Manufacturing process

Materials

- **Includes the core (drug particles), the wall (polymeric in nature) and miscellaneous materials.**
- **The core may be water soluble or water insoluble, may be single or mixture of drug, stabilizer, diluent and other excipients.**
- **The polymeric coating or wall material are selected depending on different factors related to the aim of microencapsulation, the available equipment and the selected method.**

- **As ideal properties for wall materials, we have**
  - **They are capable of forming a film that is cohesive with the core materials.**
  - **Must be chemically compatible and non reactive with the core materials.**
  - **Must provide the desired coating properties like the strength, flexibility and stability.**

Types of wall materials

- **Water soluble polymers like acacia, gelatin, starch, sodium alginate, Chitosan, HPMC, Na-CMC and PVA.**
- **Water insoluble polymers like EC, some Eudragits, polyethylene and polyamide (Nylon).**
- **Enteric polymers like shellac, some Eudagits and CAP**
- **Waxes and lipids like hard paraffin, carnauba wax, stearic acid and bees wax.**

Miscellaneous materials

- Hardening agent or cross-linking agent like formaldehyde, glutraldehyde and calcium chloride.
- Surfactants : specially hydrophilic polymer (?) and non ionic types??
- Solvents: like water, dichloromethane, ethanol, liquid paraffin and n- Hexane. (for dissolving, dispersing or washing)
- Plasticizers: like PG, glycerol, sorbitol, Castor oil
- pH modifiers or buffers
- Electrolytes as precipitating agents : like NaCl or Na_2SO_4

Methods of microencapsulation

- The selection of particular process depend on the physical and chemical nature of the core as well as the aim of microencapsulation.
- There is no definite method can be used for encapsulation of all drugs and vice versa.
- The methods are generally divided into physical and chemical methods.

Table 13-7 (H.w.) for following (Your textbook)

The physical methods like:

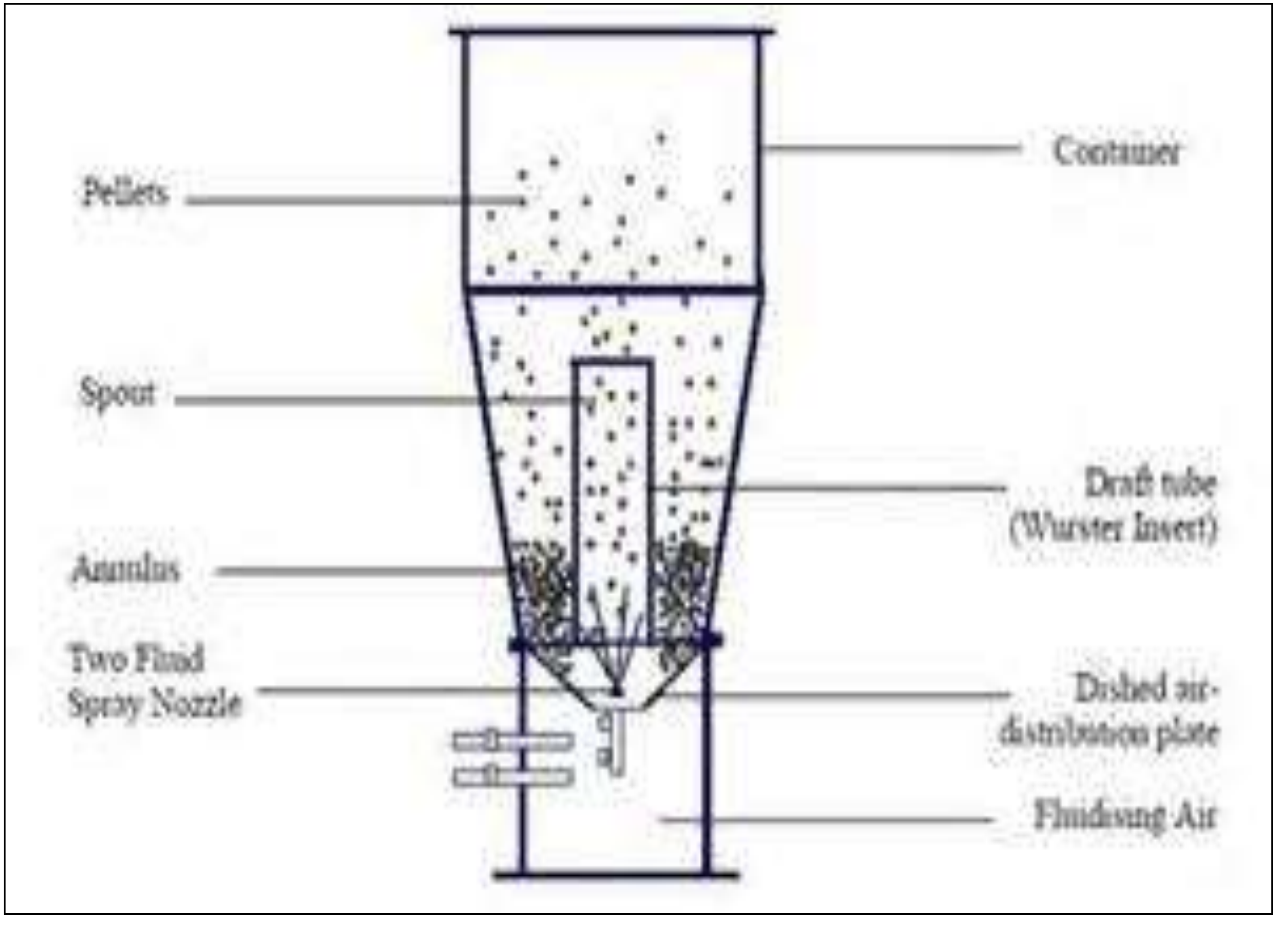
- Air suspension method
- Pan coating (As in tablet coating steps, but used for powders)
- Spray drying

