

Excelsus Structural Solutions as an example of technology transfer of SR based analytical services

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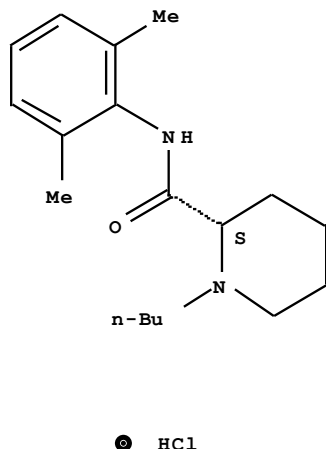
Outline

- I. Importance of structural analyses in the pharmaceutical industry
- II. Fast and efficient Synchrotron XRPD versus lab-XRPD
- III. SR-XRPD key applications
- IV. Excelsus Structural Solutions' milestones
- V. What does Excelsus Structural Solutions offer?
- VI. Conclusion

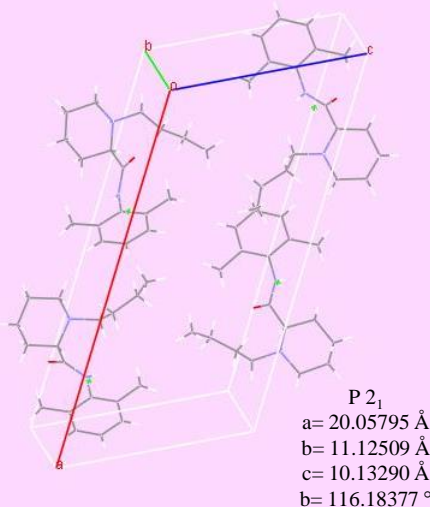
Why is structural analysis relevant to the pharmaceutical industry?

- Polymorphism and the relation between **structure** ↔ **properties**
- Microstructural properties (e.g. influence of stress and strain, particle size and domain)

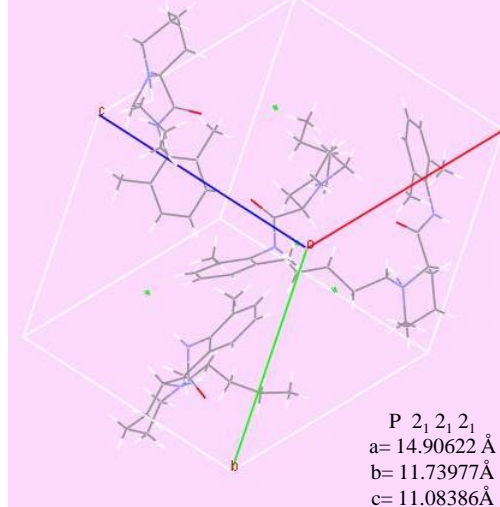
Example of
Bupivacaine Hydrochloride



Form B at 112 °C, monoclinic



Form D at 20 °C, orthorhombic



Gozzo, Masciocchi, Griesser, Niederwanger, 2010. Personal Communication

Properties influenced by the solid state structure of substances and, therefore, influenced by polymorphism:

- Solubility
- Pharmacokinetics and pharmacodynamics
- Thermodynamic properties (e.g. stability of drugs) → **in-situ non-ambient time-resolved studies**
- Mechanical properties (e.g. hardness, compressibility, tableting, tensile strength)

Polymorphic studies play a key role throughout the whole life-cycle of products

Early development

- Support to the selection of the appropriate form(s)



Technical development

- Development of manufacturing processes to ensure high and reproducible content of desired polymorphic form
- Polymorphic studies for impurity detection and stability studies
- Crystal engineering (e.g. co-crystallization*)



Commercial production

- Polymorphic characterization to support (1) process validation, (2) comparability studies following process changes, and (3) investigations to assess impact of deviation on product quality

Intellectual Property (IP)

Fight against counterfeit drugs

X-ray Powder Diffraction,
in particular with
synchrotron radiation is a
unique and powerful
technique for such studies

* Example of carbamazepine (see *Organic Crystal Engineering*, Eds. Tiekink, Vittal & Zaworotko, Wiley 2010)

What makes **synchrotron-XRPD**
such a powerful analytical tool?



