

PHASE EQUILIBRIA AND THE PHASE RULE



PHARMACEUTICAL TECHNOLOGY-II
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THE PHASE RULE

1

- This is a rule formulated by J. Willard Gibbs
- By applying phase rule, «**relationship between variables that can be changed without changing the equilibrium state of a system**» can be defined
- The independent variables can be **temperature, pressure, density, concentration**, etc..
- The rule is expressed as follows:

$$F = C - P + 2$$

F: The number of degrees of freedom of the system

C : The number of components

P : The number of phases present

Phase (P):

$$F = C - P + 2$$

2

is a homogeneous, physically distinct portion of a system that is separated from other portions of the system by bounding surfaces.

For example,

- a system containing water and its vapor is a two-phase system.
- an equilibrium mixture of ice, liquid water, and water vapor is a three-phase system.

Number of components (C):

$$F = C - P + 2$$

3

- It is the number of chemically independent materials in a system.

Ex 1 : In a system consisting ice, water and water vapour, **C=1** .

All phases have similar chemical formulation (H_2O).

Ex 2: In the three-phase system of $\text{CaCO}_3 = \text{CaO} + \text{CO}_2$, **C= 2**.

- if we choose to use $\text{CaCO}_3 + \text{CO}_2$, we can write CaO as $\text{CaCO}_3 - \text{CO}_2$.

Number of degrees of freedom (F)

It is the least number of intensive variables that must be fixed/known to describe the system completely.

4

Ex 1: Consider a given volume of water vapor

$$F = C - P + 2 \\ = 1 - 1 + 2 = 2$$

According to the phase rule, two independent variables are required to define the system. Variable like temperature or pressure must be known to define the system completely.

Ex 2: water in equilibrium with its vapor.

$$F = C - P + 2 \\ = 1 - 2 + 2 = 1$$

By stating the temperature, we define the system completely because the pressure under which liquid and vapor can coexist is also defined.

Ex 3: Suppose that we cool liquid water and its vapor until a third phase (ice) separates out.

$$F = C - P + 2 \\ = 1 - 3 + 2 = 0$$

system is completely defined, and the rule gives. In other words, there are no degrees of freedom.

This is known as the critical point.

The relation between the number of phases and the degrees of freedom in one-component systems is summarized in Table 1.




5

System	Number of phases	Degrees of freedom	Comments
Gas Liquid Solid	1	$F = C - P + 2$ $F = 1 - 1 + 2 = 2$ F = 2	Bivariant system Two variants must be fixed to define the system
Gas + Liquid Liquid + Solid Gas + Solid	2	$F = C - P + 2$ $F = 1 - 2 + 2 = 1$ F = 1	Univariant system One variant must be fixed to define the system
Gas + Liquid + Solid	3	$F = C - P + 2$ $F = 1 - 3 + 2 = 0$ F = 0	Invariant system System lie only at the point of intersection of the three phases.

According to the component number,



example

- Systems containing 1 component  water
- 2 component systems
(condensed systems)  alcohol-water
phenol-water
thymol-salol
- 3 component systems  emulsions

One-Component Systems:


7

Ethyl alcohol and ethyl alcohol vapour mixture

Phases : 1. Ethyl alcohol }
 2. Ethyl alcohol vapour } $P = 2$

Both phases are C_2H_5OH } $C = 1$

$$F = C - P + 2 = 1 - 2 + 2 = 1$$

- ✓ $F = 1$  system can be defined with one variable.
- ✓ This variable can be temperature or pressure etc.

Completely miscible 2 component systems

8

Example: Water, Water vapour and Ethyl alcohol mixture

Phases : 1. Water + Ethyl alcohol
2. Water vapour } P = 2

(Ethyl alcohol and water are completely miscible both as vapors and liquids)

Components: 1. H₂O
2. C₂H₅OH } C=2

$$F = C - P + 2 = 2 - 2 + 2 \quad \longrightarrow \quad \mathbf{F = 2}$$

system can be defined with two variables.

Partially or immiscible 2 component systems

9

Example: Water, Water vapour and Liquid benzyl alcohol

Phases : 1. Water
2. Water vapour
3. Benzyl alcohol } $P = 3$

(water and benzyl alcohol are only partially miscible)

Components: Both 1st and 2nd phases are H₂O } $C=2$
3rd phase is benzyl alcohol

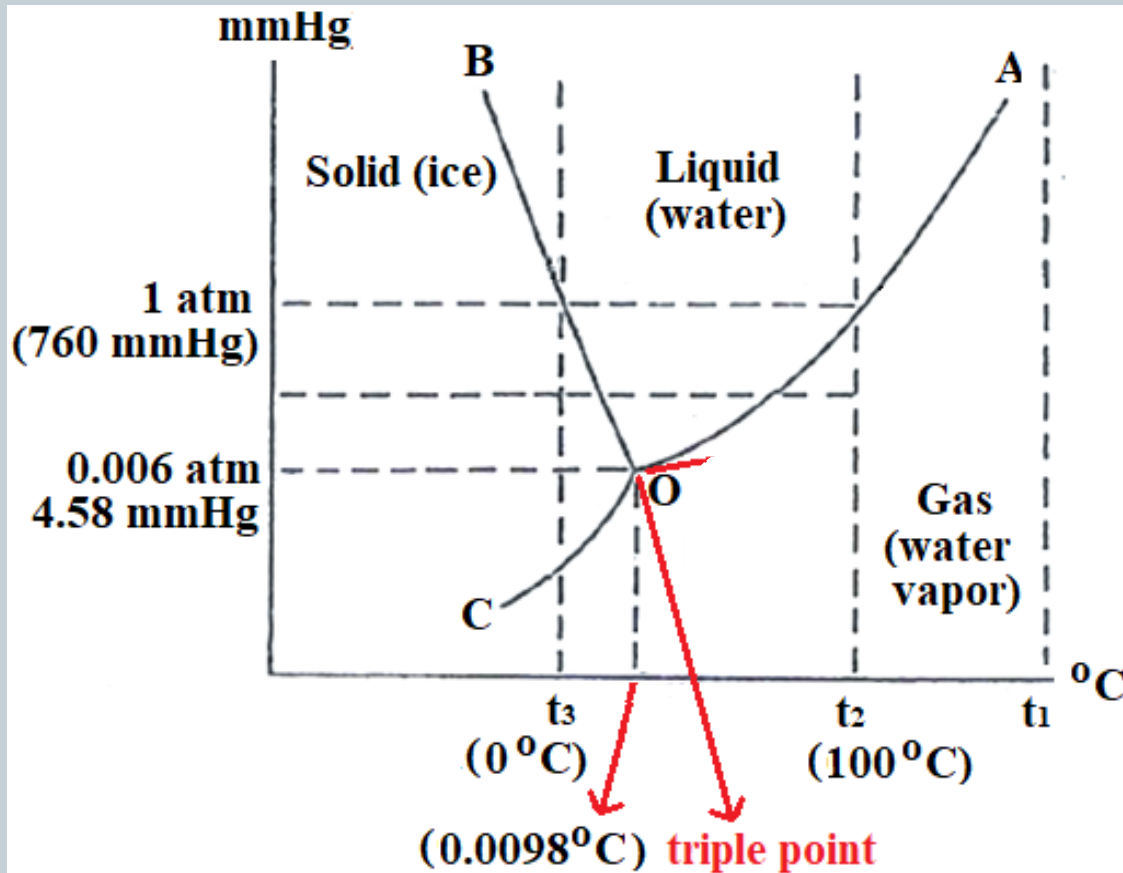
$$F = C - P + 2 = 2 - 3 + 2 \quad \longrightarrow \quad \mathbf{F = 1}$$

