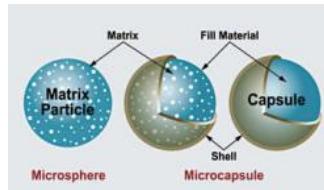




Microencapsulation

What is microencapsulation?

- It is a process in which tiny particles or droplets of liquid are surrounded by a coating to give small capsules
- In a relatively simplistic form, a microcapsule is a small sphere with a uniform coat wall around it



2

It differs from other coating methods because microencapsulation process is used to coat the particles having a particle size range from 1 to 5000 μ .

When the particle size is below 1 μ m the particles are known as nanoparticles, nanocapsules or nanospheres.

Particles greater than 5000 μ are known as macroparticles

3

Need for microencapsulation (Advantages)

Prevent oxidation of active ingredient

Retarding evaporation of active ingredient.

Conversion of liquids to powders and improving the handling properties.

To avoid the chemical incompatibility of ingredients within the same formulation.

Masking of chewable tablets, powders and suspension.

To get targeted release of the drug.

To avoid adverse effects like gastric irritation of the drug e.g. aspirin is the first drug which is used to avoid gastric irritation.

Modify the rate of drug release i.e. sustained, controlled etc

4

Disadvantages

No single process is adaptable to all core material

Incomplete or discontinuous coating

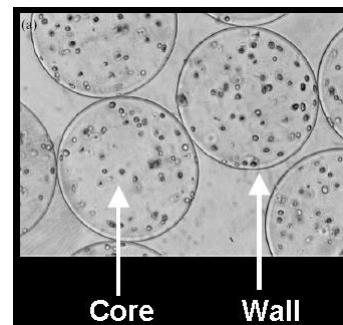
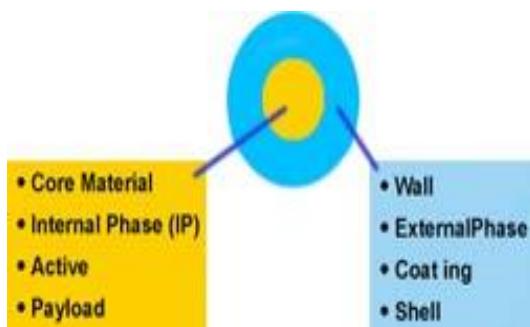
Inadequate stability or shelf life of sensitive APIs

Non-reproducible and unstable release characteristics of encapsulated product

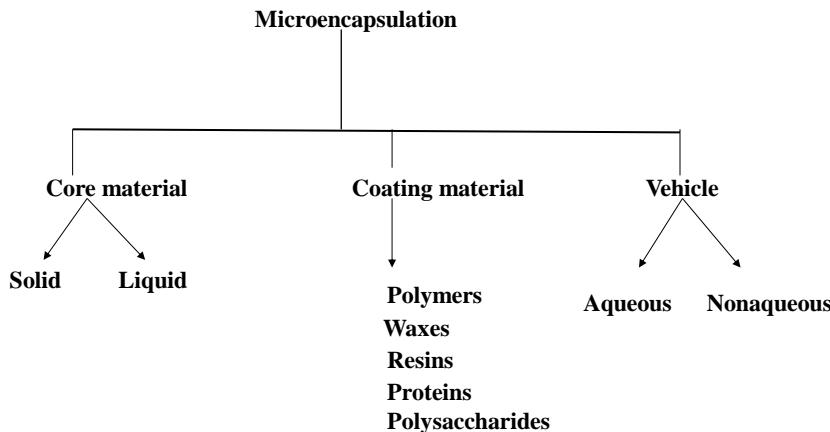
Not economic

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Microparticle



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Core material

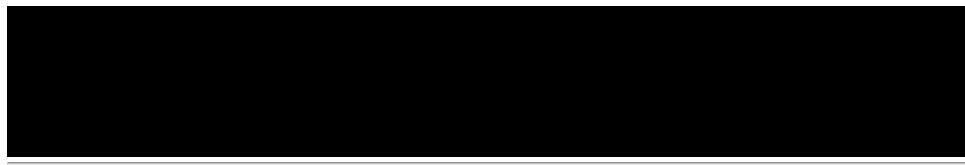
The core material, defined as the specific material to be coated, can be liquid or solid in nature.

The composition of the core material can be varied, as the liquid core can include dispersed and/or dissolved materials.

The solid core can be active constituents, stabilizers, diluents, excipients, and release-rate retardants or accelerators.

The ability to vary the core material composition provides definite flexibility and utilization of these characteristics often allows effectual design and development of the desired microcapsule properties

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Sr. no.	Core material	Property	Purpose	Final product
1	Paracetamol	Slightly water soluble solid	Taste masking	Tablet
2	Aspirin	Slightly water soluble solid	Taste masking, SR, reduced gastric irritation	Tablet or capsules
3	Menthol/ methyl salicylate/ camphor mixture	Volatile solution	Reduce volatility	Lotion
4	Vitamin A palmitate	Nonvolatile liquid	Stabilisation to oxidation	Dry powder

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Coat

The selection of appropriate coating material decides the physical and chemical properties of the resultant microcapsules/microspheres

What is the specific dosage form or product requirements-stabilization, reduced volatility, release characteristics, etc?

What coating material will satisfy the product objectives and requirements?

What microencapsulation method is best suited to accomplish the coated product objectives?

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Properties of coating material

- Should be capable of forming a film that is cohesive with the core material
- Chemically compatible and non reactive with the core material
- Strength
- Flexibility
- Impermeability
- Solubility
- Clarity
- Moisture sorption
- Optical properties
- Stability

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Selection of coating material

- Stabilization of core material.
- Inert toward active ingredients.
- Controlled release under specific conditions.
- Film-forming, pliable, tasteless, stable.
- Non-hygroscopic, no high viscosity, economical.
- Soluble in an aqueous media or solvent, or melting.
- The coating can be flexible, brittle, hard, thin etc.

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Types of coat material

Water soluble resins

- Gelatin, Gum Arabic, Starch, PVP, CMC, HEC, MC, Arabinogalactan, PVA, Polyacrylic acid.

Water insoluble resins

- Ethylcellulose, Polyethylene, Polymethacrylate, Polyamide (Nylon), Poly (Ethylene Vinyl acetate), Cellulose nitrate, Silicones, Poly lactideco-glycolide.

Waxes and lipids

- Paraffin, Carnauba, Spermaceti, Beeswax, Stearic acid, Stearyl alcohol, Glyceryl stearates

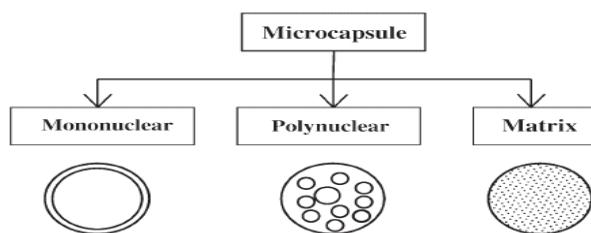
Enteric coating

- Shellac, Cellulose acetate phthalate, Zein

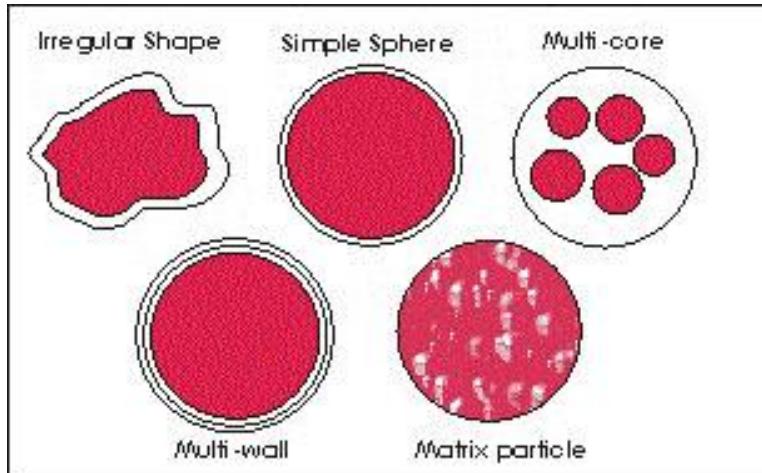
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Morphology of microcapsules

- Morphology depends on:
 - The core material
 - Process of deposition of the shell
- They may have regular or irregular shapes
- Classified as:



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- Mononuclear microcapsules contain the shell around the core
- Polynuclear capsules have many cores enclosed within the shell.
- In matrix encapsulation, the core material is distributed homogeneously into the shell material.
- Multi-wall particle, more than one layer of coating

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Microencapsulation technologies

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Choice of technology

The ability to incorporate reasonably high concentrations of the drug.

Stability of the preparation after synthesis with a clinically acceptable shelf life.

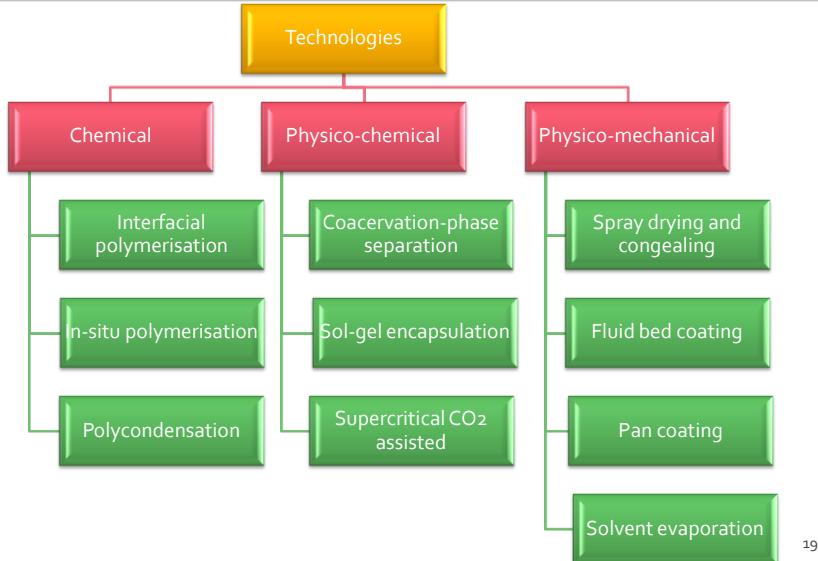
Controlled particle size and dispersability in aqueous vehicles for injection.

Release of active reagent with a good control over a wide time scale.

Biocompatibility with a controllable biodegradability and susceptibility to chemical modification

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Classification of technologies



Among these techniques fluidized bed or air suspension method, coacervation and phase separation, spray drying and spray congealing, pan coating, solvent evaporation methods are widely used.

