ELDICO SCIENTIFIC
THE ELECTRON DIFFRACTION COMPANY

Electron Diffraction: Advancing Mechanical Chemistry

save time, resource and material

Solid state research

Solid state research is an important step in the development of a new drug. From a regulatory perspective, an assessment of the solid state characteristics of an active pharmaceutical is required[1]. Risk management, on the other hand, is also an important driver to study the solid state behaviour of a drug in development.

The appearance of a different polymorph at later stages of development or the transformation from amourphous to crystalline of a product on stability can be very costly. Different bioavailability of the drug product or the drug substance will entail redeveloping the drug or formulation from the beginning. Selecting the right solid form, one that will not change on stability, whether it is a developable polymorph, a salt, co-crystal or stabilized amorphous state, is crucial in the further development and formulation.

Diversity in experimental set up is necessary for maximizing success in form discovery and therefor many varied crystallization techniques are used for solid state screening. One of the methods is mechanochemical synthesis.

Mechanochemical synthesis

Mechanochemical synthesis (mechanochemistry) involves the use of mechanical energy (such as grinding, milling, or shearing) to induce chemical transformations in solid-state materials. This method is often used as one of the first screening methods to produce new crystalline forms of new polymorphs, salts or co-crystal forms of pharmaceutical active ingredients.

The material is often characterized using conventional X-ray powder diffraction. However, with this method it is often very difficult to characterize if new forms are present since the sample can be a mixture of different nanocrystalline phases or the sample is partly or fully amorphous.

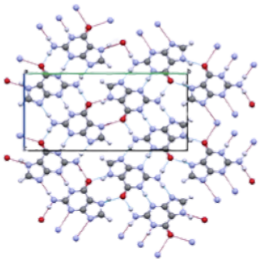
Electron diffraction

Electron diffraction (3D ED, MicroED) is a powerful technique used to analyse the chemical and structural changes induced by milling grinding or shearing as it can obtain diffraction information from nanocrystals as small as 100 nm and it can also detect a few crystals present in a predominantly amorphous phase. Electron diffraction is particularly useful to study mixed phases of single nanocrystals and can provide valuable results for the full characterisation of materials produced using mechanochemistry

Mechanochemistry

ELDICO *ED-1*

Crystal structure



[1] ICH Q6A Guideline, see: http://www.ich.org/LOB/media/MEDIA430.pdf and http://www.ich.org/LOB/media/MEDIA431.pdf

Case study: Quininium aspirinate, a glass-forming drug–drug salt [2]

Quininium aspirinate is a drug-drug salt prepared as amorphous material by ball milling or manually grinding powders of quinine and aspirin without liquid additives. While quininium aspirinate remains amorphous for months when kept in a closed vessel, it recrystallizes within hours upon exposure to solvent vapors

Microcrystal electron diffraction (microED) at ELDICO Scientific, Switzerland, was used to investigate diffraction from individual particles in the amorphous sample. While most particles did not diffract, two of 35 did, and unit cell parameters were calculated.

These studies could be fundamental in predicting the stability of drug products, as any crystal could potentially act as a seed for crystallinity conversion over time.
The lattice was the same as that of crystalline quininium aspirinate confirming the salt was formed under ball milling.

Conclusion

This finding advances our understanding of the structural properties of amorphous materials prepared by mechanochemistry. MicroED emerges as a new tool for providing detailed data on single nano- and micro-crystallites, effectively complementing bulk measurements. In certain cases, crystallinity can be viewed as an impurity, and MicroED stands out as the tool with the minimum limit of detection possible. If a crystal exists within an amorphous material, MicroED will identify it, particularly with the help of automation to detect sufficient quantities of crystals.

