Elucidating Polymorphism of Pharmaceutical Organic Crystals using in-situ Electron Microscopy Methods

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Polymorphism is the existence of more than one crystal structure for one compound upon changing specific conditions to influence the nucleation and crystallisation process.[1] This phenomenon has previously threatened and halted production of a number of pharmaceutical products, e.g. ritonavir (aka. Norvir), a common drug for the treatment of AIDS, where the detection of an alternate and more stable crystal structure caused the product to crystallise and possess reduced bioavailability compared to the soluble initial form.[2] An alternative crystal structure alters the inhernet properties of the compound such as; lattice energy, melting point, diffraction pattern and solubility. In the context of pharmaceutical products solubility is one of the most important property as it directly influences the bioavailability of the product upon administration.[3] Alternatively, if a new polymorph of common pharmaceutical product is discovered, it has the potential to have implications for improved methods of administration.

It has been previously shown that formerly unkown polymorphs of pharmaceutical compounds form when in the presence of a magnetic field.[4] Through collaboration this project aims to fundamentally understand the growth of these magnetic field induced polymorphs at the nanoscale. Electron microscopy methods are used such as *in-situ* microscopy, as a new and novel way of characterising the polymorphs and analysing how they develop in real-time. Due to the organic nature of the pharmaceutical crystals, they are prone to radiation damage and effects from the electron beam. For example radicals produced in the aqueous sample due to localised heating in the liquid-cell holder can introduce artefacts and uncontrolled side-reactions.[5] To overcome these effects, and minimise beam induced effects, methods such as using low a smaller aperture size, cryogenic temperature control are implemented.

To facilitate the work in this project a complimentary suite of peripheral equipment was used, consisting of an aberration corrected FEI TITIAN Themis^3, fitted with GATAN K2 direct detector capable of 1600 fps detector with a detective quantum efficiency (DQE) of up to 80% for *in-situ* analysis, appropriate for low-dose imaging where poor contrast and low signal-to-noise can be a limitation.

This project aims to highlight the necessity of characterising alternative polymorphs of common pharmaceutical products, which can impact their production and also to thoroughly and fundamentally analyse their growth at the nanoscale, as it is not yet fully understood.[6]

References

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