For industrial applications, it is of great interest to understand and determine the crystal structure, identify / characterize several possible polymorphs and to detect / quantify the crystallinity / amorphous phase of final products, since many important chemical and physical properties depend on the crystal structure properties.

Carbamazepine (CBZ), is a drug used primarily in the treatment of epilepsy and neuropathic pain. It may be used in schizophrenia along with other medications and as a second line agent in bipolar disorder. CBZ exists in several polymorphic forms.

Electron Diffraction Tomography analysis with TEM using ultrasensitive Timepix detector with no cooling holder allowed to collect diffraction tomography data from individual nanocrystals (size about 200 nm) and reconstruct the reciprocal space.

Unit cell determination and structure solution from the measured intensity helped to identify same crystal structure as reported by X-ray diffraction.

Unit cell:  
\[ a = 7.53 \text{ Å} \]  
\[ b = 11.14 \text{ Å} \]  
\[ c = 14.06 \text{ Å} \]  
\[ \beta = 92.80^\circ \]  

SPG : P21/n

Crystal structure of CBZ solved with X-Ray diffraction

3D reciprocal space reconstruction of CBZ and studied crystal (about 200 nm size)

Solved crystal structure of carbamazepine using 3D electron diffraction tomography (50° continuous tilt, 3823 reflections , 0.8° resolution)

Electron Diffraction Tomography technique by TEM microscope is particularly useful in case of polyphasic systems (several polymorphs), nm size crystals, and poorly crystalized samples

CM 30 Philips electron microscope and Timepix ultrasensitive detector (insert) at CcIT Univ of Barcelona (Spain) where CBZ ED data collection was made.

High Resolution Virtual Dark Field (VDF) in TEM is a technique that enables detection of very small trace of crystalline material; in the example shown above, trace crystals of very small sizes (e.g., 10 nm) can be observed at very low quantity (< 0.01%). Structure characterization (like phase confirmation) of such small crystals can be done using Electron Diffraction on individual crystallites.

Electron Crystallography is considered as the method of choice for structure determination of nanocrystalline compounds (crystals as small as 20 nm to several microns). Such nano-crystallites reveal typically “X-Ray amorphous” powder diffraction patterns (for sizes < 10 nm) where it is very difficult to identify and characterize their structures using X-Ray diffraction techniques.

Use of precession 3D electron diffraction (PED) with TEM makes possible unit cell and structure determination on individual nanocrystals. Using 3D diffraction tomography, a 3D reconstruction of the reciprocal space can be performed by tilting the sample and recording ED patterns (Fig. 1) (typically ±45° every 1°). Collected electron diffraction (ED) patterns can be processed to precisely determine the unit cell and reveal the space group symmetry of the API crystal. Full atomic crystal structure can also be performed after collection and precise measurement of ED intensities.