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Excelsus
Structural Solutions

WIR SCHAFFEN WISSEN – HEUTE FÜR MORGEN

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Absolute quantification of pharmaceuticals: The search of suitable internal standards

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PPXRD Website – www.icdd.com/ppxrd   ICDD Website - www.icdd.com

- QPA on absolute scale of traces in organic mixture
- Internal standard method

- Constraints for the choice of an internal standard:
  - Internal standard method in itself
  - Synchrotron radiation

Which strategy for absolute QPA via SR-XRPD?

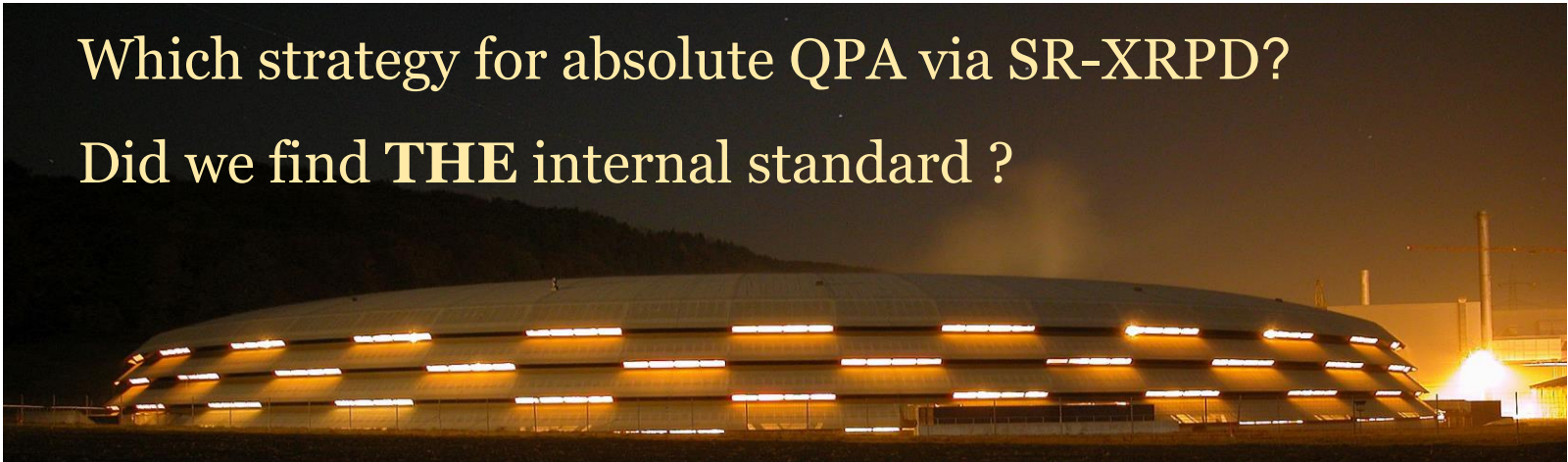Did we find **THE** internal standard ?
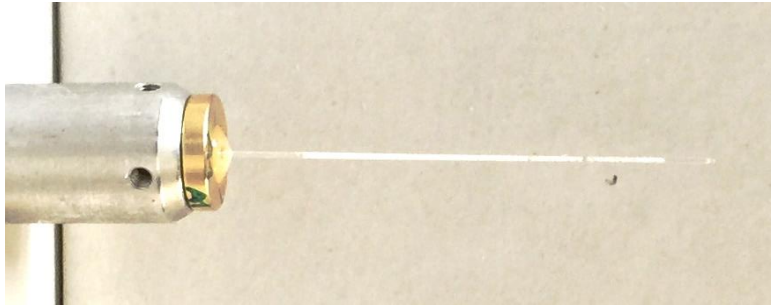
Photo: Paul Scherrer Institute

Outlook

1. Internal standard for pharmaceuticals and SR-XRPD
2. Search of the internal standard
3. Challenges/Preliminary results

On going project!

- Small volume analyzed

vs

- Small volume analyzed
- Restrictions on capillary diameter

- Capillaries : transmission, angular resolution, modelling, highly potent and/or reactive
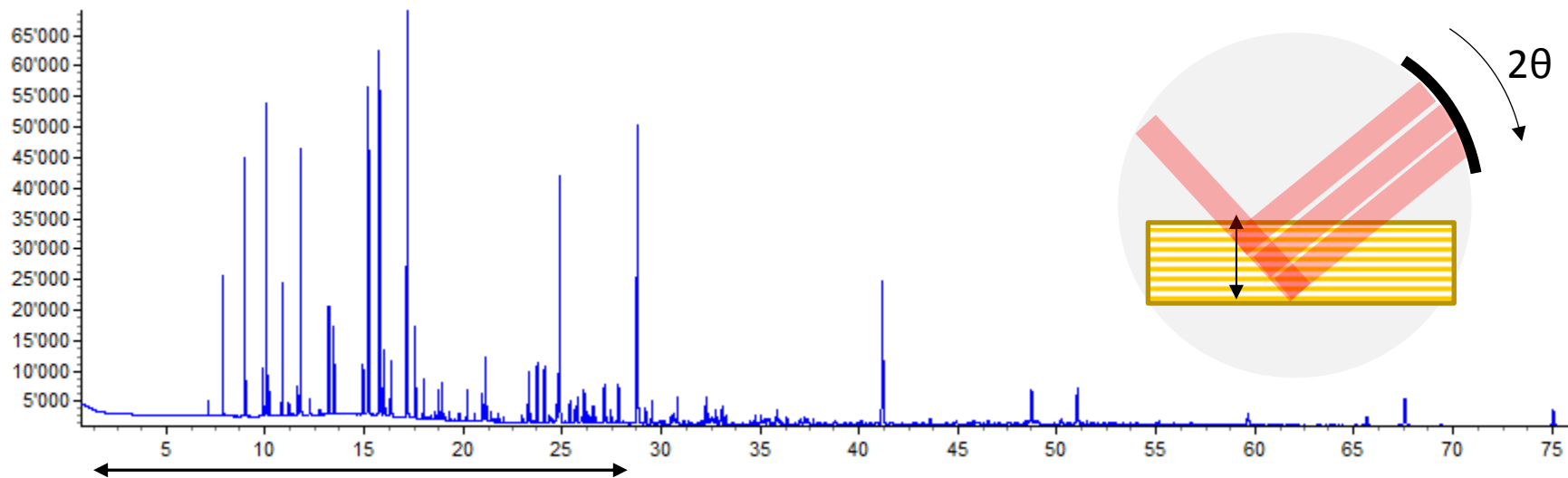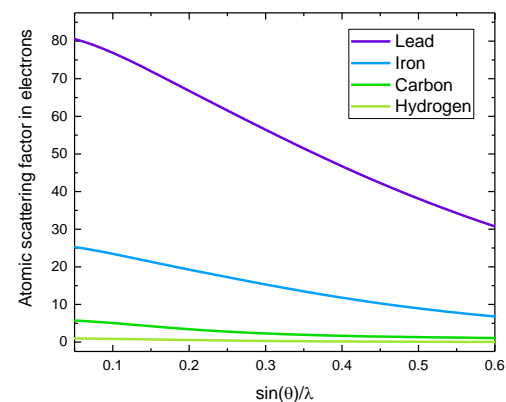- Fast measurement, high angular (FWHM) resolution/tunability

