

Solubility.

Solubility gas/liquid,
liquid/liquid, solid/liquid

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- **formation of the solution** depends on **the mutual solubility** solute and solvent – on the physical and chemical properties
- 9 types of mixtures (solutions):

solute	solvent	example	eg. of medical form
gas	gas	air	gas inhalation anesthetics in cylinders
liquid	gas	fog	aerodispersions
solid	gas	iodine vapor in the air	aerodispersions
gas	liquid	$H_2O + CO_2$	solution of effervescent tablets
liquid	liquid	ethanol + H_2O	medical solutions
solid	liquid	salicylic alcohol	medical solutions
gas	solid	hydrogen in palladium	-
liquid	solid	mineral oil paraffin	ointments
solid	solid	solid solutions	capsules with solid solutions

- **saturated solution** - solute is in equilibrium with solid phase of this substance
- **solubility** - concentration of solute in the saturated solution at a given temperature
- **unsaturated solution** - solute concentration is lower than in a saturated solution at a given temperature
- **supersaturated solution** - is one that contains more of the dissolved solute than it would normally contain at a definite temperature, were the undissolved solute present
- **degree of solubility according to Czech Pharmacopoeia** – see previous presentation
- **solubility** (at const. T, p) **depends on** the **chemical properties** (H-bridges (H-bonds), the ratio of polar and nonpolar groups, ...), the **size of molecules** (dissolved substances and solvents), **el. charge** (solution of electrolytes) and the **polarity of molecules** (dipole moment)

- water-soluble substances forming H-bonds with water:
phenols, alcohols, aldehydes, ketones, amines, etc.
- Straight-chain monohydroxy alcohols, aldehydes, ketones, and acids with more than four or five carbons cannot enter into the hydrogen-bonded structure of water and hence are only slightly soluble.
- When additional polar groups are present in the molecule, water solubility increases greatly.
- Branching of the carbon chain reduces the nonpolar effect and leads to increased water solubility.
- according to polarity – polar X semipolar X nonpolar

- **mechanism of action of polar solvents (water):**
 1. high dielectric constant (relative permittivity) reduces the attractive force between oppositely charged ions
 2. polar solvents break covalent bonds by acid-base reactions. example: $\text{HCl} + \text{H}_2\text{O} \longrightarrow \text{H}_3\text{O}^+ + \text{Cl}^-$
 3. polar solvents are capable of solvating molecules and ions through dipole interaction forces (particularly H-bonds), which leads to the solubility of the compound

- **nonpolar solvents:**
 - **are unable** to reduce the attraction between the ions of strong and weak electrolytes because of the solvents' **low dielectric constants**

- **cannot** break covalent bonds and ionize weak electrolytes, because they belong to the group known as **aprotic** solvents (can not receive or give H^+)
- **cannot form hydrogen bridges** with nonelectrolytes
 - ionic and polar substances are insoluble
- **can** dissolve nonpolar solutes **with similar internal pressures** through induced dipole interactions (results from the cohesive forces of liquid molecules). The solute molecules are kept in solution by the weak **van der Waals type of forces**.
 - alkaloidal bases, fatty acids, etc. dissolve in nonpolar solvents

■ **semipolar solvents** (ketones, alcohols):

- can induce a certain degree of polarity in nonpolar solvent molecules (benzene, which is readily polarizable, becomes soluble in alcohol).
 - can act as intermediate solvents to bring about miscibility of polar and nonpolar liquids.

Solubility of gases in liquids

- eg. $\text{HCl} + \text{H}_2\text{O}$, $\text{NH}_3 + \text{H}_2\text{O}$, $\text{CO}_2 + \text{H}_2\text{O}$, ...
- the solubility of gas in liquid is the concentration of the dissolved gas when it is **in equilibrium with the gas above the solution**
- the solubility **depends** primarily on the **pressure, temperature, presence of salts**, and **chemical reactions** that the gas sometimes undergoes with the solvent
- **1. The pressure of a gas above the solution**
 - the effect of the pressure on the solubility of a gas is expressed by **Henry's law**:
$$c = \sigma \cdot p$$
 - c = concentration of dissolved gas, σ = constant (solubility coefficient),
 p = partial pressure of the gas above the solution

