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Pharmaceutical polymorph characterization by high resolution low loss EELS spectroscopy and electron diffraction tomography

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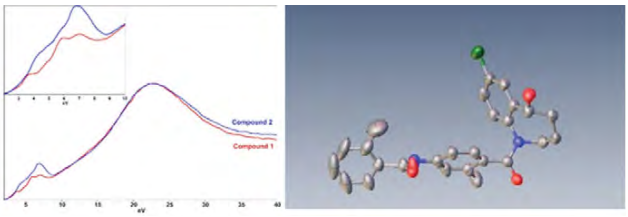
Polymorphism is critically important in the pharmaceutical industry, as different polymorphic forms usually have different physical properties like solubility, bioavailability etc... Undesired polymorphic forms (usually as "trace" quantities) can co-exist with main polymorphic forms during the synthetic process. Standard diffraction based techniques like conventional powder X-ray diffraction or spectroscopic techniques like IR/Raman may fail to reliably identity and characterize them at nm scale. Transmission Electron Microscopy (TEM) technique has the capability to characterize nm size crystals. Recently, a study of several organic/pharmaceutical compounds was carried out using conventional EELS where it was established its utility for drug molecules characterization [1]. In this work we present high resolution (monochromated) EELS-low loss (2-40 eV) characterization of two different pharmaceutical drug molecules (Compound 1 & 2) (Titan 60-300 low base at 300 keV, monochromated, 0.2 eV energy resolution) Fig. 1 shows comparison of EELS low loss signature for the two pharmaceutical drug compound. While a plasmon peak at 23eV is almost identical for both compounds, a region at 3-9 eV shows clear differences in the spectra, which could be used as possible fingerprint of the phases. Alternatively, crystalline compounds can be characterized using 3D Electron Diffraction (ED) Tomography, where a series of electron diffraction patterns are recorded with a fixed tilt step around an arbitrary axis from a nanometer size crystal [2]. From this 3D diffraction pattern dataset, unit cell parameter and symmetry can be determined and the crystal structure can be solved using ED extracted intensities dataset. In this work we present structure solution of two important pharmaceuticals compounds (Compound 3 and 4) [3]. Low dose 3D diffraction tomography data was collected using 120 KeV Zeiss Libra Microscope and Timepix camera.



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