Characterization of amorphous pharmaceuticals – what can you do in the home lab?

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PPXRD Website – www.icdd.com/ppxrd

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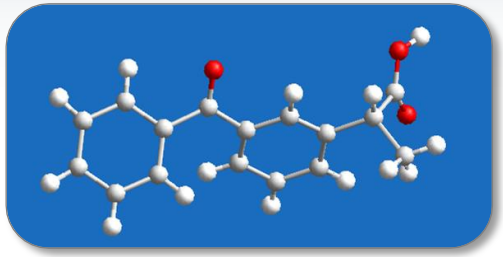
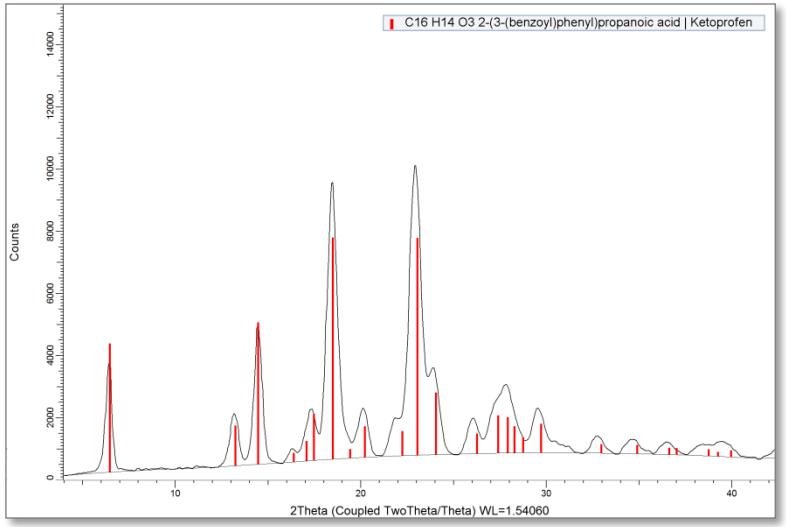
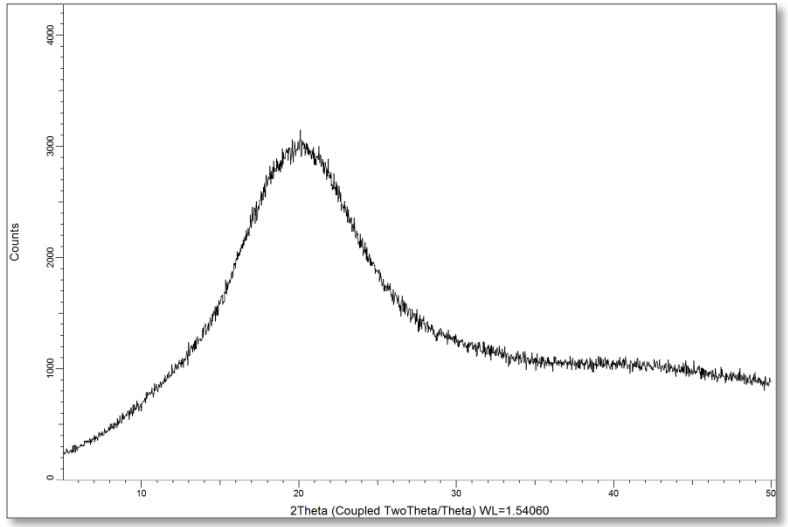
Motivation
Fingerprinting APIs

- Powder X-ray diffraction (PXRD) is a powerful tool to characterize active pharmaceutical compounds in the solid state
  - This is typically limited to crystalline compounds





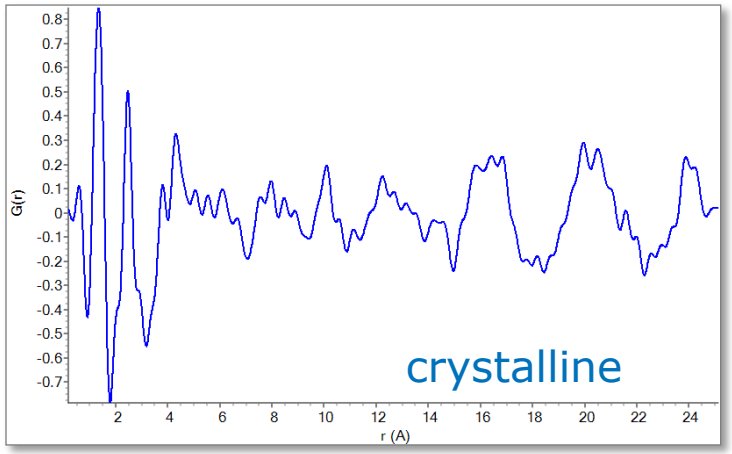
Crystalline ketoprofen

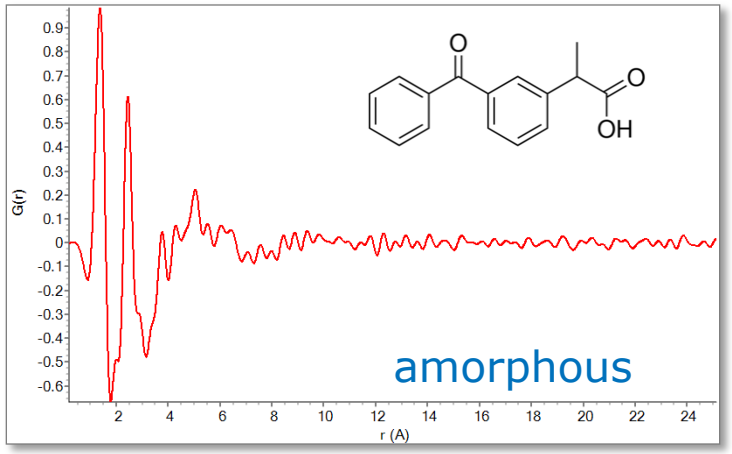


Amorphous ketoprofen

Motivation
Fingerprinting Amorphous APIs

- The pair distribution function (PDF) provides structural information for amorphous materials, enough to allow for a fingerprint [1-3]:



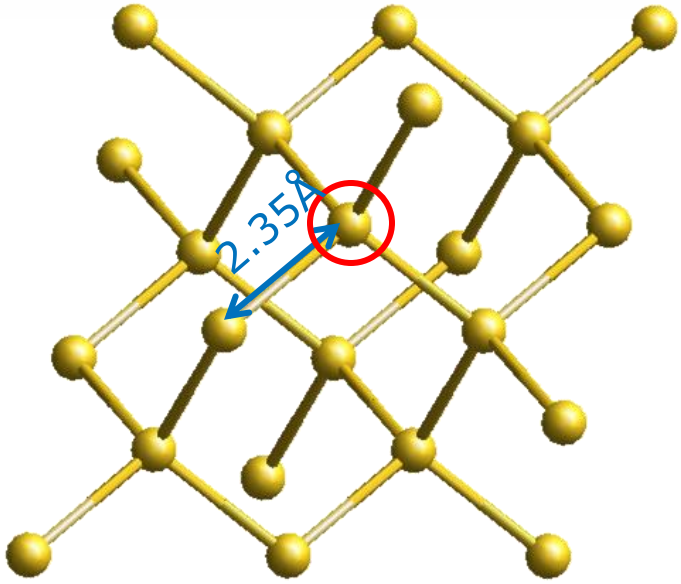


- Measurements carried out at a synchrotron (30 min) [1,2], or potentially a lab source, but requiring very long measurement times (hours - days)
- Is it possible to collect PDFs of APIs on a lab instrument, fast enough to allow screening?

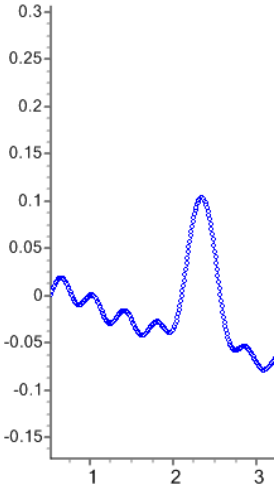
[1] Billinge S.J.L. et al., CrystEngComm, 2010, 12, 1366-1368
[2] Dykhne T., Taylor R., Florence A., Billinge S.J.L., Pharm. Res., 2011, 28:1041-1048
[3] Total Scattering Pair Distribution Functions (TSPDF) for Fingerprinting Amorphous Pharmaceuticals S. Billinge, PPXRD-10 (2011)

What is PDF?

Si lattice



Radial atomic **P**air **D**istribution **F**unction (PDF) gives the interatomic distance distribution, or "probability" of finding atomic pairs of distance *r* apart.

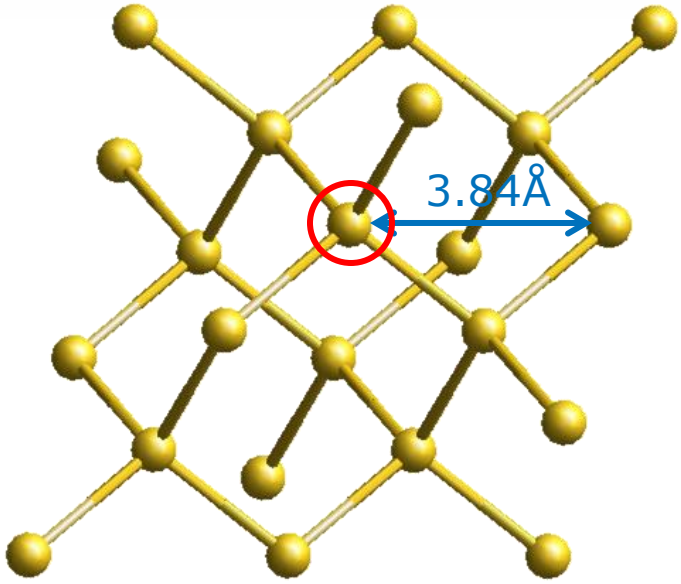


Start at an arbitrary atom, and look outward

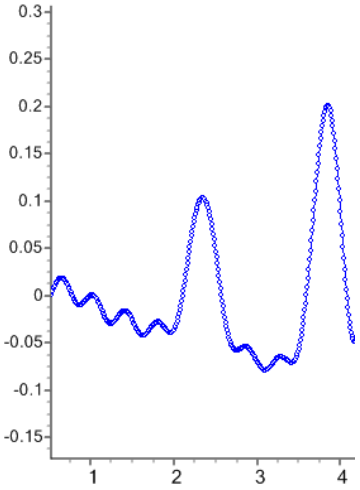
Peak appears at nearest neighbor

What is PDF?

Si lattice



Radial atomic **P**air **D**istribution **F**unction (PDF) gives the interatomic distance distribution, or "probability" of finding atomic pairs of distance *r* apart.

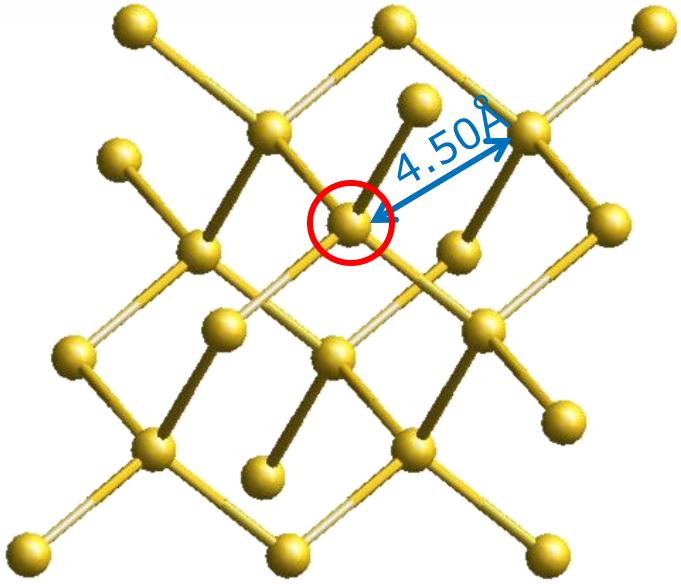


Start at an arbitrary atom, and look outward

Another peak appears at the next neighbor

What is PDF?

