CrystalBreeder
Crystal16
Crystalline

APPLICATION NOTE

IMPROVE AND ACCELERATE YOUR CRYSTALLIZATION SCREENS

Every day, new compounds are produced within food, personal care, dye, agro and pharmaceutical industry. These compounds are getting more and more complex, making dosage determination and formulation more difficult. In order to obtain the solid state form with desired properties, solid state screening needs to be performed. Polymorph, co-crystal, salt screening, amorphous solid dispersion are most common solid state screening methods of which, polymorph screening is still most widely applied. The CrystalBreeder and Crystal16 provide the perfect tool to automate the execution of crystallization experiments, improving reproducibility while drastically increasing productivity and efficiency without compromising on flexibility.

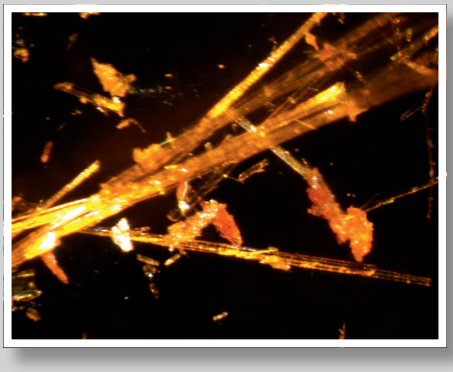
Basic steps into crystallization screening

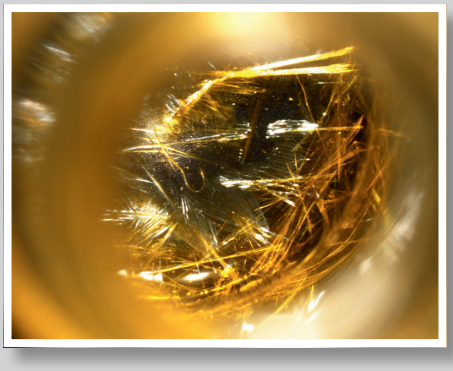
Automating your solid state screening process enables you to perform the crystallization experiments with just a small amount of effort. One **Crystal16** can run up to **16 experiments** in parallel at **1-mL scale**. The **CrystalBreeder** can run up to **32 experiments** in parallel at **0.1-mL scale**. Reproducibility and controllability enable you to perform good science and meet regulatory requirements.

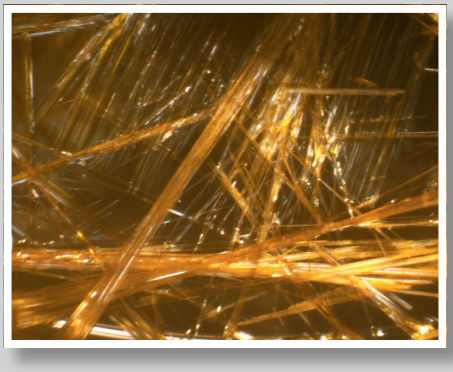
The **solubility of your compound** in organic solvents or water plays an important role when designing a crystallization screen. Knowing the solubility will allow you to **select suitable solvents for the different crystallization methods**. In addition, a selection of solvents and mixtures that spans the **range of possible chemical functionalities** will maximize the chances of finding new, interesting and developable solid forms.

Both CrystalBreeder and Crystal16 are the perfect tools for determining solubility in an easy and efficient manner. Additionally, the **CrystalClear™ software** package allows the user to graphically **visualize the data and to generate reports** that can be exported to Word.

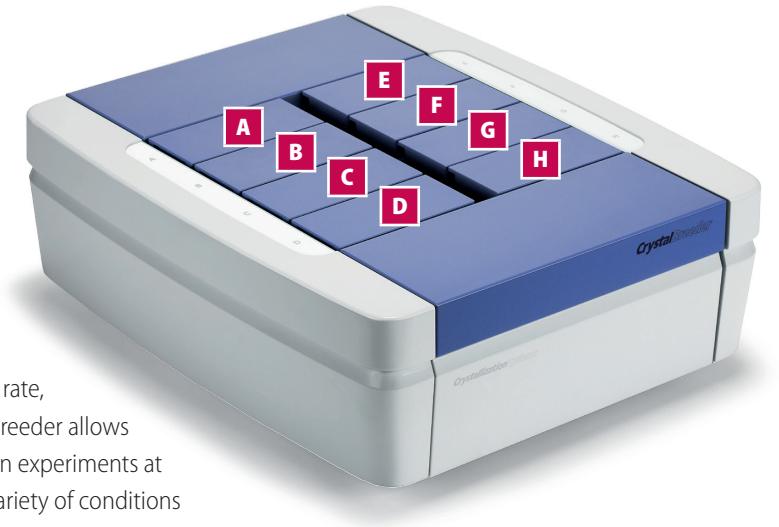
General rule of thumb: solubility should not be too high causing depletion and not to low, making crystallization too slow.







