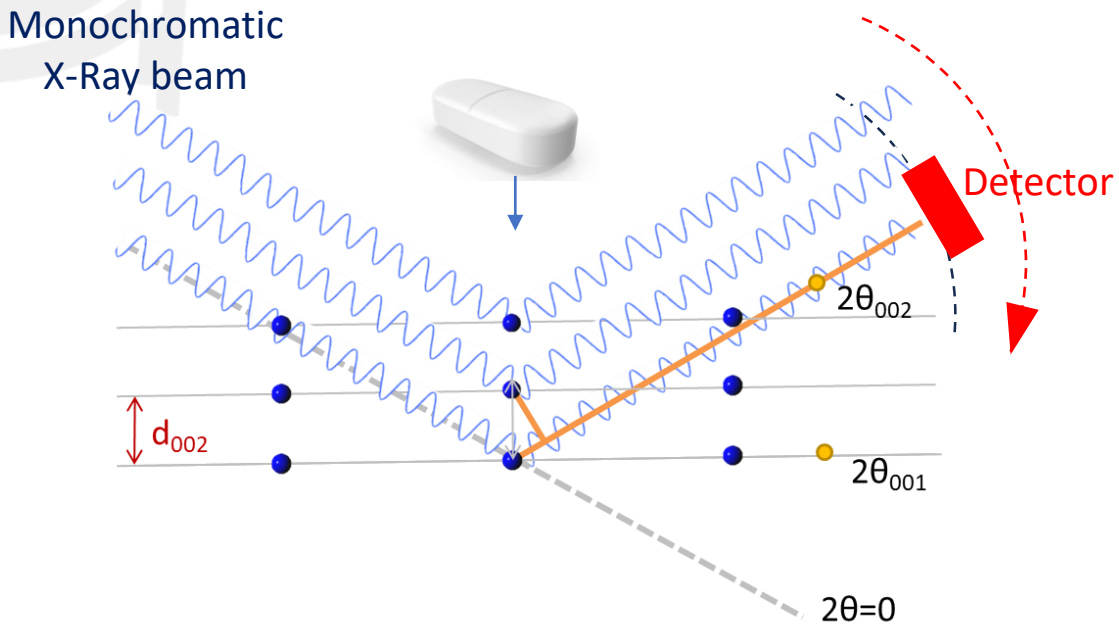
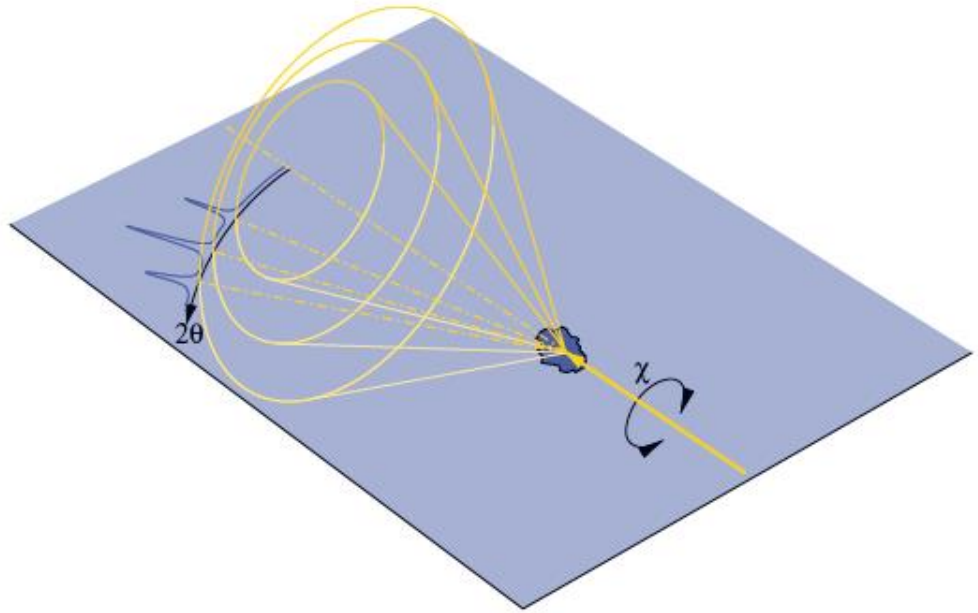
EXCELSUS
STRUCTURAL SOLUTIONS

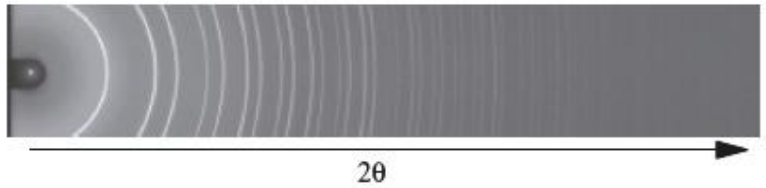
Synchrotron X-Ray Powder Diffraction to support pharmaceutical drug development

