THE ELECTRON DIFFRACTION COMPANY

3D ED analysis of agrochemical nanocrystals.

From spray-droplet crystallisation – a Syngenta & ELDICO case study on mesotrione.

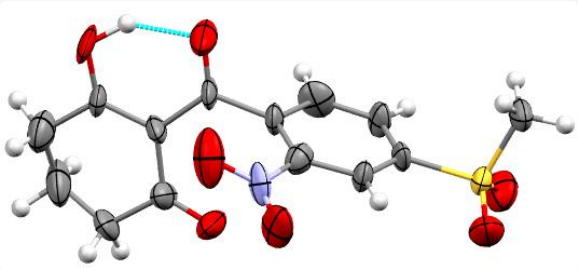

Fig. 1 Molecular structure of mesotrione form 1 from ED data.

EXPERIMENTAL

ED crystal mapping

Instrument	**ELDICO ED-1**
Collaboration	**Syngenta**
Particles screened	**38**
Form 1 identified in	**36 crystallites**
Other polymorphs	**none found**
Datasets merged	**4**
Structure	**solved ab initio**

A typical way of deploying agrochemicals is spraying crops with diluted formulations of the active ingredient. Analysis of the solid form obtained upon evaporation of spray droplets is crucial for understanding bioefficacy, but also challenging, because the crystallisation conditions usually produce nanocrystalline material that is mixed with other components of the formulation. Electron diffraction crystal mapping is the perfect tool to analyse such samples and study the solid form of active ingredients under these conditions.

Introduction

The solid form of agrochemical active ingredients (AIs) is very important for product stability and controlling uptake, just like for active pharmaceutical ingredients (APIs). For instance, if a product contains a metastable polymorph, over time there will be crystal growth causing blockages in nozzles and changes to bioefficacy. Knowing whether the AI can change to a different solid form when it is deployed on the crops is important for formulation design, because spraying a diluted formulation leads to very different crystallisation conditions than standard laboratory protocols. Even when the AI is a suspension on dilution, mechanical stress (spraying through a nozzle) and changes in humidity can still lead to a change in solid form. Unlike the controlled conditions of a laboratory, the evaporation of spray droplets cannot be precisely controlled in a real-life environment.

The analysis of the obtained residue is challenging for multiple reasons. First, the fast crystallisation produces nanocrystals that are too small for single-crystal X-ray diffraction (SC-XRD). Second, the low levels of AI and other formulation components lead to multi-phase mixtures that make obtaining sufficient-quality powder XRD (PXRD) for phase matching very challenging. Third, sampling from the plant leaves introduces additional complications such as the epicuticular wax of the leaf and environmental material.

Simulating spraying on leaves

In a cooperation between Syngenta and ELDICO we simulated the spraying of an AI formulation on leaf surfaces by spraying directly onto the grid (continuous carbon film on copper grid) used as sample support for electron diffraction (ED) measurements. The crystallites can then be analysed directly, as they formed upon evaporation of the droplets. A commercial formulation was prepared and diluted with water to the correct application rate that a farmer would use, then sprayed using a handheld atomiser to replicate a typical spray-droplet size (nanolitre) from a large boom sprayer.

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CASE STUDY

Mesotrione.

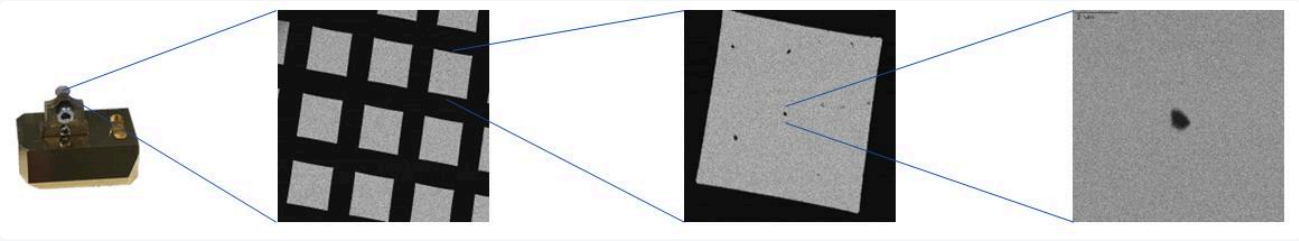

Fig. 2 Sample holder with the prepared grid and STEM (scanning transmission electron microscopy) images at different fields of view: 400×400 µm², 100×100 µm² and 10×10 µm² (left to right).

CRYSTALLOGRAPHIC DATA – MESOTRIONE FORM 1 (4 MERGED DATASETS)

a, b, c (Å)	**10.41(10), 11.52(11), 12.31(11)**	Resolution	**0.80 Å**
α, β, γ (°)	**90, 94.965(19), 90**	Completeness	**88.8%**
Space group	**$P2_1/c$**	Rint	**16.96%**
Formula	**$C_{14}H_{13}NO_7S$**	R1 [I>2σ]	**17.20%**
Independent reflections	**2233**	wR2 [all data]	**45.84%**
Parameters	**211**	Goodness-of-fit	**1.06**
Restraints	**0**		

Mesotrione is a broad-spectrum HPPD (4-hydroxyphenylpyruvate dioxygenase) inhibitor used to control pre- and post-emergence broadleaf weeds and some grasses, protecting corn and other crops such as sugarcane. A sample of mesotrione was prepared as described and measured on an ELDICO ED-1 electron diffractometer. Out of 38 particles, the unit cell of anhydrous mesotrione form 1 was identified in 36 crystallites, and no other polymorphs were found; in the other particles the data quality was not sufficient for unit-cell determination. Form 1 is indeed the technical product used in the formulation, and the results confirm that the same form is also obtained after spraying and evaporation in air.

Although a unit cell is already sufficient for identification by matching with literature data, the collected data were of high quality and the structure could easily be solved ab initio. Refinement required no restraints and allowed the location of hydrogen atoms, and therefore the determination of the tautomeric form of the mesotrione molecule. Even though no unknown polymorphs were present, the data quality shows that the method would also be capable of solving the crystal structures of new polymorphs that could form during spray-droplet crystallisation.

Conclusion. ED crystal mapping is a powerful tool to analyse phase mixtures, as it can collect data from individual nanocrystals – which can be used not only to identify known forms, but also to determine crystal structures of minor species such as other polymorphs, contaminants or decomposition products. In this case study we solved the crystal structure of mesotrione form 1 from a nanolitre spray-droplet crystallisation experiment of a diluted formulation. This experimental setup simulates the crystallisation of agrochemical active ingredients for foliar application and can thus help in formulation development.

Case study in cooperation with Syngenta International AG, Basel. ELDICO Scientific AG · Allschwil, Switzerland.