- ✓ Partially mixed benzyl alcohol-water system can be defined with only one variable.

Systems Containing One Component

- Water -

10



OA: vapor pressure curve

OB: melting point curve

OC: sublimation curve

Phase diagram for water at moderate pressures

OA: Vapor and liquid are in equilibrium. At A (374°C), and at O (0.0098°C)

OB: Vapor and solid are in equilibrium. The negative slope of OB shows that the freezing point of water decreases with increasing external pressure.

OC: Liquid and solid are in equilibrium.

- Above the critical temperature (t_1 : 374°C), water is in the gaseous state and the system remains as a gas.
- Below the critical temperature (t_2), water vapor is converted into liquid water by an increase of pressure .
- Below triple point (t_3 ; 0.0098°C), an increase of pressure on water in the vapor state converts the vapor first to ice and then at higher pressure into liquid water.

- Liquid water exhibits two degrees of freedom ($F=2$)
- Along OA, OB or OC curves, two phases exist in equilibrium. Thus, **one variable** is required to define the system ($F=1$)
- At the triple point, all phases are in equilibrium, that is, the only equilibrium is at this pressure at temperature of 0.0098°C (with respect to $F=0$).

12

System	P	F	Variants
Water Ice Vapour	1	$F = C - P + 2$ $F = 1 - 1 + 2$ F = 2	<u>Pressure and temperature</u> must be fixed to describe the system completely. (Bivariant system)
Vapour+Water (OA) Vapour+Ice (OB) Water+Ice (OC)	2	$F = C - P + 2$ $F = 1 - 2 + 2$ F = 1	<u>Pressure or temperature</u> must be fixed (Univariant system)
Vapour+Ice+Water	3	$F = C - P + 2$ $F = 1 - 3 + 2$ F = 0	At the triple point, all phases are in equilibrium. (Invariant system)

CONDENSED SYSTEMS

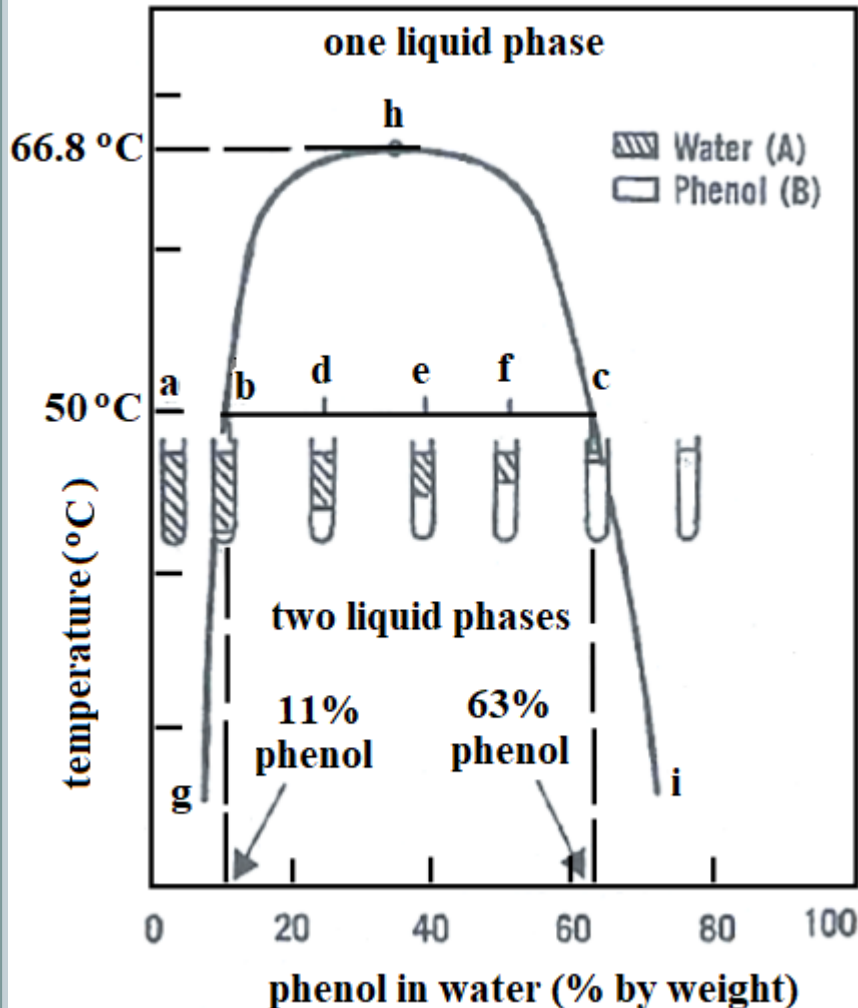
13

- These are partially miscible two-component systems having one liquid phase when certain amounts are mixed.
- In these systems, **the vapor phase is ignored** and only solid and/or liquid phases are considered. In these systems **$F = 2$** .
- There are only two variables (**temperature and concentration**) remain in condensed systems, and we are able to portray the interaction of these variables by the use of planar figures on rectangular-coordinate graph paper.

