Rapid Characterization of Formulated Pharmaceuticals Using Fast MAS ^{1}H Solid-State NMR Spectroscopy

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Introduction

Active pharmaceutical ingredients (APIs) can be prepared in many different solid forms and phases that affect their physicochemical properties and suitability for oral dosage forms. ^{13}C Solid-state NMR (SSNMR) spectroscopy is widely employed to characterize solid APIs, however, ^{13}C SSNMR experiments on dosage forms with low API loading are often challenging due to low sensitivity, unfavorable NMR relaxation times and interference from excipients. Here, fast MAS ^{1}H SSNMR experiments are shown to be applicable for the rapid characterization of low drug load formulations.[1]

Experimental

All fast MAS ^{1}H experiments were performed at the NHMFL with a Bruker 1.3 mm HCN probe and 18.8 T magnet.

Results and Discussion

1D ^{1}H SSNMR experiments on the antihistamine API meclizine dihydrochloride (mecl) and a commercial Dramamine® tablet with 12.5 wt% mecl loading illustrate the challenges of analyzing formulations with low API loads (Figure 1A). A MAS frequency of 50 kHz is sufficient to provide a well-resolved ^{1}H SSNMR spectrum of pure mecl at 18.8 T. The ^{1}H SSNMR spectrum of the mecl tablet is dominated by the intense NMR signals from the excipient molecules, namely microcrystalline cellulose (MCC). The intense MCC signals obscure most of the mecl signals, however, the ^{1}H NMR signal of the ammonium group of mecl is resolved at 12.7 ppm (Figure 1A, inset). The ammonium group chemical shift is identical in the tablet and pure API, immediately suggesting that the same polymorph is present.

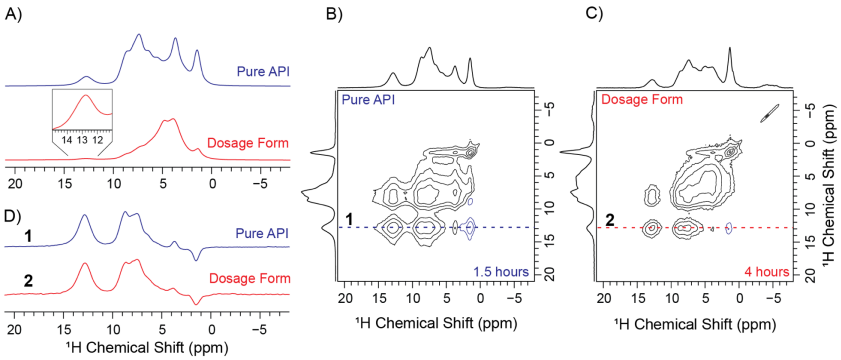

Figure 1. MAS ^{1}H SSNMR spectra of pure **mecl** and a commercial 12.5 wt% **mecl** tablet acquired at B_0 = 18.8 T with ν_{rot} = 50 kHz. A) 1D DEPTH NMR spectra. DEPTH was used to suppress probe background NMR signals. B), C) 2D ^{1}H SD NMR spectra acquired with a selective saturation pulse applied at 3.5 ppm and a 20 ms spin diffusion time. D) ^{1}H NMR spectra extracted from rows of the 2D NMR spectra (dashed lines in B and C).

2D ^{1}H NMR spectra with selective saturation pulses (SSPs) and spin diffusion periods can be used to eliminate NMR signals from the excipients and obtain resolved, diagnostic ^{1}H SSNMR spectra of the API in formulations. SSPs applied in the region of 3-5 ppm will eliminate signals from most excipients. 2D ^{1}H SD NMR experiments with SSPs were performed on pure mecl and the mecl tablet (Figures 1B and 1C). Spin diffusion only occurs between ^{1}H nuclei that are proximate,[34,35] therefore, the NMR spectrum of the mecl tablet extracted from the ammonium peak at 12.7 ppm will only show ^{1}H NMR signals from the API (dashed lines in Figure 1). Figure 1D clearly shows that the same API phase is present in pure mecl and the tablet, in agreement with ^{13}C SSNMR experiments (not shown).

Conclusions

High-field fast MAS ^{1}H SSNMR experiments can be used to rapidly detect APIs in dosage forms with better sensitivity than ^{13}C SSNMR. This will allow dilute APIs with unfavorable T_1 relaxation times to be characterized in drug products. We are currently performing ^{1}H SSNMR experiments on additional APIs to demonstrate the generality of this approach.

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References

[1] Hirsh, D.A., *et al*., Manuscript in Preparation.