

Microencapsulation

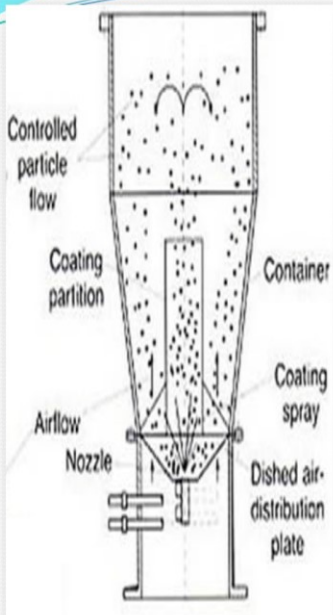
Methodology

- 1) Air suspension
- 2) Coacervation /Phase separation
- 3) Multiorifice centrifugation
- 4) Pan coating
- 5) Spray drying and congealing
- 6) Solvent evaporation
- 7) Interfacial polymerization

Microencapsulation Processes and Their Applicabilities

<i>Microencapsulation Process</i>	<i>Applicable Core Material</i>	<i>Approximate Particle Size (μm)</i>
Air suspension	Solids	35–5000*
Coacervation-phase separation	Solids & liquids	2–5000*
Multiorifice centrifugal	Solids & liquids	1–5000*
Pan coating	Solids	600–5000*
Solvent evaporation	Solids & liquids	5–5000*
Spray drying and congealing	Solids & liquids	600

*The 5000- μm size is not a particle limitation. The methods are also applicable to macrocoating, i.e., particles greater than 5000- μm in size.



Air suspension

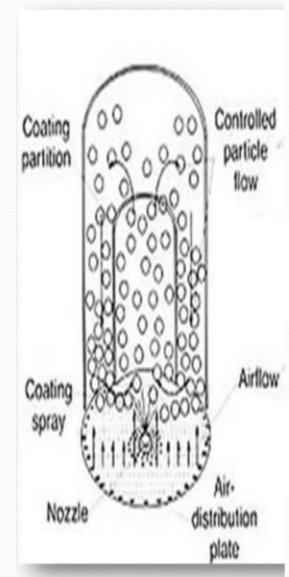
It is known as *wurster process*

- Consist of the **dispersing of solid (particulate core material)** in a supporting circulating air stream and spray coating including (polymer aq. or solvent solution, emulsion, dispersion or hot melt) of the air suspended particles.

- Within the coating chamber, particles are suspended on an **upward moving air stream**



 - Coating** material usually a polymer solution is spray-applied to the **moving particles several hundred of times**.
 - The supporting air stream also **serve to dry the product** while it is being encapsulated.
- Applicable core material (solids D.F.) and the approximate particle size 35-5000 μm .
- Processing variables:**
 - A- Density, M.P., S.A., solubility, friability, crystallinity, flowability of **core material**
 - B- **Coating material** conc.
 - C- Volume of air to fluidize core material
 - D- Amount of core material
 - E- Inlet and outlet operating temp.



Coacervation/Phase separation

- Coacervation (P.S. 2-5000 μm) of solids and liquids core materials occurs in three steps under **continuous agitation**:
 - 1) Formation of three immiscible chemical phases
 - 2) Deposition of coating material
 - 3) Rigidization of coating material

Step 1)

1) Formation of three immiscible chemical phases

Three immiscible phases are:

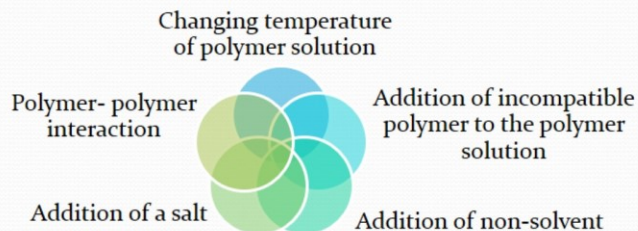
- 1) liquid manufacturing vehicle phase
- 2) core material phase
- 3) coating material phase

To form the three phases:

The core material is dispersed in a solution of coating polymer

The solvent for the polymer being the liquid manufacturing vehicle phase.

