Excelsus Structural Solutions

PPXRD15

Hyderabad – India

19th August 2017

An internal standard for **pharmaceuticals**

The Art of dealing with compromise

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This document was presented at PPXRD - Pharmaceutical Powder X-ray Diffraction Symposium

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PPXRD Website – www.icdd.com/ppxrd

ICDD Website - www.icdd.com

Quantifying small traces of pharmaceuticals on an absolute scale

MOTIVATION

Why small traces?

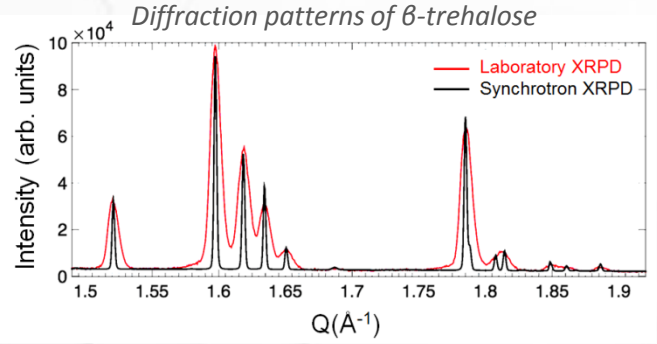
(Early detection contaminants/degradation products/ crystalline seed/highly potent)

Actual status of QPA of **pharmaceuticals**?

Why quantifying on an **absolute** scale?

CHALLENGES

Pushing **instrumentation** limits



Tailoring methodology to characteristics of pharmaceuticals

Choice of quantification method

Quantifying small traces of **pharmaceuticals** on an absolute scale

MOTIVATION

Why **small** traces?

Actual status of QPA of **pharmaceuticals**?

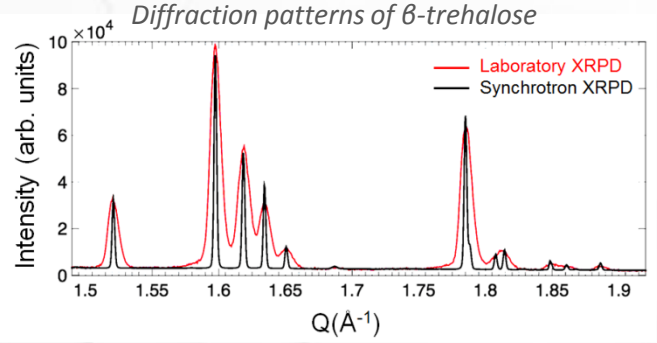
(Tailored properties, Alumina?, unique vs. set of standards, PONKCS)

Why quantifying on an **absolute** scale?

N. V. Y. Scarlett & I. C. Madsen, Powder Diffraction, **21**, 4, 278-284 (2006). PONKCS method

CHALLENGES

Pushing **instrumentation** limits



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Why **small** traces?

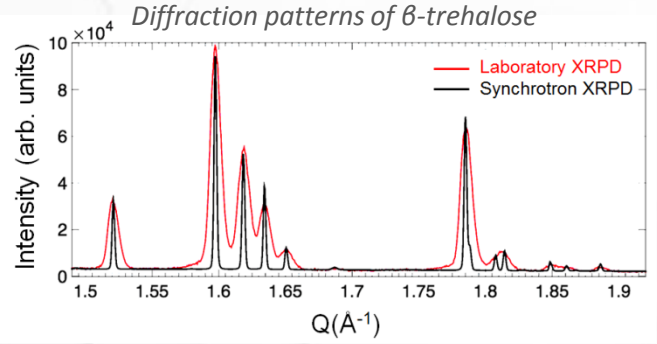
Actual status of QPA of **pharmaceuticals**?

Why quantifying on an **absolute** scale?

(relative scale: invisible amorphous/unknown, ex: interconversion to amorphous)

CHALLENGES

Pushing **instrumentation** limits



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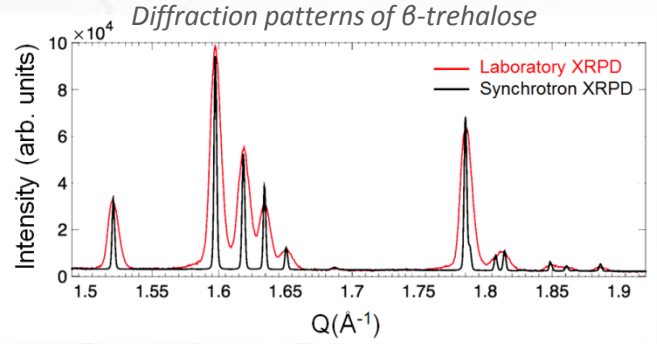


