

MUNI
PHARM

Phase equilibria

Physical chemistry

Basic concepts

Phase equilibria - between two or more phases in a heterogeneous system (thermodynamic equilibrium).

Phase - homogeneous part of a heterogeneous system separated from other phases of the phase boundary, where the observed property step-changed.

Component - chemically pure substance (chemical entity - the element, compound).

Phase transition – process in which a certain quantity of a substance passes from one phase to another.

State variable - p , T , c (concentrations in multicomponent systems).

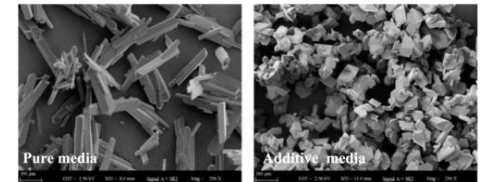
Degree of freedom of the system - number of state variables that can be changed while maintaining the phase equilibria.



ice- water

Basic concepts

| Type of phase transition | Name of action |
|-----------------------------------|------------------------|
| liquid → gas (vapor) | boiling |
| gas (vapor) → liquid | condensation |
| solid → liquid | melting |
| liquid → solid | solidification |
| solid → gas | sublimation |
| gas → solid | desublimation |
| crystal form → other crystal form | change in crystal form |

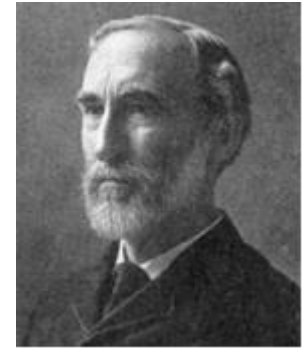


In multicomponent systems, more actions may take place. For example, in the phase transition gas – liquid: dissolving gas in liquid occurs, in the transition solid – liquid: dissolving the solids in a liquid. In multicomponent systems may occur transitions from one liquid phase to another liquid phase - extraction.

Phase

- (1) **Pure substances.** *It must be remembered that a phase may or may not be continuous.* Thus, whether ice is present in one block or many pieces, it is considered one phase.
- (2) **Mixtures of gases.** All gases mix freely to form homogeneous mixtures.
- (3) **Miscible liquids.** Two completely miscible liquids yield a uniform solution (e.g. a solution of ethanol and water is a 1-phase system in liquid phase).
- (4) **Non-miscible liquids.** A mixture of two non-miscible liquids on standing forms two separate layers (2-phase system in liquid phase).
- (5) **Solutions** (e.g. an aqueous solution of a solid substance is 1-phase system).
However, a saturated solutions 2-phase systems .
- (6) **Polymorphism.** By definition, **a phase must have throughout the same physical and chemical properties.** Thus mixture of two polymorph is a 2-phase system.
- (7) **A mixture of two or more chemical substances contains many phases.** Each of these substances having different physical and chemical properties makes a separate phase.
E.g. Decomposition of Calcium carbonate:
 $\text{CaCO}_3 \rightarrow \text{CaO} + \text{CO}_2$
(solid) (solid) (gas) There are two solid phases and one gas phase (3-phase system).

The Gibbs Phase Rule



Josiah Willard Gibbs

- allows to determine the number of degrees of freedom (F), i.e. the largest number of state variables (p, T, c) that can be varied simultaneously and arbitrarily without determining one another.

$$F = C - P + 2$$

F – number of degrees of freedom; C – number of components; P – number of phases

Sample Problems:

- gas-gas** $F = 2 - 1 + 2 = 3$ (variables T, p, concentration; to describe the system, you must specify all three variables)
- water-water vapor** $F = 1 - 2 + 2 = 1$ (variables T, p; to describe the system it is necessary to specify one variable, second variable is determined by the first)
- saturated solution NaCl** $F = 2 - 3 + 2 = 1$ (system is fully described by temperature; the other variables (vapor pressure and composition of the solution i.e. solubility) are determined by the temperature.)

One-component system

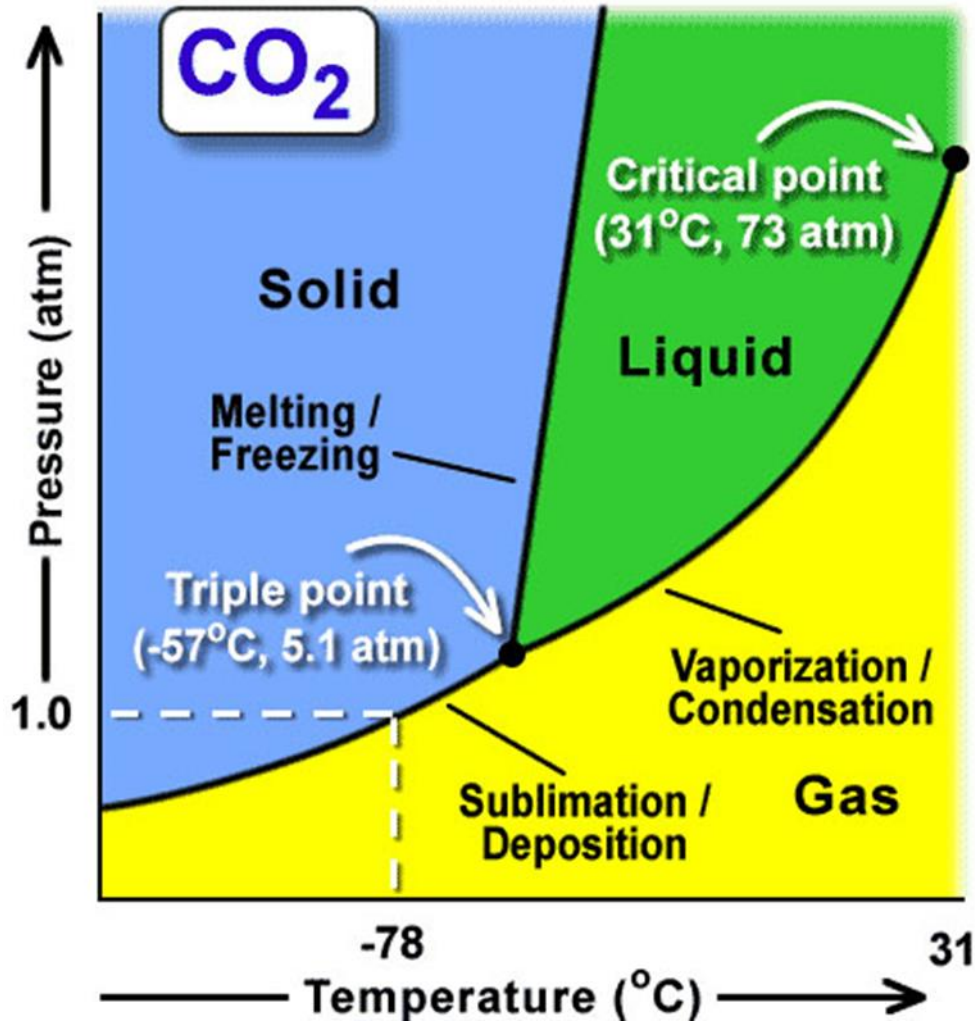
$$C = 1; F = C - P + 2; F = 3 - P$$

The number of phases in the one-component system cannot be greater than 3.

In one-component system three cases can occur :

- 1) system consists of one phase (e.g. gas) with 2 degrees of freedom (we can change 2 variables (p, T) independently without changing the number of phases)
- 2) system consists of 2 phases with 1 degree of freedom (one variable we can choose, second variable is determined by the first)
- 3) system consists of 3 phases and has no degree of freedom (we cannot arbitrarily choose any variable – triple point)

Phase equilibrium - one-component system



In the **triple point** the three phases coexist, the number of degrees of freedom = 0. The change in temperature or pressure will reduce the number of coexisting phases.

When the **critical temperature** is reached, the substance cannot exist in the liquid phase at any pressure (supercritical fluid).

Clausius–Clapeyron equation

$$\int_{p_1}^{p_2} d \ln p = \Delta H_{m,vap} / R \int_{T_1}^{T_2} dt / T^2 \quad - \textit{integral form}$$



Pressure cooker

$$\ln p_2 / p_1 = - \Delta H_{m,vap} / R \cdot (1/T_2 - 1/T_1)$$

- valid for small temperature differences ($\Delta H_{m,vap}$ is constant)
- with large temperature differences is $\Delta H_{m,vap}$ function of temperature: **Antoine's equation**: $\ln p = A - B / (T + C)$
(constants A, B, C are tabulated for a large set of substances)

- **equilibrium solid phase - vapor**

Instead of $\Delta H_{m,vap}$, sublimation enthalpy $\Delta H_{m,subl}$ is used in the equation.

- **equilibrium solid phase - liquid**

$$p_2 = p_1 + \Delta H_{m,melt} / \Delta V_{m,melt} \cdot \ln T_2 / T_1$$

Clausius–Clapeyron equation

Sample Problem

T_{melt} of water at normal pressure (101 325 Pa) 0°C. Melting enthalpy $\Delta H_{\text{melt}} = 6008 \text{ J/mol}$, molar volumes of liquid water and ice are $V_{\text{m}}^{(\text{l})} = 18.0 \text{ cm}^3/\text{mol}$ and $V_{\text{m}}^{(\text{s})} = 19.8 \text{ cm}^3/\text{mol}$.

Calculate the pressure at which the melting temperature of the water is -1°C (assuming that the melting enthalpy and molar volumes do not change with temperature).

$$p_2 = p_1 + \Delta H_{\text{melt}} / \Delta V_{\text{melt}} \times \ln T_2 / T_1$$

$$\Delta V_{\text{melt}} = 18.0 \times 10^{-6} - 19.8 \times 10^{-6} = -1.8 \times 10^{-6} \text{ m}^3/\text{mol}$$

$$p_2 = 101\,325 + [(6008 / -1.8 \cdot 10^{-6}) \times \ln (272.15/273.15)]$$

$$p_2 = 12.2 \times 10^6 \text{ Pa} = 12.2 \text{ MPa} (\approx 120 \text{ atm})$$

Two-component systems

$$C = 2; F = C - P + 2; F = 4 - P$$

- two-component system is able to form a maximum of 4 phases
- 4 cases may occur :
 - 1) components form one phase = 3 degrees of freedom (T, p, composition)
 - 2) components form two phases = 2 degrees of freedom (T and p or T and composition or p and composition can vary independently without equilibrium break)
 - 3) components form three phases = 1 degree of freedom (univariate)
 - 4) components form four phases = no degree of freedom (invariant)
- the maximum number of degrees of freedom is equal to 3 => three-dimensional phase diagrams
- one of the variables (p, T) is considered to be constant
 - p = const. – **isobaric diagrams** of two-component systems
 - T = const. – **isothermal diagrams** of two-component systems

Two-component systems

For a two-component system may occur in such cases:

- 1) equilibrium liquid - gas
- 2) equilibrium liquid - vapor
- 3) equilibrium liquid - liquid
- 4) equilibrium gas - solid
- 5) equilibrium liquid - solid

