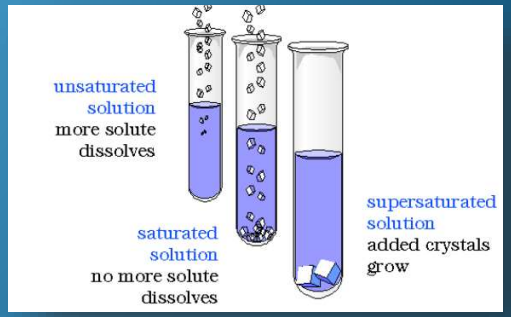
Solubility and Distribution Phenomena

Chapter 9



In This Chapter

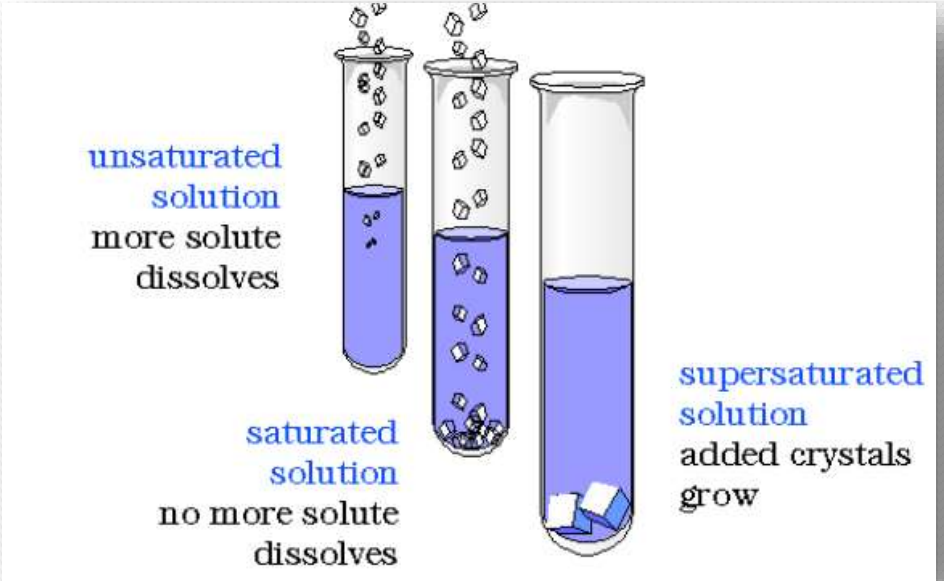
- Define Saturated, unsaturated solutions, Solubility , Polar and non polar solvents
- Examples of Polar and non polar solvents
- Introduce some solubility rules
- Understand factors affecting the solubility of weak and strong electrolyte
- Define the Partition coefficient and its importance in pharmaceutical formulations

Importance of studying solubility

- Many drugs are available as solutions (topical, oral, Parenteral)
- Select best solvent or solvents for solubilizing a drug
- Overcome problems arising in formulations(pptn.)
- Solubilizing of non polar drugs in aqueous solutions
- Many drugs shows pH dependent solubility(pH effect)
- Molecular structure effect on solubility(predicting solubility according to structure)

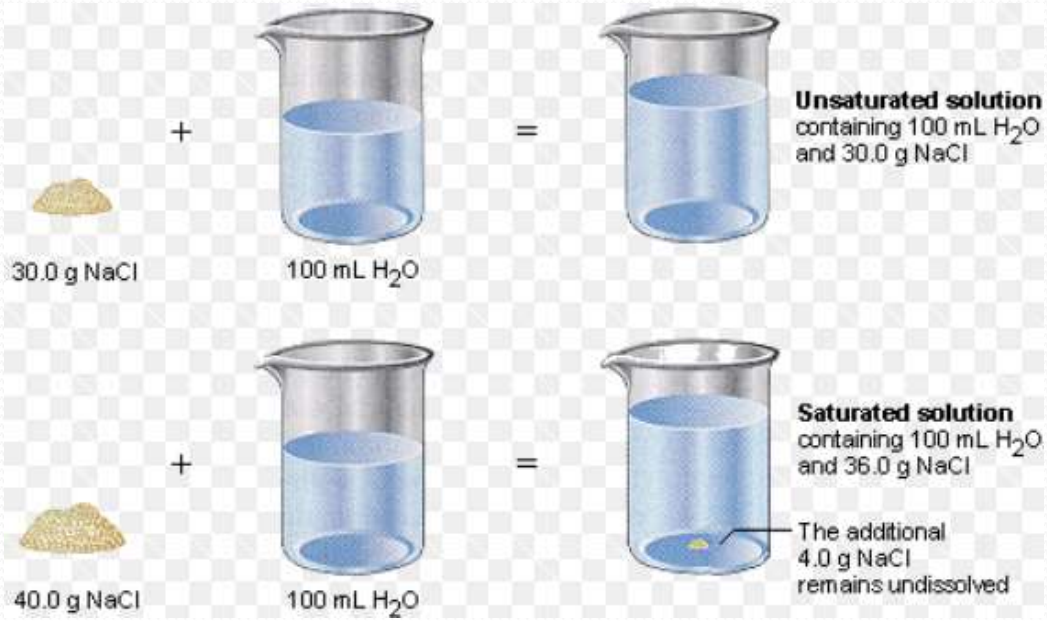
Definition

- A *saturated solution* is one in which the solute in solution is in equilibrium with the solid phase
- A *supersaturated solution* is one that contains more of the dissolved solute than it would normally contain at a definite temperature
- Solubility of metastable forms may be higher, but when changed to stable form a precipitate will form(formulation problems)



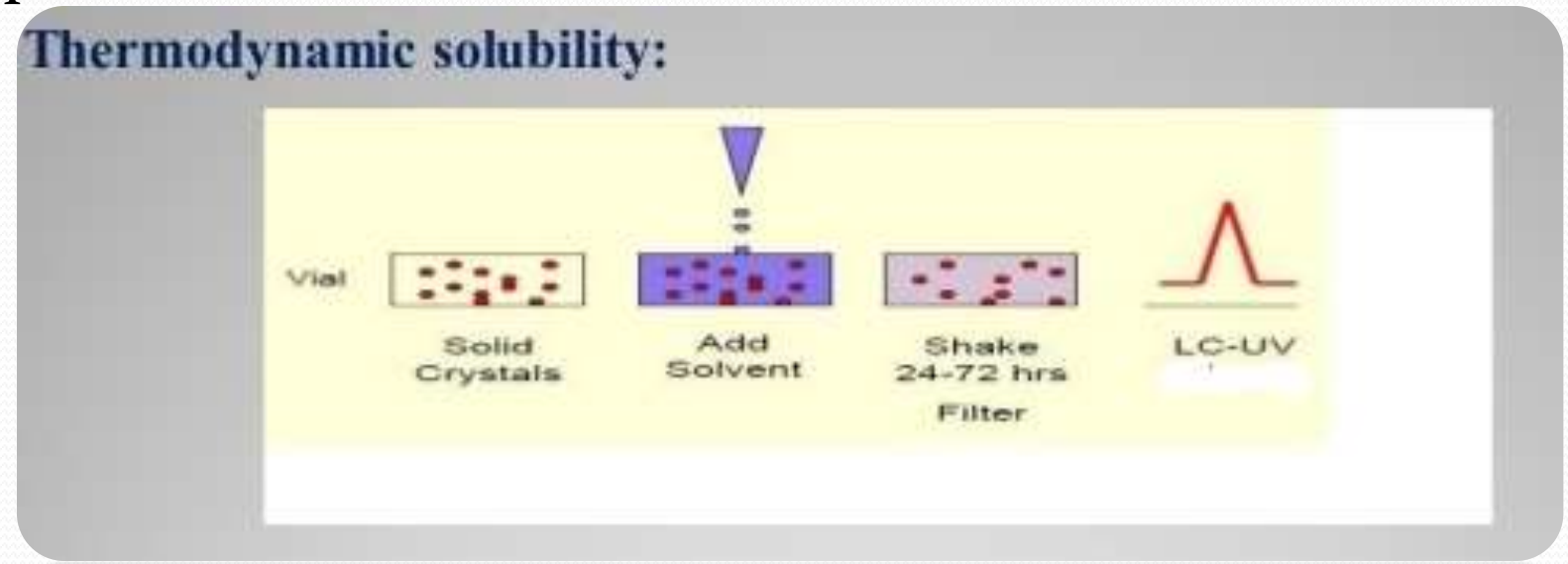
Definitions

- *Solubility* (in quantitative terms) as the concentration of solute in a saturated solution at a certain temperature
- Solubility (in a qualitative) way, it can be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion



Definitions

- Thermodynamic solubility of a drug in a solvent is the maximum amount of the most stable crystalline form that remains in solution in a given volume of the solvent at a given temperature and pressure under equilibrium conditions



Solubility & Dissolition

- **Dissolution:** The process by which a drug particle dissolves is termed dissolution