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

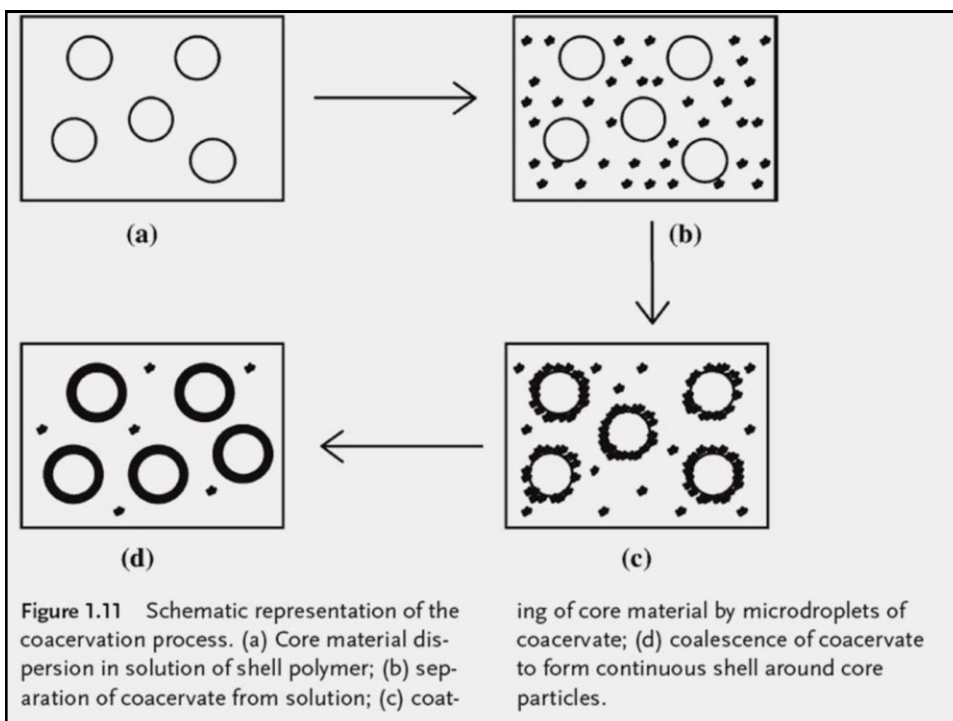


Step 2)**Deposition the coating material (adsorption phenomenon- prerequisite of effective coating)**

Depositing liquid polymer coating upon core material; if the polymer is adsorbed at the interface formed between core material and liquid vehicle phase. The continued deposition of coating material is promoted by reduction the total free interfacial energy of the system brought about by the decrease of the coating material surface area during coalescence of the liquid polymer droplets.

Step 3)**Rigidizing the coating material**

By crosslinking (with formaldehyde), desolvation techniques or thermal treatment to form a self-sustained microcapsules.



The coating material phase is formed by utilizing one of the methods of phase separation coacervation:

a) Temperature changes

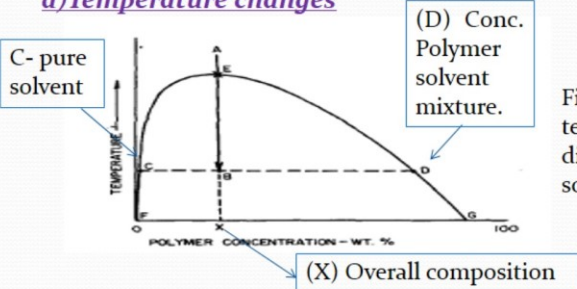
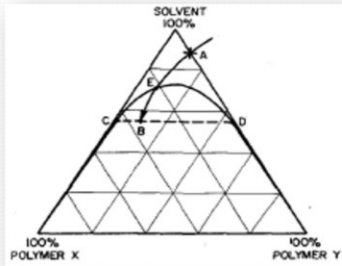


Figure: illustrate a general temp.-composition phase diagram of polymer and solvent

- It is a binary system–polymer (ethylcellulose) and solvent phase (cyclohexane) diagram
- Above FEG polymer solution exists as homogeneous phase. When temperature decreases (A) it crosses phase boundary (E) and polymer get separated as immiscible liquid droplet from vehicle phase. Under proper polymer conc., temp. and agitation, the liquid polymer droplet coalesces (rigidization) around core particle (Acetaminophen) and microencapsulation occurs

E.g. Microencapsulation of acetaminophen using ethyl cellulose in cyclohexane solution.

b) By adding incompatible polymer

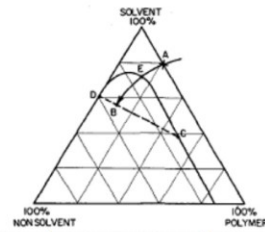


- Liquid phase separation of a polymeric coating material and microencapsulation can be accomplished by utilizing the incompatibility of dissimilar polymers existing in a common solvent.
- It involve a ternary system consisting of solvent and two polymer x and y .
- Immiscible core material (point A) is dispersed in a solution of polymer Y.
- Polymer X is added to the system (arrowed line), the phase boundary will be crossed at point E.

