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Determination of solubility by gravimetric method: A brief review

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Abstract
Therapeutic effect of drug depends upon the bioavailability and the solubility of drugs molecules. Solubility is the most important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. It represent a fundamental concept in field of research. About 40% of drugs with market approval and nearly 90% of molecules in the discovery pipeline are poorly water-soluble.

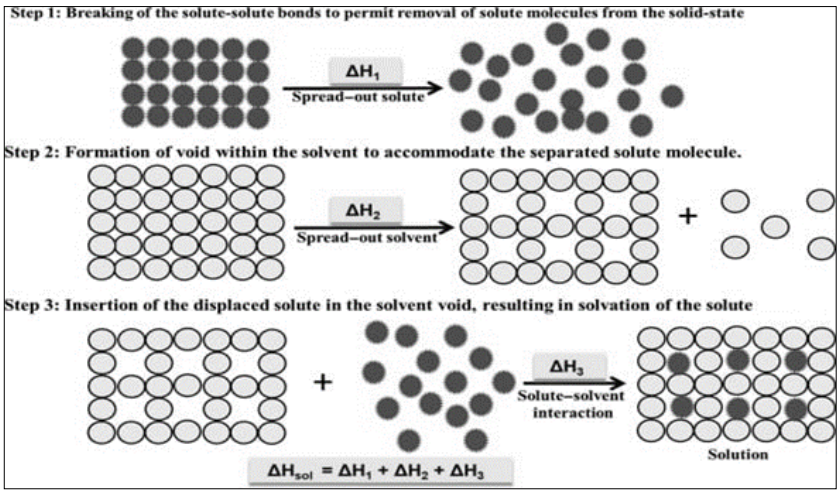
History: Generally, Poorly water soluble drugs often require high doses in order to reach the therapeutic plasma concentrations after oral administration. The drug with low aqueous solubility is the major problem in the formulation development of new chemical entities as well as generic development. The solubility of a substance fundamentally depends on the physical and chemical properties of the solute and solvent as well as on pressure, temperature and also changes to the pH of the solution. Poor solubility is an ongoing challenge in pharmaceutical development. A drug must be in solution form for it to be absorbed regardless of the route of administration. The solubility of an API, therefore, plays a crucial role in bioavailability given that drug absorption is a function of solubility and permeability. There are various techniques to enhance the drug solubility such as particle size reduction, use of surfactants, salt formation, nano-suspension, solid dispersion, etc. The solid dispersion is an important approach for improvement of bioavailability of poor water-soluble drugs.

Keywords: Gravimetric method, drugs molecules, poorly water-soluble

Introduction
Solubility in quantitative terms as concentration of solute in concentrated solution at a certain temperature, and in qualitative way it is a spontaneous interaction of two or more substance to form a homogeneous molecular dispersion.

Solubilization is a preparation of thermodynamically stable isotropic solution of a substance normally insoluble or slightly soluble in a given solvent by introduction of an additional component or components.

Process of Solubilization



There are two direct factors that affect solubility: temperature and pressure. Temperature affects the solubility of both solids and gases, but pressure only affects the solubility of gas. Solubility is based on the highest-dose strength of an immediate release product. A drug is considered highly soluble when the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range of 1 to 7.5.

Method of enhancement of solubility

physical modification	**Chemical Modifications**
A)particle size reduction • Micronization • Sonocrystalisation • Nanosuspension • Supercritical fluid process B) Modification of crystal habit • Polymorphs • Pseudopolymorphs C) Drug dispersion in carriers • Eutectic mixtures • Solid dispersion D) Solubilization by surfactants • Microemulsions	• Changein PH • Use of buffer • Derivatization (transforms a chemical compound into a product) **Other Methods** • Co-crystalisation (crystalline structure composed of at least two components) • Co-solvency (solvent that in conjunction with another solvent can dissolve a solute). • Solubilizing agents • Solventdisposition • Selective absorption on insoluble carrier • Using soluble prodrug

Principal: Mathematically it is expressed as the concentration of solute in a solution, which is in equilibrium with the solute (solid). That means the concentration of solute in a saturated solution is its solubility.
The pharmacopoeial expression of solubility is the number of milliliter of solvent in which 1 gram of solute will dissolve to make a saturated solution. When the exact solubility has not been determined, the solubility may be expressed in descriptive terms:

Expression for approximate solubility: (IP)

The simplest way of solubility determination is to determine the concentration of solute in a saturated solution and work out the quantity of solvent in volume and quantity of solute in weight to express solubility.

