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From crystal to tablet – linking structure to function through compression studies

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Pharmaceutical tablets are the most widely used oral solid dosage form worldwide. They have a convenient design that favours high patient compliance, display good stability to atmospheric conditions, and can be manufactured at a large scale with the correct formulation. [1] During the tablet manufacturing process, the pharmaceutical powder blend is subjected to applied pressure at various stages of the production line, usually up to 0.3 GPa. Key properties of the crystalline components in the formulation (mechanical properties, solid state properties, chemical stability) directly impact the behaviour the components exhibit during processing, and define the quality and nature of the final product.

Currently, the relationship between the structural characteristics of crystalline pharmaceuticals and their behaviour under pressure is not well understood. In our study, we begin to investigate this relationship between structure and function by exploring alternative strategies to analyse and understand the compressibility observed in high-pressure crystallographic datasets. Active slip planes are reported to be responsible for plastic deformation in organic pharmaceutical crystals. [2] Additionally, their presence is shown to correlate with superior tabletability. [2] To investigate the potential impact of slip planes during the compression of systems of pharmaceutical relevance, we present a new approach to mapping molecular movement upon compression, and tracking the movement against slip planes predicted using the CSD-Particle tool (Cambridge Structural Database). [2]

We illustrate the outcome of this approach on a study of the racemic and chiral crystal structure of an active pharmaceutical ingredient used as an antibiotic: ofloxacin and levofloxacin. The difference in chirality between both crystals give rise to differing solid state landscapes [3][4], making them exciting candidates to examine under pressure. X-ray diffraction data has been collected on ofloxacin, levofloxacin hemihydrate and levofloxacin anhydrous under moderate pressures using a medium pressure sapphire capillary pressure cell on beamline I19 at Diamond Light Source ($\leq$ 0.12 GPa) [5], and at high pressures using standard diamond anvil cells in-house and on beamline ID15B at the European Synchrotron Radiation Facility ($\leq$ 7 GPa). We present data on the compressibility of these systems at tabletting pressures and beyond in an effort to determine the impact of chirality on their structural behaviour under pressure, and relate these to our present understanding of slip planes.

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