To Solvate or Not To Solvate? – A Crystallographic Evaluation of the Isostructural Solvated and Non-Solvated Crystal Forms of an Active Pharmaceutical Ingredient

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Active Pharmaceutical Ingredients (APIs) are typically developed as a solid dosage form, which can exist as a wide range of crystalline solids such as polymorphs, solvates, salts and co-crystals. Crystalline solid form screening and characterization of APIs are an essential part of the development of new drug substances since the physicochemical properties of the drug molecules are closely related to the crystal packing and intermolecular interactions of a particular form in the solid-state. This work illustrates an example of the detailed crystalline form screening studies of a pharmaceutically active compound BMS-817399 using various organic solvent systems. From crystallization trials, a series of isostructural hydrated channel solvate forms were identified. While maintaining the framework based on API and water molecules, the crystal structures of these forms feature unique solvent channels whose sizes are dictated by the volume of the solvent molecule used in the crystallization. Despite the influence to the channel volume, the presence of solvents within the cavity was determined to be inconsequential to the physical stability of the form. Moreover, solid state characterization studies revealed all forms undergo dehydration or desolvation to result in the same neat phase whose structure maintains many similarities of the hydrate/solvate precursors. The presentation will discuss how the crystallographic analysis supported the selection of a physically and chemically stable crystalline form to enable robust and reproducible scale-up production of an API in support of the drug development.