Excipient Compatibility as Predicted by ASAP

A Case Study

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Getting To Know Faster

Outline

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3. Accelerated Stability Assessment Program (ASAP)
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Introduction

- Provide a rational for excipient selection
- ICH Q8(R2): Pharmaceutical Development
  - The compatibility of the drug substance with excipients listed should be evaluated
- Impact on stability of API
  - Risk management
- Regulatory Requirement
  - QOS: What evidence supports compatibility between the excipients and the drug substance?

Traditional Excipient Compatibility Studies

- Binary mixture of active pharmaceutical ingredient (API) and excipient prepared in a 1:1 ratio
- Excipients showing incompatibility at the 1:1 ratio tested at a ratio more typical of the final formulation
- Two vial types (duplicate vials for each) prepared for each drug-excipient blend
  - Assay vial (pre-weighed for moisture)
  - Composite vial (for additional tests)

Traditional Excipient Compatibility Study

- Three controlled conditions
- 200 vials prepared for 7 excipients studied open dish

One Excipient = 25 Vials	T=0			T=2 weeks			T=4weeks			T=8 weeks		
Test Conditions	Assay	Dupl.	Comp.	Assay	Dupl.	Comp.	Assay	Dupl.	Comp.	Assay	Dupl.	Comp.
Accelerated - 40ºC / 75% RH	X	X	X	X	X	X	X	X	X	X	X	X
CRT - 25ºC / 60% RH	X	X	X	X	X	X	X	X	X	X	X	X
Light	2 X	X	X	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total Vial Counts =	4	3	3	2	2	2	2	2	2	2	2	2
Grand Totals =	10			6			6			6		

Traditional Excipient Compatibility Studies

- The analytical testing includes:
  - Assay
  - Impurities
  - Description
  - Loss on Drying (LOD)
- Results compared to a control (API) across all time points and conditions to look for any trending
- Any unexplained or unexpected loss in potency, or increase in impurities over time mandated further investigations
  - Excipient ratio screening, at the levels typical of the final formulation.

Traditional Excipient Compatibility Studies

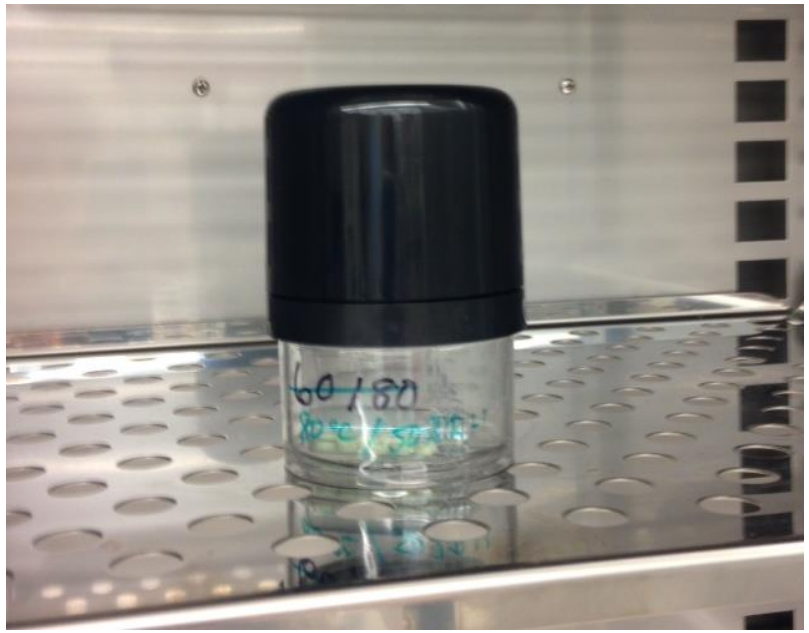
- Limitations
  - 1:1 Binary blends not representative of formulation
    - May not pick up on incompatibilities
  - Manufacturing
    - Processing
    - Tableting
  - Sample Load
  - Resources
  - Increased time-line
  - Inconclusive results
  - Not an indicator of formulation stability

Accelerated Stability Assessment Plan: Excipient Compatibility Study

- Rapid approach to determine incompatibilities
- Multiple prototype formulations screened simultaneously
- Provides greater understanding of drug product stability
  - Impurity profile
- Allows rapid entry in full formulation development
- Predicts impact of container/closure on product stability

