Advances in Synchrotron XRPD for the Enhanced Characterization of Pharmaceuticals

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Outlook

I. Role of structural analysis in the pharmaceutical industry

II. Synchrotron Radiation X-Ray Powder Diffraction (SR-XRPD)

III. Synchrotron XRPD in the field of pharmaceuticals

IV. Conclusions
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**

<table>
<thead>
<tr>
<th>Form B at 112 °C, monoclinic</th>
</tr>
</thead>
<tbody>
<tr>
<td>P 21, a= 20.05795 Å, b= 11.12509 Å, c= 10.13290 Å, β= 116.18377°</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Form D at 20 °C, orthorhombic</th>
</tr>
</thead>
<tbody>
<tr>
<td>P 2 2 2, a= 14.90622 Å, b= 11.73977 Å, c= 11.08386 Å</td>
</tr>
</tbody>
</table>

_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) \(\rightarrow\) in-situ non-ambient time-resolved studies
- Spectroscopic properties
- Mechanical properties (e.g. hardness, compressibility, tableting, tensile strength)
Polymorphic studies play a key role throughout the whole life-cycle of products

**Compound selection**
- Identification and characterization of individual polymorphic forms and selection of desired form

**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**

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

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*Example of carbamazepine (see Organic Crystal Engineering, Eds. Tiekink, Vittal & Zaworotko, Wiley 2010)*
What makes synchrotron-XRPD such a powerful analytical tool?
II. Synchrotron Radiation X-Ray Powder Diffraction (SR-XRPD)

Our 3 ingredients for state-of-the-art SR-XRPD

A. An efficient synchrotron facility and beamline optics

B. State-of-the-art diffractometers

C. Outstanding detection systems
II. Synchrotron Radiation X-Ray Powder Diffraction (SR-XRPD)

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Hodeau et al, 1998


Multicrystal Analyser

MYTHEN II
II. Synchrotron Radiation X-Ray Powder Diffraction (SR-XRPD)

A. Synchrotron facility and beamline optics

Properties:

- High Spectral Brightness: $10^{12}-10^{15}$ photons/sec in small beams ($\mu$m$^2$ to mm$^2$)
- Tunable and monochromatic photon energy
- Polarization
- Time structure
- Coherence

Benefits

- Efficient data collection, high statistics
- Time-resolved in-situ non ambient XRD
- Photon-consuming experimental set ups
- Penetration of highly absorbing materials
- Variable d-spacing resolution
- Large unit cells (many reflections at very low angles)
- XRD near absorption edges (anomalous dispersion)
B. State-of-the-art diffractometers

Properties:
Resolution: 1 arcsec
Accuracy: ±2 arcsec
Precision: ±1 arcsec

Large working space and flexibility

Benefits
- Great mechanical stability
- Highest flexibility to accommodate all kinds of sample environments
C. Outstanding detection systems

**Properties:**
- Angular selection of diffracted beam
- Fluorescence suppression

**Benefits:**
- Ultra-high resolution (better than 0.003°)
- Angular resolution independent of sample dimension and position
- Independence of transparency effect
- High S/N and S/B

**Trade-off:**
- Long measurements (min to hours) → radiation damage

**Multicrystal Analyser**

**MYTHEN II**

**Properties:**
- Solid state modular microstrip detector
- Large dynamic range (24 bits)
- Single photon counting read out
- Fluorescence suppression
- Very fast acquisition times (subsec)

**Benefits:**
- 120° angular coverage at SLS
- High d-spacing resolution
- 0.004° inherent angular resolution
- Capable of simultaneously detecting strong and weak signals
- Sub-sec time resolution XRPD for in-situ kinetic studies

**Trade-off:**
- Resolution limited by sample dimension
- Sensitive to the uniformity of powder distribution in sample holder, granularity, statistical orientation

**Hodeau et al, 1998**

**Schmitt et al, 2003,**

**Bergamaschi, Schmitt et al, 2010**
Synchrotron XRPD in the field of pharmaceuticals

- Indexation, structural solutions & microstructural analyses
- Fast and dose-controlled SR-XRPD
- Quantitative Phase Analysis (L.o.D, L.o.Q)
- In-situ kinetic studies

- Bruni, Gozzo et al, *Thermal, spectroscopic, and ab initio structural characterization of carprofen polymorphs*, J. Pharm. Sci.2011, 100(6), 2321-2332
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!
III. Synchrotron XRPD: Dose-controlled SR-XRPD

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
Why is Quantitative Phase Analysis relevant to the pharmaceutical industry?

- **Polymorphic purity**: detect and quantify unwanted polymorphic forms in both drug substance and drug product
  - Level of Detection (LoD)
  - Level of Quantitation (LoQ)

- Assess the **polymorphic composition** in drug substance and product

- In formulated materials, the **API/excipients relative proportion** is paramount and needs to be kept under control

- **Degree of Crystallinity** in amorphous/crystalline mixtures
Quantification of organic compound mixtures can be achieved via different methods (e.g. spectroscopic, thermal and diffraction methods)

Diffraction methods are direct methods → diffraction information is directly produced by the crystal structure of the component phases in the mixture

Quantitative phase analysis with conventional lab-XRPD is widely used and an established practice in the pharmaceutical industry → LoD and LoQ down to very few % wt is achieved 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
III. Synchrotron XRPD: Quantitative Phase Analysis

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

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

Minority phase: Indomethacin

Diffracted intensity (a.u.)