Solubility is an Intrinsic property

- Solubility is an *intrinsic* material property that can be altered only by chemical modification of the molecule
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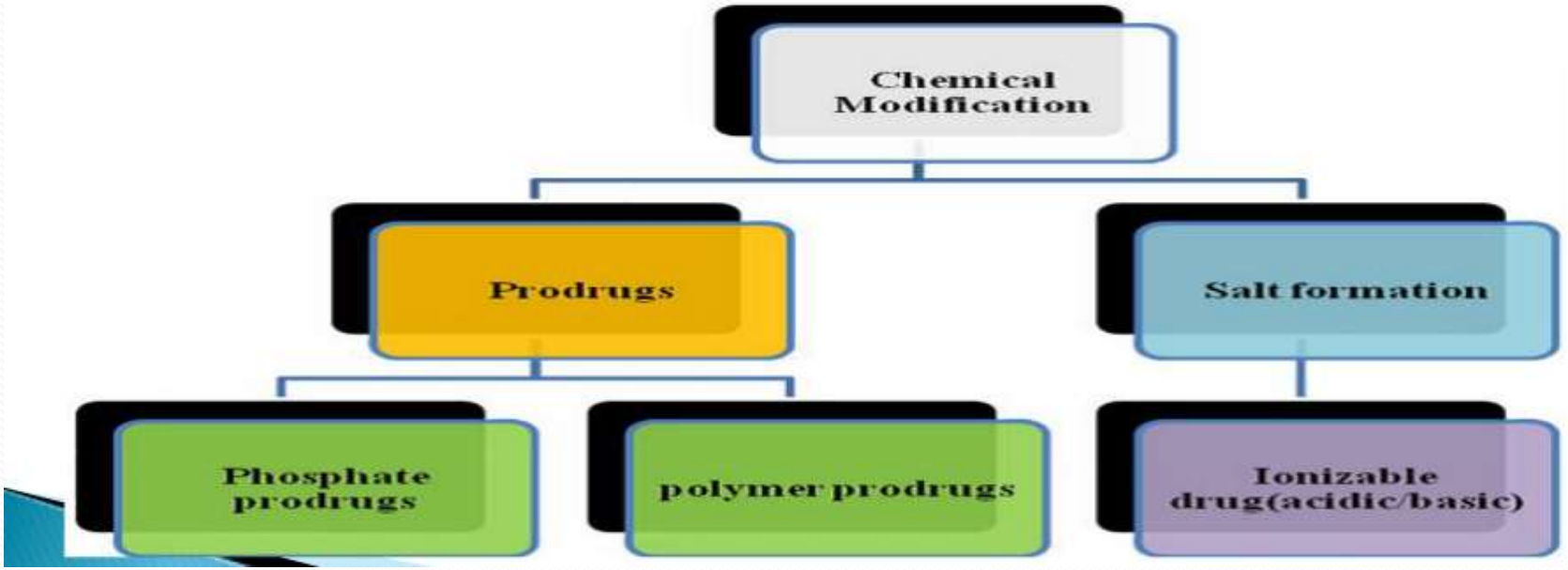
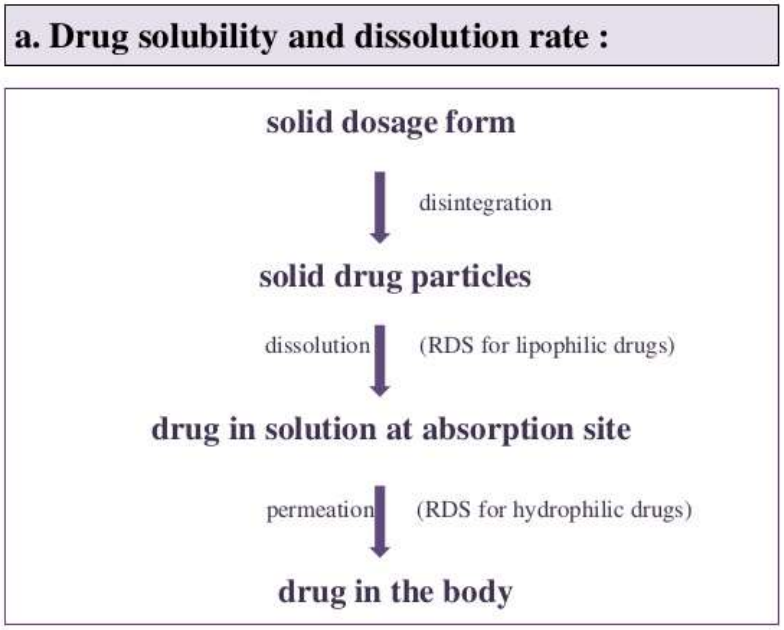


The solubility of a compound depends on
the properties of the solute and the solvent
temperature pressure, the pH of the solution,

Dissolution an extrinsic property

- dissolution is an *extrinsic* material property that can be influenced by various chemical, physical, or means such as complexation, particle size, surface properties, crystal properties

An extrinsic (or relational) **property** is a **property** that depends on a thing's relationship with other things.

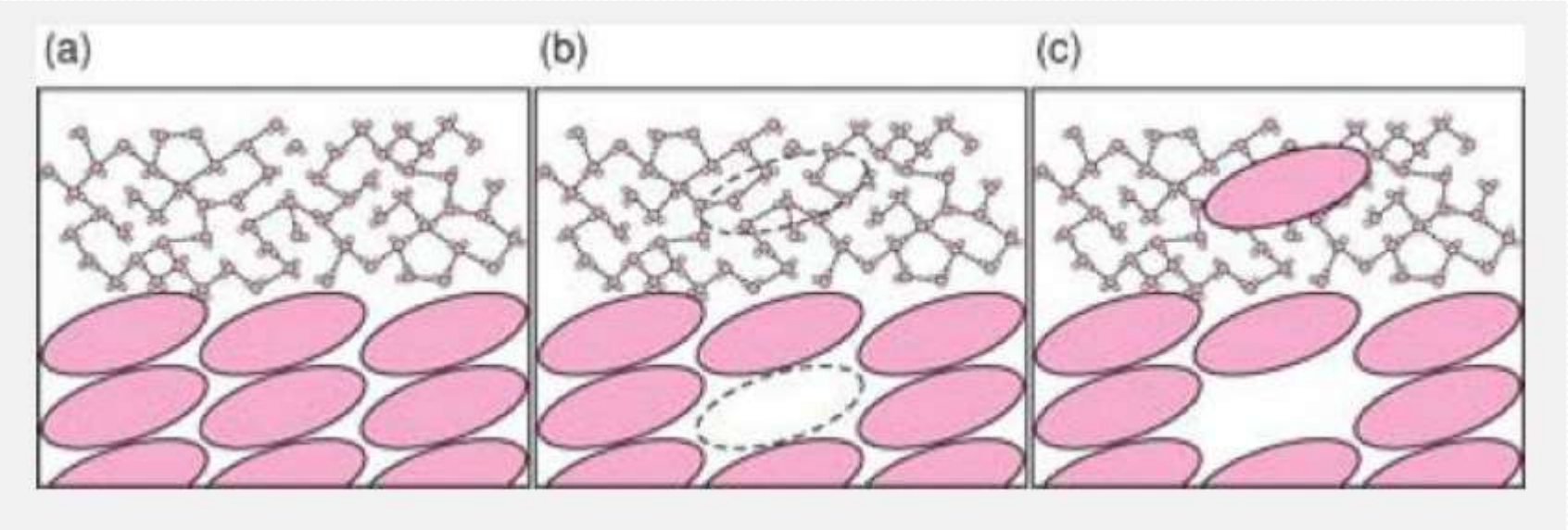


- Former Definition: Thermodynamic solubility of a drug in a solvent is the maximum amount of the most stable crystalline form that remains in solution in a given volume of the solvent at a given temperature and pressure under equilibrium conditions

- This Thermodynamic equilibrium involves a balance of the energy of three interactions against each other:
- (1) solvent with solvent,
- (2) solute with solute, and
- (3) solvent and solute

Steps of solid going into solution.

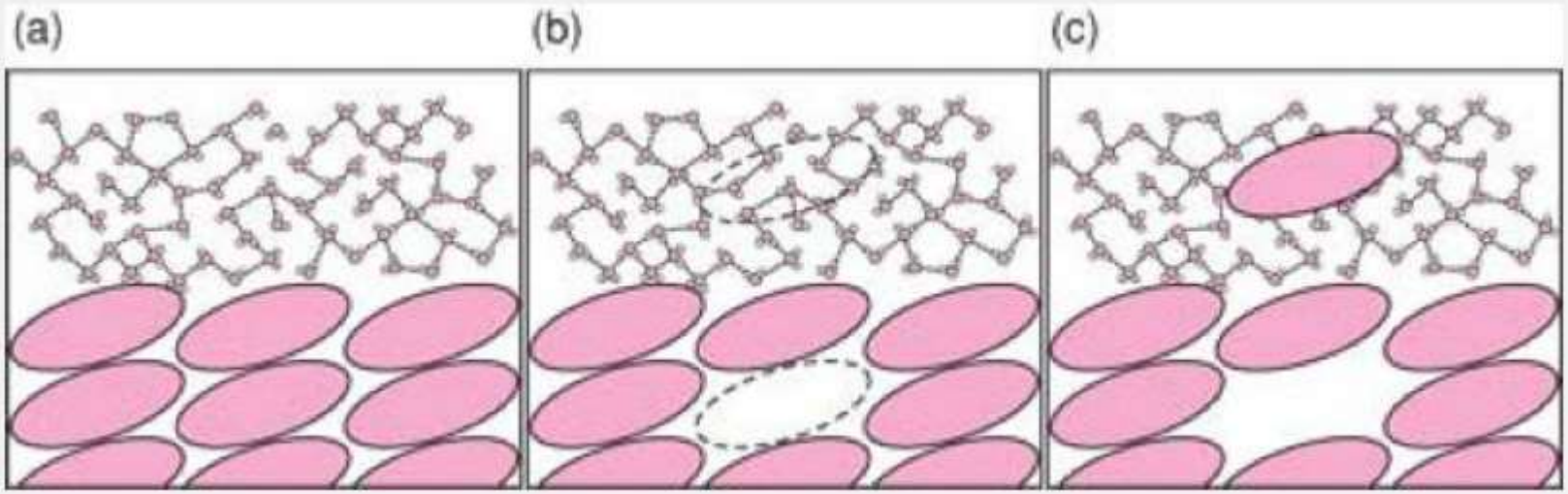
1. Step 1: Hole open in the solvent
2. Step 2: One molecule of the solid breaks away from the bulk
3. Step 3: The solid molecule is enter into the hole in the solvent



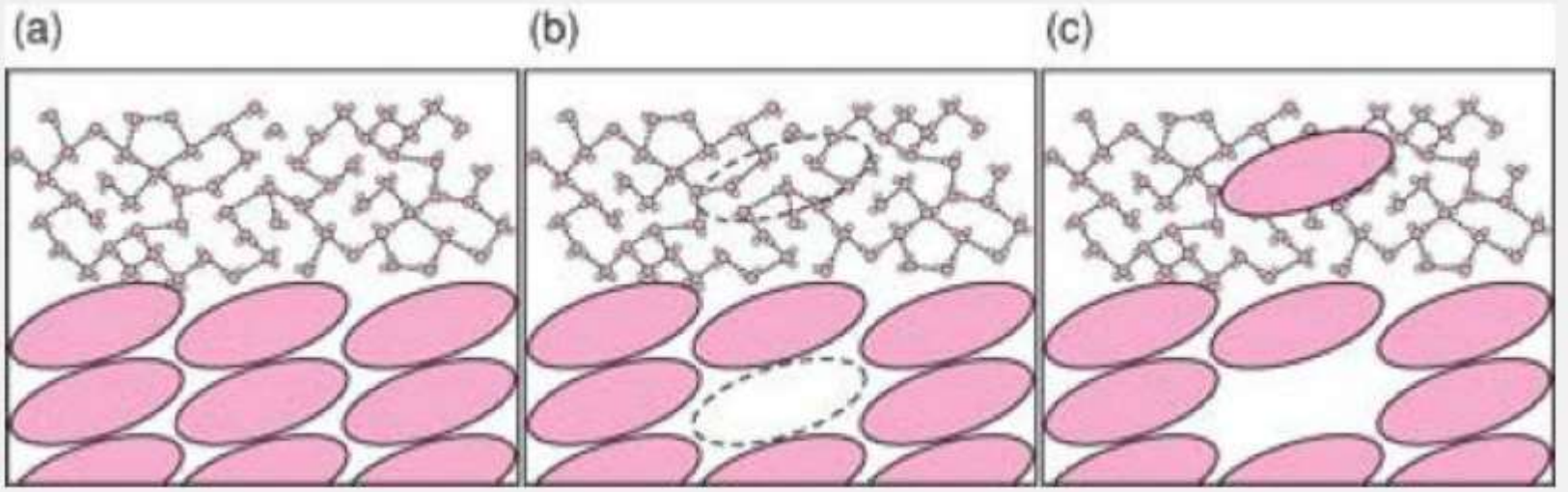
- (*a*) At first Solvent and solute are segregated, each interacts primarily with other molecules of the same type