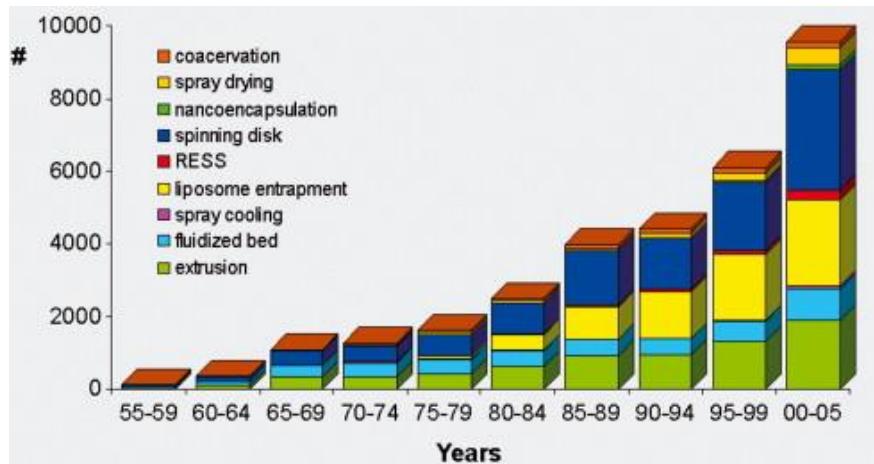
Depending on the physical nature of the core substance to be encapsulated the technique used will be varied and the equipment used varies from complex to simple processing equipment.

The specific processing equipment employed depends on the final product form desired and on the microcapsule properties.

All processing and formulation operations must be conducted with continual caution to avoid possible adverse effects (rupture, attrition or dissolution) upon the thin microcapsule coating.

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Trends in microencapsulation



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Microencapsulation processes and their applicability.

Microencapsulation Process	Nature of core material	Approximate Particle size (μm)
Air suspension	Solids	35-5000*
Coacervation-phase separation	Solids and liquids	2-5000*
Multi orifice centrifugation	Solids and liquids	1-5000*
Pan coating	Solids	600-5000*
Spray and congealing	Solids and liquids	600
Solvent evaporation	Solids and liquids	5-5000*

*The 5000 μm size is not a particle size limitation. The Methods are also applicable for macro coating

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Fluidised bed coaters

Mainly for encapsulation of solid core

Indirectly liquids can be encapsulated by adsorbing the liquid on to porous solids

They function by suspending or dispersing of solid, particulate core materials in a supporting air stream and the spray-coating of the air suspended particles

In the coating chamber, particles are suspended in moving air stream as each pass through coating zone, the core material receives an increment of coating material

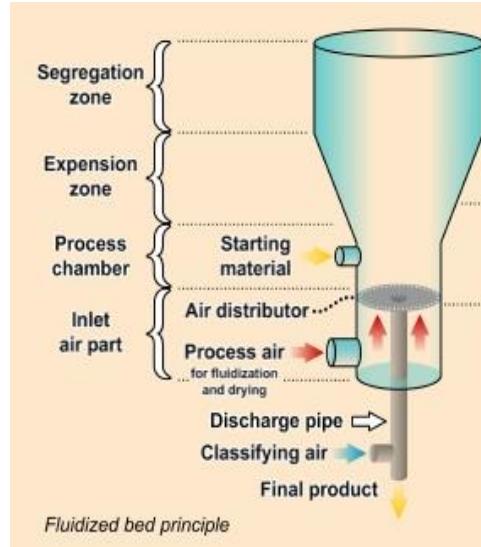
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The cyclic process is repeated several hundred times during processing, depending on the purpose of microencapsulation, the coating thickness desired, or whether the core material particles are thoroughly encapsulated.

The supporting air stream also serves to dry the product while it is being encapsulated.

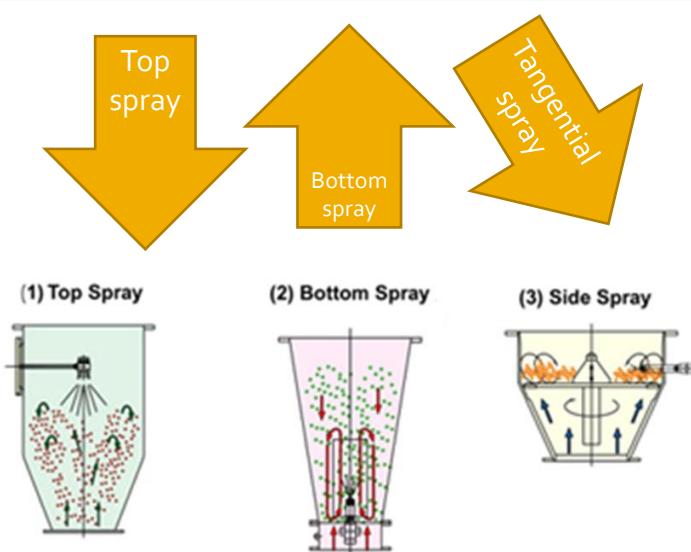
Drying rates are directly related to the temperature of the supporting air stream.

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Types of fluid bed coaters



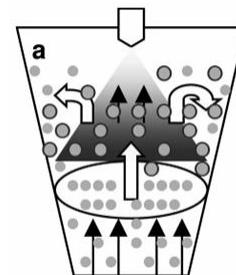
26

Top spray

Coating material is sprayed downwards on to the fluid bed such that as the solid or porous particles move to the coating region they become encapsulated.

Increased encapsulation efficiency and the prevention of cluster formation is achieved by opposing flows of the coating materials and the particles.

Produce higher yields of encapsulated particles than either bottom or tangential sprays.



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Tangential spray

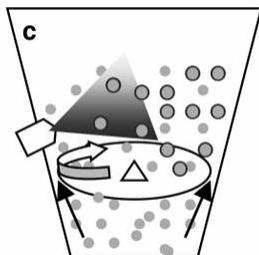
Consists of a rotating disc at the bottom of the coating chamber, with the same diameter as the chamber.

During the process the disc is raised to create a gap between the edge of the chamber and the disc.

The tangential nozzle is placed above the rotating disc through which the coating material is released.

The particles move through the gap into the spraying zone and are encapsulated.

As they travel a minimum distance there is a good yield of encapsulated particles



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Bottom spray (Wurster air suspension technique)

Developed by Prof. D.E. Wurster.

Uses a coating chamber that has a cylindrical nozzle and a perforated bottom plate.

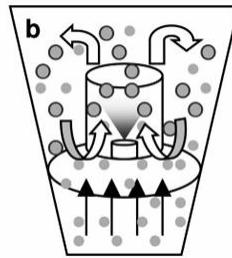
The cylindrical nozzle is used for spraying the coating material.

As the particles move upwards through the perforated bottom plate and pass the nozzle area, they are encapsulated by the coating material.

The coating material adheres to the particle surface by evaporation of the solvent or cooling of the encapsulated particle.

This process is continued until the desired thickness and weight is obtained.

Although it is a time consuming process, the multilayer coating procedure helps in reducing particle defects.



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Processing variables

1. Density, surface area, melting point, solubility, friability, volatility, crystallinity, and flowability of the core material.
2. Coating material concentration.
3. Coating material application rate.
4. Volume of air required to support and fluidize the core material.
5. Amount of coating material required.
6. Inlet and outlet operating temperatures.

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Spray drying and spray congealing

Both the processes involve dispersing of core material in a liquefied coating substance and spraying or introducing the core-coating mixture into some environmental condition, whereby relatively rapid solidification and formation of the coating is effected.

The principle difference between both the methods is the means by which the coating solidification is accomplished

Coating solidification in case of spray drying is effected by rapid evaporation of a solvent in which the coating material is dissolved.

In spray congealing method it is done by thermally congealing a molten coating material or by solidifying a dissolved coating and by introducing the coating-core material mixture into a non-solvent.

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Spray drying

Conducted by dispersing the core material in a coating solution, in which the coating substance is dissolved and in which the core material is insoluble and then by atomizing the mixture into an air stream.

The heated air supplies the latent heat of vaporization required to remove the solvent from the coating material, thus forming the microencapsulated product.

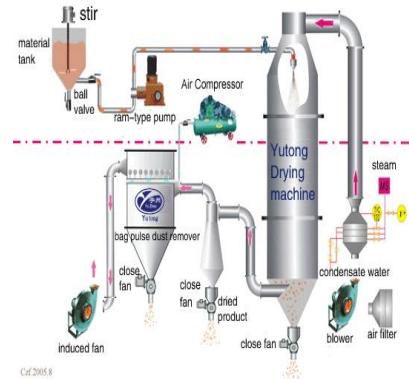
This process produces microcapsules of size range of 5 to 60 microns.

This process is commonly employed in microencapsulation of liquid flavors yielding dry, free flowing powders for use in food and pharmaceuticals

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Process variables for spray drying

1. Feed material properties such as viscosity, uniformity, and conc. of core and coating material
2. Feed rate
3. Method of atomization
4. Drying rate controlled by inlet and outlet temp.
5. Air stream solvent conc



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Spray congealing

Can be done with spray drying equipment when the protective coating is applied as melt i.e core material is dispersed in a coating material melt rather a coating solution.

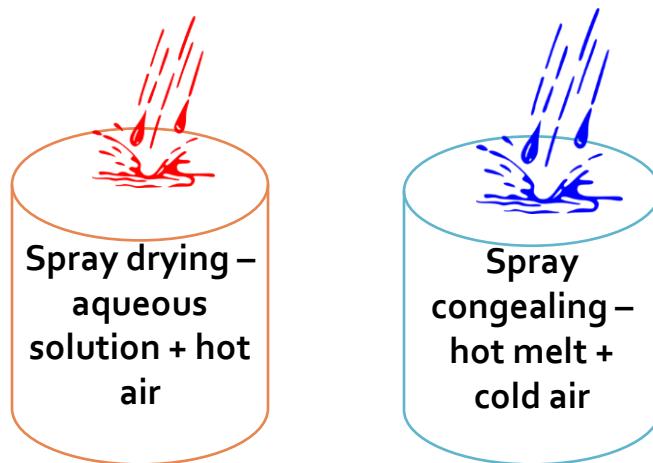
Coating solidification is accomplished by spraying the hot mixture into a cool air stream.

Waxes, fatty acids and alcohols, polymers and sugars, which are solids at room temp. but meltable at reasonable temp. are applicable to spray congealing techniques.

Process variables and conditions are similar to spray drying techniques.

