AstraZeneca

UKRI Innovate UK

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Knowledge Transfer Partnership (KTP) helps AstraZeneca to improve product quality and manufacturing processes

Background

There is often uncertainty about the position of atoms within the crystal structure of an active pharmaceutical ingredient (API) – known as "crystallographic disorder." Such crystallographic disorder can affect physiochemical properties and make an API difficult to manufacture consistently. Problems may also be seen with physical and chemical stability, dissolution rate, solubility and bioavailability. All of which challenge the requirement for a stable medicine with consistent quality and performance.

Challenge

A Knowledge Transfer Partnership (KTP) was initiated between AstraZeneca and the University of Warwick to mitigate some of the problems of crystallographic disorder in active pharmaceutical ingredients.*

KTPs aim to help businesses improve their competitiveness and productivity through better use of knowledge, technology, and skills within the UK academic knowledge base. The focus of this KTP was the application of experimental solid-state Nuclear Magnetic Resonance (NMR) and complementary density-functional theory (DFT) calculations of NMR parameters, in a so-called 'NMR crystallography' approach to such systems.

NMR is a powerful form of spectroscopy that uses a strong magnetic field to gain information on the electronic - and hence chemical environment of certain nuclei, notably carbon, hydrogen, and nitrogen. It is one of the few experimental techniques that can be used to understand crystallographic disorder.

One of the aims of the KTP partnership was to work on delivering new and sector-leading innovation to give an improved understanding of the range of models and molecular motions that best describe the crystallographic disorder, as well as to identify the causes of the disorder. These insights would enable AstraZeneca to design approaches to reduce the risks often associated with disordered systems. Furthermore, a better understanding of the atomic-level structure of crystallographically disordered active pharmaceutical ingredients would expedite AstraZeneca's ability to develop pharmaceutical formulations.

The challenge was for the knowledge gained from this KTP to lead to better quality products and improved manufacturing processes. Better designed products and processes would result in fewer batch failures during manufacturing, and less waste. This aligns with AstraZeneca's aim for superior science led products, improved outcomes for patients, and environmental sustainability.

Solution

Dr Patrick Szell, a University of Ottawa graduate, was recruited as the KTP Associate on this two-year project, and embedded within a multi-disciplinary team working at the interface between industry and academia. The project was funded by UK Research and Innovation (UKRI) through Innovate UK.

Patrick started by applying solid-state NMR experiments on compounds currently in AstraZeneca's development phase[1]. Improvements were made in performing the NMR calculations (running the calculations, extracting and interpreting the results[3]), understanding the influence of crystallographic packing on crystallographic disorder, and leveraging less-employed "exotic" nuclei - such as chlorine[5] - to gain information on the crystallographic disorder[1, 2, 4].

One of the challenges faced by the partnership was how to relate the NMR response to the disorder. To help address this, Patrick was able to leverage Warwick's expertise in investigating dynamics to provide insights into the influence of crystal packing on molecular motion in a representative pharmaceutical and its cocrystals. Patrick used cutting-edge technology at the University of Warwick, such as the UK's first 1 GHz NMR spectrometer that was brought to field in 2020 and operates as part of Warwick-hosted UK High-Field Solid-State NMR Facility.

Patrick also created a series of computational tools designed to automate the task of performing NMR calculations and analysing the results, thereby providing AstraZeneca scientists with a harmonised way of working and providing significant time savings.

Patrick said: "Having had the opportunity to work with AstraZeneca, a pharmaceutical giant, and contributing to the development of medicines that save lives has been an immensely rewarding experience. The combination of an excellent team, access to a world-class NMR facility at the University of Warwick, and the resources available at AstraZeneca resulted in rapid advancements in understanding crystallographic disorder in pharmaceuticals."