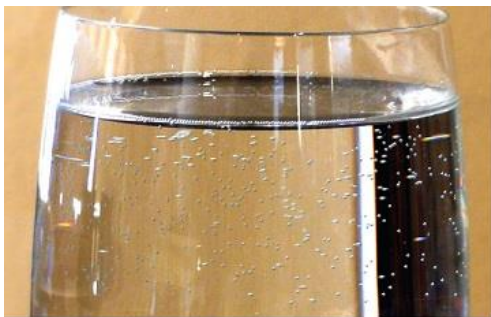
Two-component systems: liquid - gas

- Dissolving gas in liquid (2 degrees of freedom; the concentration of gas in solution is determined at a given T and p).
- Amount of gas dissolved at a given temperature in a liquid is directly proportional to gas pressure (Henry's law):

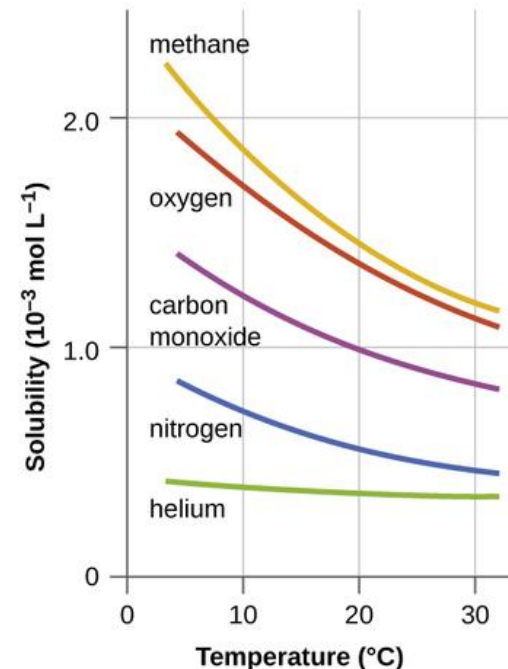
$$c = k_H \cdot p \quad k_H - \text{Henry's law constant}$$

valid at low concentrations, and if there is no reaction between gas and solvent.

- Gas solubility typically decreasing as temperature increases.

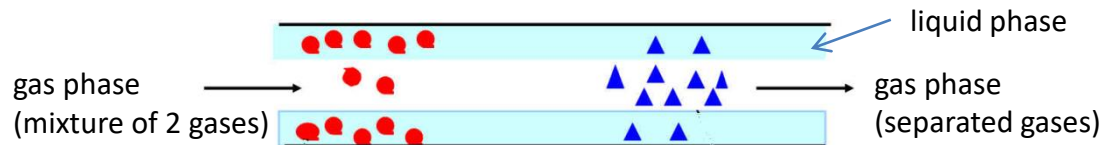


The small bubbles of air in this glass of chilled water formed when the water warmed to room temperature and the solubility of its dissolved air decreased.



Two-component systems: liquid - gas

- Mixture of gases – the content of the gases in the liquid phase differs from the composition of the gas phase (different k_H) - practical use in separation of the gaseous components (**gas chromatography**).



- Atmospheric pressure affects the dissolution of oxygen in the blood.
Acute mountain sickness: $pO_2 < 4.7 \text{ kPa}$ = brain disorders.
Max. height without breathing apparatus is 4 km.



O_2 poisoning during diving: $pO_2 > 220 \text{ kPa}$ = surfactant damage occurs in the lungs, convulsions and loss of consciousness.

Max. immersion depth when diving with compressed air is 100 m.



Two-component systems: liquid - vapor

- dependence between temperature, vapor pressure and composition of the liquid (description of distillation)

Partial pressures of saturated vapors of components of ideal mixture of two volatile fluids corresponds to the composition of the liquid mixture

- **Raoult's law** $p_A = x_A \cdot p_A^0$

p_A^0 – the vapor pressure of pure component A
 p_A – vapor pressure of component A above the solution

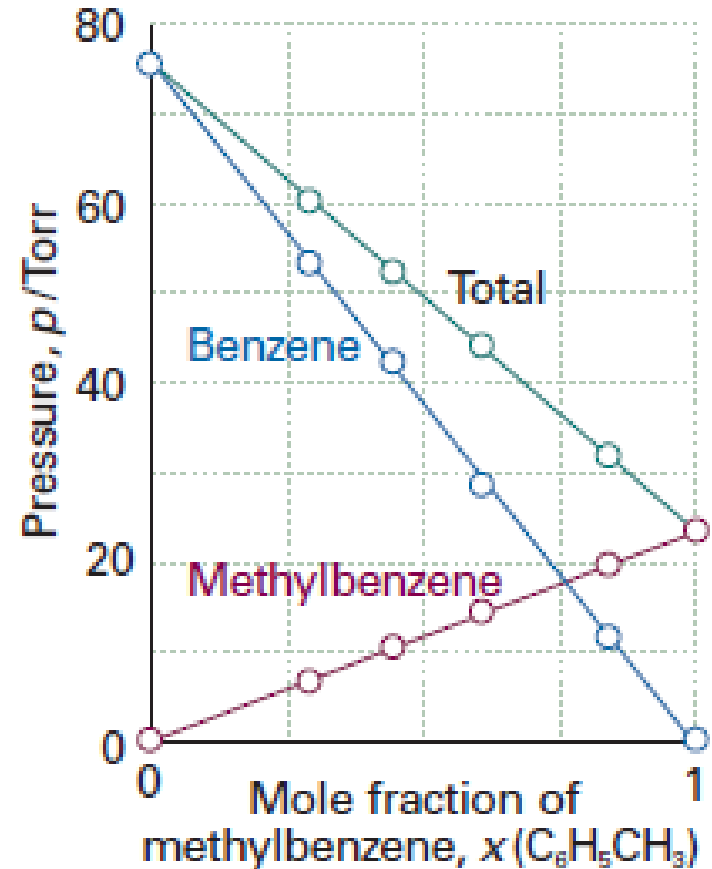
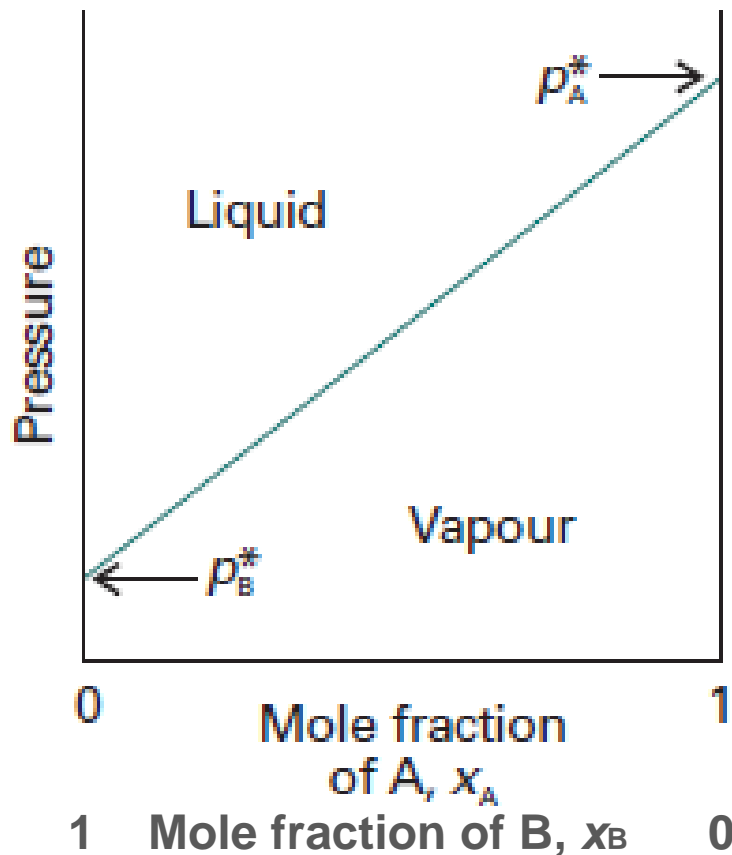
x_A – the mole fraction of component A in solution

- vapor pressure of the component above the solution is directly proportional to its amount in the solution (i.e. its molar fraction)
- the more of the component will be represented in a liquid solution, the greater the vapor pressure of this component above the solution

Graphical representation of Raoult's law (T = const.)

$$p = p_A + p_B$$

$$p_A = x_A \cdot p_A^0 \quad p_B = x_B \cdot p_B^0$$

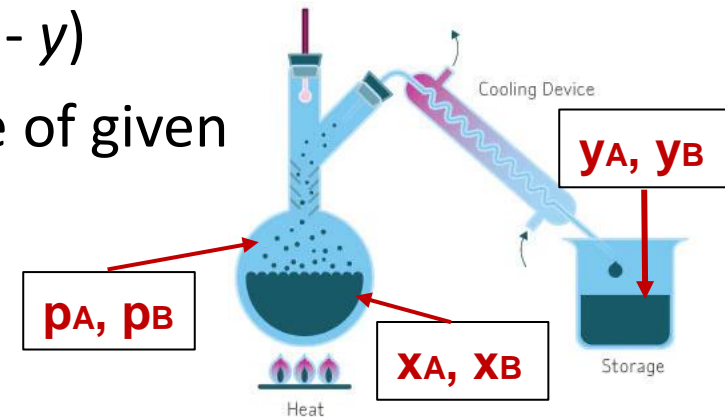


The composition of the gas phase (Raoult's law)

- gas phase composition (mole fraction - y) is expressed using the partial pressure of given substance and total pressure

$$y_A = p_A / p$$

$$y_B = p_B / p$$



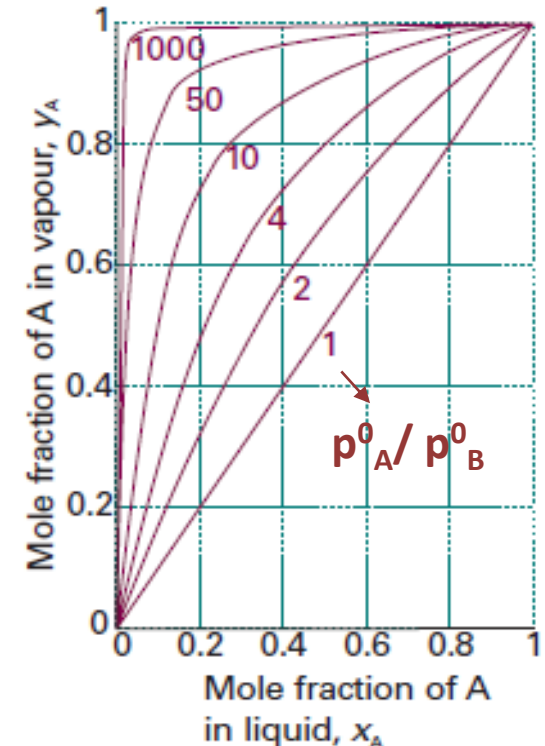
- for an ideal mixture of two components (A, B) is valid that their mole fractions in the gas phase can be expressed by the following relations:

