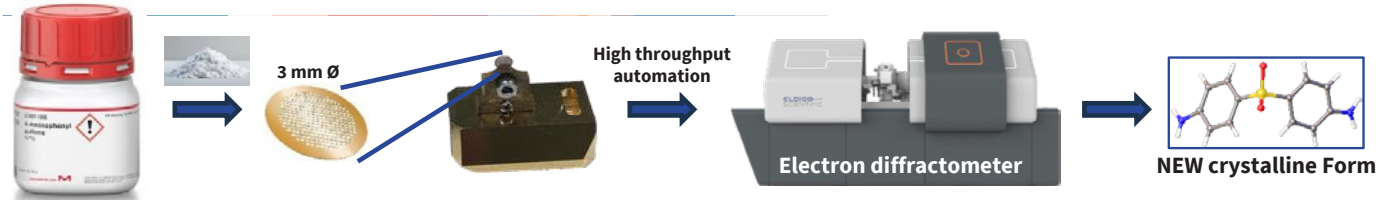
New Polymorphic Form of Dapsone Found with Automated Electron Diffraction (microED) experiments on a commercial sample



In the pharmaceutical industry, understanding the crystal structure of Active Pharmaceutical Ingredients (APIs) and formulations is fundamental to ensuring quality, performance, and manufacturability. The solid form of an API determines its physical and chemical behavior—including solubility, dissolution rate, bioavailability, stability, and mechanical performance. Even subtle differences in molecular packing or polymorphism can lead to marked variations in drug efficacy and processability, with major implications for patient safety and regulatory compliance.[1]

In modern times, Pharmaceutical companies increasingly use Crystal Structure Prediction (CSP) to explore the polymorphic landscape and de-risk the selection of undesired forms. Yet, CSP predictions must be experimentally validated. Only direct structure elucidation confirms which crystalline form is present and whether it remains stable throughout formulation, scale-up, and storage.[2]

Introduction

Dapsone, known as diaminodiphenyl sulfone (DDS) exists for more than 100 years. The antimicrobial activity of it was recognized 90 years ago; it is also used for treatment of leprosy and in dermatology. Up to date, 5 forms of the pure drug have been crystallographically characterized. Form III believed to be the most stable polymorphic form.

Recent CSP studies on Dapsone predict some ~ 40 forms in the energy landscape and provide evidence that a new form, namely Form V is the most thermodynamical stable.[3]

With the aid of Electron Diffraction (3D ED / microED) as a complementary method to SCXRD,[4] crystalline materials with dimensions below 1 µm can readily be employed for structural elucidation. Owing to the strong interaction between electrons and matter, the small crystal size does not impede the acquisition of high-quality diffraction data.[5,6] Moreover, unit cell determination and structure solution are as straightforward as in conventional SCXRD experiments.

Furthermore, Automated Electron Diffraction enables the analysis of hundreds of particles in significantly less time compared to manual data collection. By acquiring diffraction data from a large number of nanoparticles, it also increases the likelihood of discovering new crystalline forms that may be overlooked by other analytical techniques or missed during manual analysis.

Automated Electron Diffraction Experiments on Dapsone

Dapsone was bought from Sigma Aldrich. The bottle was opened and a tiny portion of sample was placed on a 3 mm Ø TEM grid. The grid was placed inside the ELDICO *ED-1* electron diffractometer.

Fully automated ED experiments were conducted. In this context, “fully automated” refers to the instrument software enabling the operator to define the number of grid meshes to be analysed and the number of particles to be irradiated per mesh. The system automatically locates each selected area, identifies suitable crystals, centers a chosen crystal in the electron beam, and collects a short continuous rotation diffraction series.

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Case Study: DAPSONE New Polymorphic Form

This procedure is iterated either until the desired number of meshes or crystals has been measured, or until the operator terminates the run.
Data processing is performed via an integrated batch script utilizing the DIALS software suite.[7] Once all diffraction data have been indexed and integrated, the resulting unit cells are clustered according to lattice similarity. Data corresponding to each unit cell cluster are then scaled together to produce final .hkl and .ins files. Structure determination is subsequently carried out using standard crystallographic software packages on the resulting datasets.

