Cambrex

Case study
Analytical services

Selective crystallization of a novel polymorph

Sarah Bethune, PhD
Sr. Director, Pharmaceutics & Formulation

Managing the emergence of a new polymorph without interrupting clinical supply.

See what success looks like: Preventing polymorphs from sabotaging early clinical trials

When success in early trials creates a demand for new batches of API, the emergence of an unexpected polymorph can be a major setback to meeting critical clinical timelines.

Different polymorphs of the same API can exhibit different physical properties including stability, solubility, and bioavailability in the body. Isolating the stable polymorph reliably in each batch is vital to the success of API manufacturing and formulation. Ideally, the optimal polymorph is selected early in development to steer formulation strategies. However, it's not uncommon for a new polymorph to arise after API manufacturing is underway.

Here's a look at how Cambrex applied rigorous characterization standards and expert knowledge of critical water activity to isolate a previously undiscovered and uncharacterized polymorph. At the same time, they were challenged with supplying the original polymorph to maintain batch production in order to meet a critical need for an ongoing clinical trial.

Early indicators: Shifting peaks

After adopting the manufacture of an API from a CMO to produce new batches required for a clinical trial, the XRPD release test indicated shifting diffraction peaks. X-ray diffraction is a standard characterization tool to provide definitive fingerprinting in the identification of crystalline structures. On its own, the variation in diffraction peaks was not evidence of a polymorph, but the XRPD release test of a fourth manufacturing batch indicated distinctly new and not just shifted XRPD diffraction peaks. This was a sufficient deviation from the strict reproducibility standards at Cambrex to warrant further investigation.

With limited polymorph studies conducted before the previously manufactured batches, further testing was performed to determine whether there might be a mixture of multiple forms to explain the XRPD pattern.

Clinical continuity.

How do you manage the emergence of a new polymorph while maintaining reliable reproduction of the approved form?

About Cambrex

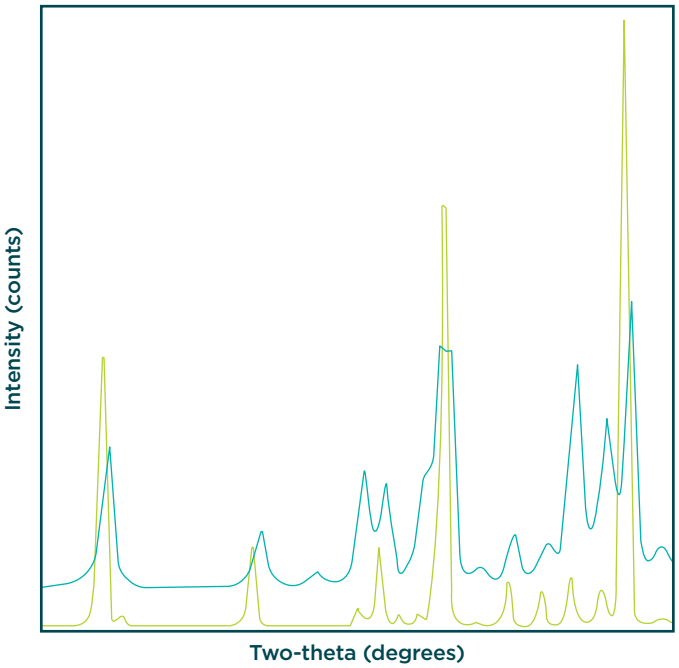
Cambrex is a leading global contract development and manufacturing organization (CDMO) that provides drug substance, drug product, and analytical services across the entire drug lifecycle.

With over 40 years of experience and a growing team of over 2,200 experts servicing global clients from North America and Europe, Cambrex is a trusted partner in branded and generic markets for API and finished dosage form development and manufacturing.

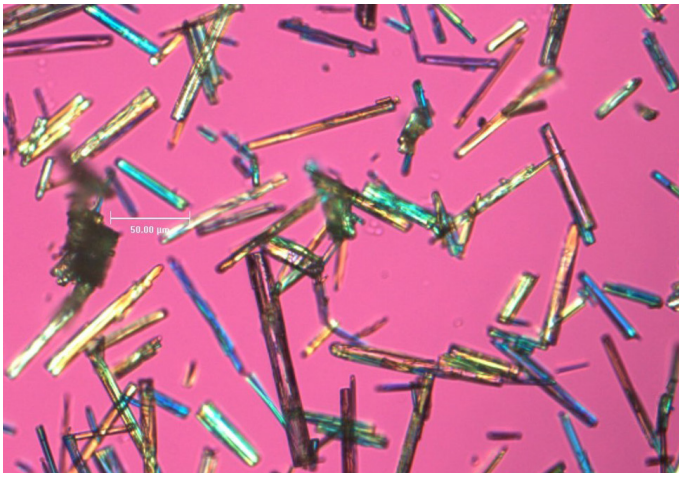
"We were able to determine that the known monohydrate was in fact a variable hydrate and set out to characterize the new polymorph,"

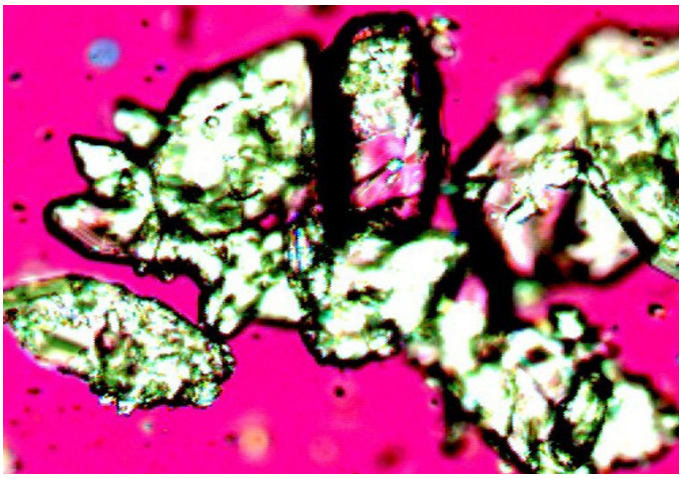
Explained Sarah Bethune, PhD, Sr. Director, Pharmaceutics & Formulation Development.

