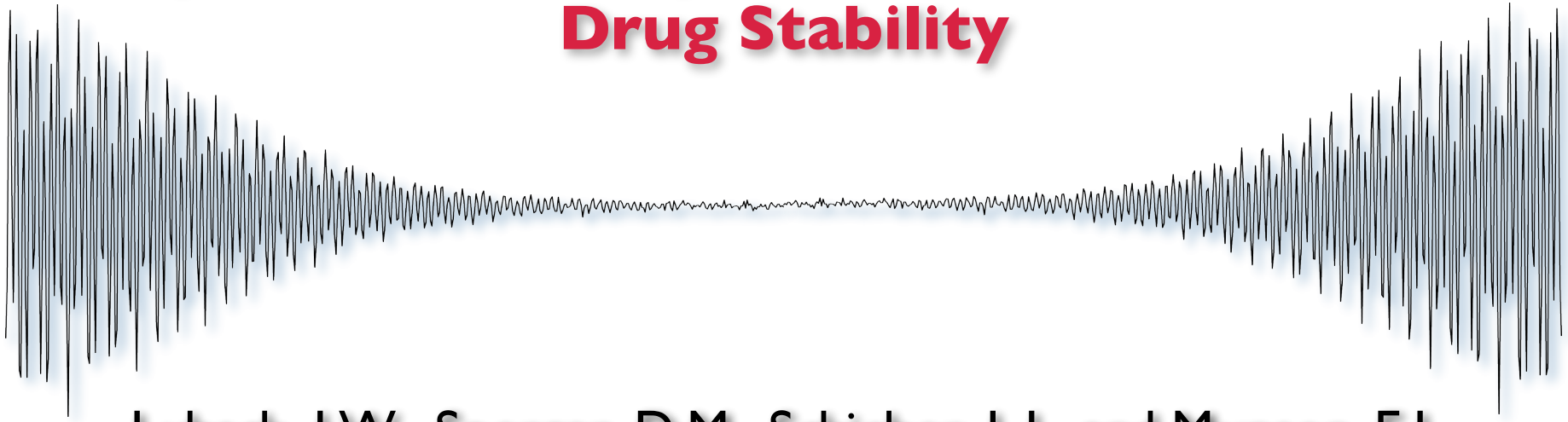
Solid-State NMR Studies of the Effects of Pharmaceutical Processing on Relaxation Dynamics and Implications to Solid-State Drug Stability



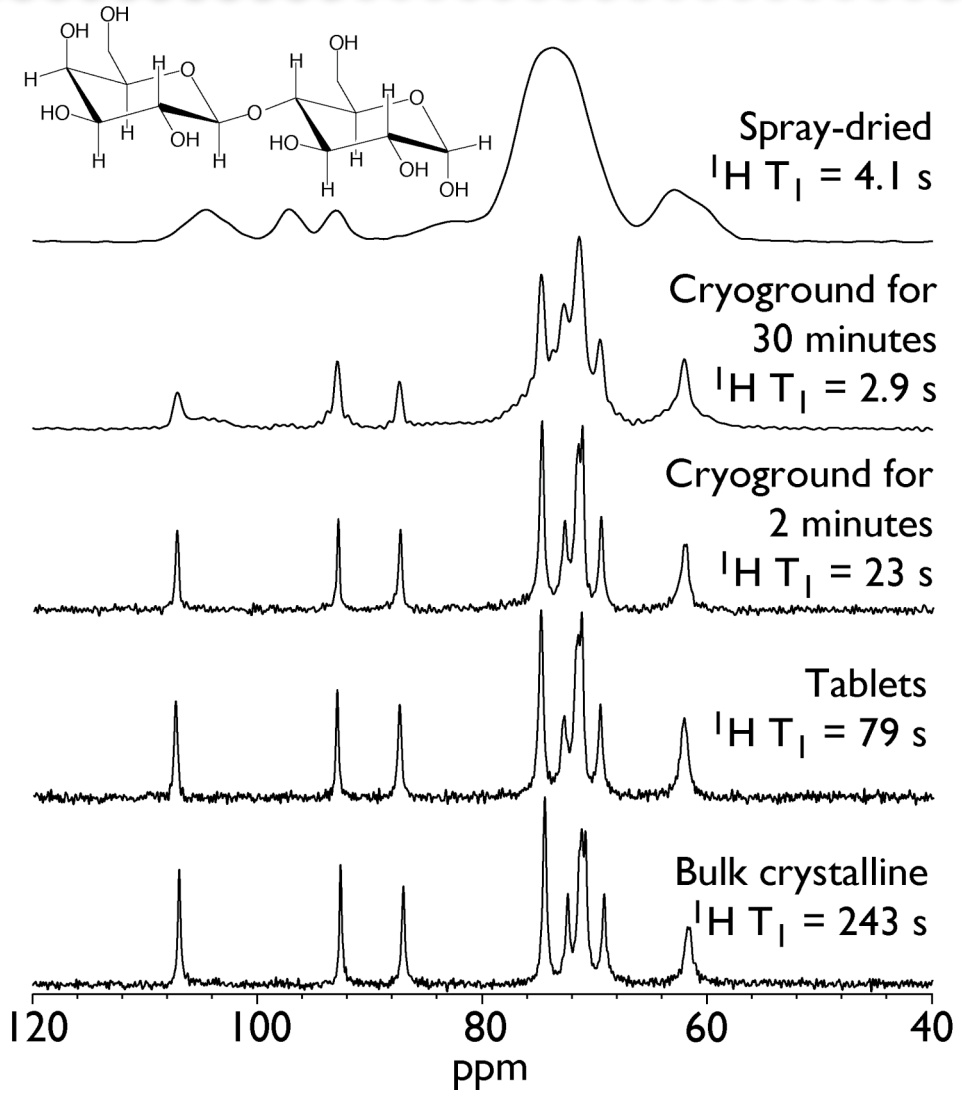
Lubach, J.W., Sperger, D.M., Schieber, L.J., and Munson, E.J.
The University of Kansas
Department of Pharmaceutical Chemistry

Introduction

- Lactose and acetylsalicylic acid (aspirin) were subjected to various formulation and processing conditions, and the effects upon CPMAS NMR spectra and relaxation dynamics were investigated.
- Relaxation dynamics can provide valuable insight into physicochemical properties and stability of bulk drugs and solid-state formulations
- Particle size reduction and introduction of highly mobile domains (i.e. crystal defect sites and amorphous material) results in much faster overall ^{1}H T_1 relaxation for the entire sample
- Detection of amorphous material is critical to the pharmaceutical industry, as it can have drastic effects on formulation stability, efficacy, and safety
- Effects of processing on relaxation dynamics may provide insight into the long-term stability of formulations