We have only

- Solvent-solvent interaction (intermolecular forces)
- And solute-solute interaction



- To move a solute molecule into solution, the interactions among solute molecules in the crystal (lattice energy) and among solvent molecules in the space required to incorporate the solute (cavitation energy) must be broken.
- This means that Solute- solute interaction and solvent solvent interaction must be broken



- Anew interaction begins:
- Once the solute molecule is surrounded by solvent, new stabilizing interactions between the solute and solvent are formed (solvation energy)
- The system disorder increases owing to the mixing of solute and solvent (entropy of mixing)

Solubility USP

- Molarity
- Molality mole/kg
- USP/BP/EP
- Merck Index
- Encyclopedia of pharmaceutical excipient

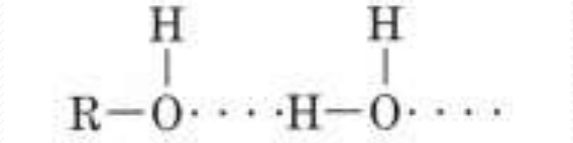
Table 9-1 Solubility Definition in the United States Pharmacopeia

escription 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

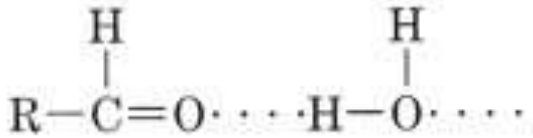
Polar Solvents

- The solubility of a drug is due in large measure to the polarity of the solvent
- But dipole moments alone is not adequate to explain the solubility of polar substances in water. The ability of the solute to form hydrogen bonds is a far more significant factor
- Polar solvents dissolve ionic solutes and other polar substances

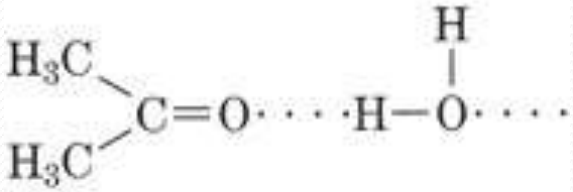
- Water dissolves phenols, alcohols, aldehydes, ketones, amines, and other oxygen- and nitrogen-containing compounds that can form hydrogen bonds with water:



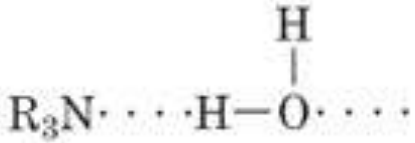
Alcohol



Aldehyde



Ketone



Amine

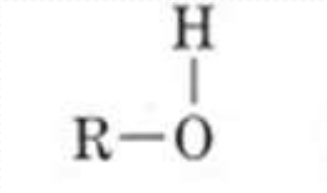
Solubility rules (Polar Solvents)

- As the length of a nonpolar chain of an aliphatic alcohol increases, the solubility of the compound in water decreases

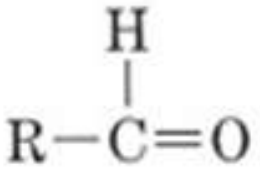
Alcohol	Solubility in H_2O (mol/100 g H_2O at 20°C)
CH_3OH (methanol)	
CH_3CH_2OH (ethanol)	
$CH_3CH_2CH_2OH$ (propanol)	
$CH_3CH_2CH_2CH_2OH$ (butanol)	
$CH_3CH_2CH_2CH_2CH_2OH$ (pentanol)	
$CH_3CH_2CH_2CH_2CH_2CH_2OH$ (hexanol)	
$CH_3CH_2CH_2CH_2CH_2CH_2CH_2OH$ (heptanol)	

Solubility rules (Polar Solvents)

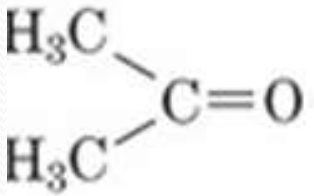
- Straight-chain monohydroxy alcohols, aldehydes, ketones, and acids with more than four or five carbons cannot enter into the hydrogen-bonded structure of water and hence are only slightly soluble



Alcohol



Aldehyde

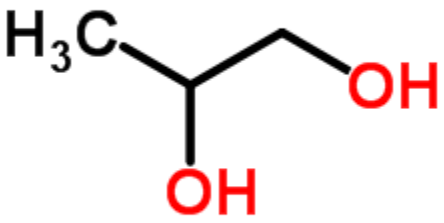


Ketone

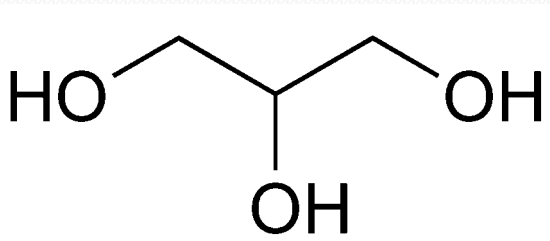
R>4 or 5

Solubility rules (Polar Solvents)

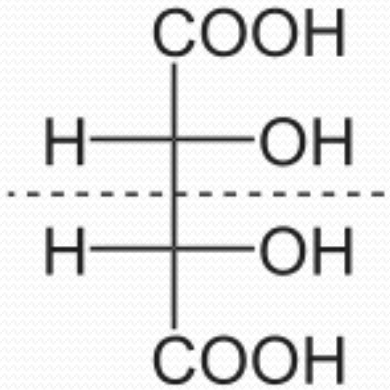
- When additional polar groups are present in the molecule, as found in propylene glycol, glycerin, and tartaric acid, water solubility increases greatly.



Propylene Glycol



Glycerin

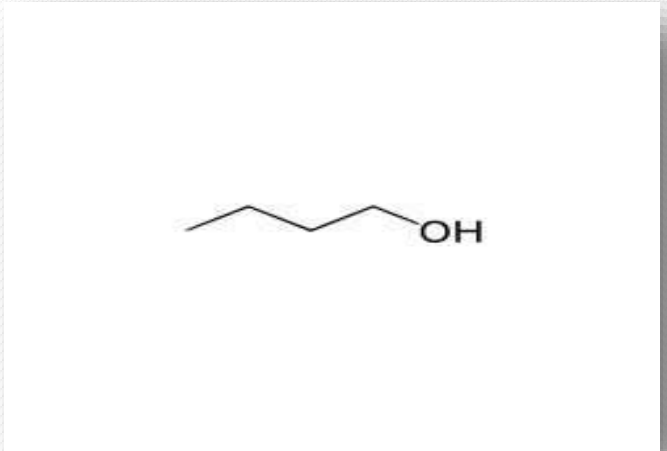


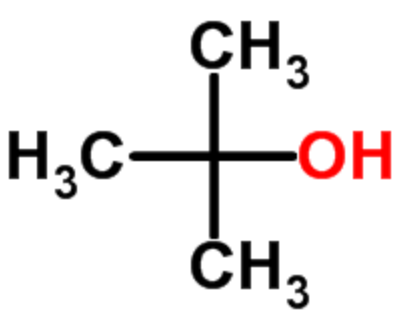
Tartaric acid

Solubility rules (Polar Solvents)

- Branching of the carbon chain reduces the nonpolar effect (due to hydrocarbon chain)n and leads to increased water solubility.

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.





Nonpolar Solvents

Nonpolar solvents

- Unable to reduce the attraction between the ions
- Cannot form hydrogen bridges.
- Ionic and polar solutes are not soluble or are only slightly soluble in nonpolar solvents.
- Nonpolar compounds, however, can dissolve nonpolar solutes through induced dipole interactions
- The solute molecules are kept in solution by the weak van der Waals– London type of forces
- Hexane, ethyl ether

Semipolar Solvents

- semipolar compounds can act as *intermediate solvents* to bring about miscibility of polar and nonpolar liquids
- **They can induce certain polarity in non-polars**
- Ex: Ketones, alcohols
- alcohol on water–castor oil mixtures (intermediate solubility
- Propylene glycol has been shown to increase the mutual solubility of water and peppermint oil and of water and benzyl benzoate
- Acetone: increase solubility of ether in water
- Mechanism: Induction of polarity in non polar solvent

