XRPD Line Broadening Analyses to Study Micronization Induced Disorder and Environmental Annealing

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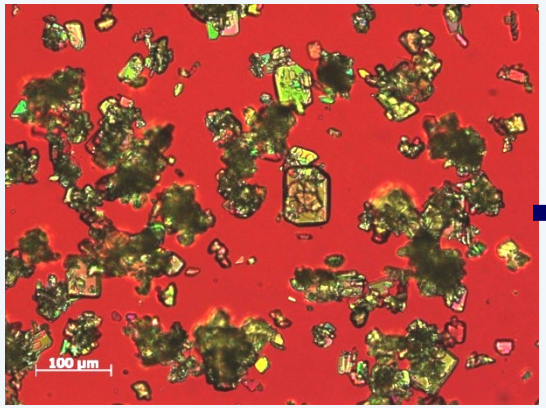
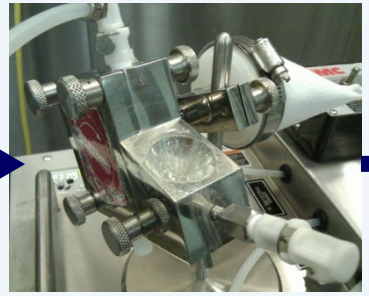
GlaxoSmithKline

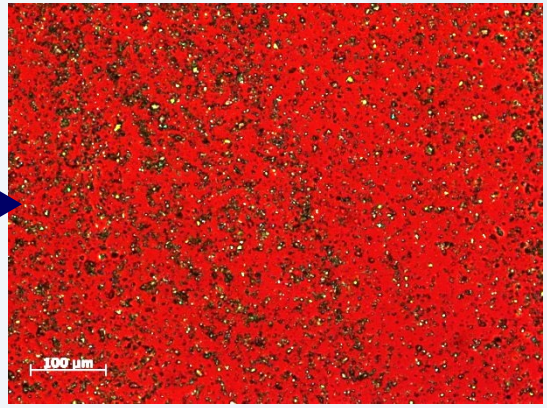
Why Study Micronization Induced Disorder?



Non-Micronized



Milling

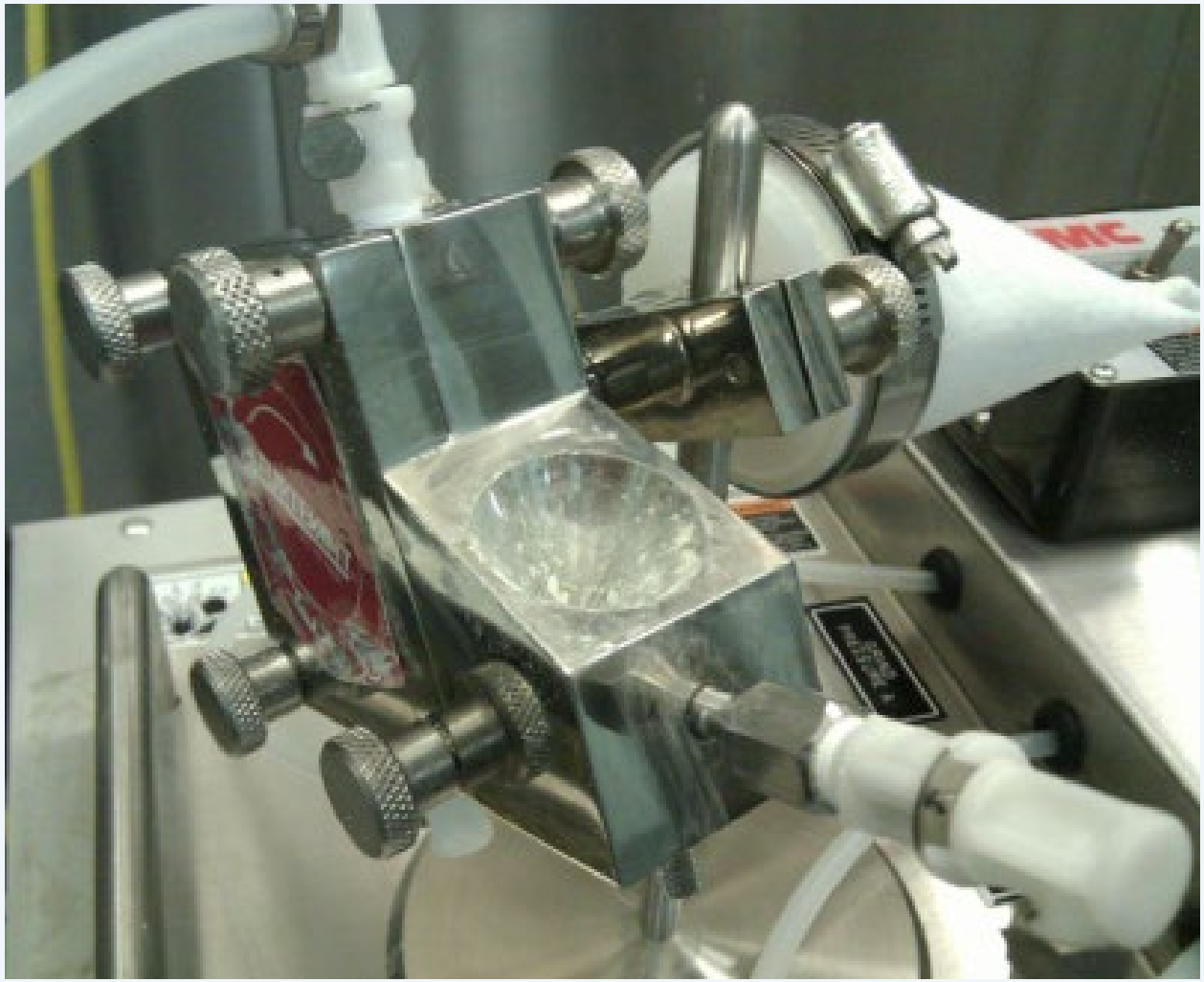


Micronized

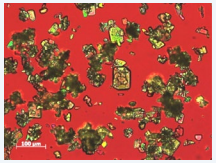
Process of micronization results in significant attrition with consistent micron size particles, but the high energy process may also induce an element of "disorder" in the material.

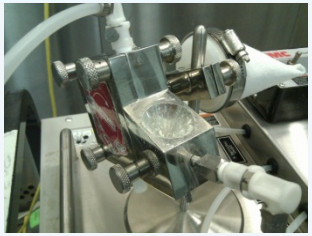
While this process **improves dissolution and particle uniformity** of the API the resulting "disorder" may affect stability and physicochemical properties, ultimately with a potential *effect on dissolution and particle uniformity??*

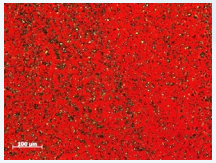
Micronization Mill

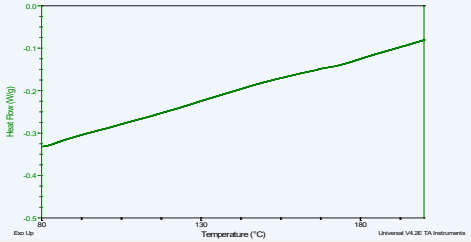


Changes in Physical Properties



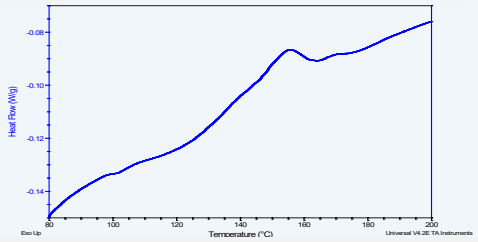


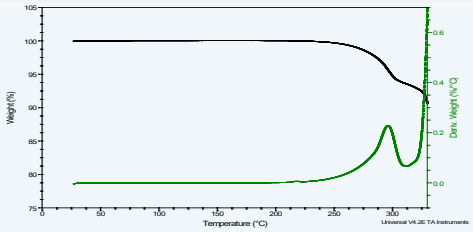




Surface Area

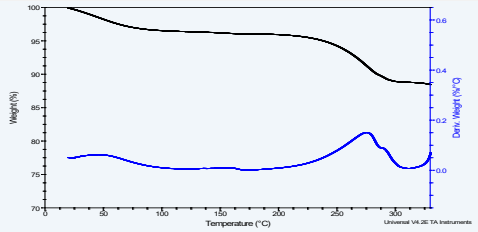
Surface Energy

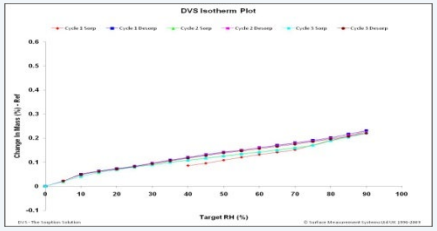




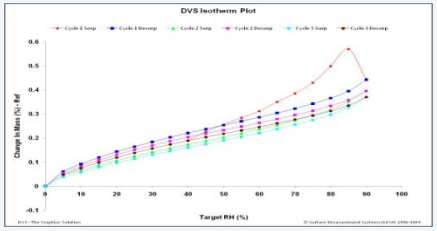
Crystallinity
XRPD

Thermal
DSC, TGA





Moisture Sorp.
GVS



Are we investigating all the possible changes that may occur and the impact of those changes on the final formulation/processing and product?

“Disorder”?


Amorphous


FRACTURED


Defective


Disordered

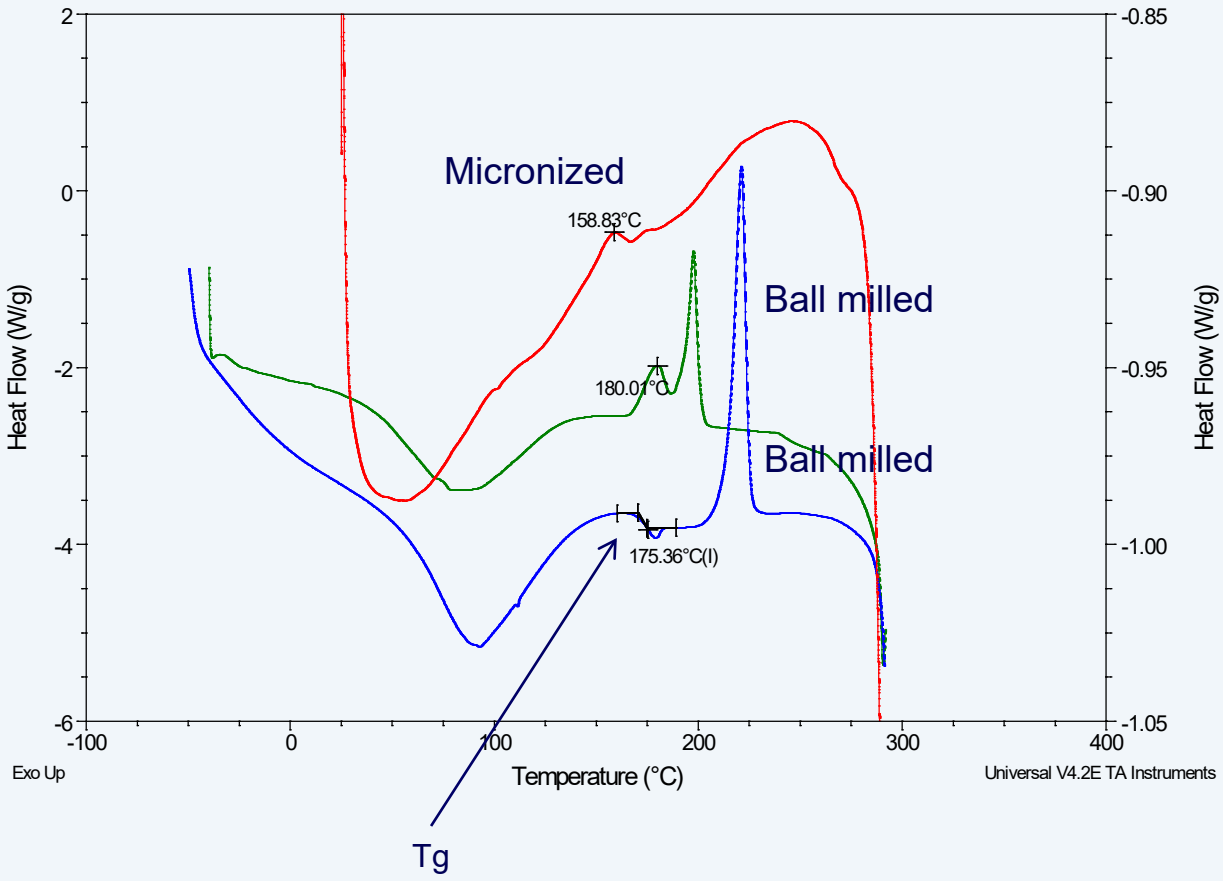

Non-
crystalline

Crystal “healing” or environmental “annealing” is often observed in aged/environmentally exposed materials

