**Uncovering the Invisible: Controlling Polymorphic Impurities in Active Pharmaceutical Ingredients**

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Polymorphism is a critical quality attribute of active pharmaceutical ingredients (APIs). While the identification and control of the primary polymorphic form are well established in the pharmaceutical industry, the detection and management of polymorphic impurities remain a significant challenge due to limitations in conventional analytical techniques. Trace levels of these impurities can persist undetected in pharmaceutical products, potentially altering the physicochemical properties and therapeutic performance of APIs. At Eurofins CDMO Alphora, we developed a sensitive and robust detection method capable of identifying and monitoring polymorphic impurities at trace levels. This technique has been successfully integrated into process development workflows, enabling real-time monitoring and control of polymorphic transformations. Coupled with a deeper understanding of polymorph conversion mechanisms, this approach has led to the design of more robust commercial manufacturing processes, ensuring consistent product quality by controlling previously undetectable polymorphic impurities.

**Purpose:**

Our client presented a critical issue in their pharmaceutical manufacturing process: although the synthetic route yielded chemically acceptable material, the final Active Pharmaceutical Ingredient (API) exhibited performance failures due to the presence of a trace-level polymorphic impurity. This impurity, undetectable by conventional solid-state characterization techniques such as Powder X-Ray Diffraction (PXRD), Differential Scanning Calorimetry (DSC), and even high-resolution Brockhouse X-ray Diffraction and Scattering sector Wiggler Low Energy beamline (BXDS-WLE). The polymorphic impurity exhibited a significantly higher melting point than the desired polymorph. As a result, it failed to melt during the drug product formulation process, leading to downstream product failures. The central challenge was to identify and eliminate this polymorphic impurity despite the absence of a reliable analytical method to detect its origin or presence in the bulk API.

**Methods:**

To assess the presence of the polymorphic impurity throughout the process, bulk API solids were placed between glass slides and melted using a hot-stage system (Mettler Toledo HS82) The melted samples were then examined using polarized light microscopy to observe residual unmelted solids indicative of the impurity. A semi-quantitative classification system was employed to estimate the relative abundance of the impurity. This approach enabled comparative analysis across multiple process stages, facilitating the identification of operations or conditions associated with increased or decreased levels of the polymorphic impurity. Multiple iterations of the process were run at a 10 g scale to assess the impacts of various conditions. Polymorph conversion studies were conducted with in-situ imaging (Technobis Crystalline) and ex-situ PXRD testing.

**Results:**

It was established that the impurity was present in the process from the first crystallization of the API. Polish filtration of the API solution demonstrated significant removal of the polymorphic impurity which was insoluble at elevated temperatures. Pore size during this polish filtration was a significant attribute, as the impurity particles were very fine (<1 µm). The filtered solution was observed to form solids on the reactor above the solvent level. These solids were enriched in the polymorphic impurity. Pre-treatment of the reactor by reflexing solvent helped to reduce the formation of these solids, but they could not be eliminated. Seeding the filtered solution with the desired polymorph facilitated controlled crystallization of the API but did not mitigate impurity already present in solution. It was observed that the polymorphic impurity was increasing in cases where the API was in contact with the solvent at ambient temperatures. A study was conducted to investigate the interconversion between polymorphs at various temperatures. The impurity was found to be thermodynamically favored at higher temperatures, while conversion to the desired polymorph occurred slowly at 5 °C and more rapidly at −5 °C. This enantiotropic relationship was complicated by the impurity’s low solubility, even at elevated temperatures, which limited the rate of transformation. With this finding it was possible to convert the impurity to the desired polymorph at low temperatures. The conversion could not be implemented directly after the API crystallization as the chemical impurities present in the solution were isolated with the API at low temperatures. To resolve this issue, the API solids were isolated by filtration, then slurried in neat solvent at -5°C before final isolation. This process proved to be successful by demonstrating isolation of the API with acceptable drug product performance at a 500 g scale. There were some traces of the impurity that formed during the filtration and drying process, but the levels were acceptable for use in the final drug product.

**Conclusions:**

Observations of the trace polymorphic impurities using a non-traditional method allowed for the observation and tracking of the polymorphic impurity. This allowed for identification of conditions that were causing the polymorphic impurity to increase in the API manufacturing process. The temperature dependence of interconversion of the polymorphs was further explored, and lead to condition that was favorable towards the desired polymorph. The findings underscore the importance of integrating solid-state characterization with process development to resolve polymorphic challenges, particularly when analytical detection is limited. The implemented control strategy provided a scalable and scientifically sound solution for ensuring the quality of the API.

**Keywords:**

Polymorphism, API, Solid-State, Process Development