The 3D Electron Diffraction Revolution : when a complete crystal structure with details similar to that obtained with X-ray diffraction data is achieved but from a crystal one million times smaller

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Abstract

Characterization of the physical state of solid drug substances is a critical issue in the development of pharmaceuticals. Crystalline active pharmaceutical ingredients (API) are generally preferred over amorphous compounds because they usually present better stability and more consistent bioavailability. Structure determination of the crystalline phase is then a key parameter for the development of this API. The most commonly used method for such analysis is single crystal X-ray diffraction (SCXRD). However, growing crystals suitable for SCXRD (ca. 10 to 20 microns) remains a bottleneck with some of API.

Fortunately, crystallography of nanocrystalline materials has recently witnessed a true revolution since the use of electron diffraction (ED) has grown rapidly over the past decade. Recent technical improvements, such as low dose parallel ED beam (reducing the annoying dynamical scattering) and the development of algorithms for treating datasets, makes ED able to provide single-crystal data with successful structure solution and refinement quality. ED is now a reliable alternative to X-ray diffraction when only nanometer-sized crystals are available.

In this communication, we will present how ED, in combination with high resolution X-ray diffraction on powder, help us to solve crystal structures of highly complex pharmaceutical molecules when large single crystals were not available for X-ray diffraction.