Aging - API “hold times”

Determination of the true contributions/components of disorder is necessary to understand and predict the effects on physicochemical properties and pharmaceutical processing

Thermal Analysis Comparison of Milled API



Tg of amorphous standard higher than exotherm in micronized API

Surface vs Bulk Amorphous

Wu, T.; Sun, Y.; Li, N.; de Villiers, M.; Yu, L. *Langmuir 2007, 23, 5148*

Lei Zhu & Janan Jona & Karthik Nagapudi & Tian Wu Pharm Res (2010) 27:1558–1567

Sayantan Chattoraj, Chandan Bhugra, Chitra Telang, Li Zhong and Zeren Wang, Changquan Calvin Sun. Pharm Res, 2012, Volume 29, Number 4, Pages 1020-1032

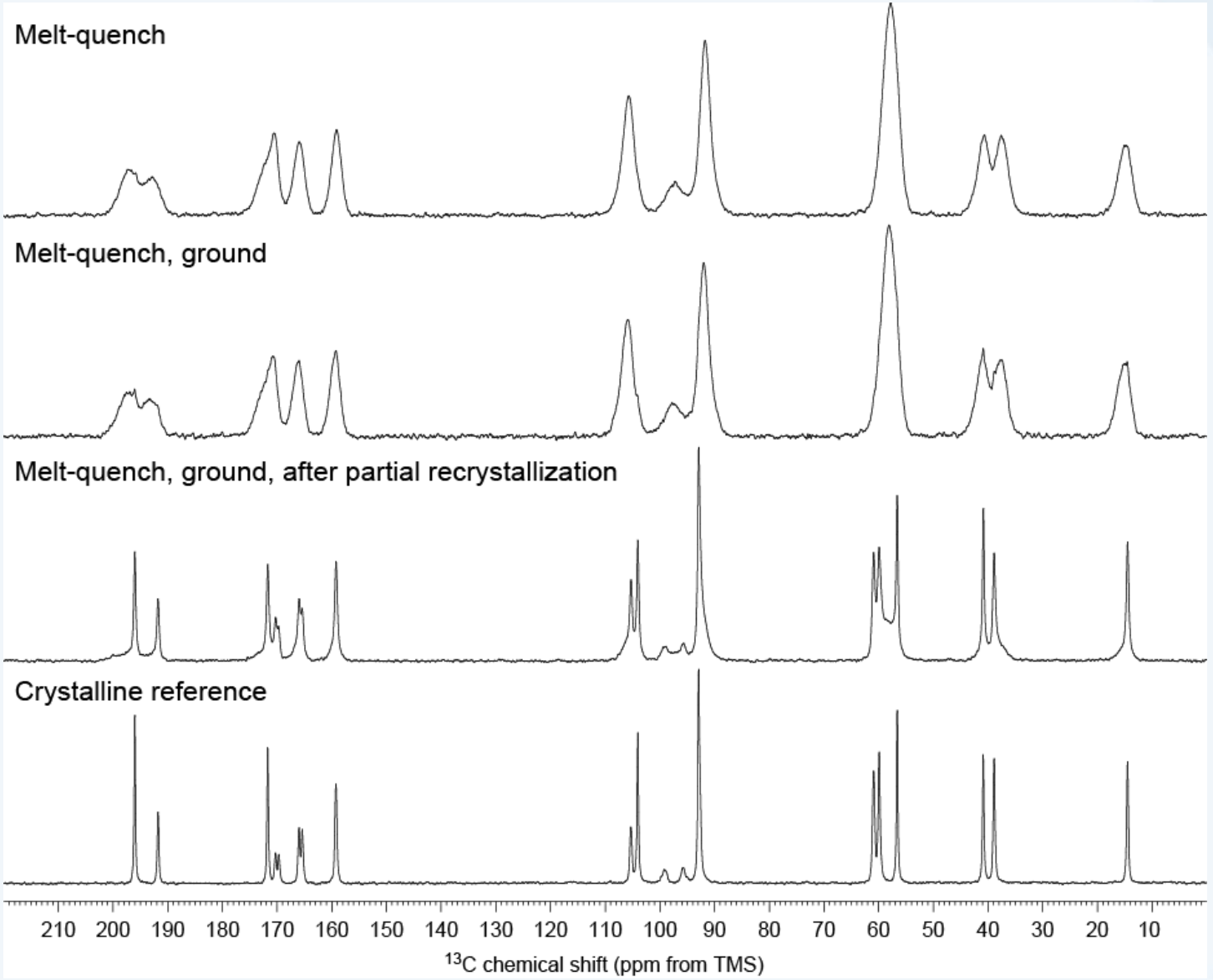
Amorphous griseofulvin ^{13}C T_1 and $T_{1\rho}$ measurements

	^{13}C T_1	^{13}C $T_{1\rho}$
Melt-quench (initial)	1.60 ± 0.12 s	78 ± 13 ms
Melt-quench (ground)	0.74 ± 0.18 s	45 ± 13 ms

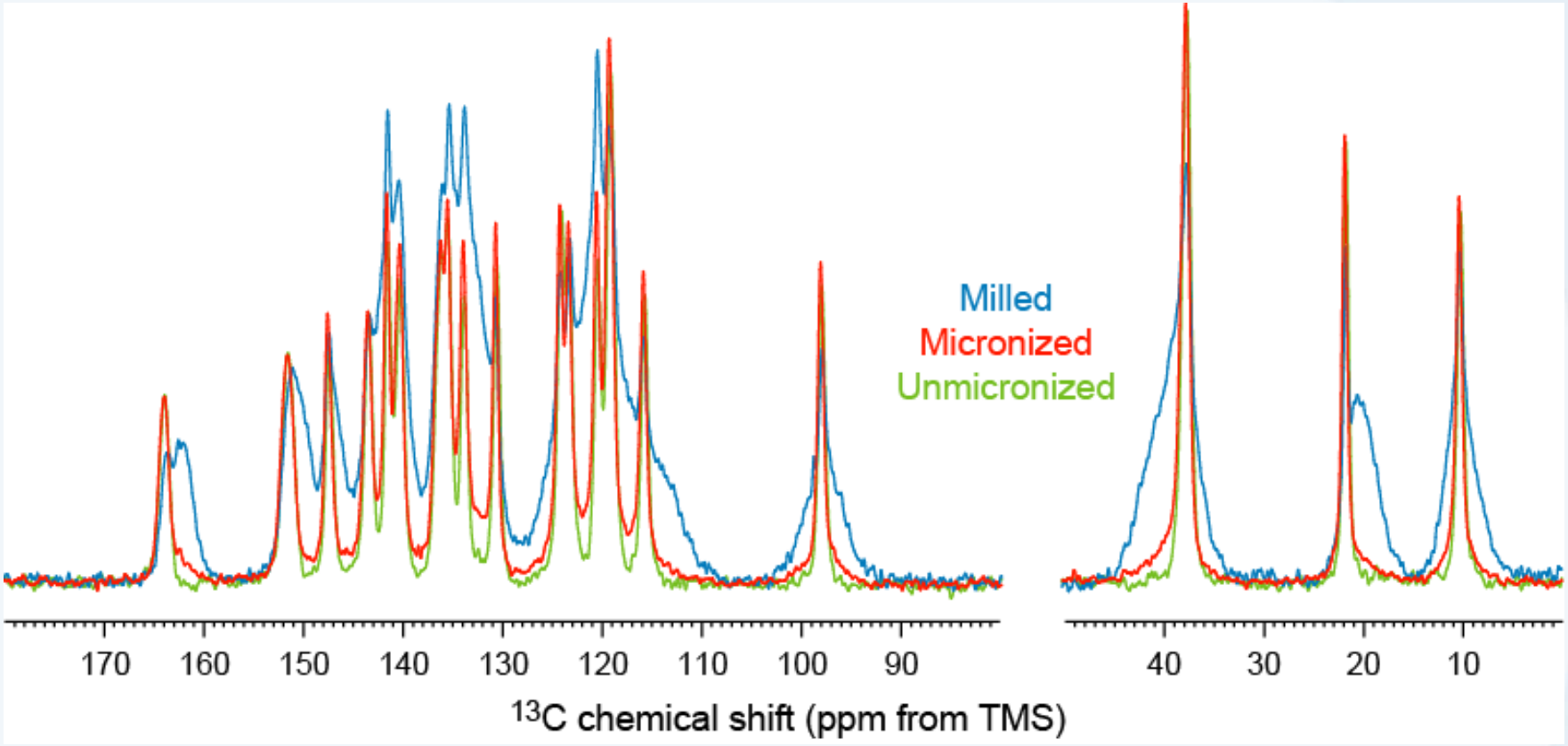
Lower ^{13}C $T_{1\rho}$ and T_1 values are consistent with higher molecular mobility in the ground sample

Variable temperature measurements were not performed because of “ground” sample instability – recrystallization occurs rapidly under MAS spinning conditions

