Physical Pharmacy (0510219)

Unit 2
Phase Equilibria
and the Phase Rule Solutions

Phase Equilibria and the Phase Rule

- The three primary phases (solid, liquid, and gaseous) of matter are often defined individually under different conditions, but in most systems we usually encounter phases in coexistence.

- For example, a glass of ice water on a hot summer day comprises three coexisting phases: ice (solid), water (liquid), and vapor (gaseous).

- The amount of ice in the drink depends heavily on several variables including the amount of ice placed in the glass, the temperature of the water in which it was placed, and the temperature of the surrounding air.

- This one-component example can be extended to the two-component system of a drug suspension where solid drug is suspended and dissolved in solution and evaporation may take place in the headspace of the container.

- The suspended system will sit at equilibrium until the container is opened for administration of the drug, and then equilibrium would have to be reestablished for the new system.

- A new equilibrium or nonequilibrium state is established because dispensing of the suspension will decrease the volume of the liquid and solid in the container. Therefore, a new system is created after each opening, dispensing of the dose, and then resealing.

It is important to understand how phases coexist , and what are the rules that governess their existence and number of variables required to define the state of mater present under defined conditions

Phase Equilibria and the Phase Rule

Phase rule:

- Phase is a homogeneous, physically distinct portion of a system that is separated from other portions of the system by bounding surfaces
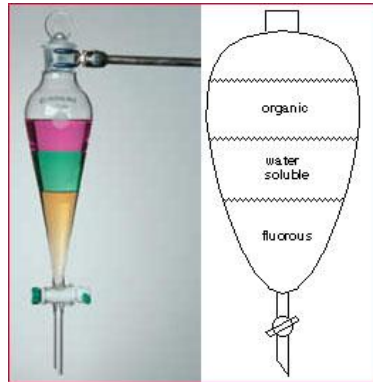
- Phases coexistence can only occur over a limited range. For example, ice does not last as long in boiling water as it does in cold water.

- Examples of phases coexistence:

1) The mixture of ice and water = have two phase which is solid and liquid

2) The mixture of oxygen gas and nitrogen gas = have one phase which is gas phase (the system is homogeneous)

3) The mixture of oil and water = have 2 same phase (liquid). Oil and water are not homogeneous and have the boundaries to separate both phase

Number of components

The number of components of a system is the number of constituents expressed in the form of a chemical formula.

For example in the 3-phase system ice, water, water vapour, the no of components is 1, since each phase is expressed as H20.

A mixture of salt and water is a 2 component system since both chemical species are independent but one phase .

Phase rule

- *Phase rule*, which is a relationship for determining the least number of independent variables (e.g., temperature, pressure, density, and concentration) that can be changed without changing the equilibrium state of the system

- i.e. The number of variables that may be changed independently without causing the appearance of a new phase or disappearance of an existing phase

- i.e. The *number of degrees of freedom* is the *least* number of intensive variables that must be fixed/known to describe the system completely

The Phase Rule

$F = C - P + 2$

- F : the number of degrees of freedom of the system (number of independent variables **(e.g. <u>temperature</u>, <u>pressure</u>, and <u>concentration</u>) that may affect the phase equilibrium**)

- C: number of components

- P: Number of phases

Systems Containing One Component

Consider a system containing one component, namely, water.

In the phase diagram of water, (the *P-T* (pressure–temperature) diagram):
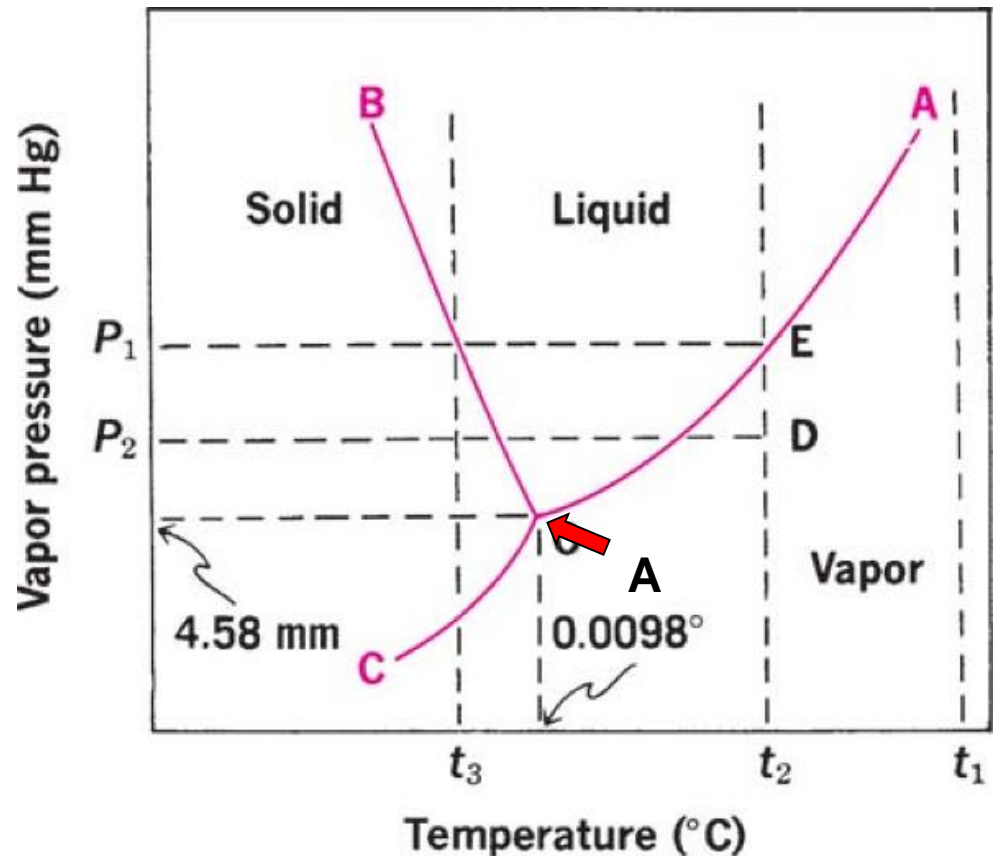
Phase diagram for water at moderate pressures.

Systems Containing One Component

The phase diagram for the ice-water-water vapour system

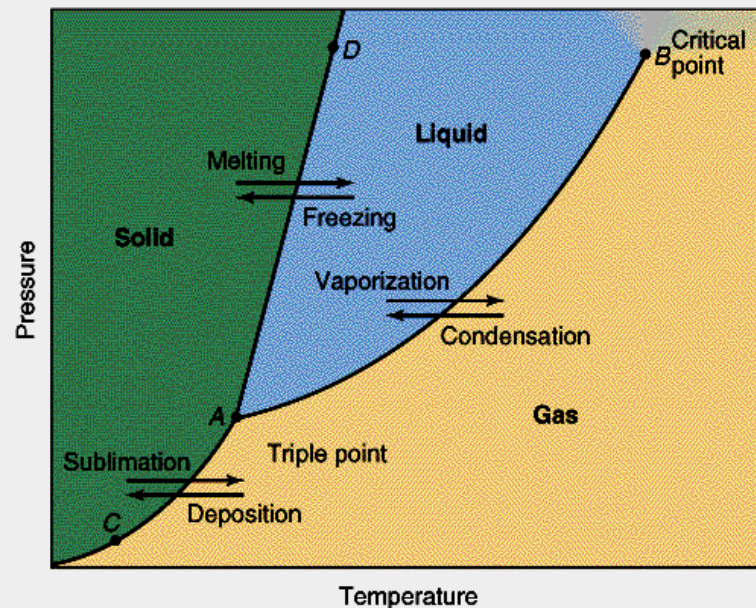**(phase diagram = graphical representation which indicates the phase equilibrium)**

Each area correspond to a single phase.
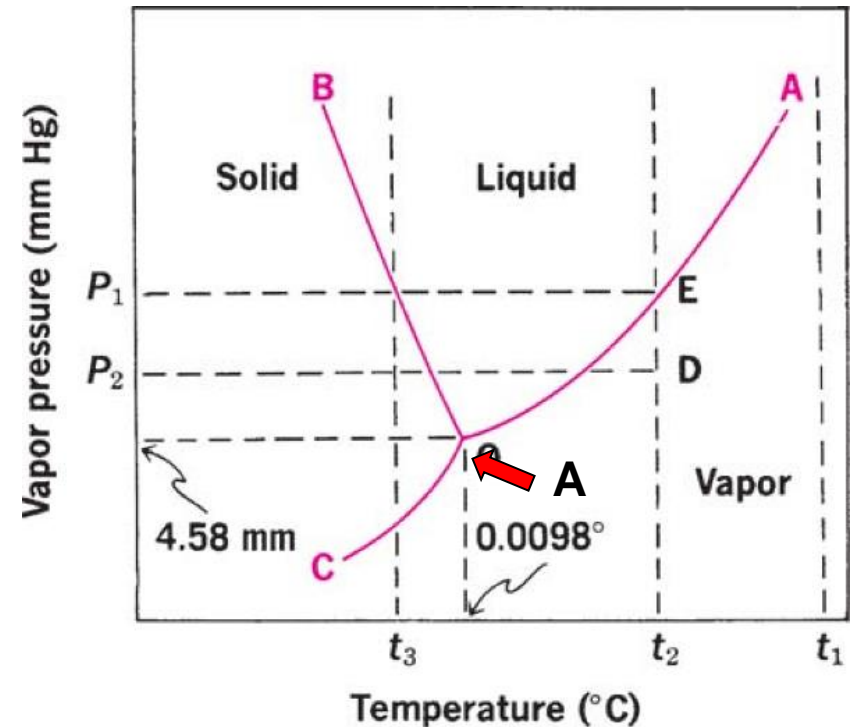**The number of degrees of freedom in each area is :**
F = C - P + 2
F = 1 – 1 +2 = 2

This means that temperature and pressure , volume and temperature , volume and pressure can be varied independently within these areas without change in number of phases

- For one phase (gas, liquid, or solid) we need to know two of the variables to define the system completely

- If the temperature of the gas is defined, it is necessary to know the pressure, or some other variable to define the system completely.

- No. of freedom = 2

- Example:
- water vapor confined (limited) to a particular volume.
- **F = C – P + 2**
- **F** = 1 - 1 + 2 = 2
- Using the phase rule only <u>two independent variables</u> are required to define the system.
- Because we need to know two of the variables to define the gaseous system completely, we say that the system has two degrees of freedom.

