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Solubility & Distribution Phenomena

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Outlines

- Objectives
- Solubility & Dissolution
- Solubility Expression
- Solvent-Solute Interaction

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Objectives

1. Define saturated solution, solubility, and unsaturated solution.
2. Describe and give examples of polar, nonpolar, and semipolar solvents.
3. Define complete and partial miscibility.
4. Understand the factors controlling the solubility of weak electrolytes.
5. Describe the influence of solvents and surfactants on solubility.
6. Define thermodynamic, kinetic, and intrinsic solubility.
7. Measure thermodynamic solubility.
8. Describe what a distribution coefficient and partition coefficient are and their importance in pharmaceutical systems.

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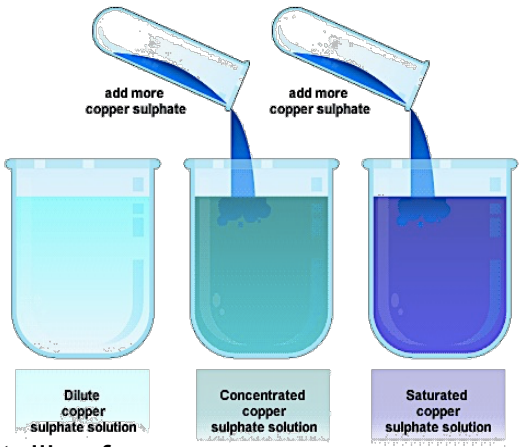
Solubility

1-Quantitative: ?

2-Qualitatives: ?



➢Unsaturated or subsaturated solution.

➢Supersaturated solution

➢Thermodynamic solubility: most stable crystalline form

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Case study

- Example: **Ritonavir**: HIV protease inhibitor 17
- 1992 –discovered
- 1996 – launch of capsule/polymorph I
- 1998 – polymorph II appears ↓ solubility →PRODUCT WITHDRAWN FROM THE MARKET
- 1998-1999 – Reformulation of the compound ↑costs
- New softgel capsule launched

RESULT :

NEW product
Increased costs
Time loss

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Differences between Solubility & Dissolution

Solubility	Dissolution
Intrinsic dynamic properties	Extrinsic Kinetic properties
Depends on:	Depends on:
Chemical and physical properties of the solute & solvent	Chemical and physical properties of external phase
pH	Complexation
Temperature	P.S. & S.A.
Pressure	Solubilizing agent

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Solubility Expression

Description forms (solubility definition)	Parts of solvent required for one part of solute	Solubility range (mg/ml)	Solubility assigned (mg/ml)
Very soluble (VS)	<1	>1000	1000
Freely soluble (FS)	From 1 to 10	100-1000	100
Soluble	From 10 to 30	33-100	33
Sparingly soluble (SPS)	From 30 to 100	10-33	10
Slightly soluble (SS)	From 100 to 1000	1-10	1
Very slightly soluble (VSS)	From 1000 to 10,000	0.1-1	0.1
Practically insoluble (PI)	>10,000	<0.1	0.01

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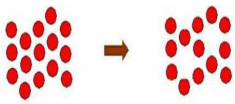
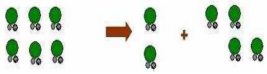
Mechanism of solubility

Step 1



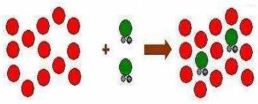
Holes open in the solvent

Step2



Molecules of the solid breaks away from the bulk

Step 3



The freed solid molecule is integrated into the hole in the solvent

- Accordingly , there will be endothermic and exothermic process of solubilization.
- The solubility of carbonated water is …….

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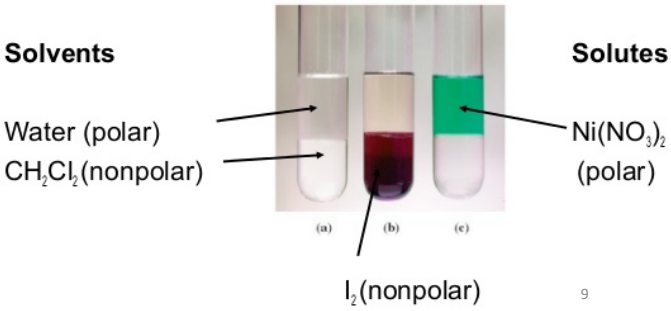
Solvent-Solute Interactions

Like dissolves Like

- ***Water for salts and sugars***
- ***Mineral oils for substances that are slightly soluble in water***

	Solvent	
Solute	**Polar**	**Nonpolar**
Ionic	Soluble	Insoluble
Polar	Soluble	Insoluble
Nonpolar	Insoluble	Soluble



