THE ELECTRON DIFFRACTION COMPANY

Unlocking the crystal structures of marketed drugs.

A case study of febuxostat – a long-missing crystal structure solved from nanocrystals by electron diffraction.

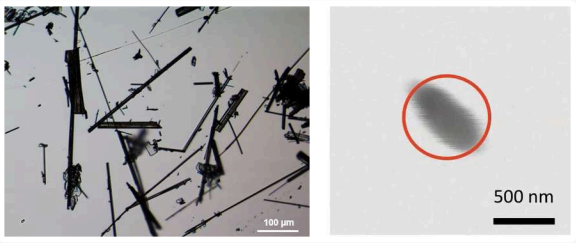

Fig. 1 (a) Febuxostat crystals used for SC-XRD (100 µm scale); (b) a febuxostat crystal used in the ED experiments (500 nm scale).

EXPERIMENTAL

Febuxostat Form A

Instrument	**ELDICO ED-1**
Compound	**febuxostat (gout)**
Reported solid forms	**>40**
Smallest ED crystal	**0.75 × 0.3 × 0.2 µm³**
SC-XRD needs	**≥ 10–15 µm**
ED dataset	**collected in minutes**

Many marketed drugs lack a determined crystal structure because their crystals are too small for single-crystal X-ray diffraction (SC-XRD) analysis. Structural information plays a very important role in solid-state properties, stability and formulation behaviour – critical factors for pharmaceutical development, regulatory approval and intellectual-property protection. The ELDICO ED-1, a dedicated electron diffractometer optimised for organic materials, overcomes this limitation by enabling crystal structure determination from nanometer-sized crystals. This study demonstrates how electron diffraction (ED) successfully determined the long-missing crystal structure of febuxostat Form A, a widely used drug for gout treatment, despite the previous failure of SC-XRD.

Furthermore, during this study, bigger crystals of Form A were obtained by serendipity, and for the first time the structure was also elucidated from X-ray diffraction experiments. A comparison of both structures reveals no difference in the lattice parameters, the packing or the molecular structure – so it also shows that an ED structure is equivalent to an SC-XRD structure, while the time and effort required for ED is clearly an advantage over the SC-XRD process.

Challenges in febuxostat structure determination

Febuxostat, a selective xanthine oxidase inhibitor, has a rich polymorphic landscape, with over 40 solid forms reported. Despite its commercial availability, the crystal structure of its marketed polymorph (Form A) remained undetermined, because crystals large enough for SC-XRD could not be grown: SC-XRD requires crystals ≥ 10–15 µm, yet Form A was never characterised by SC-XRD; X-ray powder diffraction (XRPD) confirmed phase identity but lacked the resolution for full structure determination; and attempts to grow larger single crystals failed.

A breakthrough for structure determination

Using the ELDICO ED-1, the crystal structure of febuxostat Form A was successfully determined from nanocrystals as small as 0.75 × 0.3 × 0.2 µm³. The ED-1 is a game-changer for organic materials: it is designed for electron diffraction on beam-sensitive organic compounds; it needs no large single crystals, so structures are obtained from nanoscale material; data collection is fully automated and requires no electron-microscopy expertise; its accuracy is comparable to SC-XRD; and complete datasets are collected within minutes.

[1] D. T. Ungur et al., *CrystEngComm* 2024, 26, 4295–4304. [2] J. A. Yadav et al., *Mol. Pharmaceutics* 2017, 14, 866–874.

CASE STUDY

Febuxostat – SC-XRD vs ED.

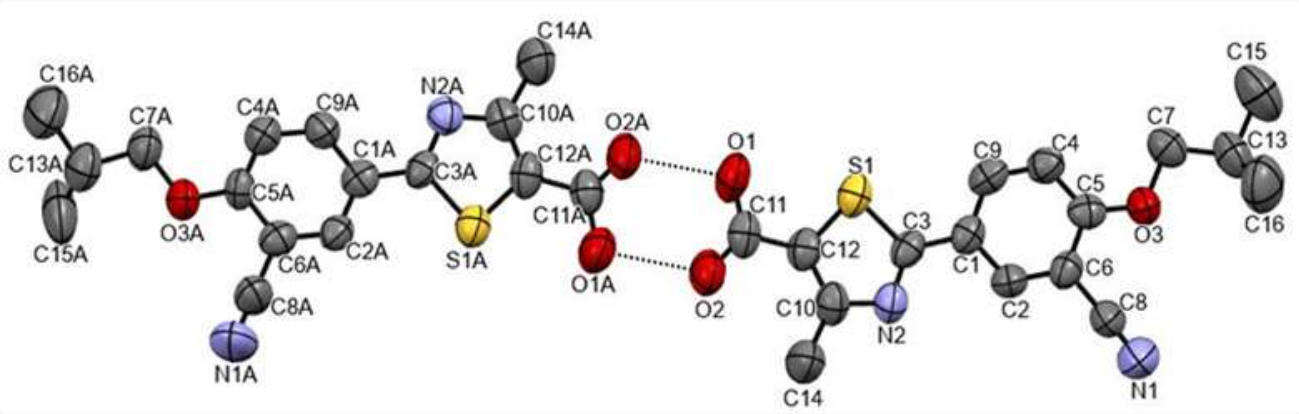

Fig. 2 ED molecular structure of febuxostat Form A. For clarity, all hydrogen atoms have been omitted; the intermolecular hydrogen bonding is represented by dotted lines.

CRYSTAL DATA – FEBUXOSTAT FORM A (SC-XRD / ED)

Formula	$C_{16}H_{16}N_2O_3S$	Cell volume (Å^3)	**3283.9(4) / 3267.9(10)**
Crystal system	**orthorhombic**	Z, Z′	**8, 2**
Space group	**$Pna2_1$**	Refined parameters	**405 / 410**
a (Å)	**8.9872(6) / 8.9860(15)**	R1 [I>2σ]	**6.29% / 16.15%**
b (Å)	**13.7547(9) / 13.742(3)**	Crystal growth	**~30 days / minutes**
c (Å)	**26.5649(17) / 26.464(4)**		

The table compares the crystallographic data obtained from SC-XRD and ED, demonstrating the high accuracy and reliability of electron diffraction for determining pharmaceutical crystal structures. The lattice parameters, packing and molecular structure are effectively identical between the two methods – but where SC-XRD needed about 30 days to grow suitable crystals, the ED datasets were collected in minutes.

Implications for pharmaceutical development. Determining crystal structures directly from nanocrystals is fast and unlocks new possibilities: polymorph screening and selection, so key solid forms are not missed; regulatory compliance with structural-characterisation requirements; intellectual-property protection based on determined structures; and formulation optimisation informed by the stability and solubility behaviour of different polymorphs.

Conclusion. For pharmaceutical companies facing solid-state characterisation challenges, the ELDICO ED-1 provides a dedicated, high-performance solution for rapid and reliable crystal structure determination – as febuxostat Form A shows, delivering an SC-XRD-equivalent structure from crystals far too small for X-ray, in a fraction of the time.

[1] D. T. Ungur, et al., *CrystEngComm* 2024, 26, 4295–4304.