The chemical methods like:

- Coacervation phase separation
- Solvent evaporation
- Gelation
- Interfacial polymrerization

Air suspension method (Wurster)

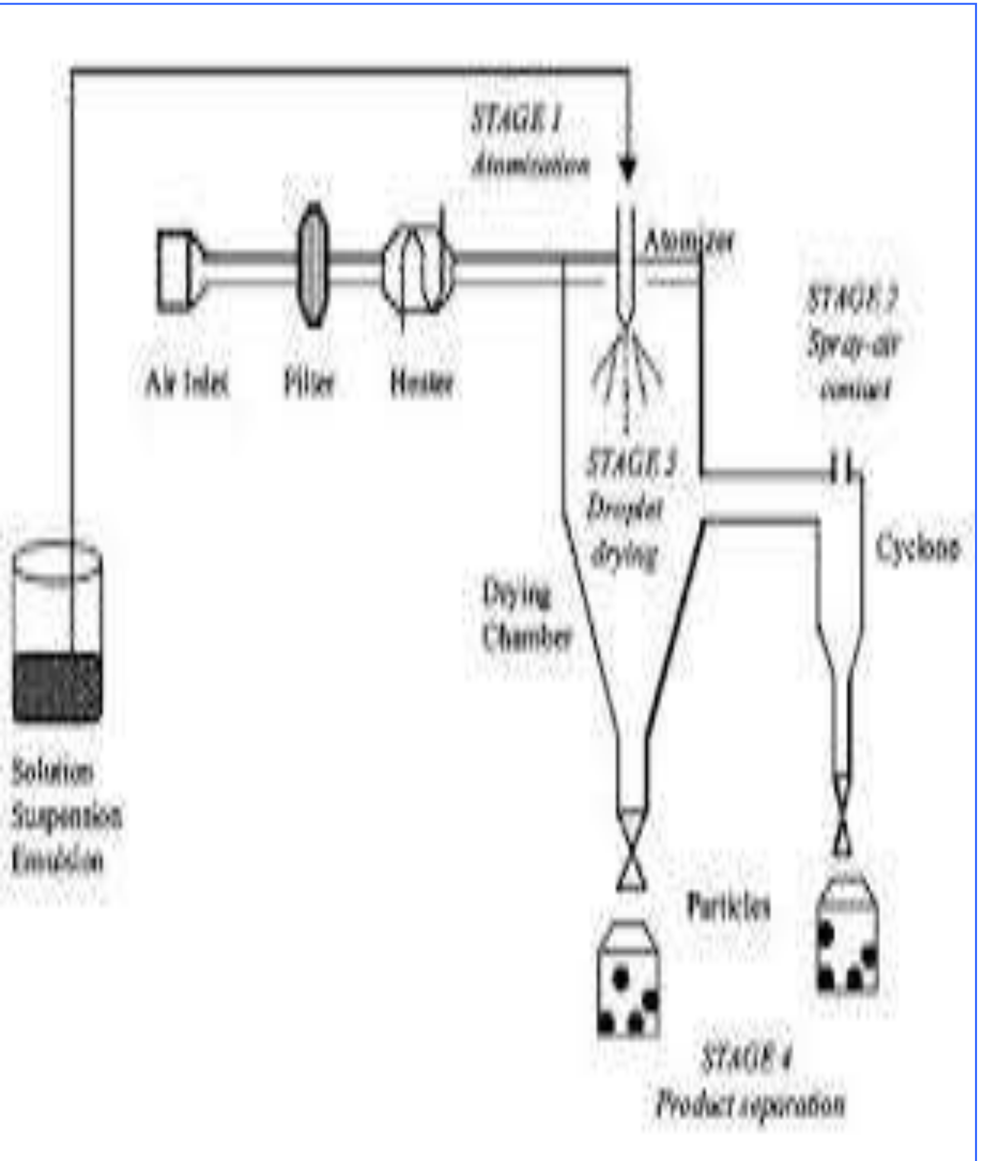
- It is down-word type fluidized bed system

