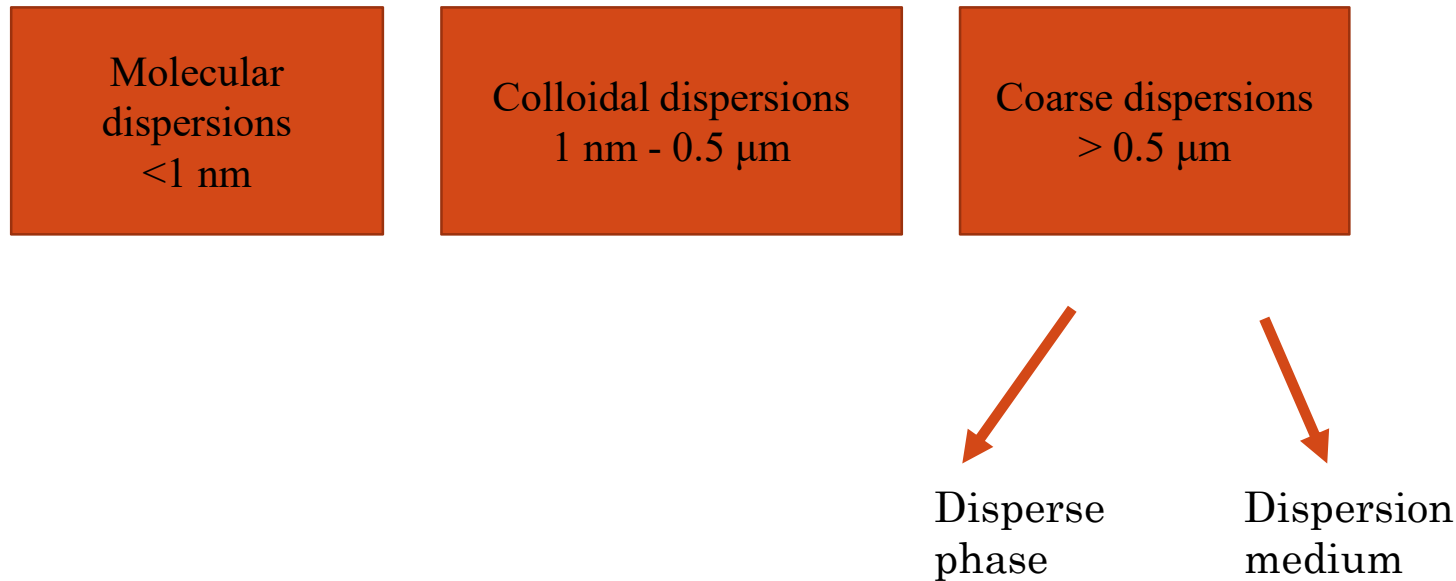


SOLUTIONS

Disperse Systems

***Dispersion

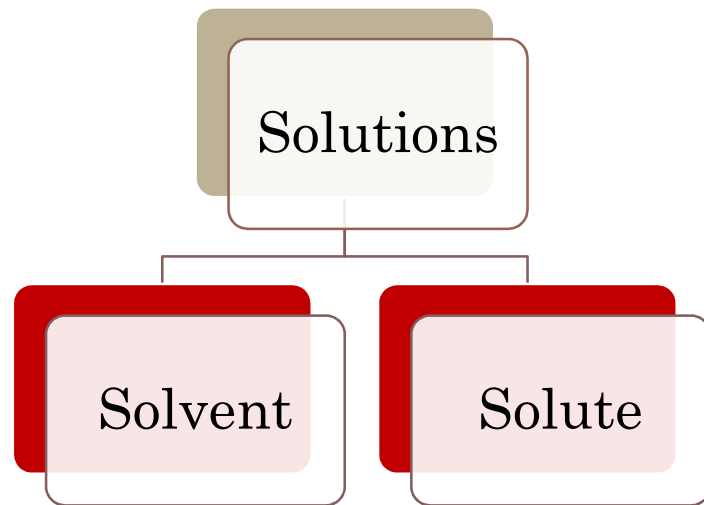


In molecular dispersions, the dispersed phase consists of individual molecules.

If the size of the molecules is smaller than the colloidal size, **true solutions** forms.

Definition (USP 29)

- Solutions are liquid preparations that contain one or more chemical substances dissolved, i.e., molecularly dispersed, in a suitable solvent or mixture of mutually miscible solvents.



* True Solutions

In true solutions, the solute is dissolved in the dissolution medium and is invisible. The solute is dispersed as small molecules or ions within the solvent.

Pharmaceutical Solutions

Aromatic water, syrup, parenteral solutions, mouthwashes, gargles, drops,...etc.

Advantages of Solutions

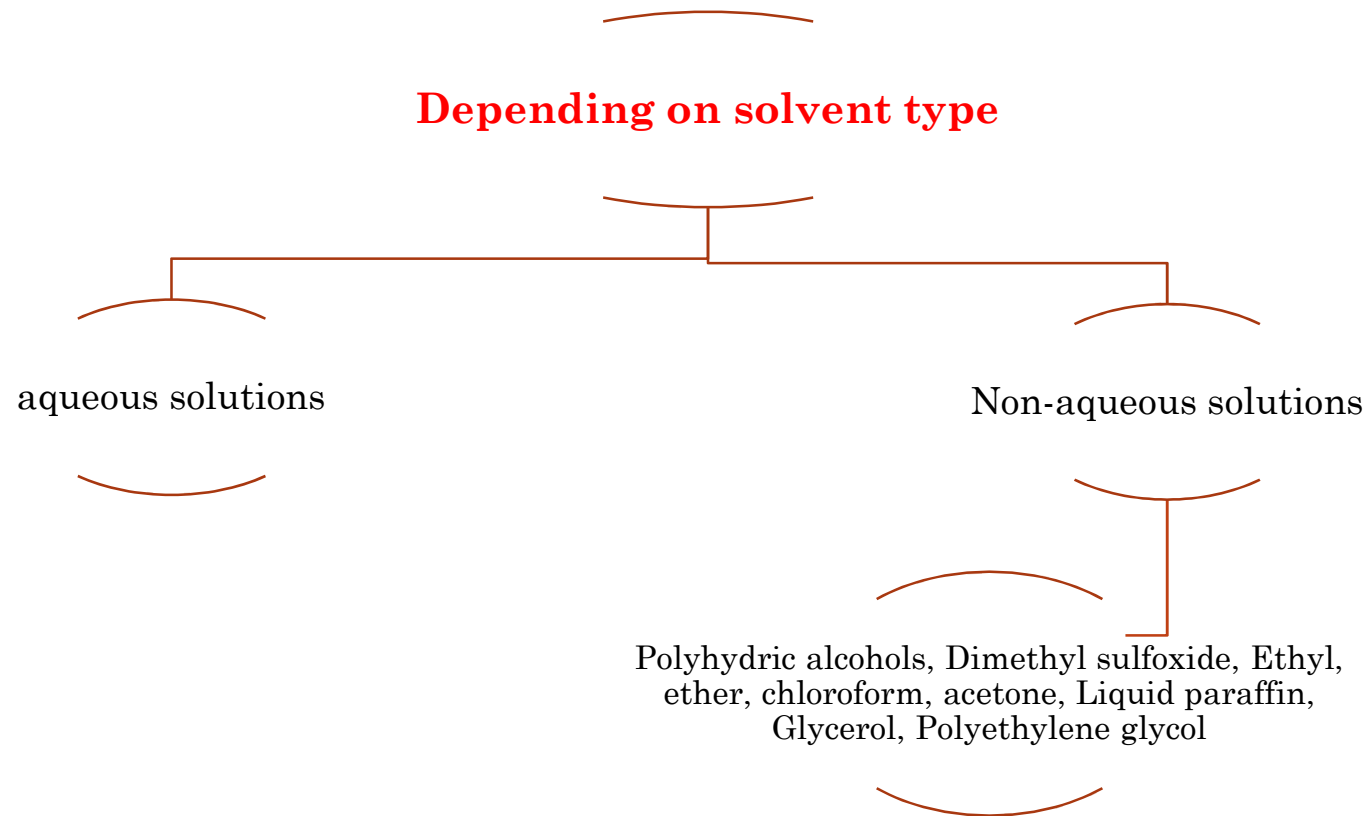
- Ease of administration (pedatric and geriatric patients)
- High absorption
- Dosing uniformity
- Easy and economic production