- As the two phase region is penetrated with further addition of polymer X (liquid polymer) then crosses the phase boundary and phase separation occur (immiscible droplets of polymer Y) then polymer Y coalesce around core material resulting in microencapsulation.
- The polymer that is more strongly adsorbed at the core material-solvent interface, in this case polymer Y (conc. Sol.), becomes the coating material (point B).
- To accomplish solidification by further penetration into 2 phase sys. or crosslinking or washing microcapsules with a liquid that is nonsolvent for polymer Y and solvent for polymer X.

E.g. Microencapsulation of **crystalline methylene blue HCl** (insoluble in toluene) using **ethylcellulose** dissolved in toluene solution (4:1) then add the incompatible liquid polymer- **polybutadiene** [quite soluble in toluene] (25:1) ethylcellulose slowly to achieve phase separation of ethylcellulose from polybutadiene and subsequent microencapsulation of core results. the ethylcellulose is solidified by adding nonsolvent (hexane) and decanted then collect coated core by filtration or drying technique.

c) By adding non-solvent to polymer



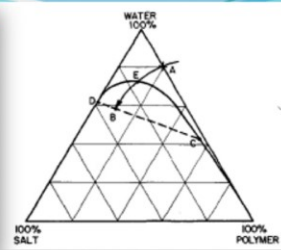
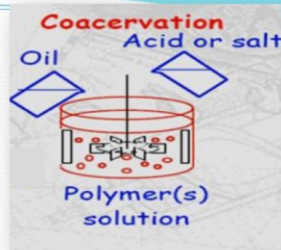
- A liquid that is nonsolvent for a given polymer can be added to a solution of the polymer to induce phase separation.

E.g: **Microencapsulation of methylscopolamine HBr using cellulose acetate butyrate (2:1) by heating to 55°C**
Solvent: methyl ethyl ketone

Nonsolvent: isopropyl ether (added slowly then cooling system to RT (25°C) for phase separation)

Then separation of microcapsules by centrifugation, washed with isopropyl ether and dried.

d) By adding salt

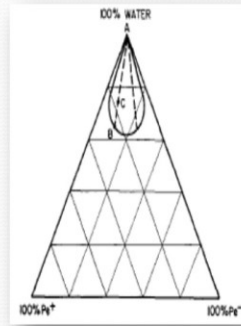


soluble inorganic salt is added to aqueous solution of certain water soluble polymers to cause phase separation.

E.g.: **oil soluble vitamin** (dissolve in corn oil) and emulsified with gelatin solution and water at (50°C) then microencapsulation induced by adding **Inorganic salt – sodium sulphate solution** and regidized at 19°C with continuous agitation. The microencapsulate product is collected by filtration and washed with water, chilled below gelatin temp. (to remove salt) and voided water by spray drying.

e) Polymer-Polymer interaction

- The interaction of oppositely charged polyelectrolyte can result in the formation of a complex having such reduced solubility that phase separation occurs .
- E.g.: Gelatin and gum arabia are typical polyelectrolytes that can be caused to interact.
- Gelatin at pH conditions below its isoelectric point 8.9, possesses a **net positive** charge , whereas the acidic gum arabia is **negatively** charged.
- Under the proper temperature (40-45°C), pH (4.5) and concentrations (2%), the two polymers can interact forming a complex that exhibit phase separation /coacervation and microencapsulation on methyl salicylate is achieved by cooling to 25°C and regidized by cooling the mixture to 10°C.



Coacervation phase separation could be aq. or non-aq.

Depending on the properties of the core materials. If the drug is water insoluble then the coating polymer used is water soluble like gelatin and acacia , this is called aqueous type coacervation.

If the drug is water soluble(as salbutamol sulphate) then water insoluble coating polymer is used (as ethyl acetate)and organic solvent (as cyclohexane) is used to dissolve the polymer .