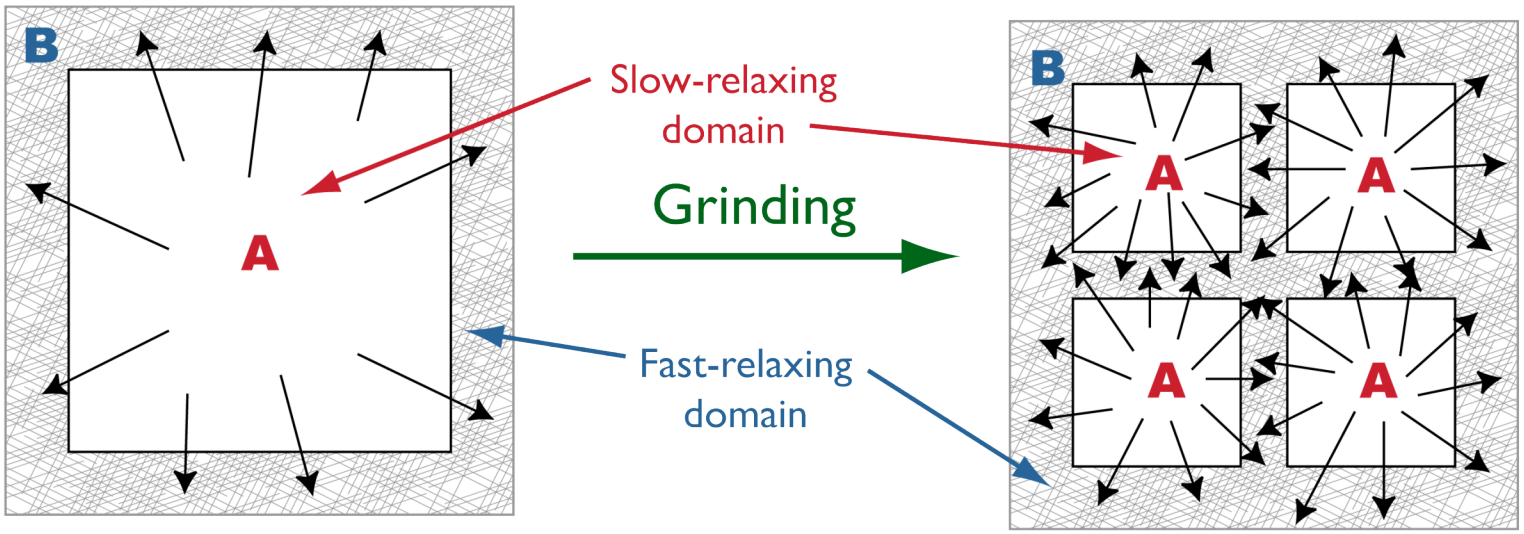
Changes in Relaxation Dynamics Upon Processing

- Lactose chosen due to its wide usage as an excipient
- Rigid crystalline system with no natural relaxation sinks (methyl groups)
- Large changes in T_1 observed with little change in spectra for compressed and 2-minute cryoground samples
- Cryogrinding for 30 minutes gave lower T_1 than pure amorphous lactose



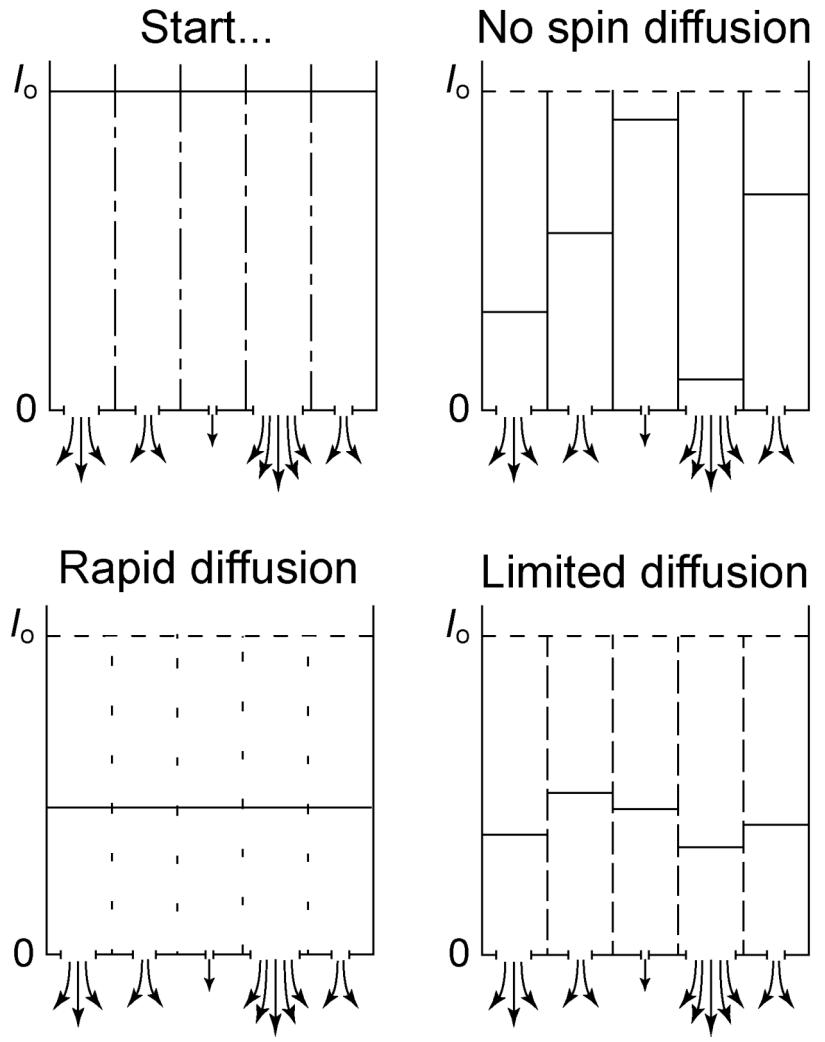
Model of Processing Effects

- Region A represents the part of the sample that relaxes the slowest, or the crystalline part of the sample
- Region B represents the parts of the sample where mobility is greatest, for example the surface of a crystal, defect sites, or amorphous regions
- During grinding Region A gets broken into small pieces, and Region B gets bigger because crystal defects and amorphous material are created under the stress of grinding
- This means that energy can be transferred more efficiently from Region A to Region B and the entire sample can relax much faster