Disadvantages of Solutions

- Packaging, storage and transport difficulties
- Difficulty of masking the bad taste and odors of active agents
- Low stability (hydrolysis, oxidation, microbiological contamination)
- Short shelf life

Solute	Solvent	Sample
Liquid	Liquid	Water - acetone ★
Solid	Liquid	Salt – water ★
Gas	Liquid	Perhidrol, soda ★
Liquid	Solid	mercury-silver (Amalgam)
Solid	Solid	Copper-gold(12 Carat YellowGold)
Gas	Solid	Hydrogen in Palladium
Liquid	Gas	Water vapor in the air
Solid	Gas	I ₂ vapor in the air
Gas	Gas	Air

Classification of Pharmaceutical Solutions



Concentration units in solutions

Percent (%) concentration

Weight percentage (% w / w) (solid and semi-solid mixtures)

Volume percentage (% v / v) (liquid-liquid)

Weight in volume percentage (% w / v) (solid-liquid or gas-liquid)

Molarity (M)	The number of moles of solute per liter of solution (mol / L)
Normality (N)	The number of mole equivalents per liter of solution
Molality (m)	the number of moles of solute per kilogram of solvent (mol / kg)
Mole Fraction (x or N)	The ratio of the number of moles of one of the components in the solution to the total number of moles
Mili equivalents (mEq)	Molecular weight /valence
ppm	The amount of solute in mg per kilogram of solution

Sample 1:

What is the molarity of the solution containing 5 gr NaOH in 250 mL? ($MW_{\text{NaOH}} = 40 \text{ g / mol}$)

- 5 g NaOH ?mol Moles (n) = m/MW

$$n = 5/40 = 0.125 \text{ mol}$$

- $M = n / V$

$$= 0.125 \text{ mol} / 0.25 \text{ L} = 0.5 \text{ M (mol/L)}$$

Sample 2:

🔥 How can you prepare 1 liters of 0.1 M CuSO_4 solution? (MW $\text{CuSO}_4 = \underline{159.6}$ g/mol)

- Calculate the mole of CuSO_4
- $M = n / V \Rightarrow 0.1 = n / 1 \Rightarrow n = 0.1 \text{ mol } \text{CuSO}_4$
- $n = X / \text{MW} \Rightarrow 0.1 = X / 159.6 \Rightarrow X = 15.96 \text{ g } \text{CuSO}_4$

$$\text{Weight percent (w/w)} = \frac{\text{Weight of the solute (g)}}{\text{Weight of the solution (g)}} \times 100$$

Eg: As 0.892 g KCl is dissolved in 54.6 g of water:

$$\text{Weight percent of KCl (w/w)} = \frac{0.892 \text{ g}}{0.892 + 54.6} \times 100 = 1.6\%$$

$$\text{Volume percent (w/w)} = \frac{\text{Volume of the solute (ml)}}{\text{Volume of the solution (ml)}} \times 100$$

Eg: Ethanol solution (70 °, 70 %) contains 70 ml ethanol in 100 ml

$$\text{Weight/volume percent (w/v)} = \frac{\text{Weight of the solute (g)}}{\text{Volume of the solution (ml)}} \times 100$$

Eg: 8 % of sugar solution: 8 g sugar in 100 ml solution

Eg: In 50 ml of 8 % sugar solution the sugar amount can be calculated as follows:

100 ml	8 g Sugar
<u>50 ml</u>	<u>x=4 g Sugar</u>

Solubility

- Amount of the solute that dissolves in a unit volume of a solvent to form a saturated solution under specified conditions of temperature and pressure.

Descriptive Term	Parts of Solvent Required for 1 Part of Solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble, or Insoluble	10,000 and over

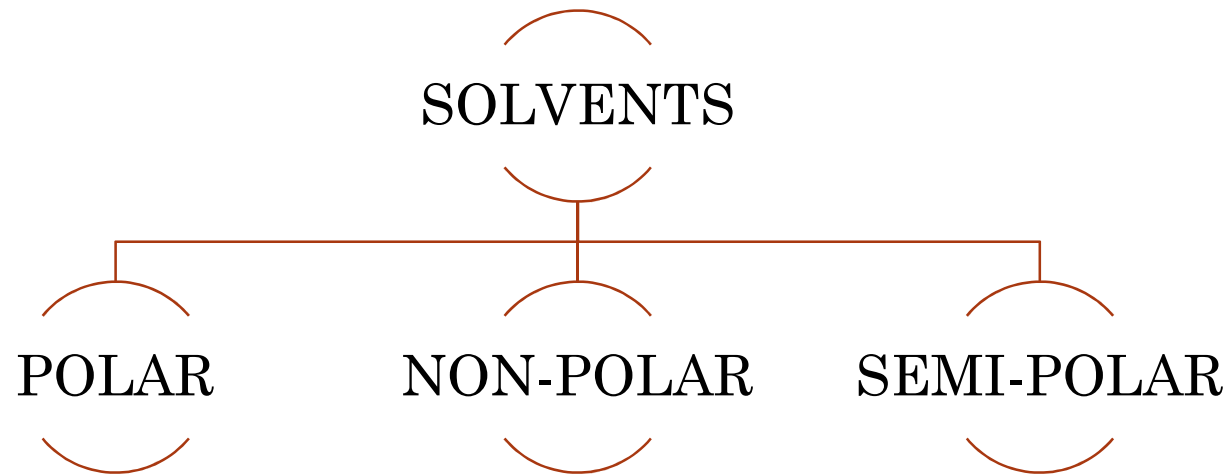
1 Part Boric acid
16 Parts Ethanol

- Ideal Solubility depends on:
 - The crystal structure of the solute
 - Solvent type
 - Solvent **polarity** and the **dipole moment**

The crystalline structure of the dissolved solute molecules is dissociated. This dissociation is accompanied by free energy exchange.

- energy required for dissociation ↑
- solubility ↓

Solvent-solute Interactions



- The polarity of the solvent is also effective on solubility and is divided into 3 classes according to their polarity.

Polarity



The charge distribution and shape of a molecule determine the polarity of the molecule. One of the bond between two atoms is the **covalent bond**. This covalent bond is formed by a pair of electrons that the two atoms jointly use. These bond electrons are attracted by atoms of different electronegativity.

