**Using 35Cl Solid-State NMR at Ultra-High Magnetic Fields to Study Active Pharmaceutical Ingredients: Polymorphs and Dosage Forms**

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**Introduction**

 The differentiation of polymorphs of active pharmaceutical ingredients (APIs) is of great importance in the pharmaceutical industry; distinct polymorphs may exhibit different physicochemical properties such as bioavailability, shelf life, stability, and each unique polymorph can be patented.1 Since most APIs are prepared as solids, it is crucial to structurally characterize and identify polymorphs and impurities in both their initial bulk forms and their final dosage forms (e.g., pills, capsules, tablets, etc.). Polymorphs are most commonly differentiated with the use of X-ray diffraction (XRD) and 13C solid-state NMR (SSNMR) techniques.2 Our group has demonstrated in 2008 that 35Cl SSNMR can serve as a complementary technique to these conventional characterization methods.3 In 2014, we published a comprehensive study of the relationship between 35Cl NMR parameters and molecular structures in a series of 20 APIs and related polymorphs.4 The current work describes the use of 35Cl SSNMR for identifying the solid phases of APIs, along with impurities, in a variety of dosage forms. The 21.1 T NMR system at the MagLab has been crucial for the success of this work.

**Experimental**

35Cl SSNMR experiments were conducted at the NHMFL in Tallahassee, FL using the 900 MHz NMR spectrometer and a 3.2 mm HX MAS probe. Spectra were acquired with the QCPMG5 and BRAIN-CP/WURST-CPMG (BCP) pulse sequences.6 Samples were purchased from Sigma-Aldrich or prepared according to literature methods.

**Results and Discussion**

35Cl SSNMR spectra of two polymorphs of **isoxsuprine** **HCl** (**IsoxI** and **IsoxII**) were acquired in short experimental times at 21.1 T (figs. **b** and **d**). The polymorphs are easily differentiated with simulations (figs. **c** and **e**) due to the different quadrupolar parameters for each polymorph. During the production of dosage forms, the API is generally mixed into an excipient matrix (cellulose, binders, etc.), which often renders 13C NMR spectra unhelpful due to overlap of signals from the excipient and API. Since the excipient does not contain chlorine atoms, undistorted 35Cl SSNMR powder patterns arising purely from the API are observed, allowing easy identification of the phase in the dosage form (**IsoxI**, fig. **a**).The use of an *ultra-high magnetic field* (UHF) allows for *rapid* *acquisition* of 35Cl SSNMR spectra of APIs in any form – this is very helpful for dosage forms, where the wt% of API is often very low. Our lower detection limit is currently less than 0.5%. We believe that UHF NMR, along with pulse sequences designed in our laboratory, will be of great use in many future studies of APIs, polymorphs, impurities, drug discovery and improving formulation processes.

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