- **This means that temperature and pressure , volume and temperature , volume and pressure can be varied independently within these areas <u>without change in number of phases</u>**
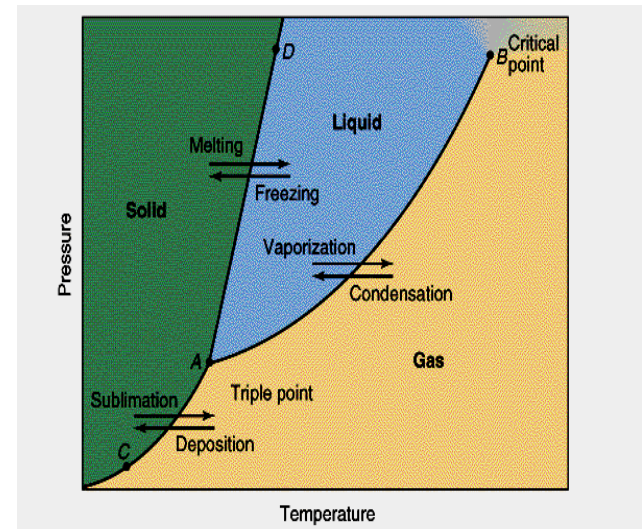
Equilibrium boundaries

For points that lie on one of the lines AB , AC, or AD, these lines form the boundaries between different phases

2 phases exist in equilibrium with each other.

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

1 variable exists when equilibrium is established between 2 phases.

➔ if the _pressure is altered_ _the temperature will change to assume a particular value_ and vice versa

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- **Independent variation will alter number of phases**

- **To keep the no. of phases constant P and T must be changed at the same time. By stating the temperature, we define the system completely**

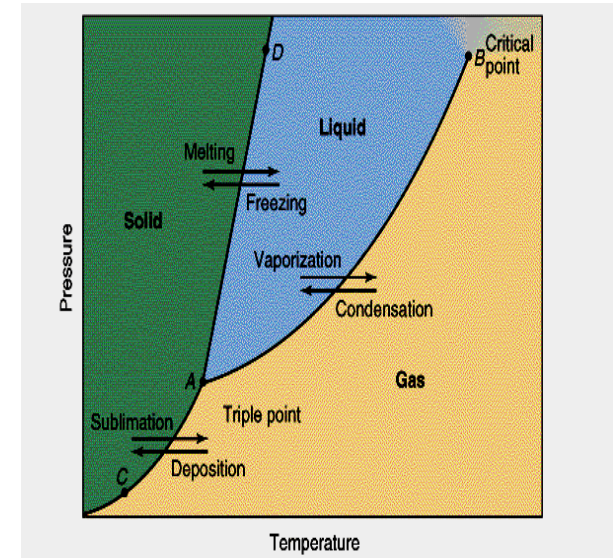- **Equilibrium boundaries represents**

⇨ **melting point**

⇨ **Freezing point**

⇨ **Vaporization point (Boiling point)**

⇨ **Condensation point**

⇨ **Sublimation point**

⇨ **Deposition point**

- **Independent variation will alter no. of phases**

- **To keep the equilibrium if P changed T must be changed at the same time**

- **By stating the temperature, we define the system completely**

- Example:
- Consider a system comprising a system comprising a liquid, water, in equilibrium with its vapor.
- **F** = 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. If we decide to work instead at a particular pressure, then the temperature of the system is automatically defined.
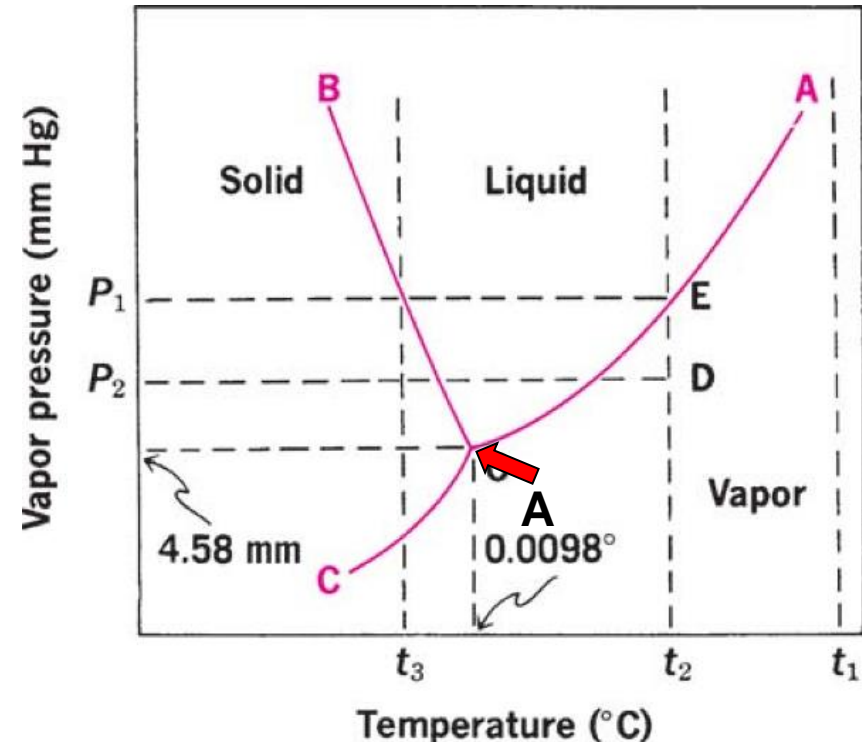
Triple Point

★The boundary lines meet at A, which is the only point in the diagram where 3 phases may coexist in equilibrium and it is therefore termed a triple point.

★**F = 1 – 3 + 2 = 0**

The system is <u>invariant;</u> i.e., any change in P or T will result in an alteration of the number of phases that are present.
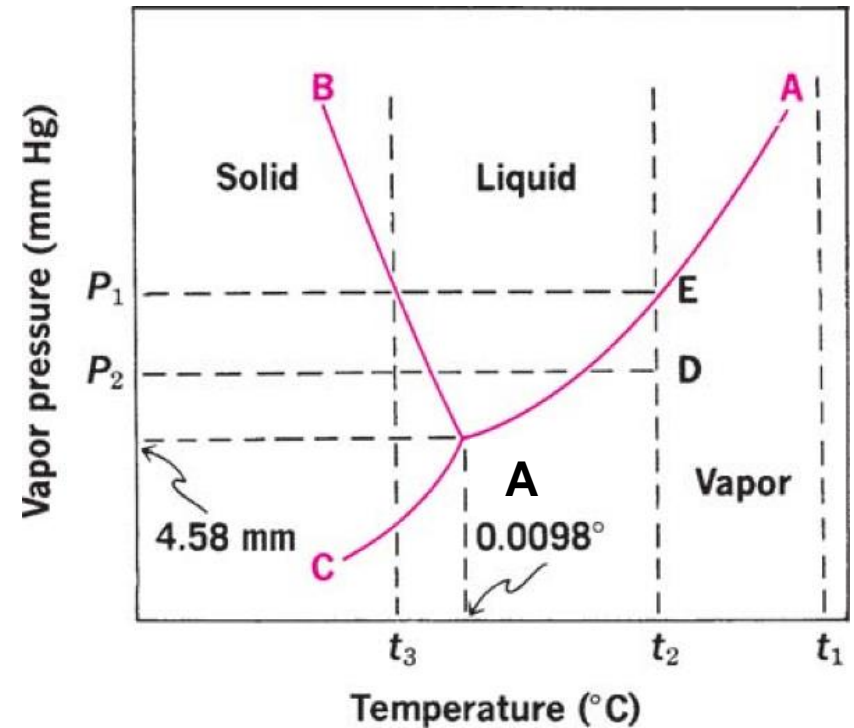
T = 0.0098°C
P = 4.58 mmHg

- Suppose we cool liquid water and its vapor until a third phase (ice) separates out.

- If we attempt to vary the particular conditions of temperature or pressure necessary to maintain this system, we will lose a phase.

- If we prepare the three-phase system of ice–water–vapor, we have no choice as to the temperature or pressure; the combination is fixed and unique. This is the **critical point.** No. of freedom = 0

Application of the Phase Rule to Single-Component Systems

System	Number of Phases	Degrees of Freedom	Comments
Gas, liquid, or solid	1	$F = C - P + 2$ $= 1 - 1 + 2 = 2$	System is *bivariant* ($F = 2$) and lies anywhere within the area marked vapor, liquid, or solid in Figure 2-22. We must fix two variables, e.g., P_2 and t_2, to define system D.
Gas–liquid, liquid–solid, or gas–solid	2	$F = C - P + 2$ $= 1 - 2 + 2 = 1$	System is *univariant* ($F = 1$) and lies anywhere along a *line* between two-phase regions, i.e., AO, BO, or CO in Figure 2-22. We must fix one variable, e.g., either P_1 or t_2, to define system E.
Gas–liquid–solid	3	$F = C - P + 2$ $= 1 - 3 + 2 = 0$	System is *invariant* ($F = 0$) and can lie only at the *point* of intersection of the lines bounding the three-phase regions, i.e., point O in Figure 2-22.

- as the number of components increases, so do the required degrees of freedom needed to define the system.

- The greater the number of phases in equilibrium, the fewer are the degrees of freedom.