Griseofulvin ^{13}C CP-TOSS spectra

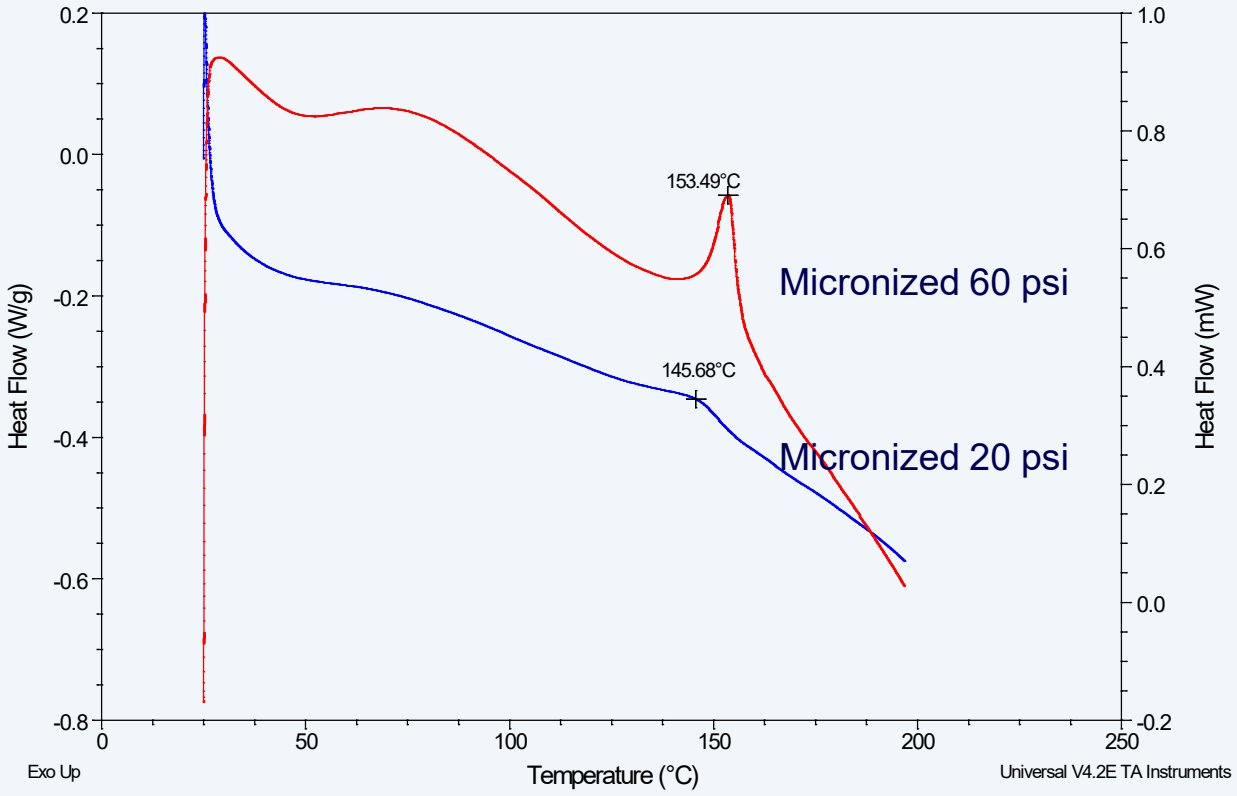


^{13}C CP-TOSS spectra



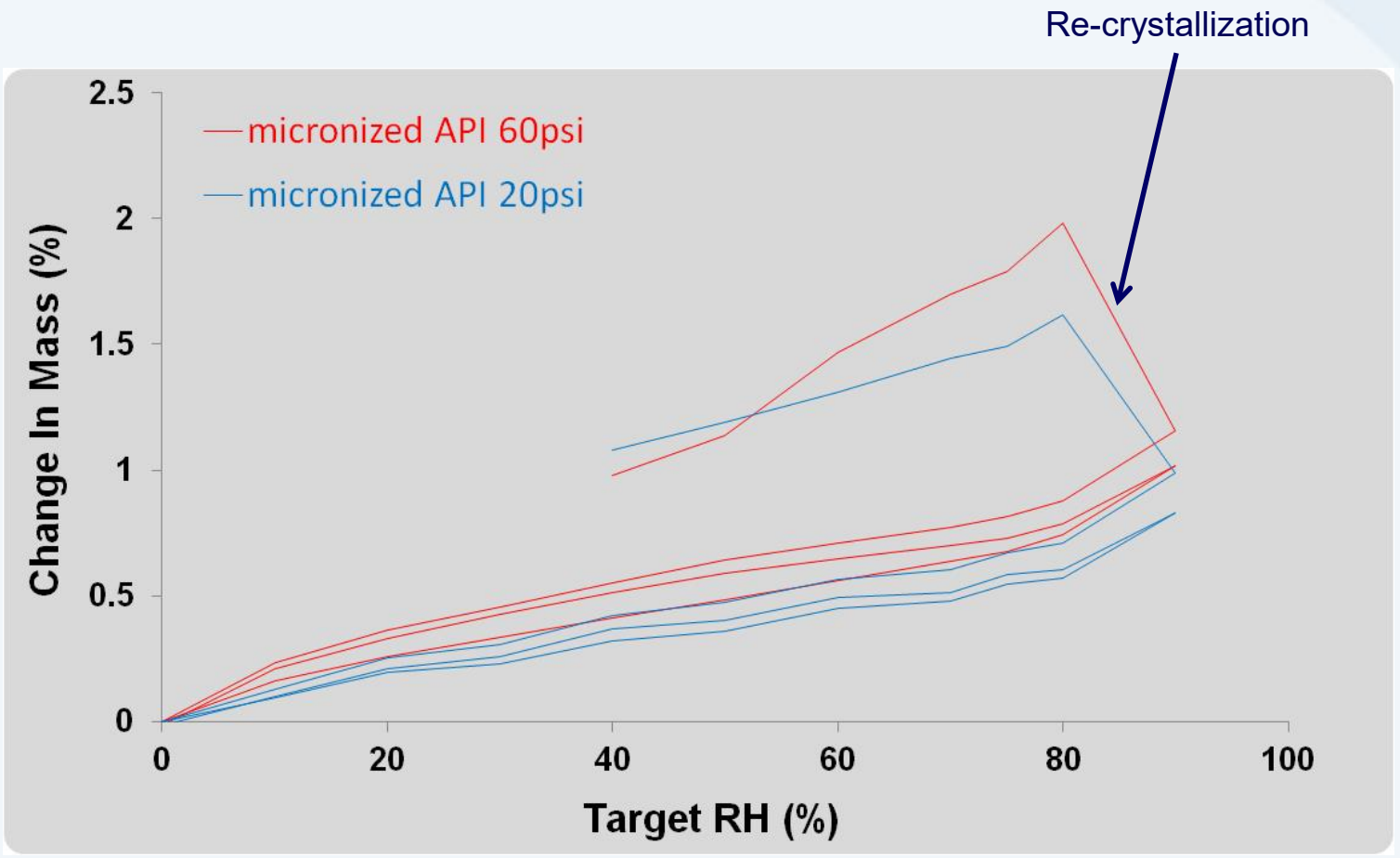
Micronized API(red trace) shows the signature of amorphous material

Thermal Analysis Comparison of API with Varied Micronization Energy

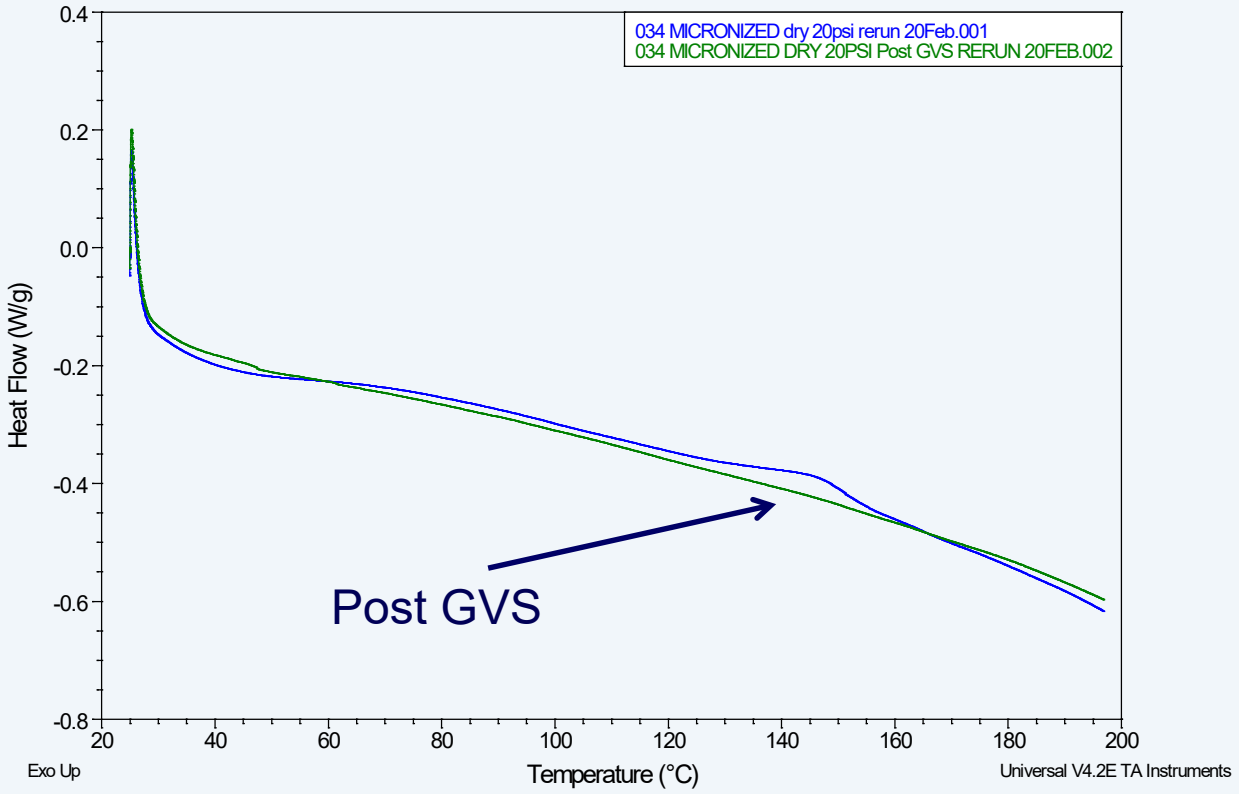


Amorphous component (exotherm) increases with increased micronization energies

Gravimetric Vapor Sorption



Post Gravimetric Vapor Sorption



After one GVS cycle the re-crystallization event is gone – consistent with amorphous recrystallization

Separating Components of Disorder

Amorphous

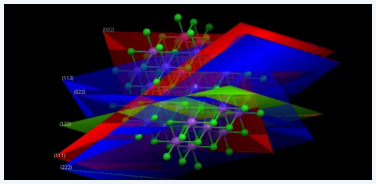
Thermal analysis
GVS-recrystallization
SS-NMR

Nano-crystalline content

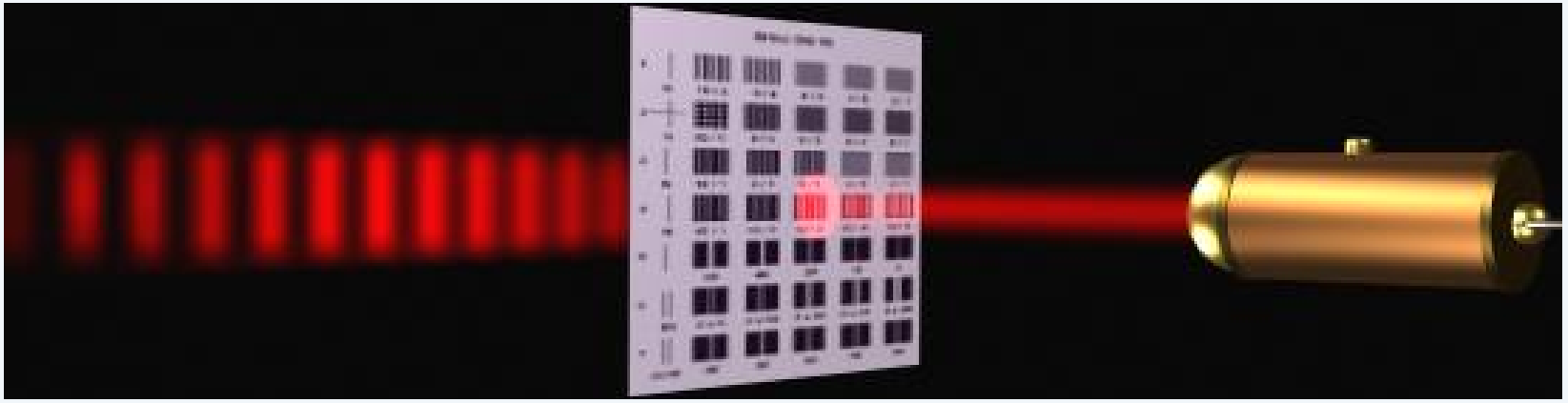
XRPD – line broadening
GVS/porosity
Surface area

Why XRPD Line Broadening?

