
[<1236> Solubility Measurements](#)

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Expert Committee: General Chapters-Physical Analysis

Input Deadline: October 31, 2016

Suggested audience: Suppliers and manufactures of excipients, drug substances, drug products, veterinary products and regulatory agencies.

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Background and objectives:

The solubility of one substance in another is a measure of the degree of molecular mixing between the two pure substances at thermodynamic equilibrium. The composition of a saturated solution, expressed as a proportion of a designated solute in a designated solvent, represents this thermodynamic limit of solubility. Solubility may be stated in units of concentration such as molality, mole fraction, mole ratio, weight/volume, or weight/weight.

Accurate determination of the aqueous solubility of pharmaceutical materials is important for understanding both quality control and drug delivery issues for pharmaceutical formulations. The ability to accurately measure the aqueous solubility of a material is affected by the physico-chemical properties of the material (e.g., surface area, particle size, crystal form), the properties of the solvent (e.g., pH, polarity, surface tension, added surfactants, co-solvents, salts), and the control of the solubility measurement parameters (e.g., temperature, time, agitation method). Control of these factors during solubility measurements is key to obtaining accurate, reliable values for the equilibrium solubility of a material.

This General Chapter will begin with a discussion of the concepts and equations that are relevant to solubility measurements. Understanding these relationships is fundamental to accurate evaluation of solubility. This will be followed by a brief description of typical experimental methods used to assess solubility of pharmaceutical materials. Finally, the use of solubility measurements to obtain bio-relevant solubility data (for human products) and species-dependent solubility data (for veterinary products) will be discussed.

Description of scope and application:

The new General Chapter is intended to provide additional tools for determination of degree of solubility of excipients and drug substances, and the establishment of bio-relevant solubility measurements for applications such as Biopharmaceutical Classification (BCS).

Preliminary outline:

- Introduction
- Background
- Methods of estimating aqueous solubility
- Factors that affect solubility and solubility measurements
 - Effect of pH
 - Effect of salts and counter-ions
 - Effect of co-solvents
 - Effect of surfactants
 - Effect of complexing agents
 - Effect of surface area (Dissolution rate)
 - Effect of surface energy (Nanoparticles)
- Experimental Methods
 - Methods for Determination of Equilibrium Solubility
 - Saturation Shake-Flask method
 - Methods for Determination of Apparent Solubility
 - Potentiometric Titration
 - Turbidimetry
 - Miniaturization, High-Throughput, and Automation in Solubility Measurement
- Solubility Measurements in Bio-relevant Media
 - Human (Simulated Gastric and Intestinal Fluids)
 - Canine (Simulated Gastric and Intestinal Fluids)
 - Bovine (Simulated Gastric and Intestinal Fluids)

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- Glossary
 - References

Anticipated proposed design phase activities: The General Chapter will be developed based on conclusions from workshops performed by the Solubility Criteria for Veterinary Products Expert Panel, in joint collaboration with the Solutions Subcommittee from the General Chapters–Physical Analysis Expert Committee.

Anticipated implementation timing: Routine.

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