An Investigation of Non-Crystalline Materials Using X-ray Powder Diffraction

PPXRD 12 Beijing May 2013

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This document was presented at PPXRD - Pharmaceutical Powder X-ray Diffraction Symposium

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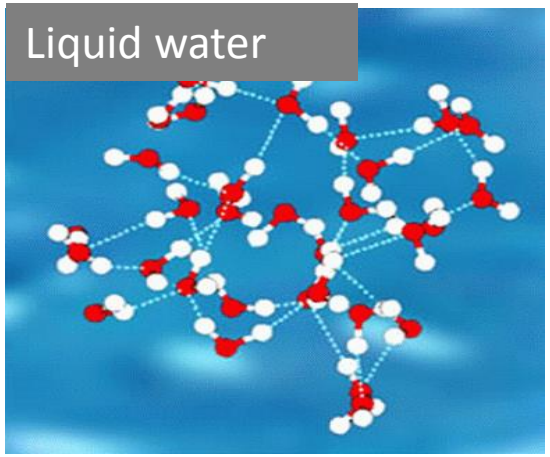
Outline of presentation::

- 1.) Crystalline and Non-crystalline.
- 2.) Application 1: residual water in lyophilizates.
  - Normalization and background modeling
  - Variance analysis
  - Full pattern fitting
  - ‘Vainshtein’s law’ and absolute quantification
- 3.) Application 2: milling induced disorder
  - Conversion to absolute electron units
  - Modeling sources of diffuse X-ray scattering
  - Defect scattering profiles

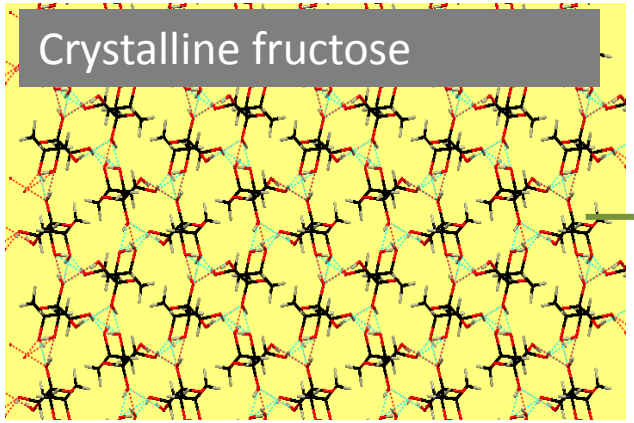
Crystalline and non-crystalline diffraction

