AL-Mustaqbal university college
Pharmacy department

Physical pharmacy II

lec2

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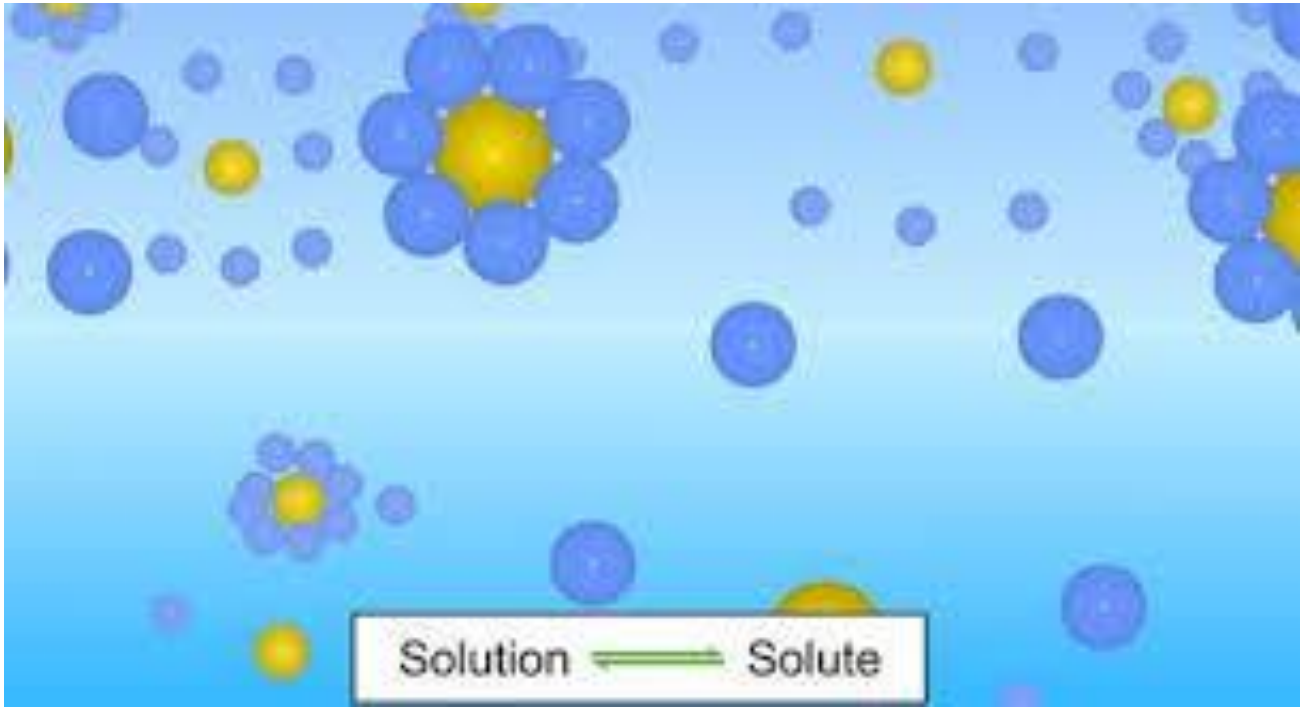
objective

- Understand the factors controlling the solubility of weak electrolytes.
- Describe the influence of solvents and surfactants on solubility.
- Define thermodynamic, kinetic, and intrinsic solubility.
- Measure thermodynamic solubility.
- Describe what a distribution coefficient and partition
- coefficient are and their importance in pharmaceutical systems

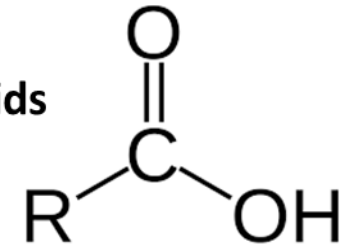
Solubility of solids in liquids

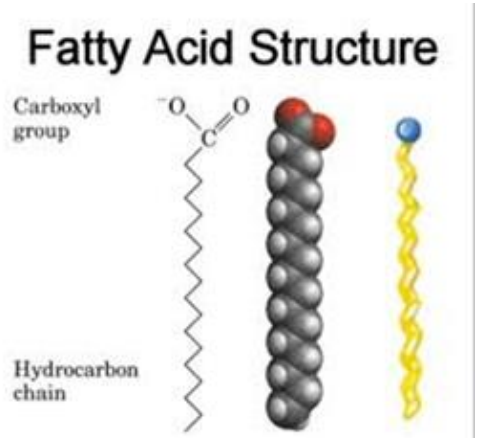
Systems of solids in liquids include the most frequently encountered and probably the most important type of pharmaceutical solutions. Many important drugs belong to the class of weak acids and bases. They react with strong acids and bases and, within definite ranges of pH, exist as ions that are ordinarily soluble in water.