Majority phase: Haloperidol

Minority phase: Indomethacin

20-24 May, 2013
Beijing, China
API mixtures are often characterized by an inhomogeneous distribution of the phase components

SR-XRPD in Debye-Scherrer geometry (transmission in glass capillaries) probes relatively small powder volumes

SR-XRPD patterns were recorded at several locations on the glass capillary and the effect on the accuracy of our QPA was studied
Whole-patterns QPA Methods

**Rietveld Method**

Rietveld, JAC (1969). 2, 65
Hill & Howard, JAC (1987). 20, 467-474

- all phases should be crystalline and a valid structure model available for all phases in the mixture
- amorphous or unknown phases quantified as a group by generating absolute phase abundances for the analyzed phases (e.g. internal standard)

**Rietveld-like Methods (PONKCS and Quanto+)**

Scarlett & Madsen, Powder Diffr. 21(4), 2006, 278-284

→ real structure factors substituted with empirical values derived from whole patterns refinement on pure phases

**Requirements:**

- pure phases available (PONKCS & Quanto+), spiked pure phases (PONKCS)

**Benefits:**

- Rietveld-like QPA with only partial structural knowledge (PONKCS & Quanto+), with NO structural knowledge (PONKCS), application to amorphous materials (PONKCS)
III. Synchrotron XRPD: Quantitative Phase Analysis

Whole-pattern QPA refinements on very diluted API mixtures

Measured (wt%) vs Weighed (wt%) graph showing the comparison of measured and weighed quantities for different methods: Rietveld, PONKCS, Quanto+. The graph illustrates the average over multiple powder volumes.
Whole-pattern QPA refinements on very diluted API mixtures

The average of %wt values at individual capillary powder volumes was consistent with %wt values from merged diffraction patterns.
Whole-pattern QPA refinements on very diluted API mixtures

The average of %wt values at individual capillary powder volumes was consistent with %wt values from merged diffraction patterns.
III. Synchrotron XRPD: fast SR-XRPD vs HR-SR-XRPD and Lab-XRPD

5% Indomethacin + 95% Haloperidol

Minority phase

Fast- SR-XRPD
2 min

HR- SR-XRPD
100 min

Lab-XRPD
17 min

Diffracted intensity (a.u.)

1/d (Å⁻¹)

HR-XRPD: A.Fitch, ID31, ESRF
Lab-XRPD: I. Madsen, CSIRO, Australia
III. Synchrotron XRPD: fast SR-XRPD vs HR-SR-XRPD and Lab-XRPD

1% Indomethacin + 99% Haloperidol

1/d (Å⁻¹)

Diffracted intensity (a.u.)

Fast- SR-XRPD
4.5 min

HR- SR-XRPD
60 min

Lab-XRPD
17 min

Minority phase
III. Synchrotron XRPD: fast SR-XRPD vs HR-SR-XRPD and Lab-XRPD

0.05% Indomethacin + 99.95% Haloperidol

Diffracted intensity (a.u.)

1/d (Å⁻¹)

0.16 0.17 0.18 0.19 0.20 0.21 0.22 0.23 0.24 0.25

Fast- SR-XRPD

20 min

HR- SR-XRPD

80 min

Lab-XRPD

17 min

Minority phase

HR-XRPD: A. Fitch, ID31, ESRF
Lab-XRPD: I. Madsen, CSIRO, Australia
III. Synchrotron XRPD: an example of \textit{in-situ} kinetic study

\textbf{In-situ dynamic study of the LaNi$_5$ hydrogen absorption process}

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


\textbf{hydrogen uptake} \hspace{1cm} \textbf{diffraction pattern} \hspace{1cm} \textbf{phase content}

\textbf{New beamline optics+ Mythen II $\rightarrow$ 10 faster}

\textbf{t (s)} \hspace{1cm} \textbf{2$\theta$ (°)} \hspace{1cm} \textbf{t (s)}

0 5 10 15 20 25 30 35 40
0 5 10 15 20 25 30 35 40
0 5 10 15 20 25 30 35 40

0 1 2 3 4 5 6
0 1 2 3 4 5 6
0 1 2 3 4 5 6

0 10 20 30 40
0 10 20 30 40
0 10 20 30 40

0 20 40 60 80 100
0 20 40 60 80 100
0 20 40 60 80 100

$\alpha$ $\beta$ $\gamma$

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\textbf{PPXRD-12}
20-24 May, 2013
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IV. Conclusions

- Polymorphic forms may have a significant impact on the quality or performance of pharmaceutical and chemical products.
- For pharmaceuticals, a careful characterization of the polymorphism of substances and drug product should therefore play a key role throughout the whole life-cycle of products.
- Polymorphic studies have also started to play a key role during patent litigations and in the fight against counterfeit drugs.
- Synchrotron-Radiation Powder Diffraction has become a unique and very powerful tool for polymorphic studies, such as kinetic analyses, the identification of closely related polymorphic forms and high-sensitivity quantitative phase analyses.
- This use is in line with the regulatory expectations (ICH guidelines and FDA guidance) that newly available analytical technologies are used for continuous improvements in process understanding and product characterization.

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