Medicinal Chemistry
The first stage
College of Dentistry

Assistant teacher

HAZIM SAAD JABBAR AL-MALIKI

University of Basra - College of Dentistry - Department of Basic Sciences

MSc. Medicinal Biochemistry from Malaysian National University (UKM) – Malaysia

Email:- hazim.saad@uobasrah.edu.iq and hazzmrn@yahoo.com

SOLUBILITY AND DISSOLUTION FOR DRUG

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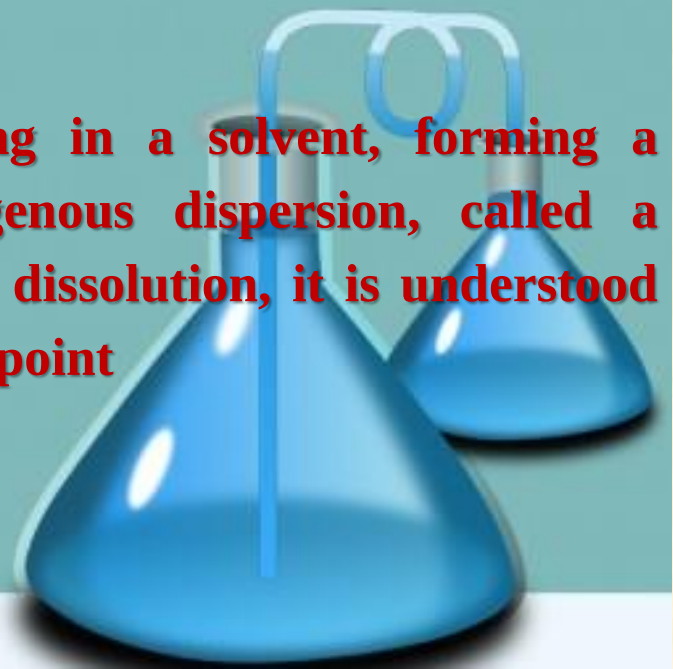
INTRODUCTION

Solubility

The term ‘Solubility’ is defined as maximum amount of solute that can be dissolved in a given amount of solvent to form a homogenous system at specified temperature. The solubility of a drug is represented through various concentration expressions such as parts, percentage, molarity, molality, volume fraction, mole fraction.

Dissolution

it is the process of a solute dispersing/dissociating in a solvent, forming a molecular-level, chemically and physically homogenous dispersion, called a solution. In contrast to solubility, when we speak of dissolution, it is understood that rate is a major consideration. Solubility is an endpoint



IMPORTANCE OF SOLUBILITY

Methods Pertaining to Drug Solubility

1- Solubility of a drug is one of its important physico-chemical properties.

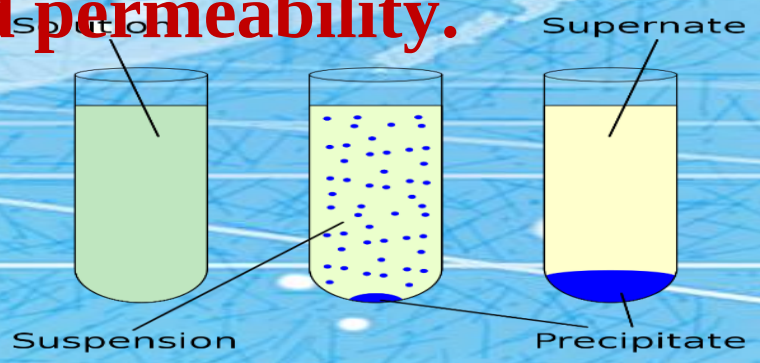
2- The solubility in non-aqueous solvents is not too important from clinical viewpoint however these solubilities play curious roles in drug discovery and development investigations.

3- The solubility behaviors of drugs remains one of the most challenging aspects in formulation development.

Therefore, when talking about solubility, there are two concepts which might be confused with each other: solubility and dissolution.

How much a solute is molecularly dispersed in the solvent is called solubility and the rate of dissolving is called dissolution.

The solubility is important in stable forms including liquid formulations and dissolution is important in transient states including the release of the drug from its formulation to biological fluids and permeability.