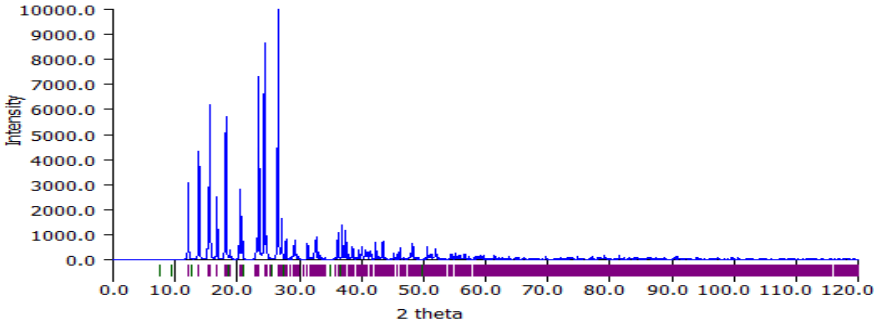
Mathilde Reinle-Schmitt - Excelsus Structural Solutions

How does X-Ray Powder Diffraction (XRPD) work?









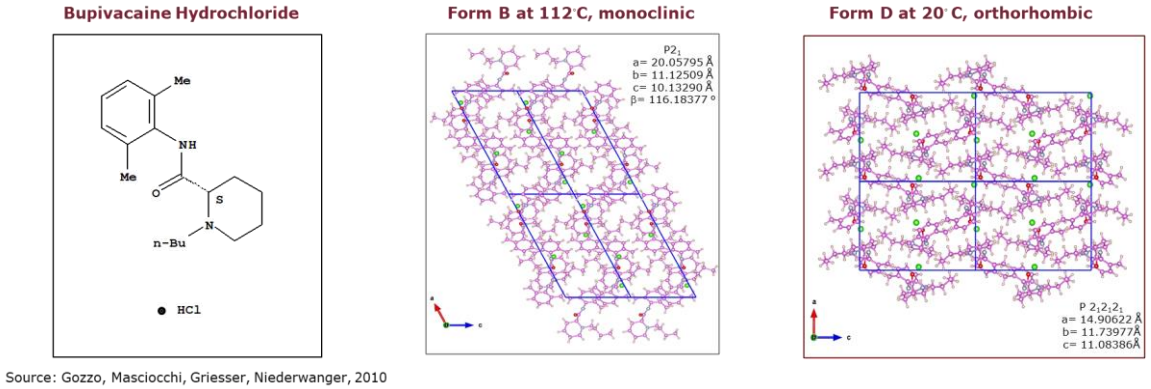
- Position of the diffracted peaks → size and dimension of the unit cell
- Intensity ratios of the diffracted peaks → type and location of atoms in the unit cell
- Full Width at Half Maximum (FWHM) of the diffracted peaks → intrinsic properties of the materials (i.e. microstructural analysis)

What are the typical applications of XRPD for pharmaceuticals?

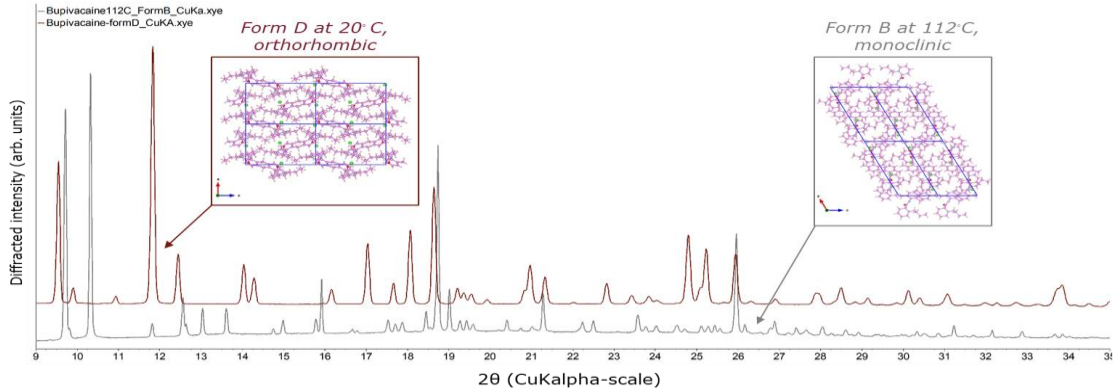
- Used all along the drug development cycle
- 90% of pharma compounds → >1 solid form
- XRPD → gold standard for the identification of solid forms

- Examples of applications?

Polymorph characterization



Source: Gozzo, Masciocchi, Griesser, Niederwanger, 2010



Rodríguez, I.; Gautam, R.; Tinoco, A.D. Using X-ray Diffraction Techniques for Biomimetic Drug Development, Formulation, and Polymorphic Characterization. Biomimetics **2021**, 6, 1.