Although **carboxylic acids** containing more than five carbons are relatively insoluble in water, they react with dilute sodium hydroxide (NaOH), carbonates, and bicarbonates to form soluble salts. The **fatty acids** containing more than **10 carbon** atoms form soluble soaps with the **alkali metals** and insoluble soaps with other **metal ions**. They are soluble in solvents having **low dielectric constants**; for example, oleic acid ($C_{17}H_{33}COOH$) is insoluble in water but is soluble in alcohol and in ether

carboxylic acids





alkali metals

any of the six chemical elements that make up Group 1 (Ia) of the periodic table—namely, lithium (Li), sodium (Na), potassium (K), rubidium (Rb), cesium (Cs), and francium (Fr). The alkali metals are so called because reaction with water forms alkalies (i.e., strong bases capable of neutralizing acids)

Hydroxy acids, such as tartaric and citric acids, are quite soluble in water because they are solvated through their hydroxyl groups. The potassium and ammonium bitartrates are not very soluble in water, although most alkali metal salts of tartaric acid are soluble. Sodium citrate is used sometimes to dissolve water-insoluble acetylsalicylic acid because the soluble acetylsalicylate ion is formed in the reaction. The citric acid that is produced is also soluble in water, but the practice of dissolving aspirin by this means is questionable because the acetylsalicylate is also hydrolyzed rapidly .

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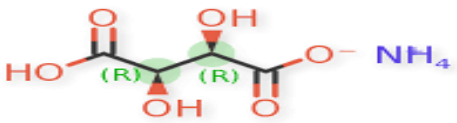
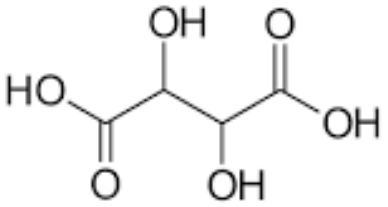
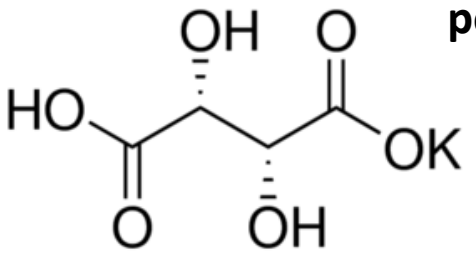


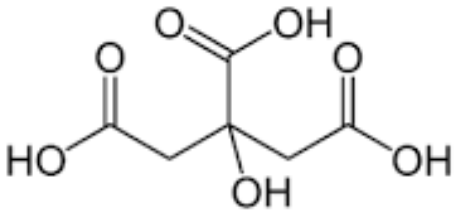
ammonium bitartrates



Tartaric acid



potassium bitartrates

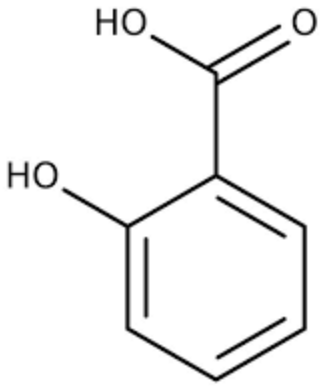


Citric acid

Aromatic acids react with dilute alkalies to form water soluble salts, but they can be precipitated as the free acids if **stronger acidic** substances are added to the solution. They can also be precipitated as heavy metal salts ,should **heavy metal ions** be added to the solution. **Benzoic acid** is soluble in **sodium hydroxide solution**, **alcohol**, and **fixed oils**.