Bruker D8 Advance
Synchrotron with Mythen

ACP (Paracetamol) gently grounded

- Much higher S/N and S/B
- LoQ<0.05 wt%, LoD<0.01 wt%

Majority phase (intensity up to 1.5 M counts): Haloperidol
Minority phase: Indomethacin

Indo % wt
5 %
1.0 %
0.1 %
0.05 %

F. Gozzo, PPXRD 12th, Beijing, China

0.01% ACP
0.05% ACP
0.1% ACP
1% ACP

F. Gozzo, PPXRD 13th, Bad Herrenhalb, Germany

- Poor scattering power (H, B, C, N, Si, P, S, O)
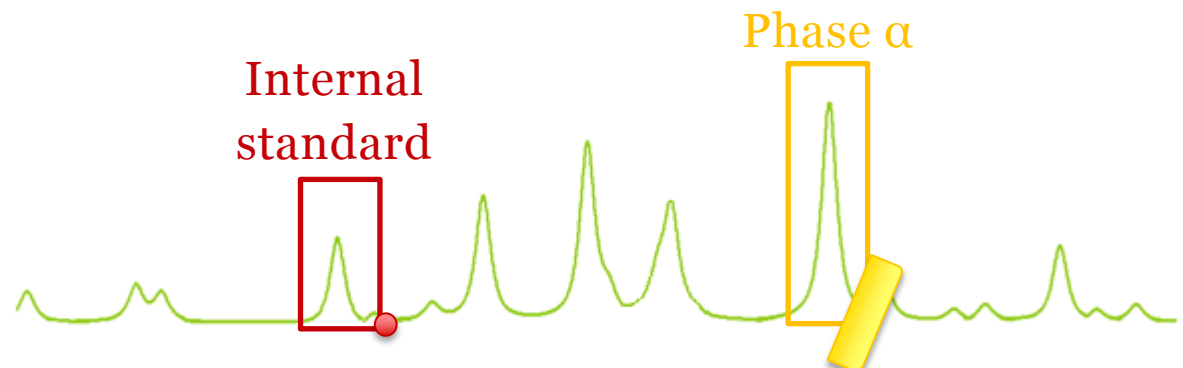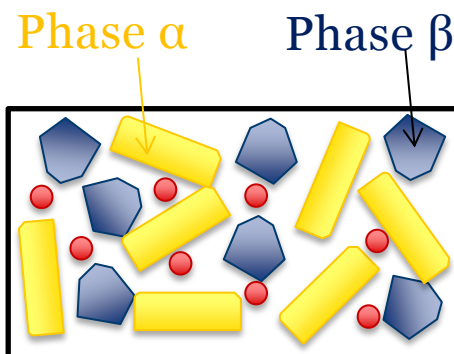- Radiation sensitive
- Low absorption
- Low symmetry

- Addition of a known weight ratio of internal standard to the mixture to analyze – known reference to scale all phases
- Use of intensity ratios:

$$SINGLE\ PEAK\ METHOD \quad w'_\alpha = \frac{I_{(hkl),\alpha}}{I_{(hkl),S}} \frac{K_{(hkl),S}}{K_{(hkl),\alpha}} . \frac{\rho_\alpha}{\rho_S} . w_S$$

$$RIETVELT\ METHOD \quad w_\alpha' = \frac{S_\alpha (ZMV)_\alpha}{S_S (ZMV)_S} . w_S$$

Phase α   Phase β

Phase α

Internal standard

- Direct correction for instrumental effects
- Comparable matrix effects
- Unknown compounds
- Amorphous quantification, Absolute scale
- Universal

- Internal standard tailored to analyte
- Time consuming powder processing
- Powder samples only
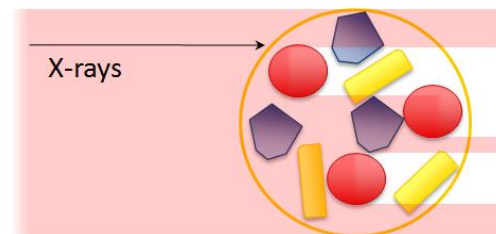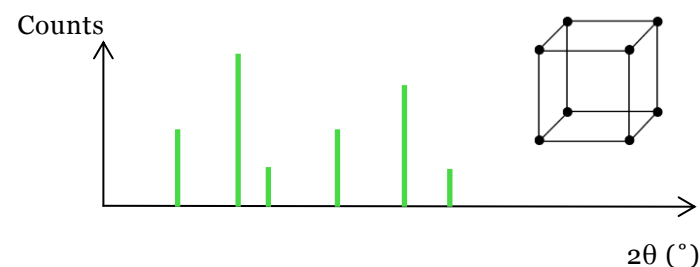- Analyte mixture contamination

- ## Constraints/requirements:

  - High symmetry, high crystallinity
  - Well-known structure
  - Well known amorphous component
  - Comparable dimensions

  - Small isometric particle, density
  - Similar mass absorption coefficient
  - Small crystallite size
  - Comparative intensities (wt %)

  - Stable, not reactive
  - Affordable, easily available

Crystallite diameter (μm)	40	10	1
Crystallites (20 mm^3)	5.97×10^5	3.82×10^7	3.82×10^{10}
Number diffracting	12	760	38 000
σ_{PS}	0.289	0.036	0.005

Robert E. Dinnebier and Simon J. L. Billinge, Print ISBN: 978-0-85404-231-9, DOI:10.1039/9781847558237
adapted from: D. K. Smith, Adv. X-Ray Anal., 1992, 35, 1-15

'Most severe limitation to QPA accuracy is particle statistics'
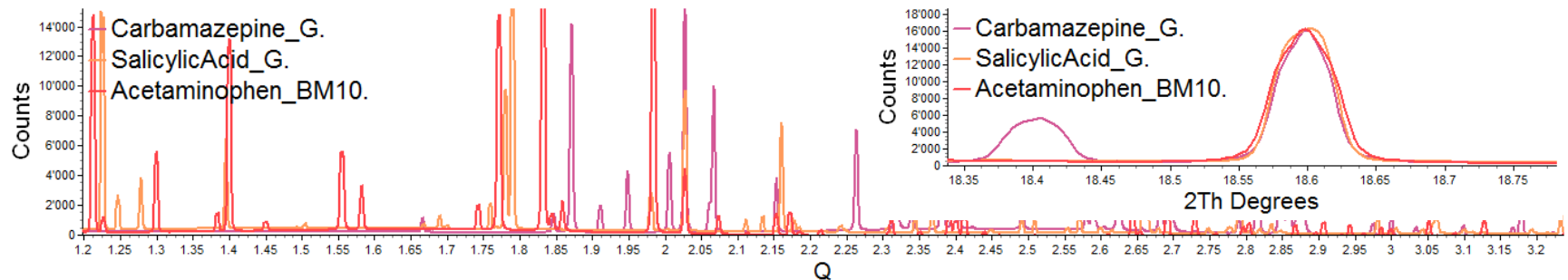
Deane K. Smith Powder Diffraction, 16, pp 186-191, (2001), doi:10.1154/1.1423285.

- Individual volumes representative of general phase distribution in the whole sample requires
  - Homogeneity of the analyte
  - Homogeneity of the mixture with Internal Standard
  - Consistent sampling

- Measure entire sample??

