Peptide Crystallization

Peptide crystallization introduces greater complexity due to molecular flexibility and size. Each peptide requires unique insight to optimize crystallization conditions. There is no substitute for expertise, and Cambrex's understanding of crystal formation and thermodynamics allows us to develop custom, scalable crystallization processes for peptides. We leverage the right tools with the best experts to bridge success from the bench to the plant.

Challenges with Peptides

Peptides present increased complexity for crystallization due to the large size and flexibility of the molecules, leading to a much smaller crystallization operating range compared to other less flexible small molecules. They have a high risk of gelling, fibrillation and aggregation, often leading to low purity results and high residual solvent contents. If solids are recovered, they are often isolated as amorphous solids, which can be difficult to handle – both during production and during further formulation steps.

Peptide molecules have very high production costs due to the complexity of synthesis and isolation. Purification is usually completed through column chromatography, which is costly to carry out and often leads to material losses during this process step.

Clear Advantages of Peptide Crystallization

Having a crystalline solid form of a peptide offers clear advantages compared to the amorphous form:

- Significant impurity rejection
- Improved processability
- Reduced hygroscopicity
- Increased stability
- Control of aggregation & gelling
- Cost advantage of crystallization when compared to column chromatography methods for purification
- Full structural determination

An in-depth understanding of the thermodynamic and kinetic processes that drive the crystallization for a specific peptide is required before the critical process parameters can be altered to achieve control over nucleation and crystal growth. Typically, crystallization operating ranges for larger peptides are much tighter than for smaller molecules, so the design and assessment of initial screening can make or break scale-up efforts.

Hannah McLachlan, Ph.D.
Project Scientist 4

There is no substitute for expertise.

Peptide crystallization introduces greater complexity than smaller molecules.

Each peptide requires unique insight to optimize individual conditions.

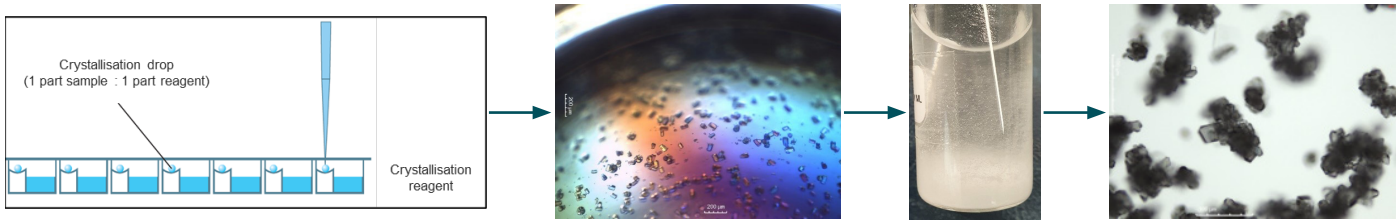
Trust the team at Cambrex to deliver successful, scalable results.

About Cambrex

Cambrex is a leading global contract development and manufacturing organization (CDMO) that provides drug substance development and manufacturing across the entire drug lifecycle, as well as comprehensive analytical and IND enabling services.

With over 40 years of experience and a team of 2,000 experts servicing global clients from North America and Europe, Cambrex offers a range of specialized drug substance technologies and capabilities, including continuous flow, controlled substances, liquid-phase peptide synthesis solid-state science, material characterization, and highly potent APIs.

Successful workflow from initial plate-based screening to vial-scale crystalline material



Bespoke Strategies

Cambrex employs a stepwise strategy to deliver crystallized peptides:

- **Milestone 1:** Initial high throughput crystallization assessment through solubility evaluation (solvents, pH, temperature, counterion inclusion and additives more than excipients), small-scale crystallization trials (free peptide or salt form) and single crystal growth.
- **Milestone 2:** Process development to deliver a controlled, robust and scalable crystallization, through investigation of the scalable elements of the process and assessment of the critical process parameters and conditions to achieve optimized yields, purity and filtration and drying efficiency efficiency.
- **Milestone 3:** Technology transfer to ensure a successful crystallization process in the client's facility. Our experts use data from in-house experiments as well as state-of-the- art modeling software and process analytical tools to ensure consistent results in the plant.

Deliverables

- **Isolation and scale-up of crystalline peptide**
- **Enhanced chemical purity/impurity profile**
- **High process yields**
- **Effective isolation and drying**
- **Improved downstream processing**
- **Successful technology transfer**

Process Development Workflow

- Solubility/identification of appropriate solvent matrix
- High throughput screening for locating initial crystals
- Initial crystallization trials of most promising conditions, including metastable zone width measurements
- Crystallization process development for identification and control of critical crystallization parameters
  - DynoChem scale-up/scale-down modeling in conjunction with use of PAT tools including BlazeMetrics and other analysis techniques
- Filtration and drying studies
- Design of Experiment (DoE) studies

While crystallization efforts are traditionally associated with smaller molecules, the stepwise approach employed by Cambrex has proven to be a successful strategy to tackle the design of peptide crystallization processes, adding to our command in this space of drug development. The increased understanding provided by these studies is a powerful tool for our clients to assess the potential of their peptide and to reveal its viability as a candidate for crystallization. Knowing whether the properties of a specific crystallized peptide will offer advantages over the amorphous material can prevent wasted scale-up efforts. Speak to Cambrex to find out how we are equipped with the expertise and tools to locate, understand and robustly scale-up crystalline solids of your peptide.