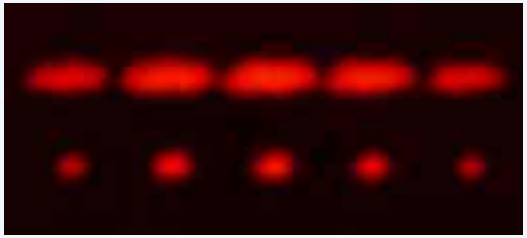
Why study micronized materials by XRPD?



Crystal is essentially a 3D *molecular* diffraction grating



http://physics-animations.com/Physics/English/DG10/

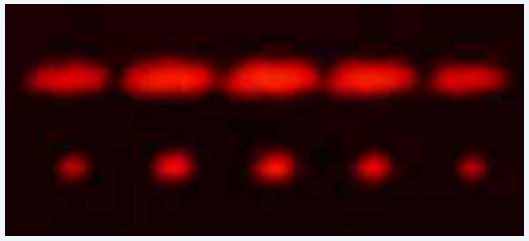


The Scherrer Equation

$$B(2\theta) = \frac{K\lambda}{L\cos\theta}$$

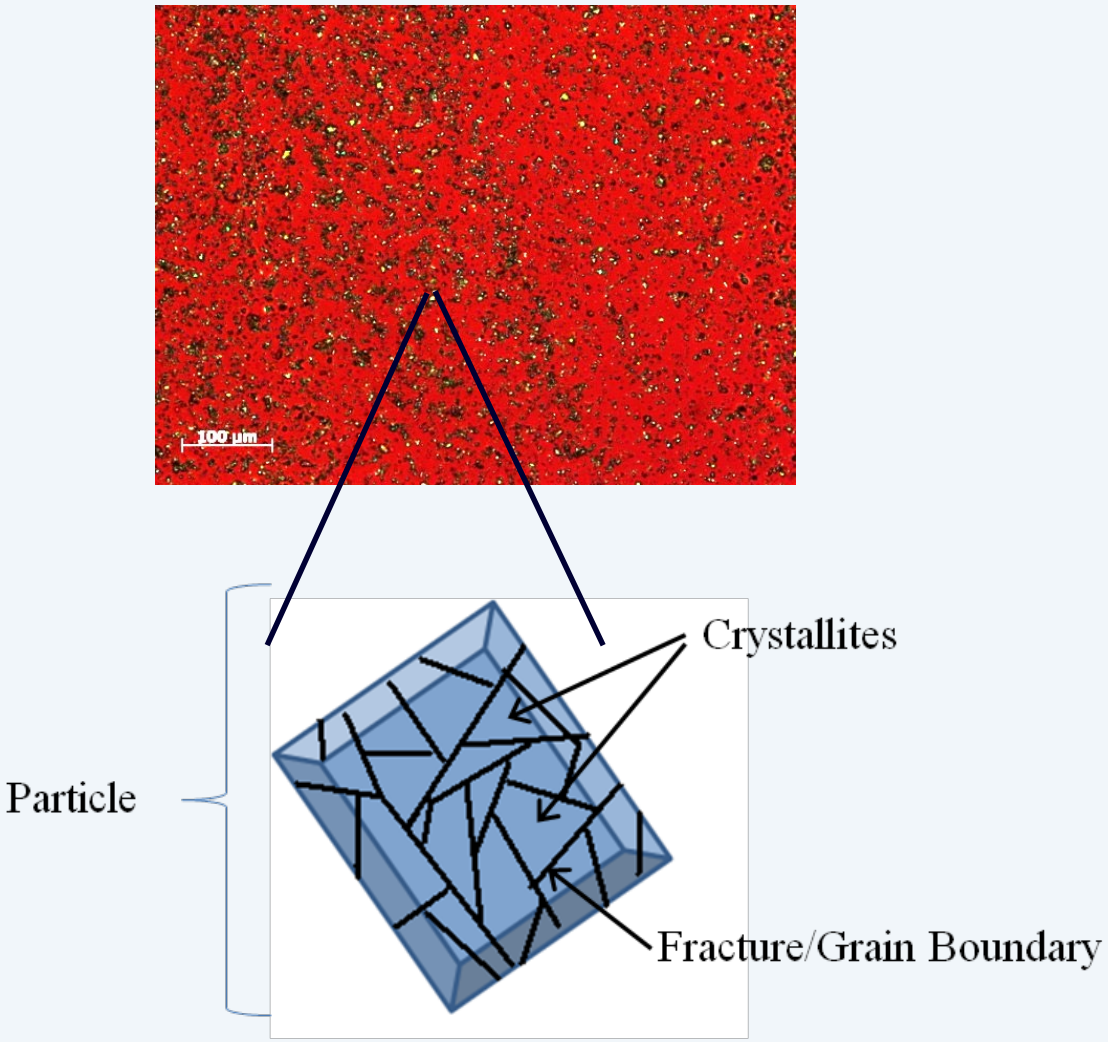
Peak width (B) is inversely proportional to the crystallite size (L)

Short Range vs. Long Range Order

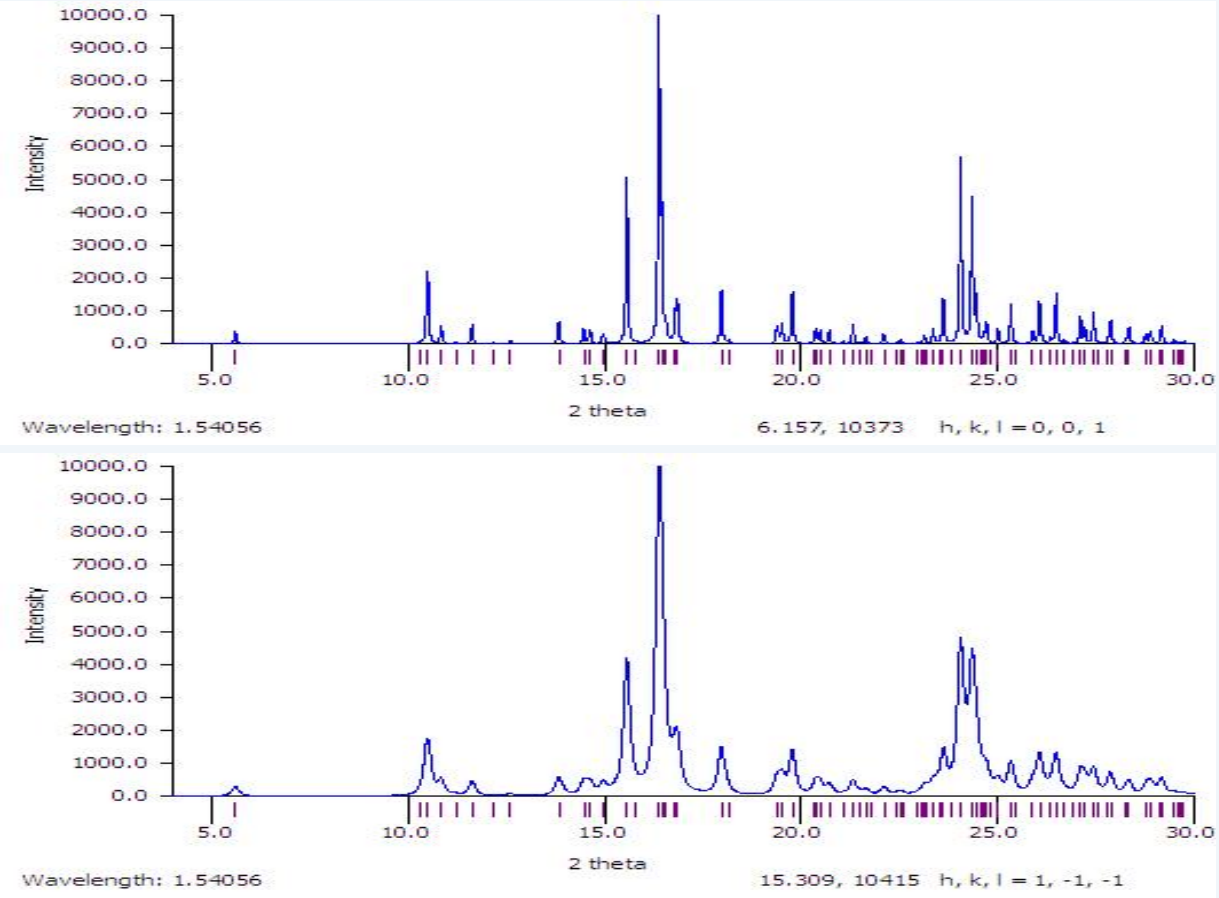


P. Scherrer, “Bestimmung der Grösse und der inneren Struktur von Kolloidteilchen mittels Röntgenstrahlen,” *Nachr. Ges. Wiss. Göttingen* **26** (1918) pp 98-100.

XRPD – Particle vs. Crystallite



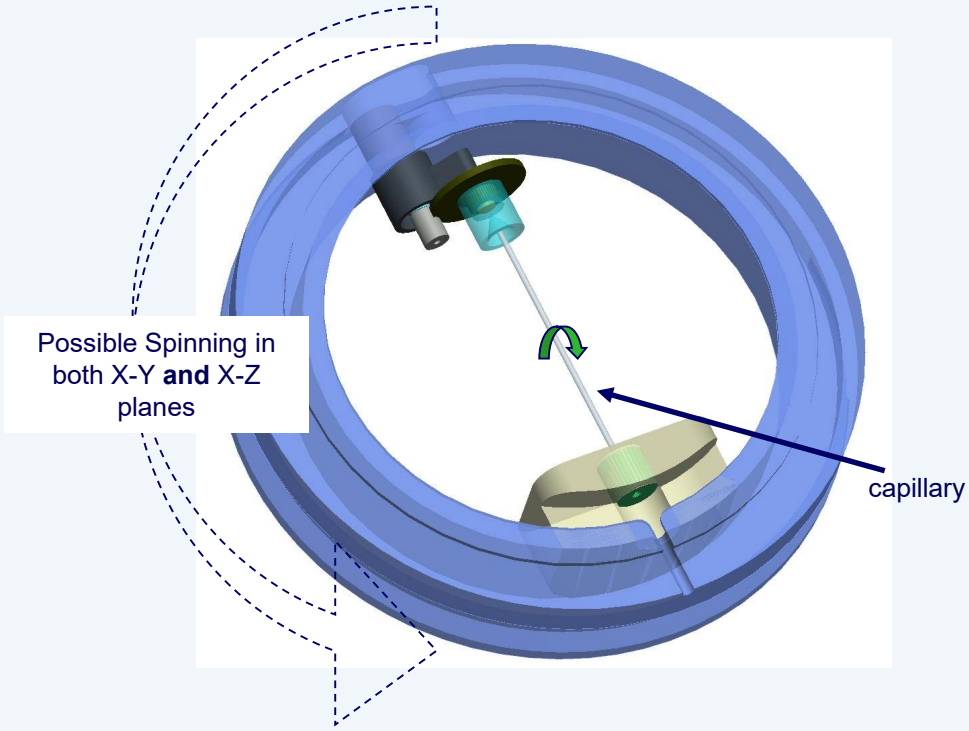
XRPD – Instrumental Factors

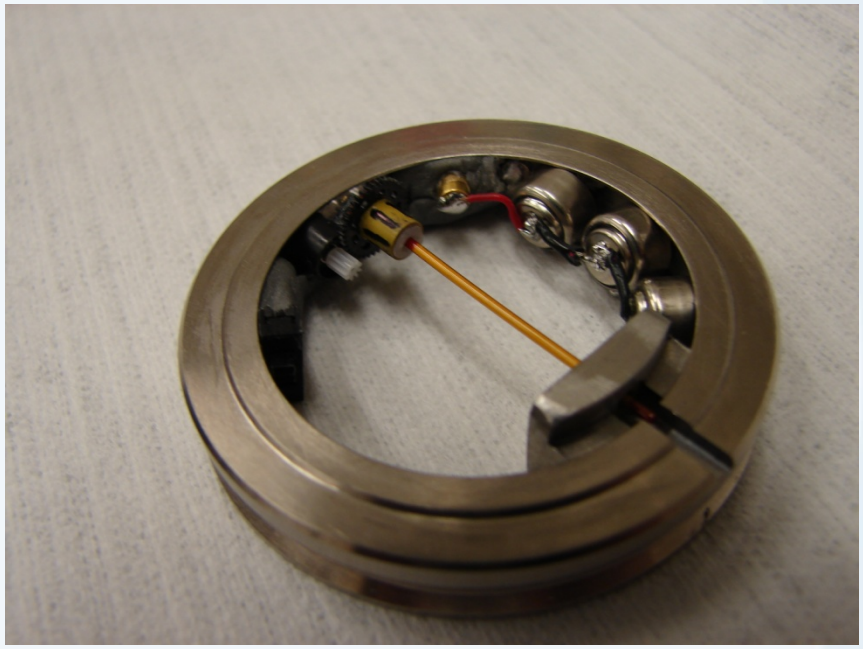


Same sample – Different instrument settings
Need quality and consistent data collection

