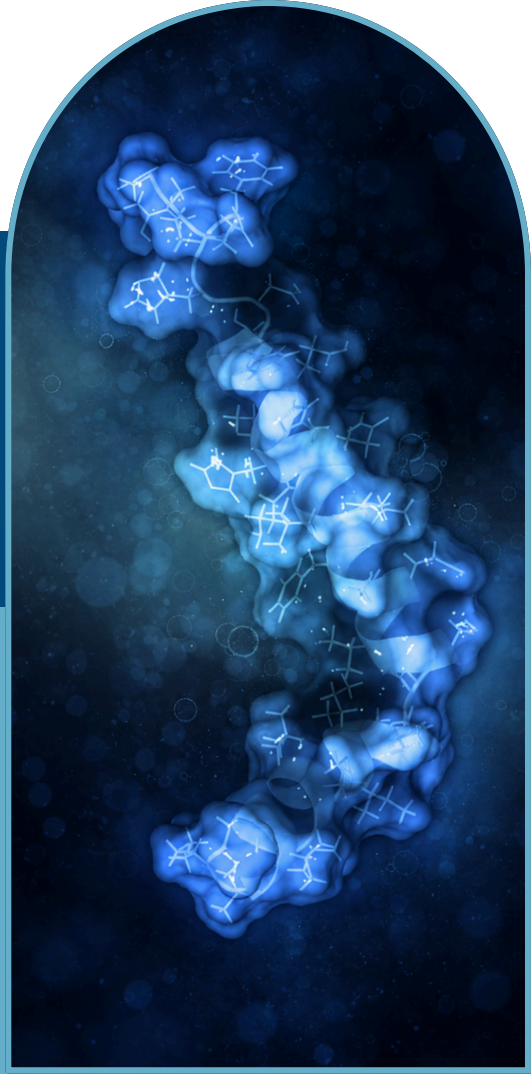
solvias



When Scaling Up Isn't Straightforward:

DEVELOPING A ROBUST CRYSTALLIZATION PROCESS FOR A HIGH-MOLECULAR-WEIGHT PEPTIDE

A pharmaceutical company developing a peptide therapeutic (MW ~1,200 Da) needed to establish a robust crystallization process suitable for large-scale manufacturing. Several solid forms of the API had already been identified, including a dihydrate, a channel hydrate (the desired form), an anhydrous form, and an amorphous form. Unfortunately, the desired crystalline form frequently crystallized together with an undesired polymorph, making it difficult to consistently produce material of the required quality. The customer also wanted to replace the solvent system in the existing crystallization process with lower molecular weight solvents to simplify manufacturing, improve process robustness, shorten filtration times, and decrease the residual solvent content. To overcome these challenges and deliver a scalable manufacturing process, the company partnered with Solvias.

THE CHALLENGES

Multiple Solid Forms
The peptide was already known to exist in several polymorphic forms, with the desired channel hydrate frequently crystallizing alongside an undesired anhydrous form. Achieving consistent polymorphic purity was essential for process robustness and product quality.

Difficult Crystallization Behavior
Attempts to directly convert either the amorphous material or the dihydrate into the desired crystal form by seeding were unsuccessful, limiting conventional process development options.
In addition, the products of the existing process typically contained residual solvent levels that fell outside the ICH Q3C limits.

Scale-Up Requirements
Beyond obtaining the correct crystal form, the final process needed to be reproducible, economical, scalable and transferable to manufacturing, and capable of delivering the required yield, purity, and particle size distribution.

OUR COLLABORATIVE APPROACH

Alternative Crystallization Pathway
Since direct conversion to the desired polymorph proved challenging, Solvias identified an ethanol solvate intermediate that enabled controlled conversion into the target crystal form and explored the stability of this form in various solvent–antisolvent mixtures.

***In Situ* Process Monitoring**
Using an automated platform for controlled crystallization together with *in situ* imaging and focused beam reflectance measurement (FBRM) probes, the team continuously monitored crystal formation and process behavior throughout development. Although unexpected phase separation initially resulted in the formation of a gel-like intermediate that could not be detected using conventional FBRM monitoring, adjustment of the conditions eventually led to a controlled process.

Process Optimization
Experimental conditions were systematically refined by reducing solution concentration to eliminate phase separation while deliberately slowing crystallization kinetics to prevent formation of the gel-like intermediate. Although the reduction in concentration necessarily decreased the volume efficiency, the resulting process was controlled, robust, and high-yielding with optimal particle properties and a dramatic reduction of the filtration time.

Scalability Focus
Process parameters were optimized not only for laboratory success but also for reproducibility, technology transfer, and manufacturing.

THE RESULTS

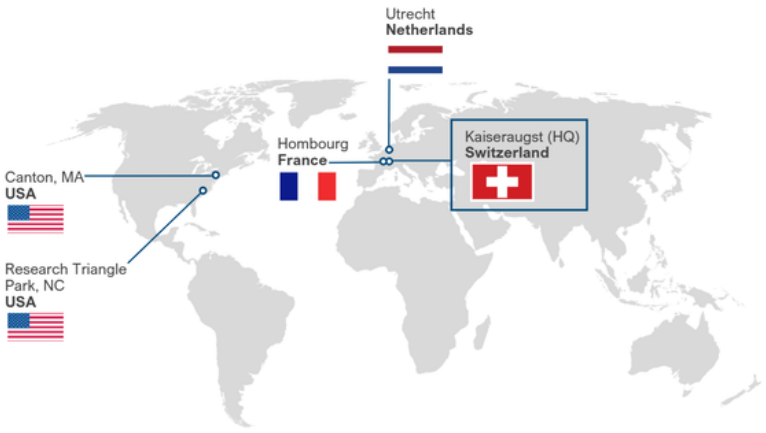
- Robust crystallization process delivering the desired polymorphic form.
- Improved process robustness while transitioning to lower molecular weight solvent systems.
- Successful mitigation of phase separation and gel formation.
- Reproducible conversion through a controlled ethanol solvate intermediate.
- Successful crystallization process suitable for technology transfer and manufacturing.

CONCLUSION

By combining advanced solid-state expertise with in situ process monitoring and systematic process optimization, Solvias established a reproducible crystallization process capable of consistently producing the desired polymorph. The resulting manufacturing-ready process reduced technical risk, supported technology transfer, and provided a reliable foundation for commercial peptide production.

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



Contact us to speak with an expert: info@solvias.com

solvias.com

solvias