Experimental Results on Dapsone

- Approx. 650 crystals were measured in 24 h (30° total rotation range, 0.5° slicing, 2 s / °, 30 µA emission current).
- Around 47 % of the crystals correspond to the known Form III.
- Around 3 % of the crystals analysed gave another unit cell (see Table 1).
- The unit cell found is monoclinic $P2_1$, with 4 independent molecules in the asymmetric unit (Fig. 1).
- This unit cell has not been predicted by CSP studies.[3]
- The structure was solved and refined successfully.[8] (see Table 2.)

	Automated ED	Clusters from unit cells found
Crystals measured	~650 in 24 h	--------
Data processing	~650 in 3 h	--------
Total crystals analysed	~650	--------
Crystals belonging to **Form III**	~300	Cluster 1: Unit cell of Form III
Crystals belonging to **NEW FORM (FORM VI)**[9]	~20	Cluster 2: Unit cell not known in any Form
Crystals indexed, but not usable	~50 %	-------

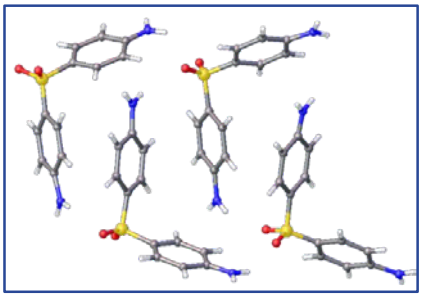


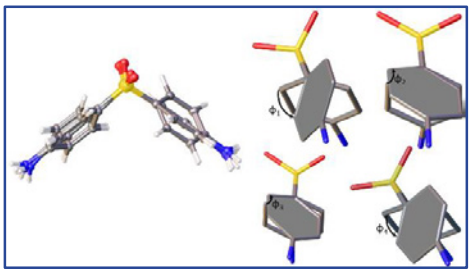
Figure 1. Asymmetric unit of: **NEW DAPSONE FORM, Form VI,** showing 4 molecules in the asymmetric unit (view along the 100 plane).

The crystal structure reveals four crystallographically independent molecules within the asymmetric unit (Fig. 1). An overlay of these molecules (Fig. 2) highlights variations in the orientations of their aromatic rings within the unit cell (i.e., different dihedral angles are observed).

Table 2: Crystal Data and Structure Refinement of **Dapsone NEW FORM**

Temperature/K	298(2)
Crystal system	monoclinic
Space group	$P2_1$
a, b, c (Å)	5.8144(12), 26.182(5), 15.395(3)
α , β, γ (°)	90, 90.43(3), 90
Volume/Å^3	2343.6(8)
Z', Z	4, 8
Radiation	(λ = 0.02851 Å)
Reflections collected	83064
Independent reflections	4254 [R_{int} = 0.4434, R_{sigma} = 0.1057]
Data/restraints/parameters	4254/919/542
Goodness-of-fit on F^2	1.183
Final R indexes [I>=2σ (I)]	R_1 = 0.1541, wR_2 = 0.3811
Final R indexes [all data]	R_1 = 0.1603, wR_2 = 0.3846

Figure 2. (left) Overlay of the 4 independent molecules found in the asymmetric unit of a **NEW DASPSONE FORM**. (right): Different dihedral angles seen for each molecule found.



Conclusions

- **Automated Electron Diffraction** (microED) enables data collection from a significantly larger number of crystals compared to manual operation.
- Analysing hundreds of crystals enhances detection of datasets that might have been overlooked by manual collection.
- Automated processing of numerous datasets allows efficient grouping based on similar unit cells.
- By clustering and analysing these related datasets, a **NEW DAPSONE FORM** was discovered from a commercial sample.
- This newly identified Dapsone polymorph crystallizes in the monoclinic $P2_1$ space group (Z' = 4), a structure not reported in the previously CSP study.

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