Particle size of the spray congealed products is function of feed rate, the atomizing wheel velocity, dispersion of feed material viscosity and other variables.

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Pan coating

Done when the desired particle size is greater than 600μ

Medicaments are usually coated onto various spherical substrates such as nonpariel sugar seeds, and then coated with protective layers of polymers.

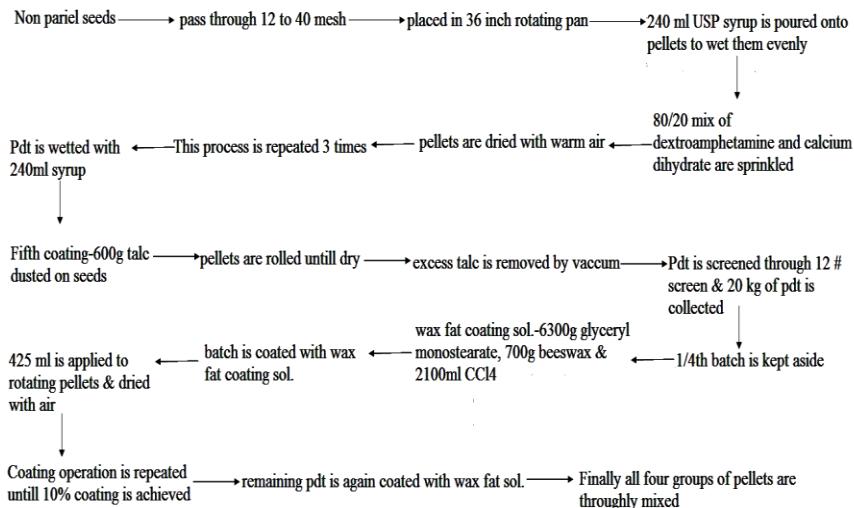
the coating is applied as a solution, or as atomized spray, to the desired solid core material in the coating pan

To remove the coating solvent warm air is passed over the coated material in the coating pan and in some cases final solvent is done in drying oven



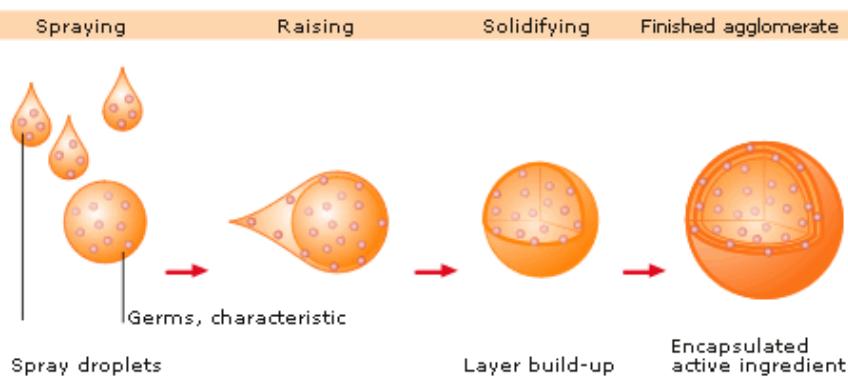
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Eg. Coating of dextroamphetamine



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Mechanism of pan coating



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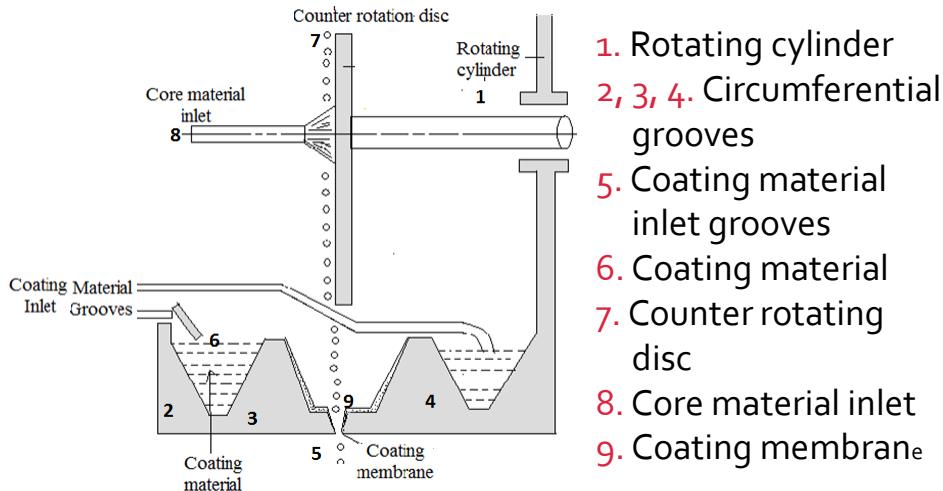
Multi-orifice centrifugal process

The Southwest Research Institute (SwRI) has developed a mechanical process for producing microcapsules that utilizes centrifugal forces to hurl a core material particle through an enveloping microencapsulation membrane thereby effecting mechanical microencapsulation.

This process is capable of microencapsulating liquids and solids if the solids are dispersed in liquids of varied size ranges with variety of coating materials.

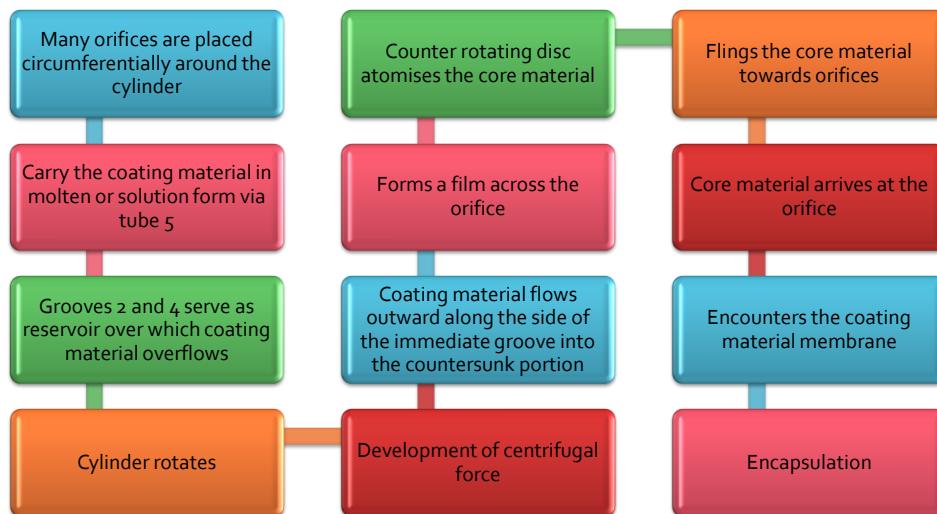
Production rate of 50 to 75 pounds per hour have been achieved with this process.

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Process



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Solidification and Rigidization of coating

Heated counter current air

- The microcapsules can be flung into a heated countercurrent air stream to harden or congeal coatings containing residual solvent.

Hardening bath

- The microcapsules can be forced into a rotating hardening or congealing bath.

Cool liquid

- The coating material if a melt can be hurled into a cool liquid (nonsolvent for the coating material) decreasing the temperature below the melting point of the coating

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Hardening bath

Hardening bath which contains the coating non-solvent that is capable of extracting the coating solution solvent

The rotating hardening bath not only provides a coating desolvation or congealing function, but serves as means of removing the microcapsules from their impact points thus reducing agglomeration tendencies.

It also provides a means of accumulating the coated product

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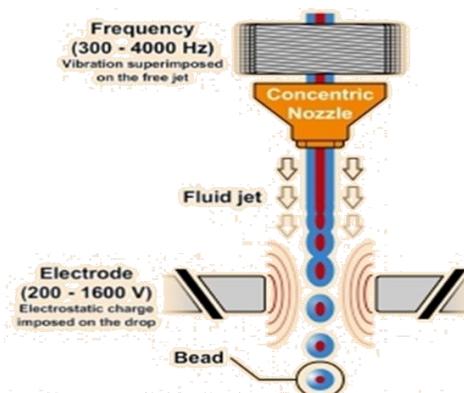
Process variables

1. Rotational speed of the cylinder.
2. Flow rate of the core and coating material.
3. Concentration and viscosity of coating material.
4. Viscosity and surface tension of core material

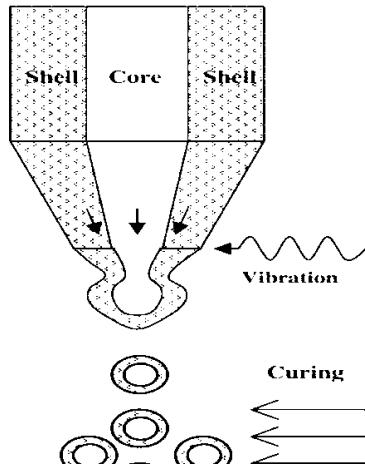
45

Vibrational Nozzle (Co-extrusion)

- The process works very well for generating droplets between **100–5,000 µm**
- Units are deployed in industries and research mostly with capacities of **1–10,000 kg per hour** at working temperatures of **20–150 °C**.
- Various nozzles heads are available.

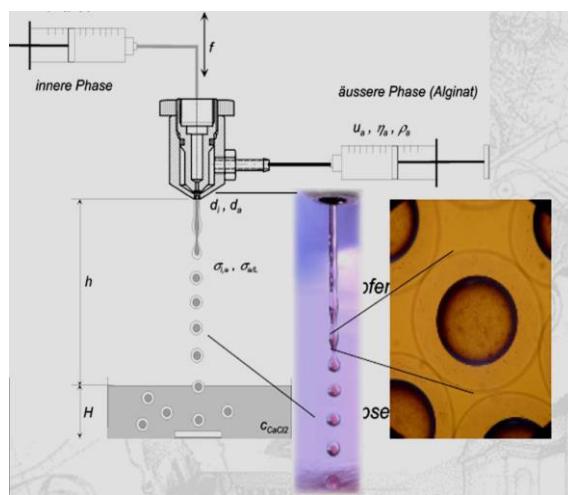
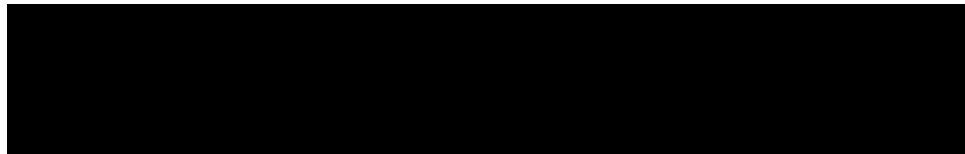


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- A dual fluid stream of liquid core and shell materials is pumped through concentric tubes and forms droplets under the influence of vibration.
- The shell is then hardened by chemical cross linking, cooling or solvent evaporation.

