The Hashemite University
Faculty of Pharmaceutical Science

Physical Pharmacy I
Solubility and distribution phenomena

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Learning objectives

- Define the terms used in solubility
- Define the solubility expressions
- Describe the solute-solvent interactions
- Understand the factors affecting the solubility
- Determine the different systems related to the solubility
- Describe what a distribution coefficient and partition coefficient are and their importance in pharmaceutical systems.

Introduction

- **Solution:** System in which molecules (solutes) are dissolved in a solvent.
- **Solubility** is defined in **quantitative terms** as the **concentration of solute** in a saturated solution at a certain temperature.
  - in **a qualitative** way, solubility is the spontaneous interaction of two or more substances to form **a homogeneous molecular dispersion.**
- Solubility is an **intrinsic** material property that can be altered only by **chemical modification** of the molecule

Introduction

- **Dissolution:** the rate at which the drug dissolves from the solid state.
- dissolution is an **extrinsic material property** that can be influenced by the following modifications:
  1. – Chemical
  2. – Physical
  3. – Crystallographic means such as complexation
  4. – Particle size
  5. – Surface properties
  6. – Solid-state modification
  7. – Solubilization enhancing formulation strategies

Introduction

- **Saturated solution** is one in which the solute in solution is **in equilibrium** with the solid phase at defined **temperature and pressure.**

Solubility Expressions

- The solubility of a drug may be expressed in a number of ways
  - molality, molarity, and percentage.
- USP list the solubility as the number of milliliters of the solvent required to dissolve 1 g of solute.
- Descriptive solubility terms according to the USP

SOLUBILITY DEFINITION IN THE UNITED STATES PHARMACOPEIA

Description Forms (Solubility Definition)	Parts of Solvent Required for One Part of Solute	Solubility Rang (mg/mL)
Very soluble (VS)	<1	>1000
Freely soluble (FS)	From 1 to 10	100–1000
Soluble	From 10 to 30	33–100
Sparingly soluble (SPS)	From 30 to 100	10–33
Slightly soluble (SS)	From 100 to 1000	1–10
Very slightly soluble (VSS)	From 1000 to 10,000	0.1–1
Practically insoluble (PI)	>10,000	<0.1

SOLVENT–SOLUTE INTERACTIONS

- **like dissolves like**
  - Examples:
    - Water: good solvent for sugars and salts
    - Mineral oil: Solvent for substances that are normally only slightly soluble in water
  - **Factors determine the solubility:**
    1. Polarity of the solvent
    2. Dielectric constant
    3. Interactions between the solvent-solute:
       - The ability of the solute to form hydrogen bond with the solvent
       - Water dissolves compounds that can form hydrogen bonds with it (e.g. phenols, alcohols, aldehydes, ketones, amines, and other oxygen- and nitrogen containing compounds)
       - Lewis electron donor–acceptor sense also contributes to specific interactions in solutions
       - The ratio of the polar to the nonpolar groups of the molecule

SOLVENT–SOLUTE INTERACTIONS

- 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**
- If **additional polar groups** are present in the molecule, as found in propylene glycol, glycerin, and tartaric acid, **water solubility increases greatly**.
- **Branching** of the carbon chain **reduces the nonpolar effect** and **leads to increased water solubility**. ??? Why
  - **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.

SOLVENT–SOLUTE INTERACTIONS

- **Polarity of the solvent**
- Polar solvent:
  - High dielectric constant
  - break covalent bonds and ionize weak electrolytes
  - Form H-bonding with the compounds
  - Water dissolves salts, sugars
- Non-polar solvents:
  - Low dielectric constant
  - Cannot break covalent bonds and ionize weak electrolytes
  - They cannot form hydrogen bridges with nonelectrolytes
  - Nonpolar compounds, however, can dissolve nonpolar solutes with similar internal pressures through **induced dipole interactions (Vander waal, London)**
  - Examples: oils and fats dissolve in carbon tetrachloride and benzene

SOLVENT–SOLUTE INTERACTIONS

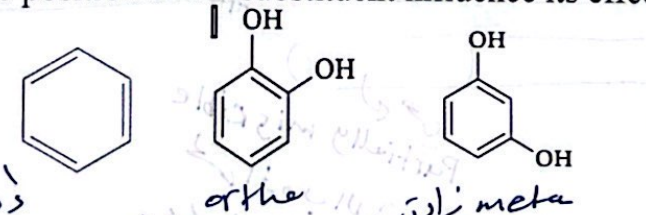
- Semi-polar solvents:
  - ketones and alcohols
  - Can induce a certain degree of **polarity in nonpolar** solvent molecules
  - Semipolar compounds can act as **intermediate solvents** to bring about miscibility of polar and nonpolar liquids.
  - acetone increases the solubility of ether in water

