Solubility and Supersaturation - A Brief Introduction

Solubility is a key pharmaceutical parameter. For pharmaceuticals, the solubility in two types of media are important: aqueous based fluids such as the gastrointestinal tract fluid and blood, and lipid based media such as cell membranes and micelles. Most biochemical and pharmacological processes occur in aqueous media and determining the solubility of a drug in an aqueous based medium is a very important part of drug development. This application note briefly introduces some relevant terminology and methods of determining solubility.

General Terminology

It is important to clarify terminology when discussing solubility and the following definitions are generally accepted:

**Equilibrium solubility** is the concentration of compound in a saturated solution when excess solid is present and solution and solid are in equilibrium. It is pH dependent for ionizable drugs.

**Intrinsic solubility** is the equilibrium solubility of the free acid or base of an ionizable compound at a pH where it is fully unionized.

The **kinetic or turbidimetric solubility** is the concentration of the compound in solution when an induced precipitate first appears.

Solubility can be expressed in a number of ways but is typically expressed as μg/mL, moles L⁻¹ or LogS (logarithm of solubility expressed as moles L⁻¹).

**Supersaturation** describes a solution in which the concentration of solute exceeds the equilibrium concentration. A supersaturated solution is a necessary condition for crystallisation.

The apparent solubility of a compound varies with pH for an ionizable compound. Charged species are usually orders of magnitude more soluble than the corresponding neutral species. This is illustrated in Figure 1 which shows the solubility versus pH profile for the base imipramine.

Measuring Solubility

There are a number of ways to measure solubility and the choice of method depends upon the information required. The classical approach to measure equilibrium solubility is the shake flask method. There are a number of variables associated with this method including buffer composition, pH, shaking and settling times and the detection method used to measure the analyte concentration.

A number of high throughput screening methods are also widely used. There are typically based on chromatographic methods and used to classify compounds into relatively broad solubility classes for the purposes of early compound selection in drug development.

![Solubility Versus pH Profile](image)

**Figure 1.** The equilibrium solubility versus pH profile for imipramine, a weak base with a pKₐ of 9.54. At low pH, it is fully ionized and is soluble at very high concentrations. For a base, solubility decreases as the pH increases due to the increasing proportion of neutral species generated. At pH >> pKₐ, the compound is fully neutral and its equilibrium solubility corresponds to the intrinsic solubility.

**Solubility: IUPAC Definition**

The analytical composition of a saturated solution, expressed in terms of the proportion of a designated solute in a designated solvent, is the solubility of that solute. The solubility may be expressed as a concentration, molality, mole fraction, mole ratio, etc.
Sirius Methods and Terminology

Sirius has developed a novel titrimetric method for measuring solubility. The CheqSol\textsuperscript{1,2} method provides a fast method of obtaining both the equilibrium and kinetic solubility of ionizable compounds.

The CheqSol method is a valuable tool for investigating the supersaturation and precipitation behaviour of drugs, for example when the drug undergoes a pH transition in solution when it transits from gastric pH to intestinal pH. A basic drug may therefore become supersaturated as it enters the higher pH environment of the upper intestine. Both the duration of supersaturation and the solubility of the precipitate are important to understand absorption. Compounds are described as Chasers or Non-Chasers according to the way they behave in CheqSol assays.

The differences between Chasers and Non-Chasers are indicated in Figure 2. In order to crystallize, a compound must first attain a supersaturated state, and differences between the kinetic (KS) and equilibrium (ES) solubility show how the compound will crystallize and how supersaturation may be maintained.

It is possible to influence the supersaturation behaviour of compounds through the use of specific excipients, for example, dipyridamole can be prevented from Chasing by the addition of HPMCAS-LF. In this case supersaturation is maintained at approximately the estimated amorphous solubility level for the dipyridamole.

Supersaturation has recently been described through the “Spring and Parachute” model\textsuperscript{3,4} (Figure 3). This model describes short lived and sustained supersaturation behaviour relative to the equilibrium solubility of the crystalline form.

**Conclusion**

Solubility can be a challenging parameter to measure and it is difficult to predict accurately. It is important to ensure that the conditions of analysis are fully defined and that data are generated in a similar way. However, there are now a number of rapid and reliable ways to measure solubility and supersaturation; these give valuable insight into these key physicochemical properties.

**References**

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