Systems Containing One Component

- Examples:
- Liquid water + vapor
- Liquid ethyl alcohol + vapor
- Liquid water + liquid ethyl alcohol + vapor mixture
- (*Note*: Ethyl alcohol and water are completely miscible both as vapors and liquids).
- Liquid water + liquid benzyl alcohol + vapor mixture
- *(Note*: Benzyl alcohol and water form two separate liquid phases and one vapor phase).
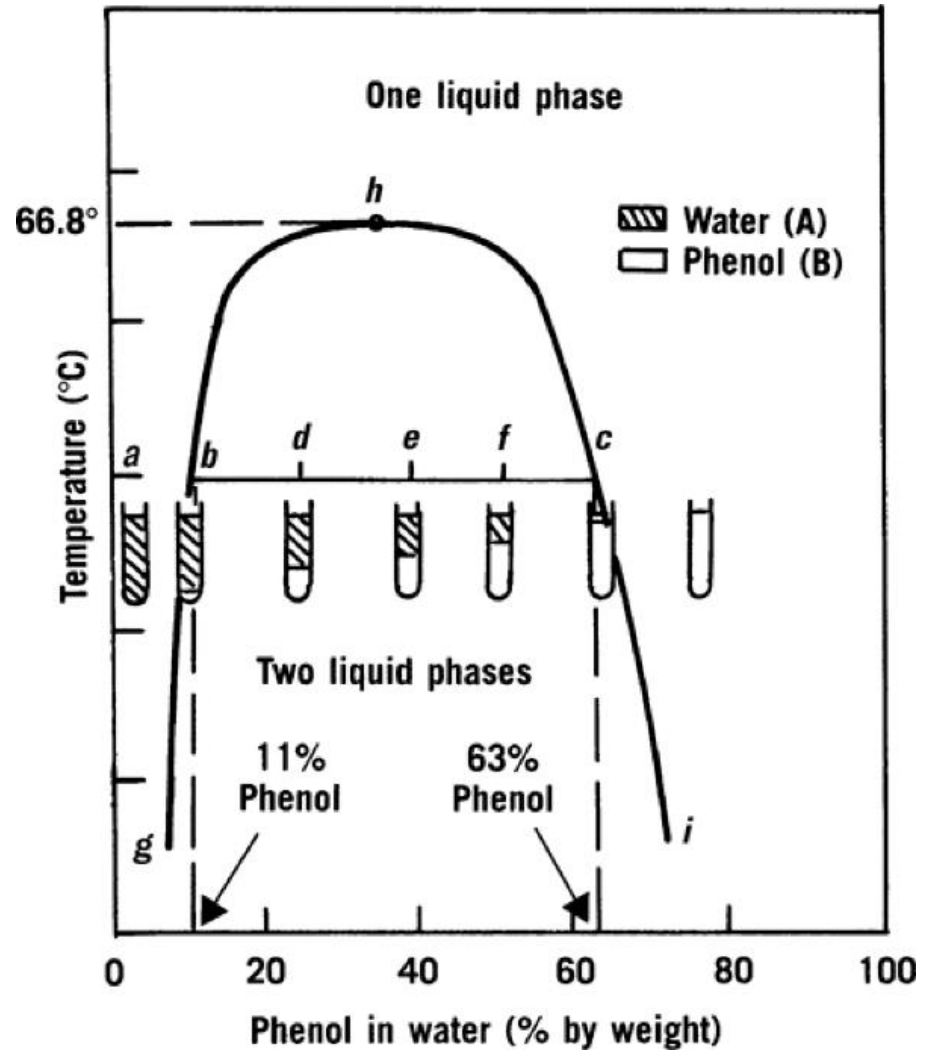
Two-Component Systems Containing Liquid Phases

- ethyl alcohol and water are <u>miscible</u> in all proportions.

- water and mercury are, for all practical purposes, completely <u>immiscible</u> regardless of the relative amounts of each present.

- Between these two extremes lies a whole range of systems that exhibit <u>partial miscibility</u> (or immiscibility).

- Phenol and water exhibit partial miscibility (or immiscibility).

- Curve *gbhci* shows the limits of temperature and concentration within which two liquid phases exist in equilibrium.

- The region outside this curve contains systems having but one liquid phase.
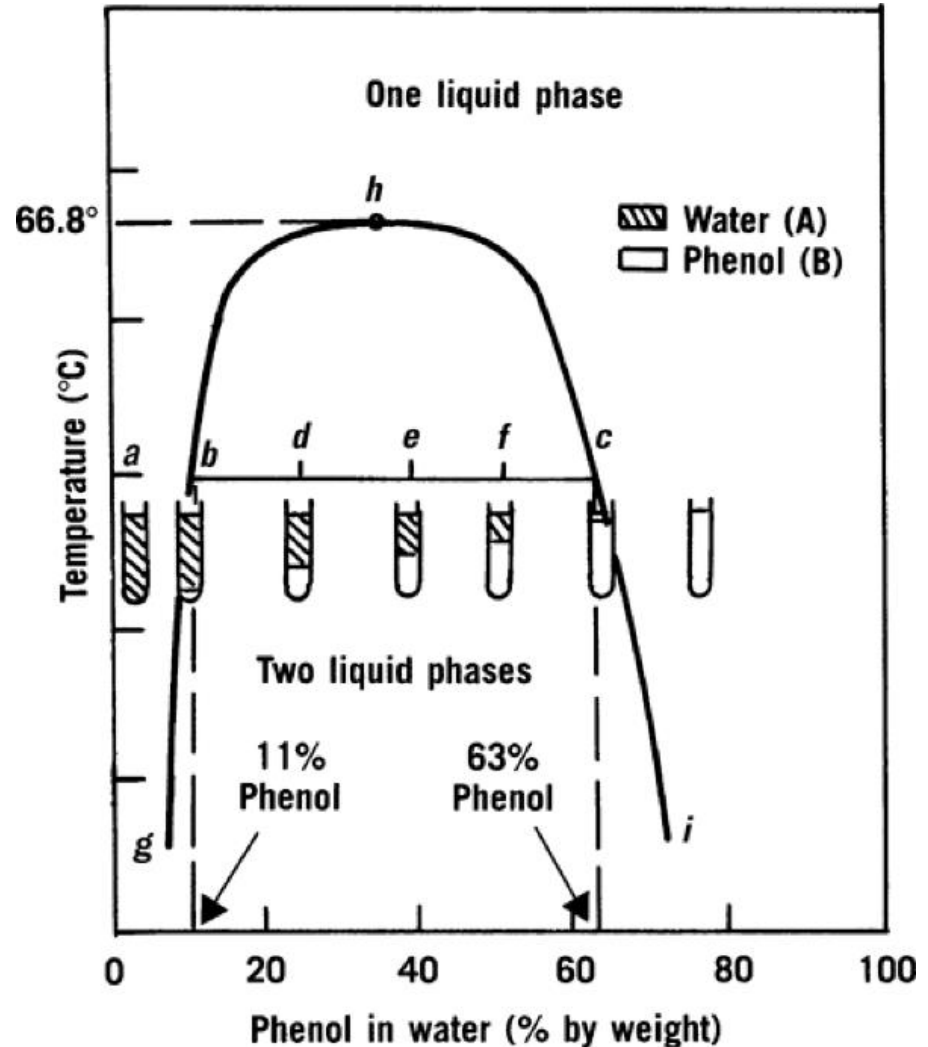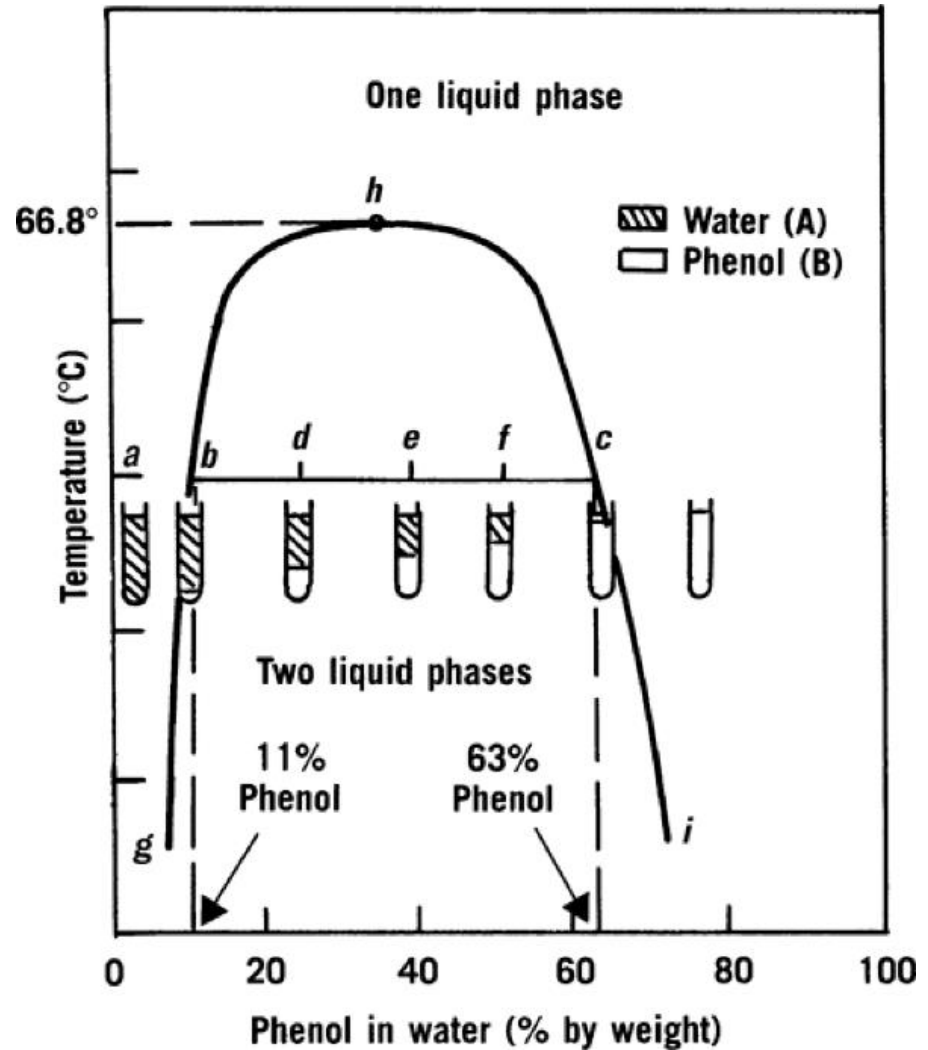
- Starting at the point *a*, equivalent to a system containing 100% water (i.e., pure water) at 50°C, adding known increments of phenol to a fixed weight of water, the whole being maintained at 50°C, will result in the formation of a single liquid phase until the point *b* is reached, at which point a minute amount of a second phase appears.

