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Detecting Low-Level Crystallinity in ASD-like Samples Using ssNMR Techniques

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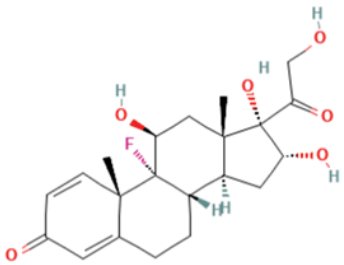
Goal / Motivation

Compare different analytical techniques (ssNMR, XPRD, DSC) for detection and characterization of crystalline phase impurities in spray-dried dispersions (SDD) using the model compound Triamcinolone.



- Triamcinolone was the model compound chosen for the project, and its structure is pictured[1], has ^{13}C and ^{19}F nuclei in its structure. Nearly all APIs contain ^{13}C in their structure, with between 20 – 30% of pharmaceutical compounds also containing ^{19}F.[2] ^{19}F is very attractive to form / polymorph identification, crystallization in SDD, amorphous detection / quantification, etc.

Methods

Comparison of XRPD, DSC, NMR. For additional information please see AAPS poster M1230-09-62.

Results and Discussion

Images 1 and 2 (^{19}F ssNMR): paragraph or bullets about what it is

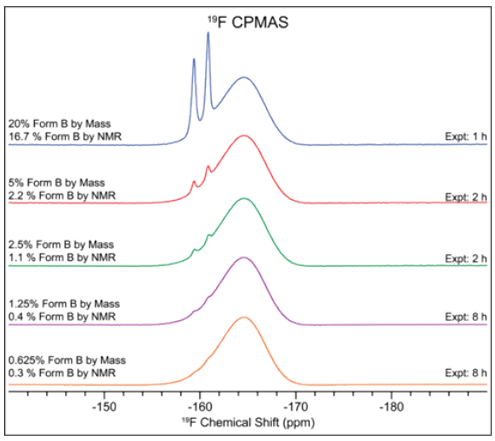


Image 1: ^{19}F ssNMR

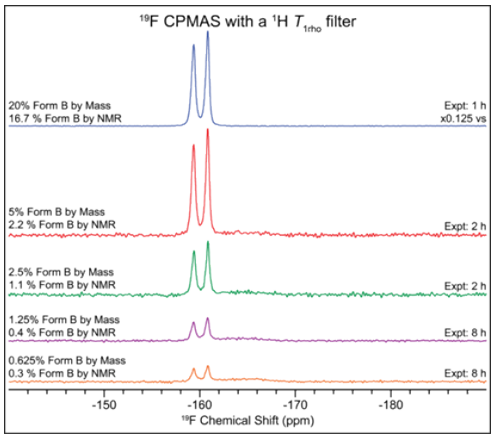


Image 2: ^{19}F ssNMR

(A) Image 1: ^{19}F Cross Polarization (CP) spectrum for prepared samples. This shows both the SDD amorphous signal (broad peak) and the crystalline peaks (sharp resonances).

(B) Image 2: ^{19}F spectrum, with the ^{1}H T_{1rho} filter to selectively eliminate the amorphous signal, allowing for the detection of crystalline signals at low levels in the formulation (0.3%).

Image 3: Direct comparison of the CP spectra with (blue) and without (red) filtering experiment.

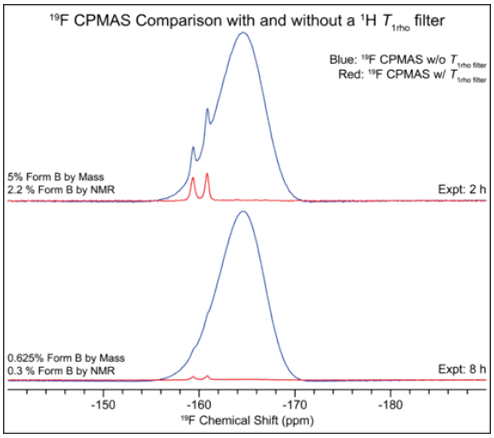


Image 3: Direct comparison of the CP spectra with (blue) and without (red) filtering experiment.

(A) Top: ~2.2% Form B (by ^{19}F ssNMR) spiked into the 20% SDD sample. See the peaks in the blue spectrum. In the red, the amorphous is filtered out, leaving only the crystalline peaks.

(B) Bottom: ~0.3% Form B (by ^{19}F ssNMR) spiked into the 20% SDD sample. Barely see the bumps on the blue spectrum, but when filtering is applied, see the crystalline material remaining in the sample.

Image 4: ^{13}C ssNMR CP data.