In pharmaceutical sciences

designing a stable liquid formulation requires the knowledge on the solubility value and an effective drug delivery to the body mostly depends on the dissolution rate which is affected by the solubility. However, they both affect each other based on Noyes-Whitney equation.

$$\frac{\mathrm{d}m}{\mathrm{d}t} = A\frac{D}{d}(C_s - C_b)$$

Where:-

- **dm/dt =** solute dissolution rate ($kg.s^{-1}$)
- **m =** mass of dissolved material (kg)
- **t =** time (s)
- **A =** surface area of the solute particle (m^2)
- **D =** diffusion coefficient ($m.s^{-1}$), which is related, in part, to the viscosity of the solvent.
- **d =** thickness of the concentration gradient (m)
- C_s = particle surface (saturation) concentration (kg or moles/L)
- C_b = concentration in the bulk solvent/solution (kg or moles/L).

NEED OF IMPROVING SOLUBILITY

There are variety of new drugs & their derivatives are available. But less than 40 % of lipophilic drugs candidates fail to reach market due to poor bioavailability, even though these drugs might exhibit potential pharmaco-dynamic activities.

The lipophilic drug that reaches market requires a high dose to attain proper pharmacological action.

The basic aim of the further formulation & development is to make that drug available at proper site of action within optimum dose.

Solubility of drug is largely due to,

1. Polarity of the solvents, that is, to its dipole moment. A polar solvent dissolve ionic solutes and other polar substances.
2. The ability of solute to form hydrogen bond with solvent.
3. Also depends on the ratio of the polar to non polar groups of the molecule.

- As the length of a non-polar chain of an aliphatic alcohol increases, the solubility of the compound in water decreases.
- Straight chain monohydric alcohols, aldehyde, 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.

TECHNIQUES OF SOLUBILITY ENHANCEMENT

Process of solubilisation

1) The separation of the molecule of the solvent to provide space in the solvent for solute.

2) The breaking of intermolecular ionic bonds in the solute.

3) The interaction between the solvent and the solute molecule or ion.

Measuring solubility

In pharmaceutical practice, one important task is to measure the solubility of solids in liquids. The following precautions serve as guidelines when running solubility tests:

- The solvent and the solute must be pure.
- The sample is removed for analysis after confirmation of saturation.
- Sample separation from saturated solution with un-dissolved solute must be reliable and satisfactory.
- The method used to analyses the solution must be reliable and reproducible.
- Temperature must be adequately controlled

Traditionally, the equilibrium solubility at a given pH and temperature is determined by the shake flask method .

According to this method the compound is added in surplus to a certain medium and shaken at a predetermined time, usually 24h or longer .

Due to the growing need to determine solubility faster new devices and automated methods have been developed.

1- Miniaturized shake-flask method can be used for almost all compounds .

2- Semiautomated potentiometric acid/base titrations method is a very economical method and is able to create a pH/solubility profile with one single determination .

3- A computational screening model is used for the prediction of intrisic solubility, which is based on lipophilicity and molecular surface areas .

4- Another devise, simply called miniature device, was developed for measuring aqueous and non-aqueous equilibrium solubility during drug discovery. With only ≈ 1mg of compound, it was possible to determine the entire pH-solubility profile .

The drug can be prepared in another way;

1. added in alkaline solution like sodium hydroxide, ammonium hydroxide.
2. A solution of β- Cyclodextrin is then added to dissolve the joined drug.
3. The clear solution obtained after few seconds under agitation is neutralized using HCl solution until reaching the equivalence point.
4. At this moment, the appearance of a white precipitate could be appreciated, corresponding to the formation of the inclusion compound.
5. The precipitate is then filtered and dried.

Biopharmaceutics classification system

- **The Biopharmaceutics classification system (BCS) is a framework for classifying a drug substance based on its aqueous solubility and intestinal permeability.**
- **Solubility is based on the highest dose strength and is considered highly soluble if soluble in 250 mL or less of aqueous media over the pH range of 1.0-7.5, otherwise considered to be poorly soluble.**
- **Permeability is based indirectly on the measurement of the rate of mass transfer across the human intestinal membrane.**



APPLICATION OF SOLUBILITY

1) **Solubility is represents a fundamental concept in fields of research such as chemistry, physics, food science, pharmaceutical, and biological sciences.**
2) **The solubility of a substance becomes specially important in the pharmaceutical field because it often represents a major factor that controls the bioavailability of a drug substance.**
3) **Solubility is commonly used to describe the substance, to indicate a substance's polarity, to help to distinguish it from other substances, and as a guide to applications of the substance.**
4) **Solubility of a substance is useful when separating mixtures.**
5) **Moreover, solubility and solubility-related properties can also provide important information regarding the structure of drug substances, and in their range of possible intermolecular interactions.**

thank you