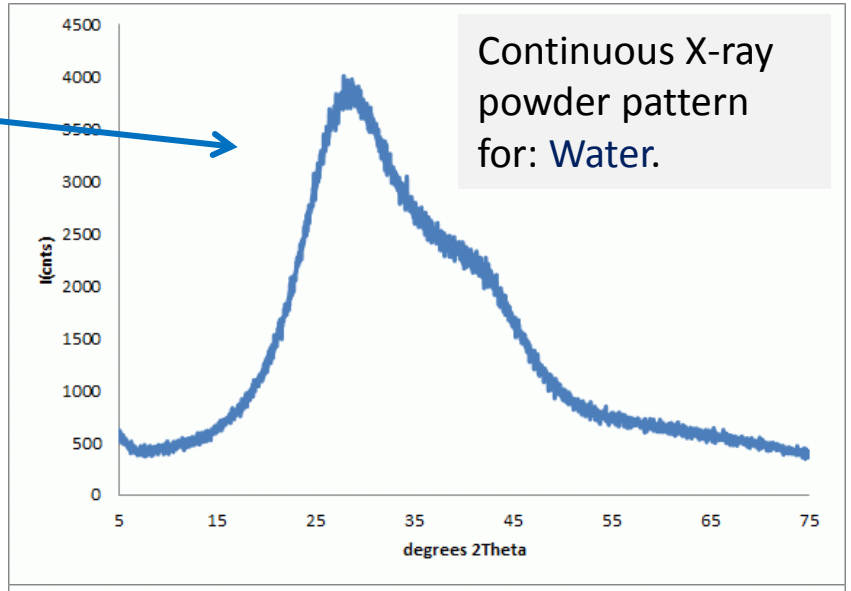
Liquid water

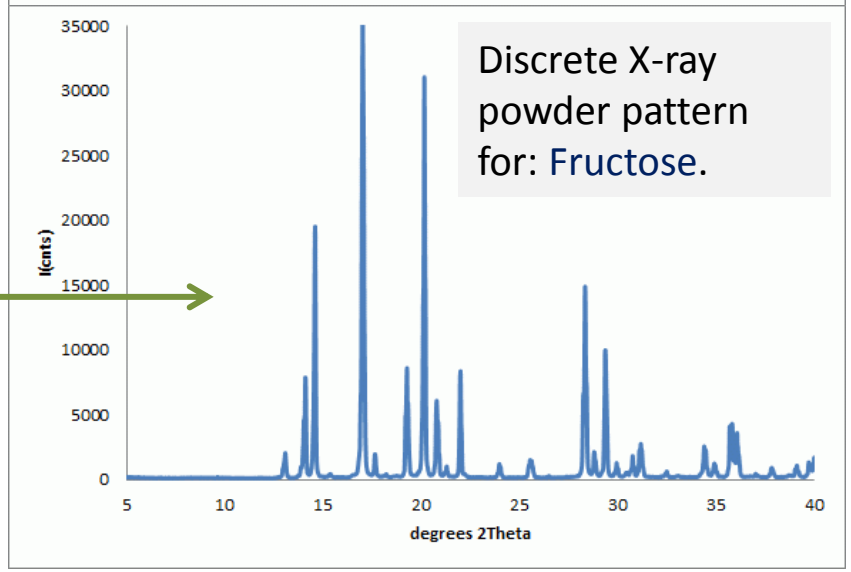


Crystalline: “any solid having an essentially discrete diffraction diagram” IUCr 1992