An efficient synchrotron facility and beamline optics

- Extremely high beam intensity: 10^{12} - 10^{15} photons/sec in small beams (μm^2 to mm^2)
- Tunable photon wavelength



- ✓ Efficient data collection
- ✓ Time-resolved studies
- ✓ XRD near absorption edges

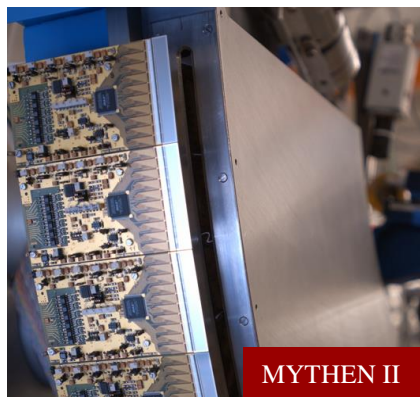


State-of-the-art diffractometers

- Great mechanical stability: resolution, accuracy and precision of the order of ± 1 -2 arcsec
- Highest flexibility to accommodate all kinds of sample environments



- ✓ Broad range, non-standard experiments



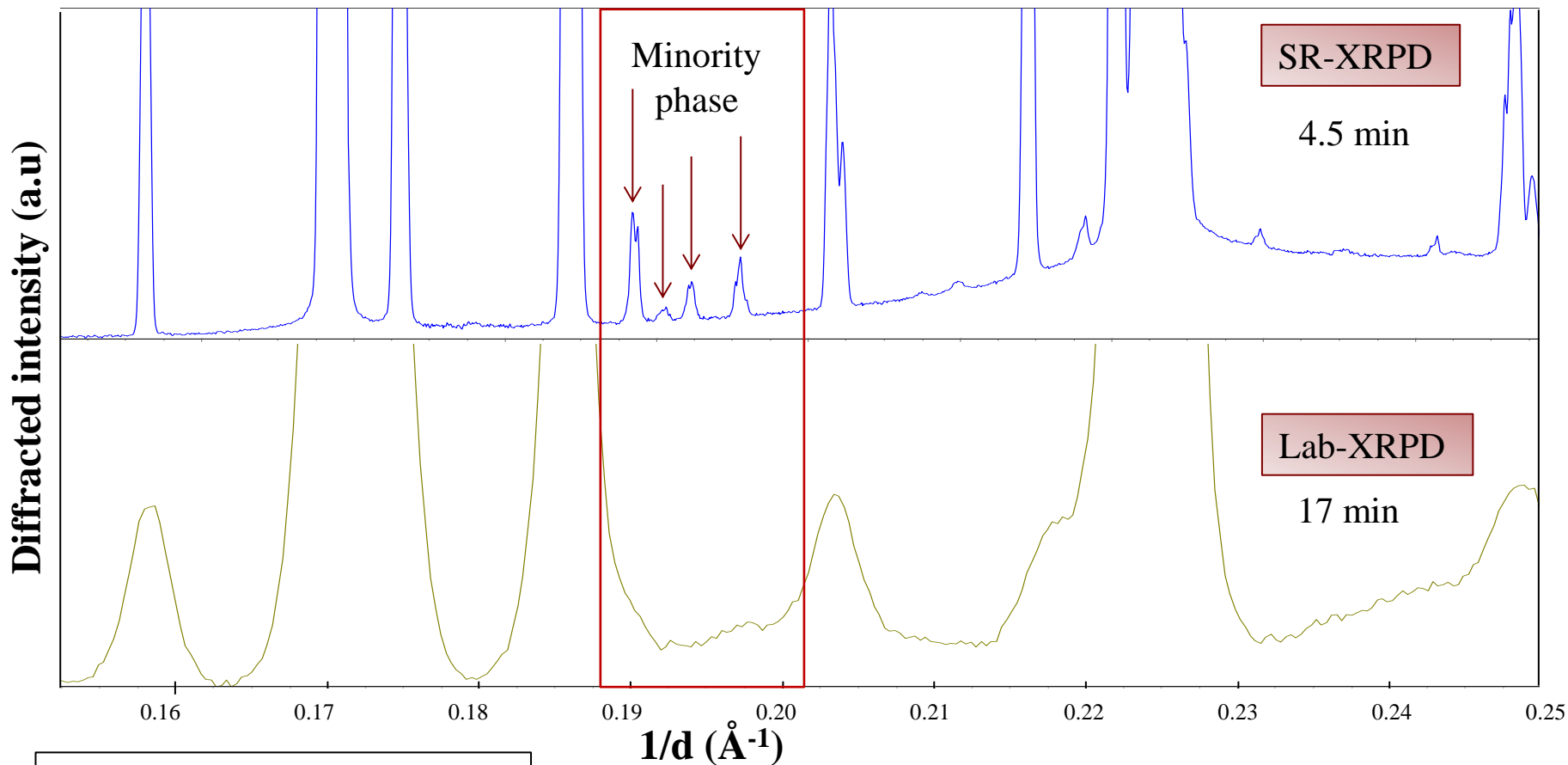
Outstanding detection systems

- Extremely fast and efficient → full diffraction patterns in milliseconds with good statistics, millions of counts in few seconds
- 120° angular coverage
- 0.004° inherent angular resolution
- Simultaneous detection of strong and weak signals