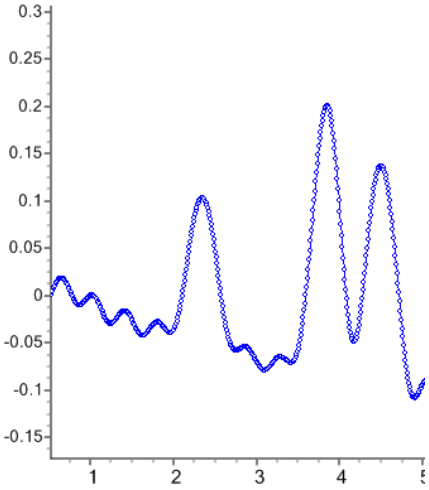
Si lattice



Start at an arbitrary atom, and look outward

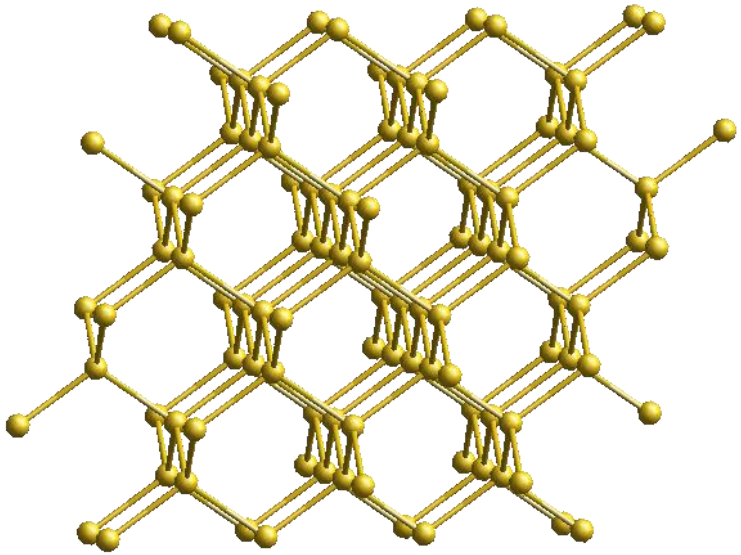
And so on…

Radial atomic **P**air **D**istribution **F**unction (PDF) gives the interatomic distance distribution, or "probability" of finding atomic pairs of distance *r* apart.

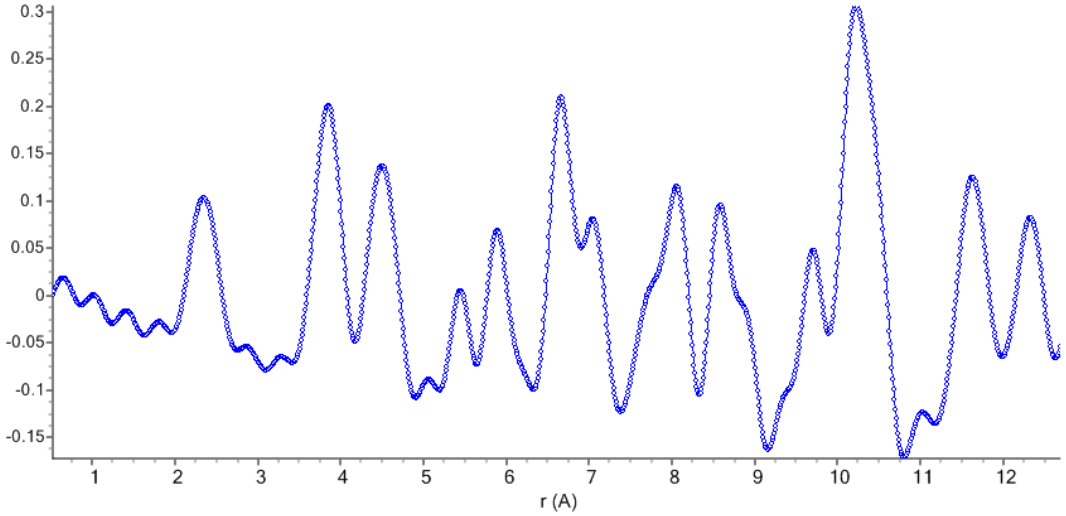


What is PDF?

Si lattice



In another way, it's a histogram of interatomic distances, normalized by the scattering contribution of each atom (form factor)



This process is repeated for all atoms, leading to a probability distribution as a function of interatomic distance

PDF data collection
Challenges

Some requirements:

