PXRD INVESTIGATION OF CHANGES IN DEHYDRATION BEHAVIOR OF GSK241572 HYDRATE AFTER MICRONIZATION

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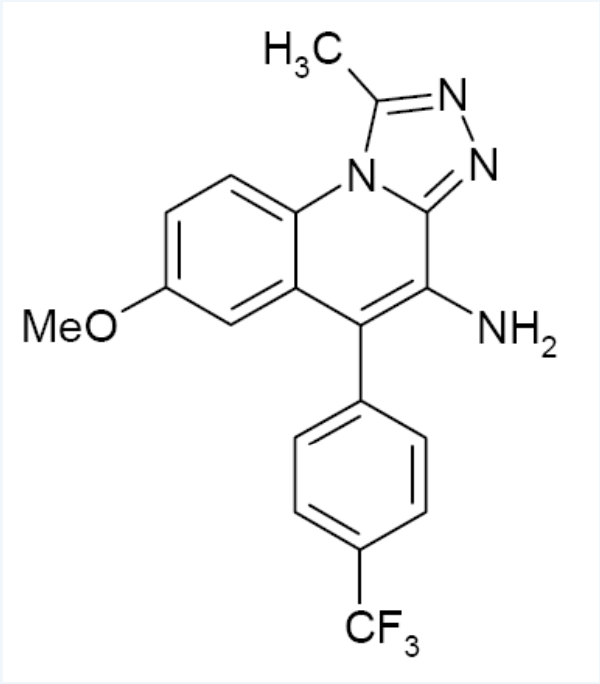
Outlines

- Background and Objectives
- Methodologies on Dehydration Analysis
  - Thermal analysis
    - DSC/TGA
    - Hot-stage microscopy
  - Gravimetric vapour Sorption
    - Isothermal dehydration
    - Kinetics modelling
  - PXRD analysis
    - Reflection vs. transmission
    - Variable temperature PXRD
    - Rieveltd refinement
- Conclusions

Background

- Many pharmaceuticals exist in both hydrated and anhydrous forms.
- The physicochemical, mechanical, processing, and biological properties of hydrates may differ significantly from those of the corresponding anhydrates.
- Understanding of dehydration behavior is required for process control and predicting stability of drug substance and drug product.
- Variable hydrates present relative complex dehydration behavior compared to stochiometrirc hydrates.

Compound in Study



- Form B, a hydrated form of this free base was chosen for development.
- Theoretical monohydrate 4.6%wt
- Classified as a variable, or non-stoichiometric hydrate
- Displays complex dehydration behavior pre and post size reduction

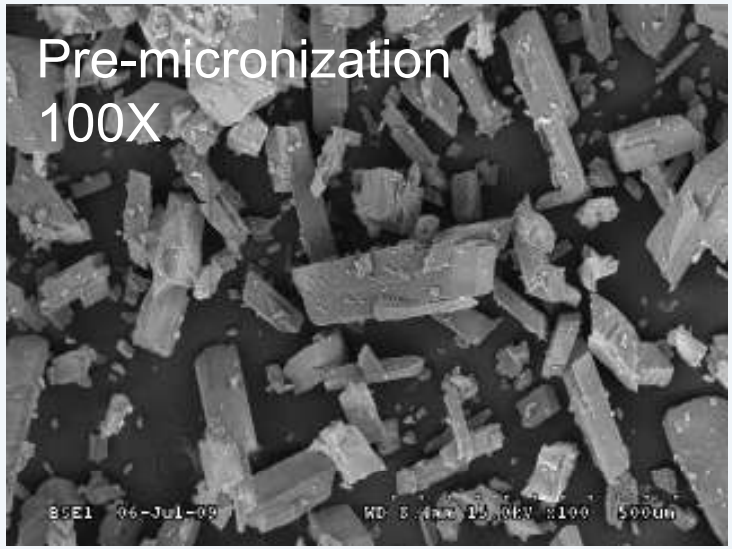
7-methoxy-1-methyl-5-(4-(trifluoromethyl)phenyl)-[1,2,4]triazolo[4,3-a]quinolin-4-amine

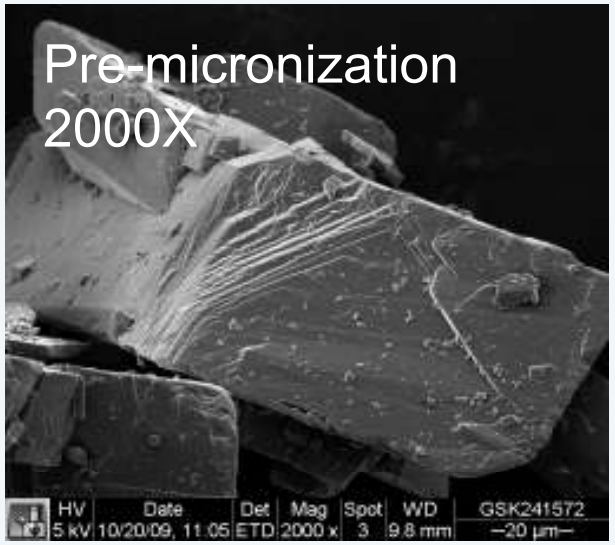
(GSK241572)

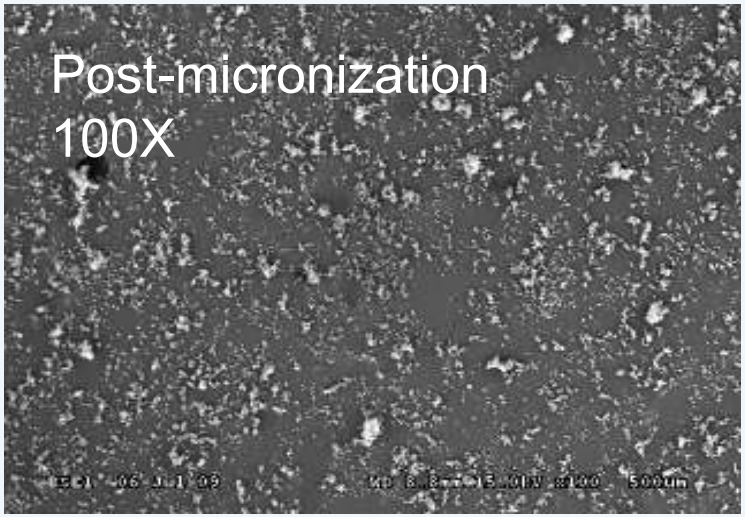
Objectives

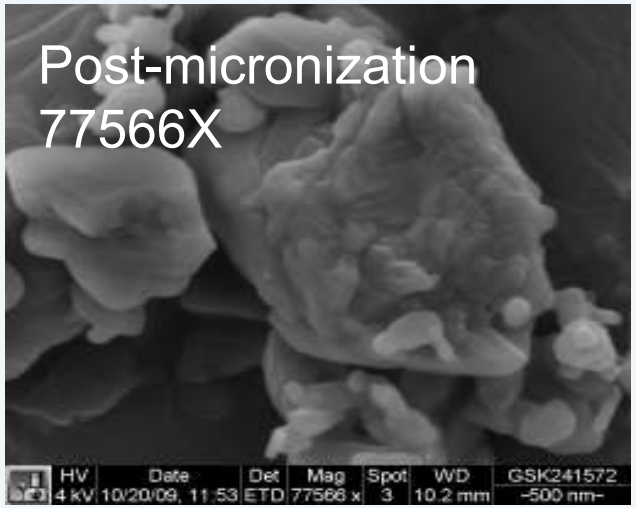
- Characterize dehydration of the system pre- and post-micronization
  - Various techniques were utilized including DSC, TGA, HSM, GVS, VT-PXRD etc.
- Study dehydration mechanism by the following approaches
  - Solid state kinetics modeling
  - Rietveld analysis
  - Crystal structural analysis

