Solid-State NMR of ^{35}Cl: A Novel Approach to the Study of Active Pharmaceutical Ingredients

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Most active pharmaceutical ingredients (APIs) are manufactured, distributed and consumed as solids. Many APIs have multiple polymorphic forms, each of which can have distinct physicochemical properties such as solubility, melting point, and dissolution rate. In addition, APIs can also form pseudopolymorphs, which are the various hydrates and solvates with distinct sets of structures and bulk properties. Each of these unique forms may have widely varying bioavailability and stability, and also represent unique intellectual property. Therefore it is essential for the pharmaceutical industry to have reliable techniques for characterization of APIs at every stage in their development, including the bulk forms and the final dosage formulations (i.e., tablets and capsules).

Common methods for the characterization of solid APIs are thermal analysis methods, powder X-ray diffraction (PXRD) and ^{13}C solid-state NMR (SSNMR)[1]. While all of these methods are adequate for characterizing bulk forms of APIs, they have serious limitations. For instance, pXRD can only be applied to crystalline samples, ^{13}C SSNMR is limited in its capacity to distinguish peaks arising from structural differences and/or impurities. Additionally, these three techniques are not particularly useful for dosage forms, due to their complexity and interfering signals arising from the multiplicity of molecules within their excipient matrices.

More than 50% of APIs are manufactured as HCl salts, for the purposes of stabilizing their crystalline forms, while allowing for a high degree of bioavailability upon dissolution. The chloride ions in HCl APIs sit in unique environments with intricate hydrogen bonding arrangements. Interestingly, there is an excellent NMR handle capable of providing a unique spectral fingerprint for each polymorph or pseudopolymorph containing ^{35}Cl. Of the two NMR-active isotopes of chlorine, ^{35}Cl is preferred for its higher receptivity (n.a. 75.33%), and has a frequency close to 15N, making it accessible on many standard X-tuning ranges on commercial NMR probes. The acquisition, processing and simulation of 35Cl central transition (+½↔–½, CT) spectra allow for determination of ^{35}Cl electric field gradient (EFG) tensor parameters, which are normally expressed as the quadrupolar coupling constant, C_Q, and the asymmetry parameter, η_Q. The EFG tensor along with the chemical shift (CS) tensor are extremely sensitive to the network of hydrogen bonds about the chloride ions. Therefore, ^{35}Cl SSNMR spectra provide unique spectral

fingerprints for each API and their respective polymorphs, with the possibility of identifying impurities and other byproducts[2]. Additionally, relationships between the quadrupolar parameters and numbers and types of short Cl···H hydrogen bonds have been established, and can be used to aid in molecular-level structural refinement[3].

The static (i.e. non-spinning) CT powder pattern provides a direct way of measuring the CS tensor and its relative orientation to the EFG tensor. However, broad CT patterns that have high sensitivity and are uniformly excited can make acquisition challenging. Therefore, conventional experiments (e.g., Hahn-echo) require extensive signal averaging and extremely high-power rectangular pulses to address these two issues respectively. In the latter case, ^{35}Cl CT patterns are often broad enough that it is not possible to achieve uniform excitation. Moreover, since APIs in dosage forms (i.e., tablets, capsules, etc.) represent a small fraction of the total weight, conventional ^{35}Cl SSNMR experiments at moderate field strengths either require very long experimental times or are simply not possible. Fortunately, the increased availability of ultra-high field NMR systems, high-sensitivity probes, and the development of signal-enhancing pulse sequences for ultra-wideline powder patterns have made ^{35}Cl SSNMR spectroscopy an excellent option for the investigation of APIs, in both their bulk and dosage forms.[4,5] The WURST-CPMG pulse sequence[6,7] incorporates wideband uniform-rate smooth truncation (WURST) pulses for broadband excitation[8], within the context of a Carr-Purcell Meiboom-Gill (CPMG) echo train[9] for sensitivity enhancement. The resulting spectrum is composed of multiple narrow spikelets whose manifold traces out the static CT powder pattern. ^{35}Cl SSNMR experiments results are typically conducted without sample rotation, alleviating difficulties associated with rotor packing required for magic angle spinning (MAS).

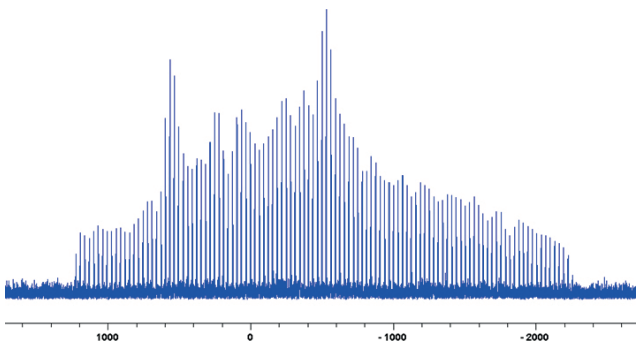
Experimental Set-Up

Below, we demonstrate the set-up of a direct excitation WURST-CPMG experiment. The parameter set ***WCPMG_35Cl*** is used with the associated pulse sequence ***wcpmg***. The WURST pulse length (P11) is set to 50 µs, sp1 is set to the power level equivalent to RF field of 18 kHz, and the pulse shape is *W_50us_500kHz_500*. The transmitter frequency (O1) is set on resonance with the 35Cl signal of NaCl (δ = 0 ppm) and the spectral width (*SWH*) is set to 1 MHz. The echo time *d6* is set to 200 µs, the dead time d3 varies from 10 to 100 µs, depending on the probe characteristics. The number of echoes (*l22*) acquired is 50 and the ^{1}H decoupling field is set to 100 kHz, but 50 kHz is sufficient. The post-acquisition treatment includes exponential multiplication with a line broadening of 50 Hz followed by Fourier transform. The subsequent spectrum is then processed with magnitude calculation (mc). Phasing these spectra, if needed, requires a second-order phase correction; hence, magnitude processing is recommended for simplicity.