- 2. Effect of temperature
 - as the temperature increases, the solubility of most gases decreases (owing to greater tendency of the gas to expand)
- 3. Effect of salts = Salting out effects
 - adding of salts (e.g. NaCl) causes decreasing in gas solubility (attraction of salt ions for the water molecules reduces the density of the aqueous environment adjacent to the gas molecules)
- 4. Effect of chemical reaction
 - chemical reaction causes usually increase in solubility (e.g. solubility HCl is 10 000 times more higher than is O₂)
- Solubility of gases in liquids calculations:
 - - Henry's law constant σ
 - - Bunsen absorption coefficient α : $V_{\text{gas}} / V_{\text{solution}} = \alpha \cdot p$
(volume of gas in liters that dissolves in 1 liter of solvent under a partial pressure of 1 atmosphere of the gas at a definite temperature)

Solubility of solids in liquids

■ Ideal solutions

- The equation derived from thermodynamic considerations is (from Clausius Clapeyron equation):

$$-\log X_2^i = \frac{\Delta H_f}{2,303.R} \left(\frac{T_0 - T}{T_0.T} \right)$$

- X_2^i = ideal solubility of the solute expressed in mole fraction
- ΔH_f = molar heat of fusion (the heat absorbed when the solid melts,
- T_0 = melting point of the solid solute
- T = temperature of the solution
- ideal solubility is **not affected by** the nature of the **solvent**
- at temperatures **above** the **melting point**, the solute is in **liquid state**, and, in an ideal solution, the liquid solute is **miscible** in all proportions with the solvent

- **Nonideal solutions** (Hildebrand):

- activity $a_2 = X_2 \cdot \gamma_2 \longrightarrow \log a_2 = \log X_2 + \log \gamma_2$

- in an ideal solution, $a_2 = X_2^i$, because $\gamma_2 = 1$:

$$-\log a_2 = -\log X_2^i = \frac{\Delta H_f}{2,303 \cdot R} \left(\frac{T_0 - T}{T_0 \cdot T} \right)$$

$$\longrightarrow -\log X_2 = \frac{\Delta H_f}{2,303 \cdot R} \left(\frac{T_0 - T}{T_0 \cdot T} \right) + \log \gamma_2$$

- the activity coefficient depends on the nature of both the solute and the solvent as well as on the temperature of the solution

- $\log \gamma_2$ is obtained by:

1. the removal of a molecule from the solute phase: $+\omega_{22}$
2. the creation of a hole in the solvent: $+\omega_{11}$
3. the solute molecule is placed in the hole: $-2\omega_{12}$
4. the activity coefficient is proportional also to the volume of the solute V_2 , the volume of solvent Φ_1 and temperature T :

$$\ln \gamma_2 = (\omega_{22} + \omega_{11} - 2\omega_{12}) \frac{V_2 \Phi_1^2}{RT}$$

– R is the gas constant

- ω is related to the cohesion forces (internal pressures)
- in nonpolar and moderately polar solutions cause weak Van der Waals forces:

$$\omega_{12} = \sqrt{\omega_{11}\omega_{22}}$$

$$\longrightarrow \ln \gamma_2 = (\omega_{11} - 2\sqrt{\omega_{11}\omega_{22}} + \omega_{22}) \frac{V_2\Phi_1^2}{RT}$$

$$\longrightarrow \ln \gamma_2 = \left[(\omega_{11})^{1/2} - (\omega_{22})^{1/2} \right]^2 \frac{V_2\Phi_1^2}{RT}$$

$$\longrightarrow \log \gamma_2 = (\delta_1 - \delta_2)^2 \frac{V_2\Phi_1^2}{2,303RT}$$

δ = solubility parameters

$$-\log X_2 = \frac{\Delta H_f}{2,303RT} \left(\frac{T_0 - T}{T_0 T} \right) + (\delta_1 - \delta_2)^2 \frac{V_2\Phi_1^2}{2,303RT}$$

- the solubility parameters may be calculated from heats of vaporization and molar volume of liquid compound (it is the square root of the internal pressure):

$$\delta = \left(\frac{\Delta H_v - RT}{V_m} \right)^{1/2}$$

EXTENDED HILDEBRAND SOLUBILITY APPROACH

- allows to calculate the solubility of **nonpolar and polar solutes in solvents** ranging from nonpolar hydrocarbons to highly polar solvents such as alcohols, glycols, and water.
- polar systems** - various strong interactions – **irregular systems** – self association of solute or solvent, solvation of the solute by the solvent molecules, complexation
- is valid not only for solid-liquid systems but also for liquid-liquid and gas-liquid.