Scanning Electron Microscopy



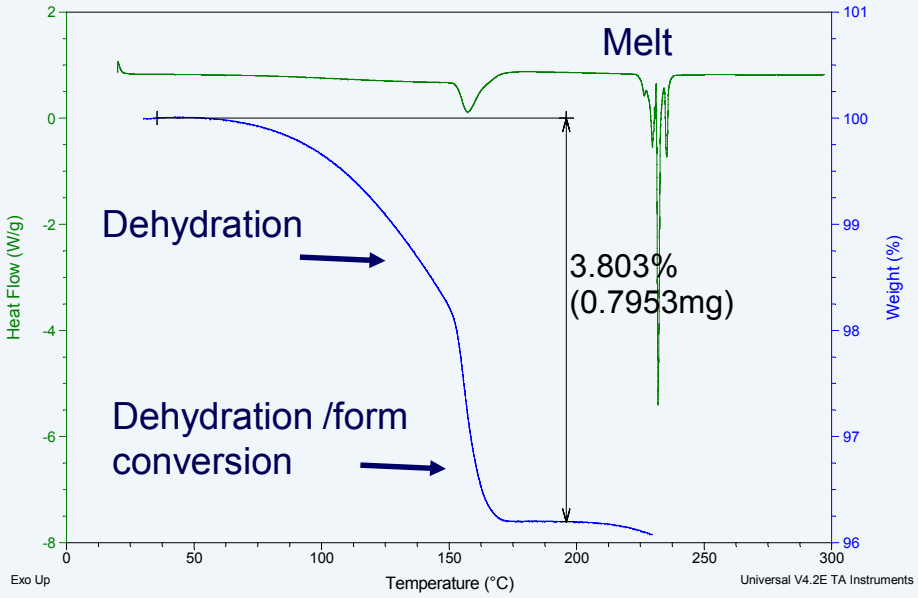




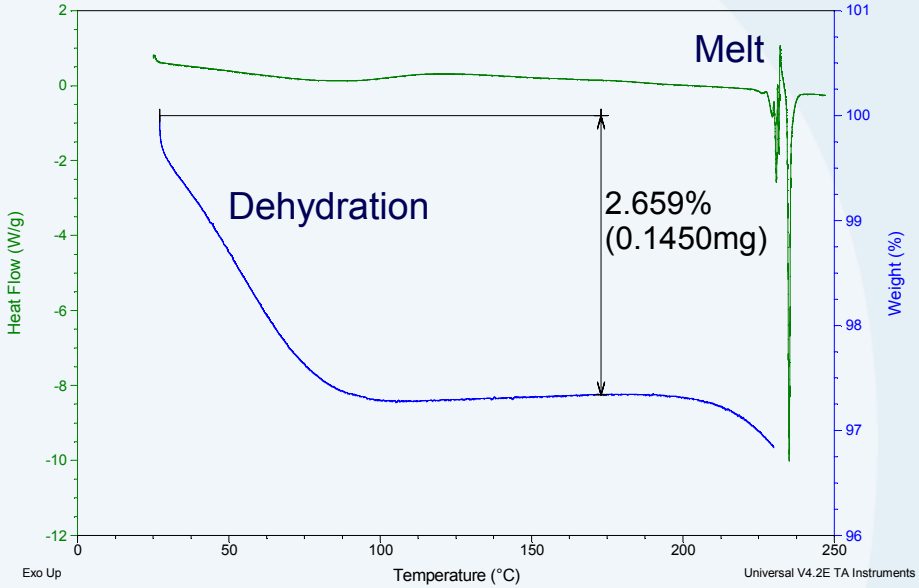


DSC/TGA

Pre-micronization

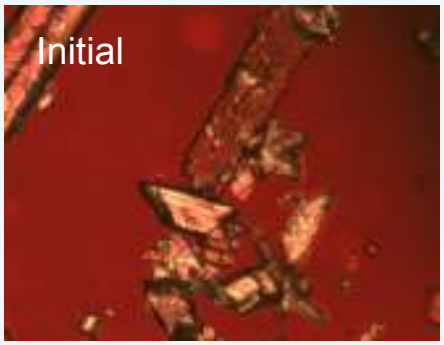
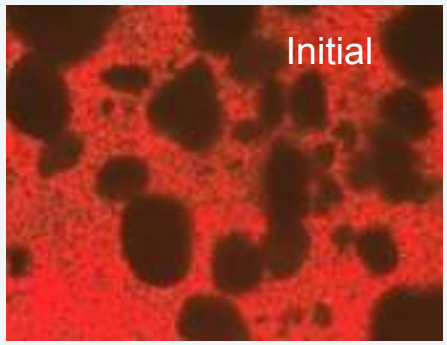
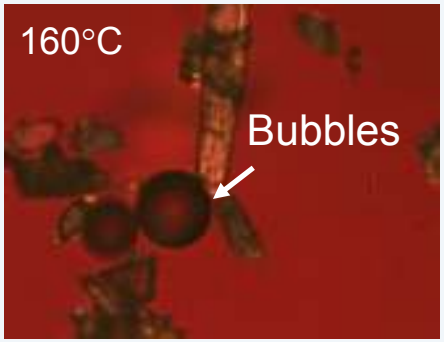
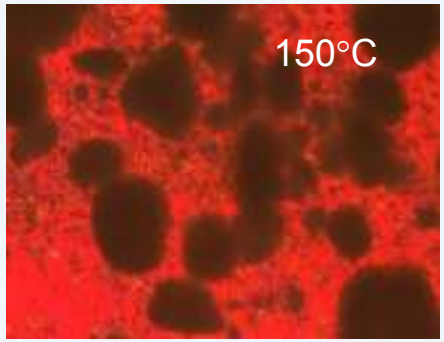
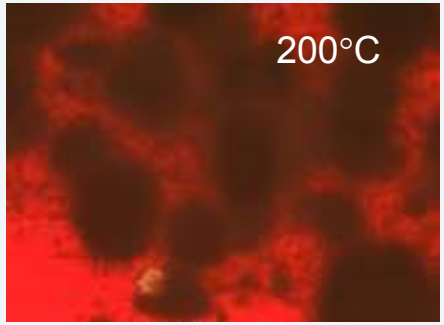


Post-micronization

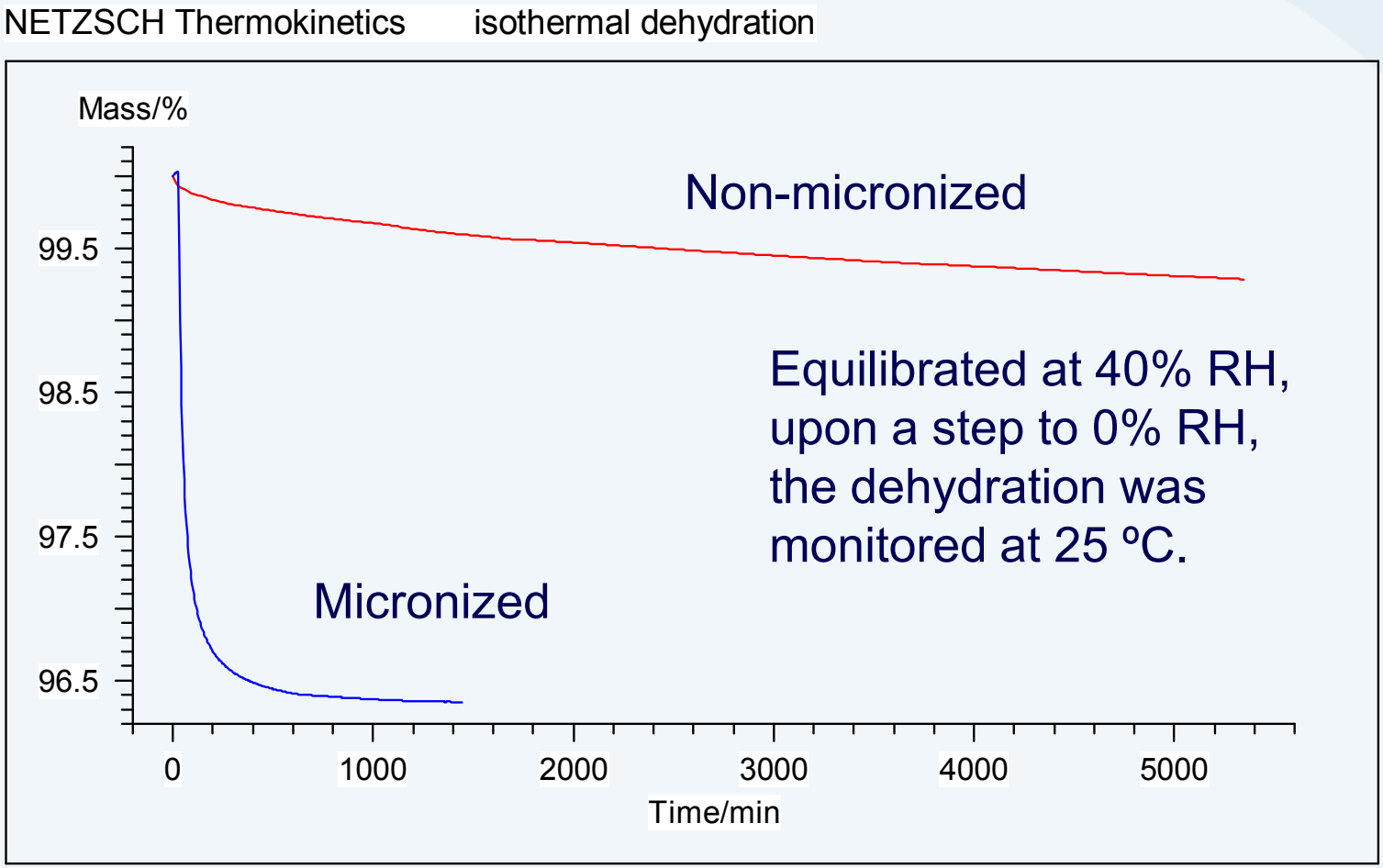


Distinct dehydration processes observed between non-micronized and micronized samples.