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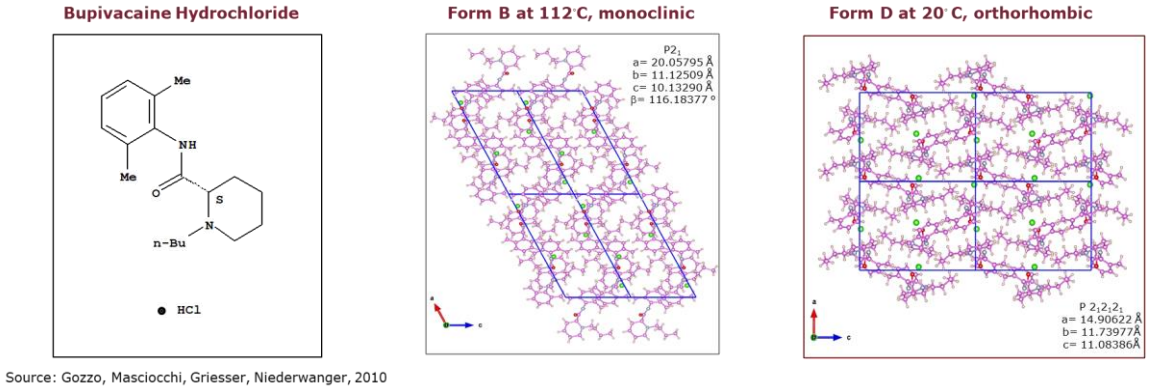

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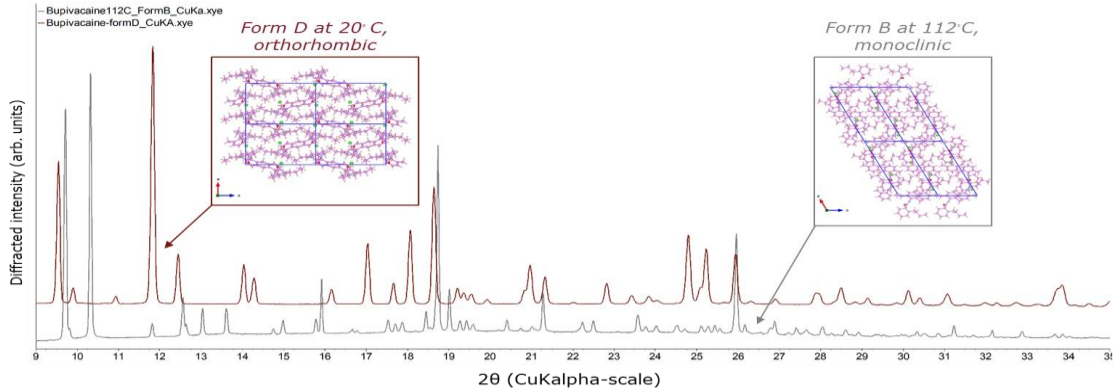


- Examples of applications?

Polymorph characterization

Minority phase detection

Degree of crystallinity

Quality control (monitoring production batches)

Effect of manufacturing/formulation on phys/chem stability

Coating efficiency

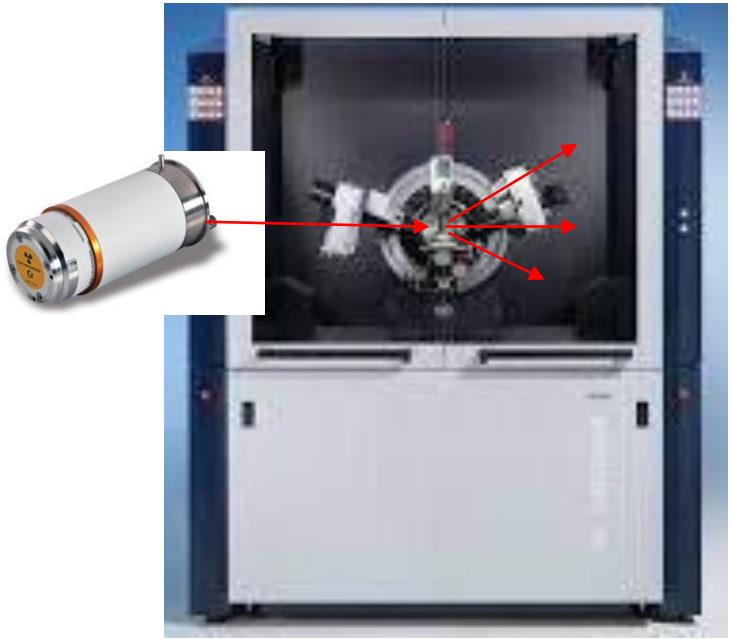
Orthogonal protocol validation

Exclude the presence of API/excipient interaction

Rodríguez, I.; Gautam, R.; Tinoco, A.D. Using X-ray Diffraction Techniques for Biomimetic Drug Development, Formulation, and Polymorphic Characterization. Biomimetics **2021**, 6, 1.

