Industrial Applications of Powder X-ray Diffraction

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PPXRD-17

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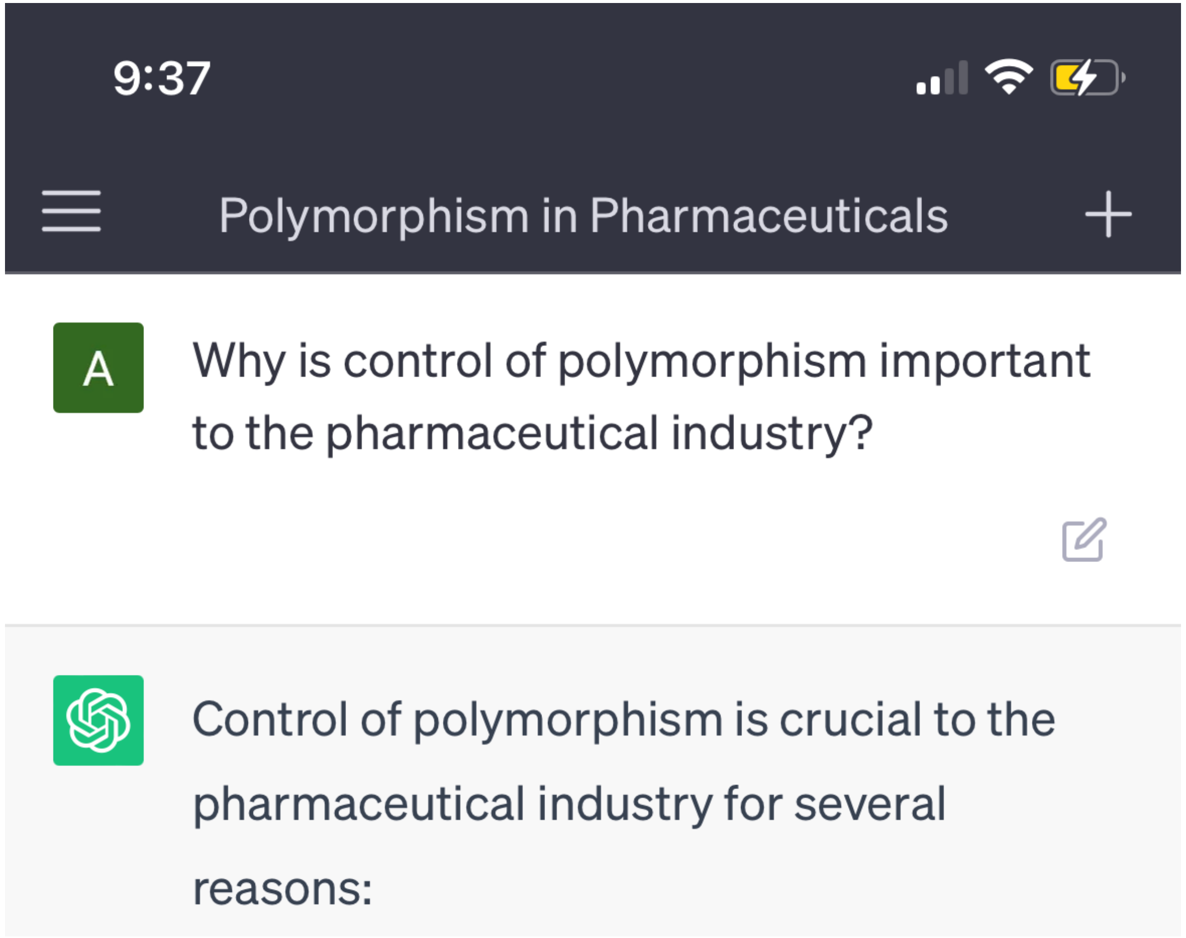
Outline

- Why is Control of Polymorphism Important to the Pharmaceutical Industry?
- Case Studies of PXRD in Industry
- Pros/ cons of PXRD and other solid-state methods for observing polymorph changes
- Stage-appropriate validation of XRPD method
- Commentary on “New” XRPD Adjacent Techniques

Let's ask ChatGPT…



Why is Control of Polymorphism Important to the Pharmaceutical Industry?

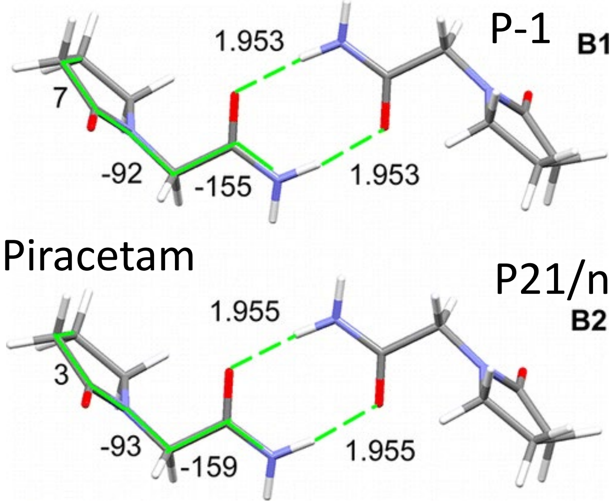
- Drug efficacy and bioavailability:
  - Polymorphism refers to the ability of a compound to exist in different crystalline forms or solid-state structures. Different polymorphs can have distinct physicochemical properties, such as solubility, stability, and dissolution rate. These properties can significantly impact the drug's bioavailability and efficacy. Therefore, the pharmaceutical industry aims to identify and control the polymorphic forms of a drug to ensure consistent therapeutic outcomes.
- Manufacturing efficiency and cost-effectiveness:
  - Polymorphism can affect various aspects of drug manufacturing, including crystal growth, purification, formulation, and stability. By understanding and controlling polymorphism, pharmaceutical companies can optimize manufacturing processes, enhance yield, and reduce production costs. Consistent control over polymorphs helps maintain batch-to-batch reproducibility, which is critical for regulatory compliance and quality assurance.
- Stability and shelf life:
  - Polymorphic forms can exhibit different stability profiles, affecting a drug's shelf life and storage conditions. Uncontrolled polymorphism can lead to unexpected changes in drug properties over time, including decreased potency or increased toxicity. By understanding and controlling polymorphism, pharmaceutical companies can optimize drug stability, extend shelf life, and ensure product quality and safety.
- Regulatory compliance:
  - Regulatory agencies, such as the U.S. Food and Drug Administration (FDA), require pharmaceutical companies to demonstrate the control and characterization of polymorphic forms during drug development and manufacturing. Documentation of polymorphism studies and regulatory submissions ensure compliance with guidelines and regulations, enabling drug approval and market access.
- Intellectual property protection:
  - Polymorphism can have a substantial impact on a drug's patent protection. Obtaining a patent for a new polymorphic form of a known drug can provide exclusivity and extend the commercial life of the drug. Pharmaceutical companies invest significant resources in research and development to discover and protect unique polymorphs, as they represent valuable intellectual property assets.

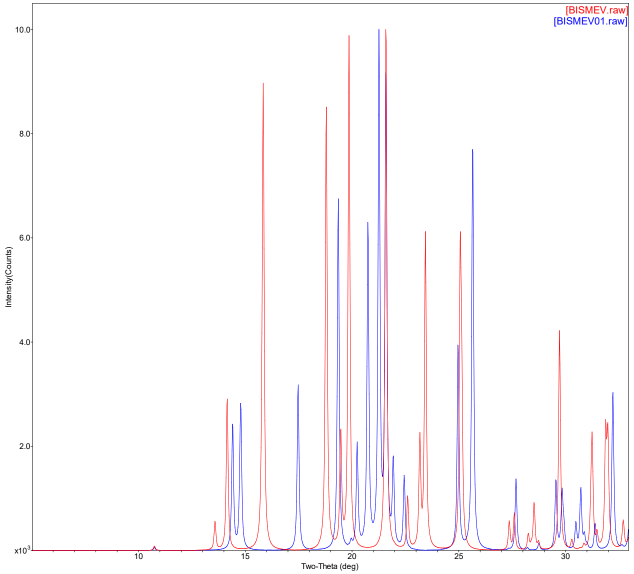
Polymorphism and XRPD

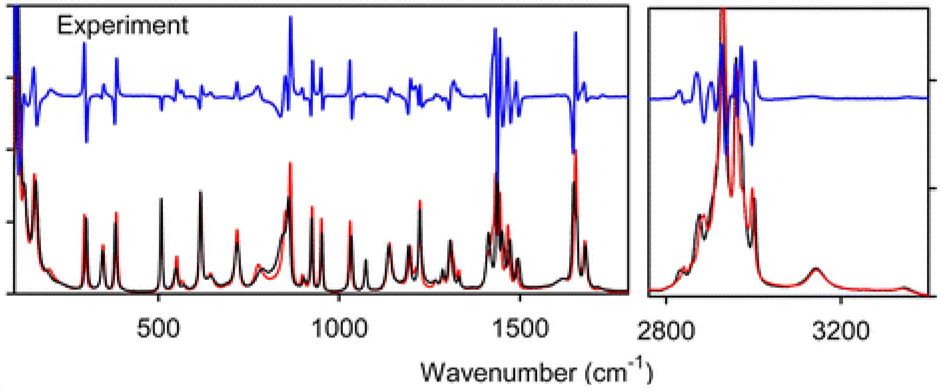
It should be emphasized that the definitive criterion for the existence of polymorphism is via demonstration of a nonequivalent crystal structure, usually by comparison of the x-ray diffraction patterns.
Microscopy, thermal analysis methodology, and solid-state NMR are generally considered as sources of supporting information.

https://www.fda.gov/ohrms/dockets/ac/02/briefing/3900B1_04_Polymorphism.htm

XRPD – Comparison to Other Techniques



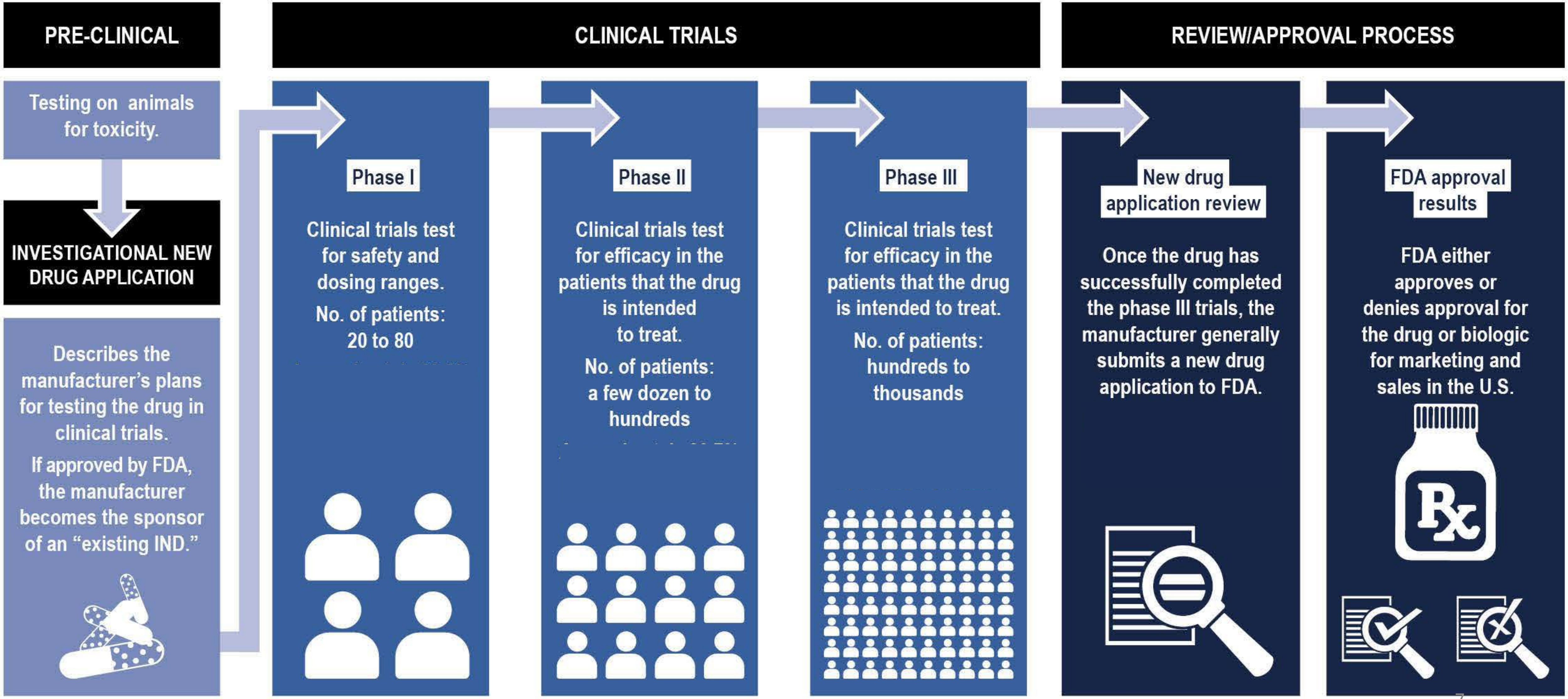




- XRPD is specific to packing changes
- Other spectroscopic techniques (raman) are not specific to polymorphs with similar conformations

Admiraal, G., Eikelenboom, J. C. & Vos, A. (1982). Acta Cryst. B38, 2600-2605.
Dračínský M., *The Journal of Physical Chemistry B* 2013 *117* (24), 7297-7307
Mazzo, D.J.,Analytical Profiles of Drug Substances Volume 15, 1986, Pages 1-34
Jozwiakowski, M.J., International Journal of Pharmaceutics Volume 91, 1993, Pages 195-207

Drug Development



Source: GAO analysis of FDA data and a 2016 collaborative study by Biotechnology Innovation Organization, Biomedtracker, and Amplion.[a] | GAO-17-564

Applications of XRPD in Drug Development

PRE-CLINICAL	CLINICAL TRIALS	REVIEW/APPROVAL PROCESS
Isolation of crystalline phase (yield, purification, solubility)	Final polymorph identification	Commercial specification justification
Fit-for-purpose polymorph identification	Polymorph risk assessments	Process understanding
	DS/ DP unit operation monitoring and control	Post-approval changes
	DS/ DP release testing and stability	Forensics (complaints, counterfeits, extraneous matter)
	Synthetic intermediate, raw material, excipient characterization and control	Intellectual property
	Clinical specification support	
	IND filing information	

Case Studies of PXRD in Industry

High-Throughput Crystallization

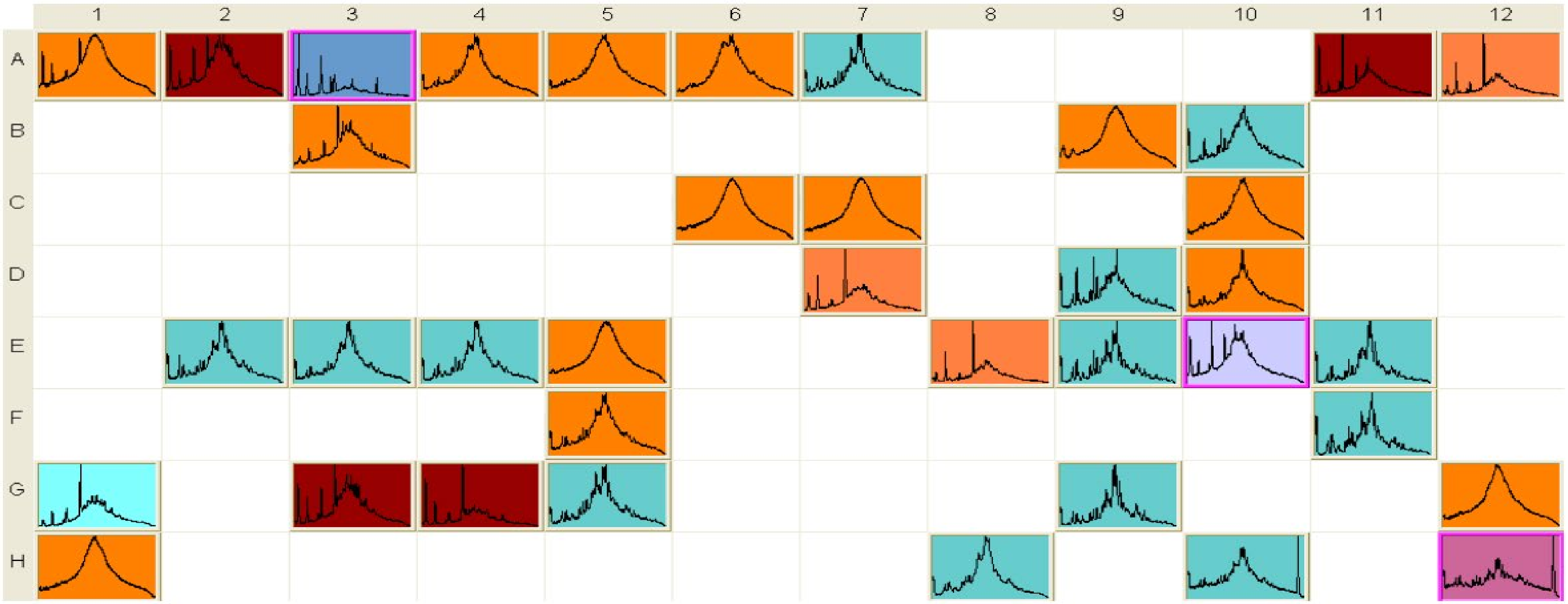
	1	2	3	4	5	6	7	8	9	10	11	12
A	MeOH/ H2O (1:1)	EtOH/ H2O (1:1)	1-PrOH/ H2O (1:1)	2-PrOH/ H2O (1:1)	MeOH/ Toluene	EtOH/ Toluene	1-PrOH/ Toluene	2-PrOH/ Toluene	Cyclopentanone/ Toluene	1,1,1-TCE	1,2-DCE	1-BuOH
B	MeOH/ H2O (1:3)	EtOH/ H2O (1:3)	1-PrOH/ H2O (1:3)	2-PrOH/ H2O (1:3)	DMF/ Toluene	DMA/ Toluene	NMP/ Toluene	DMSO/ Toluene	EtOAc/ Toluene	1-Chloro- butane	2-BuOH	MEK
C	DMF/ H2O (1:1)	DMA/ H2O (1:1)	NMP/ H2O (1:1)	DMSO/ H2O (1:1)	THF/ Toluene	Acetone/ Toluene	MeCN/ Toluene	1,2-DME/ Toluene	i-BuOH/ Toluene	2-MeTHF	n-BuOAc	Butyl Ether
D	DMF/ H2O (1:3)	DMA/ H2O (1:3)	NMP/ H2O (1:3)	DMSO/ H2O (1:3)	1,4-Dioxane/ Toluene	Formamide/ Toluene	PG/EtOH/ Toluene	t-BuOH/EtOH/ Toluene	IPAC/ Toluene	Anisole	Cyclo- hexane	Cyclopent- anone
E	THF/ H2O (1:1)	Acetone/ H2O (1:1)	MeCN/ H2O (1:1)	1,2-DME/ H2O (1:1)	TrifluoroEtOH/ Toluene	2-Methoxy- EtOH/Toluene	1,2-DCE/ Toluene	1-BuOH/ Toluene	MIBK/ Toluene	Diethoxy- methane	EtOAc	Heptane
F	THF/ H2O (1:3)	Acetone/ H2O (1:3)	MeCN/ H2O (1:3)	1,2-DME/ H2O (1:3)	2-BuOH/ Toluene	MEK/ Toluene	2-MeTHF/ Toluene	n-BuOAc/ Toluene	n-BuOAc/ Toluene	i-BuOH	IPAC	MeOAc
G	1,4-Dioxane/ H2O (1:1)	Formamide/ H2O (1:1)	PG/EtOH/ H2O (1:1)	t-BuOH/EtOH/ H2O (1:1)	Trichloroethene	Trifluoro- toluene	PG/EtOH	t-BuOH/EtOH	n-PrOAc/ Toluene	Me-Cyclo- hexane	MIBK	MTBE
H	1,4-Dioxane/ H2O (1:3)	Formamide/ H2O (1:3)	2-MethoxyEtOH/ H2O (1:3)	TrifluoroEtOH/ H2O (1:3)	Octane	Perfluoro- heptane	t-BuOAc	TAME	Toluene	n-BuOAc	Nitro- methane	n-PrOAc

PPT Plate Anti-solvents:

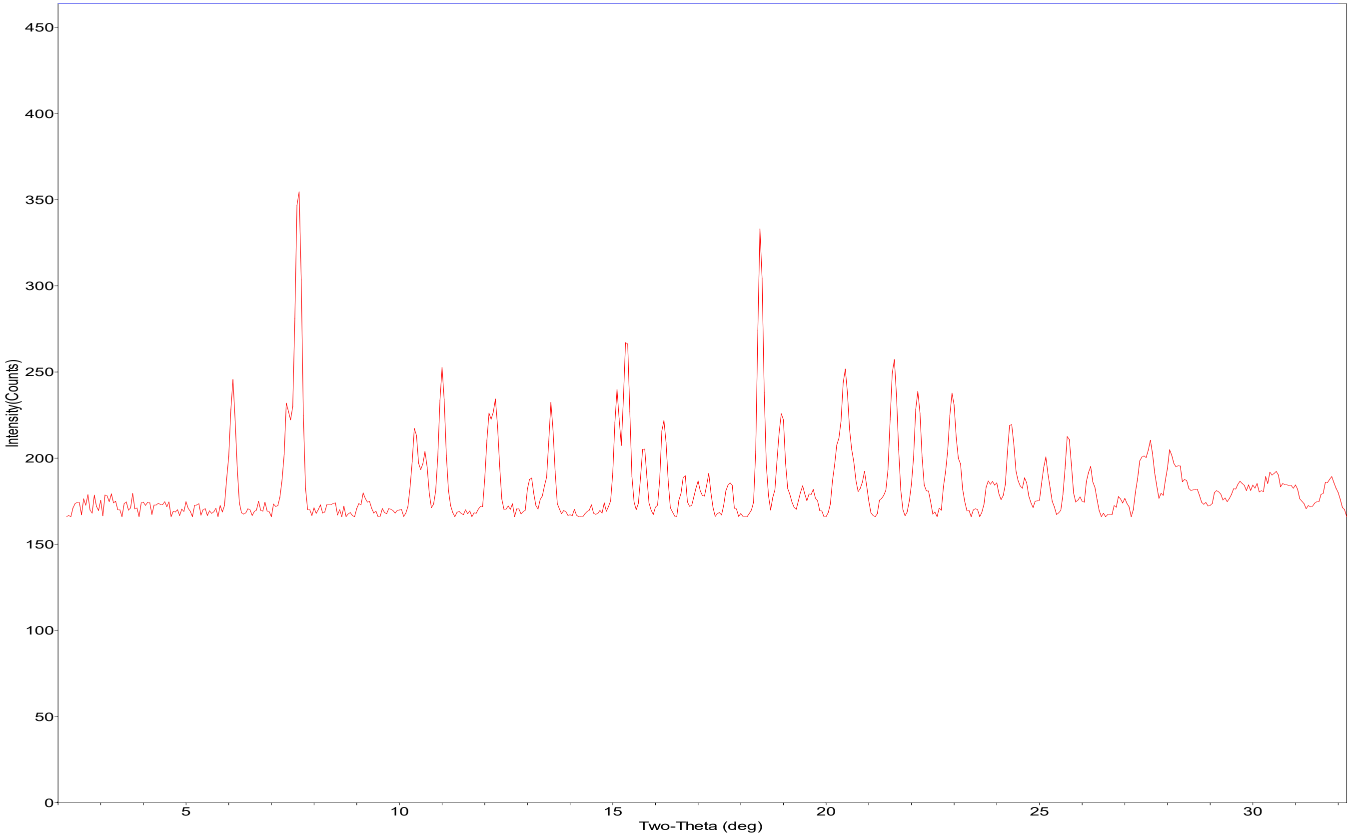
Water	Heptane	Butyl Ether

High-Throughput – Well Plate PXRD

High-Throughput - Grouping

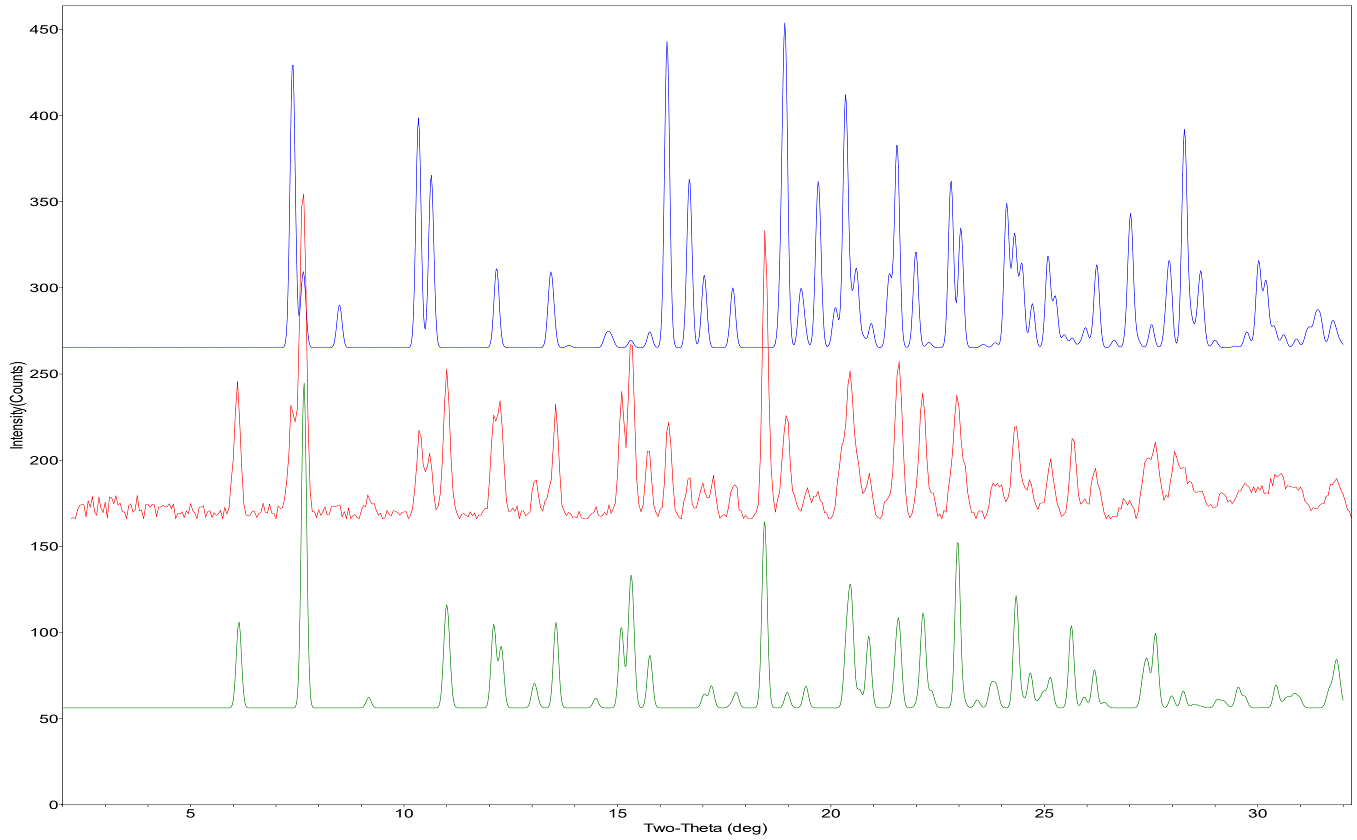


Phase Purity and Composition



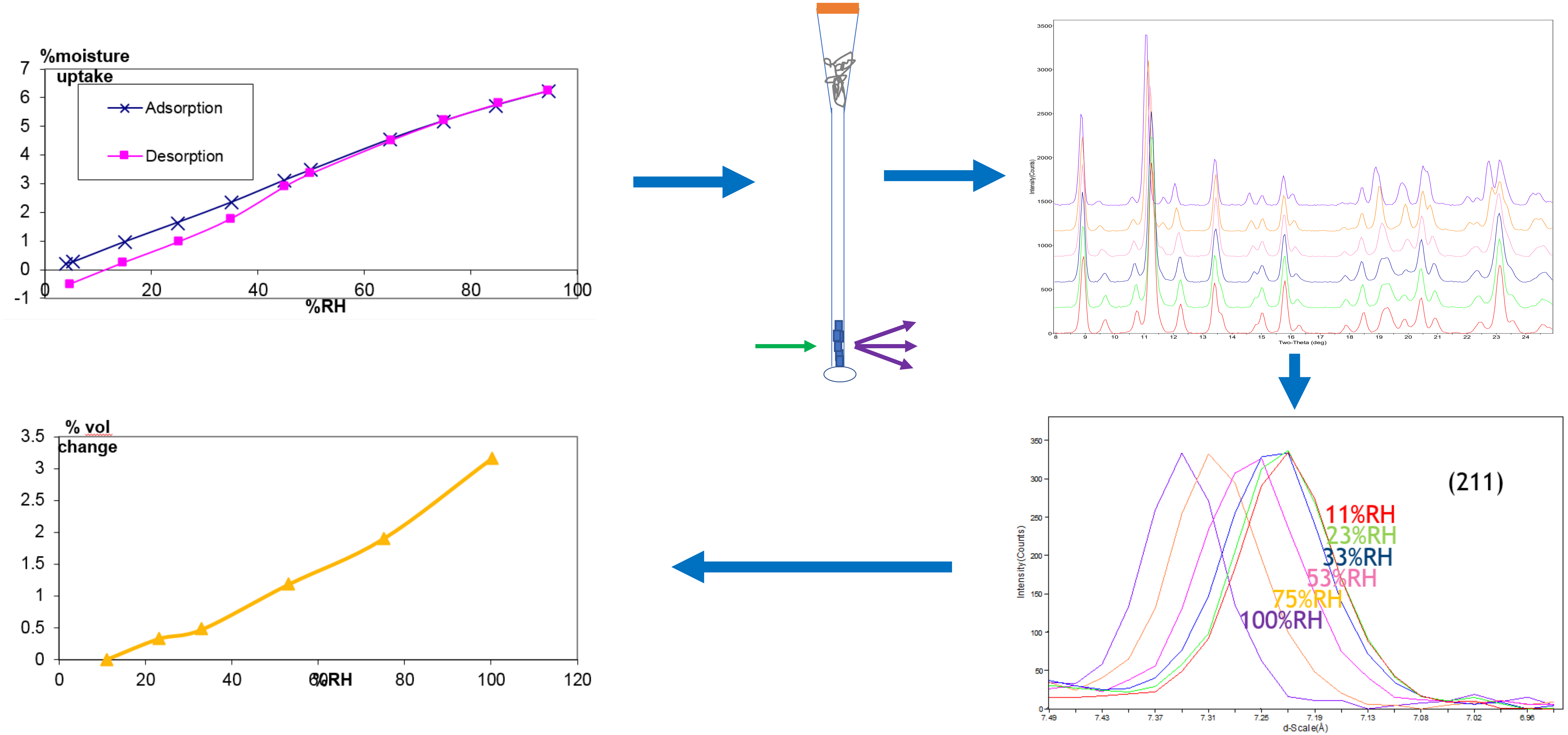
- Single phase?

