Q&A with Ardena Experts

Design of Experiments (DoE) and its relevance in API crystallization process development

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What are the main challenges in the development of an API crystallization process?

The crystallization process of an API should lead reliably to a material with the desired quality attributes. However, there can be challenges that have to be addressed:

- Polymorphic form: Some APIs have a complex polymorphic landscape. It can be difficult to develop a crystallization method that reliably results in the required polymorphic form in such a case.
- Particle size distribution (PSD): The PSD is determined during the crystallization procedure, and it impacts several properties of an API:

a. Solubility, Bioavailability and Formulation: Small particles are more soluble than large particles. The bioavailability can often be increased by using smaller particles. A different PSD can necessitate the development of a new formulation.
b. Flowability: which impacts the unloading, transfer, dosing, and mixing of the API as a powder.
c. Bulk density: Determines the size of equipment and containers, and influences transport costs.

- Critical process parameters (CCPs): Some process parameters during crystallization influence the quality of the API. The result can be a higher impurity content or a higher residual solvent content.

What is Design of Experiments (DoE)?

DoE is a systematic approach to set up an experimental design. Input variables (factors) are defined with a low and a high value (level). After completion of the experiments, the influence of the factors on the output variables (response) is tested using statistical software.

How can DoE help to solve challenges in pharmaceutical crystallization?

Understanding the influence of input parameters on a crystallization experiment and how to control critical process parameters is typically a challenge. Yet it is important to identify the parameters that are critical for the quality of the API, whether it is the polymorphic form, the PSD or morphology of the particle or the impurity or residual solvent content.

Traditional approaches often rely on iterative experiments based on trial and error. With DoE, a structured and statistically-driven approach can be applied to understand a process and to find the optimal conditions to deliver the product with the target specifications. The range of operation that delivers a good product can be determined with DoE. The outcome is the development of a robust process, which avoids OOS (out-of-specification) batches or other surprises (e.g. failed formulation).

What equipment does Ardena utilize for DoE?

Different equipment is used for process development, depending on the scale of the crystallization experiments:

- Crystal16 by Technobis
  Crystallization systems (300 µL – 2 mL);
- Crystalline by Technobis
  Crystallization systems (1 – 8 mL);
- Mya 4 reaction station by Radleys
  (100 - 400 mL);
- Atlas HD by Syrris (50 – 1000 mL).

The obtained solids are analyzed using XRPD, TGMS, HPLC, and 1H-NMR. Most frequently used analytical techniques are: DSC, PSD, DVS, KF, PLM, and SEM.

How does Ardena use DoE to develop and improve a crystallization process?

An example where DoE can be useful is in resolving issues that occur during the production of APIs. For instance, the manufacturing process is affected by batch-to-batch variability in PSD leading to issues with solubility or the formulation process, or reproducible crystallization of the desired polymorph appears difficult, or the residual solvent content is out-of specifications.

In most cases, a solubility study, including determination of the meta-stable zone width (MSZW), is conducted. Furthermore, a batch record screening can identify factors that should be evaluated in the DoE. And depending on the issue and the current crystallization process, the input variables (factors) are identified and the low and high value (levels) of the factors are determined.

The experiments are designed and executed according to the DoE, and the obtained solids are analyzed. The study timelines vary and depend on the number of crystallization experiments and the scale. When all experiments are completed and the values of the responses are collected, the main effect and interaction plots are prepared. The analysis of the DoE results shows then clearly which factor has the biggest impact, and within which range an optimal result can be achieved.

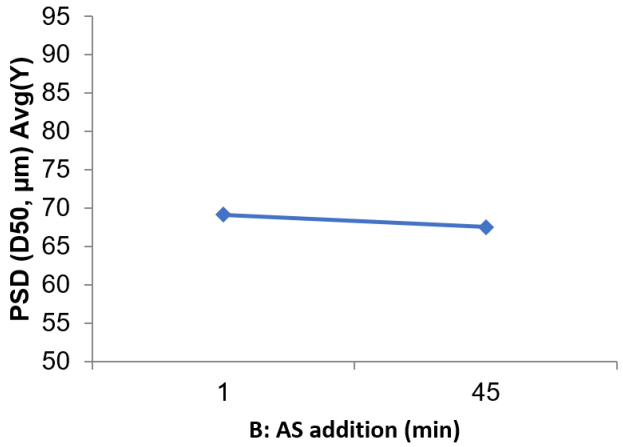
A demonstration batch on an appropriate scale is then conducted.

How many experiments are needed for a DoE?

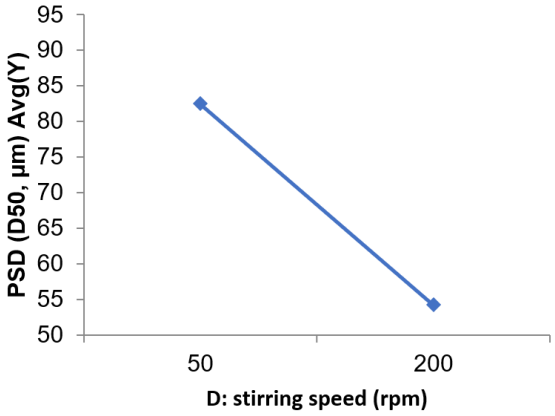
The number of experiments of a full factorial design is determined by the number of factors (n) and it is equal to 2n. Additionally, 3 center point experiments are conducted, which would lead to a total of 19 experiments for a design with 4 factors. However, evaluating 8 factors needs 259 experiments for a full factorial design. It is, however, possible to conduct a fractional factorial design for 8 factors which would require only 19 experiments. Fractional factorial designs allow for the investigation of a broad range of factors, which could potentially influence the crystallization, while being cost and time efficient.

Can you provide examples of DoE results?

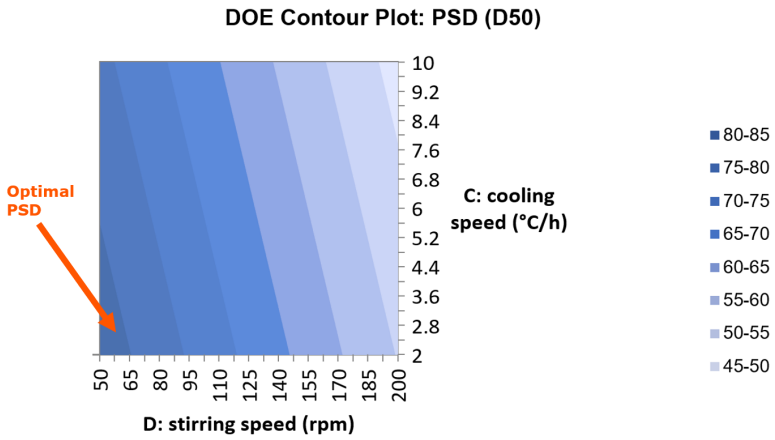
The image below shows an example of a factor (antisolvent addition time) that has hardly any impact on the response (PSD, d50), as almost no variation in PSD was observed for fast or slow antisolvent addition:



The image below shows an example of a factor (stirring speed) that strongly influences the response (PSD), as the determined PSD significantly decreases for high stirring speeds:



A contour plot of the most significant factors can help to determine the optimal settings of factor during the crystallization. In the shown case study, slow stirring and slow cooling did optimize the particle size to 80 – 85 µm (indicated by the arrow). The contour plot reveals the range in which the optimal PSD could be obtained (50 – 65 rpm with 2°C/h or up to 4°C/h with 50 rpm).



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