$$y_A = p_A^0 \cdot x_A / (p_A + p_B)$$

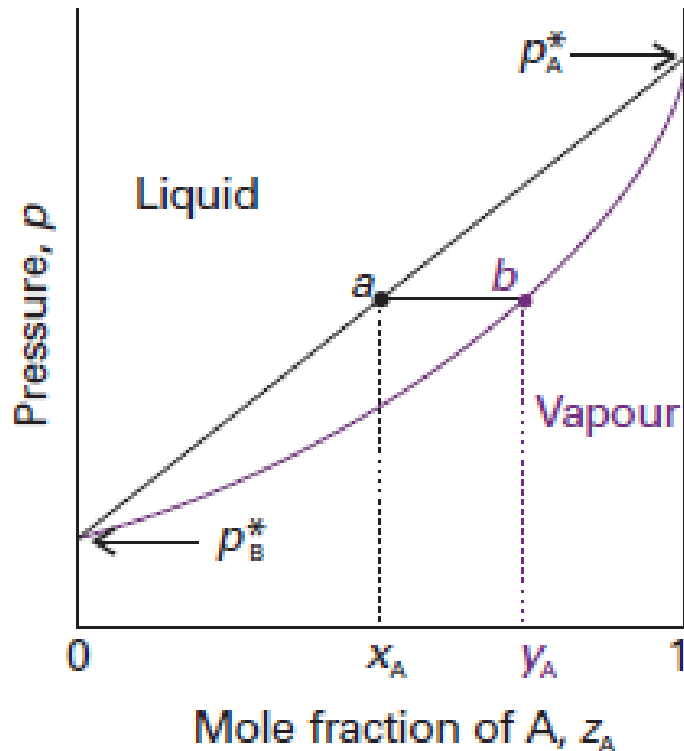
$$y_B = p_B^0 \cdot x_B / (p_A + p_B)$$

- in gas phase is more of the more volatile substance (thus having a lower boiling point or greater vapor pressure):

$$\text{separation factor} = p_A^0 / p_B^0$$



The composition of the gas phase (Raoult's law)



- point **a** indicates the vapor pressure of the mixture composition x_A and point **b** indicates the composition of the vapor

$$y_A = p_A / p$$

$$p = p_A + p_B$$

$$p_A = x_A * p_A^0$$

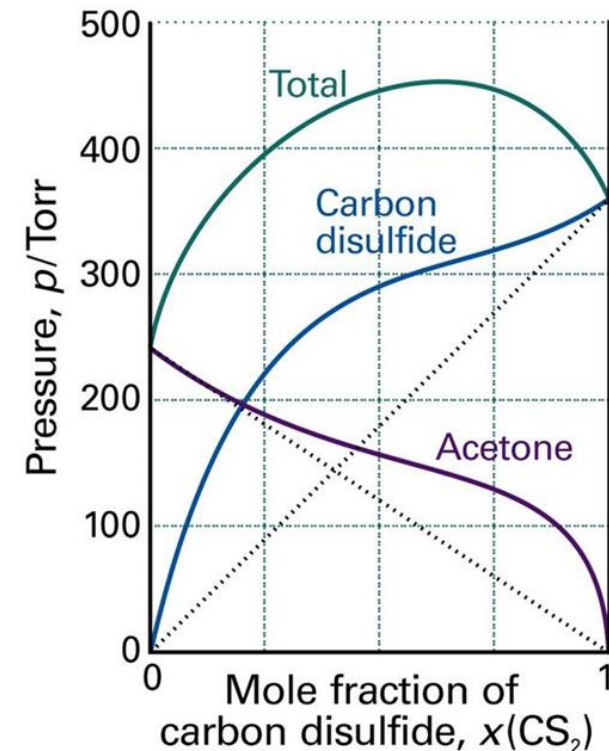
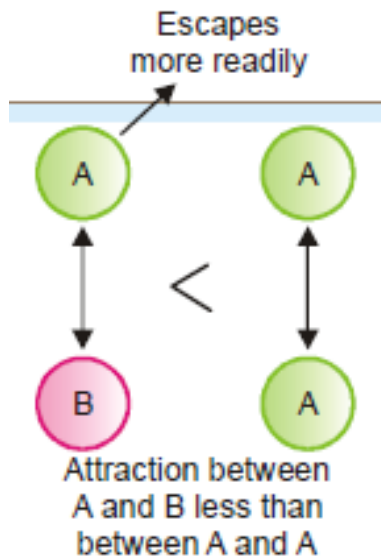
- if the composition of liquid is set by the value x_A then the composition of vapor is given by value y_A

Deviations from Raoult's law

- non-ideal behavior of liquids
- **positive deviation** from Raoult's law

The pressure above the solution is greater than calculated from RL (there is small interaction between different molecules in the mixture; components are easily separated from each other).

Above the solution, there is higher vapor pressure, the boiling point of the mixture occurs at a lower temperature.

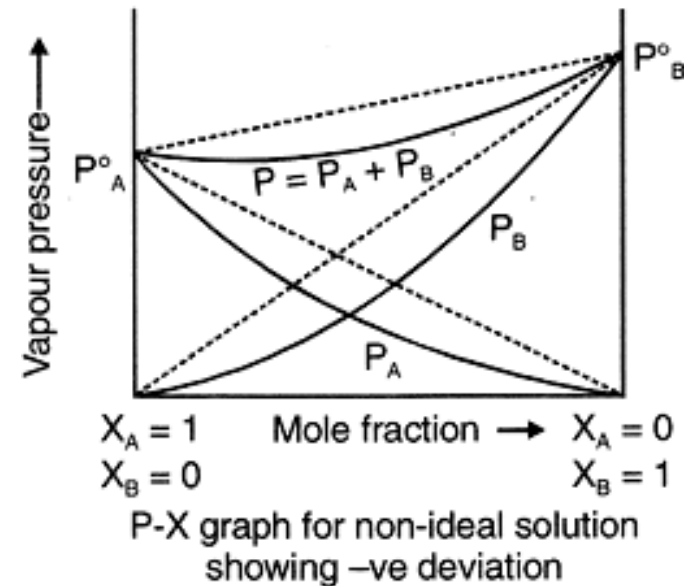
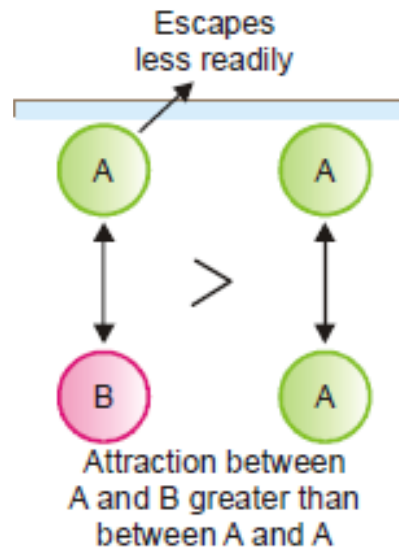


Deviations from Raoult's law

- non-ideal behavior of liquids
- **negative deviation** from Raoult's law

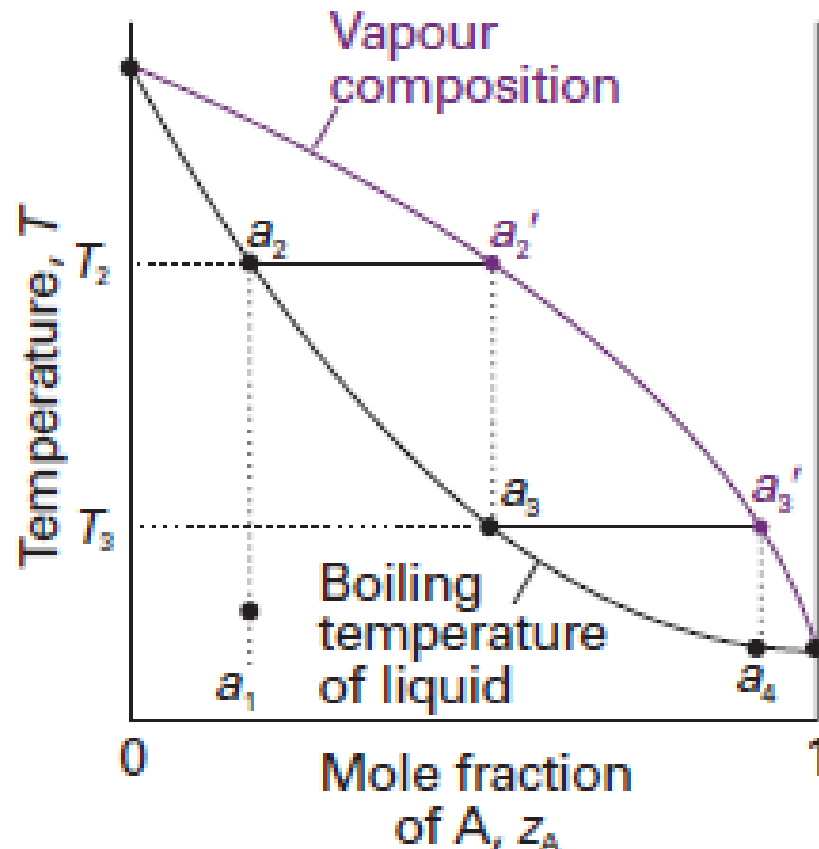
The pressure above the solution is lower than calculated from RL (molecules in the solution interact each other; components are worse separated from each other).

Above the solution, there is lower vapor pressure, the boiling point of the mixture occurs at a higher temperature.



Phase diagrams (isobaric)

- dependence of the boiling point of individual phases on their composition (at constant pressure)
- on the x-axis is plotted composition (mole fractions of the individual components) and on the y-axis is plotted temperature



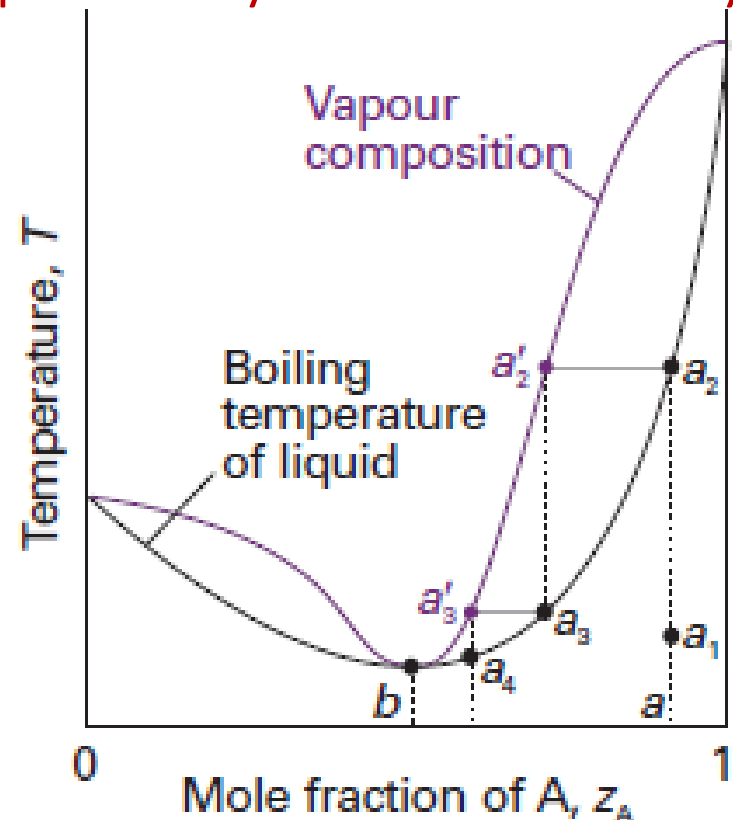
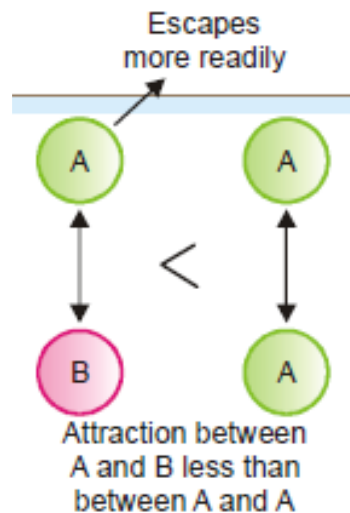
Deviations from Raoult's law

- **positive deviation** from Raoult's law

Above the solution, there is higher vapor pressure, the boiling point of the mixture occurs at a lower temperature.