XRPD – Sample Analysis

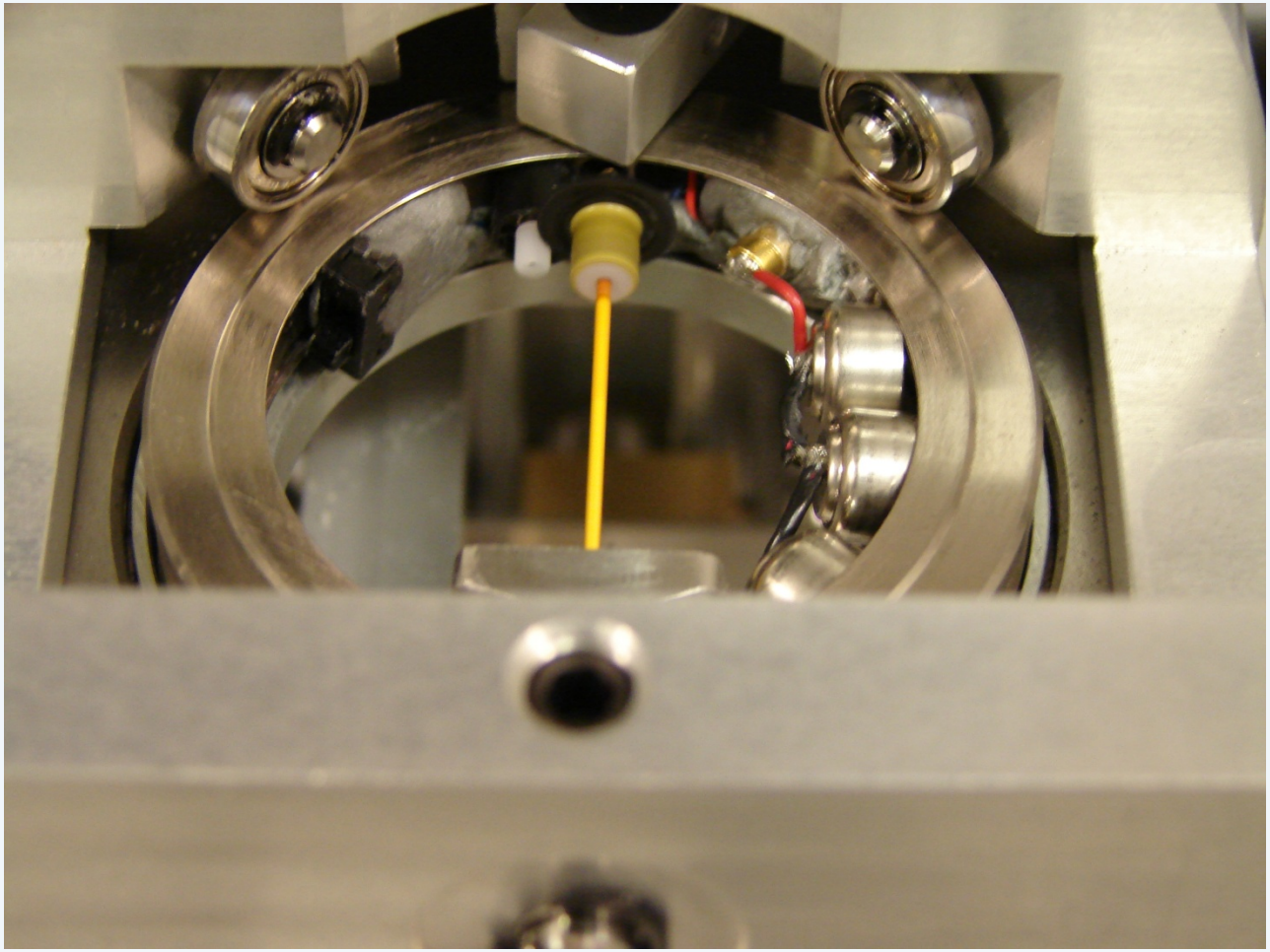
Convenient Capillary Analysis Setup



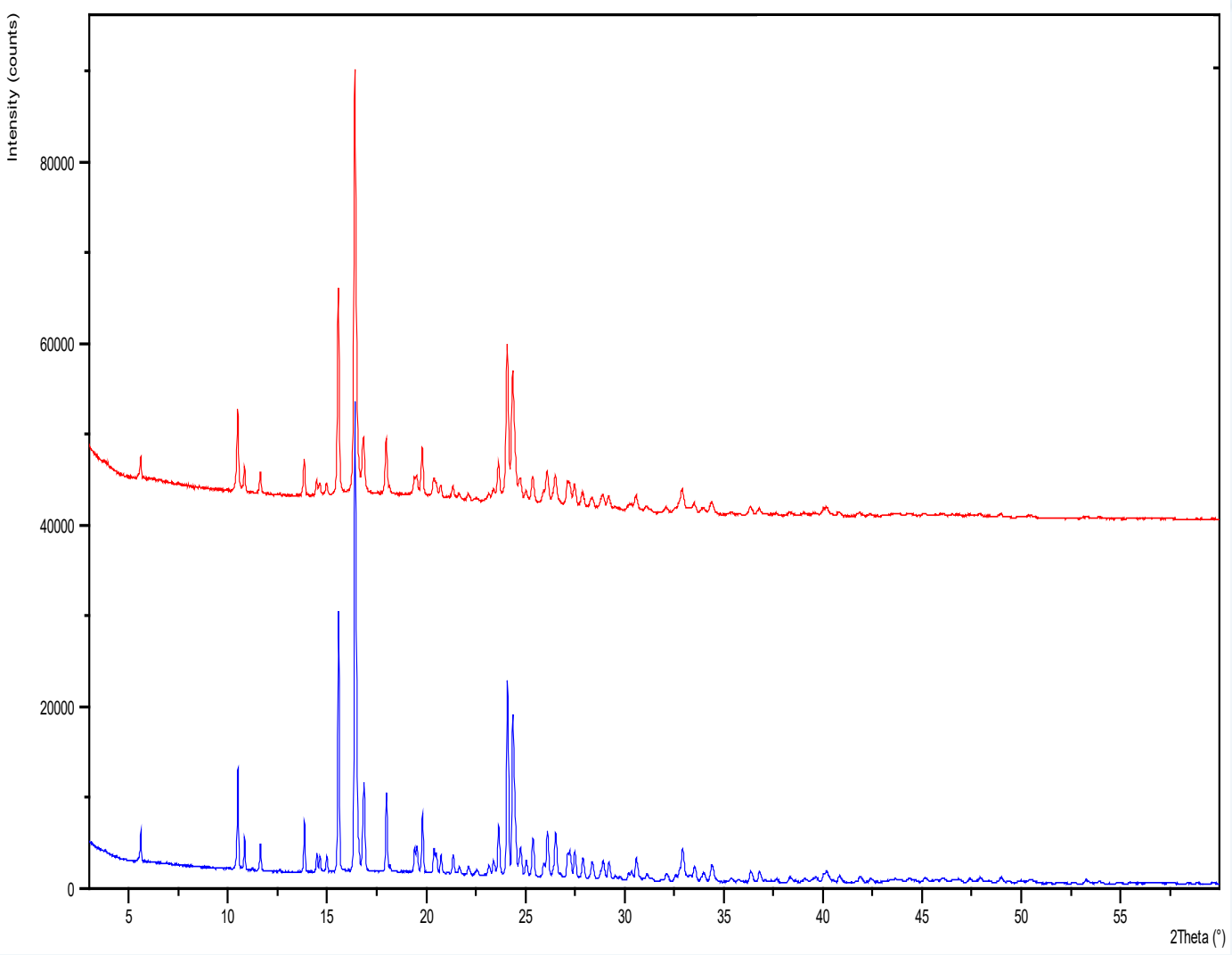


Capillary sample may be loaded into holder (pre-aligned) and analyzed in standard transmission setup with auto-changer and without need for instrument reconfiguration to capillary analysis with standard goniometer heads.

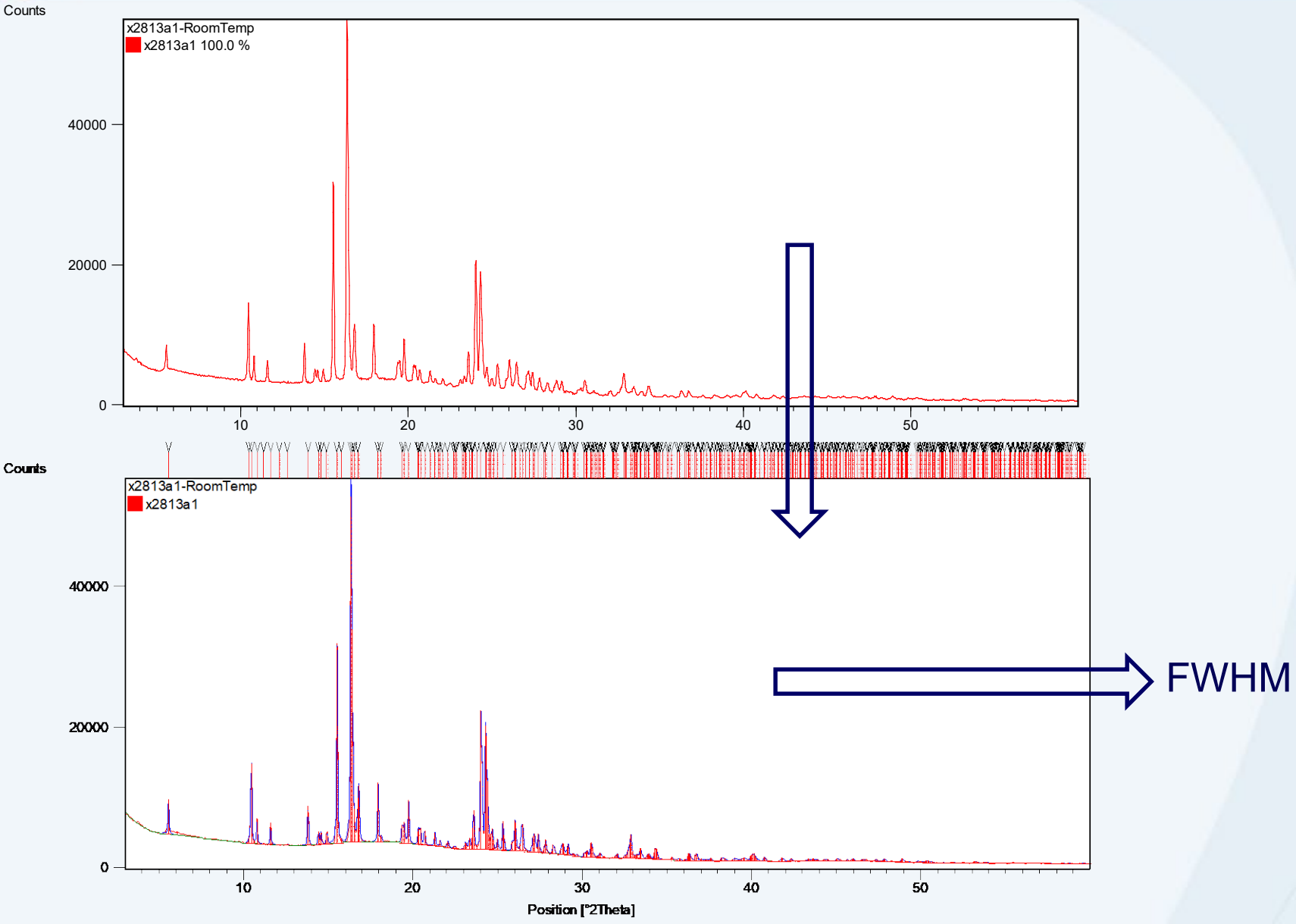
XRPD – Sample Analysis – Transmission Setup