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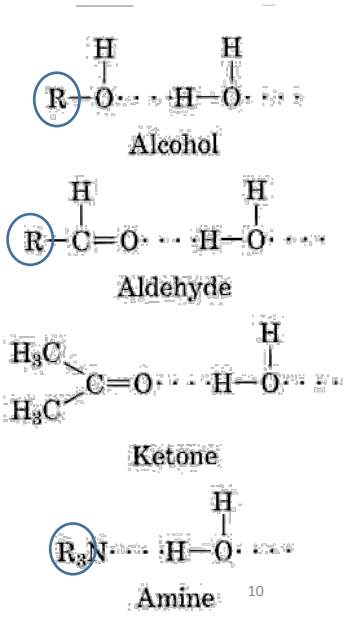
Polar solvents

Water can dissolve solutes by different mechanisms

- ***Dipolar interaction (eg: Water dissolves ionic solutes)***
- ***H-bonding (eg: Water dissolves Alcohols, phenols, aldehydes, ketones and amines.***
- ***What are the effect of R group on water miscibility?***



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Polar solvents

Effect of R- Group:

- ***Ratio of polar to non-polar part in the molecules: (eg: increase the chain of the aliphatic molecules resulted in ..... Water solubility).***
- ***Increase number of polar group leads to increase in water solubility (e. propylene glycol has two –OH groups).***
- ***Branching of the aliphatic chain reduce the non polar properties and so increase the water solubility. (eg: butyl alcohol in water e.g. tertiary butyl alcohol is miscible with water in all proportions while n-butyl dissolve in extent of about 8g/100mL at 20°C.***

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Non-Polar solvents

CCl_4, Benzene, Mineral oils

- ***They are not capable to reduce the attraction between ions of strong or weak electrolytes because of low dielectric constant.***
- ***They can dissolve the nonpolar cpd by:***
  1. ***Induced dipole interaction.***
  2. ***VDW-London type of interaction (interaction between uncharged atoms).***
- ***They can dissolve oils, fats, fatty acids, alkaloids such as morphine.***

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Semipolar solvents

Alcohol, Acetone, PG

- ***They induce a certain degree of polarity in nonpolar solvents. e.g benzene in alcohol***
- ***They also Known as (intermediate solvents)***
- ***e.g.***
  1) ***Acetone increases the solubility of ether in water.***
  2) ***Alcohol on water-caster oil mixtures.***
  3) ***Propylene glycol on water-peppermint oil and on water benzyl benzoate, (here they can be called Cosolvent)***

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TABLE 9-2

POLARITY OF SOME SOLVENTS AND THE SOLUTES THAT READILY DISSOLVE IN EACH CLASS OF SOLVENT

	Dielectric Constant of Solvent, ε (Approximately)	Solvent	Solute	
Decreasing Polarity	80	Water	Inorganic salts, organic salts	Decreasing Water Solubility
↓	50	Glycols	Sugars, tannins	↓
	30	Methyl and ethyl alcohols	Caster oil, waxes	
	20	Aldehydes, ketones, and higher alcohols, ethers, esters, and oxides	Resins, volatile oils, weak electrolytes including barbiturates, alkaloids, and phenols	
	5	Hexane, benzene, carbon tetrachloride, ethyl ether, petroleum ether	Fixed oils, fats, petrolatum, paraffin, other hydrocarbons	
	0	Mineral oil and fixed vegetable oils		

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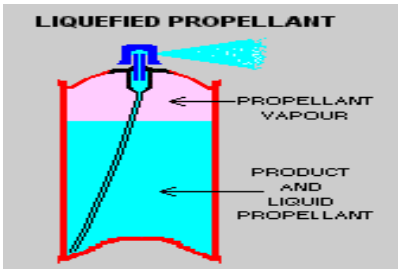
Solubility of Gases in Liquids

- Ex: Carbonated water: is exothermic process.
- Ex: Pharmaceutical aerosols: Liquefied gas under pressure “Propellant”



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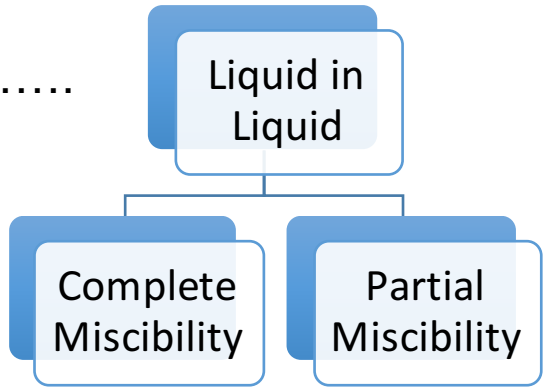
Solubility of Liquids in Liquids

- Ex: Hydroalcoholic solution: ……..
- Ex: Aromatic water: …….
- Ex: Spirits: ……



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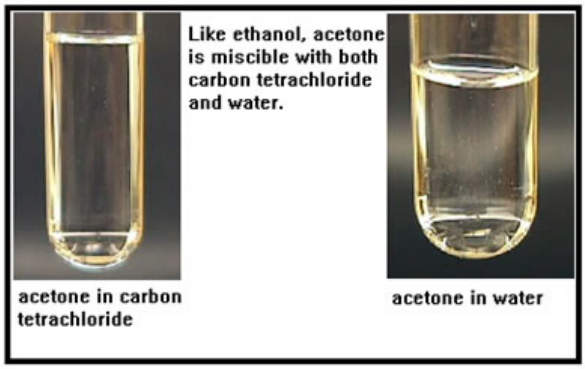
Complete miscibility