Eg: In case of HF:

Since electronegativity of fluorine is greater than hydrogen atom, bond electrons are more attracted by fluorine atom. For this reason, fluorine atom will attract negative charges. The positive charges will be on hydrogen atom side.

These type of molecules in which negative and positive ends are separated called **polar molecules**.

Dipole moment

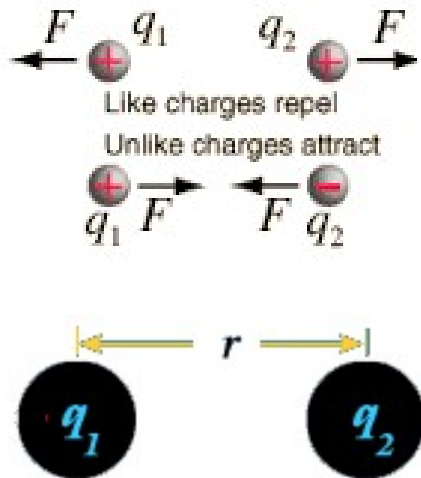
- Dipole : bipolar
- Dipole moment (μ) is the measure of net molecular polarity, which is the magnitude of the charge Q at either end of the molecular dipole times the distance r between the charges.

Substance	Dielectric Constant	Dipole Moment (debye)
Formamide	110.0	3.37
Water	78.5	1.85
Dimethyl sulfoxide	48.9	3.96
Methanol	32.6	1.66
Ethanol	24.3	1.68
Acetone	20.7	2.72
Ammonia	16.9	1.47
Chloroform	4.8	1.15
Diethyl ether	4.3	1.15
Benzene	2.3	0.00
Carbon tetrachloride	2.2	0.00
Hexane	1.9	0.00

Source: Brey, W.S., *Physical Chemistry and Its Biological Applications*, p. 26, Academic Press (1978).

Dielectric constants and permanent molecular dipole moments of some common solvents

Coulomb's Law and Dielectric Constant



	Substance	Dielectric Constant	Dipole Moment (debye)
POLAR	Formamide	110.0	3.37
	Water	78.5	1.85
	Dimethyl sulfoxide	48.9	3.96
SEMI-POLAR	Methanol	32.6	1.66
	Ethanol	24.3	1.68
	Acetone	20.7	2.72
NON-POLAR	Chloroform	4.8	1.15
	Diethyl ether	4.3	1.15
	Benzene	2.3	0.00
	Carbon tetrachloride	2.2	0.00
	Hexane	1.9	0.00

Source: Brey, W.S., *Physical Chemistry and Its Biological Applications*, p. 26, Academic Press (1978).

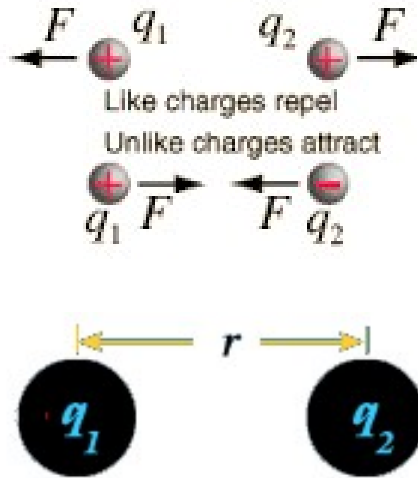
force (N) $f \propto \frac{q_1 q_2}{D r^2}$ charges in coulombs
dielectric constant of medium D distance between point charges (m)

Note: a positive value of f indicates repulsion

- q_1 and q_2 , are two oppositely charged particles standing at a distance of « r » from each other. According to Coulomb's law, they attract each other in inverse proportion to the square of their distance. If a dielectric medium (such as solvent) enters between them, the attraction force will decrease at certain rate called a «dielectric constant».

Coulomb's Law and Dielectric Constant

NaCl/water



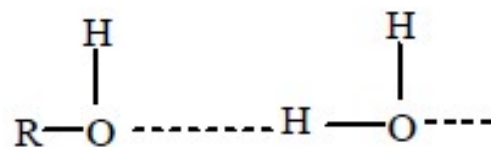
	Dielectric Constant	Dipole Moment (debye)
Formamide	36.6	3.37
Water	78.5	1.85
Dimethyl sulfoxide	46.7	3.96
Methanol	32.6	1.66
Ethanol	24.3	1.68
Acetone	20.7	2.72
Chloroform	4.8	1.15
Diethyl ether	4.3	1.15
Benzene	2.3	0.00
Carbon tetrachloride	2.2	0.00
Hexane	1.9	0.00

- Dielectric constant varies for different solvents.
- For example, the dielectric constant of water is known as 78.54. This value indicates that the coulomb force between the ions in water is 78.54 times lower compared to the force in the air. Eg: The attraction between Na and Cl in NaCl is 78.5 times lower in water. Therefore, it is readily soluble in water.
- Under vacuum, DC is 1. For other environments it is more than 1.
- Another important reason for water to be a good solvent is the high dielectric constant.

Source: Brey, W.S., *Physical Chemistry and Its Biological Applications*, p. 26, Academic Press (1978).

POLAR SOLVENTS

- They dissolve ionic and other polar compounds.
- Eg: Water, Dimethyl sulfoxide (DMSO), Formamide
- Water (dissolves: aldehyde, ketones, alcohol, phenols)



Alcohol with water

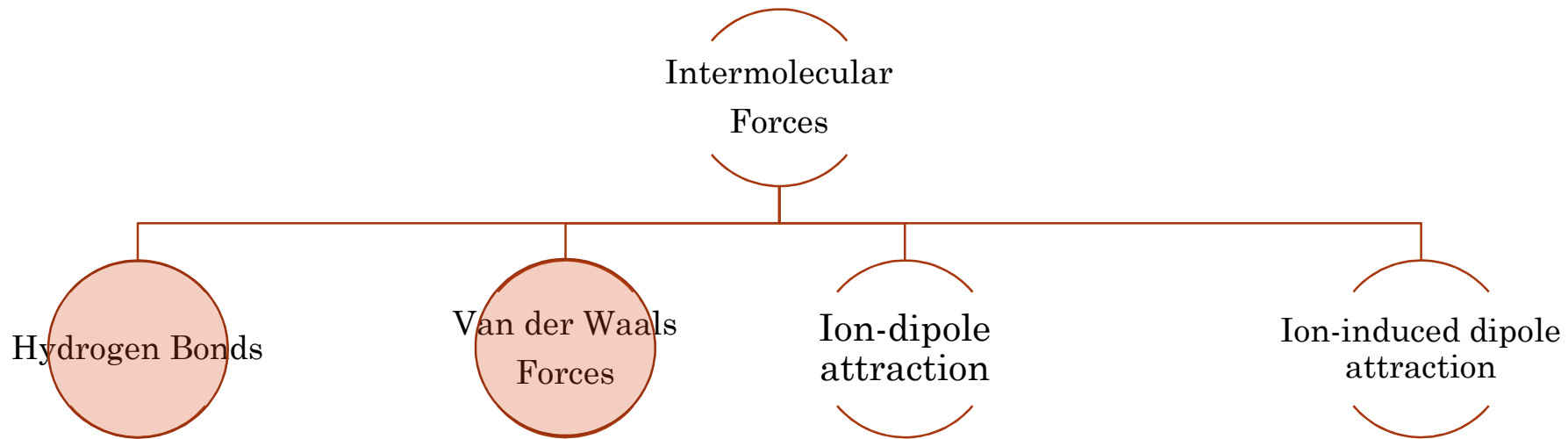
NON-POLAR SOLVENTS

- Have low dielectric constant
- Do not reduce attraction between weak or strong electrolytes
- Can not disrupt covalent bonds
- Can not dissolve ionic or polar compounds

