TECHNICAL NOTE

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Novel Non-Crystalline Materials Analysis: New Strategies to De-risk Amorphous Material Formulation Development.

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The latest approaches for characterizing non-crystalline (amorphous) materials and determining physical stability under typical storage conditions.

Amorphous forms consist of disordered arrangements of molecules that do not possess a distinguishable crystal lattice. Different forms of a drug substance can have different chemical and physical properties, including melting point, chemical reactivity, apparent solubility, dissolution rate, optical and mechanical properties, vapor pressure, and density. These properties can have a direct effect on the ability to process and/or manufacture the drug substance and the drug product, as well as on drug product stability, dissolution, and bioavailability. Instability of non-crystalline materials is of particular concern to regulatory bodies within companies and national agencies.

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Introduction

Active pharmaceutical ingredients (APIs) with poor aqueous solubility continue to represent a significant challenge for oral delivery. Non-crystalline solid dispersions (ASDs) have attracted attention and commercial success in the pharmaceutical industry over the last two decades. ASDs can provide an increase in API dissolution rate that is orders of magnitude higher than that of the crystalline counterpart, thereby potentially increasing the therapeutic effect. ASDs can be made in a variety of ways including mechanical treatment (cryo-grinding), heating (quench cooling or hot-melt extrusion) and various solvent-based processes (rotary evaporation, lyophilization, precipitation, and spray-drying). Understanding whether a non-crystalline drug or dispersion is stable with respect to crystallization over the storage and/or shelf life of the drug product is critical for development.

There are many techniques that can be used to determine the structure and properties of a non-crystalline material. X-Ray Powder Diffraction (XRPD) and vibrational spectroscopy have been used to quantify the amount of crystalline component in non-crystalline formulations for stability prediction and in order to set specifications for manufacturing. Differential Scanning Calorimetry (DSC) can be used to determine the temperature dependence of heat capacity and to identify the glass transition temperature (Tg), where (on heating) a non-crystalline material changes from a state where it experience relaxation (glass) to an equilibrium high density liquid state without relaxation..

Characterization of non-crystalline phases through measurement of relaxation times, heat capacities, residual water/solvent contents, and other characteristics provides key information for prediction of timescales and temperature/humidity conditions under which crystallization will occur. If ASD instability is introduced by processing, such information can be used change processing steps in order to achieve a more stable ASD.

To address the challenges of developing non-crystalline materials and to provide tools to more effectively guide development, Triclinic Labs has developed a comprehensive approach to ASD materials characterization and analysis that can be broadly divided into three categories:

What techniques can be used to determine non-crystalline stability?

1.) **Total Diffraction Modelling allowing direct ranking of relative physical stabilities for non-crystalline solid forms.**

Non-crystalline solids can exist in a broad range of physical states depending on thermal history and the production processes used to make them. When manufacturing non-crystalline solids, a common challenge is how to select the appropriate production process and thermal annealing conditions to maximize physical stability. A new Total Diffraction Modelling approach using X-ray powder diffraction (XRPD) data allows determination of the inter-molecular order that characterizes non-crystalline solid forms.

Most people utilize Bragg peaks in XRPD patterns to determine the crystalline form of substances. William Henry and Lawrence Bragg (father and son) formulated their law of X-ray diffraction from crystals in 1913. At about the same time, Peter Debye, considered the founder of materials science, became interested in how X-rays could be used to probe molecular structure. He developed, among many other things, the Debye scattering equation, which can be used to predict the X-ray diffraction patterns of gases, liquids, and amorphous solids. Our Total Diffraction Modelling system utilizes the prediction of XRPD patterns by the Debye scattering equation with more-recently developed methods to model molecular structures. This new capability has revealed that the relative stabilities of non-crystalline states can be related to changes in observed local orders. More-stable states exhibit increased local packing densities and reduced residual order length scales compared to less-stable states.

2.) **Total Diffraction Modeling plus Chemometric Variance Analysis for formulation optimization.**

In addition to selection of production process and thermal annealing conditions, excipient selection and formulation processing can impact the physical stability of final products or drug product intermediates. At Triclinic Labs, we have found that the combination of Total Diffraction Modelling with chemometric variance analysis is a powerful tool for teasing out the influence of excipients and formulation on the local state of amorphous APIs and the potential for long-term stability issues. For example, the chemometric approach has been used to characterize the impact of residual water and solvents within formulated products.

3.) **Total Diffraction Modeling plus Thermal Analysis for prediction of physical stability of non-crystalline material**

Understanding the solid-state structure of non-crystalline solids at a molecular level is an ongoing endeavor. It is clear that the physical behavior of non-crystalline solids of a specific compound can vary considerably depending on the method used to produce them, suggesting the
underlying solid state structures are different. Of primary interest to the

pharmaceutical industry is whether a non-crystalline API or drug product will crystallize during the shelf life of the product. Traditionally, that issue has been approached as suggested by Hancock, Shamblin, and Zografi (*Pharm. Res*. **1995**, *12*, 799-806). They reported that "For all our materials the data indicate that for the molecular motions detected by DSC to be slowed to a point where they are insignificant over the normal lifetime of a pharmaceutical product it is necessary to cool to temperatures at least 50K below the glass transition temperature." The underlying assumption is that crystallization is governed solely by molecular mobility.

We have developed a model based on experimental data that includes not only molecular mobility but other physical characteristics that describe crystallization potential. Data essential to the model are afforded by XRPD and DSC analyses. The derived transformation model allows prediction of physical changes occurring within a non-crystalline solid form over a wide range of storage conditions. Physical properties captured by the model include, for example, phase separation, collapse, flow and crystallization. The model provides accurate predictions of the lifetimes of non-crystalline solids. Stability differences of non-crystalline solids manufactured by different processes can be clearly established. Details of the model and approach are currently proprietary but will be revealed in future publications.