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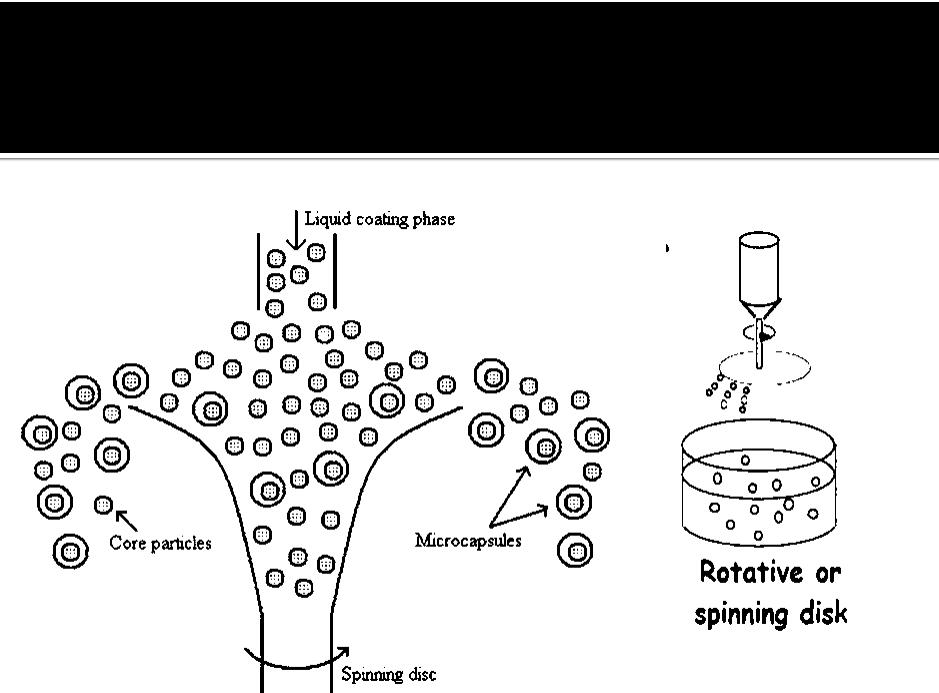


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Spinning disk

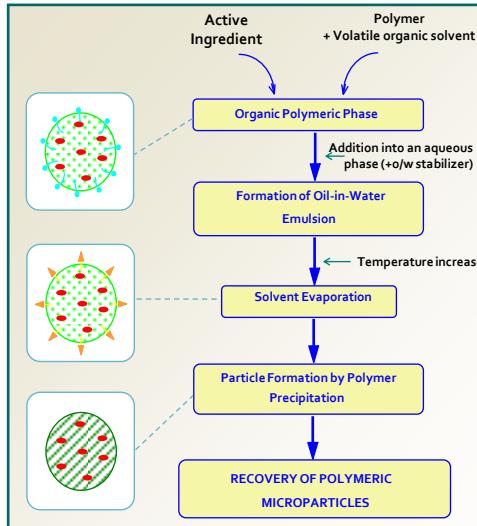
- Suspensions of core particles in liquid shell material are poured into a rotating disc.
- Due to the spinning action of the disc, the core particles become coated with the shell material.
- The coated particles are then cast from the edge of the disc by centrifugal force.
- After that the shell material is solidified by external means (usually cooling).
- This technology is rapid, cost-effective, relatively simple and has high production efficiencies.

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Solvent evaporation



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.

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Process parameters

- Method of forming dispersion
- Evaporation rate of solvent
- Temperature cycle
- Agitation rates
- Choice of LMVP
- Choice of solvent recovery technique

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Phase separation - coacervation

Temperature change
Salt addition
Non-solvent addition
Incompatible polymer addition
Polymer – polymer interaction

53

- The name derives from the Latin word coacervare, meaning "**to assemble together or cluster**".
- The term coacervation was introduced in 1929 by Bungenberg de Jong and Kruyt, for a process in which aqueous colloidal solutions separate, upon alteration of the thermodynamic condition of state, into two liquid phases, one rich in colloid, i.e., the coacervate, and the other containing little colloid

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Types of coacervation

Simple

- Salting out
- Non-solvent addition
- Temperature change

Complex

- Driven by the attractive forces of oppositely charged polymers

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3 stages

Formation of 3 immiscible chemical phases

Deposition of liquid polymer coating on core

Rigidization of coat

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STAGE 1

3 phases

Liquid manufacturing vehicle phase (LMVP)

Core material

Coating material

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Formation of coating solution in LMVP

Dispersion of core in coating solution

Coating material is separated out by a suitable method

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Methods of separation of coating material

Simple

Complex

Temperature change

Salt addition

Non-solvent addition

Incompatible polymer addition

Polymer-polymer interaction

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Stage 2

Controlled physical mixing of core and coating material in LMVP

Polymer is adsorbed at the interface between core and LMVP

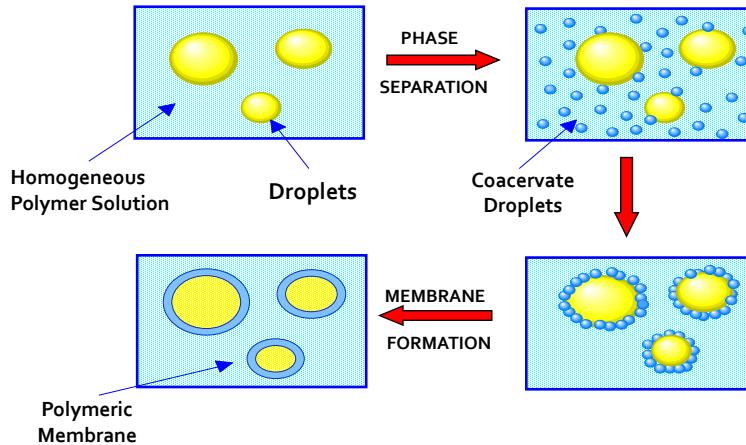
Liquid polymer coats the core

Continued deposition of the coating material

Reduction in the total free interfacial energy of the system

Decrease of the coating material surface area during coalescence of the liquid polymer droplets

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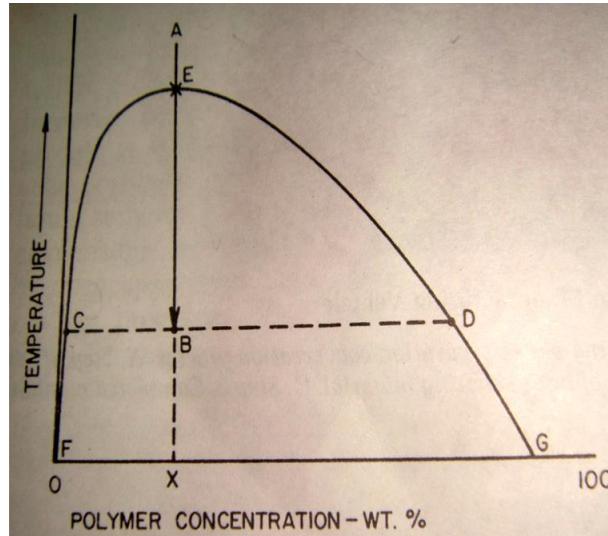
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Stage 3

- Done by:
 1. Thermal – cooling
 2. Crosslinking – formaldehyde, glutaraldehyde
 3. Desolvation technique – drying

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Temperature change



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The system exist as a single homogenous solution at all the points above the phase boundary or binodal curve FEG.

Embryonic microcapsules

At point B the segmented tie-line suggests that

As the temperature of the system is decreased from point A along the arrowed line AEB the phase boundary is crossed at point E

If a core material is present in the system under proper polymer concentration, temp. and agitation conditions the liquid polymer droplet coalesce around the dispersed core particles

Point C – pure solvent

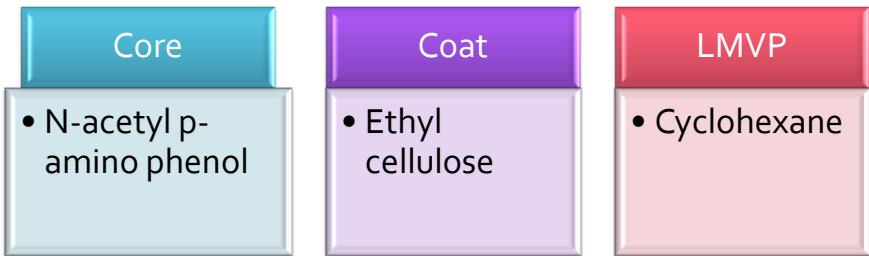
The two phase region is entered

Phase separation of the dissolved polymer occurs in the form of immiscible liquid droplets

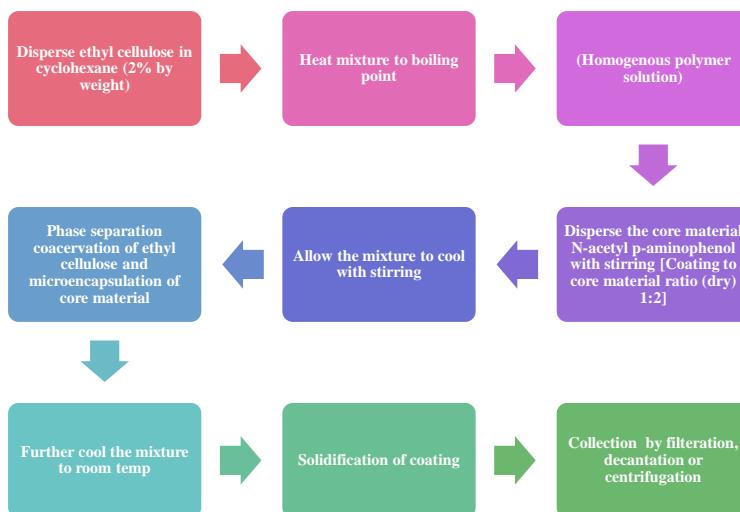
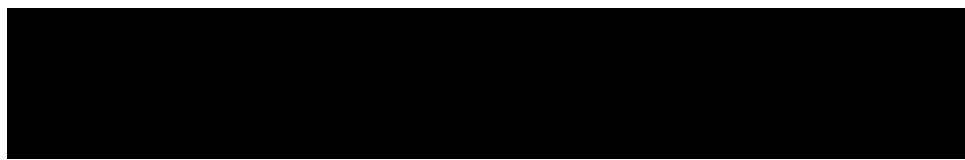
Point D - concentrated polymer solvent mixture