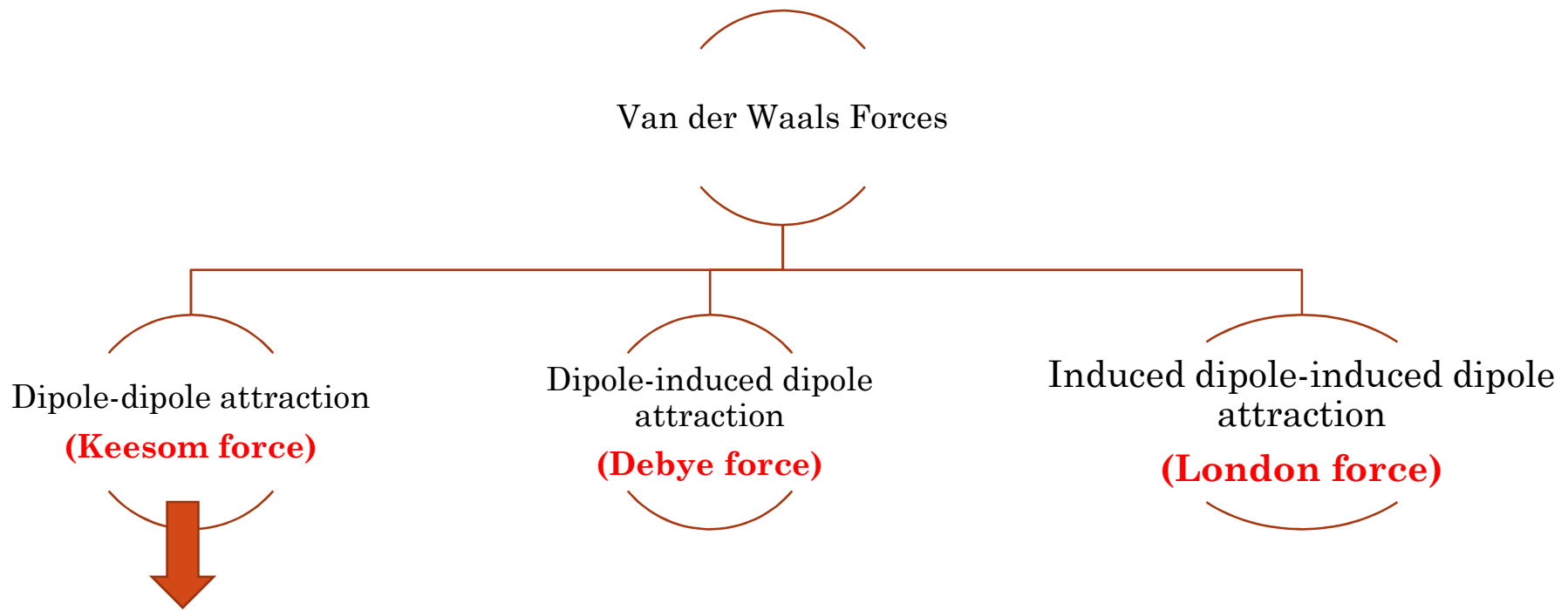
- Eg: Chloroform, diethyl ether, benzene, toluene

SEMI-POLAR SOLVENTS

- Also called intermediate solvents
- Miscible with polar and non-polar solvents
- Eg:
 - Acetone: (Ether solubility in water ↑)
 - Propylene glycol: (Water solubility of peppermint oil ↑)

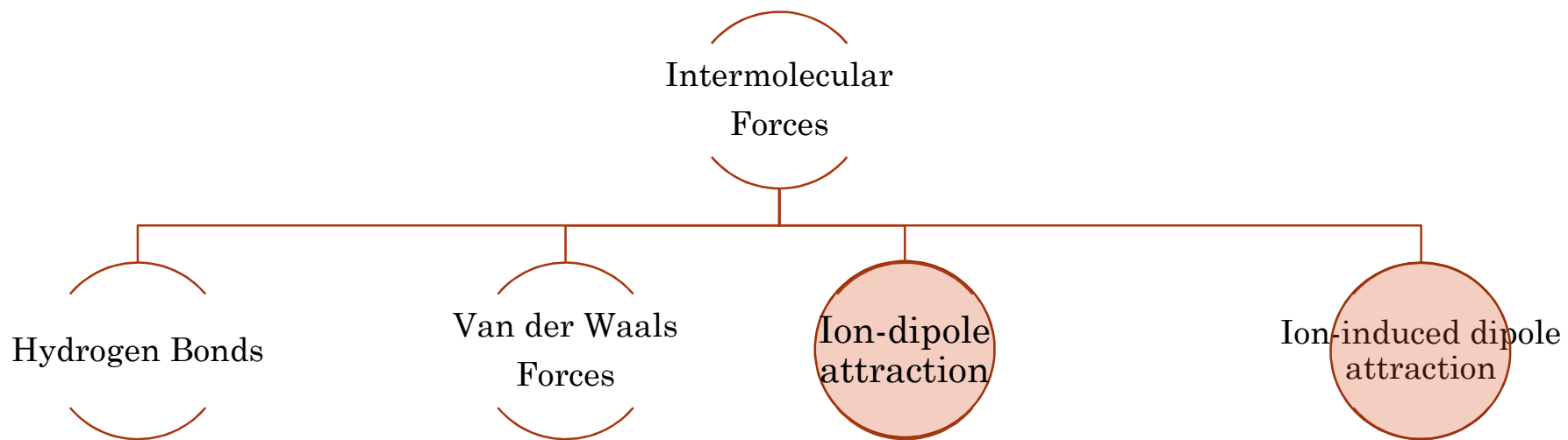


- Hydrogen is a small molecule and has a large electromagnetic field. For this reason, it can reach to electro-negative atoms and make electrostatic bond with them which we call **hydrogen bond**.
- alcohol, carboxylic acid molecules aldehydes, esters and polypeptides
- ICE-WATER-WATER VAPOR



Ethanol-water
Sugar-Water

- Van der Waals bonds are between molecules and are a physical interaction. They are not as strong as intramolecular bonds.
- The **dipole-dipole** bonds form as a result of the electrostatic attraction force between the partial charges of a polar molecule and the partial charges of another polar molecule.
- The dissolution of liquids consist of polar molecules is carried out by dipole-dipole interaction.



A non-polar molecule (Iodine) or atom may become polarized by an electron cloud of an ion (iodide). In this way, it can form a bond with the induced dipole ion. Such bonding is called **ion-induced dipole bonds**.

Solubility of gases in liquids

- Ammonia, carbon dioxide

Pressure →

Dissolution in water

Aerosol

- Nitrogen, carbon dioxide, propellant

Pressure →

Dissolution

Pressure:
Henry Law

Temperature: Usually
reduces the solubility
of gases in liquids

Presence of dissolved
electrolyte in liquid:
NaCl

Chemical reaction
between gas and liquid

Henry's Law- Effect of Pressure

$$c = k P$$

c = solubility of the gas (M)

k = Henry's Law Constant

P = partial pressure of gas

Henry's law is a gas law that states that the amount of dissolved gas is proportional to its partial pressure in the gas phase.

