NASDAQ: MRTX

MIRATI THERAPEUTICS

Targeting the genetic and immunological drivers of cancer

Application of DD-WPPF Method to Accurately Determine Minor Amorphous/Polymorph Impurities in Pharmaceutical Material

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Outline

- Challenges with Quantitative XRD method in Pharmaceutical Analysis
- DD-WPPF method
- Case studies
- Summary

Quantitative XRD method in Pharmaceutical Analysis

- Application of quantitative XRD in pharmaceutical analysis
  - Phase composition/purity in QC release of API and drug product
  - Monitor polymorph changes in stability studies
- Common methods
  - Calibration curve using peak intensity from standard mixtures
  - Reference Intensity Ratio (RIR with internal standard)
  - Rietveld refinement

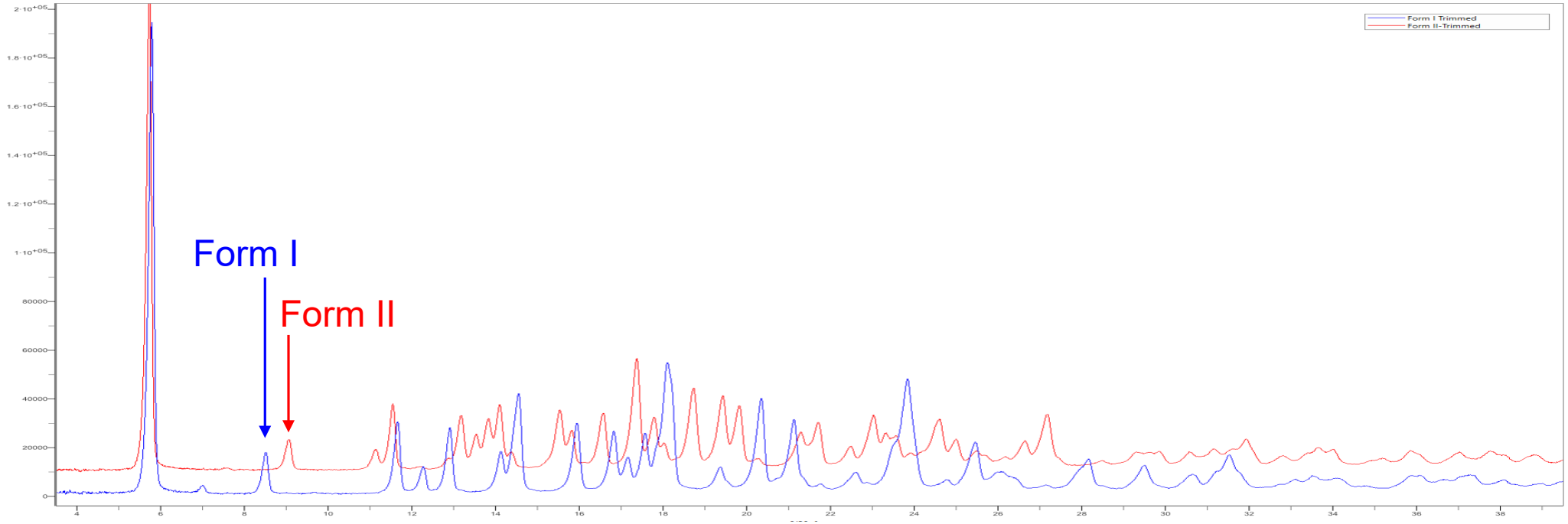
Direct Derivation-Whole-Powder Pattern Fitting (DD-WPPF) method

- Published by Hideo Toraya et al from Rigaku and Implemented in Rigaku Smartlab Studio II Software
- Brief workflow for the DD-WPPF method
  - Create measured phase profiles
    - Patterns of individual components
  - Evaluate mixture sample data
    - Phase identification
    - Select refinement parameters
    - Set data range for refinement
  - Results evaluation
    - Visual evaluation
    - Rwp%, Rp%, S and χ^2

Case Study #1: Minor Polymorph Impurity in API

- The API has two polymorphs of similar energy level, different ratios of the two polymorphs can be generated depending on the crystallization conditions and solvents used.
- Current quantitative analytical method utilizes single peak intensity and calibration curve to quantify the undesired form in API batches. Due to variability of sample prep and XRD analysis, two different calibration curves (high and low range) are used depending on the actual composition of the sample with LOQ determined at 19% and 30%.
- Can a simpler and more accurate method be developed with DD-WPPF?

Form I and Form II XRD Pattern of MRTX A

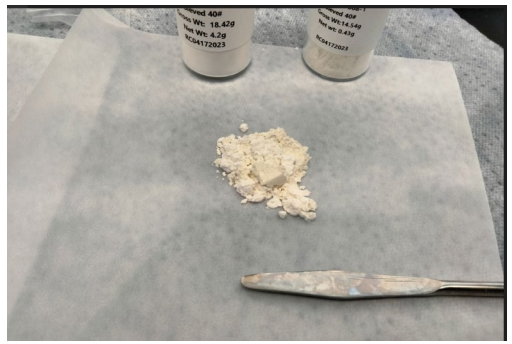


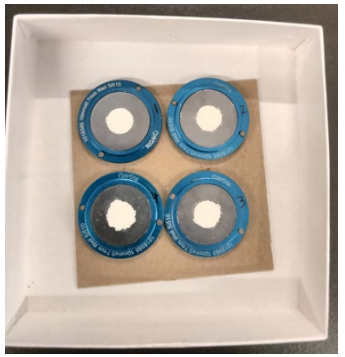
- There are distinct form I and form II peaks. Why the method LOQs were so high?