2. Search of internal standard: Analyte mixture

- QPA on the analyte mixture with internal standard candidates
- Demonstrate a method: negligible impact of test mixture
- Acceptable peak overlaps
- Particle/crystallite size

- QPA of a ternary organic mixture: APIs well-known structure
  – Majority phase: Acetaminophen (Ball milled) – 75 to 96 %w/w
  – Medium phase: Salicylic Acid (Ground) – 3 to 20 %w/w
  – Minority phase: Carbamazepine (Ground) - 0.1 to 5 %w/w

- **Organic?**

- **Al_2O_3**
  - Naproxen, Danazol, 10% and 50% wt mixing, Lab-machine
  - Urinary stone constituents =, 30-40 %wt mixing, Lab-machine, failure

- **LiF**
  - Sodium salt amorphous vs crystalline, 5%
  - Tolnaftate in microspheres, 20%
  - Racemic compound of ibuprofen, 20% wt mixing

- **Diamond powder, $Ca(OH)_2$, $CaSO_4.2H_2O$, ZnO, Silicon powder...**

Internal Standard	Chemical formula	Density (g.cm^{-3})	Crystal structure
Hexamethylene-tetramine	$(CH_2)_6N_4$	1,33	Cubic
Diamond	C	3,51	Cubic
Lithium fluoride (precipitated, 99,995%, Sigma Aldrich)	LiF	2,635	Cubic
Monosodium citrate (Jungbunzlauer)	$NaH_2C_6H_5O_7$	1,5	Two known polymorphs: monoclinic & orthorombic
Sodium carbonate (anhydrous, ≥99,9999%, Sigma Aldrich)	Na_2Co_3	2,54	monoclinic or orthorombic
Zeolite (Faujasite)	$[Na_{28.8}Ca_{14.4}(H_2O)_{263}]$ $[Si_{134.4}Al_{57.6}O_{384}]$	1,93	Cubic
Corundum (as a reference)	Al_2O_3	4,02	Trigonal-hexagonal

Internal Standard	Chemical formula	Density (g.cm^{-3})	Crystal structure	
Hexamethylene-tetramine	$(CH_2)_6N_4$	1,33	Cubic	Selected
Diamond	C	3,51	Cubic	Very hard
Lithium fluoride (precipitated, 99,995%, Sigma Aldrich)	LiF	2,635	Cubic	Selected
Monosodium citrate (Jungbunzlauer)				Low symmetry
Sodium carbonate (anhydrous, ≥99,9999%, Sigma Aldrich)				Low symmetry
Zeolite (Faujasite)	$[Na_{28.8}Ca_{14.4}(H_2O)_{263}]$ $[Si_{134.4}Al_{57.6}O_{384}]$	1,93	Cubic	Later stage
Corundum (as a reference)	Al_2O_3	4,02	Trigonal-hexagonal	Selected

- Particle size distribution: 1-5 microns

- Dry microsieving 5 to 20 microns:
  - As received, ground and ball-milled HMTA and LiF
  - agglomeration or too large *psd*

- Ball-milling

- Characterization techniques:
  - Laser granulometry
  - Optical microscope
  - Scanning electron microscopy

APIs

Internal standard
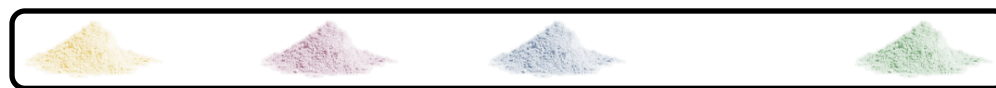
Amorphization ?

Electrostaticity ?
Agglomeration ?
Water uptake ?

CONSISTENT SAMPLE
PREPARATION !

- Organic
  - similar density
  - similar mass absorption coefficient
- Cubic symmetry, highly crystalline
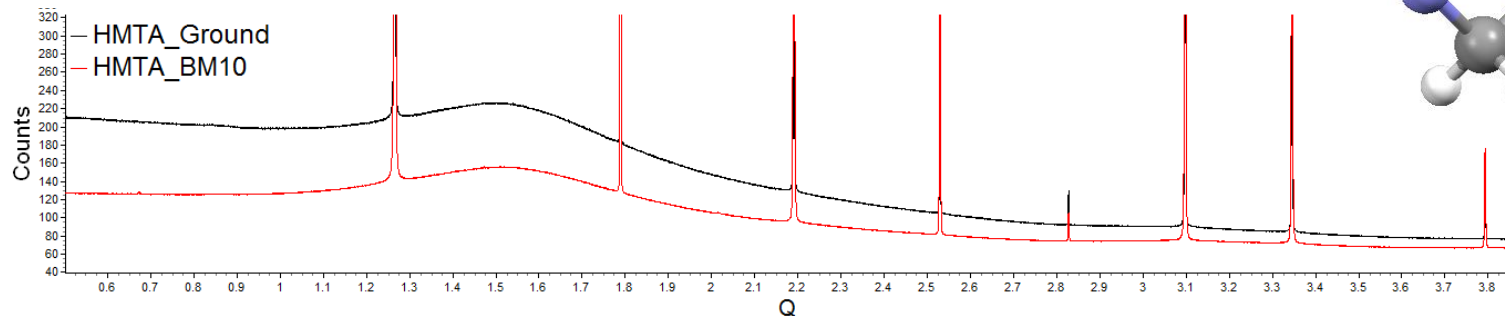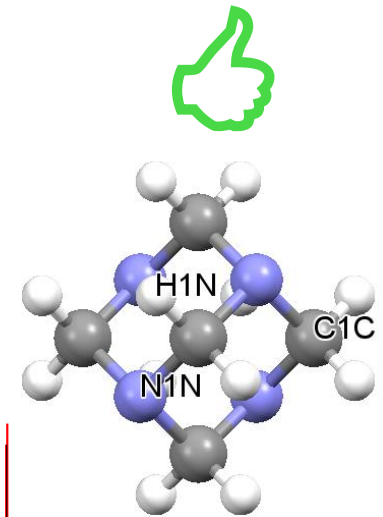
- Resistant to milling
  - reduced particle size distribution
  - reduced crystallite size
  - amorphization: in progress
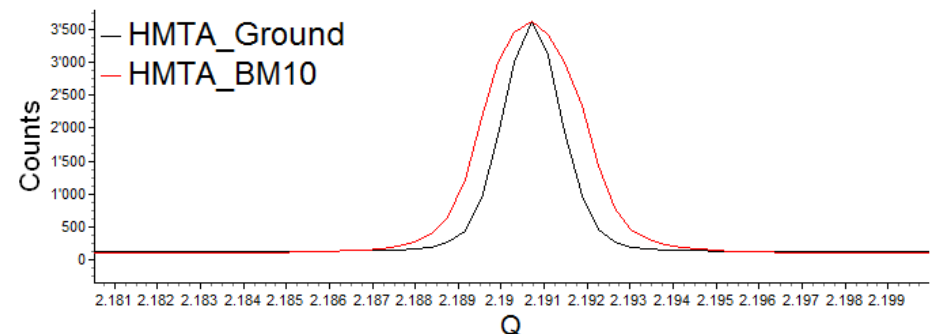
- Not stable in mixture
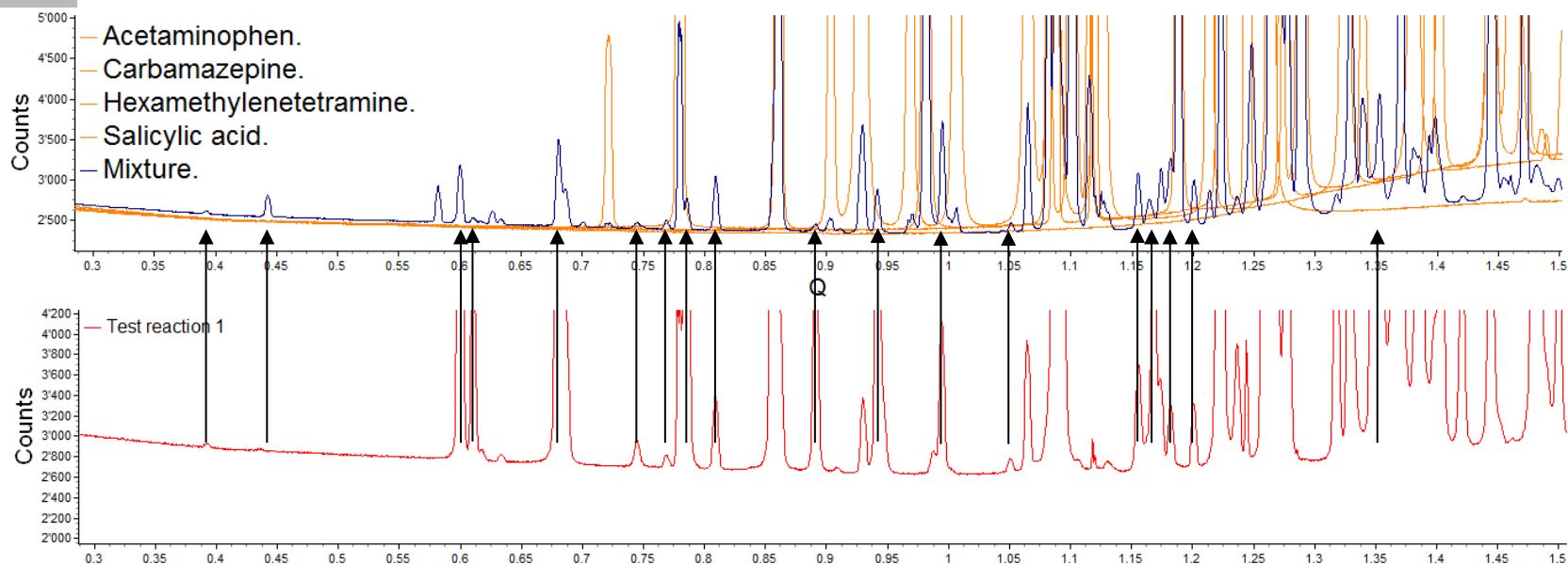
HMTA + *SA*	*HMTA*⁺*SA*⁻