Mixtures cannot be completely separated by distillation – they create **azeotrope**.

First fraction with the lowest boiling point will have a constant composition.



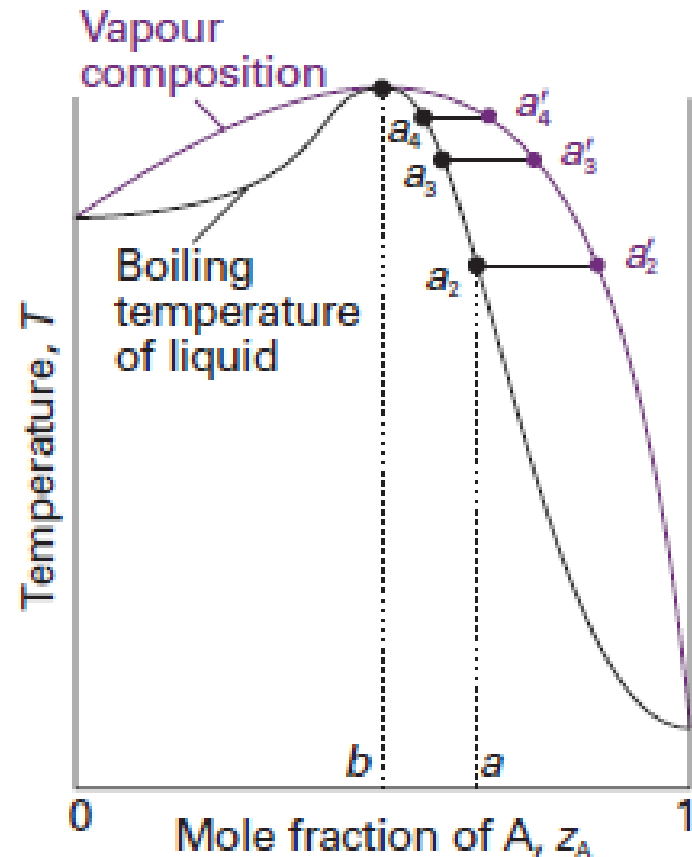
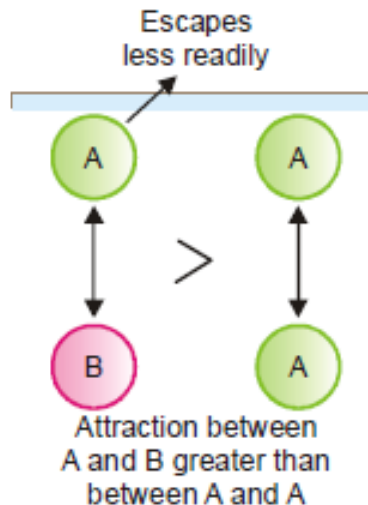
Deviations from Raoult's law

- **negative deviation** from Raoult's law

Above the solution, there is lower vapor pressure, the boiling point of the mixture occurs at a higher temperature.

Mixtures cannot be completely separated by distillation – they create **azeotrope**.

First fraction with the highest boiling point will have a constant composition.



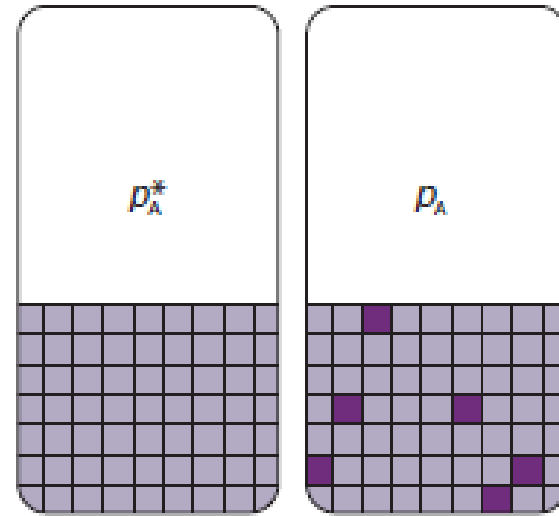
Effect of non-volatile substance on the vapor pressure and boiling point

Colligative properties (dilute solutions of non-volatile substances):

- Lowering the vapor pressure (Raoult's law)
- Elevation of the boiling point
- Depression of the freezing point
- Osmotic pressure

$$p_A = x_A \cdot p_A^* \quad (x_A + x_B = 1; x_A < 1)$$

$$p_A < p_A^* \quad \Rightarrow \quad T_b^{\text{solution}} > T_b^{\text{solvent}}$$



Ebulioscopy – determining the molecular weight of the solute from the difference in boiling point

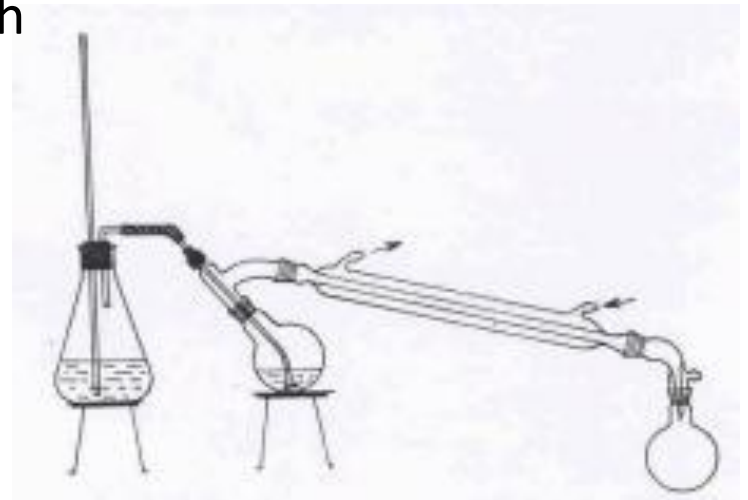
$$\Delta T = T_{b,\text{solution}} - T_{b,\text{solvent}} = K_b \cdot i \cdot m_{\text{solute}} / M_{\text{solute}} \cdot m_{\text{solvent}}$$

K_b – ebullioscopic constant ; i – van't Hoff's factor (actual number of particles in solution after dissociation)

Immiscible liquids

$p = p^0_A + p^0_B$ Dalton's Law

- total pressure above the solution is equal (the immiscible liquids) to the sum of in the vapor pressures above their pure solutions
- if the total vapor pressure above the solution (p) is equal to the ambient pressure, the boiling occurs
- mixture of immiscible liquids boils at a lower temperature than its individual components
- steam distillation (distillation of labile substances which have high boiling point)
- the distilled mixture is not miscible with water – easy separation after condensation



Two-component systems

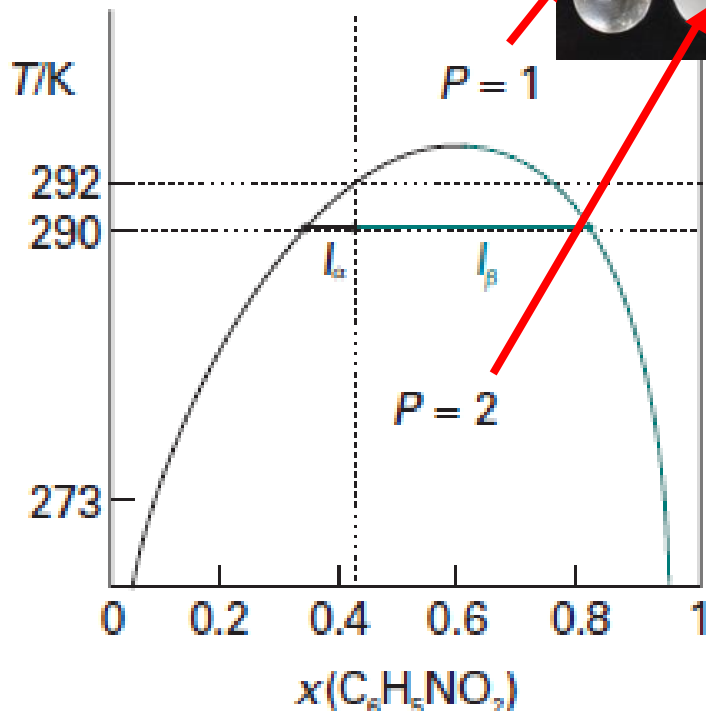
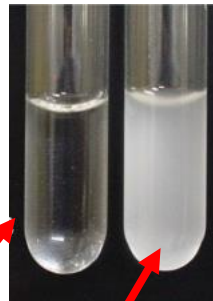
For a two-component system may occur in such cases:

- 1) equilibrium liquid – gas
- 2) equilibrium liquid - vapor
- 3) equilibrium liquid - liquid
- 4) equilibrium gas - solid
- 5) equilibrium liquid - solid

Two component systems: liquid - liquid

Phase diagrams of limited miscible liquids

- When liquids are mixing (whose mutual solubility is limited), two separate liquid phases are formed after exceeding the solubility of one liquid in the other.



