Using Ultra-High Magnetic Fields to Study Isoxsuprine HCl and Mexiletine HCl Using ^{35}Cl Solid-State NMR: Polymorphs and Dosage Forms

Schurko, R.W.; Veinberg, S.L.; Jaroszewicz, M.J.; Sandre, A.R.; Namespetra, A.M. (U. of Windsor, Chemistry); Frydman, L. (Weizmann Institute, Chemical Physics/NHMFL); Hung, I.; Gan, Z. (NHMFL)

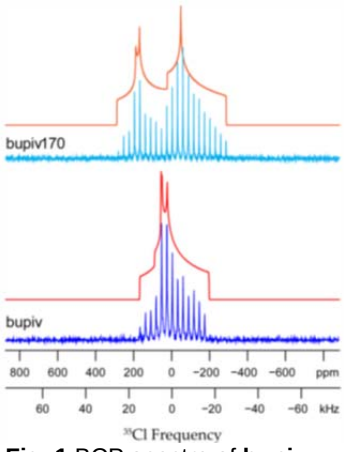

Fig. 1 BCP spectra of **bupiv** and **bupiv170** and corresponding analytical simulation in red.

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, etc., and each unique polymorph is patentable.[1] Since most APIs are prepared as solids (in many cases packed, shipped and added to excipients as solids), it is crucial to structurally characterize and identify polymorphs and impurities in both their initial bulk forms and their final dosage forms. Polymorphs are most commonly differentiated with the use of X-ray diffraction (XRD) and ^{13}C solid-state NMR (SSNMR) techniques.[2] In a 2008 publication, our group demonstrated that ^{35}Cl SSNMR can serve as a complementary technique to conventional characterization methods.[3] In 2014, we worked with the NHMFL to publish a comprehensive study of the relationships between ^{35}Cl NMR parameters and molecular structures in a series of 20 APIs and related polymorphs.[4] New studies are currently in progress on the detection of APIs in dosage forms (e.g., pills, capsules, etc.), identification of impurities, and 2D methods for separating complex overlapping patterns.

Experimental

^{35}Cl SSNMR experiments were conducted at the NHMFL facility in Tallahassee, FL using the 900 MHz ultra-wide bore NMR spectrometer and a 3.2 mm ^{1}H-X MAS probe. Spectra were acquired with the Hahn-echo (HE) pulse sequence as well as the WURST-CPMG (DE) and BRAIN-CP/WURST-CPMG (BCP) pulse sequences.[4,5] Samples were purchased from Sigma-Aldrich or prepared according to methods outlined in the literature.

Results and Discussion

^{35}Cl SSNMR spectra of two polymorphs of **bupivacaine HCl** were acquired in short experimental times using the BCP pulse sequence (*Figure 1*). The polymorphs can easily be differentiated with ^{35}Cl SSNMR due to different ^{35}Cl quadrupolar parameters (C_Q and η_Q) in both compounds. During the chemical formulation of the dosage forms, the API is generally mixed into an excipient matrix (cellulose, binders, etc.) which often render ^{13}C NMR spectra unhelpful due to overlap of signals from the excipient and API. Fortunately, the excipient does not contain chlorine atoms, which results in undistorted ^{35}Cl SSNMR powder patterns arising purely from the API, allowing for easy indentification of the API in the dosage form (**mexilitene HCl**, *Figure 2*). The use of an ultra-high magnetic field allows for ***rapid acquisition*** of ^{35}Cl SSNMR spectra of APIs in any form in very short experimental times – 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%.

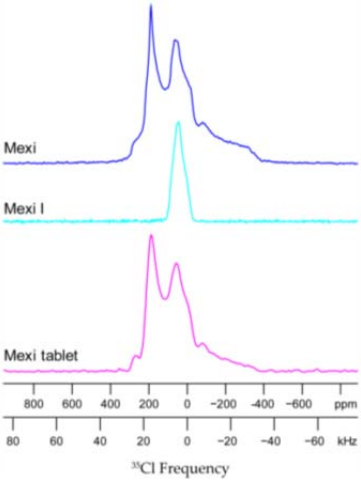

Fig. 2 ^{35}Cl SSNMR spectra of **mexi**, **mexi I** and a **mexi tablet.**

Acknowledgements

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