

Crystallization – Understanding and developing the process

In order to achieve controlled production of a desired polymorphic form it is essential to primarily understand the product and be intimately familiar with the process. Furthermore, scaling up the crystallization process requires an expert team of experienced scientists working closely together to ensure reliable and seamless development.

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Crystallization processes are presently the most widely used techniques for purifying solid drug substances. Independent of chemical or chiral purity enhancement, specially designed crystallization processes are the best choices for processing. Compared to separation by chromatography, crystallization processes, in most cases, also have economic benefits. But not only purity aspects favor the use of crystallization techniques, even the controlled production of a desired polymorphic form, typically via seeding processes, can be achieved.

In active pharmaceutical ingredients, several polymorphs and solvates may be present. A change of the crystalline form and/or the presence of an amorphous part may induce important changes concerning the physical properties such as dissolution rate, bioavailability, stability or processability of the corresponding drug product.

Needless to say, an ideal crystallization process must be robust, reproducible and scalable. Therefore, for the development of robust processes it is mandatory to determine the influence of significant parameters such as temperature and solvents of crystallization, drying, milling, and storage conditions on the crystalline form and on its crystallinity.

To guarantee reliable and seamless development and scale up of a crystallization process, a team of experienced scientists should closely collaborate. Starting from the initial crystallization screening process to kg-scale production and the final supply of material (GMP and non-GMP), a multidisciplinary team is required.

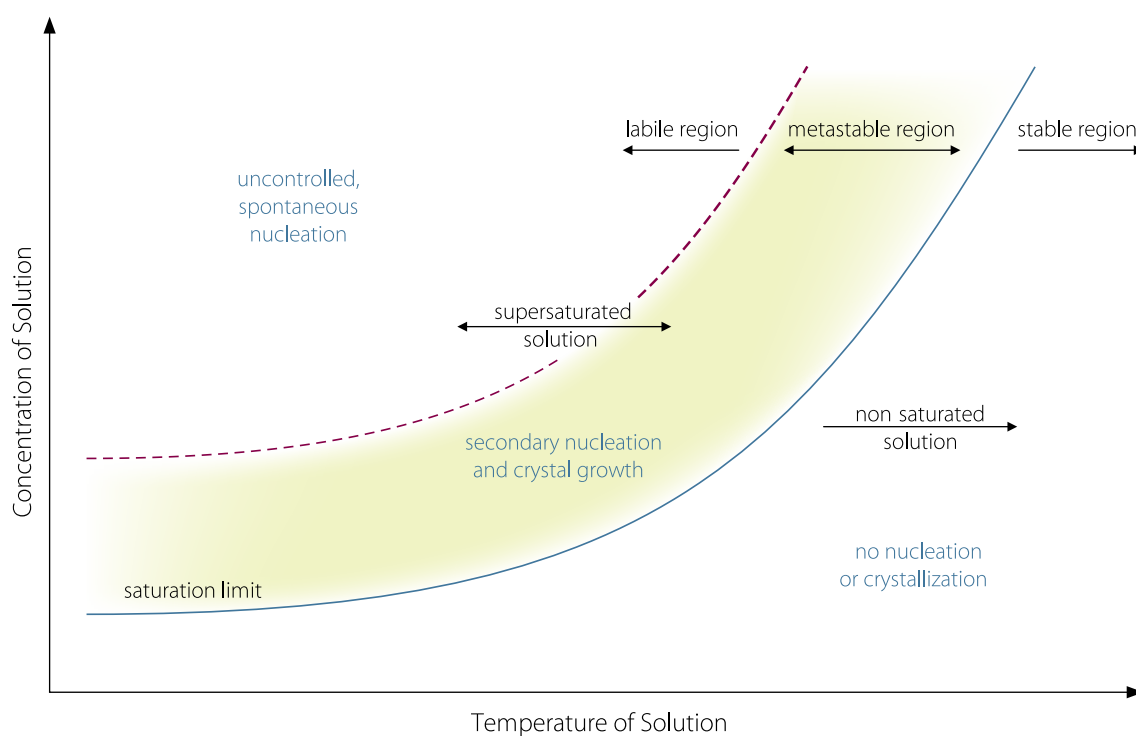


^ Figure 1: A crystallization process for a nonspecified pharmaceutical drug substance

INVESTIGATING POLYMORPHISM – IDENTIFYING AND UNDERSTANDING THE PROFILE

The key step towards a robust crystallization process is a detailed solid-state characterization and polymorphism investigation which provides an overview of the polymorphic transformations, including the identification of the most thermodynamically stable form at a given temperature, and an understanding of the temperature-dependent behavior of all forms. For example, an important part of a polymorphism profile is to determine whether the thermodynamic stability ranking of polymorphs changes with temperature (i.e., enantiotropy). To control reactions in an enantiotropic system, determining the transition temperature at which the ranking of polymorphs changes is of great significance, especially if this temperature is within the range of operation (e.g., between the temperature of cold filtration and the boiling point of the solvent).