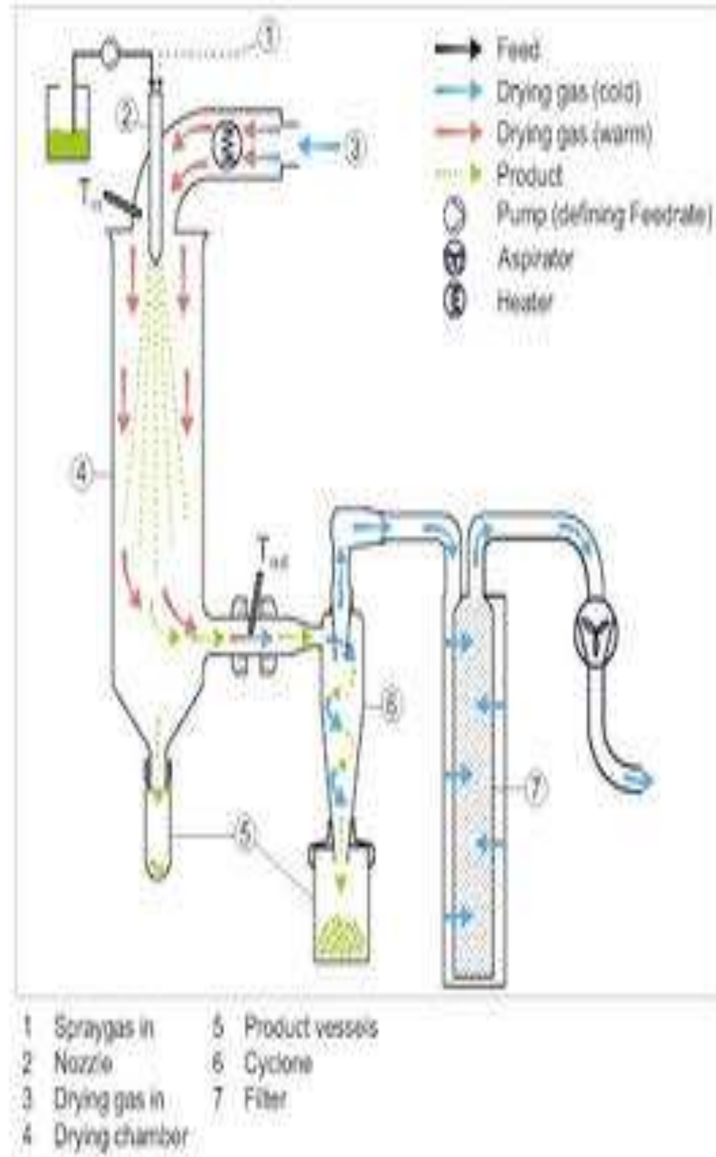


- Involves dispersing of the solid particulate core materials in a supporting air stream. (used for most of drugs)
- Then, spraying of the coating material (polymeric solution) using atomizer (application of the coating solution)
- Drying using fresh or hot air.
- Collection of the coated particles (microcapsules), containing one or more coating layers depending on the aim and the times of application.

Q/ What are the factors affecting this method?? = are related to materials, equipment and steps like ………..??

Spray drying





- Involve dissolving of the wall material in a volatile solvents, and the core material is **dispersed** within it.