Solubility expression: Solubility is also expressed quantitatively in terms of percentage, molality and molarity. Molality is expressed as a number of moles of solute dissolved in 1000 g of solvent and Molarity is expressed as a number of moles (gram molecular weight) of solute dissolved in 1000 g of solvent. There are three concentration terms are used in the pharmaceutical field.

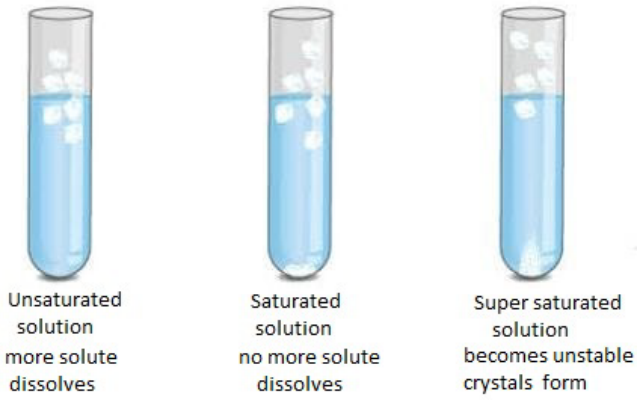
These are

1. % w/w is the number of grams of solute dissolved in 100 g of solution.
2. % v/v is the number of ml of solute dissolved in 100 g of solution.
3. % w/v is the number of gram of solute dissolved in 100 ml of solution.

The concentration can be determined by gravimetric, titrimetric or by any instrumental method of analysis.

Types of solution

Unsaturated solution: A solution with less solute than the saturated solution that completely dissolves, leaving no remaining substances.
Saturated solution: A solution with solute that dissolves until it is unable to dissolve anymore, leaving the undissolved substances at the bottom.
Super Saturated solution: A solution (with more solute than the saturated solution) that contains more undissolved solute than the saturated solution because of its tendency to crystallize and precipitate.



Procedure: Clean all the glassware apparatus with detergent solution or chromic acid solution. Wash all the glassware apparatus with distilled water (2 to 3 times). Around 20 g of sodium chloride is added with 50 ml of water in a conical flask, with Constant stirring using glass rod. The stirring is continued till a saturated solution is obtained. A part of solid is left undissolved in a conical flask. The solution is filtered and 10 ml of the filtrate is pipetted out into a preweighed watch glass. The watch glass containing 10 ml of filtrate (Saturated solution of sodium chloride) is weighed. Then the filtrate is evaporated and dried at about 100°C in a hot air oven. Then it is cooled and

weighed. The drying is continued till a constant weight is obtained.
Observation: Room Temperature: 25 °C
Weight of empty dish in g: wI
Weight of dish + 10 ml solution in g: w^2
Weight of dish + dry solution in g: w^3

Calculation
Weight of solute in 10 ml solution in g = w3-w1
Weight if solvent in 10 ml solution in g = w2-w1

Volume of solvent in ml = $\frac{\text{Weight of solvent}}{\text{Density of solvent (water)}} = \frac{w2-w3}{\text{Density of water}}$

Density of water at room temperature can be referred from the appendix (for rough calculation density of water may be considered as 1 g/ml).
Solubility is the parts of solvent required for 1 part of solute.

(w3-w1) g of solute requires $\frac{(w2-w3)}{\text{Density of water}}$ ml of water.

1g of solute will require $\frac{(w2-23)}{(w3-w1)\ \text{Density of water}}$ ml of water.

Report: The solubility of sodium chloride is 1 in 2.8 ml water at 25 °C.

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