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Example

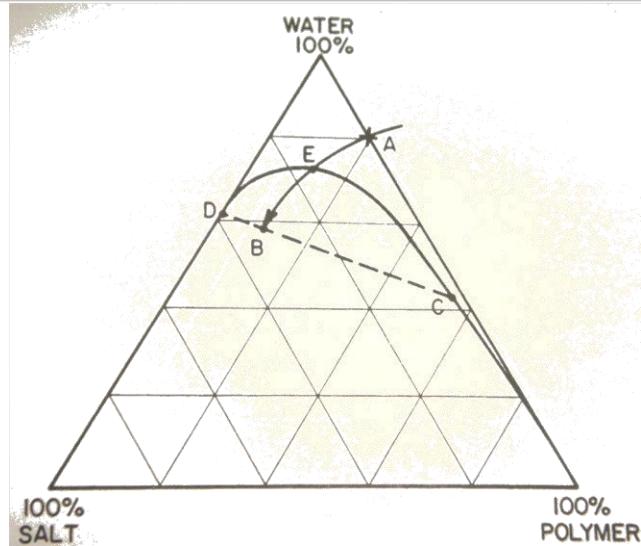


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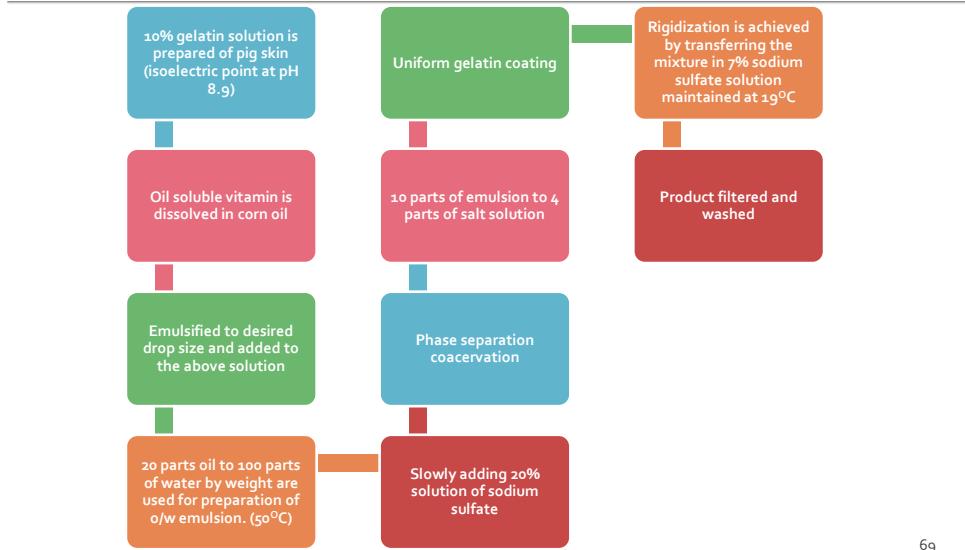
Salt addition



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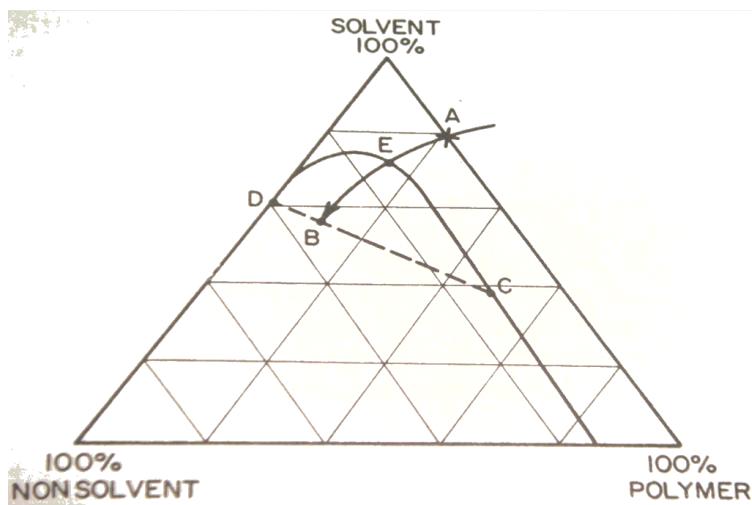


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Non-solvent addition

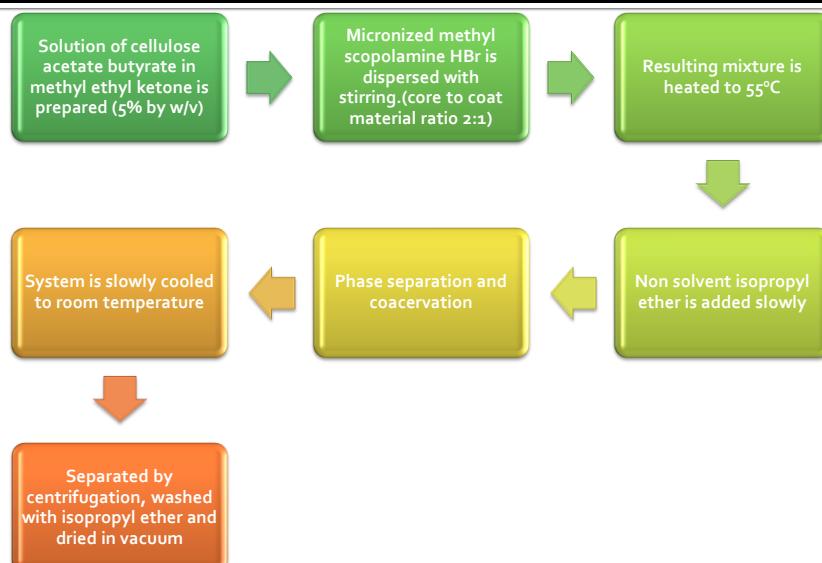
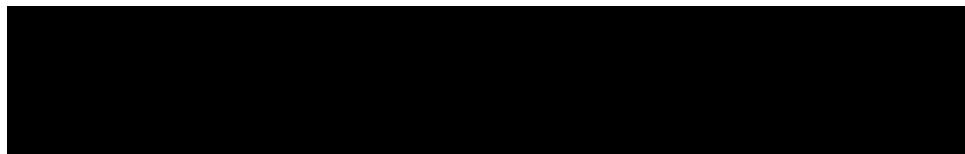


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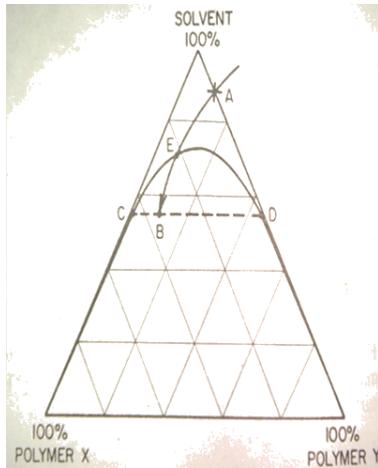
Core	Coat	LMVP	Non solvent
• Methylscopolamine HBr	• Cellulose acetate butyrate	• Ethyl methyl ketone	• Isopropyl ether

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Incompatible polymer addition

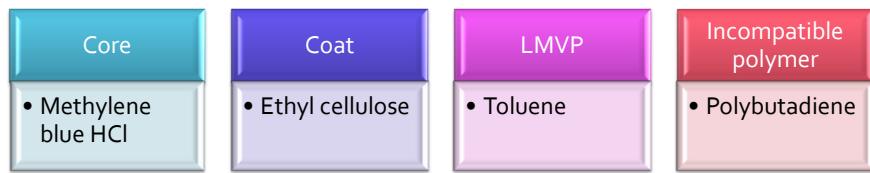


- Utilizes the incompatibility of dissimilar polymers existing in a common solvent.
- At point B – polymer Y dispersed in solution of polymer X
- Polymer Y is more strongly adsorbed on the surface of core

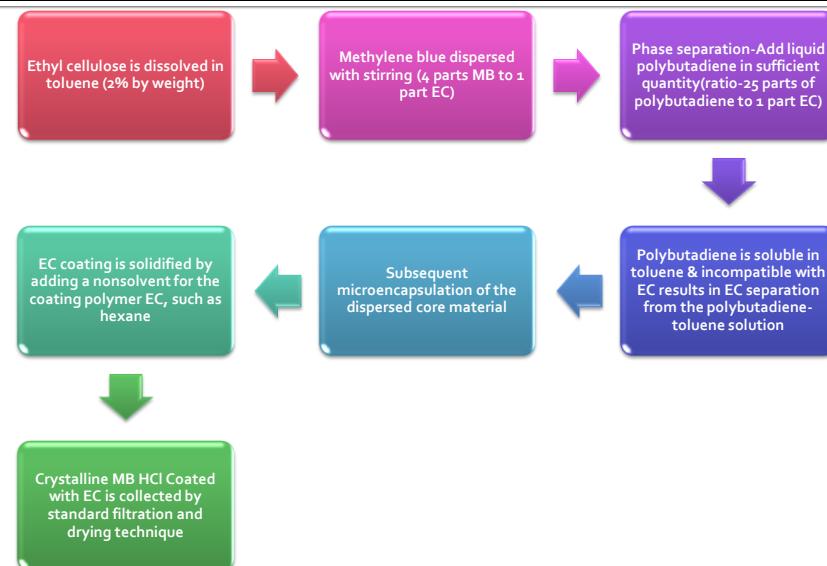
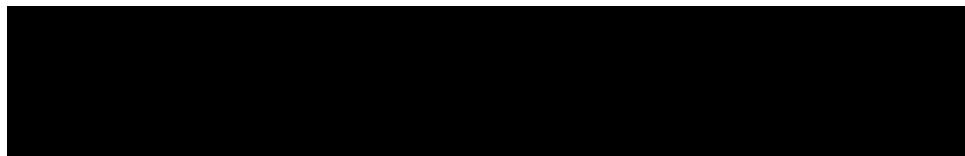
73

- Solidification of the coating material is accomplished by:
 - Further penetration into two phase region
 - Chemical cross linking, or
 - Washing the embryonic microcapsules with a liquid that is a non solvent for the coating polymer Y, and that is a solvent for polymer X.