Tailoring methodology to characteristics of pharmaceuticals

Choice of quantification method

Quantifying small traces of pharmaceuticals on an absolute scale

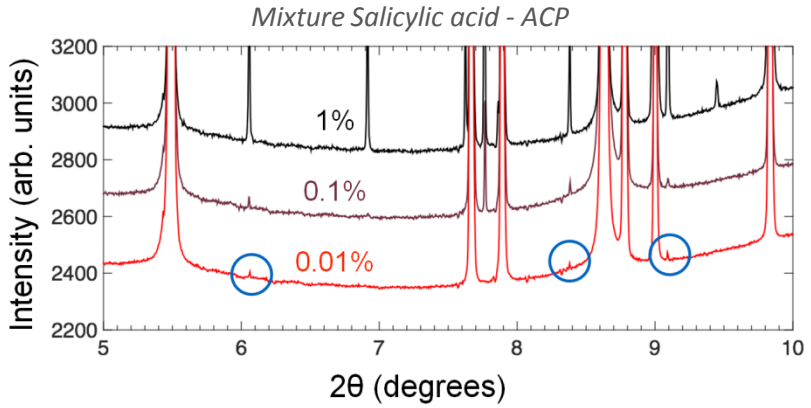
CHALLENGES

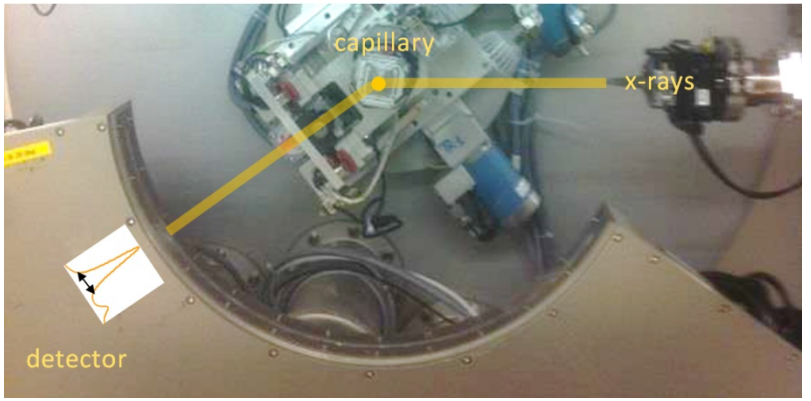
Pushing **instrument** limits

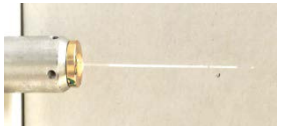
Synchrotron radiation +
Position sensitive detector +
capillary geometry

LoQ<0.05 wt%, LoD<0.01 wt%
High angular (FWHM) resolution
Data collection efficiency
Data modelling
No transparency effect
Tunable wavelength

Particle statistics/homogeneity of distribution
Low scattered intensity
Reproducibility cap. patterns







vs

Quantifying small traces of pharmaceuticals on an absolute scale

CHALLENGES

Tailoring methodology

Know your sample: **organics**

Light molecules, poor scattering power, large unit cells, low symmetry, peak overlapping, radiation sensitive, low absorption…

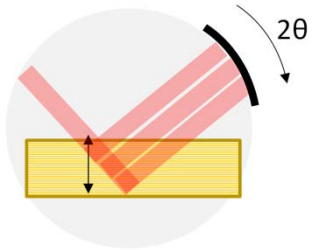
Spatial inhomogeneities

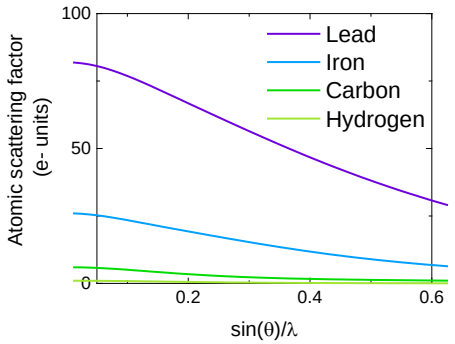
⇨ sample more powder volumes

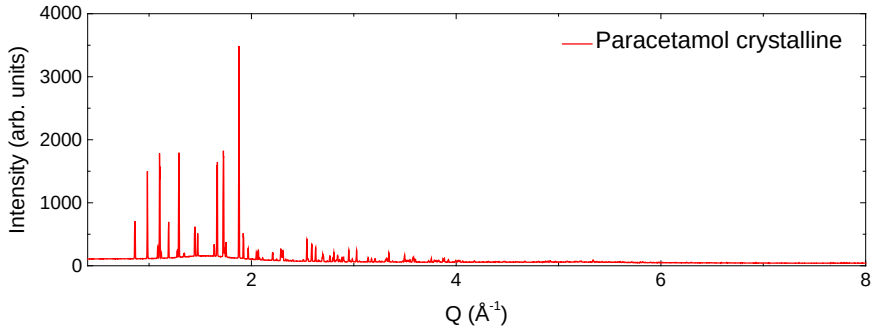
Semi-crystalline materials

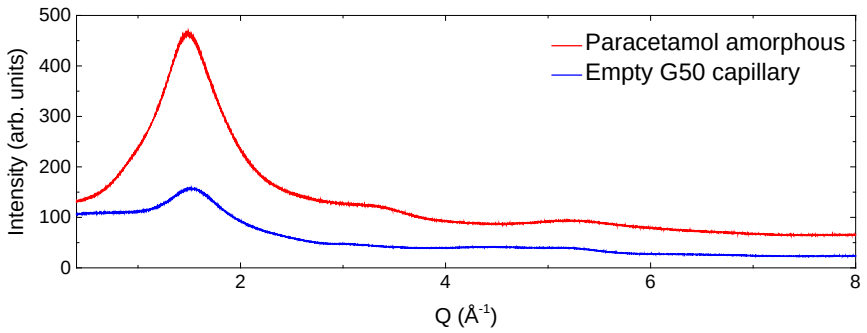
Degree **o**f **C**rystallinity (DoC)

Correlation amorphous contributions sample vs container









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Quantifying small traces of pharmaceuticals on an absolute scale

CHALLENGES

Choice of quantification method

Internal standard method

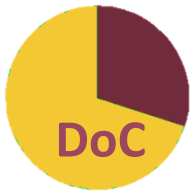
Calibration curve: Y/N

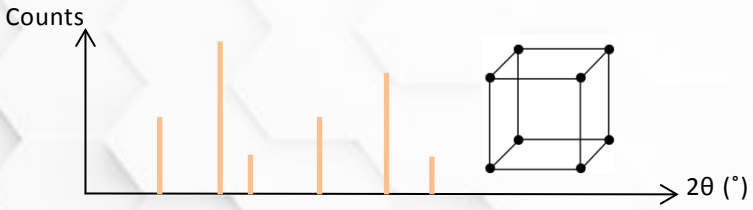
- Direct correction for instrumental effects
- Comparable matrix effects
- Unknown compounds
- Amorphous quantification, Absolute scale
- Universal

