

Solubility and distribution phenomena

Introduction

- A *solution* can be defined as a system in which molecules of a solute are dissolved in a solvent vehicle.
- Solubility is defined as the maximum solute concentration in a certain solvent at a certain temperature.

Solute concentration < solubility → undersaturated solution

Solute concentration = solubility → saturated solution

Solute concentration > solubility → supersaturated solution

Expressions of solubility

- The solubility of a drug can be expressed in terms of concentration such as:
 - Molarity
 - Normality
 - Molality
 - Mole fraction
 - percentage (% w/w, % w/v, % v/v).

Expressions of solubility

- The pharmacopeias used the following less specific way to denote to solubility

Descriptive term	Approximate volume of solvent in milliliters per gram 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	more than 10 000

Prediction of solubility

- Solubility depends on chemical, electrical & structural effects that lead to mutual interactions between the solute and the solvent.
- “**like dissolves like**”.
- **A solute dissolves best in a solvent** with similar chemical properties. i.e.
 - Polar solutes dissolve in polar solvents. e.g **salts & sugar dissolve in water** .
 - Non polar solutes dissolve in non polar solvents. Eg. **naphtalene dissolves in benzene**.

Prediction of solubility

- If the solvent is A and the solute B and the forces of attraction are represented by A—A, B—B and A—B, one of three conditions will arise:
 1. If $A-A \gg A-B$, i.e. the affinity of a solvent molecule for its own kind is markedly greater than its affinity for a solute molecule, the solvent molecules will be attracted to each other and form aggregations from which the solute is excluded (e.g. benzene in water).
 2. If $B-B \gg A-B$, the solvent will not be able to break the binding forces between solute molecules and disperse them (e.g. sodium chloride in benzene).
 3. If $A-B > A-A$ or $B-B$, or the three forces are of the same order, the solute will disperse and form a solution.

Factors influencing solubility

Polar solvents

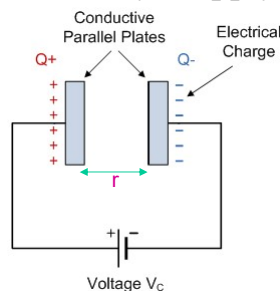
- Polar solvents dissolve ionic solutes and polar substances.
- The solubility of a drug in polar solvent depends on:
 1. **The polarity of the solvent (measured by dielectric constant)**
 2. **The ability of the solute to form hydrogen bonds.**
 - Water dissolves Phenols, alcohols, aldehydes, ketones, amines, and other oxygen- and nitrogen-containing compounds that can form hydrogen bonds with water
 3. **The ratio of polar to nonpolar groups of the molecule**
 - As the length of a nonpolar chain of an aliphatic alcohol increases, the solubility in water decreases (e.g. Straight chain monohydroxy alcohols, aldehydes, and acids with more than 4 carbons cannot enter into the hydrogen-bonded structure of water and hence are only slightly soluble).

Dielectric constant

- A molecule can maintain a separation of electric charge either through induction by an external electric field or by a permanent charge separation within a polar molecule.
- Dielectric constant (relative permittivity) of a material is its (absolute) permittivity expressed as a ratio relative to the permittivity of vacuum.

Dielectric constant

- Consider two parallel conducting plates, such as the plates of an electric condenser, which are separated by some medium across a distance r and apply a potential across the plates.
- Electricity will flow from the left plate to the right plate through the battery until the potential difference of the plates equals that of the battery supplying the initial potential difference.



Dielectric constant

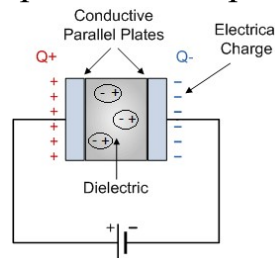
- The *capacitance*, C (in farads), is equal to the quantity of electric charge, q (in coulombs), stored on the plates, divided by the potential difference, V (in volts), between the plates:

$$C = q/V$$

- The capacitance of the condenser depends on the type of medium separating the plates as well as on the thickness r .
- When a vacuum fills the space between the plates, the capacitance is C_0 .
- This value is used as a reference to compare capacitances when other substances fill the space.

