Poster

Investigating Pharmaceutical Solid Forms at High Pressure

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The selection of a crystalline solid form for a new Active Pharmaceutical Ingredient (API) is a critical milestone in the development of many commercial drug products. The final selection must be robust and manufacturable as well as provide the desired bio-performance, indeed the expectation to ensure control of the solid form in the specific drug product is described in regulatory guidance [1].

The performance of the API in the drug product is complicated by factors such as chemical stability and the different types of interaction with the excipients, but also significantly by its exposure to the environmental conditions experienced during manufacturing. One key processing step is that of compaction, an operation which applies pressures in the 0.1 – 0.4 GPa range to produce tablets from loose powders. Under these pressure conditions, some APIs undergo polymorphic phase changes, reducing control of the form in the final drug product and therefore controls of the bio-performance.

Understanding a material's propensity to undergo such a phase transformation and the development of new small-scale, process-relevant experiments enable the early identification of this risk and allows for mitigation plan to be built while designing the final crystallisation steps. High-pressure crystallography has been demonstrated to be a powerful tool that can be used to explore a material solid-form landscape, e.g., chlorpropamide and galunisertib [2, 3]. In a typical experiment, sample in the form of a crystal or crystalline powder is loaded into a Diamond Anvil Cell and then exposed to high-pressure. The sample under study can then be monitored by diffraction or spectroscopic means to allow for the identification of discontinuities during compression (and decompression), which may indicate a pressure-induced change to the solid form.

A pharmaceutically-relevant case study is presented demonstrating the usefulness of high pressure measurements to the understanding of phase changes in API under tabletting conditions. This will illustrate how such studies will help the pharmaceutical industry moving forwards.

[1] ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances. (2000) In *ICH Harmonized Tripartite Guideline*.

[2] Zakharov, B. A., Seryotkin, Y. V., Tumanov, N.A., Paliwoda, D., Hanfland, M., Kurnosov, A. V. & Boldyreva, E. V. (2016) *RSC Adv*, **6**, 92629.

[3] Bhardwaj, R. M., McMahon, J.A., Nyman, J., Price, L. S., Konar, S., Oswald, I. D. H., Pulham, C. R., Price, S. L. & Reutzel- Edens, S. M. (2019). *J. Am. Chem. Soc.*, **141**, **35**, 13887.