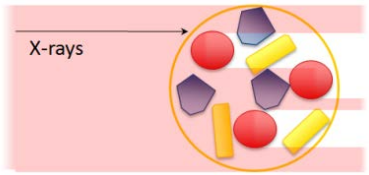
- Internal standard tailored to analyte
- Time consuming powder processing
- Powder samples only
- Analyte mixture contamination

Which internal standard?

```
;
 Structure of Sucrose
;
_journal_name_full                 'Personal communication to COD'
_journal_year                      2013
_chemical_formula_moiety           'C12 H22 O11'
_chemical_formula_sum              'C12 H22 O11'
_chemical_formula_weight           342.30
_space_group_IT_number             4
_symmetry_cell_setting             monoclinic
_symmetry_Int_Tables_number        4
_symmetry_space_group_name_Hall    'P 2yb'
_symmetry_space_group_name_H-M     'P 1 21 1'
_atom_sites_solution_hydrogens     geom
 atom sites solution primary       direct
```







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

C Madsen and N. V. Y. Scarlett in 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
Deane K. Smith Powder Diffraction, 16, pp 186-191, (2001), doi:10.1154/1.1423285

Quantifying small traces of pharmaceuticals on an absolute scale

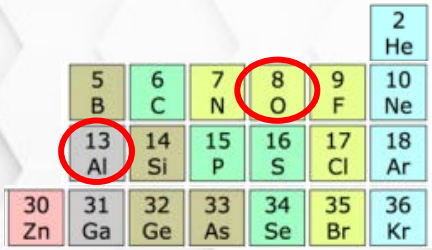
CHALLENGES

Compromises …

Alumina

Nice peak shape

Known DoC (NIST standard SRM676 series)



Density ca. 3.9 g.cm^{-3}

LAC (12.4 keV) = 37.3 cm^{-1}

Small wt% ⇨ weighting errors

Quantifying small traces of pharmaceuticals on an absolute scale

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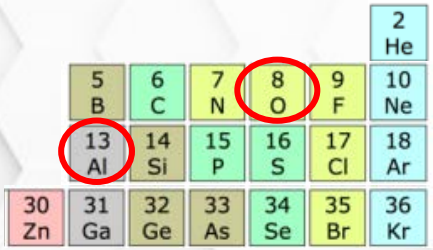