$$-\log X_2 = -\log X_2^i + A(\omega_{11} + \omega_{22} - 2\omega)$$

$$A = \frac{V_2 \Phi_1^2}{2,303RT}$$

$$(\omega_{11})^{\frac{1}{2}} = \delta_1 \dots \dots \dots (\omega_{22})^{\frac{1}{2}} = \delta_2$$

$$-\log X_2 = -\log X_2^i + A(\delta_1^2 + \delta_2^2 - 2\omega)$$

$$\log X_2^i - \log X_2 = A(\delta_1^2 + \delta_2^2 - 2\omega)$$

$$\frac{\log\left(\frac{X_2^i}{X_2}\right)}{A} = \frac{\log \gamma_2}{A} = \delta_1^2 + \delta_2^2 - 2\omega$$

$$\omega = \frac{1}{2} \left(\delta_1^2 + \delta_2^2 - \frac{\log \gamma_2}{A} \right)$$

δ_1^2, δ_2^2 : are known quantities

γ_2 : is obtained from a knowledge of the drug's ideal solubility

SOLVATION AND ASSOCIATION

- it can be shown from thermodynamic consideration that the heat change (ΔH_2) when 1 mole of solute is added to a large quantity of regular solution = $RT \ln \gamma_2$

- also applies :
$$\log \gamma_2 = (\delta_1 - \delta_2)^2 \frac{V_2 \Phi_1^2}{2,303RT}$$

- all intermolecular forces are of approximately equal size (nonpolar solutions) - released heat is absorbed by the solution (the squared term can lead only to positive values):

$$\Delta H_2 = RT \ln \gamma_2 = (\delta_1 - \delta_2)^2 V_2 \Phi_1^2$$

SOLVATION AND ASSOCIATION

- in polar solutions can be variously strong interactions:

$$\Delta H = RT \ln \gamma_2 = (\omega_{22} + \omega_{11} - 2\omega_{12})V_2\Phi_1^2$$

- when $2\omega_{12} > \omega_{11} + \omega_{22} \dots \Delta H < 0 \dots$ **solvation**
- (negative deviation from Raoult's law – applies when specific interactions, such as hydrogen bonding occur between the solute and the solvent)
- when $2\omega_{12} < \omega_{11} + \omega_{22} \dots \Delta H > 0 \dots$ **association**
- (positive deviation from Raoult's law – applies when the interaction occurs between like molecules of one of the components in a solution – e.g. dimerization of benzoic acid in some nonpolar solvents or the interlinking of water molecules by hydrogen bonding)

MULTIPLE (PARTIAL) SOLUBILITY PARAMETERS HANSEN

- In order to better account the polar nature of solvent Hansen partitioned Hildebrand solubility parameters into three parameters.

$$\frac{\Delta E}{V} = \frac{\Delta E_D}{V} + \frac{\Delta E_P}{V} + \frac{\Delta E_H}{V}$$

$$\delta^2 = \delta_D^2 + \delta_P^2 + \delta_H^2$$

δ_D^2 ... nonpolar and dispersion interactions

δ_P^2 ... permanent dipole-permanent dipole interactions

δ_H^2 ... hydrogen bonding and all varieties of strong donor-acceptor interaction between solute and solvent

- The sum of these energy terms divided by molar volume gives the total cohesive energy density

MULTIPLE (PARTIAL) SOLUBILITY PARAMETERS FEDORS

- Fedors proposed a method of group contributions for estimating the total solubility parameters the atom and chemical group contributes to ΔE and ΔV

$$\delta^2 = \frac{\sum \Delta E}{\sum \Delta V}$$

method of group contributions – e.g.:

CH₃-CH₂-OH

CH₃-... E₁... is known quantities

CH₂-... E₂... is known quantities

OH-... E₃... is known quantities

$$E_1 + E_2 + E_3 = \sum \Delta E$$

MULTIPLE (PARTIAL) SOLUBILITY PARAMETERS SNYDER

Snyder divided Hansen's parameter of δ_H into 3:

$\delta_b - H^+$ (proton) acceptor

$\delta_a - H^+$ (proton) donor

δ_{in} - parameter for induced dipolar interaction

+ $\delta_d + \delta_p$ - together 5 solubility parameters

- enable better approximation of real state