Spin Diffusion

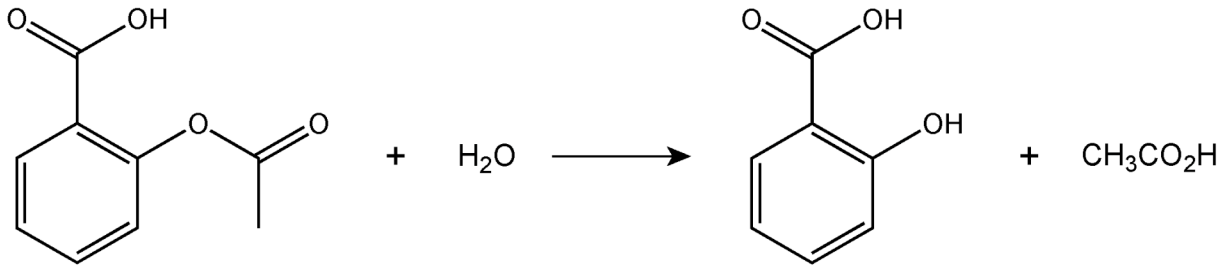
- Through-space dipolar interaction enabling energy transfer between like spins
- Spin-lattice relaxation dominated by the fastest relaxing species present
- Magnetization is transferred from slow-relaxing domains to fast-relaxing domains
- With efficient magnetization transfer, a common T_1 is observed for entire sample



Adapted from Stejskal, E.O. and Memory, J.D. *High Resolution NMR in the Solid State*. ©1994 Oxford University Press, Inc. p. 106.

Relaxation and Stability

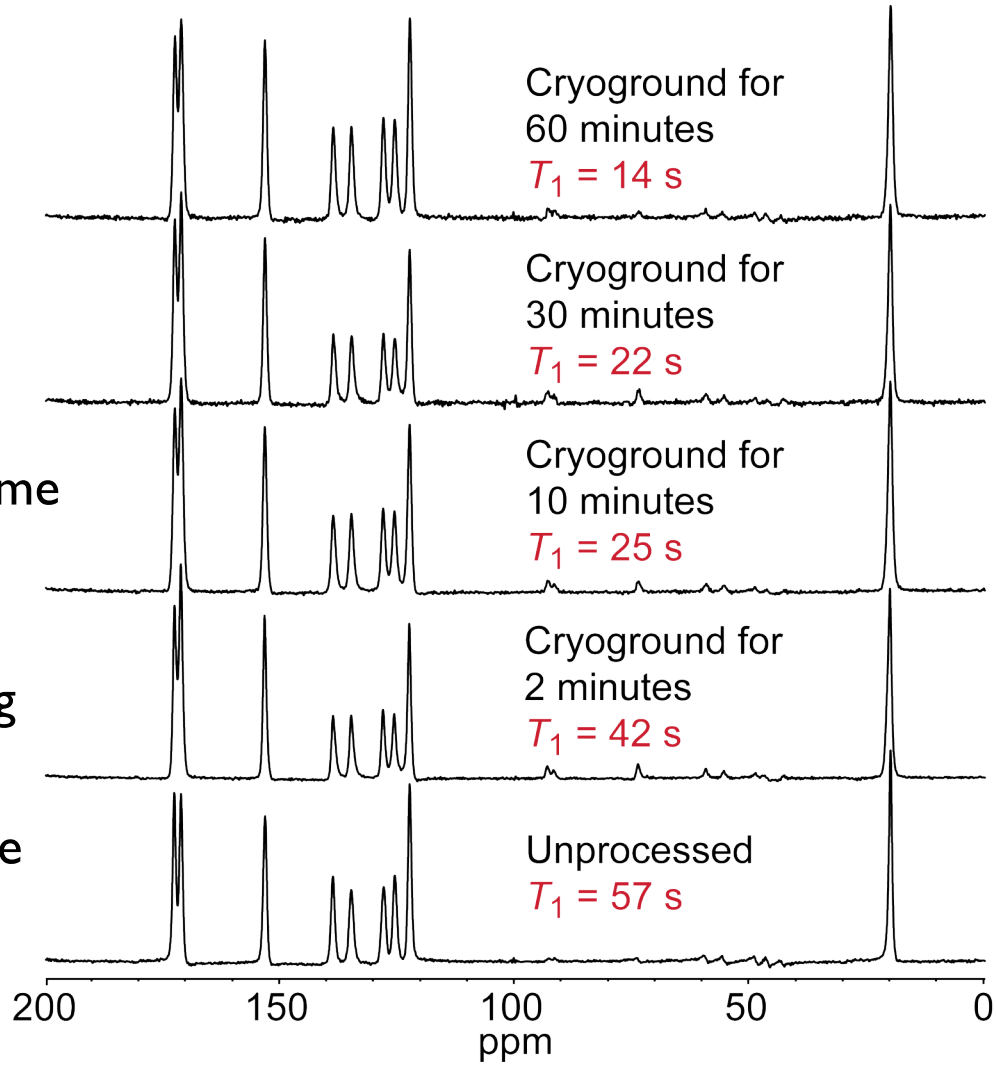
- What does relaxation have to do with drug stability?
  - Relaxation is directly correlated with sample mobility, and mobility is correlated with reactivity, so measuring relaxation times may tell us which drug formulations are going to be least stable over time
  - More mobile drugs are more likely to react, because it takes motion and energy for two molecules to encounter each other and undergo a chemical reaction
  - These degradation reactions occur over time, and the time it takes for 10% of a drug to degrade is its viable shelf life
  - The FDA requires marketed drug products to have at least a two-year shelf life, so finding the most stable formulation of a drug is crucial to the pharmaceutical industry