The number of moles of individual coexisting phases can be expressed using the **lever rule**:

$$\frac{n_\alpha}{n_\beta} = \frac{l_\beta}{l_\alpha} = \frac{(x_\beta - x)}{(x - x_\alpha)}$$

x - total molar fraction of a component in the system

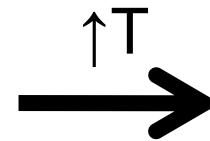
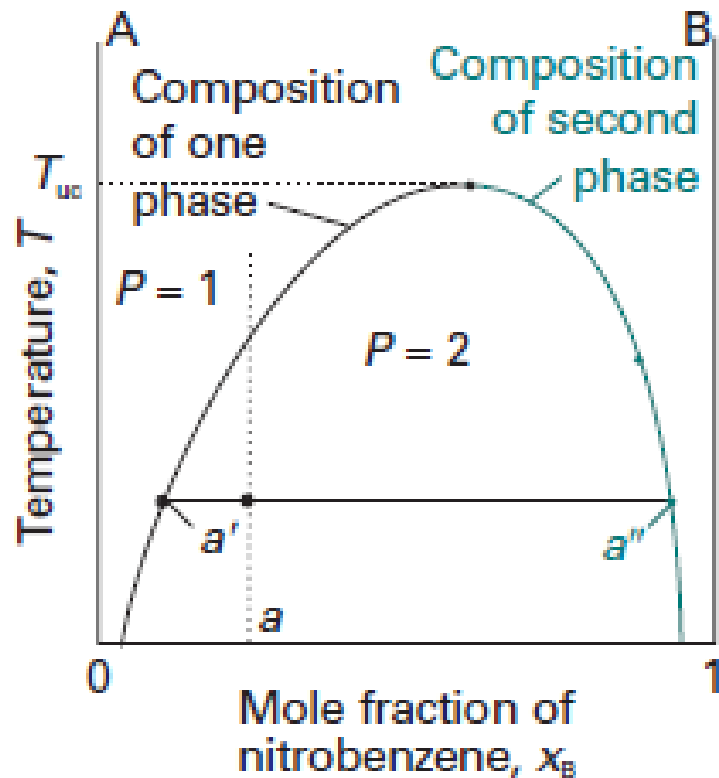
x_α - mole fraction of the component in the first phase

x_β - mole fraction of the component in the second phase

The critical solubility temperature

- temperature at which the second phase occurs / disappears

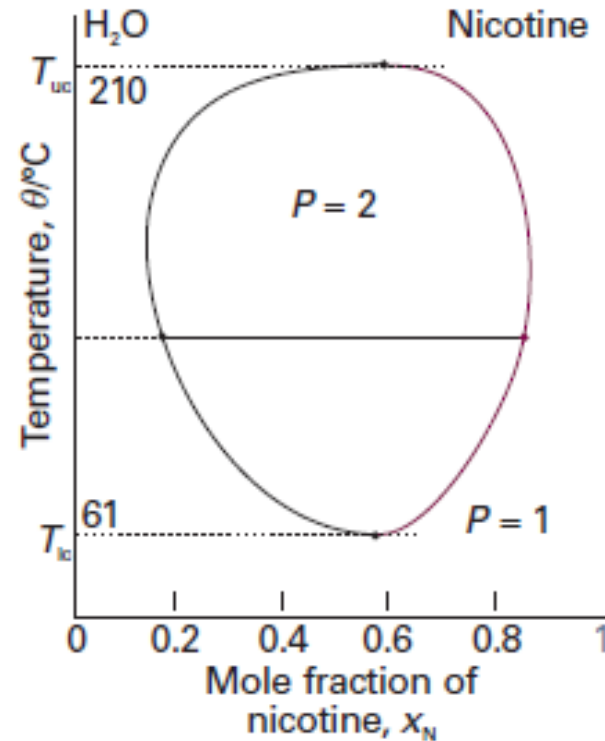
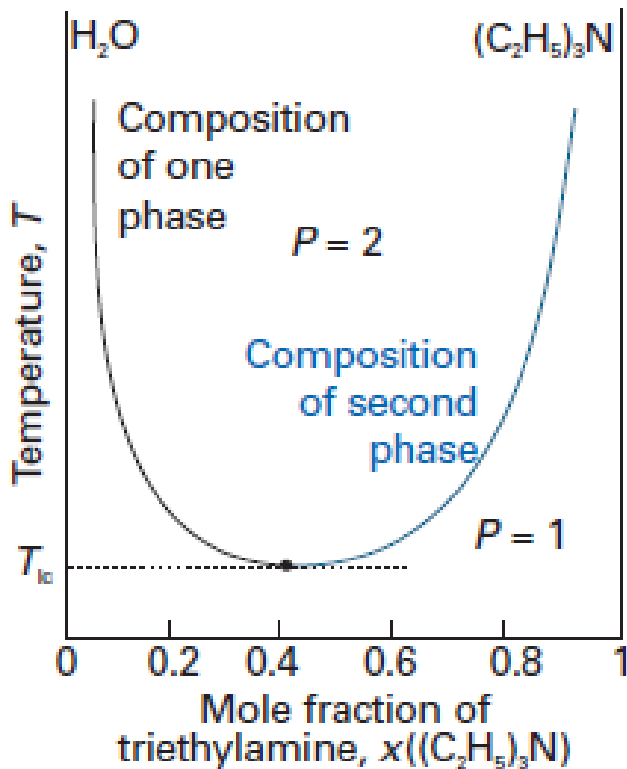
Systems with upper critical solubility temperature



The critical solubility temperature

Systems with lower critical solubility temperature

Systems with upper and lower critical solubility temperature



Two-component systems

For a two-component system may occur in such cases:

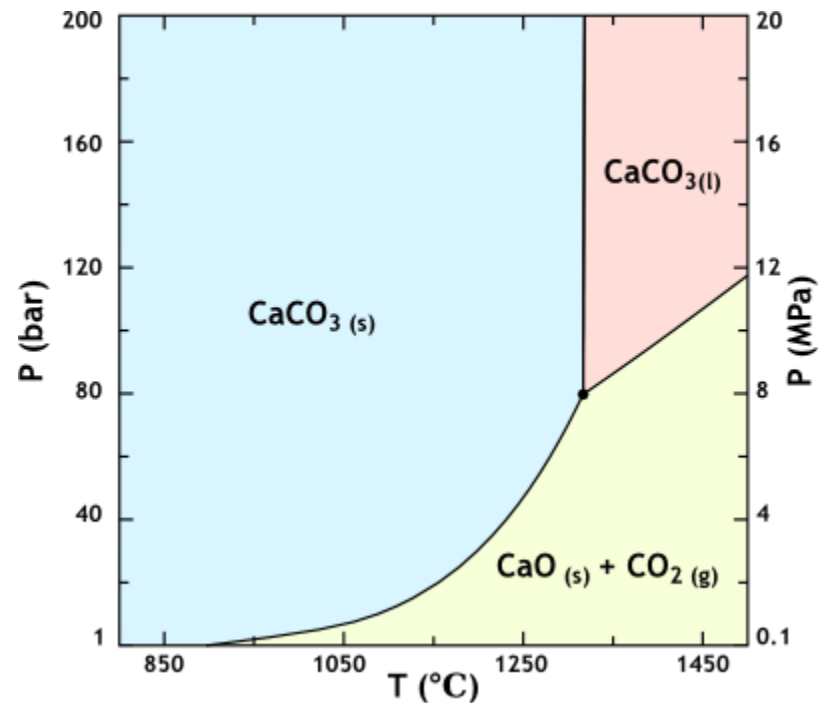
- 1) equilibrium liquid - gas
- 2) equilibrium liquid - vapor
- 3) equilibrium liquid - liquid
- 4) **equilibrium gas - solid**
- 5) equilibrium liquid - solid

Two component systems: gas – solid

- most often occur with the thermally dissociating substances or hydrates (solvates) – pseudopolymorphism

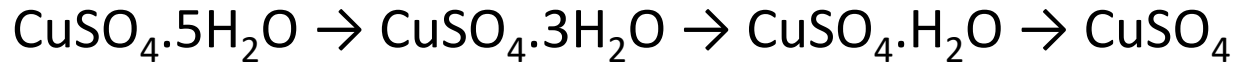
1. Thermally dissociating substances

$\text{CaCO}_3 \rightarrow \text{CaO} + \text{CO}_2$ 3-phases system – variables are pressure and temperature



Two component systems: gas – solid

2. Hydrates (solvates)



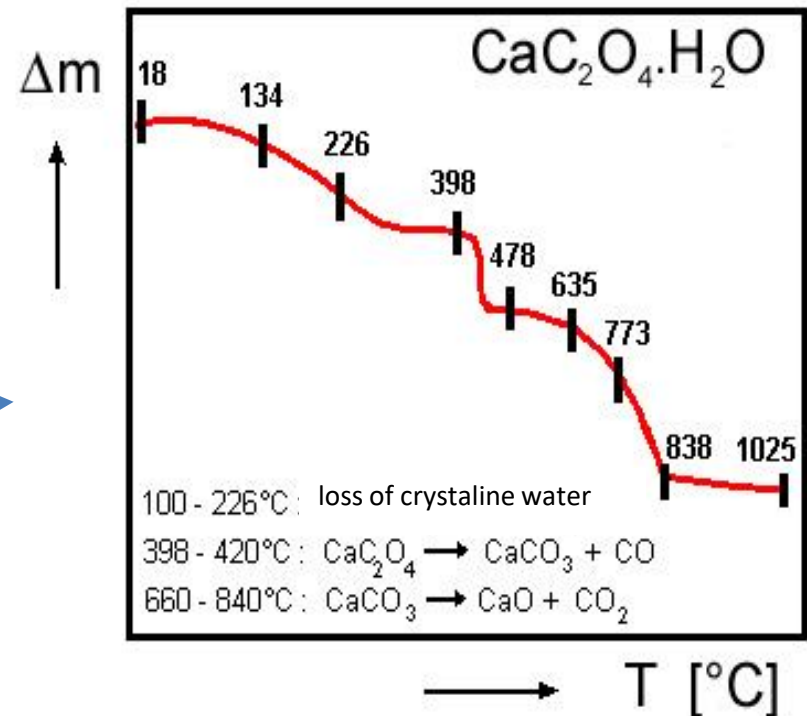
Pseudopolymorphism is the phenomenon wherein a compound is obtained in crystalline forms that differ in the nature or stoichiometry of included solvent molecules.

Pseudopolymorphism of drugs:

different solubility, rate of absorption, stability - pseudopolymorphism must be controlled (eg. thermogravimetry)

Thermogravimetry

is based on continuous recording of mass changes of a sample, as a function of temperature (in time).



