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CRYSTALLIZING A COMPLEX, HIGH-MOLECULAR-WEIGHT AMORPHOUS API

Identifying a developable crystalline form and establishing process-relevant crystallization conditions

A pharmaceutical company was developing a complex synthetic API with a molecular weight of approximately 900 Da, placing it at the upper end of the small-molecule range and approaching the molecular complexity typically associated with larger molecules. The compound also had many rotational degrees of freedom and had only ever been obtained as an amorphous oil containing residual solvent, creating challenges for crystallization, purification, stability, and handling. The drug developer wanted to identify at least one crystalline solid form to improve stability and reduce residual solvent content. If multiple crystalline forms were discovered, the team needed to determine which offered the most suitable properties for development and evaluate potential conditions for its crystallization. To identify an optimal crystalline form and establish a path toward a practical crystallization process, the company partnered with Solvias.

THE CHALLENGES

Large and Complex Molecule
Although the molecule was a synthetic compound, it had a relatively high molecular weight and many degrees of rotational freedom, making crystallization a challenge.

Oily Consistency
The compound had only ever been obtained as an oil that contained residual solvent. The oily consistency of the compound made it difficult to purify, subject to degradation during storage, and challenging to handle in downstream processing steps.

OUR COLLABORATIVE APPROACH

High-Throughput Screening Experiments
192 microscale experiments were performed in 2 microtiter plates to explore the crystallization parameter space and to rapidly identify the conditions that were most likely to lead to crystallization.

Complementary Laboratory-Scale Experiments
In addition to the high-throughput screening, focused laboratory-scale experiments were also performed. These experiments included complementary crystallization approaches such as vapor diffusion, slow cooling followed by temperature cycling, and suspension equilibration at more extreme temperatures. Furthermore, attempts were made to reproduce the best leads from the high-throughput screening on a scale that permitted physico-chemical characterization.

Selection of the Optimal Polymorph
Three crystalline or partially crystalline forms were isolated and characterized within the project, including 2 anhydrous forms and 1 solvate. The more thermodynamically stable of the 2 anhydrous forms at room temperature was identified.

Initial Crystallization Development
Although the most stable anhydrous form at room temperature was discovered using solvents that were not suitable for process development, a seeded cooling and antisolvent dosage process for producing this form was developed on a laboratory scale using pharmaceutically acceptable solvents.

THE RESULTS

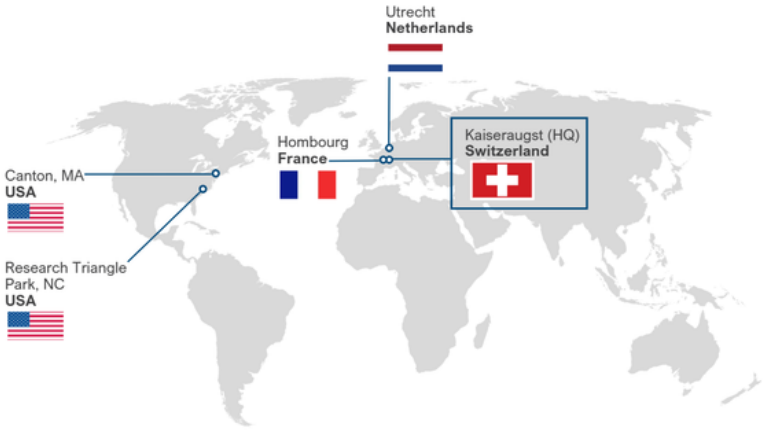
- Crystallization of the amorphous material.
- Removal of residual solvent.
- Identification and characterization of multiple crystalline polymorphic forms.
- Determination of the most stable anhydrous form at room temperature.
- Development of a small-scale crystallization process using pharmaceutically acceptable solvents.
- Gram-scale production of a crystalline, white powder in place of an oil.

CONCLUSION

While larger molecules are more challenging to crystallize than smaller ones, crystallization screenings can be fruitful. A hybrid approach combining high-throughput screening to rapidly explore a large parameter space along with targeted laboratory-scale experiments to fine-tune parameters is useful. Even if many of the screening conditions are far from process-relevant, once a crystalline form has been discovered, a practical seeded process for obtaining it from pharmaceutically acceptable solvents can generally be developed.

WHY PARTNER WITH US?

- CRO
- Founded in 1999
- 800+ team members
- 175+ PhD-level scientists
- GMP, GLP, ISO9001 certified
- 23K m^2 of lab capacity
- 700+ customers worldwide
- 5 centers of excellence



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