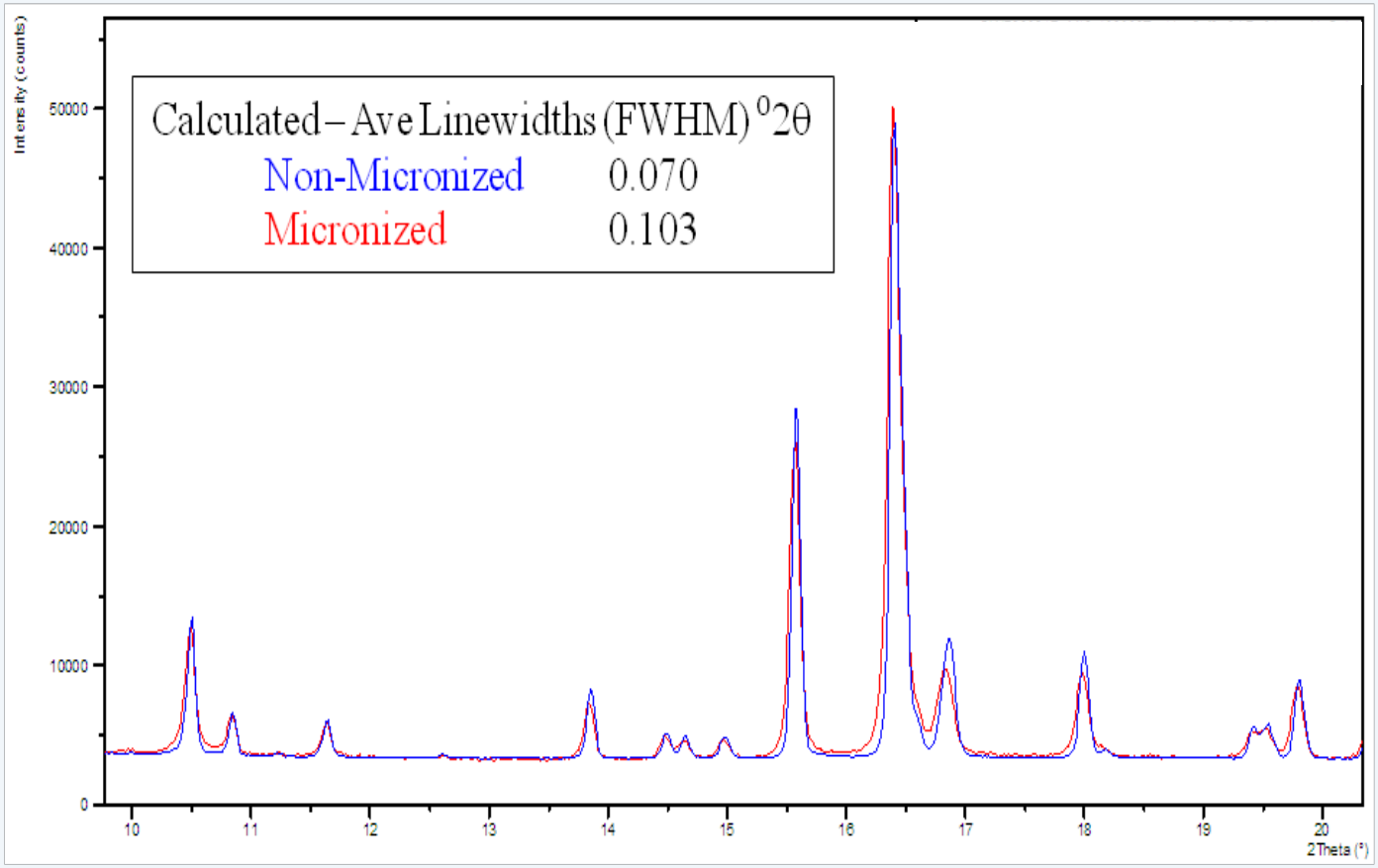
Visual Comparison of Raw Patterns



Profile Fitting To Obtain FWHM



XRPD – Sample Analysis



Non-micronized and freshly micronized materials show significant differences in linewidth – consistent and suitable for analysis

“Annealing” Studies

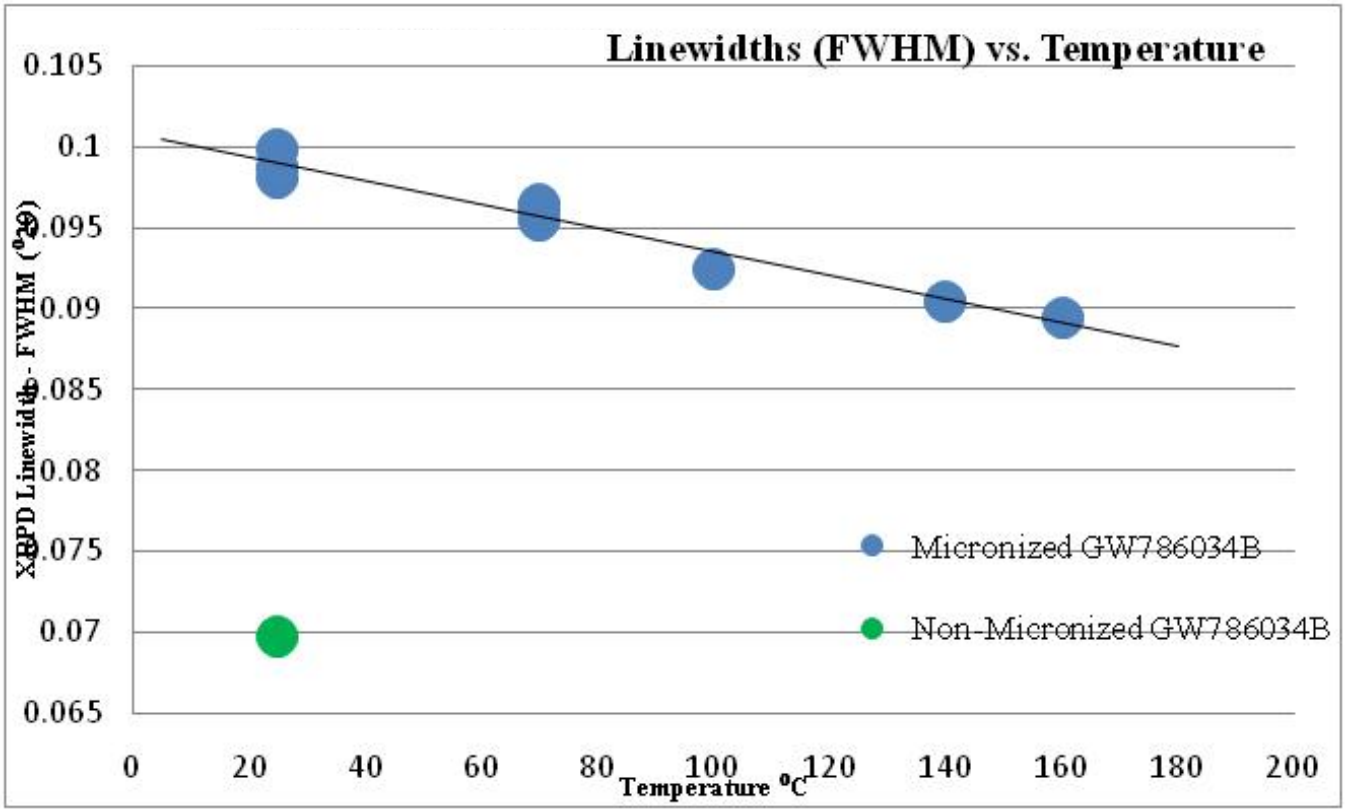
Annealing

1. To subject (glass or metal) to a process of heating and slow cooling in order to toughen and reduce brittleness.
2. To strengthen or harden.

Study 1

Samples of fresh micronized material were equilibrated at 6 different temperatures. Samples were heated in the DSC cell, in open DSC pans, and held isothermal for at least 60 min.

Study 1 Results



Linear relationship observed with increasing temperature and XRPD linewidth (FWHM) – Increase in **crystallite** size as increase temperature

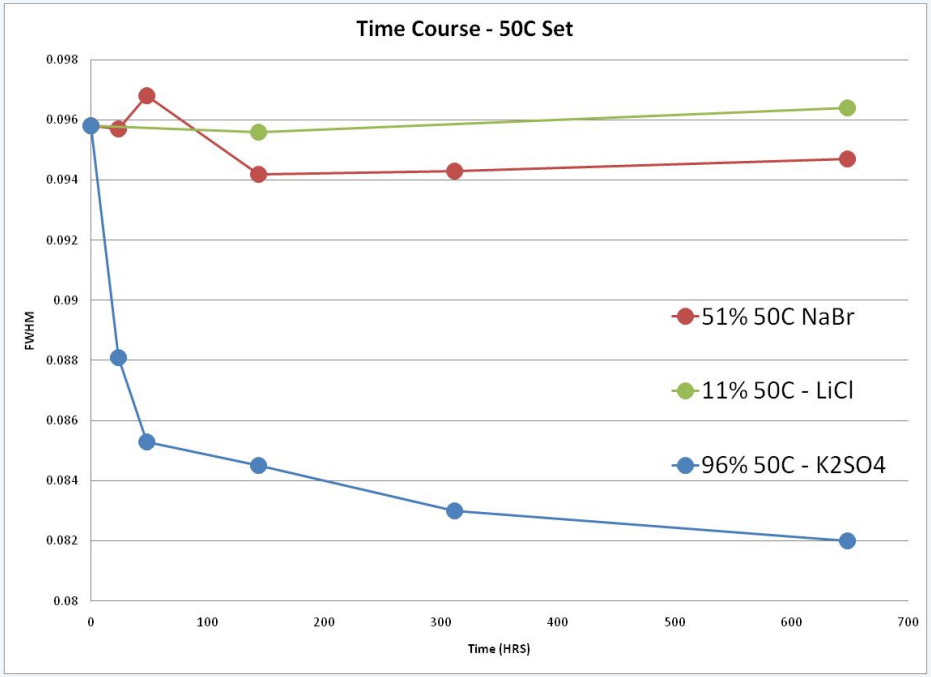
Environmental “Annealing”

