Real-time monitoring of mechanochemical formation of pharmaceutical cocrystals using synchrotron X-ray diffraction

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The synthesis of cocrystals composed of active pharmaceutical ingredients (APIs) is a rapidly growing research field, and one of the central topics of modern pharmaceutical materials science.[1] A number of different approaches have been developed to screen and synthesize such pharmaceutical cocrystals, including solution cocrystallization,[2] accelerated aging,[3] and mechanochemistry.[4] The latter has not only proven to be an extremely efficient route for cocrystal discovery, but is also a powerful method for bulk synthesis of solid phases that are metastable or even impossible to attain by other means.[5] Furthermore, mechanochemistry enables the synthesis and screening of pharmaceutical cocrystals regardless of the solubility of the individual components.[6] However, the mechanisms of mechanochemical cocrystallization remain poorly understood: the first technique for real-time, *in situ* monitoring of ball milling mechanochemistry was introduced very recently and applied in the evaluation of the reaction mechanisms of microporous framework formation.[5,7]

Here, we describe the results of real-time X-ray powder diffraction monitoring of mechanochemical cocrystallization using a novel, high-resolution setup at the X04SA beamline (SLS, Villigen).[8] The high data quality enabled us to conduct the first detailed analysis of the appearance of metastable polymorphs and stoichiometric variations in a library of related cocrystals. New cocrystal and polymorphic crystal structures were solved using *ab initio* methods and verified using complementary methods.

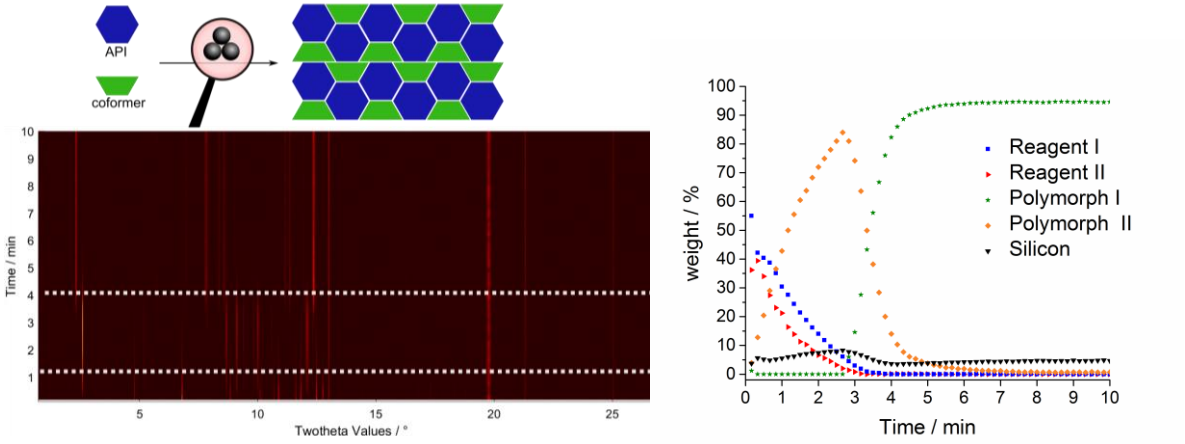

Figure 1: *In situ* monitoring of the formation of different cocrystal phases, measured at the X04SA beamline at SLS, Villigen.

Keywords: cocrystals, mechanochemistry, *in situ* X-ray powder diffraction

[1] Tan *et al.*, *Chem. Commun.*, **2016**, *52*, 7760; [2] Rodríguez-Hornedo *et al.*, *Mol. Pharm.*, **2006**, 3(3), 362; [3] Huskić *et al. Chem. Comm.*, **2016**, 52, 5120; [4] Friščić, Jones *Cryst. Growth Des.*, **2009**, *9*, 1621; [5] Katsenis *et al.*, *Nature Comm.*, **2015**, *6*:6662; [6] Karki *et al.*, *CrystEngComm.*, **2009**, *11*, 470; [7] Friščić *et al.*, *Nat. Chem.*, **2013**, *5*, 66; [8] Ban *et al.*, *Anal. Chem.*, **2017**, *89*, 13176;