Amorphous Solid Forms: The Use of X-ray Powder Diffraction (XRPD)

Simon Bates  2010
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Amorphous Forms: XRPD

Methods You can Apply in Your Own Laboratory

• What do we mean by Amorphous Solid Forms?
• How to Collect the Best Powder Patterns?
• Simple Graphical Analysis Methods
• Information Content of X-ray Amorphous data.
• Direct Methods.
What do we mean by "Amorphous Solid Forms"?

• Traditional view points:
  – From classical thermodynamics, an amorphous solid is one that manifests no long-range inter-molecular order.
  – "X-ray amorphous" is a solid form whose powder pattern contains no crystalline diffraction peaks.

• More extreme paradigm:
  – A kinetically frustrated form, with a random and chaotic arrangement of molecules
What do we mean by "Amorphous Solid Forms"?

• Although lacking long-range order, there is no fundamental restriction on the types of short range inter-molecular order that might exist.
  – The appearance of an X-ray Amorphous powder pattern is driven by the characteristic short range order.
  – The density of amorphous forms (usually within a few percent of the crystalline density) implies significant close packing.
What do we mean by "Amorphous Solid Forms"?

• Two traditional theoretical models of the amorphous state give some perspective on the types of local order that might exist.
  – Continuous Random Network (CRN)
  – Random Close Packed (RCP)
Amorphous Solid Forms?

- Crystalline
- Low Temperature
- X-ray Amorphous
- Glass
- Defects
- RCP
- Melt
- High Temperature
- Order/Entropy
- Temperature/Energy
- CRN
- Amorphous

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XRPD Data Collection

• To collect the best powder patterns for amorphous material analysis:
  – Reduce all sources of background scatter as far as possible.
  – Accurately determine the background signal over the analysis range and remove.
  – Collect data from background at low angles to background at high angles (VIP).
  • Start at 1 or 2 degrees and measure up to 60, 70, 80 or 90 degrees depending on where the diffraction signal from the sample falls to background.
The modeling and removal of a realistic background contribution is perhaps the most important pre-processing step in analysis X-ray amorphous data.
X-ray amorphous halo widths increase with 2Theta according to universal equation: halo width = 4 E tan(θ) (E~0.125).

Universal halo width:

\[ \Delta 2\Theta = 4 E \tan(\theta) \]

\[ E = \text{strain} = 0.125 = \frac{d1-d0}{d0}. \]
Universal Halo width:
4 E tan(θ)
E ~ 0.125
(Δd/d ~ 10%) → by 10 atomic steps, the atom position uncertainty is the size of a single step.
Corresponds to ~15Å maximum correlation length.
Crystallinity index ~ 7.5.
As a direct consequence of the universal peak width for X-ray amorphous materials, the PDF transform performed on the measured powder pattern will show essentially the same damping and correlation length ~ 10 Å to 15 Å.

The PDF calculation gives a characteristic correlation length $R_p$ that is consistently 10 Å to 15 Å for all amorphous materials tested.
Rc, The correlation length determined from the universal width is <15Å. Only atomic features defined by distances less than Rc will diffract coherently.
Visual Analysis of Data

Modeling XRPD from the HSA molecule shows well defined low angle peaks below 6 degrees that correlate well with crystalline diffraction. The measured diffuse scattering shows nothing at low angles.
The characteristic position of a dominant halo in the measured data, can in principle be read straight from a graphical display of the measured data.

However, the diffraction halo from randomly arranged small local clusters will be shifted to high angles. The shift must be corrected for in order to determine 'd' values from X-ray amorphous halo positions.

\[
d_{\text{effective}} \sim \frac{d}{1.13}
\]
Visual Analysis of Data

2 Amorphous raffinose profiles!

Change in x-ray amorphous profile as a precursor to re-crystallization.

Change in local order to accommodate water.

PCRM chemometric analysis isolates 2 distinct X-ray amorphous profiles

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Direct analysis: Crystalline - Amorphous

Raffinose Pentahydrate

- Diffuse profile extracted by frequency filtering
- Use of equal area rule to estimate ratio of crystalline to non-crystalline diffraction.
- Digital filter used to isolate the crystalline from the non-crystalline diffraction.

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Direct analysis: Crystalline - Amorphous

• The Equal Area Rule:
  – The relative total diffraction signal from two phases is proportional to the electron density difference between the phases. (No preferred atomic absorption).
  – For mixed organic systems with the same atoms and similar electron densities, the relative total diffraction will be proportional to the weight% of the phases present in the mixture.

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Direct analysis: Crystalline - Amorphous

Thermodynamics and kinetics of re-crystallization to R5H

Re-crystallization from amorphous (dry) raffinose requires the addition of water. Amorphous dry → amorphous wet → crystalline. A 2 step phase transition. RH > ~45%

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Direct analysis: Crystalline - Amorphous

Using rule of equal areas, diffuse scattering intensity can be quantified with respect to crystalline diffraction.


Extracted diffuse profiles for disordered raffinose pentahydrate
Direct analysis: Crystalline - Amorphous

Vacuum Oven @ 60ºC

- Activated crystal?
- Random single amorphous nucleation events
- Amorphous%
- Defects normalised to crystalline%
- Random single defect nucleation events

Hours

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Dextran-Trehalose: Miscible or Phase Separated

Single Tg

PCRM chemometric method finds NO inter-species molecular interaction

PCRM semi-Quant analysis of Trehalose content

Trehalose composition ratio: calculated vs known

Nano Suspension

PCRM2 - Dextran

PCRM1 and Trehalose reference

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Dextran-Trehalose: Re-crystallization event

- Re-crystallization of the trehalose-dextran dispersion gives another measure of the phase separated domain size. The width of crystalline peaks can be used to calculate the effective size of the crystalline regions.