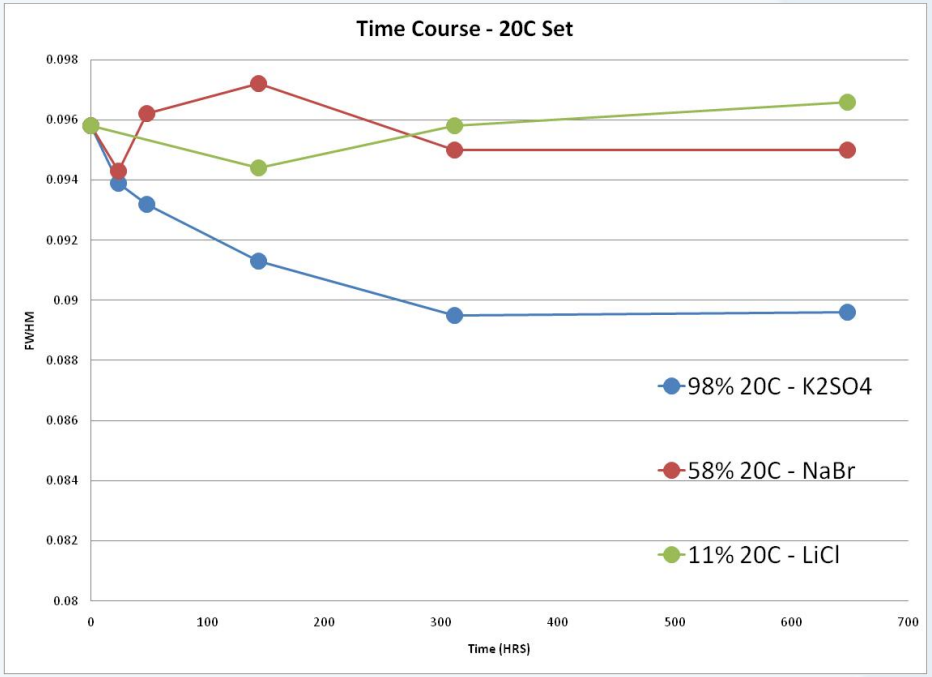
Study 2

Samples of micronized material lot stored at 3 different RHs and at 2 different temperatures. Samples were pulled periodically over a several week period of time.

LiCl (~10 %)	NaBr (~50 %)	K_2SO_4 (~95%)
Ambient	Ambient	Ambient
50 °C	50 °C	50 °C

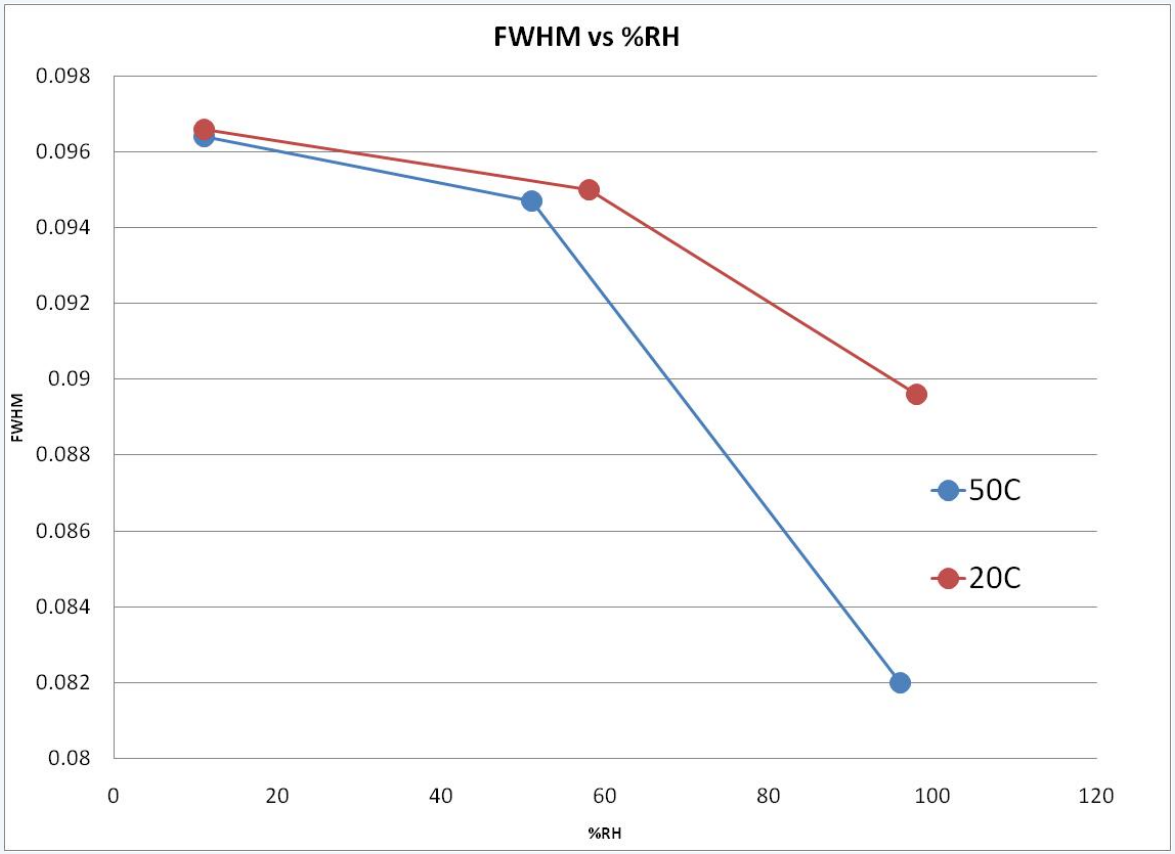
Study 2 – Time Course





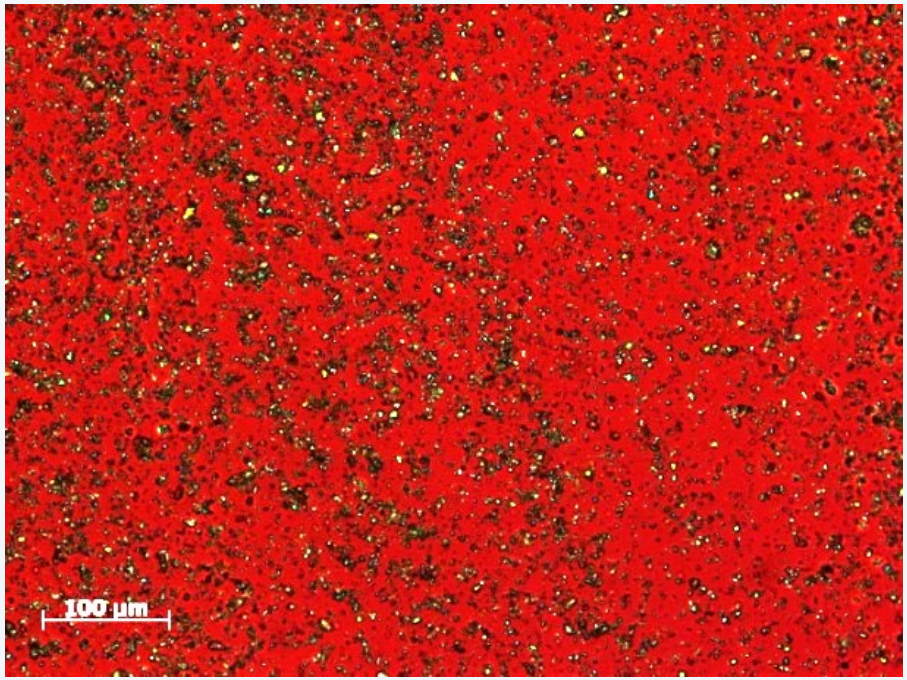
Within 2 weeks all conditions appear to have reached an equilibrium with respect to a reduced FWHM

Study 2 – Temperature Humidity Effect

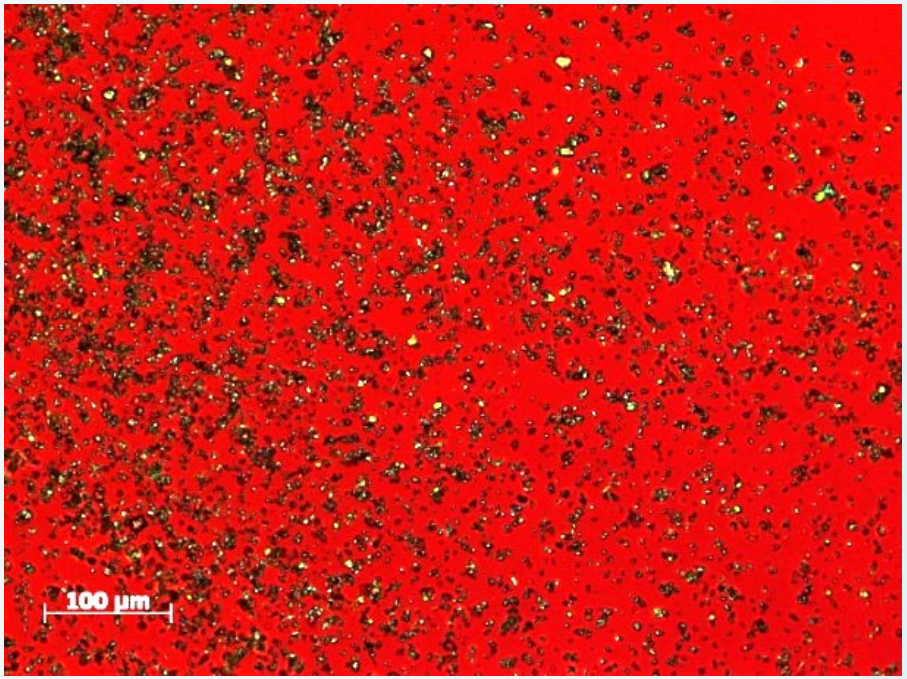


A **synergistic** effect on annealing is apparent with increased temperature **and** relative humidity