- High energy X-rays to collect data to high Q

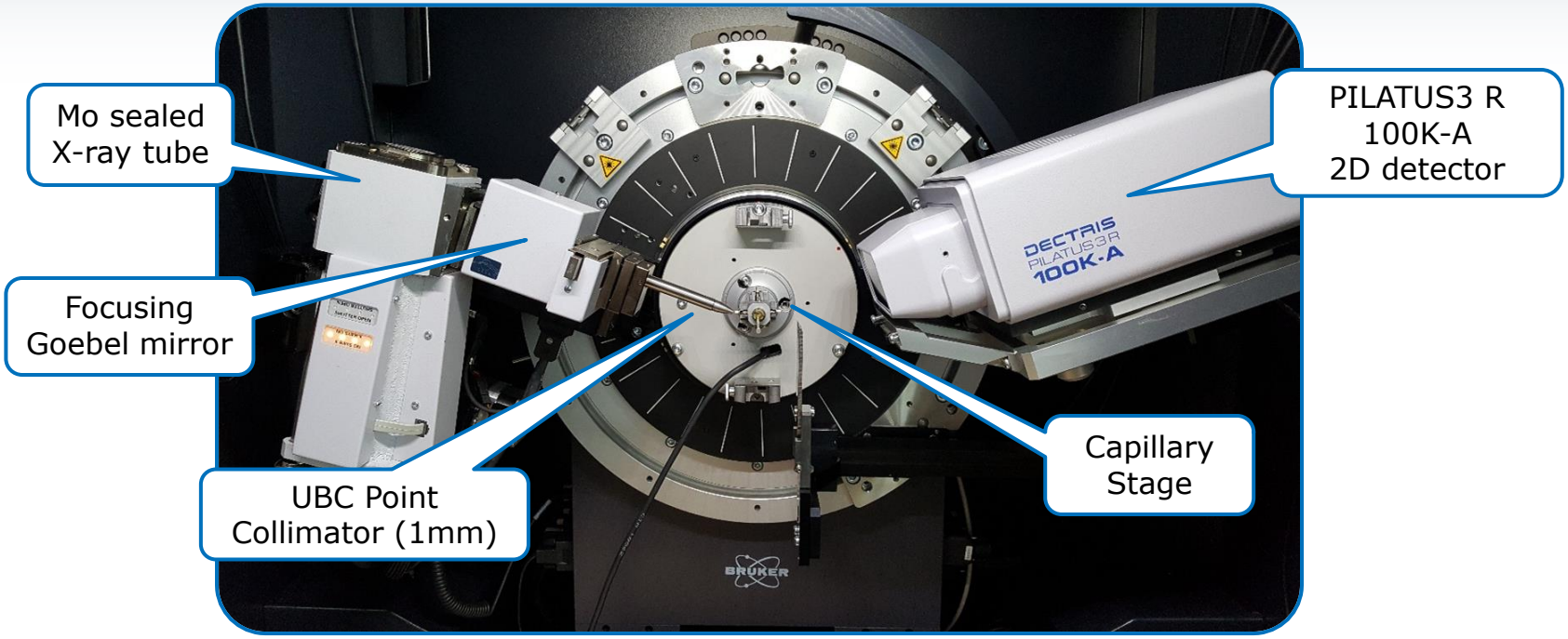
$$Q = \frac{4\pi \sin\theta}{\lambda}$$

Short wavelength X-rays allows measurements to high Q

- Good counting statistics
- Low instrument background

- These points (particularly the first 2) are why measurement times are typically so long

Experimental Setup
D8 ADVANCE

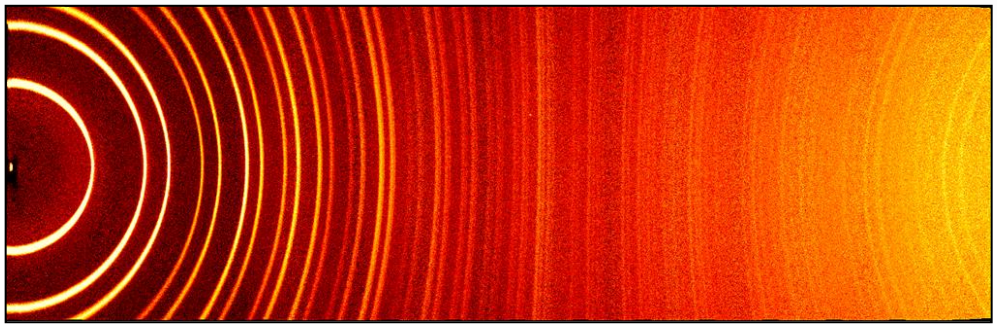


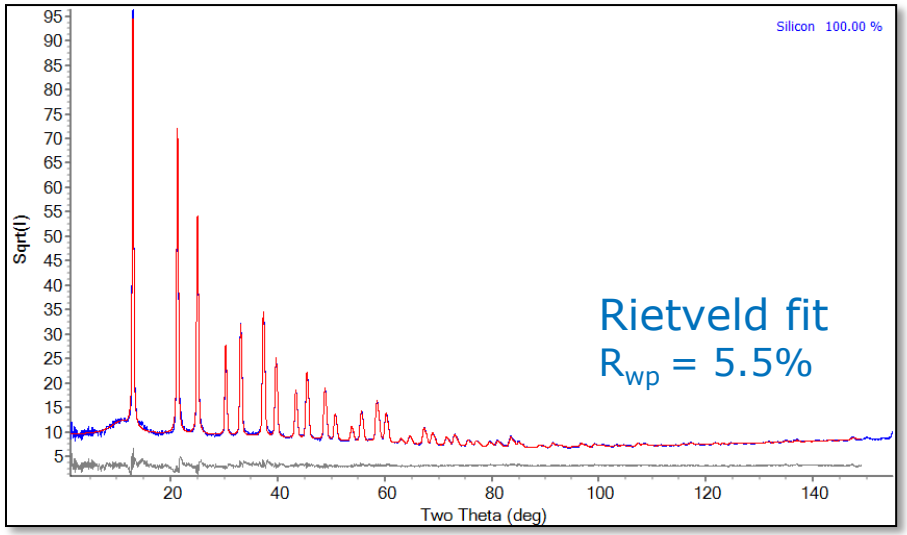
- Mo radiation is in the 'sweet spot' for PDF on pharmaceuticals
  - λ = 0.7108 Å; $Q_{max} \approx 17$ Å^{-1} (minimum necessary for PDF analysis)
  - Stronger interaction with weak scatterers (compared to Ag, synchrotron)

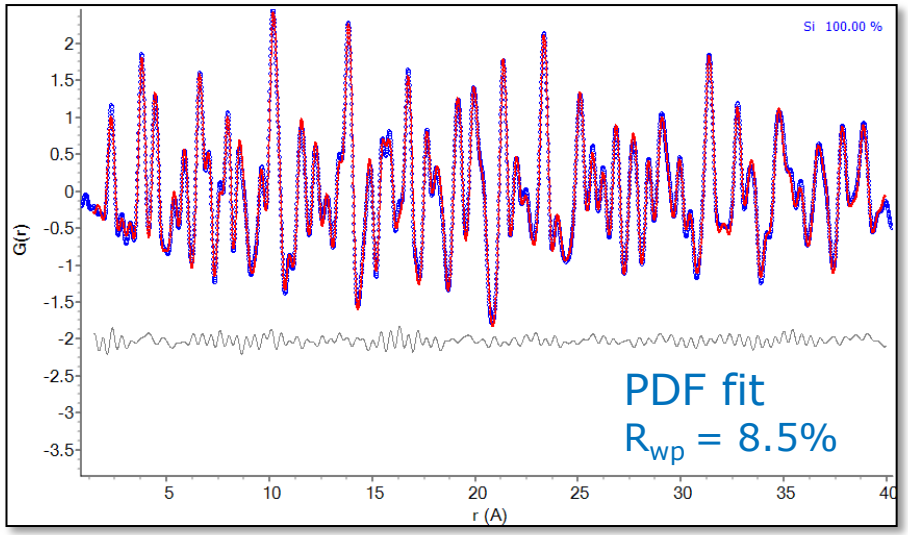
Validation of experimental setup
Silicon powder