Factors influencing the solubility

- The chemical nature of the compound
  1. Polar to nonpolar groups ratio
  2. Substitution
- The surface area of the molecules
- Structural features and aqueous solubility:
  - Size, shape, and surface area are important to predict the solubility
  - Crystallinity
  - Hydration and solvation
  - Chain branching influences the solubility
  - Other solubility predictors could be the melting point and the boiling point.
    - ↑Boiling point ↓ solubility
    - ↑Melting point ↓ solubility

Factors affecting the solubility

- Substituents
- Substituents affect the solubility of molecules in water
- Hydrophilic or hydrophobic type (depending on their polarity)
- The position of the substituent influence its effects on the solubility



ortho: 4 mole/L, m.p 105 °C
meta: 9 mole/L, m.p 111 °C
Para: 0.6 mole/L, m.p 170 °C

The ability of OH to interact with water decreases in the ortho position so it has a lower solubility than the meta

Factors affecting the solubility

- The effect of pH on the solubility of the ionized drugs
- The great majority of the drugs are organic electrolytes, there are 4 parameters determine their solubility:
  1. – Their degree of ionization
  2. – Their molecular size
  3. – Interactions of substituent groups with the solvent
  4. – Their crystal properties

Solubility of solids in liquids

- The most common and important type
- Factors determine the solubility of solids in liquids

1. pH

- Acidic drugs
  - Low solubility in acidic solutions and higher solubility in basic solutions
  - pH below which the acidic drugs begins to precipitate
- Basic drugs
  - High solubility in acidic solutions and lower solubility in basic solutions
  - pH above which the acidic drugs begins to precipitate
- **The predominant undissociated species can not interact with water molecules like the ionized form which is readily hydrated**

Calculating the Solubility of Weak Electrolytes as Influenced by pH

- If we represent the drug as HA and the total saturation solubility of the drug as S and if S_o is the solubility of the undissociated species HA.
- Then the total solubility is the sum of the solubility of ionized and unionized forms that is

$S = S_o$ + concentration of the ionized species

- $pH_p = pka + \log \frac{S - So}{So}$

Example:

- What is the pH below which sulfadiazine (acid, pka=6.48) will begins to precipitate in an infusion fluid, when the initial molar concentration of sulfadiazine sodium is 4×10^{-2} M and the solubility of sulfadiazine is 3.07×10^{-2} M?

$$pH = 6.48 + \log \frac{4\times10^{-2} - 3.07\times10^{-2}}{3.07\times10^{-2}}$$

$$= 8.6$$

- For basic drugs:
  - Such as ranitidine are more soluble in acidic solution, where is the ionized form of the drug is predominant.

$$pH_p = pka + \log \frac{So}{S - So}$$

- Amphoteric drugs
  - Several drugs and amino acids, peptides, and proteins are amphoteric: displaying both acidic and basic characteristics
  - Use the equation for **basic drugs** at pH values **below** the isoelectric point
  - Use the equation for **acidic drugs** at pH values **above** the isoelectric point

2. Solvents

- Frequently, a solute is more soluble in a mixture of solvents than in one solvent alone (cosolvency)

3. Particle size

Techniques to enhance the solubility

- Complexation
- Solubilization by surfactant:
  - Micellar solubilization
  - Microemulsion
  - self emulsifying drug delivery system
- Chemical modification
  - Salt formation
- Cosolvency
  - Mixed of solvent

Complexation

- Cyclodextrins (CD): enzymatically modified starch
- Glucopyranose unit forms the ring
  - α-CD: a ring of 6 units
  - β-CD: a ring of 7 units
  - γ-CD: a ring of 8 units
- The ring is a cylindrical, the outer surface being hydrophillic and the internal surface of the cavity being non-polar
- Appropriately sized lipophilic molecules can be accommodated wholly or partially in the complex.
  - The host-guest ratio is usually 1:1

Complexation

- Encapsin: HPβ-CD is available for pharmaceutical use
  - 10% can enhance the solubility of **betamethasone by 118 times**, of **diazepam 21 time**, and of **ibuprofen 55 times**