Aspirin hydrolyis degradation reaction

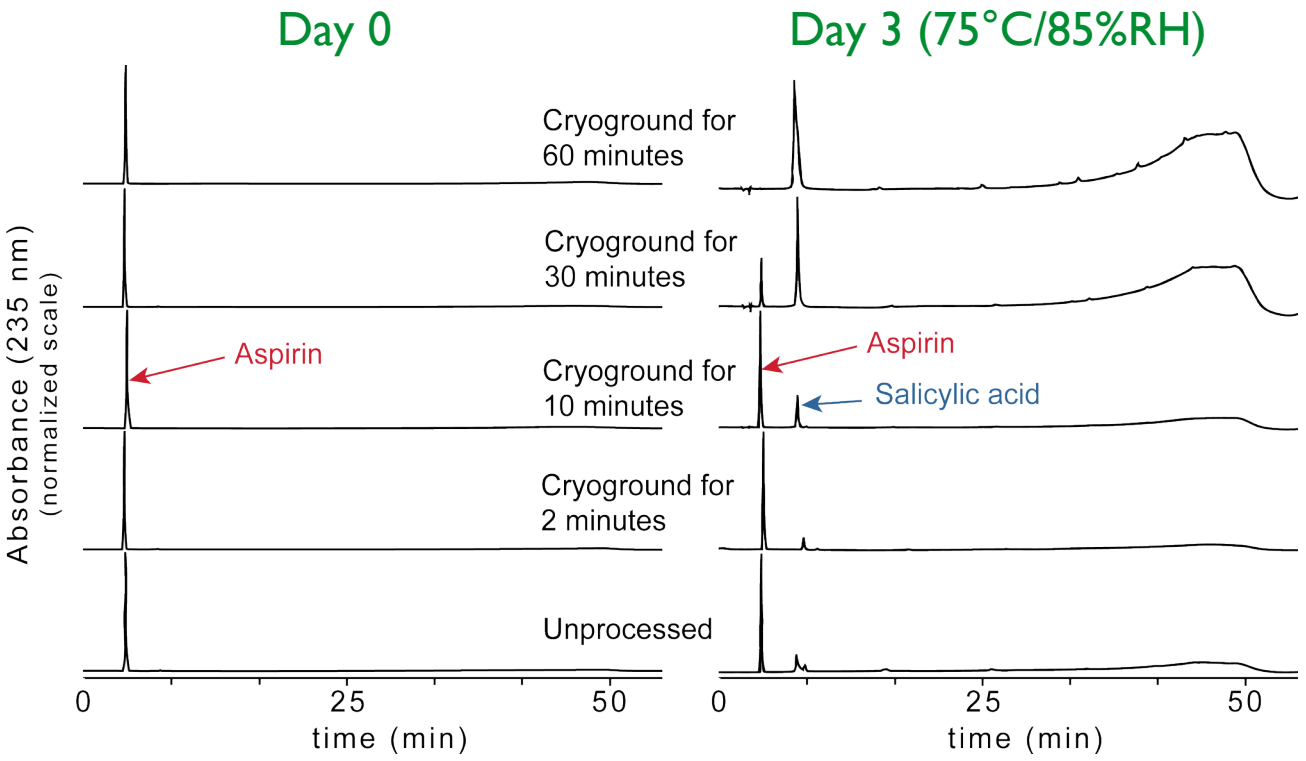
Cryoground Aspirin

- Bulk (unprocessed) aspirin has a relaxation time of 57 s
- As was the case with lactose, cryogrinding reduced T_1 times of aspirin, with longer grinding times giving lower relaxation times
- All five spectra are nearly identical, indicating that aspirin does not become amorphous upon cryogrinding
- Amorphous aspirin would be manifested as broad peaks underlying the sharp crystalline peaks
- The T_1 reduction is likely entirely due to reducing the particle size and introducing many crystal defect sites



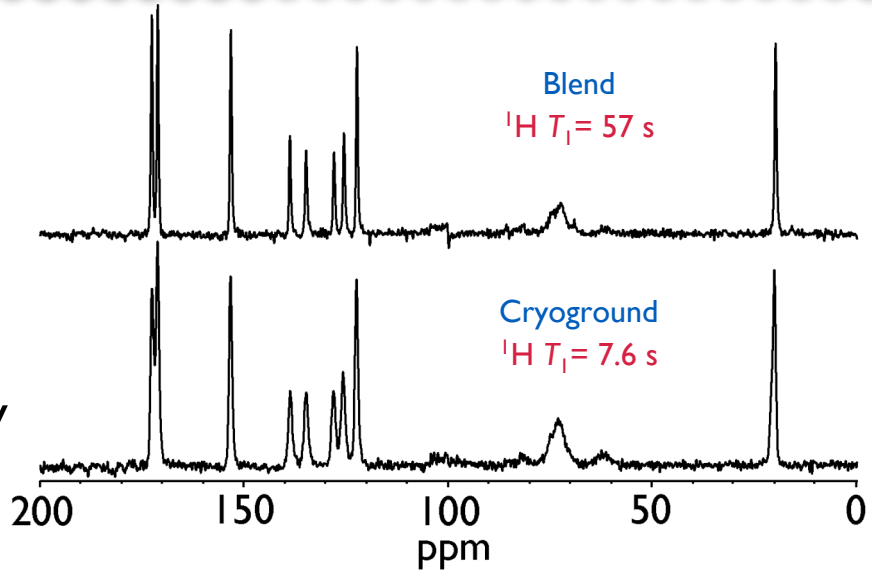
Aspirin Stability

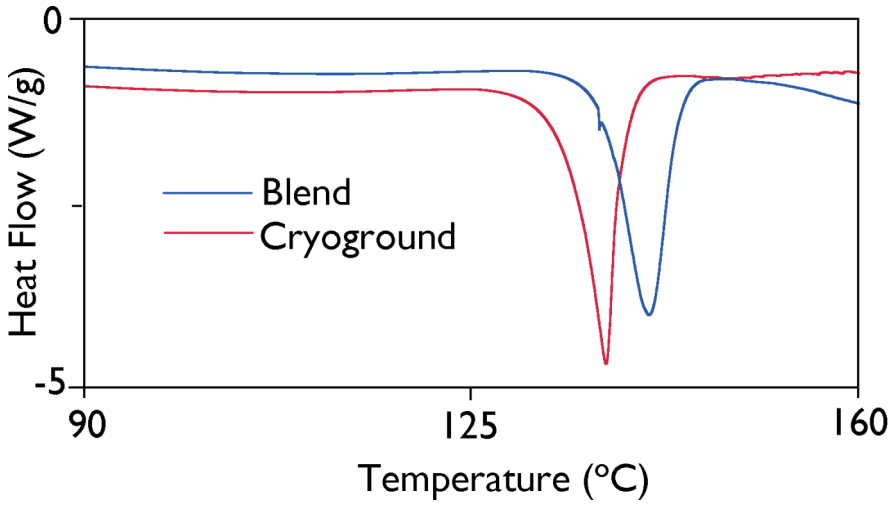
- On the left are HPLC chromatograms for bulk aspirin and aspirin immediately after cryogrinding
- The single aspirin peak indicates that no degradation occurred during cryogrinding
- On the right are aspirin HPLC chromatograms run after 3 days in a stability chamber at 75 °C and 85% relative humidity
- The salicylic acid peak increases in samples ground for longer times, and the sample ground for 60 minutes has no aspirin remaining at all
- This shows that the samples ground for longer periods of time are much less stable than unprocessed aspirin



Aspirin and Starch Mixtures

- 50:50 physical mixture of aspirin and Starch 1500 was prepared and cryoground for 30 minutes
- Unprocessed blend of aspirin and starch used as control
- ^1H T_1 of cryoground material significantly less than control
- DSC showed melting point of cryoground material (133.97 °C) less than that of control (137.02 °C)
- Water vapor sorption at 90% RH showed weight gain of 9.1% for cryoground material, while control gained 6.25%
- All data indicates faster degradation of cryoground material