- ✓ Time-resolved kinetic studies
- ✓ Control of radiation damage

1% Phase A+ 99% Phase B



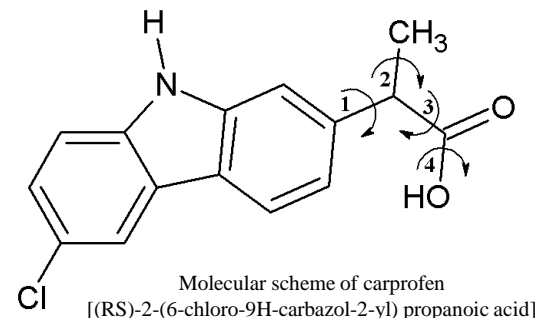
Lab-XRPD: I. Madsen, CSIRO, Australia

CARPROFEN: a tricky case of polymorphism

- Non-steroidal anti-inflammatory drug (Rimadyl, Imadyl, Novox, Imafen and Rovera)
- Comprehensive physicochemical characterization of carprofen still missing, in particular the study of possible polymorphs and their structural characterization

We therefore performed:

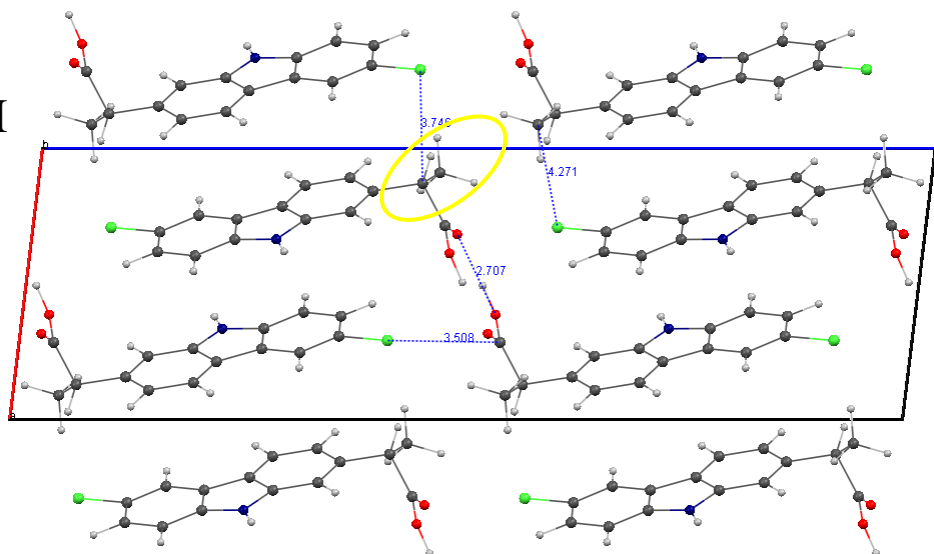
- Re-crystallization from various hot solutions of commercial solid form → isolated two new forms:
 - ❖ Re-crystallization in ethanol (Form I)
 - ❖ High-Temperature as solid-solid transformation (Form II)
- Thermal, spectroscopic, lab-XRPD and *ab-initio* SR-XRPD and post-experimental DFT calculations
- Low-T measurements and high-pressure investigations