Two-Component Systems Containing Liquid Phases

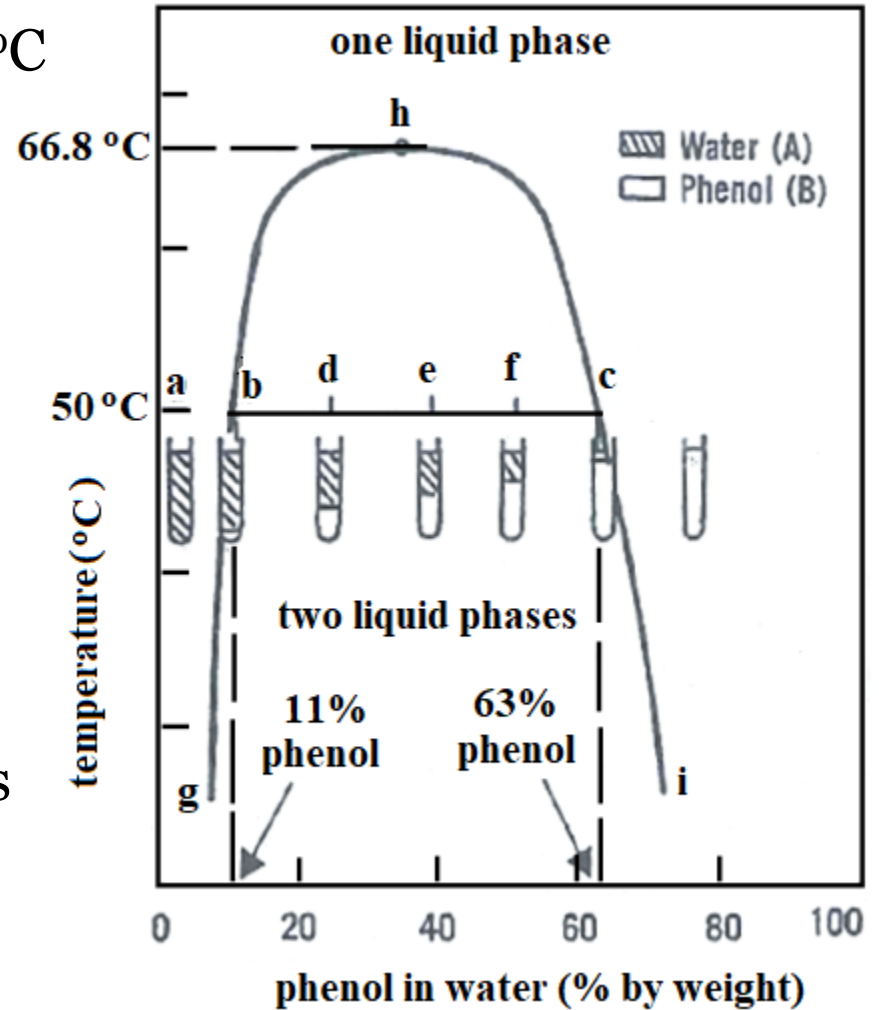
Example: Phenol and Water

14



- ❖ When a certain amount of water and phenol mixed, two liquid phases produced.
- ❖ Each liquid phase consists the other liquid as solubilized, this amount depends on temperature.
- ❖ The curve (*gbhci*) shows **two liquid phases exist in equilibrium at 50C.**
- ❖ The region outside this curve contains **one liquid phase**

- Point «a» has 100 % water at 50°C
- When phenol is added between 11-63 % at 50°C (*points b to c*) **two phases appear.**
- When the total concentration of phenol exceeds 63% at 50°C, a **single phenol-rich liquid phase** is formed.
- The max °C (**66.8°C–point h**) at which the two-phase region exists is termed as **critical solution (upper consolute, critical °C).**



- All combinations of phenol and water above this temperature are **completely miscible and yield one-phase liquid systems.**

- At «*d*» there is 24% w/w phenol in the system. The weight of water (A) is greater than phenol (B) at point *d*. Phenol has a higher density than water. Thus, there will be more of water-rich phase in the tube.

1. «*dc*» and «*bd*» can be measured with a ruler in cm from the diagram.

$$\frac{\text{Weight of phase A}}{\text{Weight of phase B}} = \frac{\text{Length } dc}{\text{Length } bd}$$

2. Or, the percentage weight of phenol can be found from the figure.

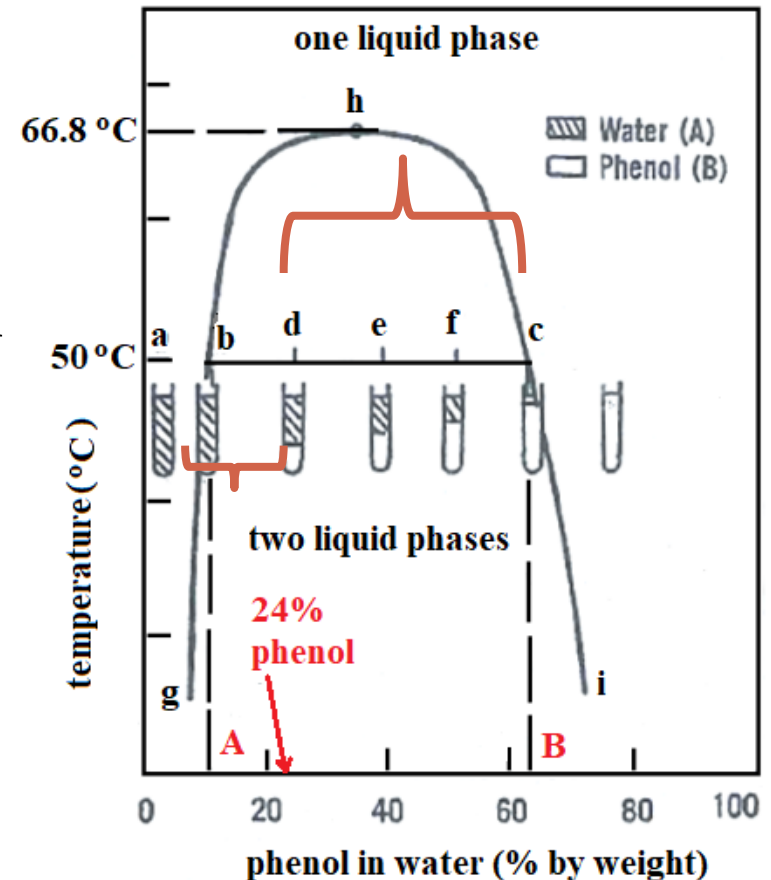
$$b=11\%, c=63\%, d=24\%$$

$$dc/bd = (63-24)/(24-11) = 39/13 = 3/1$$

For every 10 g of a liquid system in equilibrium represented by *point d*, one finds

7.5 g of phase A (75%)

2.5 g of phase B (25%)



■ Example,

Let us suppose that we mixed 24 g of phenol with 76 g of water, warmed the mixture to 50°C and allowed it to reach equilibrium at this temperature.