- Spraying of dispersion (the mixture) as droplets into the warmed chamber of equipment.
- Drying at low temperature, so can be used for encapsulation of heat sensitive drugs (like proteins).
- Collection of the free flow, dry microcapsules (with spray dried particles properties) within a cyclone.

Coacervation phase separation

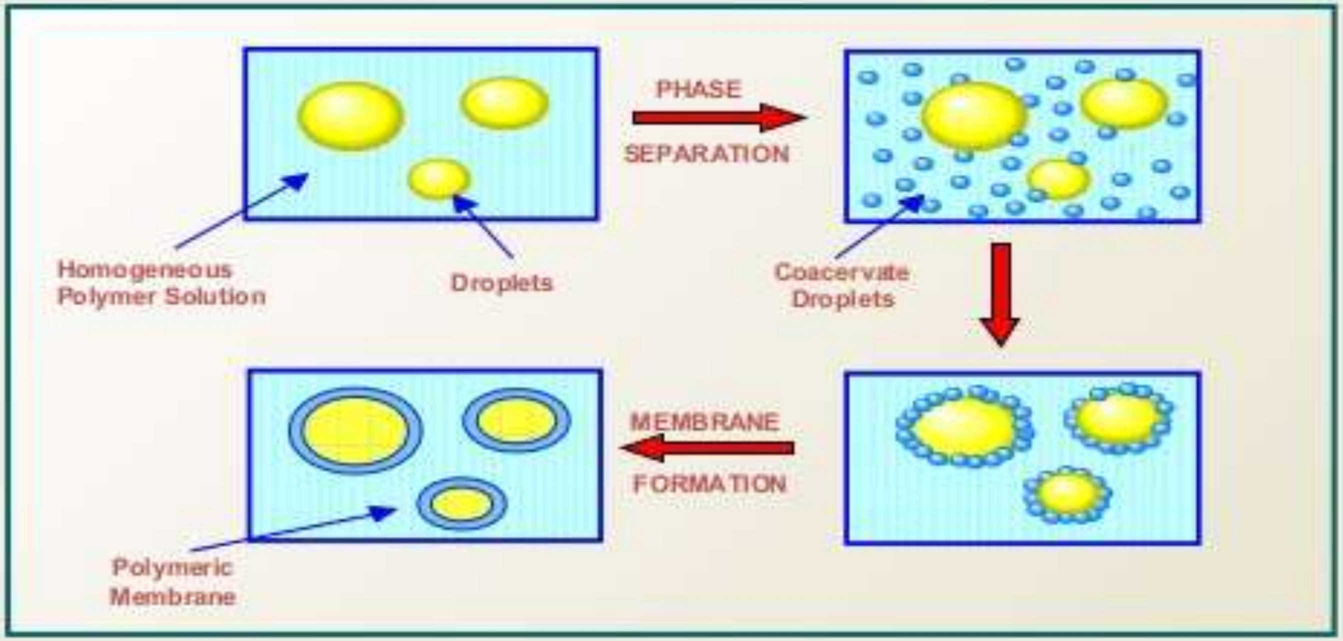
- Involves three main steps,

1) Stabilization of three phase system ?? by coacervation, in which the core materials are coated with the wall material and the resulted microcapsules are dispersed in the liquid carrier medium.

