^{35}Cl Solid-State NMR of HCl Pharmaceuticals: Pure Samples, Polymorphs and Dosage Forms

A. Namespetra, D. Hirsh, A. Sandre (U. of Windsor, Chemistry and Biochemistry); I. Hung, Z. Gan (NHMFL);
R. W. Schurko (U. of Windsor, Chemistry and Biochemistry)

Introduction

50% of active pharmaceutical ingredients (APIs) contain chlorine and many are classified as HCl salts. In HCl APIs, the chloride ion (Cl^-) acts as a counterion and is coordinated by nitrogen- and oxygen-bound protons. The prominence of HCl pharmaceuticals suggests the use of ^{35}Cl solid-state (SSNMR) a powerful probe for their structural characterization. We have previously demonstrated the capability of ^{35}Cl SSNMR for the differentiation of polymorphs of HCl APIs, in compliment with more conventional ^{13}C SSNMR and powder-X-ray diffraction (pXRD) experiments.[1] ^{35}Cl SSNMR spectra reveal the number of crystallographically distinct sites, and also provide information on the coordination environments of the Cl^- anions. Furthermore, ^{35}Cl SSNMR experiments can be applied to both crystalline and amorphous phases, and are therefore capable of identifying phases and/or polymorphs that cannot be observed in pXRD patterns.

Crucial to the success of this work is the application of ultra-high magnetic field (UHMF) NMR spectrometers (18.8 T or higher). NMR experiments at UHMFs on bulk samples are completed with great rapidity, and allow for the study of real dosage forms (i.e., pills, capsules, etc.) in which the pharmaceutical compound is diluted. In addition, acquisition of ^{35}Cl NMR spectra at two fields permits the accurate extraction of both anisotropic chemical shielding and quadrupolar parameters, as well as their relative orientation; this provides a unique fingerprints for each API (and each polymorph), and acts as a structural probe of each Cl^- environment.

At present, we have collected ^{35}Cl SSNMR data on more than 25 different APIs and several sets of polymorphs. We have also commenced investigations on dosage forms, and established lower detection limits for such experiments. In the coming year, we will publish several papers describing: (i) the correlation of ^{35}Cl NMR parameters to a series of distinct Cl^- anion hydrogen bonding environments, and the use of these correlations in predicting unknown structures; (ii) the use of ^{35}Cl SSNMR for investigating impurity phases and mixes of pharmaceutical compounds; (iii) the development of ^{35}Cl SSNMR as a high-throughput method for polymorph differentiation, and quality assurance control for real dosage forms of APIs.

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

^{35}Cl SSNMR spectra of 20 mg nicardipine HCl capsules (manufactured by Mylan) under conditions of MAS (left) and on stationary samples (right) are shown in Figure 1. Comparable spectra are acquired for bulk samples (bottom) and dosage forms (middle), along with spectral simulations (top). The static ^{35}Cl spectra were acquired using the WURST-QCPMG pulse sequence, which allows for broadband excitation and T_2-driven signal enhancement, allowing for rapid acquisition of high-quality, ultra-wideline spectra.

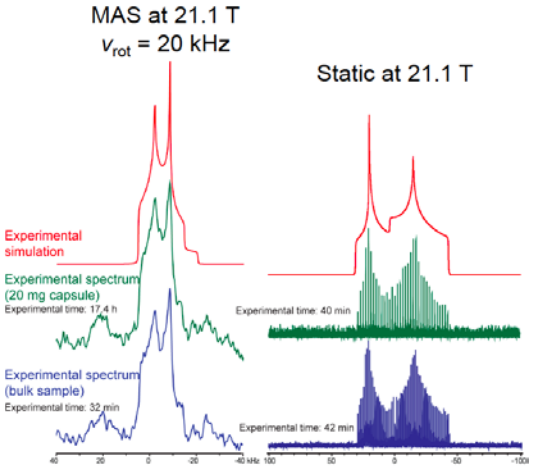

Figure 1. ^{35}Cl MAS and static NMR spectra and simulations of nicardipine HCl at two different fields.

Conclusions

The sensitivity of the ^{35}Cl EFG and CS tensor parameters to the chlorine environments holds much promise for application to a wide variety of HCl pharmaceuticals. Methods are being developed for examination of mixtures, impurities and a variety of dosage forms.

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References

[1] Hamaed, H., *JACS*, ***130***, 11056 (2008).