Sample Prep Challenges

- Plate selection

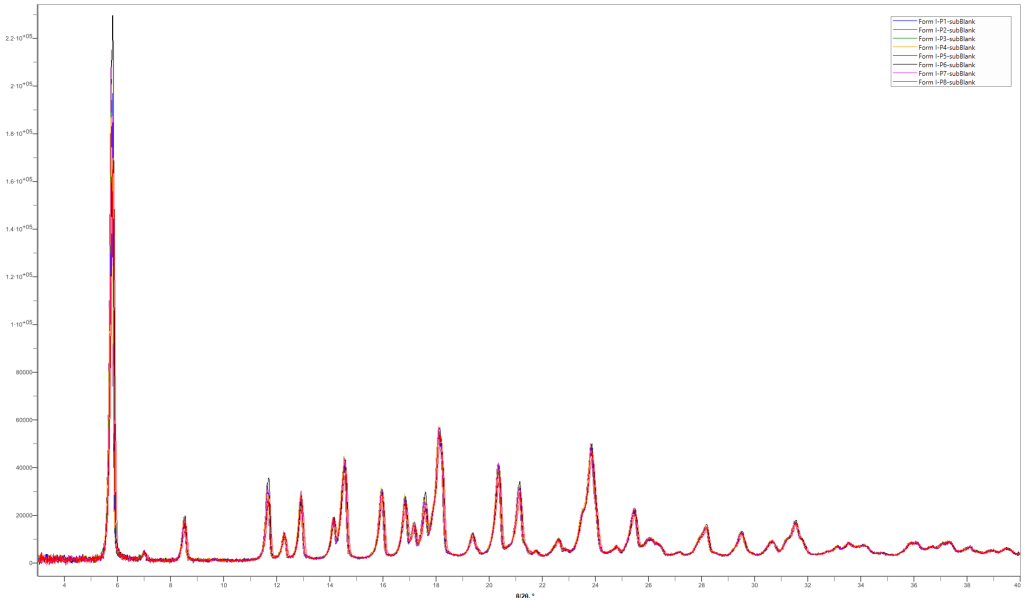
- Preparation of sample mixtures with known composition
  - Both form I and form II are fluffy, fine, and sticky powder that aggregates easily and turn static in dry environment
  - Quite challenging to prepare an accurate and uniform mixtures

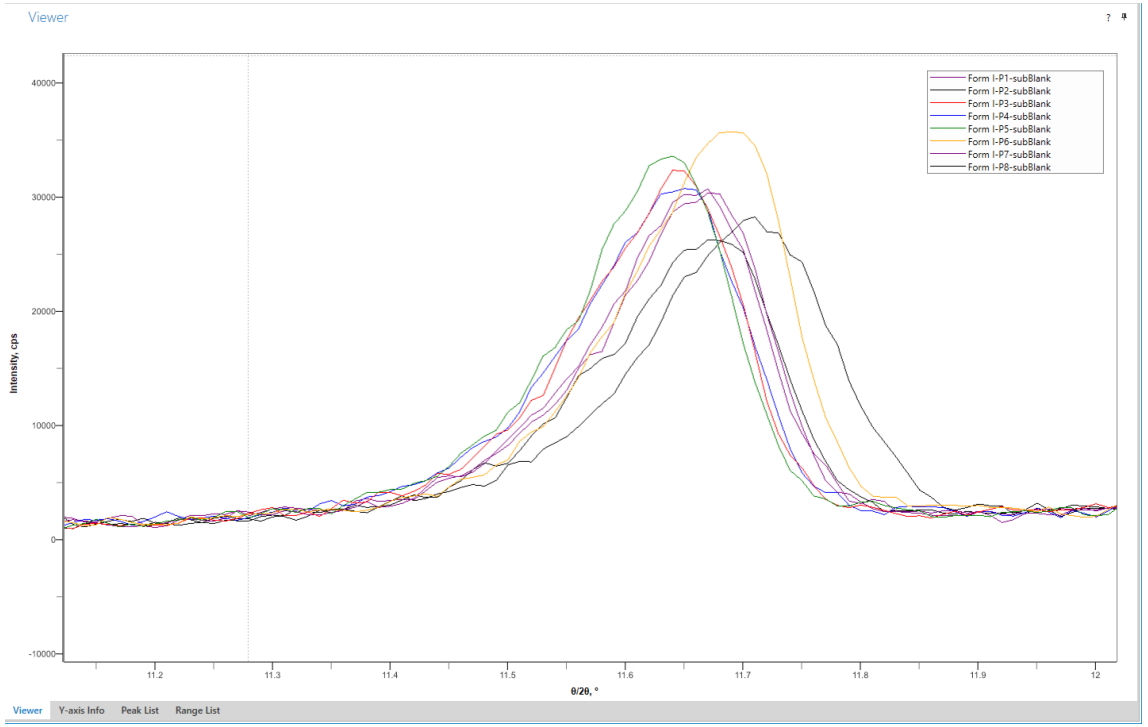




XRD Analysis Challenges

- MRTX A powder sample has strong tendency for preferred orientation
- Bench top Rigaku MiniFlex 6G Diffractometer was used
  - No auto Z-alignment so 2-theta position can be variable due to sample packing