HMTA + SA → HMTA⁺SA⁻

LAG in EtOH (50µL)

10 min grinding in agate mortar

The salt was not pure
[reactant as contaminant]

LAG in EtOH

- NIST Quantitative Analysis Powder Diffraction Standard
- Few intense peaks
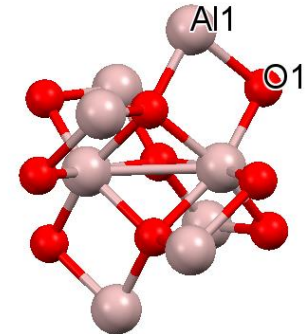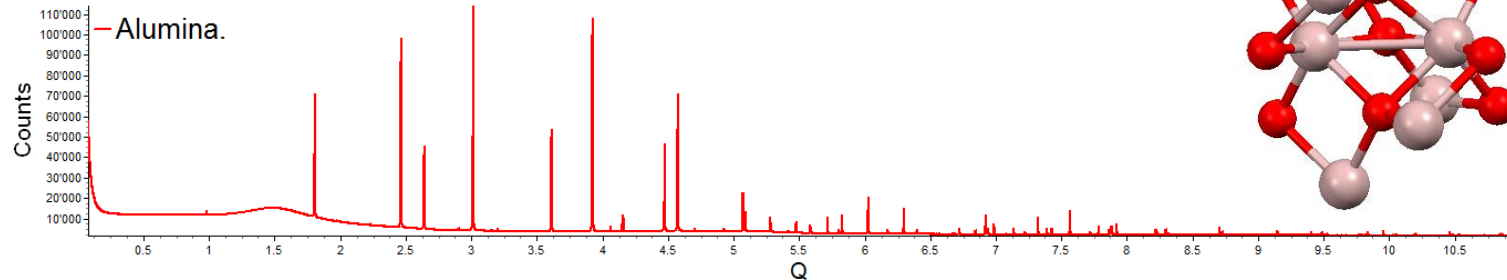
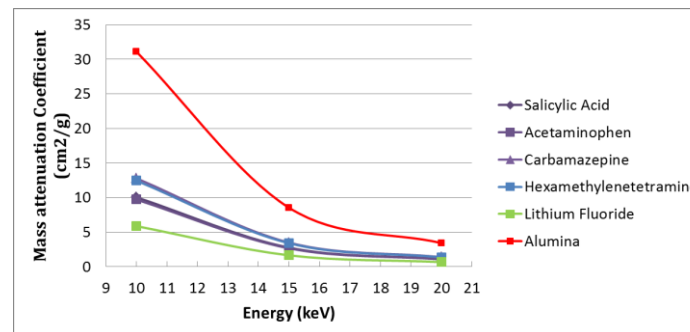- Known structural model
- Mean particle size below 2 microns
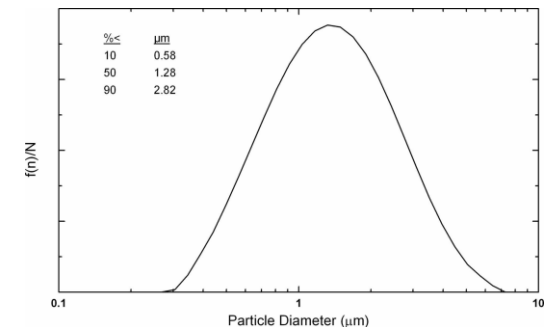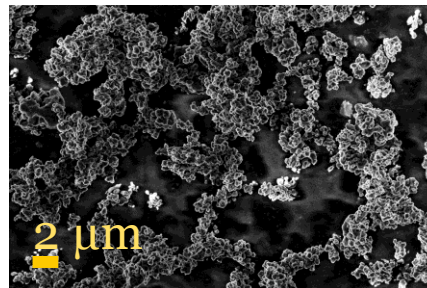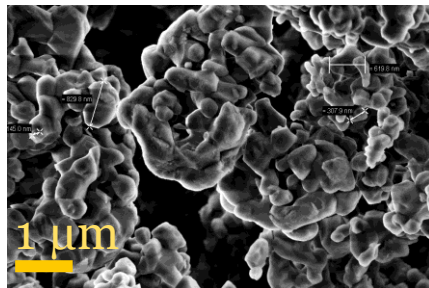
- Well-known amorphous content (99,2% crystalline)

Cline, J. P., Von Dreele, R. B., Winburn, R., Stephens, P. W. & Filliben, J. J. (2011). Acta Cryst. A67, 357-367.