Si powder
1 hour data collection

Measurement strategy:
- frames every 10° 2θ
- *count longer at high angles*

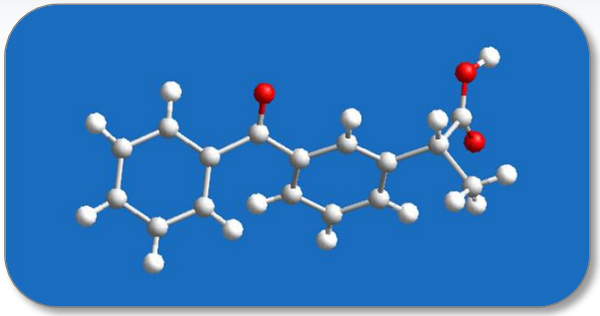




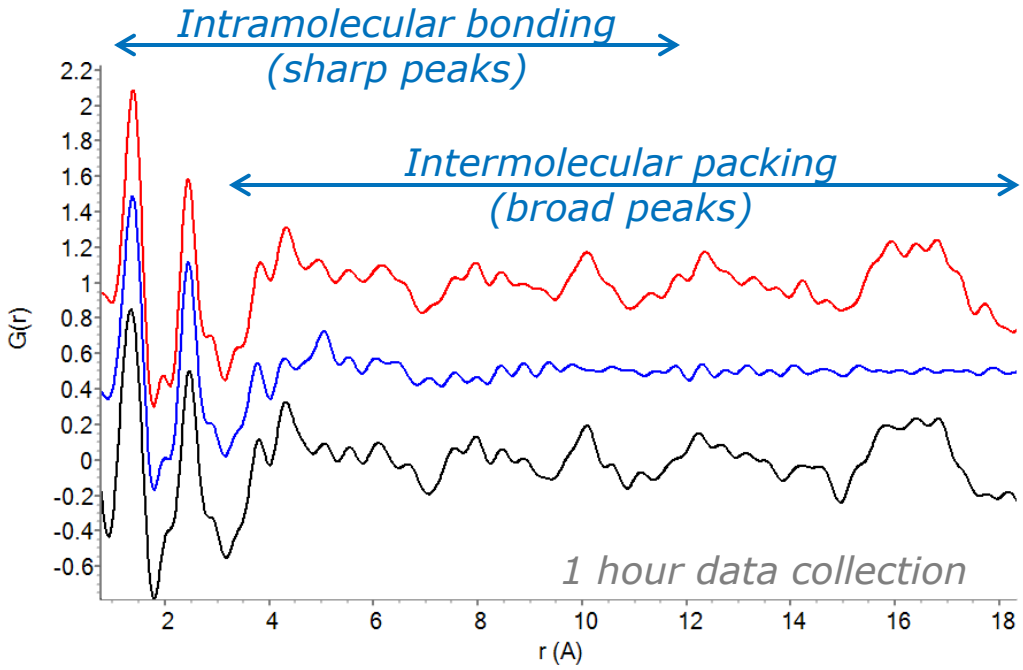


Information content of the PDF
Ketoprofen

- 2 main regions of bonding for molecules
- Small differences between 4 – 6 Å (cryst. vs amorph.)
- No packing signal (beyond 10 Å) in amorphous



Ketoprofen, nonsteroidal anti-inflammatory drug



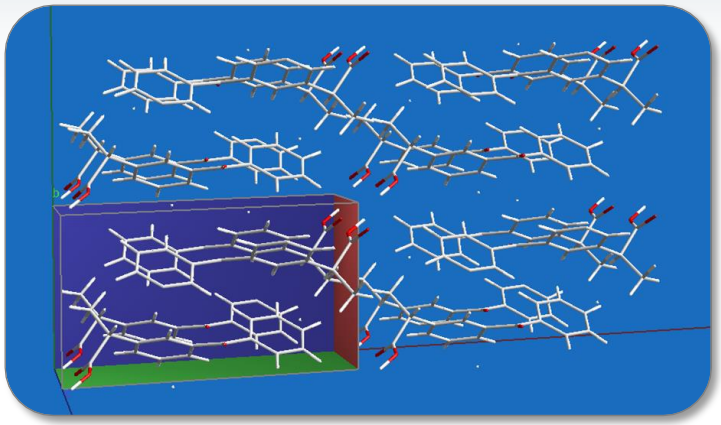
re-crystallized (from amorphous)

amorphous (melt-quenched)

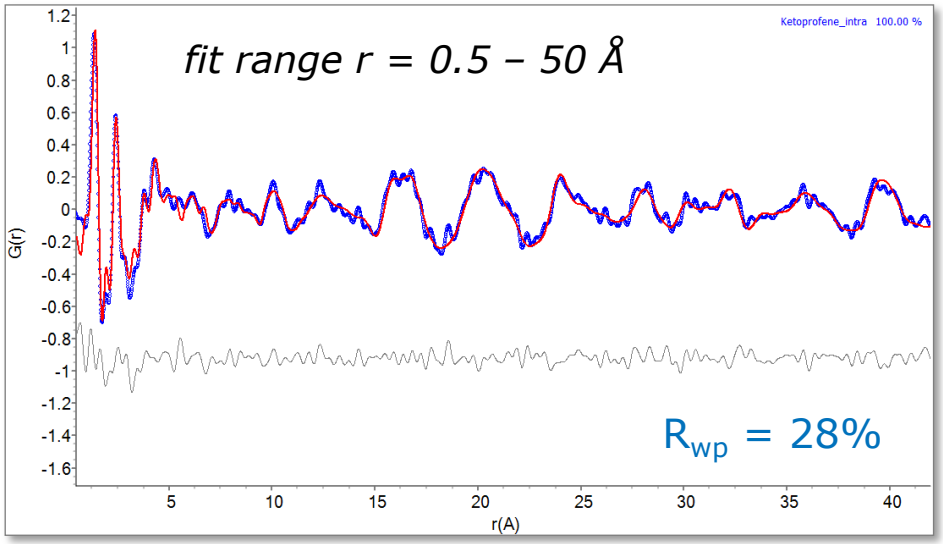
crystalline (as received)