Crystalline fructose







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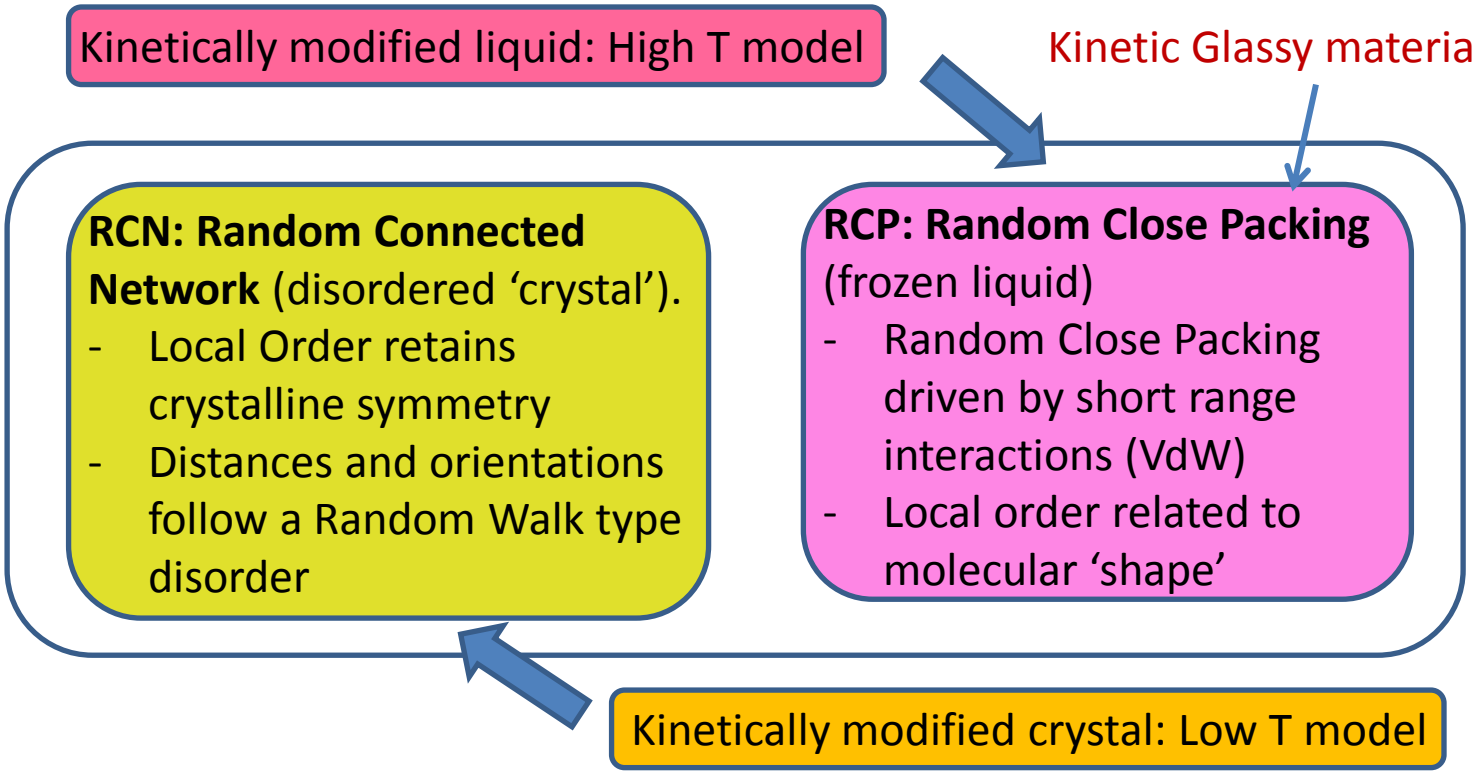
Non-Crystalline Materials