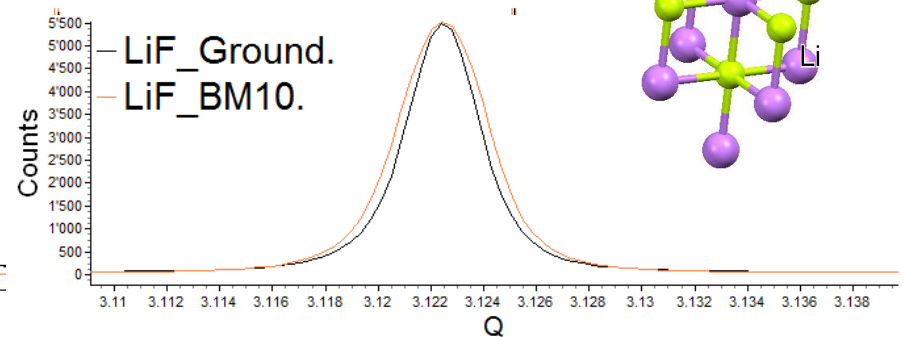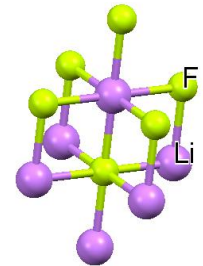- High density, inhomogeneity along capillary

ACP reflection

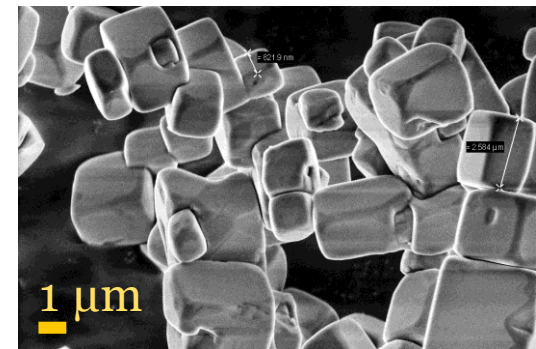Al_2O_3 reflection
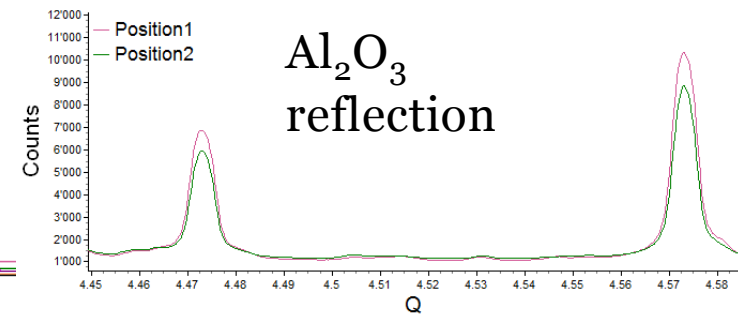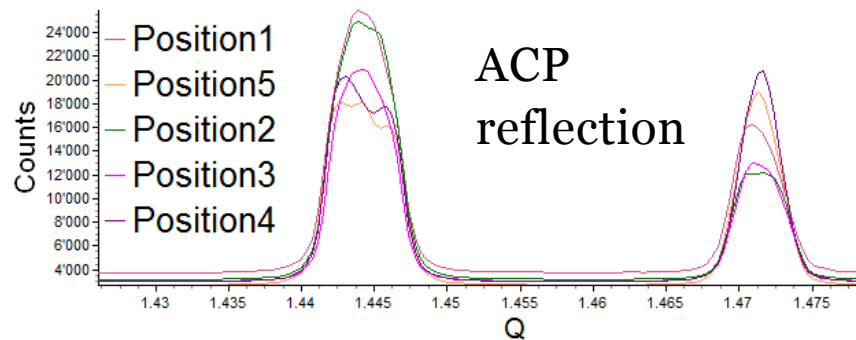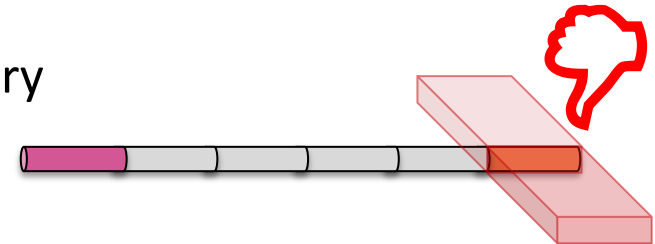
- Absorption contrast, high mass attenuation coefficient:

- Previous experiment: effect of microabsorption with 20% Al_2O_3

- Excellent structural model (special positions)
- No preferential orientation
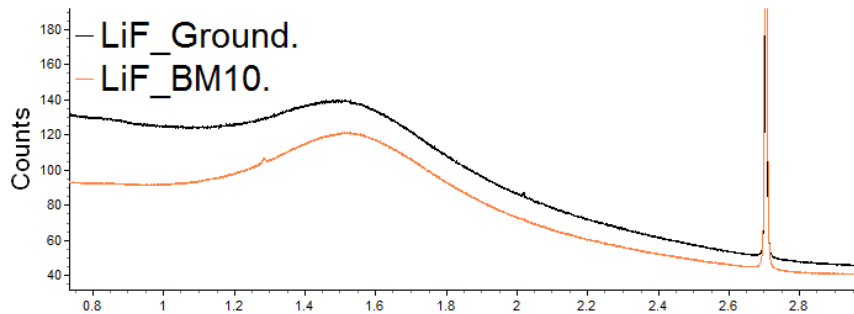
- Resistant to milling
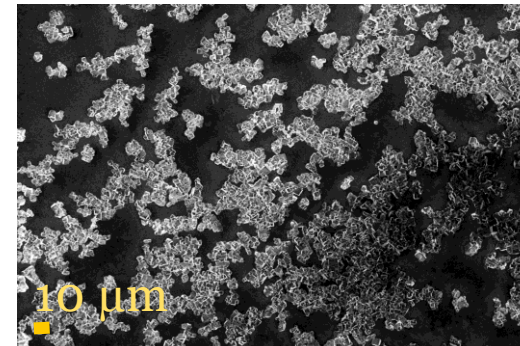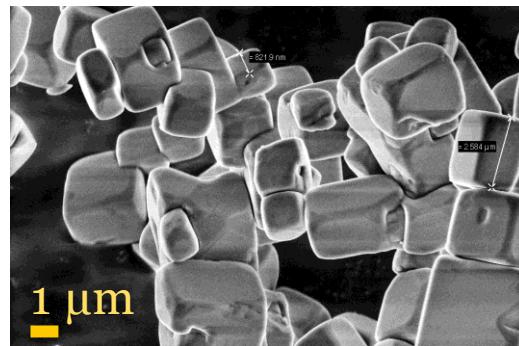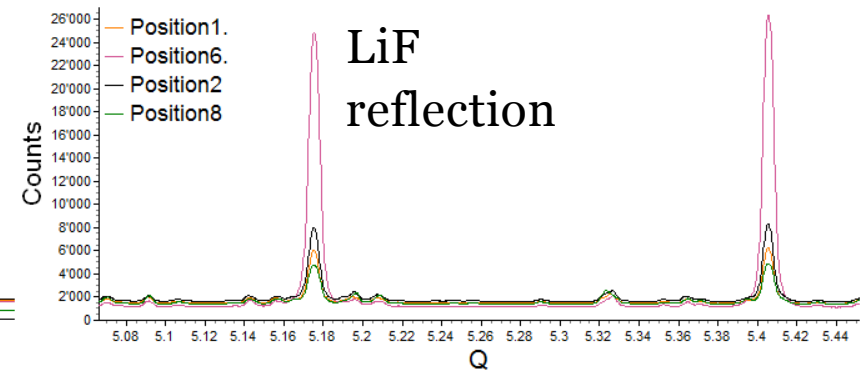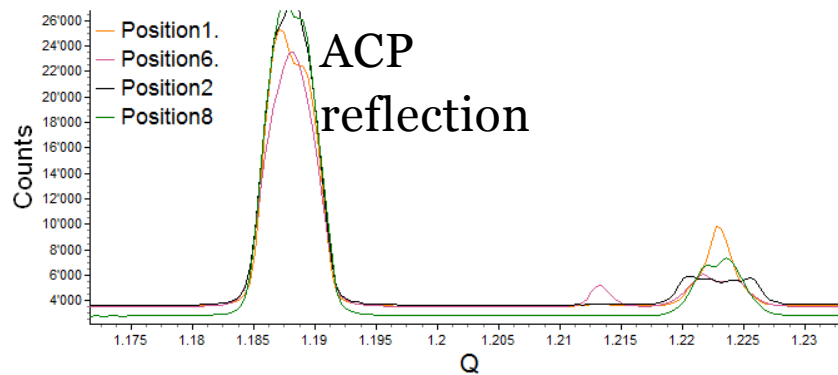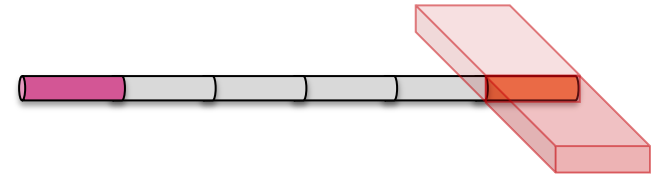 - Particle size distribution < 5 microns
  - reduced crystallite size
  - amorphization: in progress

