Impact of Coformer Substitution on the Formation and Polymorphism of Pharmaceutical Cocrystals

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Cocrystallization is a widely applied strategy to enhance the physicochemical properties of active pharmaceutical ingredients (APIs), with some pharmaceutical cocrystals already approved and commercialized [1]. However, selecting suitable coformers remains a major challenge due to the complexity of intermolecular interactions and the limitations of current virtual screening methods. This study investigates the cocrystallization behavior of two model APIs, metronidazole (MNZ) and griseofulvin (GRF), using structurally related coformers to better understand the impact of coformer substitution on cocrystal formation. Additionally, the selected combinations enabled the study of temperature-dependent phase transformations in three cocrystal polymorph systems.

Building on previous work with MNZ and gallic and gentisic acids [2], this presentation expands the screening to include various dihydroxybenzoic acids, gallates, and benzenetriols, resulting in the discovery of four new cocrystals and polymorphic forms of one of these cocrystal systems. For GRF, a range of phenolic coformers were explored [3], leading to the discovery of three new cocrystals. Substituent effects are evident for both systems. In case of GRF, carbon substituents at *ortho* or *meta* positions hinders cocrystallization, while chlorine substituents, especially at *ortho* and *para* positions, promotes it through electron-withdrawing effects that enhanced hydrogen bonding interactions.

Experimental screening methods, including liquid-assisted grinding (LAG), slurry-mediated transformations, and microscopic contact preparation, were complemented by virtual screening tools to assess their predictive power. Virtual methods, such as molecular complementarity [4], multi-component hydrogen-bond propensity [5], and molecular electrostatic potential analysis [5], suggested possible coformers but showed limited predictive consistency. In contrast, crystal structure prediction [7] emerged as the most reliable tool, successfully identifying all observed cocrystal combinations and providing valuable structural insights. Experimental characterization techniques, including X-ray diffraction, infrared spectroscopy, and thermal analyses (DSC and TGA), alongside pairwise intermolecular energy calculations, further elucidated key interaction motifs responsible for cocrystal stability.

These findings highlight the critical role of integrated experimental and computational approaches in advancing rational cocrystal design, understanding polymorphic transformations in cocrystals, and improving coformer selection strategies.

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