X-ray amorphous powder patterns are continuous in nature (**non-crystalline**) indicating that the sample has no long-range order and is macroscopically isotropic in nature. However, **the non-crystalline X-ray pattern itself is a finger print of the short-range order.**

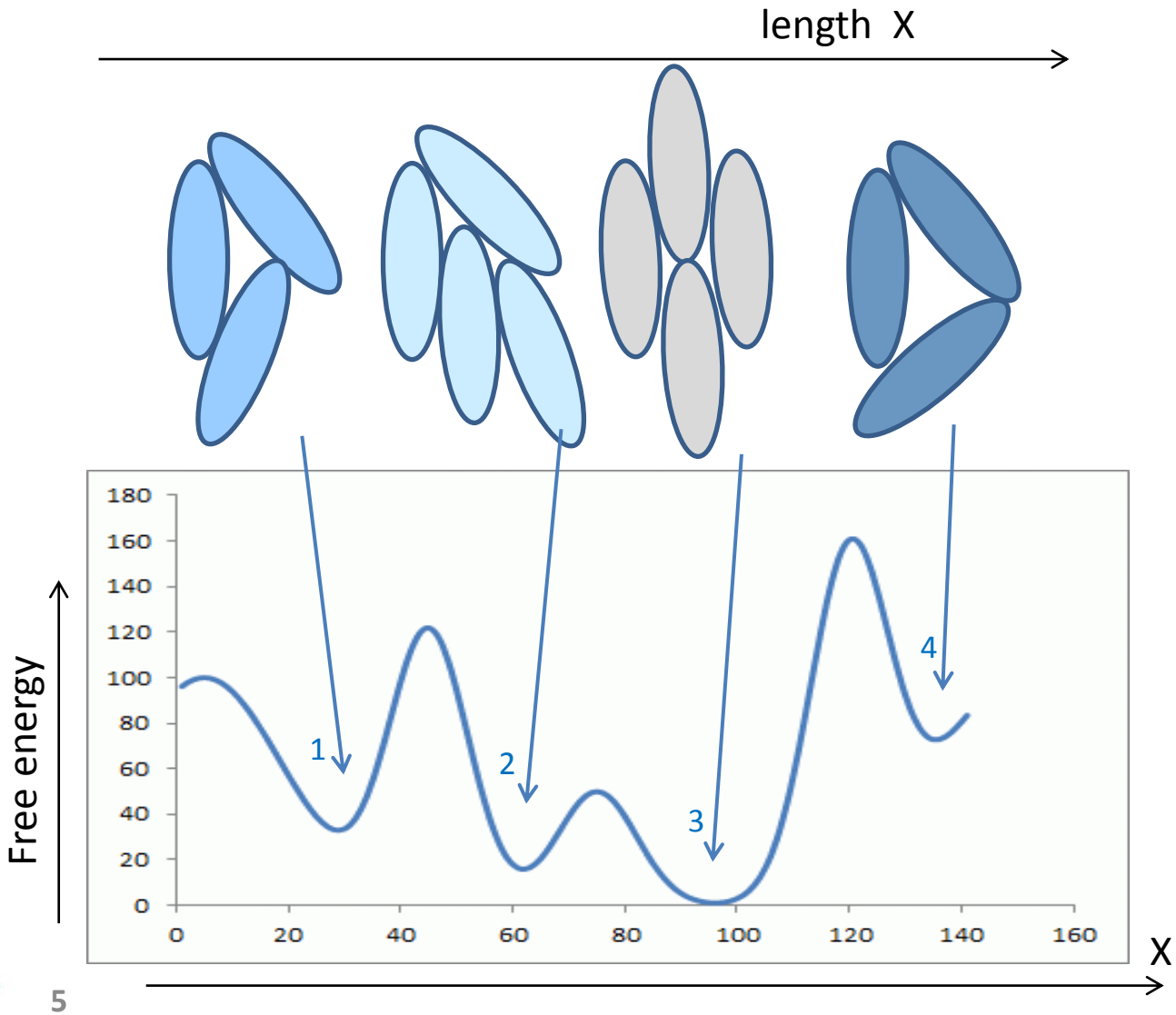


Nature of ‘Glassy’ local order

Spatially, a super-cooled liquid can be considered to be a mosaic of locally ordered regions (each of which represents a local energy minima) isolated from each other by high energy barriers

Configurational Entropy
Sc ~ log(Nf)/Nf
‘Nf’ ~ number of different free energy states available.

Experimental determination of local order will average over the huge number of local states



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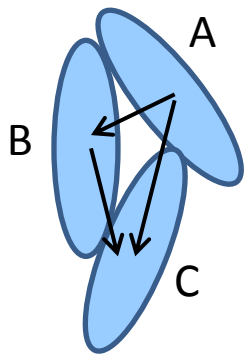
Debye Diffraction Model



Pair relationships:

1 A-A : d == 0.0

1 B-B : d == 0.0

1 C-C : d == 0.0

2 A-B : d = d_{AB}

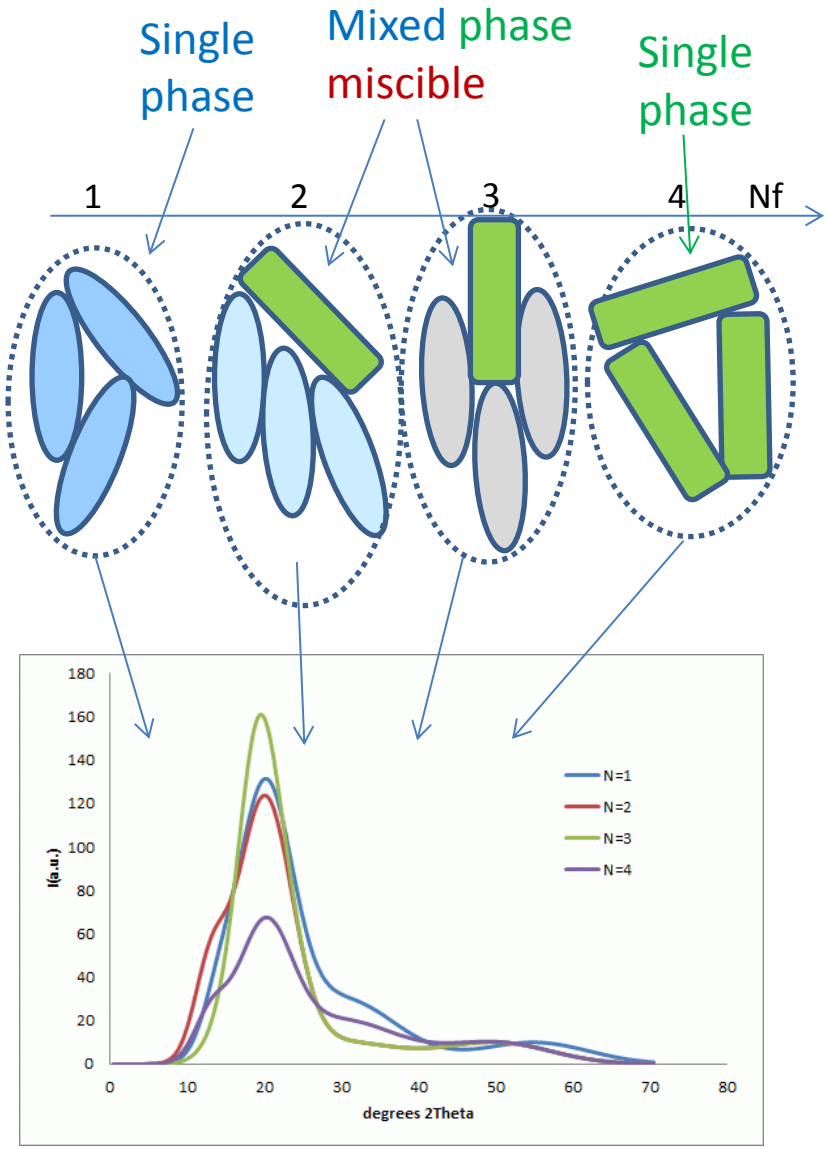
2 A-C : d = d_{AC}

2 B-C : d = d_{BC}

Diffraction Intensity:

$$I_{DM} = \sum_i F_i^{2\square} + 2\sum_i \sum_{j \neq i} F_i F_j \sin(Q.d_{ij})/(Q.d_{ij})$$

Each Locally ordered region, single phase or mixed, gives it's own unique 'coherent' diffraction response given by atom-atom pair coordination. Measured powder pattern is a sum of all such responses.



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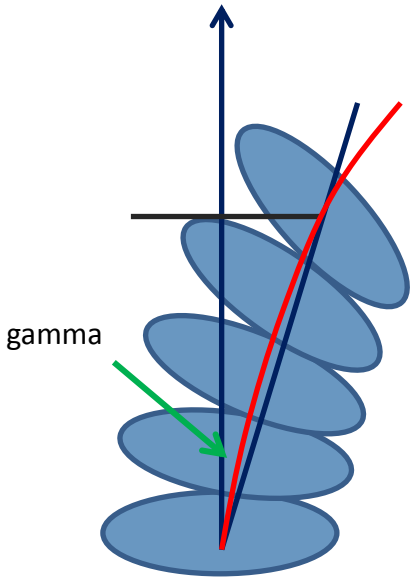
What extent of local order is observed?

Consider random close packing as a self-avoiding random walk

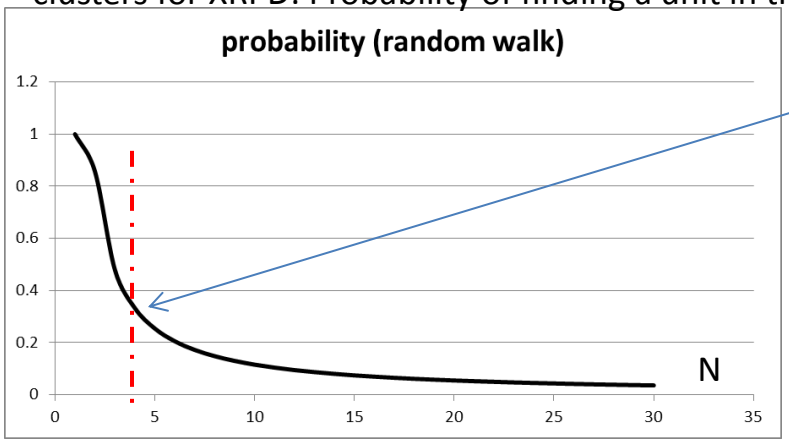


Half cone angle:: gamma
From self avoiding random walk

Cos(gamma) = (1/(N^(1-x))

