



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



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What do we mean by "Amorphous Solid Forms"?

- Although lacking long-range order, there is no fundamental restriction on the types of short range intermolecular 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)





### **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.



### **XRPD** Data Collection



The modeling and removal of a realistic background contribution is perhaps the most important pre-processing step id analysis X-ray amorphous data.



X-ray amorphous halo widths increase with 2Theta according to universal equation: halo width =  $4 \text{ E} \tan(\theta)$  (E~0.125).





Universal Halo width:  $4 \text{ E} \tan(\theta)$ E ~ 0.125  $(\Delta d/d \sim 10\%) \rightarrow by 10$ atomic steps, the atom position uncertainty is the size of a single step. Corresponds to ~15Å maximum correlation length. Crystallinity index ~ 7.5.

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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  $\sim$  10 Å to 15 Å







Effective size IMC 1.1nm



Effective size piroxicam 1.2nm

The PDF calculation gives a characteristic correlation length Rp 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.



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 Xray amorphous halo positions.

d\_effective ~ d/1.13











- 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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S. Bates, R. Kelly, P. Shields, I. Ivanesvic, G. Zografi, A. W. Newman, J. Pharm. Sci., 96(5): 1418-1433, 2007.



#### Vacuum Oven @ 60°C





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#### Dextran-Trehalose: Miscible or Phase Separated



#### Dextran-Trehalose: Recrystallization 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



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  $\rightarrow$  nanosuspension



#### Information Content of X-ray Amorphous Data



Due to limited information content of the measured data. Data MUST be modeled within physically realistic limits.



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to place 3 or 4

atoms at most.

#### 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, 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.



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.

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

 Para-crystalline modeling treats the Xray 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.





- Two common crystalline polymorphs:
  - Form BETA: Monoclinic P21/c (CCDC: BIYSEH01)
  - Form ALPHA: Orthorhombic Pca21 (CCDC:





- 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:  $9.302 \rightarrow 9.137$ b:  $10.968 \rightarrow 10.644$ c:  $9.756 \rightarrow 10.241$  $a:69.36 \rightarrow 68.68$ be:  $110.83 \rightarrow 106.21$ ga: 92.75 → 85.29 Volume: 867  $\rightarrow$  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



- Calculation of the PDF from a measured powder pattern:
  - The PDF transform is just a Fourier sine transform and is straight forward 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





