Case Study Template

1. Title of Case Study: NMR Crystallography in Pharmaceutical Development

2. Grant Reference Number: Contract: PR140003

3. One sentence summary: ^{1}H, ^{13}C and ^{14}N two-dimensional Nuclear Magnetic Resonance (NMR) spectra obtained at the UK 850 MHz Solid-State NMR Facility enable the refinement of crystal structures of pharmaceuticals by an NMR crystallography approach that combines experiment with calculation of NMR parameters.

4. One paragraph summary:

Nuclear magnetic resonance (NMR) spectroscopy is a powerful analytical tool for characterising the structure of molecules with atomic resolution via the chemical shift and quadrupolar interaction (for spin $I \geq 1$) that are sensitive to the local electronic environment of the atomic nucleus and dipolar and J couplings of nuclear spins that inform on through-space proximities and through-bond connectivities. Employing the technique of magic-angle spinning (MAS) enables NMR analysis to be performed for samples in the solid state. This case study describes the application of experimental MAS NMR to characterise the packing of molecules of an active pharmaceutical ingredient in the solid state, notably benefitting from the enhanced resolution and signal to noise provided by working at the high magnetic field of the UK 850 MHz Solid-State NMR Facility. By combining experiment with calculation of NMR parameters using density-functional theory, the output of a single-crystal X-ray diffraction analysis was checked. Specifically, the study refined the position of a key hydrogen atom, thus providing valuable insight into the intermolecular hydrogen bonding that governs the adopted structure. Such fine detail in structural analysis is of importance for regulatory approval, as well as for predicting stability of the active ingredient when delivered as a medicine.

5. Key outputs in bullet points:

- *Access for a leading UK pharmaceutical company to state-of-the-art solid-state NMR experimental characterisation*
- *Use of NMR crystallography (comparison of experiment to NMR chemical shifts and quadrupolar parameters calculated using density-functional theory) to refine and validate crystal structures solved by X-ray diffraction*
- *Atomic-level understanding of key intermolecular hydrogen-bonding interactions that govern the packing of an active pharmaceutical ingredient molecule in the solid state; this insight is critical information for predicting stability during manufacture, and for regulatory approval*

6. Main body text

Solid-state NMR characterisation was performed at a magnetic field strength of 20 Tesla (corresponding to a ^{1}H Larmor frequency of 850 MHz) for an active pharmaceutical ingredient within development at AstraZeneca: one-dimensional ^{1}H and ^{13}C MAS NMR spectra and two-dimensional ^{1}H-^{13}C and ^{14}N-^{1}H MAS NMR correlation spectra were recorded, hence allowing the resolution and assignment of ^{1}H and ^{13}C chemical shifts and the determination of ^{14}N quadrupolar parameters. Starting from the output of a single-crystal X-ray diffraction structure determination, NMR parameters were calculated using density functional theory. In an NMR crystallography analysis, a

comparison was then made between the experimental and calculated NMR parameters. A particular focus was on the NMR parameters for hydrogen and nitrogen atoms involved in intermolecular hydrogen bonding interactions that drive the adopted packing of the molecules in the solid state. Importantly, the study refined the understanding of the co-crystal/ salt categorisation of the structure – this comes down to a question as to whether a particular hydrogen atom is close to one of two different heteroatoms. Since X-rays are diffracted by electrons, it is a challenge, as in this case, to determine precisely such hydrogen atom positions in an X-ray diffraction experiment; by comparison, the NMR parameters are very sensitive to such a change in the structure.

Data from the 850 MHz spectrometer at Warwick combined with GIPAW predictions enables us to refine structural models derived from diffraction data. This includes the position of hydrogen atoms. Better structural models enables AstraZeneca to make more reliable property predictions.

7. Names of key academics and any collaborators:

Professor Steven P. Brown, Department of Physics, University of Warwick
Dr Helen Blade and Dr Leslie P. Hughes, AstraZeneca UK

8. Sources of significant sponsorship (if applicable):

Contract for the High-Field Solid-State Nuclear Magnetic Resonance Facility (EPSRC)
AstraZeneca

9. Who should we contact for more information?

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