

**MS25-2-2 Structural Study of Organic Cocrystals Using 3D Electron Diffraction**  
**#MS25-2-2**

V.E. Agbemeh <sup>1</sup>, D. Sonaglioni <sup>2</sup>, I. Andrusenko <sup>2</sup>, E. Husanu <sup>2</sup>, M. Gemmi <sup>2</sup>

<sup>1</sup>Istituto Italiano Tecnologia (IIT) & University of Parma - Pontedera (Italy), <sup>2</sup>Istituto Italiano Tecnologia (IIT) & University of Pisa - Pontedera (Italy)

**Abstract**

One of the main limitations on the effectiveness of Active Pharmaceutical Ingredients (APIs) is their low solubility in water resulting in low oral bioavailability. To improve this, one of the proposed solution is cocrystallization with compounds known as Generally Recognized As Safe (GRAS) <sup>1</sup>. APIs cocrystals are composed of two molecules in the same lattice bonded by noncovalent bonds<sup>2</sup>.

This work addresses the structural study of lamotrigine and oxyresveratrol cocrystals formed by mechanosynthesis. Ethyl maltol, isonicotinamide, and nicotinamide were used as GRAS cofomers.

Mechanosynthesis often leads to the formation of crystals too small for single-crystal X-ray diffraction (SCXRD) hence finding structural information is an extremely hard task.

3D electron diffraction is the most suitable to solve this task with some unique advantages in the analysis of small crystals. In 3D ED single crystal diffraction data of structure solution quality can be collected on grains as small as few hundreds of nanometres<sup>3,4,5</sup>. Thanks to a new generation of single electron detectors this kind of experiment can be performed in low dose, therefore beam sensitive crystals like organics do not amorphized during the duration of the experiment. With the knowledge obtained from the crystal structure, modifications can be made during the intermediate crystallization steps or to the final compounds which can be crucial for the commercialization of APIs.

Our preliminary results show changes in the unit cell parameters of the newly formed cocrystals with respect to their initial precursors which indicate that the process of cocrystallization was achieved.

PXRD has been performed to cross-check the structure derived with electrons diffraction. Despite submicrometric crystals size and a strong stacking disorder their unit cell parameters were successfully determined and used for further crystal structure elucidations.

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**References**

Reference

1. Sakamoto N., Tsuno N., Koyama R., Gato K., Titapiwatanakun V., Takatori K., Fukami T. Four Novel Pharmaceutical Cocrystals of Oxyresveratrol, Including a 2 : 3 Cocrystal with Betaine. *Chem Pharm Bull (Tokyo)*. 2021;69(10):995-1004. doi: 10.1248/cpb.c21-00375. PMID: 34602581.
2. Aitipamula S., Banerjee R., Bansal K. A. et. al Polymorphs, Salts, and Cocrystals: What's in a Name? *Crystal Growth & Design* 2012 12 (5), 2147-2152 doi: 10.1021/cg3002948
3. Andrusenko I., Potticary J., Hall S.R., Gemmi M. A new olanzapine cocrystal obtained from volatile deep eutectic solvents and determined by 3D electron diffraction. *Acta Crystallogr B Struct Sci Cryst Eng Mater*. 2020 Dec 1;76(Pt 6):1036-1044. doi: 10.1107/S2052520620012779. Epub 2020 Nov 12. PMID: 33289715.
4. Gemmi, M., Mugnaioli, E., Gorelik, T. E., Kolb, U., Palatinus, L., Boullay, P., Hovmöller, S., & Abrahams, J. P. (2019). 3D Electron Diffraction: The Nanocrystallography Revolution. *ACS central science*, 5(8), 1315–1329. <https://doi.org/10.1021/acscentsci.9b00394>
5. Brázda P, Palatinus L. Babor M. Electron diffraction determines molecular absolute configuration in a pharmaceutical nanocrystal 2019J Science P667-669 V 364 6441 doi:10.1126/science.aaw2560