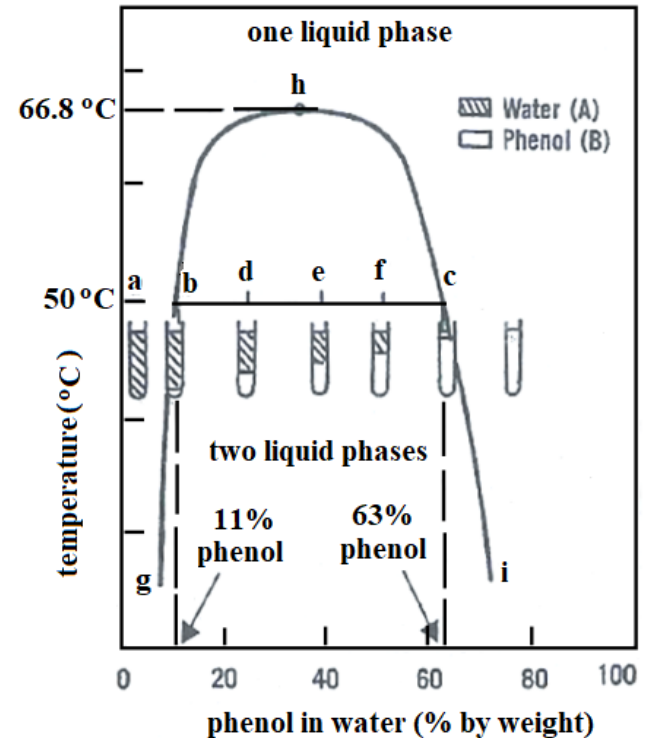
On separation of the two phases, we would find 75 g of phase A (containing 11% by weight of phenol) and 25 g of phase B (containing 63% by weight of phenol).

Phase A contains ,
 $(11 \times 75)/100 = 8.25$ g of phenol

Phase B contains,
 $(63 \times 25)/100 = 15.75$ g of phenol

This gives a sum total of 24 g of phenol in the whole system.

- It is left to the people to confirm that *phase A* contains 66.75 g of water and *phase B* 9.25 g of water.
- The phases are shown at *b* and *c* in this figure.



Eutectic Mixtures

These are 2-component systems containing solid and liquid phases.

18

- An eutectic mixture is the composition of two or more compounds that exhibits a melting temperature lower than that of any other mixture of the compounds. The components are completely miscible when they are in liquid state but completely immiscible as solids.
- In these systems, there is an eutectic point at which the liquid and solid phases have the same composition (*the eutectic composition*).
- Examples; 56% by weight of salol in camphor eutectic point is 6°C. acetaminophen-propyphenazone system, camphor, chloral hydrate, menthol, and betanaphthol can also form eutectic mixtures

Eutectic systems are examples of solid dispersions.

- solid dispersions may offer a means of facilitating the dissolution and frequently, therefore, the bioavailability of poorly soluble drugs when combined with freely soluble “carriers” such as urea or polyethylene glycol.

