CRYSTAL STRUCTURE ANALYSIS OF PHARMACEUTICALS WITH ELECTRON DIFFRACTION

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X-Ray powder diffraction (XRPD) has already successfully been used for a long time in the field of pharmaceuticals for polymorph screening (fingerprinting) and more recently for the structural and microstructural analysis of active pharmaceutical ingredients (API) and excipients. Large enough single crystals are in fact very difficult to grow or do not represent well the properties of the polycrystalline pharmaceutical compounds. Furthermore, quantitative phase analyses can only be performed with powder materials. Although XRPD is well established, there are often limitations in its successful application, in particular when facing complex structures whose XRPD patterns are characterized by many overlapping peaks and the determination of the cell parameters and the extraction of the diffracted intensity is very difficult and often unsuccessful. In such cases the use of synchrotron radiation and advanced experimental methods need to be explored (e.g. texture method [1], anisotropic thermal expansion [2]) but the determination of the crystal structure is never guaranteed and far from being routine.

Transmission Electron Microscope (TEM) combined with precession 3D electron diffraction tomography technique [3] has produced very promising results in the field of crystal structure determination and has the great advantage of requiring very small single crystals (from 25-500 nm) and very small quantity of material (few crystals on a TEM grid). This technique consists of collecting a series of patterns every 1° (usually from -45° to + 45°) while the sample is tilted around the goniometer axis. Reciprocal space reconstruction and subsequent cell parameter determination and diffraction intensity extraction are automatically performed by ad-hoc software [3,4]. The structure of several organic compounds has been recently solved this [5]. In addition to diffraction tomography, a novel TEM-based orientation imaging technique (ASTAR) has been recently developed [6] with high spatial resolution (1-25 nm) enabling the mapping of phases and orientations even for radiation sensitive organic nanocrystals. By rapidly scanning the beam on the specimen area, in fact, diffraction information can be collected before the radiation damage occurs and nanometer size orientation/phase maps can be successfully obtained. Diffraction information from different locations of the crystal reveals crystal cell parameter information and detailed crystalline/amorphous texture characterizing the samples. These two advanced techniques will be presented and pilot experimental results will be discussed.

![Image](a) TEM-STEM image showing fibers of haloperidol pharmaceutical compound (b) crystal structure (c) and (d) Typical electron diffraction patterns collected automatically from different parts of the crystal shown in (a).