Poster

On the Mechanism of Cocrystal Formation by Mechanochemical Reaction via Low Melting Eutectic: A Time-Resolved In Situ Monitoring Investigation

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Cocrystals are multicomponent crystalline molecular materials made of different chemical entities that crystallize within the same crystal structure held together by intermolecular noncovalent interactions. Cocrystallisation has been largely investigated in the modern literature since the novel intermolecular networks established between the molecular species involved can tune their ultimate physical properties (*e.g.,* solubility, volatility, melting point) of the single molecular entities when in their pure form. They are typically obtained in bulk through mechanochemical protocols. Whereas the macroscopic aspects of grinding are becoming clear, the fundamental principles that underlie mechanochemical cocrystallisation at the microscopic level remain poorly understood and the description of the step-by-step mechanism of the overall cocrystallisation process are often neglected [1]. In the present communication, a class of cocrystals between two solid coformers that proceeds through the formation of a metastable low melting binary eutectic phase is reported. The overall cocrystallisation process has been monitored by Time Resolved In situ (TRIS)-XRPD with a customized ball milling setup and low-energy synchrotron beam [2]. Although the reaction is completed in less than 5 seconds the metastable eutectic phase is clearly observed thanks to the combination of fast data acquisition time (500 ms) and microstructure analysis performed through the use of ad-hoc modified line profile functions [3]. Complementary TRIS-Raman Spectroscopy was used to finely described the first steps of the cocrystal growth from the eutectic phase for crystal sizes below the limit of detection of XPRD within the first seconds of the reaction. Thermal analysis (DSC, and Hot stage microscopy) completed the overall description of the mechanochemical protocol under investigation, even providing the binary phase diagram of the systems.

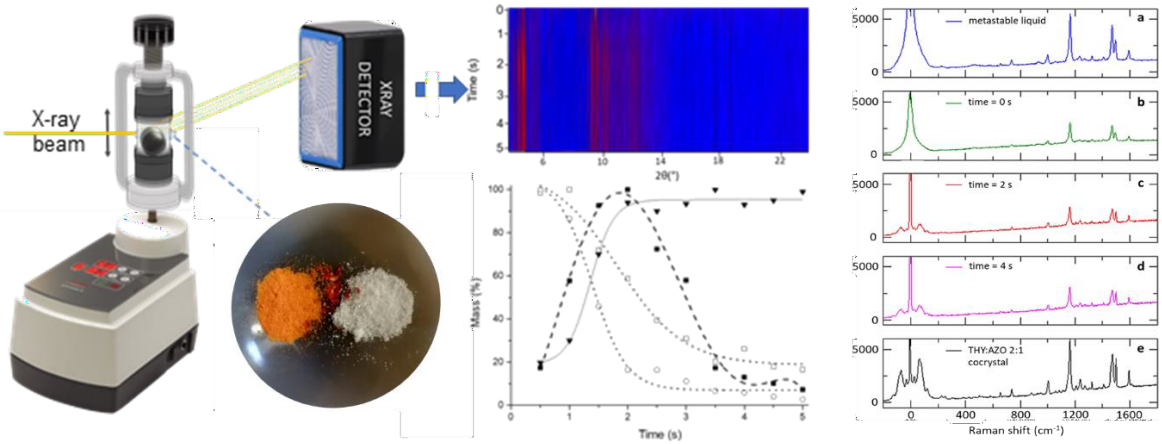

Figure 1. Schematic representation of the TRIS-XRPD experimental setup with an insight of the Rietveld Refinement data analysis and TRIS-Raman Spectroscopy study.

[1] Lampronti, G. I.; Michalchuk, A. A. L.; Mazzeo, P. P.; Belenguer, A. M.; Sanders, J. K. M.; Bacchi, A.; Emmerling, F. *Nat. Commun.* **2021**, *12* (1), 1–9.

[2] Mazzeo, P. P. M.; Prencipe, M.; Feiler, T.; Emmerling, F.; Bacchi, A. *Cryst. Growth Des* **2022**, *22* (7), 4260–4267.

[3] Mazzeo, P. P.; Lampronti, G. I.; Michalchuk, A. A. L.; Belenguer, A. M.; Bacchi, A.; Emmerling, F. *Faraday Discuss.* **2023**, *241*, 289–305.