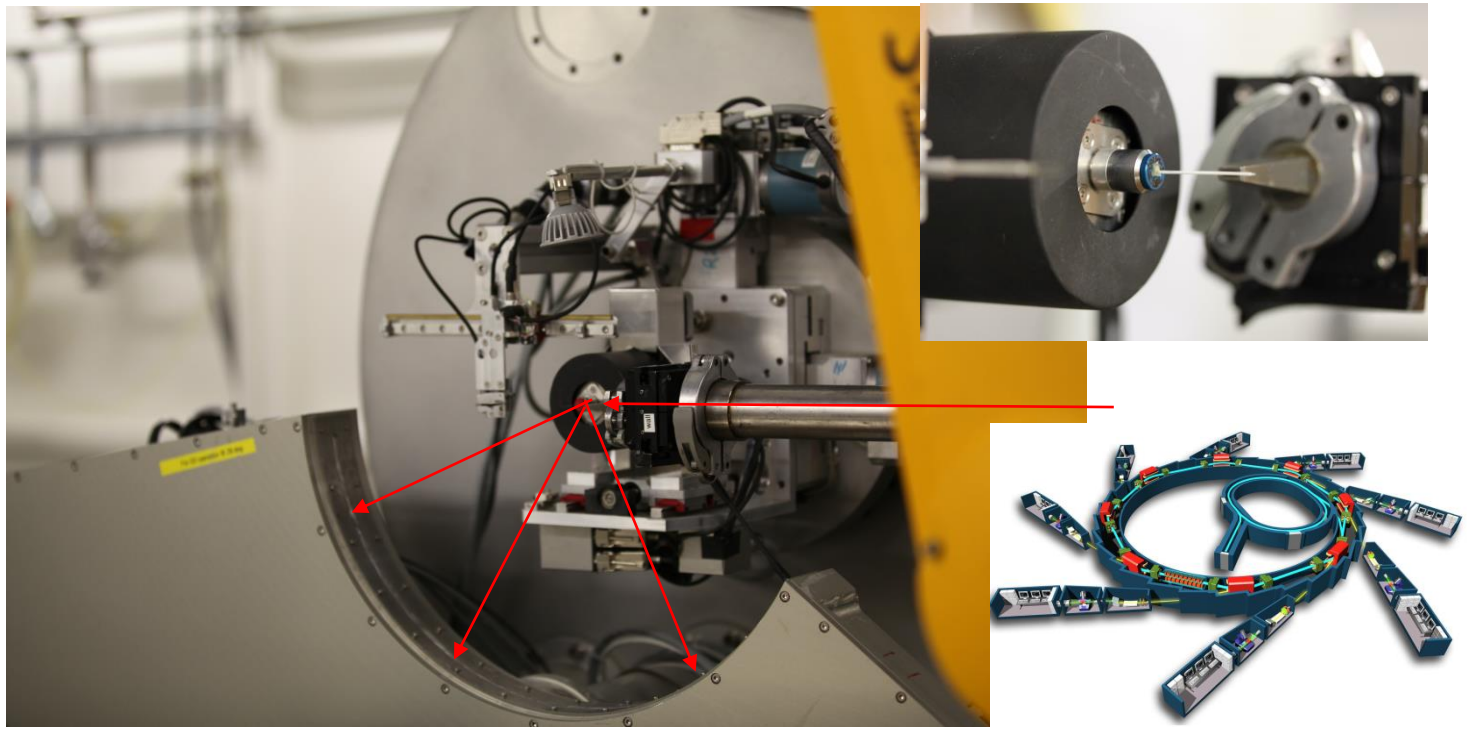
Laboratory vs Synchrotron source of X-rays

