MS28-1-9 Navigating crystal forms in pharmaceutical compounds by 3DED/microED
#MS28-1-9

M. Lightowler [1], S. Li [2], X. Ou [2], G. Hofer [1], J. Cho [1], X. Zou [1], M. Lu [2], H. Xu [1]
[1]Stockholm University - Stockholm (Sweden), [2]Sun Yat-sen University - Guangzhou (China)

Abstract
Three-dimensional electron diffraction (3DED), also known as microcrystal electron diffraction (MicroED) has recently emerged as a promising method for crystal structure determination of pharmaceutical compounds[1,2]. The method complements existing methods by providing the opportunity to study small organic molecules from crystals too small for conventional single crystal X-ray diffraction and too complex for powder X-ray diffraction. In our lab, structures of several pharmaceutical compounds have been determined and various studies indicate that 3DED/MicroED is capable of (i) rapid structure determination at atomic resolution[2,3], (ii) solving crystal structures of new polymorphs[4,5], (iii) studying polymorphism evolution[6,7], and (vi) phase analysis by high-throughput 3DED/MicroED. However, comparing to X-ray diffraction, 3DED/MicroED is still in its infancy. Further optimization and innovations in new software and hardware are required to make it more robust and more accessible to the structural chemistry and pharmaceutical research community. In EMC33, I would like to present our latest development in specimen preparation, data collection and processing routine, and future perspective of 3DED/MicroED.

References
1. Clabbers, M. T. B. & Xu, H. Microcrystal electron diffraction in macromolecular and pharmaceutical structure determination. Drug Discov. Today Technol. S1740674920300354 (2020) doi:10.1016/j.ddtec.2020.12.002.

2. Jones, C. G. et al. The CryoEM Method MicroED as a Powerful Tool for Small Molecule Structure Determination. ACS Cent. Sci. 4, 1587–1592 (2018).

3. Gruene, T. et al. Rapid Structure Determination of Microcrystalline Molecular Compounds Using Electron Diffraction. Angew. Chem. Int. Ed. 57, 16313–16317 (2018).

4. Andrusenko, I. et al. Structure determination, thermal stability and dissolution rate of δ-indomethacin. Int. J. Pharm. 608, 121067 (2021).

5. Lightowler, M. et al. Indomethacin Polymorph δ Revealed To Be Two Plastically Bendable Crystal Forms by 3D Electron Diffraction: Correcting a 47-Year-Old Misunderstanding**. Angew. Chem. Int. Ed. 61, (2022).

6. Broadhurst, E. T. et al. Polymorph evolution during crystal growth studied by 3D electron diffraction. IUCrJ 7, 5–9 (2020).

7. Broadhurst, E. T., Xu, H., Parsons, S. & Nudelman, F. Revealing the early stages of carbamazepine crystallization by cryoTEM and 3D electron diffraction. IUCrJ 8, 860–866 (2021).

8. Wang, Y. et al. Elucidation of the elusive structure and formula of the active pharmaceutical ingredient bismuth subgallate by continuous rotation electron diffraction. Chem. Commun. 53, 7018–7021 (2017).

A summary of 3DED/MicroED applications in studying crystal forms of pharmaceutical compounds in our lab. a) structure determination of API bismuth Subgallate[8], b) Polymorphism evolution of glycine[6], c) Crystallization of carbamazepine[7], d) Discovery of indomethacin form θ, correcting a 47-year-old misunderstanding[5], e) Structure determination of five phases of vemurafenib, and f) Phase analysis by high throughput 3DED/MicroED