ASAP: Excipient Compatibility Study

- Sample count depends on study
  - 21 samples for 3 batches tested
- Amebis Incubation System
  - Incubation flask controls temperature/humidity



Case Study

- aNDA program
- Presence of lactose in reference listed drug (RLD)
  - Maillard reaction
    - Chemical reaction between amine and sugar
- One known degradation product
- Specification limit defined by ICH Q3B(R2) and monograph
- Drug product: oral tablet
- Strength: 0.5mg, 1mg, and 2mg
- Commercial packaging configuration: 100 and 1000 count HDPE bottle
- Timeline
  - 12 months to develop final formulation

Case Study

- API determined to be stable
- Three prototype formulations pressed into tablets
- Manufactured at bench scale
- Formulation 1 approximates RLD formulation

Prototype Formulation	**1**	**2**	**3**
Ingredient			
API	X	X	X
Microcrystalline Cellulose	X	X	X
Lactose	X		
Dicalcium Phosphate		X	
Starch 1500			X
Magnesium Stearate	X	X	X

Case Study

- ASAP design parameters
  - 7 samples per prototype formulation
  - Container closure system selected based on appropriate sized bottle for 100 tablets

Product Type:	Tablet
Length:	14 days
Number of Analyses:	7
Specification Limit:	0.2% label claim
Container:	75cc HDPE bottle/HIS cap

Case Study

- Testing design
  - Screening design for excipient selection
    - Minimal approach taken comparing three prototypes
    - Once prototype formulation selected and optimized then additional more robust ASAP study conducted

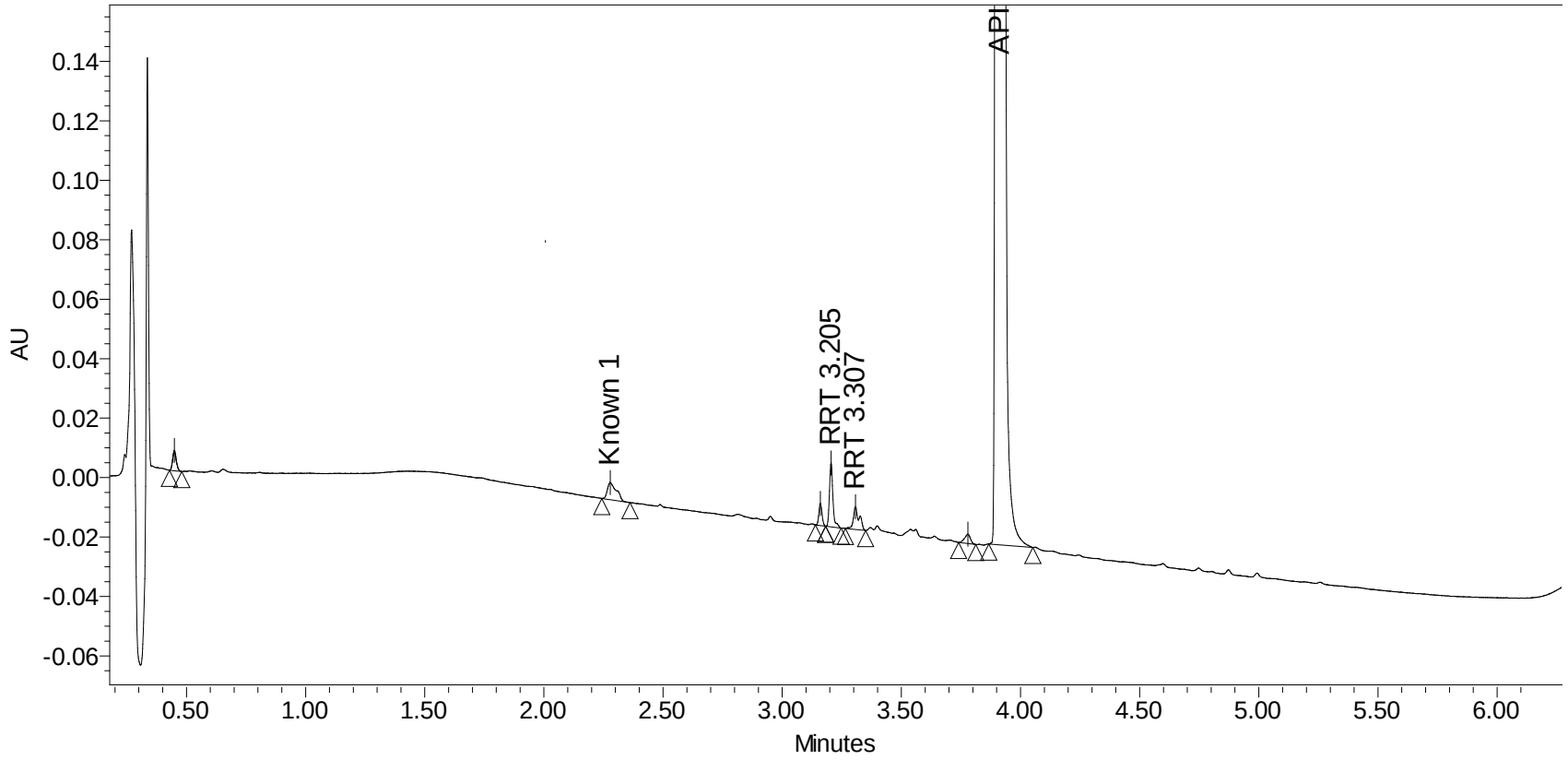
T (ºC)	%RH	Time(Days)
50	75	14
60	50	14
70	10	14
70	75	1, 3
80	30	2