Microscope Comparison



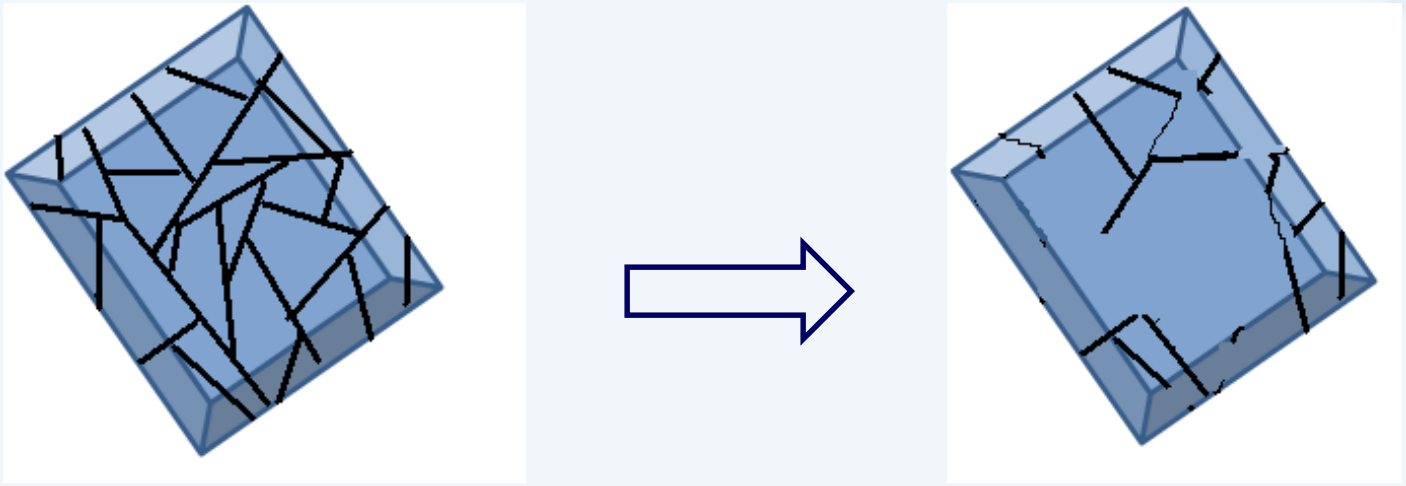
Freshly Micronized

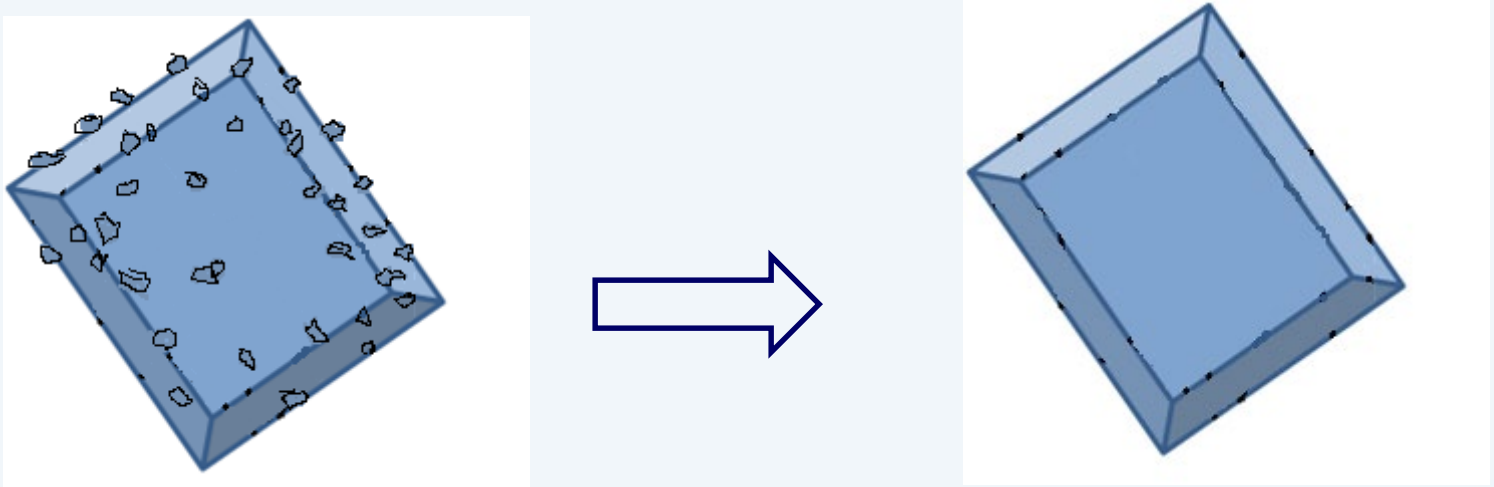


“Annealed”

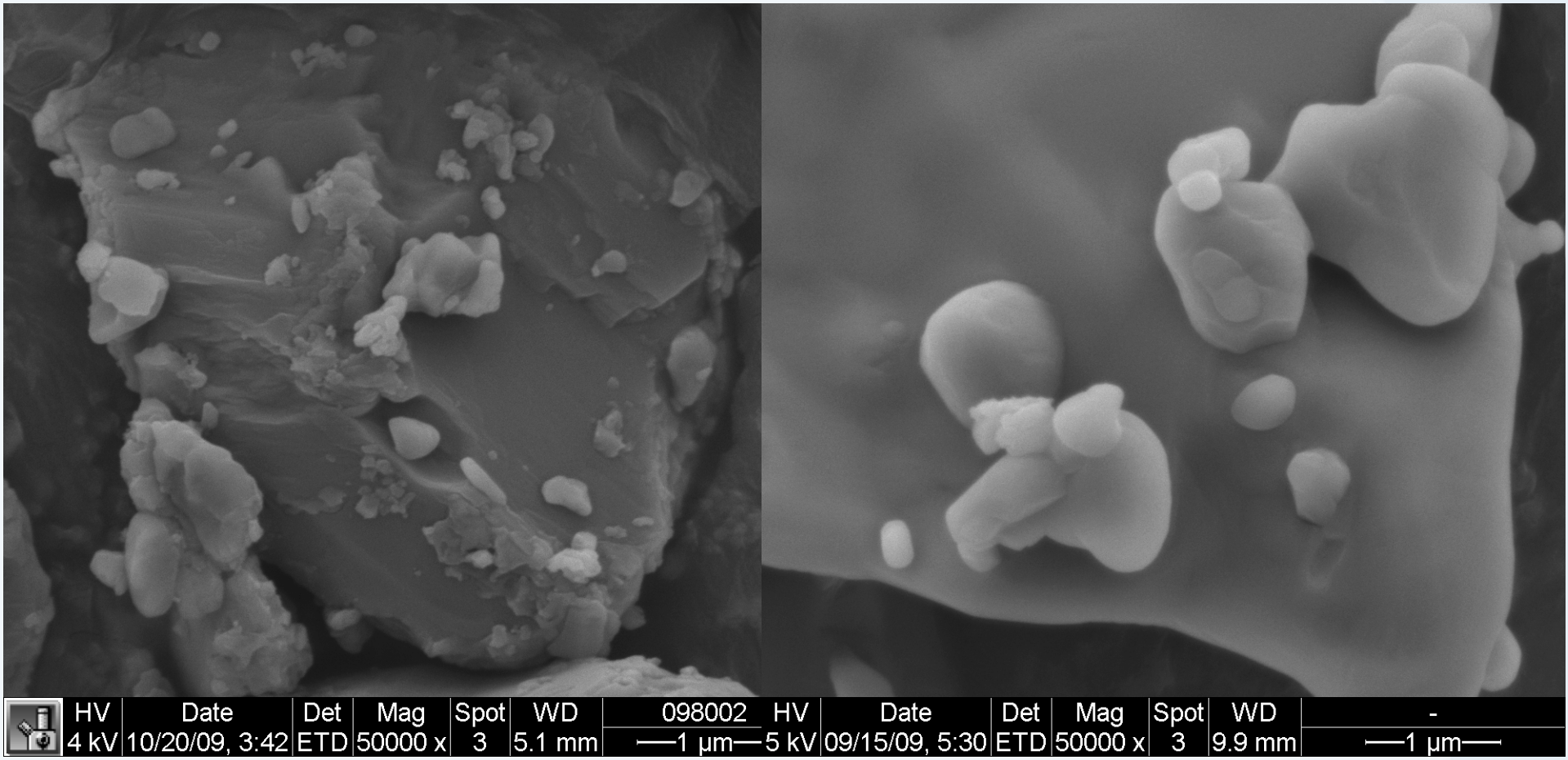
No **obvious** difference in particles post “annealing” - Consistent with healing of fractures/fines.

Healing of Fractures



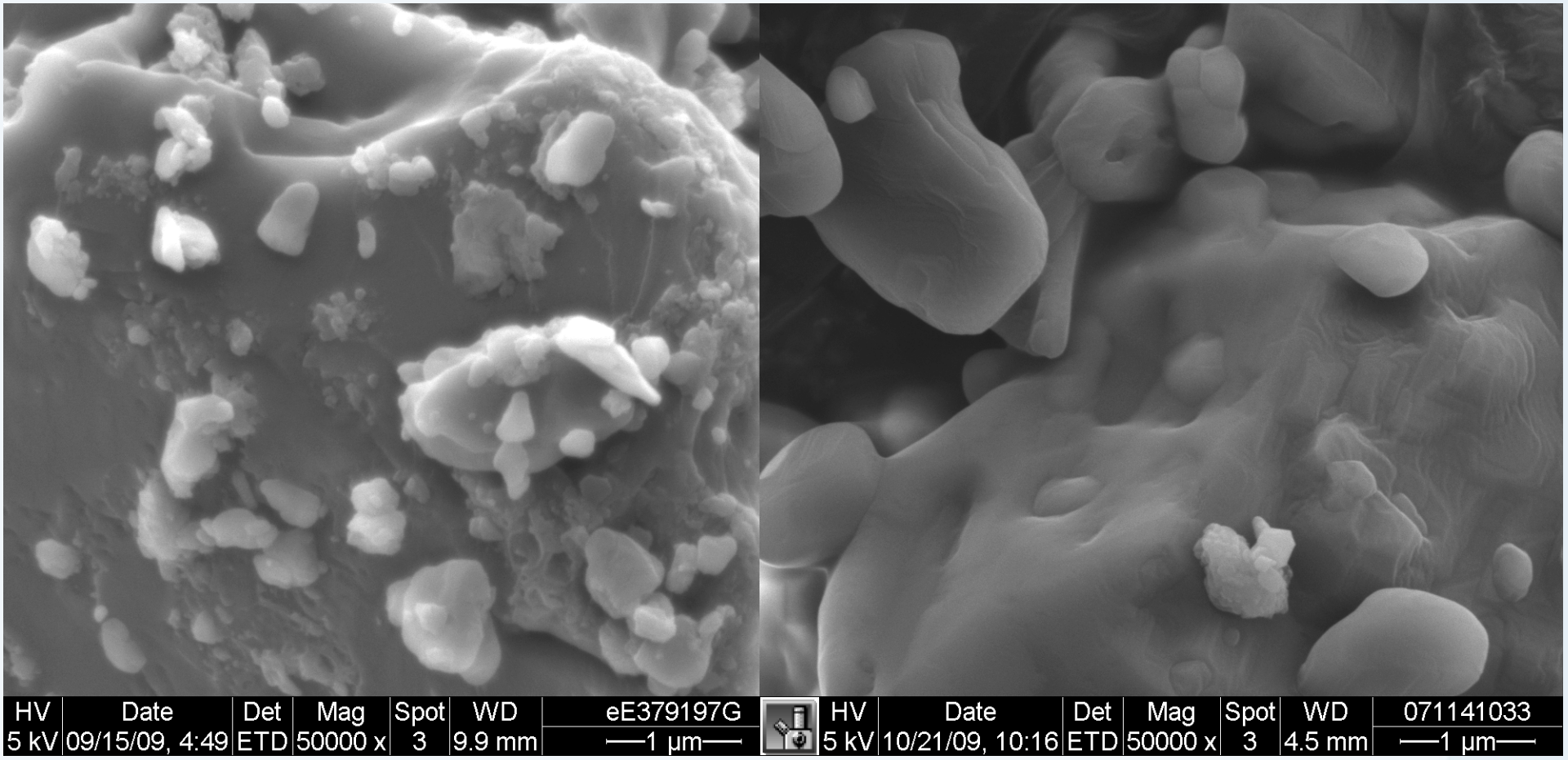


Increase in averaged crystallite size


HV
4 kV
Date
10/20/09, 3:42
Det
ETD
Mag
50000 x
Spot
3
WD
5.1 mm
1 µm
098002
HV
5 kV
Date
09/15/09, 5:30
Det
ETD
Mag
50000 x
Spot
3
WD
9.9 mm
-
1 µm

“Fresh”

“Aged”


HV
5 kV
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1 µm
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5 kV
Date
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ETD
Mag
50000 x
Spot
3
WD
4.5 mm
071141033
1 µm

“Fresh”

“Aged”

Conclusions

With further study we may be able to better understand **“disorder”** generated in micronized API’s and separate the contributions of true glassy **amorphous** and nano-crystalline content.

We are currently evaluating the physiochemical changes that are associated with this observed crystal “healing” - related moisture sorption, surface area and porosity, thermal, XRPD, and ssNMR data.

We are applying this same methodology to other projects with similar observations/results.

Acknowledgements

Jeff Brum

Rachel Forcino

Fred Vogt (SS-NMR)

Robert Carlton (SEM)