Streamlining Pharmaceutical Molecule Cocrystallization

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Abstract: Developing drug products requires precise control over the physical properties of active pharmaceutical ingredients (APIs). Utilizing multi-component phase systems, like cocrystals, offers a means to enhance critical physicochemical properties of APIs, such as stability and solubility [1,2]. However, predicting which coformers will form cocrystals with a specific compound is challenging. Additionally, cocrystals can exhibit polymorphism, existing in different ratios of API:coformer, and may contain solvents (solvates) or water (hydrates). Both computational [3,4] and experimental techniques [5] have been developed to estimate cocrystal formation and synthesize cocrystals. However, there is limited consistency in the application of the proposed protocols, especially as numerous methods can be employed to produce cocrystals. Common approaches include solvent-based methods, neat and liquid-assisted grinding, as well as contact preparation, hot-melt extrusion, freeze-drying, spray drying techniques, etc., all of which have been used successfully. Consequently, the current state-of-the-art cocrystal discovery remains a time-consuming process. This talk aims to provide new insights into cocrystal screening and the solid form landscapes of cocrystals of model pharmaceuticals.

Metronidazole cocrystals were employed for evaluating commonly used virtual cocrystal screening methods, including assessments of molecular complementarity, multi-component hydrogen bond propensity, and molecular electrostatic potentials. This allowed for the identification of both the strengths and limitations inherent in the readily available virtual tools [6]. Carbamazepine, acetylsalicylic acid, and acetaminophen were selected as test compounds to assess crystal structure prediction (CSP) for cocrystal screening against a range of potential coformers, to ascertain the most stable cocrystal form, and to evaluate the feasibility of cocrystallization [4]. Finally, the cocrystal landscapes of dapsone [7] were systematically elucidated using state-of-the-art approaches. The combined experimental and computational screening led to the discovery of novel multicomponent solid-state forms and provided insights into their stability order.

Overall, the significance of employing a combination of computational and analytical techniques to gain a deeper understanding of cocrystal formation and cocrystal stability will be discussed, allowing finally to assess the potential of specific cocrystals for the use in pharmaceutical products.

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