Application of Solid-State ^{35}Cl NMR Spectroscopy for the Detection of Polymorphism in Hydrochloride Anaesthetic Pharmaceuticals

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Introduction

Hydrochloride local anaesthetic (LA) compounds are a group of drugs with common structural features which determine their pharmaceutical function and activity. These features allow conformational flexibility in their structures which lead to the possibility of formation of different polymorphs, as well as hydrates and solvates (pseudopolymorphs). Polymorphism can lead to drastic effects on the bulk properties of these drugs, including dissolution rate, bioavailability and chemical and physical stabilities, all of which can affect performance and shelf-life. Traditionally, single-crystal and powder X-ray diffraction (XRD) have been the primary methods for solid-state characterization of pharmaceuticals. For many standard pharmaceuticals, isolation of crystals suitable for single-crystal XRD studies can be very difficult. Powder XRD is useful for distinguishing polymorphs in microcrystalline samples, but lends little to identification of slight structural or conformational changes, and fails to identify disordered or amorphous phases.[1] Solid-state NMR (SSNMR) spectroscopy is a powerful complementary technique for the study of structural polymorphism and pseudo-polymorphism.[2] In this project, we utilize ^{35}Cl SSNMR spectroscopy to study microcrystalline forms of select LA HCl pharmaceuticals. The sensitivity of the ^{35}Cl chemical shielding (CS) and electric field gradient (EFG) tensors to subtle changes in the Cl^- environments is reflected in the ^{35}Cl SSNMR powder patterns. Coupled with standard ^{13}C and ^{1}H NMR experiments, XRD and *ab initio* calculations of NMR parameters, ^{35}Cl SSNMR provides a powerful probe of polymorphism in HCl pharmaceuticals.

Experimental

^{35}Cl SSNMR experiments were carried out on a Varian Infinity Plus spectrometer with an Oxford 9.4 T wide-bore magnet using 5mm HX static probe at the University of Windsor. High field ^{35}Cl NMR data were collected on an ultra-wide bore 900 MHz (21.1 T) superconducting NMR magnet (NHMFL) using a 3.2 mm MAS HX probe and flat coil HX static probe.

Results and Discussion

The ^{35}Cl NMR spectra of LH (Figure 1) reveal one chlorine site in agreement with the crystal structure. Experiments at 21.1 T are crucial for (i) obtaining high-resolution MAS NMR patterns and (ii) isolating anisotropic CS parameters. Simulations reveal a quadrupolar coupling constant, C_Q, of 4.67 MHz, and asymmetry parameter, η_Q, of 0.77. The LH polymorph, LH1, does not have a known crystal structure. ^{35}Cl NMR spectra of LH1 provide an exquisite probe of molecular structure, revealing two overlapping second-order patterns, corresponding to two distinct chlorine environments. Site 1, which is distinguished by a narrower central pattern, has values of C_Q =2.52 MHz and η_Q = 0.95, consistent with a Cl^- ion surrounded by three short hydrogen-chlorine contacts.[3] Site 2 has a broad pattern with two clearly visible discontinuities, arising from a larger C_Q = 5.32 and η_Q closer to zero. These values reveal a Cl^- ion with only one short hydrogen-chlorine bond.[3]

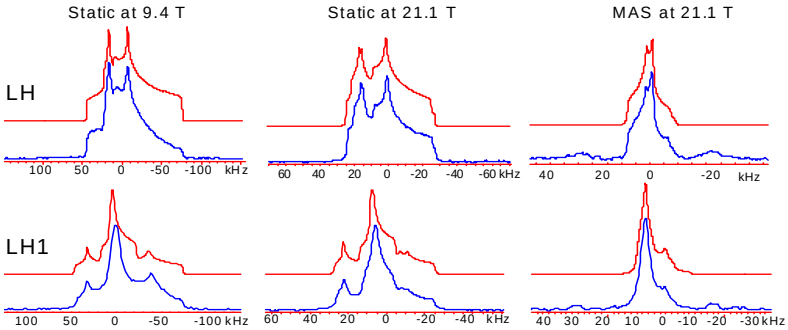

Figure 1. ^{35}Cl NMR spectra and simulations of lidocaine HCl monohydrate (LH) and its polymorph (LH1) at two different fields.

Conclusions

The sensitivity of the ^{35}Cl EFG and CS tensor parameters to the chlorine chemical environment, and the potential to model these sites with *ab initio* calculations, holds much promise for application to a wide variety of HCl pharmaceuticals.

References

[1] B. E. Padden, et al., *Anal. Chem.* **1999**, *71*, 3325.
[2] R. K. Harris, *Analyst* **2006**, *131*, 351.
[3] D. L. Bryce, M. Gee, R. E. Wasylishen, *J. Phys. Chem. A* **2001**, *105*, 10413.