Understanding of the cocrystal formation by anti-solvent crystallization process

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Co-crystals are being intensively studied nowadays primarily due to the potential of improving pharmaceutical properties including the dissolution behavior for BCS class-II drug substances such as indomethacin (IMC). Recently, we discovered a new method using anti-solvent addition method to prepare indomethacin-saccharin (IMC-SAC) co-crystals. In this study, we investigated the solubility behavior of IMC-SAC cocrystal in methanol-water cosolvent and the phase solubility diagram (PSD) of cocrystal was determined to comprehend cocrystallization. The criterion for pure IMC-SAC cocrystals formation was proposed and verified through supporting experiments performed with different concentrations. The anti-solvent co-crystallization process of IMC-SAC was monitored using an in-line NIRS and spectra were analyzed by a principal component analysis (PCA) method. By integrating the PCA results with off-line characterization data, it was confirmed that there are distinct difference in the cocrystallization pathways.