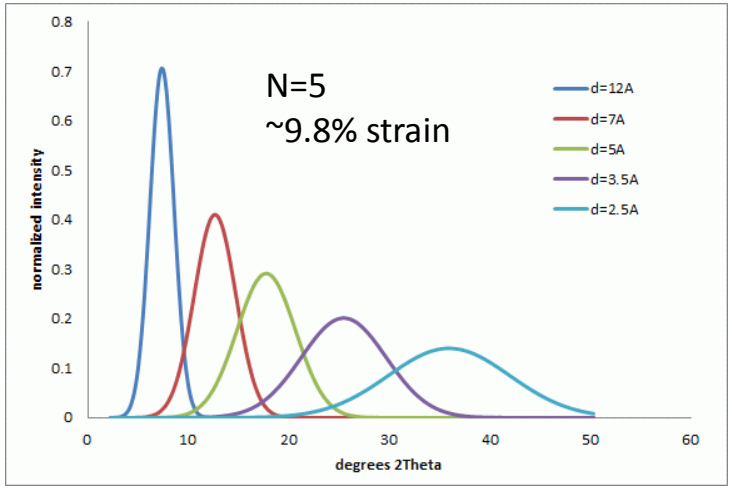
Where N is number of units and
(x) typically lies between 0.5 and 0.8

Evolution of gamma gives effective size limit to coherently diffracting clusters for XRPD: Probability of finding a unit in the correct place.



coherent limit ~ N d
Where N = number of units
and 'd' is size of packing unit

Scherrer equation
Peak_broadening ~ K λ/(N d cos(2θ)) (peak broadening in radians)



XRPD from a randomly close packed material will have a universal form where peak width is only a function of its position

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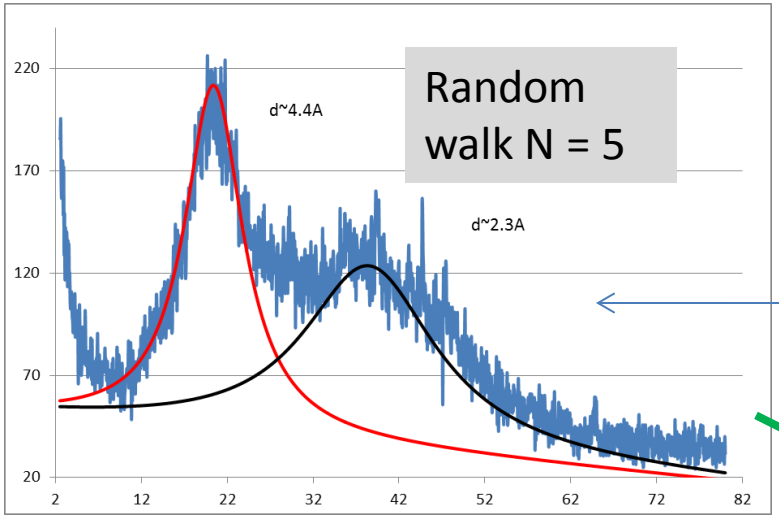
Universal Peak width for random packing



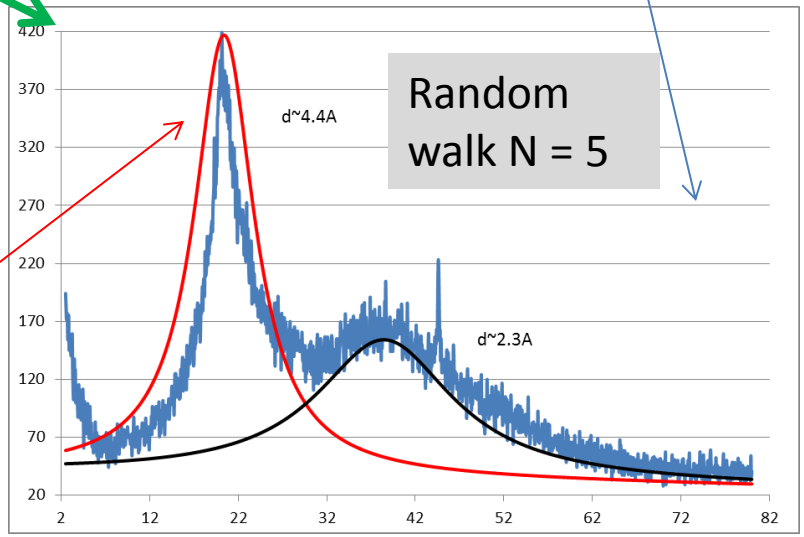
The universal nature of XRPD patterns from random systems is only with respect to the peak width as a function of peak position.

