THE ELECTRON DIFFRACTION COMPANY

# Precision in powder analysis.

Electron diffraction for milled pharmaceuticals – detecting residual crystallinity that PXRD can miss.

EXPERIMENTAL

### ED crystal mapping

| | |
|---|---|
| Instrument | **ELDICO ED-1** |
| Collaboration | **RCPE Graz** |
| Particles / sample | **~100** |
| Melt quench | **fully amorphous** |
| Ball milled | **crystallinity present** |
| Ball-mill run | **91 measured · 26 crystalline** |
| Match | **Carvedilol (CSD)** |

Milling is widely utilised in the pharmaceutical industry, serving several critical applications, including enhancing solubility and bioavailability, particle-size reduction, and controlled-release formulations. The product of milling can sometimes be difficult to analyse with traditional techniques such as powder X-ray diffraction (PXRD). Here we show how electron diffraction (3D ED / microED) is the ideal tool for the analysis of milled products.

Milling enhances the solubility and bioavailability of poorly soluble drugs by producing amorphous materials that dissolve more readily than their crystalline counterparts. It also plays a key role in particle-size reduction, ensuring uniformity in active pharmaceutical ingredients (APIs) and excipients, which is vital for consistent drug formulation and enhanced absorption. Additionally, milling is crucial for developing controlled-release formulations, as it helps to achieve the particle sizes and distributions necessary to maintain therapeutic drug levels over extended periods. Overall, milling not only improves the physical and chemical properties of pharmaceutical compounds but also supports the development of advanced drug-delivery systems, ultimately contributing to more effective and reliable medications.

## Why electron diffraction

Analysing the powder by PXRD is the state-of-the-art method for milled samples for several reasons: confirming the amorphous state, detecting residual crystallinity, ensuring batch consistency, and meeting regulatory compliance. However, PXRD has a detection limit of 1–2%, which can sometimes overlook low levels of residual crystallinity or impurity phases. To address this limitation, electron diffraction has emerged as a promising solution: with its higher sensitivity, it can detect even minimal crystalline residues, ensuring a more accurate characterisation of milled materials. The ELDICO ED-1 is optimised for this purpose, as it can analyse powders in a fully automated fashion using the so-called electron-diffraction crystal-mapping method.

Case study in collaboration with the Research Center Pharmaceutical Engineering GmbH (RCPE), Graz.

CASE STUDY

# Carvedilol – ball milling vs melt quenching.

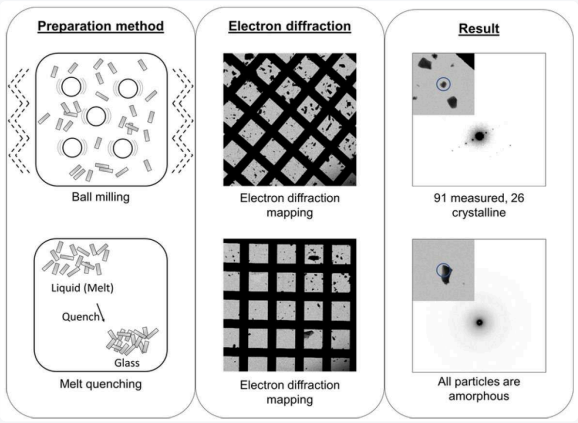


**Fig. 1** Overview of results from crystal mapping of carvedilol – preparation method, electron-diffraction mapping and result for ball milling (top) and melt quenching (bottom).

UNIT CELL – CRYSTALLINE CARVEDILOL (BALL-MILLED)

| | |
|---|---|
| a | **9.20 Å** |
| b | **15.20 Å** |
| c | **15.45 Å** |
| α | **90°** |
| β | **101.67°** |
| γ | **90°** |
| Volume | **2115 Å³** |
| System | **monoclinic P** |
| Match | **Carvedilol CSD entry** |

In collaboration with the Research Center Pharmaceutical Engineering GmbH (RCPE) in Graz, we conducted a case study to compare different sample-preparation methods. Carvedilol was used as an example to assess two different preparation techniques for amorphous APIs: melt quenching and ball milling. To investigate the resulting crystallinity from both techniques, samples were prepared on a TEM grid, and for each sample about 100 particles were tested using the automated crystal-mapping method.

Whereas the sample from melt quenching was fully amorphous, crystallinity was still found to be present in samples prepared by ball milling (Fig. 1). Continuous-rotation data collection allowed the determination and matching of the unit cell with carvedilol. The results indicate that the ball-milling time needs to be increased to ensure 100% amorphisation.

**Conclusion.** Electron-diffraction crystal mapping emerges as a powerful tool for precise characterisation of milled pharmaceutical samples. This technique excels in detecting crystalline phases even at extremely low levels of detection, making it invaluable for assessing the amorphous nature of milled materials. By combining particle screening with continuous-rotation diffraction, it detects and identifies crystalline impurities and unknown crystal forms within pharmaceutical formulations – crucial for ensuring product quality and efficacy, as well as meeting stringent regulatory standards in the pharmaceutical industry.



Sample preparation and crystal mapping performed at ELDICO Scientific AG with RCPE, Graz.