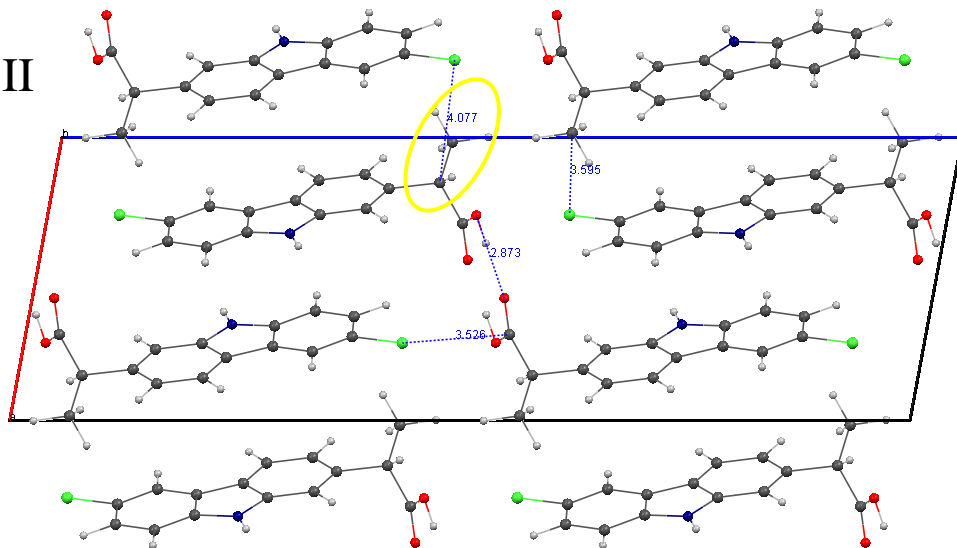
Lab-XRPD could ONLY indicate that Form I and II might have been different forms:

- No indexation possible
- No purity assessment

Form I



Form II



Conclusions from SR-XRPD

- Form I → Form II is a subtle **isostructural transformation**
- The structure **ONLY** differs by the torsional angle of the methyl group
- Form I and II are **conformational polymorphs**
- Evidence for **configurational disorder**
- Commercial form made of a 40/60 % mixture of Form I and II

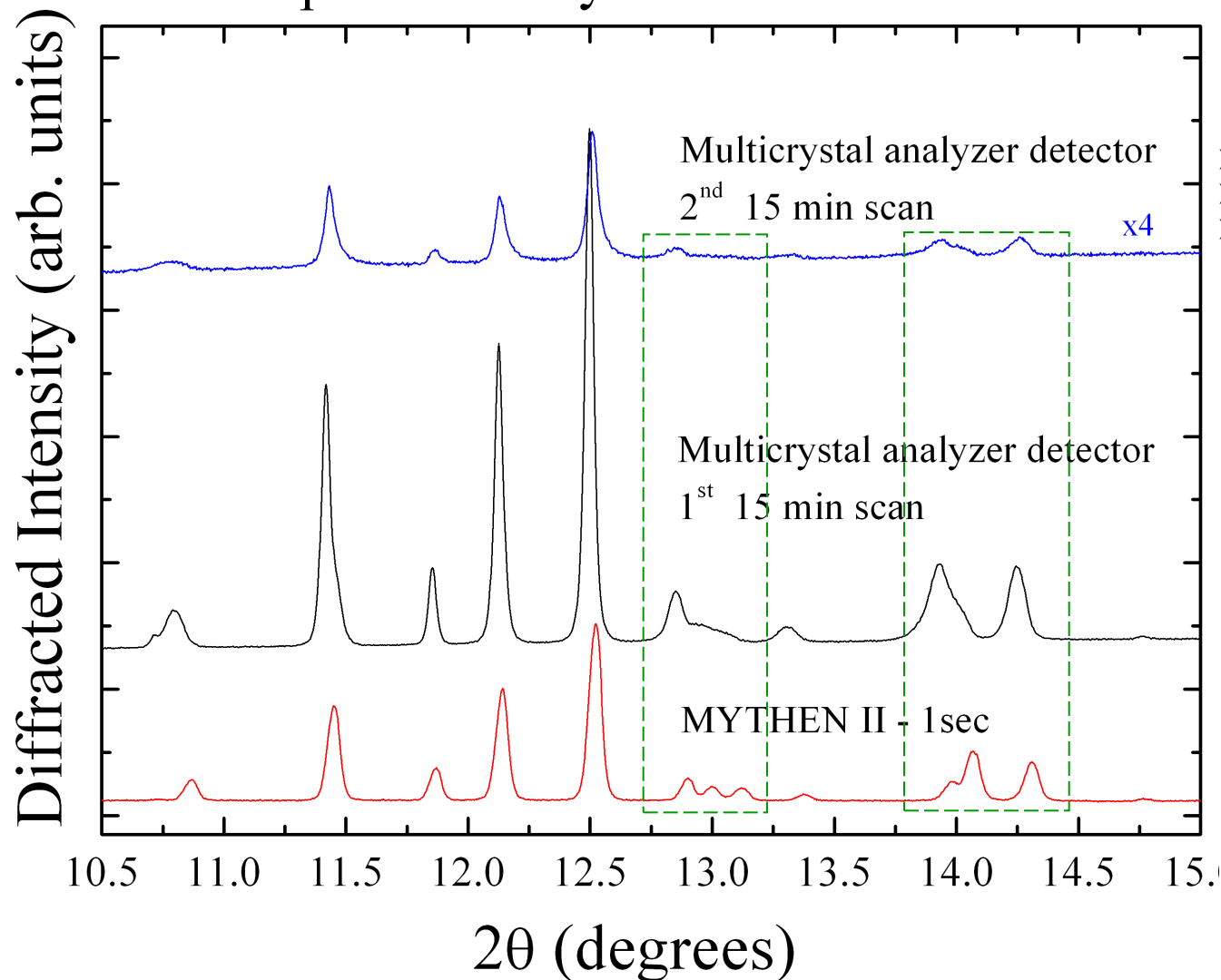
Minimization of radiation damage control with fast and dose-controlled SR-XRPD