Phase Purity and Composition



- Mixture of phases
- scXRD -> Simulated XRPD Neat Form and Hydrate
- Material will have residual water

VRH-PXRD - Observe Lattice Changes



Anisotropic expansion/ contraction as a function of temperature, pressure, solvent/ water activity

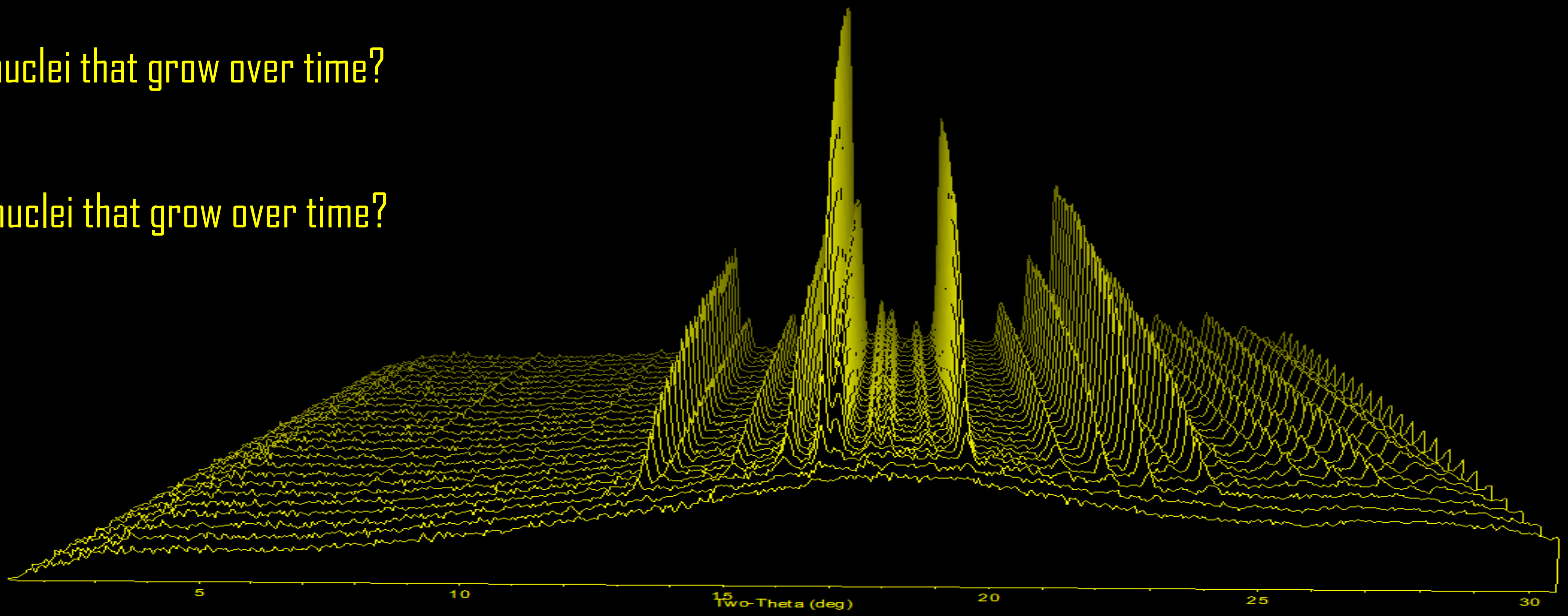
In-Situ Crystallization

Observe crystallization over time.

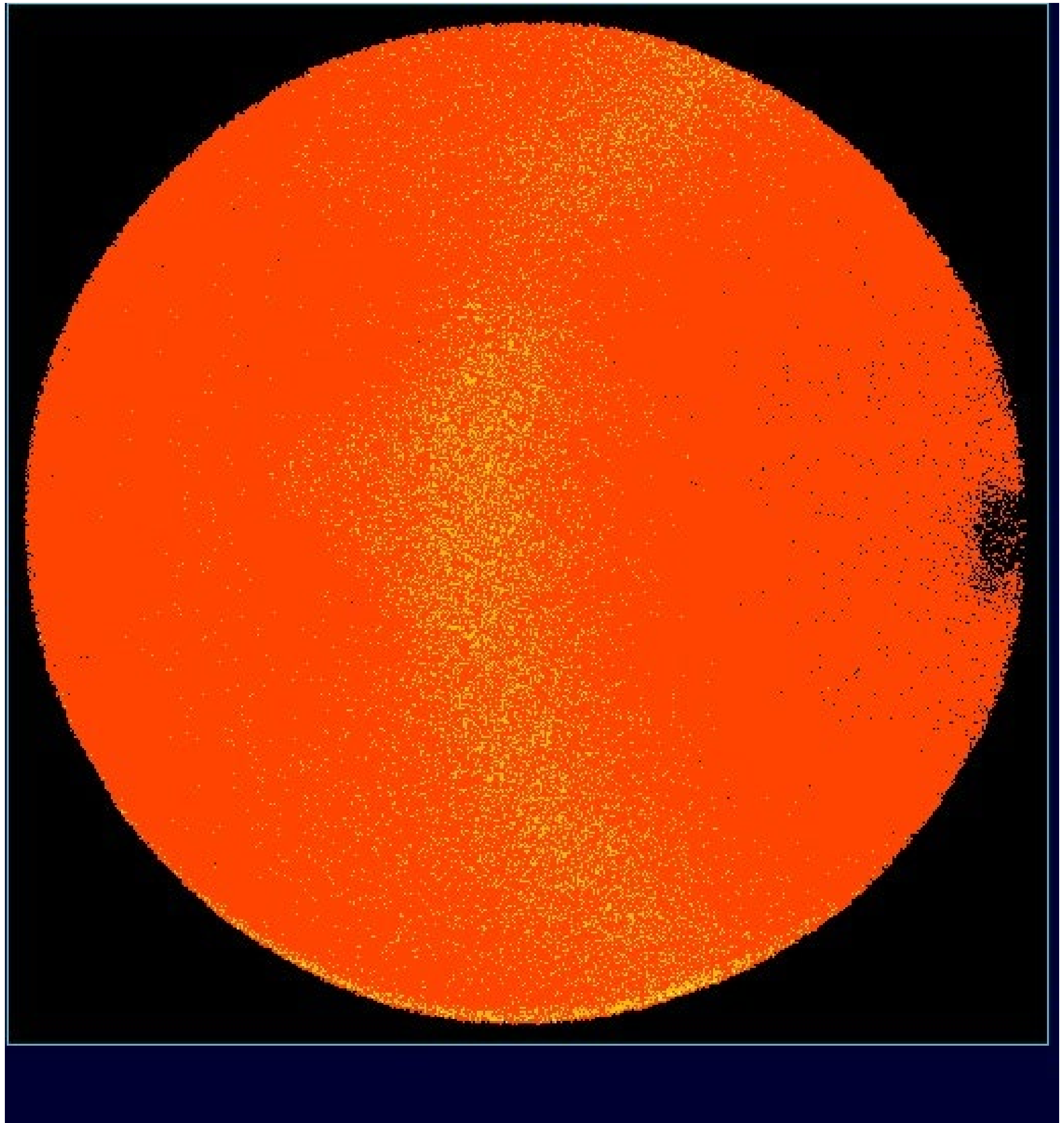
Small number of nuclei that grow over time?

OR

Large number of nuclei that grow over time?



2D: Observe In-Situ Crystallization Mechanism



Texture from 2 D data

- Small domains
- Randomly orientated
- Many Nuclei

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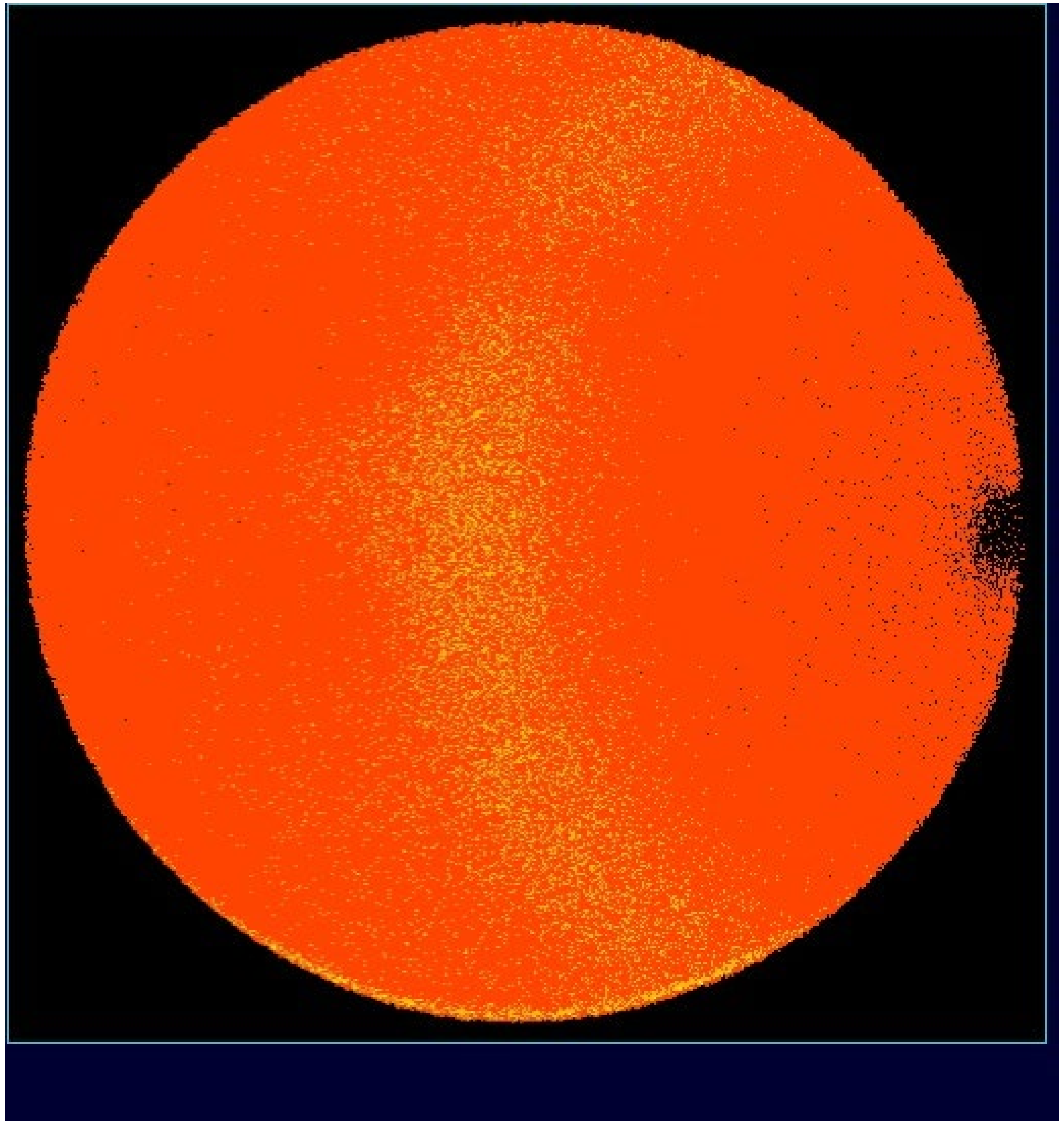

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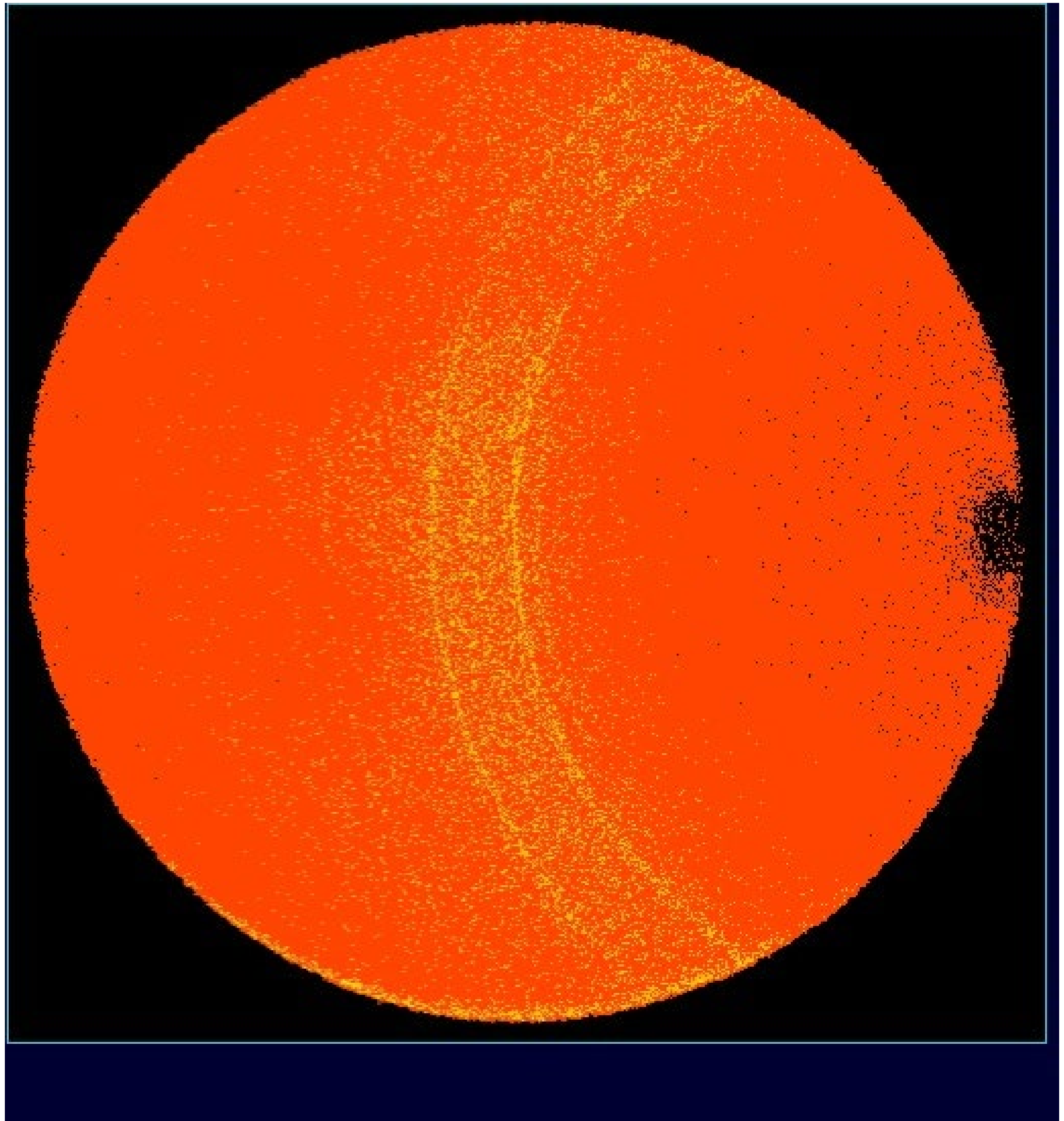

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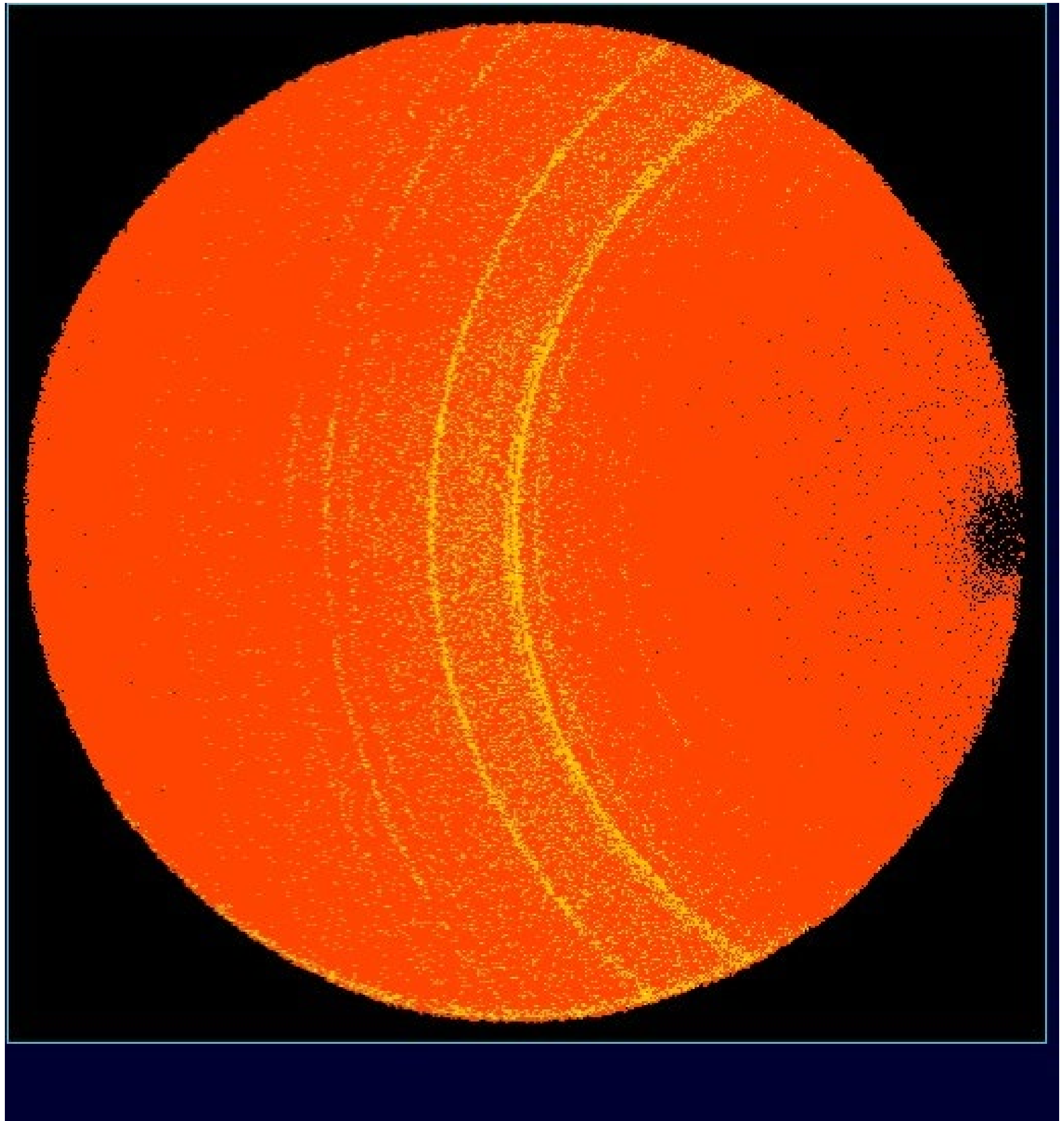

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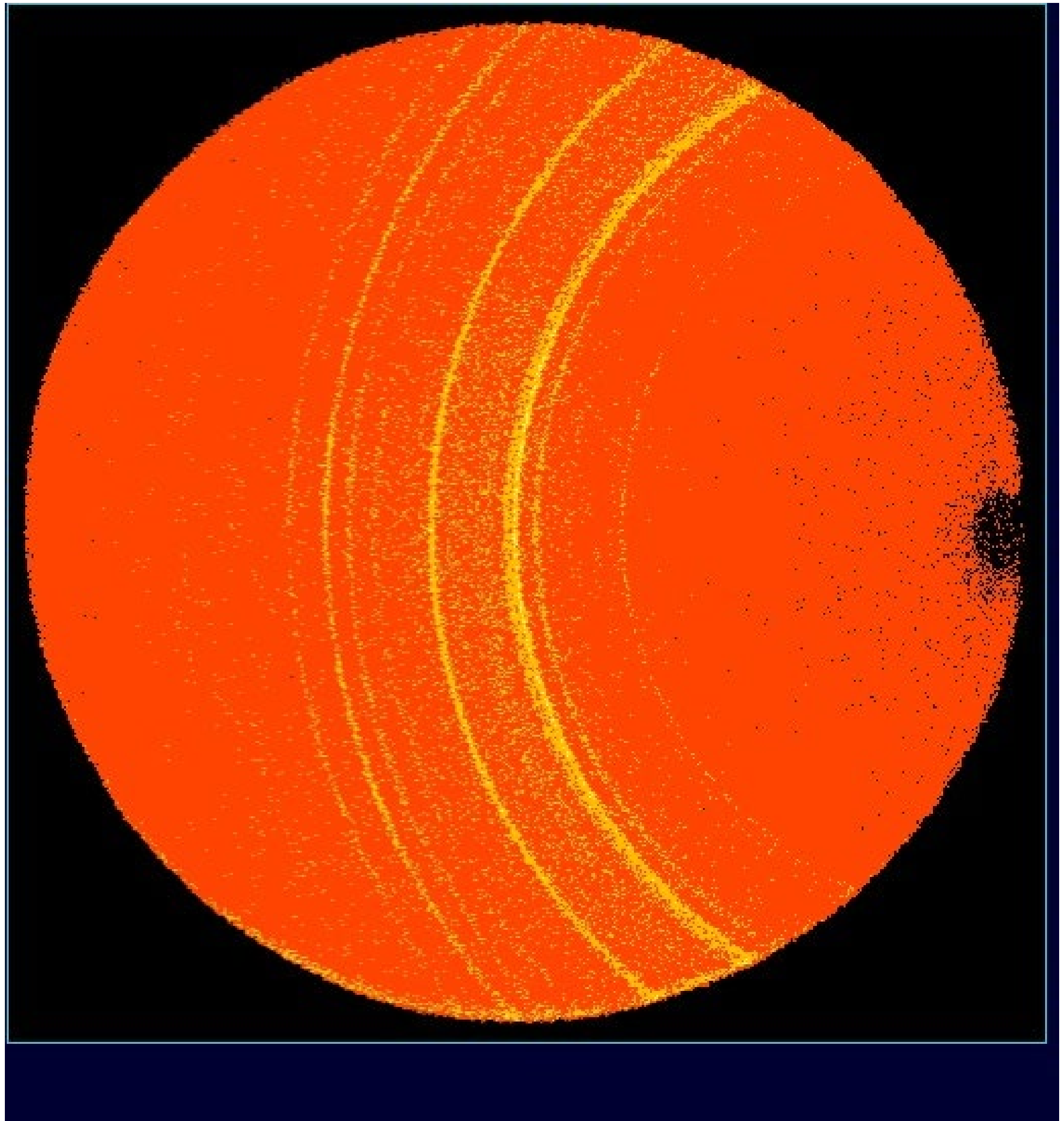

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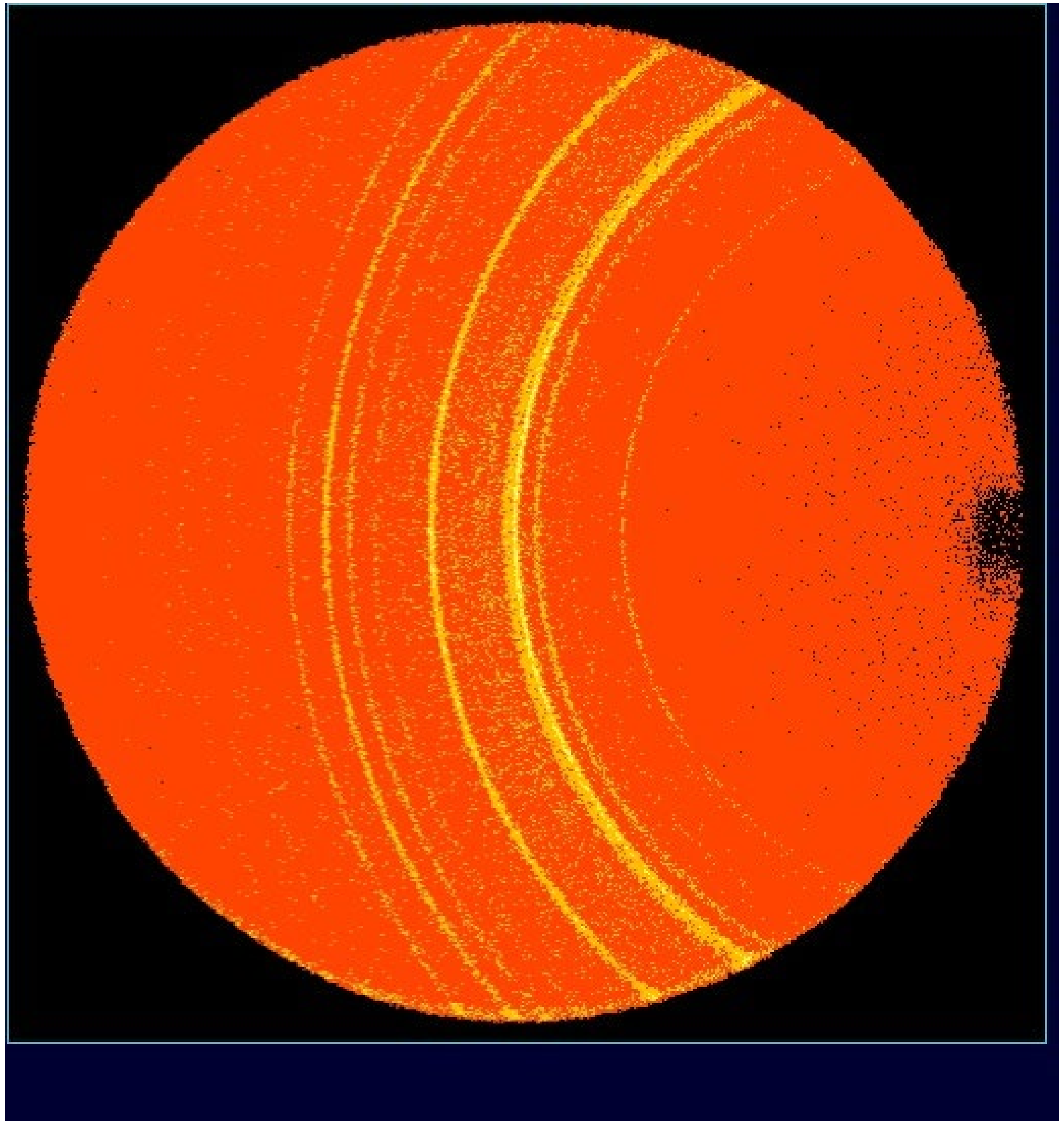

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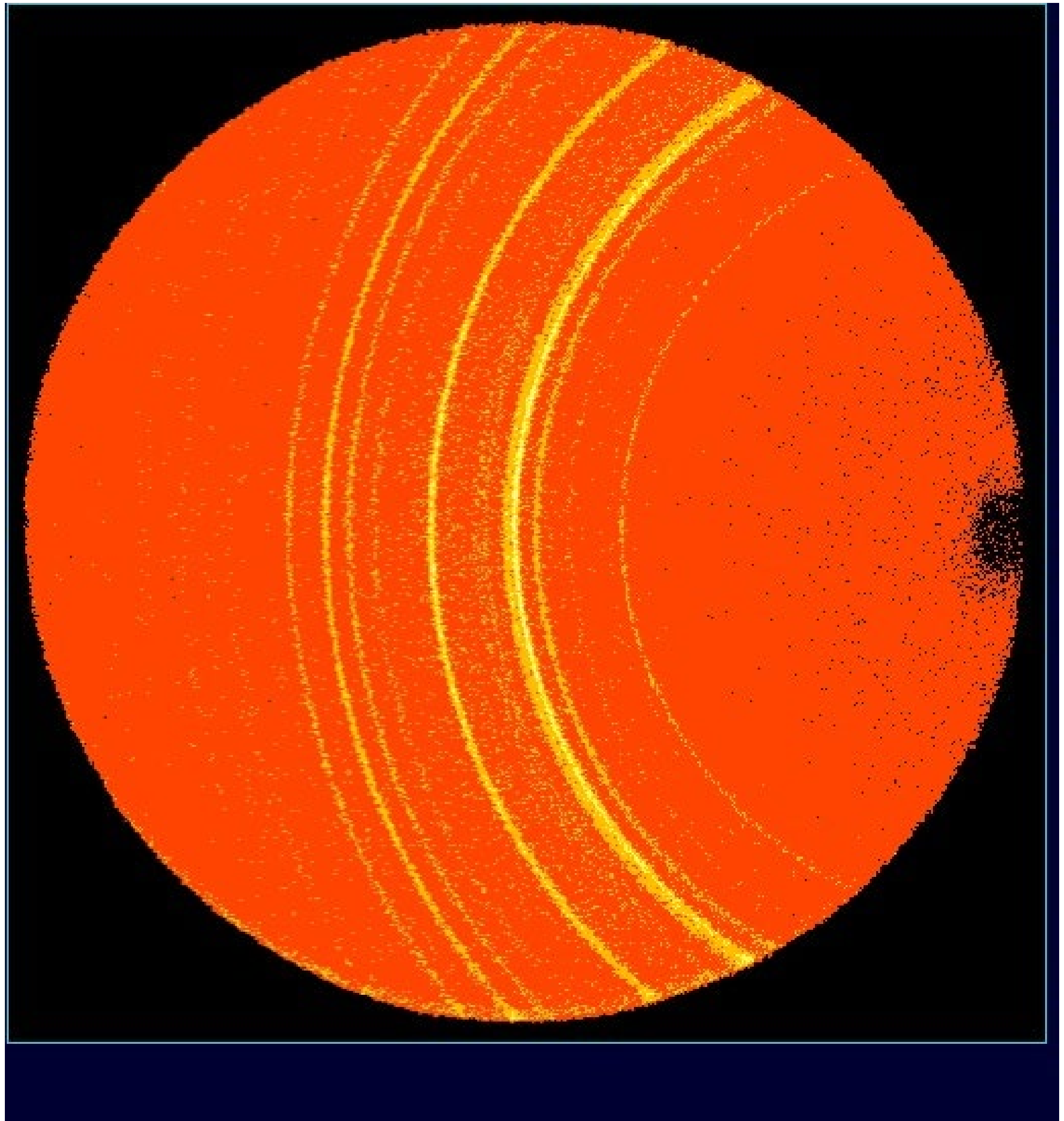