- Inhomogeneous distribution in spite of milling and careful mixing
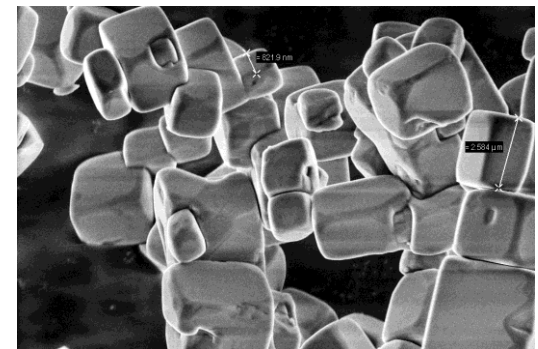- Strong agglomeration, hygroscopic

ACP reflection

LiF reflection

1 μm

10 μm

3. Preliminary results: LiF

High Statistics (ALL)

Medium Statistics (MS)

Low Statistics (LS)

Single Position (PX)
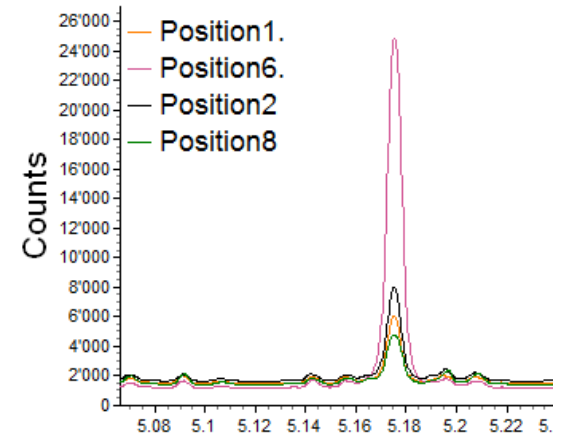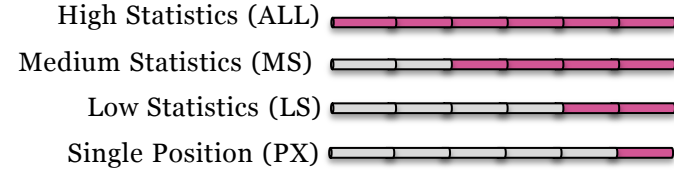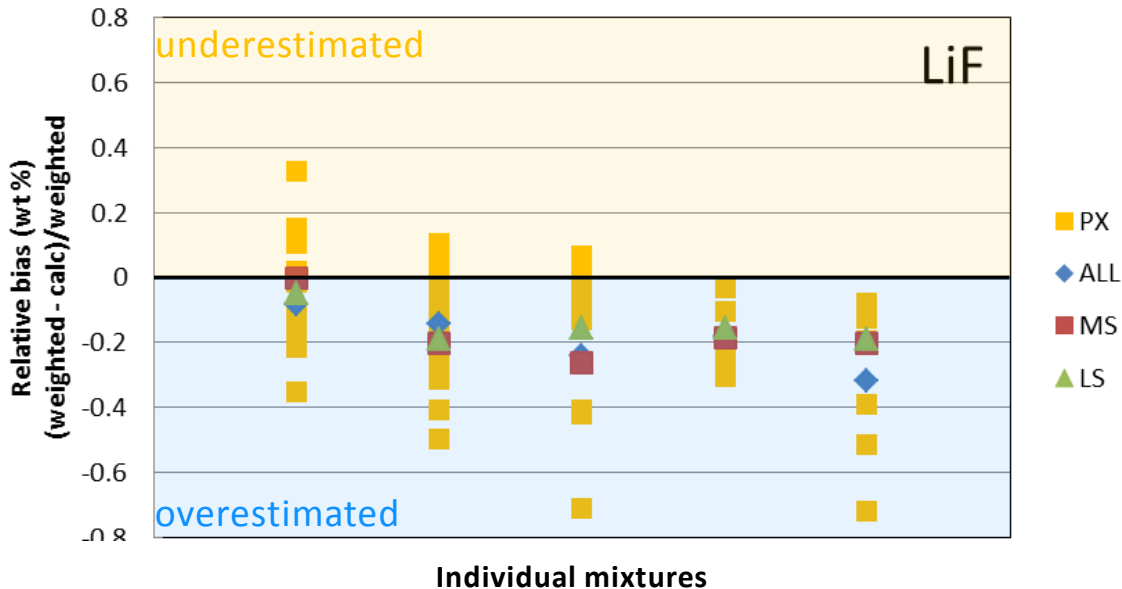
- Confirm inhomogeneity of LiF
- Improving the statistics, insufficient volumes collected

$$Relative\ bias\ (wt\%) = \frac{weighted - refined}{weighted}$$
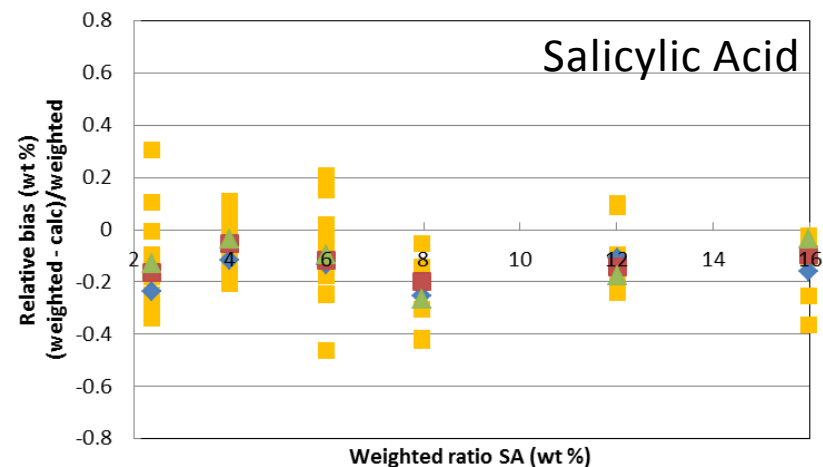
Relative bias wrt calculated (Rietvelt) weight ratios for LiF