Density ca. 3.9 g.cm^{-3}

LAC (12.4 keV) = 37.3 cm^{-1}

Small wt% ⇨ weighting errors

Beyond Alumina

Diamond

LAC (12.4 keV) = 3.2 cm^{-1}

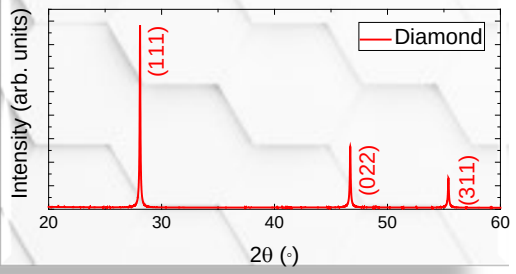
Density ca. 3.5 g.cm^{-3}

Small wt% ⇨ weighting errors

Very few peaks <60° 2θ

⇨ limited redundancy for peak overlap

Purity of grinding media

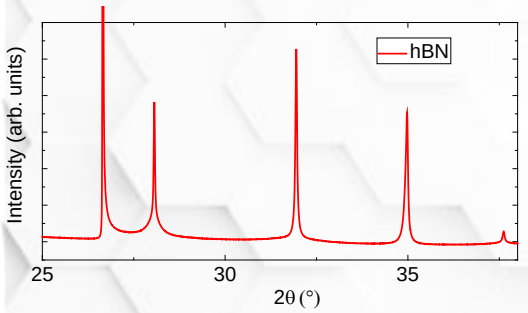


hBN

Density ca. 2.1 g.cm^{-3}

LAC (12.4 keV) = 2.9 cm^{-1}

Helps to homogenize blends



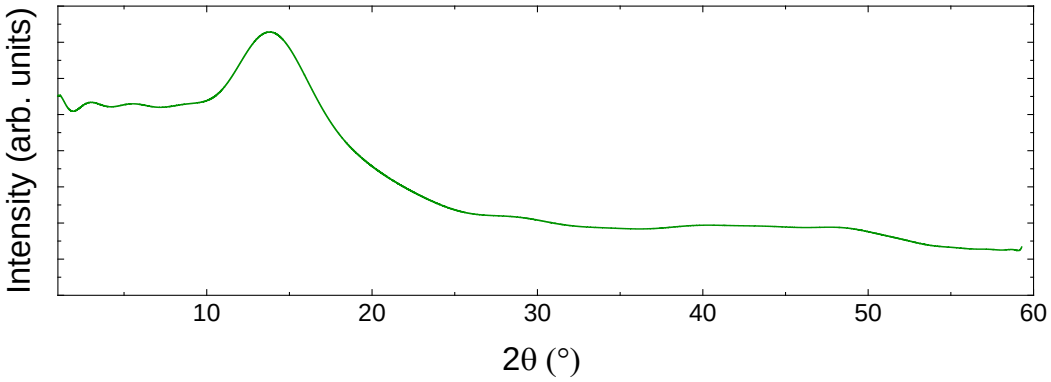
Flakes ⇨ difficult peak shape

Standard Rietveld refinement won't work

Alternative analysis strategy

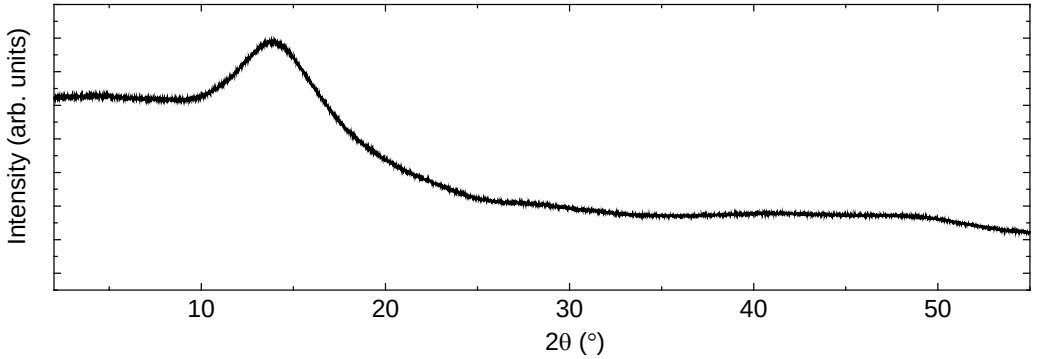
Assessing the DoC – Background fit

- High order polynomial:



- Main separate contributions (physically-based background):

Empty

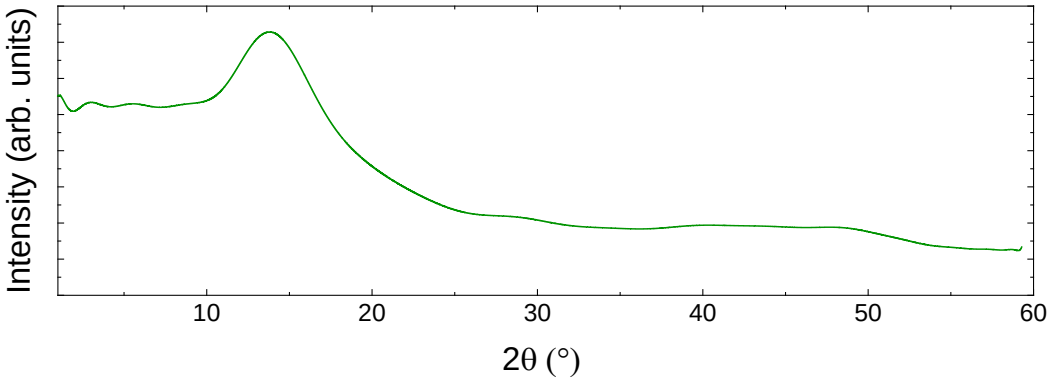


- Modelling or subtracting?
- REAL samples: Amorphous pattern **not always** available

(i.e. calibration curve amorphous/crystalline not an option)

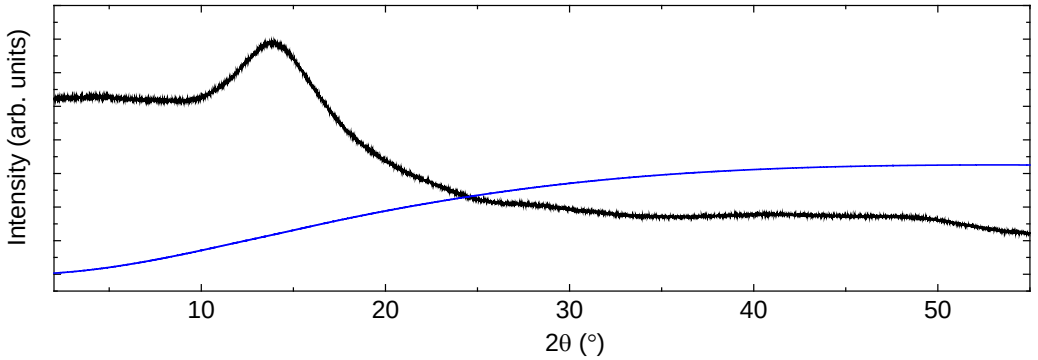
Assessing the DoC – Background fit

- High order polynomial:



- Main separate contributions (physically-based background):

Empty
Compton



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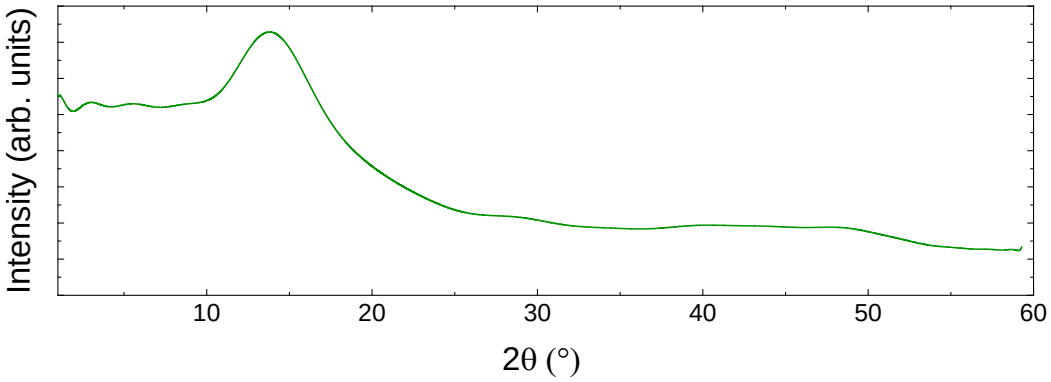
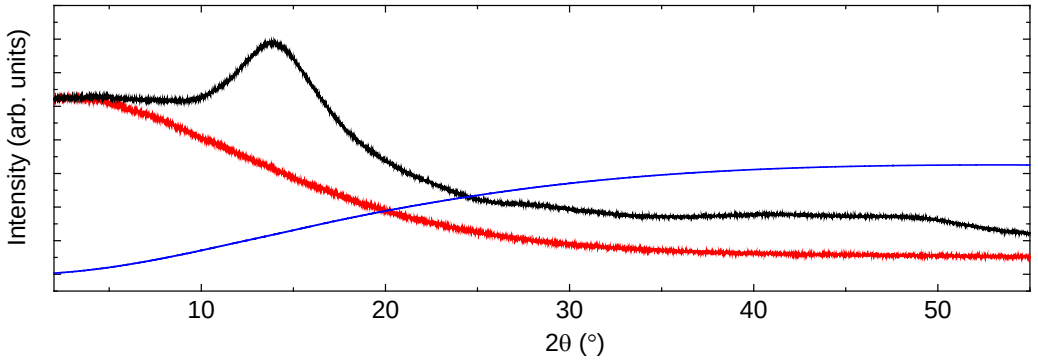