PDF refinement in TOPAS v6
Crystalline Ketoprofen

- Molecules can be difficult to model (due to overlap region)
- Rigid body for molecule including torsion angles
- Small FWHM < 15 Å (≈ size of molecule)
- Larger FWHM for entire range



Packing motif of ketoprofen



PDF fit of crystalline ketoprofen in TOPAS

```
'inter and intramolecular interactions
prm intra  0.18713`
prm inter  0.87715`
pdf_for_pairs * * pdf_only_eq_0
   pdf_gauss_fwhm = If(X<15, intra, 0);
pdf_for_pairs * *
   pdf_gauss_fwhm = inter;
```

Section of TOPAS input file

Cluster Analysis
Are amorphous phases distinguishable?

- Cluster analysis partitions data into sets based on their similarity
  - Similar patterns end up in the same cluster, dissimilar ones in different clusters
  - Quick way to analyze and compare sets of data
  - We looked at several different APIs (and one excipient), and tried to also make the amorphous form of each (8 samples in total)

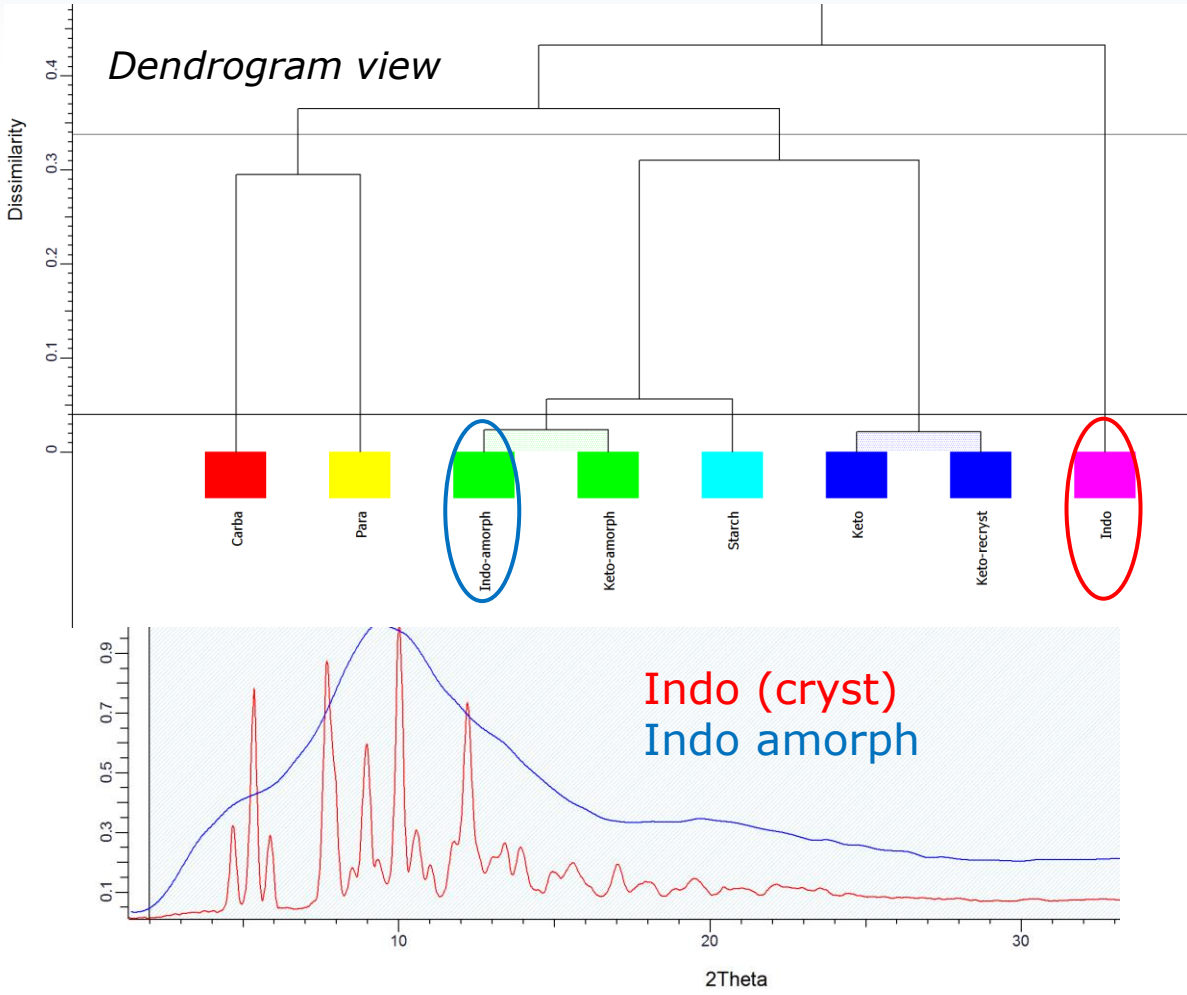
Compound	Abbrev.	Formula	Form	Amorph?
Carbamazepine	Carba	$C_{15}H_{12}N_2O$	III	No
Paracetamol	Para	$C_8H_9NO_2$	I	No
Ketoprofen	Keto	$C_{16}H_{14}O_3$		Yes*
Indomethacin	Indo	$C_{19}H_{16}ClNO_4$	γ	Yes
Corn-starch	Starch	$C_{27}H_{48}O_{20}$		Nano