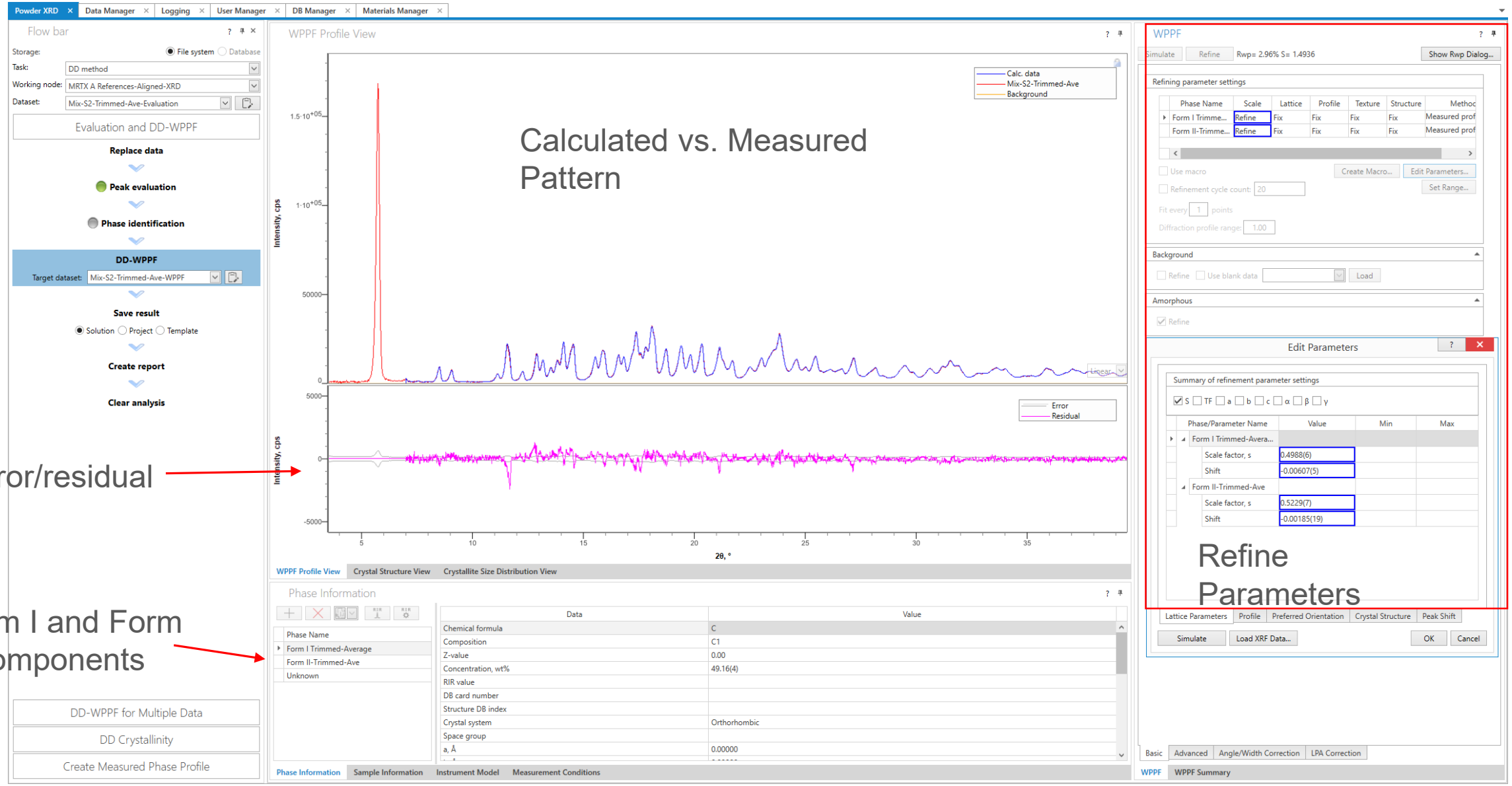




Sample Preparation and Raw data processing

- Manual mixing of accurately weighed form I and form II on paraffin paper with spatula.
  - Eight sample mixtures of different ratios were prepared via geometric dilution
- Eight replicates of each sample mixture were run and the average of the 8 replicates is used for quantification
  - Subtract blank from the raw data
  - Realignment of the 8 replicates to correct 2-theta shift with sample packing variation
  - Trimmed the data to the same 2-theta range
  - Average the trimmed data set