Case Study

- Stability indicating UHPLC method
- Reporting impurities equal or greater then 0.02% label claim
- 2 days for analytical analyses with a developed method

Mobile Phase	A:	0.1% TFA in H2O	
	B:	Acetonitrile	
Gradient Program (Linear)	Time (min)	%A	%B
	Initial	90	10
	0.50	90	10
	5.00	25	75
	5.50	25	75
	5.55	90	10
	6.50	90	10
Column	Type:	Waters Acquity BEH C18, 50 x 2.1 mm, 1.7 µm particle size	
	Temperature:	40 ºC	

Chromatogram



Raw Data: % Impurity

Formulation 1: Lactose

Deg Product	Control	50ºC/75%RH 14 days	60ºC/50%RH 14 days	70ºC/11%RH 14 days	70ºC/75%RH 1 days	70ºC/75%RH 3 days	80ºC/30%RH 2 days
Known 1	ND	0.032	0.078	0.076	0.039	0.065	0.099
RRT 3.21	ND	0.141	0.262	0.108	0.150	0.325	0.192
RRT 3.31	ND	0.058	0.256	0.064	0.086	0.059	0.179

Formulation 2: Dicalcium Phosphate

Deg Product	Control	50ºC/75%RH 14 days	60ºC/50%RH 14 days	70ºC/11%RH 14 days	70ºC/75%RH 1 days	70ºC/75%RH 3 days	80ºC/30%RH 2 days
Known 1	0.024	0.392	0.621	0.622	0.314	0.614	0.629

Formulation 3: Starch 1500

Deg Product	Control	50ºC/75%RH 14 days	60ºC/50%RH 14 days	70ºC/11%RH 14 days	70ºC/75%RH 1 days	70ºC/75%RH 3 days	80ºC/30%RH 2 days
Known 1	ND	0.055	0.036	0.043	0.046	0.115	0.040

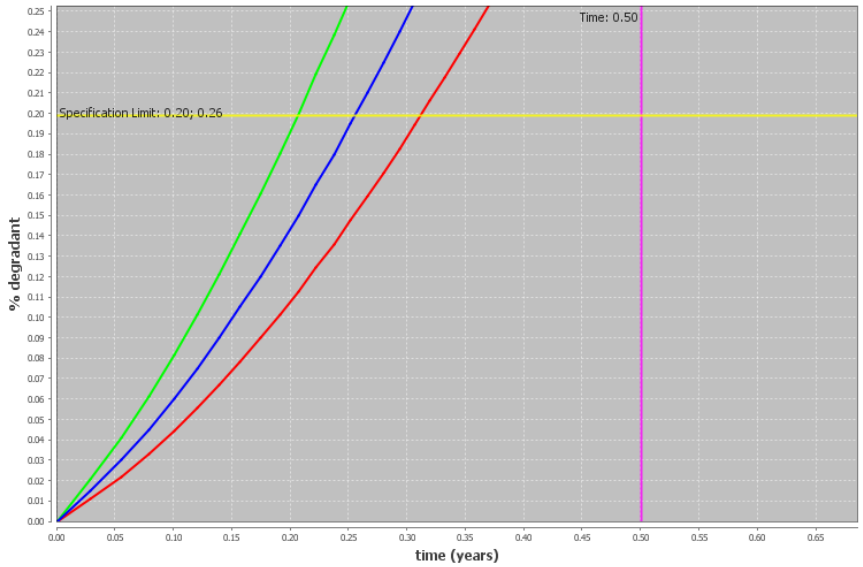
Case Study

- Predicted results from ASAP®Prime meeting acceptance criteria of 0.2% label claim
  - All degradation products
- Packaging assessed
  - With and without desiccant
- ICH accelerated and CRT
- RRT 3.31 poor correlation
  - Potential secondary degradation