Dielectric constant

- If **water** fills the space, the capacitance is increased, since the water molecule can orientate itself so that its negative end lies nearest the positive condenser plate and its positive end lies nearest the negative plate.
- This alignment provides additional movement of charge because of the increased ease with which electrons can flow between the plates.
- Thus, additional charge can be placed on the plates per unit of applied voltage.



Dielectric constant

- The capacitance of the condenser filled with some material, C_x , divided by the reference standard C_0 , is referred to as the *dielectric constant*, $1/\epsilon$:

$$\epsilon = C_x / C_0$$

- The dielectric constant ordinarily has no dimensions, since it is the ratio of two capacitances.

Vacuum	1.0 (by definition)
Metals	Infinite
Gases	1.00xx (at one atmosphere)
Water	87.9 (0°C) to 55.5 (100°C)
Hexane	1.8865 (20°C)
Cyclohexane	2.0243 (20°C)
Benzene	2.285 (20°C)
Hydrocarbon lubrication oils	2.1 to 2.4 (room temperature)

Table 1. Dielectric Constant of Common Materials

Dielectric constant

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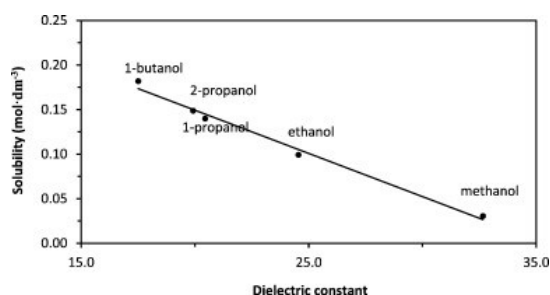
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Table 1. Dielectric Constant of Common Materials

Dielectric constant

- The dielectric constants *of* solvent mixtures can be related to drug solubility:

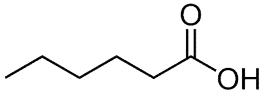
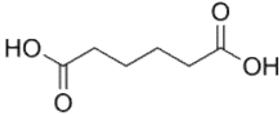
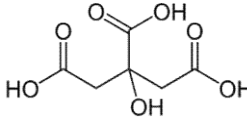


Solubility of morin flavonoid in alcohols (Journal of Molecular Liquids, Volume 233, 2017)

Factors influencing solubility

Polar solvents

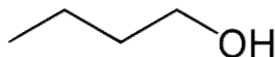
- When additional polar groups are present in the molecule, water solubility increases greatly.

Name	Chemical formula	structure	Solubility
Hexanoic acid	$C_6H_{12}O_2$		1 g/100 ml
Adipic acid	$C_6H_{10}O_4$		24 g/100 ml
Citric acid	$C_6H_8O_7$		148 g/100 ml

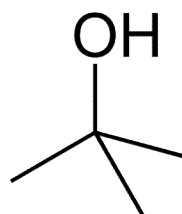
Factors influencing solubility

Polar solvents

- Branching of the carbon chain reduces the nonpolar effect and leads to increased water solubility (E.g. Tertiary butyl alcohol is miscible in all proportions with water, whereas n-butyl alcohol dissolves to the extent of about 8 g/100 mL of water at 20°C).



n-butanol

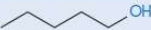
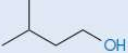
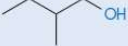
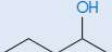
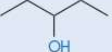
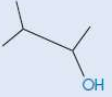


tert-butanol

Factors influencing solubility

Polar solvents

Table 5.2 Solubilities of pentanol isomers in water^a

Compound	Solubility (molality, <i>m</i>)	Surface area (nm ²)	Boiling point (°C)	Structure
<i>n</i> -Pentanol	2.6×10^{-1}	3.039	137.8	
3-Methyl-1-butanol	3.11×10^{-1}	2.914	131.2	
2-Methyl-1-butanol	3.47×10^{-1}	2.894	128.7	
2-Pentanol	5.3×10^{-1}	2.959	119.0	
3-Pentanol	6.15×10^{-1}	2.935	115.3	
3-Methyl-2-butanol	6.67×10^{-1}	2.843	111.5	
2-Methyl-2-butanol	1.403	2.825	102.0	

Factors influencing solubility

Nonpolar solvents

- Non polar solvents are unable to reduce the attraction between the ions due to their *low dielectric constants*.
- They are unable to form hydrogen bonds with non electrolytes.
- Non polar solvents can dissolve non polar solutes through weak van derWaals forces
- Example: solutions of oils & fats in carbon tetrachloride or benzene.