Hot-Stage Microscopy

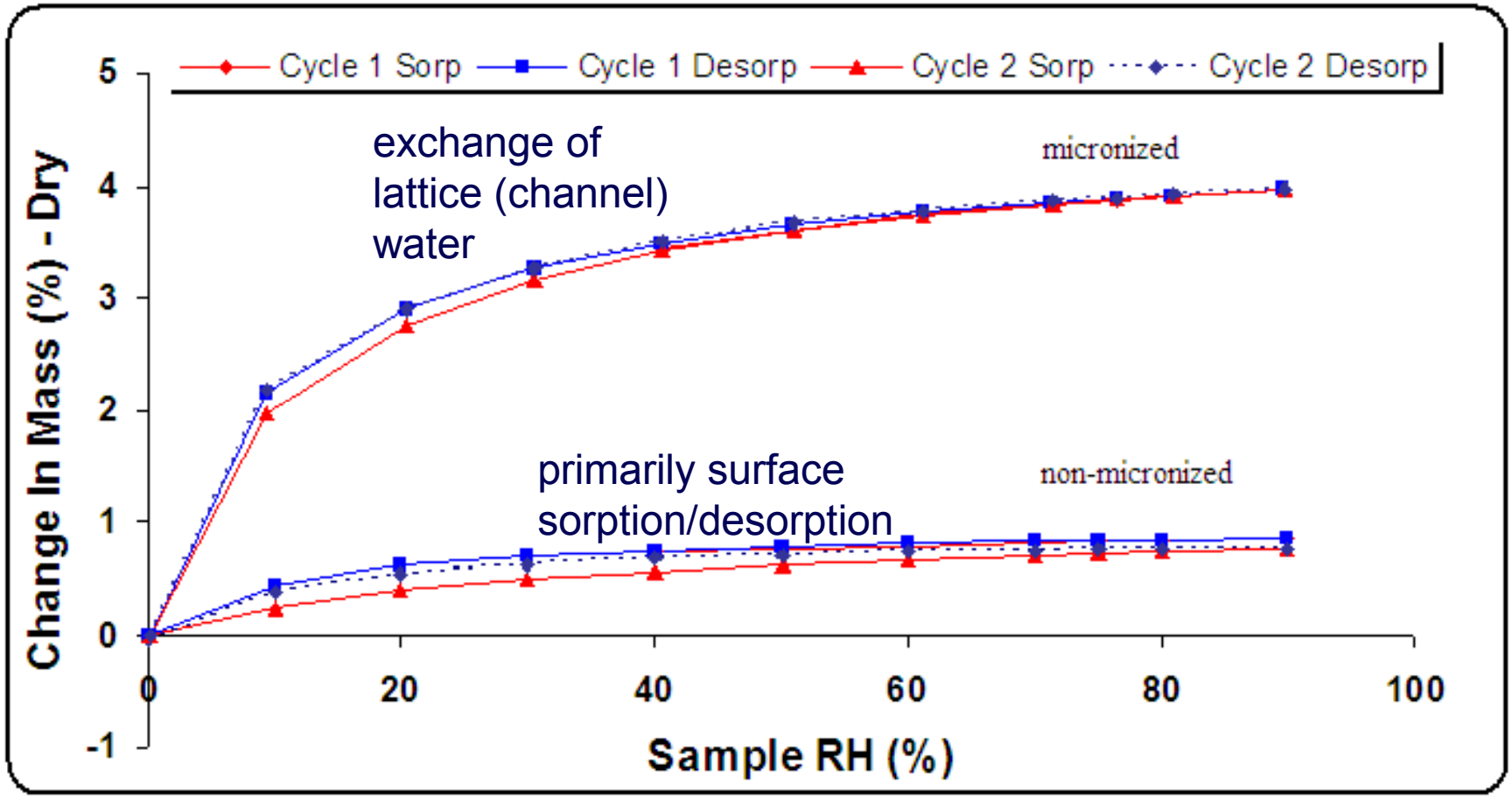
	Pre-micronization	Post-micronization	
			
Start re-crystallization to needle-like crystals (anhydrous form)			Start re-crystallization to needle-like crystals (anhydrous form)
Converted to anhydrous form			Converted to anhydrous form

Isothermal Dehydration



Drastically different behavior displayed with regards to the loss of water content over time. The rate of loss of non-micronized material is slower by ~ two orders of magnitude.

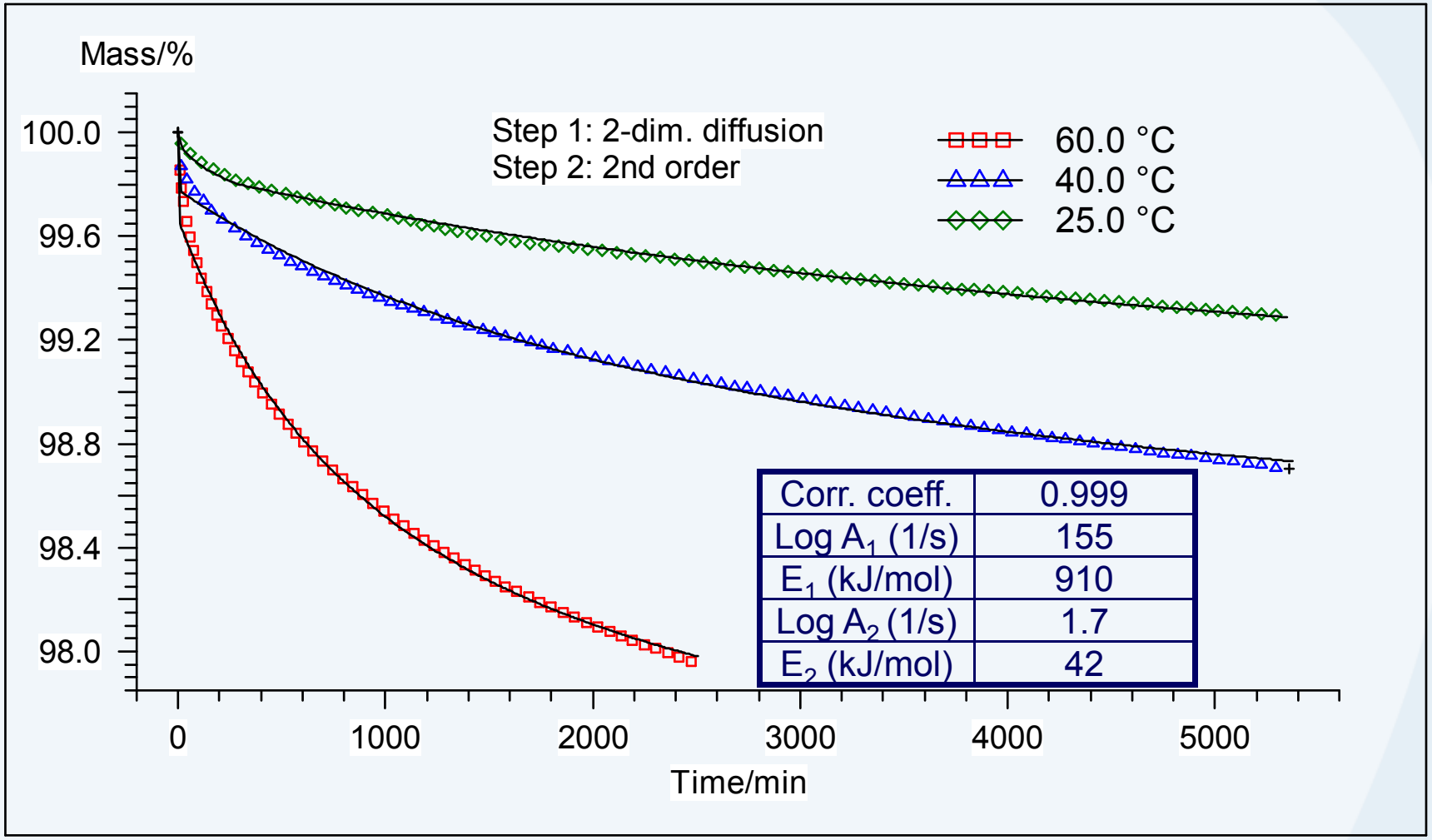
GVS Isotherms



GVS isotherms (25°C) for the interaction of water with micronized and non-micronized FormB.

