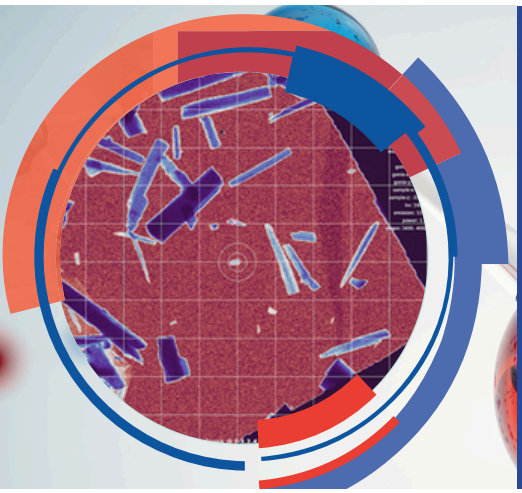
ELDICO SCIENTIFIC
THE ELECTRON DIFFRACTION COMPANY



Precision in Powder Analysis: Electron Diffraction for Milled Pharmaceuticals

solve problems by saving time, resources and material

Milling

Milling is widely utilized in the pharmaceutical industry, serving several critical applications, including enhancing solubility and bioavailability, particle size reduction, controlled release formulations. The product of milling can sometimes be difficult to analyse for traditional techniques such as PXRD or X-ray. We show here how electron diffracion is ideal for analysis of milled products.

Milling enhances the solubility and bioavailability of poorly soluble drugs by producing amorphous materials that dissolves more readily than their crystalline counterparts. Milling 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 drug absorption. Additionally, milling is crucial for developing controlled-release formulations, as it helps achieve the desired particle sizes and distributions necessary to maintain therapeutic drug levels over extended periods**.**

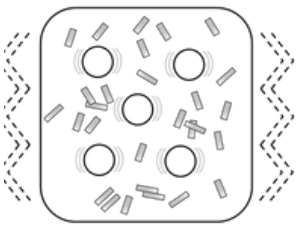
Overall, milling not only improves the physical and chemical properties of pharmaceutical compounds but also supports the development of advanced drug delivery systems, ultimately contributing to more effective and reliable medications.

Analyzing the powder using X-ray powder diffraction (XRPD) is vital for milled samples for several reasons:-

1. Confirming Amorphous State
2. Detecting Residual Crystallinity
3. Ensuring Batch Consistency
4. Regulatory Compliance

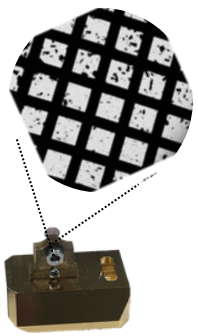
However, XRPD has a detection limit of 1-2%, which can sometimes overlook low levels of residual crystallinity or impurity phases. To address this limitation, electron diffraction has emerged as a promising solution. With its higher sensitivity, electron diffraction can detect even minimal crystalline residues, ensuring a more accurate characterization of the milled materials. This advancement supports the development of more effective and reliable pharmaceutical formulations.

The ELDICO *ED-1* from ELDICO Scientific is optimized for this purpose as it has the ability to analyze powders fully automated using the so called electron diffraction crystal mapping method.

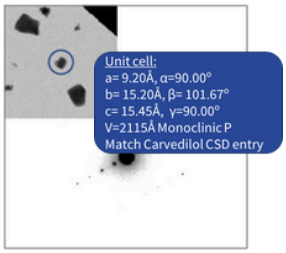


Ball milling

ELDICO *ED-1*



Crystal mapping



91 measured, 26 crystalline

Result

Case study: Carvedilol, comparison ball milling and melt quenching.

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 preparation techniques, samples were prepared on a TEM grid. 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.

Unit cell:
a= 9.20Å, α=90.00°
b= 15.20Å, β= 101.67°
c= 15.45Å, γ=90.00°
V=2115Å Monoclinic P
Match Carvedilol CSD entry

The results indicate that ball milling time would need to be increased to ensure 100% amorphization.

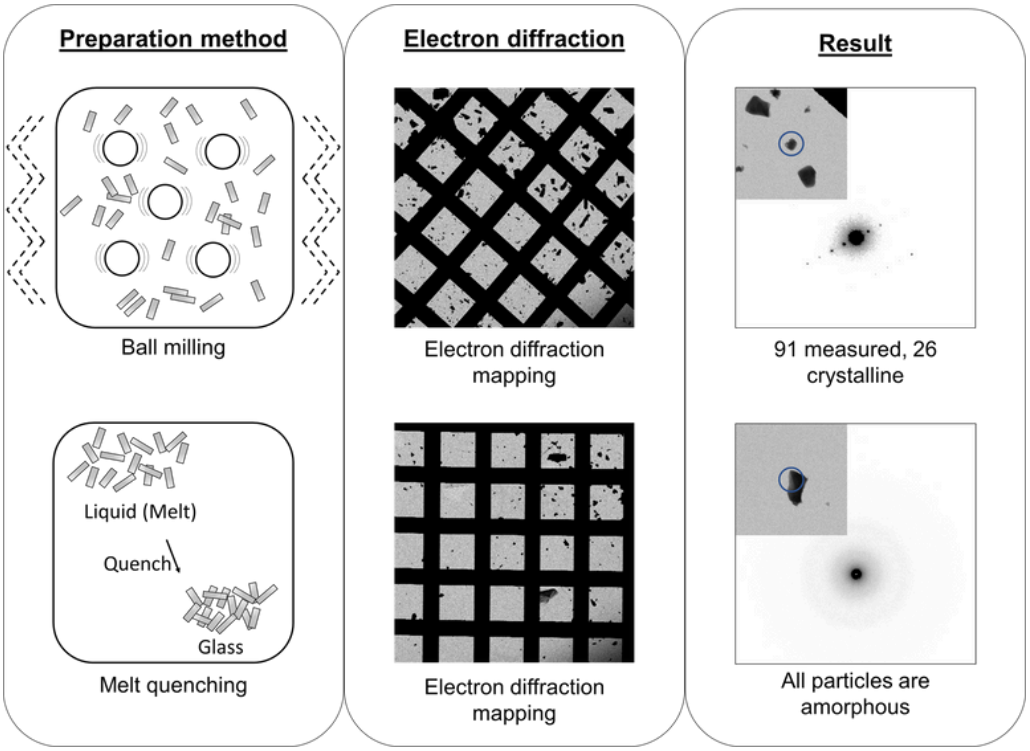


Fig. 1: Results electron diffraction mapping

Conclusion:
Electron diffraction crystal mapping emerges as a powerful tool for precise characterization 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, electron diffraction crystal mapping identifies and identifies crystalline impurities and unknown crystal forms within pharmaceutical formulations. This capability is crucial for ensuring product quality and efficacy, as well as meeting stringent regulatory standards in the pharmaceutical industry.