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# Effect of Functional Group Position in Co-Formers and Solvent on Cocrystal Polymorphism/Stoichiomorphism: A Case Study

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**Abstract :** In recent years, there has been an increase in the number of reports on cocrystal polymorphism and stoichiomorphism. However, the research on the factors that influence these phenomena is limited. Herein, picolinamide (PAM), nicotinamide (NAM), and isonicotinamide (INA) were selected as co-formers to form multicomponent solids with 4-chloro-3-sulfamoylbenzoic acid (CSBA). Six new cocrystal forms of CSBA were discovered, and their crystal structures were determined. It was found that PAM and NAM can only form one cocrystal with CSBA, while INA can form up to four cocrystals, including both cocrystal polymorphism and stoichiomorphism. Molecular electrostatic potential analysis and crystal structure analysis showed that the functional group position of PAM limited the diversity of cocrystal synthons, while the lattice energy limited the diversity of cocrystal synthons when NAM acted as a co-former. Only INA was not subject to these restrictions when forming cocrystals. Finally, the influence of solvents on cocrystals was illustrated by determining the ternary phase diagrams. The mechanism of two similar solvents, ethyl acetate, and acetone, controlling the crystallization of cocrystal polymorphism was analyzed by molecular simulations.

**Keywords :** cocrystal polymorphism, cocrystal stoichiomorphism, phase diagram, molecular simulation
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