Permanent dipole-Induced dipole force

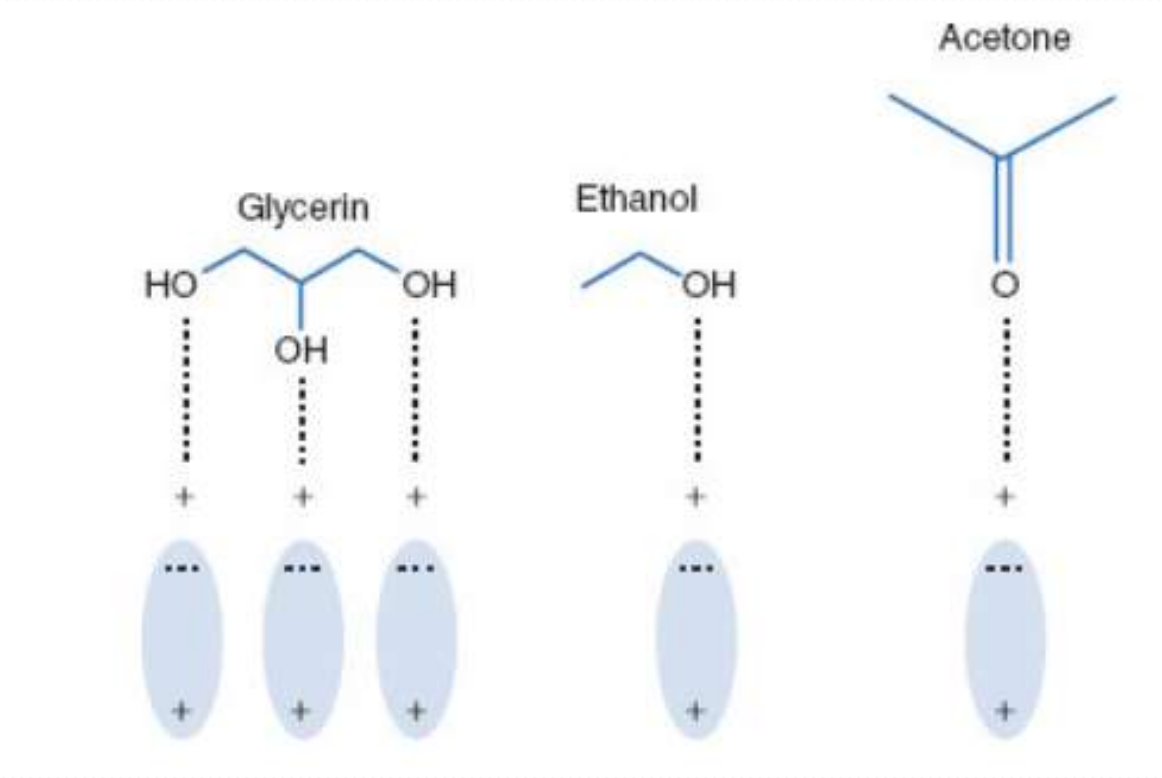

Glycerin
HO
OH
OH
Ethanol
OH
Acetone
O

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		

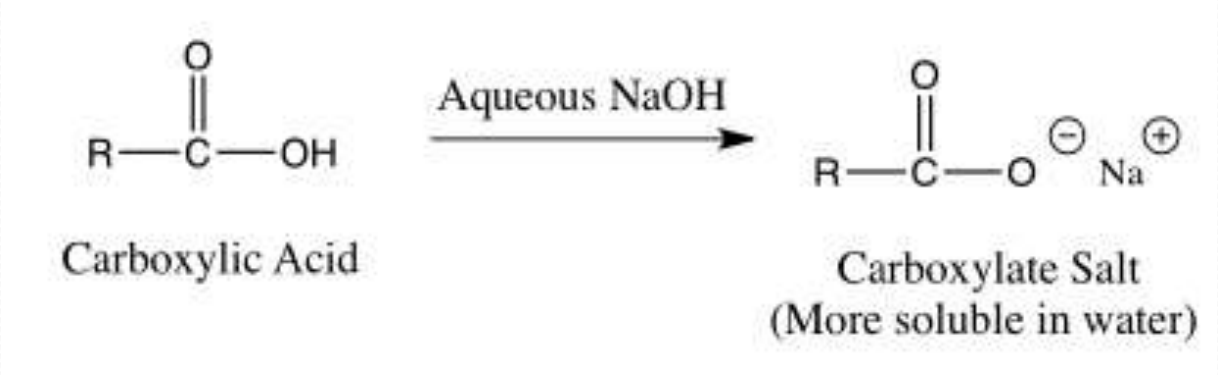
- 50-80 polars
- 20-50 semipolar solvents
- 0-20 non polar solvents

Completely and partially miscible

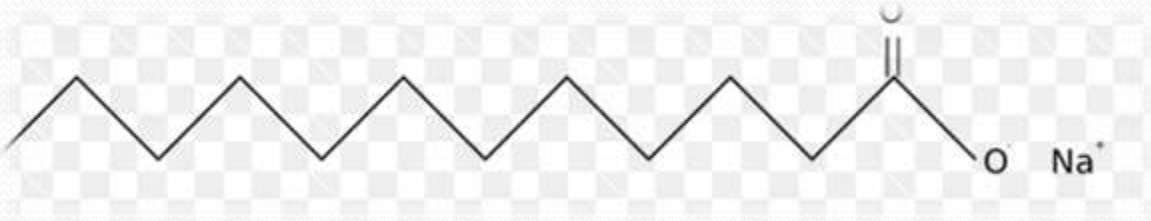
- Polar and semipolar solvents, such as water and alcohol, glycerin and alcohol, and alcohol and acetone, are said to be completely miscible because they mix in all proportions
- When certain amounts of water and ether or water and phenol are mixed, two liquid layers are formed, each containing some of the other liquid in the dissolved state (Partially miscible)

Solubility of solids in Liquids (pH)

- Many important drugs belong to the class of weak acids and bases
- carboxylic acids containing more than five carbons are relatively insoluble in water, they react with dilute sodium hydroxide, carbonates, and bicarbonates to form soluble salts

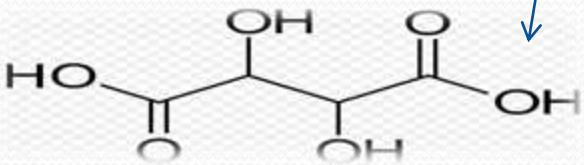


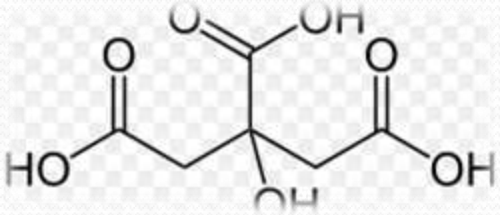
- The fatty acids containing more than 10 carbon atoms form soluble soaps with the alkali metals(Na,K) and insoluble soaps with other metal ions.



- Fatty acids 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

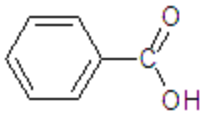
- **Hydroxy acids**, such as tartaric and citric acids, are quite soluble in water because they are solvated through their hydroxyl groups



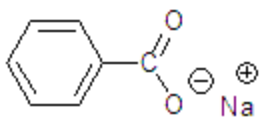


- **Aromatic acids** react with dilute alkalies to form water-soluble salts, but they can be precipitated as the free acids if stronger acidic substances are added to the solution or by heavy metals

Benzoic acid is soluble in sodium hydroxide solution, alcohol, and fixed oils



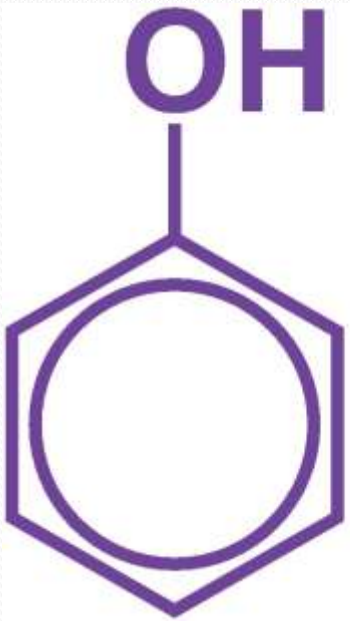
benzoic acid
acid form:
sol. in organic



sodium benzoate
salt form:
sol. in water

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

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



C_6H_5OH

Solubility of Weak Electrolytes as Influenced by pH

- ***Acidic drugs**, such as the non-steroidal anti-infl ammatory* agents, **are less soluble in acidic solutions** than in alkaline solutions
- because the predominant undissociated species cannot interact with water molecules to the same extent as the ionised (weak solvent solute interaction)
- ***Basic drugs** such as ranitidine are more* soluble in acidic solutions where the ionized form of the drug is predominant

Calculating the Solubility of Weak Electrolytes as Influenced by pH

- As we know solubility of weak electrolytes is strongly influenced by the pH of the solution
- **Example**, a 1% solution of phenobarbital sodium is soluble at pH values high in the alkaline range.
- The soluble ionic form is converted into molecular phenobarbital as the pH is lowered, and drug begins to precipitate from solution at room temperature

$$HP + H_2O \leftrightarrow H_3O^+ + P^-$$

$$K_a = \frac{[H_3O^+][P^-]}{[HP]} \longrightarrow \log K_a = \log[H_3O^+] + \log(\frac{[P^-]}{[HP]})$$

$$\longrightarrow -\log[H_3O^+] = -\log K_a + \log(\frac{[P^-]}{[HP]})$$

S The total solubility of drug (un-ionized + ionized) $S = [HP] + [P^-]$

$S_\circ$ solubility of the un-ionized form of drug in solution $S_\circ = [HP]$

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

So: is the solubility of the undissociated form of the drug.
(molar interensic solubility)
S : total solubility of drug

- The equation relating the solubility, *S*, *of an acidic drug to the* pH of the solution is:

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

- *So is the solubility of the* undissociated form of the drug.
- S : total solubility of drug
- pH: the pH **below** which the drug separates from solution as the undissociated acid.

henderson hasselbalch equation

So: is the solubility of the undissociated form of the drug. (molar interensic solubility)
S : total solubility of drug

- **Example**
- **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*o, of phenobarbital is 0.0050 and the p*K*a is 7.41 at 25°C. The molecular weight of sodium phenobarbital is 254.

The molar concentration of salt initially added is

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

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

$$\text{pH}_p = 7.41 + \log\frac{(0.039 - 0.005)}{0.005} = 8.24$$

So: is the solubility of the undissociated form of the drug. (molar interensic solubility)
S : total solubility of drug

- ***Basic drugs*** *such as ranitidine are more* soluble in acidic solutions where the ionized form of the drug is predominant. The equation relating the solubility, *S*, *of* a basic drug to the pH of the solution is:

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

is the pH *above* which the drug begins to precipitate from solution as the free base.

Ionization and pH Summary

Strong vs. weak acids and bases

1. Strong – ionized at all pHs
2. Weak – only ionized at certain pHs (most drugs are weak acids or weak bases
3. Ionized drugs are not very lipid soluble- only nonionized form of drug crosses membrane readily
4. Percent ionization is pH dependent
5. pKa is the negative log of the ionization constant and is equal to the pH at which a drug is 50% ionized
6. Weak acids become highly ionized as pH increases
7. Weak bases become highly ionized as pH decreases

The Influence of Solvents on the Solubility of Drugs(nonelectrolytes and the undissociated molecules of weak electrolytes.)

