

APPLICATION NOTES

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Polymorph and salt screening

Crystallization processes and crystal structures are often complex and unpredictable. Regulatory authorities worldwide, however, increasingly require pharmaceutical companies to demonstrate absolute control over their production processes. The Crystal16™ offers an invaluable tool to automate the execution of crystallization experiments, improving reproducibility while drastically increasing productivity and efficiency and without compromising on flexibility.



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.

The challenges of polymorph and salt screening

- Crystallization processes and crystal structures are often complex and unpredictable. It is therefore not unusual for crystallization experiments to involve a fair amount of trial and error. Testing a large diversity of conditions (solvents, solvent mixtures, concentration, cooling profiles, ripening times, etc.) requires a flexible experimental setup.
- In the preclinical stage of development, when only small amounts of expensive compound are available, crystallization screening focuses on the selection of the optimal crystal form for further development. Experiments can range from targeted studies to identify a stable polymorph, to bringing about a more drastic alteration of the physicochemical properties by creating a new salt form.
- In the later stages of drug development when increased attention is given to enhancing patent protection, more comprehensive programs are undertaken in order to pinpoint as many crystal forms as possible, polymorphs as well as salts.
- Regulatory authorities worldwide require pharmaceutical companies to demonstrate that they have absolute control over the substance (API) and all stages of its production process. This in turn requires companies to understand interconversions and to produce consistent quality (i.e. ensure constant composition of chemical as well as physical purity). The solid forms produced should be stable, not only during production, but also in their formulation and subsequent end-use.

Increased efficiency with Crystal16™

- Automating the execution of crystallization experiments means more experiments can be carried out in the same timeframe, but also, the results are much more reproducible and controllable, which is essential for good science and answering the requirements put forward by the regulatory authorities.
- Superior flexibility
One Crystal16™ can run up to 16 experiments in parallel. The 1-ml scale is sufficiently small and the smallest scale compatible with commercially available standard analytical equipment. The reactor vials are grouped into 4 independently temperature-controlled reactor blocks allowing different cooling profiles to be applied to each block. In each block, crystallization conditions such as solvents and solvent mixtures, compound concentrations, acids and bases or, for salt formation, ratios of API/salt former can be varied. Experiments can be planned efficiently and, being automated, left to run overnight as well, reducing the experimentation time even further.

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- Online analysis

The Crystal16™ not only runs 16 crystallizations in parallel, it also analyzes them. In-situ turbidity measurements can provide information about the apparent solubility and the dissolution rate of the various salts and polymorphs obtained (see Application Note 3). The optional CrystalClear™ software package allows the user to graphically visualize the data and to generate reports that can be exported to Word.

- Polymorph versus salt screening

The execution of salt screening studies is similar to that of polymorph screening. It should be noted, however, that the key to salt screening is not solely to identify the salt formers (formation of a salt can often be predicted based on pKa differences between the API and the acid or base), but also to determine the optimum conditions under which the salts are crystallized. The resulting solids are readily recovered by solvent evaporation and/or off-line filtration.

Examples

- Polymorph screening

A typical polymorph screening project of 96 experiments would be run using, for example, 2 different concentrations of the API in 8 solvents and 4 solvent mixtures, applying 2 different cooling profiles (e.g. a fast and a slow cooling rate of 5 °C/min. and 0.1 °C/min. respectively) in combination with 2 ripening times (short ripening to capture unstable or kinetically stabilized forms and long ripening to allow more stable forms to appear). Using the Crystal16™, 96 experiments could be run in less than 2 weeks using only a few grams of sample.

- Salt screening

For a salt screening study, instead of using, for instance, 12 solvents or solvent mixtures, the number of solvents could be reduced to, for instance, 6 but combined with 8 different counter ions (acids or bases). Given a cooling profile and ripening time and using 2 different concentrations for each solvent, the total number of experiments would again be 96. Run on a Crystal16™ the salt screening study would be completed in approximately 2 weeks.

The Crystal16™ is a useful tool to generate and identify new crystal forms and to help solve problems related to polymorphism and crystallization. Using minimal amounts of material, each screening project is carefully designed to meet its specific objectives. To fully characterize the solid forms obtained, screening experiments executed on the Crystal16™ are typically followed by extensive off-line analytical work using x-ray powder diffraction, spectroscopic techniques (Raman) and thermal analysis.

Please contact us for more information:

Info@crystallizationsystems.com

www.crystallizationsystems.com

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Technobis Crystallization Systems B.V.

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



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