[MS24-P29] Experimental and Computational Approaches Towards Solid Form Screening of Pharmaceuticals.

Rajni Miglani Bhardwaj[#], Louise S. Price[†], Sarah L. Price[†], Susan M. Reutzel-Edens[$], Gary J. Miller[‡], Iain D. H. Oswald[#], Blair F. Johnston[#], and Alastair J. Florence[#].

[#]*Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow-G4 0RE,* [†]*Department of Chemistry, University College London, 20 Gordon Street, London-WC1H 0AJ.* [$]*Eli Lilly and Company, Indianapolis, Indiana-46285.* [‡]*Analytical Sciences, Manchester Metropolitan University, Chester Street, Manchester, M1 5GD, U.K.*
E-mail: rajni@strath.ac.uk

Experimental screening is often used to explore the range of possible solid forms (polymorphs, solvates, salts, co-crystals) of pharmaceuticals [1-2], so that the appropriate solid form can be taken forward as a clinical candidate. The purpose of this work was to demonstrate the effectiveness of combined experimental and computational approaches for solid form screening of active pharmaceutical ingredients (API). An effective methodology of high throughput crystallisation (HTC) for solid form screening using quartz 96/48 multi well plate with an automated system for collecting high quality Raman spectra was also developed. This methodology offers various advantages including reduced material requirements (1 mg per well), fast data collection, no separate sample preparation, and analysis of sample in suspension. High throughput crystallisations of API were carried out on 96/48 multi well plates under various conditions i.e. solvents, antisolvents, concentrations, different counter ions. In one example of HTC, 96 crystallisations utilizing 144 mg of a model API and ~20 ml of 48 solvents yielded 21 novel forms. HTC results were used as guide to scale up experiments to fully characterise the physical forms using XRPD, SXD, DSC and TGA. Other crystallisation methods yielded forms which were not observed during HTC, highlighting the fact that no one crystallisation method ensures all physical forms. Crystal structure prediction (CSP) studies were used to rationalise the observance of large number of physical forms and plausible explanation for the inability to obtain the metastable forms II and III separately. PIXEL calculations were used to rationalise the observance of key centrosymmetric dimer in all 35 experimental crystal structures. CSP calculations find that structures that do not contain the observed dimer are thermodynamically feasible, suggesting that kinetic effects are responsible for all the observed structures being based on the dimer. In another example of HTC, 96 crystallisations utilizing a total of 230 mg of a model API and ~24 ml of 48 solvents yielded only 3 novel physical forms. The results of HTC were used as guide to scale up experiments to fully characterize the 3 novel physical forms. Computational approaches were used for interpreting the experimental crystal energy landscape of this API and rationalise the varied solid state behaviour of both API under study.

[1] Florence, A.J., (2009). Harry G. Brittain, Informa Healthcare, New York. 2: 139-184.
[2] Morissettea, S.L., Almarssona, O., Petersona, L.M, Adv. Drug Deliv Rev, 2004, 56, 275– 300.

Keywords: Solid form screening, high throughput crystallisation, crystal structure prediction