Dr Leslie Hughes, AstraZeneca said: "A highly successful KTP between the University of Warwick and AstraZeneca has resulted in improved tools for modelling and calculating NMR parameters associated with disordered pharmaceuticals," with Professor Steven P. Brown, University of Warwick commentating that: "The placement of the KTP Associate for the two-year project duration with AstraZeneca, working on live compounds and with day-to-day interaction with AstraZeneca scientists, provides a direct channel for rapid and effective exchange of knowledge and ideas between academia and industry. This is quantitatively different to what can be achieved working on representative generic compounds in, for example, industry-supported PhD projects."

Dr Russ Bromley, Knowledge Transfer Adviser from the Knowledge Transfer Network added: "Despite difficult circumstances as a result of the Covid pandemic, Dr Szell was able to continue his experimental work with the world-class NMR facility at the University of Warwick. He significantly reduced the time taken to analyse NMR output that increased experimental productivity for the project and AstraZeneca's NMR facilities. Project outcomes in quality and quantity advanced AstraZeneca's knowledge of crystallographic disorder and seven significant publications from a two-year KTP project sets a new record."

Impact

The KTP's impact has been wide and far-reaching and has led to the following:

- Confirmation of the structural model and characterisation of the disorder in several compounds currently in development
- Automation of NMR calculations in a single mouse-click. This has been beneficial in harmonising ways of working, increasing accessibility to non-specialists, improving robustness, and creating significant time savings for AstraZeneca employees and other UK industrial NMR users.
- The ways of working developed by Patrick have also generated substantial interest in AstraZeneca, as well as in other companies to implement these methods in work practices.
- Seven external publications have and will come out of this KTP, resulting in a significant scientific contribution.
- Pharmaceutical industry and business impact: An improved ability to use NMR crystallography to model and hence understand the disorder present in many pharmaceuticals, removes some of the risk associated with developing such systems into commercially viable medicines.
- Knowledge transfer across AstraZeneca has been extensive and has taken place through four communications pathways: (i) internal AstraZeneca publications, (ii) presentations, internally and externally through conferences and industrial gatherings and webinars, (iii) training sessions for AstraZeneca employees, (iv) manuals and training videos.
- Paving the way for the production of better quality medicines (more stable /consistent quality/ with consistent performance) and improved manufacturing processes.

Footnotes

* awarded the highest grade of "Outstanding" by the KTP Grading Panel for its achievement in meeting KTP's Objectives.

1. P.M.J. Szell, S.P. Brown, L.P. Hughes, H. Blade, S.O. Nilsson Lill, A Curious case of dynamic disorder in pyrrolidine rings elucidated by NMR crystallography. *Chem. Commun.* 2020, 56, 14039-14042. **https://doi.org/10.1039/D0CC05236A**
2. P.M.J. Szell, J.R. Lewandowski, H. Blade, L.P. Hughes, S.O. Nilsson Lill, S.P. Brown, Taming the dynamics in a pharmaceutical by cocrystallization: investigating the impact of the coformer by solid-state NMR. *CrystEngComm*, 23, 2021, 6859-6870. **https://doi.org/10.1039/D1CE01084K**
3. P.M.J. Szell, S.O. Nilsson Lill, H. Blade, S.P. Brown, L.P. Hughes, A toolbox for improving the workflow of NMR crystallography. *Solid State Nuclear Magnetic Resonance*, 116, 2021, 101761. **https://doi.org/10.1016/j.ssnmr.2021.101761** with WRAP dataset **http://wrap.warwick.ac.uk/156679/**
4. A.J. Al-Ani, P.M.J. Szell, Z. Rehman, H. Blade, H.P. Wheatcroft, L.P. Hughes, S.P. Brown, C.C. Wilson, Combining X-ray and NMR Crystallography to Explore the Crystallographic Disorder in Salbutamol Oxalate. *Under Review*
5. P.M.J. Szell, Z. Rehman, B. Tatman, L.P. Hughes, H. Blade, S.P. Brown, Exploring the potential of ^{35}Cl solid-state NMR to characterize disorder in pharmaceutical hydrochlorides. *Article in preparation.*