- Main separate contributions (physically-based background):

Empty
Compton
Air

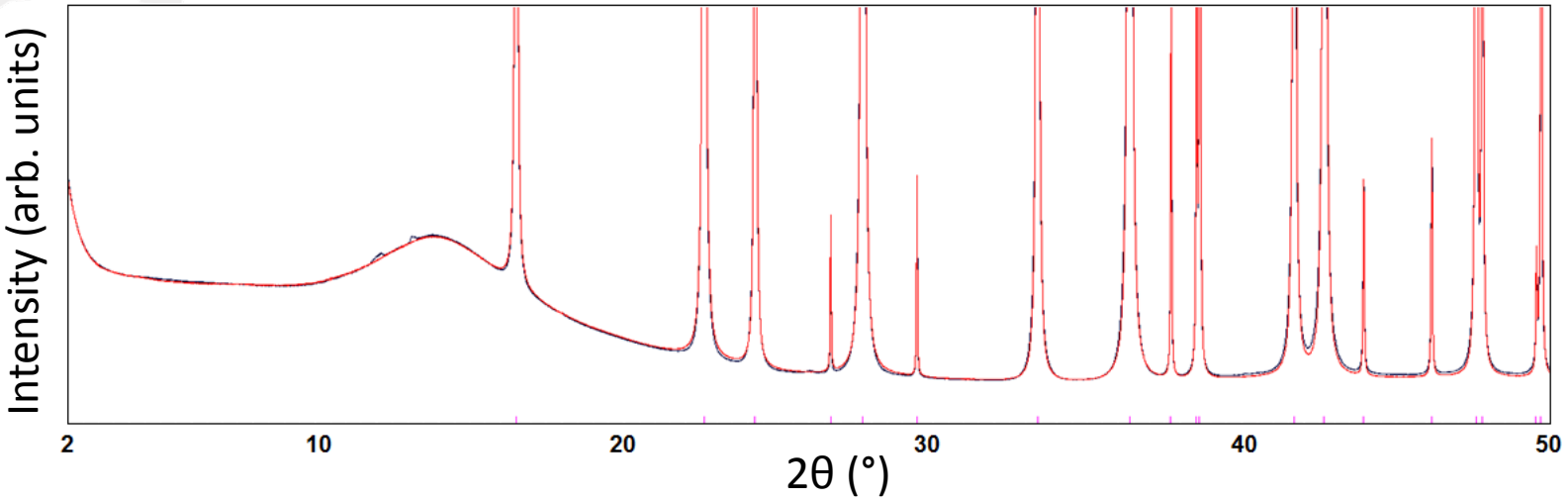


- Modelling or subtracting?
- REAL samples: Amorphous pattern **not always** available

(i.e. calibration curve amorphous/crystalline not an option)

Assessing the DoC – 'Testimonial' example of Alumina

- Alumina DoC

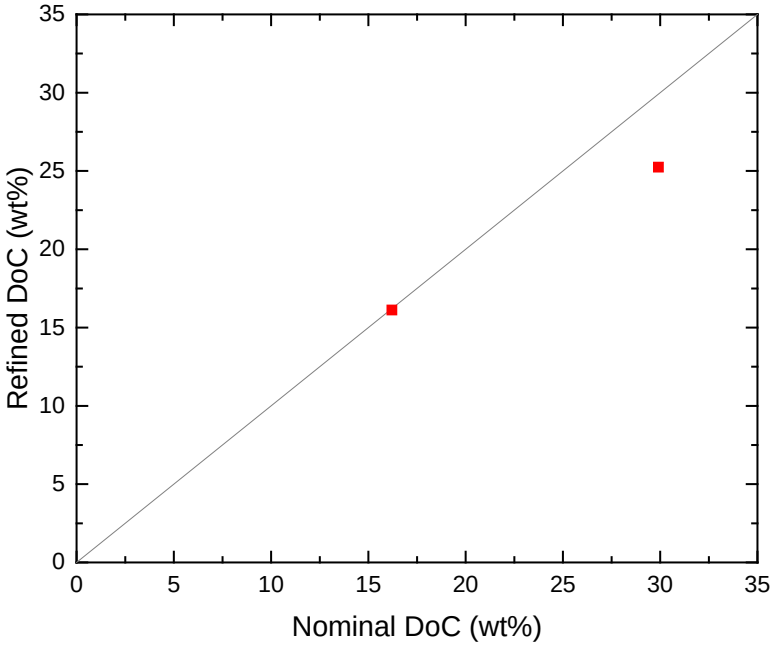


Background fits nicely with identified diffuse contributions

Expected DoC between 99 and 100 wt%:
we are NOT sensitive to <1 wt% amorphous content

Assessing the DoC – Consistency with *ad-hoc* mixtures

- Test method against ***ad-hoc* physical mixtures** of amorphous /crystalline lactose



