Application of Solid-State ^{35}Cl NMR Spectroscopy for the Detection of Polymorphism in a Variety of Hydrochloride Pharmaceutical Drugs

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Introduction

In our recent publication,[1] we show that ^{35}Cl solid-state NMR (SSNMR) spectroscopy is a powerful complimentary technique to XRD and ^{13}C SSNMR experiments for the study of pharmaceutical polymorphs. It provides clear information on the number of chlorine sites and shows great utility for identifying sites in non-crystalline, disordered or even impurity phases, especially in cases where the solid-state ^{13}C NMR spectra or powder XRD data are unable to differentiate polymorphs. Due to the usefulness of the ^{35}Cl SSNMR in identifying different polymorphs, the fact that 50% of all pharmaceutical salts are HCl salts and that chlorine is present ca. 25% of drugs, we are extending this work to include a variety of HCl pharmaceuticals and their polymorphs. Our previous work has also shown that the use of ultrahigh field NMR spectrometers is crucial for the success of such work, for both fast acquisition of high *S*/*N* NMR spectra and accurate determination of anisotropic quadrupolar and chemical shift parameters. In this project, we utilized ^{35}Cl SSNMR spectroscopy, at 9.4 and 21.1 T, to study a number of 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. When coupled with standard ^{13}C and ^{1}H NMR experiments, XRD and *ab initio* calculations of NMR parameters, ^{35}Cl SSNMR is an excellent probe of HCl pharmaceuticals and their polymorphs.

Experimental

^{35}Cl SSNMR experiments were carried out on a Varian Infinity Plus spectrometer with an Oxford 9.4 T wide-bore magnet using 5 mm 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 mexiletine HCl (MH) (Figure 1) reveal two different chlorine sites, 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 quadrupolar coupling constants, C_Q, of 5.45 & 3.1 MHz, and asymmetry parameter, η_Q, of 0.40 & 0.55 for the two sites. The ^{35}Cl NMR spectra of two polymorphs of MH, which have no known crystal structures, were also obtained. ^{35}Cl NMR spectra of MH polymorphs show very different chlorine environments; modeling with *ab initio* calculations should provide much insight into their structures.

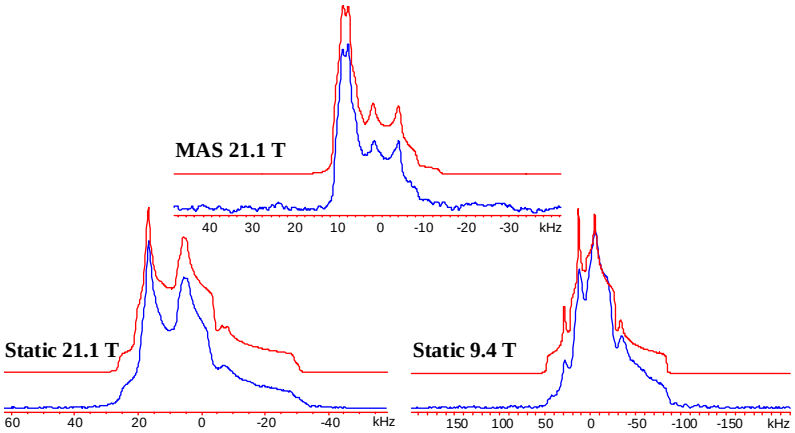

Figure 1. ^{35}Cl MAS and static NMR spectra and simulations of mexiletine HCl at two different fields

Conclusions

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

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References

[1] H. Hamaed, J. M. Pawlowski, B. F. T. Cooper, R. Fu, S. H. Eichhorn, R. W. Schurko, *JACS* **2008**, *130*, 11056.