Technobis
crystallization systems



The CrystalBreeder can run up to 32 experiments

Control your crystallization parameters

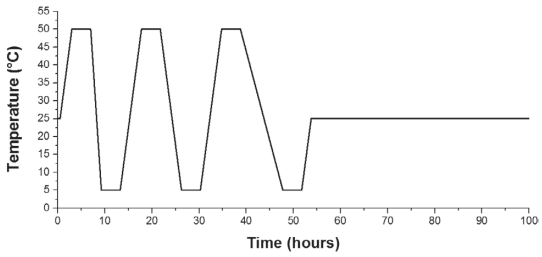
Performing your polymorph screen using the CrystalBreeder or Crystal16 enables control over the temperature, cooling/heating rate, stirring rate, concentration and solvent. Additionally, the CrystalBreeder allows you to perform evaporation crystallization or cooling evaporation experiments at a controlled evaporation rate. This enables you to apply a wide variety of conditions including the most used crystallization methods:

CrystalBreeder

- Cooling crystallization
- Temperature cycling
- Slurry experiments
- Cooling evaporation
- Vapor diffusion
- Evaporation crystallization
- Crystallization by layering

Crystal16

- Cooling crystallization
- Temperature cycling
- Slurry experiments



CrystalBreeder	
A	Fast cooling crystallization
B	Slow cooling crystallization
C	Slurry 5°C
D	Slurry 30°C
E	Temperature cycling
F	Evaporation crystallization
G	Vapor diffusion solvents
H	Vapor diffusion anti-solvents

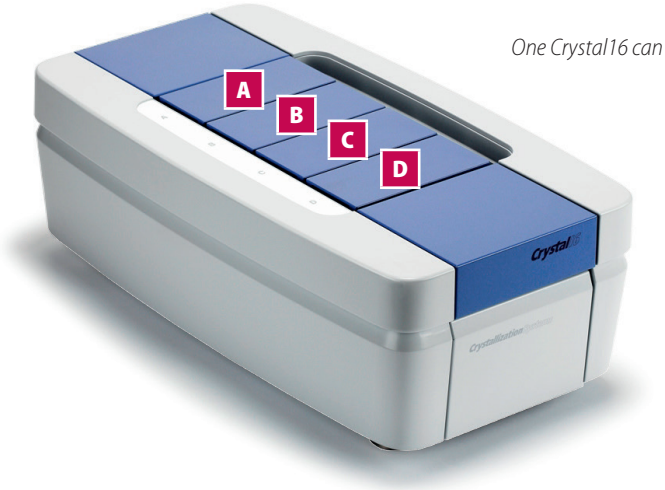
Typical crystallization set-up

A typical polymorph/crystallization screen of 32 experiments performed on a CrystalBreeder would run by using 5 crystallization methods as shown at the right.

A typical polymorph/crystallization screen on the Crystal16 would include at least 16 experiments by using 3 crystallization methods: cooling crystallization, slurry and temperature cycling.

Crystal16	
A	Slow cooling crystallization
B	Fast cooling crystallization
C	Slurry
D	Temperature cycling

Four different solvents could be chosen for the crystallization experiments. Two different cooling profiles could be applied for cooling crystallization (*e.g.* a fast and a slow cooling rate of 5 °C/min and 0.1 °C/min). Additionally, one can also choose for 2 ripening times (short ripening to capture unstable or kinetically stabilized forms and long ripening to allow more stable forms to appear). Different concentrations and different crystallization temperatures can also be considered while designing the crystallization experiments. To fully characterize the solid forms obtained, screening experiments executed on the Crystal16 and CrystalBreeder are typically followed by analytical work using X-ray diffraction, microcopy, spectroscopic techniques and thermal analysis.



One Crystal16 can run up to 16 experiments

AN EXAMPLE OF POLYMORPH SCREENING

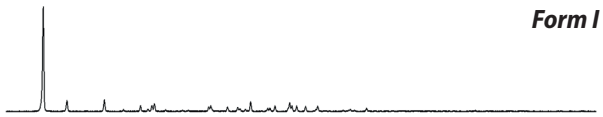
A crystallization/polymorph screening was conducted at Radboud University Nijmegen on isoxazolone dye. The compound is used as filter dye in photographic films and known to have two polymorphs: needles (form I), rhombic blocks (form II)*. The screen was performed on both **CrystalBreeder** and **Crystal16** systems in parallel.

