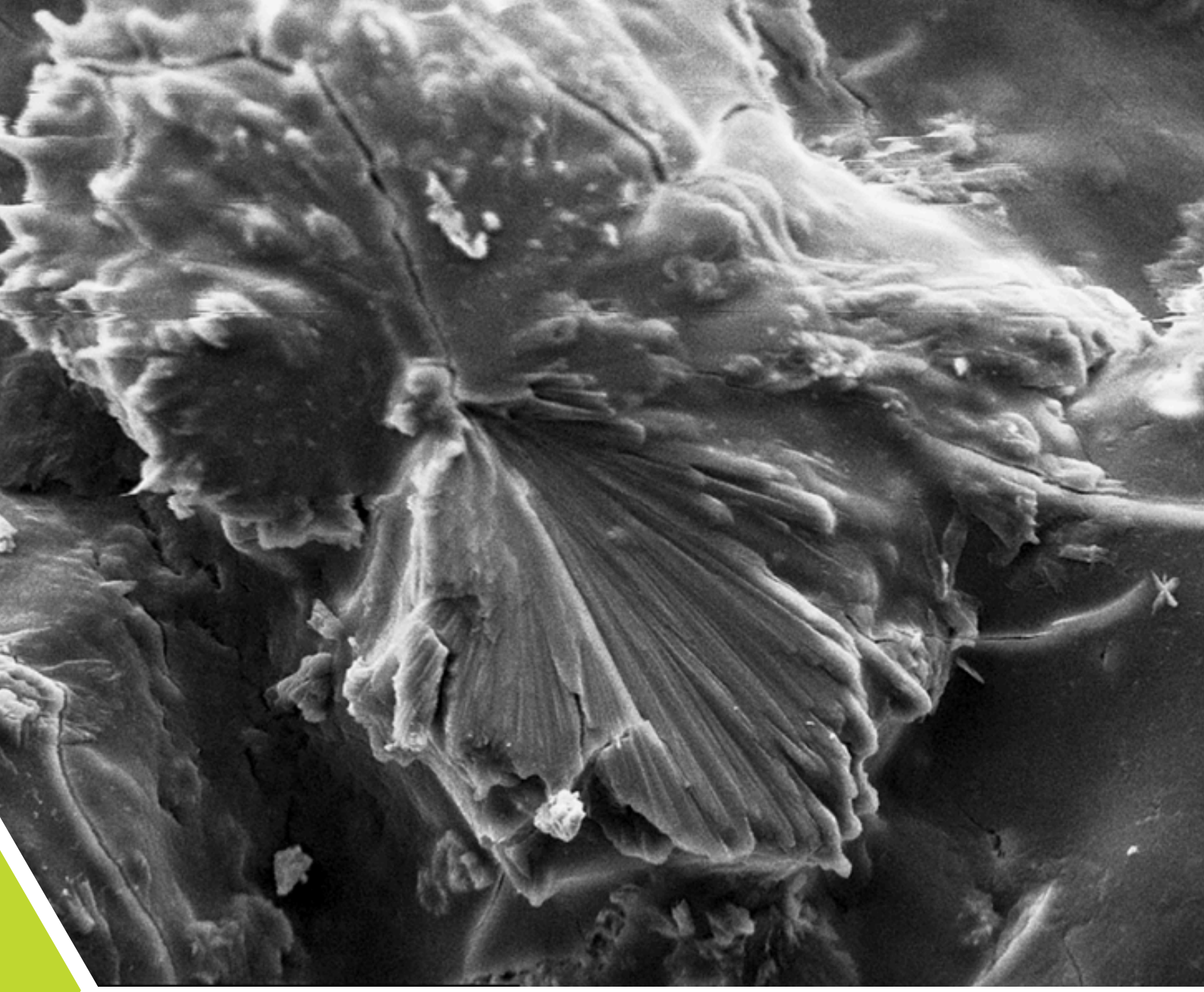


Crystal Clear Vigilance:

The Importance of Detecting Crystallization in Amorphous Solid Dispersions

White Paper

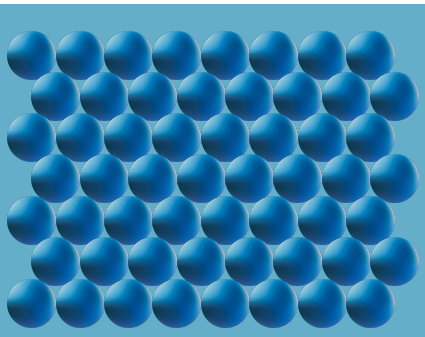
solvias

Executive Summary

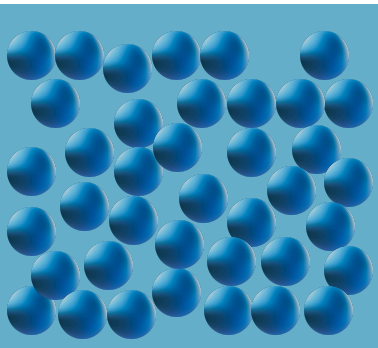
Amorphous Solid Dispersions (ASDs) are a transformative approach to improving bioavailability in drug formulations. In ASDs, the drug doesn't form well-defined crystals, but instead exists uniformly dispersed in the polymeric carrier in a sub-divided state, ideally molecularly dispersed. Due to this, it forms a disordered, non-crystalline state. This innovative technique holds great promise for enhancing drug solubility, ultimately leading to improved bioavailability. Despite their effectiveness in addressing therapeutic limitations, ASD formulation creates challenges, in particular the risk of crystallization and stability issues. Therefore, ASDs require knowledgeable testing to ensure consistent product quality and efficacy throughout its lifetime.

Crystallization Tendency: Critical Analysis for Stability

ASDs can crystallize on variable time scale due to the inherent thermodynamic instability of the amorphous state. The crystalline form is characterized by a well-ordered molecular structure, whereas the amorphous form lacks this order.



Crystalline



Amorphous

Crystallization poses a substantial risk to a drug's bioavailability and efficacy. Detecting crystallization in early development is essential to ensure the stability of formulations. ASDs are susceptible to physical changes during various stages, including preparation, storage, and dissolution. Even minimal crystalline zones can act as nuclei, destabilizing your product. Early API and polymer compatibility testing, coupled with the selection of appropriate polymers, is crucial to minimizing the risk of an unstable product. Quantifying amorphous content and assessing crystallization propensity are fundamental for maintaining pharmaceutical quality. The performance of ASDs relies on the Amorphous/Crystalline (A/C) ratio, emphasizing the importance of precise determination and analysis of crystallization kinetics for stability and consistent pharmacological responses. Depending on the specific ASD system under investigation, the most suitable technique can be chosen.

Dosing Precision and Bioavailability

Consistent dosage is a critical component for patient safety and thus of pharmaceutical formulation development. Recrystallization-induced particle growth leads to a decline in product quality, and impacts characteristics such as flowability, caking, and mechanical properties. These changes directly influence critical quality attributes (CQAs) in drug delivery systems, especially in Metered Dose Inhalers (MDIs) and Dry Powder Inhalers (DPIs). Developing analytical methods to detect crystallization not only maintains dosage reliability but also plays a vital role in upholding the overall quality and performance of pharmaceutical products. The presence of crystals can disrupt uniform drug delivery within a batch, posing challenges to maintaining bioavailability and dose efficacy. By conducting tests to identify and mitigate crystallization, pharmaceutical manufacturers can safeguard the reliability of each dose.

Crystallization in ASDs undermines their intended purpose of improving bioavailability. The recall of multiple lots of an immunosuppressive therapy, Cyclosporine, in November 2023 highlights the consequences of unexpected crystallization. Although not an ASD, this incident reinforced the potential of crystallization to cause both underdosing and overdosing, compromising patient safety and outcomes through uneven drug distribution. The transition from an amorphous to a crystalline state can decrease solubility, alter dissolution kinetics, and introduce unwanted variability in drug absorption. Undoubtedly, there is a need to address crystallization risk early to ensure that efforts towards enhancing drug effectiveness aligns with patient safety.

Recrystallization-induced particle growth leads to a decline in product quality.

The recall of multiple lots of Cyclosporine in 2023 highlights the consequences of unexpected crystallization.

Crystallization can cause both underdosing and overdosing, compromising patient safety and outcomes.

Regulatory Perspectives on Crystallization

Regulatory bodies are increasingly concerned by the impact of crystallization on ASD drug performance. Standards outlined by the United States Pharmacopeia (USP), including the recent addition to chapter 941 focusing on the "characterization of crystalline and partially crystalline solids by x-ray powder diffraction (XRPD)" and chapter 696 regarding "characterization of crystalline solids by microcalorimetry and solution calorimetry", highlight the demand for specific testing. The rationale of ASD composition can be discussed and the choice of polymer and optimal drug–polymer ratio identified.