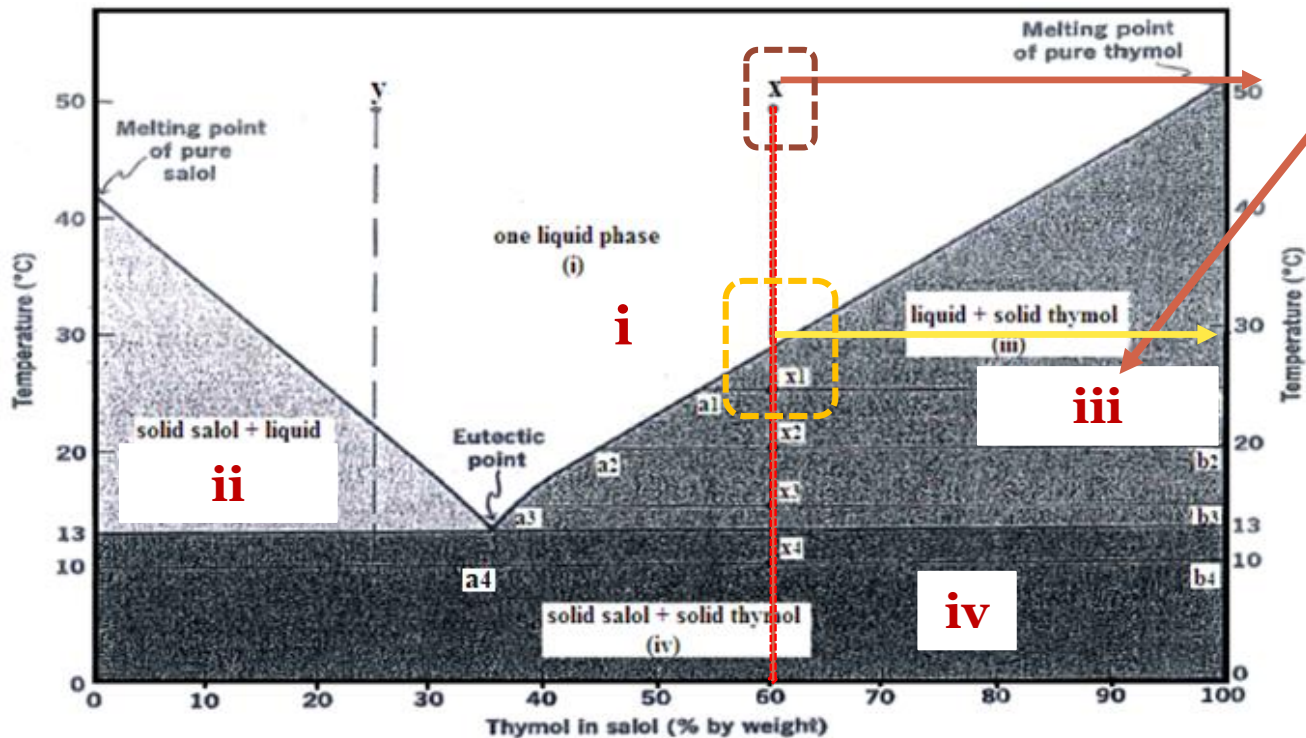
Example: Salol-thymol mixture

19

- When the mixture has **34% thymol in salol**, over a temperature of **13°C** system will be in a single liquid form.
- This point (13°C) on the phase diagram is known as the *Eutectic Point* for the given concentration of salol-thymol mixture.
- At the eutectic point, three phases (liquid, solid salol, and solid thymol) coexist. The eutectic point therefore denotes an invariant system because, in a condensed system,

$$F=2-3+1=0.$$

100 %
salol



$$F=2-2+1$$
$$F=1$$

100 %
thymol

- i. A single liquid phase,
- ii. A region containing solid salol and a conjugate liquid phase,
- iii. A region in which solid thymol is in equilibrium with a conjugate liquid phase, and
- iv. A region in which both components are present as pure solid phases.

- System containing **60%** of thymol in salol at 50 °C is represented by **x**.
- This system remains as single liquid until 29 °C.
- At (x1) solid thymol separates out to form two-phase system.
- Below **13°C**, the liquid phase disappears altogether and the system contains **two solid phases of pure salol and pure thymol**

Phase Equilibria in Three-Component Systems

21

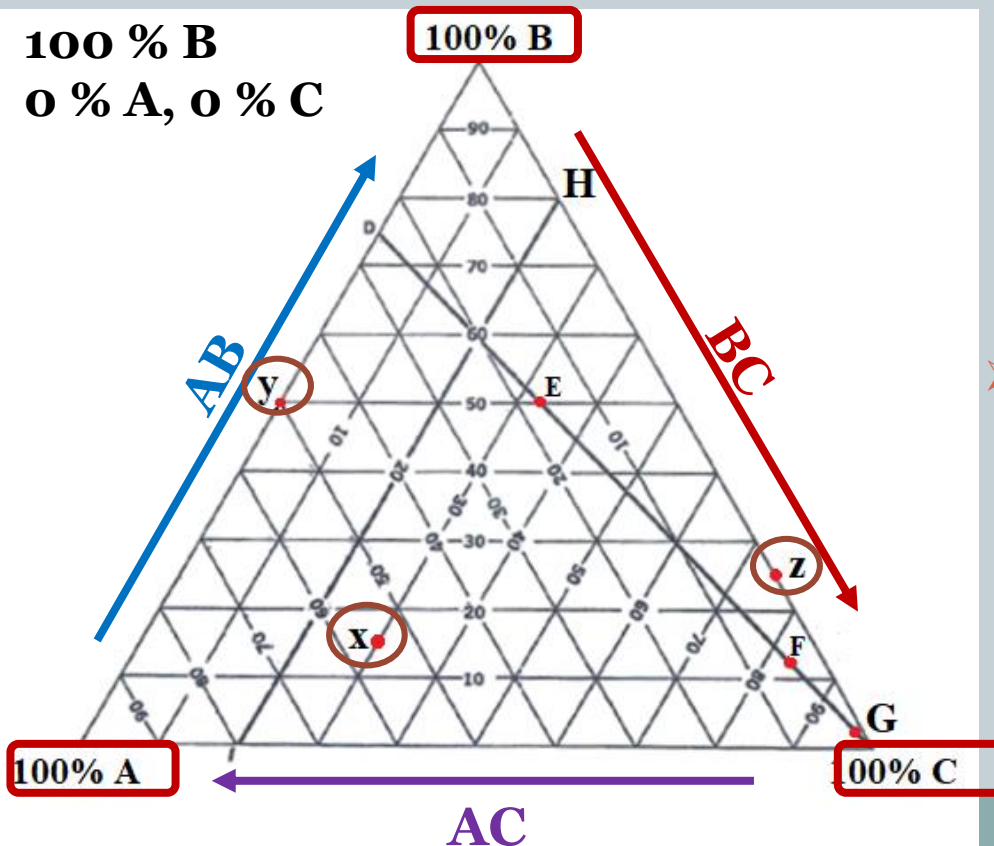
- In a **non-condensed system** containing three components but only one phase, $F=C-P+2=3-1+2=4$
(F: temperature, pressure, and the concentrations of two of the three components)
- Only two concentration terms are required because the sum of these subtracted from the total will give the concentration of the third component.
- If we regard the system as condensed and hold the temperature and pressure constant, $F=2$, thus we can use a planar diagram (generally triangular graphs are used) to illustrate the phase equilibria.
- Several areas of pharmaceutical processing such as Crystallization, Salt form selection, and Chromatographic analyses rely on the use of ternary systems for optimization

Rules Relating to Triangular Diagrams

The concentration in ternary systems are expressed on a weight basis.

22

- ✓ Each of the three corners represent 100% by weight of one component
- ✓ The lines AB , BC , and AC are used for **two-component mixtures** and can be divided into 100 equal units.



- ✓ Point y , on the line AB , represents a system containing 50% of B (and hence 50% of A).
- ✓ Point z , along BC , signifies a system containing 75% of C .
- The point x lies on the lines parallel to AB and gives 30% of C and parallel to AC and gives 15% of B . Therefore, the concentration of A is $=100-(B+C)$
 $=100-(15+30)=55\%$.

