APPLICATION NOTE 5

Co-crystallization studies

Co-crystallization brings new opportunities for preformulation and is a first step towards crystal engineering. Indeed, where traditional approaches such as salt screening fail, co-crystallization often still manages to solve the crystallization problems or improve a drug substance's physicochemical properties. The Crystal16™ offers a systematic and effective method to discover new stable co-crystal forms based on easy-to-measure solubility data of the pure components.

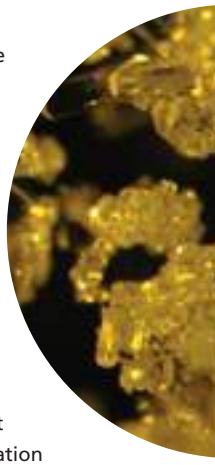
Improve and accelerate your crystallization research

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 and challenges of co-crystallization

- With an increase in the size and complexity of the molecules that enter into drug development, companies face a larger number of compounds that are either poorly soluble, difficult to crystallize or problematic with respect to physicochemical properties for successful development. Traditional approaches such as salt formation may no longer offer sufficient opportunities to provide a solution and new strategies are actively being explored.
- Crystal engineering has been identified by pharmaceutical scientists as a means of improving and tailoring the physicochemical properties of active pharmaceutical ingredients (API). The properties of an API may be modified through salt formation using a limited number of available counter ions. Co-crystals offer further potential for changing the API properties by using a much more extensive range of co-crystallizing molecules (co-builders).
- A co-crystal is defined as a crystal that is built up of two or more organic compounds which, in their pure form, are solid at ambient conditions. A co-crystal can have improved properties such as longer shelf life, improved dissolution rate and increased bioavailability.
- The ability of an API to form a co-crystal is dependent on a range of variables, including the types of co-former, the API co-former ratio, the solvents, the temperature, the pressure, the crystallization technique, etc. A systematic exploration of the combination of relevant variables increases the chance of discovering a co-crystal with the desired properties.
- Traditional experimental methods tend to overlook a significant number of co-crystals as the range of experimental co-crystallization conditions is often too limited and thermodynamic information is neglected.



Solubility as key to co-crystal screening

This application note describes a systematic and effective method to discover new stable co-crystal forms based on easy-to-measure solubility data of the pure components. The key to optimizing the probability of finding co-crystals is to determine solubility, starting with the solubilities of the pure components.

- The graph overleaf (see Figure A) shows a simplified phase diagram of a 1:1 AB co-crystal at two temperatures T_1 and T_2 in a solution.
- Typically, the solubility of a component drops when other components are added to the mixture and this should be observed when small amounts of co-builder B are added to the solution or when small amounts of A are added to a solution containing co-builder B. To simplify the representation, we assume that the solubility of the pure components A and B and the solubility product of the co-crystal A:B are constant; this results in a straight vertical and horizontal line (black) for the solubility of the pure components A and B respectively. The solubility product $(xA \bullet xB)^*$ for a stable co-crystal is smaller than the product of the pure component solubilities $xA^* \bullet xB^*$.

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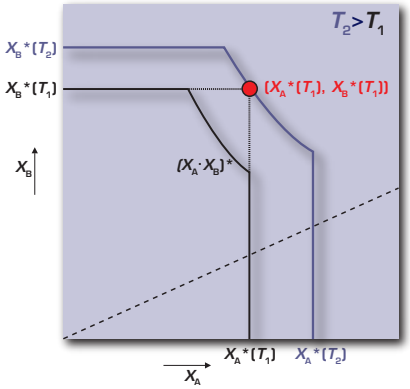

Figure A

T[°C]	X_{CBZ} [mmol/mol]	X_{INA} [mmol/mol]	molar ratio CBZ:INA	T_S [°C]
10	2.9	21.8	0.12	26.8
15	3.7	25.2	0.13	34.2
20	4.6	29.0	0.13	36.9
25	5.7	33.3	0.14	42.0

Figure B

Note: to maximize the probability of co-crystal formation, not only is it important to choose the appropriate component ratio, it is also important to choose an appropriate solvent as both components should be sufficiently soluble and competition between co-crystallization and solvation of the API should be minimal.

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The solubility line of a stable co-crystal will intersect the rectangular envelope of the pure component solubilities xA*(T_1) and xB*(T_1) below its upper right point (indicated in red) with composition (xA*(T_1),xB*(T_1)).

- In principle, at temperature T1 with corresponding component solubilities xA*(T_1) and xB*(T_1), a solution with overall composition (xA*(T_1),xB*(T_1)) will generally be well-positioned to obtain co-crystals. For co-crystal screening this principle has the important consequence that a solution with composition (xA*(T_1),xB*(T_1)) will have a saturation temperature T_2 (of the co-crystalline phase) above the pure component saturation temperature T_1. These saturation temperatures are experimentally easily accessible.

Example

The Crystal16™ can be used to design a co-crystal screening program by measuring the clear points of a series of co-builders and the API. The possibility for co-crystallization can be checked by measuring the saturation temperature of the mixtures, based on the individual components' solubilities. As an example, the co-crystallization of carbamazepine (CBZ) with iso-nicotinamide (INA) was studied on a Crystal16™, using the following approach:

- In a first experiment, different concentrations of the pure components were slurried in ethanol and from the measured solubility curves the solubility of the individual components CBZ (XCBZ) and INA (XINA) were read at 10, 15, 20 and 25 °C.
- In the next experiment, mixtures of CBZ and INA were prepared based on the solubility data of the pure components. The prepared slurries were dissolved and recrystallized after which the saturation temperature (clear point) was determined upon heating at 0.3 °C/min. The saturation temperatures TS of the mixtures of CBZ and INA are listed in the table (see Figure B) and are all significantly higher than the pure component saturation temperatures (e.g. 42 °C versus 25 °C), indicating that a more stable and therefore less soluble co-crystal phase was recrystallized. The conclusion is that CBZ and INA most likely can form co-crystals. Note that a large excess of INA (at least a factor 6 based on molar ratio) is needed to successfully co-crystallize, the solubility of INA being much higher than that of CBZ.
- This example illustrates that a systematic screening method can be applied to investigate several combinations of API, co-builders and solvents, optimizing the probability of discovering co-crystalline materials. Matching solution with co-crystal stoichiometry should be set aside, and co-crystal screening should be designed based on easily accessible pure component solubilities.