Henry's Law- Effect of Pressure

HIGH PRESSURE	LOW PRESSURE
HIGH CO ₂ SOLUBILITY	LOW CO ₂ SOLUBILITY

$$c = k P$$

c = solubility of the gas (M)
k = Henry's Law Constant
P = partial pressure of gas

Solubility of liquids in liquids

- Water-alcohol
- Water-essential oil

• Raoult's Law

$$P = X P^{\circ}$$

vapor pressure of solution
mole fraction of solvent
vapor pressure of pure solvent

- Ideal solutions:
- The liquid mixture that meets Raoult's law at all concentrations is called **ideal solutions**.
- **True solutions**: they show a positive or negative deviation from the Raoult law.

- Evaporation event: the number of molecules passing between the liquid phase and the vapor phase is equal
- The gas phase becomes saturated with the evaporating solvent molecules and this vapor forms pressure on the liquid depending on the temperature. This pressure is called the **vapor pressure of the liquid**.
- **Over time, more gas molecules pass through the space on the surface of the liquid, and the pressure of vapor from these molecules increases.**

Raoult's Law

The vapor pressure of the pure solvent is higher than the vapor pressure of the solution.

The presence of foreign molecules in the solvent causes a decrease in vapor pressure.

This reduction is related to the relative number of solute molecules.

Positive deviation:
carbon disulfide and acetone
(propanone) mixture

Negative deviation
acetone-chloroform
mixture

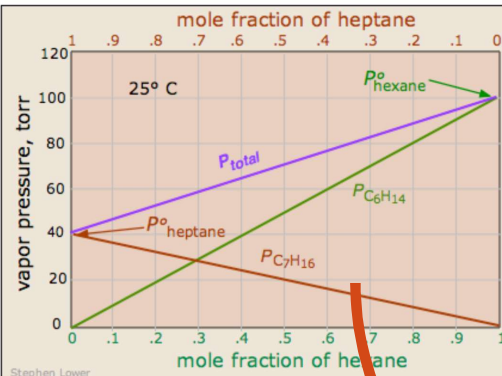
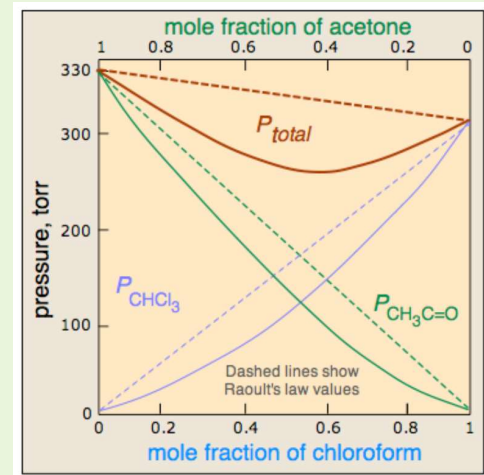
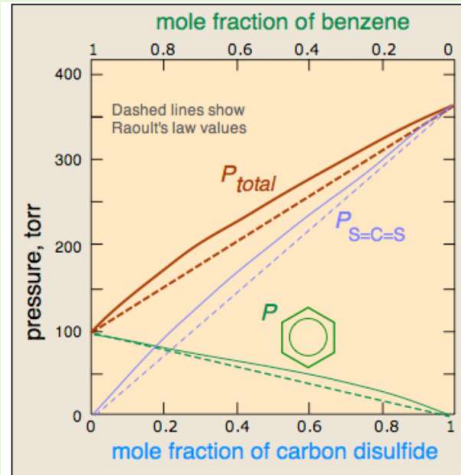


Figure 8.8.1: Raoult's law plot for a mixture of hexane and heptane.



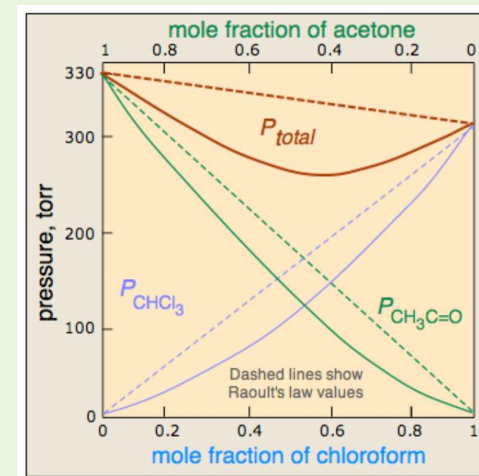
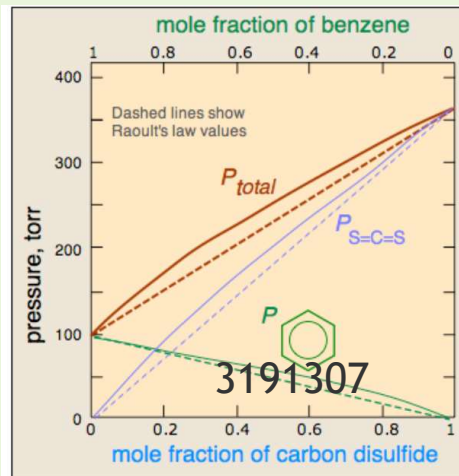
According to Raoult's law
Vapor Pressure-Mol
Fraction are linear

**Ideal
Solutions**

True Solutions

Positive deviation:
carbon disulfide and acetone
(propanone) mixture

Negative deviation
acetone-chloroform
mixture



Negative deviations from Raoult's law arise when the forces between the particles in the mixture are stronger than the mean of the forces between the particles in the pure liquids. The converse is true for positive deviations.

True Solutions

Percentage of ethyl alcohol Density(g/ml)

Alcohol:

95.1-96.9 % v/v 0.8051-0.8124

92.6-95.2 % w/w

Absolut (or anhydrous) alcohol:

99.5 % v/v 0.7907-0.7932

99.2 % w/w

Diluted alcohol

69.1-71.0 % v/v 0.8860-0.8883

61.5-63.5 % w/w

Eg: Prepare 100 ml of 70° alcohol using Ethanol.

$$V_1.d_1=V_2.d_2$$

V1: Volume required=100 ml

d1:Percentage of alcohol required=70 v/v

d2:Percentage of alcohol used=96 v/v

$100*70/96=72.9$ ml of 96 v/v alcohol is diluted to 100 ml with water in a graduated cylinder

Hydrogen Peroxide (Perhydrol) Calculations

Oxygenated water

100 ml 100V 30 g H₂O₂

100 ml 10V 3 g H₂O₂

10 ml 10 V X g H₂O₂

X = 0.3 g H₂O₂

100 ml H₂O₂ 30g H₂O₂

X 0.3 g H₂O₂

X = 1 ml of Pehydrol is diluted to 10 ml with water
in a graduated cylinder

Liquids that can be mixed with each other or mixed at a certain rate

A homogeneous part of a system which is separated from the other parts with certain borders is called **the phase**.

Phase diagrams are graphical representation of the physical states (solid, liquid, gas) of a substance or changes of the physical properties of mixtures composed of several substances as a function of temperature, pressure or mixture content.