One liquid phase

66.8°

h

☒☒☒ Water (A)
☐ Phenol (B)

Temperature (°C)

a *b* *d* *e* *f* *c*

Two liquid phases

11% Phenol   63% Phenol

g   *i*

0   20   40   60   80   100
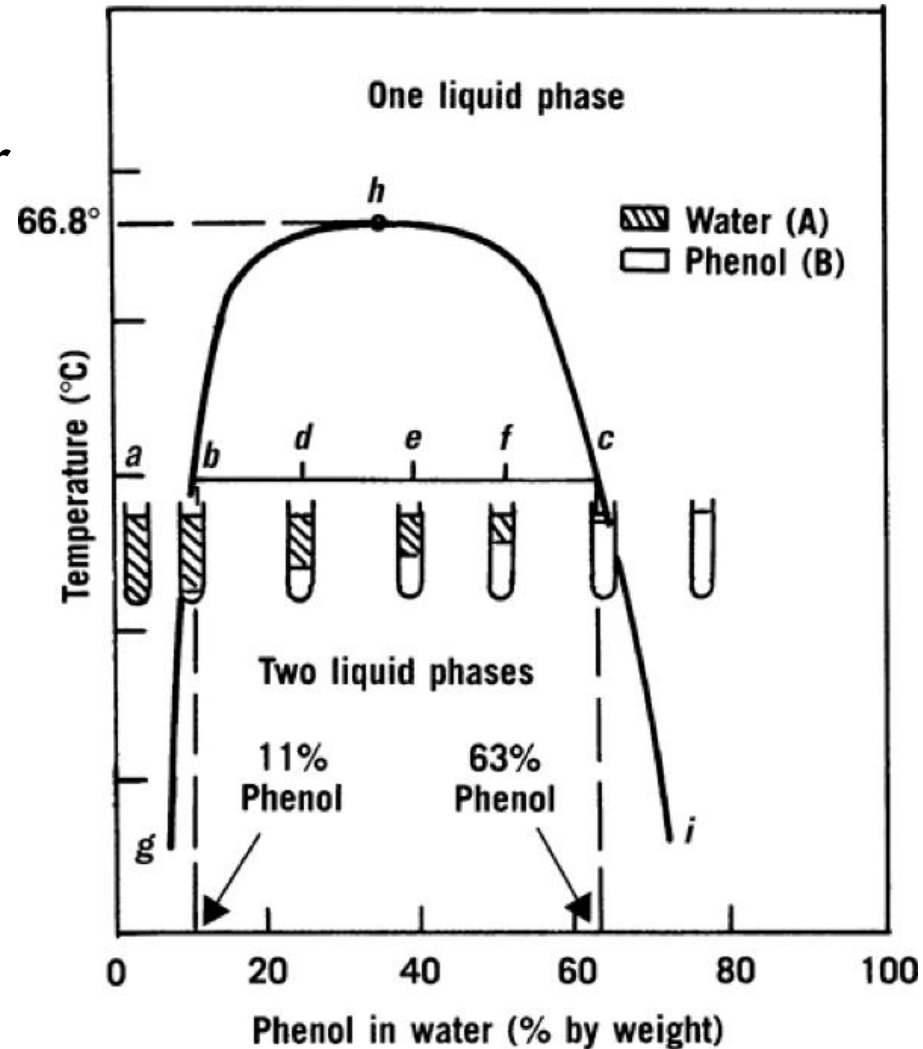
Phenol in water (% by weight)

- The concentration of phenol and water at which this occurs is 11% by weight of phenol in water. Analysis of the second phase, which separates out on the bottom, shows it to contain 63% by weight of phenol in water.

- This phenol-rich phase is denoted by the point c .

One liquid phase

66.8°

h

Water (A)
Phenol (B)

Temperature (°C)

a b d e f c

Two liquid phases

11% Phenol

63% Phenol

g

i

0   20   40   60   80   100

Phenol in water (% by weight)

- Mixtures (b to c) are containing increasing amounts of phenol. Thus, systems in which the amount of the phenol-rich phase (B) continually increases and the amount of the water-rich phase (A) decreases.

- Once the total concentration of phenol exceeds 63% at 50°C, a single phenol-rich liquid phase is formed.
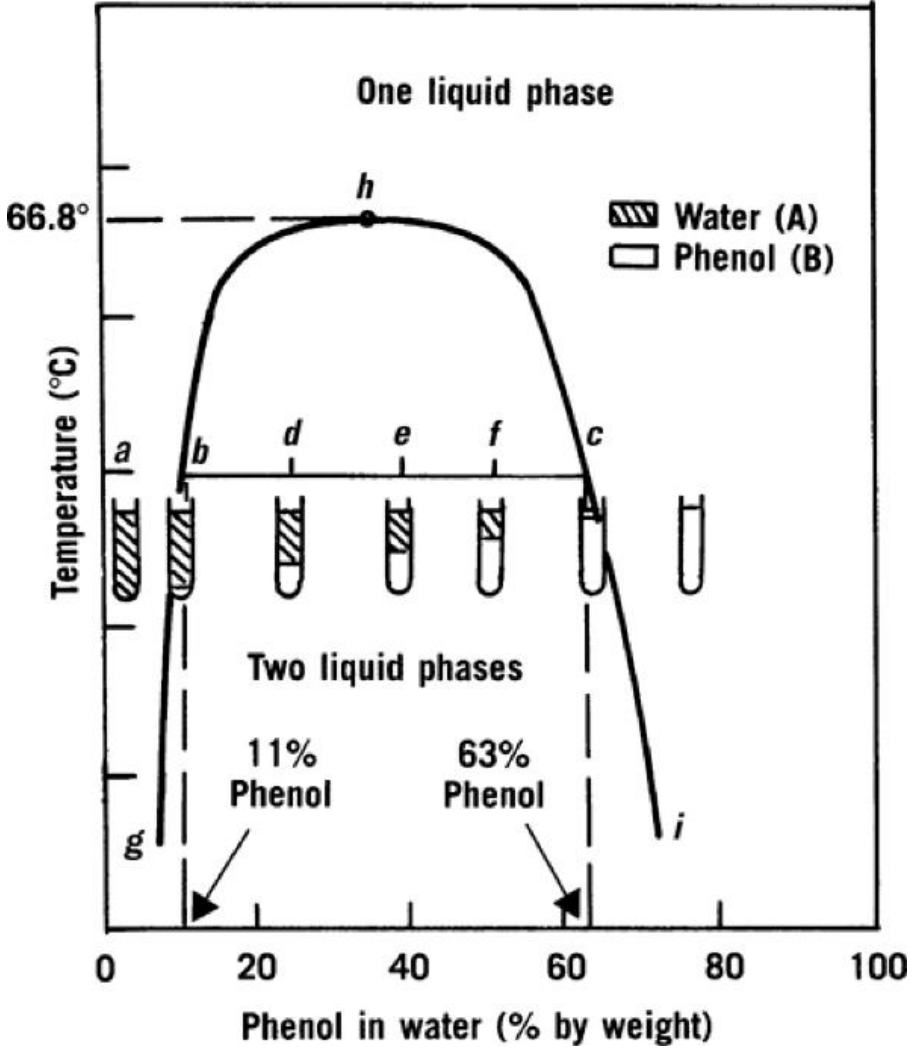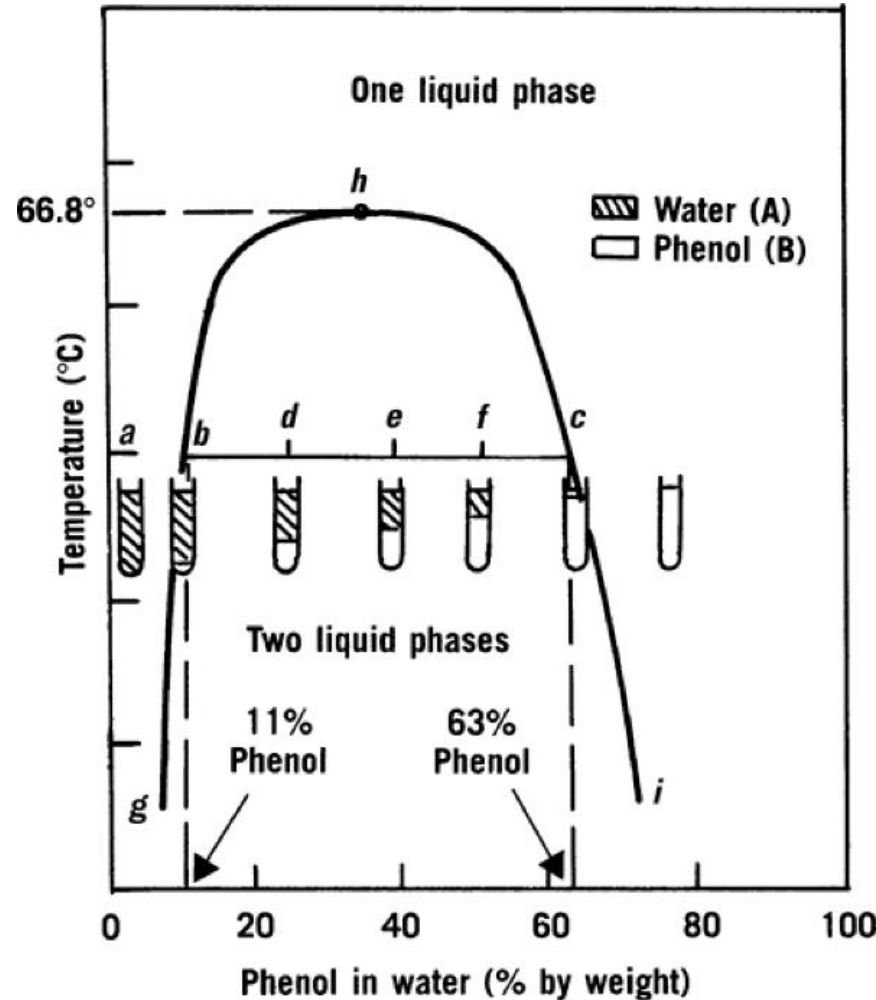
- The maximum temperature at which the two-phase region exists is termed the *critical solution*, or *upper consolute*, *temperature* (point *h)*

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

- The line *bc* drawn across the region containing two phases is termed a *tie line*.