- Ex: Polar and semipolar solvents:
  - water-alcohol,
  - glycerin-alcohol,
  - alcohol-acetone
- Ex: Nonpolar solvents:
  - benzene and CCl4



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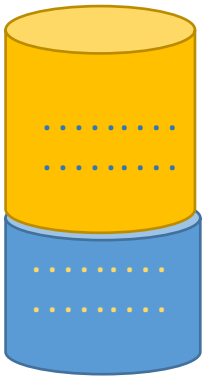
Partial miscibility

- Ex: Water + ether,
  Water + phenol
- The system will separated into 2 layers, each containing some of the other solvent.
- The temperature might **affect** such systems as shown in the following examples



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Water + Phenol

- At 50ºC they are miscible at conc below 11% and above 63%.
- At Temp > 66.8ºC, They are miscible at all proportions.
- Consolute temperature: …….

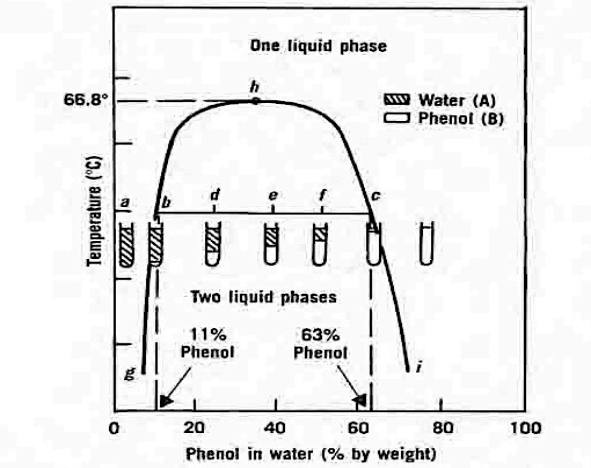

Fig. 2–23. Temperature–composition diagram for the system consisting of water and phenol. (From A. N. Campbell and A. J. R. Camp-

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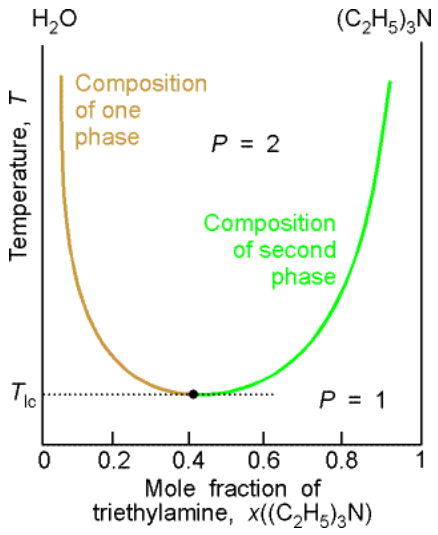
Water + Triethylamine

- They are miscible below consolute temperature.
- Consolute temp around 20ºC



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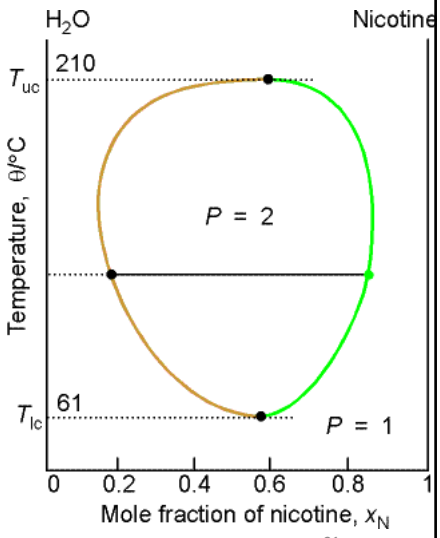
Water + Nicotine

- This system has upper (210ºC) and lower (61ºC) consolute temperature.
- Between 61-210ºC, the system will be partially miscible.



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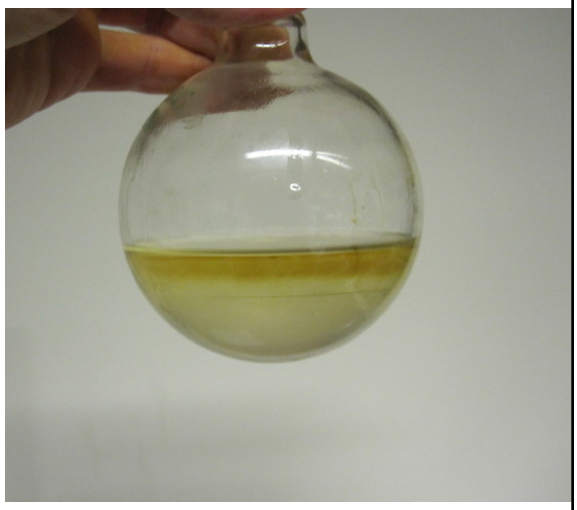
Water + Ethylether

- They don't have consolute temperature.
- They are partially miscible at any temperature



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EXAMPLE 9–1

Component Weights

A mixture of phenol and water at 20°C has a total composition of 50% phenol. The tie line at this temperature cuts the binodal at points equivalent to 8.4% and 72.2% w/w phenol. What is the weight of the aqueous layer and of the phenol layer in 500 g of the mixture and how many grams of phenol are present in each of the two layers?