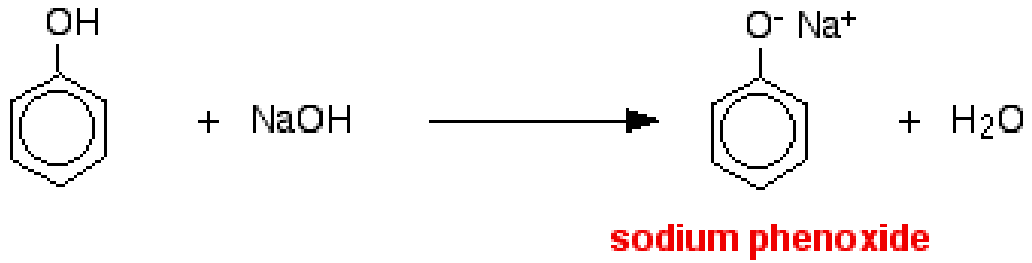
Salicylic acid is soluble in **alkalies** and in **alcohol**. The OH group of salicyclic acid cannot contribute to the solubility because it is involved in an intramolecular hydrogen bond.

Salicylic acid



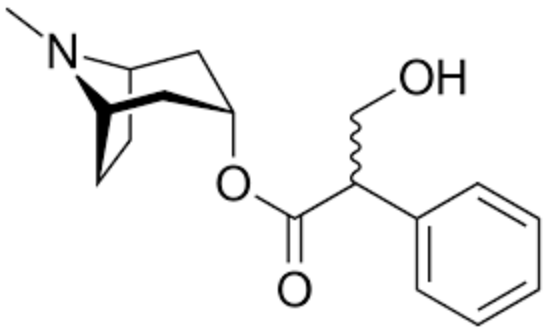
Phenol is weakly acidic and only slightly soluble in water but is quite soluble in dilute sodium hydroxide solution,

$$C_6H_5OH + NaOH \rightarrow C_6H_5O^- + Na^+ + + H_2O$$

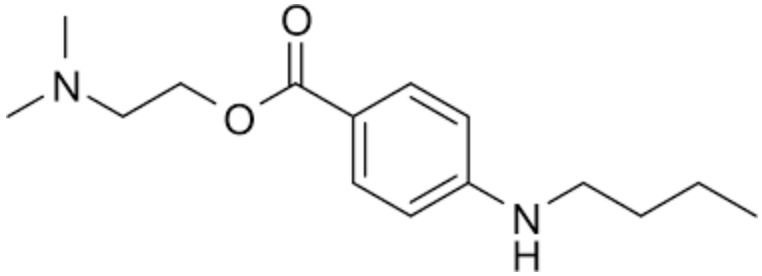


Phenol is a weaker acid than H_2CO_3 and is thus displaced and precipitated by CO_2 from its dilute alkali solution. For this reason, carbonates and bicarbonates cannot increase the solubility of phenols in water.

Many **organic compounds** containing a basic nitrogen atom in the molecule are important in pharmacy. These include the alkaloids, sympathomimetic amines, antihistamines, local anesthetics, and others. Most of these **weak electrolytes** are not very soluble in water but are **soluble** in dilute solutions of acids; such compounds as **atropine sulfate** and **tetracaine hydrochloride** are formed by reacting the basic compounds with acids. Addition of an **alkali** to a solution of the salt of these compounds **precipitates** the free base from solution if the solubility of the base in water is low.