The U.S. Food and Drug Administration (FDA) has emphasized the significance of exploring all potential solid-state forms of a drug substance. They recommend "that applicants investigate whether the drug substance in question can exist in polymorphic forms", referring to crystalline and amorphous forms, as well as solvate and hydrate forms. Thorough investigation into the conditions influencing their formation, conversion, or equilibration is also required. Adopting a generic approach for such studies carries risks; instances have arisen where inadequate methods for identifying crystallinity were utilized in regulatory filings, leading the FDA to request supplementary information for a more thorough evaluation.

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Trusted Solutions

Navigate Your Analytical Challenges with Solvias

Analytical approaches to quantify crystallinity in amorphous substances have their own advantages and limitations. Due to ASD's intentional design, lacking crystalline structures, traditional analytical methods that rely on long-range order like it is present in crystals prove to be less effective. Detection sensitivity becomes a hurdle as the crystalline content within ASDs is often minimal, demanding highly sensitive analytical approaches for accurate identification and quantification. The amorphous state's thermodynamic instability poses a risk of inducing crystallization during analysis, potentially leading to inaccurate results. The selection of analytical techniques is critical, demanding methods that effectively characterize without inducing sample changes. This requires expertise in both advanced analytics and analytical method validation.

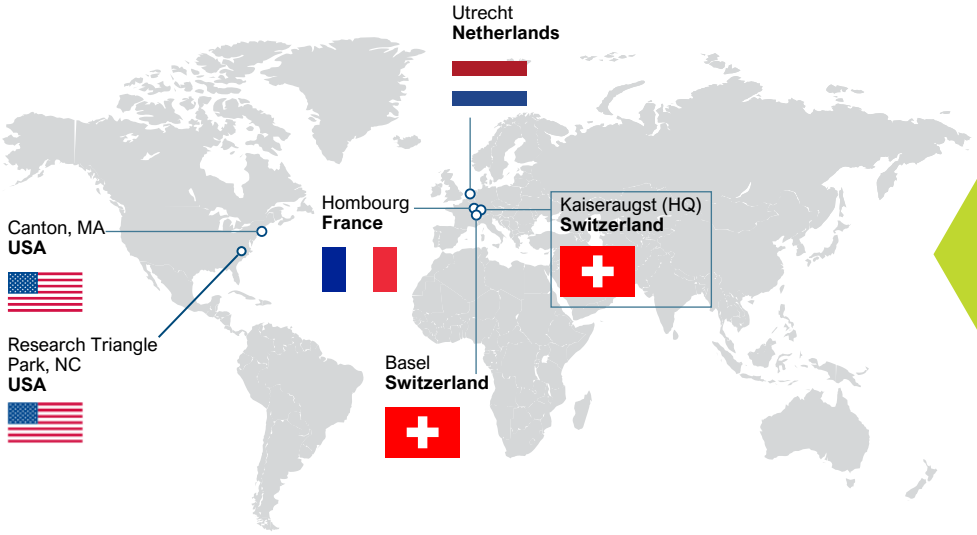
Solvias offers unparalleled analytical services with a proven track record in reliable and thorough detection of crystalline material in ASDs. We leverage cutting-edge technologies and a commitment to precision, to ensure tailored and precise assessments of unique formulations. Our experts also routinely perform long term and accelerated stability studies to ensure your molecule's integrity over time. Collaborating closely with our customers, we design analytical strategies that have consistently gained approval from regulatory authorities. As partners in quality, we enable pharmaceutical developers to navigate the regulatory landscape with confidence, knowing that their ASD formulations are consistently reliable and compliant with the highest industry standards.

Have Confidence in Your ASD Formulations

While ASDs offer revolutionary benefits in pharmaceuticals, the risk of crystallization demands vigilant, early detection and precision in formulation. The delicate interplay between drug substance and carrier on the molecular level highlights its complexity, impact on dosage reliability and overall quality. Regulatory scrutiny reinforces the need for thorough investigations. Partnering with Solvias ensures reliable detection of crystalline material, enabling developers to meet industry standards confidently.

Why partner with us?

- CDMO/CRO
- Founded in 1999
- 800+ team members
- 175+ PhD-level scientists
- GMP, GLP, ISO9001 certified
- 22.5K sqm of lab capacity
- 700+ customers worldwide
- 6 centers of excellence



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

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