Although some liquids are mixed with each other, it is practically impossible to mix some of them. Most of the liquids are between these two states and homogeneous mixtures can be obtained by using different ratios. Phase diagrams are used to determine these ratios.

When examining the equilibrium between phases, the equation proposed by Gibbs is used:

$$F = C - P + 2$$

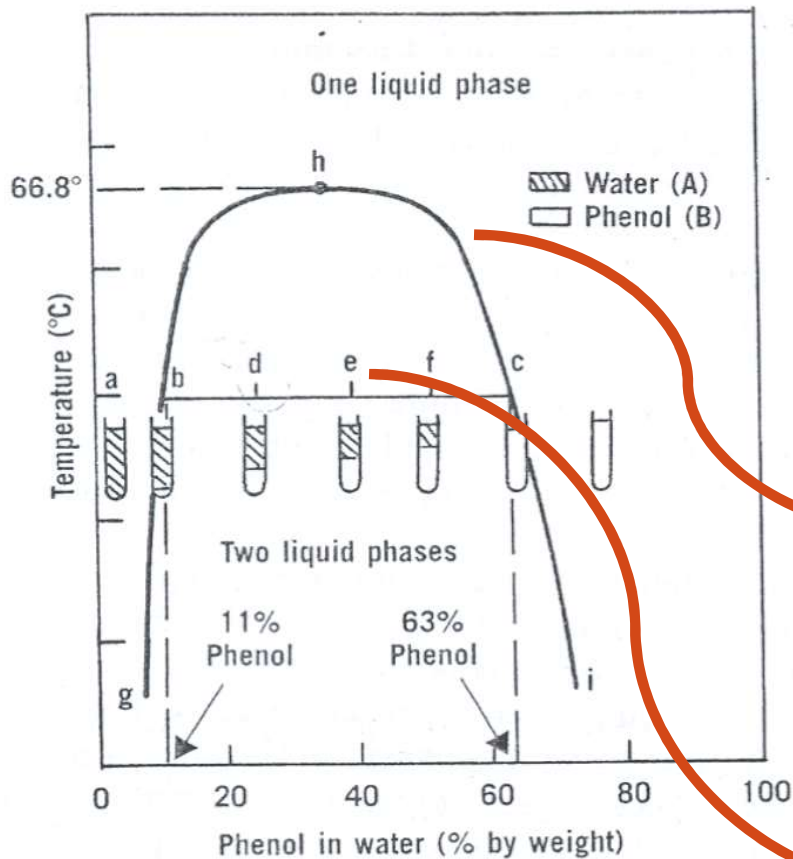
A: Number of components or component types in the system

P: number of phases in the system

F: degree of freedom (the minimum number of variables that must be known in order for the system to maintain its current state or to be able to fully identify the system)



Ratio of pressure, temperature or system components

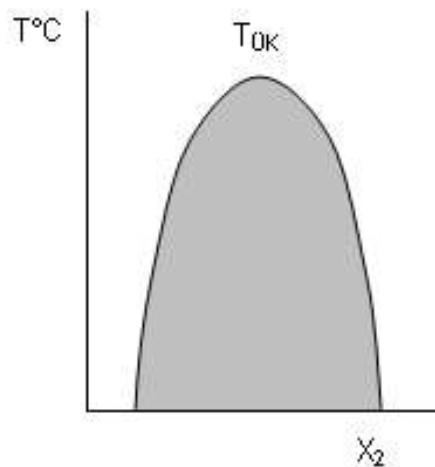


- gbhci "curve": separates the single-phase and two-phase region, gives the temperature and phenol concentration values showing that the two liquid phases are in equilibrium with each other.
- Outside of the curve: the region where both components form a single mixture
- $F = C - P + 2$
 $= 2 - 1 + 2$
 $= 3$ (pressure, temperature and concentration)
- The inside of the curve: the area in which two fluids
- do not mix
- $F = C - P + 2$
 $= 2 - 2 + 2$
 $= 2$ (temperature and concentration)

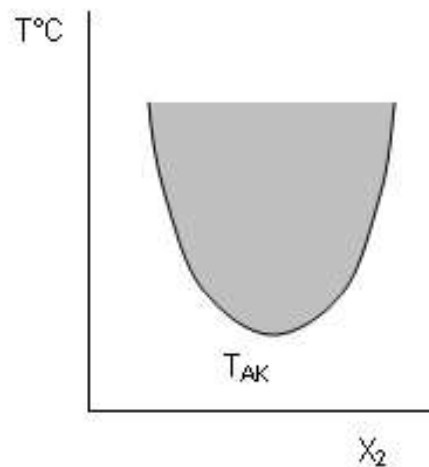
Depending on the pressure and temperature, the two liquids which give both homogeneous and heterogeneous mixture are called **partially mixable liquids**.

The upper limit of the temperature at which the two liquids are mixed in each ratio is called the **upper critical temperature**.

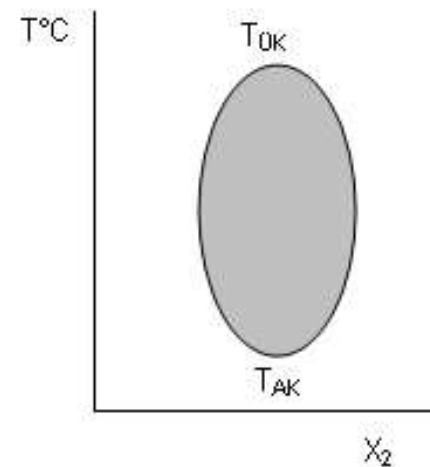
The lower limit of the temperature at which the two liquids are mixed in each ratio is called the **lower critical temperature**



The mixture does not have a lower critical temperature. This means that there is no low temperature at which components can be mixed at all ratios. The regions outside the curve are single phase in all three.



The mixture does not have an upper critical temperature but there is a lower CT.



There are both upper and lower CT at which mixtures can be mixed at all ratios. Or, in other words, the mixture can only be mixed in certain temperature ranges.

Solubility of solids in liquids

- The solubility of the solid in ideal solutions depends on the temperature, the melting point of the solid and the **molar melting heat** of the solid.
- **molar melting heat**: Amount of heat required to melt one mole of a solid

$$-\log X_2^i = \frac{\Delta H_f}{2.303R} \left(\frac{T_0 - T}{T_0 T} \right)$$

T = absolute temp. of the solution

T_0 = melting point of the solid solute

X_2^i = ideal solubility of the solute expressed in mole fraction

ΔH_f = Heat of solutions \rightarrow Heat of fusion

- For non-ideal solutions activity can be used instead of concentration and ideal solution laws can be applied

$$-\log X_2 = \frac{\Delta H_f}{2.303 R} \left(\frac{T_0 - T}{TT_0} \right) + \log \gamma_2$$

γ_2 : activity coefficient

ΔH_f : Molar melting heat

X_2^i : Ideal solubility of solids in moles

T_0 : Melting degree of solid in absolute temperature

T : Temperature of the solution in absolute temperature

Non-colligative properties of solutions

Non-colligative properties are properties that depend on the identity of solute and solvent.

- Viscosity, surface tension, taste, color...etc

Colligative properties of solutions

Colligative properties are mainly those properties that depend on the number of ions or molecules of a substance dissolved in a solvent.