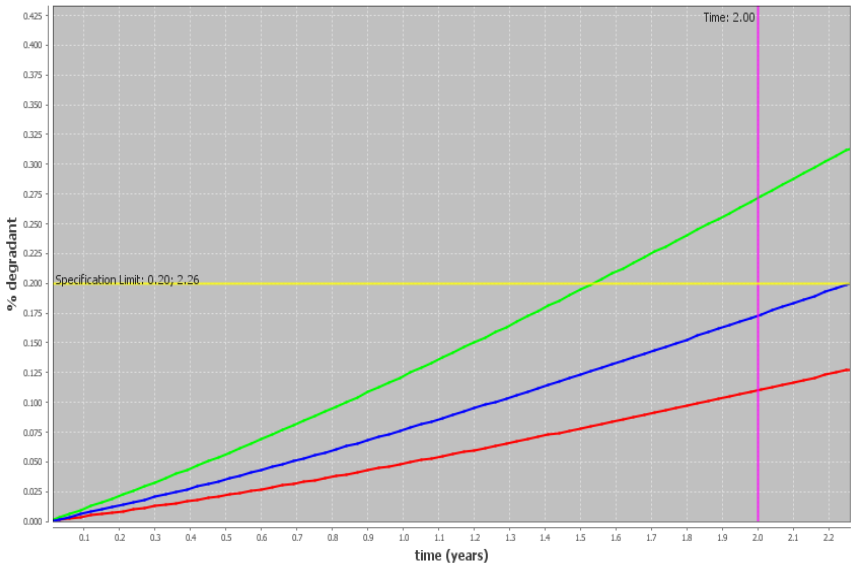
Formulation	1	1	1	2	3
Degradation Product	Known 1	RRT 3.21	RRT 3.31	Known 1	Known 1
Model correlation	0.96	0.97	0.62	0.99	0.95
Condition	% Probability of Passing				
40°C/75%RH 6 month no desiccant	98	90	77	0	99
40°C/75%RH 6 month 1g desiccant	99	100	90	36	100
25°C/60%RH 24 month no desiccant	99	100	90	73	99
25°C/60%RH 24 month 1 g desiccant	99	100	94	97	100
25°C/60%RH 36 month no desiccant	98	100	79	30	98
25°C/60%RH 36 month 1 g desiccant	99	100	87	80	99