2) The dispersed particles of core are continuously coated with the wall materials.

3) Hardening of the microcapsules wall using a suitable hardening agents

COACERVATION / PHASE SEPARATION



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

- **Other steps may be involved like:**

1) **Washing with suitable solvent (aq. Or organic)**
2) **Drying at suitable conditions .**
3) **Collection of yield to be evaluated**

Monitoring of microcapsules formation within process is needed using microscopes to get idea about the time required for process and microcapsules quality.

- The coacervation or phase separation can be induced by different effects resulting into simple (containing single wall material) or complex (contain complex wall material) coacervation:

1) Temperature change ------------simple
2) Addition of non-solvent---------simple
3) Addition of salt (salting out)---------simple
4) Incompatible polymer addition---------simple
5) Polymer-polymer interaction (complex coacervation)

Temperature Change effect

- The phase separation of the dissolved polymer particles occurs in the form of immiscible liquid droplets and if the core materials are present in the system, under proper conditions (polymer concentration, temperature and agitation), the liquid polymer droplets coalesce around the dispersed core particles, thus forming microcapsules (simple coacervates).

- The temperature change alone is used to induce phase separation, assuming a mono-disperse polymer system, so decrease the temperature may result in formation of two phases: one phase becomes polymer-poor (the microencapsulation vehicle phase) and second phase (the wall material phase) becomes polymer-rich.

Ex. For Binary system of EC+ Cyclohexane for water soluble drug X (EC:X ratio is 2:1)

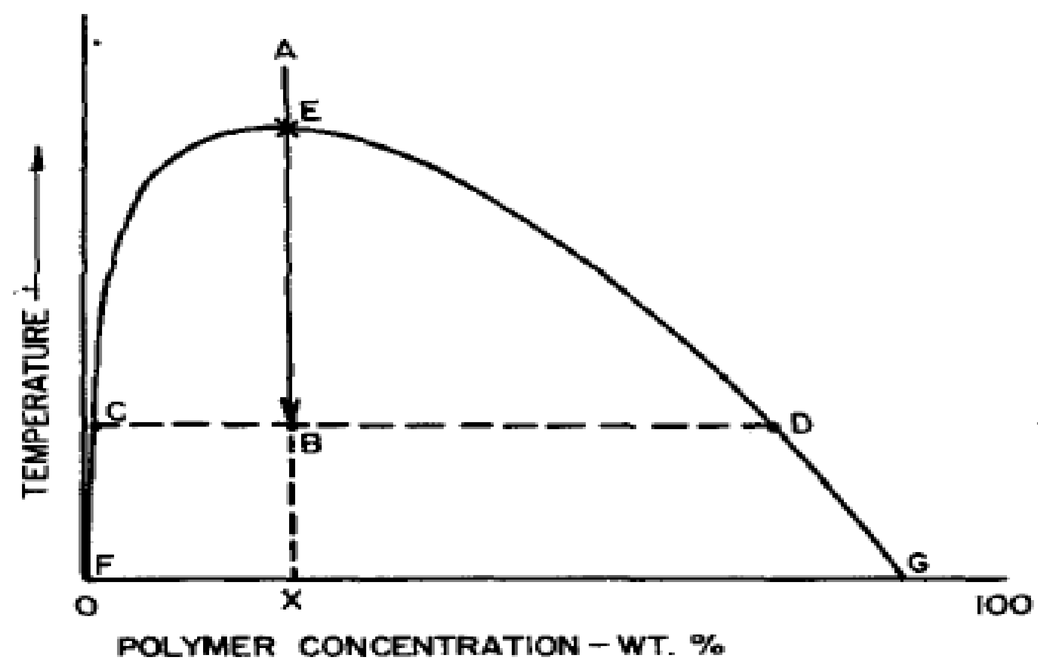


FIG. 13-39. *General phase diagram—coacervation induced thermally. (From Bakan.[28])*