Ternary Systems with One Pair of Partially Miscible Liquids:

23

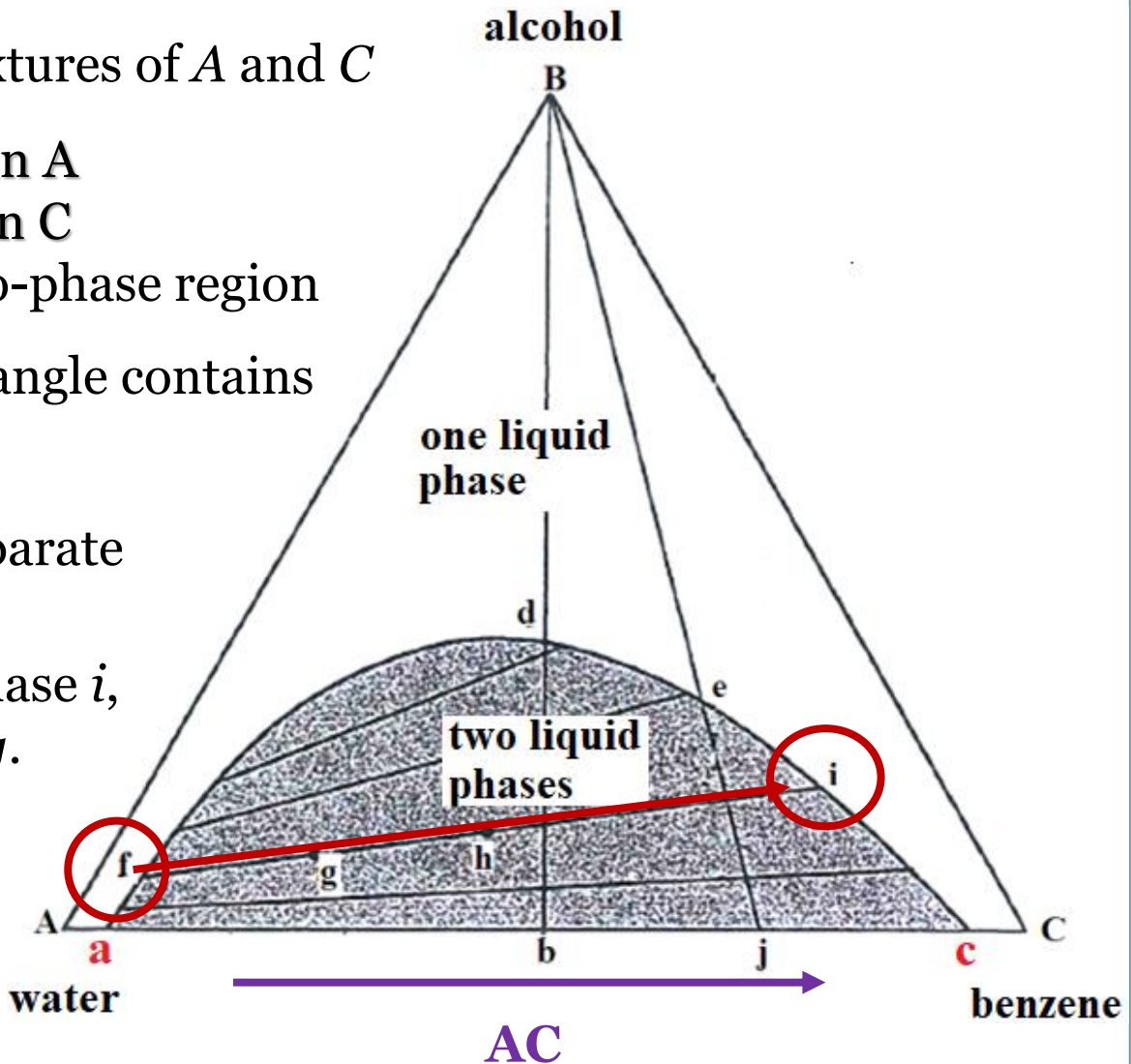
Example: Water and benzene

- ✓ are slightly miscible and usually produces a **two-phase system**.
- ✓ The heavier of the two phases consists of water saturated with benzene; while the lighter phase is benzene saturated with water.
- ✓ Alcohol is completely miscible with both benzene and water. Here, addition of alcohol serves **as a co-solvent**.
- ✓ Alcohol shifts the electronic equilibrium of the highly polar water and nonpolar benzene solutions to provide solvation.
- ✓ **Addition of sufficient alcohol to a two-phase system of benzene and water would produce a single liquid phase in which all three components are miscible.**

- The **line AC**: binary mixtures of A and C
- *Point a* : solubility of C in A
- *Point c* : solubility of A in C
- binodal curve *afdeic* : two-phase region
- The remainder of the triangle contains one liquid phase.

«*g*», in equilibrium, will separate into two phases, *f* and *i*:

- The ratio of phase *f* to phase *i*, on a weight basis, is $gi:fg$.
- System *h* contains equal weights of the two phases.

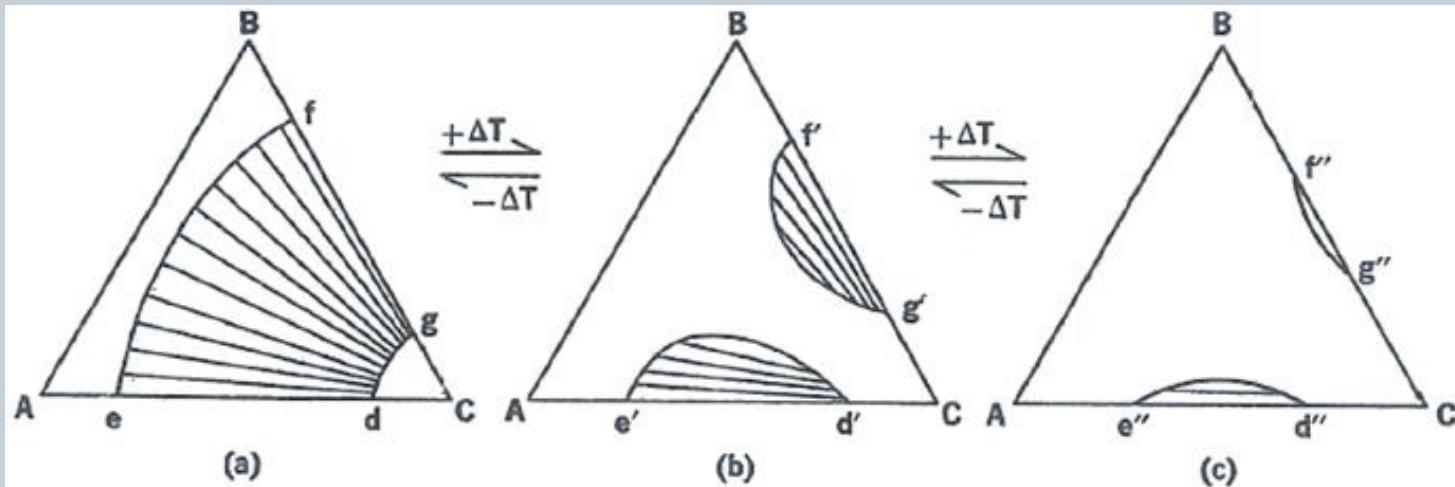


- Addition of component *B* to a 50:50 mixture of A+C will produce a phase change from a two-liquid system to a one-liquid system at point *d*.