For solvates and hydrates, both thermodynamic parameters and solvent activity must be examined. In particular, it is crucial to determine whether a given polymorph results directly from the chosen process conditions or whether it is obtained by the desolvation of an intermediate solvate or hydrate while drying. In the latter case, the choice of solvent for the final crystallization step will be restricted and the product may be difficult to dry, leading to elevated levels of residual solvent. Dehydrated hydrates often have the disadvantage of being hygroscopic and can tend to rehydrate (dependent upon moisture levels or water activity).



^ Figure 2: T/C graph of solubility and MSZW

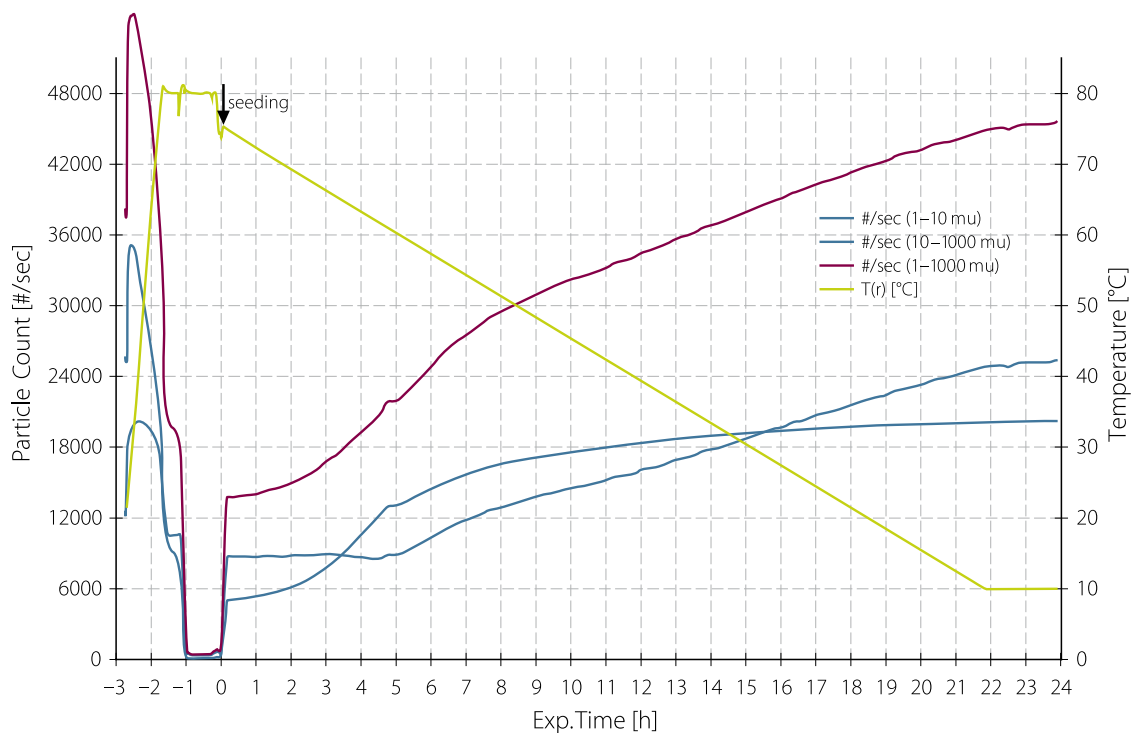
DESIGNING THE PROCESS

Based on the polymorph landscape and the chemical compatibility of the drug substance with various solvents, a first set of solvents or solvent mixtures is selected to determine the temperature-dependent solubility of relevant polymorphs. This screening type of process provides the metastable zone width (MSZW) of the system and is the basis of a preferable seeding process for a robust crystallization. Seeding is the most favored technique for crystallization of pharmaceutical drug substances as it ensures a controlled and reproducible process.