Analysis of a crystalline monohydrate



Shifting of select XRPD diffraction peaks during analysis of a crystalline monohydrate that had been previously discovered suggested the possibility of a variable or channel hydrate.





Microscopy comparison of the crystal forms of the monohydrate original API (top) alongside the isolated anhydrous crystal (bottom) revealed two distinct morphologies.

Finding the solution: Selective polymorph screen

When a starting material is suspected to be a mixture, the use of selective properties of solvents to activate crystallization and separate the materials in the mixture was taken.

By designing a polymorph study to screen against a panel of various organic solvents, Sarah's team confirmed the presence of a new anhydrous crystalline polymorph. Analysis of the data revealed two distinct polymorphs which were successfully isolated as single phases.

Sophisticated characterization techniques of the solid forms also included XRPD, DSC, TGA, PLM, DVS, KF, and NMR. Characterization data became part of the intellectual property package for the client.

Optimizing stability: Critical water activity

The thermodynamic stability of both anhydrous and hydrate polymorphs is dependent upon the critical water activity of the solvent system. Therefore, distinct phase boundaries can be identified by comparing stability across various water activity media, much like the approach to determining the critical transition temperature between a monotropic and enantiotropic polymorph.[1]

Cambrex exceeds current industry standards by applying this principle through the use of competitive slurries to definitively assign thermodynamic stability. Reliance upon thermal data alone can present an incomplete picture of a stability profile. In this case, examination of the critical water activity revealed larger thermodynamic stability space for the anhydrous form, which was later chosen to replace the original API for scale-up.

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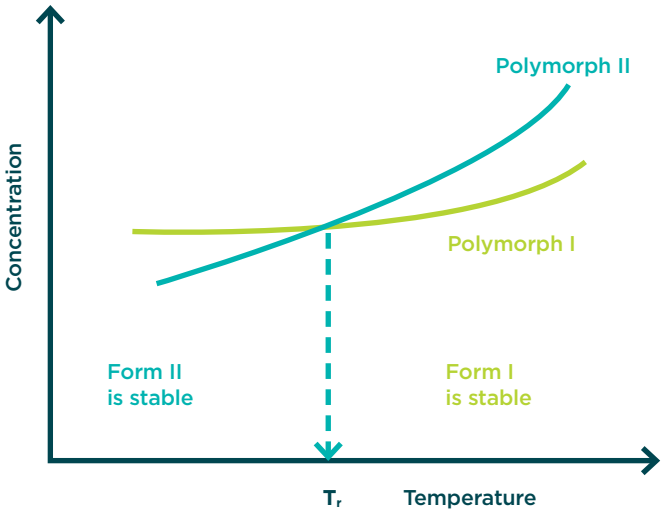
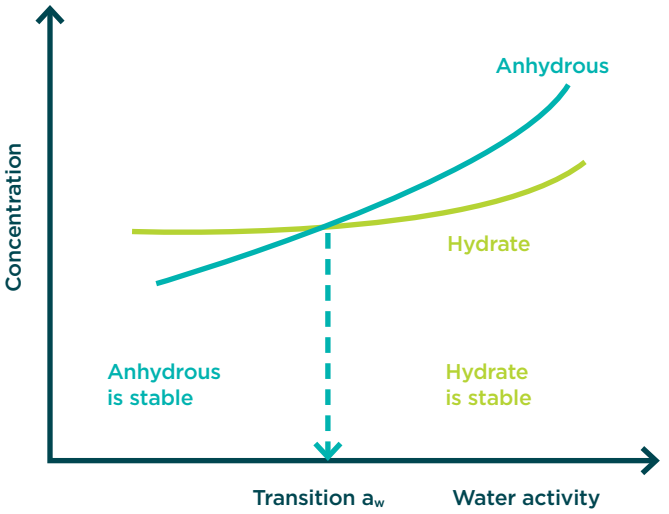
Enantiotropic/monotropic stability



Anhydrous/hydrate stability



The phase boundary and stability window for each polymorph was determined experimentally using competitive slurries of various water activity media. The anhydrous polymorph was found to be stable at a_w<80% and was selected for scale-up.

Competitive confidence.

Does your CMO use thorough methods to definitively assign thermodynamic stability?

Parallel delivery: Meeting clinical demand

Polymorphism is typically viewed as a complication during API development, but it can also present opportunities. The profile of the newly isolated polymorph spearheaded a new scale-up effort with confidence in its favorable stability.

However, the clinical trial underway required timely manufacture of the original polymorph to continue delivery to patients. In parallel with scaling up production of the new anhydrous form, the manufacturing team applied the results of the polymorph study to optimize production of the original polymorph. Accounting for the critical water activity in the manufacturing process yielded the monohydrate exclusively, thus enabling critical clinical studies to continue without interruption.

Confronting and resolving challenges in the early stages of API development is part of Cambrex's mission to improve the yield and purity of products. Rapid delivery of the original API while characterizing a new polymorph for optimal production is the kind of response to dual challenges that has built a strong record of client success.

Authors

Sarah Bethune, PhD
Sr. Director, Pharmaceutics & Formulation Development

Terry J. Harper
Director, Material Characterization

References

1. On the polymorphism of pharmaceuticals and other molecular crystals. II Applicability of Thermodynamic Rules. Burger, A. & Ramberger, R. Mikrochim Acta (1979) 72: 273-316.