

I believe that I should be considered for the 2012 PANalytical Thesis Prize in Physical Crystallography as a large part of my PhD studies were devoted to making advances in the crystallographic analysis of organic materials, and in particular pharmaceutical samples, by transmission electron microscopy (TEM). Among the key developments that I made during this work was the development of a new approach to crystal structure determination which enables structures to be obtained from crystals with sub-micron and even nano-sized dimensions, equating to picogram amounts of material, and from crystal phases which are present as minor components in mixtures. In addition, I was able to demonstrate that TEM, a technique which is already commonly used for characterising inorganic materials, is also widely applicable to the study of pharmaceutical crystals.

The new approach to crystal structure determination for molecular compounds combines crystal structure prediction and transmission electron microscopy (TEM), and was developed for use with samples which are not suitable for conventional single crystal or powder X-ray diffraction approaches. This crystal structure determination method requires a small number (1 to 3) of experimental electron diffraction patterns to be recorded from a sample, which are then used to identify the corresponding crystal structure from a calculated set of potential low energy crystal structures generated by crystal structure prediction. Importantly, it is possible to obtain these electron diffraction patterns from one crystallite with sub-micron or even nano-sized dimensions, and before significant beam damage is caused by the electron beam (explain due to the properties of TEM). This methodology was first tested on known crystal form, and was then used to identify a novel crystal phase of the pharmaceutical compound theophylline. The crystal structure of this new polymorph was determined from TEM analysis of a single crystallite with an approximate mass of 3 pg and despite this phase occurring as a minor component in a mixture with a second crystal form of theophylline at an estimated concentration of less than 0.1 %w/w, a value below the limits of detection of analytical methods routinely used for pharmaceutical characterisation.

The use of TEM for the characterisation of pharmaceutical samples prior to the start of my PhD was very limited, largely due to the difficulties associated with the preparation of appropriately thin samples, and issues with sample damage caused by the electron beam. I developed strategies for overcoming these issues which have enabled characterisation of a variety of pharmaceutical compounds, including theophylline, paracetamol and aspirin, and also pharmaceutical salts and cocrystals. A range of relevant crystallographic information about these compounds was derived including morphology, polymorph identification, characterisation of crystal defects and mapping of crystal habit to crystal structure, with advantages over more commonly used analytical methods. For example, crystals of theophylline were observed to contain defects which were associated with the fracturing of the crystals.

In conclusion, the work described in my thesis represents a significant contribution to the field of physical crystallography, and would therefore be worthy of the 2012 PANalytical Thesis Prize.