Laboratory X-ray source



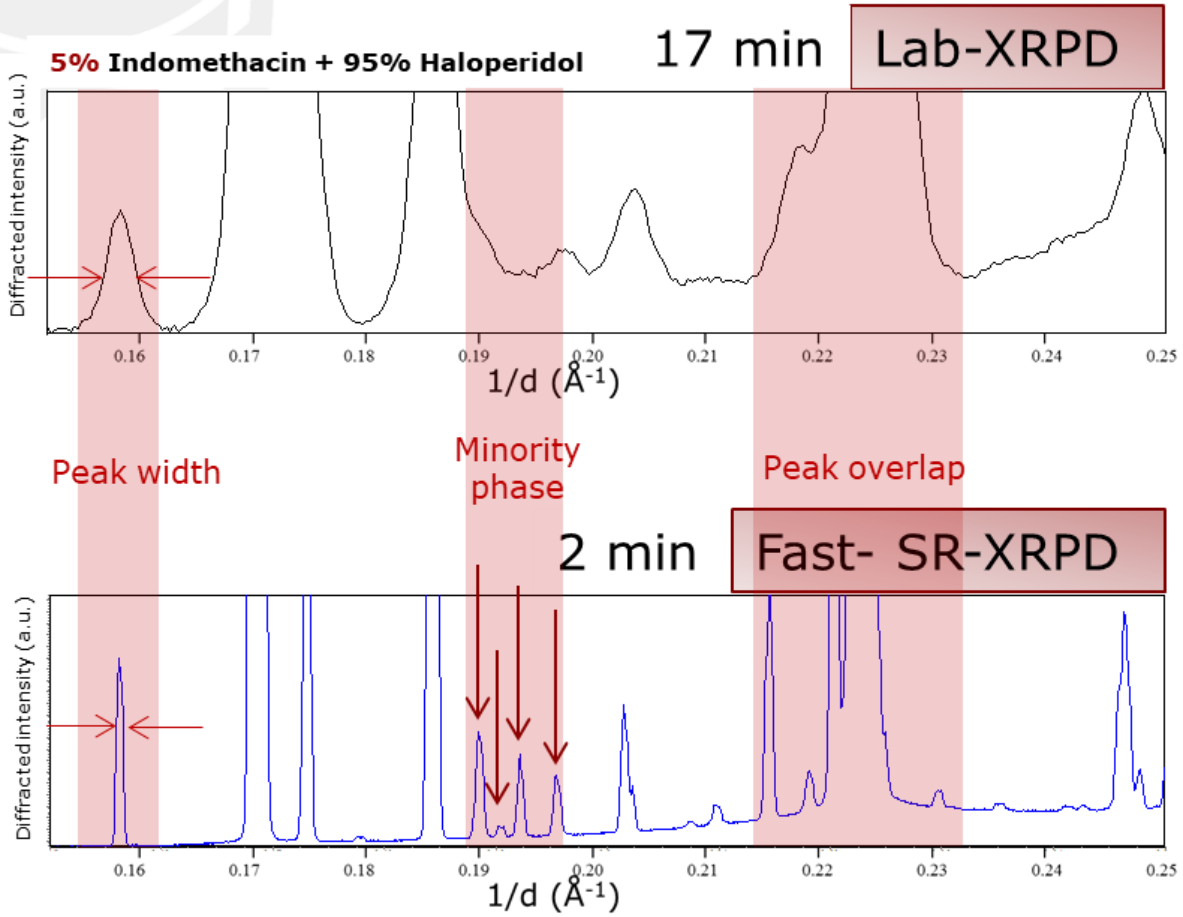
Source: https://www.bruker.com/en/products-and-solutions/diffractometers-and-x-ray-microscopes/x-ray-diffractometers.html

Synchrotron source



Picture: MS beamline @ SLS

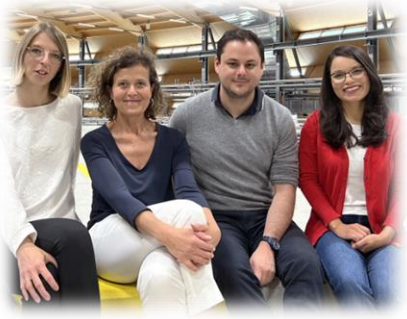
Advantages of using synchrotron light

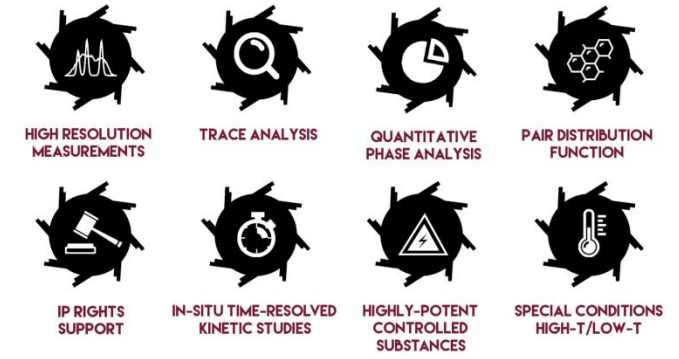


- Pushing the limits of powder diffraction!
- Efficient Technology Transfer offices exist
  → industrial customers can access SR facilities relatively fast and without submitting proposals.
- Executing a measurement for industry is however RARELY enough
  → synergy between the synchrotron expert and the industrial partner is paramount and the key of success!
- Specificities of organic materials to take into account

About ESS

- Who we are
- What we do? Who are our customers?
  - Large, medium and small companies, primarily pharmaceutical and chemical companies (70% Europe, 20% USA, 10% Asia)
  - Experts in the field of Intellectual Property Rights (pharmaceuticals) - mainly attorneys offices
- Where do we measure?
- What makes us different?
  - Aligned with specificities of Bio/Pharma industries