Factors influencing solubility

Semipolar solvents

- Semipolar solvents, such as ketones can induce a certain degree of polarity in non polar solvent molecules.
- They can act as intermediate solvents to bring about miscibility of polar & non polar liquids.
- Example: acetone increases solubility of ether in water.

Solubility of gases in liquids

- Examples of pharmaceutical solutions of gases include: HCl, ammonia water & effervescent preparations containing CO₂ maintained in solution under pressure.
- The solubility of a gas in a liquid *is the concentration of dissolved gas when it is in equilibrium with some of the pure gas above the solution.*
- The solubility depends on:
 - molecular weight of gas
 - the pressure
 - temperature
 - presence of salts
 - chemical reactions that sometimes the gas undergoes with the solvent

Solubility of gases in liquids

Effect of molecular weight of gas

- The solubility of gas molecules typically increases with increasing molecular weight of gas due to stronger London and Debye forces between gas and solvent molecules.

Effect of pressure

- The effect of the pressure on the solubility of a gas is expressed by *Henry's law*, which, states that in a very dilute solution at constant temperature, the concentration of dissolved gas is proportional to the partial pressure of the gas above the solution at equilibrium.

Solubility of gases in liquids

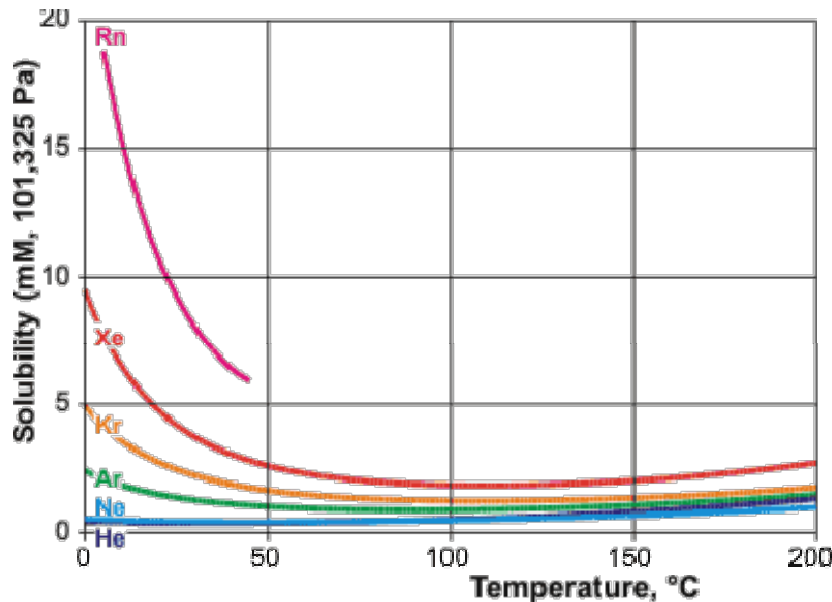
Effect of temperature

- As the temperature increases, the solubility of most gases decreases, owing to the greater tendency of the gas to expand, increased kinetic energy of gas molecules, leading to breaking of intermolecular forces.

Presence of salts

- Gases are often liberated from solutions in which they are dissolved by the introduction of an electrolyte such as sodium chloride and sometimes by a nonelectrolyte such as sucrose. This phenomenon is known as *salting out*.

Solubility of gases in liquids



Solubility of gases in liquids

Effect of chemical reactions

- Henry's law applies strictly to *gases* that are only slightly soluble in solution and that do not react in any way in the solvent.
- Gases such as **hydrogen chloride**, **ammonia**, and **carbon dioxide** show deviations as a result of chemical reaction between the gas and solvent, usually with a resultant increase in solubility.
- Accordingly, hydrogen chloride is about 10,000 times more soluble in water than is oxygen.