- *vapor pressure lowering*
- *boiling point elevation*
- *freezing point depression*
- *osmotic pressure*

1.0 M aqueous sugar solution to a 0.5 M solution of table salt (NaCl) in water.

Solubility of salts in water

Solubility of solutes by absorbing heat: INCREASE WITH TEMPERATURE



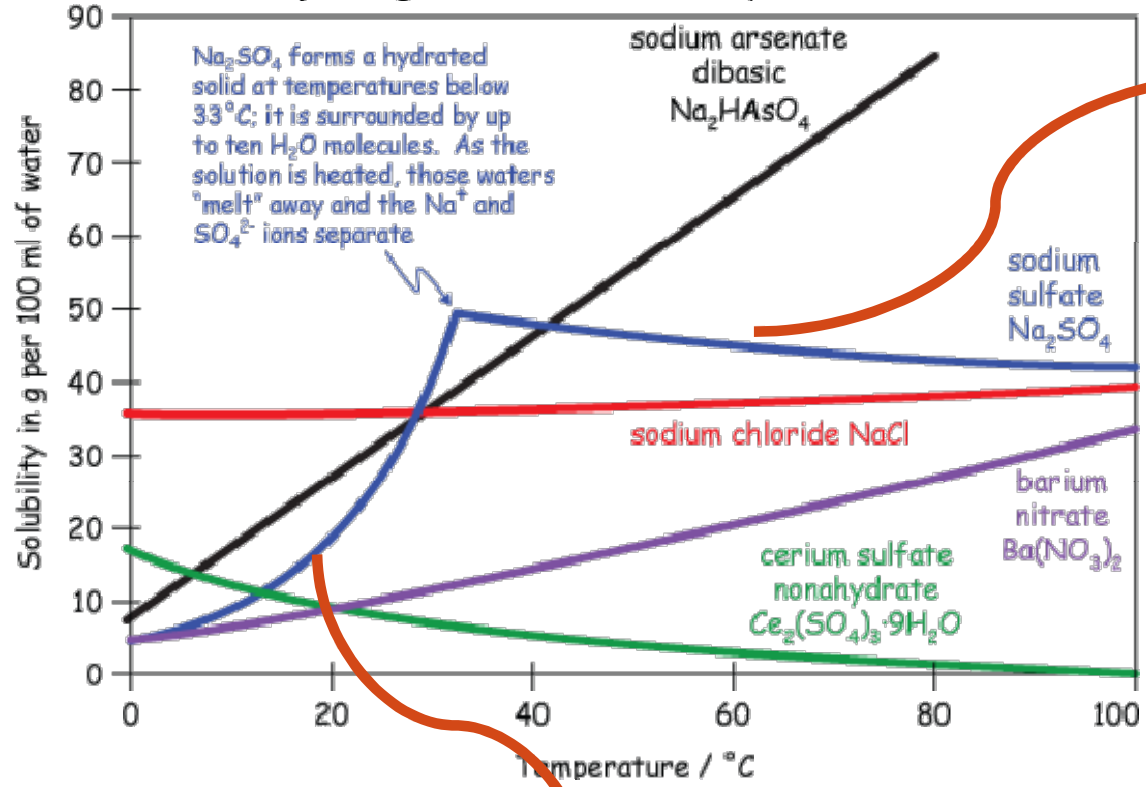
ENDOTHERMIC DISSOLUTION

Solubility of solutes by releasing heat: REDUCE WITH TEMPERATURE



EXOTHERMIC DISSOLUTION

Solubility changes as a function of temperature for a few salts

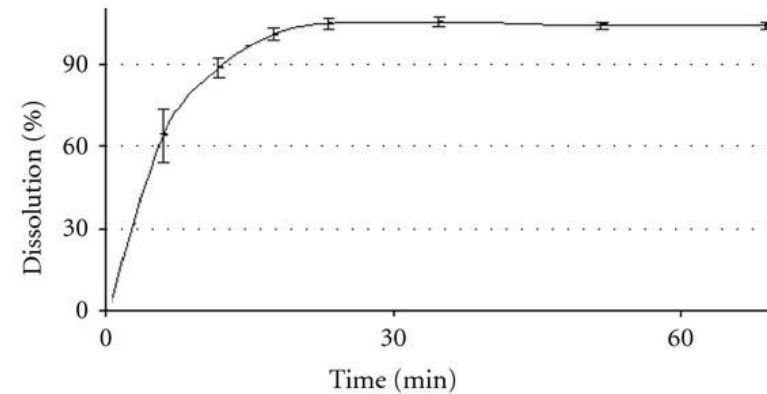


EXOTHERMIC

ENDOTHERMIC

Dissolution Rate

- Amount of solute dissolved in unit time in a given dissolution medium under certain pressure and temperature



Solubility

- Maximum amount of solute that can be dissolved under a certain pressure and temperature in a given dissolution medium
- **Ex:** Solubility of acetyl salicylic acid in water at 37 ° C is 10mg/mL.

Factors affecting the dissolution rate

- Particle size

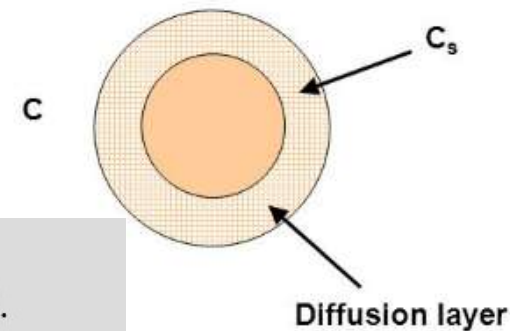
- Mixing

Noyes-Whitney equation

$$\frac{dC}{dt} = \frac{D \cdot A(C_s - C)}{h}$$

- Temperature

dc/dt = Dissolution rate.
 k = Dissolution rate constant (1st order).
 D = Diffusion coefficient/diffusivity
 C_s = Saturation/ maximum drug solubility.
 C = Con. Of drug in bulk solution.
 $C_s - C$ = concentration gradient.
 h = Thickness of diffusion layer.



- Generally, the rate of dissolution of substances in solvents is slow. Therefore, in order to achieve complete dissolution and **increase the rate of dissolution**:
- the temperature application may be carried
- Size can be reduced
- solubilizing agents can be used
- mixing can be applied

Generally, because of the **endothermic** properties of the substances, their solubility is higher at temperatures above room temperature. Therefore, if the dissolution is accelerated by increasing the heat, make sure that the material is stable and not volatile.

Factors affecting solubility

- Molecular size
- Solvent type
- Temperature
 - ★ Stability and volatile property should be checked
 - Endothermic reaction (sugar-water)
 - Exothermic reaction (methyl cellulose-water)
- Solvent pH
- Cosolvents
- Surface Active Agents

Molecular size

- It is reported that large and organic molecules have less solubility in water than small molecules and that the solubility decreases with increasing molecular weight.

pH and pKa effect

- SOLVENT: Water
- SOLUTE: Weak acid or weak base

Water is generally used as solvent in formulation studies. The active substances are generally weak acid or weak base. Water sometimes ionizes these substances without sometimes decomposing them into ions

pH ve pKa effect

- SOLVENT: Water
 - SOLUTE: Weak acid or weak base
- Dissolved by ionization ★ pH
- Dissolution without ionization

If there is better solubility in acidic medium compared to water: **Weak base**

If there is better solubility in basic medium compared to water: **Weak acid**

If there is better solubility is obtained both in asidic and basic medium compared to water: **amphoteric structure or zwitterion behavior**

The **intrinsic solubility** is the equilibrium **solubility** of the free acid or base form of an ionizable compound at a pH where it is fully non-ionized.