Cosolvency

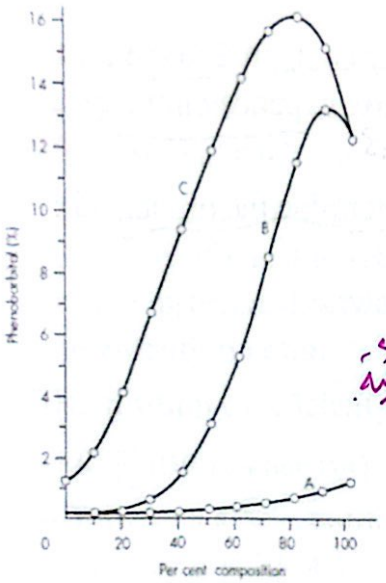
- Common water miscible solvents used in pharmaceutical formulations
  - Ethyl alcohol
  - Propylene glycol
  - Glycerol
  - Polyoxyethylene glycol (PEG)

اهم Cosolvent
و يقدر اخذهم orally

- Toxicity consideration

يعني لو حقنتي البنزين بذوب بس orally ما بقدر اخذه لانه toxic

Cosolvency



The solubility of phenobarbital in:
(A)Glycerol-water
(B)Ethanol-water
(C)Ethanol-glycerol

As a function of the percentage composition of the mixture

Salt formation

- Most commonly used method to enhance the solubility of weak acidic and weak basic drugs
- pH-solubility curves must be determined to investigate the solubility enhancement by salt formation

Drug	ml of water to dissolve 1 g of drug
Atropine	455
Atropine sulfate	0.5
Codeine	120
Codeine sulfate	30
Codeine phosphate	2.5
Morphine	5,000
Morphine sulfate	16
Sulfadiazine	13,000
Sodium sulfadiazine	2

Salt formation

- Salt formation increase the solubility compared to the free drug. However, the **extent of increase** depends on the type of salt formed.
- Properties must be considered to determine the proper salt:
  1. – Stability
  2. – Polymorphism
  3. – Hygroscopicity
  4. – Mechanical properties
  5. – **Solubility**
  6. – Route of administration

Salt formation

– Route of administration

Drug substance	Oxprenolol		Metoprolol	
Dosage form	Conventional tablet	OROS	Conventional tablet	OROS
salt	Hydrochloride	Succinate	Tartarate	Fumarate
Solubility in H_2O (mg/ml) at RT	720	496	750	435

Oral solutions: stability and taste

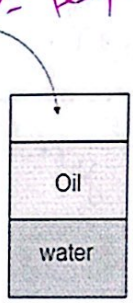
Parenteral: solubility

Diclofenac sodium: oral and parenteral

Diclofenac diethylamine: topical gel

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.**
- **Distribution coefficient (K)**
  - $K=\frac{C1}{C2}$ **(Distribution law)**
  - **Distribution ratio, distribution coefficient, or partition coefficient.**



Distribution of solutes between immiscible solvents

- **Example:**
- When boric acid is distributed between water and amyl alcohol at 25°C, the concentration in **water** is found to be 0.0510 M and in **amyl alcohol** it is found to be **0.0155** M. What is the distribution coefficient?
- $K=\frac{C_{H2O}}{C_{alco}}=\frac{0.0510}{0.0155}=3.29$
- $K=\frac{C_{alco}}{C_{H2O}}$???
- **One should always specify, which of these two ways the distribution constant is being expressed.**

Application of Kin the pharmaceutical field

- Preservation of oil–water systems
- Drug action at nonspecific sites, and the
- Absorption and distribution of drugs throughout the body.

Application of K in the pharmaceutical field

- In pharmaceutical discovery and pre-formulation studies, the n-octanol/water partition coefficient of drugs is calculated

$$P=\frac{C_{octanol}}{C_{water}}$$

- This partition coefficient is used as a measure of drug lipophilicity
- In drug delivery, the lipophilicity/hydrophilicity balance has been shown to be a contributing factor for the rate and extent of drug absorption
- In practice logP value is calculated and used
  - LogP>1 lipophilic drug
  - LogP<1 hydrophilic drug

Application of K in the pharmaceutical field

- n-octanol properties reassemble the lipid bilayer membrane. Therefore, distribution of substance into the octanol represent, to a certain extent, their ability to passively diffuse across the biological membranes
- For ionizable drugs, logP will be pH-dependent
- The required logP value depends on the route of administration of the drug (its different for different membranes that the drug has to cross)
- As a general rule, maximum flux will occur at log P value=3

The End