Essential for such a seeding process is the addition of the seeding crystals at a temperature at which the system enters the metastable region. *Figure 1*. If seeding crystals are added at higher temperatures (= stable region), they will dissolve without nucleation. If seeding crystals are added in the labile region, nucleation will start spontaneously and the system will crystallize in an uncontrolled manner.

Figure 2 shows a typical cooling crystallization supplemented by the addition of seeding crystals. After complete dissolution of the starting material, the temperature (green line) is lowered till the system enters the metastable zone. Seeding crystals are added and the temperature is continuously reduced. The controlled crystallization is monitored by focused beam reflectance measurement (FBRM) to determine the number and diameter of particles generated (purple, blue and orange lines).

Within cooling crystallization processes the addition of antisolvent, pH shifts or salt formation are also appropriate supporting tools. At this point, other crystallization processes such as azeotropic distillation may also be considered in order to broaden the knowledge of the crystallization process.



^ Figure 3: Seeding process monitored by FBRM

Even at this early stage of crystallization process design, later specifications for large-scale production will be taken into account. Variation of solvent systems (e.g. technical solvent quality versus highly pure solvent), exchange of solvents (e.g. class-1 or class-2 to class-3 solvents), stirring time and speed or variation of substrate concentration will be tested on a ml scale to generate necessary information for further optimization and production to ensure rapid development and feed the production chemists with information necessary to guarantee reproducible results.

OPTIMIZING THE PROCESS

Once an initial crystallization process is established further work has to be carried out for process optimization. Even small changes in a crystallization process may lead to undesirable events such as agglomeration, polymorphic conversion, and nucleation. The systematic variation of relevant process parameters such as cooling profile, stirring (type of stirrer, speed), seeding, purity (spiking with relevant side products) and water activity will identify the critical factors that influence the characteristics of the solid product and form the basis for a robust crystallization process design.

Beside these parameters, space volume yield, compression and filterability of the crystallization process or crystallization product will be varied and optimized.

A further important step is the harvesting and drying of the crystalline product which may include drying hydrates to the desired hydration level. Comprehensive analysis of the solid product – by HPLC, headspace GC, X-ray powder diffraction, particle size distribution, microscopy, or other techniques – will provide all the information needed to optimize both the crystallization of the desired polymorphic form within the defined product specifica-

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tions (crystal size, shape, and purity) and a high productivity of the overall crystallization process (e.g., good yield, short batch cycle time).

SCALING-UP FROM MULTIGRAM TO KG SUPPLY

The designed process is repeated on a larger scale (250 g to >1 kg) for proof of concept or direct delivery. As all relevant information was previously gained during the design and optimization stage, involving specialists from all disciplines, production of the desired quantity can start immediately. By implementing this integrated approach for crystallization development and scale-up, a fast and reliable process is guaranteed without time-consuming technical transfer efforts from one company to another.

As our target is always to ensure the best, cheapest and most effective production method, we offer production under both GMP but also non-GMP quality standard. For non-GMP material (e.g. for formulation development or toxicology studies), substance-specific validations for test methods can be avoided by using general methods according to ICH, pharmacopeia test methods or through one of the ready-to-use Solvias standard methods. If the material should be used for GMP processes, the production will be accordingly under full GMP quality standard. *Figure 3*. It is worthwhile to note that in most of the cases crystallization demands a substrate which is also produced under GMP. The use of a non-GMP starting material in such case will not result in a GMP-compliant product.



^ 100L GMP reaction vessel

For every crystallization process under GMP an ICH-conform release testing will be performed either with customer-specific methods, analytical methods transferred to our laboratories, or by in-house validated methods. As Solvias is equipped with production facilities under certified GMP quality standard, we could either just crystallize your substrate or even further produce the starting material in our own facility ensuring complete GMP coverage. In addition, our scientific experts are always available for consultation at any stage of the process and can advise the client how best to utilize our extensive portfolio of products and services to complete the technology transfer.

WHY WORK WITH SOLVIAS?

The unique combination of Solvias' expertise in solid-state development, crystallization process development, pilot plant production scale under GMP and non-GMP and state-of-the-art instrumentation enables us to tackle the majority of drug development candidates. Our approach to set up crystallization projects right from the start with a team approach comprising physicochemists, organic and analytical chemists guarantees seamless process development for your drug candidate without time- and money-consuming technology transfers at this stage.