- **Radiation Damage** is the **alteration of the structural and chemical properties** of the material under investigation induced by its exposure to electromagnetic radiation. It is **dose** and **energy** dependent
- In XRD patterns we observe shift (usually anisotropic) and broadening of reflections and their progressive disappearance → it usually undermines the success of structural solution

The effect is very serious at 3rd generation synchrotron facilities and affects the study of organic compounds, in particular pharmaceuticals

Our high-resolution, fast and dose controlled SR-XRPD measurements have opened a new gate to the systematic structural analyses of organic compounds!

Bupivacaine Hydrochloride - form D



- 1 mm capillary,
- Mythen data at 50% reduced intensity
- No radiation damage up to 3min



Large counting statistics
in subsec acquisition times



In-situ kinetic studies of organic
compounds!

Gozzo F. , 2008
See: Bergamaschi et al, J. Synchrotron
Rad. (2010). 17, 653–668

Quantitative Phase Analysis (QPA): why is it relevant?

- ❑ **Polymorphic purity**: Level of Detection (LoD), Level of Quantitation (LoQ)
- ❑ Assess the **polymorphic composition** in drug substances (API purity) and products (API/excipients composition)
- ❑ **Degree of Crystallinity** in amorphous/crystalline mixtures

QPA with lab-XRPD widely used and an established practice → LoD and LoQ down to very few % wt achievable with reasonable acquisition time and powder volumes

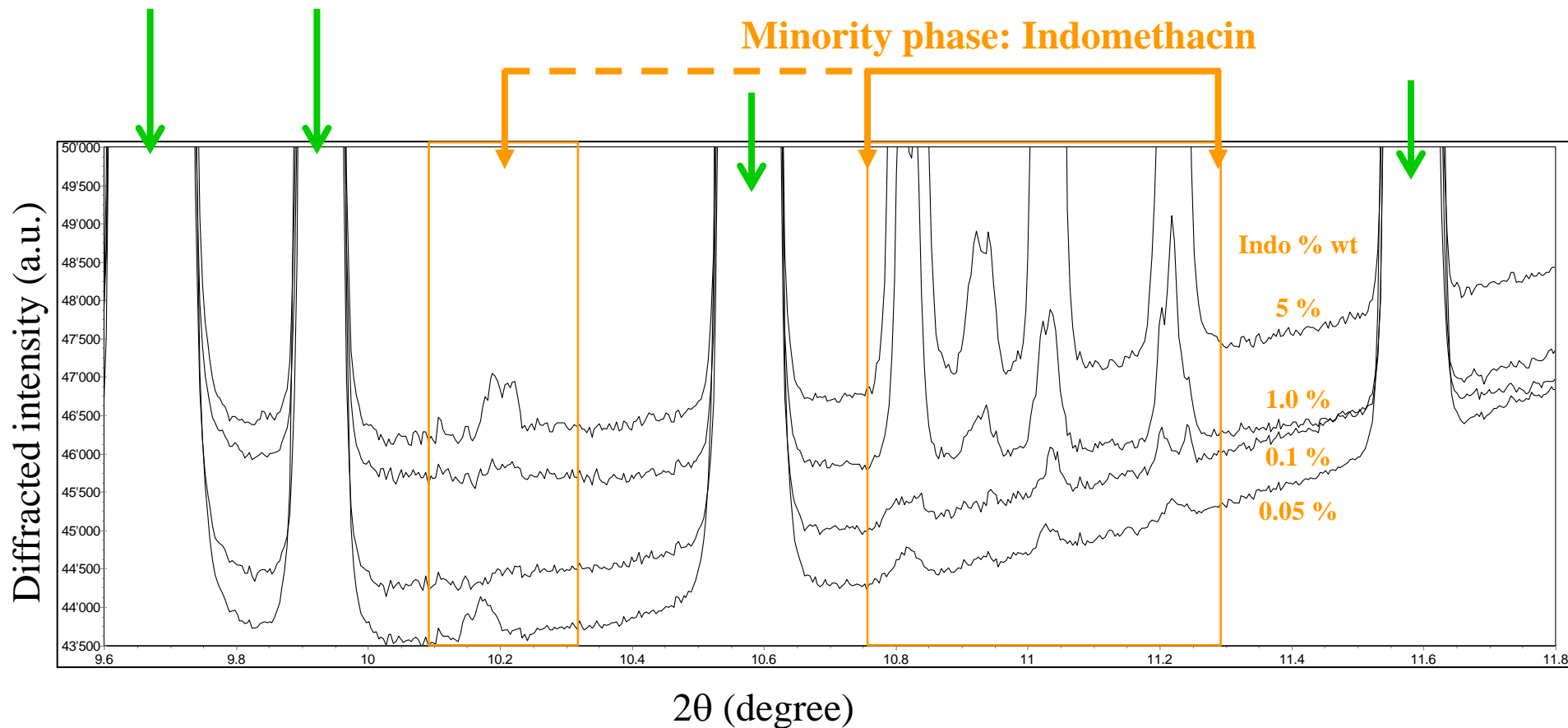
Can SR-XRPD achieve considerably lower LoD and LoQ without increasing costs and complexity?