- a solute is more soluble in a mixture of solvents than in one solvent alone. This phenomenon is known as *cosolvency*,
- the solvents that, in combination, increase the solubility of the solute are called *co solvents*.
- PG,PEG, Glycerine, Alcohol.

The Influence of Solvents on the Solubility of Drugs

- if we have Weak electrolyte (example weak acid in water): Ionized and non ionized species soluble in water (S,So)
- Adding alcohol affects the solubility of a weak electrolyte in a buffered solution in two ways:

HP+Alcohol+H2O

- (*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.
- (Non ionized Solubility) 

(as Alcohol less polar than water)

The Influence of Solvents on the Solubility of Drugs

- (*b*) But Alcohol 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 (p*K*a is increased).
- But Net change is increased solubility
- so that the pH for weak acids can be reduced more somewhat before precipitation occurs.

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

Influence of Other Factors on the Solubility of Solids

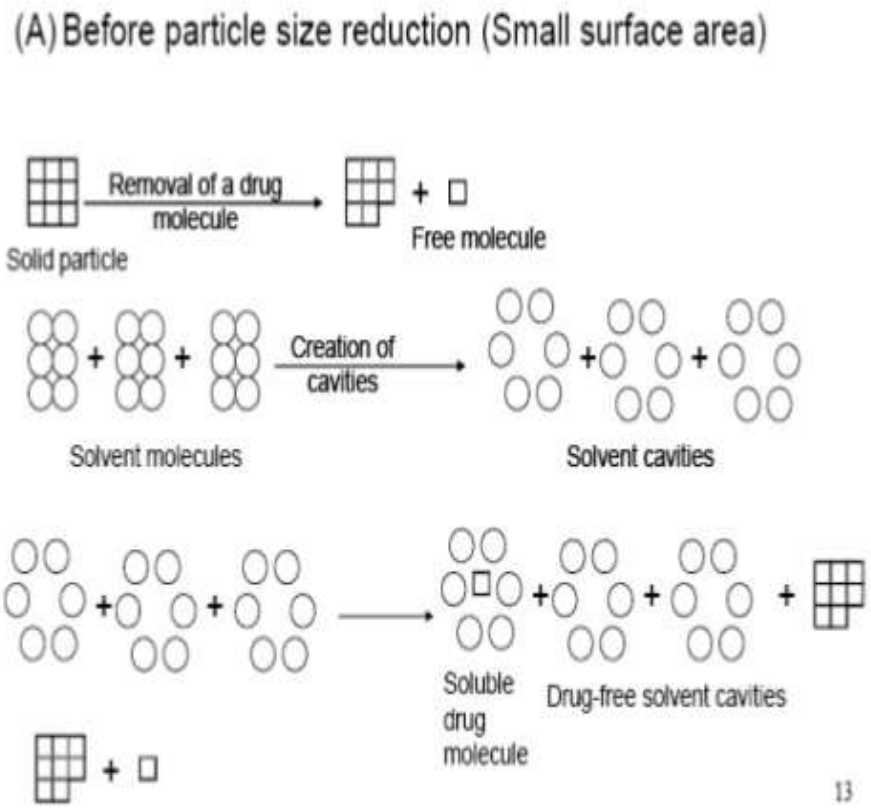
- type of arrangement in the crystal

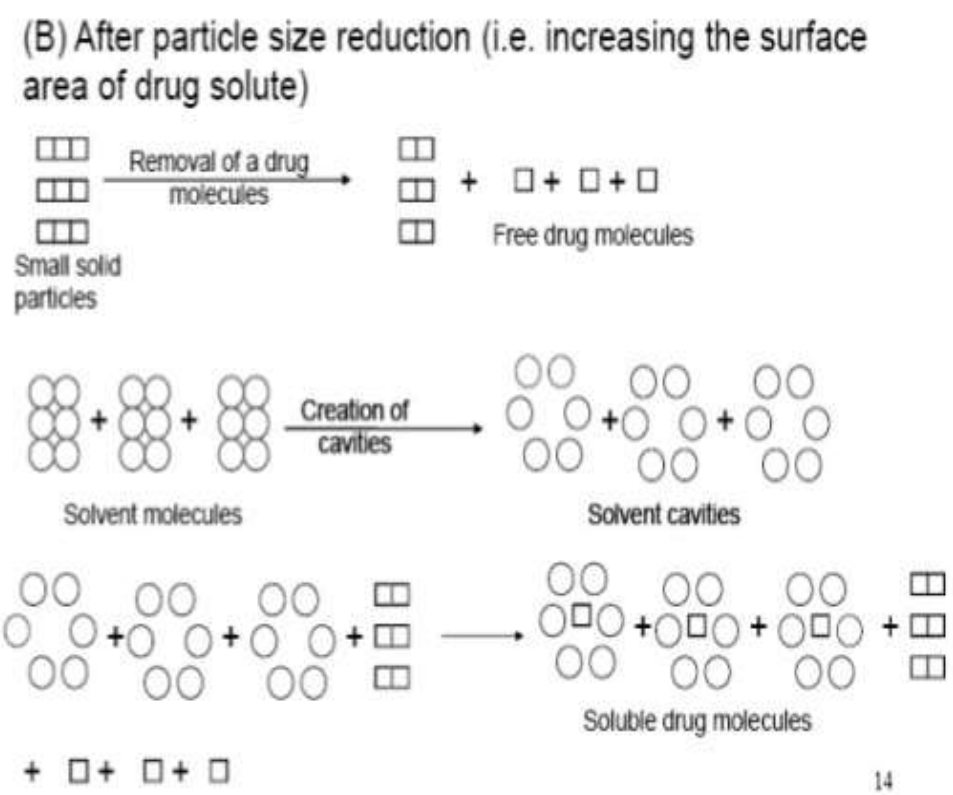
This is because solubility depends in part on the work required to separate the particles of the crystalline solute

- The molecules of the amino acid α-alanine form a compact crystal with high lattice energy and consequently low solubility
- Lattice energy high or low

Effect of particle size on rate solubility

↓Particle size → ↑ surface area→ ↑Solubility





Biopharmaceutical Classification system (drug absorption)

- The **Biopharmaceutics Classification System** is a system to differentiate the drugs on the basis of their solubility and permeability

- Class I - high permeability, high solubility
- Class II - high permeability, low solubility
- Class III - low permeability, high solubility
- Class IV - low permeability, low solubility

- A drug substance is considered HIGHLY SOLUBLE when the highest dose strength is soluble in < 250 ml water over a pH range of 1 to 7.5
- A drug substance is considered HIGHLY PERMEABLE when the extent of absorption in humans is determined to be > 90% of an administered dose,.

BCS Class I: High Solubility and High Permeability

- Compounds belonging to this class are normally expected to dissolve quickly in gastric and intestinal fluids, and readily cross the intestinal wall through passive diffusion
- BCS Class I are unlikely to show bioavailability or bioequivalence issues
- Therefore, for BCS class I drugs, in vitro dissolution studies are thought to provide sufficient information to assure in vivo product performance making full in vivo bioavailability / bioequivalence studies unnecessary

BCS Class II: Poor Solubility and High Permeability

- By definition, poor solubility and/or slow dissolution are the rate-limiting steps for oral absorption of BCS class II compounds

- In other words, the compounds may dissolve quickly enough to reach their equilibrium solubility, but the solubility is too low to establish a wide enough concentration gradient to drive passive diffusion (we have to modify solubility)

BCS Class II: Poor Solubility and High Permeability

- Formulations designed to overcome solubility problems:
  - Salt formation
  - Particle size reduction
  - Metastable forms

BCS Class III: High Solubility and Low Permeability

- Since passive diffusion is the rate-limiting step for oral absorption of BCS class III compounds, the most effective way to improve absorption and bioavailability of this class of compounds is to increase the membrane permeability

- Approaches to improve permeability:
  - Prodrugs
  - Permeation enhancers

BCS Class IV: Low Solubility and Low Permeability

- Class IV compounds exhibit both poor solubility and poor permeability, and they pose tremendous challenges to formulation development
- Different dosage form is needed (injection)

CLASS	SOLUBILITY	PERMEABILITY	EXAMPLES
Class – I	High	High	Metoprolol , Propranolol
Class – II	Low	High	Nifedipine, naproxen
Class – III	High	Low	Cimitidine, Metformin
Class – IV	Low	Low	Taxol,