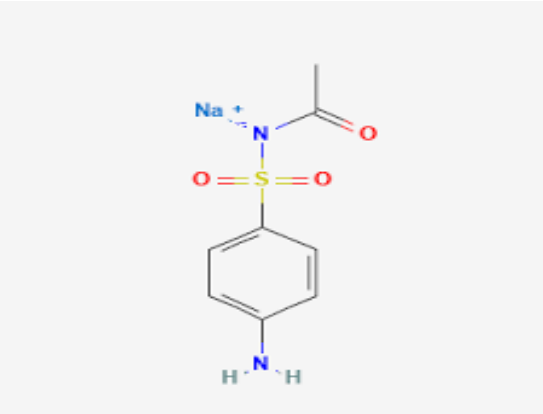


atropine sulfate

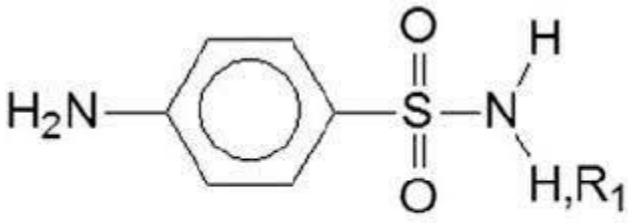


tetracaine hydrochloride

The aliphatic nitrogen of the sulfonamides is sufficiently negative so that these drugs act as slightly soluble **weak acids** rather than as **bases**. They form water-soluble salts in alkaline solution by the following mechanism; The oxygens of the sulfonyl (SO_2) group withdraw electrons, and the resulting electron deficiency of the sulfur atom results in the electrons of the N:H bond being held more closely to the nitrogen atom. The hydrogen therefore is bound less firmly, and, in alkaline solution, the soluble sulfonamide anion is readily formed. The **sodium salts** of the sulfonamides are precipitated from solution by the addition of a **strong acid** or by a salt of a strong acid and a weak base such as ephedrine hydrochloride

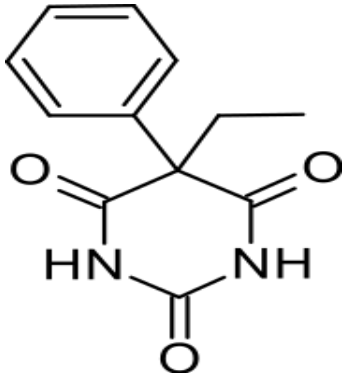


sulfonamides



R_1 = aromatic heterocycle

The **barbiturates,** like the sulfonamides, are **weak acids** because the electronegative oxygen of each acidic carbonyl group tends to withdraw electrons and to create a positive carbon atom. The carbon in turn attracts electrons from the nitrogen group and causes the hydrogen to be held less firmly. Thus, in **sodium hydroxide solution**, the hydrogen is readily lost, and the molecule exists as a soluble anion of the weak acid. In highly alkaline solutions, the second hydrogen ionizes. The p*K*1 for phenobarbital is 7.41 and the p*K*2 is 11.77. Although the barbiturates are soluble in alkalies, they are precipitated as the free acids when a stronger acid is added and the pH of the solution is lowered.

