Case Study Template

1. Title of Case Study: Solid-State NMR of Pharmaceuticals

2. Grant Reference Number: EP/F017901/1, NS/A000061/1 & EP/T015063/1

3. One sentence summary: ^{1}H, ^{13}C and ^{14}N two-dimensional Nuclear Magnetic Resonance (NMR) spectra obtained at the UK High-Field Solid-State NMR Facility provide structural and dynamic insight at atomic resolution for pharmaceuticals, often employing 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 structure and dynamics 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 High-Field 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 can be validated. By focusing in on key hydrogen atoms, valuable insight is obtained 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 leading UK and international pharmaceutical companies to state-of-the-art solid-state NMR experimental characterisation*
- *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*
- *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, and quantify the effect of specific key intermolecular interactions, hydrogen bonding and pi interactions, on NMR parameters*

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 active pharmaceutical ingredients, in projects of relevance to AstraZeneca, Bristol-Meyers Squibb, Daiichi Sankyo, and GlaxoSmithKline. One-dimensional ^{1}H and ^{13}C MAS NMR spectra and two-dimensional ^{1}H-^{1}H, ^{1}H-^{13}C, ^{14}N-^{1}H and ^{35}Cl-^{1}H MAS NMR correlation spectra allow the resolution and assignment of ^{1}H and ^{13}C chemical shifts and the determination of ^{14}N and ^{35}Cl quadrupolar parameter, as well as the identification of specific H-

H, C-H and N-H proximities, notably key intermolecular proximities associated with hydrogen bonding.
In an NMR crystallography analysis, starting from the output of a single-crystal X-ray diffraction structure determination, NMR parameters can be calculated using density functional theory. Considering a comparison between experimental and calculated NMR parameters, a particular focus is 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. As an example, this is important for understanding of the co-crystal/ salt categorisation of a system – 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.
References:
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7. Names of key academics and any collaborators:

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9. Who should we contact for more information?

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