DD-WPPF Method Workflow Interface

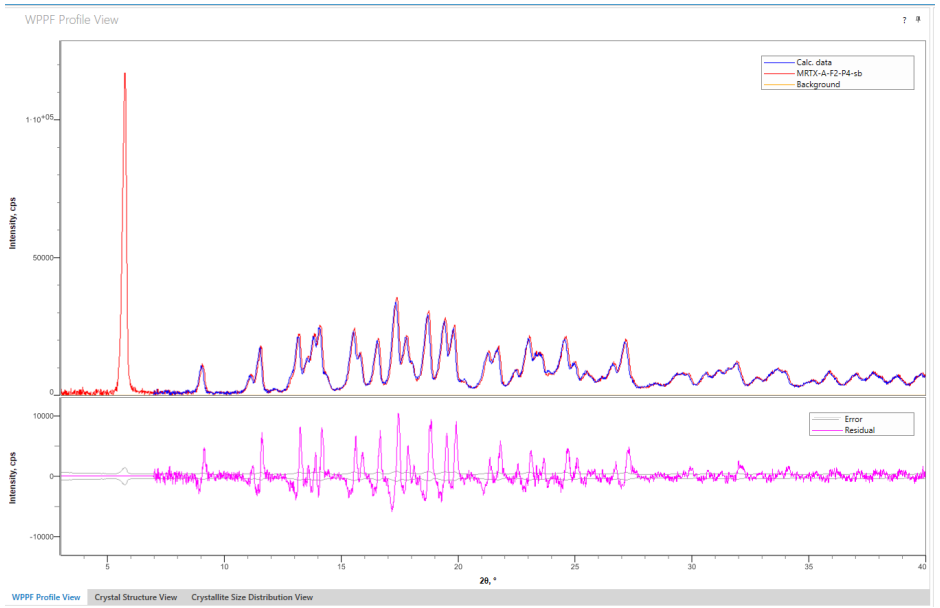


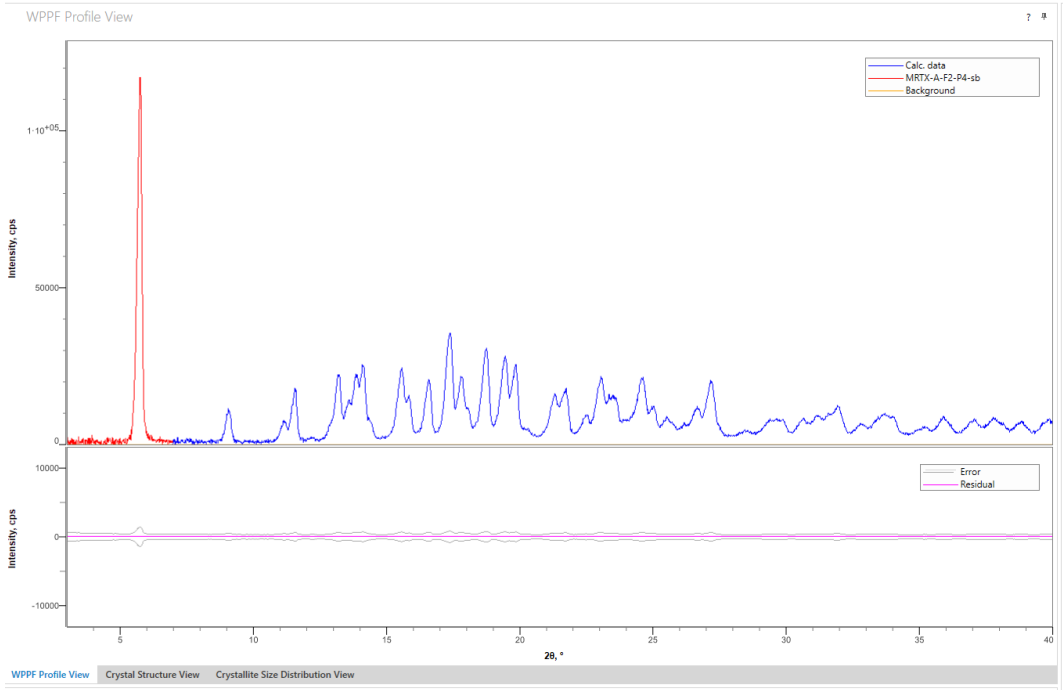
Error/residual

Form I and Form II components

Refine Parameters

Find the Global Minimum During Refinement





Phase / Dataset	MRTX-A-F2...
Rwp, %	16.45
Rp, %	12.99
S	3.1798
χ^2	10.1108
MRTX-A-F1-P4...	
Weight frac...	3.2(3)

Summary of refinement parameter settings

☑ S ☐ TF ☐ a ☐ b ☐ c ☐ α ☐ β ☐ γ

Phase/Parameter Name	Value
MRTX-A-F1-P4-sb	
Scale factor, s	0.032(3)
Shift	-0.01021(9)
MRTX-A-F2-P4-sb	
Scale factor, s	0.947(4)
Shift	-0.0502491(9)

WPPF Summary

Phase / Dataset	MRTX-A-F2...
Rwp, %	0.00
Rp, %	0.00
S	0.0000
χ^2	0.0000
MRTX-A-F1-P4...	
MRTX-A-F2-P4...	
Weight frac...	100.00

