Dapsone cocrystals through experiment and theory: polymorphism, hydrate formation and different stoichiometric ratios rationalised

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Controlling the physical properties of solid forms for Active Pharmaceutical Ingredients (APIs) through cocrystallisation is an important step in drug product development [1]. However, it is difficult to know a priori which coformers will form cocrystals with a given compound. Furthermore, cocrystals may exist with different coformer ratios, can exhibit different packing arrangements with the same composition (polymorphism) and may also incorporate a solvent (solvates) or water (hydrates). Several computational [2,3] and experimental methods [4] have been developed to estimate cocrystallisation and the synthesis of cocrystals, although with little consistency in the application of the proposed experimental protocols. Thus, the current state-of-the-art cocrystal discovery remains a time-consuming process.

The cocrystal solid form landscapes of dapsone with five coformers (2,2’-bipyridine, 4,4’-bipyridine, caffeine, ε-caprolactam and caffeine) were systematically elucidated, using cutting-edge experimental and computational approaches. The computationally generated (co)crystal energy landscapes had the experimental forms (API, coformers and cocrystals) as lowest energy structures. Both, the experimental and computational screen, reproduced the literature known cocrystal forms [5,6,7] and lead to novel multicomponent solid-state forms. For dapsone/2,2’-bipyridine the first cocrystals were found. Cocrystal polymorphism was confirmed for the combinations of dapsone with 2,2’-bipyridine, ε-caprolactam and flavone. Furthermore, the dapsone/flavone system was found to form a non-stoichiometric hydrate in molar ratios ranging from 1:1:0 to 1:1:0.66 (dapsone:flavone:water).

Finally, for dapsone/4,4’-bipyridine and dapsone/caffeine different cocrystal stoichiometries were rationalized. The experimental structures of the novel cocrystals were solved form PXRD data. Solution calorimetry and lattice energy calculations unravelled the thermodynamic driving force for cocrystal formation. The obtained materials were thoroughly characterised with advanced analytical techniques (thermal analysis, isothermal calorimetry, X-ray diffraction, spectroscopy, moisture sorption, solubility) in order to understand the dapsone cocrystal forms.

This study demonstrates the importance of applying complimentary computational and analytical techniques for understanding cocrystal formation, cocrystal stability and the correlation between structural features and pharmaceutical applicability.