With our **fast** and **dose-controlled** SR-XRPD we were able to **directly** detect and **quantify** traces of API as low as **0.05% wt** in mixtures

QPA of a binary API physical mixtures with fast SR-XRPD

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

Minority phase: Indomethacin



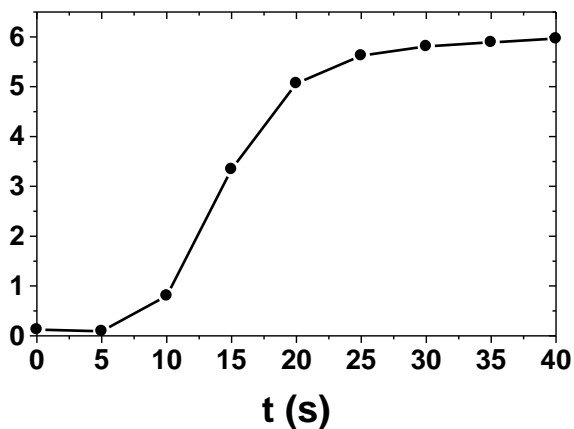


In-situ dynamic study of the LaNi_5 hydrogen absorption process

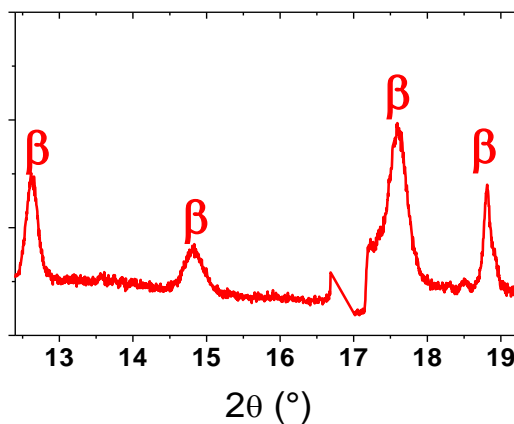
- *In-situ* hydrogen absorption at 15 bar
- *In-situ* desorption by connecting the cell to a vacuum pump
- Continuous measurements using the μ strip detector while the reaction takes place
- Acquisition times between 5 and 20 sec per pattern, depending on the reaction kinetic.