Let Z be the weight in grams of the aqueous layer. Therefore, $500 - Z$ is the weight in grams of the phenol layer, and the sum of the percentages of phenol in the two layers must equal the overall composition of 50%, or $500 \times 0.50 = 250$ g. Thus,

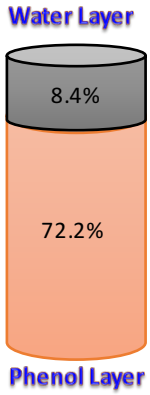
$$Z(8.4/100) + (500 - Z)(72.2/100) = 250$$

Weight of aqueous layer, $Z = 174$ g

Weight of phenol layer, $500 - Z = 326$ g

Weight of phenol in the aqueous layer, $174 \times 0.084 = 15$ g

Weight of phenol in the phenolic layer, $326 \times 0.722 = 235$ g



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Three components systems

- Examples:
  - Water +CCl_4+ acetic acid
  - Water + Phenol+ acetone
  - Water + castor oil + alcohol
  - Water + peppermint oil + PG

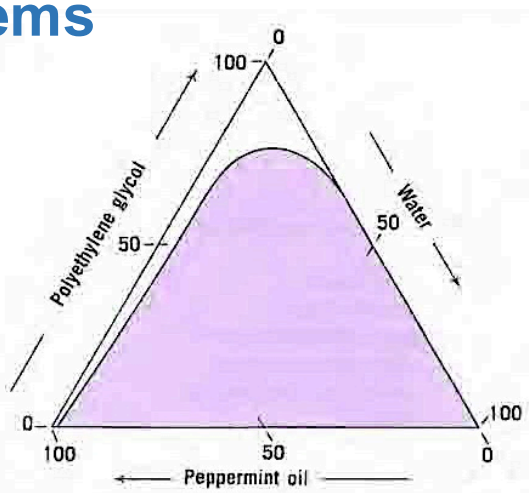

Fig. 9–2. A triangular diagram showing the solubility of peppermin oil in various proportions of water and polyethylene glycol.

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Solubility of solids in liquids

Acids:

- Carboxylic acid more than 5c are insoluble in water but soluble in ……
- Hydroxyl acid: eg: Citric and tartaric acids are soluble in water due to: ……
- Aromatic acid : eg: benzoic acid is soluble in …….
- Phenol is …… in water but ……. In dilute hydroxide solution

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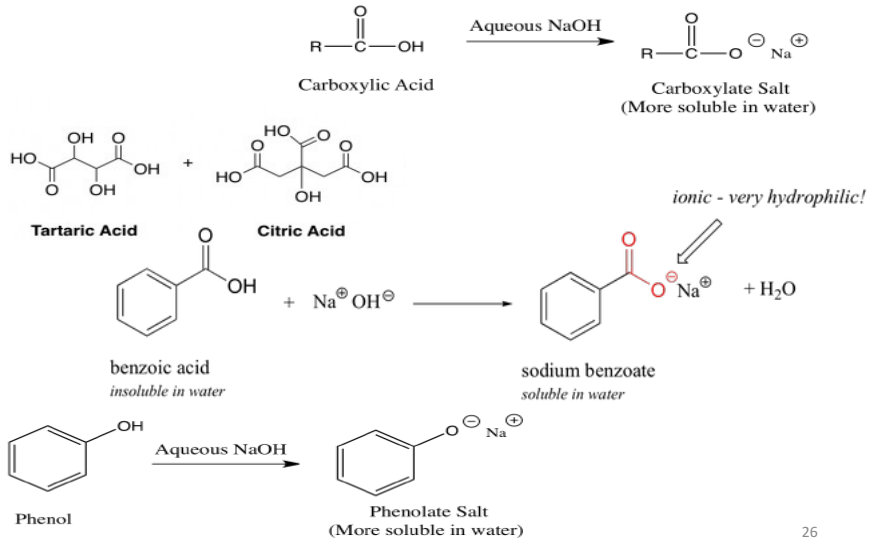
Solubility of S in L

- Carboxylic acid
- Hydroxyl acid
- Aromatic acid
- Phenol



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Solubility of S in L

Bases:

- Alkaloids and N- containing cpd are soluble in …… but not in water
- Barbiturates are insoluble in acids but soluble in NaOH
- Sulfonamide "sulfa drug" can form water soluble salt in alkaline solution

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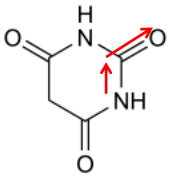
Solubility of S in L