One liquid phase

66.8°

Temperature (°C)

h

░░░ Water (A)
☐ Phenol (B)

a　*b*　　*d*　　*e*　　*f*　　　*c*

Two liquid phases

11% Phenol

63% Phenol

g

i

0　　20　　40　　60　　80　　100
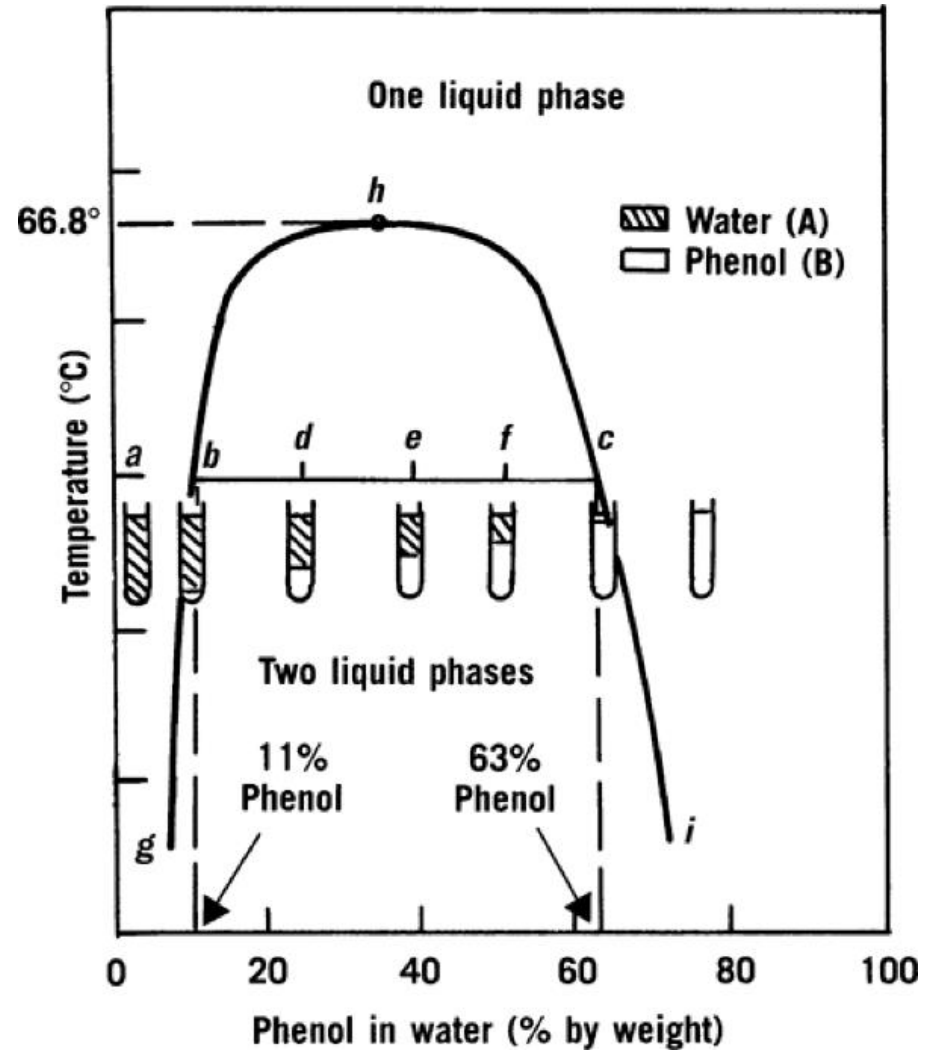
Phenol in water (% by weight)

- An important feature of phase diagrams is that all systems prepared on a tie line, at equilibrium, will separate into phases of constant composition.

- These phases are termed *conjugate phases*. For example, any system represented by a point on the line *bc* at 50°C separates to give a pair of conjugate phases whose compositions are *b* and *c*.
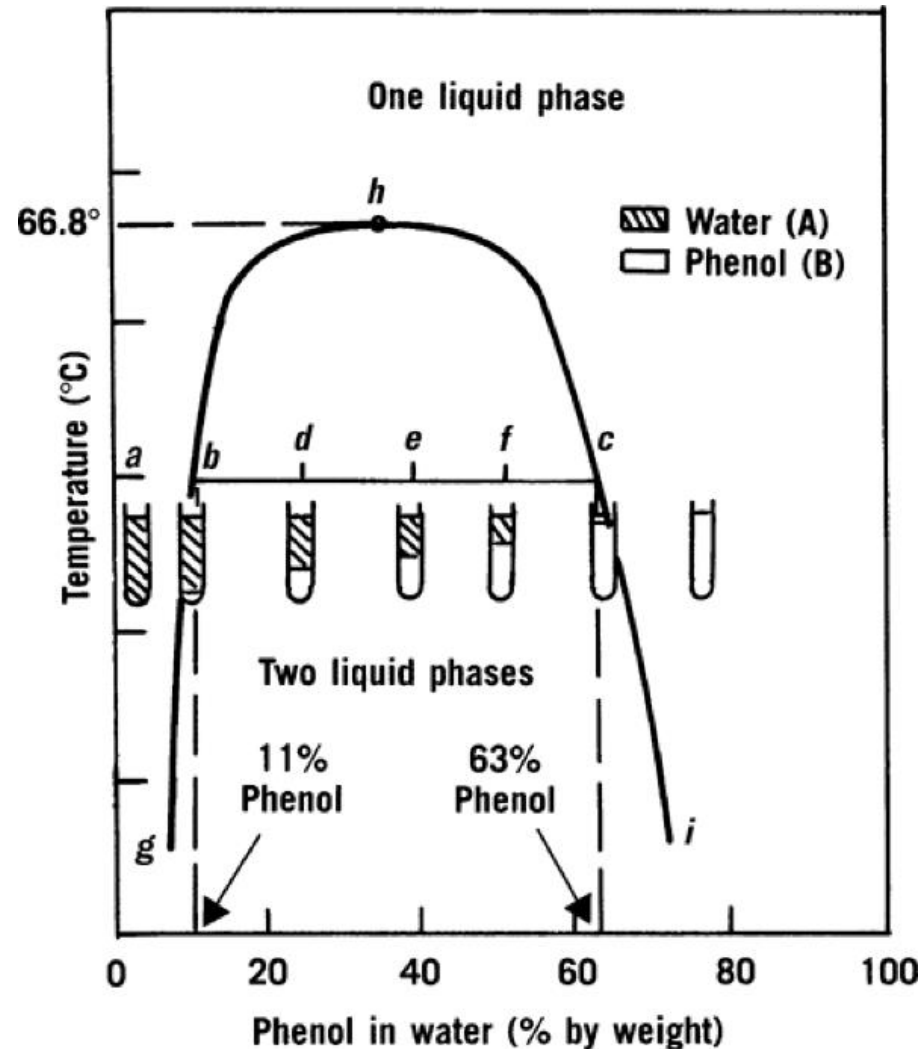
- **Applying the phase rule shows that with a two-component condensed system having one liquid phase, F = 3.**

- **Because the pressure is fixed, F is reduced to 2, and**
- **it is necessary to fix both temperature and concentration to define the system.**

- **When two liquid phases are present, F = 2; again, pressure is fixed. We need only define temperature to completely define the system because F is reduced to 1.**

One liquid phase

66.8°

h

Water (A)
Phenol (B)

a b   d   e   f   c

Two liquid phases

11% Phenol   63% Phenol

g   i

Temperature (°C)

0   20   40   60   80   100
Phenol in water (% by weight)

- It is seen that if the temperature is given, the compositions of the two phases are fixed by the points at the ends of the tie lines, for example, points *b* and *c* at 50°C.

- The compositions (relative amounts of phenol and water) of the two liquid layers are then calculated by the following method .

One liquid phase

66.8°

h

Water (A)
Phenol (B)

Temperature (°C)

a *b*   *d*   *e*   *f*   *c*

Two liquid phases

11% Phenol   63% Phenol

g   *i*

0   20   40   60   80   100

Phenol in water (% by weight)

Example 1:

- If we prepare a system containing 24% by weight of phenol and 76% by weight of water (point *d*), at equilibrium we have two liquid phases present in the tube.

- The upper one, A, has a composition of 11% phenol in water (point *b* on the diagram), whereas the lower layer, B, contains 63% phenol (point *c* on the diagram).
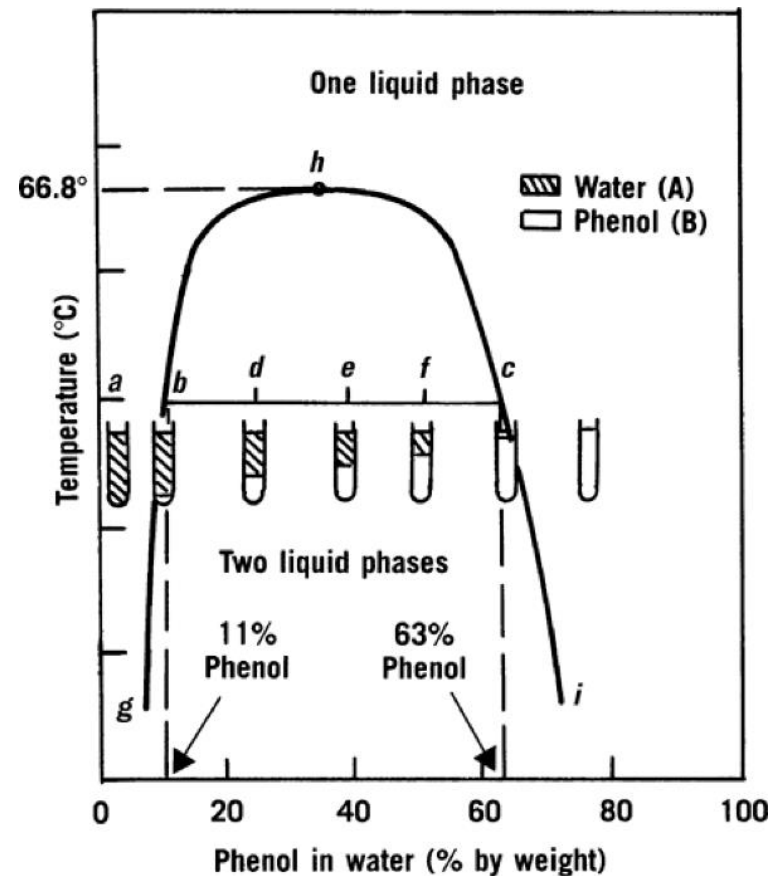