Courtesy of Prof. Cerny, Uni. Geneva - Joubert et al. Acta Materialia, **54** (2006), 713-719

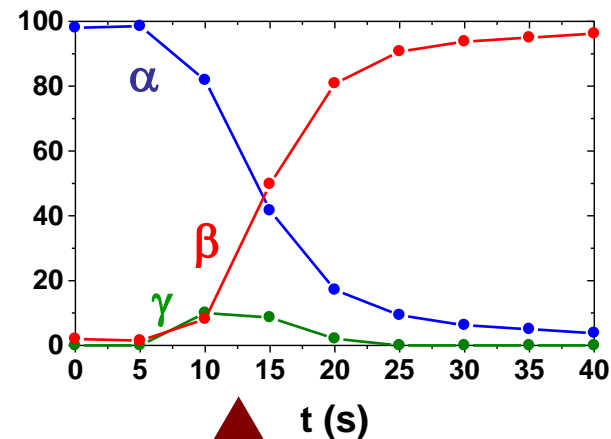
hydrogen uptake



diffraction pattern



phase content



New beamline optics+ Mythen II → 10 faster

t = 40 s

September 2011- February 2012:

- Development of concept, benchmarking
- Partnership with Excelsus Scientific Engineering (ESE) in San Francisco, USA
- Agreement with the Paul Scherrer Institute: ESS as a PSI spin off company
- Join network of ‘young’ entrepreneurs in Brussels
- Financial plan, administrative aspects
- Understanding customers needs (interviews, discussions, meetings, literature)

March 26th, 2012:

- Foundation of Excelsus Structural Solutions in Brussels

January 2012 – June2012:

- ESS web site concept
- Development of ESS activities (search of customers, what can we offer that nobody else does?)
- Industrial oriented research projects (e.g. Quantitative Phase Analyses of organic compounds, LoD, LoQ, amorphous vs crystalline quantitation)
- Pilot customers

July 2012 – December 2012:

- ESS web site realization and publication (www.excels.us), company brochures, ESS+ESE webinar (October 30th, 2012) permanently available on line

http://www.excels.us/index/pages/id_page-161/news-3/lang-en/

- Development of ESS activities (continued)
- Industrial oriented research projects (continued)
- Services to first customers: 2 contracts

January 2013 – June 2013:

- Development of ESS activities (continued)
- Industrial oriented research projects (continued)
- Participation to key meetings: PPXRD in Beijing, CrystalForm@Bologna, BASF diffractionist meeting, Topas Meeting in Gaithersbourg, Biovalley Meeting, International School of Powder Diffraction in Greece, XRD training to ECHA
- Presentations at companies

July 2013 – present:

- Publication on Science Omega with testimonials of Novartis and BASF
- Design of 2 complex SR-XRPD experiments for companies → generation of 2 long term contracts
- Additional 8 work orders, data analyses included
- Coordination of other-than-SR-XRPD measurements via ESS network

Level I:

You internally analyze your synchrotron data.

- we assist you in the choice of the appropriate experimental conditions;
- we prepare the samples
- organize and perform the synchrotron measurements
- deliver the data to you with a written report