Ternary Systems with Two or Three Pairs of Partially Miscible Liquids

25

- There are **two binodal curves** with two pairs of partially miscible liquids.
- Increasing the temperature leads to a reduction in the areas of the two binodal curves (Fig. c). Reduction of the temperature expands the binodal curves to form a **single band of immiscibility**.

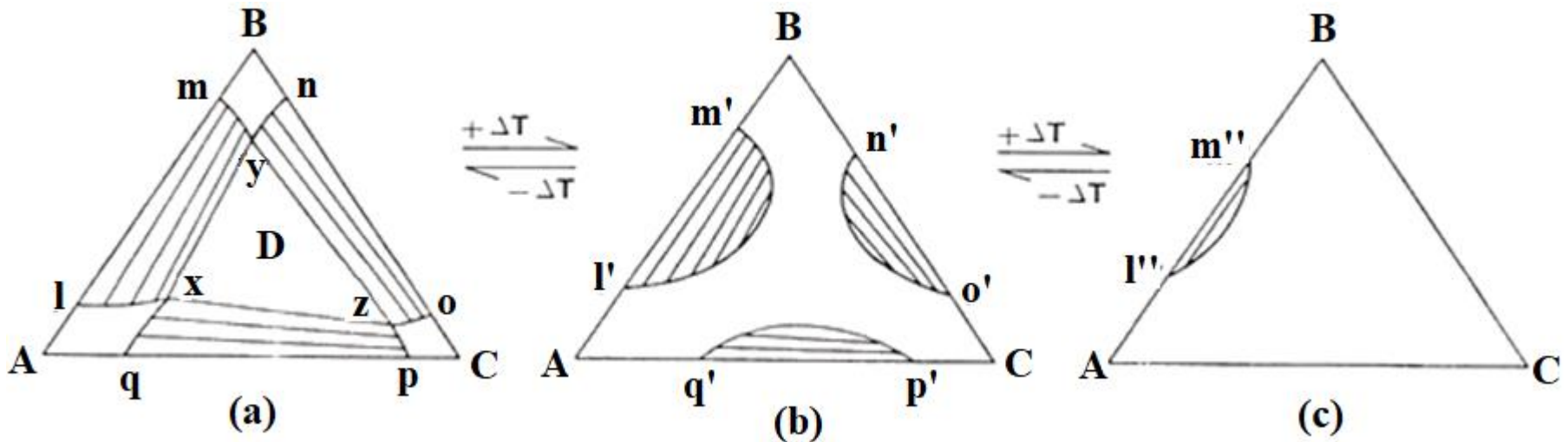


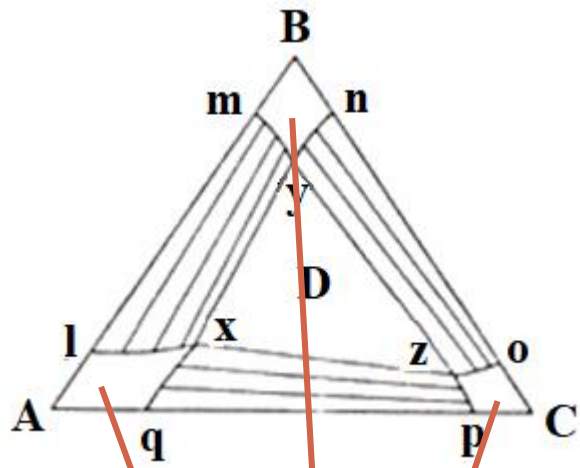
Effect of temperature changes on the binodal curves representing a system of two pairs of partially miscible liquids

Three pairs of partially miscible liquids

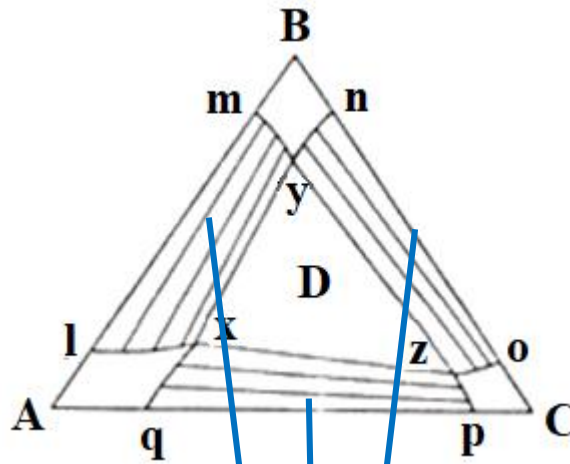
26

- **Three binodal curves** meet a central region (D) appears in which *three* conjugate liquid phases exist in equilibrium.
- In this region, *D*, which is triangular, **F=0** for a condensed system under isothermal conditions.
- *all* systems lying within this region consist of three phases whose compositions are always given by the points *x*, *y*, and *z*.