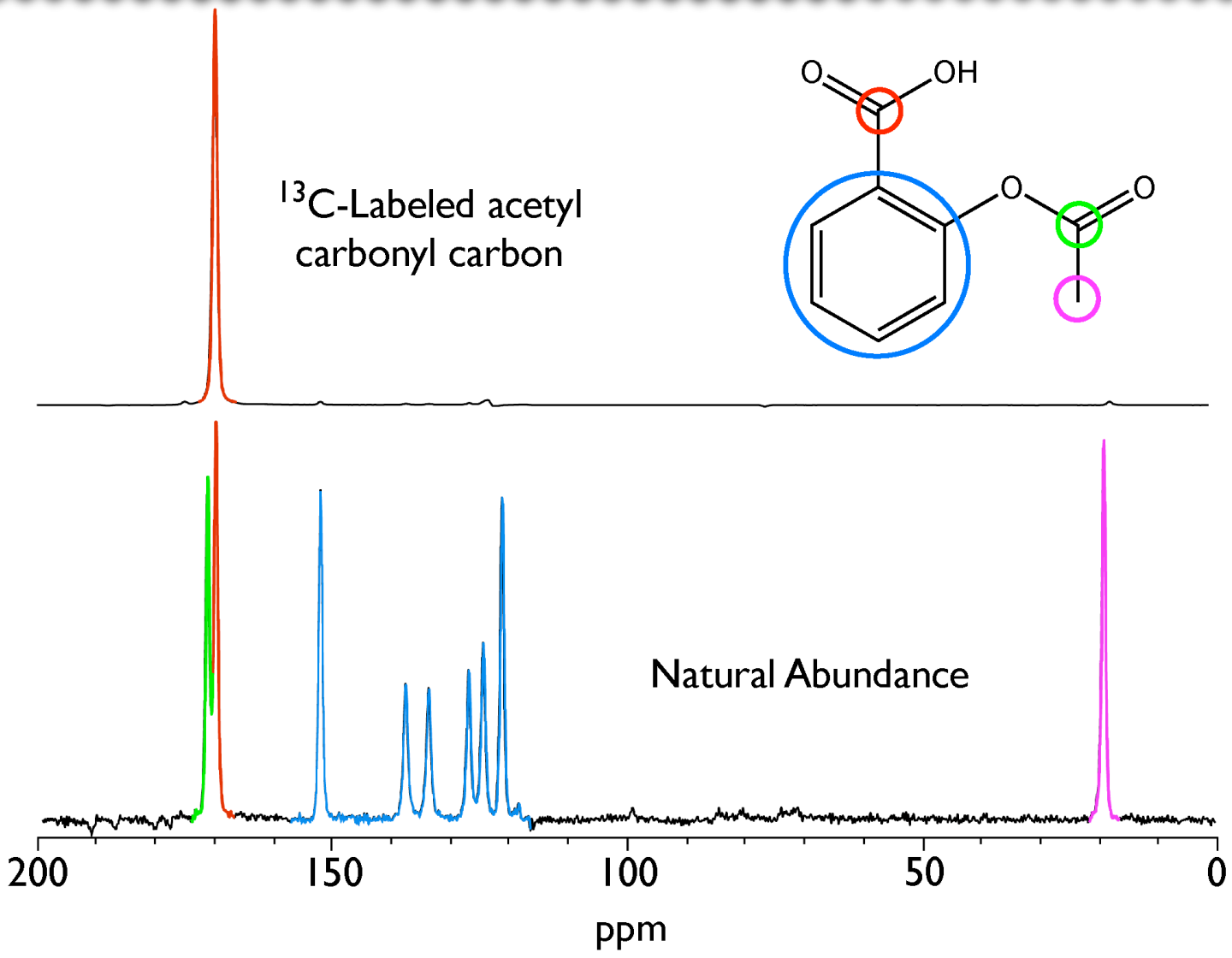
Degradation of Aspirin Mixed With Starch

- The aspirin/starch blend and cryoground material were stored at 75 °C and 55% RH
- Samples were removed and analyzed by HPLC at various time points
- Hydrolysis to salicylic acid was monitored, and found to occur at a faster rate in the cryoground material compared to the control
- These stability results correlate nicely with the relaxation times, melting points, and hygroscopicity of each sample

50:50 Aspirin:Starch Blend (Control)		
	% Area	
	Aspirin Peak	Salicylic Acid Peak
t=0	99.93	0.07
t=1 week	81.44	18.56
t=2 weeks	71.87	28.13

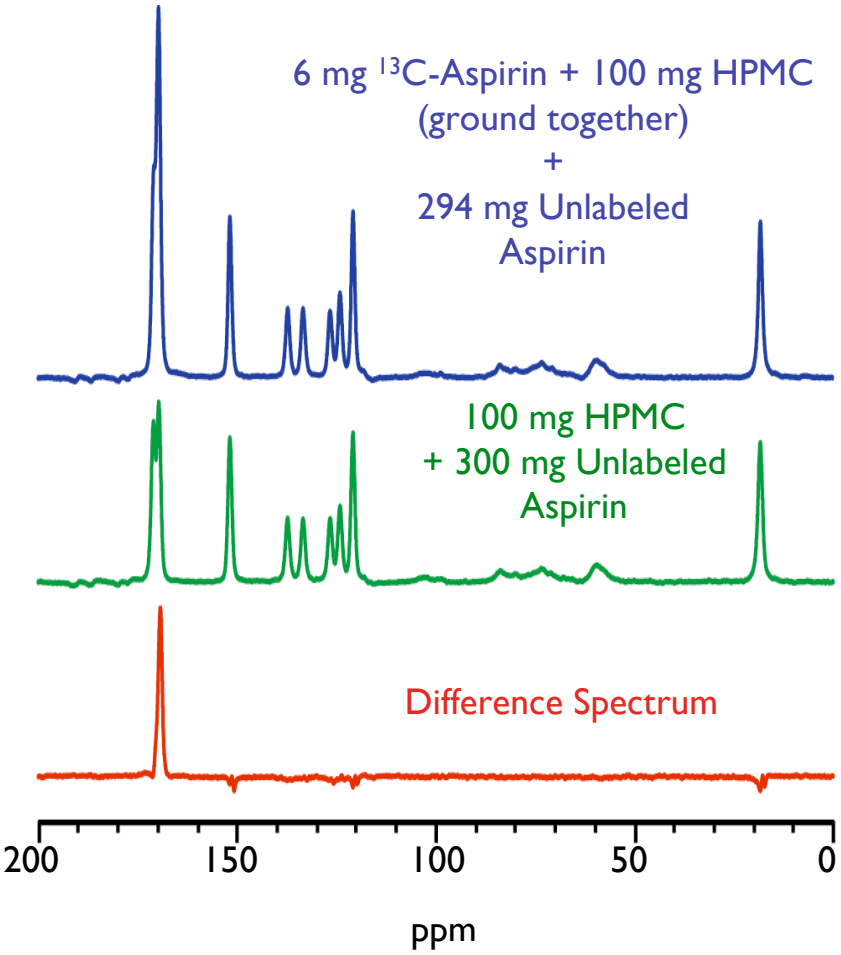
50:50 Aspirin:Starch Cryoground 30 min.		
	% Area	
	Aspirin Peak	Salicylic Acid Peak
t=0	99.84	0.16
t=1 week	59.89	40.11
t=2 weeks	3.88	96.12

