^{35}Cl Dynamic Nuclear Polarization Solid-State NMR of Active Pharmaceutical Ingredients

David A. Hirsh,[1] Aaron J. Rossini,[2] Lyndon Emsley,[3] and Robert W. Schurko[1,*]

[1]Department of Chemistry & Biochemistry, University of Windsor, Windsor, ON, Canada N9B3P4
[2]Department of Chemistry, Iowa State University, Ames, IA 50011-3111
[3]Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland CH-1015
* Corresponding author: rschurko@uwindsor.ca

The identification of solid forms of active pharmaceutical ingredients (APIs) plays an important role in drug development, both in the discovery of new forms and quality assurance. Each polymorph, pseudopolymorph (such as a hydrate or solvate), cocrystal, or salt of an API is uniquely patentable, and can have substantially different psychochemical properties (stability, solubility, bioavailability etc.) that make it more (or less) desirable for future development of a dosage form. Once a final formulation has been chosen for the dosage form, it must be screened for the presence of impurities and polymorphs that can limit the drug's effectiveness or produce a costly (and dangerous) undesired form of the drug.

Solid pharmaceuticals are commonly characterized using X-ray diffraction, ^{1}H and ^{13}C solid-state NMR (SSNMR), and thermogravimetric methods. In many cases, these techniques provide adequate characterization of the bulk forms of APIs, but they often fail to distinguish between forms of an API that have similar structures, or to provide unambiguous identification of the API in dosage forms. The signal from such dosage forms is typically confounded by interference from the excipient (e.g., binding ingredients and fillers in the tablet or capsule), which can make data interpretation ambiguous.

Prior work in our group[1,2] has demonstrated that ^{35}Cl SSNMR is a valuable tool for characterizing the bulk and dosage forms of APIs that have been synthesized as HCl salts. As ^{35}Cl is a quadrupolar nucleus (I = 3/2), its spectra are influenced by a combination anisotropic chemical shift and quadrupolar interactions. The later are particularly sensitive to small changes in the local Cl^- anion environment (e.g., differences in hydrogen bonding), which produce ^{35}Cl SSNMR spectra that serve as distinct spectra fingerprints of each form of an API.

Given the importance of identifying even trace amounts of an alternate API structure within a dosage form, there has been a focus on improving the lower detection limit (LDL) of ^{35}Cl SSNMR spectra. Our research group has developed pulse sequences that enable the rapid acquisition of broad ^{35}Cl SSNMR patterns with high S/N even at moderate field strengths (*e.g.*, 9.4 T). The WURST-CPMG[3] and BRAIN-CP[4] pulse sequences are used for direct (^{35}Cl) and indirect (^{1}H-^{35}Cl) broadband excitation of ^{35}Cl SSNMR spectra. Despite these developments, acquiring high-quality spectra in a short amount of time can still be a challenge in some cases, especially for species in low concentrations.

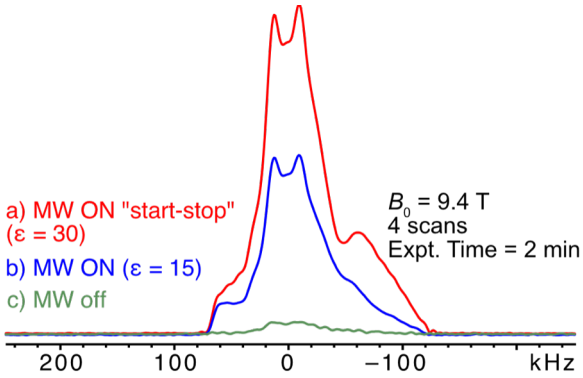

Fig. 1 ^{35}Cl BCP/WCPMG (static) DNP spectra of Ambroxol HCl. Acquired with μwaves ON a) & b) and off c). For a), the sample was slowly rotated during the recycle delay. ε = DNP enhancement

Over the past few years, dynamic nuclear polarization (DNP) has become a popular method for achieving high gains in S/N, and for probing a number of materials previously unamenable to routine study by SSNMR.[5] Recent developments in instrumentation and sample preparation have enabled signal increases in excess of 300.[6] To date, these studies have been limited to the characterization of narrow patterns (typically for the spectral acquisition of spin-1/2 nuclides such as ^{1}H and ^{13}C). In this presentation, I will discuss the first acquisition of wideline ^{35}Cl DNP SSNMR spectra, with focus on spectral quality, CP and decoupling conditions, and protocols for the acquisition of DNP NMR under static sample conditions. Such experiments have the potential to increase signals by factors of 10 to 200, which would enable the rapid acquisition of spectra of tablets and dosage forms, including those with low wt-% APIs. Such improvements will also allow us to study API domain sizes, excipient-API interactions, and to discover new polymorphic forms and impurity phases.

[1] Hamaed, H *et al. J. Am. Chem. Soc.* **2008**, 130, 11056.
[2] Hildebrand, M. *et al. CrystEngComm* **2014**, 16, 7334.
[3] O'Dell, L. A.; Schurko, R. W. *Chem. Phys. Lett.* **2008**, 464, 97.
[4] Harris, K. J. *et al. J. Magn. Reson.* **2012**, 224, 38.
[5] Bajaj, V. S. *et al. J. Magn. Reson.* **2007**, 189, 251.
[6] Rossini, A. J *et al. J. Magn. Reson.* **2015**, 259, 192.