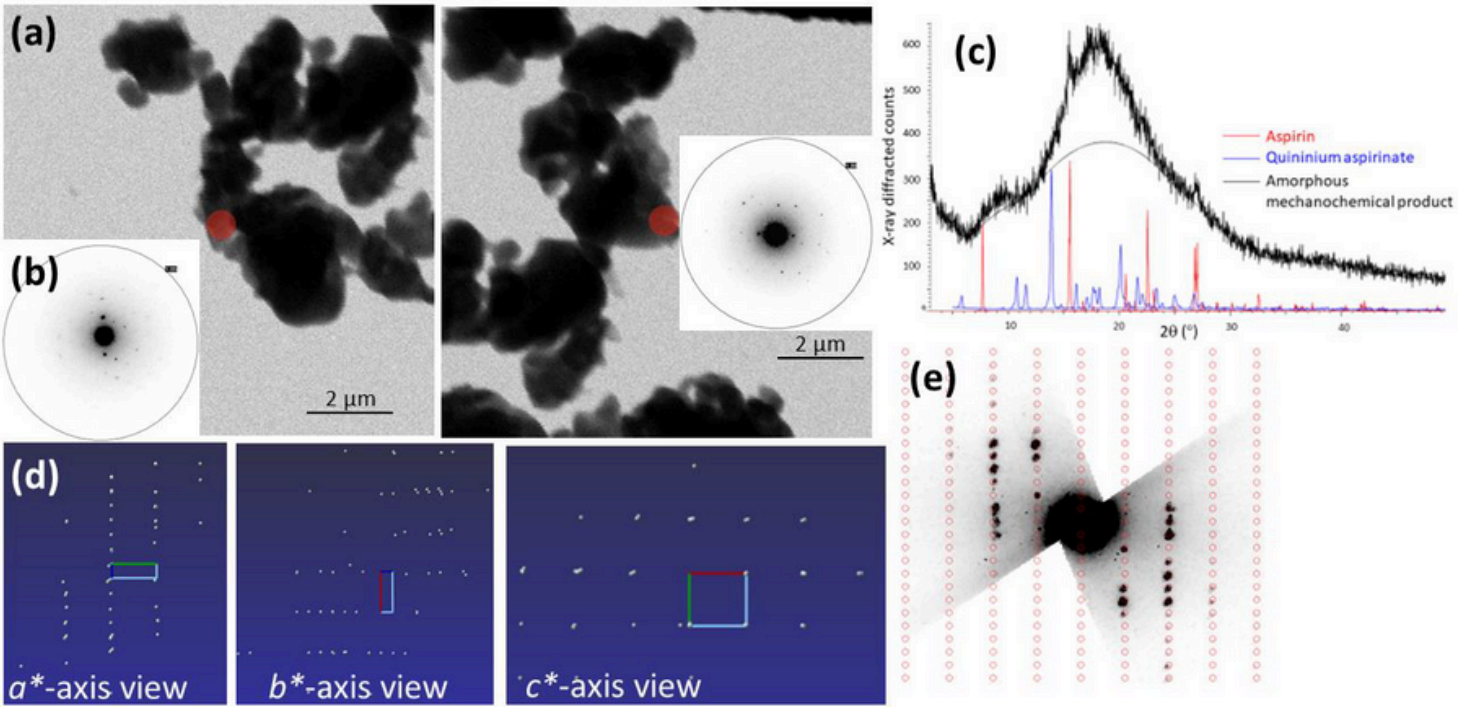


Figure 1: Diffracting particles in amorphous quininium aspirinate .
a) Scanning transmission electron microscopy (STEM) and microED data were collected on 35 areas (red circles).
(b) Two crystallites showed diffraction spots.
(c) Corresponding X ray powder diffraction data of the bulk phase (black line). Red and blue lines show the calculated patterns of aspirin and the crystalline mechanochemical product.
(d) Reciprocal space from micro ED leading to the unit cell, the same as that of crystalline quininium aspirinate .
(e) Precession image with unit cell overlay (calculated spot positions are shown with red circles)

[2] Harris, N., Benedict, J., Dickie, D. A. & Pagola, S. Acta Cryst. (2021). C77, 566–576