Two-component systems

For a two-component system may occur in such cases:

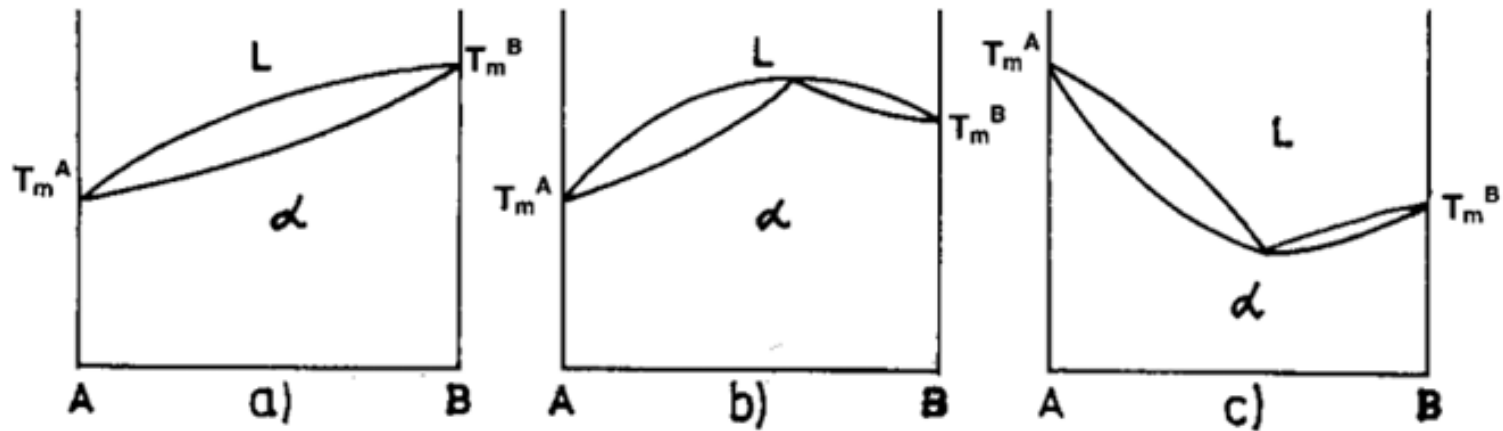
- 1) equilibrium liquid - gas
- 2) equilibrium liquid - vapor
- 3) equilibrium liquid - liquid
- 4) equilibrium gas - solid
- 5) **equilibrium liquid - solid**

Two component systems: liquid – solid

- Examples are a **saturated solution** or **solid solution**.
- The effect of pressure is minimal, it is not necessary to consider the existence of the gas phase.

Solid solutions

The components are miscible in both phases (liquid and solid).



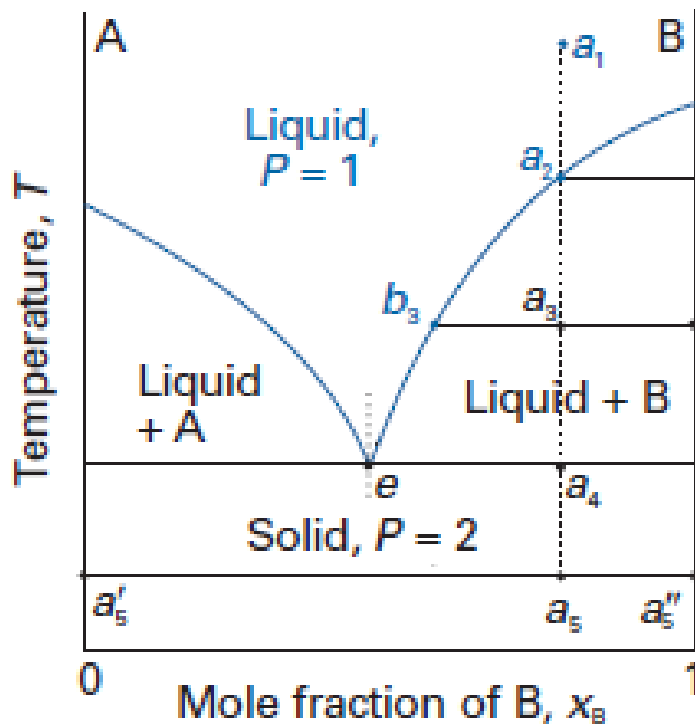
- ideal behavior (perfect solubility)
- non-ideal behavior (phase diagram with maximum)
- non-ideal behavior (phase diagram with minimum)

Two component systems: liquid – solid

Eutectic mixtures

The substances are miscible in the liquid state and immiscible in the solid state. The melting point of the mixture:

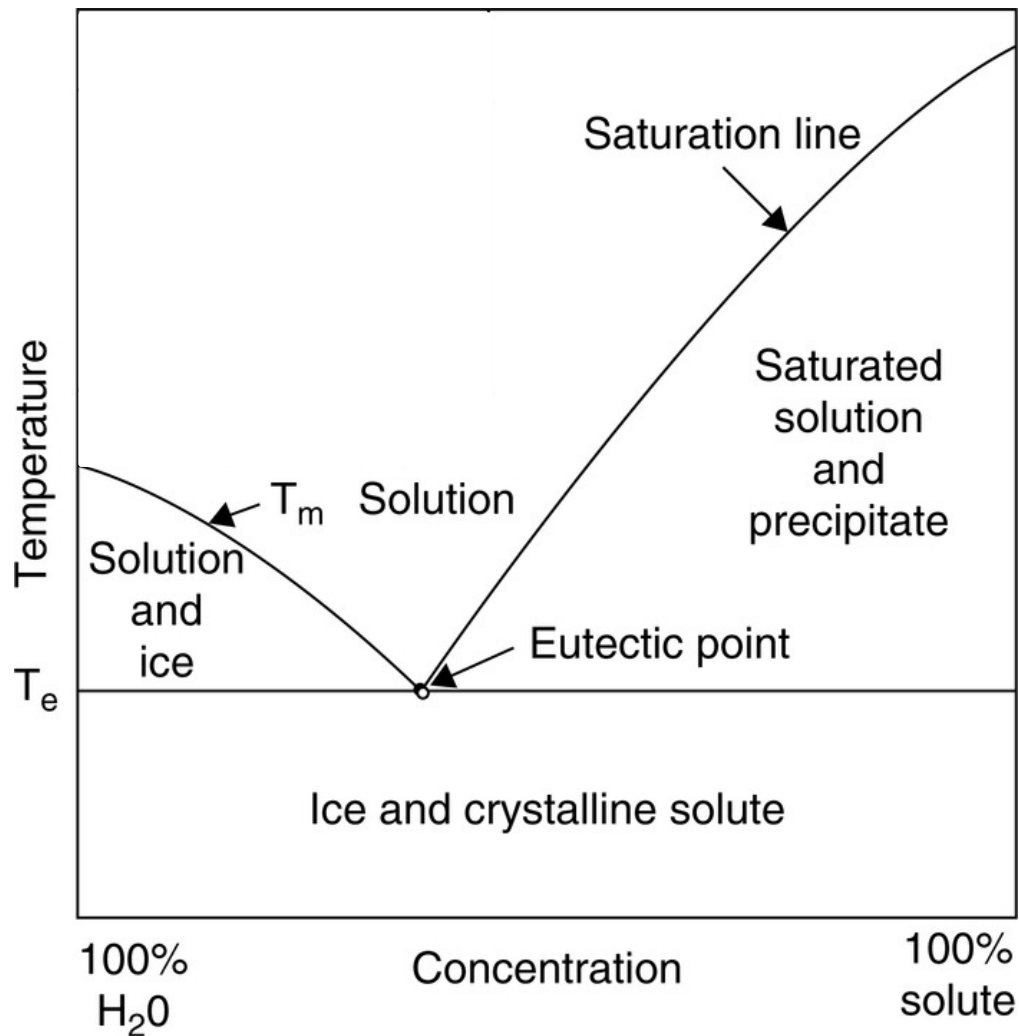
- A) does not depend on the concentration;
- B) can be lower than the melting point of the individual substances.



- $a_1 - a_2$; Pure solid B begins to come out of the solution
- $a_2 - a_3$; More of the solid forms, and the relative amounts of the solid and liquid (which are in equilibrium) are given by the lever rule, b_3 – composition of liquid phase
- $a_3 - a_4$; liquid phase start freezing, its composition corresponds to point e (eutectic) – saturated solution. Further cooling causes compounds B and A to come out of the solution in the same weight ratio they are in the eutectic point
- a_5 – in the system are two separate solid phases

Two component systems: liquid – solid

Examples is a **saturated solution** of NaCl in water (**eutectic mixture**).



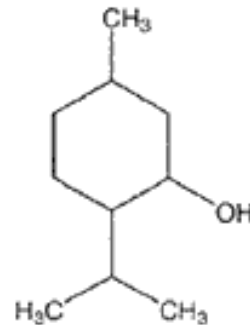
Two component systems: liquid – solid

Eutectic mixtures: Pharmaceutical applications

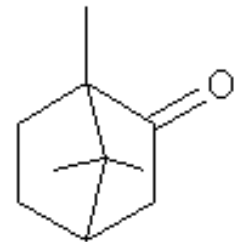
1. **Dusting powders** may contain substances forming eutectic mixture (the formation of the liquid phase is undesirable).

Problematic are solid compositions which liquefies upon mixing. **Melting points of many eutectic mixtures are lower than the room temperature.**

Mixing the components forming the eutectic mixture separately (e.g. menthol and camphor). Menthol and camphor are mixed separately with other excipients.



menthol



camphor

2. **Topical preparations** - facilitating dissolution.

Substances forming the eutectic mixture are mixed until the liquid phase is formed (crystals are abrasive). This liquid is mixed with other excipients (liquid is better incorporated to the dosage form).

Two component systems: liquid – solid

Effect of non-volatile substance to the freezing point

Colligative properties (dilute solutions of non-volatile substances):

- Lowering the vapor pressure (Raoult's law)
- Elevation of the boiling point
- Depression of the freezing point
- Osmotic pressure

Cryoscopy is the method for determining the lowered freezing points. Applications: determination of the molecular weight of the solute, osmolality determination (biochemical examination of blood serum or urine).

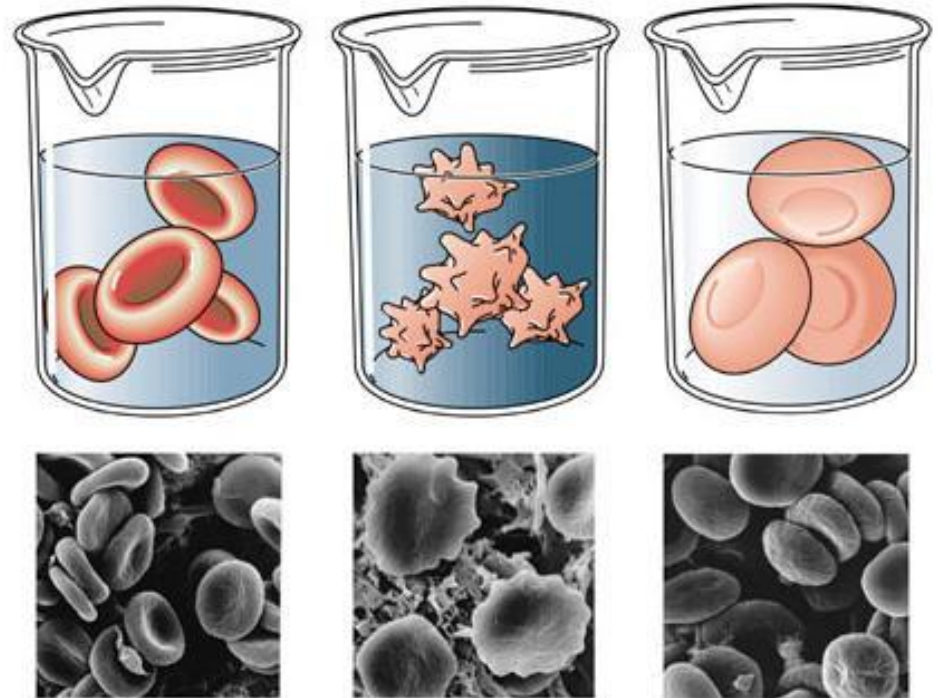
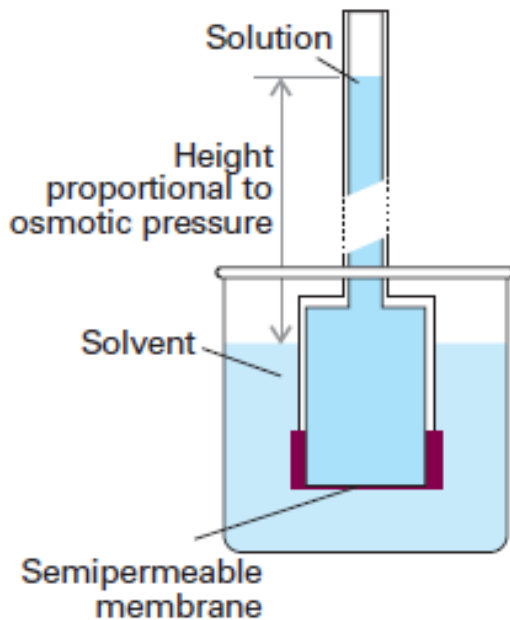
$$M_{solute} = \frac{c'_{solute} (g / kg)}{\Delta T_f} K_f i$$

K_f – cryoscopic constant

i – particle correction factor

Effect of non-volatile substance to the freezing point

Osmotic pressure: laboratory testing of osmolality is performed most frequently using cryoscopy.