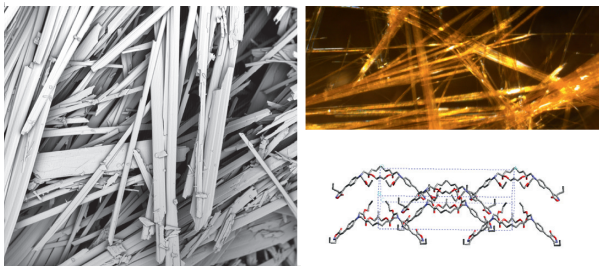
For this screen, four solvents were used as crystallization solvents. The choice of solvents was made considering the solubility information of the compound in a larger set of solvents. The investigated crystallization methods were cooling crystallization with 10.0°C/min and 0.01°C/min, slurry at 5°C and 30°C for 2 weeks, and temperature cycling.

Besides the already known form I (needles) and form II (blocks), a third form (form III) was also identified.

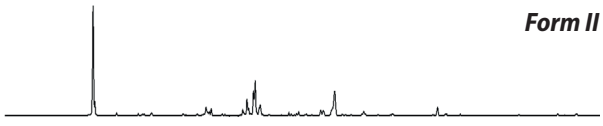
Resulting crystals of the isoxazolone dye were characterized by X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC). In addition, scanning electron microscopy (SEM) and optical microscopy images were taken to provide morphological information.

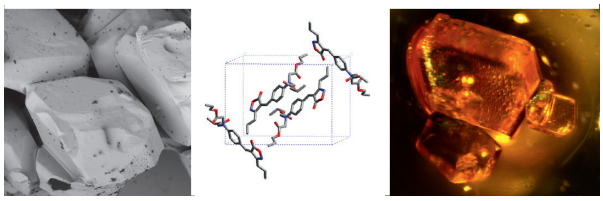
Form I





Form II





Conclusions

Both CrystalBreeder and Crystal16 have proven to be suitable for polymorph screening at 0.1 and 1 mL scale. A wide variety of parameters can be varied to perform the desired crystallization methods in a reliable, repeatable and controllable manner.

Solvent	Device	Cooling 10.0°C/min	Cooling 0.01°C/min	Slurry at 5°C	Slurry at 30°C	Termocycling
Ethanol	CrystalBreeder	I	I	II	II	II
	Crystal16	I	I	II	II	II
Methanol	CrystalBreeder	I	I	II	II	II
	Crystal16	I	I	II	II	I
2-propanol	CrystalBreeder	I	I	II	II	II
	Crystal16	I	II	II	II	II
Acetone	CrystalBreeder	I+II	I+II	II	II	II
	Crystal16	I+II	I	II	II	II+III

The study was conducted at Radboud University Nijmegen, Solid State Chemistry Department (The Netherlands). Results and pictures courtesy of Evelien Huijs and Dr. Hugo Meekes.

** Aret E., Meekes H., Vlieg E. & Deroover G. Polymorphic behavior of a yellow isoxazolone dye. Dyes and Pigments 72, 339-344, (2007).*

Aret E., Growth of organic dye crystals: morphology and polymorphism, in Solid State Chemistry, 128, (2013).

CrystalBreeder
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SCREEN MORE WITH LESS

The CrystalBreeder and Crystal16 are useful tools to perform automated and controlled solid state screens. The wide variation in experimental conditions and the separate temperature blocks enable screening with less effort and in no time. Each screening can be designed to meet its specific objectives while only using small amounts of material.

Improve and accelerate your crystallization research with the CrystalBreeder and Crystal16 parallel crystallizers, the ultimate tools for solid-state research. Designed by scientists for scientists, these tools are user-friendly multi-reactor benchtop systems with intuitive software to perform medium-throughput crystallization studies at a 0.1-mL and 1-mL scale. It offers invaluable assistance throughout the various stages of the drug development life cycle, from discovery to preclinical screening.

Specifications	Crystalbreeder	Crystal16
Reactors	32	16
Reactor Type	Commercially available, glass	Commercially available, glass
Optimal Work Volume (Ml)	0.05 to 0.25	0.25 to 1.5
Temperatures Zones	8	4
Temperature Range (°c)	-15 to 150	-15 to 150
Temperature Accuracy (°c)	0.1	0.1
Heating Rate (°c/min)	0-20	0-20
Cooling Rate (°c/min)	0-20	0-20
Stirring	Overhead or stir bar	Overhead or stir bar
Stirring Speed (RPM)	0-1250	0-1250
Evaporation Option	Yes, with evaporation flow per block of 4 reactors	No
Turbidity (%)	Every reactor	Every reactor
Data Export	CrystalClear word report XML	CrystalClear word report XML
Foot Print (dxwxh)	(49x56x20)	(49x28x20)

More information in less time

- Multiple reactor systems
- Small footprint
- Little training required
- Cheap disposable reactors
- No cleaning reactors
- No cleaning analytics
- Small volume
- Clear correlation between results
- Data consistency

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