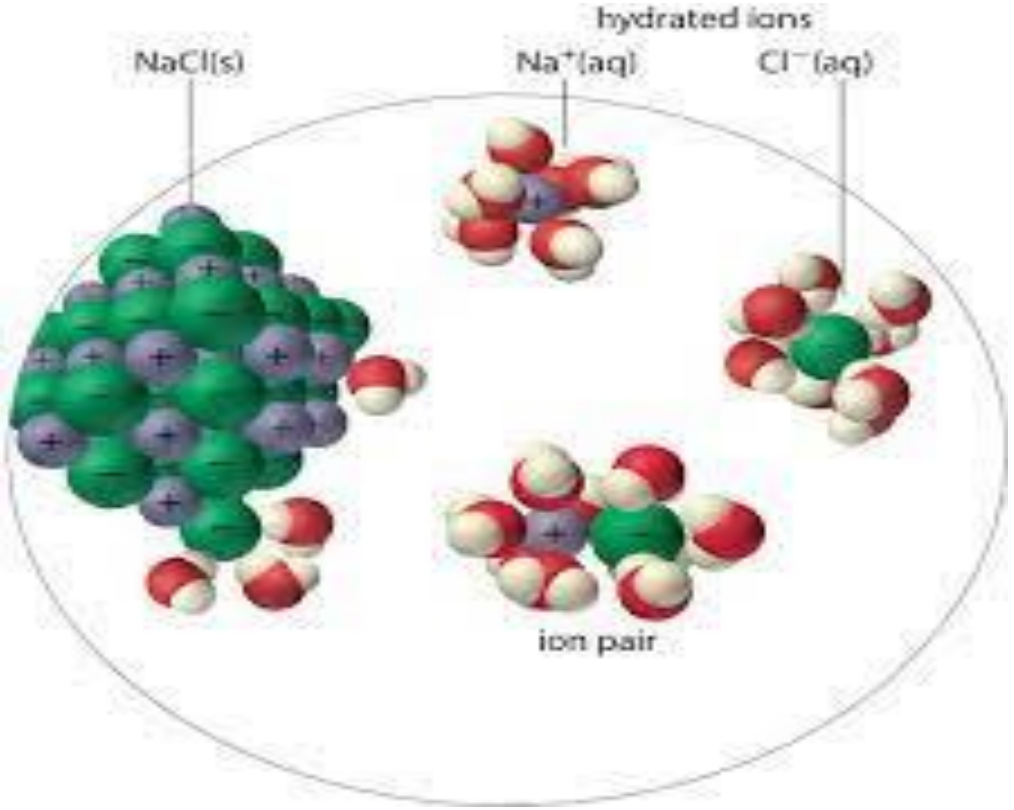


phenobarbital

The Influence of Solvents on the Solubility of Drugs

Weak electrolytes can behave like strong electrolytes or like nonelectrolytes in solution. When the solution is of such a pH that the drug is entirely in the **ionic form**, it behaves as a solution of a strong electrolyte, and solubility does not constitute a serious problem. However, when the pH is adjusted to a value at which **un-ionized** molecules are produced in sufficient concentration to exceed the solubility of this form, precipitation occurs. ,we are now interested in the solubility of nonelectrolytes and the undissociated molecules of weak electrolytes..

Frequently, a solute is more soluble in a mixture of solvents than in one solvent alone. This phenomenon is known as ***cosolvency***, and the solvents that, in combination, increase the solubility of the solute are called ***cosolvents***. Approximately 1 g of phenobarbital is soluble in 1000 mL of water, in 10 mL of alcohol, in 40 mL of chloroform, and in 15 mL of ether at 25◦C



Solvents and weak electrolytes

The solvent affects the solubility of a weak electrolyte in a buffered solution in two ways: (*a*) The addition of alcohol to a buffered aqueous solution of a weak electrolyte **increases the solubility** of the un-ionized species by **adjusting the polarity of the solvent** to a more favorable value. (*b*) Because it is less polar than water, alcohol **decreases the dissociation of a weak** electrolyte, and the solubility of the drug goes down as the dissociation constant is decreased

Influence of Other Factors on the Solubility of Solids

The size and shape of small particles (those in the micrometer range) also affect solubility. Solubility increases with decreasing particle size according to the approximate equation

$$\log \frac{s}{s_0} = \frac{2\gamma V}{2.303 RTr}$$

where s is the solubility of the fine particles; s_0 is the solubility of the solid consisting of relatively large particles; γ is the surface tension of the particles, which, for solids, unfortunately, is extremely difficult to obtain; V is the molar volume (volume in cm^3 per mole of particles); r is the final radius of the particles in cm; R is the gas constant (8.314×10^7 ergs/deg mole); and T is the absolute temperature. The equation can be used for solid or liquid particles such as those in suspensions or emulsions.

Example

Particle Size and Solubility

A solid is to be comminuted (crushing) so as to increase its solubility by 10%, that is, s/s_0 is to become 1.1. 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.

273+27=300 kelvin

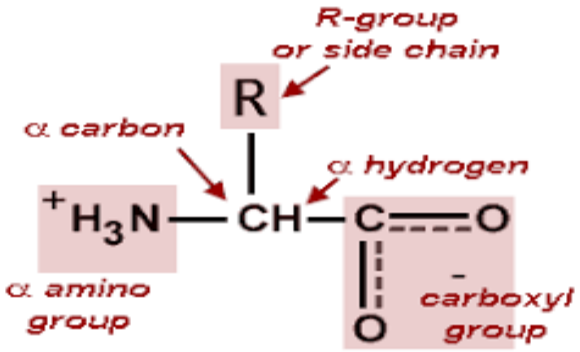
Log 1.1=0.0414

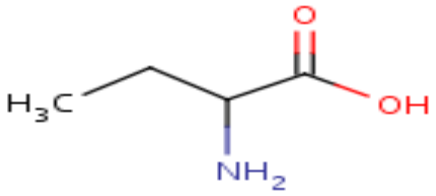
$$\log \frac{s}{s_0} = \frac{2\gamma V}{2.303 RTr}$$