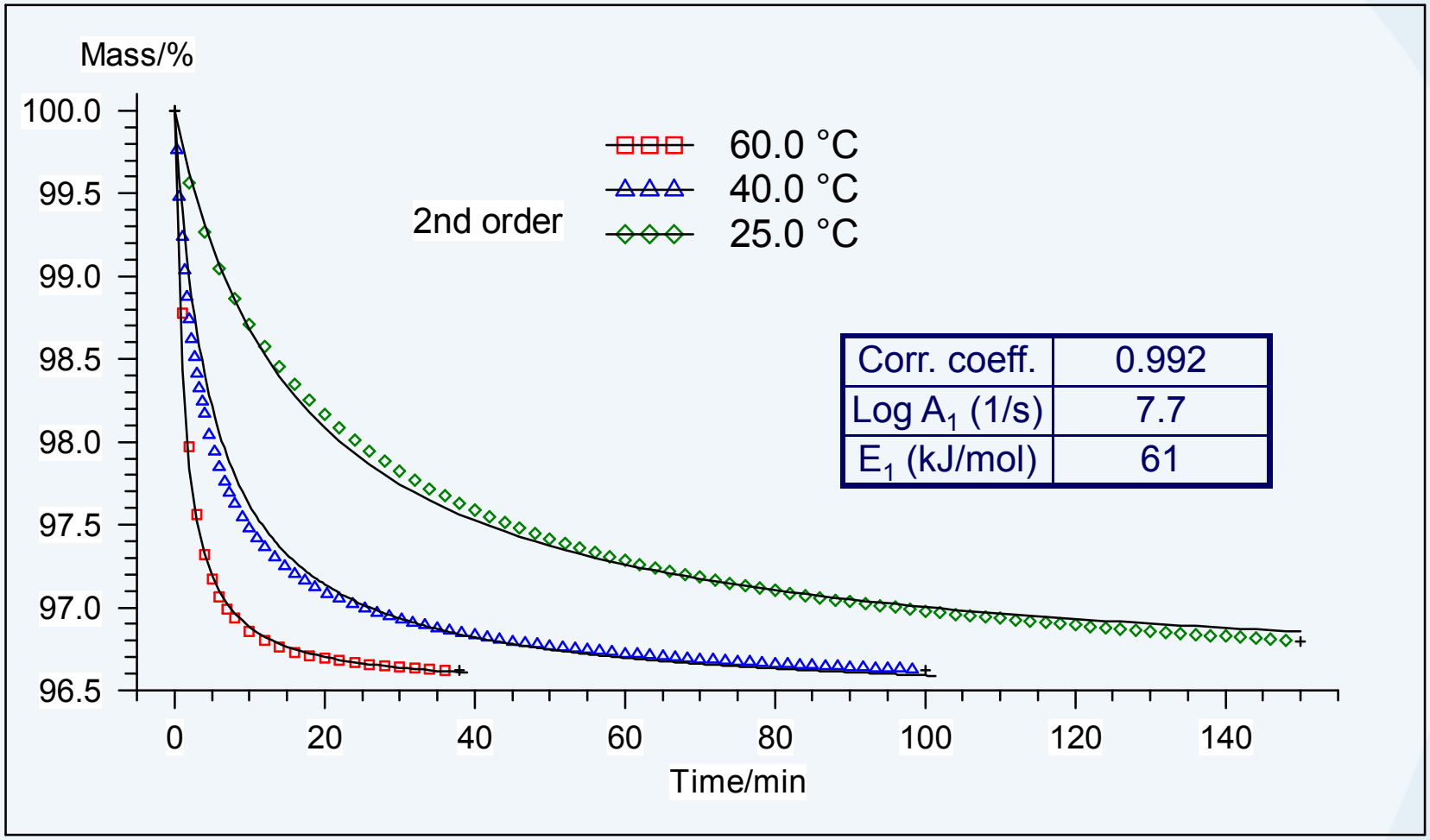
Kinetic Modeling – Non-micronized

NETZSCH Thermokinetics 241572 unmic dehydration by GVS



Kinetic Modeling – Micronized

NETZSCH Thermokinetics 241572 mic dehydration by GVS

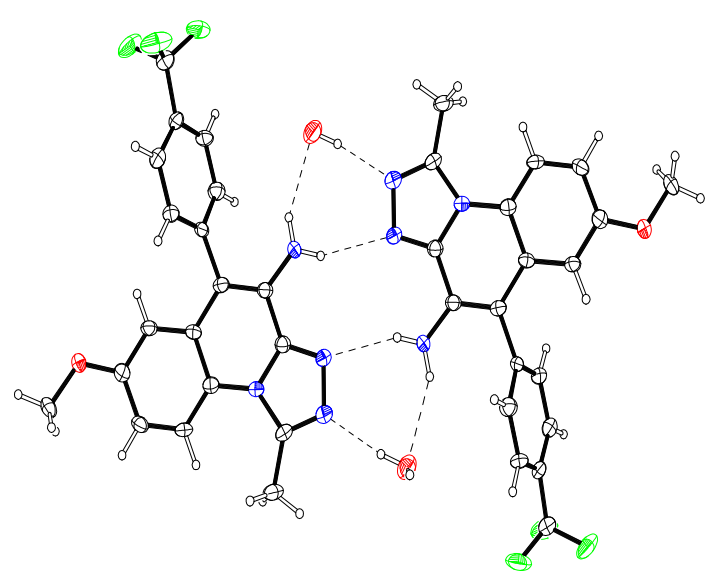


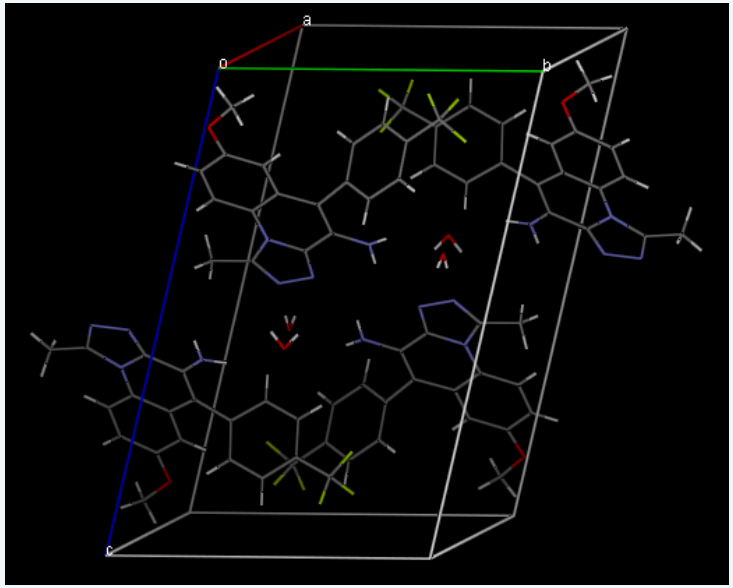
Summary so far….

- DSC, TGA, HSM, and GVS data showed distinct dehydration process between non-micronized and micronized materials.
- Kinetics modeling on dehydration showed
  - The non-micronized material exhibits a two-step dehydration process where a diffusion step is followed by a 2nd order step. The diffusion step is the rate limiting step based on that its dehydration activation energy is ~22 times higher than the 2nd step.
  - The micronized material follows a simple one-step process (2nd order)
- PXRD analysis will be discussed next to rationalize results.

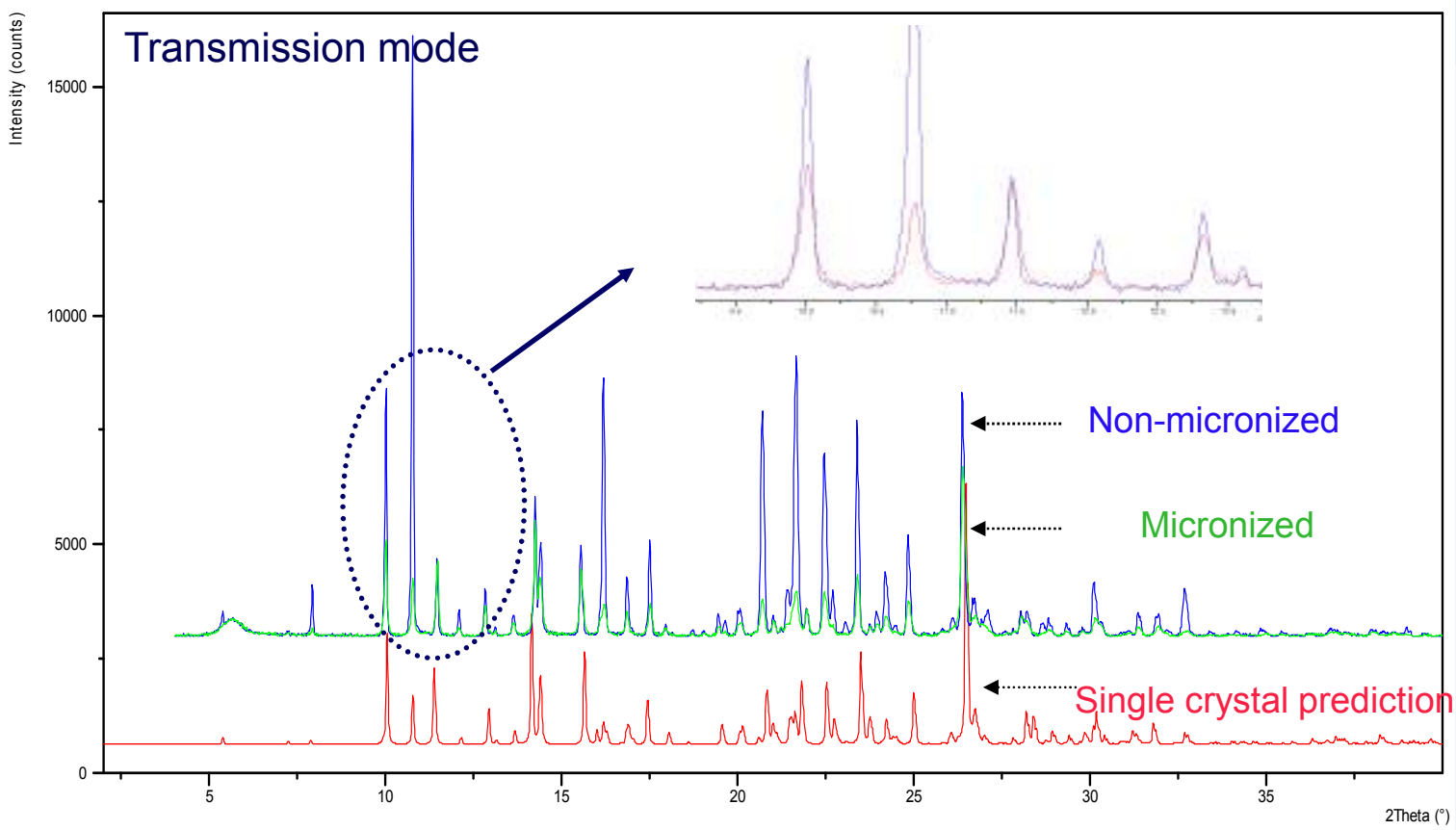
Crystallographic Data

Moiety formula	$C_{19}H_{15}F_3N_4O{\cdot}H_2O$	
Crystal system	Triclinic	
Temperature	150(2) K	
Space group	$P\bar{1}$	
Unit cell dimensions	a = 8.473(6) Å	α= 102.09(4)°
	b = 12.542(7) Å	β= 102.70(5)°
	c = 17.476(9) Å	γ = 94.86(8)°
Volume	1754.8(18) $Å^3$	
Z	4	
Density (calculated)	1.478 Mg/m^3	