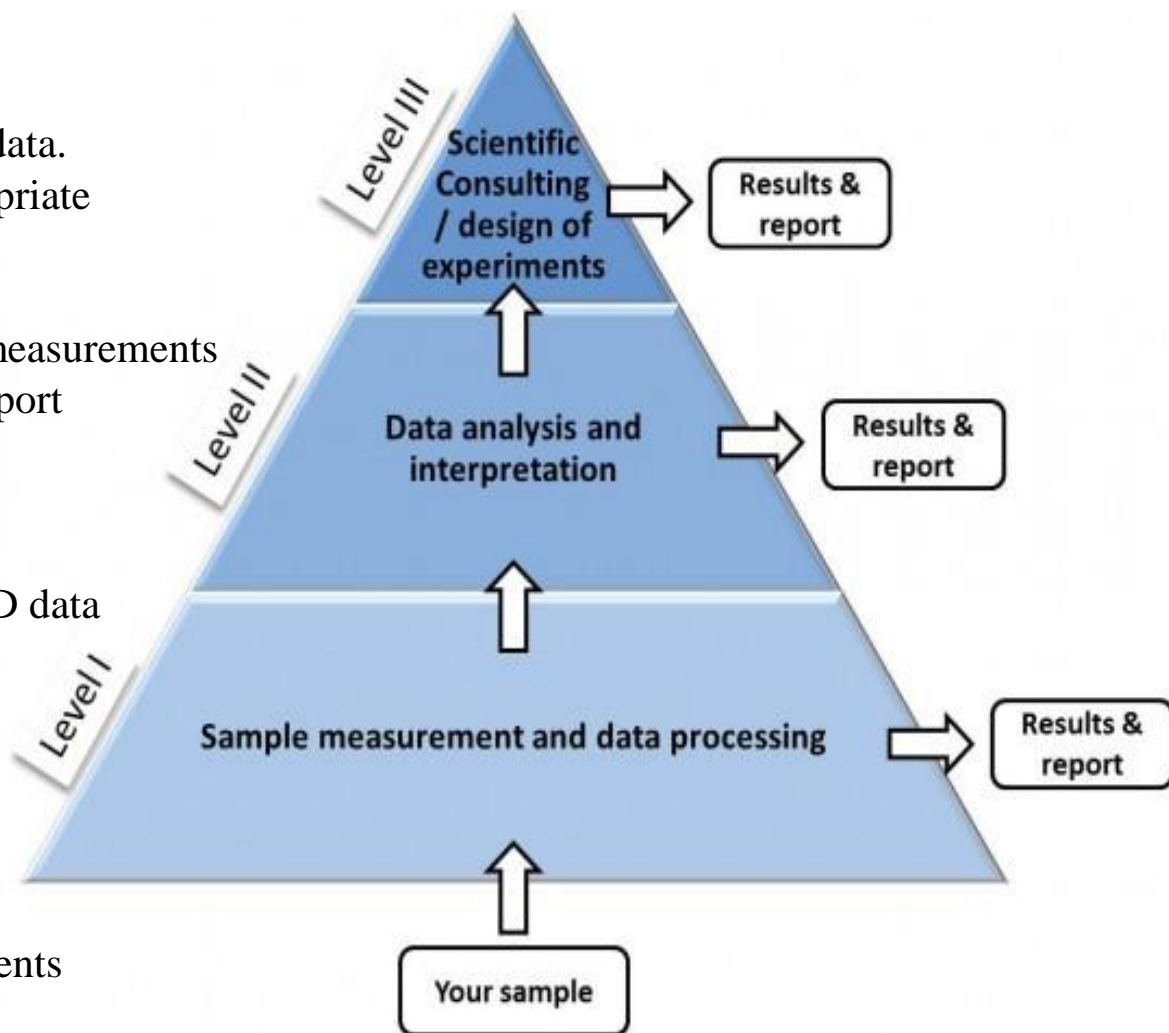
Level II:

In addition to Level I services

- we analyze and interpret your SR-XRPD data
- provide a written report

Level III:

- In addition to Level I and II services,
- we provide scientific consulting
- work in close collaboration with you
- assist you in the design of new experiments





BASF has been working with Excelsus Structural Solutions (ESS) since its inception. Synchrotron X-Ray Powder Diffraction has always been an elemental part of our analytical toolbox, but in the past the effort of accessing beam time and collecting data was exorbitant. Since our collaboration with ESS, this has become as simple as a phone call. We do not have to concern ourselves with all the details of the experimental setup, which can be impressively, but also dauntingly, complex. It is a great pleasure for us to work with a company so dedicated and professional as ESS has proven to be. ESS is our first choice when it comes to accessing SR-XRPD Data.

**Bernd Hinrichsen, Research Scientist, BASF SE,
Ludwigshafen, Germany**



Novartis owns strong technical and scientific capabilities allowing us rapidly assess and resolve problems that might arise. Each material has the potential to present different challenges and technical features. Some may be straightforward and routine, others may be complex. We have further enhanced our analytical capability by forming a partnership with Excelsus Structural Solutions (ESS). For complex tasks requiring a creative, technical or logistical solution, a specialist service such as SR-XRPD was not available worldwide. Faced with exceptionally challenging deadlines our partnership with ESS has been very successful in improving our ability to deliver quick solutions. ESS brings energy, pride and passion on everything they do, they innovate and improve. This partnership has been found to ensure a smooth transition of products during drug product development, underpinning more conventional routes.

**Arnaud Grandeury, Fellow, Pharmaceutical and Analytical Development, Novartis Campus Basel,
Switzerland**

- Synchrotron X-Ray Powder Diffraction is an extremely powerful analytical tool
- SR-XRPD opens new horizons for the characterization of pharmaceuticals throughout their lifecycle
- **Excelsus Structural Solutions**' mission is to provide affordable and easy access to this complex analytical tool

Acknowledgments

- **SLS direction** (C. Quitmann, F. van der Veen, J. Mesot) and **SLS TT AG** (S. Mueller, I. Walthert) and **PSI Technology Transfer** (G. Travaglini, A. Foglia, Ph. Dietrich)
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