- A. Isotonic solution (equal concentration of ions in solution and cell)
- B. Hypertonic solution (higher concentration of ions in solution than in cell)
- C. Hypotonic solution (lower concentration of ions in solution than in cell)

Van't Hoff equation

$$\pi = iRTc$$

Isotonization calculation

Sample Problem 1

What is freezing point depression (ΔT_f) of 100 g of isotonic solution of NaCl in water?

$$m(\text{NaCl}) = 0.817 \text{ g}$$

$$m(\text{H}_2\text{O}) = 100 \text{ g}$$

$$M(\text{NaCl}) = 58.45 \text{ g}\cdot\text{mol}^{-1}$$

$$K_f (\text{H}_2\text{O}) = 1.86 \text{ K}\cdot\text{kg}\cdot\text{mol}^{-1}$$

$$M_{\text{solute}} = \frac{c'_{\text{solute}} (\text{g} / \text{kg})}{\Delta T_f} K_f i$$

$$\Delta T_f = \frac{c'_{\text{solute}} (\text{g} / \text{kg})}{M_{\text{solute}}} K_f i$$

$$\Delta T_f = \frac{g_{\text{solute}}}{M_{\text{solute}} \times kg_{\text{solvent}}} K_f i$$

$$\Delta T_f = \frac{0.817}{58.45 \times 0.1} 1.86 \times 2$$

$$\Delta T_f = 0.52$$

Sample Problem 2

How many grams of NaCl are needed for isotonization of 1 kg of 0.125% solution of CaCl₂.

$$M(\text{CaCl}_2) = 110.98 \text{ g}\cdot\text{mol}^{-1}$$

$$M(\text{NaCl}) = 58.45 \text{ g}\cdot\text{mol}^{-1}$$

$$K_f (\text{H}_2\text{O}) = 1.86 \text{ K}\cdot\text{kg}\cdot\text{mol}^{-1}$$

1 kg of 0.125% solution of CaCl₂ contains 1.25 g of CaCl₂.

$$100\% \dots\dots\dots 1 \text{ kg}$$

$$0.125\% \dots\dots\dots x \text{ kg}$$

$$x = 0.125/100 \times 1 = 0.00125 \text{ kg} \times 1000 = 1.25 \text{ g}$$

We know that the freezing point depression (ΔT_f) of isotonic water solutions is 0.52.

The freezing point depression of CaCl₂ solution is:

$$\Delta T_f = \frac{g_{solute}}{M_{solute} \times kg_{solvent}} K_f i \quad \Delta T_f = \frac{1.25}{110.98 \times (1 - 0.00125)} 1.86 \times 3 = 0.0629$$

Current ΔT_f is 0.0629 but we want to decrease the freezing point by 0.52 to get the isotonic solution.

We need to decrease the freezing point by 0.4571 (0.52 – 0.0629 = 0.4571).

How many grams of NaCl are needed to lower the freezing point of 1 kg of CaCl₂ solution in water by 0.4571?

$$\Delta T_f = \frac{g_{solute}}{M_{solute} \times kg_{solvent}} K_f i$$

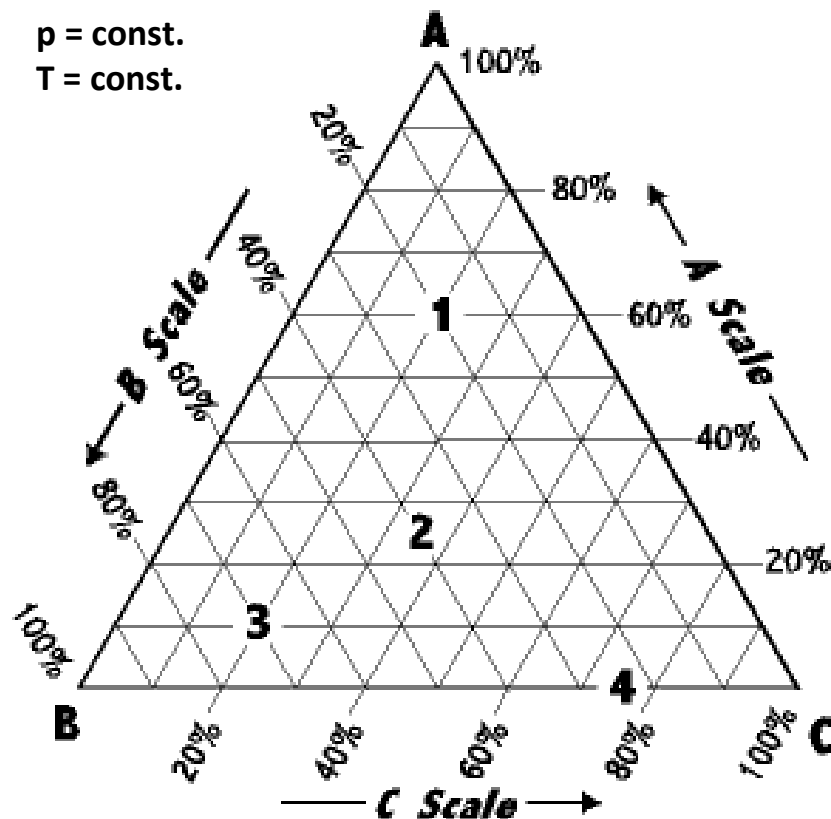
$$0.4571 = \frac{g_{solute}}{58.45 \times (1 - 0.00125)} 1.86 \times 2$$

$$g_{solute} = 7.17$$

For isotonization of 1 kg of 0.125% solution of CaCl_2 we need to add 7.17 g of NaCl.

Three component systems

- liquid-liquid equilibrium in the assessment of the **extraction of a substance** from a mixture using an suitable solvent or to describe a **system of three liquids**.



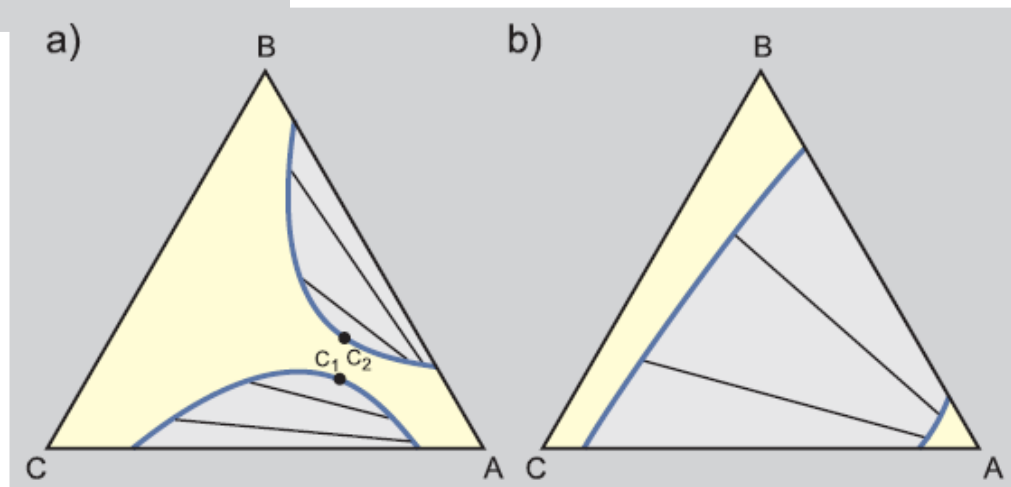
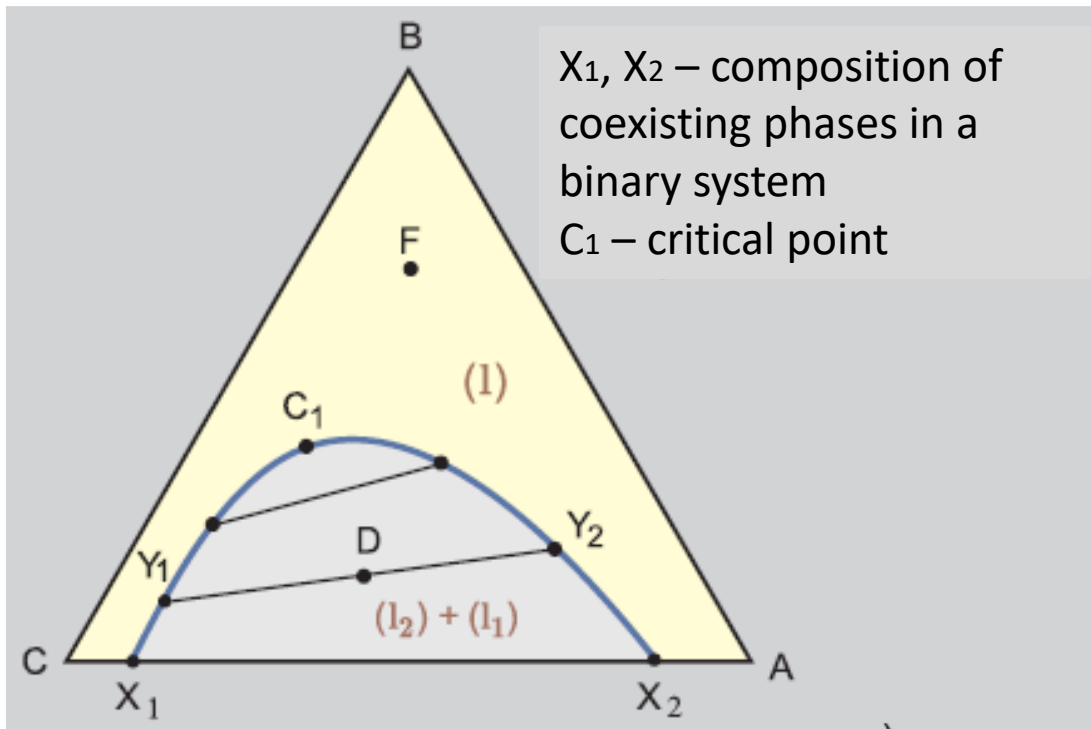
$$X_A + X_B + X_C = 1$$

The **vertices** of the triangle correspond to one pure component.

