APPLICATION NOTE 3

Solubility measurements

Solubility data are used to make crucial decisions from the earliest stages of drug discovery and throughout the entire development process. The Crystal16™ and optional CrystalClear™ software provide the ideal tools to efficiently gather and analyze solubility data at an early stage, using only minimal amounts of sample. Discover why several pharmaceutical companies have already chosen the Crystal16™ as their standard tool to determine solubility of their drug compounds.

Improve and accelerate your crystallization research

Improve and accelerate your crystallization research with the Crystal16™ parallel crystallizer, the ultimate tool for solid-state research and process development. Designed by scientists for scientists, the Crystal16™ is a user-friendly multi-reactor benchtop system with intuitive software to perform medium-throughput crystallization studies at a 1-ml scale. It offers invaluable assistance throughout the various stages of the drug development life cycle, from preclinical screening to process optimization. Developed for crystallization studies, the Crystal16™ has also been successfully used in other application areas such as polymer solubility studies and process chemistry.

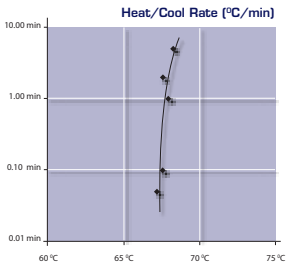
Crystal16™

The basics of solubility curves

- Solubility data are used to make crucial decisions from the earliest stages of drug discovery and throughout the entire development process. A solubility curve shows how the solubility of a substance varies with temperature. The substances are typically free bases or salts, and water is by far the most common solvent. The solubility of a substance in water depends on several factors.
- The solid-state characteristics of drugs are known to exert a potentially significant influence on the solubility. Polymorphs of a drug substance can have different measured aqueous solubility and dissolution rates. When such differences are significant, their bioavailability differs, in which case it may be difficult to formulate a bioequivalent drug product using an alternative polymorph. When solubility and dissolution rate of the relevant polymorphic forms are sufficiently high, regulatory concerns with respect to bioavailability and stability are minimal. When deciding which polymorph to develop and register, the Biopharmaceutics Classification criteria of high solubility and rapid dissolution should be considered.

Efficient determination of solubility curves

- Experimental determination of solubility curves traditionally relies on labor-intensive techniques, which is why detailed solubility data are often not available. The Crystal16™ combines automation with integrated turbidity measurement to determine cloud and clear points and is ideally suited to acquire solubility data at an early stage using only minimal amounts of sample.
- The solubility curve is a thermodynamic property of the substance-solvent system. When measuring the solubility curve using very fast heating rates, it is possible to overshoot, but at slower rates the measured clear point should be constant irrespective of heating rate. A series of measurements with the Crystal16™ show that heating rates below 0.5 °C/min generally yield consistent clear points whereas the solubility curve can be easily overshot at heating rates above 5 °C/min.



- Using a Crystal16™ with 16 vials holding 4 different concentrations of a drug substance in 4 different solvents and applying 2 temperature cycles with a heating rate of 0.5 °C/min and a cooling rate of 1 °C/min, 4 solubility curves can be measured in duplicate in half a day.

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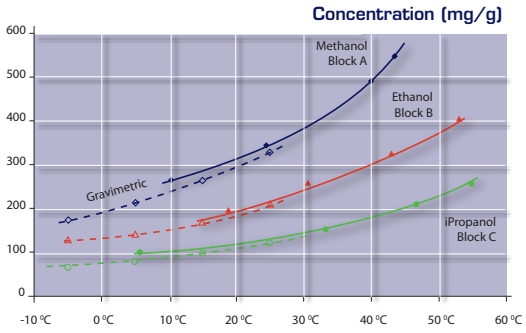

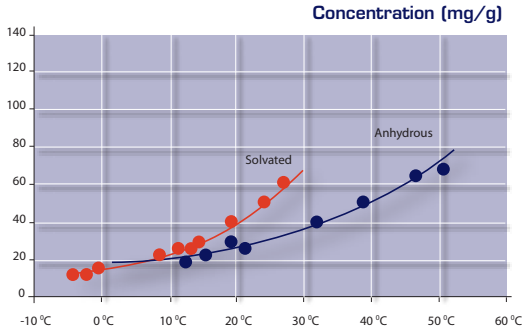

Examples

- API solubility
  Several pharmaceutical companies have chosen the Crystal16™ as their standard tool to determine solubility. The graph to the right shows the solubility curves of an API in three solvents, determined on the Crystal16™ using 3 of the 4 blocks. In each of the blocks 4 HPLC vials with different concentrations of the API were heated to 60 °C at 0.3 °C/min. The data resulting from the experiments carried out on the Crystal16™ (full lines) agreed well with the data obtained using a gravimetric method (dashed lines).
- API interconversions
  A typical experiment would consist of (i) preparing an array of slurries of varying concentrations of solid in 1 ml of a solvent or solvent mixture, (ii) heating to 75 °C at 0.3 °C/min, using magnetic stir bars to agitate the slurry, determining the dissolution temperature by turbidity measurements (iii) followed by cooling to 0 °C at 1 °C/min to observe crystallization of the sample, again by measuring turbidity. In the example shown opposite, each measurement cycle was repeated 3 times to increase confidence in the results. In the first measurement cycle, crystallization of the substance during the cooling cycle resulted in a hydrate rather than the anticipated anhydrous form. Consequently, a different solubility curve was obtained in the subsequent measurement cycles. The solvated form appears to be the thermodynamically stable form below 15 °C (i.e. lowest solubility). This example illustrates that (pseudo)polymorphic changes can be induced and observed by repeated measurements of the solubility curve. These changes may provide crucial information for the ultimate crystallization process development or downstream operations. In addition, duplicate or triplicate measurements will increase confidence in the results.

21st century manufacturing

The application of process analytical technology (PAT) to crystallization process design has always been an area of high interest for both the chemical development and manufacturing arenas. This is partly due to the growing emphasis on PAT as a tool for '21st Century Manufacturing' as described, for example, in the guideline document 'PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance' issued by the FDA in 2004. The use of in-situ turbidity measurement and automated methods to determine solubility curves significantly reduces operator workload compared to traditional methods, which should encourage the use of solubility data in the early stages of crystallization process development.

Please contact us for more information:
Info@crystallizationsystems.com
www.crystallizationsystems.com

Pyrietstraat 2
1810 SC Alkmaar
The Netherlands
Tel: +32 72 3020040

Technobis
crystallization systems

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