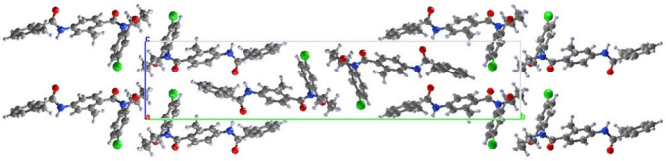
Micro to Nanometer Scale Characterization of Pharmaceutical Compounds by Electron Microscopy

P. P. Das*[1], A. Gómez Pérez[1], S. Nicolopoulos[1]

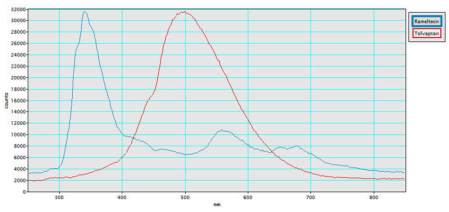
[1]NanoMEGAS SPRL, Boulevard Edmond Machtens 79, B1080, Brussels, Belgium

partha@nanomegas.com

Scientific community have shown a growing interest in using Electron Microscopy based techniques to characterize pharmaceutical compounds due to inherent advantages for structure characterization at micron to nm scale. The major advantage of using Electron Microcopy based techniques are based to the fact that imaging, diffraction and spectroscopic analysis can be combined at the same time where in case of Transmission Electron Microscope (TEM) up to 1 nm image resolution can be obtained. In our work, we have used a TEM based technique (electron diffraction tomography [1] also known as MicroED) and Scanning Electron Microscopy (SEM) based technique (Cathodoluminescence/CL) imaging and spectroscopy to characterize pharmaceutical organic compounds in nm and micro meter resolution respectively. Using electron diffraction tomography in TEM under low dose conditions and using novel pixelated detectors, we have studied ab-initio structure solution of several known and unknown pharmaceutical compounds [2,3].The principle of TEM electron diffraction tomography method is sampling the reciprocal space in small steps (usually 1 degree tilt) by focusing the electron beam on a nanometer size crystal, which can be used to determine further crystallographic information. Using this novel diffraction technique it was possible to characterize compounds with short to long with unit cell (> 35 Å) and/or up to 2 molecules in the asymmetric unit (e.g. like carbamazepine, nicotinic acid, Ramelteon, Tolvaptan, Loratadine Form II, Linagliptin etc.) [2, 3]. In the inserted above image, structure solved from ED tomography data of Tolvaptan compound is shown.



On the other hand, we have used spectroscopy based technique like CL in SEM to fingerprint several organic pharmaceutical compounds.e.g. Linagliptin, Tolvaptan, Rivaroxaban, Ramelteon, Lacosamide, Clofarabine, Piroxicam, Loratadine etc. where we found that most of the compounds show unique characteristic CL spectra [4]. Therefore a proposed strategy to characterize a pharmaceutical sample could be to first use SEM -CL spectroscopy and compare its CL spectra with reference CL spectra of known phases; in case that does not match , proceed to further analysis using TEM electron diffraction tomography for full characterization of the compound of interest. In the right image, comparison of CL spectra of Ramelteon (blue colour curve) and Tolvaptan (red colour curve) is shown.



Therefore a combination of these two techniques could be a powerful tool to monitor pharmaceutical modifications and phase identifications.

Keywords: Electron Microscopy, Diffraction Tomography, Cathodoluminescence, Spectroscopy, Imaging

References:

1) U. Kolb, T. Gorelik, C. Keble, M. T. Otten , D. Hubert, Ultramicroscopy 107, 507, 2007.
2) E. van Genderen, M.T.B. Clabbers, P. Pratim Das, I. Nederlof, A. Stewart, Q. Portillo, S. Nicolopoulos, J.P. Abrahams, Acta Crystallogr. A, 72, 236–242, 2016.
3) P. P. Das, E. Mugnaioli, S. Nicolopoulos, C. Tossi, M. Gemmi, A. Galanis, G. Borodi, M. M. Pop, Org. Process Res. Dev., 22, 1365-1372, 2018.
4) G. Nichols, European Journal of Pharmaceutical Sciences, 45, 19-42, 2012.