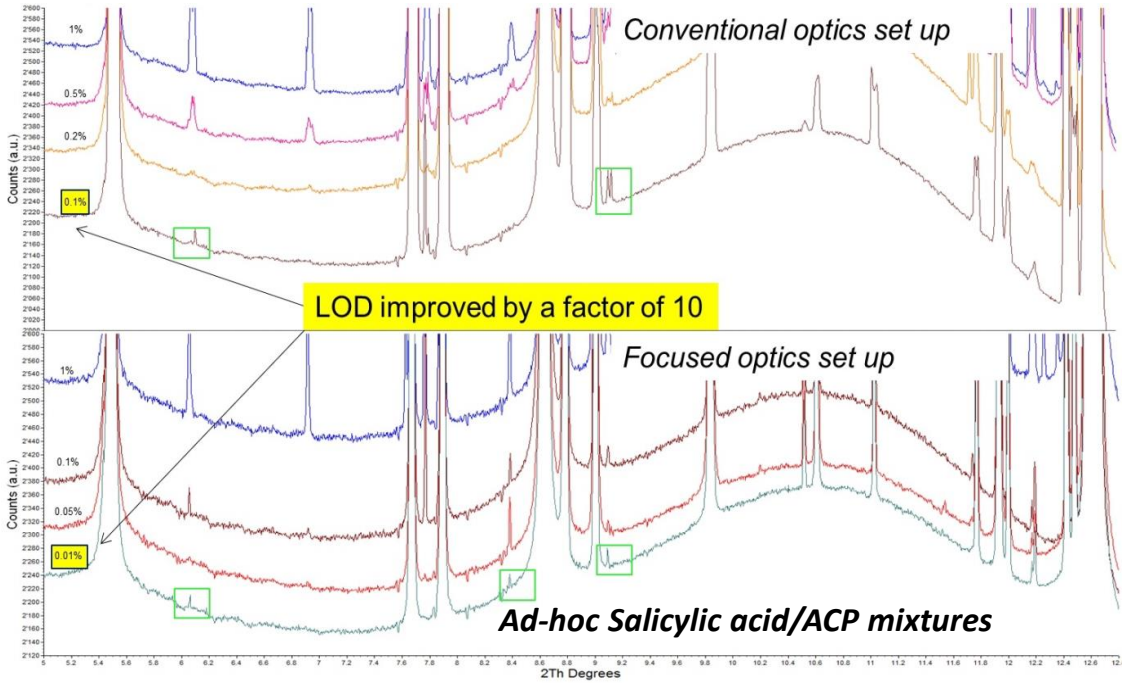


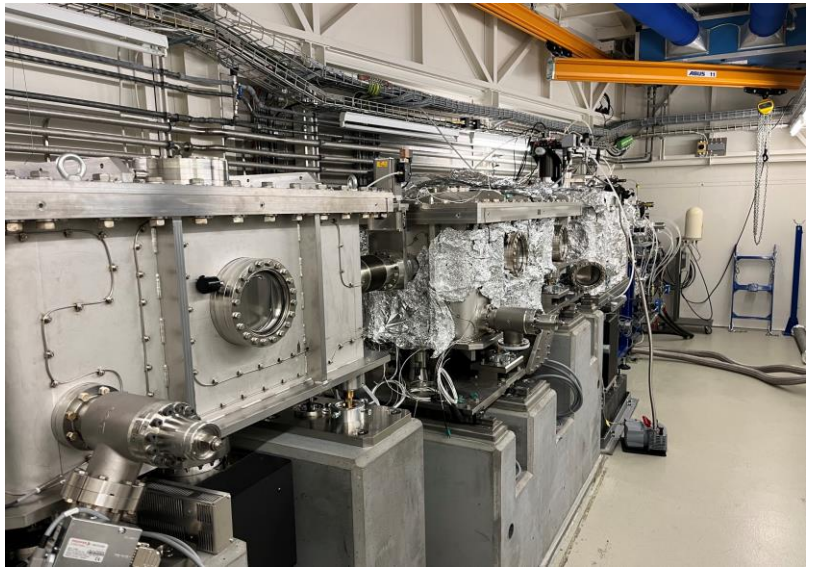


Optimizing data collection for industrial use

- Optimization of experimental setup/data collection strategies
- Cost effectiveness (evaluate S/N)
- Industrial requirements: deadlines, confidentiality

Improving data collection strategies: achieved level of detection 0.01 of wt%





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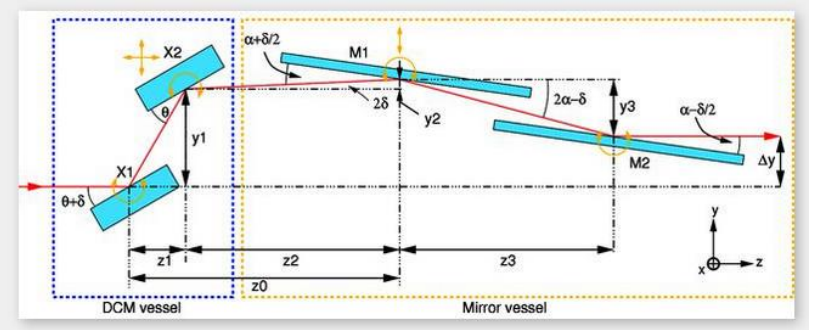