Solubility Phase diagram

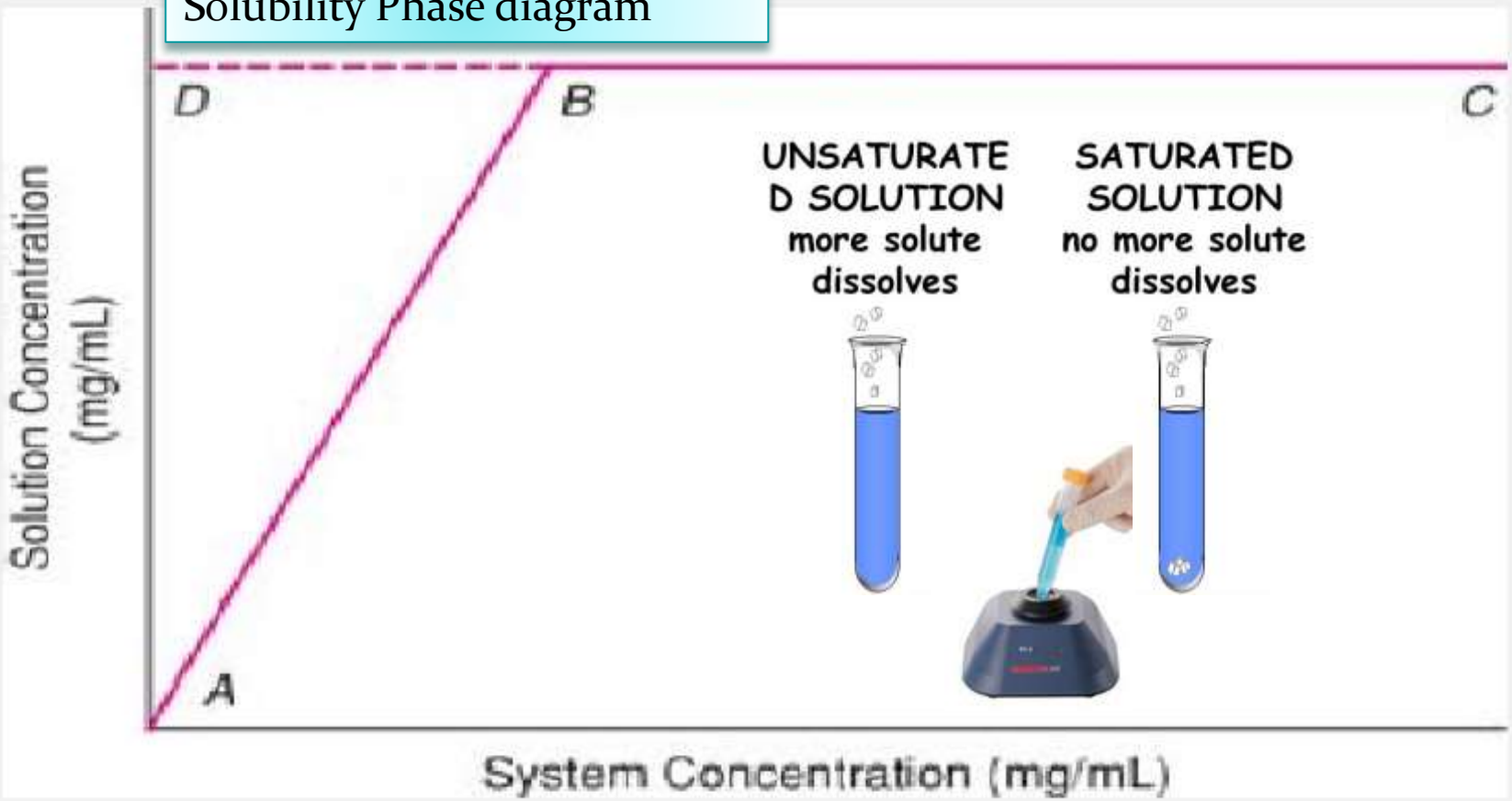


Fig. 9-6. Phase-solubility diagram for a pure drug substance. The line segment A–B represents one phase since the concentration of drug substance is below the saturation concentration. Line segment B–C represents a pure solid in a saturated solution at equilibrium. (From Remington, *The Science and Practice of Pharmacy*, 21st Ed., Lippincott Williams & Wilkins, 2006, p. 216. With permission.)

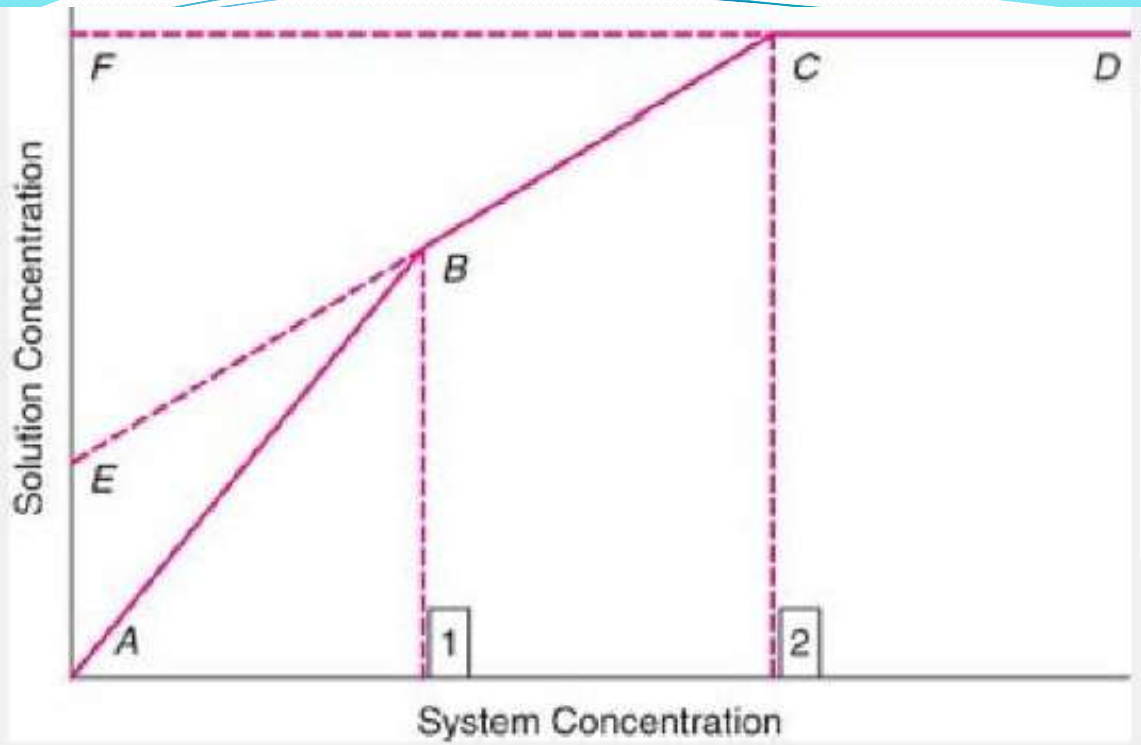


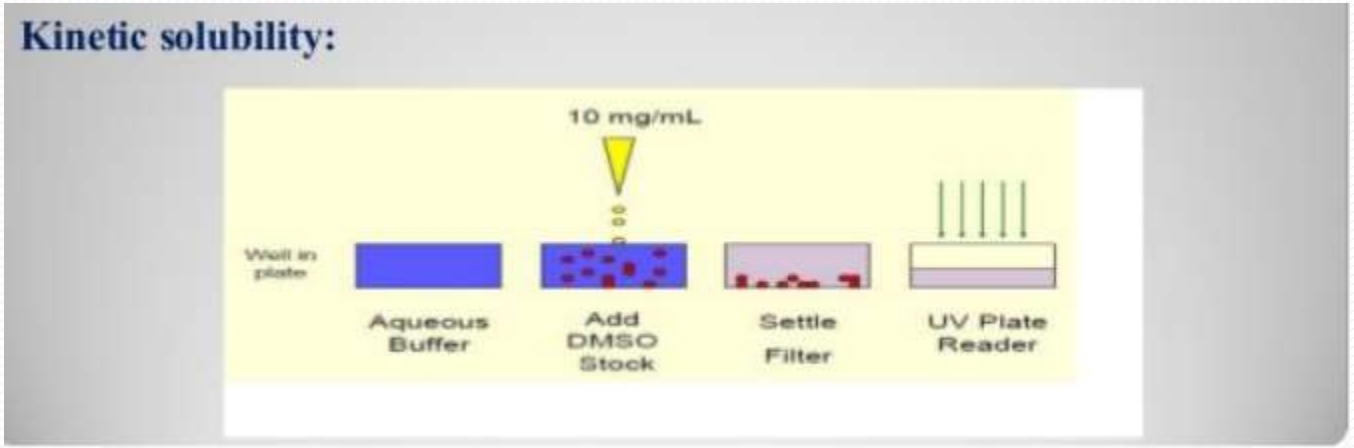
Fig. 9-7. Phase-solubility curve when the drug substance contains one impurity. At point B, the solution becomes saturated with component 1 (the drug). The segment B–C represents two phases—a solution phase saturated with the drug and some of the impurity and a solid phase of the drug. Segment C–D represents two phases—a liquid phase saturated with the drug and impurity and a solid phase containing the drug and the impurity. (From Remington, *The Science and Practice of Pharmacy*, 21st Ed.,

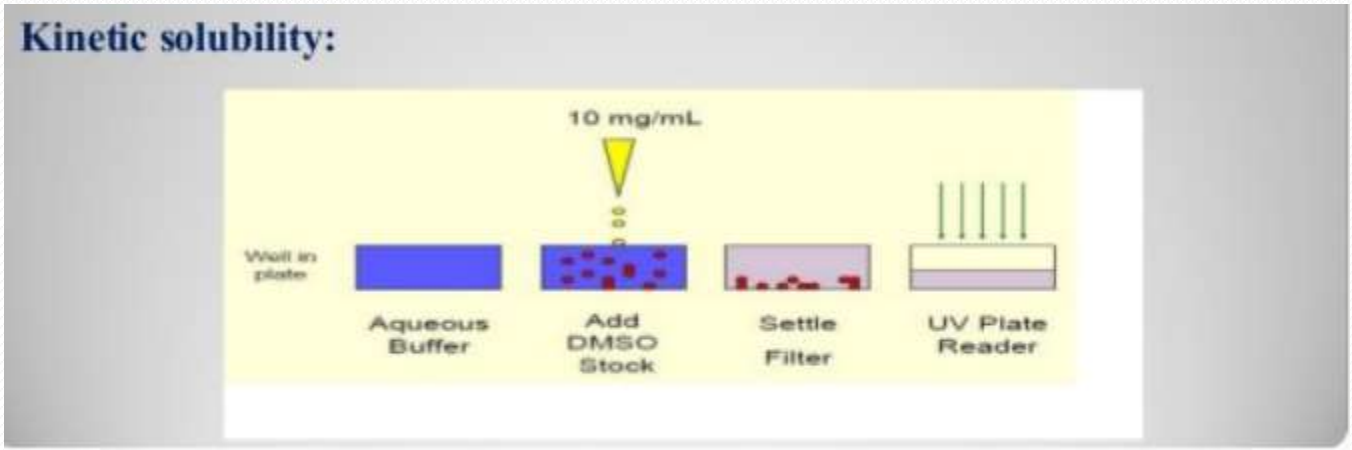
“Kinetic” Solubility

- Thermodynamic solubility determination is Time consuming
- Starting the experiment with a high purity crystalline form of the substance will give the best chance that the solubility measured after a reasonable incubation period will represent the true equilibrium solubility (hours to days) (thermodynamic) (difficult for new drg)
- Sometimes the incubation period will not be sufficient for metastable crystal forms to convert to the most stable form.(result will give solubility of different crystal forms (Not true solubility)
- Not enough drug synthesized (early drug studying)

“Kinetic” Solubility

- Misleading name : because it measures a precipitation rate rather than solubility
- Kinetic solubility: using submilligram quantities **Kinetic Solubility** is the concentration of a compound in solution when an induced precipitate first appears.