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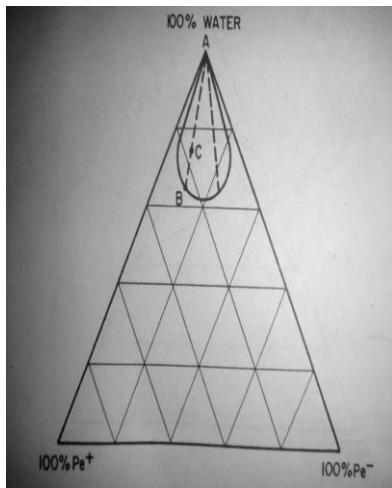


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Polymer – polymer interaction

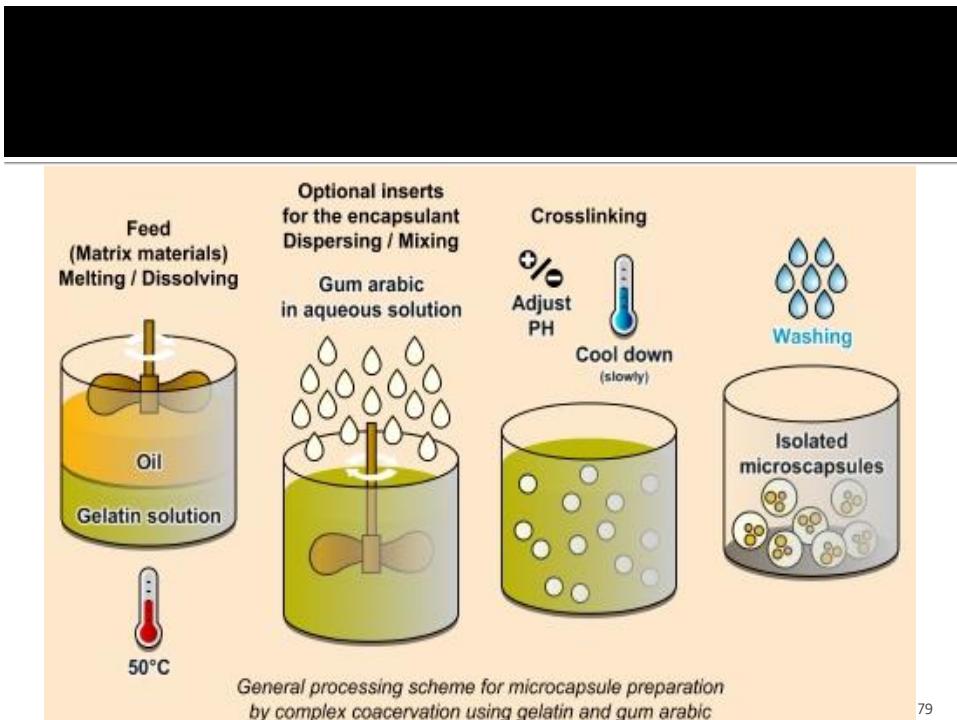


- The interaction of oppositely charged polyelectrolytes can result in formation of a complex having such reduced solubility that phase separation occurs

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- Gelatin and gum arabic are typical polyelectrolytes that can cause to interact.
- Gelatin at pH conditions below its isoelectric point ($\text{pH} < 8.5$), possesses a net positive charge, whereas the acidic gum arabic is negatively charged.
- Under proper temp., pH and conc; two polymers can interact through their opposite electrical charges forming a complex that exhibits phase separation

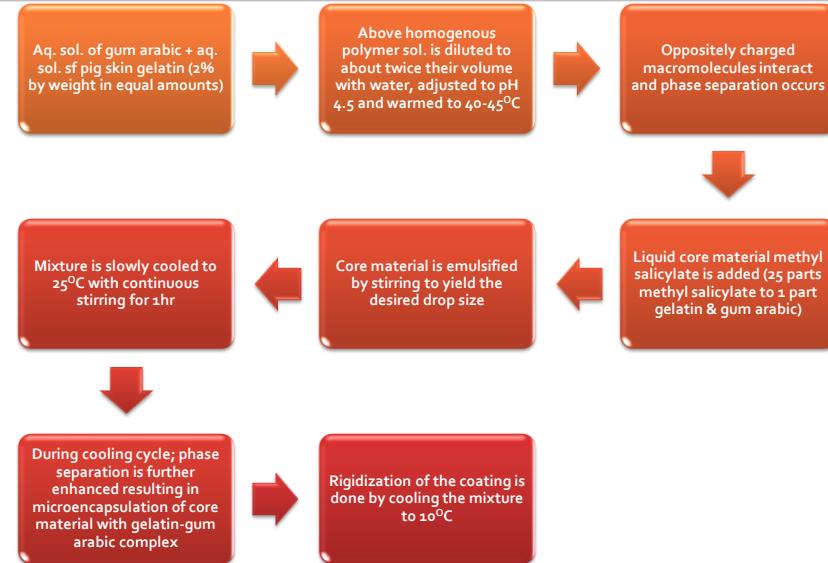
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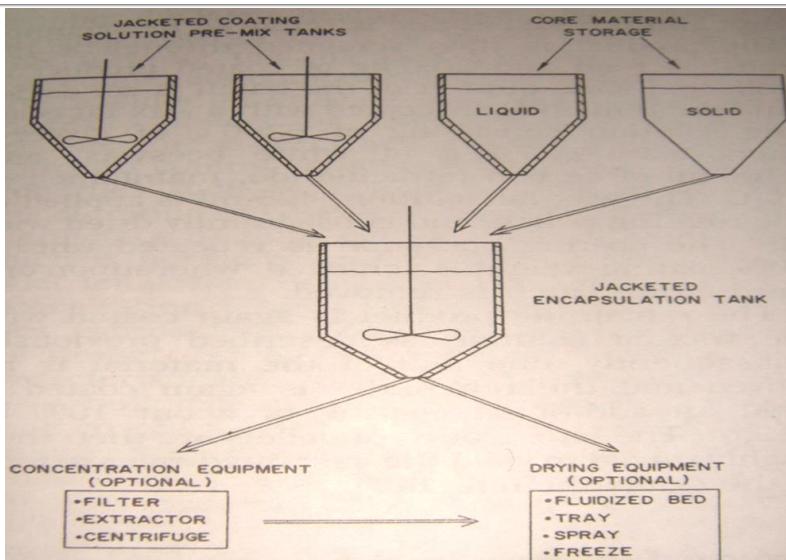


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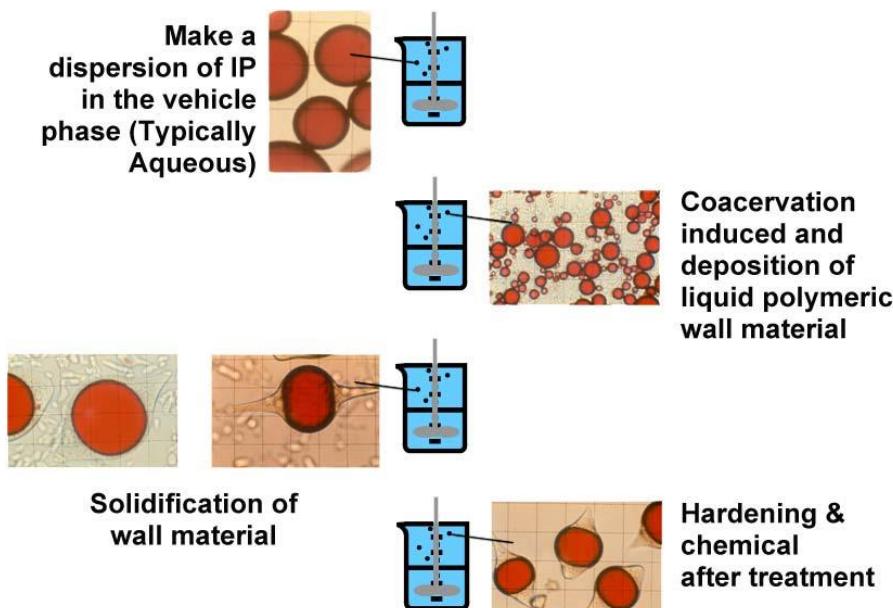
Large scale phase separation - coacervation



82

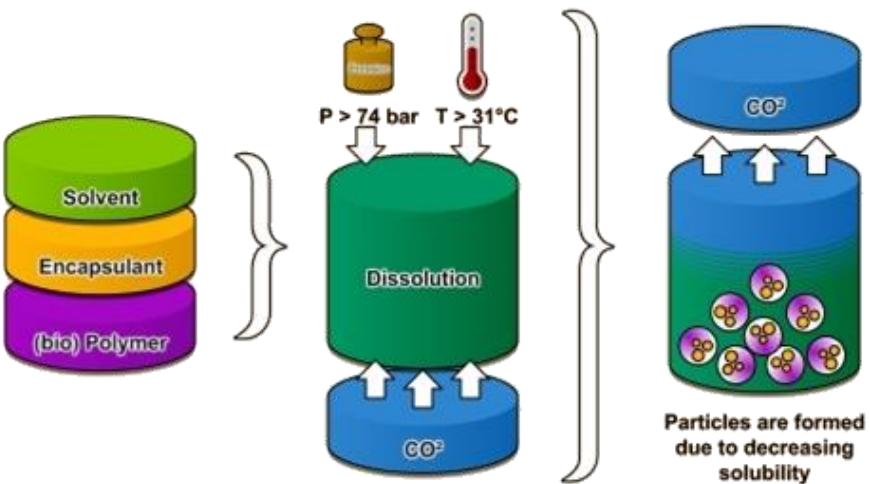
- Batch operations using common production equipments
- A wide variety of liquids, solids or suspensions can be microencapsulated in various sizes having a variety of coatings.
- Microcapsules are being manufactured in vessels upto 2000 gallons in capacity, at a multimillion pound per annum rate

83



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Supercritical fluid anti-solvent method (Gas anti-solvent method)



85

- Supercritical fluid containing the active ingredient and the shell material are maintained at high pressure and then released at atmospheric pressure through a small nozzle.
- The sudden drop in pressure causes desolvation of the shell material, which is then deposited around the active ingredient (core) and forms a coating layer.