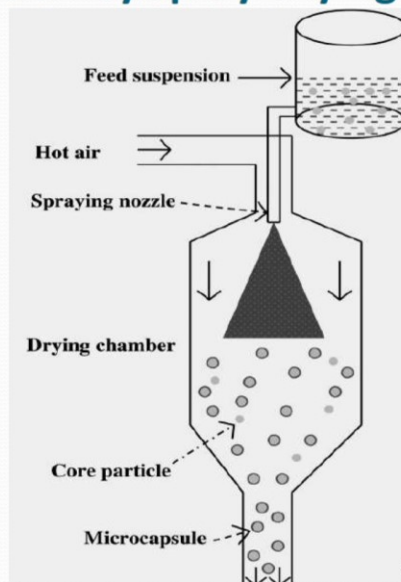
Spray-Drying & spray-congealing :

- Spray drying and spray congealing processes are similar in that both involve **dispersing of core material in a liquified coating substance** and spraying the core – coating mixture into some environmental condition, whereby rapid solidification of the coating is effected.
- Microencapsulation by **spray drying** is conducted by **dispersing the core material in a coating solution (the coating substance is dissolved and core material is insoluble)** .
- Atomizing the mixture into heated air stream to remove solvent from the coating material, thus forming microencapsulated product.

micro-encapsulation by spray-drying.

Spray drying
 spray = aqueous solution
 hot air

P.S. 600 µm



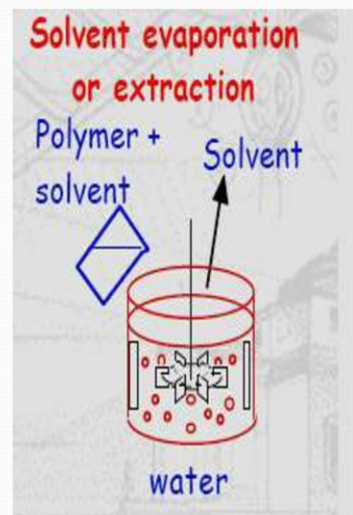
Spray-congealing:

- This technique can be accomplished with spray drying equipment when the protective coating is applied as a **melt**.
- 1- The core material is dispersed in a coating material melt.
- 2- Coating solidification (and microencapsulation) is accomplished by spraying the hot mixture into a cold air stream.
- e.g. microencapsulation of vitamins with digestible **waxes** for taste masking.

Solvent Evaporation

Formation of liquid and solid core

- The coating is dissolved in a volatile solvent (which is immiscible with the liquid manufacturing vehicle phase).
- A core is dissolved or dispersed in the coating polymer solution.
- With agitation, the core coating material mixture is dispersed in the liquid manufacturing vehicle phase
- The mixture is heated to evaporate the solvent for the polymer.
- Then the liquid vehicle temperature is reduced to ambient temp. so microcapsules are in suspension form coated on to substrate or isolated as powder.



Interfacial Polymerization

This methods involve the **reaction of monomeric unit located at the interface** existing between a core material substance 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 occur at a liquid-liquid, liquid-gas, solid-gas interface.

E.g.: Polymerization to form polyamide (nylon) membranes by the reaction occur at the liquid-liquid interface between aq. solution of aliphatic diamine (hexanediamine) and water immiscible organic solution of a dicarboxylic acid halide (sebacoyl Cl).

The polymerization starts to occur as **hexanediamine** (have P.C. toward water immiscible organic phase) diffuses to the **organic sebacoyl Cl** (water insoluble) phase and **thus polycondensation reaction occurs forming polyamide**. Because **chemical reaction rate exceeds the diffusion rate of the diamine into non-aq. phase**, the polyamide deposited at the interface exist **between 2 solutions**.

Example: Microencapsulation of protein solutions by incorporating PTN in the aq. diamine phase. Such as microencapsulation of enz. (urease) -that convert blood urea to ammonia-.

Mechanisms of drug release:

- It involves many steps according to this equation:
- $R_t = R_1 + R_2 + R_3$
- R_t = total rate of drug release
- R_1 = rate at which the solvent penetrates the wall material
- R_2 = rate at which the drug dissolved
- R_3 = rate at which the dissolved drug can penetrate the wall and release from the surface
- Therefore permeability of the coat and solubility of the drug in the dissolution medium are important to control the release. and R_3 is the controlling step (slowest).

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Factors affecting drug release:

- pH: it has great effect especially with gelatin-acacia coacervation method, if the pH is above 4 it will reduce the ME since gelatin be -ve and repulsive force produced with acacia (-ve)
- Stirring speed: it affects the size of ME. As it increased, smaller p. size of ME produced which will improve the micrometric properties of the ME including followability and fluidity as well as the surface area.
- Hardening agent (cross linking agent): sometimes added specially in aq. Colloidal dispersion method as formaldehyde or CaCl_2 . Microcapsules containing hardening agent showed highest drug release than thermally linked microcapsules.
- Drug loading (amount) and coat:core ratio: as amount of ibuprofen increased the release is decreased since the C:C ratio is changed
- Effect of additives: such as addition of surfactants during ME of ibuprofen the % of drug in the microcapsules equal to the theoretical amount (improves ME efficiency and loading)).

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