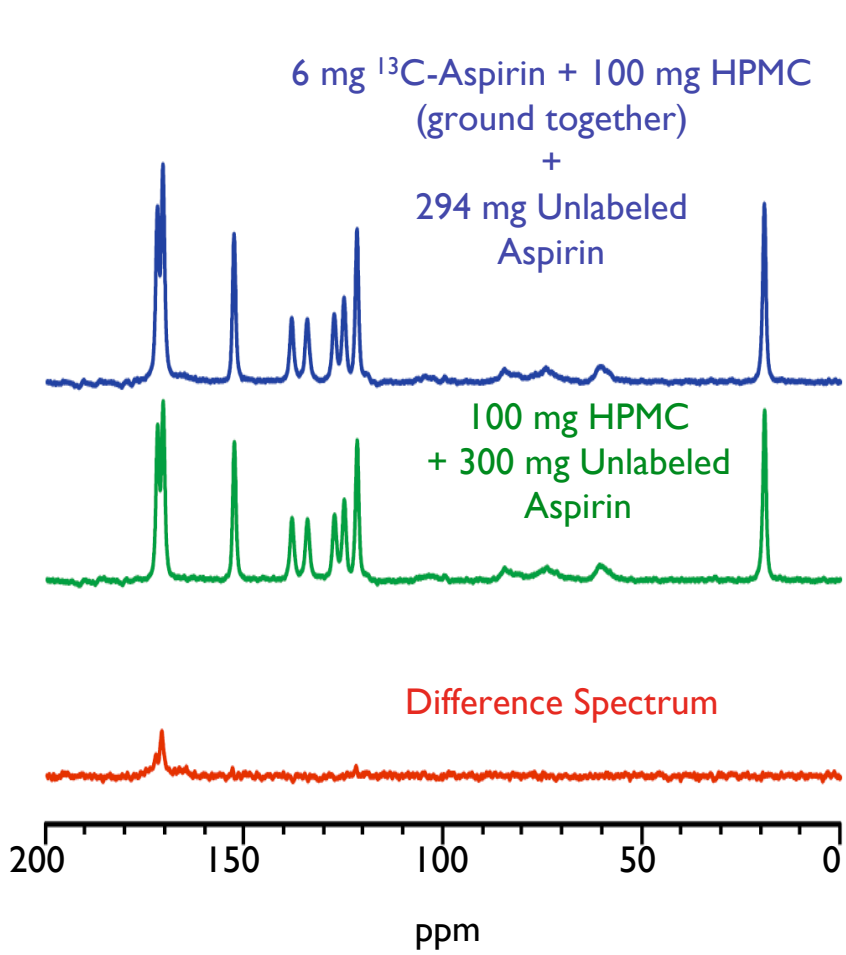
NMR Spectra of ^{13}C-Labeled Aspirin and Natural Abundance Aspirin



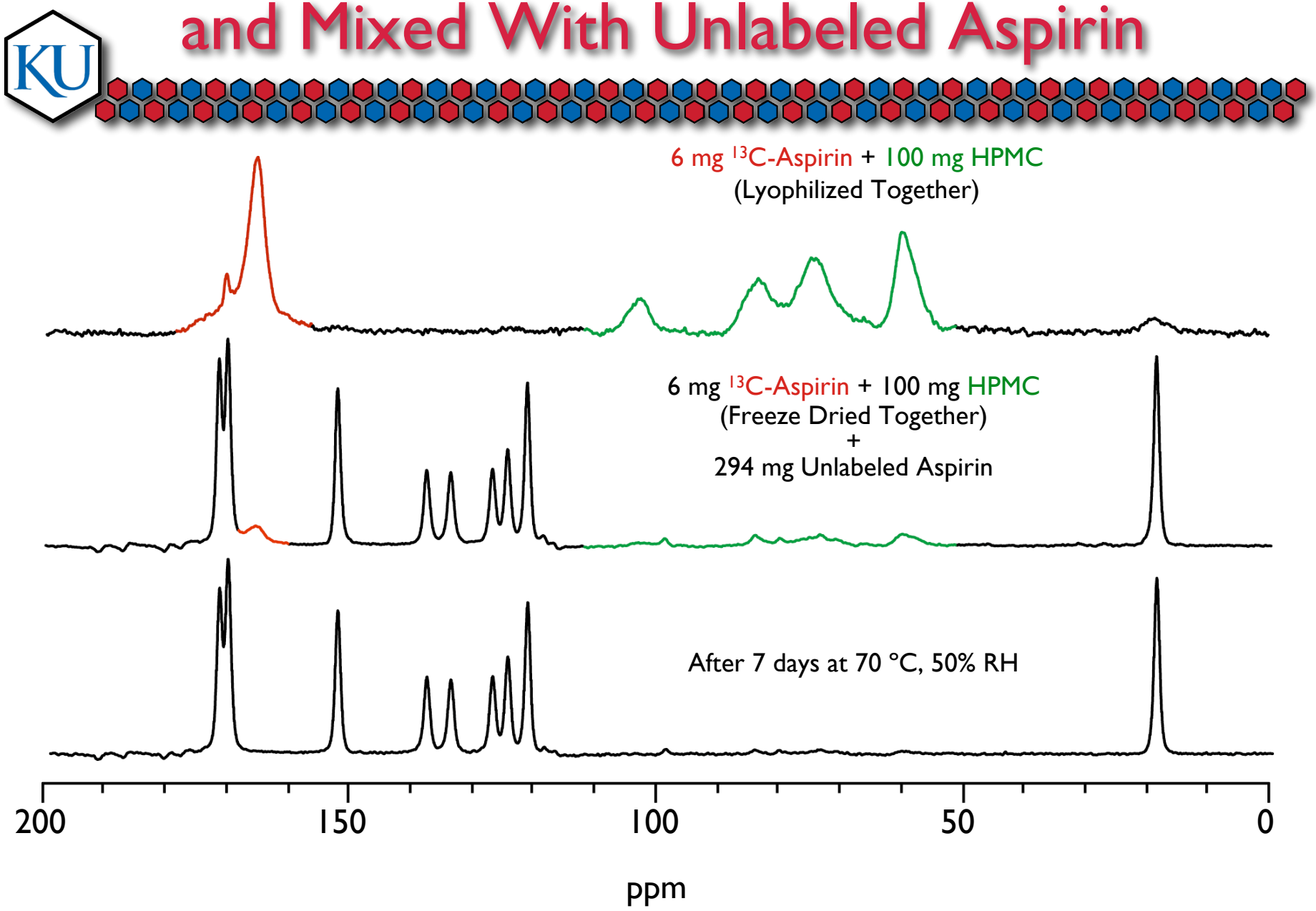
Monitoring Degradation of a Minor Component Using Solid-State NMR

