^{14}N solid-state NMR spectroscopy of pharmaceuticals and their polymorphs

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In a previous publication by our group [1], we demonstrated that ^{35}Cl solid-state NMR (SSNMR) spectroscopy is a powerful complimentary technique to powder X-ray diffraction (XRD) and ^{13}C SSNMR 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, or in cases where the solid-state ^{13}C NMR spectra or powder XRD data are unable to differentiate polymorphs. However, there are many pharmaceuticals and associated polymorphs that are not crystallized as hydrochloride (HCl) salts; hence, there is a need for additional probe nuclei.

Nitrogen is present in many pharmaceuticals and may serve as an attractive probe nucleus. Nitrogen has two NMR active nuclei (^{14}N and ^{15}N) which are 99.63 % and 0.37 % naturally abundant, respectively. Recent optimization of the WURST-QCPMG pulse sequence [2,3] and availability of high magnetic fields (21.1 T) have made direct observation of the ^{14}N nucleus possible. Nitrogen-14 is a spin-1 nucleus, has a non-zero electric quadrupole moment (eQ = 20.44 mb) and a low gyromagnetic ratio (γ = 1.93 × 10^7 rad T^{-1} s^{-1}). Previous studies have demonstrated the sensitivity of the ^{14}N solid-state NMR spectra to local nitrogen environments [2,4]; thus, we would like to explore the possibility of using ^{14}N SSNMR for pharmaceutical polymorph differentiation.

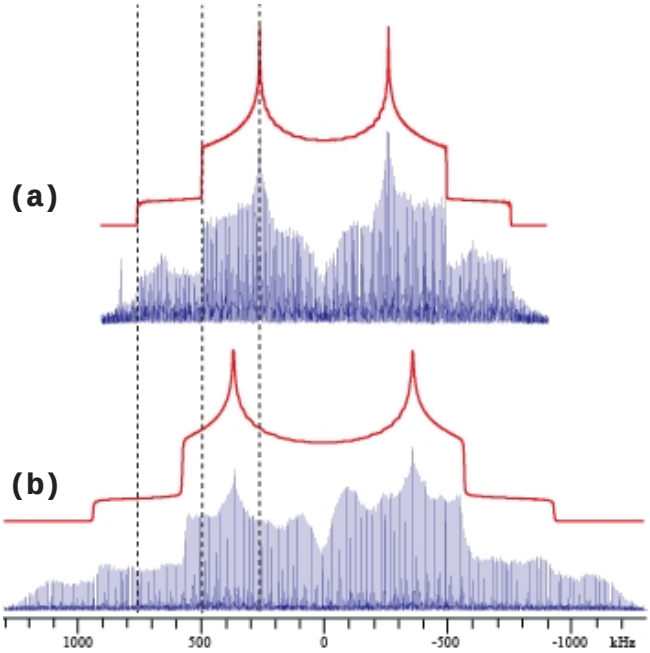

Figure 1: ^{14}N powder patterns of **(a)** bupiv I, C_Q = 1.00 MHz and η_Q = 0.31 and **(b)** bupiv II, C_Q = 1.25 MHz and η_Q = 0.22. The spectra taken at 21.1 T are composed of 2 and 4 sub-spectra, respectively, and took *ca.* 8 and 16 hours, respectively, to collect. Dashed lines highlight discontinuities of bupiv I.

In this study, a series of pharmaceuticals and their associated polymorphs have been investigated by ^{14}N SSNMR. The samples were chosen such that they all contained nitrogen atoms in pseudo-tetrahedral environments,

which have been previously demonstrated to be amenable to ^{14}N SSNMR [2]. Results from two systems are discussed below.

Bupivacaine HCl (bupiv) contains a nitrogen atom bonded to three carbon atoms and one hydrogen atom. The two polymorphs, bupiv I and bupiv II, were prepared by recrystallization from a 50/50 mixture of water and acetone and by heating to 170°C, respectively. ^{14}N SSNMR spectra for the two polymorphs show distinct discontinuities (horns, shoulders and feet) marked by the dashed lines (Figure 1). Accordingly, the C_Q and η_Q values are different for each sample. The crystal structures of both polymorph phases of bupiv are known; it is clear that the local environments of the nitrogen atoms are distinct from one another due to variation in hydrogen bond lengths and positions.

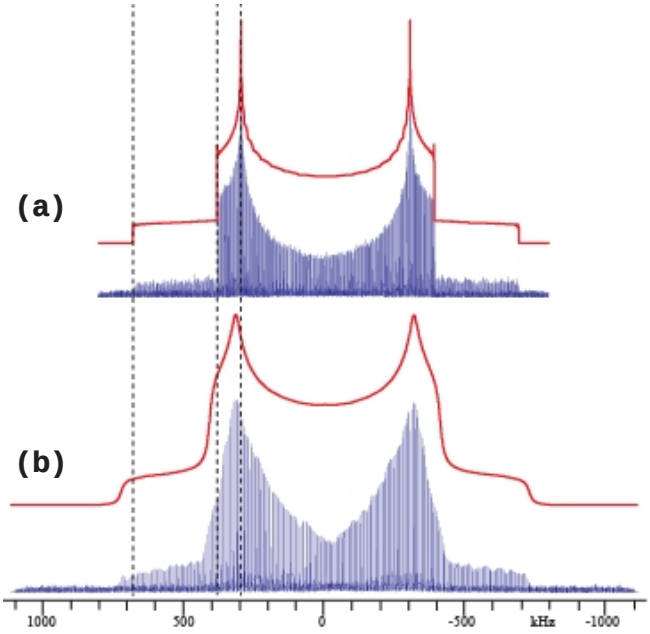

Figure 2: ^{14}N powder patterns of **(a)** mexil I, C_Q = 0.915 MHz and η_Q = 0.125 and **(b)** mexil III, C_Q = 0.97 MHz and η_Q = 0.13. The spectra recorded at 21.1 T are composed of 2 and 4 sub-spectra, respectively, and took *ca.* 2 and 5 hours, respectively, to collect. Dashed vertical lines highlight discontinuities of mexil I.

Mexiletine HCl (mexil) contains a nitrogen atom bonded to one carbon atom and three hydrogen atoms. Two polymorphs of mexil were studied; mexil I, which was recrystallized from water, and mexil III, which was produced by heating mexil I to 160 °C. Their ^{14}N powder patterns appear different, although they yield similar quadrupolar parameters (Figure 2). The mexil III powder pattern displays significant broadening, which may arise from a number of possible scenarios, including decreased long-range order, local dynamic processes, and/or an increased number of longer-range ^{14}N-^{1}H dipolar couplings (some of which may alter the relaxation characteristics of the ^{14}N nuclei in this sample). Although a crystal structure for mexil III is not available, based on the quadrupolar parameters of the two systems, it can be concluded that the nitrogen environment varies only slightly between the two polymorphs. We are currently continuing our investigation of pharmaceutical polymorph systems using ^{14}N SSNMR.

References

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