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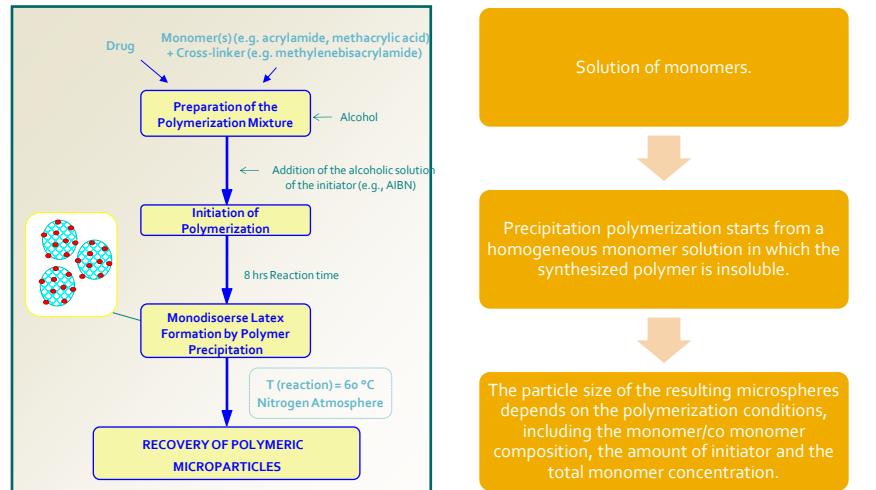
- The disadvantage of this process is that both the active ingredient and the shell material must be very soluble in supercritical fluids.
- In general, very few polymers e.g., polydimethylsiloxanes, polymethacrylates are soluble in supercritical fluids such as CO₂.

87

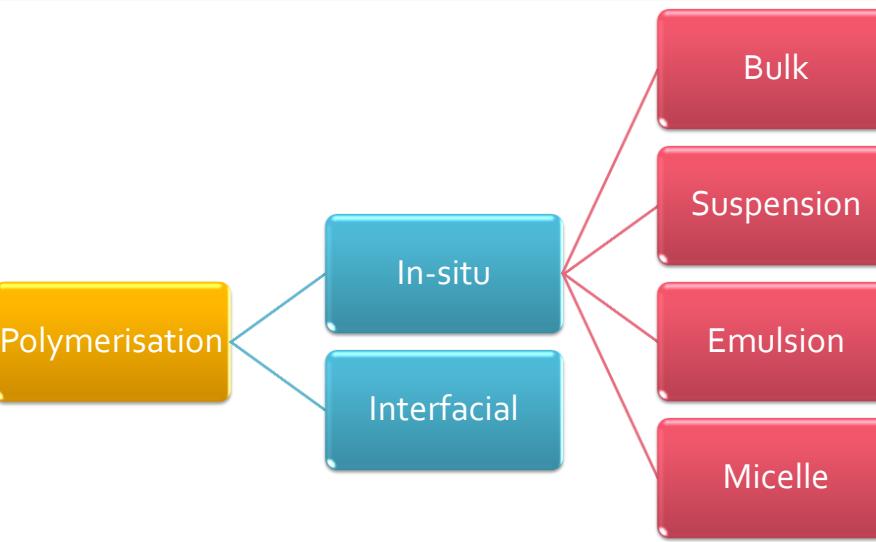
Polymerisation

- This method utilizes formation of in-situ microcapsule coating.
- The method involves the reaction of monomeric units located at the interface existing between core material and a continuous phase in which the core material is dispersed.

88



89



90

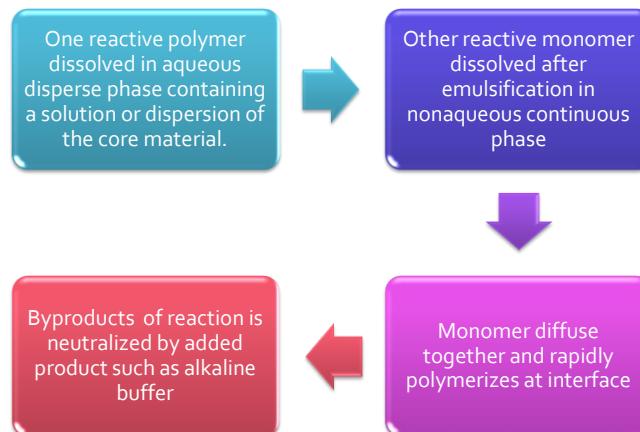
In situ polymerisation

- It is also known as **normal polymerization**.
- By this technique, one can produce capsules and particles in micrometer and nanometer range.
- Polymerization techniques of pharmaceutical interest is carried out in liquid phase and they have following types
 1. Bulk polymerization
 2. Suspension polymerization
 3. Emulsion polymerization
 4. Micelle polymerization

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Interfacial polymerisation

- It involves reaction of various monomers at the interface between two immiscible liquid phases



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Advantages:

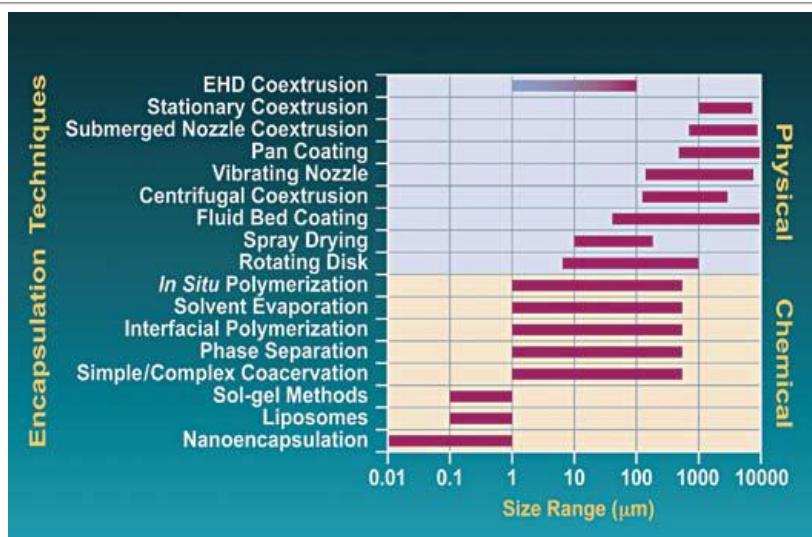
- Rapid, Products are relatively uniform in size

Disadvantages:

- Toxicity problem associated with unreacted monomer
- Excessive drug degradation caused by reaction with monomer
- Fragility of formed product
- Lack of biodegradability of product

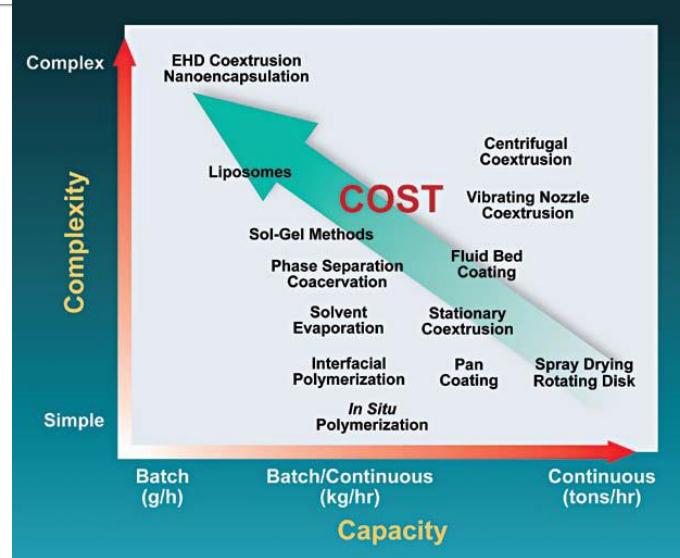
93

Size ranges



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Cost and capacity analysis



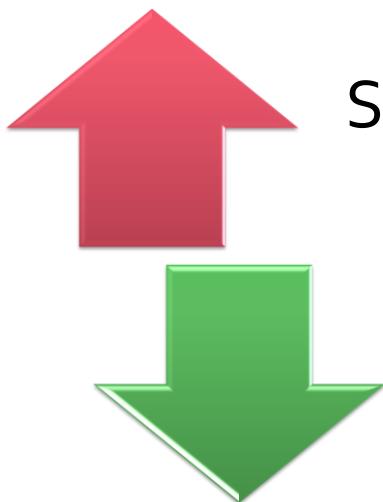
95

Factors affecting encapsulation

- Solubility of polymer in the organic solvent
- Solubility of organic solvent in water
- Concentration of the polymer
- Ratio of dispersed phase to continuous phase (DP/ CP ratio)
- Rate of solvent removal
- Interaction between drug and polymer
- Solubility of drug in continuous phase
- Molecular weight of the polymer

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Solubility of polymer in the organic solvent

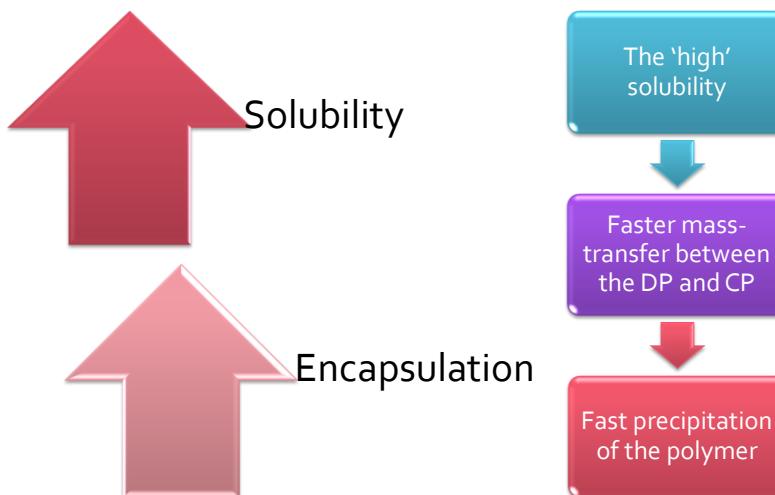


Solubility

Encapsulation

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Solubility of organic solvent in water