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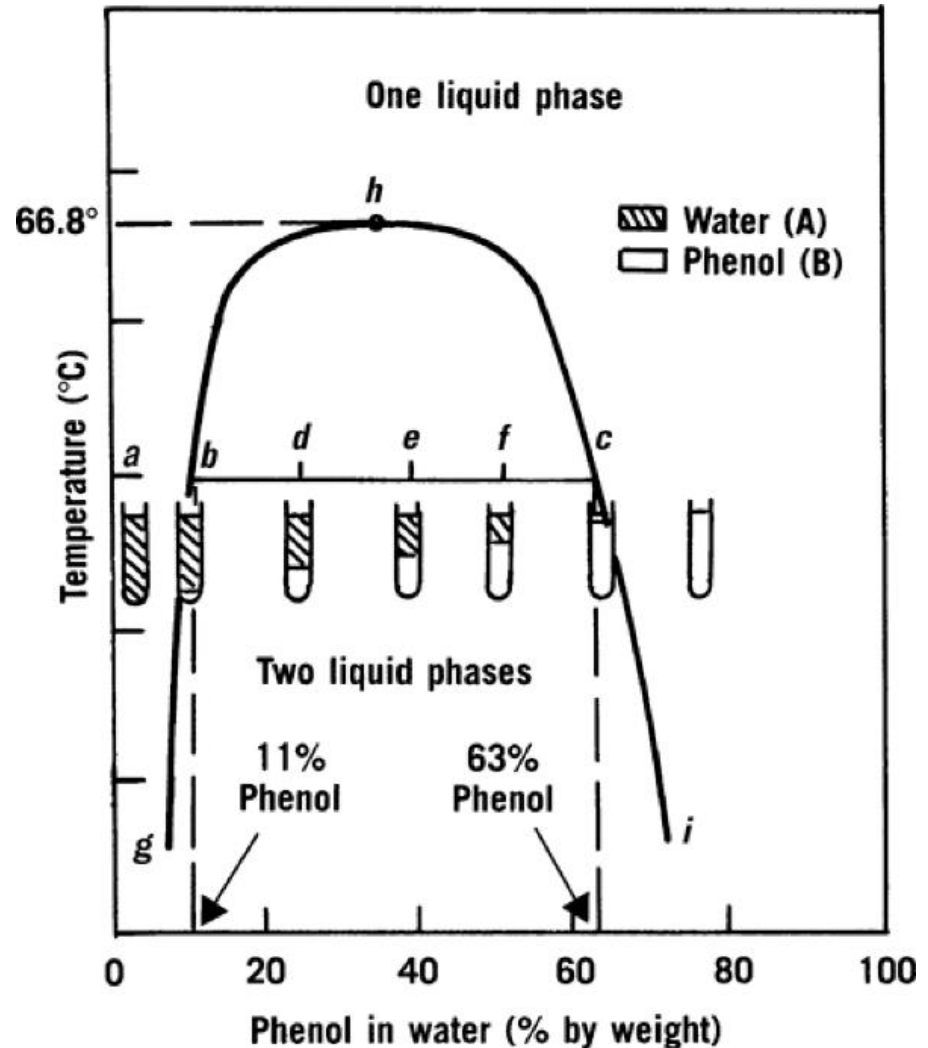
- Phase B will lie below phase A because it is rich in phenol, and phenol has a higher density than water.

- In terms of the relative weights of the two phases:

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

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


- point b = 11%,
- point c = 63%
- point d = 24%

- the ratio 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 and 2.5 g of phase B.

- Example 2:

- a system at 50°C containing 50% by weight of phenol (point f),

- the ratio of phase A to phase B is

  fc/bf = (63 - 50)/(50 - 11) = 13/39 = 1/3.

- for every 10 g of system f prepared, we obtain an equilibrium mixture of 2.5 g of phase A and 7.5 g of phase B.

- **The phase diagram is used in practice to formulate systems containing more than one component where it may be advantageous to achieve a single liquid-phase product.**

Phase diagram for the system triethylamine–water showing lower consolute temperature.
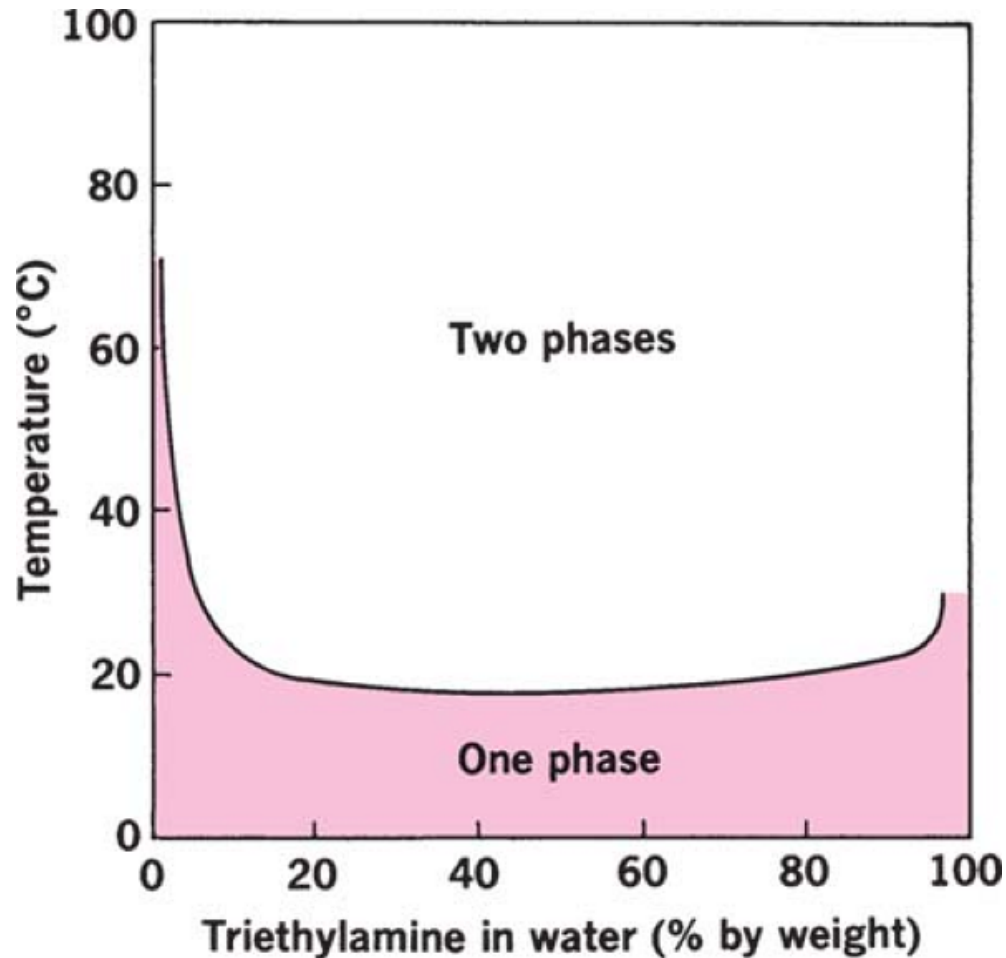
Nicotine–water system showing upper and lower consolute temperatures.
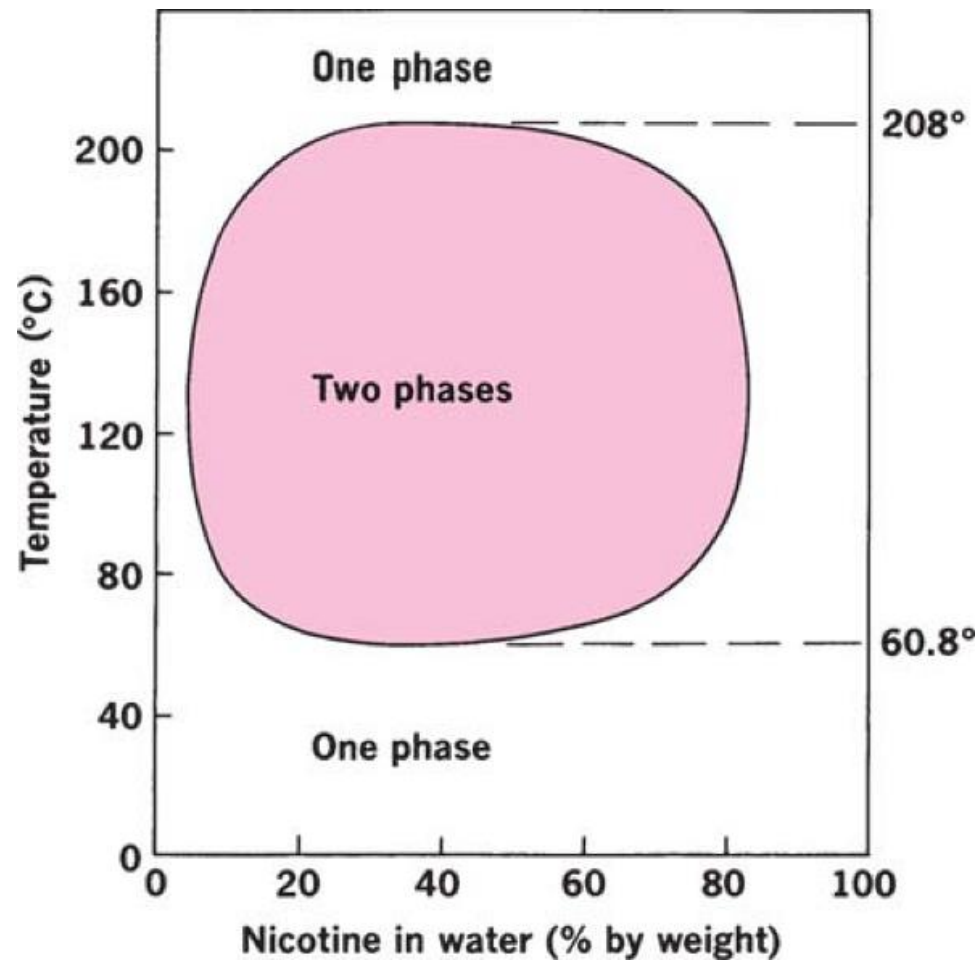
- ***Two-Component Systems Containing Solid and Liquid Phases: (Eutectic Mixtures)***

- We'll discuss solid–liquid mixtures in which the two components are completely miscible in the liquid state and completely immiscible as solids, that is, the solid phases that consist of pure crystalline components

- Examples of such systems are salol–thymol, salol–camphor, and acetaminophen–propyphenazone.

Two-Component Systems Containing Solid and Liquid Phases : Eutectic Mixtures

- solid–liquid mixtures in which the two components are completely miscible in the liquid state and completely immiscible as solids.