Solubility of gases in liquids

Table 4–3 Solubilities of some gases in water

Gas	Structure*	Polarity	Solubility in water (g/L)	Temperature (°C)
Nitrogen	$\text{N}\equiv\text{N}$	Nonpolar	0.018	40
Oxygen	$\text{O}=\text{O}$	Nonpolar	0.035	50
Carbon dioxide	$\overset{\delta^-}{\text{O}}=\text{C}=\overset{\delta^-}{\text{O}}$	Nonpolar	0.97	45
Ammonia	$\begin{array}{c} \text{H} \quad \text{H} \quad \text{H} \\ \diagdown \quad \diagup \quad \\ \text{N} \\ \diagup \quad \diagdown \quad \\ \text{H} \quad \text{H} \quad \delta^- \end{array}$	Polar	900	10
Hydrogen sulfide	$\begin{array}{c} \text{H} \quad \text{H} \\ \diagdown \quad \diagup \\ \text{S} \\ \diagup \quad \diagdown \\ \text{H} \quad \delta^- \end{array}$	Polar	1,860	40

Solubility of liquids in liquids

➤ Liquid-liquid systems may be divided into 2 categories:

- 1) Systems showing *complete miscibility* such as alcohol & water, glycerin & alcohol, benzene & carbon tetrachloride.
 - Complete miscibility occurs when the adhesive forces between different molecules (A-B) $\gg$ cohesive forces between like molecules (A-A or B-B).
- 2) Systems showing *Partial miscibility* as phenol and water; two liquid layers are formed each containing some of the other liquid in the dissolved state.

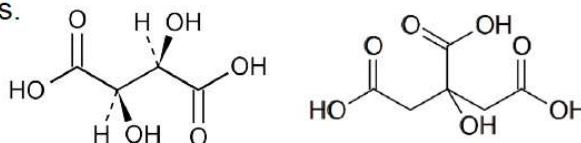
Solubility of solids in liquids

Effects of substituents

Substituents can influence solubility by affecting the solute molecular cohesion and its interaction with water molecules.

Polar groups such as $-\text{OH}$ are capable of hydrogen bonding (high solubility).

E.g. Hydroxy acids, such as tartaric and citric acids, are quite soluble in water because they are solvated through their hydroxyl groups.



Non-polar groups such as $-\text{CH}_3$ and $-\text{Cl}$ are hydrophobic (low solubility).

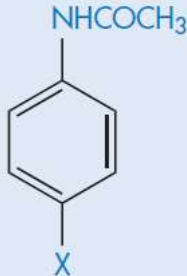
Factors influencing solubility

Table 5.4 Substituent group classification

Substituent	Classification
$-\text{CH}_3$	Hydrophobic
$-\text{CH}_2-$	Hydrophobic
$-\text{Cl}, -\text{Br}, -\text{F}$	Hydrophobic
$-\text{N}(\text{CH}_3)_2$	Hydrophobic
$-\text{SCH}_3$	Hydrophobic
$-\text{OCH}_2\text{CH}_3$	Hydrophobic
$-\text{OCH}_3$	Slightly hydrophilic
$-\text{NO}_2$	Slightly hydrophilic
$-\text{CHO}$	Hydrophilic
$-\text{COOH}$	Slightly hydrophilic
$-\text{COO}^-$	Very hydrophilic
$-\text{NH}_2$	Hydrophilic
$-\text{NH}_3^+$	Very hydrophilic
$-\text{OH}$	Very hydrophilic

Factors influencing solubility

Table 5.5 The effect of substituents on solubility of acetanilide derivatives in water

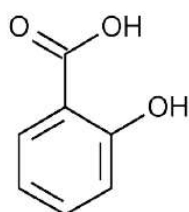
Derivative	X	Solubility (mg dm ⁻³)
	H	6.38
	Methyl	1.05
	Ethoxyl	0.93
	Hydroxyl	13.9
	Nitro	15.98
	Aceto	9.87

Solubility of solids in liquids

Effects of substituents

The position of the substituent on the molecule can affect the solute molecular cohesion and its interaction with water molecules, and hence its solubility.