Edit Parameters

Summary of refinement parameter settings

☑ S ☐ TF ☐ a ☐ b ☐ c ☐ α ☐ β ☐ γ

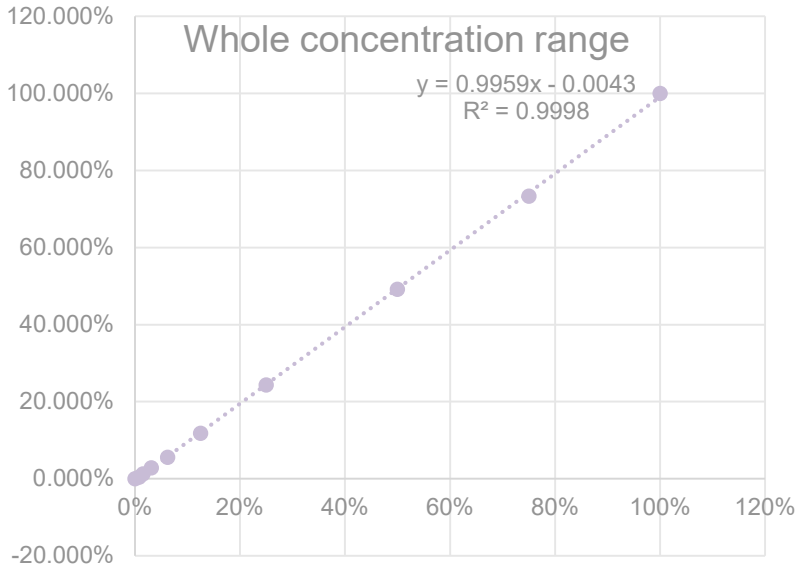
Phase/Parameter Name	Value	Min	Max
MRTX-A-F1-P4-sb			
Scale factor, s	0.0000	0.00	0.2
Shift	-0.073093(9)	-0.15	0.15
MRTX-A-F2-P4-sb			
Scale factor, s	1.0000	0.991	1.2
Shift	0.000000	-0.15	0.15

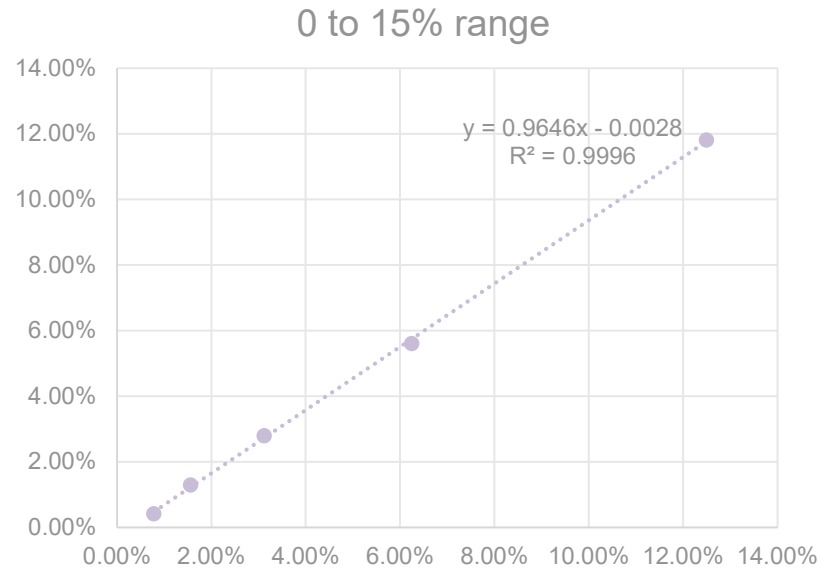
Lattice Parameters | Profile | Preferred Orientation | Crystal Structure | Peak Shift

Simulate | Load XRF Data... | OK | Cancel

DD-WPPF Results

Sample	Theoretical		DD-WPPF Results		Form I Quantification Absolute error	Form I Quantification Relative error
	F1%	F2%	F1%	F2%		
Form II	0%	100%	0.001%	99.999%		
S1	75%	25%	73.35%	26.65%	-1.65%	-2.20%
S2	50%	50%	49.21%	50.79%	-0.79%	-1.58%
S3	25%	75%	24.32%	75.68%	-0.68%	-2.72%
S4	12.50%	87.50%	11.82%	88.18%	-0.68%	-5.44%
S5	6.25%	93.75%	5.61%	94.39%	-0.64%	-10.24%
S6	3.125%	96.88%	2.80%	97.20%	-0.33%	-10.40%
S7	1.5625%	98.44%	1.30%	98.70%	-0.26%	-16.80%
S8	0.78125%	99.22%	0.42%	99.58%	-0.36%	-46.24%
Form I	100%	0%	99.999%	0.001%		