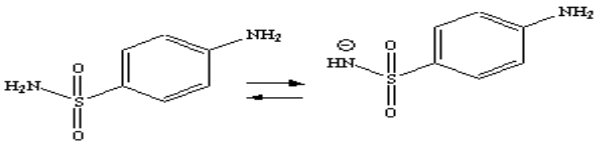
Bases:

- Alkaloids:

- Barbiturates



- Sulfonamide



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Calculating the solubility by pH

$$HP_{solid} \rightleftharpoons HP_{sol}$$
$$HP_{sol} + H_2O \rightleftharpoons H_3O^+ + P^-$$

The intrinsic solubility= S_o

$$S_o = [HP]_{sol}$$

The total solubility, S

$$S = [HP] + [P^-]$$

Soluble as undissociated

$$[P^-] = K_a \frac{[HP]}{[H_3O^+]} \quad OR \quad K_a = \frac{[H_3O^+][P^-]}{[HP]}$$

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$$S = S_0 + K_a \frac{S_0}{[H_3O^+]} \rightarrow S = S_0\left(1 + \frac{K_a}{[H_3O^+]}\right) \rightarrow (S - S_0) = K_a \frac{S_0}{[H_3O^+]}$$

$$\log (S - S_0) = \log K_a + \log S_0 - \log [H_3O^+]$$

Henderson Hasselbalch

$$pH_p = pK_a + \log \frac{S - S_0}{S_0}$$

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Henderson Hasselbalch

$$pH_p = pK_a + \log \frac{S - S_0}{S_0}$$

$$pH = pKa + \log \frac{Ionized}{Unionized}$$

For Salts of weak acid

$$pH_p = pK_w - pK_b + \log \frac{S_0}{S - S_0}$$

$$pH = pKa + \log \frac{Unionized}{Ionized}$$

For Salts of weak Base

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EXAMPLE 9–2

Phenobarbital

Below what pH will free phenobarbital begin to separate from a solution having an initial concentration of 1 g of sodium phenobarbital per 100 mL at 25°C? The molar solubility, S_0, of phenobarbital is 0.0050 and the pK_a is 7.41 at 25°C. The secondary dissociation of phenobarbital, referred to previously, can ordinarily be disregarded. The molecular weight of sodium phenobarbital is 254.

The molar concentration of salt initially added is

$$\frac{\text{g/liter}}{\text{mol.wt.}} = \frac{10}{254} = 0.039 \text{ mole/liter}$$

$$pH_p = 7.41 + \log \frac{(0.039 - 0.005)}{0.005} = 8.24$$

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Influence of the Solvents on the Solubility

- Cosolvency is .....
- The concept is used to enhance the solubility at the critical pH

The solubility of phenobarbital

Solubility	Solvents
1:1000	Water
1:10	Ethanol
1:40	Chloroform
1:15	Ether

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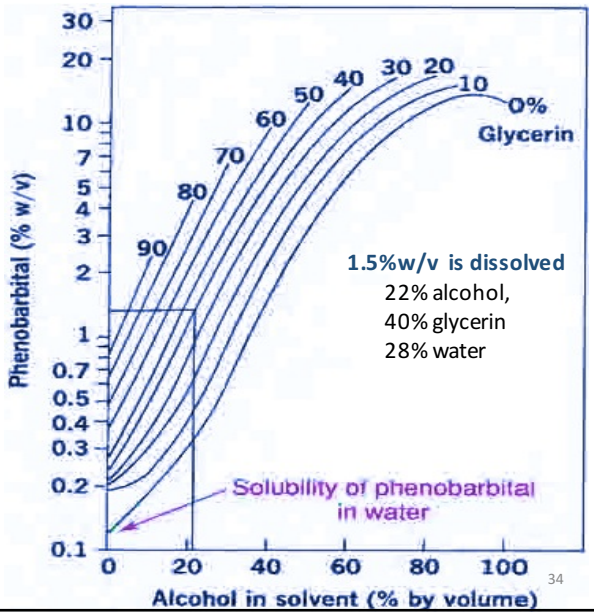
- Phenobarbital solubility in water is greatly enhanced by the addition of ethanol and glycerin



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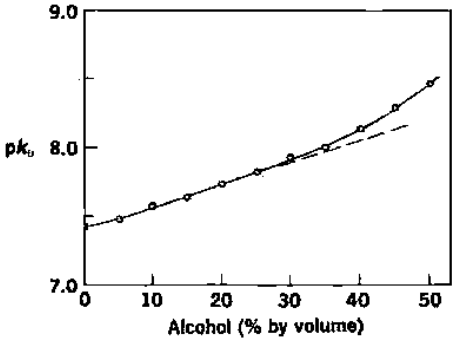
Combined effect of pH and solvents



The influence of alcohol concentration on the dissociation constant of phenobarbital