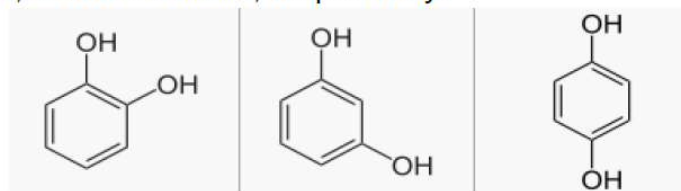
E.g. the OH group of salicylic acid cannot contribute to the solubility because it is involved in an intramolecular hydrogen bond.



Solubility of solids in liquids

Effects of substituents

E.g. the aqueous solubility of o-, m- and p-dihydroxybenzenes are 4, 9 and 0.6 mol/L, respectively.



Symmetric particles (p-dihydroxybenzenes) can be less soluble than unsymmetric ones (m-dihydroxybenzenes) because they form compact crystals (which require more work to separate the particles), while the unsymmetric particles pack less efficiently in crystals.

Solubility of solids in liquids

Effects of solid state

- The less stable solid state (e.g. metastable polymorph, amorphous or anhydrous state) will be more soluble than the stable state.

Particle size

- Above a certain size, solubility is not influenced by the particle size of the solid solute. However, the reduction in the size of particles to micron or sub-micron size can influence solubility.
- A micronized drug may have an increase in solubility if the micronization process breaks down the crystal lattice of the solid.

Solubility of solids in liquids

Effects of salt form

- The solubility of the drug in aqueous media may be markedly dependent on the salt form.

Table 5.13 Solubilities of salts of an antimalarial drug (XIX)^a

Salt	Melting point (°C) ^b	Solubility (mg cm ⁻³)
Free base	215	7–8
Hydrochloride	331	32–15
d/Lactate	172 (dec)	1800
l/Lactate	193 (dec)	900
2-Hydroxy-1-sulfonate	250 (dec)	620
Methanesulfonate	290 (dec)	300
Sulfate	270 (dec)	20

^a Reproduced from S. Agharkar, S. Lindenbaum and T. Higuchi, *J. Pharm. Sci.*, 65, 747 (1976).

^b (dec) – with decomposition.

Solubility of solids in liquids

Table 5.3 Correlation between melting points of sulfonamide derivatives and aqueous solubility

Compound	Melting point (°C)	Solubility
Sulfadiazine	253	1 g in 13 dm ³ (0.077 g dm ⁻³)
Sulfamerazine	236	1 g in 5 dm ³ (0.20 g dm ⁻³)
Sulfapyridine	192	1 g in 3.5 dm ³ (0.29 g dm ⁻³)
Sulfathiazole	174	1 g in 1.7 dm ³ (0.59 g dm ⁻³)

Solubility of solids in liquids

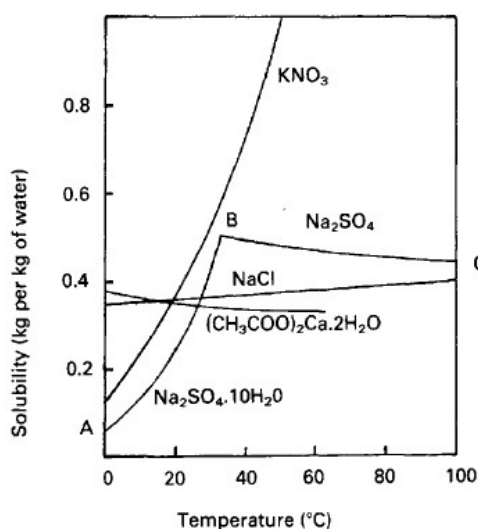
Effect of temperature

- A rise in temperature will lead to an increase in the solubility of a solid with an endothermic dissolution.
- Conversely, in the case of the less commonly occurring systems that exhibit exothermic dissolution, an increase in temperature will give rise to a decrease in solubility.
- Plots of solubility versus temperature, which are referred to as *solubility curves*, are often used to describe the effect of temperature on a given system.
- Most of the curves are continuous; however, abrupt changes in slope may be observed with some systems if a change in the nature of the dissolving solid occurs at a specific transition temperature.

Solubility of solids in liquids

Effect of temperature

- Sodium sulphate exist as the decahydrate $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$ up to 32.5°C , and its dissolution in water is an endothermic process.
- Its solubility therefore increases with rise in temperature until 32.5°C is reached.
- Above this temperature the solid is converted into the anhydrous form Na_2SO_4 , and the dissolution of this compound is an exothermic process.
- The solubility therefore exhibits a change from a positive to a negative slope as the temperature exceeds the transition value.