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

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

The **configuration of a molecule** and the type of arrangement in the crystal also has some influence on solubility, and a symmetric particle can be **less soluble** than an unsymmetric one. This is because solubility depends in part on the work required to separate the particles of the **crystalline solute**. The molecules of the amino acid *α*-alanine form a compact crystal with high lattice energy and consequently **low solubility**. The molecules of *α*-amino-*n*-butyric acid pack less efficiently in the crystal, partly because of the projecting side chains, and the crystal energy is reduced. Consequently, *α*- amino-*n*-butyric acid has a solubility of 1.80 moles/liter and *α*-alanine has a solubility of only 1.66 moles/liter in water at 25◦C, although the hydrocarbon chain is longer in *α*-amino*n*- butyric acid than in the other compound.





α-alanine

Poor aqueous Solubility

"Poor aqueous solubility is caused by two main factors: high **lipophilicity** and **strong intermolecular interactions**, which make the solubilization of the solid energetically costly. What is meant by good and poorly soluble depends partly on the expected therapeutic dose and potency of the drug. As a rule of thumb from the delivery perspective, a drug with an average potency of 1 mg/kg should have a solubility of at least 0.1 g/L to be adequately soluble. If a drug with the same potency has a solubility of less than 0.01 g/L it can be considered poorly soluble.

Hydrophobic Parameters

The pharmacologic effect of simple organic compounds was related to their oil/water partition coefficient, *P*. It later became clear that the partition coefficient was of little value for explaining specific drug activity (i.e., binding to a receptor) because specificity also relates to steric and electronic effects . The partition coefficient, *P*, is a commonly used way of defining relative hydrophobicity (also known as lipophilicity) of compounds.

Note

Hydrophobic is often used interchangeably with lipophilic

Distribution of solutes between Immiscible solvents

If an excess of liquid or solid is added to a mixture of two immiscible liquids, it will distribute itself between the two phases so that each becomes saturated. If the substance is added to the immiscible solvents in an amount insufficient to saturate the solutions, it will still become distributed between the two layers in a definite concentration ratio. If C_1 and C_2 are the equilibrium concentrations of the substance in Solvent 1 and Solvent 2, respectively, the equilibrium expression becomes

$$\frac{C_1}{C_2} = K$$

The equilibrium constant, *K*, is known as the **distribution ratio**, ***distribution coefficient***, or ***partition coefficient***. This équation which is known as the *distribution law*, is strictly applicable only in dilute solutions where activity coefficients can be neglected.

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

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

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

Extraction

To determine the efficiency with which one solvent can extract a compound from a second solvent—an operation commonly employed in analytic chemistry and in organic Chemistry .Suppose that w grams of a solute is extracted repeatedly from V_1 mL of one solvent with successive portions of V_2 mL of a second solvent, which is immiscible with the first. Let w_1 be the weight of the solute remaining in the original solvent after extracting with the first portion of the other solvent. Then, the concentration of solute remaining in the first solvent is (w_1/V_1) g/mL and the concentration of the solute in the extracting solvent is $(w - w_1)/V_2$ g/mL. The distribution coefficient is thus

