsulated contents to prevent the degradation of the product due to external environmental factors such as oxygen, light, heat, and humidity which could destroy any labile compound.

# Applications of Microencapsulation

- Aid in the addition of oily medicines to tableted dosage forms. To overcome problems related to tacky granulations while producing tablets. This was accomplished through improved flow properties. eg. The non-flowable multicomponent solid mixture of niacin, riboflavin, and thiamine hydrochloride and iron phosphate may be encapsulated and made directly into tablets.
- To protect drugs from environmental hazards such as humidity, light, oxygen or heat. eg. vitamin A and K have been shown to be protected from moisture and oxygen through microencapsulation.
- The separations of incompatible substances, eg. pharmaceutical eutectics. The stability enhancement of incompatible aspirin- chlorpheniramine maleate mixture was accomplished by microencapsulating both of them before mixing.
- Microencapsulation can be used to decrease the volatility.
- The hygroscopic properties of many core materials may be reduced by microencapsulation
- Microencapsulation has also been used to decrease potential danger of handling of toxic or noxious substances. Such as fumigants, herbicides, insecticides and pesticides

# Applications of Microencapsulation

1. Lupin launched first Cephalexin (Ceff-ER) and Cefadroxil (Odoxil OD) antibiotic tablets for treatment of bacterial infections.
2. Aspirin controlled release system ZORprin CR tablets for relieving arthritis symptoms.
3. Quinidine gluconate CR tablets are used for treating and preventing abnormal heart rhythms.
4. Niaspan CR tablet is used for improving cholesterol levels and thus reducing the risk for a heart attack.

- Glucotrol (Glipizide SR) is an anti diabetic medicine used to control high blood pressure