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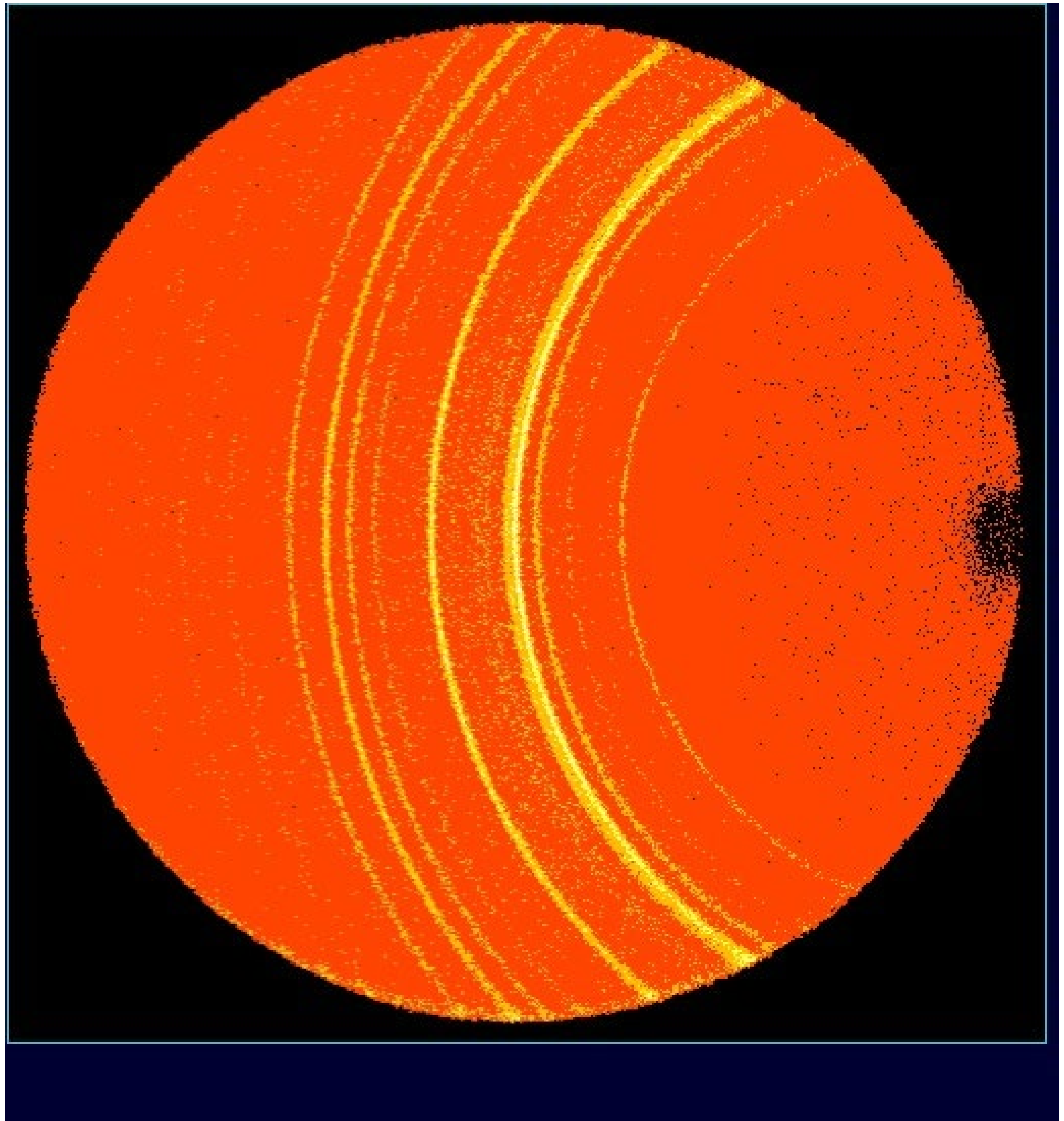

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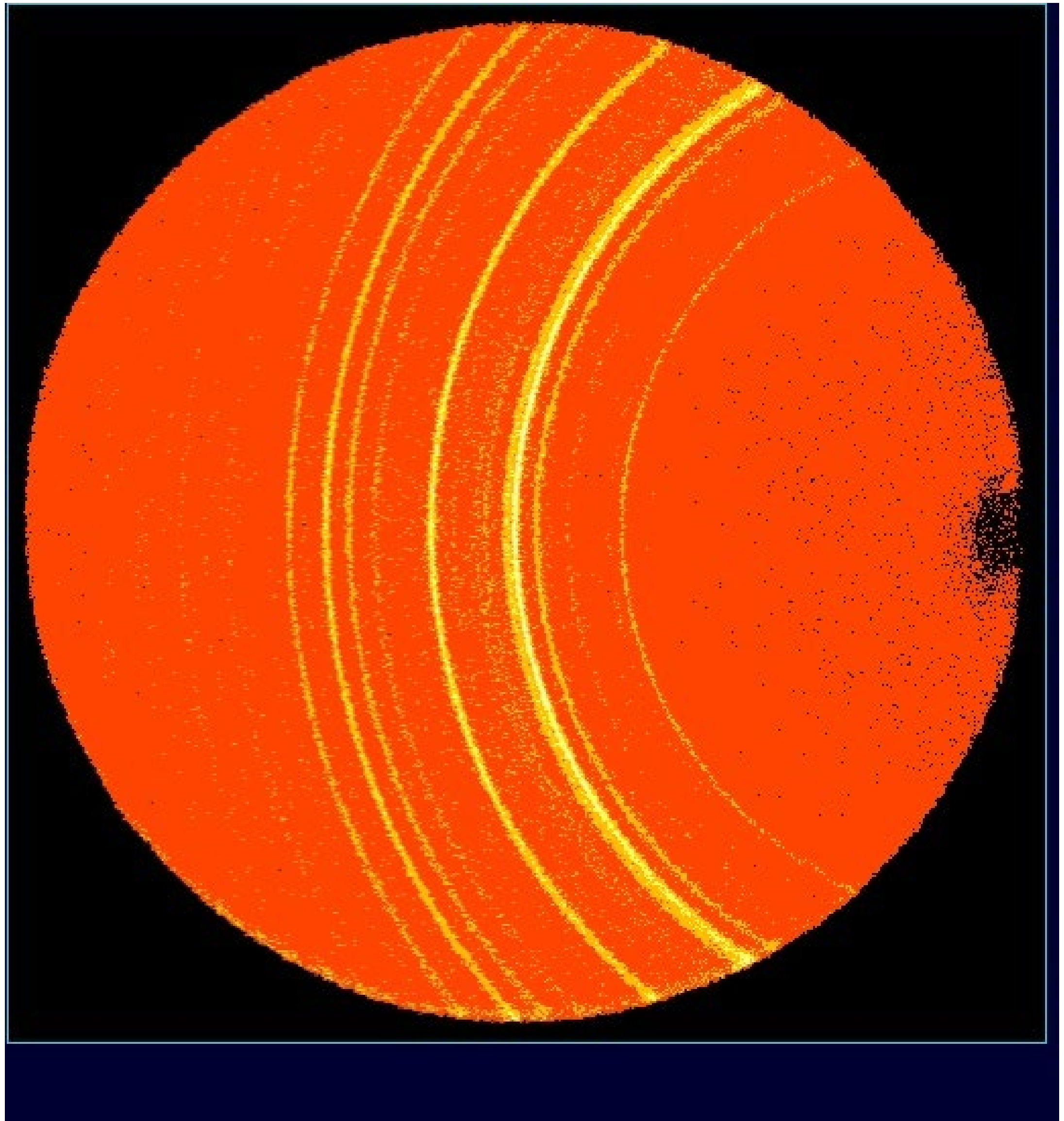

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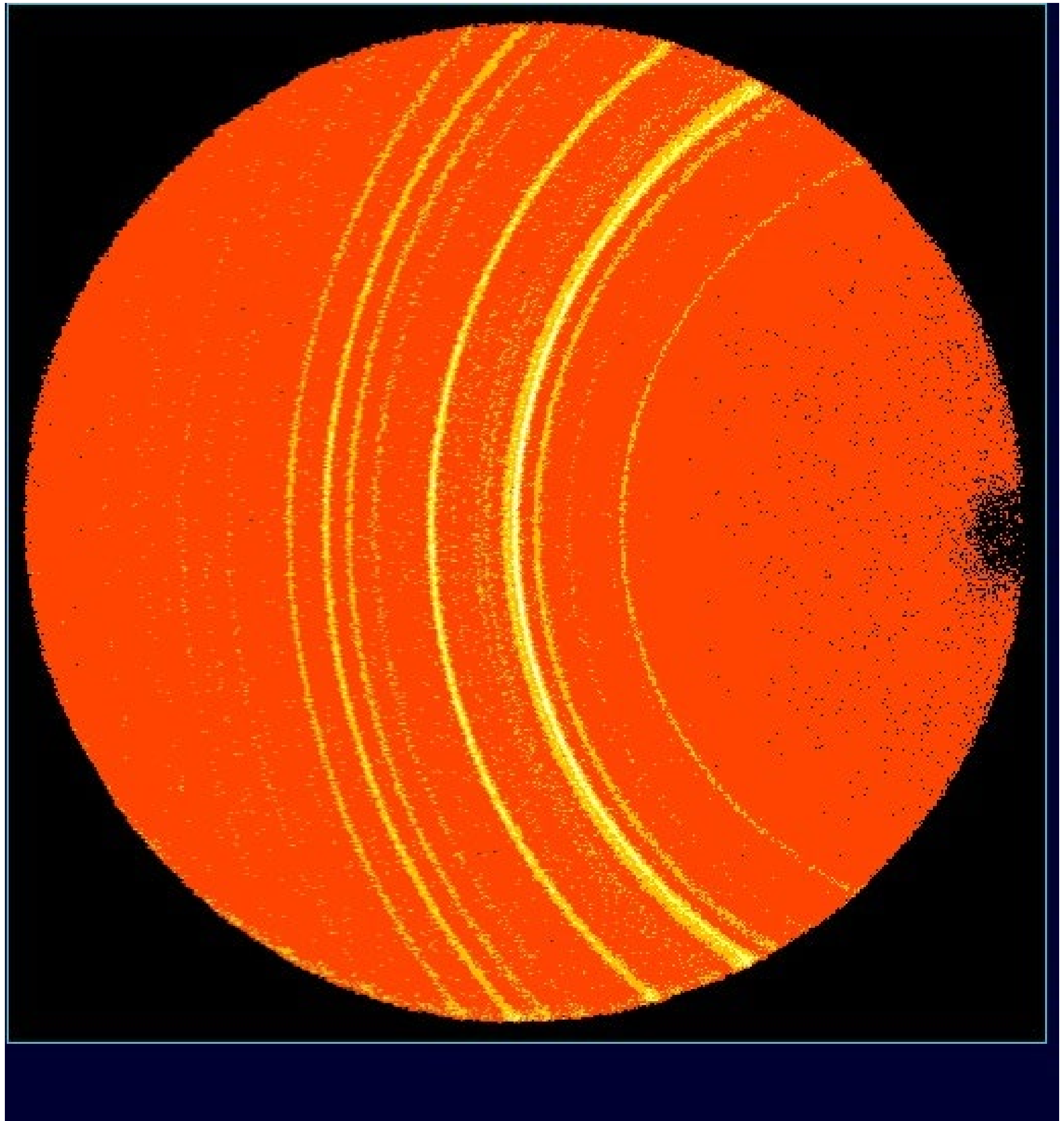

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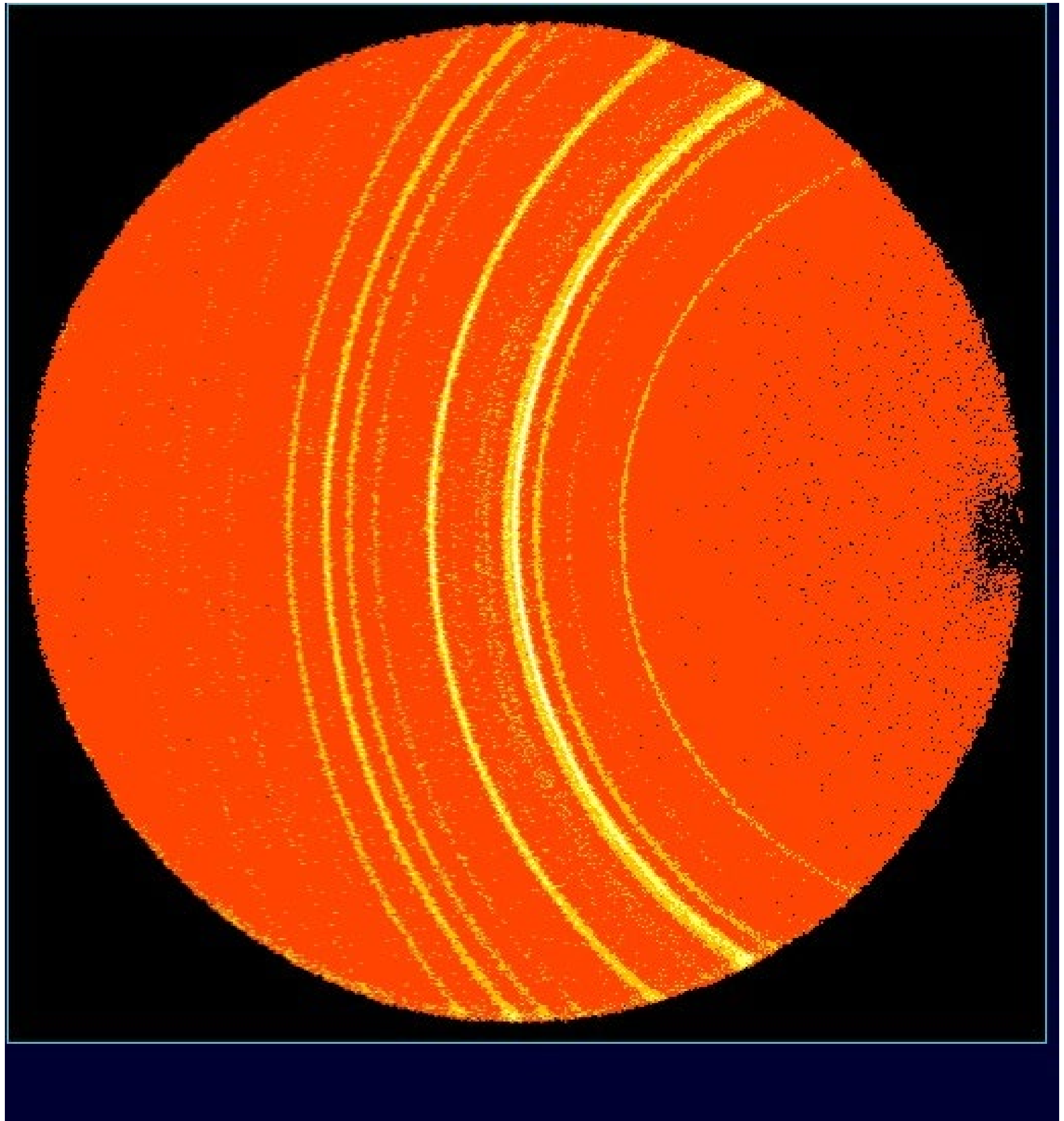

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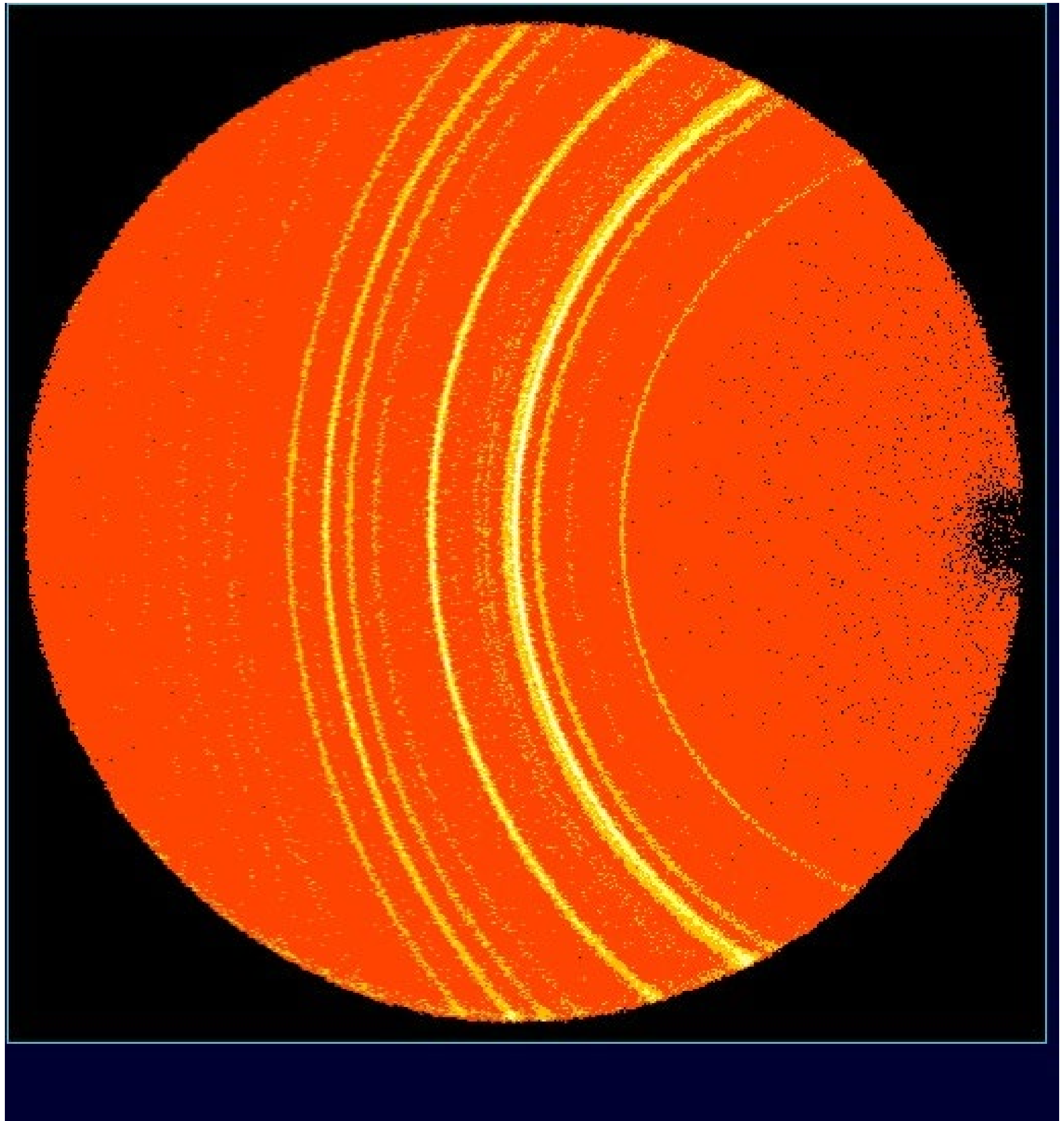

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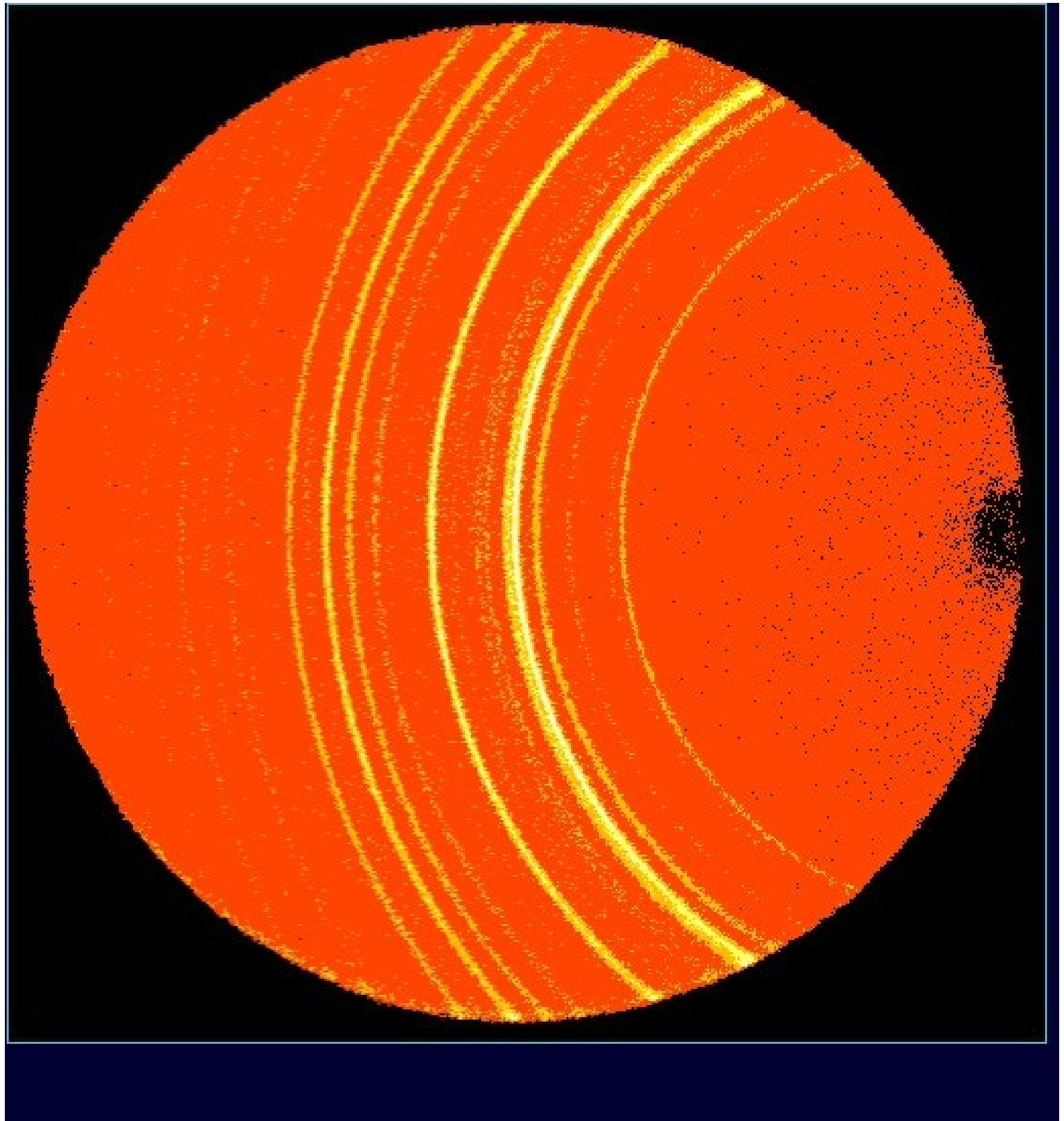

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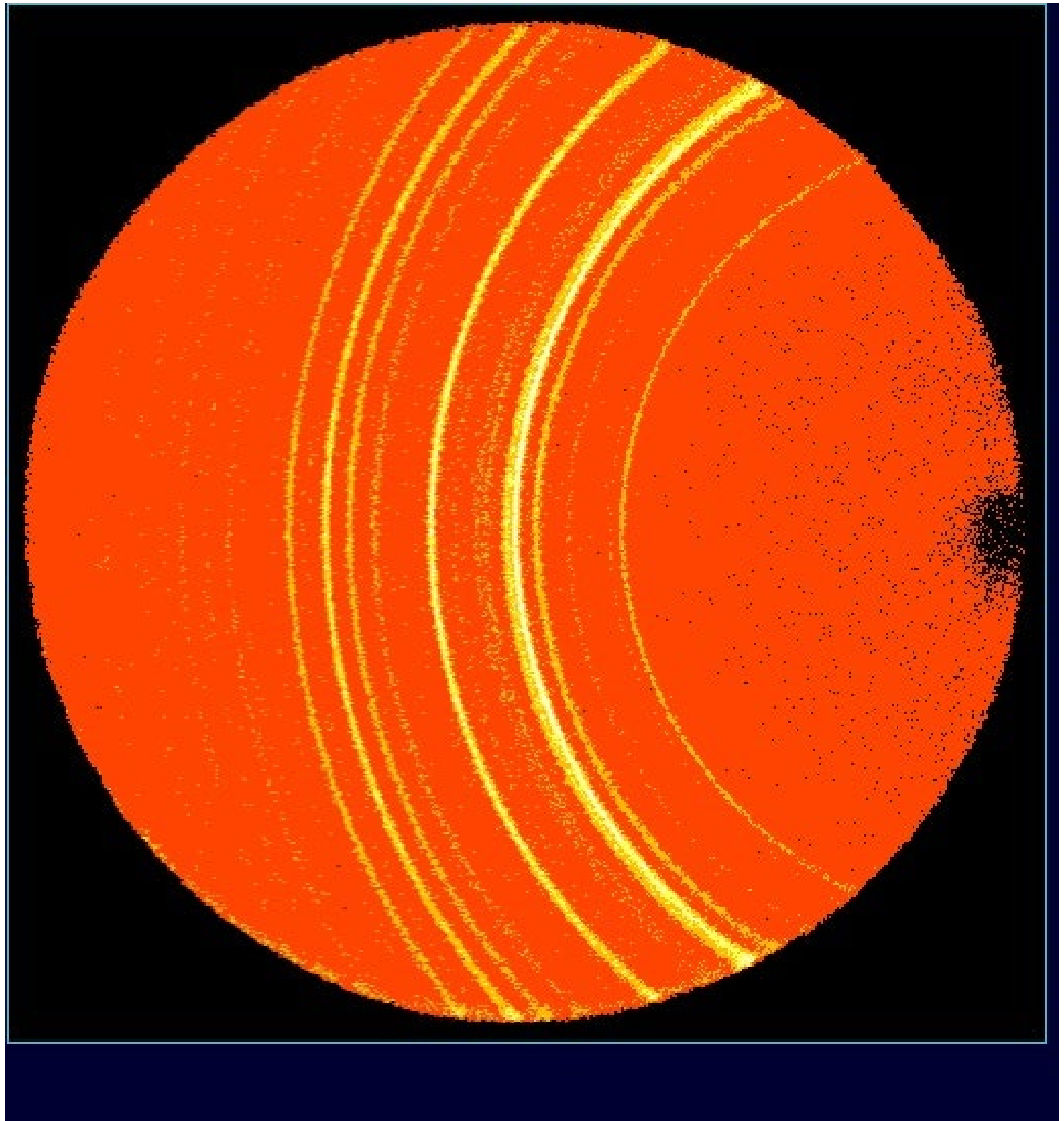

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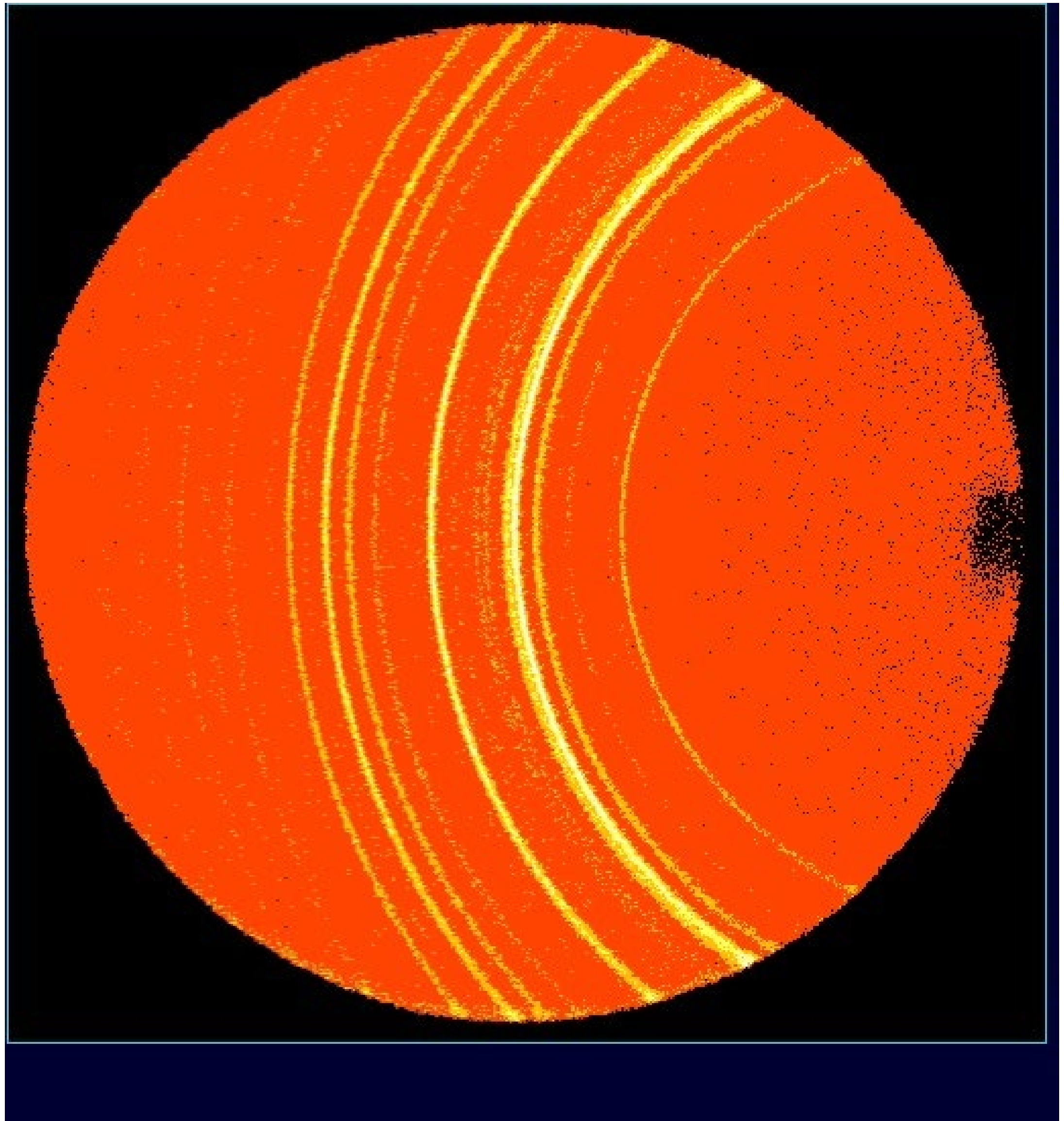