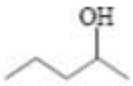
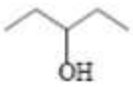
- Typically, the compound is dissolved in dimethyl sulfoxide (because it is a strong organic solvent) to make a stock solution of known concentration
- Added to aqueous solvent of interest (buffer) until the anti-solvent properties of the water drive the compound out of solution. (lattice energy Ignored)

Kinetic solubility

- The resulting precipitation is detected optically, and the kinetic solubility is defined as the point at which the aqueous component can no longer solvate the drug.
- Solubility results obtained from kinetic measurements might not match the thermodynamic solubility results perfectly
- Speed, small amount of material (early formulation study not enough API), mo pure crystalline material

Notes

- The *boiling point* of liquids and the *melting point* of solids both reflect the strengths of interactions between themolecules in the pure liquid or the solid state. Ingeneral, aqueous solubility decreases with increasing boiling point and melting point

		Boiling point (°C)	Solubility (M/l)
n-Pentanol		137.8	0.26
3-methyl-1-butanol		131.2	0.31
2-Pentanol		119	0.53
3-Pentanol		115.3	0.62

	Melting Point	Solubility
Sulfadiazine	253°C	1g in 13 dm^3
Sulfamerazine	236°C	1g in 5 dm^3
Sulfapyridine	192°C	1g in 3.5 dm
sulfathiazole	174°C	1g in 1.7 dm

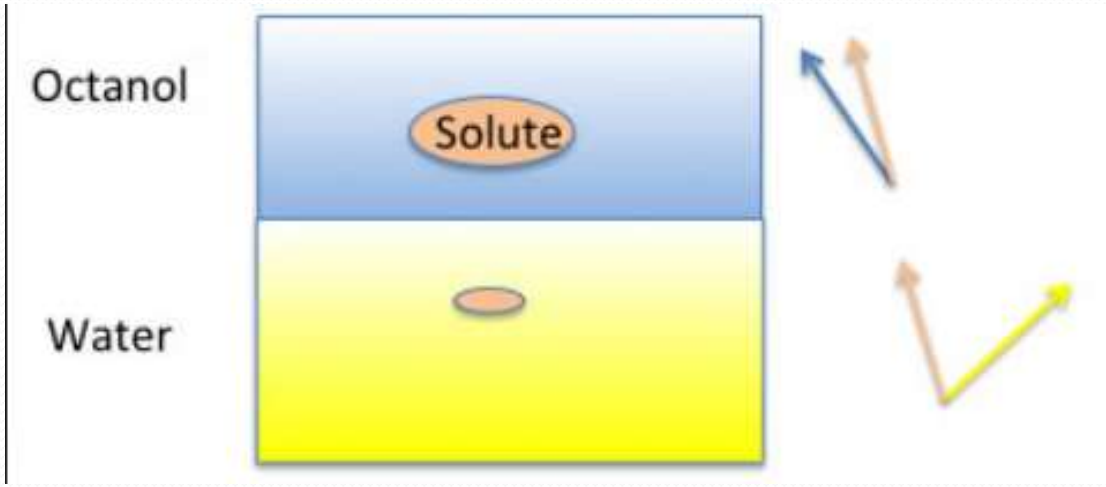

PARTICLE SIZE
TEMPERATURE
MOLECULAR STRUCTURE
SOLUBILITY
pH
CRYSTAL STRUCTURE
PRESSURE
POLARITY

Temperature effect on solubility

- Temperature (Generally ⬆ Temp ➡ better solubility" if positive heat of solution, (Absorb Heat)
- Eciption Calcium Hydroxide Topical Solution, USP. Calcium hydroxide is soluble in water to the extent of 140 mg per 100 mL of solution at 25°C and 170 mg per 100 mL of solution at 15°C (exothermic upon dissolving).

Distribution of Solutes between Immiscible Solvents

- If a of liquid or solid is added to a mixture of two immiscible liquids, it will distribute itself between the two phases (distribution)



Distribution of Solutes between Immiscible Solvents

- If C_1 and C_2 are the equilibrium concentrations of the substance in Solvent1 and Solvent2, respectively
- K, is known as the *distribution* ratio, *distribution coefficient*, or *partition coefficient*.

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

- **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?

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

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

Examples on partitioning

- **drugs 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

Importance of Partition coefficient

Knowledge of partition is important to the pharmacist

- These include preservation of oil–water systems,
- drug action at nonspecific sites (drug receptor Interaction)
- and the absorption and distribution of drugs throughout the body.

Effect of Ionic Dissociation and Molecular Association on Partition

- In partitioning
- The solute can exist partly or wholly as associated molecules in one of the phases
- or it may dissociate into ions in either of the liquid phases

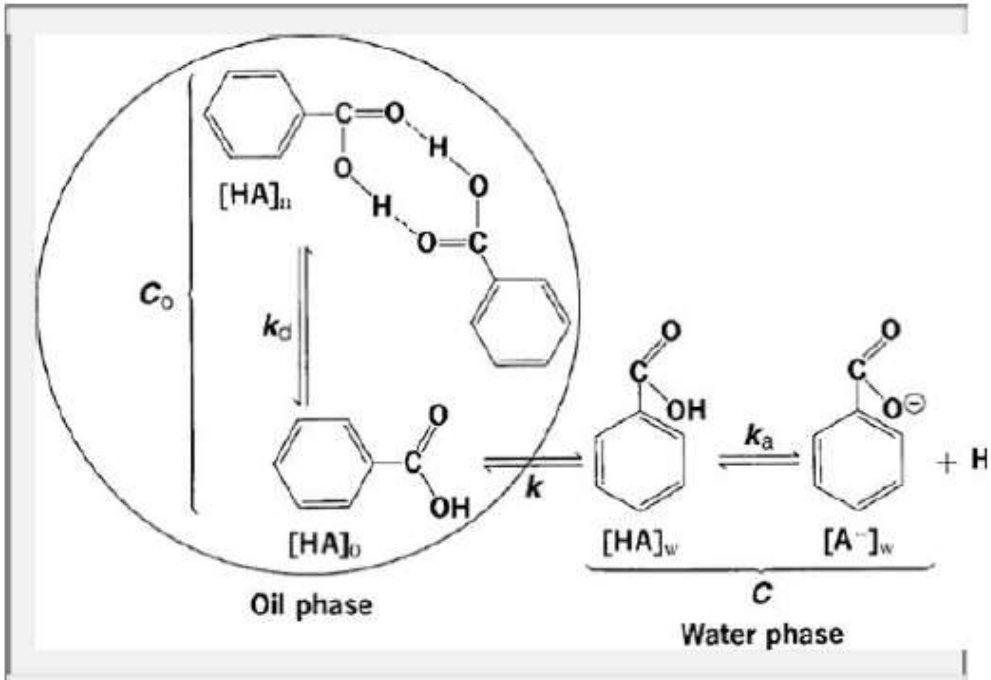


Fig. 9-9. Schematic representation of the distribution of benzoic acid between water and an oil phase. The oil phase is depicted as a magnified oil droplet in an oil-in-water emulsion.

- Water-Benzoic Acid- Oil (Peanut oil no association) only dissociation occurs
- How to calculate Partition coefficient
- 1- don't consider the dissociation

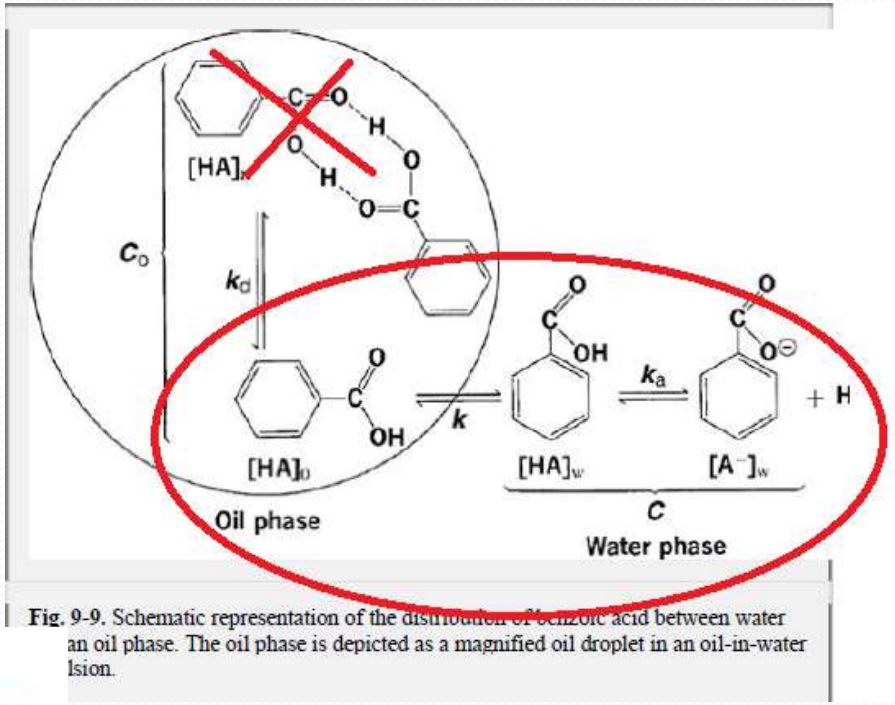


Fig. 9-9. Schematic representation of the distribution of benzoic acid between water an oil phase. The oil phase is depicted as a magnified oil droplet in an oil-in-water lsion.

$$K = \frac{[HA]_o}{[HA]_w} = \frac{C_o}{[HA]_w}$$ ⇨ Undissociated acid

- *In this case K* is called the *true distribution coefficient*

Benzoic acid (water/peanut oil)

- Emulsions contains preservative that partition between two phases (benzoic acid)
- the preservative or bacteriostatic properties of organic acids is **a function of the undissociated acid concentration** and not of the ion.
- (effective preservative is the unionized form)
- The important function is the K (Partition coefficient) not the concentration of preservative
- How to calculate K (True Partition coefficient)
- This leads to step 2

2- dissociation considered

- The concentration of benzoic acid in water is given by:

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

$$K' = \frac{[HA]_o}{[HA]_w + [A^-]_w} = \frac{C_o}{C_w}$$

- K` = apparent distribution coefficient

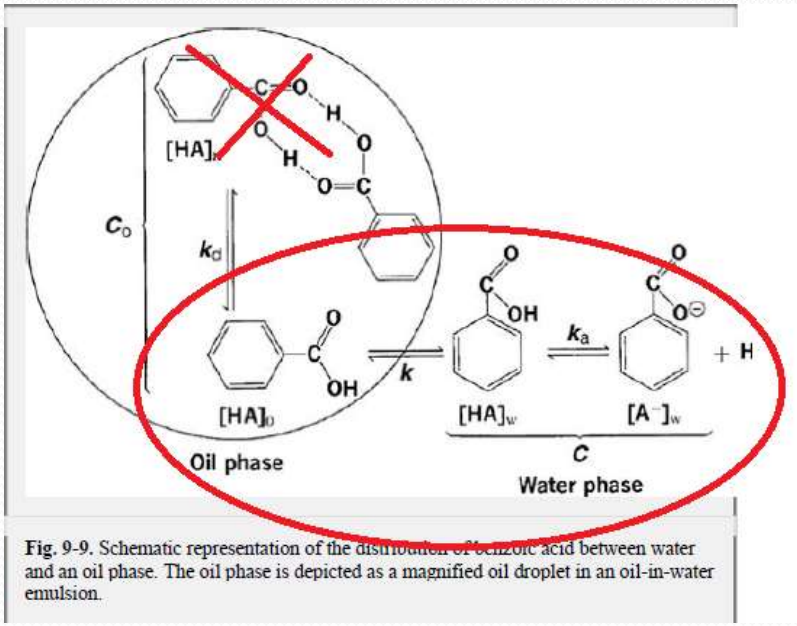


Fig. 9-9. Schematic representation of the distribution of benzoic acid between water and an oil phase. The oil phase is depicted as a magnified oil droplet in an oil-in-water emulsion.