Results and Discussion

We demonstrate first the results obtained with a suitable test sample: glycine HCl. In addition to its availability, low cost and low toxicity, glycine HCl is an excellent set-up sample for ^{35}Cl SSNMR of APIs since its central transition represents adequately the expected spectral width.[3,4] Figure 1 shows a spectrum of glycine HCl (purchased from Sigma Aldrich) at 11.7 T (48.9 MHz): 128 transients were acquired with a repetition rate of 1s, for a total acquisition time of approximately 2 minutes. The spectrum obtained spans 170 kHz at 500 MHz and demonstrates the efficiency of the WURST pulse for broadband excitation.

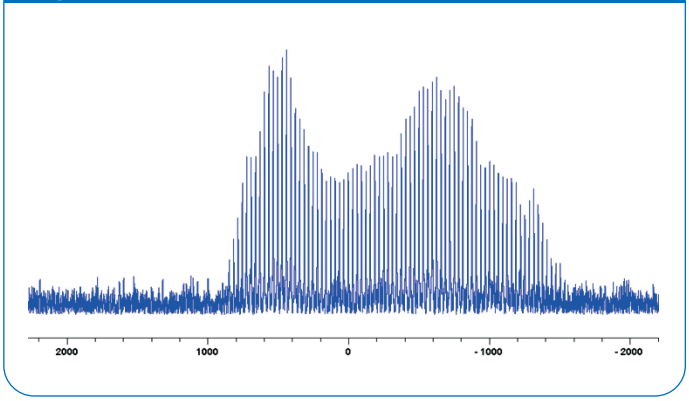
Figure 1



WURST-CPMG spectrum of glycine HCl.

Since the combination of broadband excitation pulses and CPMG echo trains play an important role in increasing experimental efficiency, we demonstrate next the application of the technique to a sample of ranitidine HCl in its final dosage formulation. Ranitidine is commonly used as a relief for heartburn symptoms. A 150 mg tablet of Zantac, purchased at a local pharmacy, was used as the dosage form. For preparation, the tablet was crushed and ground using a mortar and pestle, before transferring it into a 4mm zirconia rotor. Figure 2 shows the spectrum obtained in approximately one hour of signal averaging. The parameters used for the experiment are identical to those of figure 1, except for the number of scans, which was set to 4096.

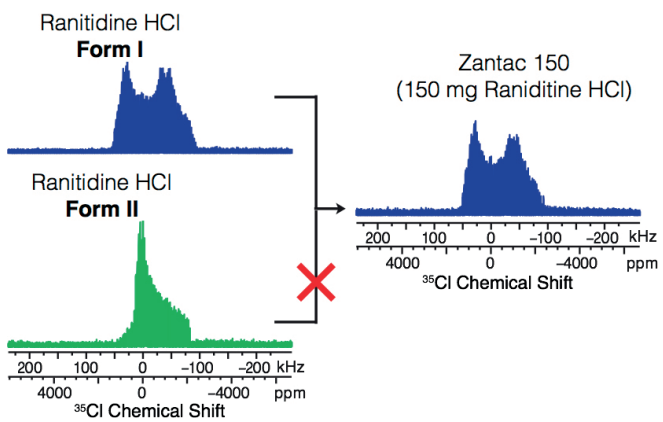
Figure 2



WURST-CPMG spectrum of a Zantac pill

The ^{35}Cl SSNMR spectrum can be simulated to obtain the ^{35}Cl EFG tensor parameters; details are described elsewhere.[3,10] However, a simple inspection of the pattern shape can provide useful qualitative information. There are two known polymorphs of ranitidine HCl, with distinct local Cl- environments. Form I has a single chlorine site involved in one close H---Cl contact,11 whereas in form II, the Cl site is involved in two close H---Cl contacts.[12] These two forms produce distinct ^{35}Cl patterns, as shown in Figure 3 (Schurko et al., unpublished results). By comparison, we can confirm that a Zantac pill purchased at the local drug store is mostly composed of ranitidine HCl form I. The ^{35}Cl powder pattern can be used as a direct assessment of the molecular polymorphism of ranitidine HCl.

Figure 3



^{35}Cl SSNMR spectra of Form I and form II of ranitidine, provided by R.W. Schurko, University of Windsor.

Conclusion

We have shown that the ^{35}Cl WURST-CPMG technique is a powerful tool for fingerprinting and characterizing the structure of APIs in their dosage forms. Using this technique, it may be possible to discover new phases or impurity products that may arise during the production and the manufacturing of formulation. Given the rapidity and ease with which spectra can be acquired, we hope the technique reported in this application note will help expand the use of ^{35}Cl SSNMR for the study of APIs in their dosage form. Furthermore, we have demonstrated that ^{35}Cl SSNMR is clearly a tool that should be added to the growing arsenal of characterization techniques used in the pharmaceutical industry, for purposes of identification, differentiation and discovery of new solid phases of APIs.

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