APPLICATION NOTES
Crystal16 ™ - 1
Polymorph and salt screening - 2
Solubility measurements - 3
Metastable zone width determination - 4
Co-crystallization studies - 5
Anti-solvents - 6
Fast track to return on investment - 7

APPLICATION NOTE 4

Metastable zone width determination with Crystal16™

The metastable zone width provides essential information for developing well-controlled crystallization processes. The gathering of the underlying solubility data traditionally relies on labor-intensive techniques, which is why these data are often not available. With the Crystal16™ and optional CrystalClear™ software, scientists have now one integrated package providing all the tools needed to easily determine the metastable zone width. The Crystal16™ being the smallest commercial scale crystallizer, only minimal amounts of sample are required.

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 data

- Solubility data are used to make crucial decisions from the earliest stages of drug discovery and throughout the entire development process.
- Clear points
  The solubility curve of a substance consists of a series of 'clear points'. A clear point is the point at which suspended solid material disappears from a solution (transmissivity of 100 %). For a solid with increasing solubility at higher temperatures, the clear point is usually measured on heating, the reverse of the cooling commonly employed for the crystallization of such substances.
- Cloud points
  The metastable limit curve consists of a series of 'cloud points'. The cloud point refers to the point at which solid material first appears in a solution from which crystallization is being carried out (decreasing transmissivity). The most common mode of crystallization from solution employs cooling to create supersaturation, the cloud point representing the point on the (falling) temperature profile at which crystal nucleation is first observable. The detection of the cloud point is important because it defines the width of the metastable zone, or the temperature corresponding to the critical supersaturation level at which crystal nucleation begins.
- MSZW
  The metastable zone width is defined as the zone between the solubility curve and the metastable limit curve and provides essential information for developing well-controlled crystallization processes.

Efficient determination of solubility data

- The Crystal16™ is the smallest scale commercial crystallizer unit with integrated turbidity measurement to determine cloud and clear points. Its operating software allows temperature programs to be defined for the crystallization experiments.
  A temperature program specifies temperature profile, sample rate, and stirring speed for each experiment. Heating and cooling rates of the slurries must be chosen carefully to determine the MSZW. Good accuracy can be obtained by duplicating measurements and repeating temperature profiles (see figure above). Technobis CrystalClear™ software can assist in identifying cloud and clear points and can automatically construct and export solubility curves and MSZW diagrams.

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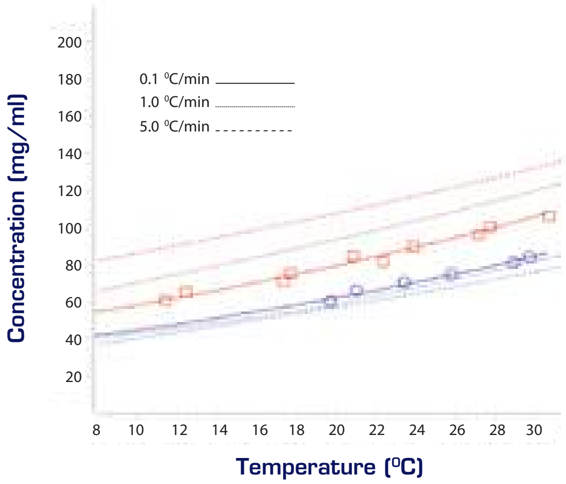

Figure A

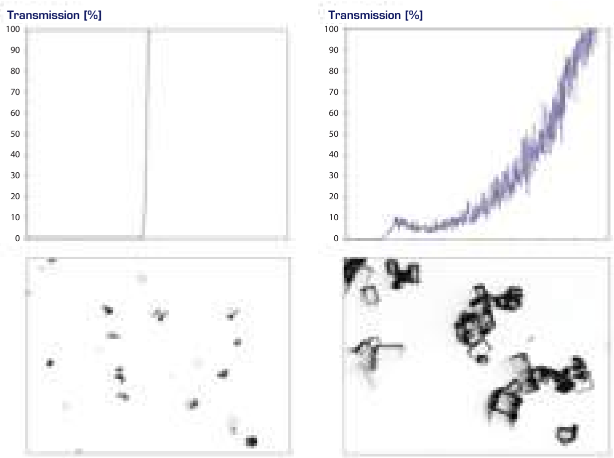

Figure B

- Identification of cloud points
  In principle an abrupt change in transmissivity is easy to detect. Nevertheless, cloud points can be difficult to identify because the appearance of the first traces of solid material in a crystallization process often occurs gradually. The first visual indication of the onset of crystallization is often a slight milkiness in the solution, corresponding to the formation of small crystal nuclei in the supersaturated solution. The milkiness increases as the number and size of nuclei increase, and eventually small crystals and particles of solid materials can be seen suspended in the liquid. Most usefully, the cloud point corresponds to the onset of nucleation, which is best identified as the point at which the transmissivity of the solution first starts to decrease. This point is detected by the Crystal16™ turbidity measurements.
- Identification of clear points
  Clear points are more easily detected because the disappearance of the solid phase often occurs more abruptly. Clear points are identified as the points where transmissivity ceases to change. These points are detected by the Crystal16™ turbidity measurements.

Examples

- Accurate detection of cloud and clear points depends on the solution cooling/heating rate. Rapid temperature changes may result in over or underestimated values. The graph (see Figure A) illustrates the impact of cooling and heating rates on the MSZW of iso-nicotinamide in ethanol. As expected, the solubility curve (blue) is less sensitive to heating rates whereas the metastable limit curve (red) shifts to lower temperatures with faster cooling. As a rule of thumb, Technobis recommends using a heating rate of 0.5 °C/min and a cooling rate of 0.3 °C/min to determine the solubility curve and the metastable limit curve, respectively.
- When looking at the raw data (see Figure B), noise on transmission curves is typically caused by larger particles or, in some cases, agglomerates. The transmission plots to the right show the dissolution of particles obtained after cooling crystallization by fast cooling (5 °C/min; left plot, no noise) and slow cooling (0.1 °C/min; right plot, substantial noise). They clearly demonstrate that slow cooling favors particle growth, the noise on the right plot being caused by larger particles. These experiments were performed on a Crystal16™ using a concentration of 100 mg/ml of iso-nicotinamide in ethanol, stirred at 700 rpm. Dissolution was studied by heating the solution at a fixed heating rate to 55 °C and keeping it at that temperature for 30 minutes, followed by cooling at the same rate to 0 °C.

Warning: MSZW can be affected by solution history, the presence of impurities or tiny amounts of seeds, mixing, etc. Characterizing these effects is important, certainly when the MSZW data are used for scale-up.

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