- The solvent that enhance the solubility of drugs (weak acids and bases) they cause a change in the dissociation constant as shown in phenobarbital.
- 30 % alcohol increases the pKa of phenobarbital from 7.41 to 7.92 and increase the S_o from 0.005M to 0.0238M

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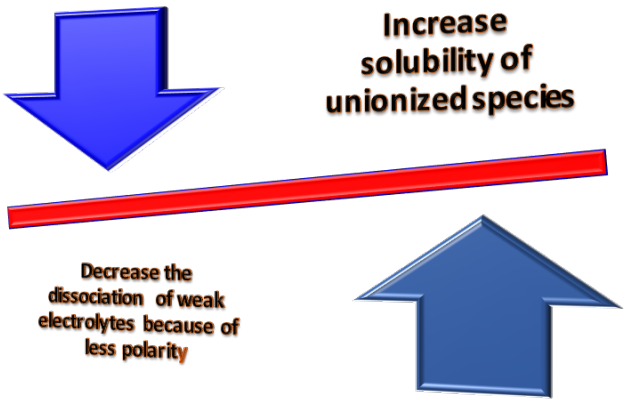
The solvent effect on the solubility of weak electrolytes by



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EXAMPLE 9–3

Minimum pH for Complete Solubility

What is the minimum pH required for the complete solubility of the drug in a stock solution containing 6 g of phenobarbital sodium in 100 mL of a 30% by volume alcoholic solution? From equation (9–9),

$$pH_p = 7.92 + \log \frac{0.236 - 0.028}{0.028}$$

0.005

$$pH_p = 7.92 + 0.87 = 8.79$$

For comparison, the minimum pH for complete solubility of phenobarbital in an aqueous solution containing no alcohol is computed using equation (9–9):

$$pH_p = 7.41 + \log \frac{0.236 - 0.005}{0.005} = 9.07$$

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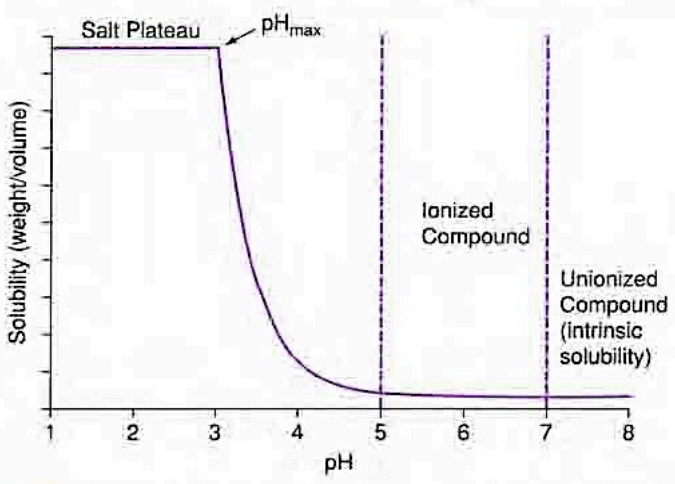

Fig. 9–8. pH–solubility profile for a compound with a single, basic pK_a value of 5. The four regions of pH-dependent solubility are the salt plateau, pH_{max}, ionized compound, and un-ionized compound. (Adapted from Bhattachar et al. 2006,[4] with permission.)

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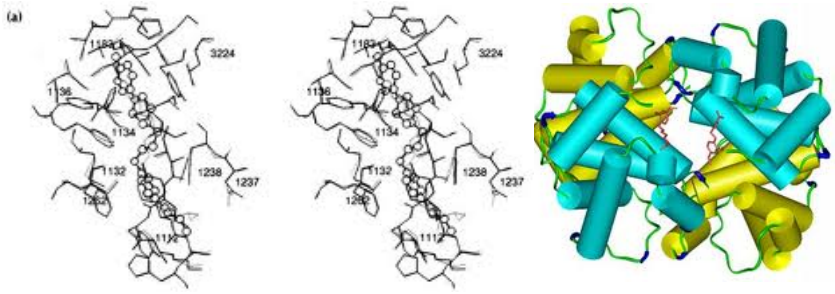
Influence of complexation

1+1 ≠ 2

Solids mixing lead to different solubilities and new experiment for mixture should be conducted



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Influence of size of particles

EXAMPLE 9–4

Particle Size and Solubility

A solid is to be comminuted so as to increase its solubility by 10%, that is, s/s_o is to become 1.10. What must be the final particle size, assuming that the surface tension of the solid is 100 dynes/cm and the volume per mole is 50 cm^3? The temperature is 27°C.

$$r = \frac{2 \times 100 \times 50}{2.303 \times 8.314 \times 10^7 \times 300 \times 0.0414}$$

$$= 4.2 \times 10^{-6} \text{cm} = 0.042\ \mu\text{m}$$

$$\log \frac{S}{S_o} = \frac{2\gamma V}{2.303RTr}$$

S= solubility of fine particles
So= solubility of relatively large particles
γ=surface tension of particle
V=molar volume (cm^3/mole)
r=radius of particle (cm)
R= gas constant $8.3*10^7$ erg/deg.mol
T= absolute temperature