* sample also recrystallized from amorphous

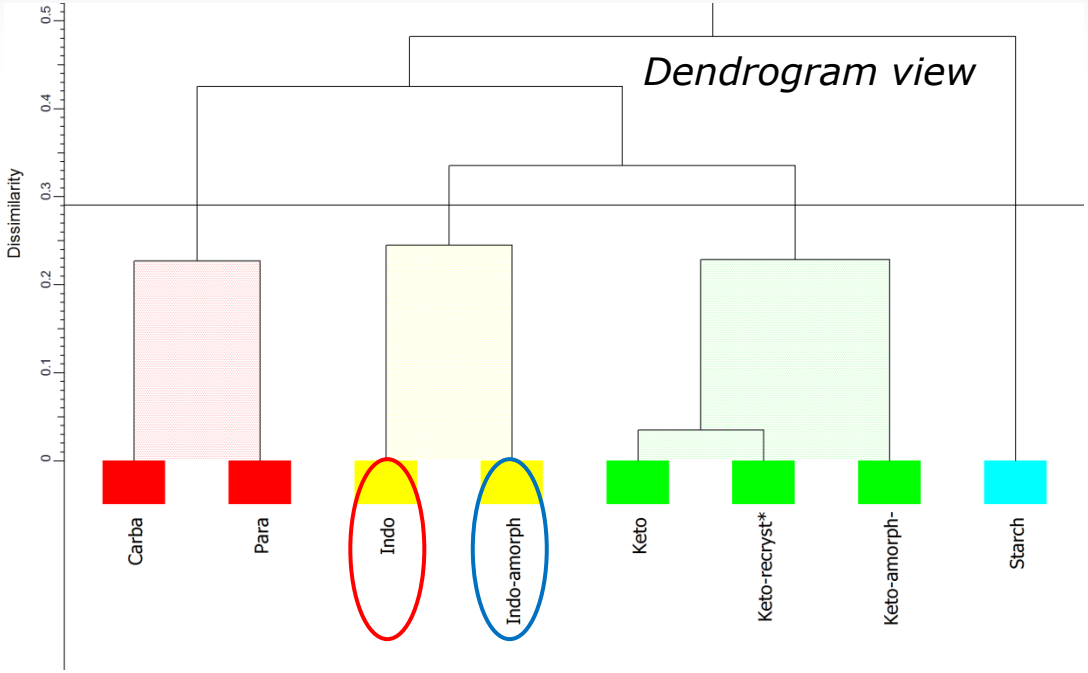
Cluster Analysis on XRD data
DIFFRAC.EVA

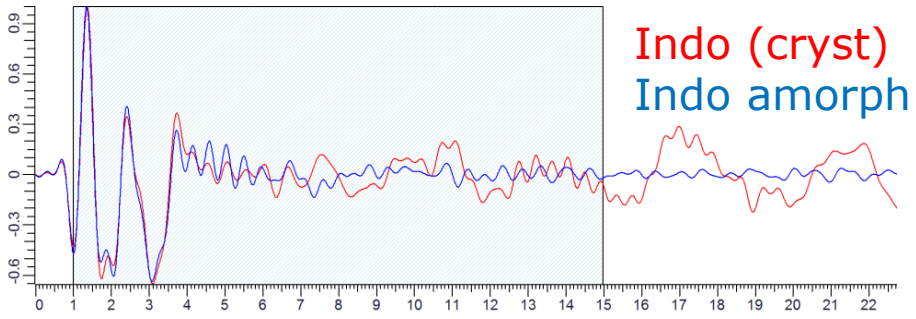
- As a frame of reference, cluster analysis on the raw XRD data
- Match range: 2 – 40° 2θ

- Obviously the direct information available in the amorphous patterns is not enough to fingerprint



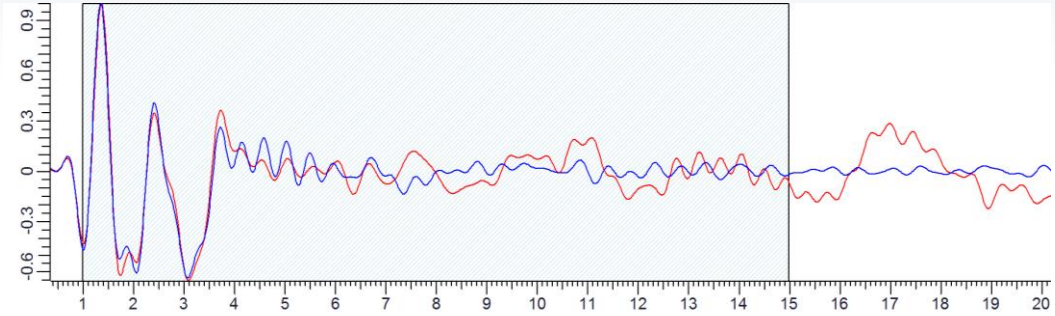
Cluster Analysis on PDF data
DIFFRAC.EVA





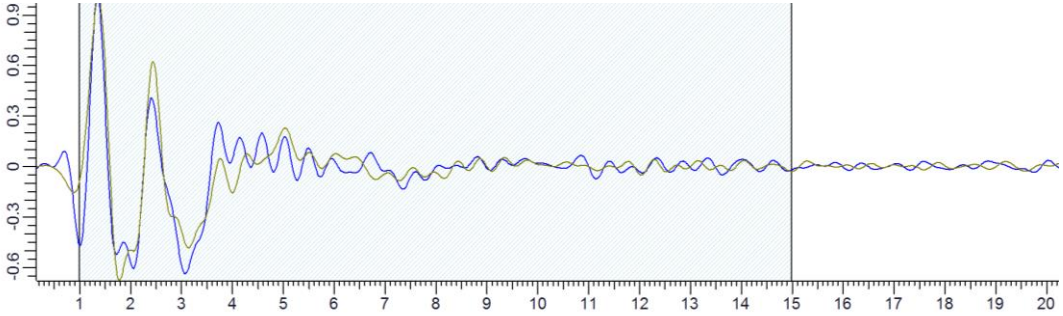
- Cluster analysis on 8 PDF datasets
- Match range: 1 – 15 Å (*intramolecular bonding and overlap region*)
- PDFs of 2 amorphous materials are different enough that they cluster with their parent crystalline PDF