<u>Step 1:</u>

DoC of pure 'crystalline' lactose: 97% DoC

<u>Step 2:</u>

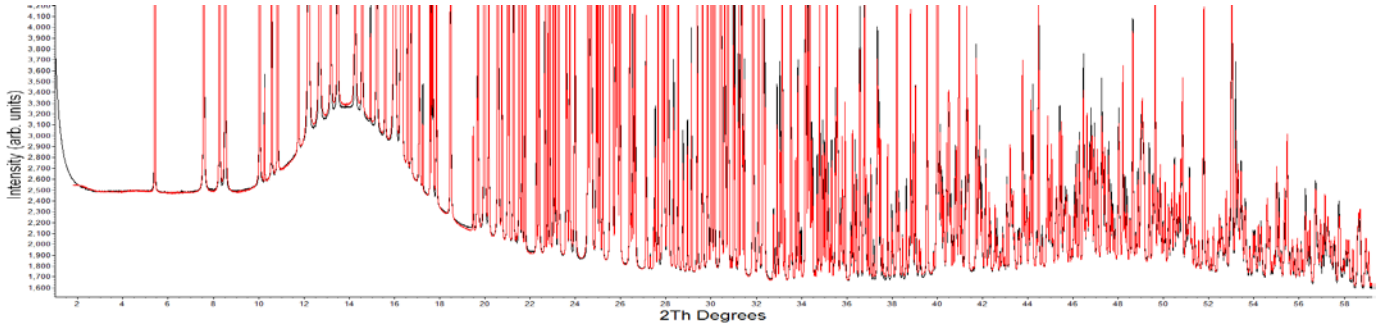
Refinement of the amorphous phase 'by difference'

Ad-hoc mixtures of lactose: relative error between weighted and refined ratio in the range 0.5 – 16 %

Assessing the DoC – for all pure phases

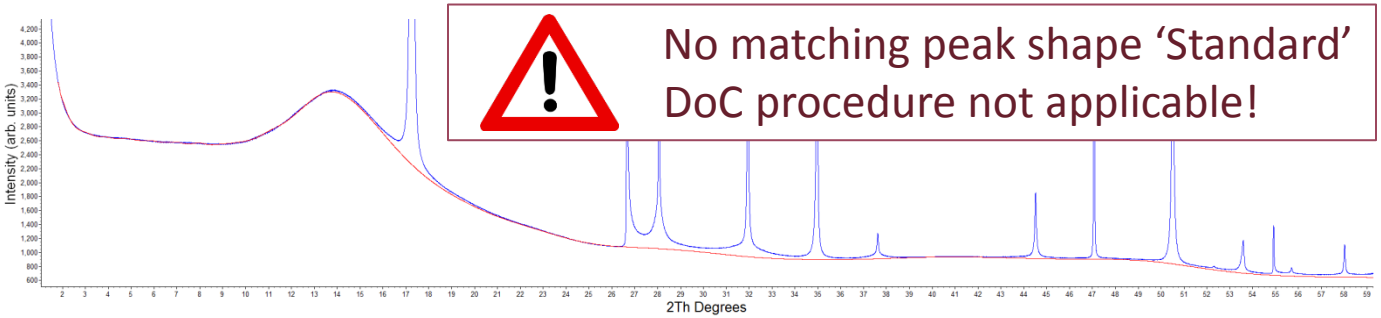
- Sucrose

DoC ca. **96.4 wt%**



- hBN

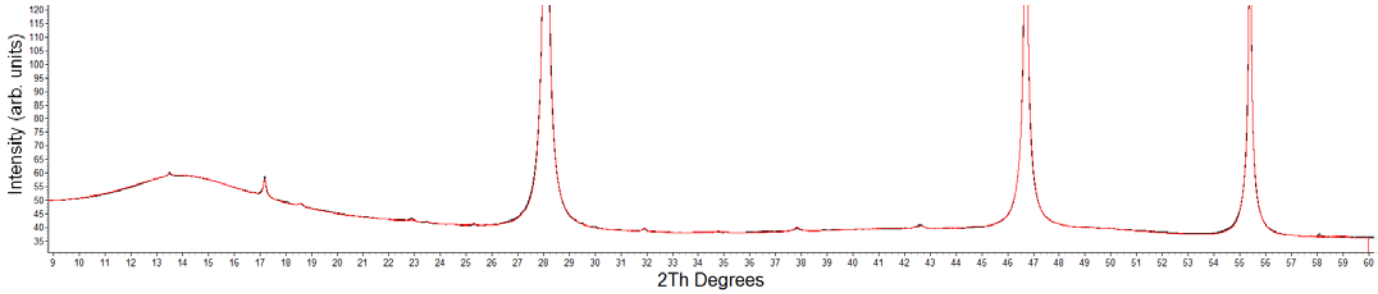
DoC ca. **99 wt%**



No matching peak shape 'Standard'
DoC procedure not applicable!