Width of crystalline peaks implies a crystalline domain size of between 10nm and 30nm.

Phase separated regions in the amorphous state will likely be of similar size or smaller → nano-suspension
Information content:

4 halos P1, P2, P3, P4. Each halo has at least 3 parameters that describe it:
- Position
- Width
- Relative Intensity

That is 9 variables for inter-molecular order. Potentially enough information to place 3 or 4 atoms at most.

Due to limited information content of the measured data. Data MUST be modeled within physically realistic limits.
Information Content of X-ray Amorphous Data

Modeling the atom positions of MCC using the Rietveld component of Topas, returns just eight (8) well defined atoms. MCC is a mesophase with more information in the measured data than in the X-ray amorphous powder pattern.

Due to the limited information content, refining atom positions with respect to measured X-ray amorphous data will return nonsense. The MCC pattern was calculated with just 8 atoms.
Bragg diffraction models are the most commonly used to calculate theoretical powder patterns.

However, the model is based upon discrete scattering events at integer (HKL) points of diffraction space.

X-ray amorphous scattering is continuous and significant error may be introduced by using a model based upon discrete diffraction events.
Direct Methods I: Para-crystalline modeling

Like the Bragg diffraction transform, the Para-Crystalline diffraction transform is a Fourier identity pair (essentially the same in diffraction and real space.).

The utility of the Para-Crystalline diffraction transform is its continuous nature.

The para-crystalline diffraction model is based upon the presence of local short range order in the sample being studied. The short range order should be linear stacks.
Direct Methods I: Para-crystalline modeling

Para-crystalline model with continuous structure factor provides a total diffraction theory for amorphous/glassy systems.

Basic unit provides a total diffraction theory for amorphous/glassy systems.

Each 1D stack forming in the solid state will give rise to a single primary halo.
Direct Methods I: Paracrystalline modeling

Component 1 real space

Direct Paracrystalline Modeling

Limited information content in x-ray amorphous pattern – use para-crystalline model to directly extract as much information as possible

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Direct Methods I: Para-crystalline modeling

- Para-crystalline modeling treats the X-ray amorphous sample as being a sum of up to 3 non-interacting linear stacks. The 'd' value of the para-crystalline model is often related to the height, width or length of the molecule.
X-ray Amorphous Form and Crystalline Parent Form

KINETIC Evolution in XRPD patterns

(a) Crystalline Form A
Kinetic disorder
20nm Crystalline
10nm Micro-crystalline
5nm 1.8nm Glassy

Correlation length (Å):
200
100
50
18

(b) buspirone HCl (ground)
buspirone HCl (calculated)

2θ [degrees]

Measured Form A melting point ~ 203°C
Calculated powder pattern evolution based on inheritance of Form A unit cell packing motif
Measured X-ray Amorphous
Glassy Form A
Predicted X-ray Amorphous

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X-ray Amorphous Form and Crystalline Parent Form

- Two common crystalline polymorphs:
  - Form BETA: Monoclinic P21/c (CCDC: BIYSEH01)
  - Form ALPHA: Orthorhombic Pca21 (CCDC: BIYSEH02)
X-ray Amorphous Form and Crystalline Parent Form

• When a crystalline powder pattern shows some correlation to an X-ray amorphous powder pattern, it is tempting to use Rietveld methods to solve for the local structure.
  – However: - Bragg calculation method not suited to X-ray amorphous powder patterns.
  – Too many variables in a typical Rietveld model when compared to the actual information content.
  – Limited refinement: reduce structure to P1 restrict refinement to the micro-structure and a single lattice parameter (maybe acceptable in some cases).
Many X-ray amorphous forms exhibit an apparent relationship to one of the crystalline polymorphs (usually the high temperature form). Can Rietveld modeling give realistic information?

Indomethacin Rietveld modeling in Maud:

- a: 9.302 → 9.137
- b: 10.968 → 10.644
- c: 9.756 → 10.241
- al: 69.36 → 68.68
- be: 110.83 → 106.21
- ga: 92.75 → 85.29

Volume: 867 → 872 (0.5%)
Mean crystal size ~20Å
Because a Rietveld model is able to describe the measured data, this in itself is not proof that the underlying molecular model is correct.
The Pair wise Distribution Function is a transformed powder pattern displayed as a function of distance.

- Shows common atom-atom pair distances as a peak.
- Long traditional use for liquid and amorphous systems to determine local coordination numbers.
- PDF matching often used as verification for molecular modeling and form similarity.
The PDF and X-ray amorphous forms

• Calculation of the PDF from a measured powder pattern:
  – The PDF transform is just a Fourier sine transform and is straightforward to execute.
  – Derivation of the required reduced structure factor from a powder pattern is the difficult part.
    • Requires correction for all instrumental sources of background and intensity modification.
    • Lorentz – Polarization, Compton Scattering, Absorption, Illuminated sample volume, air-scatter etc.
    • Best addressed by optimizing the diffractometer
The PDF and X-ray amorphous forms

PDF study of the solid forms of Piroxicam. The X-ray amorphous form shows just 3 NN PDF peaks before the signal damps out. The location of these 3 peaks and relative intensity closely matches the PDF of both the Alpha and Beta crystalline polymorphs.
The PDF and X-ray amorphous forms

As made

Amorphous

Mill 1

Mill 2

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