Solubility of solids in liquids

Influence of pH on solubility of weak electrolytes

Systems of solids in liquids include the most frequent and important type of pharmaceutical solutions.

Most drugs belong to the class of weak acids and bases. They react with strong acids or bases to form water soluble salts.

Acidic drugs (e.g. NSAIDs), are more soluble in alkaline solutions where the ionized form is the predominant.

$$pH - pK_a = \log \frac{[Ionized]}{[Unionized]}$$

Basic drugs (e.g. ranitidine), are more soluble in acidic solutions where the ionized form of the drug is predominant.

$$pH - pK_a = \log \frac{[Unionized]}{[Ionized]}$$

Solubility of solids in liquids

Influence of pH on solubility of weak acids

- If we represent the drug as HA and the total saturation solubility of the drug as S , and if S_0 is the solubility of the undissociated species HA then:

$$pH - pK_a = \log\left(\frac{S - S_0}{S_0}\right)$$

S_0 is termed intrinsic solubility

Solubility of solids in liquids

Example

What is the pH below which sulfadiazine ($pK_a = 6.48$) will begin to precipitate in an infusion fluid, when the initial molar concentration of sulfadiazine sodium is $4 \times 10^{-2} \text{ mol dm}^{-3}$ and the solubility of sulfadiazine is $3.07 \times 10^{-4} \text{ mol dm}^{-3}$?

Answer

The pH below which the drug will precipitate is calculated using equation (5.11):

$$\begin{aligned} \text{pH} &= 6.48 + \log \frac{(4.00 \times 10^{-2}) - (3.07 \times 10^{-4})}{3.07 \times 10^{-4}} \\ &= 8.60 \end{aligned}$$

Solubility of solids in liquids

Influence of pH on solubility of weak bases

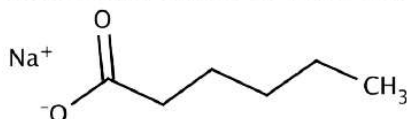
- If we represent the basic drug as B and BH^+ and the total saturation solubility of the drug as S , and if S_0 is the solubility of the unprotonated species B then:

$$\text{pH} - \text{p}K_a = \log \left(\frac{S_0}{S - S_0} \right)$$

Solubility of solids in liquids

Influence of pH on solubility of weak electrolytes

Carboxylic acids containing more than 5 carbons are relatively insoluble in water; however, they react with dilute NaOH, carbonates, and bicarbonates to form soluble salts.



The fatty acids (> 10 carbon) form soluble soaps with the alkali metals and insoluble soaps with other metal ions.

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



Solubility of solids in liquids

Boiling point and melting point

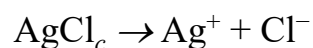
In general, aqueous solubility decreases with increasing boiling and melting point.

This is because the higher the boiling point of liquids and melting point of solids, the stronger the interactions between the molecules in the pure liquid or the solid state.

Solubility increases with decreasing particle size, due to the increased particle surface area; meaning more of the solid is in contact with the solvent.

Solubility products

- For poorly soluble materials such as silver chloride and barium sulfate the concept of the solubility product can be used.
- The following equilibrium exists in solution between crystalline silver chloride AgCl_c and ions in solution:



- An equilibrium constant K can be defined as:

$$K = \frac{[\text{Ag}^+][\text{Cl}^-]}{[\text{AgCl}_c]}$$

- At saturation the concentration of the crystalline silver chloride $[\text{AgCl}_c]$ is essentially constant and the solubility product, K_{sp} , may therefore be written:

$$K_{sp} = [\text{Ag}^+][\text{Cl}^-]$$

Solubility of slightly soluble electrolytes

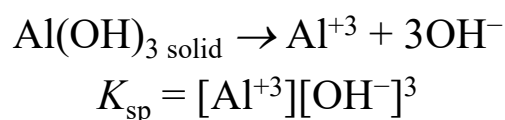
Table 5.7 Solubility products of some inorganic salts