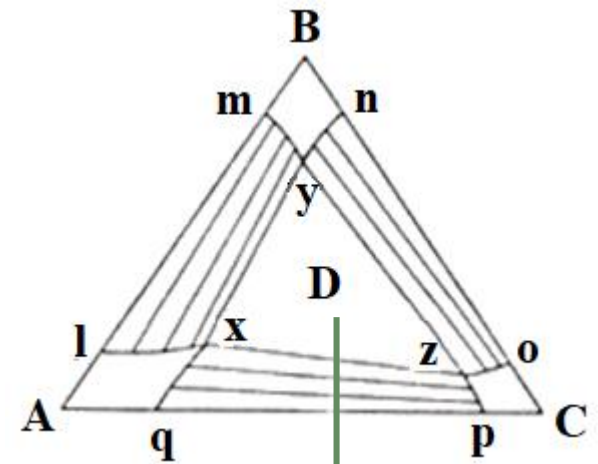




1 phase



2 phases

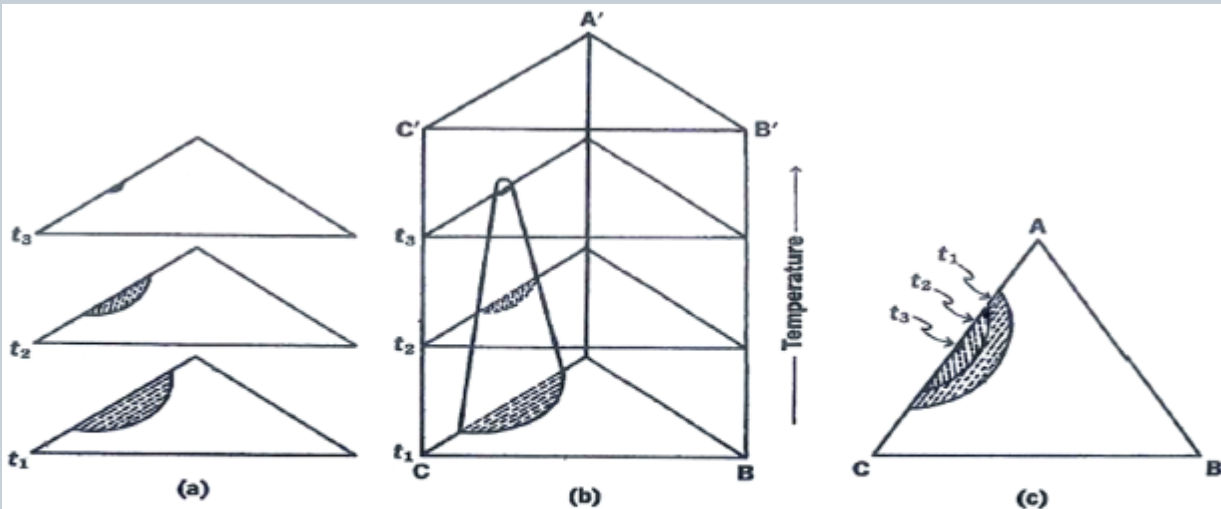


3 phases

Effect of Temperature

28

- Changes in temperature will cause the area of immiscibility
- In general, the area of the binodal decreases as the °C is raised and miscibility is promoted.



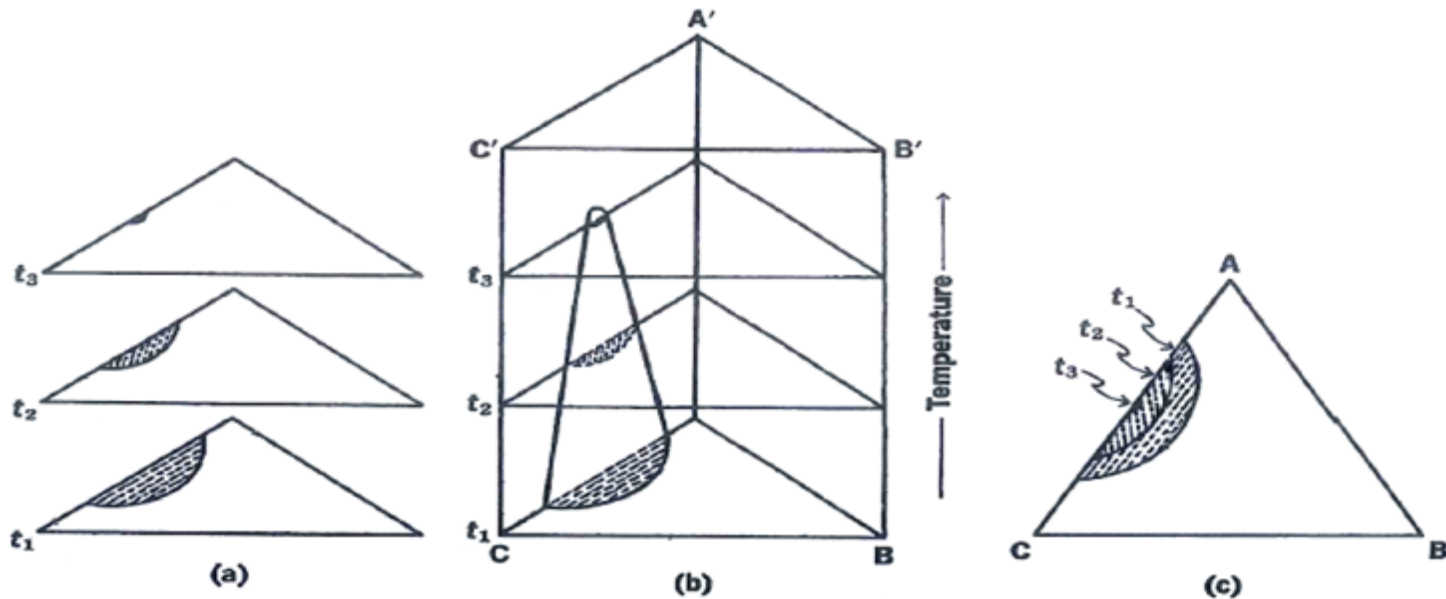
Alterations of the binodal curves with changes in temperature.

(a) Curves on the triangular diagrams at temperatures t_1 , t_2 , and t_3 .

(b) The three-dimensional arrangement of the diagrams in the order of increasing temperature.

(c) The view one would obtain by looking down from the top of (b).

- The effect of °C on phase equilibria of three-component systems are generally shown with triangular prisms.



Alterations of the binodal curves with changes in temperature.

(a) Curves on the triangular diagrams at temperatures t_1 , t_2 , and t_3 .

(b) The three-dimensional arrangement of the diagrams in the order of increasing temperature.

(c) The view one would obtain by looking down from the top of (b).

- The three planar sides of the prism are simply 3-phase diagrams of binary-component systems. Fig. shows the ternary-component system containing one pair of partially immiscible liquids (A and C).
- **As the temperature is raised, the region of immiscibility decreases.**
- The volume outside the shaded region of the prism consists of a single homogeneous liquid phase.

Application of Phase Diagrams to Pharmaceutical Systems

30

Phase diagrams were used as;

- Solubilization of two- and three- component pharmaceutical systems.
- Formulation of microcapsule, nanocapsule and emulsion type systems,
- stability studies and
- examination of biological activity.