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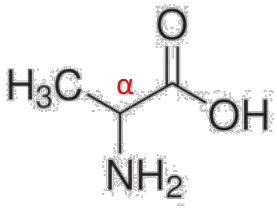
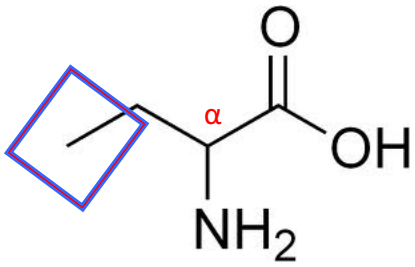
The effect of molecular configuration



α alanine
1.66 mole/Liter



α amino butyric acid
1.8 mole/Liter

- Less work is required to separate asymmetric molecules within the crystal compare with the work of symmetric ones.
- The extra carbon in side chain responsible for the asymmetry of crystal form and enhance the solubility although it's a lipophilic addition

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POOR AQUEOUS SOLUBILITY

Dose potency	Required Solubility
1mg/kg	0.1g/L

And if less than 0.01g/L is consider as poor soluble drug

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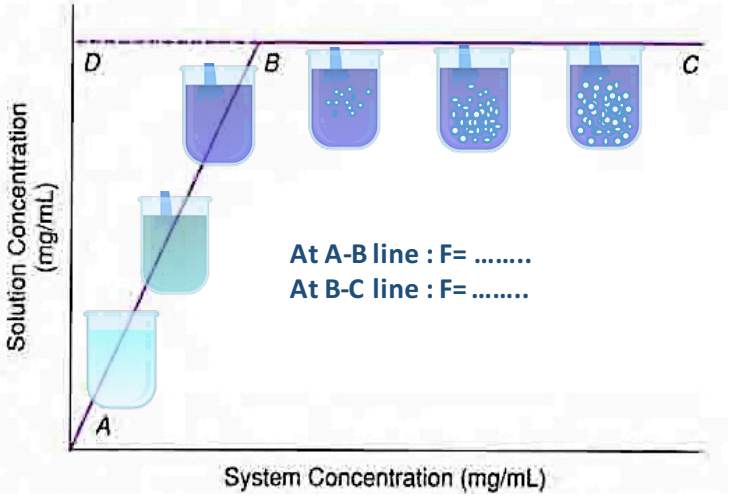
Phase rule and solubility

Phase Equilibrium and Phase Rule: By J. Willard Gibbs



At A-B line : F= ……..
At B-C line : F= ……..

$$F = C - P + 2$$

F= Degree of freedom (number of independent variable: Conc, Temp, Pressure
C= Smallest number of components
P=Number of phases

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Measurement of solubility

Thermodynamic steps of solubility are :

1. Add more drug
2. Wait for equilibrium
3. Remove excess
4. Analyze content (HPLC)

Kinetic solubility (anti solvent pption)

1. Dissolve the drug in strong organic solvent.
2. Add the stock gradually to water.
3. The drug ppt at the point when water cannot take more drug (ie solubility).
4. It measures the pption rate rather than dissolution.

Stock solution of drug in dimetyl sulfoxide

Optically detection of precipitation

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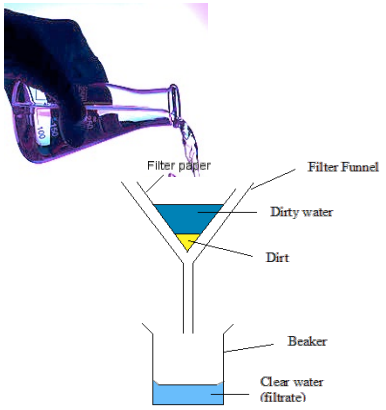
Limitations of solubility measurement

Limitation of shake-flask method:

1. Adsorption onto vial or filter
2. Incomplete phase separation
3. Compound instability
4. Slow dissolution.
5. Inaccurate pKa determination.



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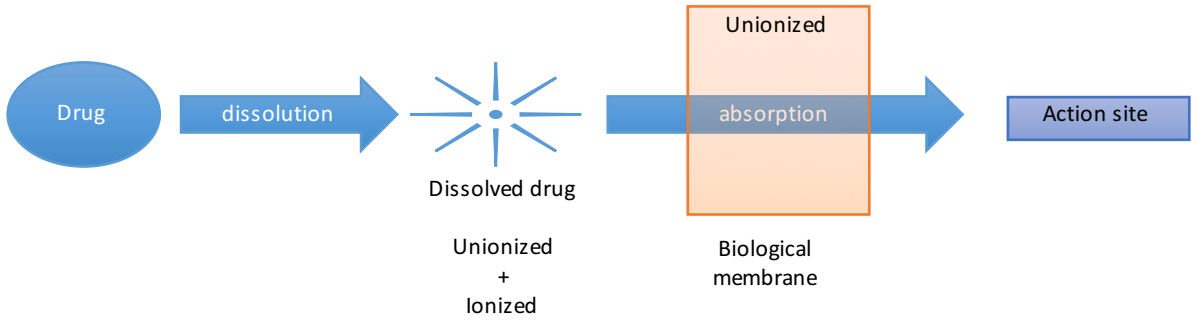
Partition Coefficient