Case Study

Formulation 2-Known-1 40°C/75% RH
no desiccant

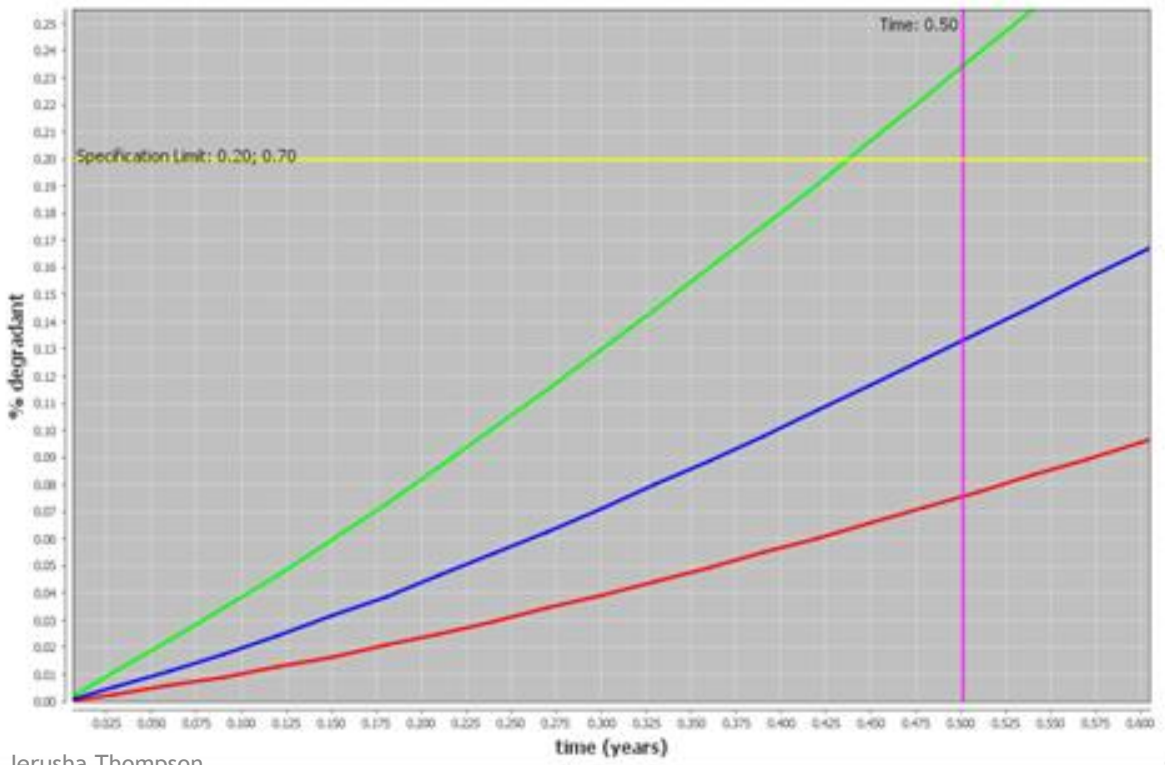


Formulation 2-Known-1 25°C/60%RH
no desiccant



Case Study

- Formulation 1- RRT 3.31 40°C/75% RH
  - Higher error propagation



Case Study

- Results
  - Formulation 1 (RLD)
    - Two unique unidentified degradation products observed
  - Formulation 2
    - Known 1 would have difficulty meeting a shelf-life of 24 months without a desiccant
    - Failure at accelerated conditions would require additional testing at an intermediate condition
  - Formulation 3
    - Highest probability of passing all conditions without desiccant
- Study results will help justify the excipient and packaging selection in CMC section of submission

Alternative Analytical Technique

- Rapid entry into full formulation development with ASAP allows decreased timeline
  - Traditional approach to excipient studies ~3-6 months
  - ASAP ~ 2-4 weeks
- Rate limiting step can become analytical technology
  - Stability indicating HPLC method can take time to develop
    - ~1-2 months
  - Response of degradation products to parent compound critical
- Quantitative NMR (qNMR)
  - One method for all drug products
    - No method development required
  - No response of degradation product needed
  - No quantitative reference standard required