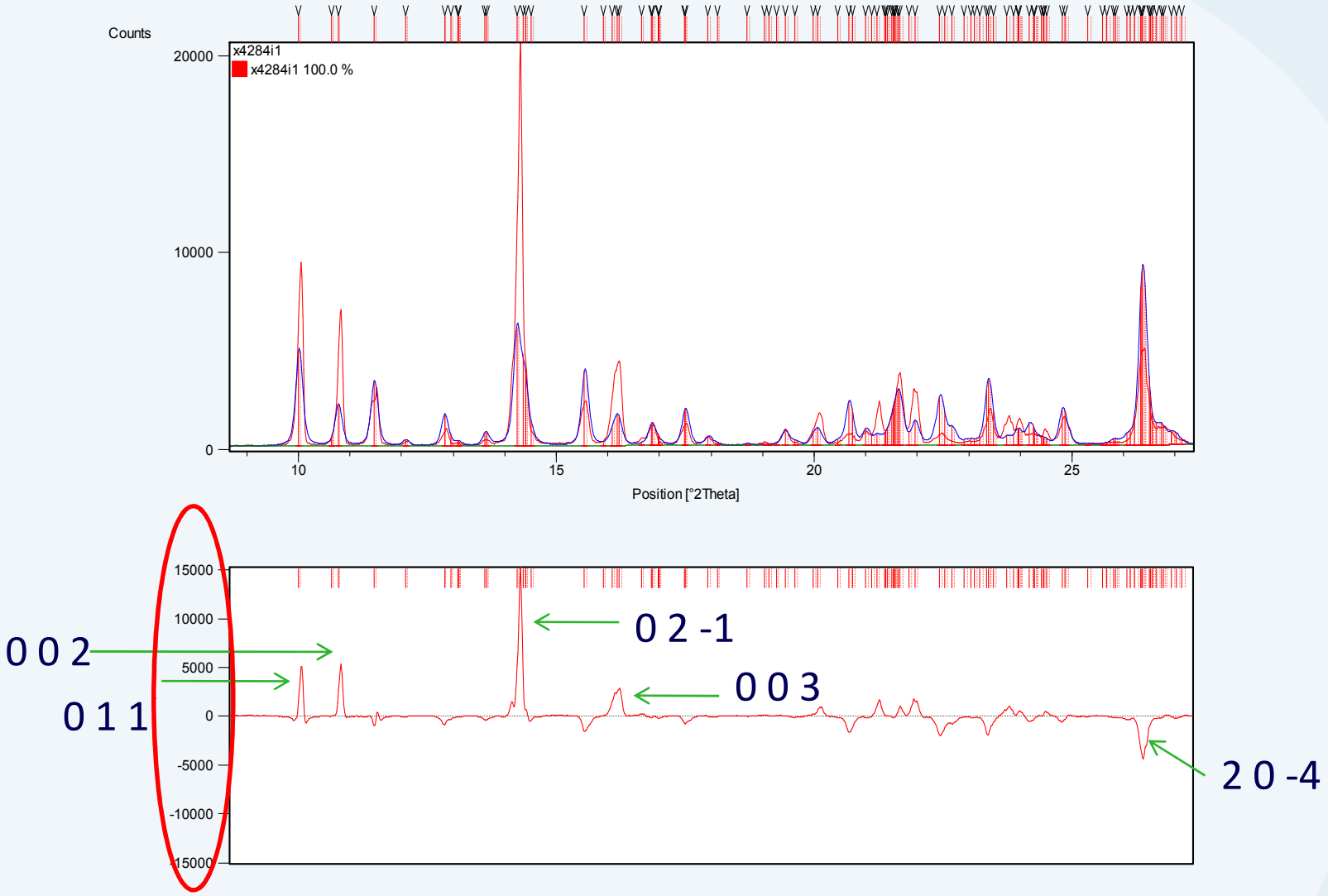
PXRD



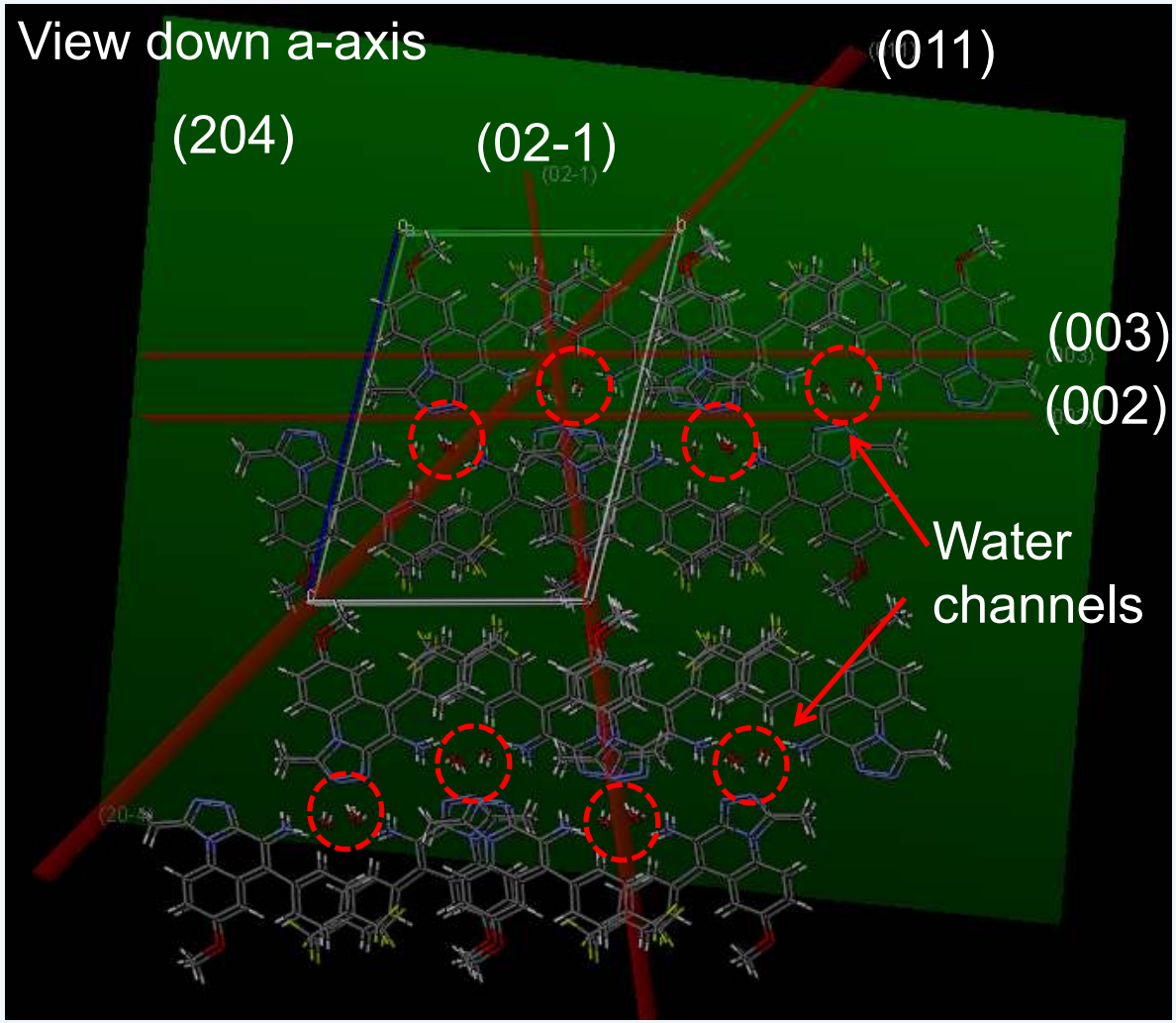
Line intensity change is due to preferred orientation

No baseline increase and peak broadening → no phase separated amorphous content or significant degradation of crystallite integrity