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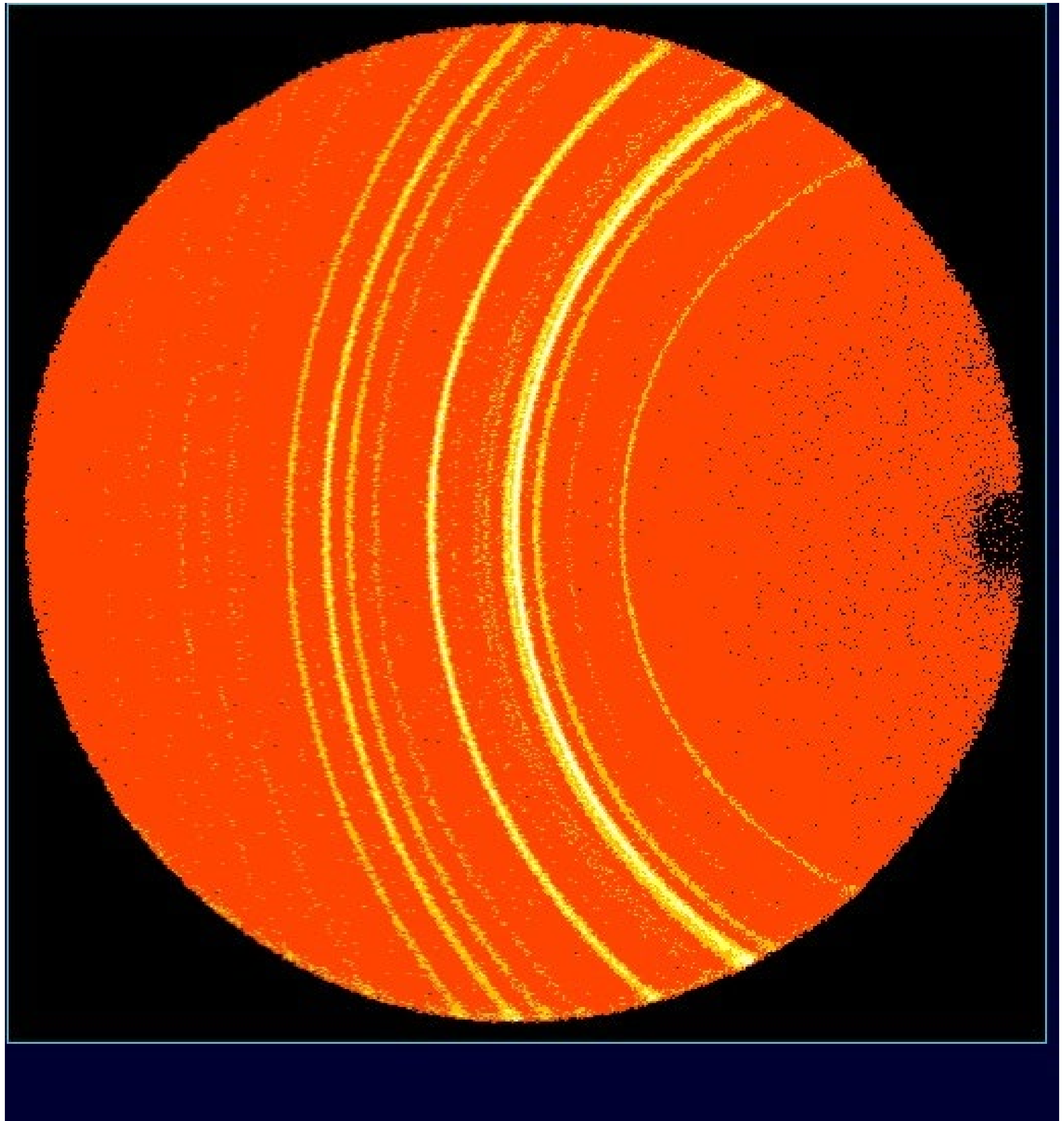

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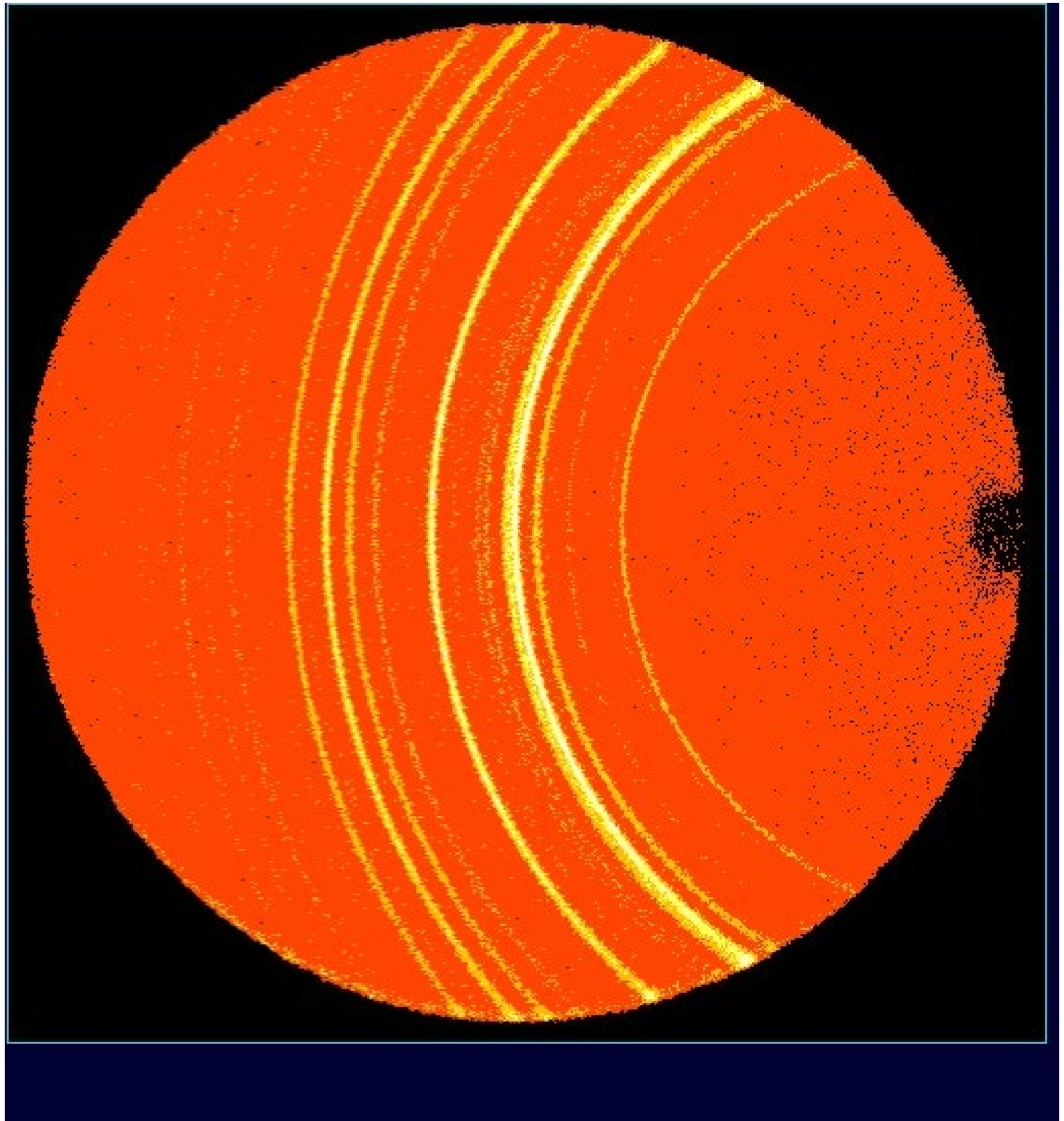

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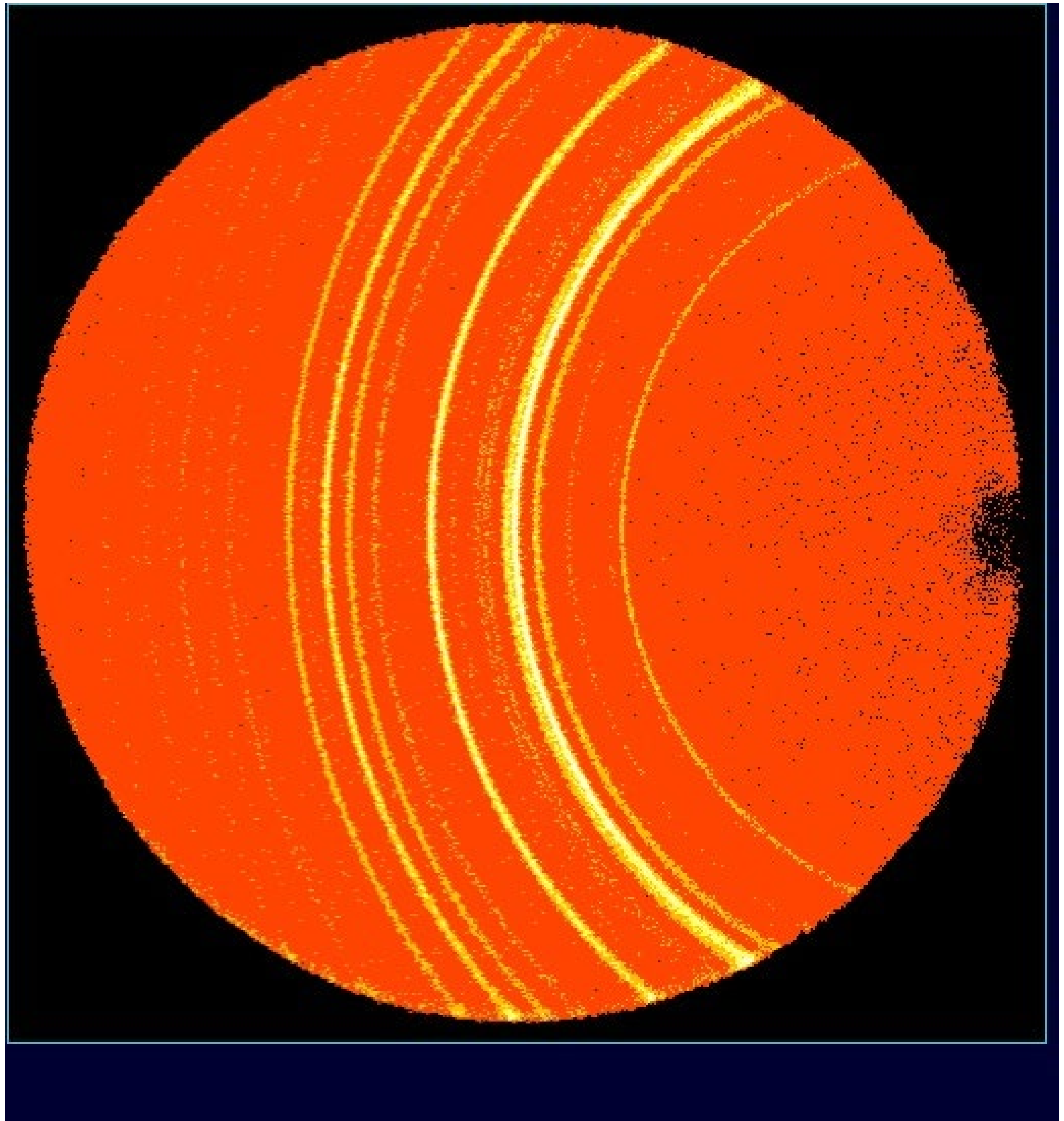

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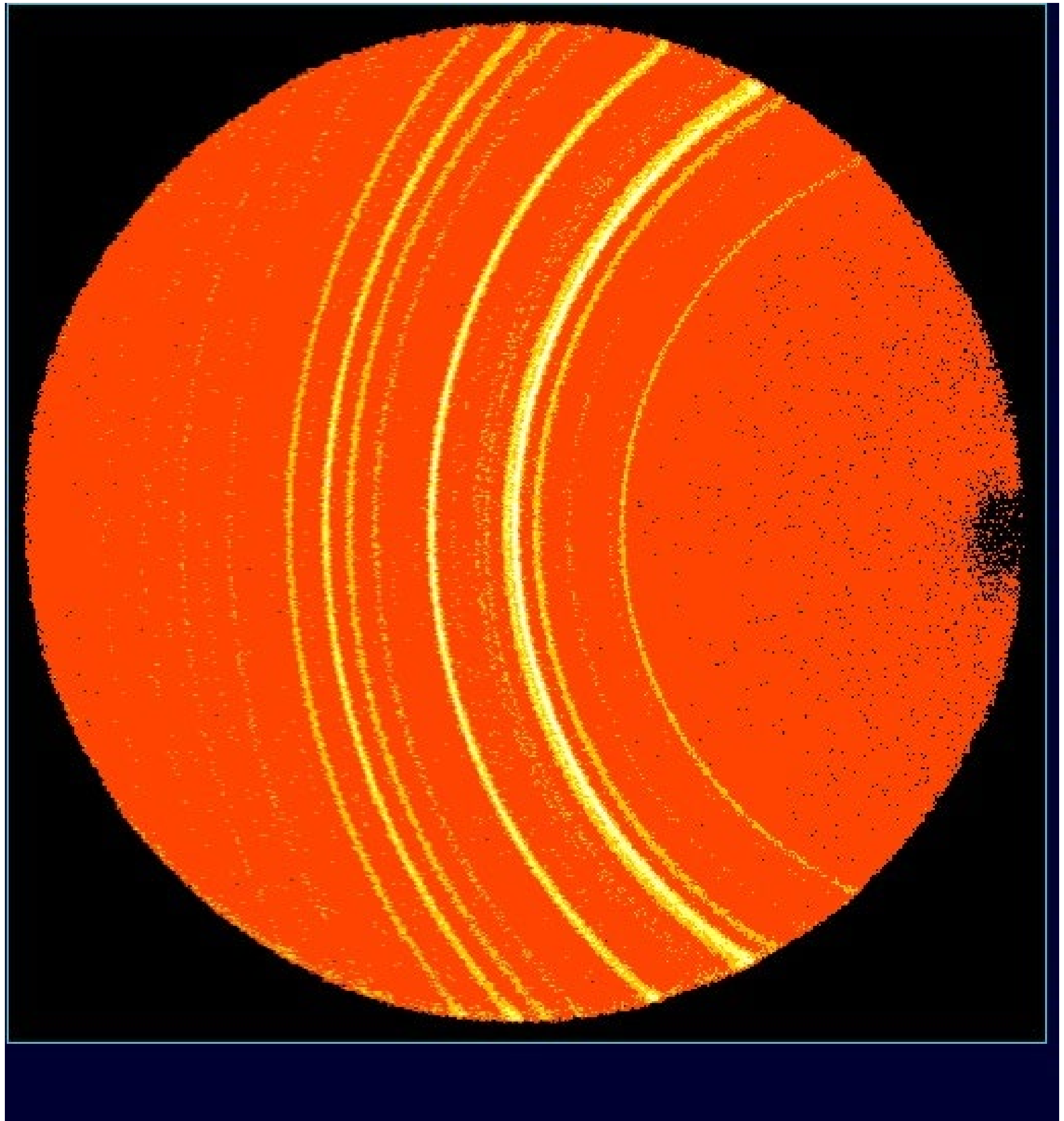

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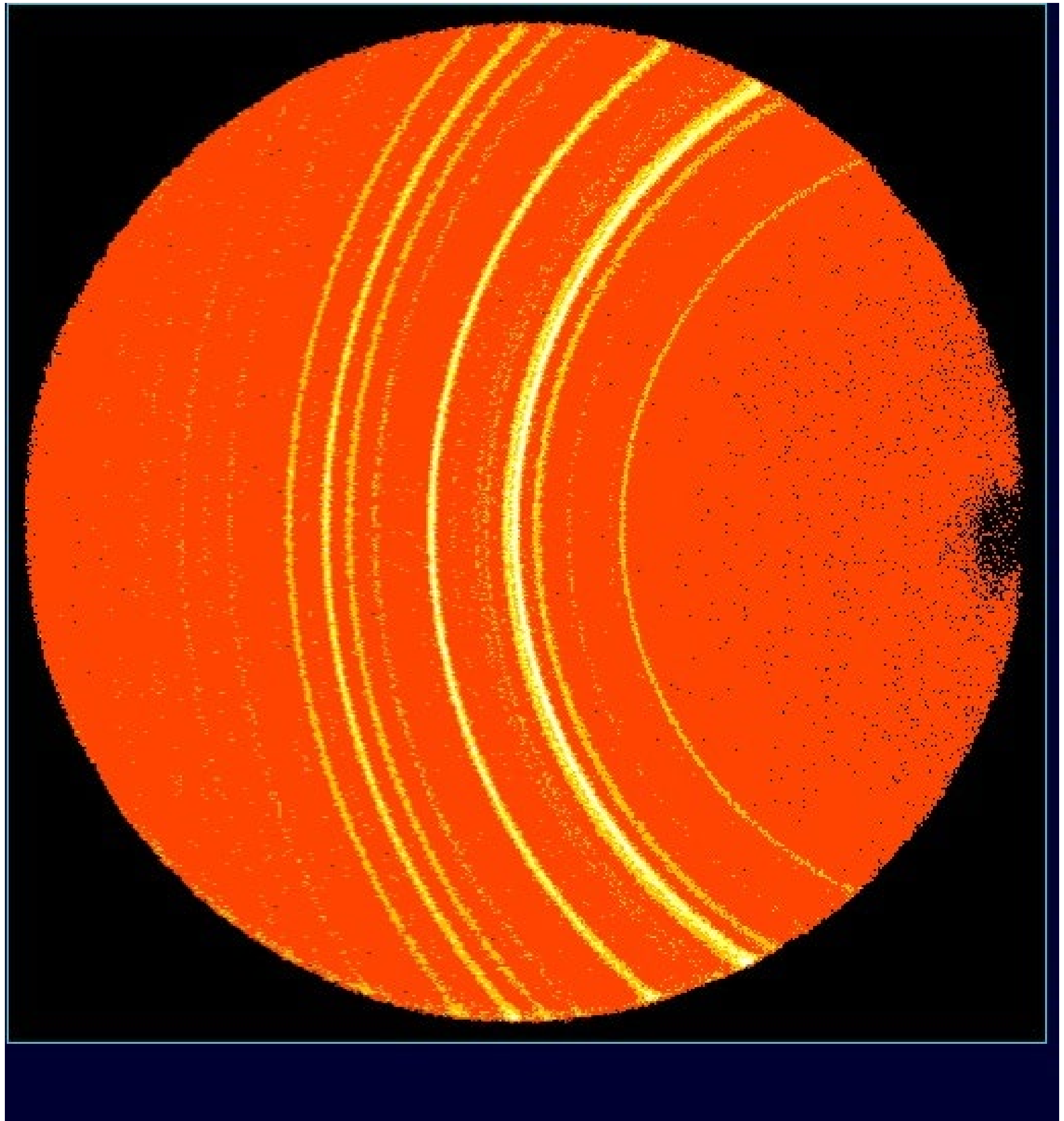

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Let's ask ChatGPT...

9:20 5G

Polymorphism in Pharmaceuticals

A What are the most important case studies of polymorphism in the pharmaceutical industry?

Polymorphism is an important phenomenon in the pharmaceutical industry that refers to the ability of a substance to exist in different crystalline forms or solid-state arrangements. These

Most Important Case Studies of Polymorphism

- ## Sulfathiazole:
  - This case is often regarded as the birth of polymorphism studies in the pharmaceutical industry. In the 1940s, it was discovered that sulfathiazole, an antibiotic, existed in two polymorphic forms (Forms I and II) with different solubility and bioavailability. This finding prompted researchers to recognize the significance of polymorphism in drug development.
- ## Carbamazepine:
  - Carbamazepine, an anticonvulsant and mood stabilizer, is another well-known case study. It has been found to exhibit multiple polymorphic forms (Forms I, III, and IV). The discovery of these different forms led to variations in drug dissolution rates and bioavailability, highlighting the importance of polymorph characterization in formulation development.
- ## Ritonavir:
  - Ritonavir, an antiretroviral medication used in the treatment of HIV, is an interesting case study due to its complex polymorphic behavior. It has been reported to exhibit at least six different polymorphs, which can significantly affect its stability and bioavailability. Understanding and controlling the polymorphic forms of ritonavir are critical for ensuring consistent drug performance.
- ## Paracetamol (acetaminophen):
  - Paracetamol is a widely used analgesic and antipyretic drug. It has been found to exhibit three polymorphic forms (Forms I, II, and III). Form II is the most stable and commercially relevant form, while Form III is less stable and has lower solubility. The understanding of these polymorphic forms is essential for ensuring the quality and efficacy of paracetamol formulations.
- ## Voriconazole:

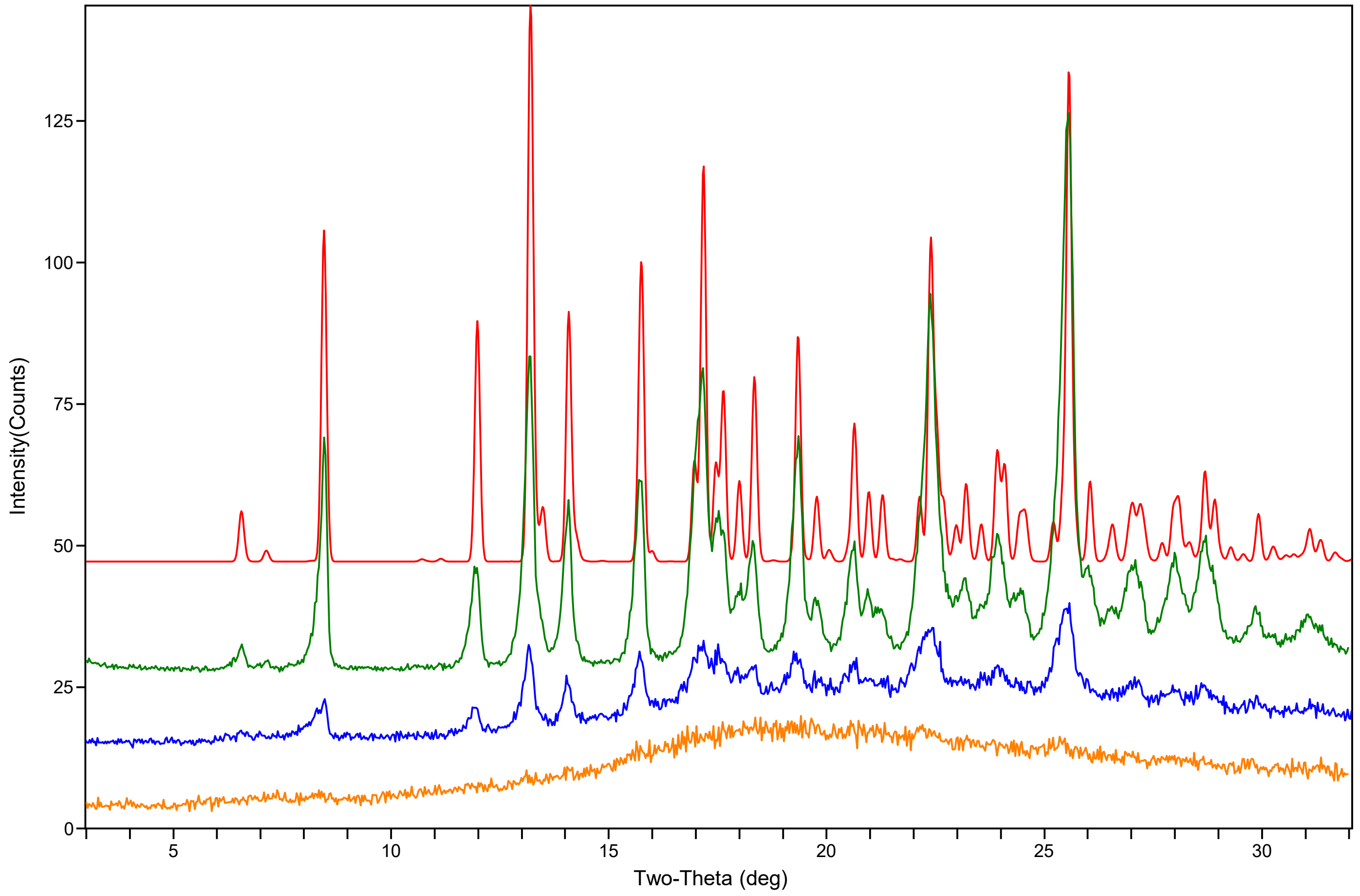
????

  - Voriconazole is an antifungal medication used to treat invasive fungal infections. It has been shown to exist in at least two polymorphic forms (Forms I and II). These forms exhibit different dissolution rates and can affect the drug's solubility and bioavailability. The selection and control of the appropriate polymorphic form of voriconazole are crucial for its therapeutic effectiveness.

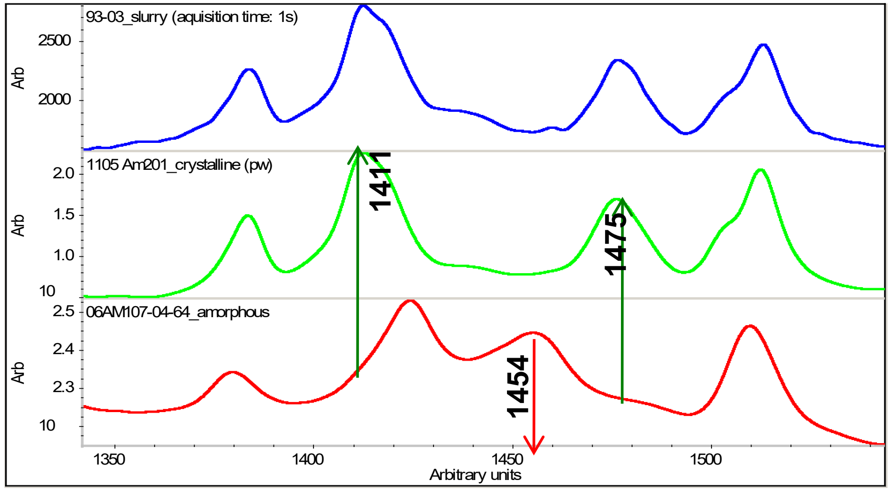
Case Study 1: DS Crystallization

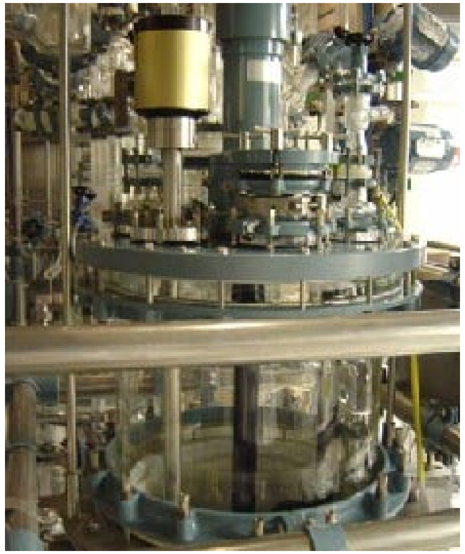
Goal: Determine end point of crystallization

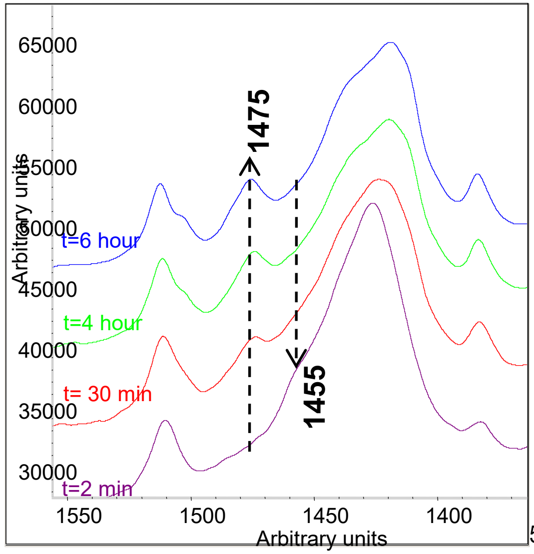
- Two-drop crystallization procedure (slurry conversion)
- Batch-to-batch variability in crystallinity by XRPD - quality concerns
- Offline capillary slurry XRPD: time consuming
- XRPD: amorphous vs solvent vs solubilized API
- Identify alternative technique

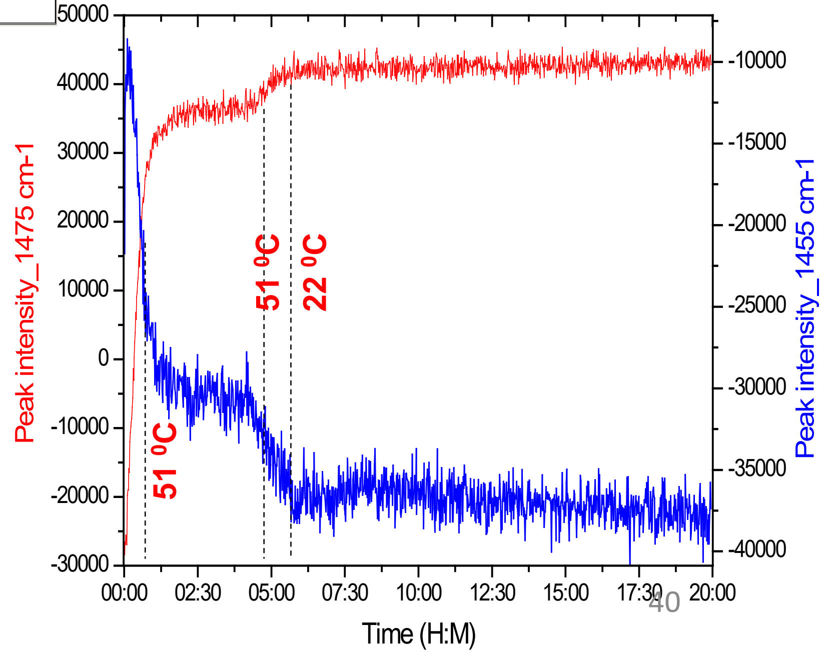


Case Study 1: DS Crystallization







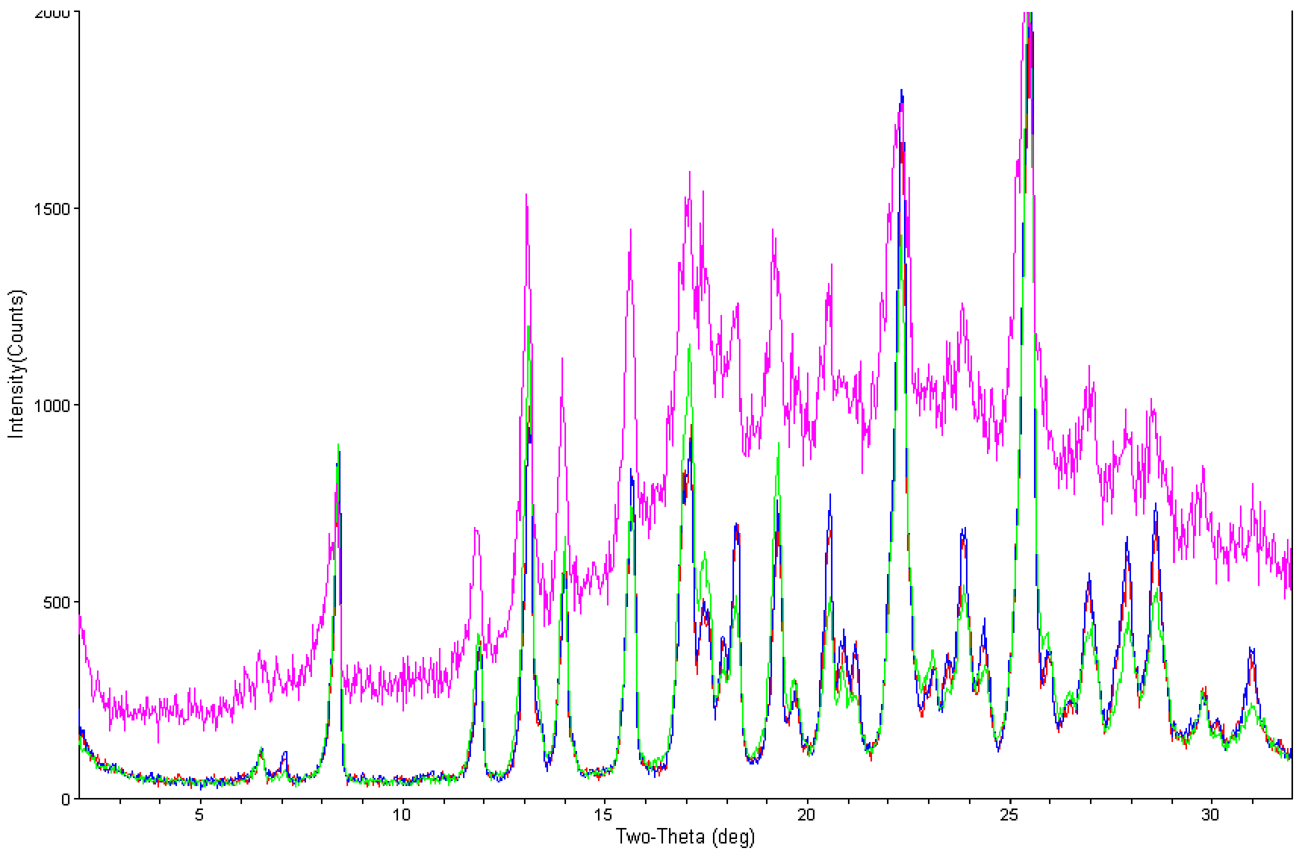


Raman specific to amorphous

In-situ probe possible

Case Study 1: DS Crystallization

- In-situ Raman probe ensures reproducible, robust crystallization with real-time form control
- XRPD used as off-line final quality check



Case Study 2: Preventing Form Change

- Early batches of API were a mixture of anhydrous form and hydrate form
- Preclinical PK data suggests form impacts to %bioavailability
- How to control form through drug substance unit operations?