J. Synchrotron Rad. (2013). 20, 667-682
https://doi.org/10.1107/S0909049513018475

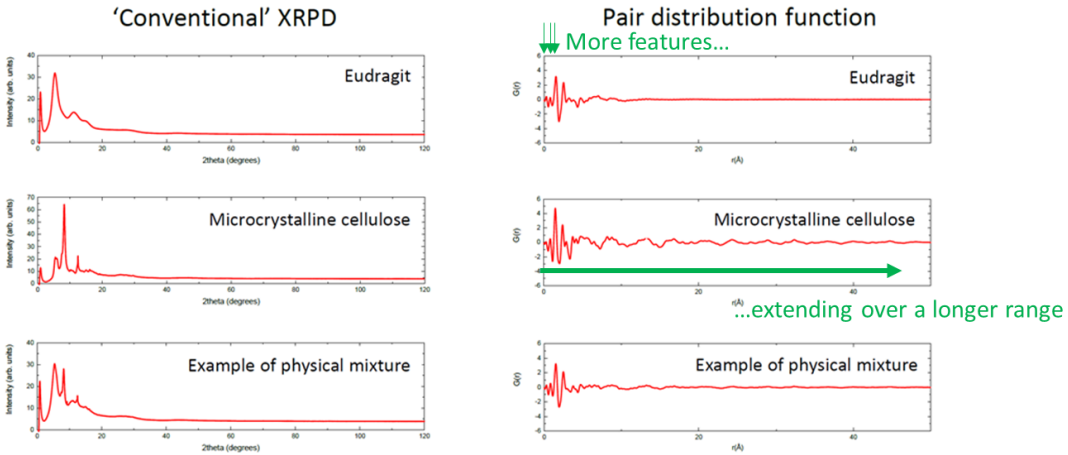
Good manufacturing practices, FDA requests/regulatory requirements

- Optimization of experimental setup/data collection strategies
- Cost effectiveness (evaluate S/N)
- Industrial requirements: deadlines, confidentiality

- Regulatory/GMP requirements → Bringing quality management into synchrotron facilities?
  - Validated analytical methods are not necessarily required
  - Nevertheless, analytical methods should be scientifically sound (e.g., specific, sensitive, and accurate) and provide results that are reliable
  - There should be assurance of proper equipment function
  - Procedures for analytical method and equipment maintenance, documentation practices, and calibration practices should be documented (SOPs)

Following trends in pharmaceutical formulations / work in progress

Dual space amorphous quantification via multivariate analysis/machine learning



Collaboration with Rocco Caliandro – Institute of crystallography, National research council of Italy, Bari
Raj Suryanarayanan, University of Minnesota and Naveen Thakral, Upsher-Smith Laboratories

Small Angle X-Ray Scattering

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Small Angle X-Ray Scattering Data Analysis and Theoretical Modelling for the Size and Shape Characterization of Drug Delivery Systems Based on Vitamin E TPGS Micelles

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[d] Novartis Pharma AG, Technical Research and Development, Chemical and Pharmaceutical Profiling, Novartis Campus, Virchow 6.3.231, 4056 Basel, Switzerland

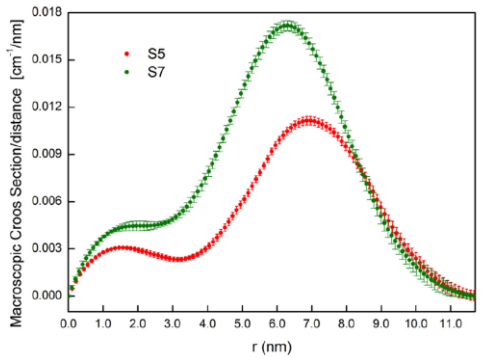


Figure 2. Pair Distance Function PDF(r) of the S5 (unloaded micelles) and S7 (micelles loaded with eltrombopag olamine powder) samples.

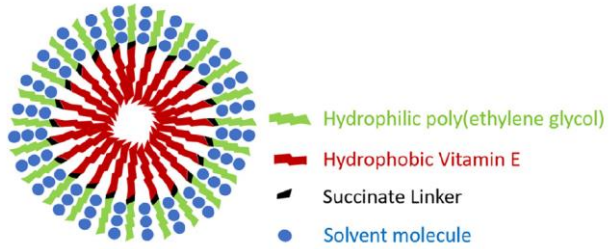
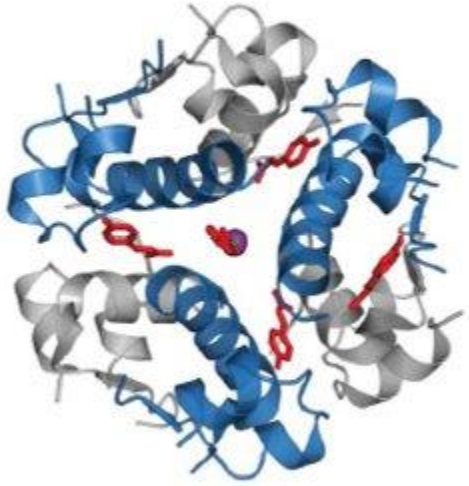