- Examples of such systems are:

- salol–thymol,

- salol–camphor,

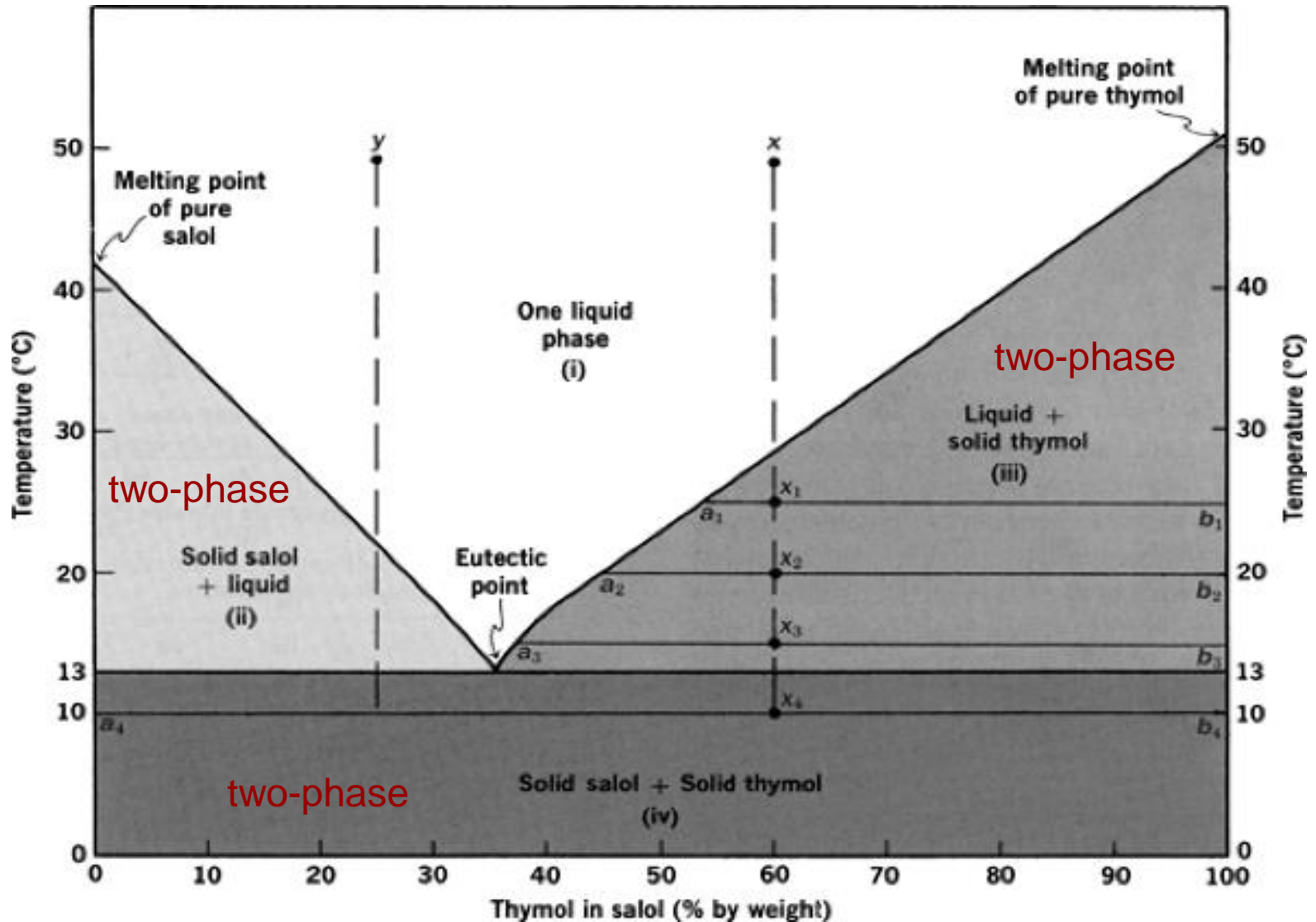- acetaminophen–propyphenazone.

thymol powder

solid salol

# Phase diagram for the thymol–salol system showing the eutectic point.

- there are four regions:
- (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.

- (iv) a region in which both components are present as pure solid phases.

- Those regions containing two phases (2, 3, and 4) are comparable to the two-phase region of the phenol–water system.

- Thus it is possible to calculate both the composition and relative amount of each phase from knowledge of the tie lines and the phase boundaries.
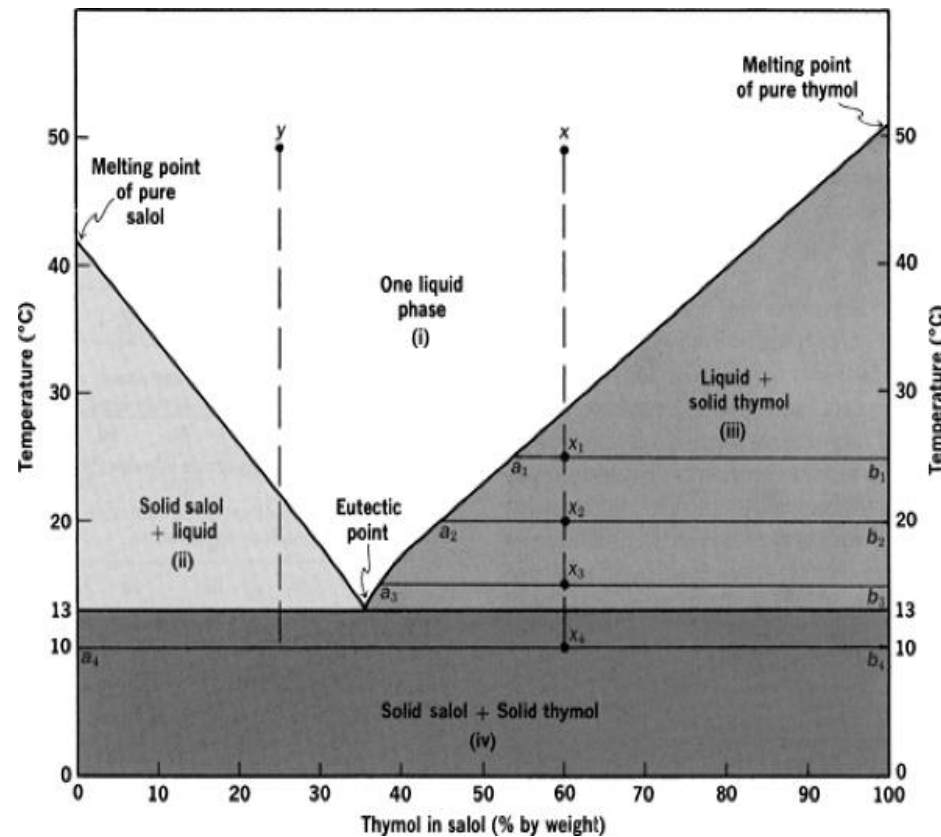
- Suppose we prepare a system containing 60% by weight of thymol in salol and raise the temperature of the mixture to 50°C. (point X)

- On cooling the system remains as a single liquid until the temperature falls to 29°C, at which point a minute amount of solid thymol separates out to form a two-phase solid–liquid system.
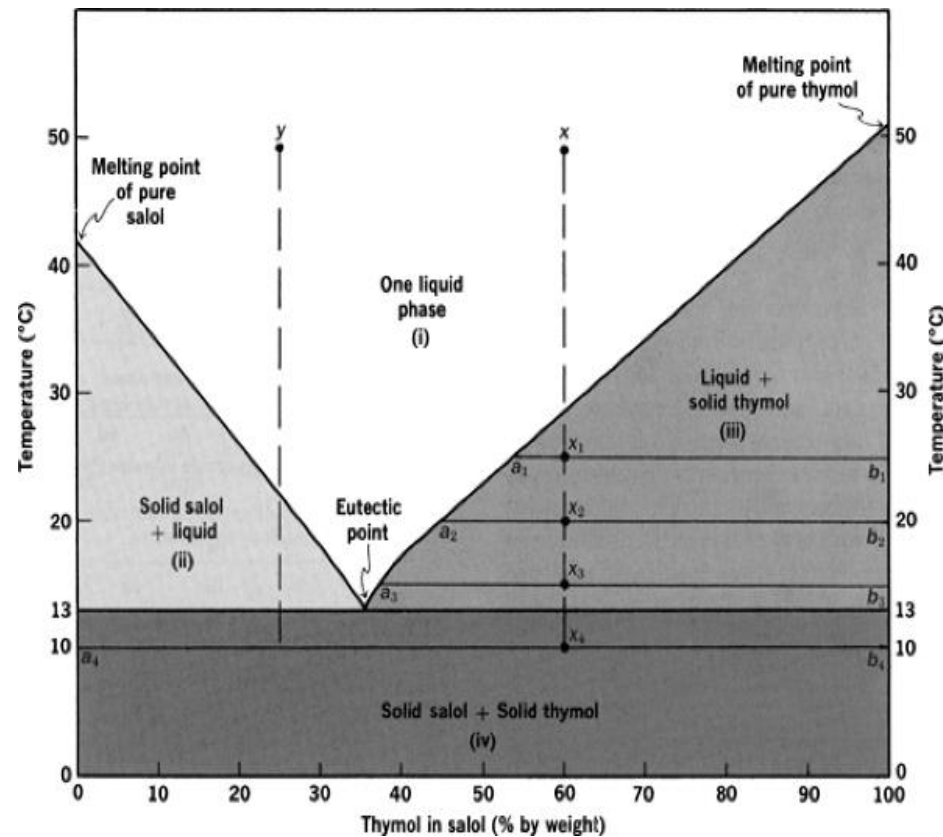
- As system *x* is progressively cooled, more and more of the thymol separates as solid.

- As system *y* is cooled the solid phase that separates at 22°C is pure salol.
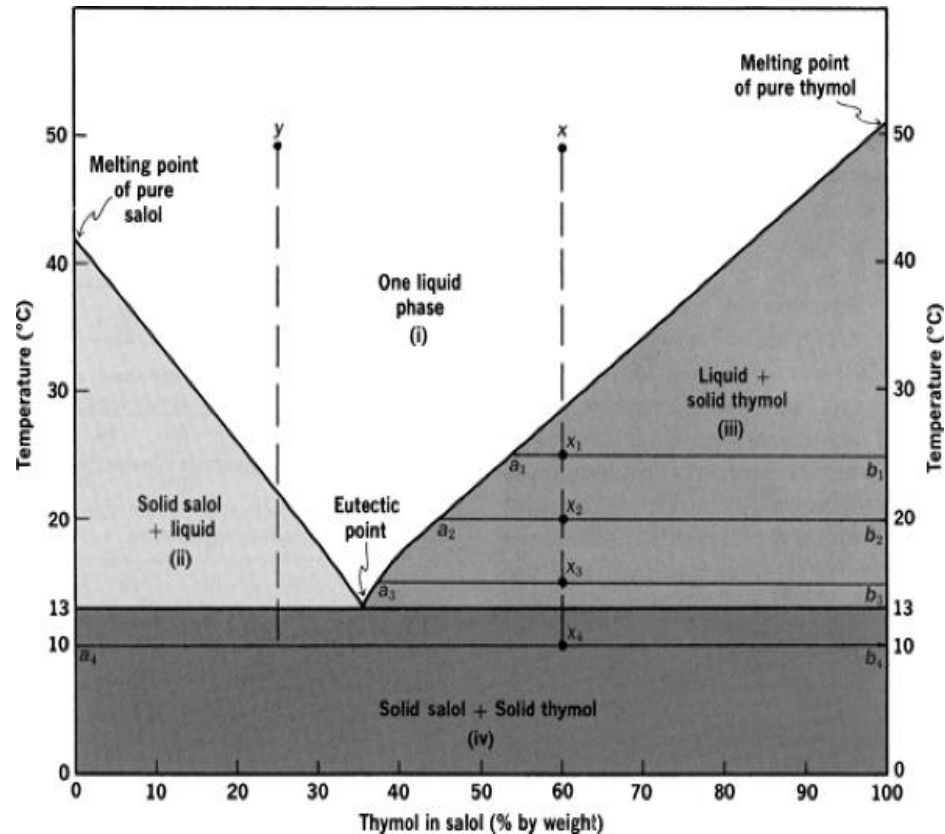
- The lowest temperature at which a liquid phase can exist in the salol–thymol system is 13°C, and this occurs in a mixture containing 34% thymol in salol.