LOD and LOQ Determination

- Standard deviation of the response from linear regression

  S_y = 0.002088

- Slope of the Linear regression

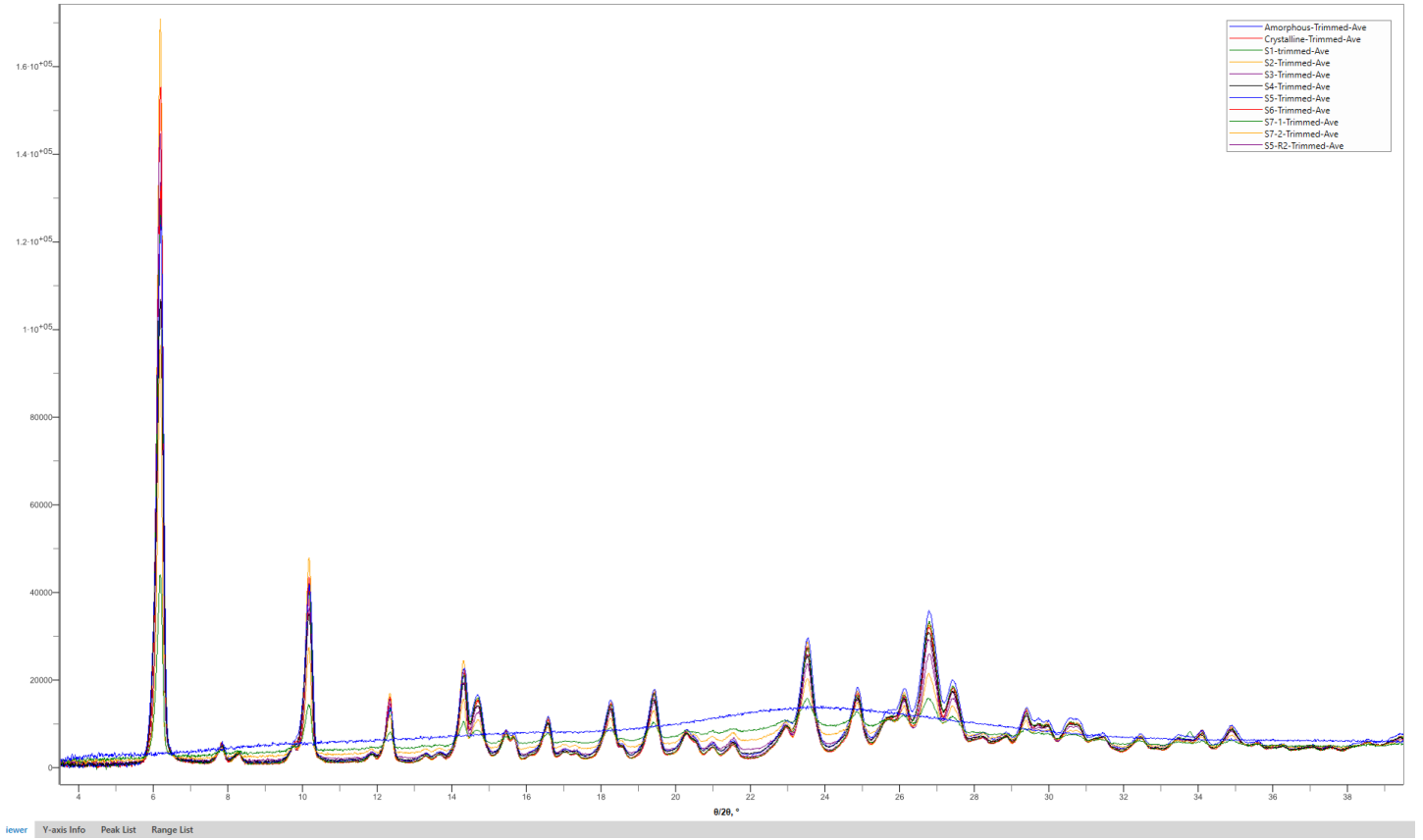
  S= 0.983858

- LOD = 3.3 * S_y /S = 0.64%
- LOQ = 10 * S_y /S = 2.12%
- Experimental confirmation with a separately prepared S6 mixture(3.125% Form I)
  - Result: 3.32%

Case # 2: Amorphous Content Determination

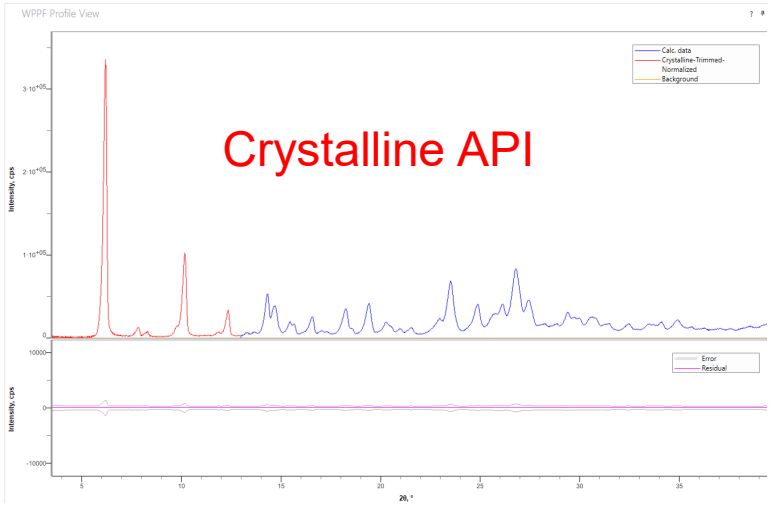
- Chiral impurity of MRTX B in tablet product was found growing during stability analysis
  - No such change was observed from stability study of the crystalline API drug substance
- Amorphous MRTX B formation during tablet compaction was suspected to be the cause
  - Analytical method to be able to quantify amorphous content in crystalline matrix is needed

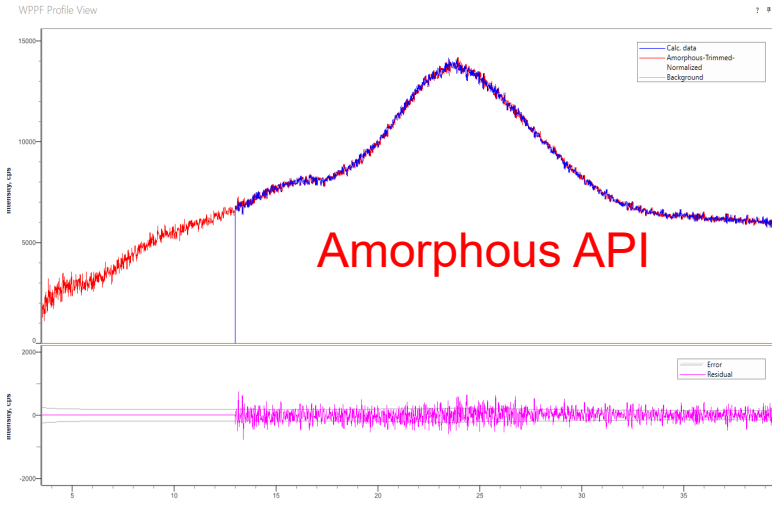
Binary Mixture of Amorphous and Crystalline MRTX B