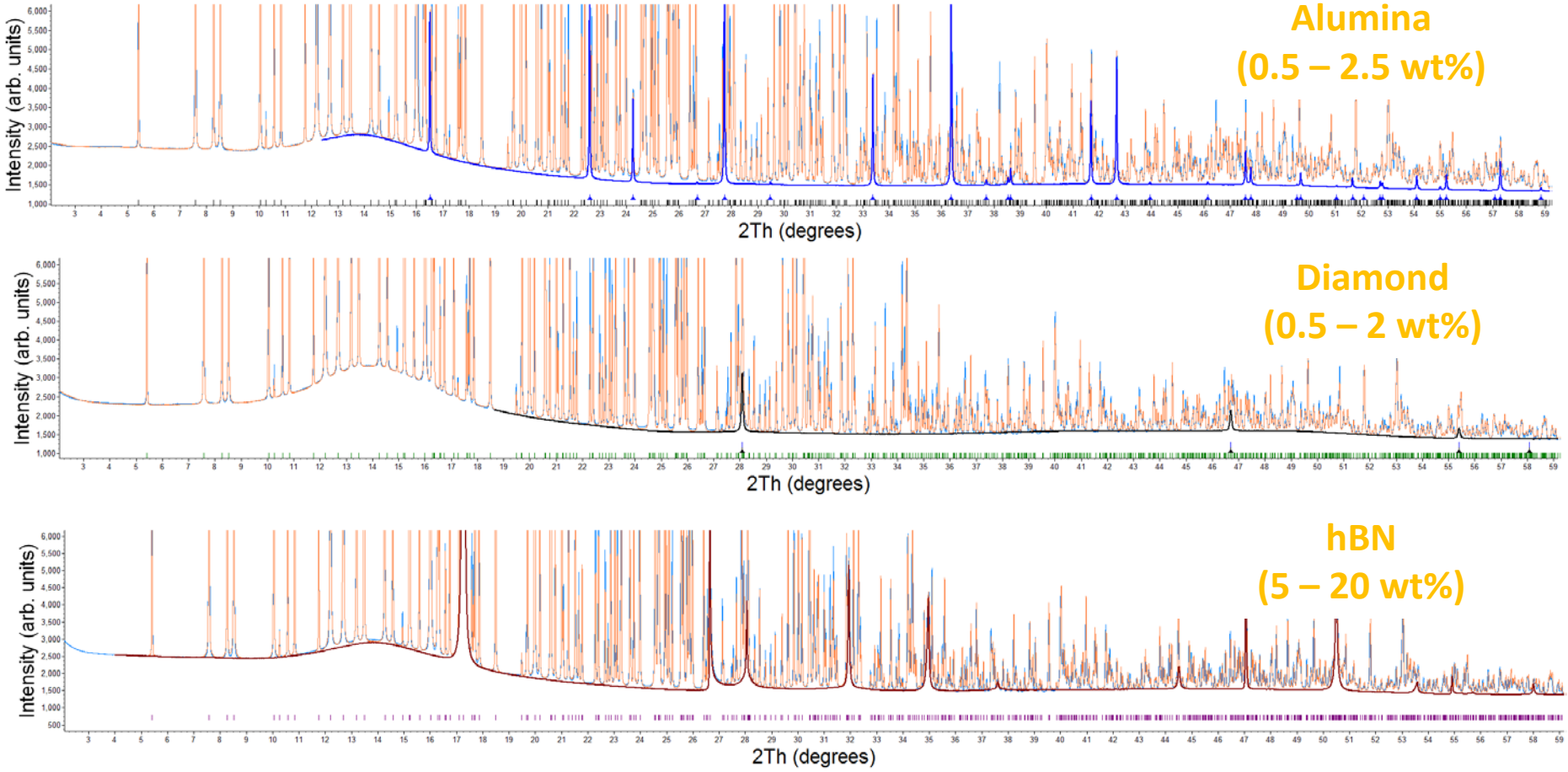
- Diamond

DoC ca. **95.8 wt%**



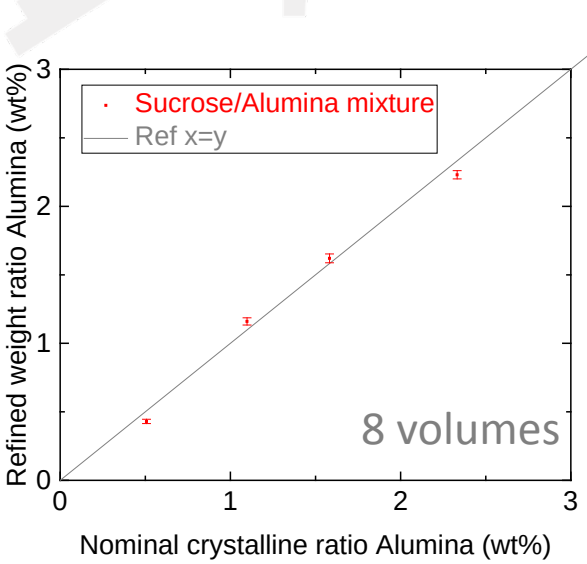
Overview calibration curve mixtures

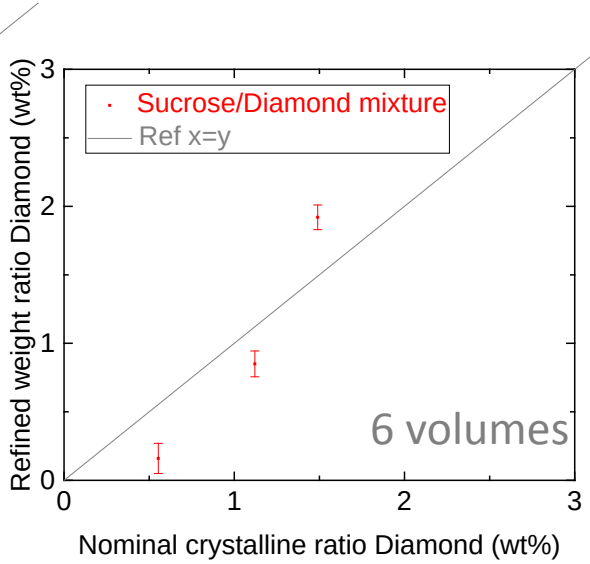
- Sucrose/Alumina-hBN-Diamond mixtures
- Small wt% to improve distribution homogeneity and adapted to scattering power

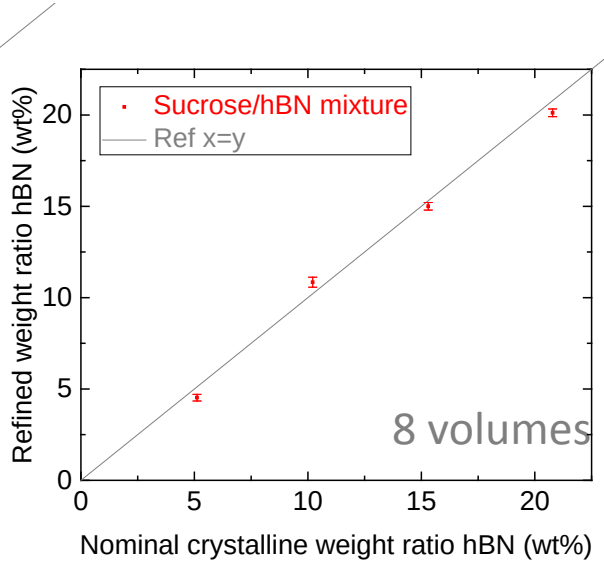


Overview calibration curve mixtures

- Comparison calibration curves internal standard/sucrose







Alumina
(0.5 – 2.5 wt%)