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

$$K = \frac{w_1 / V_1}{(w - w_1) V_2} \qquad (9\text{–}2$$

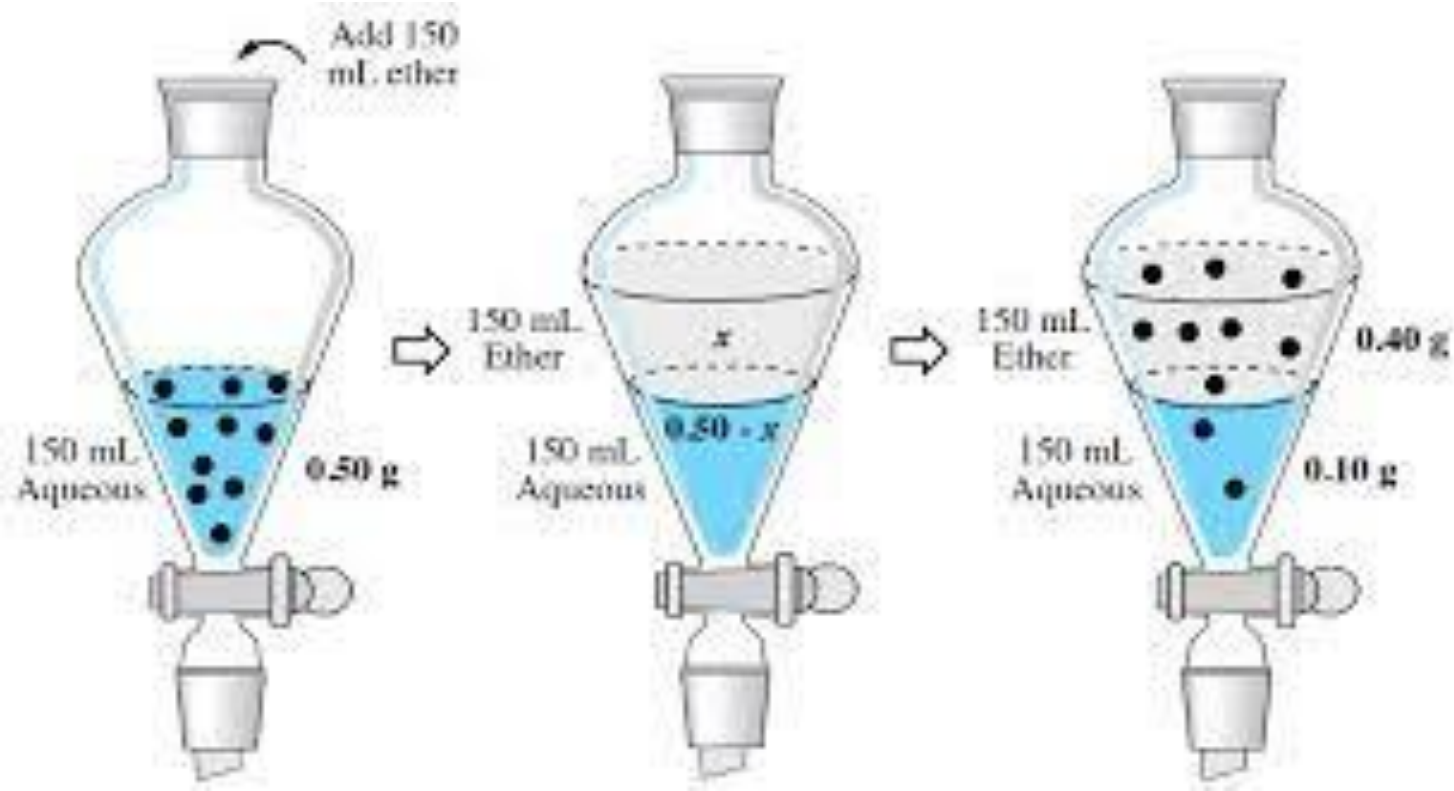
or

$$w_1 = w \frac{K V_1}{K V_1 + V_2} \qquad (9\text{–}2$$

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

$$w_n = w \left(\frac{K V_1}{K V_1 + V_2} \right)^n \qquad (9\text{–}2$$

By use of this equation, it can be shown that most **efficient extraction** results when ***n* is large** and V_2 is small, in other words, when a large number of extractions are carried out with small portions of extracting liquid. The development just described assumes complete immiscibility of the two liquids..



Distribution Coefficient

The distribution coefficient for iodine between water and carbon tetrachloride at 25℃ 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

$$w_1 = w\frac{KV_1}{KV_1 + V_2}$$

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

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

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

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

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


Thank You!

letter of the Greek alphabet.

A	α	alpha	N	ν	nu
B	β	beta	Ξ	ξ	ksi
Γ	γ	gamma	O	ο	omicron
Δ	δ	delta	Π	π	pi
E	ε	epsilon	P	ρ	rho
Z	ζ	zeta	Σ	σς	sigma
H	η	eta	T	τ	tau
Θ	θ	theta	Y	υ	upsilon
I	ι	iota	Φ	φ	phi
K	κ	kappa	X	χ	chi
Λ	λ	lambda	Ψ	ψ	psi
M	μ	mu	Ω	ω	omega

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