Formulation	%BA (NCPK)
Anhydrous microsuspension (D90 ~12um)	44.6
Hydrate nanosuspension (D90 < 0.3um)	29.3
Anhydrous tablet w cellulose (D90~12um)	55.4

Solvent Mediated Crystallization
PXRD: Hydrate? Neat?

↓

Isolation and Drying
PXRD: Hydrate? Neat?

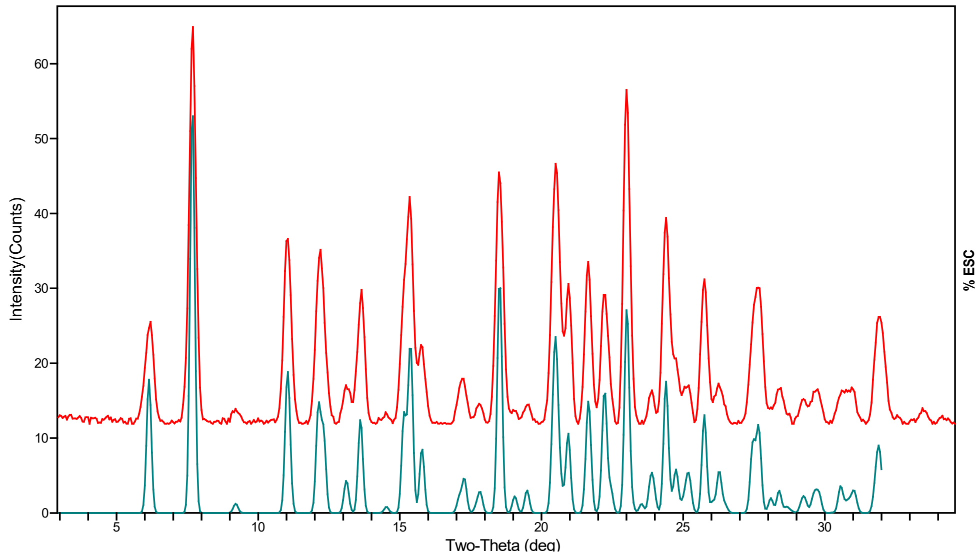
↓

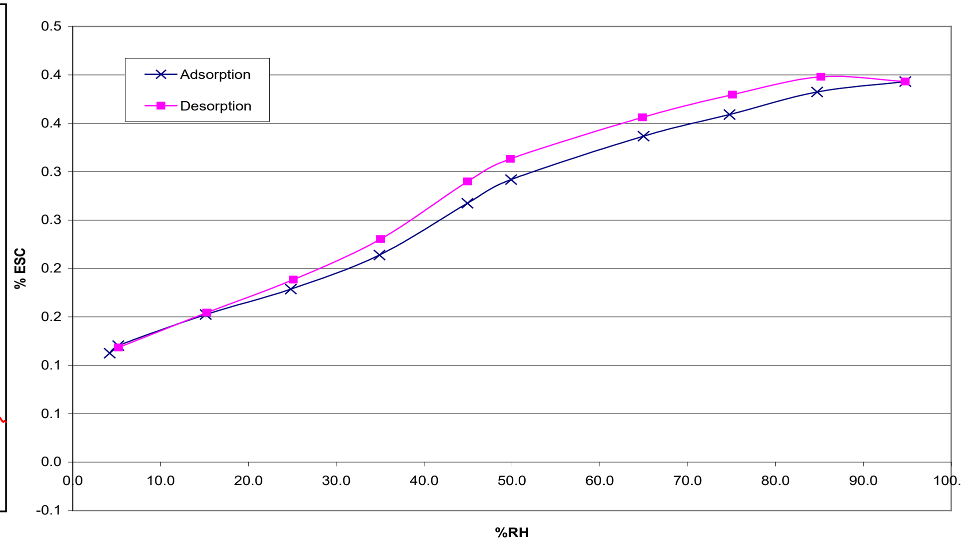
Milling
PXRD: Hydrate? Neat?

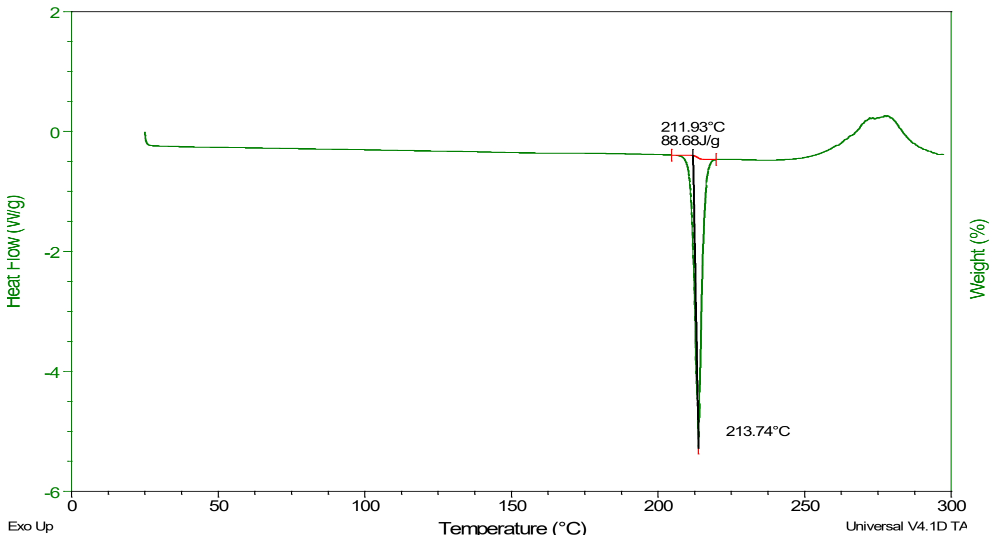
↓

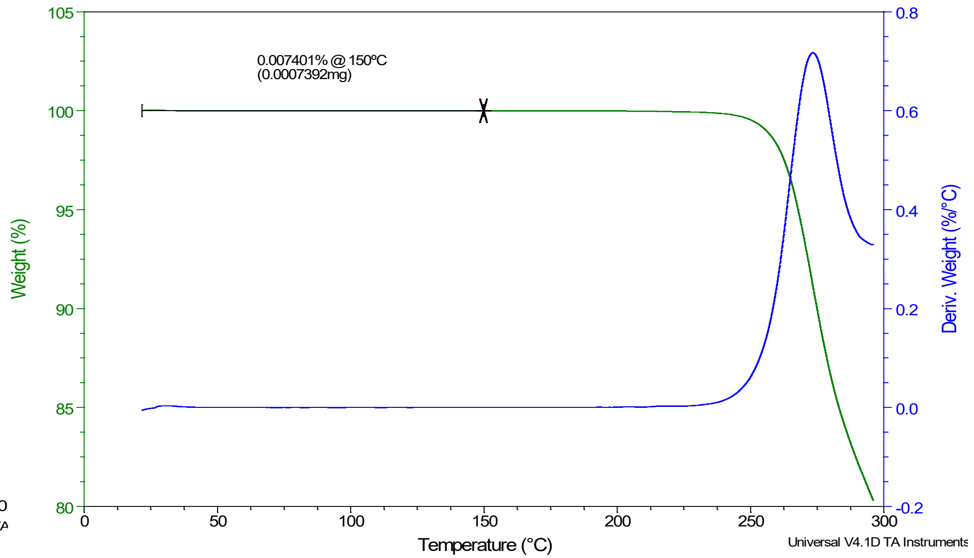
Packaging and Storage
PXRD: Hydrate? Neat?

Case Study 2: Preventing Form Change

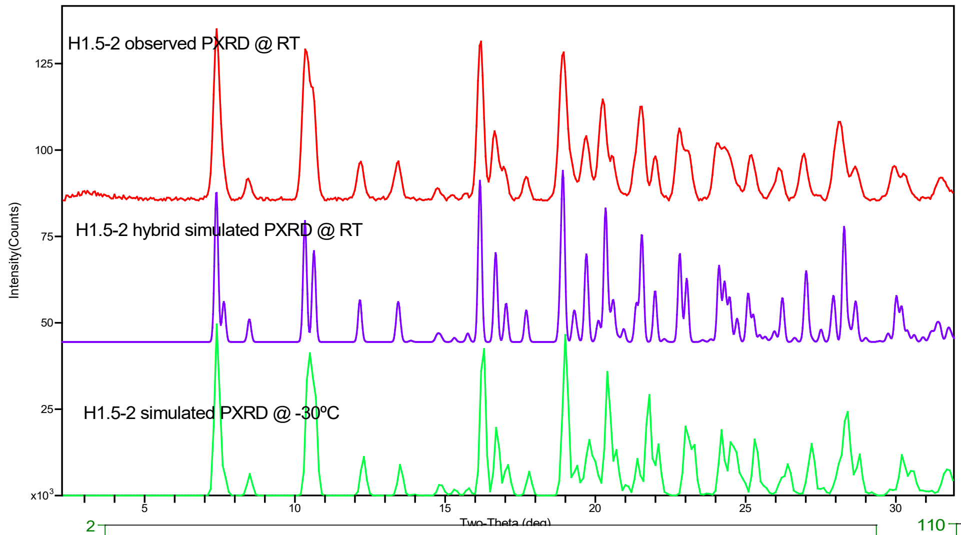


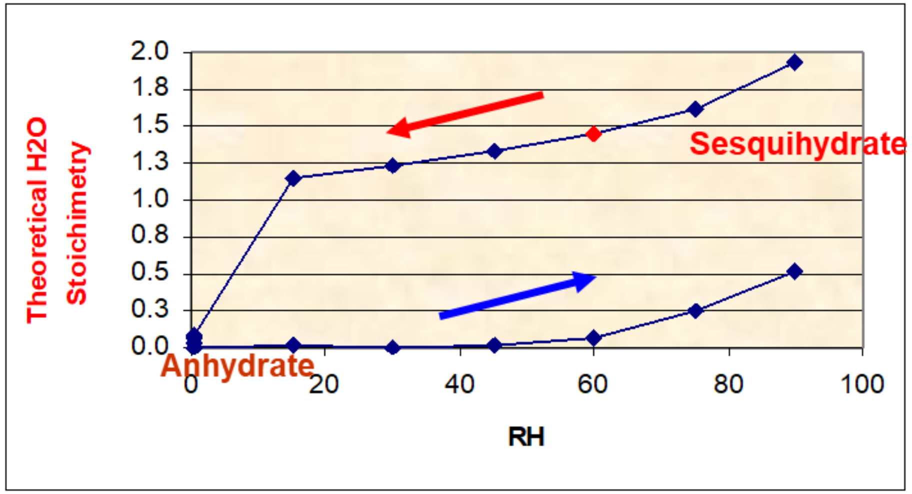


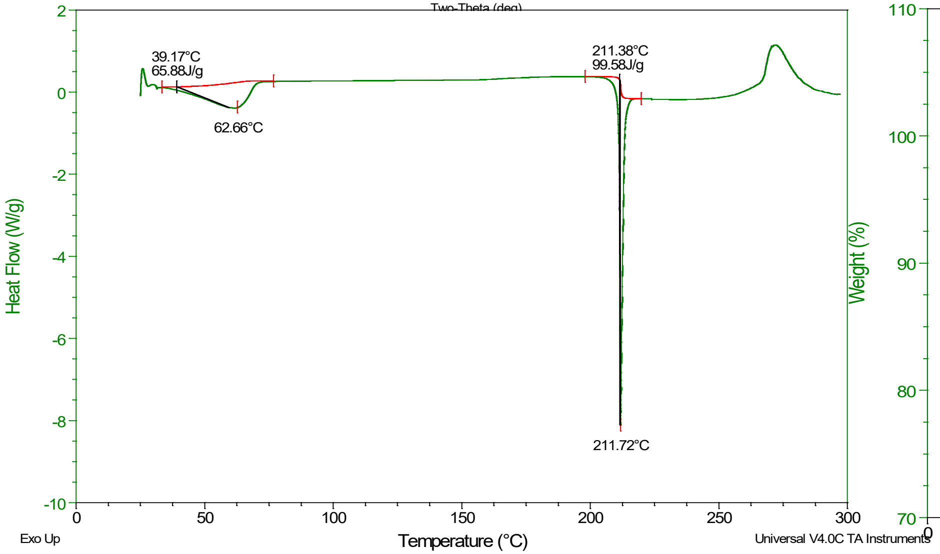


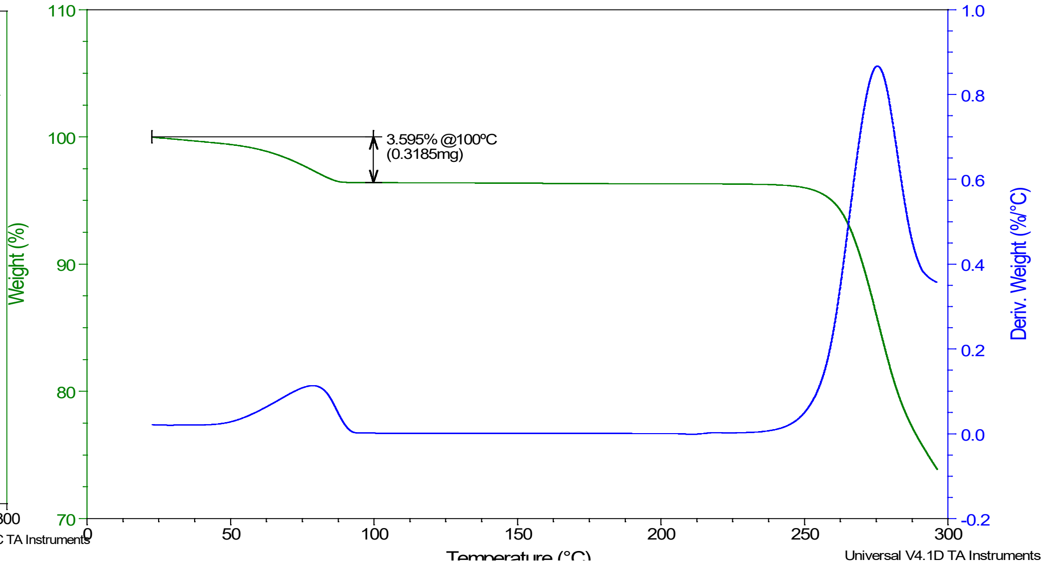


Case Study 2: Preventing Form Change



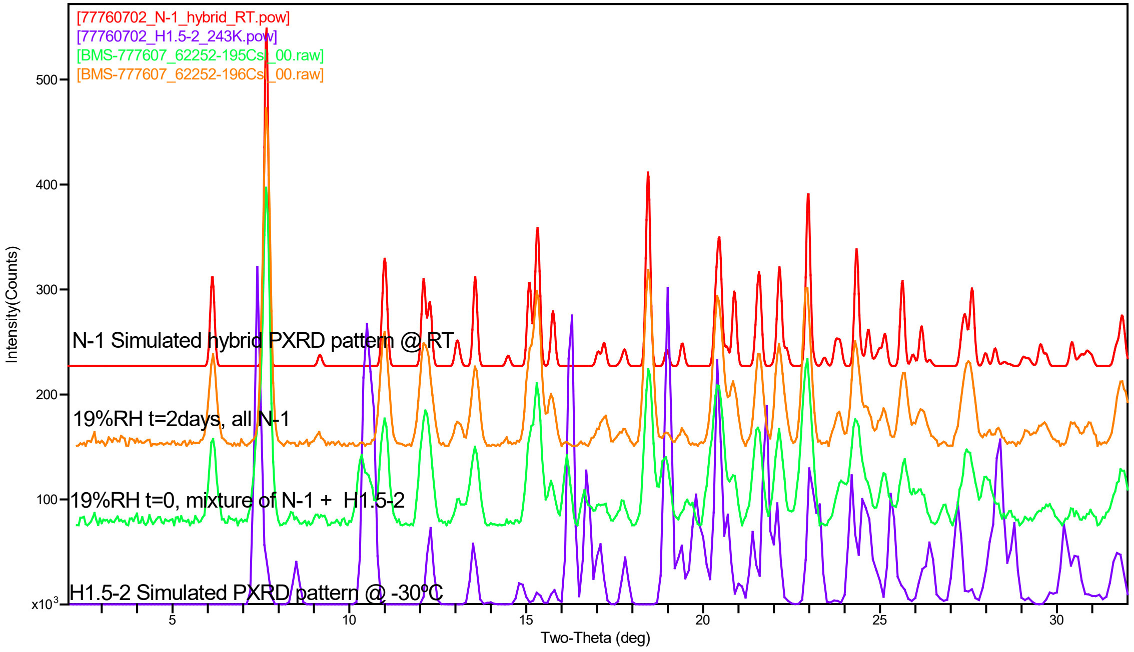






Case Study 2: Preventing Form Change

- Slurry XRPD used to determine critical water activity: $0.19 <_{awcrit}> 0.29$, RT
- DS process controlled through water activity/ desiccant



Solvent Mediated Crystallization
aw<0.19: PXRD = neat form

↓

Isolation and Drying
RH<19%: PXRD = neat form

↓

Milling
RH<19%: PXRD = neat form

↓

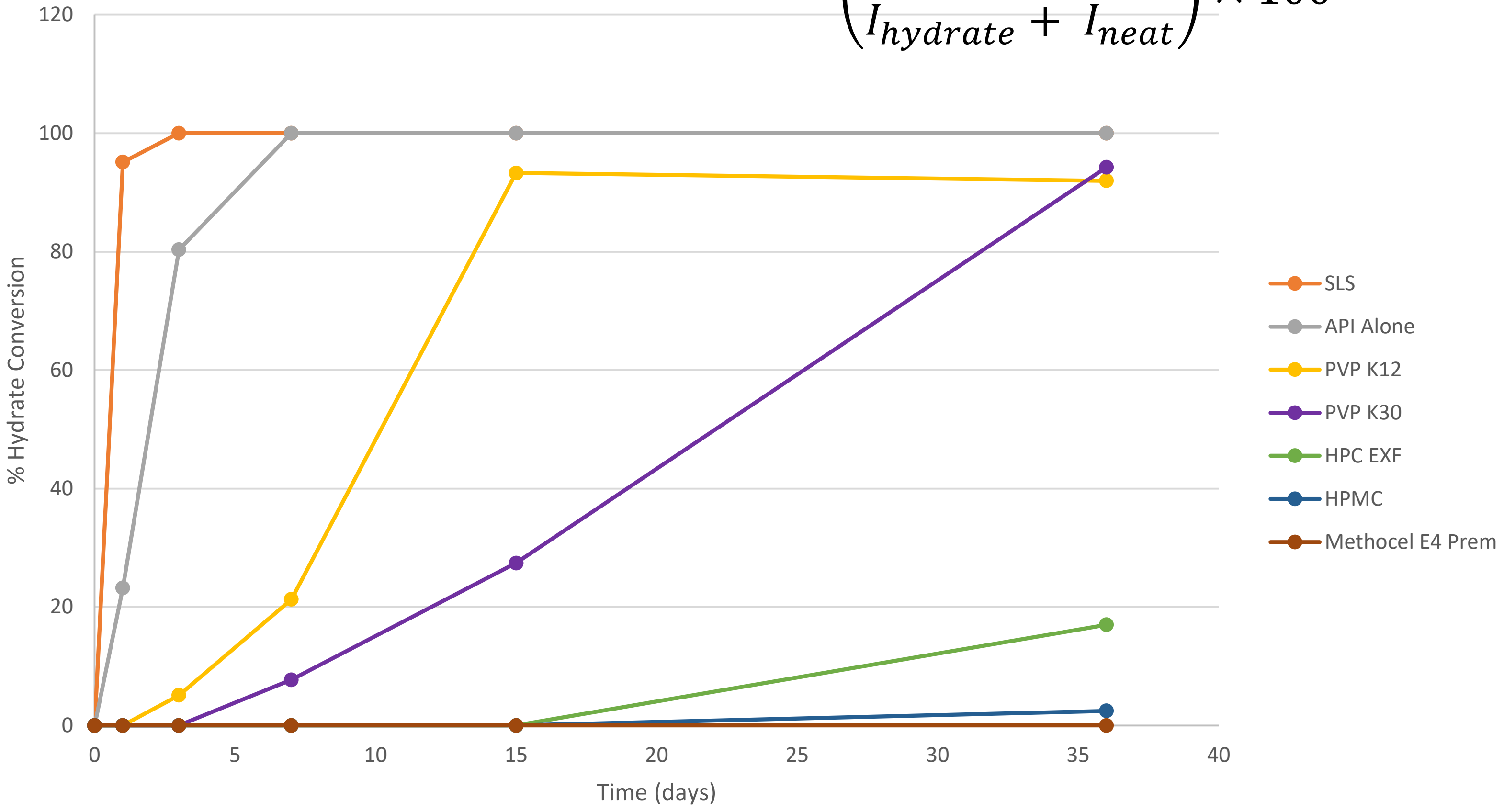
Packaging and Storage
RH<19% (desiccants): PXRD = neat form

Case Study 2: Preventing Form Change

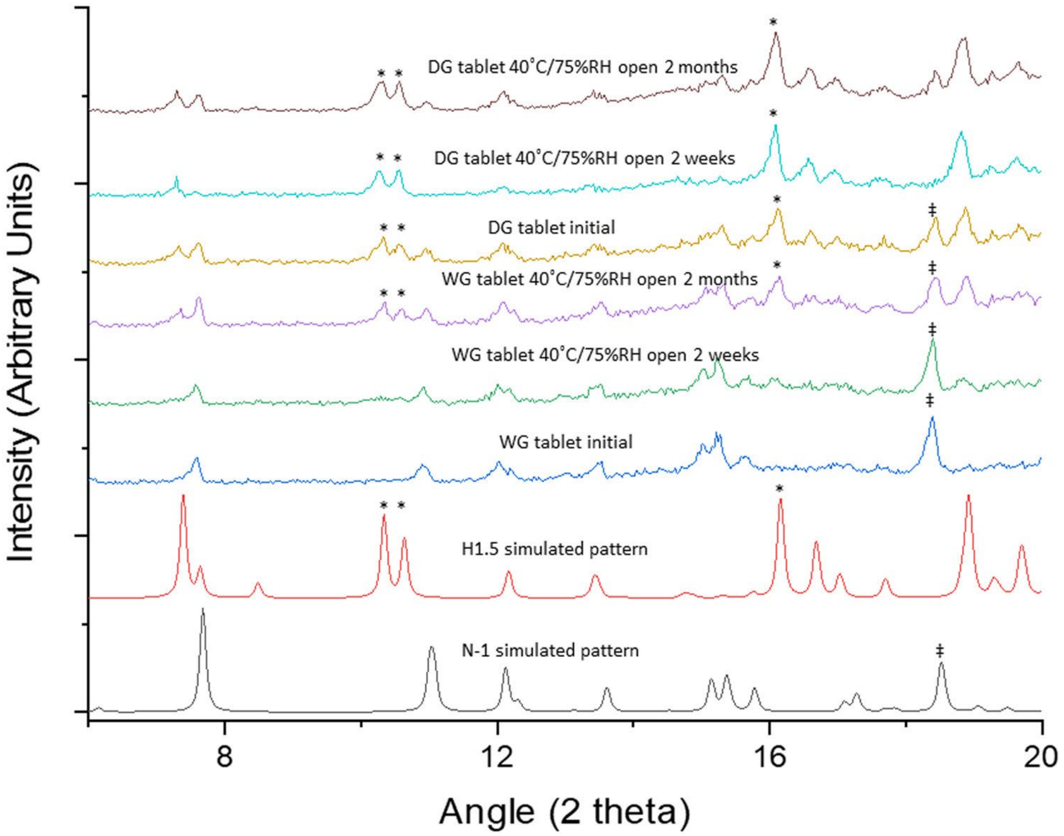
- How to prevent form change in the drug product?

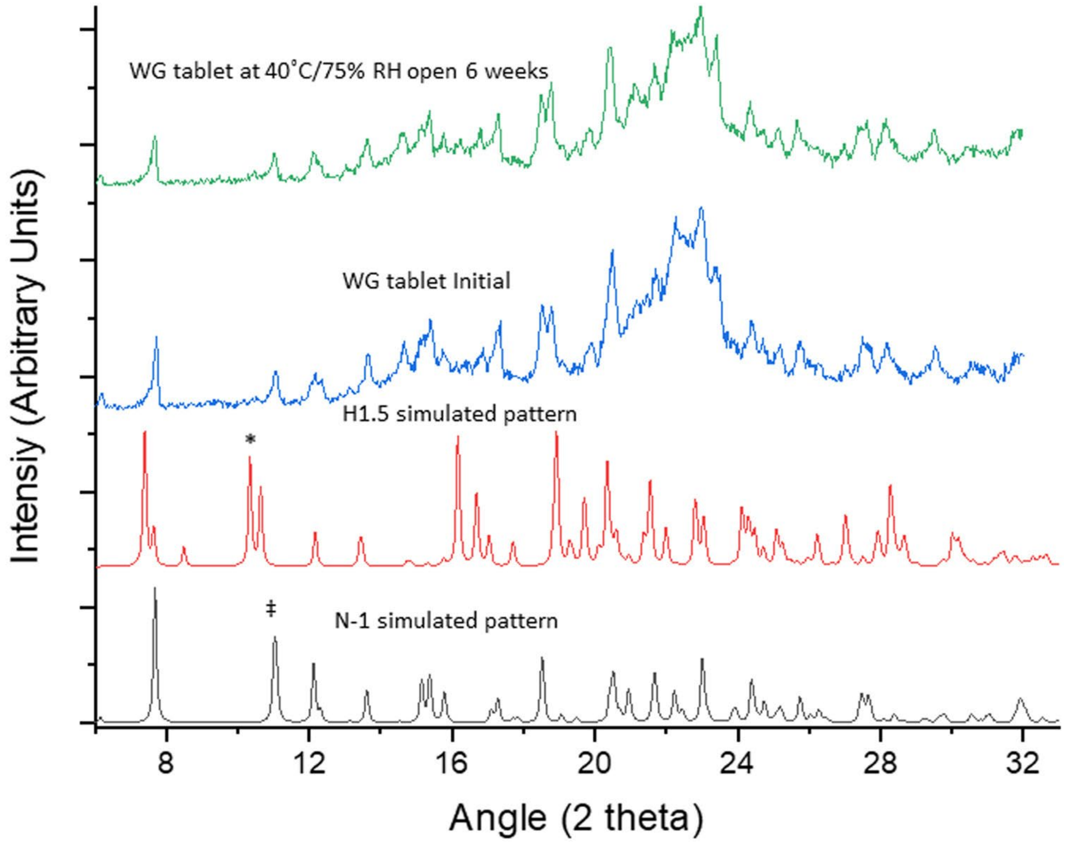
- DP aqueous suspensions (awcrit=1) would rapidly convert to the hydrate form
- XRPD used to determine that cellulosic polymers could be used to retard hydrate conversion

$$\left(\frac{I_{hydrate}}{I_{hydrate} + I_{neat}}\right) \times 100$$



Case Study 2: Preventing Form Change





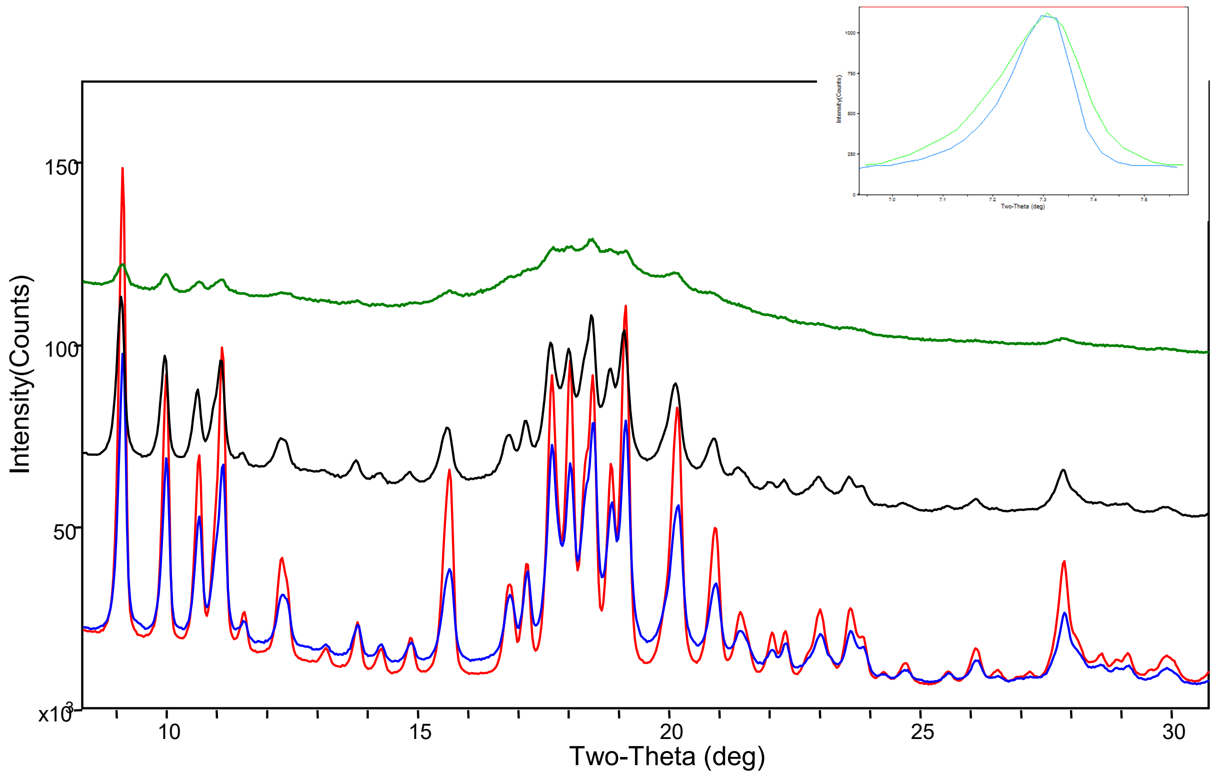
- In tablets: HPC introduced as a foam retarded hydrate conversion more than dry granulation or regular wet granulation