underestimated

LiF

Relative bias (wt %)
(weighted - calc)/weighted

- PX
- ALL
- MS
- LS

overestimated

Individual mixtures

- LiF overestimated

3. Preliminary results: LiF

- LiF overestimated
- ACP underestimated , CBZ and SA overestimated

■ PX
◆ ALL
■ MS
▲ LS
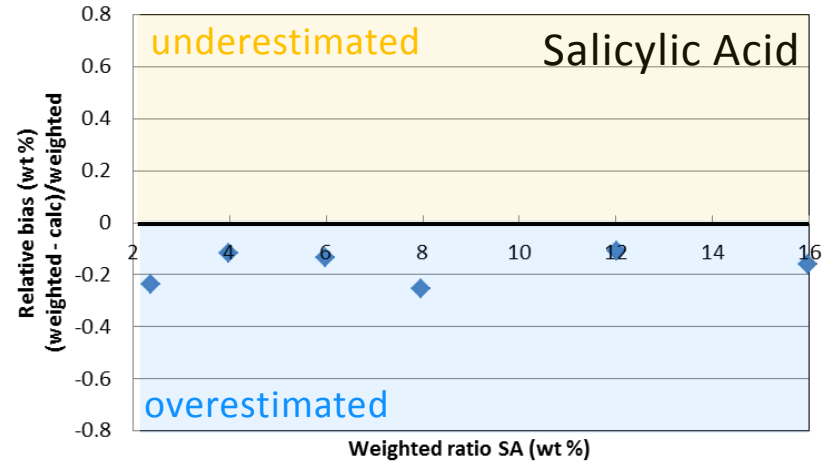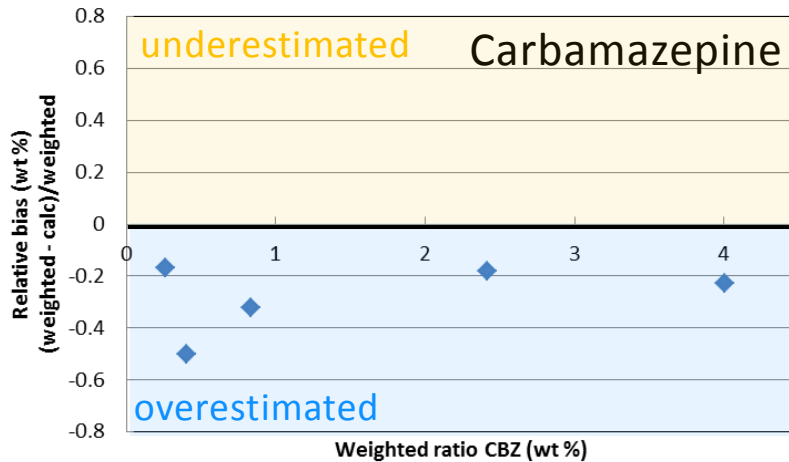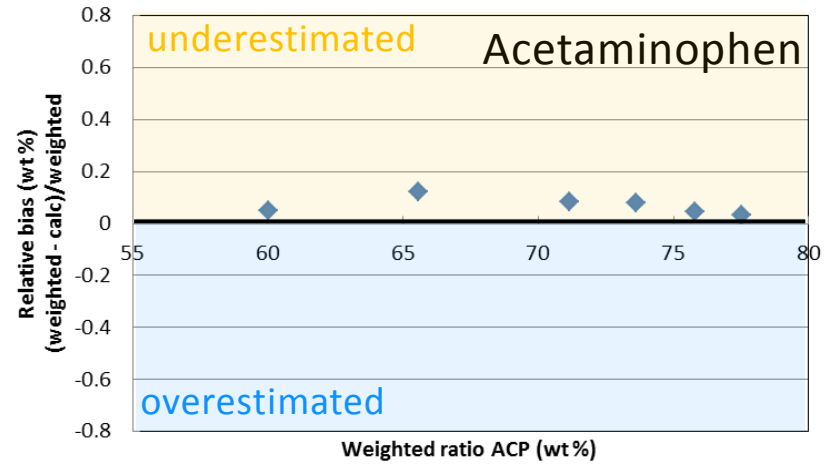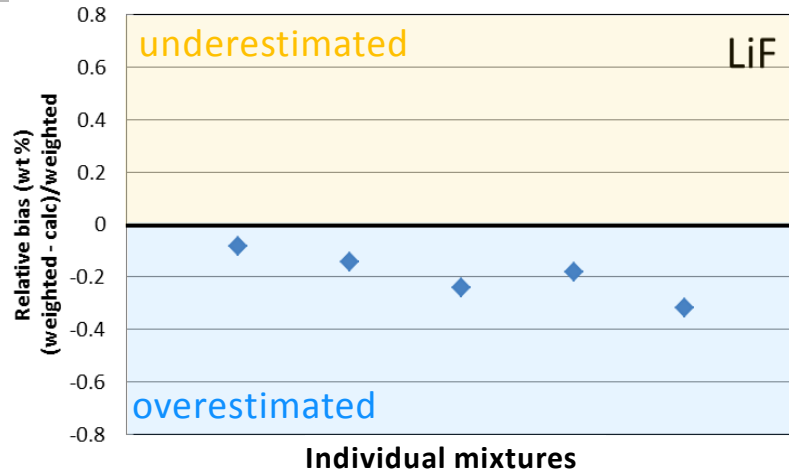
- Preferential orientation in Acetaminophen and Salicylic Acid
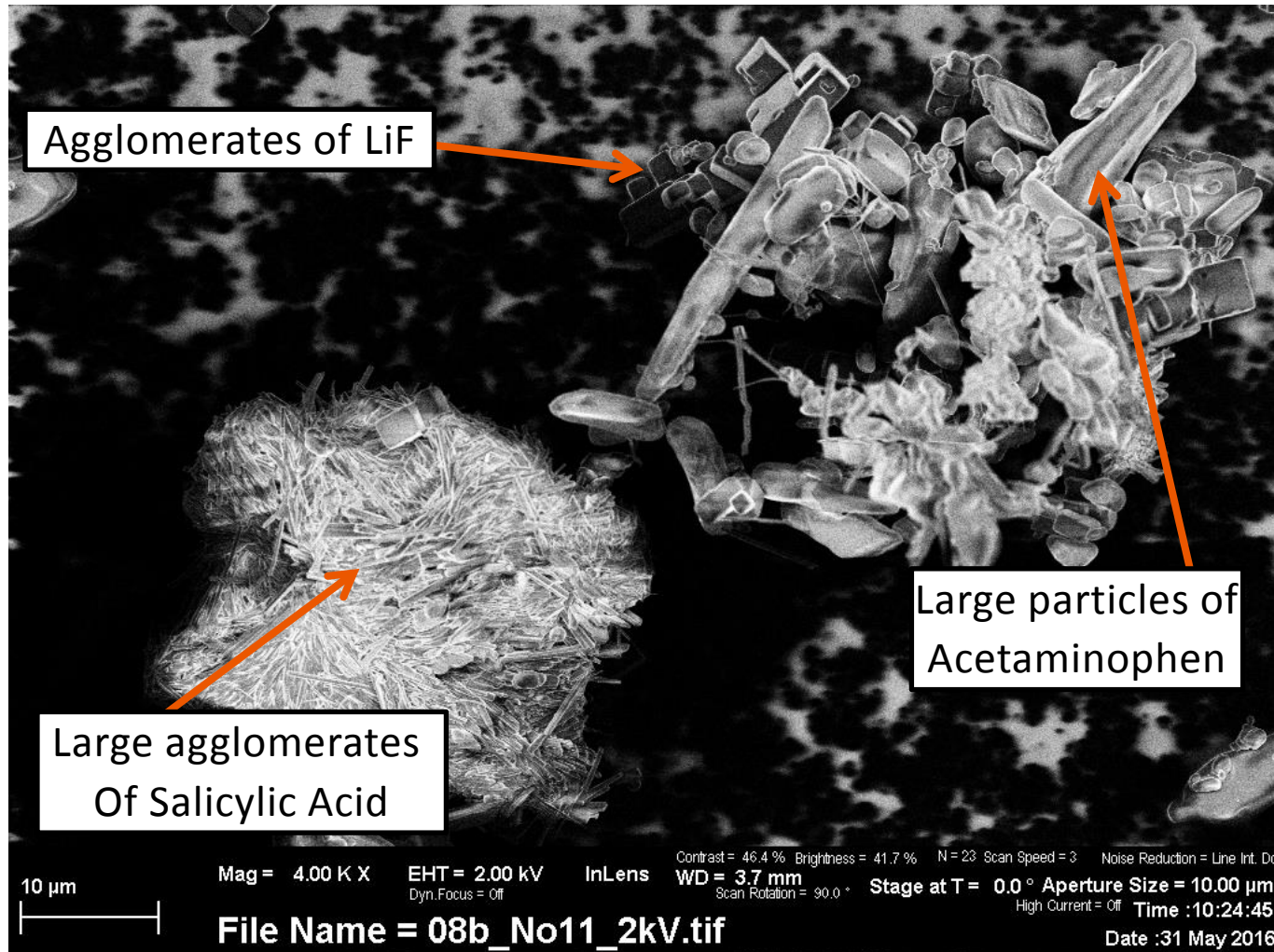
- Degree of crystallinity method – not yet convincing results
- Problem with modelling and correction of extrinsic background
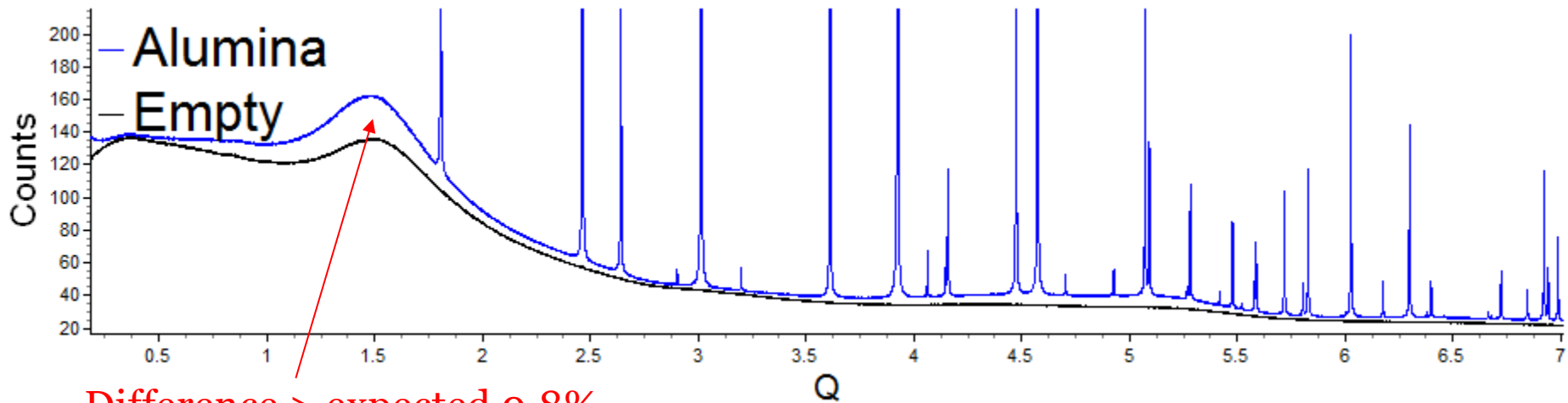
Difference > expected 0.8%