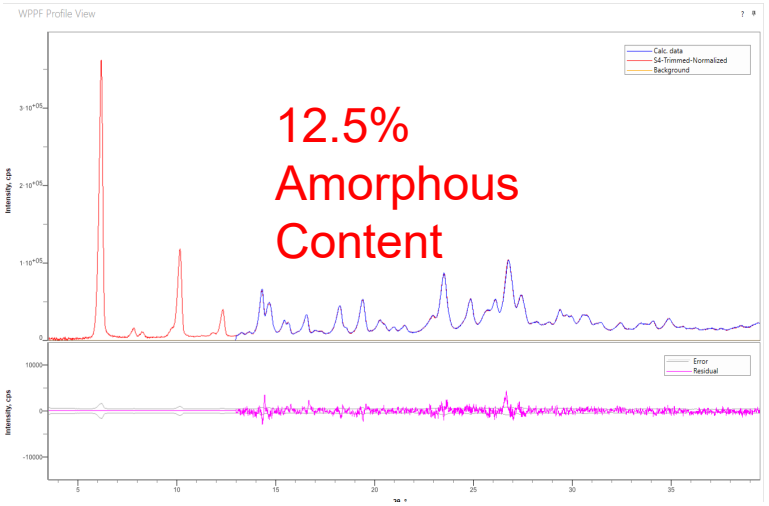


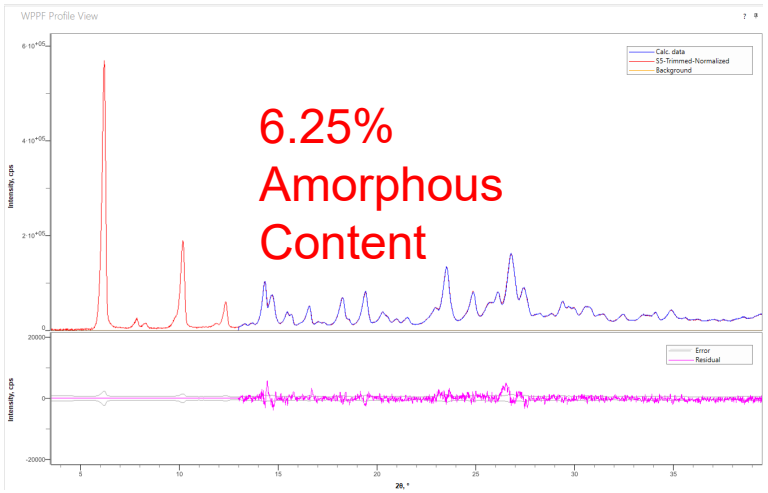
- Seven mixtures with amorphous content at 75%, 50%, 25%, 12.5%, 6.25%, 3.125% and 1.5625% were prepared