Compound	K_{sp} ($\text{mol}^2 \text{dm}^{-6}$)
AgCl	1.25×10^{-10}
$\text{Al}(\text{OH})_3$	7.7×10^{-13}
BaSO_4	1.0×10^{-10}

- The solubility product equation is not applicable to freely soluble salts (such as NaCl) and loses accuracy for sparingly soluble (1 part in 30-100 parts) or if other salts are present.
- When other salts are present activity rather than concentration should be used

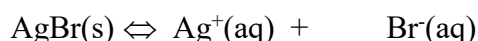
Solubility products

- As in the case of other equilibrium expressions the concentration of each ion is raised to a power equal to the number of ions appearing.
- Thus, for $\text{Al}(\text{OH})_3$



Solubility products

- Example: Calculate the solubility of AgBr in water in grams per liter if $K_{\text{sp}} = 5.0 \times 10^{-13}$
- We start with the balanced equation for the equilibrium.



We then write the solubility product expression for this reaction.

$$K_{\text{sp}} = [\text{Ag}^+][\text{Br}^-] = 5.0 \times 10^{-13}$$

- Because there is no other source of either ion in this solution, the concentrations of these ions at equilibrium must be the same.

$$[\text{Ag}^+] = [\text{Br}^-]$$

- Substituting this equation into the K_{sp} expression gives the following result. $[\text{Ag}^+]^2 = 5.0 \times 10^{-13}$
- Taking the square root of both sides of this equation gives the equilibrium concentrations of the Ag^+ and Br^- ions.

$$[\text{Ag}^+] = [\text{Br}^-] = 7.1 \times 10^{-7}M$$

Solubility products: common ion effect

- The presence of other sources of the same ions like Cl^- or Ag^+ reduces the solubility of AgCl .
- Because

$$[\text{Ag}^+][\text{Cl}^-] > K_{sp}$$

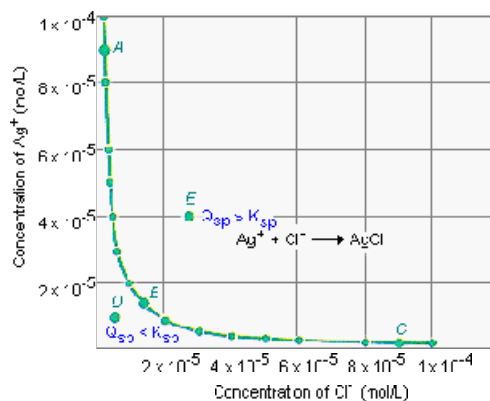
AgCl precipitates until $[\text{Ag}^+][\text{Cl}^-] = K_{sp}$

- In some cases the solubility increases when a common ion is added this is due to the formation of complexes with the compound that are soluble.

Solubility products: common ion effect

Saturated solution of AgCl to which NaCl has been added:

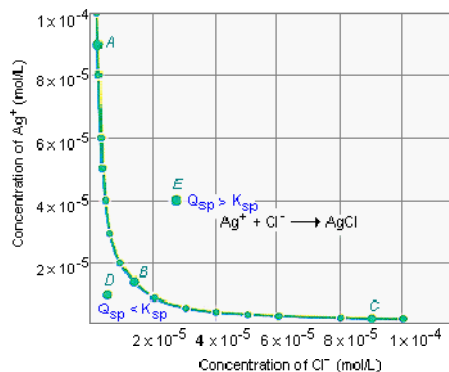
- The figure below shows a small portion of the possible combinations of the Ag^+ and Cl^- ion concentrations in an aqueous solution. Any point along the curved line in this graph corresponds to a system at equilibrium, because the product of the Ag^+ and Cl^- ion concentrations for these solutions is equal to K_{sp} for AgCl .



Solubility products: common ion effect

Saturated solution of AgCl to which NaCl has been added:

- **Point A** represents a solution at equilibrium that could be produced by dissolving two sources of the Ag^+ ion such as AgNO_3 and AgCl in water.
- **Point B** represents a saturated solution of AgCl in pure water, in which the $[\text{Ag}^+]$ and $[\text{Cl}^-]$ terms are equal.
- **Point C** describes a solution at equilibrium that was prepared by dissolving two sources of the Cl^- ion in water, such as NaCl and AgCl .