Non solvent addition

A liquid that is
a non solvent
for a given
polymer can be
added to a solution
of the polymer to
induce the phase
Separation

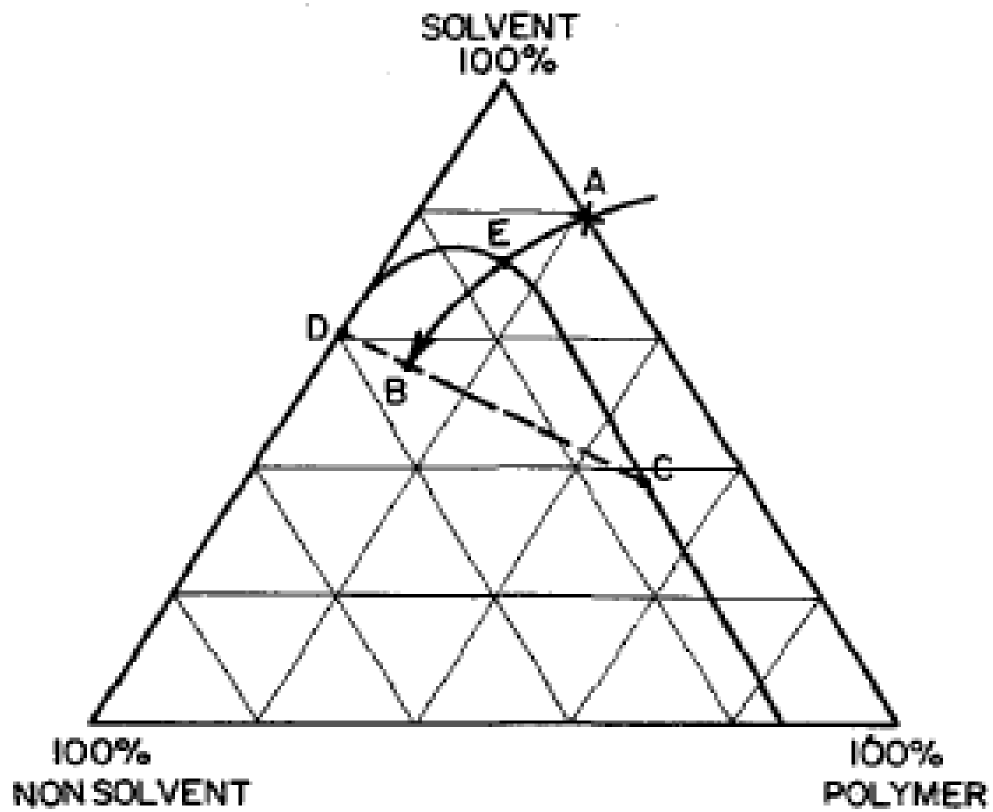
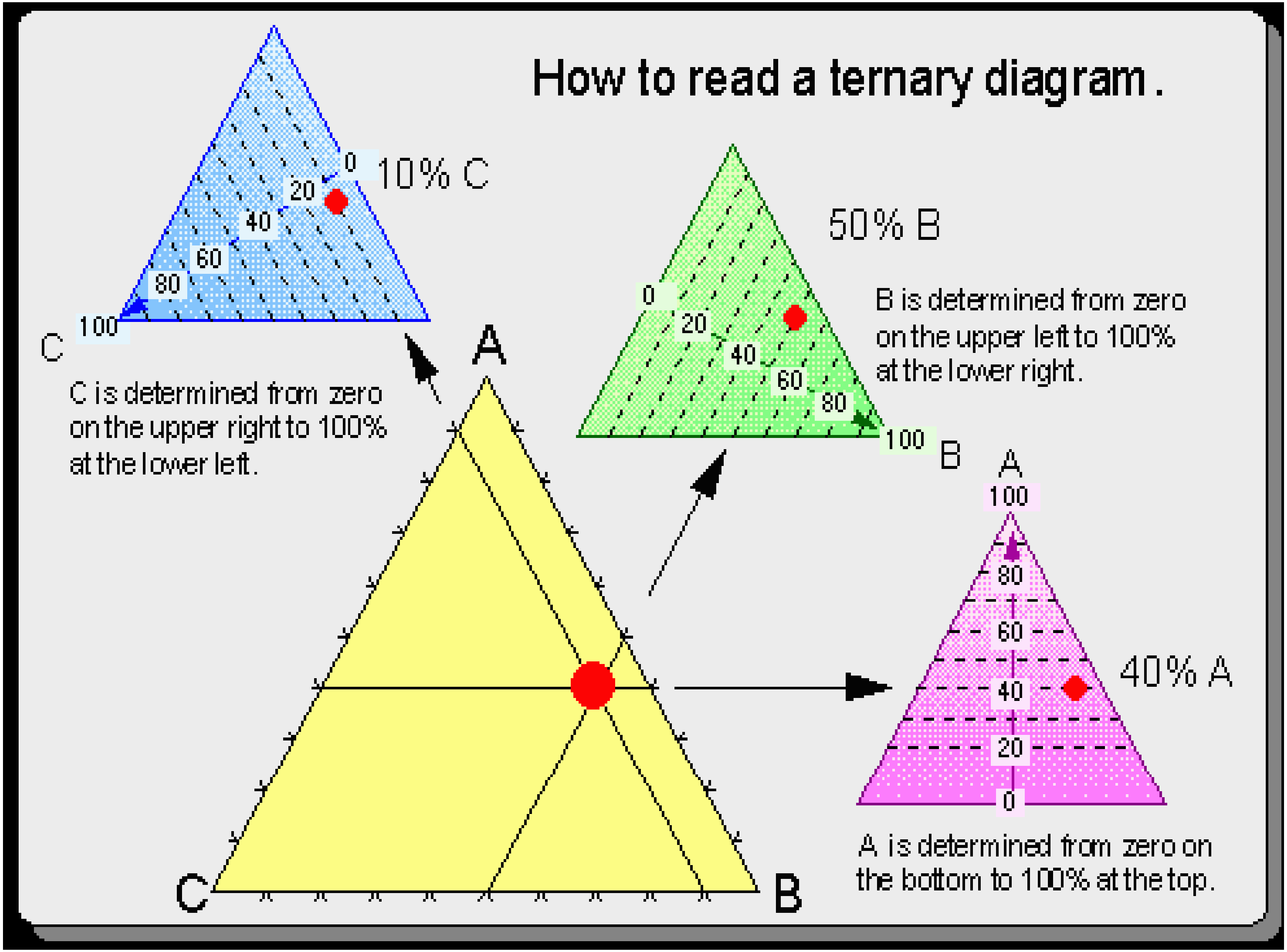