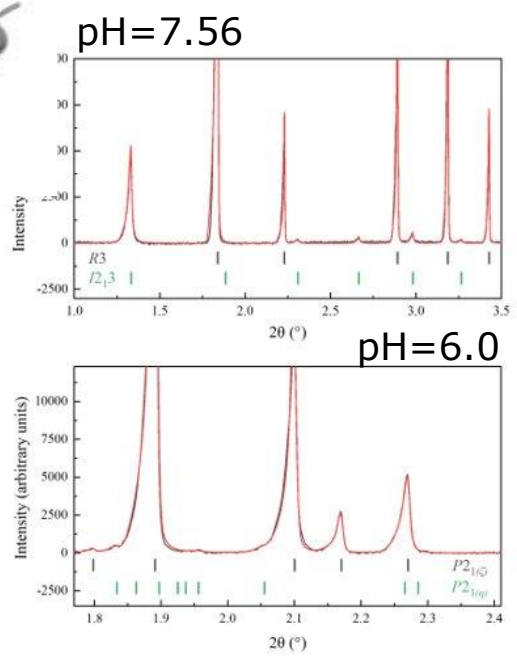
Figure 1. Micelle model system.

Following trends in pharmaceutical formulations / work in progress

Two examples of work on proteins



Polymorphism of human insulin



Triandafillidis et al, 2020
Acta Cryst. (2020). D76, 1065–1079

Collaboration with Irene Margiolaki's group, University of Patras, Greece

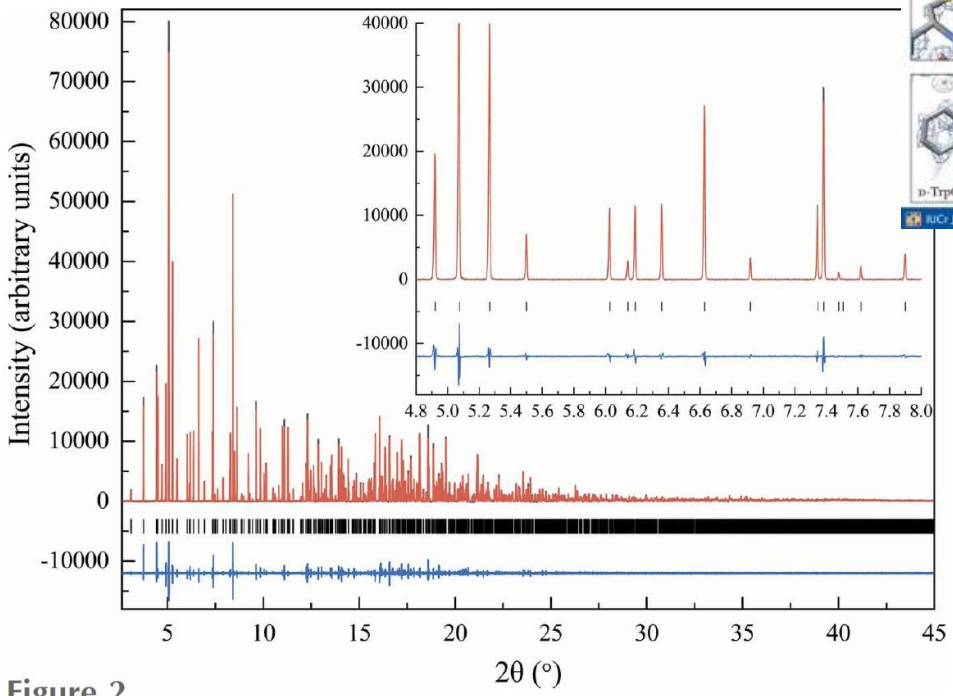
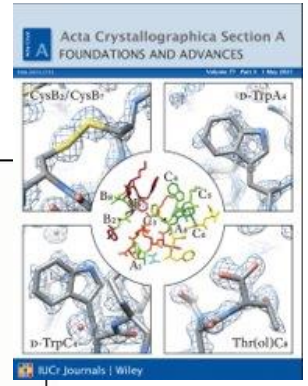


Figure 2

Pawley fit of S-XRPD data of octreotide (sample code oct_S1, space group $P2_12_12_1$). Data were collected at 298 K [SLS-X04SA, λ = 1.3004392 (8) Å]. The black, red and lower blue lines represent the experimental data, the calculated pattern and the difference between them, respectively. The vertical bars correspond to Bragg reflections compatible with the refined orthorhombic unit cell. The inset corresponds to magnification of the fit in a selected 2θ region. The extracted unit-cell parameters and agreement factors are: a = 18.52902 (3), b = 30.28875 (4), c = 39.73145 (7) Å, R_{wp} = 2.623%, χ^2 = 2.6624.



Octreotide: first detection of a second phase

Outlook

What can we do for the others?

- Characterization of polycrystalline materials
- Share insights and experience about
  - Access to synchrotron techniques
  - Technology transfer at synchrotron sources
  - Method development

Where would we need help?

- Instrumentation: I0 measurements, background control (zero-background sample holder?)
- Case studies
- Automation of data collection/ analysis strategies via GUI/scripts
- Application of machine learning/artificial intelligence

Thank you for your attention!!