Standard Rietveld refinement

Diamond
(0.5 – 2 wt%)

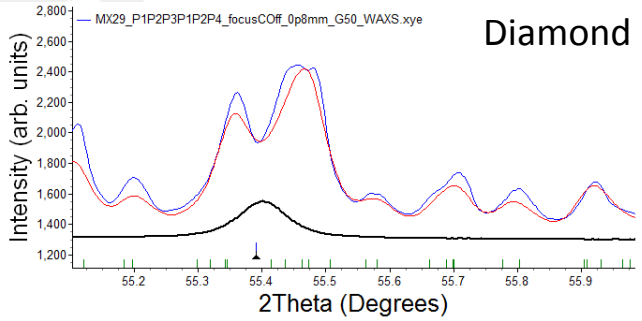
Standard Rietveld refinement

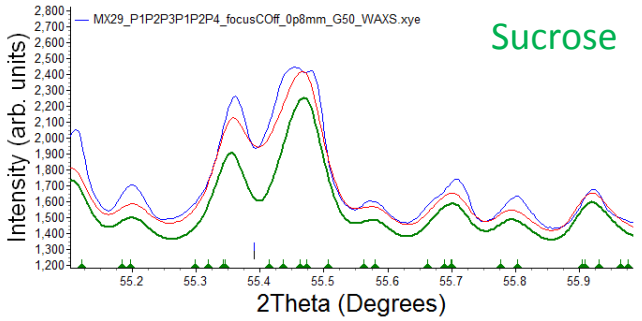
hBN
(5 – 20 wt%)

hBN modelled using observed data and calibrated versus Alumina

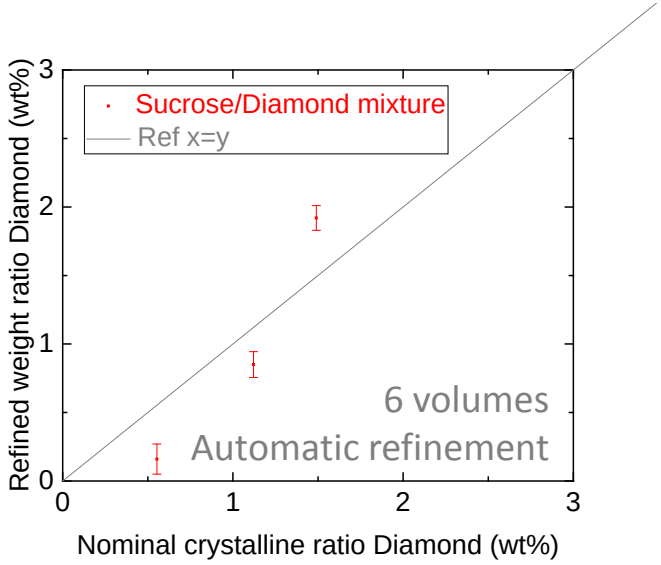
Diamond as internal standard – calibration curve

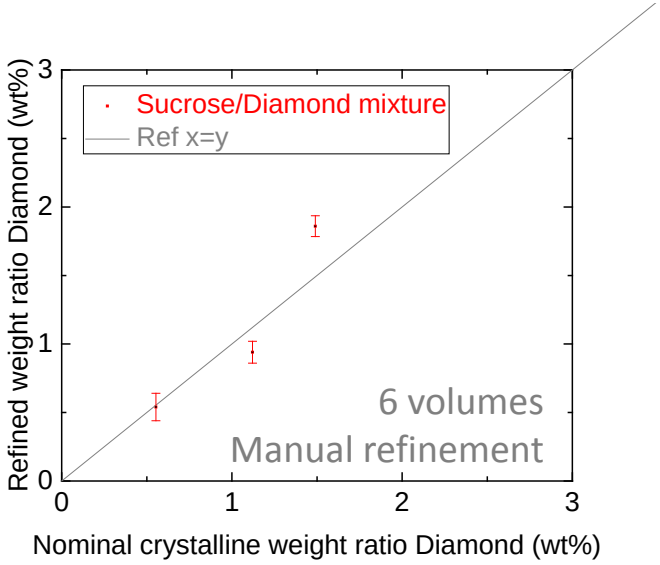
- Strongly **correlated** Diamond/Sucrose reflections





- **Limits** of the least square optimization





What next?

The three candidates can be used under favorable circumstances:

Alumina: restrained wt%

Diamond: if peak overlapping allows

hBN: if peak overlapping allows and intensity (not more than 20wt%)

- Validate DoC method
- Try DoC using the scaled amorphous phase
- Assess the lower limit of amorphous-QPA

- Ternary mixtures with each of the standards (increased Diamond wt%)
- Test of alternative analysis methods (PONKCS, 'Siroquant'-like, proper model of hBN distortions, 'Principal Component Analysis'-like)

Acknowledgments /References

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Nicola Casati & MS beamline team, Swiss Light Source
Celestino Padeste
Claire Villevieille & Cyril Marino
Paul Scherrer Institute, Villigen, Switzerland

Arnaud Grandeury
Novartis Pharma AG, Basel, Switzerland

Danysz Eustache & coworkers
Saint-Gobain, Saint-Gobain Advanced Ceramics LLC

Ian Madsen
CSIRO, Australia

Useful references

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Thank you for your attention

Questions?

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