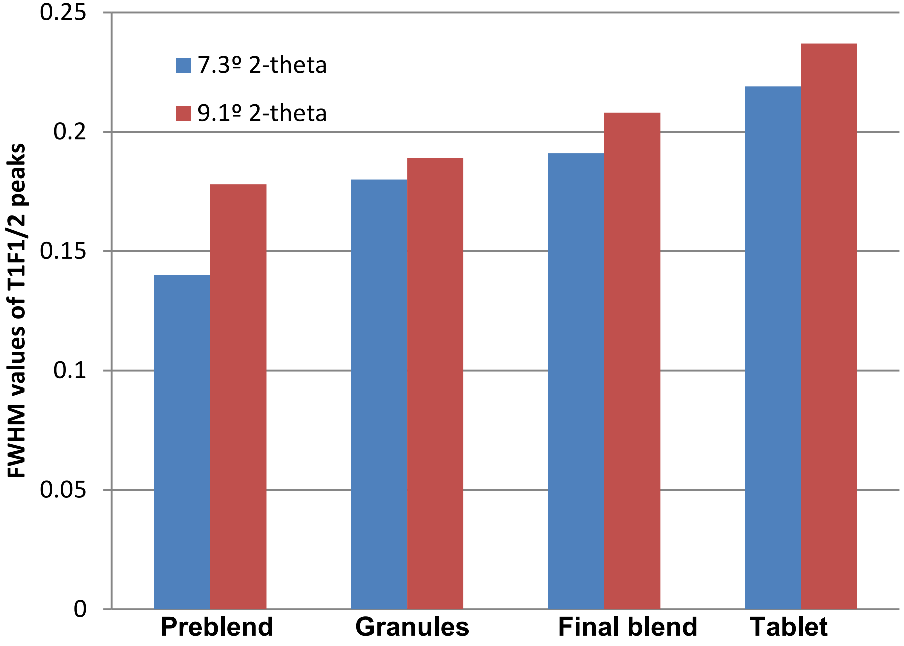
Human PK results	Formulation	AUC	Cmax
	Anhydrous tablet	22017	1895
	Hydrate nanosuspension	10763	984

Case Study 3: Crystallinity in DP

Goal: Quantify crystallinity in DP; Track crystallinity through unit ops

- API shows high propensity to lose crystallinity upon mechanical stress
- During DP manufacture: XRPD shows peak broadening

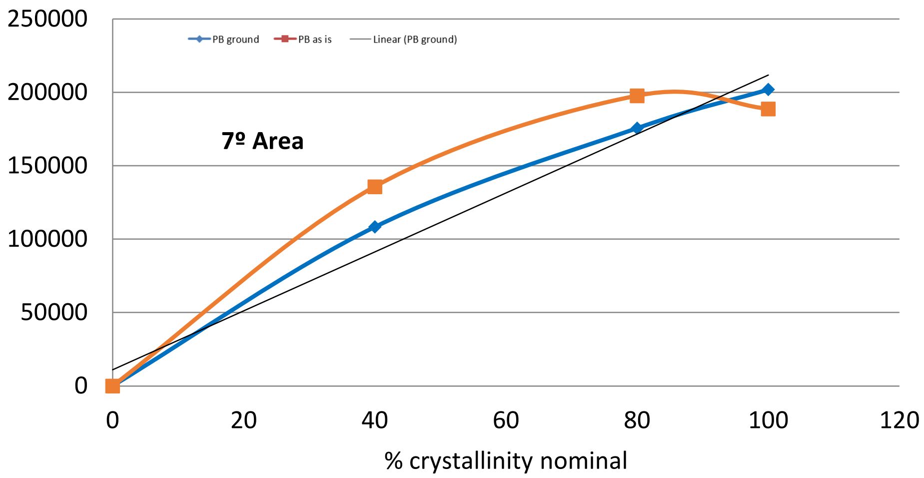


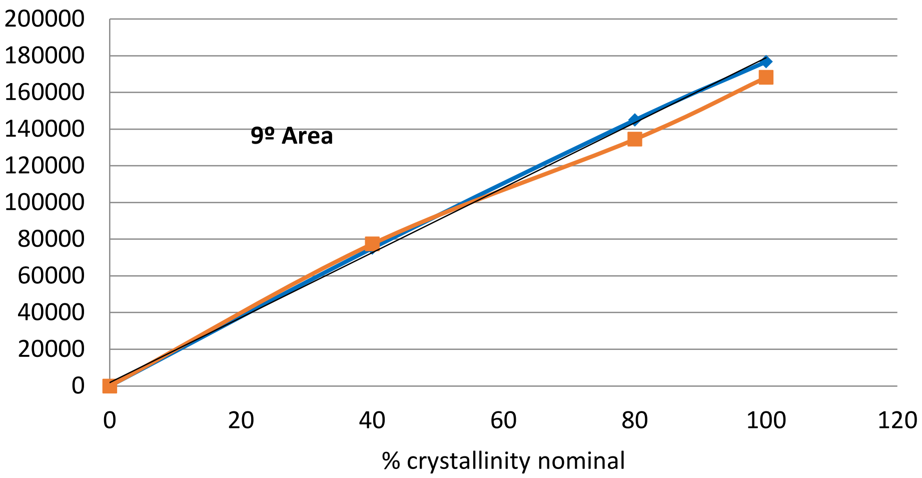


Case Study 3: Crystallinity in DP

XRPD cannot be used for quantification (sample prep):

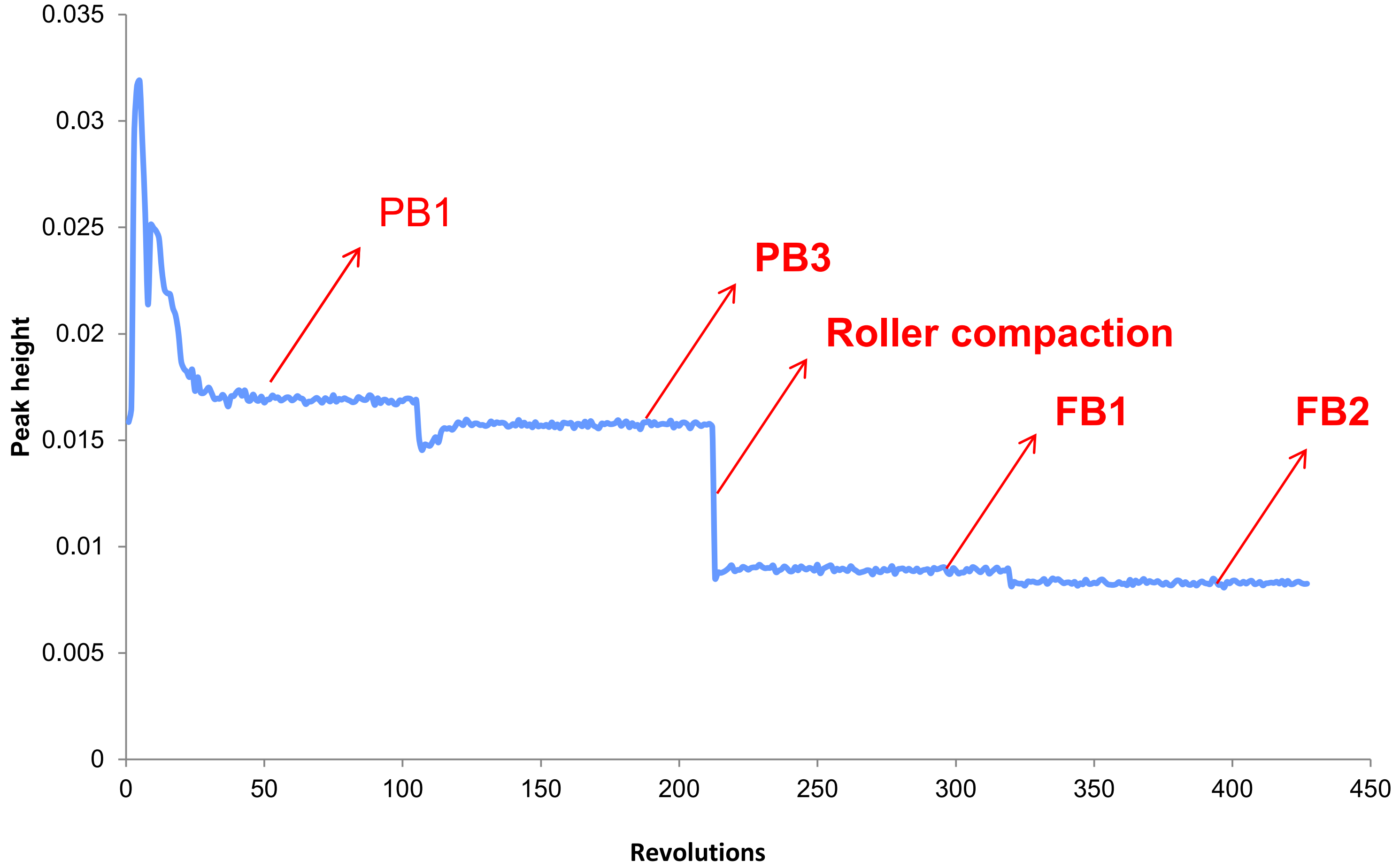
- Calibration curve: rank order changes from peak-to-peak
- Requires grinding to minimize preferred orientation
- Grinding can induce loss of crystallinity
- Limited choice of peaks (8 crystalline forms: 3 APIs and excipients)

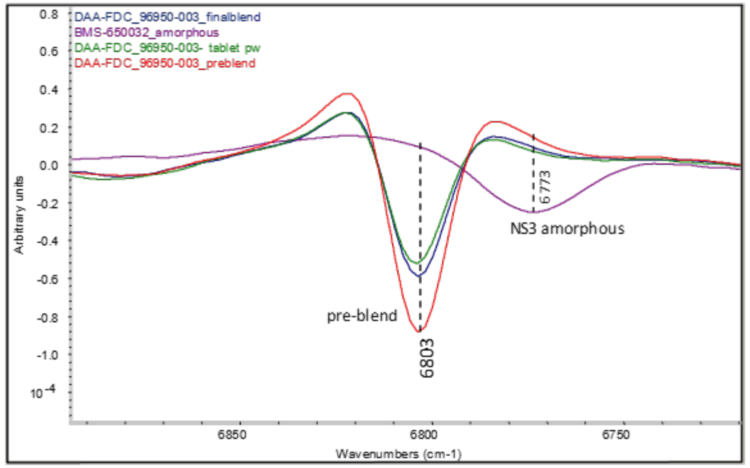




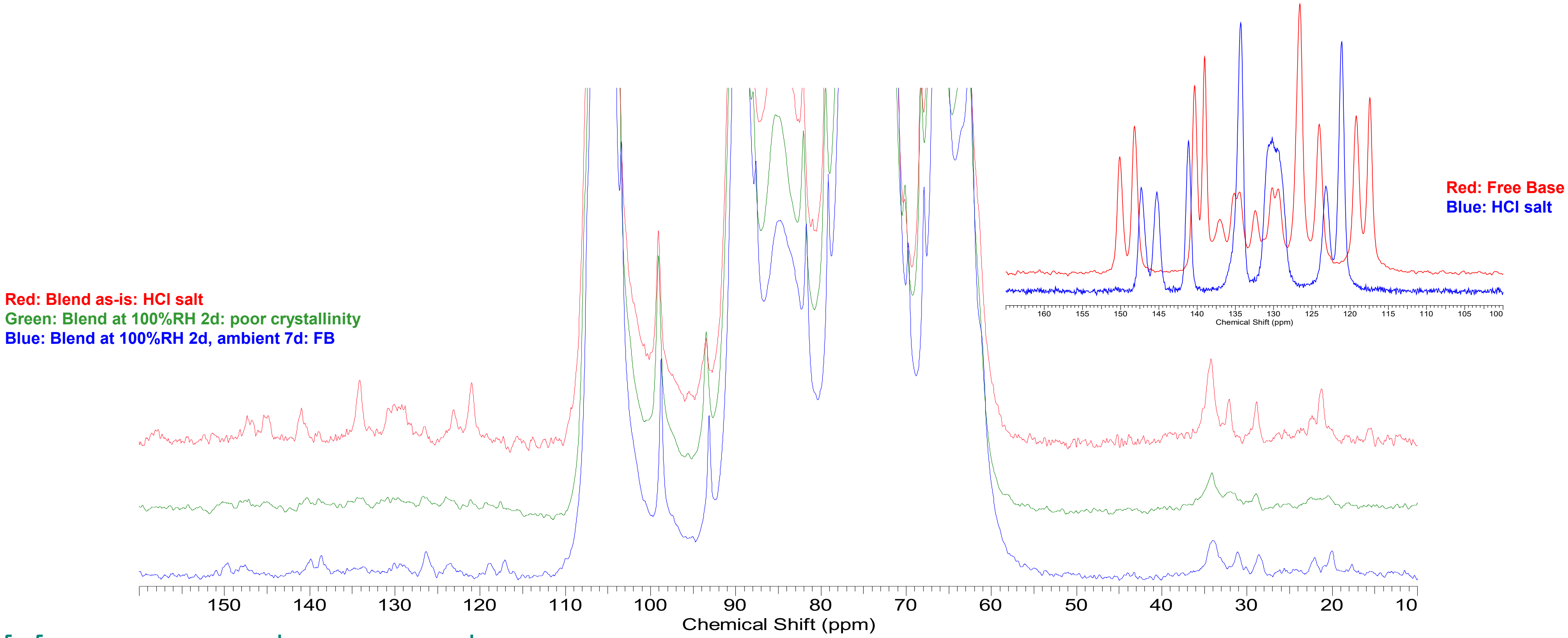
Case Study 3: Crystallinity in DP

- NIR: specific to amorphous and crystalline - Quantification feasibility shown
- NIR trends with XRPD for loss of crystallinity during processing
- Roller compaction unit operation shown as largest contributor





Case Study 4: Dissociation of Salt in DP



Goal: Identify factors impacting dissociation and mitigation strategies

- DP has 0.8% DL
- Below conventional XRPD LOD
- CP-MAS C-13 ssNMR identified dissociation of HCl salt to FB in DP
- Humidity shown to speed up conversion

Case Study 4: Dissociation of Salt in DP

HCl Salt | **HCl Salt + MgSt**

Ballmilled | **As-is** | **Compacted**

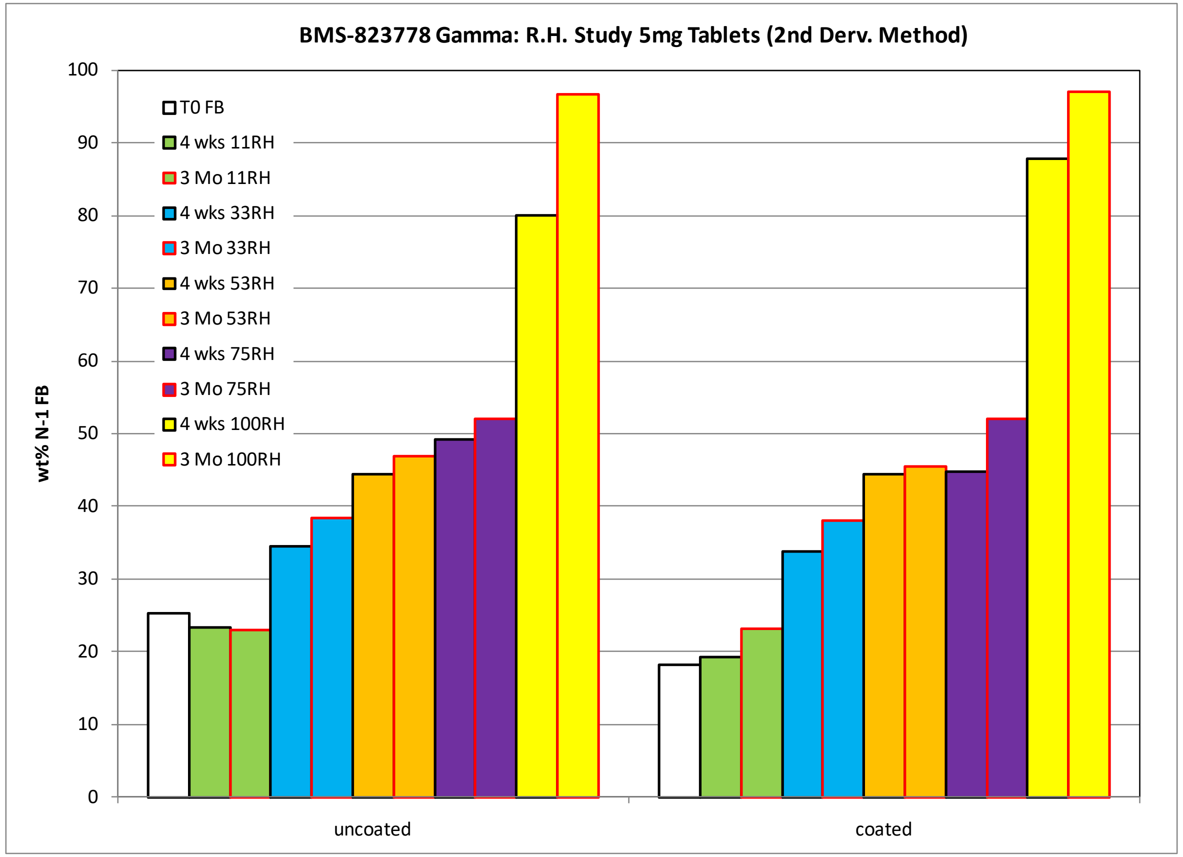
Stored at 11, 33, 53, 75, 100% RH, RT for t=x

Analyzed by XRPD

Ballmilled As-is t=2m	Ballmilled + MgSt t=1m	As-is t=2m	As-is + MgSt	Compacted As-is t=1m	Compacted + MgSt t=2/3m
11%-n	11%-n	11%-n	11%-tbd	11%-n	11%-n
33%-n	33%-y	33%-n	33%-tbd	33%-n	33%-n
53%-n	53%-y	53%-n	53%-tbd	53%-n	53%-y
75%-n	75%-y	75%-n	75%-tbd	75%-n	75%-y
100%-n	100%-y	100%-n	100%-tbd	100%-n	100%-y

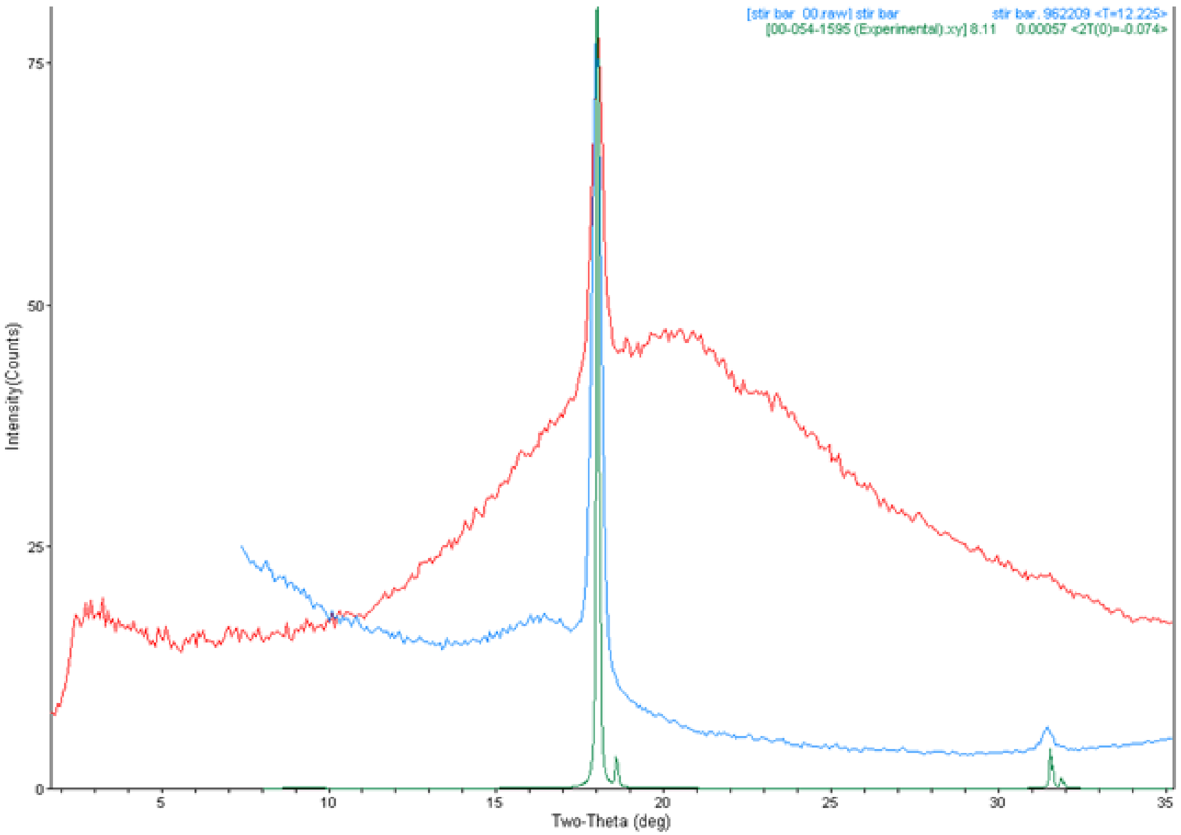
- XRPD can be used to screen the impact of excipients, mechanical processing and humidity at higher DL
- MgSt and humidity shown to increase dissociation

Case Study 4: Dissociation of Salt in DP



- XRPD humidity screening results validated in DP with NIR
- Offers potential mitigation strategy of desiccants

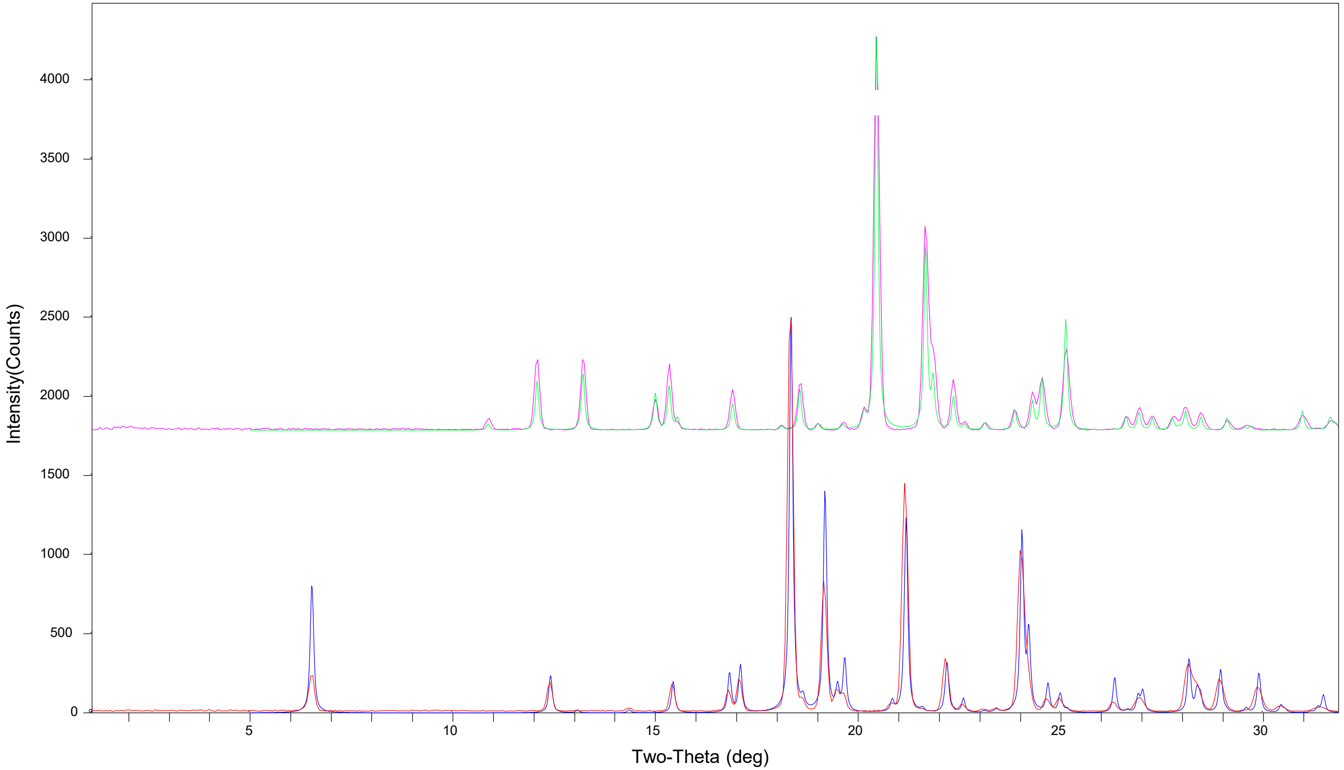
Case Study 6: Contaminant Investigation



Goal: Identify contaminant

- Extra peaks observed in API batches by centrifuged slurry PXRD
- Several programs impacted
- XRPD pattern consistent with Teflon from ICDD database and consistent with stir bars/ rods
- PTFE undetectable by routine analytical techniques
- Impacts phase purity determination
- Possible manufacturing/ safety concern

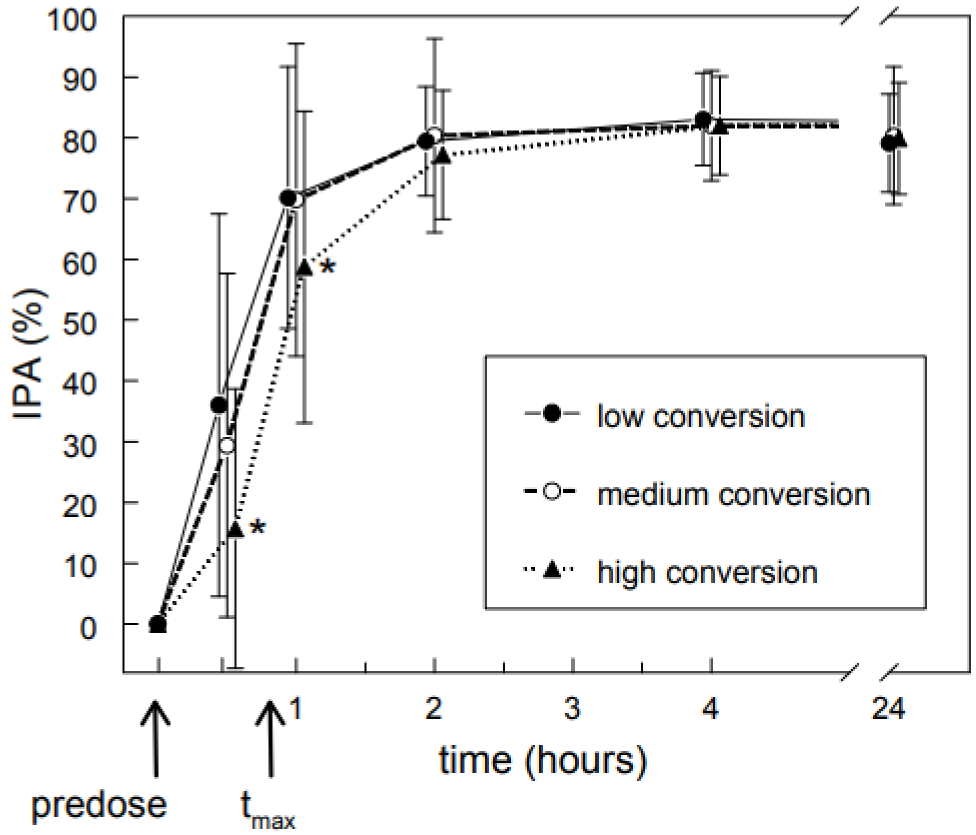
Case Study 7: Excipient Variability



- HEPES is a buffer used in biologics manufacture
- Filtration issues with one batch – poor solubility
- Overall HEPES concentration is lowered – yield impact
- Database searches of the ICDD and the CSD were conducted to find references PXRD patterns or single crystal structures of HEPES
- PXRD data was collected and compared to theoretical PXRD patterns obtained from published single crystal structures
- Batch of HEPES that had poor dissolution properties was shown to be a different polymorph

Case Study 8: XRPD Commercial Specification!!