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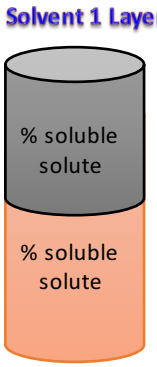
Partition Coefficient



$$\frac{C_1}{C_2} = K_a = P$$ = Distribution ratio, distribution coefficient or partition coefficient

Two immiscible solvents

Applications of log P:

1. Indication of lipophilicity
2. Drug permeation, absorption, distribution, excretion, and action
3. Drug extraction
4. Preservation of oil/water systems.

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EXAMPLE 9–5

Distribution Coefficient

When boric acid is distributed between water and amyl alcohol at 25°C, the concentration in water is found to be 0.0510 mole/liter and in amyl alcohol it is found to be 0.0155 mole/liter. What is the distribution coefficient? We have

$$K = \frac{C_{H_2O}}{C_{alc}} = \frac{0.0510}{0.0155} = 3.29$$

No convention has been established with regard to whether the concentration in the water phase or that in the organic phase should be placed in the numerator. Therefore, the result can also be expressed as

$$K = \frac{C_{alc}}{C_{H_2O}} = \frac{0.0155}{0.0510} = 0.304$$

One should always specify, which of these two ways the distribution constant is being expressed.

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Effect of the Ionic Dissociation & Molecular Association on Partition

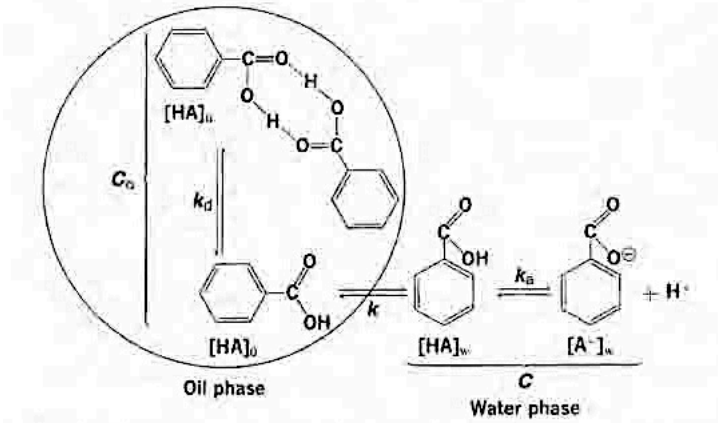

Fig. 9–9. Schematic representation of the distribution of benzoic acid between water and an oil phase. The oil phase is depicted as a magnified oil droplet in an oil-in-water emulsion.

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Extraction

To extract a solute from a solvent we need to use immiscible solvent with subsequent washing

$$K = \frac{\text{Concentration of solute in original solvent}}{\text{Concentration of solute in extracting solvent}}$$

$$K = \frac{w_1 / V_1}{(w - w_1)/V_2} \qquad (9\text{–}24)$$

or

$$w_1 = w \frac{K V_1}{K V_1 + V_2} \qquad (9\text{–}25)$$

The process can be repeated, and after n extractions,[37]

$$w_n = w \left(\frac{K V_1}{K V_1 + V_2} \right)^n \qquad (9\text{–}26)$$

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EXAMPLE 9–7

Distribution Coefficient

The distribution coefficient for iodine between water and carbon tetrachloride at 25°C is $K = C_{H_2O}/C_{CCl_4} = 0.012$. How many grams of iodine are extracted from a solution in water containing 0.1 g in 50 mL by one extraction with 10 mL of CCl_4? How many grams are extracted by two 5-mL portions of CCl_4? We have

$$w_1 = 0.10 \times \frac{0.012 \times 50}{(0.012 \times 50) + 10}$$

$$= 0.0057 \text{ g remains or } 0.0943 \text{ g is extracted}$$

$$w_2 = 0.10 \times \left(\frac{0.012 \times 50}{(0.012 \times 50) + 5}\right)^2$$

$$= 0.0011 \text{ g of iodine}$$

Thus, 0.0011 g of iodine remains in the water phase, and the two portions of CCl_4 have extracted 0.0989 g.

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Thanks for your attention

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T/F with explanation:

The rectal absorption of *p*-aminobenzoic acid **(pKa 3.3)** could be anticipated from an aqueous enema buffered at **pH (7.8)**.

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Group A

If the dose potency of a drug (A) is **10 mg/kg**, then the minimum required solubility of drug (A) oral formulation is **0.1g/L**.

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Group B

pH – ionization profile for a basic drug with pKa =7.

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Group C

Alcohol can change solubility of phenobarbital in buffer aqueous solution by two opposite effects.

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Group D

The aqueous solubility of α-alanine is higher than that of α-amino butyric acid.

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