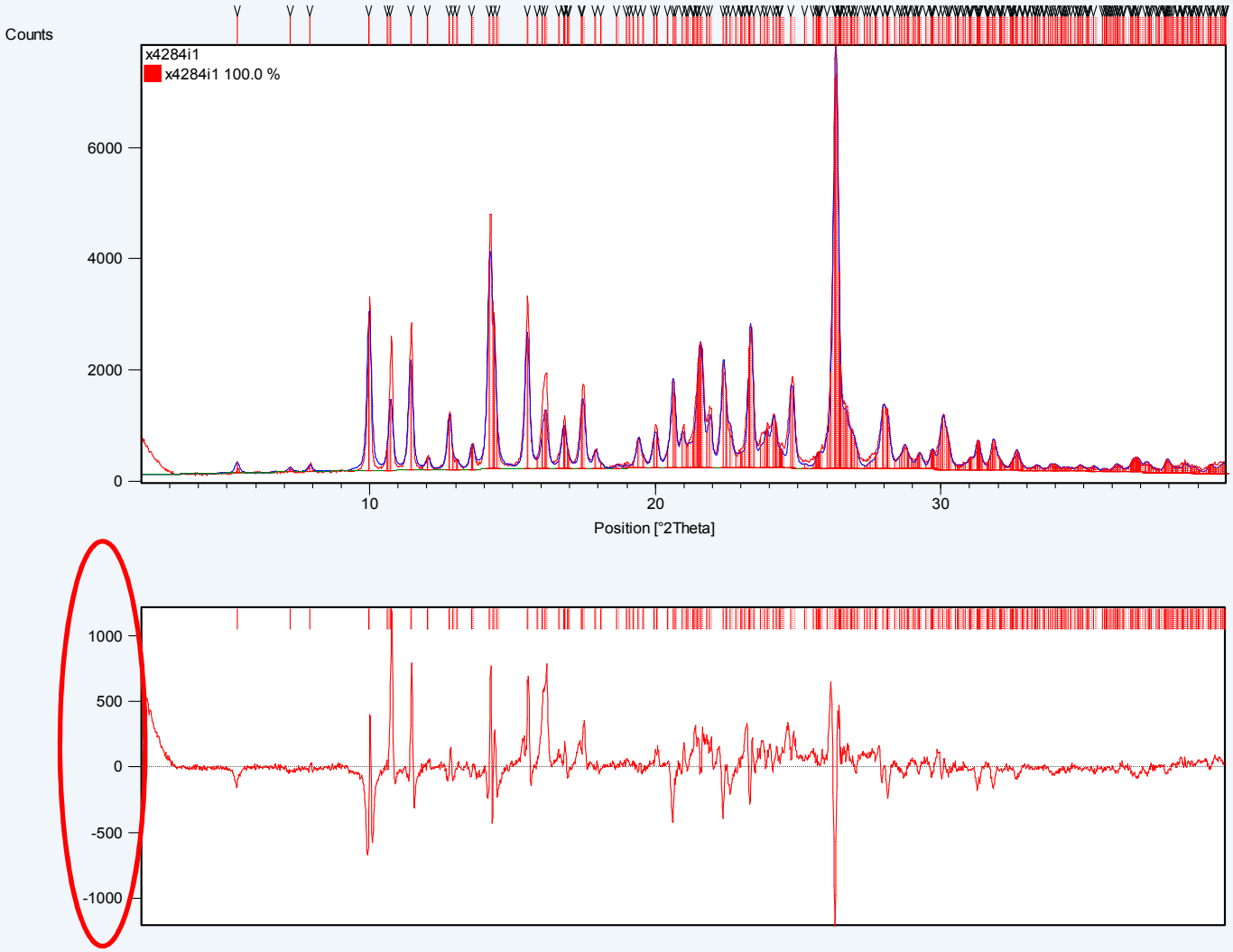
Reflection Analysis – Non-Micronized



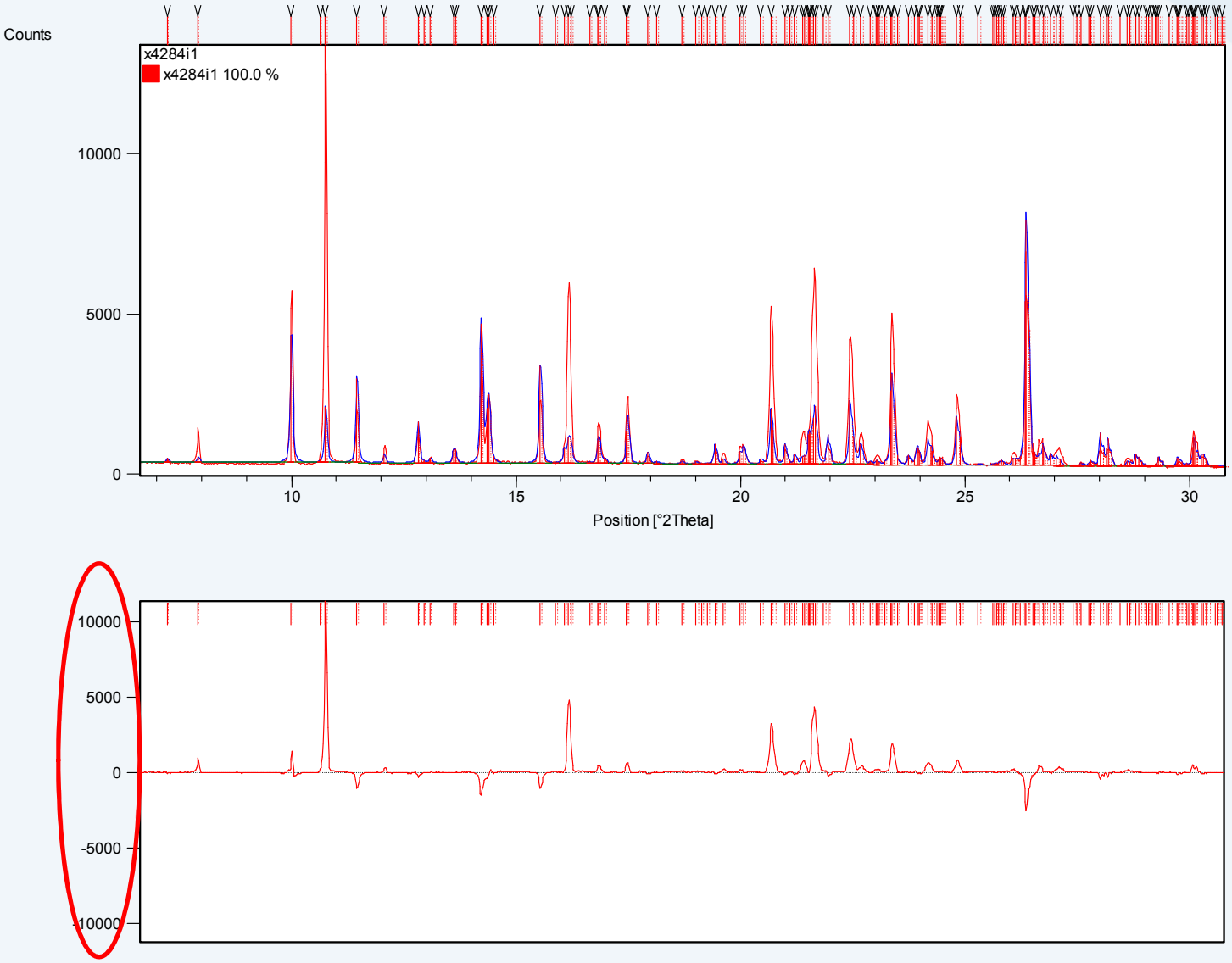
Reflection Analysis – Non-Micronized

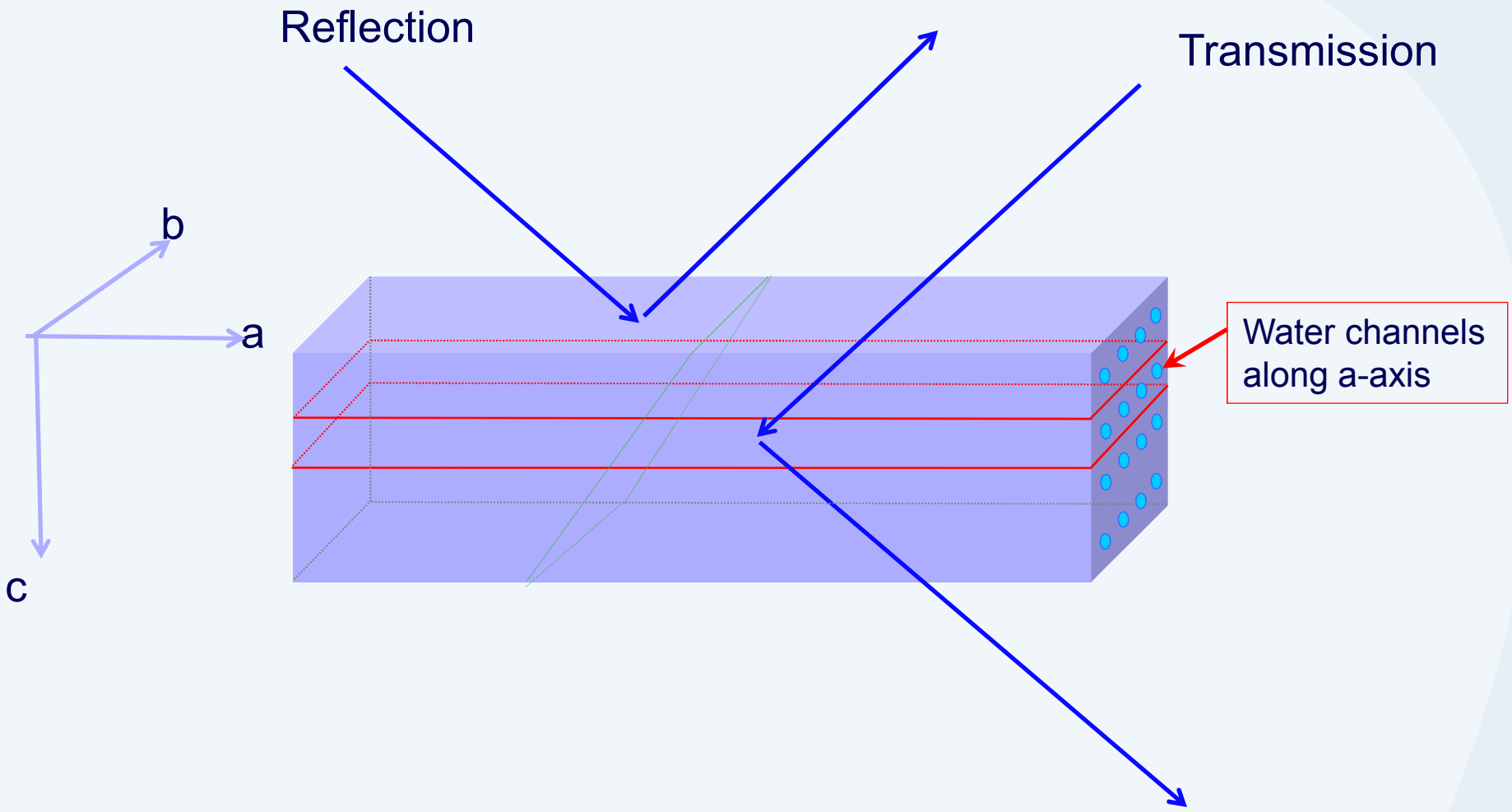


Reflection Analysis – Micronized



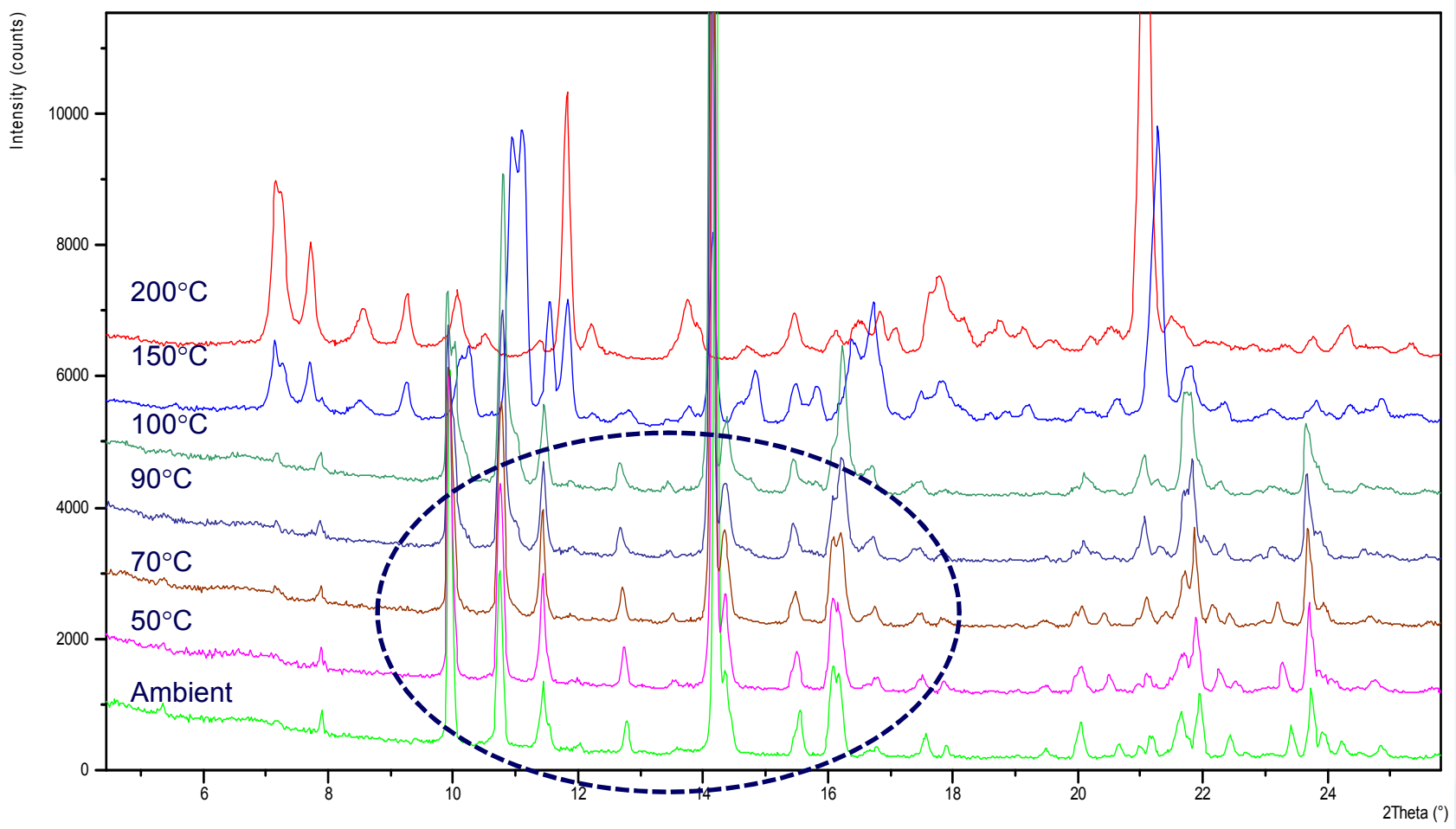