Solubility

Encapsulation

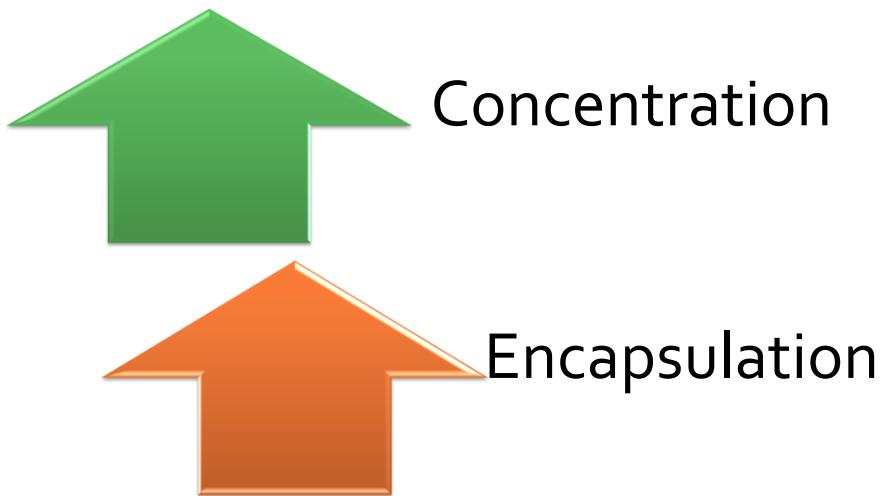
The 'high'
solubility

Faster mass-
transfer between
the DP and CP

Fast precipitation
of the polymer

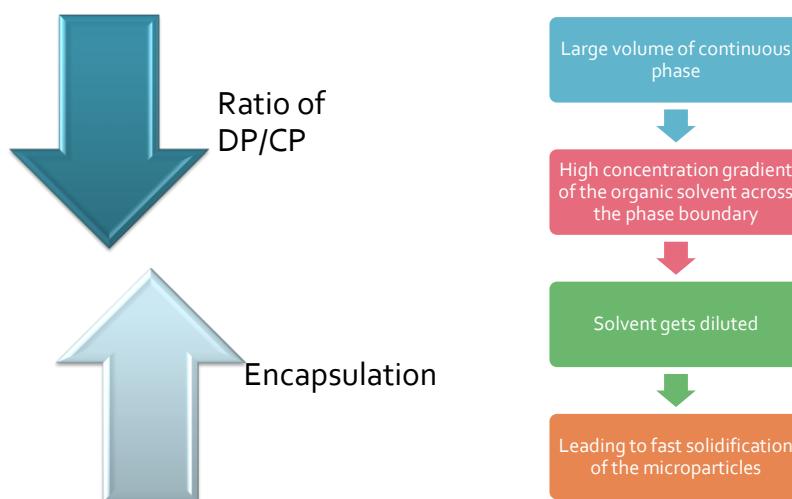
98

Concentration of the polymer



99

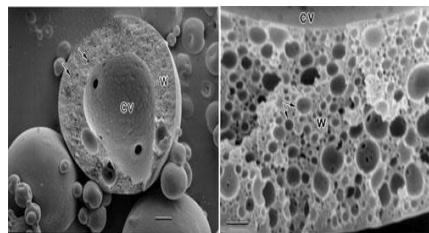
Ratio of dispersed phase to continuous phase (DP/ CP ratio)



100

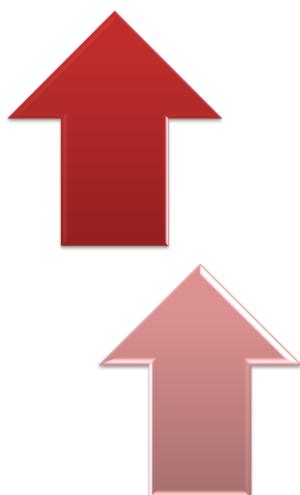
Rate of solvent removal

- The method and rate of solvent removal influence the solidification rate of the dispersed phase as well as morphology of the resulting microparticles
- A rapid rise in temperature results in a thin wall and a large hollow core



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Interaction between drug and polymer



Interaction

Encapsulation

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Solubility of drug in continuous phase

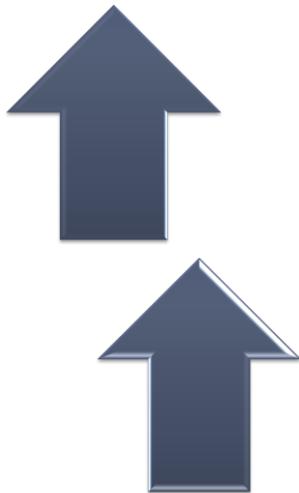


Solubility in CP

Encapsulation

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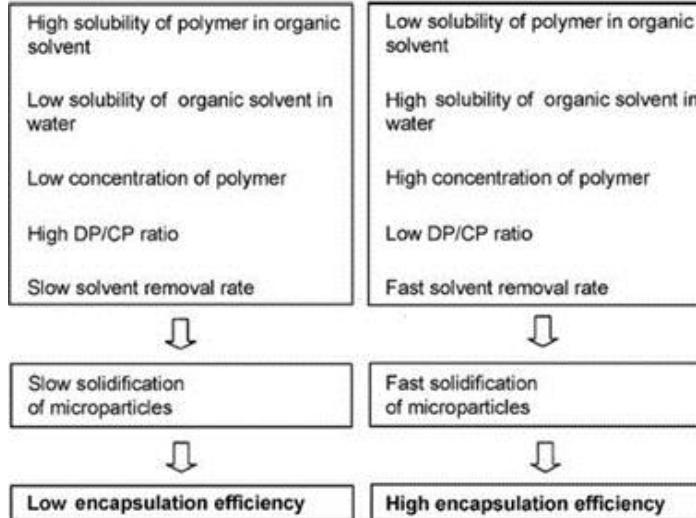
Molecular weight of the polymer



Molecular weight

Encapsulation

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In vitro evaluation



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Sieve analysis

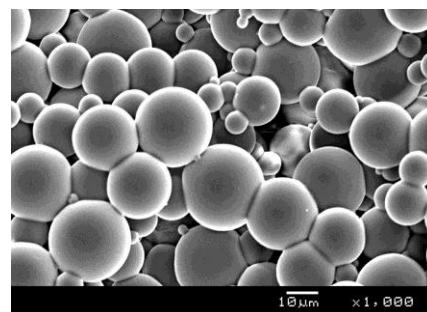
- Separation of the microspheres into various size fractions can be determined by using a mechanical sieve shaker (Sieving machine, Retsch, Germany).
- A series of five standard stainless steel sieves (20, 30, 45, 60 and 80 mesh) are arranged in the order of decreasing aperture size.
- Five grams of drug loaded microspheres are placed on the upper-most sieve.
- The sieves are shaken for a period of about 10 min, and then the particles on the screen are weighed



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Morphology

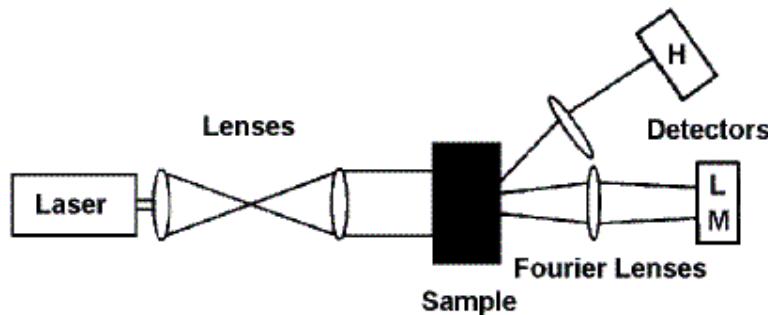
- Done by:
 1. Scanning electron microscopy
 2. Atomic force microscopy



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Particle size determination

- Laser diffractometer



9

Bulk density

- The microspheres fabricated are weighed and transferred to a 10-ml glass graduated cylinder.
- The cylinder is tapped until the microsphere bed volume is stabilised.
- The bulk density is estimated by the ratio of microsphere weight to the final volume of the tapped microsphere bed.



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Capture efficiency (encapsulation efficiency)

- The capture efficiency of the microspheres or the percent entrapment can be determined by allowing washed microspheres to lyse.
- The lysate is then subjected to the determination of active constituents as per monograph requirement.
- The percent encapsulation efficiency is calculated using equation:

$$\% \text{ entrapment} = \frac{\text{actual content}}{\text{theoretical content}} \times 100$$

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Drug release

- Beaker method
 - The dosage form in this method is introduced in the beaker containing the medium and stirred uniformly using over head stirrer.
 - Volume of the medium used in the literature for the studies varies from 50- 500 ml
 - Stirrer speed from 60-300 rpm

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- Dissolution apparatus

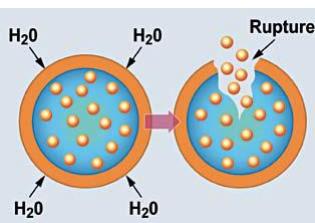


Type of release:

- Triggered release – Release occurs due to a change in environment, such as pH, temperature, moisture, pressure, electromagnetic. This is used to achieve immediate, delayed or pulsatile release profiles.
- Sustained release
- Burst release
- Combination release

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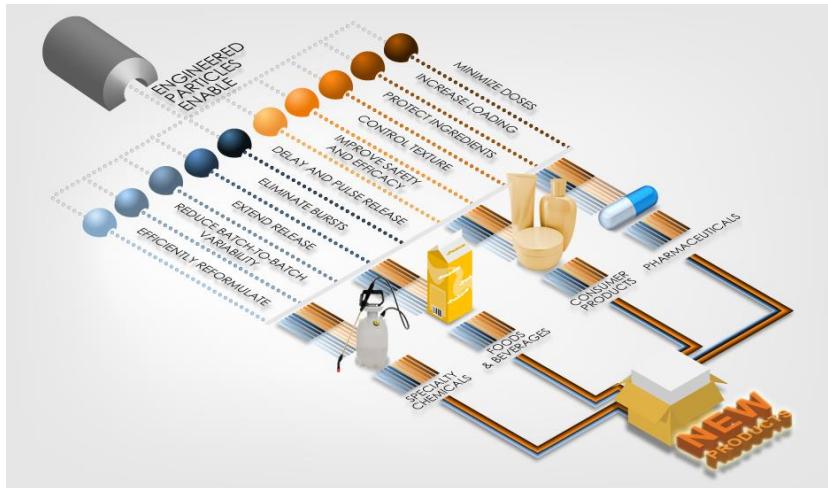
Release mechanisms



- Diffusion
- Dissolution
- Molecular trigger (such as pH)
- Biodegradation
- Thermal
- Mechanical
- Osmotic

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Applications



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To mask the bitter taste of drugs like Paracetamol, Nitrofurantoin etc.

Many drugs have been microencapsulated to reduce gastric and other G.I. tract irritations. Sustained release Aspirin preparations have been reported to cause significantly less G.I. bleeding than conventional preparations.

A liquid can be converted to a pseudo-solid for easy handling and storage. eg. Eprazinone.

Hygroscopic properties of core materials may be reduced by microencapsulation eg. Sodium chloride.

Carbon tetrachloride and a number of other substances have been microencapsulated to reduce their odor and volatility.

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Microencapsulation has been employed to provide protection to the core materials against atmospheric effects, e.g. vitamin A palmitate.

Separation of incompatible substance has been achieved by encapsulation.

Cell immobilization: In plant cell cultures, Human tissue is turned into bio-artificial organs, in continuous fermentation processes.

Beverage production.

Protection of molecules from other compounds.

Drug delivery: Controlled release delivery systems.

Quality and safety in food, agricultural & environmental sectors.

Soil inoculation.

In textiles: means of imparting finishes.

