Role of lattice disorder in the water mediated dissociation of pharmaceutical cocrystal systems.

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Purpose. Significant progress has been made in the design and synthesis of pharmaceutical cocrystals. However, there is limited work on the stability of cocrystals in the drug product environment. The formulation of cocrystals as tablets necessitates the use of excipients and entails several processing steps. It is therefore necessary to evaluate the potential impact of both API-excipient interactions and processing conditions on cocrystal stability.

Methods. Differential scanning calorimetry, thermogravimetric analysis and powder X-ray diffractometry were used for comprehensive characterization of the starting materials as well as dissociation products. Lattice disorder was quantified using powder X-ray diffractometry (measured as peak broadening), and gravimetric water sorption.

Results. Under pharmaceutically relevant processing and storage conditions, the model cocrystal system (caffeine-oxalic acid, CAFOXA) dissociated. The cocrystal-excipient (dicalcium phosphate, DCPA) binary mixtures were milled for short time durations (≤ 2 minutes) and stored at RT/ 75% RH. Even a very short milling time (10 seconds) resulted in a measurable disorder and an attendant tendency of the solid to sorb water. The milling-induced disorder is expected to be more pronounced on the surface of the particles. The proposed mechanism of dissociation is dissolution of CAFOXA and DCPA in the sorbed aqueous layer, followed by proton transfer from coformer (oxalic acid) to DCPA, and formation of caffeine hydrate and calcium oxalate. In addition to the impact of milling, the influence of co-processing on cocrystal stability was studied using two sets of cocrystal-excipient mixtures. In physical mixtures of individually milled components (i.e. milling followed by mixing), much less dissociation was observed than in co-milled mixtures (i.e. mixing and then milling). The enhanced reactivity was attributed to the combined effects of surface disorder and intimate mixing. Even at low levels of disorder, a pronounced cocrystal dissociation was observed, thereby indicating the disproportionate impact that even short milling times have on chemical reactivity. Suitable experimental controls revealed high cocrystal stability in the absence of even one of the three contributing factors – namely, water, excipient and lattice disorder.

Conclusion. While cocrystals provide an avenue to modify solid state and biopharmaceutical properties, formulating them into stable solid dosage forms can be challenging. Through this work, we were able to mechanistically understand the stability of cocrystals in a drug product environment. The design of a robust cocrystal dosage form warrants a comprehensive understanding of the impact of excipients, processing as well as storage conditions.

References.

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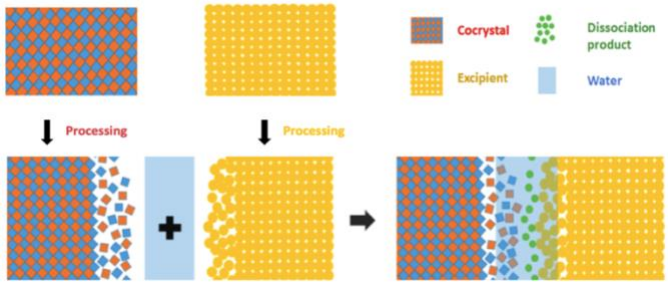

Schematic representation of the impact of lattice disorder on the water mediated dissociation of cocrystals.