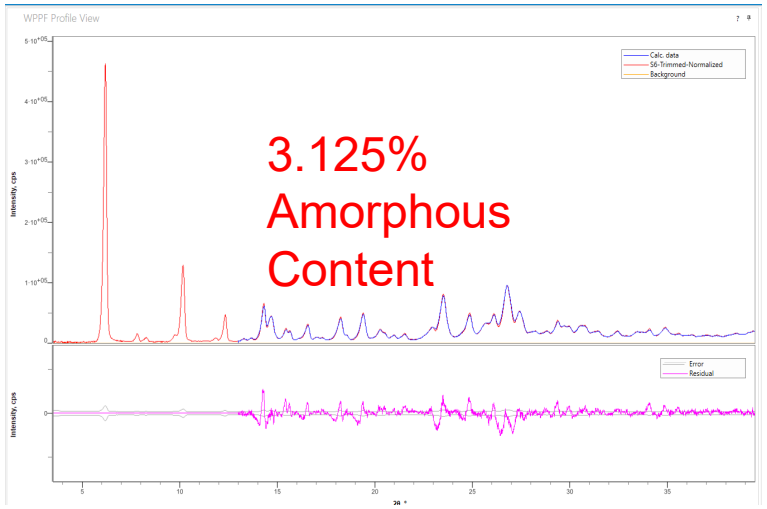
Representative WPPF Profile Views

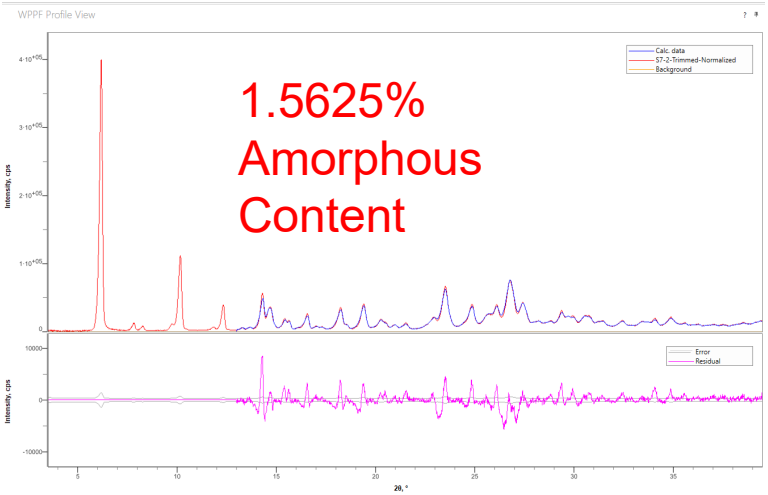






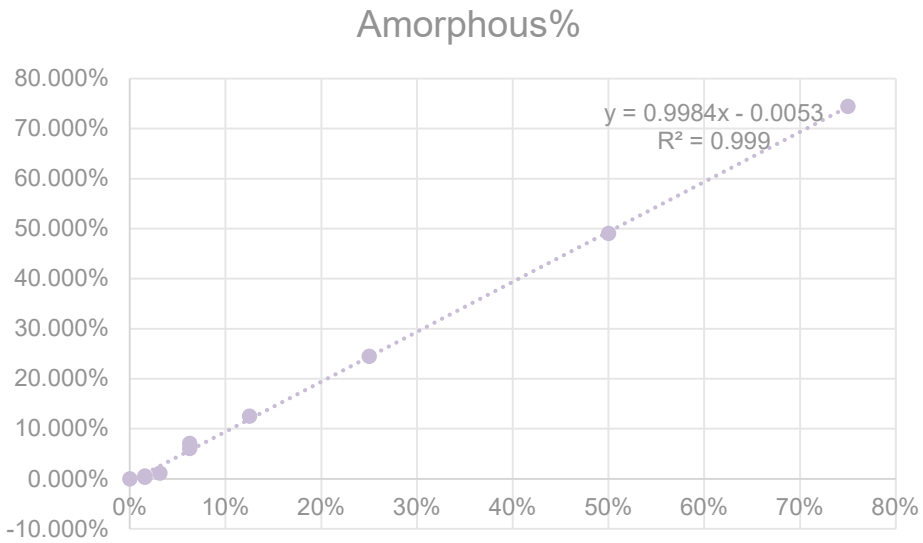


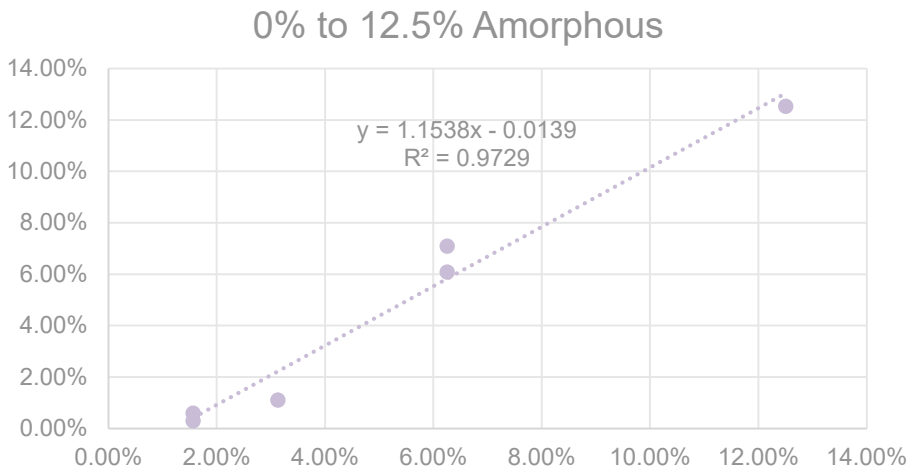




DD-WPPF Results

Sample	Theoretical Amorphous%	DD-WPPF Amorphous%	Absolute error	Relative error
Crystalline	0%	0.001%		
Amorphous	100%	99.999%		
S1	75%	74.40%	-0.60%	-0.80%
S2	50%	49.04%	-0.96%	-1.92%
S3	25%	24.47%	-0.53%	-2.12%
S4	12.50%	12.53%	0.03%	0.24%
S5	6.25%	7.09%	0.84%	13.44%
S5-2	6.25%	6.08%	0.36%	5.76%
S6	3.125%	1.11%	-2.02%	-64.48%
S7	1.5625%	0.59%	-0.97%	-62.24%
S7-2	1.5625%	0.30%	-1.26%	-80.80%





LOD and LOQ Determination

- Standard deviation of the response from linear regression

  S_y = 0.01159

- Slope of the Linear regression

  S = 0.9619

- LOD = 3.3 * S_y /S = 3.6%
- LOQ = 10 * S_y /S = 12.0%

Summary

- DD-WPPF method was applied in two case studies to quantify minor crystalline and amorphous content in API material
  - 2.2% LOQ was achieved for the quantification of minor crystalline polymorph impurity
  - 12.0% LOQ was achieved for the quantification of amorphous content in crystalline API

- Replicate sample runs were utilized to minimize quantification error due to sample prep variation

- Advantages of DD-WPPF method
  - Simple to develop and implement
  - No calibration necessary
  - Accurate and straightforward to judge the reliability of results

Acknowledgements

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