- Eli Lilly's Prasugrel: weakly basic HCl salt (pKa 5.1)
- HCl salt chosen to help with PPI patient population
- Late-stage observation of phase conversion
- 70% (by XRPD) free base dosed in the Clinic, showed similar AUC, slightly different Cmax
- Commercial XRPD specification: limit test for up to 70% free base



Human PK results	Formulation	AUC	Cmax
	5% free base	470	331
	58% free base	467	297
	70% free base	409	236

Factors to Consider
Method Selection

Attribute	XRPD	Spectroscopy (IR, Raman, NIR)	ssNMR	Dissolution

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Speed	~2-30mins	<2mins	Hours	Hours

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Chemometrics	Not trivial due to sample preparation artifacts: sample height effects, preferred orientation, etc	Multivariate approaches are typically used	Not typically used	Not applicable

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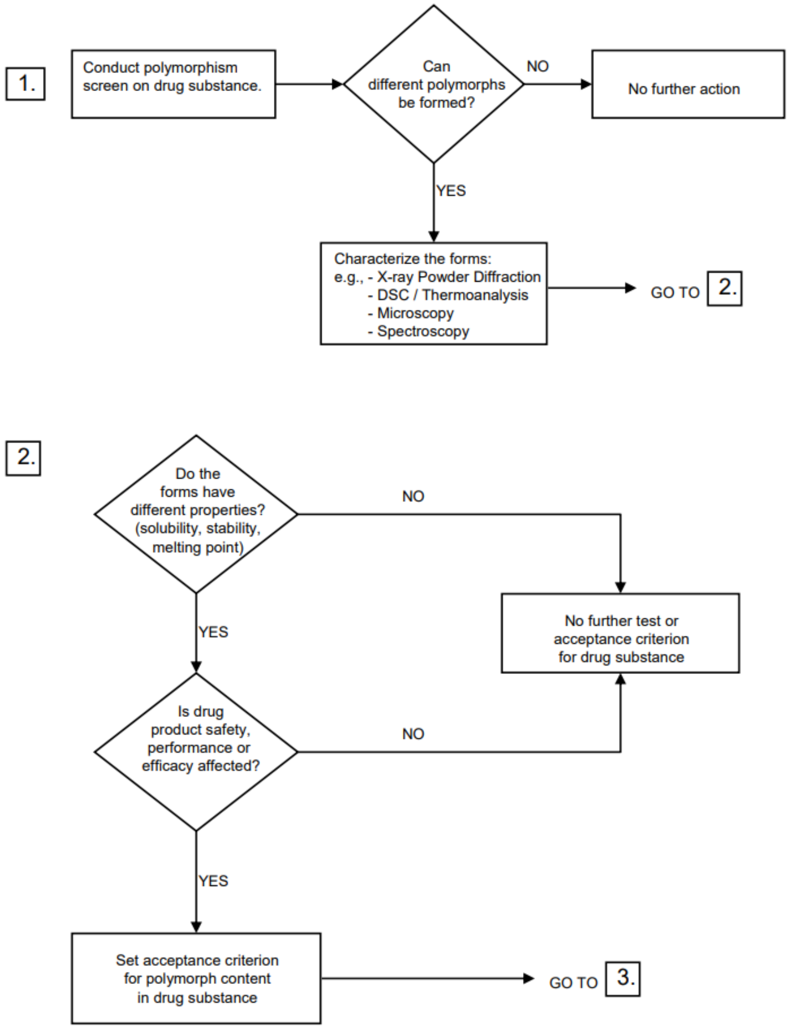
Chemometrics	Not trivial due to sample preparation artifacts: sample height effects, preferred orientation, etc	Multivariate approaches are typically used	Not typically used	Not applicable
QC-lab ready	Inherent robustness concerns	Routine	Too expensive, specialized	Routine

Factors to Consider
XRPD Method Validation

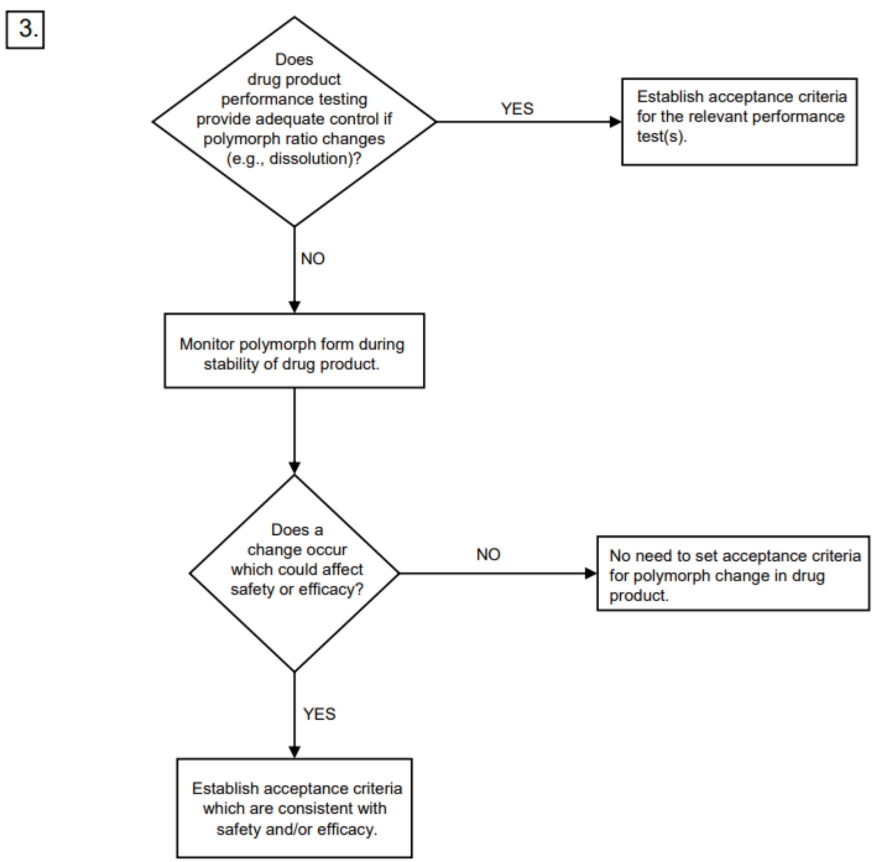
ICH Q6A Decision Tree 4

Drug Substance

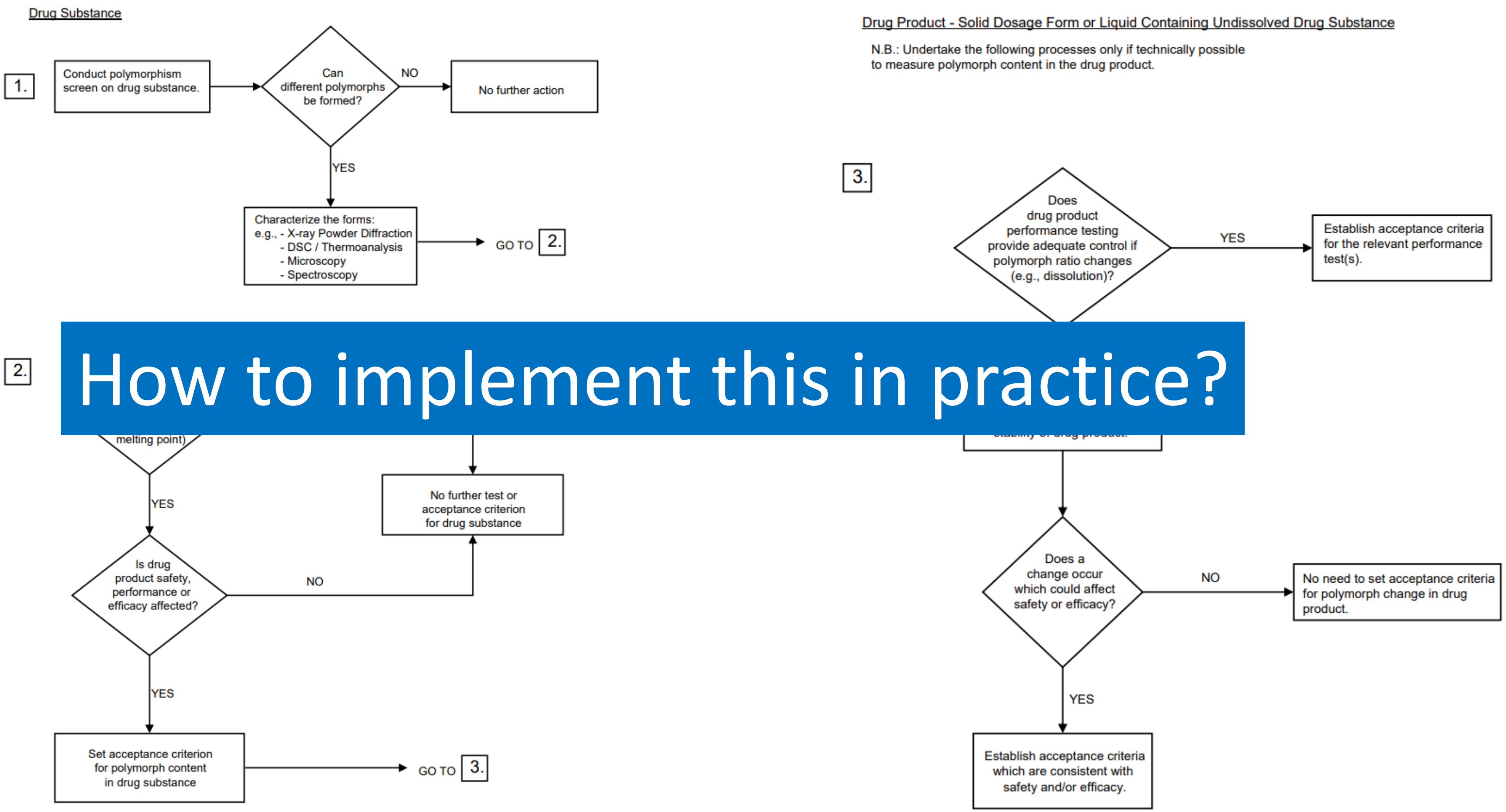


Drug Product - Solid Dosage Form or Liquid Containing Undissolved Drug Substance

N.B.: Undertake the following processes only if technically possible to measure polymorph content in the drug product.

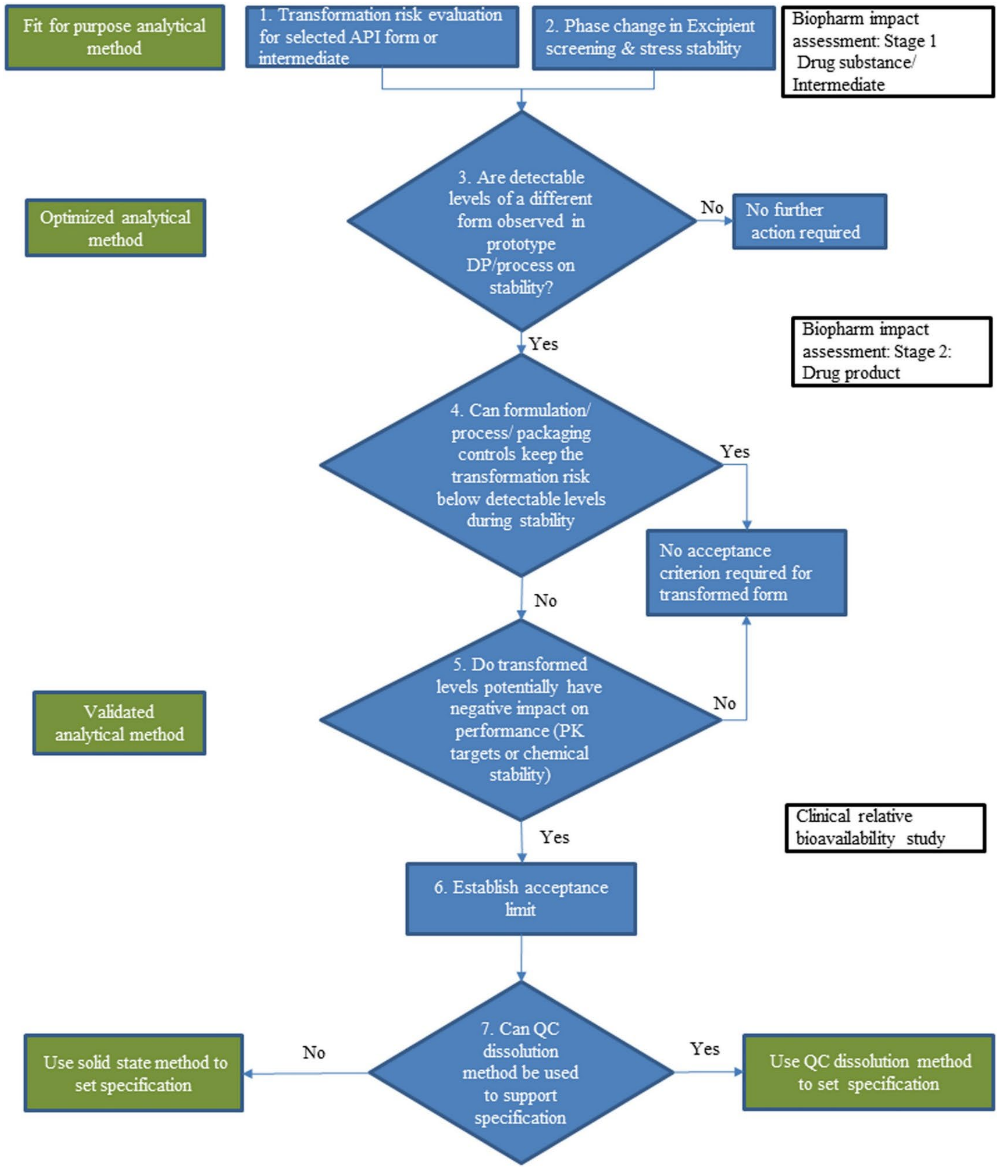


ICH Q6A Decision Tree 4



How to implement this in practice?

Strategies for Managing Solid Form Transformation Risk in Drug Product



https://doi.org/10.1016/j.xphs.2022.12.002.

Fit-for-Purpose Validation of XRPD Methods

From ICH Q2 for Chromatography ID, Assay, etc

Validation Parameter
System Suitability
Accuracy
Precision – repeatability
Robustness
Specificity
Linearity
Precision – intermediate precision
Precision – reproducibility
Detection limit
Quantitation limit
Range

Fit-for-Purpose Validation of XRPD Methods

instrument verifications and calibrations

Validation Parameter
System Suitability
Accuracy
Precision – repeatability
Robustness
Specificity
Linearity
Precision – intermediate precision
Precision – reproducibility
Detection limit
Quantitation limit
Range

Fit-for-Purpose Validation of XRPD Methods

Crystalline: consistent with simulated – no extra peaks, no significant shifts.

Amorphous: absence of crystalline peaks compared to placebo

Validation Parameter
System Suitability
Accuracy
Precision – repeatability
Robustness
Specificity
Linearity
Precision – intermediate precision
Precision – reproducibility
Detection limit
Quantitation limit
Range

Fit-for-Purpose Validation of XRPD Methods

Consistent over triplicate analysis

Validation Parameter
System Suitability
Accuracy
Precision – repeatability
Robustness
Specificity
Linearity
Precision – intermediate precision
Precision – reproducibility
Detection limit
Quantitation limit
Range

Fit-for-Purpose Validation of XRPD Methods

Pattern unaffected by grinding, spinner speed, packing height, etc

Validation Parameter
System Suitability
Accuracy
Precision – repeatability
Robustness
Specificity
Linearity
Precision – intermediate precision
Precision – reproducibility
Detection limit
Quantitation limit
Range

Fit-for-Purpose Validation of XRPD Methods

Crystalline: unique peaks can be identified (when compared to other forms or placebo)

Validation Parameter
System Suitability
Accuracy
Precision – repeatability
Robustness
Specificity
Linearity
Precision – intermediate precision
Precision – reproducibility
Detection limit
Quantitation limit
Range

Fit-for-Purpose Validation of XRPD Methods

Response is proportional to concentration

Validation Parameter
System Suitability
Accuracy
Precision – repeatability
Robustness
Specificity
Linearity
Precision – intermediate precision
Precision – reproducibility
Detection limit
Quantitation limit
Range

Fit-for-Purpose Validation of XRPD Methods

Consistent over different days, different analysts, etc

Validation Parameter
System Suitability
Accuracy
Precision – repeatability
Robustness
Specificity
Linearity
Precision – intermediate precision
Precision – reproducibility
Detection limit
Quantitation limit
Range

Fit-for-Purpose Validation of XRPD Methods

Consistent between laboratories

Validation Parameter
System Suitability
Accuracy
Precision – repeatability
Robustness
Specificity
Linearity
Precision – intermediate precision
Precision – reproducibility
Detection limit
Quantitation limit
Range

Fit-for-Purpose Validation of XRPD Methods

Lowest amount of analyte which can be detected but not necessarily quantified as an exact value

Validation Parameter
System Suitability
Accuracy
Precision – repeatability
Robustness
Specificity
Linearity
Precision – intermediate precision
Precision – reproducibility
Detection limit
Quantitation limit
Range

Fit-for-Purpose Validation of XRPD Methods

Lowest amount of analyte which can be quantitatively determined with suitable precision and accuracy

Validation Parameter
System Suitability
Accuracy
Precision – repeatability
Robustness
Specificity
Linearity
Precision – intermediate precision
Precision – reproducibility
Detection limit
Quantitation limit
Range

Fit-for-Purpose Validation of XRPD Methods

Upper and lower concentrations for which precision, accuracy and linearity have been demonstrated

Validation Parameter
System Suitability
Accuracy
Precision – repeatability
Robustness
Specificity
Linearity
Precision – intermediate precision
Precision – reproducibility
Detection limit
Quantitation limit
Range

Fit-for-Purpose Validation of XRPD Methods

Do I have form x or y?

Validation Parameter	Form Identity	
	IND	NDA
System Suitability	+	+
Accuracy	+	+
Precision – repeatability	+	+
Robustness		+
Specificity	+	+
Linearity		
Precision – intermediate precision		+
Precision – reproducibility		
Detection limit		
Quantitation limit		
Range		

Fit-for-Purpose Validation of XRPD Methods

I cannot have more than 15% of form x in my drug product or else the PK will be impacted

Validation Parameter	Form Identity		Limit Test	
	IND	NDA	IND	NDA
System Suitability	+	+	+	+
Accuracy	+	+	+	+
Precision – repeatability	+	+	+	+
Robustness		+		+
Specificity	+	+	+	+
Linearity				
Precision – intermediate precision		+		+
Precision – reproducibility				
Detection limit			+	+
Quantitation limit				
Range				

Fit-for-Purpose Validation of XRPD Methods

I need to quantify the exact amount of minority form x in a majority of form y

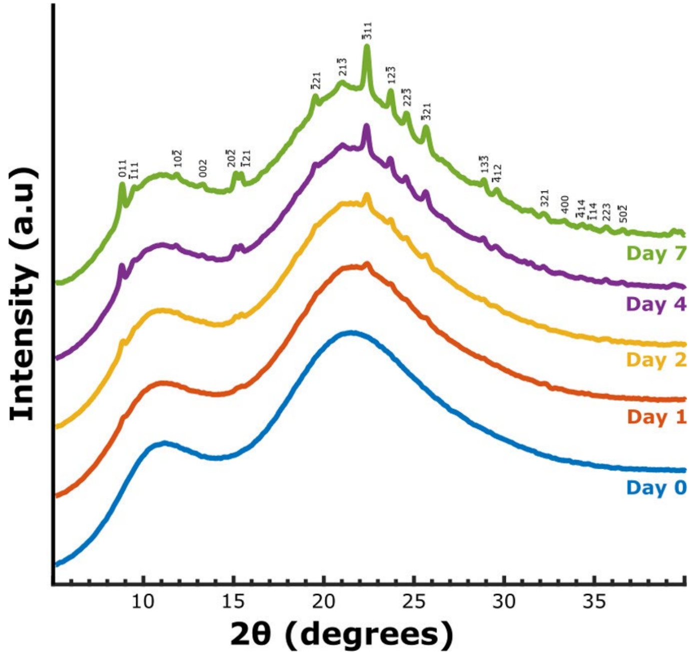
Opinion:
Difficult to think of a reason for a quantitative commercial test

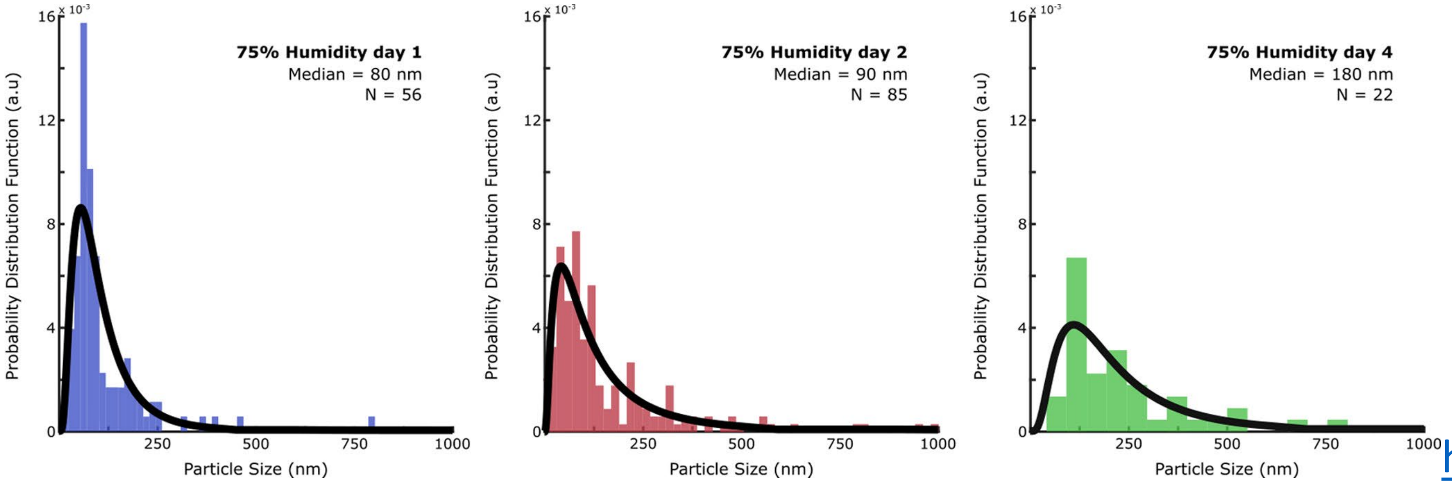
Validation Parameter	Form Identity		Limit Test		Quantitative Test	
	IND	NDA	IND	NDA	IND	NDA
System Suitability	+	+	+	+	+	+
Accuracy	+	+	+	+	+	+
Precision – repeatability	+	+	+	+	+	+
Robustness		+		+		+
Specificity	+	+	+	+	+	+
Linearity					+	+
Precision – intermediate precision		+		+		+
Precision – reproducibility						
Detection limit			+	+		
Quantitation limit					+	+
Range					+	+

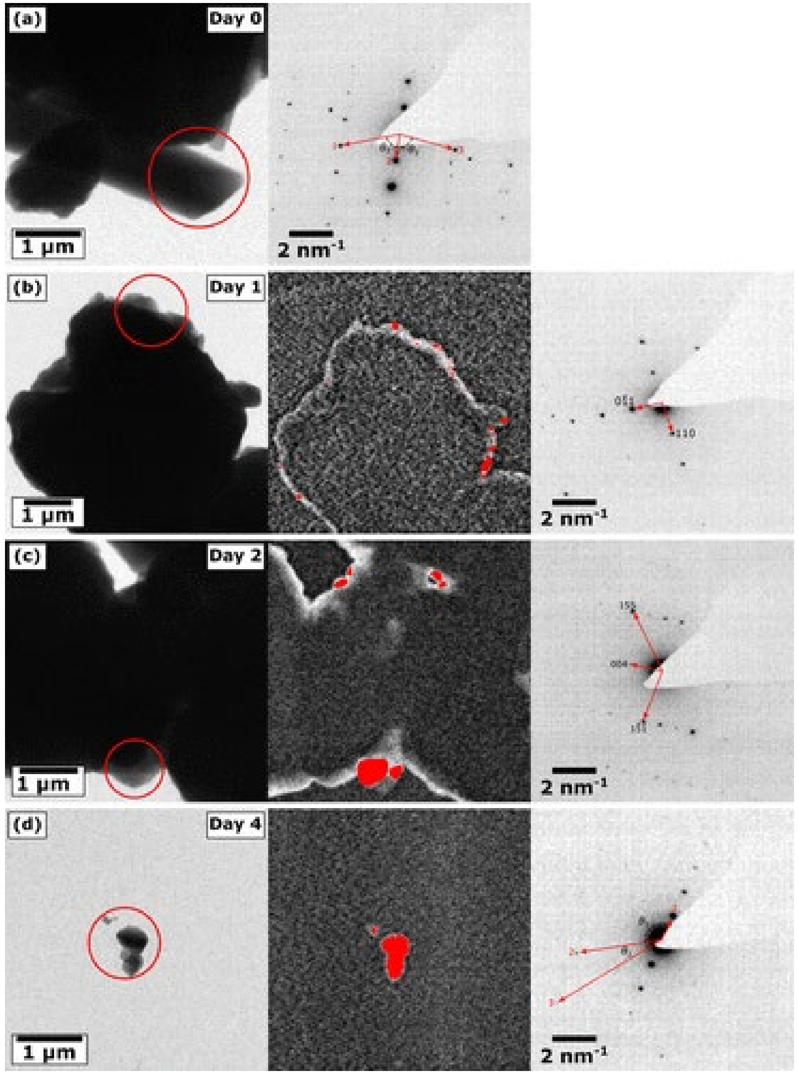
Commentary on “New” PXRD Adjacent Techniques

Micro-Electron Diffraction for Increasing LOD/ Forensics

- Crystallinity cannot be observed by XRPD or orthogonal techniques at day 0
- ED observes crystallinity at day 0
- ED can also track particle growth over time

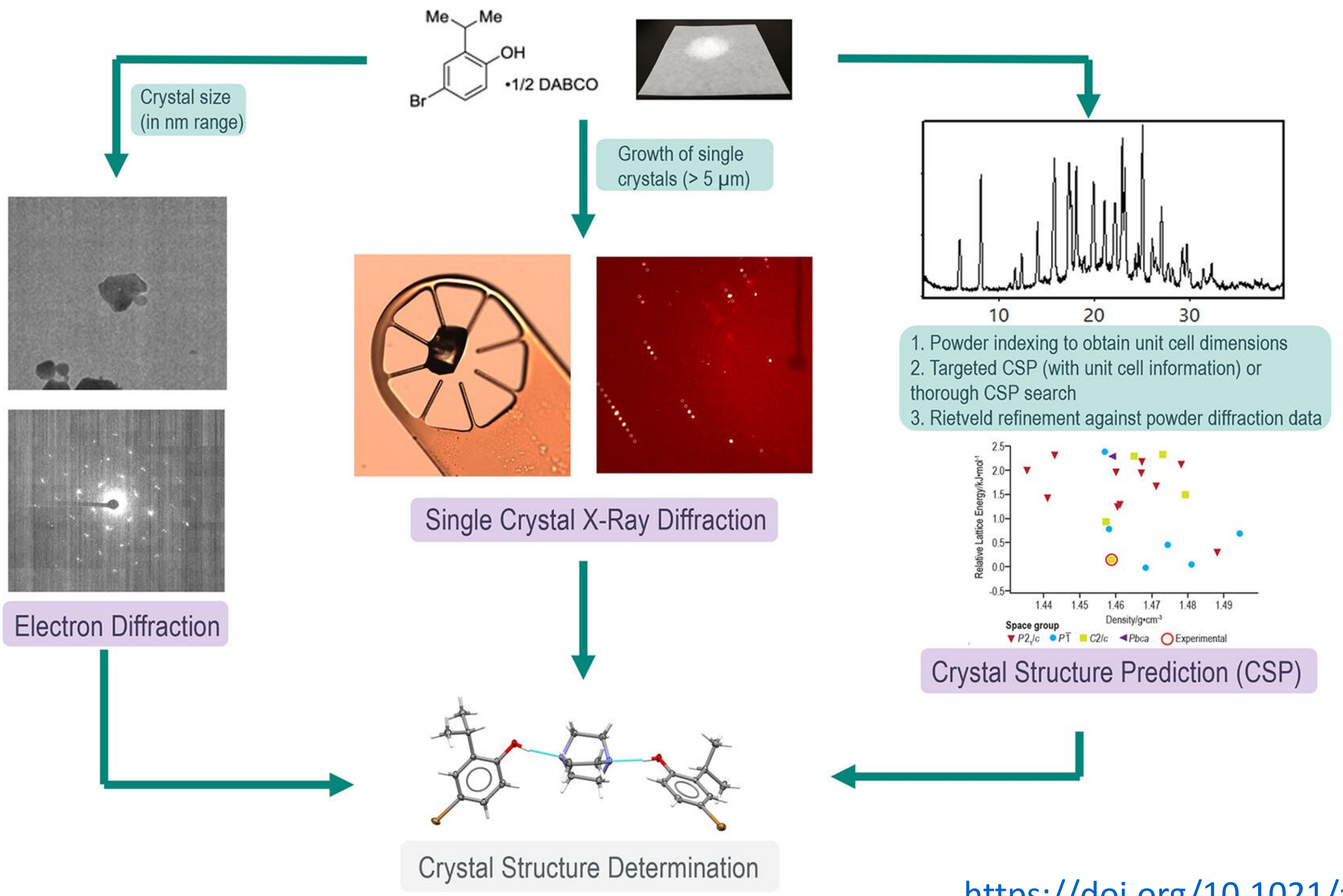






https://doi.org/10.1021/acs.molpharmaceut.0c00918

Crystal Structure Prediction and Micro-Electron Diffraction



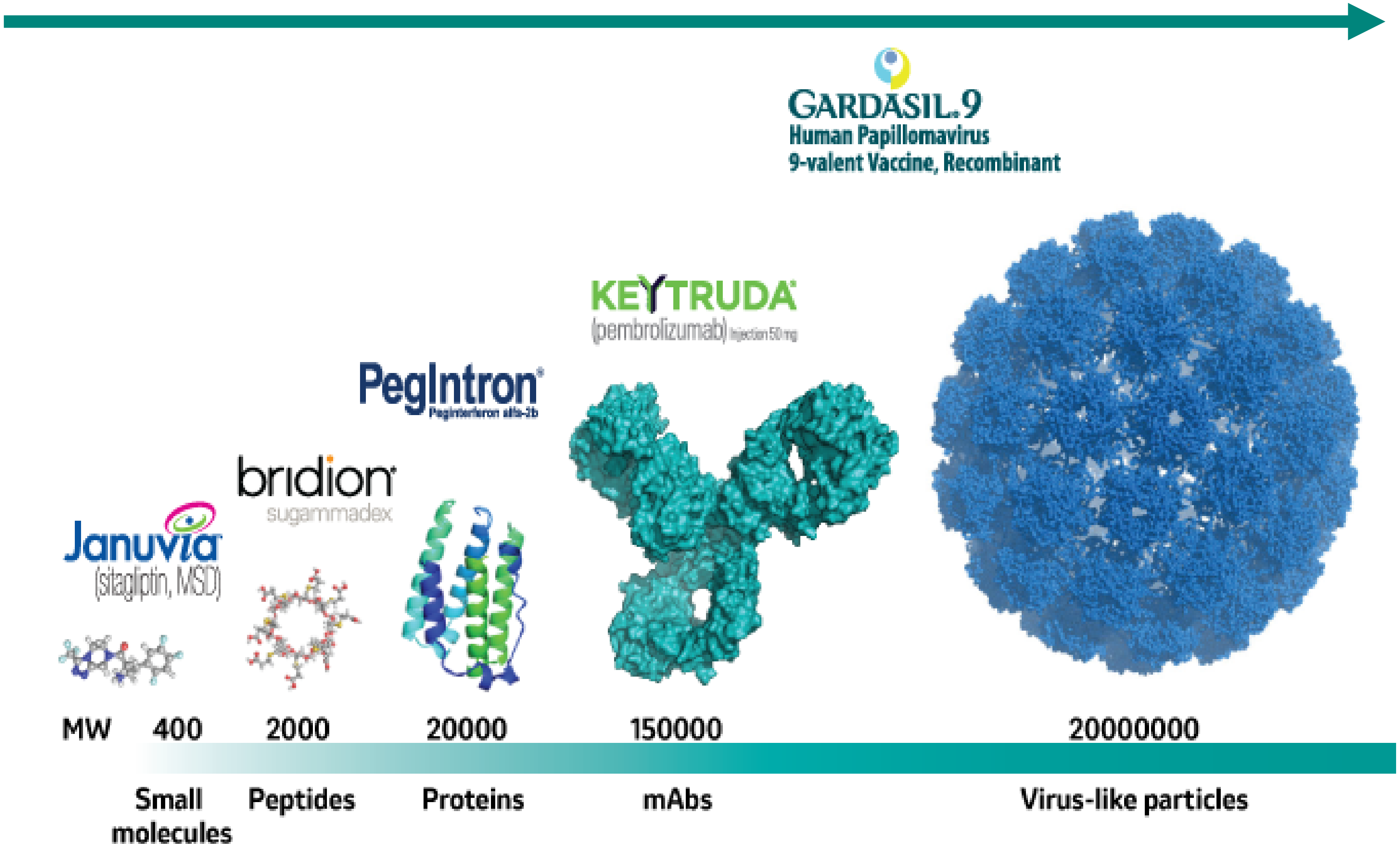
More questions?