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

$$K' = \frac{[HA]_o}{[HA]_w + [A^-]_w} = \frac{C_o}{C_w}$$

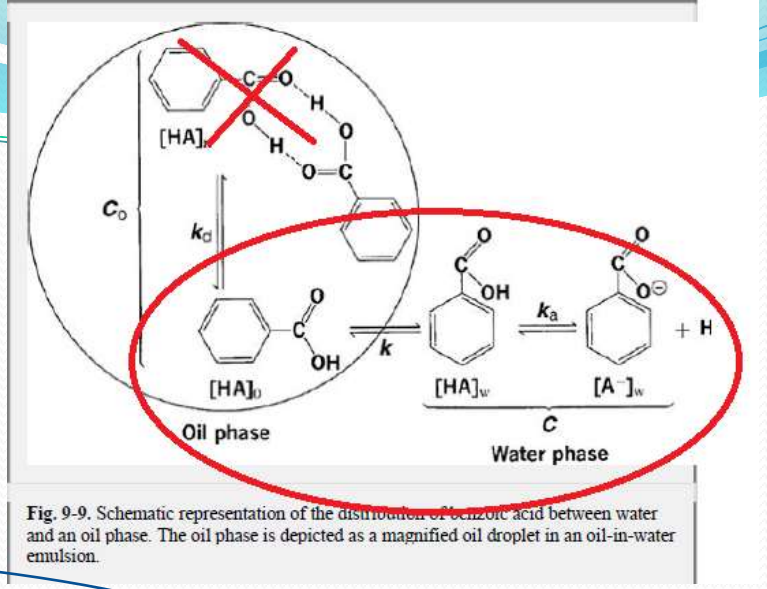


Fig. 9-9. Schematic representation of the distribution of benzoic acid between water and an oil phase. The oil phase is depicted as a magnified oil droplet in an oil-in-water emulsion.

$$K' = \frac{[HA]_o}{[HA]_w + \frac{K_a[HA]_w}{[H_3O^+]}} = \frac{[HA]_o[H_3O^+]}{[HA]_w(K_a + [H_3O^+])}$$

$$[A^-]_w = \frac{K_a[HA]_w}{[H_3O^+]}$$

To eliminate the need of (HA)o substitute (HA)w with as K= (HA)o/(HA)w

$\{HA\}_w = (HA)o/K$

K:true partition Coefficient

$$K' = \frac{[HA]_o[H_3O^+]}{[HA]_o/K(K_a + [H_3O^+])} = \frac{K[H_3O^+]}{K_a + [H_3O^+]}$$

$$\frac{K[H_3O^+]}{K_a + [H_3O^+]} = \frac{C_o}{C_w}$$

or

$$C_o = \frac{K[H_3O^+]C_w}{K_a + [H_3O^+]}$$

Total Conc in oil and water

As ➡ $C = C_o + C_w$ ➡ Then

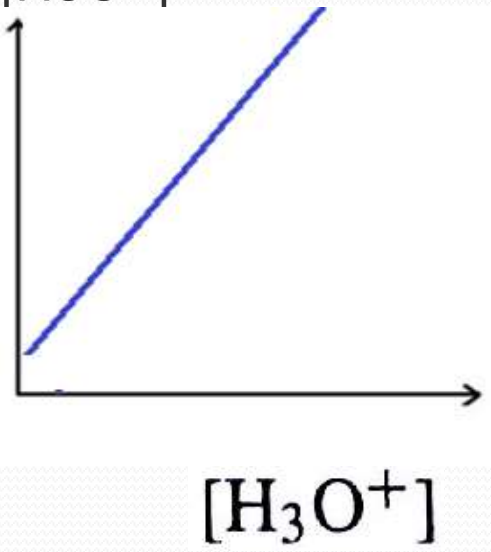
$$C = \frac{K[H_3O^+]C_w}{K_a + [H_3O^+]} + C_w$$

$$= \frac{K[H_3O^+]C_w + (K_a + [H_3O^+]C_w}{K_a + [H_3O^+]}$$

- Rearrangement of previous equation

$$\frac{K_a + [H_3O^+]}{C_w} = \frac{[H_3O^+](K + 1) + K_a}{C}$$

a linear equation of the form $y = a + bx$, and therefore a plot of (Ka + [H3O+])/Cw against [H3O+]



Ka: Acid dissociation constant
K: True Partition coefficient

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

$$C = C_o + C_w$$

$$K = \frac{[HA]_o}{[HA]_w} = \frac{C_o}{[HA]_w}$$ ⇨ Undissociated acid

a slope $b = (K + 1)/C$ and an intercept $a = K_a/C$

True partition coefficient

Example

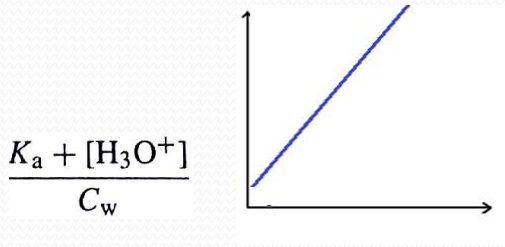
$$\frac{K_a + [H_3O^+]}{C_w} = \frac{[H_3O^+](K + 1) + K_a}{C}$$

a slope $b = (K + 1)/C$ and an intercept $a = Ka/C$

- A plot of (*K*a + [H3O])/*C*w against [H3O] for benzoic acid distributed between equal volumes of peanut oil and a buffered aqueous solution yields a slope *b* = 4.16 and an intercept *a* = 4.22 × 10-5. The *Ka* of benzoic acid is 6.4 × 10-5. Compute the true partition coefficient, *K*

(Slope): b= (K+1)/C ⟹ *K=bC-1*

(Intercept): a=Ka/C ⟹ *C=Ka/a*



(true partition coefficient)

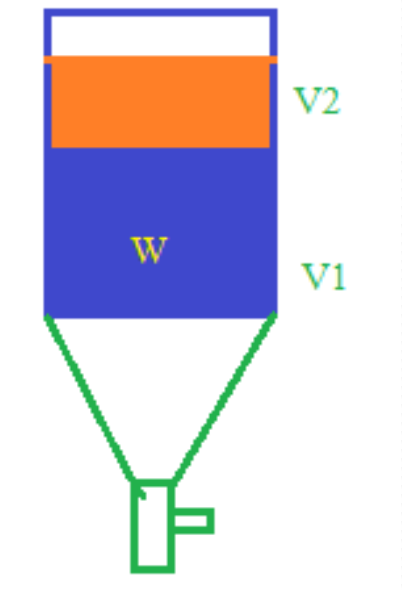
$$K = \frac{bKa}{a} - 1 \qquad K = \frac{bKa - a}{a}$$

$$\frac{(4.16 \times 6.4 \times 10^{-5}) - 4.22 \times 10^{-5}}{4.22 \times 10^{-5}} = 5.31$$

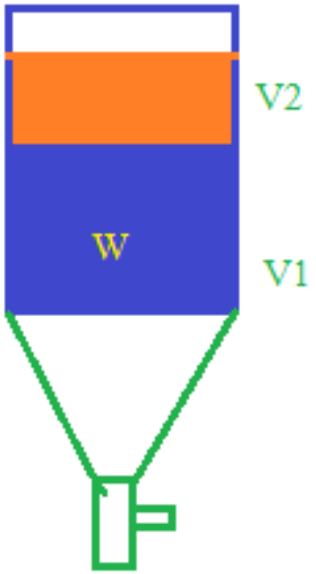
- Alternative method for K determination , the true distribution constant could be obtained according to equation $K = \frac{[HA]_o}{[HA]_w} = \frac{C_o}{[HA]_w}$ by analysis of the oil phase and of the water phase at a sufficiently low pH (2.0) at which the acid would exist completely in the un-ionized form
- One of the advantages of equation **Plot method** however, is that the oil phase need not be analyzed; only the hydrogen ion concentration and *C*w, the total concentration remaining in the aqueous phase at equilibrium, need be determined.

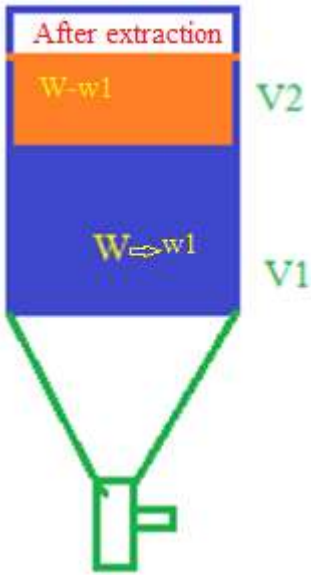
Extraction

- To determine the efficiency with which one solvent can extract a compound from a second solvent
- 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
- Then The distribution coefficient is:





$$K = \frac{w_1/V_1}{(w - w_1)V_2} \Rightarrow w_1 = w\frac{KV_1}{KV_1 + V_2}$$

- After several(n)extractions ⇒

$$w_n = w\left(\frac{KV_1}{KV_1 + V_2}\right)^n$$

$$K = \frac{w_1/V_1}{(w - w_1)V_2}$$

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

$$w_n = w\left(\frac{KV_1}{KV_1 + V_2}\right)^n$$

Distribution Coefficient

The distribution coefficient for iodine between water and carbon tetrachloride at 25°C is $K = C_{H2O}/C_{CCl4} = 0.012$. 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.