Transmission Analysis – Non-Micronized





Schematic drawing showing orientation of a non-micronized particle in x-ray sample holder

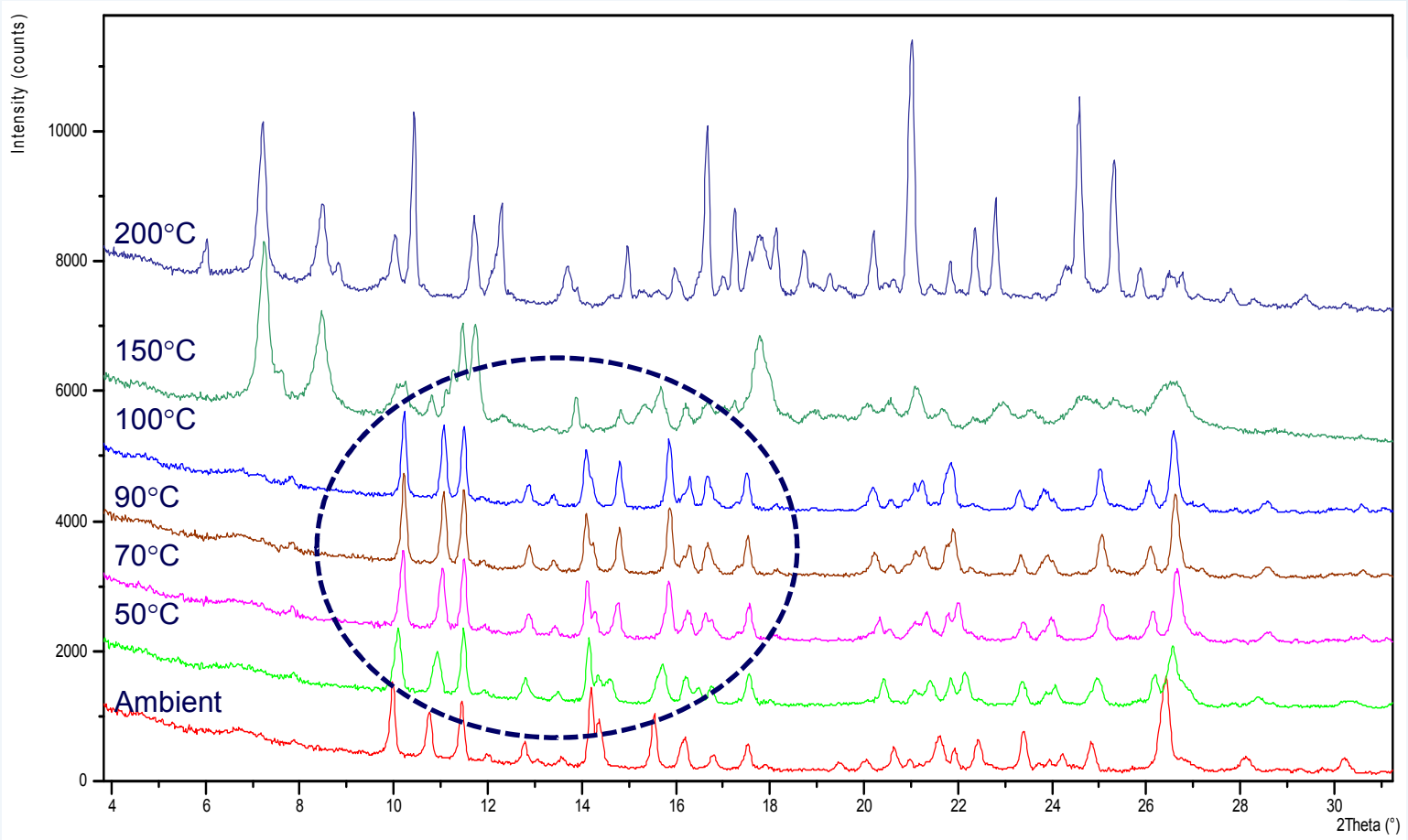
VT-PXRD – Non-Micronized



Form change observed at 150°C

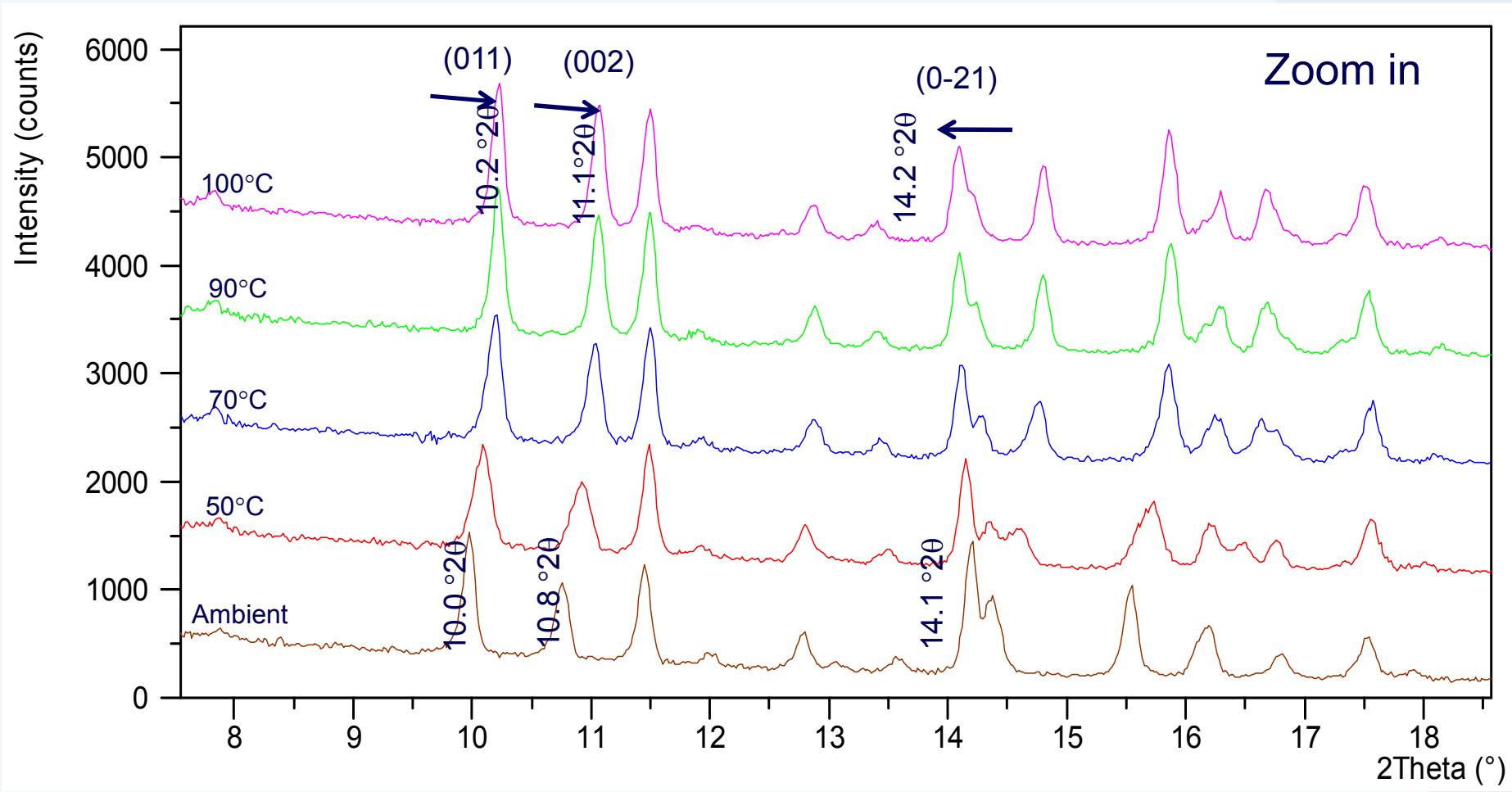
Line shifting (up to 100°C) less than 0.1 °2θ

