



The Hashemite University
Faculty of Pharmaceutical Science

Physical Pharmacy I

Solubility and distribution phenomena

Dr. Areen Alshweiat

Areen.alshweiat@staff.hu.edu.jo

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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**. *ممكن ان يحترق ذواته*

*لا بد ان يكون
ذاتيات
بعض*

- **Solubility** is defined in **quantitative terms** as the **concentration of solute** in a saturated solution at a **certain temperature**. *كم عند
تساوي*

– 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

*لأنه الحرارة
تأثر على الذائبة
كلما زادت الحرارة
تزيد الذائبة
(مقدارها)*

*إذا أعزى سolute و solvent إذا كانا السائل A - A Cohesive force
قوة صمما بقدر تزداد في solvent B
أ) Cohesive force بين A و A وبين B - B (غير صمما بقدر كل واحد كالما يتفاعل
B) Adhesive force بين A و B أقل أو مساوي*

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** *ممكن ان يحترق ذواته*
- 2 - **Physical** *معدل*
- 3 - **Crystallographic** means such as (**complexation**)
- 4 - **Particle size**
- 5 - **Surface properties** *غير صمما*
- 6 - **Solid-state modification**
- 7 - **Solubilization enhancing formulation strategies**

*ممكن ان يحترق ذواته
التي هي الكيميائية
non polar
بالمركبات
التي هي جعوية
polar
لا بد ان
ذاتياتها
تزداد*

بفعلها صفة لها في الحد ما يثبت

Introduction

لقد
يذوب
منصير
تترسب

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

حسبها انها من كبر فمقد يصير لها تعبير

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. (كم بدى m.L من المذيبات)
- Descriptive solubility terms according to the USP (كاذوب آخف solute)

SOLUBILITY DEFINITION IN THE UNITED STATES PHARMACOPEIA

Description Forms (Solubility Definition)	Parts of Solvent Required for One Part of Solute	Solubility Range (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

* دى كبرتهم بالريكون
ما يعرف اذا
داخليين

* كل ما كان القبول المى بمتصاه اقل
كل ما كانت الذائبة اعل

SOLVENT-SOLUTE INTERACTIONS

Polar يذوب Polar
ويمكننا

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

إذا كانت
تفاعل بينهم
فضلوا كل
واحد لخاله
قدرة انه
يعمل
H-bond
Solvent
ويذوبوا

انعكاس Polarity
Dielectric constant
عوامل لتحديد
النائية
المركب المستر كثير مرات بتأثيرها Position
Lewis electron donor-acceptor sense
كل قطرات ال non polar group
تتقل ذائبة
المركب
H-bond

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.

branching
ذائبة
المركب
ذائبة بزيادة
Polarity
إذا زادت
المركب
Polar group
بتزئبة ذائبة

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)

هذه الذائبة
في وسط الصالح
والصالح
non polar

مع صمغ لاصق
الذائبة
(cosolvent)

لا تذوب في الماء
non polar
أعلى من الماء

بسم
الكحول

Partially miscible
لصمغ الاثير بالماء
acetone

Factors influencing the solubility

- الطبيعة الكيميائية للمركب
- The chemical nature of the compound
 - ① Polar to nonpolar groups ratio $\frac{\text{Polar}}{\text{non}}$
 - ② Substitution $\rightarrow$ واستبدال المجموعات

The surface area of the molecules

Structural features and aqueous solubility:

- Size, shape, and surface area are important to predict the solubility
- Crystallinity $\rightarrow$
- Hydration and solvation
- Chain branching influences the solubility

Other solubility predictors could be the melting point and the boiling point.

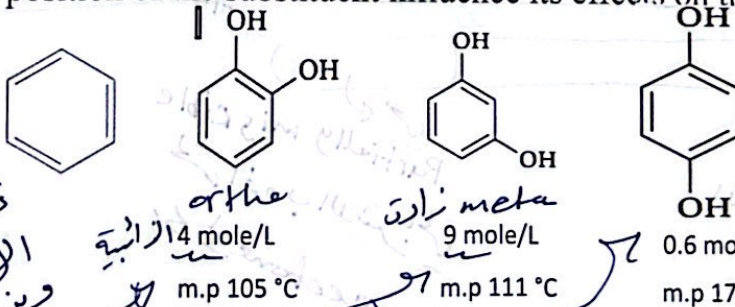
$\uparrow$ Boiling point $\downarrow$ solubility

$\uparrow$ Melting point $\downarrow$ solubility

B.P
M.P
نقطة الغليان
نقطة الانصهار

Factors affecting the solubility

- المجموعات الوظيفية
- Substituents $\rightarrow$ إذا أضفنا مجموعة
 - 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



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 * *حجم الجزيئات الجزيئية*
 - 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 $\rightarrow \text{pH} < \text{pK}_a$

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

CH_3COOH هل الذائب؟ *هل حمض الخليك الذائب؟*
 Solubility & form *الذائبية والشكل*
 ionized form *الشكل الأيونى*
 Solubility *الذائبية*
 Transic... *انتقالية...*

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_0 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)

$$S = S_0 + \text{concentration of the ionized species}$$

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

undissociated

لو صحت ايني صيغة على $pH = 2$ هل ذائب او لا؟ unionized لانه pH اقل من pKa

• 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 $4 \times 10^{-2} M$ and the solubility of sulfadiazine is $3.07 \times 10^{-2} M$?