The **points on the sides** of the triangle determine the composition of a two component system consisting of components whose vertices are at the ends of the line ($C = 2$).

The **points inside the triangle** define the composition of ternary system at constant pressure and temperature ($C = 3$).

Limited miscible componets



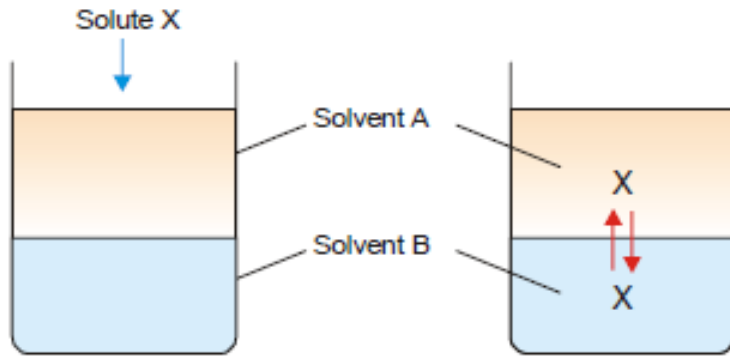
Partition equilibrium

$$a^I / a^{II} = P$$

The partition coefficient (**P**) of a substance at a given T **is constant**.

$$c^o / c^w = P$$

Nernst's distribution law



Limitations of Nernst's law:

1. T, p = const.
2. Equilibrium concentrations
3. Dilute solutions
4. Non-miscibility of solvents
5. Same molecular state
(no association or dissociation)

Application:

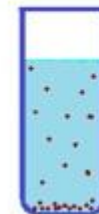
- Extraction or purification of compounds
- Simulation of drug absorption and determination of drug lipophilicity

Partition coefficient P: optimum P = 100 -1000 (log P = 2 – 3)

log P > 3 → **accumulation**

log P < 2 → **rapid elimination**

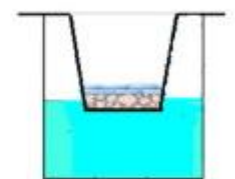
SOLUBILITY



DISTRIBUTION



MEMBRANE PERMEABILITY



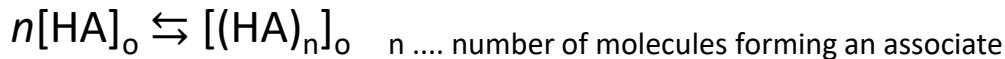
Partition equilibrium

- The ratio c^o / c^w is constant if the compound is present in solvents such as simple molecules.
- If an association or dissociation occurs, the ratio c^o / c^w is not constant.

Partition coefficient $P = \frac{[HA]_o}{[HA]_w}$

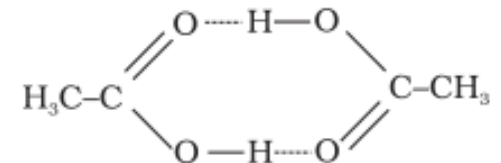
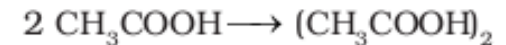
includes only the non-associated and non-dissociated part of the molecule

ASSOCIATION

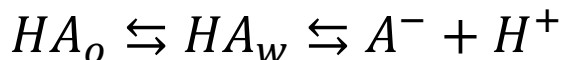


Partition ratio D: includes also associated part of the molecule

$$D = \frac{[HA]_o + [(HA)_n]_o}{[HA]_w}$$



DISSOCIATION

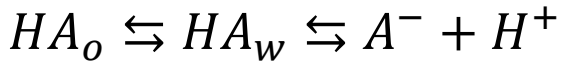


Partition ratio D: includes also dissociated part of the molecule

$$D = \frac{[HA]_o}{[HA]_w + [A^-]_w}$$

Partition equilibrium

DISSOCIATION– weak acid



Partition coefficient

$$P = \frac{[HA]_o}{[HA]_w}$$

Partition ratio

$$D = \frac{[HA]_o}{[HA]_w + [A^-]_w}$$

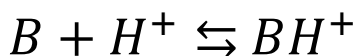
Dissociation constant

$$k_A = \frac{[H^+]_w \cdot [A^-]_w}{[HA]_w}$$

$$\frac{1}{D} = \frac{[HA]_w + [A^-]_w}{[HA]_o} \rightarrow \frac{1}{D} = \frac{1}{P} + \frac{[A^-]_w}{[HA]_o} \rightarrow \frac{1}{D} = \frac{1}{P} + \frac{k_A \cdot [HA]_w}{[H^+]_w \cdot [HA]_o}$$

$$\frac{1}{D} = \frac{1}{P} + \frac{k_A}{[H^+]_w \cdot P} \rightarrow \frac{1}{D} = \frac{1}{P} \cdot \left(1 + \frac{k_A}{[H^+]_w} \right) \rightarrow P = D \cdot \left(1 + \frac{k_A}{[H^+]_w} \right)$$

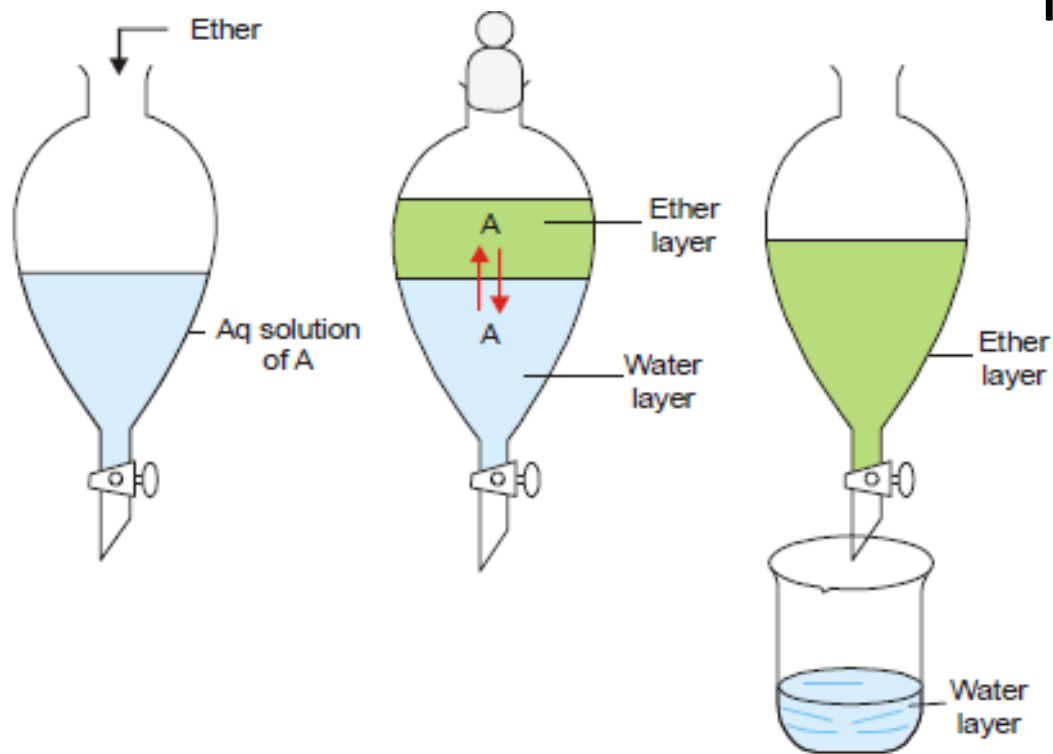
DISSOCIATION– weak base



$$P = D \cdot \left(1 + \frac{[H^+]_w}{k_A} \right)$$

The extraction between immiscible solvents

- is used in the extraction separation methods (separation of mixture of compounds)
- is used for removal of impurities or concentration increase
- usually extraction of compounds in system of water and organic solvent immiscible with water



The degree of extraction(%)

$$E = \frac{100D}{D + \frac{V_W}{V_O}}$$

The extraction between immiscible solvents

MULTIPLE EXTRACTION

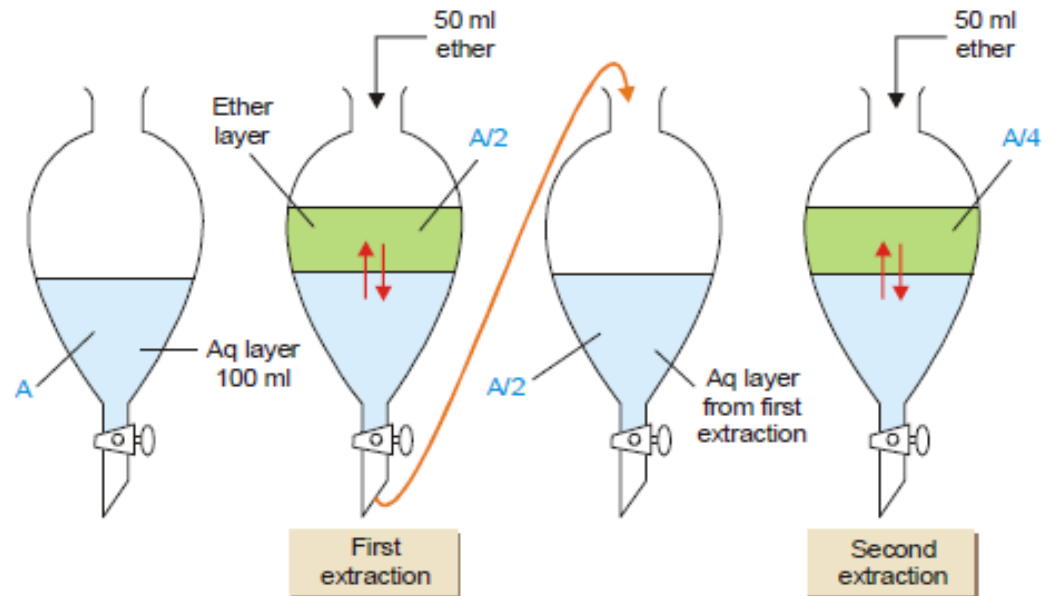
Sample problem:

$$D = 2$$

$$V_w = V_o = 100 \text{ ml}$$

$$V_w/V_o = 1$$

$$E = \frac{100.2}{2+1} = 66.6 \%$$



$$V_o = \frac{1}{2} V_w; V_o = 100 \text{ ml}$$

$$V_w/V_o = 2$$

$$E = \frac{100.2}{2+2} = 50 \%$$

1. EXTRACTION
2. EXTRACTION (50% of the rest after 1. extraction = 25 %)

TOTAL **75 %** after two consecutive extractions

The multiple stage extraction (natural compounds extraction)

Each organic fraction contain different type of natural compounds (different polarity).



Ethanolic extraction

Ethanolic extract