Ask Melissa Tan
~ Presenting Tomorrow

https://doi.org/10.1021/acs.molpharmaceut.2c00020

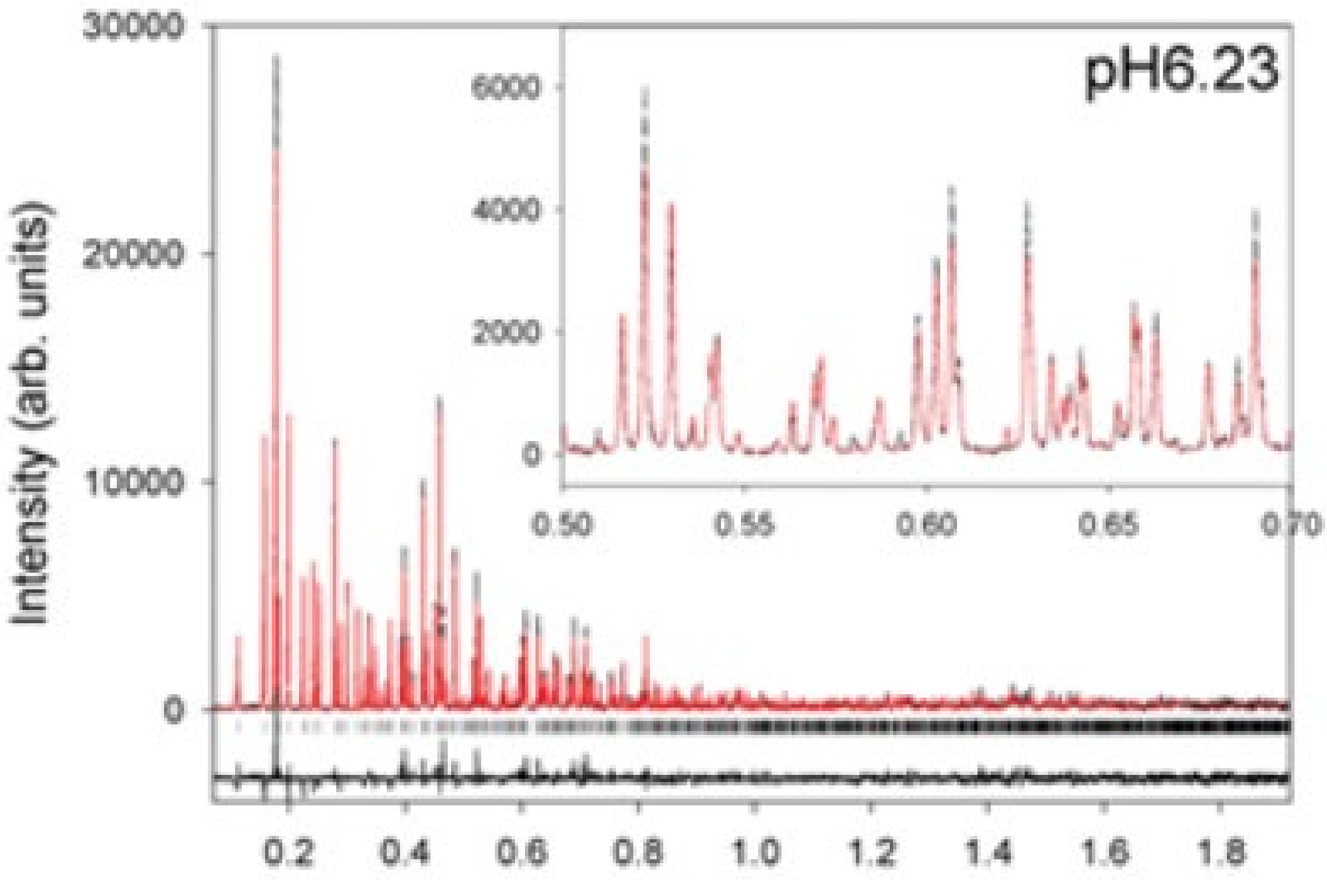
What do to for Large Molecules?

↑ d-spacings -> ↓ 2-theta postions



SAXSD for Crystalline Proteins

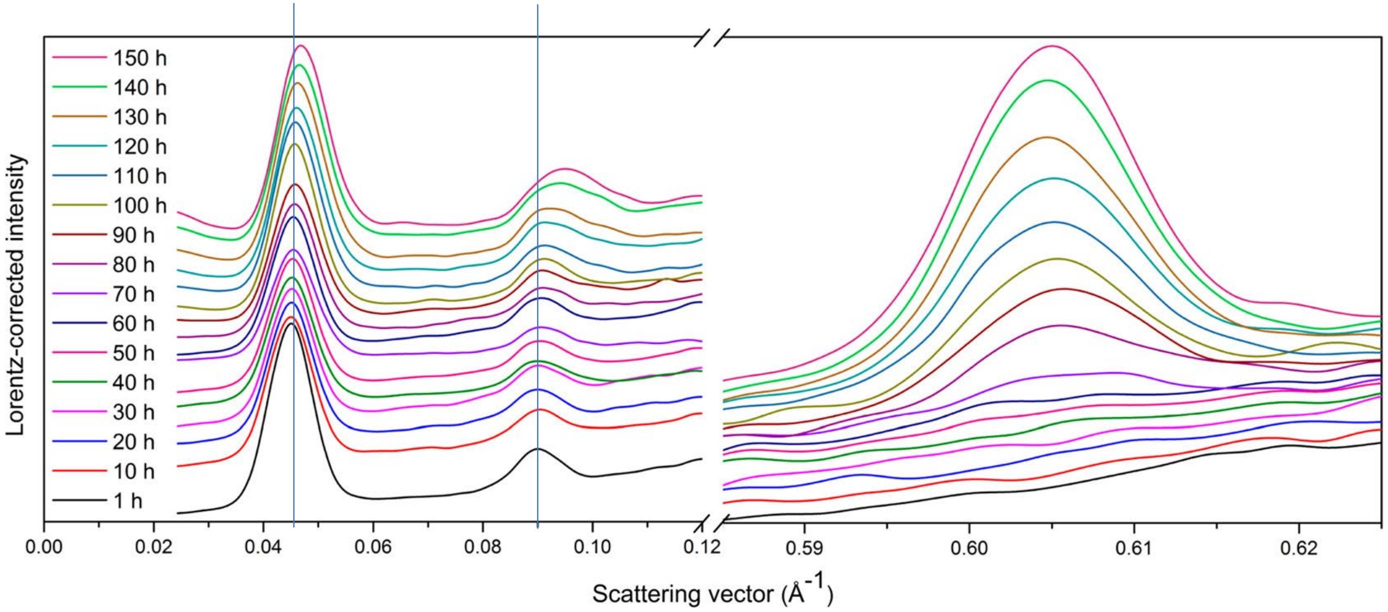
- Characterization below the typical CuKα 2θ 2º is needed due to the large d-spacings
- SAXSD can be used to look at lower angles
- Useful for crystalline proteins but even excipients – even magnesium stearate

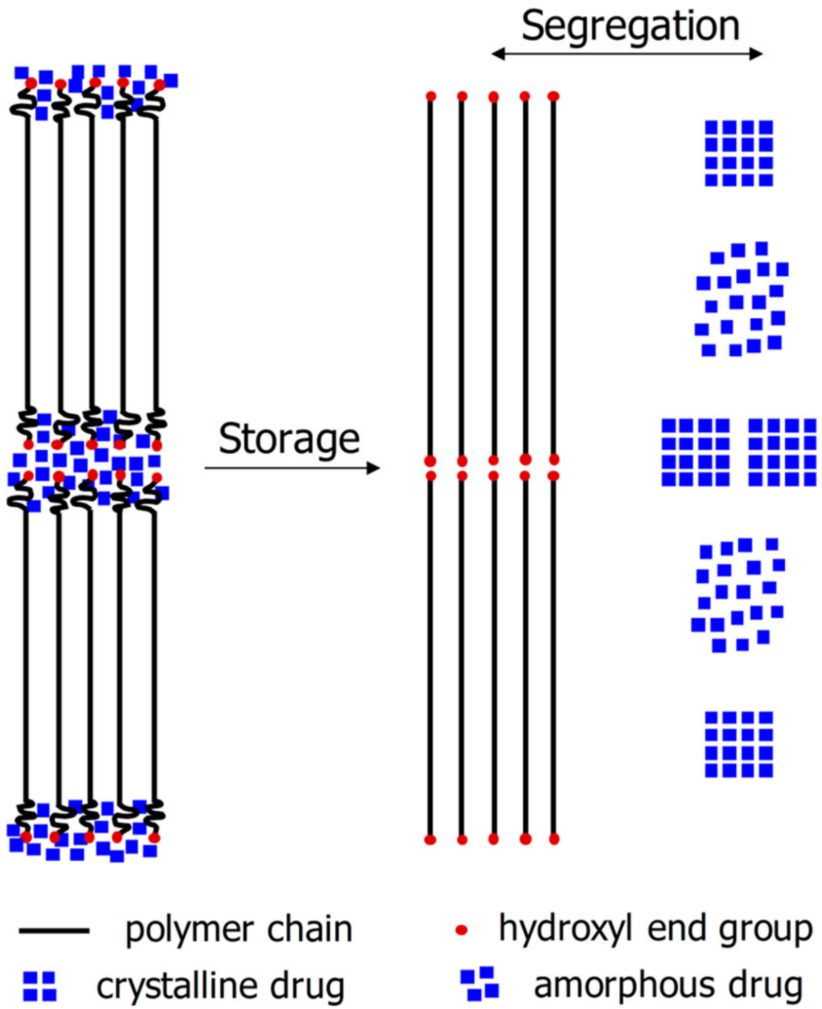


0.25 2.2 CuKalpha

https://journals.iucr.org/a/issues/2008/01/00/sc5011/sc5011.pdf

SAXSD for Microstructure Understanding



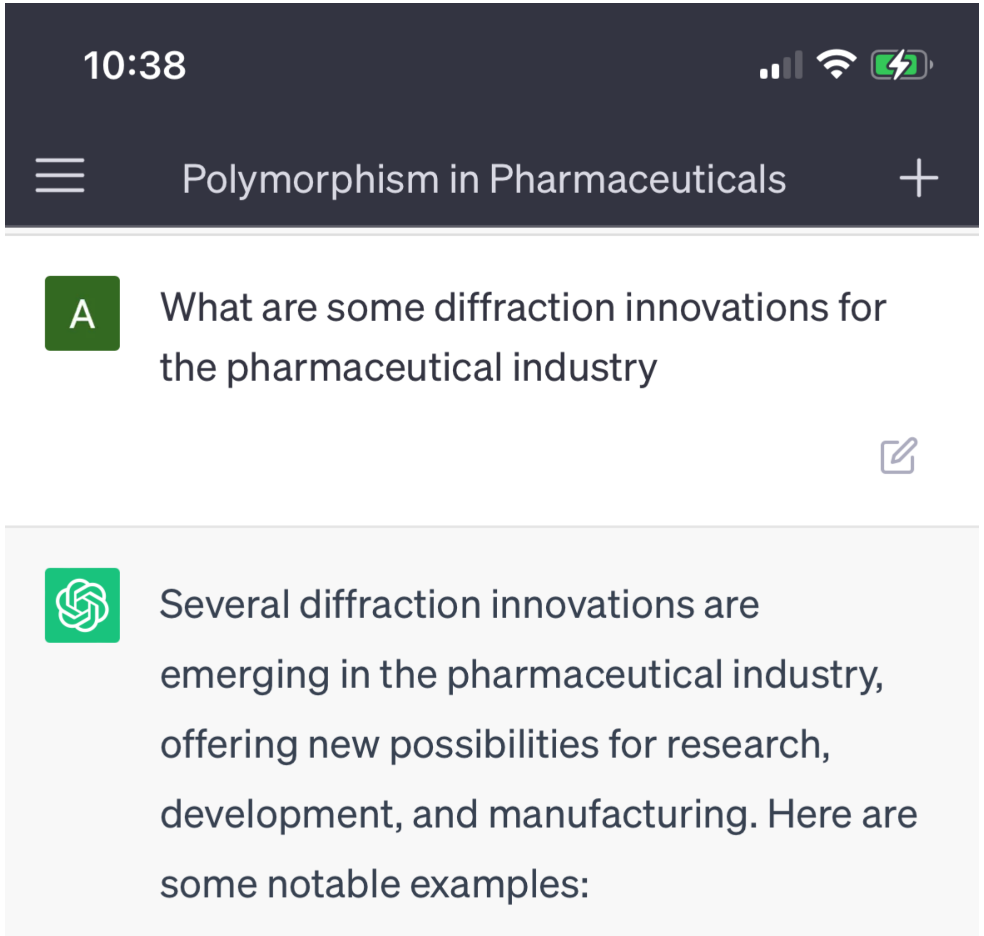


- Upon storage, the diffraction peak of PEG2000 extended chain lamellae continuously shifted to higher scattering vectors, indicating the decrease in the long period of the polymer.
- Concurrent with the evolution of a new diffraction peak at q ≈ 0.605 Å−1 due to the crystallization of Indomethacin.
- Segregation of the drug from the interlamellar region of the PEG matrix and its crystallization outside of the lamellar stacks

https://doi.org/10.1021/acs.molpharmaceut.7b01007

What are Some Diffraction Innovations for the Pharmaceutical Industry?

Let's ask ChatGPT…



What are Some Diffraction Innovations for the Pharmaceutical Industry?

- Structure determination of complex molecules:
  - Diffraction techniques, such as X-ray crystallography and electron diffraction, play a crucial role in determining the atomic and molecular structures of pharmaceutical compounds. As the pharmaceutical industry continues to develop increasingly complex molecules, diffraction methods will be essential for understanding their structures and interactions, aiding in drug design and optimization.
- Polymorph characterization and control:
  - Polymorphism remains a critical factor in drug development and manufacturing. Diffraction techniques enable the identification, characterization, and control of polymorphic forms. As pharmaceutical companies strive to enhance drug stability, bioavailability, and manufacturing efficiency, diffraction methods will continue to be indispensable in achieving these goals.
- Amorphous and nanocrystalline materials:
  - Amorphous and nanocrystalline forms of drugs are gaining attention due to their improved solubility and bioavailability. Diffraction techniques, such as wide-angle X-ray scattering (WAXS) and small-angle X-ray scattering (SAXS), enable the characterization and understanding of these non-crystalline structures. Future advancements in diffraction methods will contribute to optimizing the formulation and performance of amorphous and nanocrystalline pharmaceuticals.
- In situ and real-time analysis:
  - Traditional diffraction methods often require crystalline samples and are conducted ex situ. However, there is a growing interest in developing in situ and real-time diffraction techniques. These methods allow researchers to study dynamic processes, such as drug dissolution, crystallization, and solid-state transformations, providing valuable insights into drug behavior and formulation stability.
- Advanced instrumentation and data analysis:
  - The pharmaceutical industry is witnessing advancements in diffraction instrumentation and data analysis techniques. High-throughput screening, automation, and data-driven approaches enable efficient and rapid structure determination, polymorph screening, and characterization. Continued innovation in diffraction hardware and software will further streamline pharmaceutical research and development processes.
- Combination with other techniques:
  - Diffraction techniques are increasingly being complemented with other analytical methods, such as spectroscopy, microscopy, and computational modeling. Integrating diffraction data with data from other techniques enables a more comprehensive understanding of drug structures, interactions, and properties. Synergistic approaches will continue to advance drug discovery, formulation, and personalized medicine.

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Our perspective

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AR&D careers

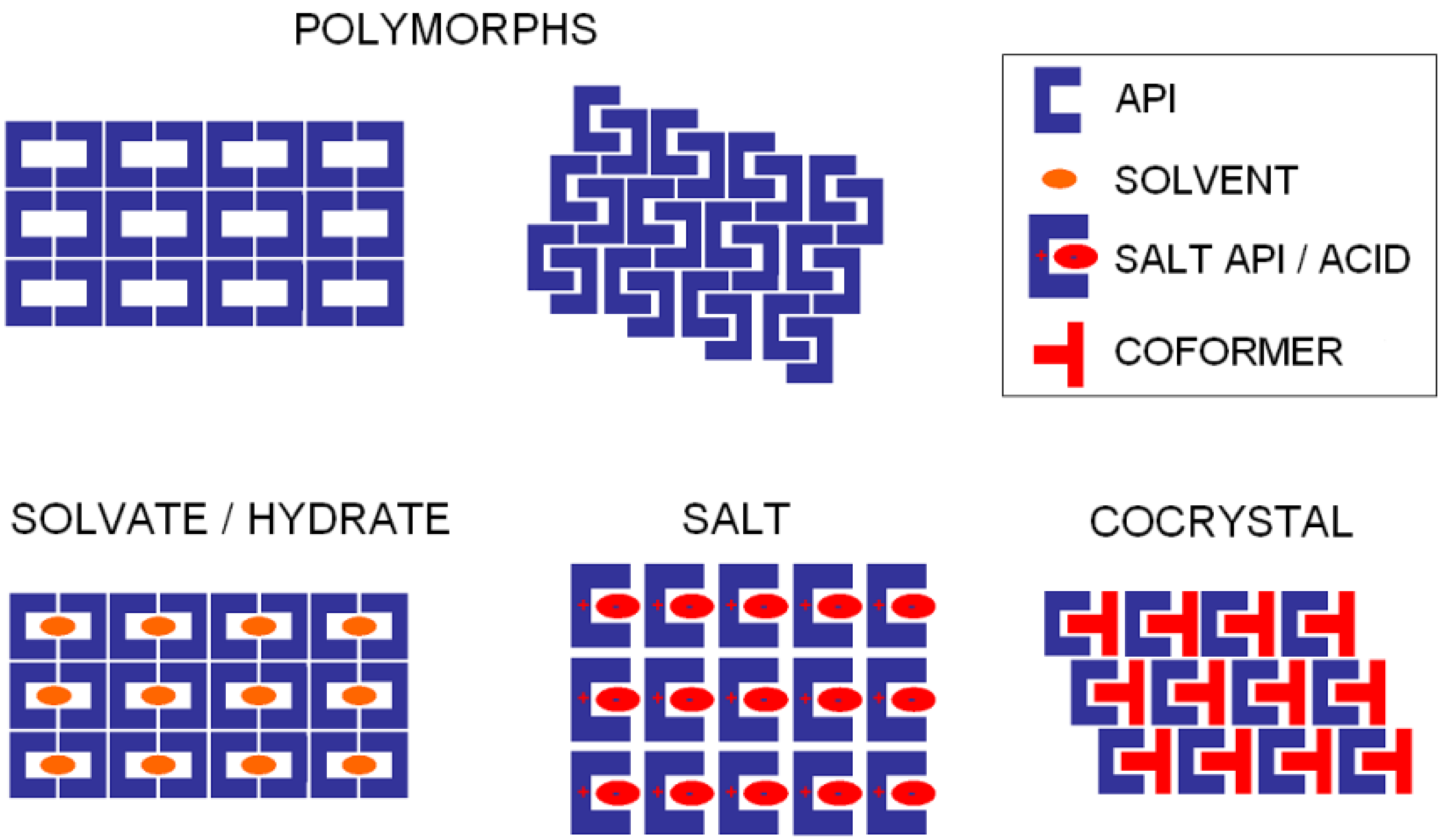
Thank you!

Questions?

PPXRD-17
Pharmaceutical Powder
X-ray Diffraction Symposium

Back-Up

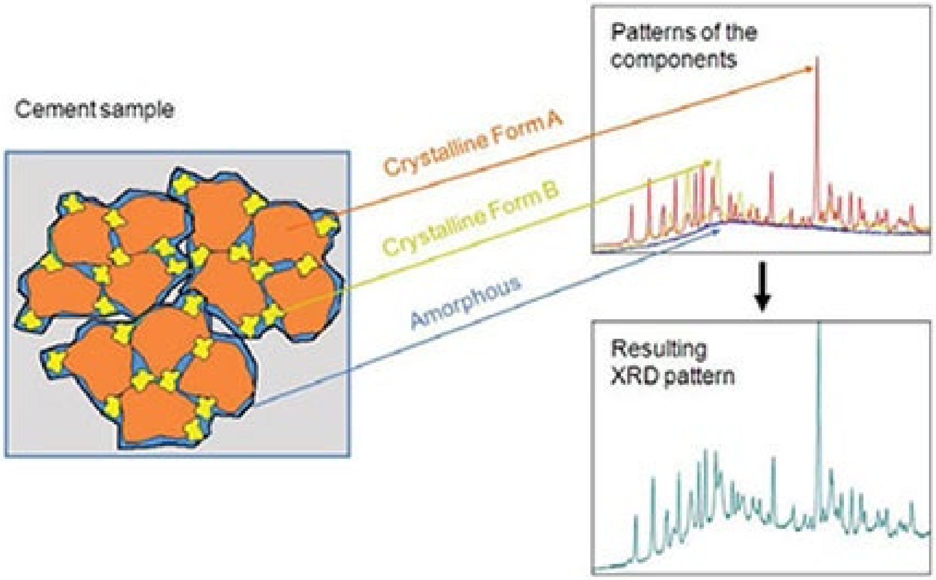
Polymorphs and Other Forms

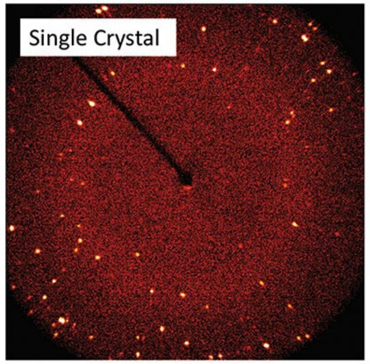


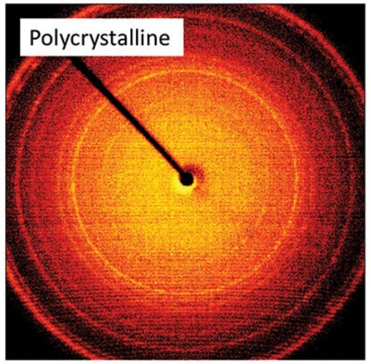
http://hdl.handle.net/2445/32128

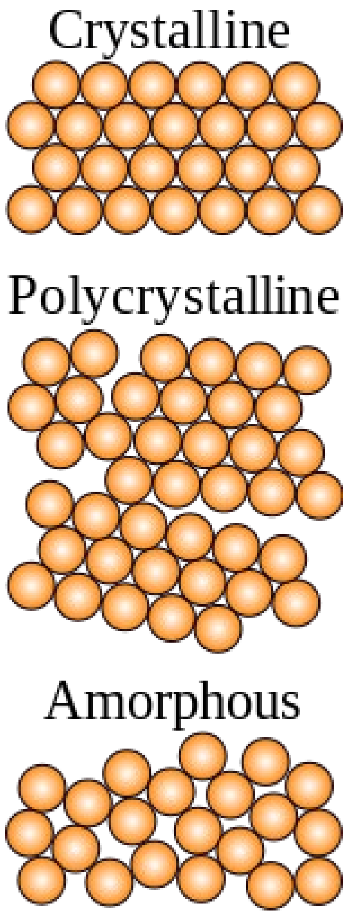
XRPD – A Primer

- Determination of crystallinity
- Identification of changes in crystalline Form (subtle and gross lattice changes)
- Texture analysis (crystallite size, orientation)



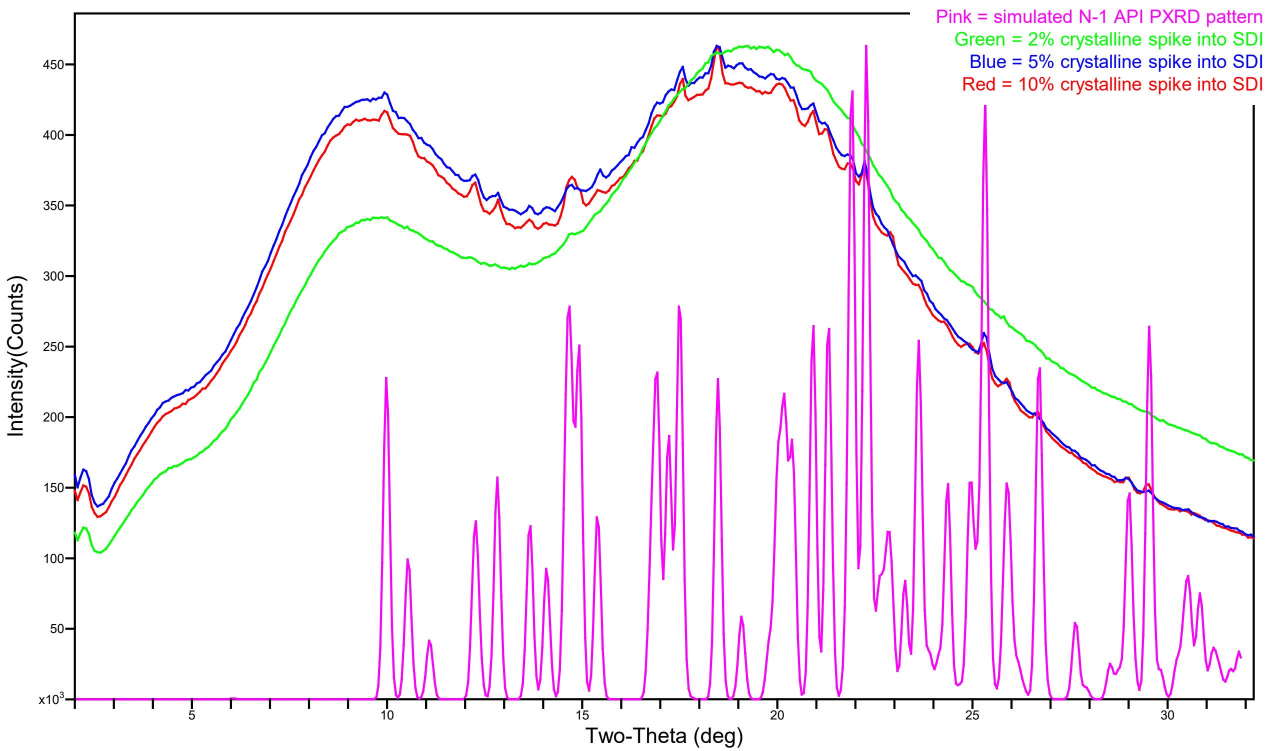






http://www.indiancementreview.com/News.aspx?nId=7IzXWlNdCOkIrYXumiJTUw==
https://www.researchgate.net/post/What_is_the_reason_for_the_amorphous_halo_in_XRD_patterns_Does_it_have_a_relation_to_clusters_in_amorph_structure
https://www.ceramicindustry.com/articles/96252-ceramic-materials-characterization-using-x-ray-diffraction
https://en.wikipedia.org/wiki/Crystallite

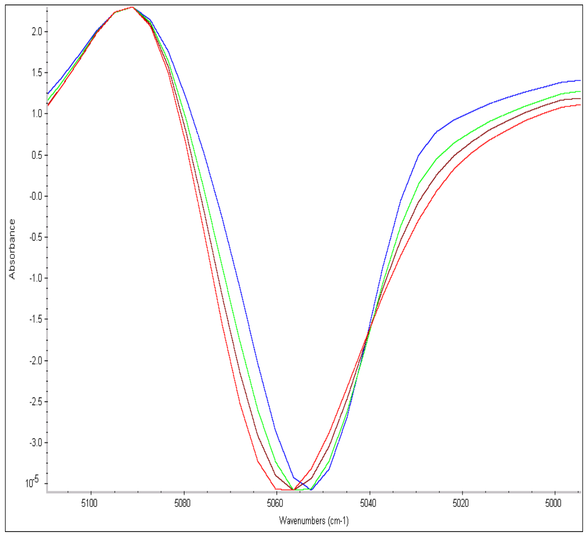
Case Study 5: Crystallization of SDI

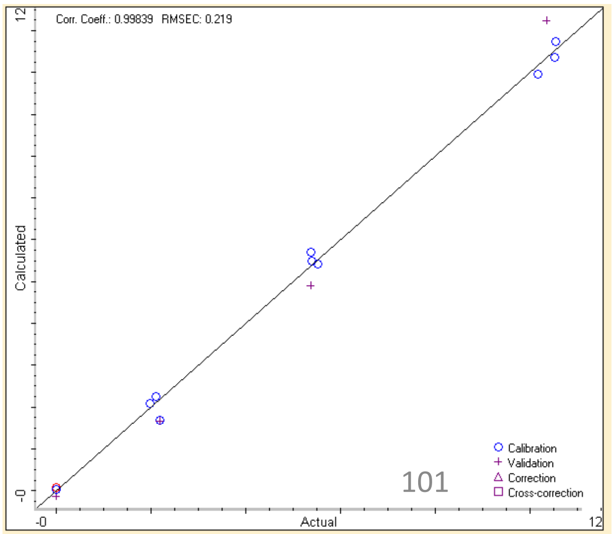


Goal: Quantify crystalline API in DP

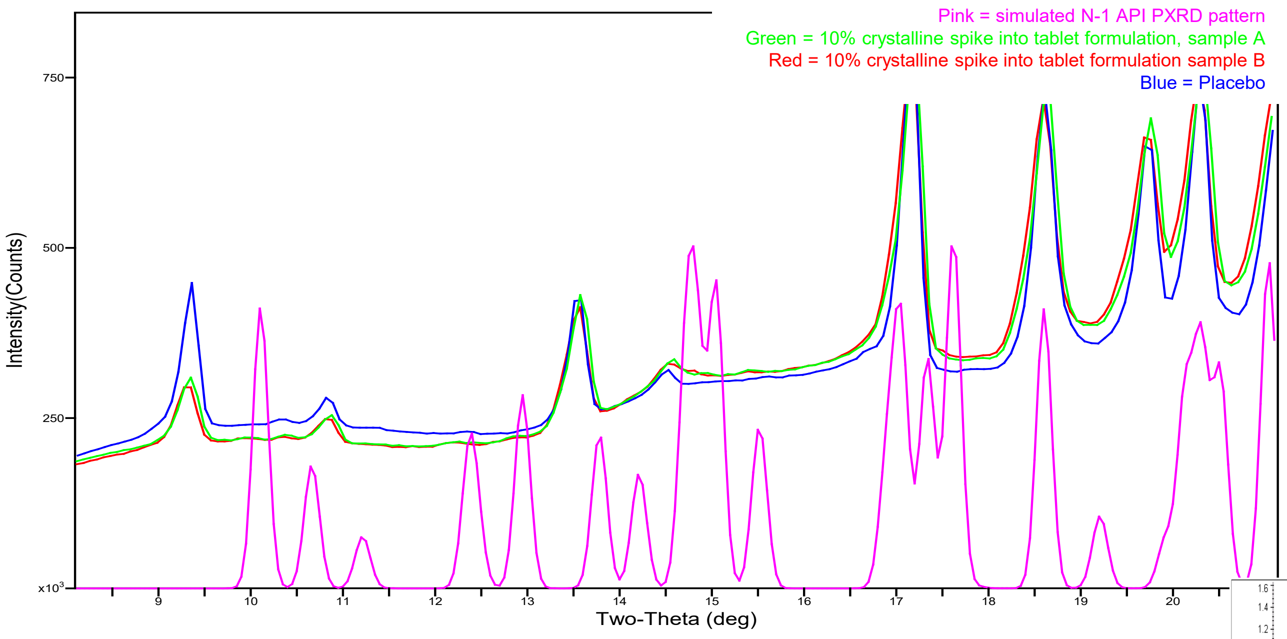
- Crystalline form shows poor solubility and therefore BA
- 25% DL SDD developed
- NIR more sensitive than XRPD

CONH2 group / C=O second overtone





Case Study 5: Crystallization of SDI



- 8% DL tablet
- XRPD cannot see crystalline 10% spike
- NIR still sensitive to crystalline 2% spike