$$pH = pKa + \log \frac{4 \times 10^{-2} - 3.07 \times 10^{-2}}{3.07 \times 10^{-2}}$$

$$= 8.6$$

معناه ان pH يكون ذائب و ionized اقل من صيغة pH بتزيد

صحت بهي pH اللي جيباش يصير عندي راسب لانه اذا كان التركيز 4×10^{-2} لل ionized form و المذايب اقل من صيغة pH

- For basic drugs:

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

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

- 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 charge in a same time

2. Solvents like dissolve like

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

3. Particle size

كلما قلت اذات السطح area
الذائبة

Techniques to enhance the solubility

أخرى لزيادة الذائبة

- Complexation
- Solubilization by surfactant:

اصنف surfactant لزيادة الذائبة

- ① Micellar solubilization
- ② Microemulsion
- ③ self emulsifying drug delivery system

لهذا / اياه ما ينبغي ان يضاف فيجاء
→ surfactant لزيادة الذائبة

- Chemical modification

– Salt formation

- Cosolvency

– Mixed of solvent

تعمل ملح
يصعب ذوب أكثر
من الدواء
الماء

في كيف تغير
ذائبة
الاسبرين
لما حلت
Surfactant

مساعدة لتذويب
المواد
التي لا تذوب في الماء
Solvent toxicity
consideration

Complexation

من ذائبة Polar ومن ذائبة non Polar

- 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

كلما زاد ال unit
زاد ال size

• The ring is a cylindrical, the outer surface being (hydrophilic) 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

بجزي الدواء
من ذائبة و يذوب
جوازة فار
CD هو
نشأ من

Complexation

- Encapsin: HP β -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

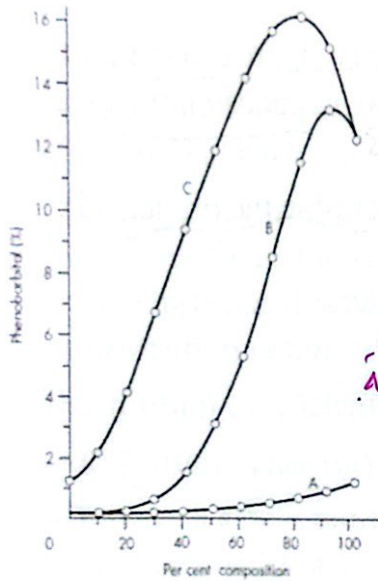
- Common water miscible solvents used in pharmaceutical formulations
 - * Ethyl alcohol
 - * Propylene glycol
 - * Glycerol
 - * Polyoxyethylene glycol (PEG)

الم
Cosolvent
و لقد را فذ هم orally

- Toxicity consideration

و بعضي لو حكت البنزين يذوب بس
عليه اضره الله
لا انه toxic

Cosolvency



Mixture of solvent
يكون المذيبات

The solubility of
phenobarbital in:

(A) Glycerol-water

(B) Ethanol-water

(C) Ethanol-glycerol

أكثر المذيبات
زيادة الذائبية

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

لأنه لا يذوب في الماء
لذا نستخدم أملاحه
وهذا بالنسبة لـ codeine

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

مسبب نفوذ بالا
الذوبانية
نقله

Salt formation

- Route of administration

Drug substance	Oxprenolol		Metoprolol	
Dosage form	Conventional tablet	OROS	Conventional tablet	OROS
salt (conventid)	Hydrochloride	Succinate	Tartrate	Fumarate
Solubility in H ₂ O (mg/ml) at RT	720	496	750	435

osmotic Release

Oral solutions: stability and taste

Parenteral: solubility

لازم
soluble

Diclofenac sodium: oral and parenteral

Diclofenac diethylamine: topical gel

طرق اعطائه

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.

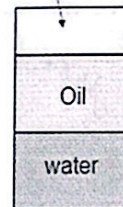
Distribution coefficient (K)

$$K = \frac{C_1}{C_2} \text{ (Distribution law)}$$

- Distribution ratio, distribution coefficient, or partition coefficient.

لا نلزم تحديد
فصل بين
بدي صيغة
K لا نلزم تحديد
oil → water
العكس

جزيئات الدواء
وغيره في
الدهان أو الماء
فقط كجزء من الزيت
تركيزه في الماء



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?

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

$$K = \frac{C_{alco}}{C_{H_2O}} ???$$

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

درجته في الماء
بأشرف النسبة
نفعنا به في
على ratio
of distribution
فلا نلزم تحديد

تركيز البوريك
أعلى في الماء
فقط K
مكون أكثر من الماء

أما العكس
فلا نلزم
3.29

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.

Emulsion
نقطة على الماء
مواد طافية
لأنه ضئيل جداً
فهو يسهل على
نحو الحبيبات
(وجوده)

منقول عن خلال
systemic circulation
منقول عن خلال
systemic circulation

K

Application of K in the pharmaceutical field

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

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

لهذا يـ اعرفه لـ اـ رـ يـ رـ مـ مـ مـ مـ M
aqueous media

- 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

بـ تـ وـ فـ تـ وـ زـ يـ هـ

octanol
water

- In practice logP value is calculated and used

* octanol مـ اـ فـ تـ يـ رـ لـ اـ نـ هـ

LogP > 1 lipophilic drug
LogP < 1 hydrophilic drug

بـ شـ بـ طـ يـ هـ مـ مـ مـ M
membrane
oil phase

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

معادلة K صيغة
PH

- 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

logp
صير
PH
dependent

بقي صير في lumen
circulation.

The End