

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

Luzia S. Germann,<sup>a\*</sup> Mihails Arhangeliskis,<sup>b</sup> Robin Stein,<sup>b</sup> Leigh Loots,<sup>b,c</sup> Cristina Mottillo,<sup>b</sup> Joseph Marrett,<sup>b</sup> Jean-Louis Do,<sup>b</sup> Nicola Casati,<sup>d</sup> Tomislav Friščić<sup>b</sup> and Robert E. Dinnebier<sup>a</sup>

<sup>a</sup>Max-Planck-Institute for Solid State Research, 70569 Stuttgart, Germany. <sup>b</sup>McGill University, Montreal, Qc, Canada. <sup>c</sup>Stellenbosch University, Stellenbosch, South Africa, <sup>d</sup>Swiss Light Source, Paul Scherrer Institute, CH-5232 Villigen, Switzerland Email: [l.germann@fkf.mpg.de](mailto:l.germann@fkf.mpg.de)

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.

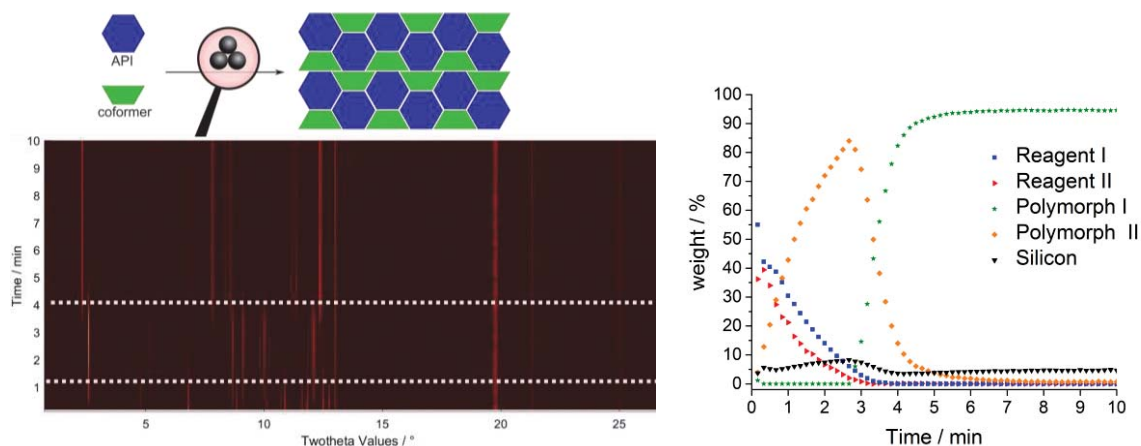


Figure 1: *In situ* monitoring of the formation of different cocrystal phases, measured at the X04SA beamline at SLS, Villigen.

**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;