Solubility problems in formulation

Mixtures of acidic and basic compounds

e.g. Septrin infusion

- **Sulfamethoxazole** is a weakly acidic substance and **trimethoprim** is a weakly basic one.
- In consequence, in an ordinary aqueous solution **sulfamethoxazole** and **trimethoprim** demonstrate a high degree of incompatibility and mutual precipitation occurs on mixing.
- To optimize mutual dissolution, an aqueous solution which includes 40% propylene glycol is utilized in the formulation of the infusion.
- On dilution, the infusion becomes less stable and at the recommended 1 in 25 dilution stability is about 7 hours.

Partition coefficient

Pharmaceutical applications

The movement of molecules from one phase to another is called partitioning. Examples of the process include:

- The absorption and distribution of drug in the body is affected by partitioning between aqueous phases and lipid biophases
- Preservative molecules in emulsions partitioning between the aqueous and oil phases
- Antibiotics partitioning into microorganisms
- Drugs and preservative molecules partitioning into the plastic of containers or giving sets
- Extraction from crude drugs.

Partition coefficient

- If a substance (liquid or solid) is added to a mixture of two immiscible liquids, it will distribute itself between the two phases in a definite concentration ratio.
- The distribution of the solute between the two phases is represented by the **partition coefficient** or **distribution coefficient**, **P**, defined as the ratio of the solubility in the nonaqueous (oily) phase, C_o , to that in the aqueous phase, C_w , i.e.

$$P = C_o / C_w$$



Partition coefficient

Example

When boric acid is distributed between water and amyl alcohol at 250 C', the concentration in water was found to be 0.0510 mole/liter and in amyl alcohol it was found to be 0.0155 Mole/liter. What is the distribution coefficient?

$$K_{w/o} = C_{H_2O}/C_{alc} = 0.0510/0.0155 = 3.29$$

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

$$K_{o/w} = C_{alc}/C_{H_2O} = 0.0155/0.0510 = 0.304$$

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

Partition coefficient

Octanol as a nonaqueous phase

- Octanol is often used as the nonaqueous phase in experiments to measure the partition coefficient of drugs.
- It most closely simulates the properties of biological fluids. Its polarity means that water is solubilised to some extent in the octanol phase (biological membranes are also not simple anhydrous lipid phases).

$$P = C_o/C_w$$

- It is usual to express the partitioning as $\log P$. The greater the value of $\log P$, the higher the lipid solubility of the solute.

Partition coefficient

$P > 1$ or $\text{Log } P > 0$ implies that the drug has affinity for lipid membranes.

$P = 1$ or $\text{Log } P = 0$ there is equal distribution between the water and oil layer.

$P < 1$ or $\text{Log } P < 0$ the drug has affinity for water or hydrophilic layer.

Structure affect the value of partition coefficient P e.g. substituent that increase P value are -alkyl, -aryl, -halogens and substituent that decrease P decrease are -OH, -COOH, -NH₂, -O, -CO.

Apparent partition coefficient (P_{app})

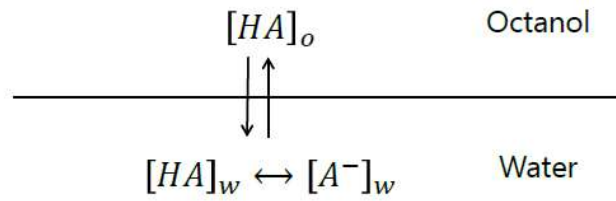
When association and dissociation of drugs occur, the situation becomes more complicated, e.g. benzoic acid associates in the oil phase and dissociates in the aqueous phase.

Drugs that are weak acids or weak bases ionize in water, depending on their pK_a s and on the pH of the aqueous phase.

In general, **ionized structures cannot partition in octanol** or other hydrophobic solvents.

P value cannot be used to assess the true distribution of the ionizable drug in the two immiscible phases, simply because its value is dependent on the ionic state of the drug (which in turn depends on pH).

Apparent partition coefficient (P_{app})



$$P = \frac{C_o}{C_w}$$

$$C_o = [HA]_o$$

$$C_w = [HA]_w + [A^-]_w$$

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