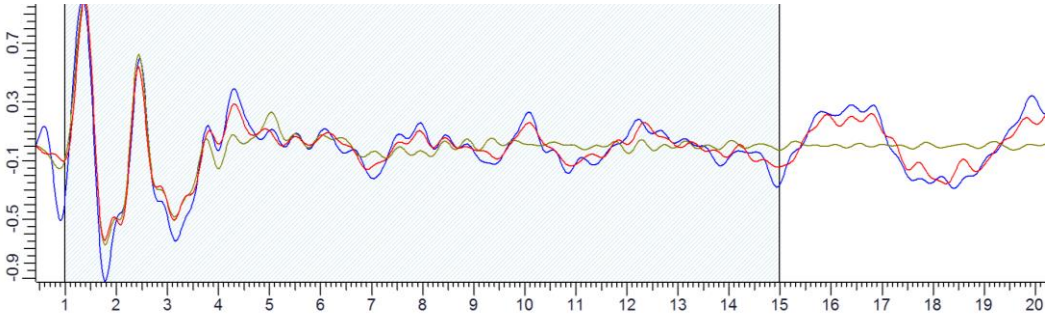
Comparison of PDFs



Indo (cryst)
Indo amorph

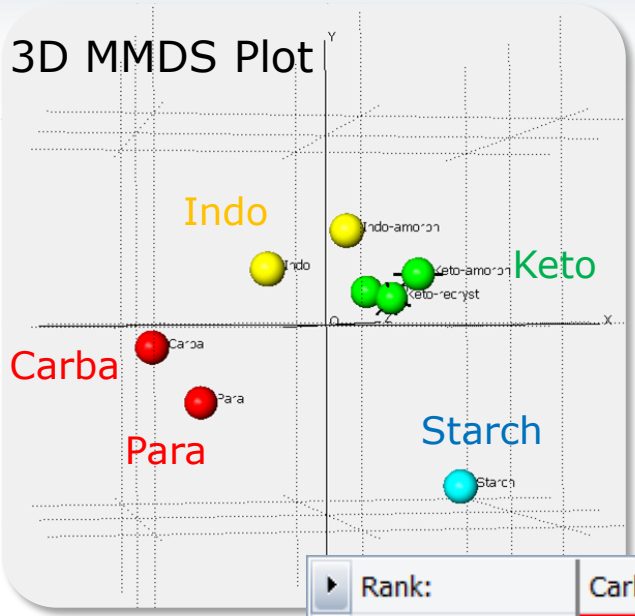
Keto amorph
Indo amorph





Keto amorph
Keto
Keto recryst

Cluster Analysis on PDF data
Visualizing the results



3D Metric Multidimensional Scaling

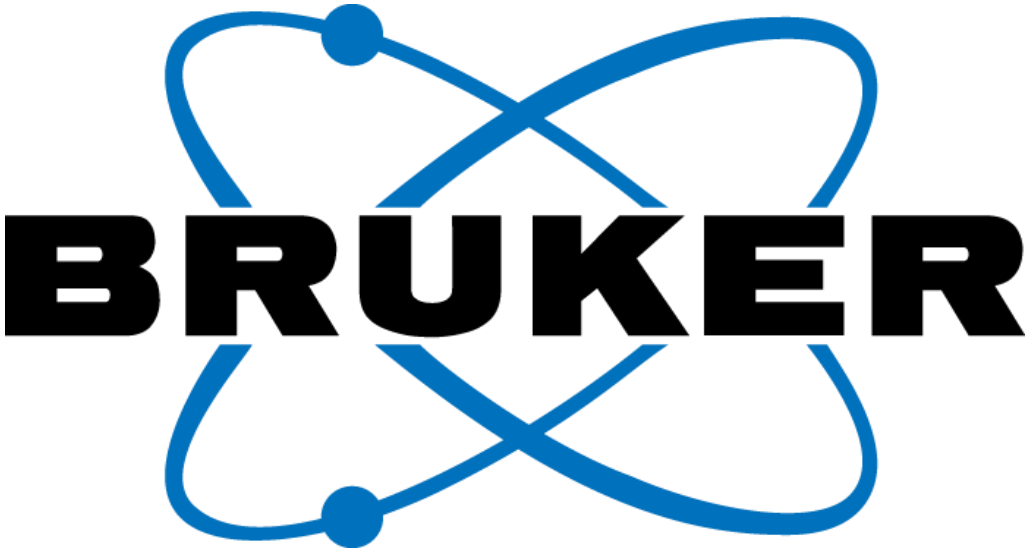
- Graphical representation of distances between objects
- Smaller distances → more similar

Correlation coefficients (> 0.80 in red)

Rank:	Carba #1	Indo #2	Indo-amorph #3	Keto #4	Keto-amorph #5	Keto-recryst #6	Para #7	Starch #8
Carba #1	1	0.7421	0.6389	0.6802	0.5265	0.6593	0.8342	0.4751
Indo #2	0.7421	1	0.8029	0.6927	0.644	0.6693	0.6589	0.5114
Indo-amorph #3	0.6389	0.8029	1	0.743	0.766	0.7471	0.6133	0.5336
Keto #4	0.6802	0.6927	0.743	1	0.8078	0.9707	0.6613	0.568
Keto-amorph #5	0.5265	0.644	0.766	0.8078	1	0.8415	0.5762	0.6114
Keto-recryst #6	0.6593	0.6693	0.7471	0.9707	0.8415	1	0.6375	0.609
Para #7	0.8342	0.6589	0.6133	0.6613	0.5762	0.6375	1	0.5094
Starch #8	0.4751	0.5114	0.5336	0.568	0.6114	0.609	0.5094	1

Summary and Outlook

- The PDF of amorphous molecular materials can provide sufficient structure information for fingerprinting.
- Data suitable for PDF analysis of organic compounds were collected in as little as 1 hour on a D8 ADVANCE diffractometer with a large 2D detector (PILATUS3 R 100K).
- Tests on other materials, particularly those with multiple polymorphs that can also be prepared in the amorphous state would be a next step.



Innovation with Integrity