- Initial Samples
- 7 days at 70 °C, 50% RH

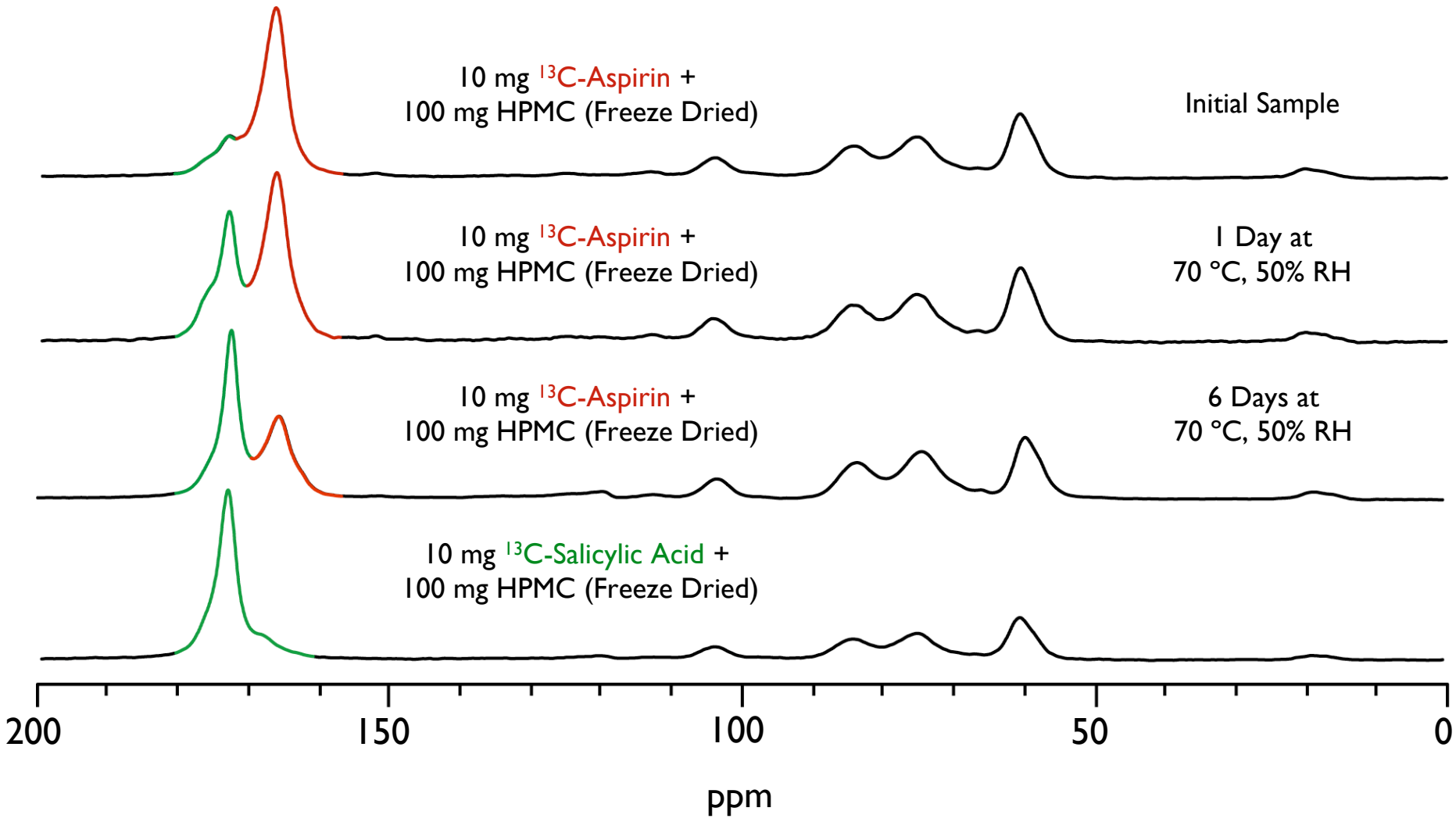




^{13}C-Labeled Aspirin Lyophilized with HPMC and Mixed With Unlabeled Aspirin

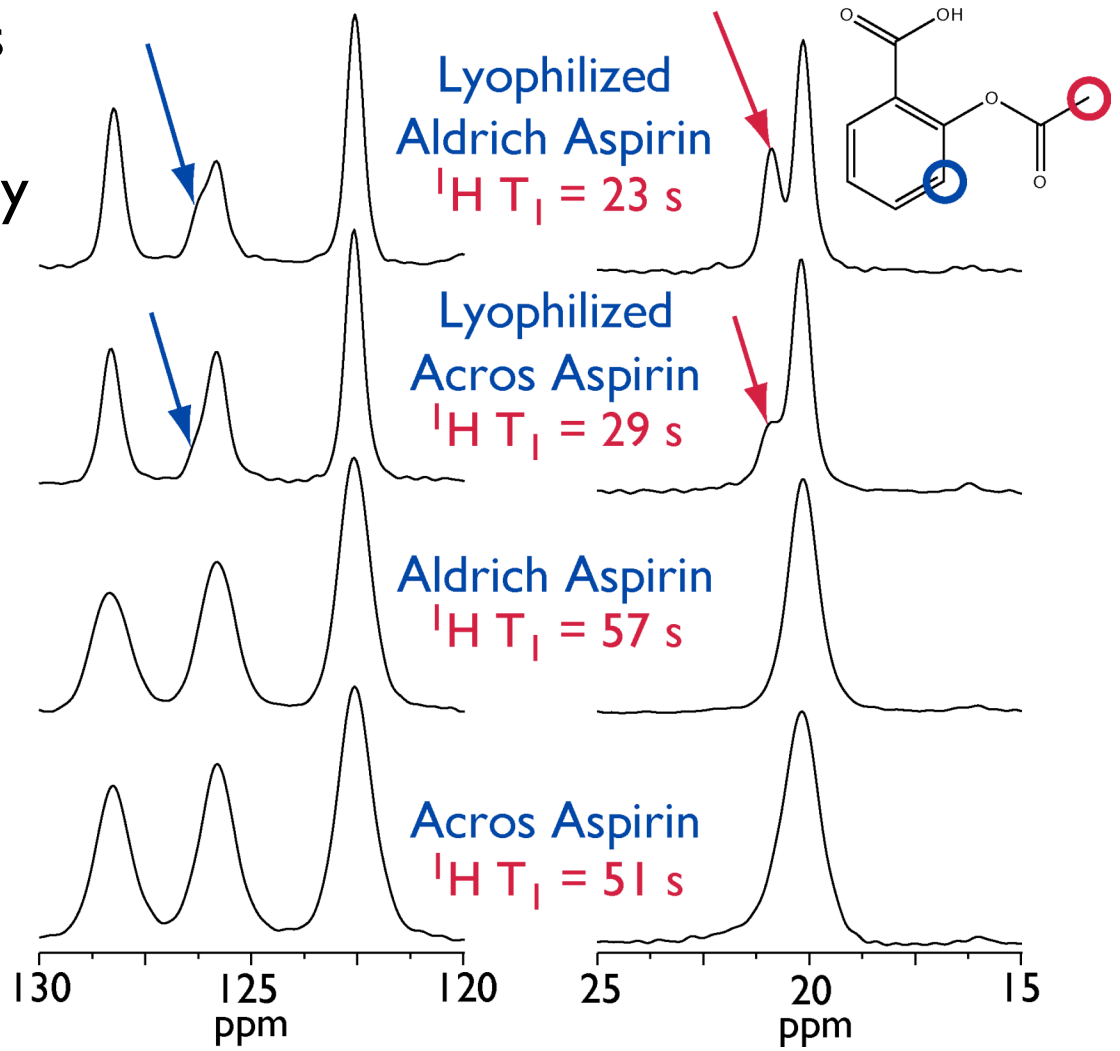


Degradation of Amorphous Aspirin



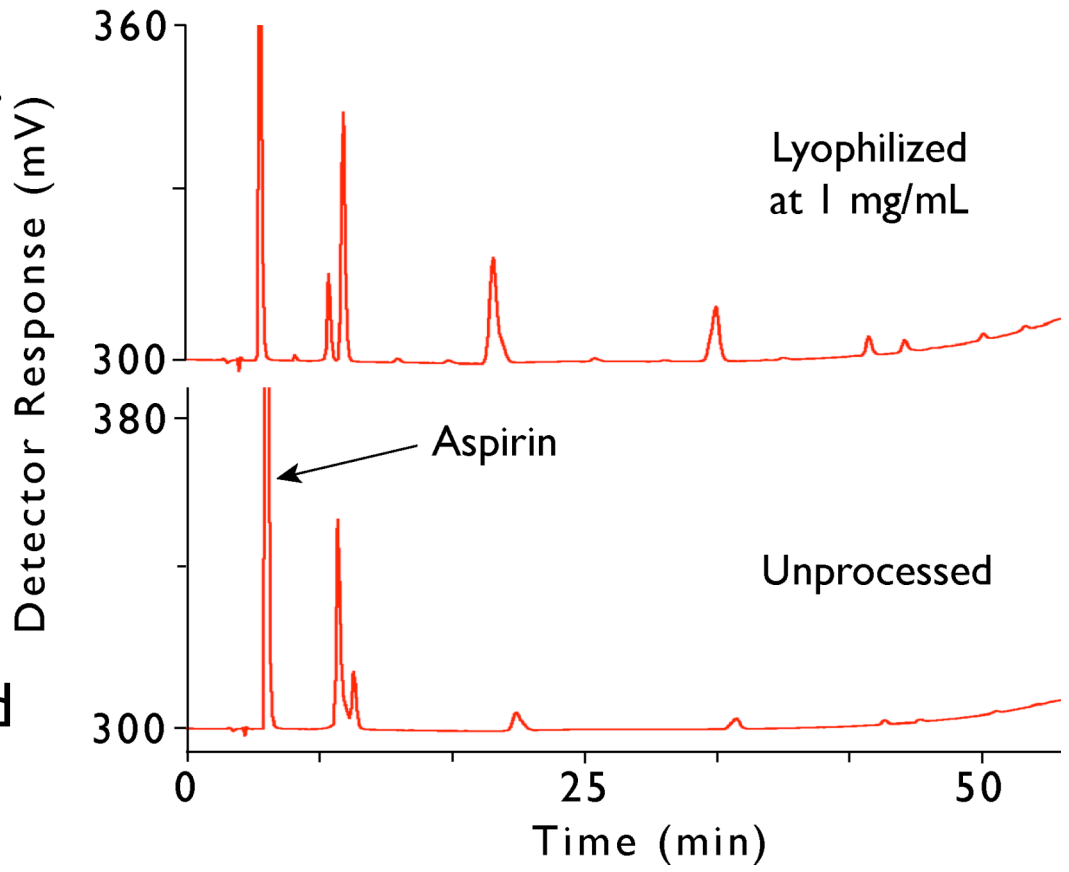
A New Form of Aspirin? Evidence from Solid-State NMR

- Aspirin from two suppliers was studied using ^{13}C CPMAS NMR spectroscopy
- Bulk and lyophilized NMR spectra are shown
- Differences between bulk and lyophilized samples:
  - New peaks
  - Changes in linewidth
  - Changes in ^{1}H T_1
- See Diana Sperger's poster for more information



Degradation of Lyophilized Aspirin

- Aldrich bulk aspirin and lyophilized aspirin submitted to 85 °C/75% RH for 15 hrs.
- Degradation studied using stability indicating HPLC method:
  - Mobile phase - MeOH/H_2O gradient
  - Column - Symmetry C18 5 μm 4.6 x 250 mm
  - UV Detection - 235 nm
- Results show that lyophilized material degrades at a faster rate



Conclusions and Future Work

- Small amounts of highly mobile domains can have a significant impact on overall sample relaxation times
- Amorphous aspirin dispersed in HPMC degrades much faster than pure crystalline aspirin
- Cryogrinding bulk aspirin does not appear to produce any significant changes in solid-state NMR spectra, however relaxation times were reduced
- Lyophilizing pure aspirin may result in a new metastable crystalline form of aspirin
- Future studies will attempt to correlate relaxation times with long term stability studies of processed aspirin formulations