Quality-by-Design Approach to Polymorphic Crystallization Development of Pyrazinamide

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Pyrazinamide is a frontline anti-tuberculosis drug and is on the World Health Organization (WHO) model list of essential medicines. It has four polymorphic forms with stability order of $\alpha > \delta > \gamma > \beta$ at ambient conditions. The stable α-form is the commercially available form. However, needle-shaped α-form easily forms a mesh-like-structure during filtration leading to inefficient filtration and long drying time. α-form also exhibits poor flowability due to its needle morphology. To avoid these problems, this study attempts to isolate one of the metastable forms which has a better morphology (plate for δ-form or prismatic for γ-form) using Quality-by-Design approach. In this talk, solvent screening results and design space development which ensures consistent production of δ-form will be presented. The robustness of the design space in the presence of various impurities will also be discussed.