FIG. 13-41. *General phase diagram for phase-separation/coacervation induced by the addition of a nonsolvent.*


How to read a ternary diagram .
0
20
40
60
80
100
C
10% C
C is determined from zero on the upper right to 100% at the lower left.
A
0
20
40
60
80
100
B
50% B
B is determined from zero on the upper left to 100% at the lower right.
A
100
80
60
40
20
0
40% A
A is determined from zero on the bottom to 100% at the top.
A
C
B

Salt addition

Soluble inorganic salts (or strong hydrophilic electrolyte) can be added into a large amount to aqueous solution of certain water soluble polymers to cause phase separation by salting out effect (abstraction of hydration water from the polymer) like addition of sodium sulfate 20%.

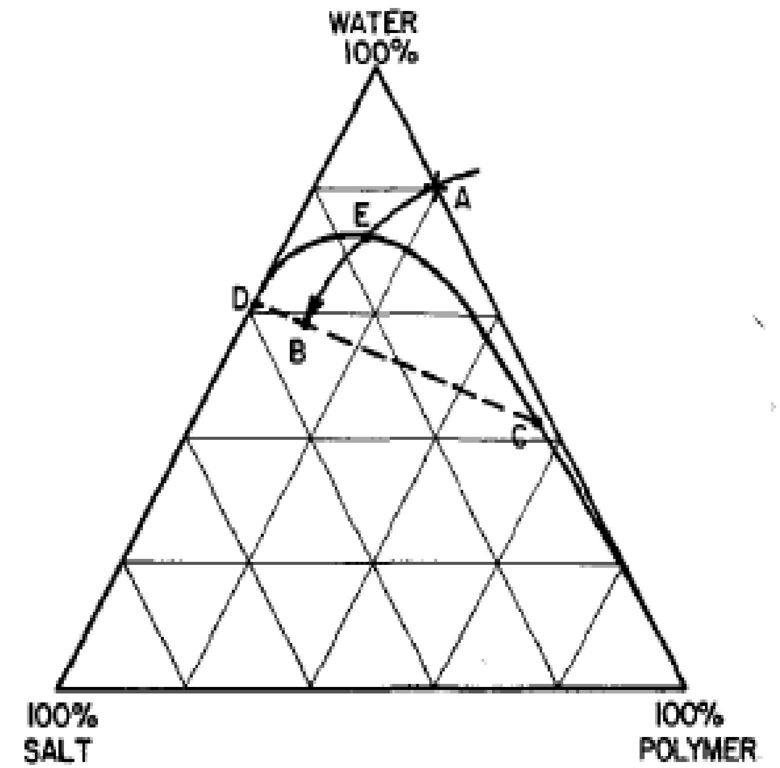


FIG. 13-42. *General phase diagram for phase-separation/coacervation induced by salt addition. (From Bakan.[28])*

Incompatible polymer addition

Liquid phase separation of a polymeric coating material can be occurred by using the incompatibility of dissimilar polymers existing in a common solvent. It does not involve any chemical reaction, one phase is rich in polymer designed to act as wall material and the other is rich in the second incompatible polymer

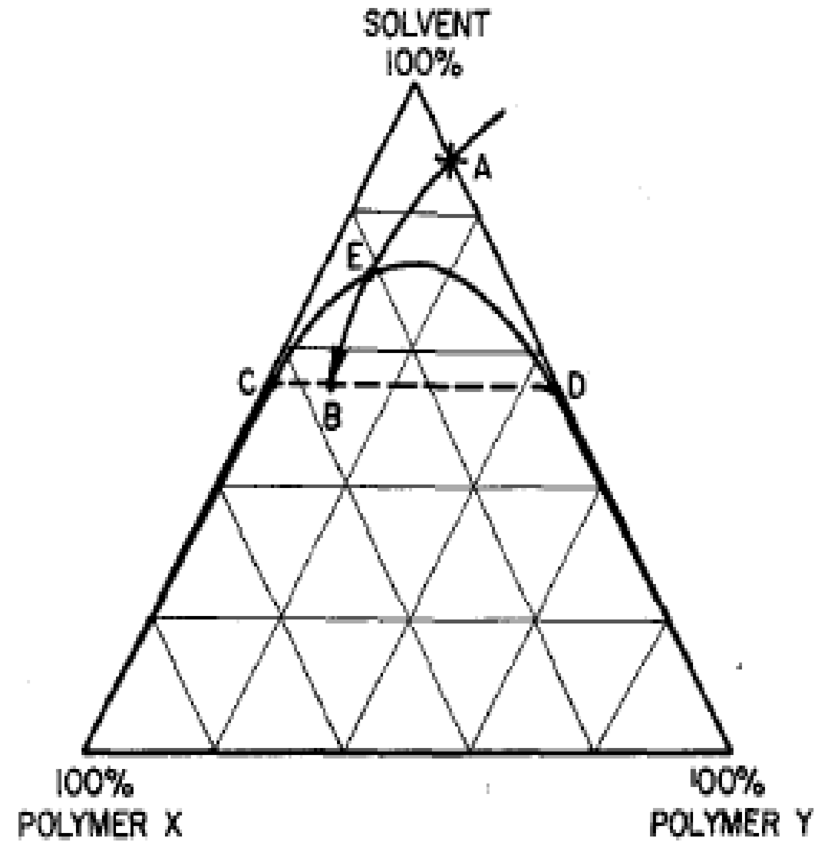


FIG. 13-40. *General phase diagram of phase-separation/coacervation induced by the addition of an incompatible polymer. (From Bakan.[28])*