Compounds do not constitute salt since they are non-ionized and therefore only themselves can be mentioned.

Henderson–Hasselbalch equation

Here, pKa can be determined from the changes in solubility or the solubility at any pH can be calculated.

Weak base, strong acid salt

$$\text{pH} = \text{pK}_a + \log \frac{[\text{B}]}{[\text{BH}^+] - [\text{B}]}$$

[B]: the molar concentration of the base moiety,
[BH⁺]: the molar concentration of the salt

Weak acid, strong base salt

$$\text{pH} = \text{pK}_a + \log \frac{[\text{AH}] - [\text{A}^-]}{[\text{A}^-]}$$

[A]: the molar concentration of the asidic moiety,
[AH]: the molar concentration of the salt

Sodium phenobarbital: Weak acid salt
Soluble in strong alkaline pH

If the pH is lowered to below 8.3, the ionized part is converted to nonionized phenobarbital and it precipitates

Cosolvent effect

- Generally, the solubility of solids in solvent mixtures is greater than the solubility in a single solvent. This is called **cosolvent effect** and the other solvents which increase the solubility are called **cosolvent**.

Surface active agents (Surfactants)

Crystal structure

AMORPHOUS > CRYSTAL

Dissolution Rate & Solubility

	Dissolution Rate	Solubility of Solids	Solubility of Gases
Heating	Increase ↑	Increase ↑	Decrease ↓
Mixing	Increase ↑	X	Decrease ↓
Increasing surface area	Increase ↑	X	X
Increasing the surface pressure of solution	X	X	Increase ↑

Classification of solutions according to the preparation methods

- Simple mixing  Simple Solutions
- Chemical reaction
- Extraction

Classification of solutions according to the preparation methods

Solutions by simple mixing

- Prepared by dissolving the solute in the solvent (by stirring or heating).



Simple Solutions

- The solvent may contain other ingredients which stabilize or solubilize the active ingredient e.g. solubility of Iodine is 1: 2950 in water however, it dissolves in presence of KI due the formation of more soluble polyiodides ($KI \cdot I_2$ $KI \cdot 2I_2$ $KI \cdot 3I_2$ $KI \cdot 4I_2$). [Strong Iodine Solution USP (Lugol's Solution)].

CONCENTRATED ETHANOL IOD SOLUTION (USP 27)

Potassium iodide		50 g
Iodine		70 g
Purified water		50 ml
Alcohol	q.s.	1000 ml

Classification of solutions according to the preparation methods

Solutions by chemical reaction

- Solutions by chemical reaction are prepared by reacting two or more solutes with each other in a suitable solvent

Calcium hydroxide + Lactic acid \longrightarrow Calcium Lactate
(Used in Ca deficiency)

- Aluminum subacetate solution
- Calcium sulfide solution

Classification of solutions according to the preparation methods

- **Solution by Extraction**

- Plant or animal products are prepared by suitable extraction process using water or other solvents. They are commonly used after filtration. Extraction process will be discussed separately. Belladon extract can be given as an example.

Excipients Used in Solution Formulations

Active Agents

- The purity and physicochemical properties of the active agent(s) should be well known.

Solvents

- ***a- Polar solvents:*** *The solvents in this group are mainly water-miscible solvents. (water, glycols, propylene glycol)*
- ***b-Semi-polar solvents*** *(ethanol, isopropyl alcohol and acetone)*
- ***c- Nonpolar solvents:*** *This group contains water-immiscible solvents. (oils, benzene, carbon tetrachloride, chloroform and liquid paraffin)*

Sweeteners

- Sucrose (often used in combination with sorbitol, glycerin and other polyols to prevent crystallization)
- Saccharin, Aspartame (phenylalanine and methyl ester of aspartic acid)

- **Saccharin** is 250-500 times sweeter than sucrose.
- However, if not properly used in the formulation, it leaves a bitter taste in the mouth.
- As an alternative **aspartame** is used as an artificial sweetener.
- Aspartame is methyl ester of aspartic acid and phenylalanine. It is 200 times sweeter than sucrose. It doesn't leave bitter taste like saccharin.

Viscosity Enhancers

- Adjustment of viscosity in solutions is important for the flowability of the preparation.
- This can be achieved by adjusting the sucrose concentration or with viscosity enhancing agents. Examples include polyvinyl pyrrolidone, various cellulose derivatives (eg, methyl cellulose, sodium carboxymethyl cellulose).

Flavors and fragrances

- They are added to oral or oramucosal solutions. They are used to mask unwanted taste and odors. The aromas that can be preferred in the selection of appropriate flavors and fragrances are given in the Table.

Felt taste	
Salty	Apricot, peach, mint, etc.
Spicy	Cherry, walnut, chocolate, anise, etc.
Sweet	Fruit, vanilla, etc.
Sour	Lemon etc.

Coloring agents

- The color and clarity of the preparation should be considered in solutions.
- Appropriate color is selected by considering the taste and odor of the solution.
- For example, for a solution with mint taste, blue or green color agents can be used. While red color is more appropriate for cherry flavor.
- Coloring agents to be used in dosage forms should be FDC (Food, Drug and Cosmetics) coded.
- Their concentration in the solutions should be less than 0.001%.

Preservatives

a) Antioxidants

b) Antibacterial agents

Antioxidants

Antioxidants are currently used as efficient **excipients** that delay or inhibit the oxidation process of molecules. Usually **antioxidants themselves** become oxidized and prevent the pharmaceutical solution.

Oil based solutions

Butyl hydroxy anisole (BHA)
Butyl hydroxy toluene (BHT)
Propyl gallate

→ (0.005-0.02%)

Tocopherol

→ (0.05-0.075%)

Aqueous solutions

Sodium sulphite
Sodium bisulfite
Sodium metabisulphite

→ (0.1-0.2%)

Ascorbic acid

→ (0.01-0.05 %)

Antibacterials:

They show bactericide effects.

Benzalkonium chloride - 0.01%,
Chlorbutanol 0.3-0.5%
Chlorocresol 0.03-0.05%
Nipa esters (methyl, ethyl and propyl esters of p-hydroxy benzoic acid) 0.1-0.3%,
Sorbic acid 0.2%
Phenol 0.5%
Mercury compounds (phenyl mercury nitrate, phenyl mercury borate, phenyl mercury acetate) 0.002-0.005%
Thiomersal% 0.001

Benzalkonium chloride: is a type of cationic surfactant. It is an organic salt classified as a quaternary ammonium compound. They are active against bacteria and some viruses, fungi, and protozoa.

Used for germicide and antiseptic purposes in the disinfection of heat sensitive instruments. Diluted aqueous solution (DF:750) and alcoholic solutions are used for disinfection of wounds and skin surfaces.

For nasal and ocular preparations, it should be diluted (DF:5000).

Chlorbutanol: Used as antiseptic and local anesthetic. It is used orally with the same therapeutic effects. In addition, there are sedative and hypnotic effects. It is used as an antiseptic and local anesthetic in the veterinary and orally as a sedative and hypnotic.

Benzoic Acid: Sodium benzoate is one of the most widely used derivatives. It is widely used in foods, syrups, solutions and similar preparations.