MS39-1-3 Rapid High-Throughput Crystallisation of Dihydropyridines
#MS39-1-3

J. Metherall [1], M. Probert [1], M. Hall [1], J. McCabe [2], P. Corner [2]
[1]Newcastle University - Newcastle upon Tyne (United Kingdom), [2]AstraZeneca - Macclesfield (United Kingdom)

Abstract
Within pharmaceutical drug development, there is a strong drive to obtain the active pharmaceutical ingredients (APIs) in the solid-state, as this enables convenient tablet or capsule drug formulation, ensuring easy usage, aiding patient compliance, and improving API stability.[1] As different solid-forms have different physical properties (including solubility), solid-form screening is an essential part of early drug development, and the ability to undertake rapid crystallisation screening is therefore very beneficial.[2]
Modern materials characterisation can be heavily dependent on the availability of suitable, high-quality crystals for analysis, as such crystals enables analysis by single crystal X-ray diffraction (SCXRD), providing atomic level structural resolution. Success in growing crystals is proportional to the amount of experimental crystallisation space explored. Approaches to the investigation of crystallisation space have undergone a 'step-change' in recent years with new techniques[3-5] becoming available *via* the use of technological advancements in liquid handling.[6] One of these 'step-change' developments is high-throughput encapsulated nanodroplet crystallisation (ENaCt). This technique permits large numbers of experimental crystallisation conditions to be screened in parallel with low overall quantities of analyte consumed. The method allows for the initiation of hundreds of individual crystallisation experiments within a few minutes of preparing solutions of the analyte in question.
We have shown that ENaCt is a capable tool for the crystallisation and subsequent SCXRD analysis of a set of six API analogues, belonging to the dihydropyridine class. Dihydropyridines are calcium channel blockers, used in the treatment of hypertension. The high-throughput crystallisation experiments presented herein were performed using a liquid-handling robot (SPT Labtech Mosquito®)[6] on the microgram scale, reducing the overall material demand to a few milligrams of total analyte. Crystals were grown from nanolitre-scale droplet solutions with each compound prepared for crystallisation in twelve common laboratory solvents. Oils were used to encapsulate the samples, with the aim to reduce the rate of solvent loss and allow a slow increase in the sample concentration up to and beyond the point of saturation. The oil encapsulation combined with the restricted number of nucleation sites available in such small droplets, aids the growth of high-quality single crystals.[1]
The six dihydropyridine compounds were successfully crystallised using the developed ENaCt protocol; single crystals of dimensions ≥ 50 μm being obtained within 2 weeks, and have been analysed via SCXRD. The results clearly demonstrate that the high-throughput crystallisation screening methods employed are beneficial in obtaining high-quality single crystals, suitable for SCXRD, in short timeframes with low overall sample requirements (~20 mg), hence providing a valuable technique for use in the drug development process.

References
1. S.L. Morissette, O. Almarsson, M.L. Peterson, J.F. Remenar, M.J. Read, A.V. Lemmo, S. Ellis, M.J. Cima and C.R. Gardner, *Adv. Drug Delivery Rev.*, 2004, **3**, 275-300.

2. L.F. Huang and W.Q. Tong, *Adv. Drug Delivery Rev*. 2004, **56**, 321-334.

3. A.R. Tyler, R. Ragbirsingh, C.J. McMonagle, P.G. Waddell, S.E. Heaps, J.W. Steed, P. Thaw, M.J. Hall and M.R. Probert, *Chem*., 2020, **6**, 1755-1765.

4. P.P. Nievergelt, M. Babor, J. Cejka and B. Spingler, *Chem. Sci.*, 2018, **9**, 3716-3722.

5. M. Hoshino, A. Khuita, H. Xing, Y. Inokuma and M. Fujita, *IUCrJ*, 2016, **3**, 139-151.

6. SPL Labtech Mosquito®, https://www.sptlabtech.com/company.