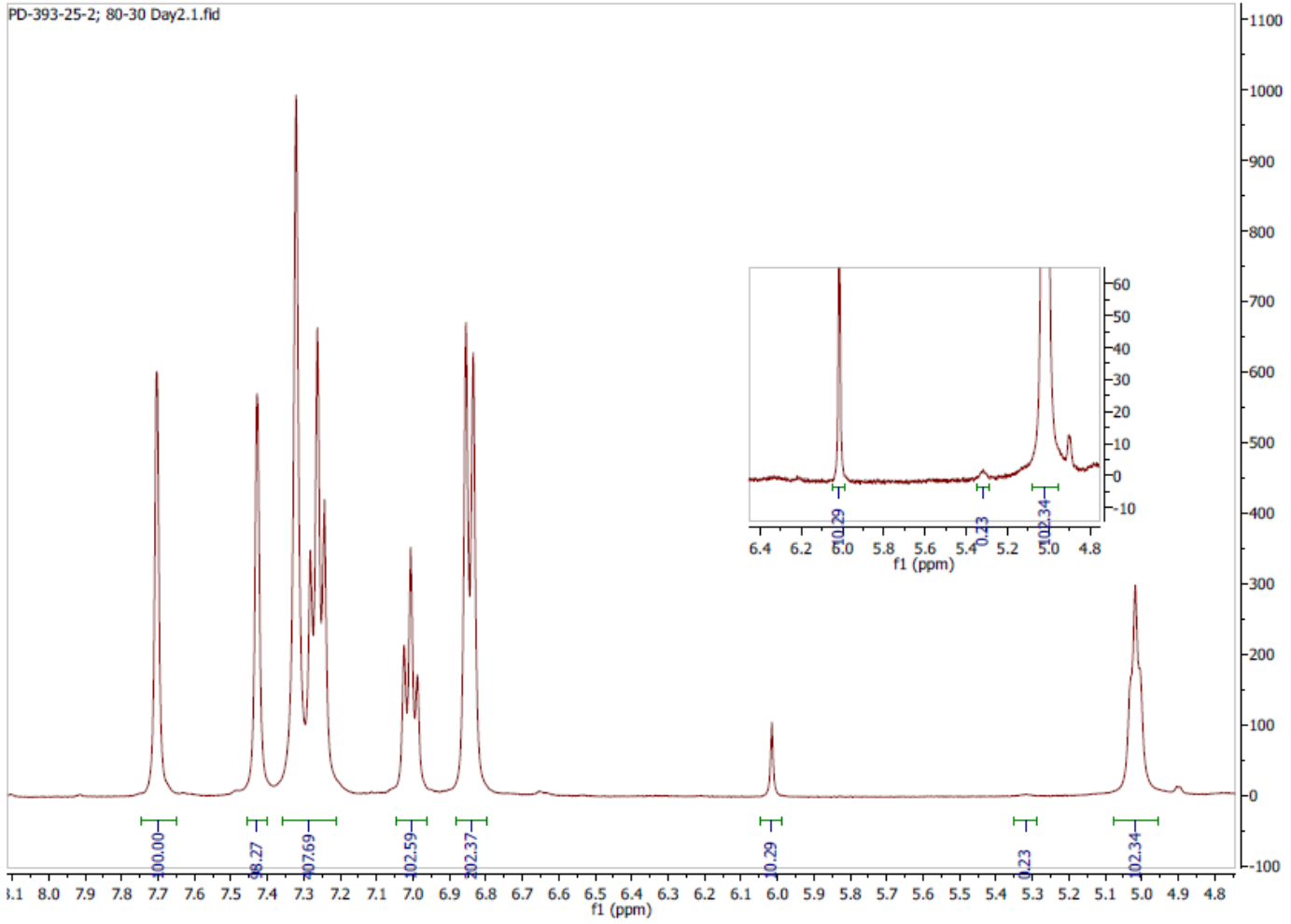
Alternative Analytical Technique

- qNMR Parameters

Field Strength	≥ 400-600 MHz
Nucleus	^{1}H
Temperature	Regulated, typically 25-30°C
Number of Scans	≥ 32
Flip Angle	≤ 45°
Spectral Width (sw)	≥ 16 ppm
Relation Delay (D1)	30 s
Solvent	Chloroform
Acquisition Time	≥ 3 s

1. Pauli, G. F. et al. J. Med Chem. 2014, 57, 9220-9231
2. Weber, M. et al. J. Pharm. Biomed. Anal. 2014, 93, 102-110

Alternative Analytical Technique



Alternative Analytical Technique

- Predicted results for meeting acceptance criteria of 0.2%

Formulation	1	2	3
Degradation Product	**Known 1**	**Known 1**	**Known 1**
Model correlation	**0.36**	**0.97**	**0.85**
Condition	**% Probability of Passing**		
40°C/75%RH 6 month no desiccant	56.4	0.0	97.6
40°C/75%RH 6 month 1g desiccant	93.0	0.03	98.7
25°C/60%RH 24 month no desiccant	94.1	7.4	94.4
25°C/60%RH 24 month 1 g desiccant	98.8	60.2	96.0
25°C/60%RH 36 month no desiccant	83.5	0.48	91.0
25°C/60%RH 36 month 1 g desiccant	95.0	21.7	93.8

Alternative Analytical Technique

- Known 1 data for each prototype formulation analyzed using qNMR
- The results of the analysis predict prototype formulation 3 (Starch 1500) would have the greatest probability of meeting an acceptance criteria of 0.2% label claim
- Analysis of unknown degradation products not performed during this analysis
- Further optimization of extraction process necessary
- Both analytical techniques selected prototype formulation 3 as the most stable formulation

Conclusion

- The data generated from the excipient compatibility study predicted prototype formulation 3 would be the best candidate to move forward into full formulation development
- Analysis of each of the prototype formulation in the ASAP study also provided an early profile of likely degradation products present in each formulation
- Both analytical techniques investigating selected prototype formulation 3
  - qNMR analysis may allow for faster determination of instabilities in a drug product
- The predictions from the ASAP study will be further monitored through the project, and confirmed through traditional ICH stability studies
- ASAP approach to excipient compatibility testing allows faster entry into full formulation development ~2-5 month

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