- Additional techniques:
  - Water sorption (gravimetric method)
  - Infrared spectroscopy
  - Calorimetry

Future directions

Analyte mixture:
- Replace ACP, SA

Internal standard
- Identify when HMTA can be used
- Reduce agglomeration in LiF
- Amorphous

Measurements @ SLS
- Determine statistically significant number of volumes
- Compare with total powder result
- Automation of measurement
- Appropriate acquisition time
- Cluster analysis of data

Success

Success

what people think it looks like

what it really looks like

References

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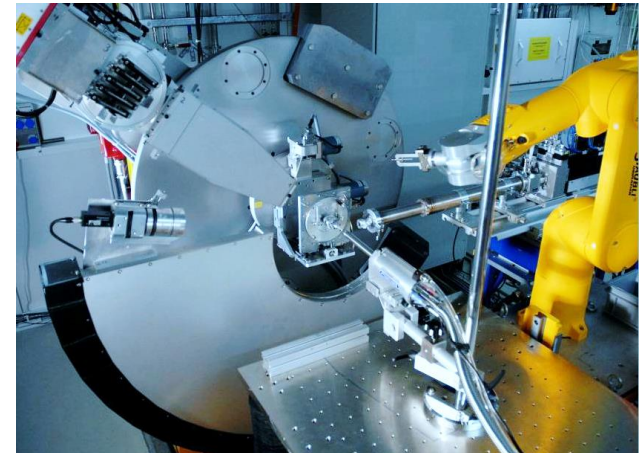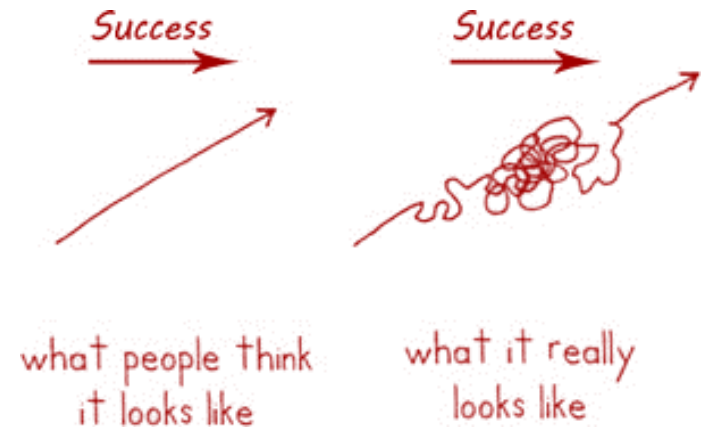Schreyer, M. et al., Journal of applied crystallography, 44, 1, 17 (2011).
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A Practical Guide for the Preparation of Specimens for X-Ray Fluorescence and X-Ray Diffraction Analysis
Victor E. Buhrke (Editor), Ron Jenkins (Editor), Deane K. Smith (Editor) , ISBN: 978-0-471-19458-3

Powder Diffraction: Theory and Practice, 2008
Robert E. Dinnebier and Simon J. L. Billinge, Print ISBN: 978-0-85404-231-9, DOI:10.1039/978184755823

Quantitative X-Ray Diffractometry, 1995
Lev S. Zevin, Giora Kimmel, ISBN: 978-1-4613-9537-9 (Print) 978-1-4613-9535-5 (Online)

X-Ray Diffraction Procedures: For Polycrystalline and Amorphous Materials, 2nd Edition, 1974
Harold P. Klug, Leroy E. Alexander, ISBN: 978-0-471-49369-3

My thanks go to

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- E. Pomjakushina
- C. Padeste

From:
Paul Scherrer Institute

Thank you for your attention!

Contact: m.reinle-schmitt@excels.us