

The role of lattice disorder in water mediated dissociation of cocrystals

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Our objective is to mechanistically understand the implications of processing induced lattice disorder on the stability of pharmaceutical cocrystal systems. Caffeine-oxalic acid was chosen to be the model cocrystal and the excipient selected was dicalcium phosphate anhydrate (DCPA). Lattice disorder was induced through cryo-milling for specified time durations. The extent of lattice disorder was characterized using X-ray peak broadening and gravimetric water sorption. In order to understand the impact of lattice disorder on cocrystal stability, binary mixtures of the cocrystal and excipient (1:1, w/w) were prepared under two conditions: (i) the two components were milled separately and mixed (referred to as physical mixture), and (ii) the two components were mixed first and then milled (referred to as comilled mixture). Both sets of binary mixtures were stored at RT/ 75% RH. The cocrystal dissociation was monitored by powder X-ray diffractometry (PXRD).

Caffeine-oxalic acid is a robust cocrystal which was observed to be stable even at elevated humidity conditions (RT/ 98% RH). However, in presence of DCPA (physical and comilled mixtures), the cocrystals dissociated to form caffeine hydrate, multiple hydrate forms of calcium oxalate and phosphoric acid. In contrast, the control samples of unmilled binary mixtures were stable at RT/ 75% RH for four weeks, thereby highlighting the role of lattice disorder in accelerating cocrystal dissociation. *In situ* PXRD analysis of binary mixtures, stored at RT/ 75% RH, revealed an increase in the extent of dissociation with an increase in milling induced lattice disorder. The dissociation was observed to be higher for the comilled mixtures compared to the physical mixtures, thereby highlighting the role of inter-particulate contact at the cocrystal-excipient interface in accelerating the cocrystal dissociation.

Through this work, we attempt to highlight a critical challenge in formulation of cocrystals i.e. compromised cocrystal stability when processed with excipients. Even seemingly robust cocrystals (caffeine-oxalic acid cocrystals in this case) can undergo dissociation when formulated with “inert” excipients, under pharmaceutically relevant processing and storage conditions. A fundamental understanding of the factors promoting cocrystal dissociation would aid rational selection of excipients and also enable optimization of processing and storage conditions. This, in turn, would enable the development of robust cocrystal dosage forms.

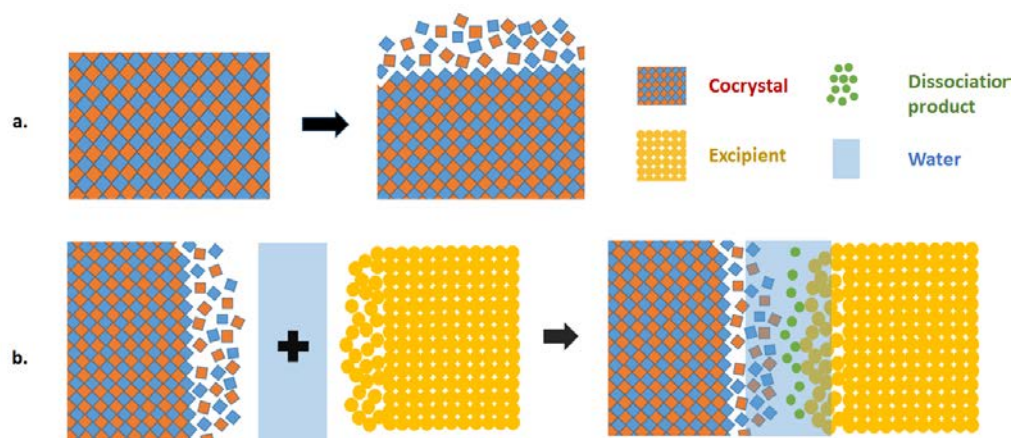


Figure 1: Schematic for (a) introduction of lattice disorder in crystals during pharmaceutical processing, and (b) the impact of lattice disorder on the water mediated dissociation of cocrystals in the presence of excipients.

References

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