VT-PXRD – Micronized



Form change observed at 150°C

VT-PXRD – Micronized



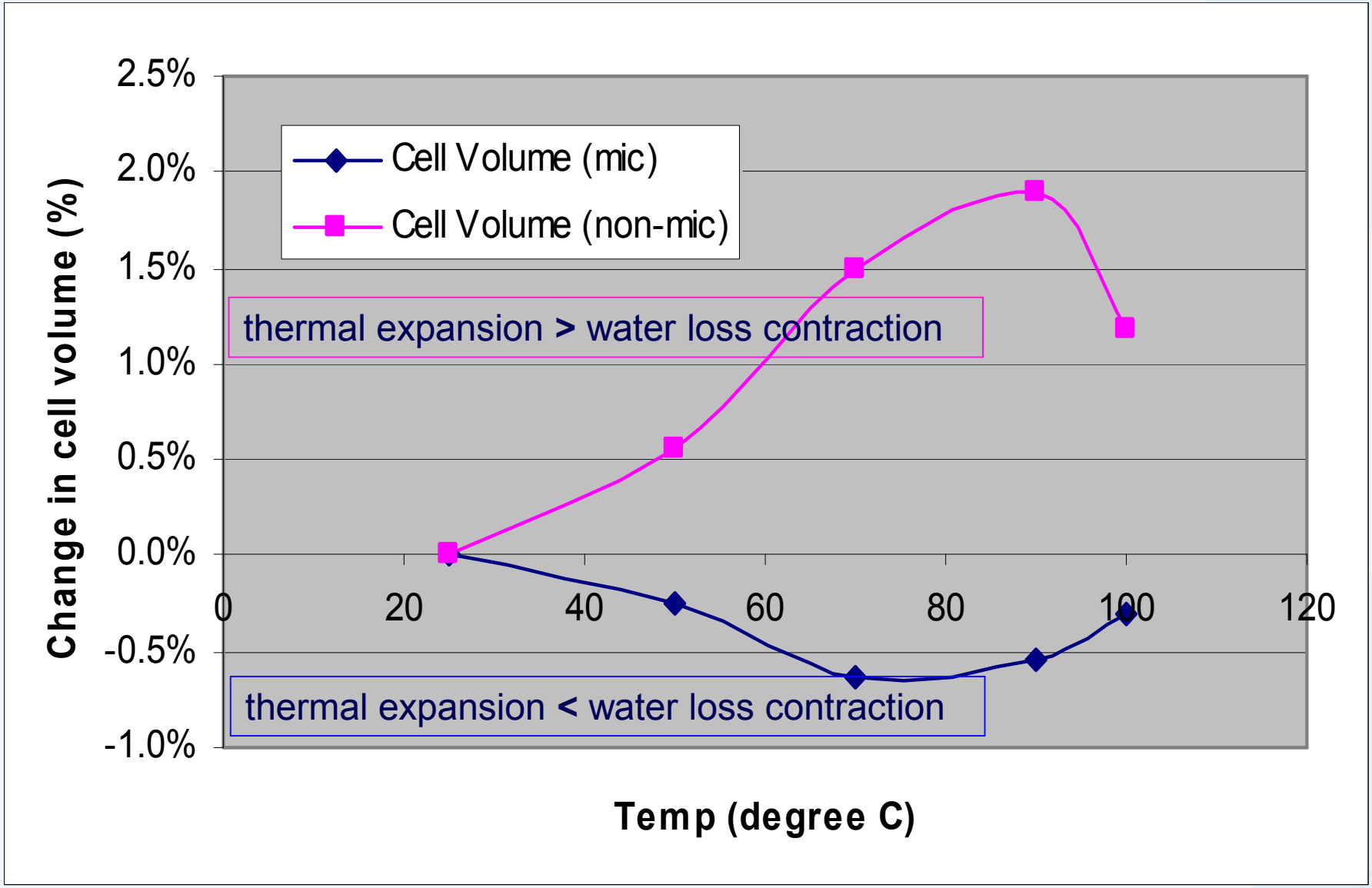
Line shifting 0.1-0.3 °2θ to both lower and higher d-spacing directions changes to the unit cell are anisotropic between the hydrated and dehydrated states

Crystal Lattice Change upon Thermal Dehydration

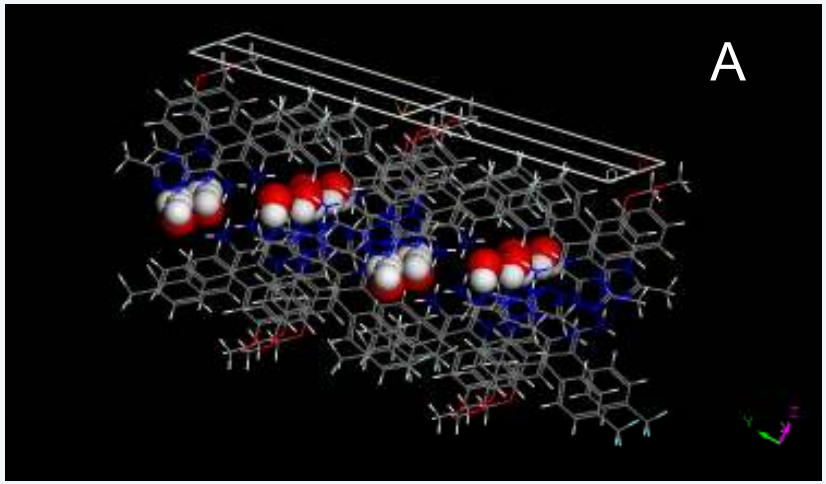
Rietveld Analysis (HighScore Plus)

	a / Å	b / Å	c / Å	α / °	β / °	γ / °	V / Å^3	V %change
mic INT	8.623	12.636	17.358	102.25	103.07	94.47	1785	0.00%
mic 50C	8.714	12.658	17.138	103.14	102.74	94.32	1780	-0.26%
mic 70C	8.750	12.667	17.036	103.98	102.72	93.74	1773	-0.63%
mic 90C	8.781	12.678	17.004	104.25	102.87	93.52	1775	-0.54%
mic 100C	8.798	12.685	17.006	104.28	102.92	93.5	1779	-0.31%
non-mic INT	8.508	12.658	17.346	101.93	102.46	95.34	1766	0.00%
non-mic 50C	8.552	12.745	17.281	101.84	101.62	96.95	1776	0.57%
non-mic 70C	8.589	12.817	17.256	102.00	101.44	97.37	1793	1.50%
non-mic 90C	8.630	12.833	17.222	102.11	101.55	97.14	1800	1.90%
non-mic 100C	8.583	12.838	17.207	102.09	101.68	97.30	1787	1.19%

Change in Cell Volume upon Thermal Dehydration

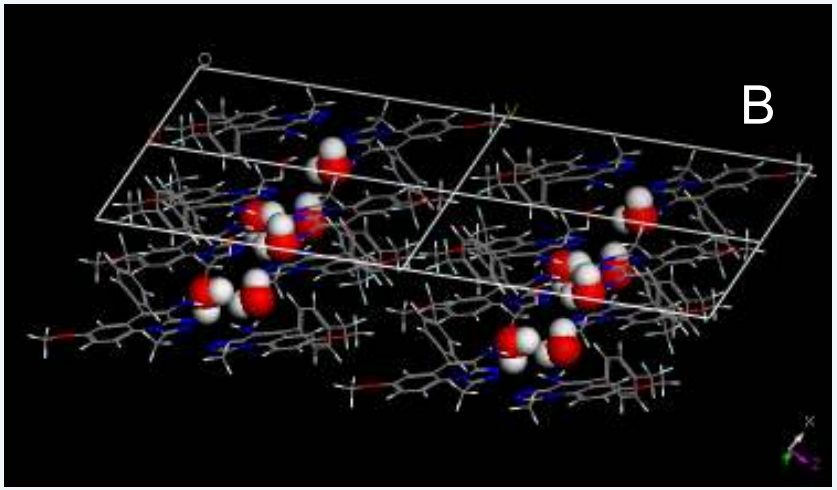


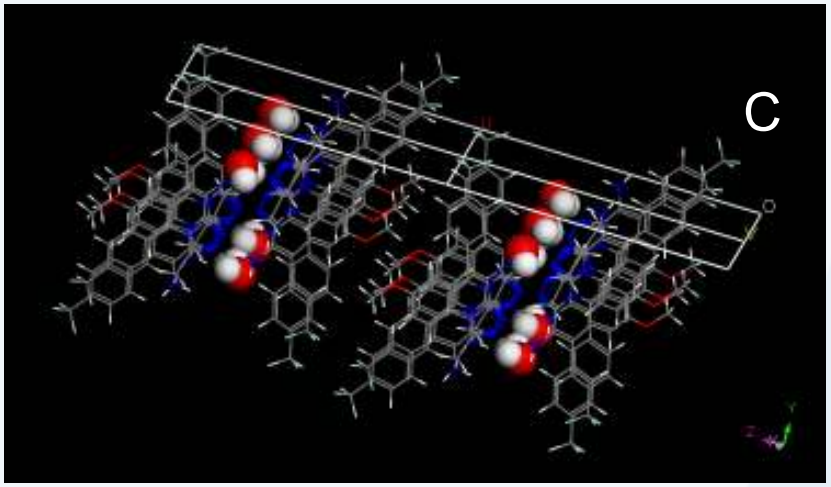
Slip Planes



A. (0 0 1) face (E_{att} = -28.3 kcal/mol), showing lack of egress channels for water

B. (0 1 0) face (E_{att} = -75.4 kcal/mol),
C. (1 0 -1) face (E_{att} = -77.6 kcal/mol), both showing egress channels for water





Calculated using the COMPASS forcefield

Conclusions

- The drastic change in dehydration behavior of the hydrate after micronization is mainly due to
  - Breakage of water channels through longest dimension (a-axis) →shorten water travel length
  - Cleavage of several crystal faces that have low attachment energy → create more channels for water to escape

- PXRD analyses provide insight into the change of dehydration behavior.

Acknowledgements

- Glenn Williams
- Fred Vogt
- Rachel Forcino
- Jeff Brum
- Roy Copley