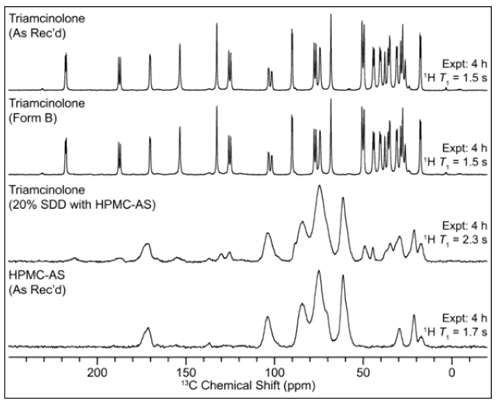


Image 4: ^{13}C ssNMR CP data.

(A) ^{13}C CP spectra acquired for the four samples. The API has sharp resonances, whereas the SDD and excipients have very broad signals. The as reiceved and Form B samples are the same.

Image 5: ^{13}C ssNMR CP

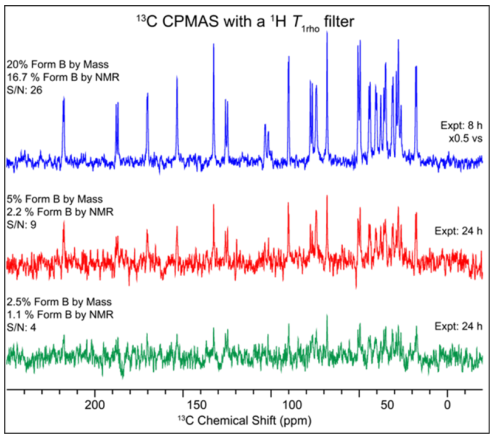


Image 5: ^{13}C ssNMR CP

(A) ^{1}H T_{1rho} filtered spectrum with ^{13}C observation. The different ^{13}C resonances are observed and can be detected (S/N of 3:1) to ~1.1% in 24 hours and quantified to ~2.2% (S/N of 10:1). This technique can be applied to other APIs that lack ^{19}F in their structure.

Image 6: XRPD Overlays of spiked samples as well as the Form B and the starting 20% triamcinolone SDD

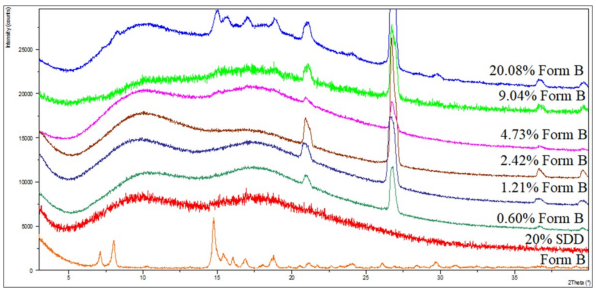


Image 6: XRPD Overlays of spiked samples as well as the Form B and the starting 20% triamcinolone SDD

(A) XRPD results for the spiked samples of Form B into the SDD. The pure form B is on the bottom. Below 10%, the PXRD was not able to detect the crystalline material with the method used. Experiment time ~ 1 hour. Peaks at 21 and 27° (2theta) are from an α-quartz internal standard.

Image 7: DSC → Overlays

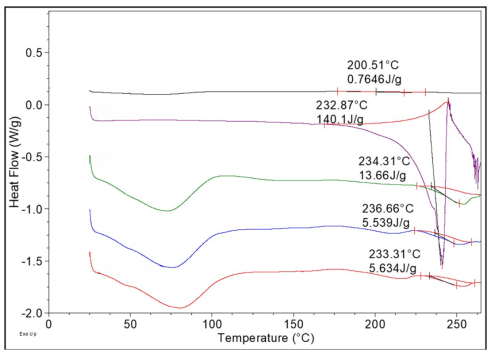


Image 7: DSC → Overlays

(A) DSC results showing the detection of crystalline material in the SDD for triamcinolone. Samples decompose above 250 °C in the DSC. Crystalline material can be detected within the spray-dried dispersion down to 0.6%. However, quantification is difficult due to the presence of polymer and absorbed solvent in the sample affecting the melting point and baseline of the spectra, respectively. Experiment time ~30 min.

Conclusions

- ^{1}H T_{1rho} filtering in ^{19}F and ^{13}C ssNMR is a powerful technique for determination of low levels of crystalline phase impurities in an ASD formulation that may not be detectable by other analytical techniques.
- ^{19}F ssNMR provides specificity between crystalline and amorphous API, without issues from excipients.
- ^{1}H T_{1rho} filtering can also be performed with ^{13}C ssNMR, which is more broadly applicable.
- The ssNMR techniques presented have much lower limits of detection and quantification over existing XRPD or DSC techniques.
- ssNMR provides additional advantages, such as resolving excipient and API signals from each other and API form identification.
- The NMR techniques used can be performed without requiring large amounts of additional experiment time.

References

[1] https://pubchem.ncbi.nlm.nih.gov/compound/Triamcinolone#section=Structures
[2] https://par.nsf.gov/servlets/purl/10356696