- This point on the phase diagram is known as the *eutectic point*.

- At the eutectic point, three phases (liquid, solid salol, and solid thymol) coexist.

- The eutectic point denotes an invariant system because, in a condensed system,

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

- The eutectic point is the point at which the liquid and solid phases have the same composition (*the eutectic composition*). The solid phase is an intimate mixture of fine crystals of the two compounds.

Application of eutectic mixture

- Lidocaine and prilocaine, two local anesthetic agents, form a 1:1 mixture having a eutectic temperature of 18°C.

- The mixture is liquid at room temperature and forms a mixed local anesthetic that may be used for topical application.
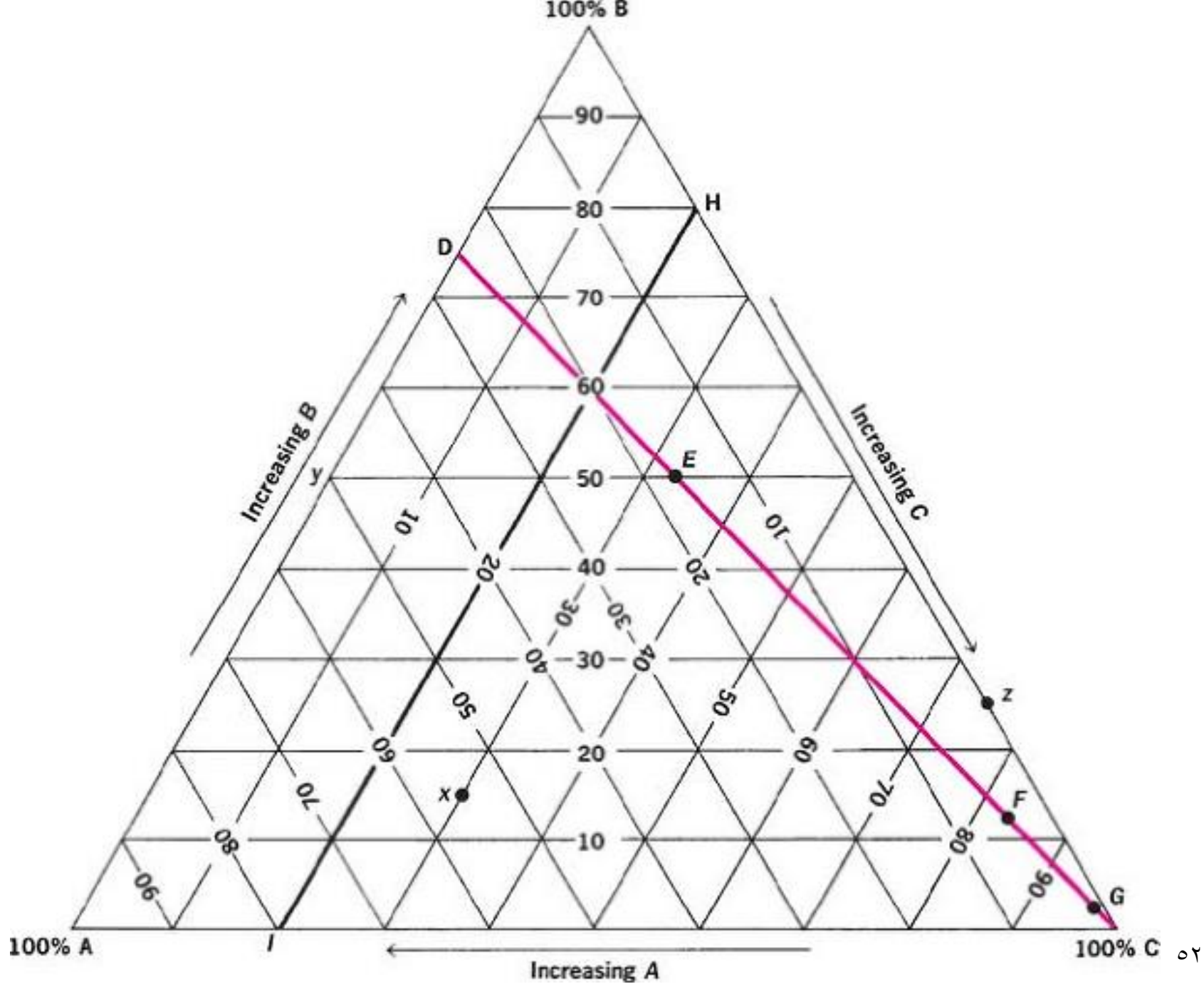
Three-Component Systems

- In systems containing three components but only one phase, **F** = 3 - 1 + 2 = 4 for a non-condensed system.

- The four degrees of freedom are 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 constant, then **F** = 2,

- Because we are dealing with a three-component system, it is more convenient to use triangular coordinate graphs,

- 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 concentrations in ternary systems are expressed on a weight basis.

- Each of the three corners of the triangle represent 100% by weight of one component (*A*, *B*, or *C*).

- that same apex will represent 0% of the other two components.

- Any line drawn parallel to one side of the triangle(for example, line *HI*) represents ternary system in which the proportion (or percent by weight) of *one* component is constant.

- In this instance, all systems prepared along *HI* will contain 20% of *C* and varying concentrations of *A* and *B*.

Ternary Systems with One Pair of Partially Miscible Liquids

- Water and benzene are miscible only to a slight extent, a mixture of the two 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.

- On the other hand, alcohol is completely miscible with both benzene and water.

- the 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.

B **Alcohol**

One liquid phase

d

e

i

Two liquid phases

h

Water *f*

g

Benzene

A *a* *b* *j* *c* **C**
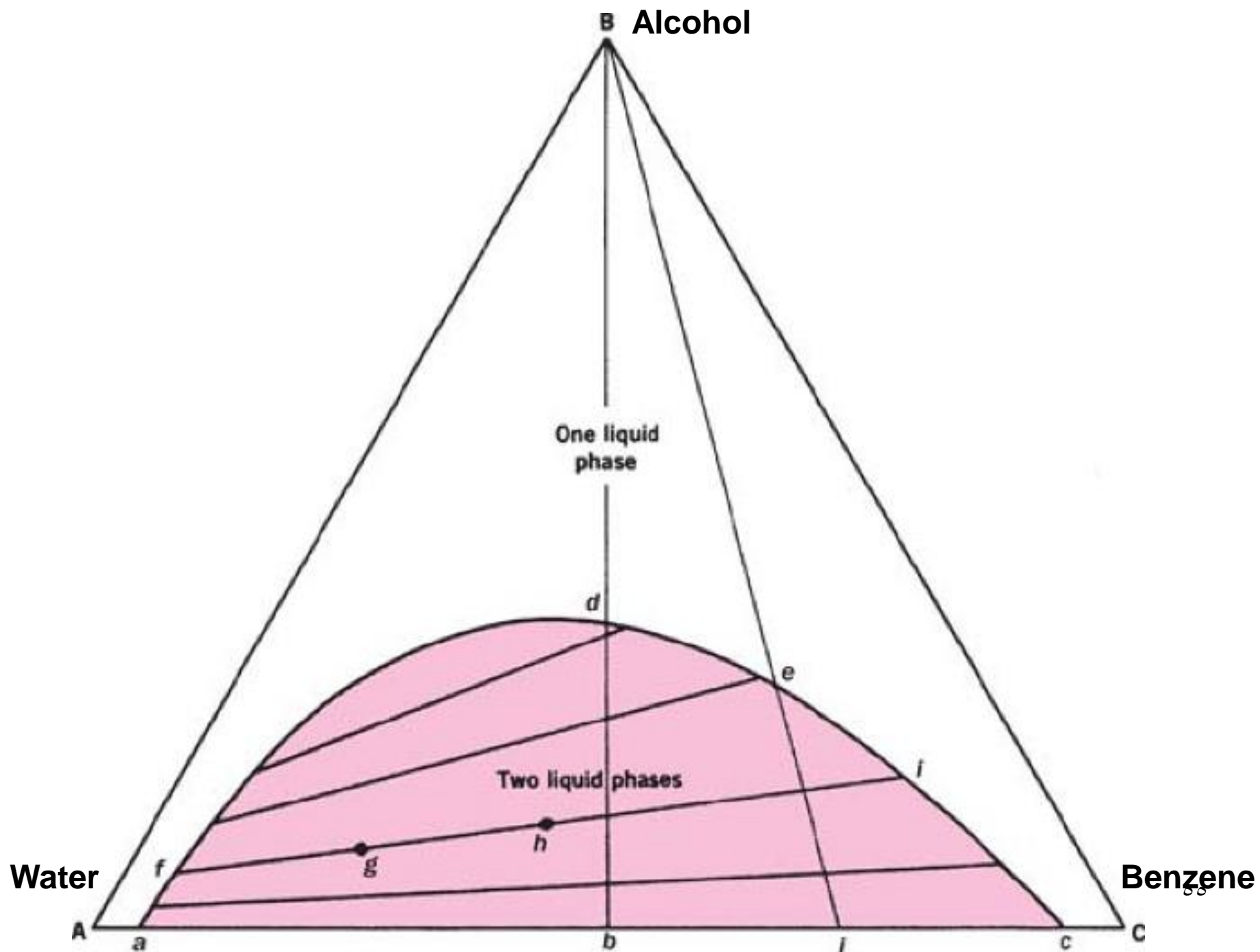
- The curve *afdeic*, (*binodal curve)*, marks the extent of the two-phase region.

- The remainder of the triangle contains one liquid phase.

- The tie lines within the binodal are not necessarily parallel to one another or to the base line, *AC*, as was the case in the two-phase region of binary systems.

- the directions of the tie lines are related to the shape of the binodal, which in turn depends on the relative solubility of the third component (in this case, alcohol) in the other two components.

- Only when the added component acts equally on the other two components to bring them into solution will the binodal be perfectly symmetric and the tie lines run parallel to the baseline.

Alterations of the binodal curves with changes in temperature

(a) (b) (c)