Confidently guide your non-crystalline product development!

The major benefit of the new analytical approaches described above is a straight forward methodology that can be used to not only rank order the stabilities of non-crystalline forms produced by different production methods but also fine tune the formulated product. The results are robust enough that the ideal formulations and production methods to achieve enhanced physical stability can be identified without extensive aging studies. In fact, accelerated aging studies can actually modify the local order within a non-crystalline formulation and give non-representative results with respect to physical stability under different storage conditions. Those non-representative results can be misleading unless built within our more-comprehensive transformation model. (Figure 1)

The methodology above has been proven with exiting pharmaceutical non-crystalline formulations (e.g. hot melt extrusion, spray drying) and has allowed clients to guide their production and regulatory strategies.

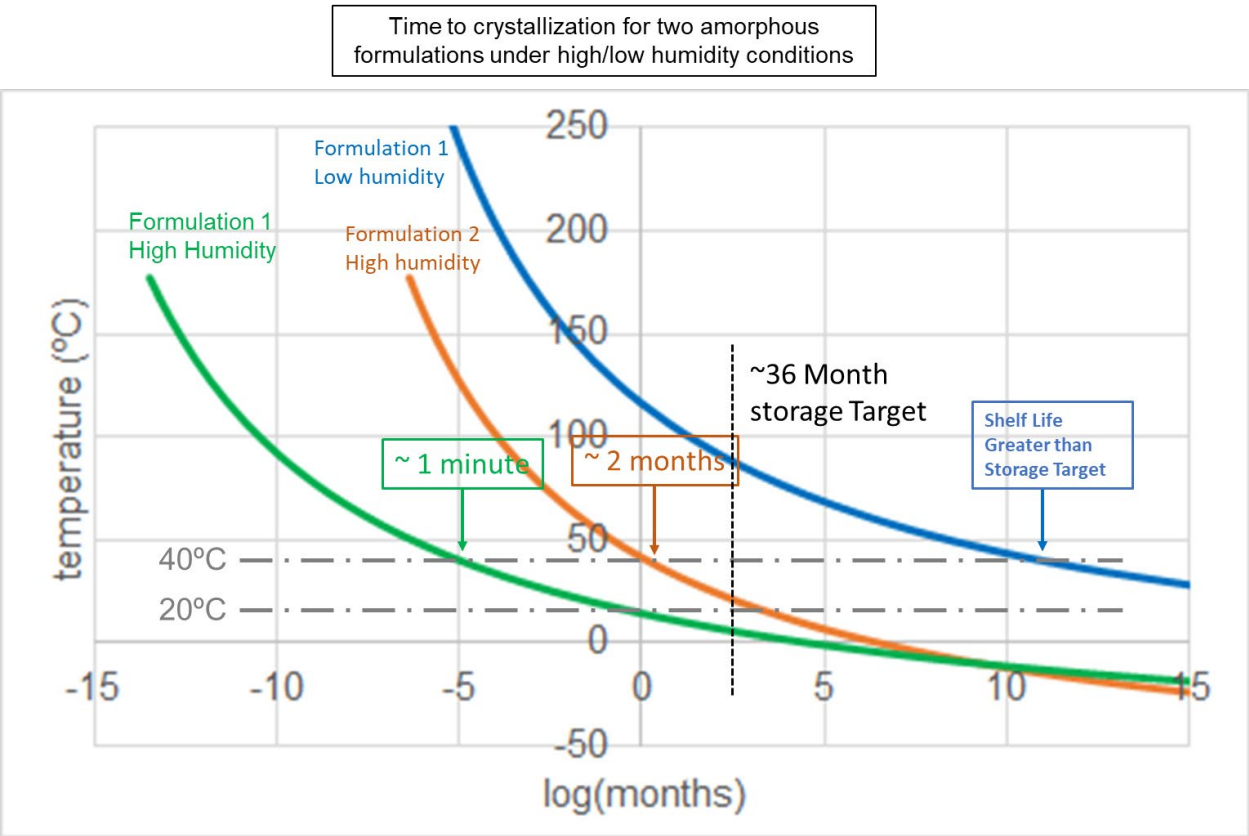

Figure 1. All amorphous formulations will eventually re-crystallize if there is an available crystalline form. The question is "how long will it take at any given storage temperature and will humidity impact the time line?". Both 40°C and 20°C storage conditions and a target storage time (about 3 years) are shown in the figure. Formulation 2 at high humidity does exceed the target storage time before crystallization is likely to occur provided that the temperature is below about 30°C. Once the temperature exceeds 30°C at high humidity, formulation 2 will re-crystallize during the target storage time. Formulation 1 at high humidity needs to be kept below 10°C in order to avoid crystallization in the target storage time. The stability of both formulations if kept dry far exceed the target storage times.

The approaches described herein were developed by the Computational Chemistry group at Triclinic Labs under the direction of Dr. Simon Bates.

About the Author

Dr. Simon Bates has over 30 years of experience working with X-ray and neutron diffraction characterization of the solid state. For the last 10 years, he has been working on characterization and molecular modeling of API and drug product pharmaceutical materials. Before moving to Triclinic Labs, Dr. Bates worked at SSCI as a Research Fellow and a Principal at Aptuit Consulting. His work on pharmaceutical systems has led to 28 peer reviewed publications and 10 patent applications.

Dr. Bates' expertise includes computational modeling of molecular systems, methods for IR Spectroscopy, Thermal Analysis, and Chemometrics and he has worked as a scientific expert in numerous patent litigation and patent prosecution cases. Dr. Bates has been an invited speaker at many scientific conferences.

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