A multi-technique approach for gaining insight into 3APS solvates

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Exploring various solid states in crystalline molecular solids is essential for assessing their diverse physical and chemical properties. This often leads to the formation of multicomponent crystals, which are significant in drug design and material chemistry. In pharmaceuticals, for example, examining solvate-solid forms is vital for understanding the stability of formulations under various storage conditions or the tendency of an API to incorporate residual solvents during synthesis or crystallization. [1] This requires a detailed analysis of the factors influencing solvate formation and stability, considering their structural characteristics and environmental conditions. To enhance our understanding of the solid form landscape of 3,3'-diaminophenyl sulfone (3APS) [2], we investigated a series of its solvates in both mono and polycrystalline forms. Our interest in the solid-state investigation of 3APS arises from its close structural similarity to dapsone (4,4'-diaminophenyl sulfone), an antibiotic which displays a wide array of solid forms, including various isostructural solvates. [3] Specifically, for 3APS, we identified a monoclinic phase solvated with acetonitrile (3APS•ACN_m) and two solvates with dioxane (3APS•DX_m and 3APS•DX_o). The structural characteristics, including the strength of intermolecular interactions, the tendency to incorporate (selectively, as well) these solvents, and the stability during desolvation, were examined using a combined experimental and computational method. In particular, structural analyses were performed using Single Crystal X-ray Diffraction (SCXRD), Powder X-ray Diffraction (PXRD), and in silico methods. We assessed the stability of the solvate phases through Variable-Temperature Single Crystal X-ray Diffraction (VT-SCXRD) and thermal analysis (DSC). (Figure 1) Additionally, quantitative phase analysis using PXRD allowed us to determine the composition percentages of solid forms with varying degrees of solvation. Our findings were then compared with previously documented dapsone solvates.

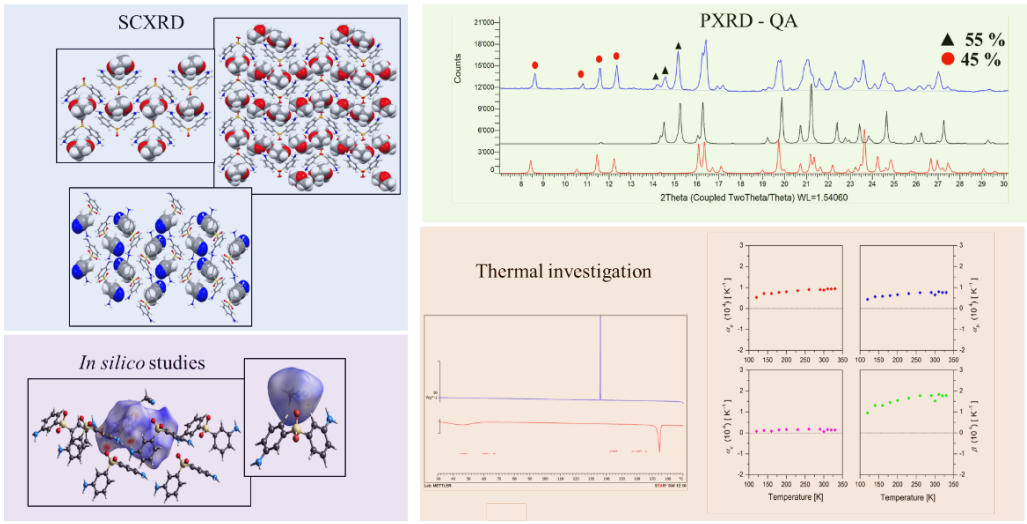

Figure 1. Representation of the multi-technique approach used in this work.

[1] ICH guideline Q3C (R6) on impurities: guideline forresidual solvents, Committee for Human Medicinal Products, 2019, European Medicines Agency.

[2] P. Paoli, M. Lippi, S. Milazzo, P. Rossi, J. Ceccharelli, L. Chelazzi, A. Ienco, L. Conti, Cryst. Growth Des. **2022**, 12, 7176-7186.

[3] D.E. Braun, T. Gelbrich, U. J. Griesser, CrystEngComm **2019**, 21, 5533-5534.