The actual peak position and peak area will be unique to the system of interest!

Change processing conditions

Crystalline materials also have a universal peak width determined by the instrument alone. For crystalline materials, peak broadening is related to 'micro-structure'.

Random materials also have a universal peak width where peak sharpening is related to 'micro-structure'.



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Measurement and Analysis of Non-Crystalline XRPD

- Typically requires a different approach than crystalline materials characterization.
  - Think more in terms of a quantitative type analysis rather than identification.
  - Knowledge of instrumental background and intensity function can be critical
  - Consistent sample preparation and measurement conditions (collect data to high angles)
  - **Normalization procedure**

Application I: Sucrose Lyophilizates – Characterization of Water Content

- Lyophilization routinely used to prepare bio-pharmaceuticals.
  - Residual water is a critical processing parameter.
  - Related to stability of formulation and maintaining protein function
  - Is residual water free or bound?
  - How much residual water present?
- Example of multicomponent amorphous drug product

Application I: Sucrose Lyophilizates – Samples (Baxter Pharmaceutical Solutions, IN)

11 sucrose lyophilizates selected by thief sampling at different times during the freeze drying cycle.

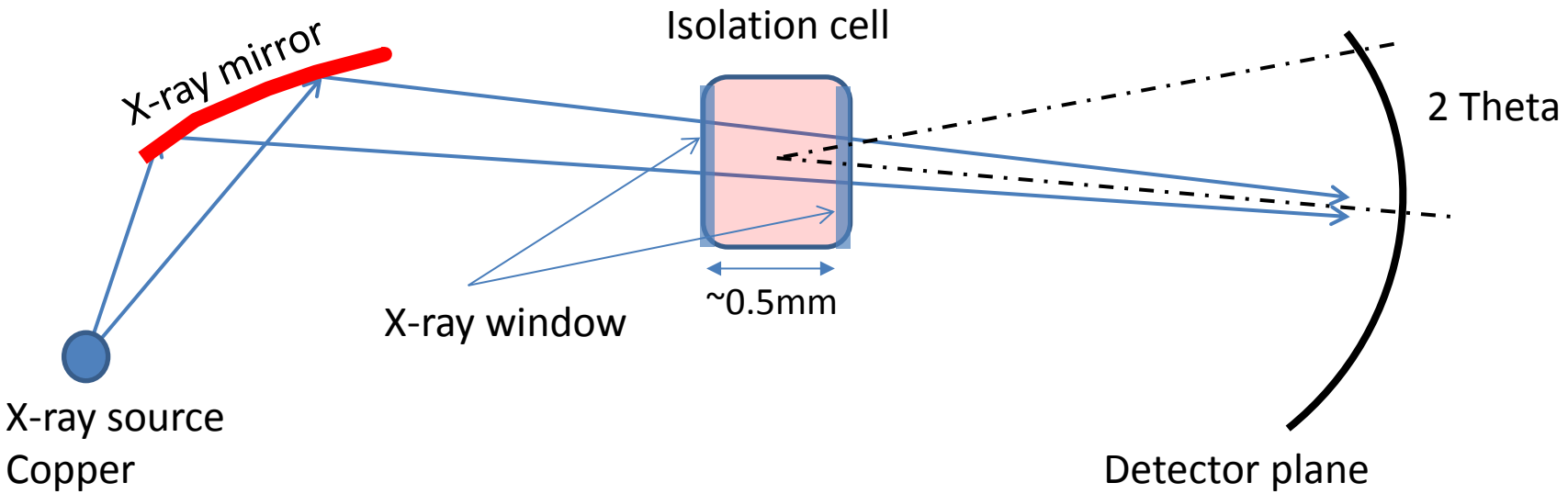
Residual water content taken as mean between KF and NIR measurements.

sample:	water %w/w
Lyophilizate 1	0.13
Lyophilizate 2	0.14
Lyophilizate 3	0.33
Lyophilizate 4	0.27
Lyophilizate 5	0.88
Lyophilizate 6	1.05
Lyophilizate 7	2.04
Lyophilizate 8	2.90
Lyophilizate 9	2.95
Lyophilizate 10	5.36
Lyophilizate 11	4.46

Application I: Sucrose Lyophilizates – Instrument Configuration

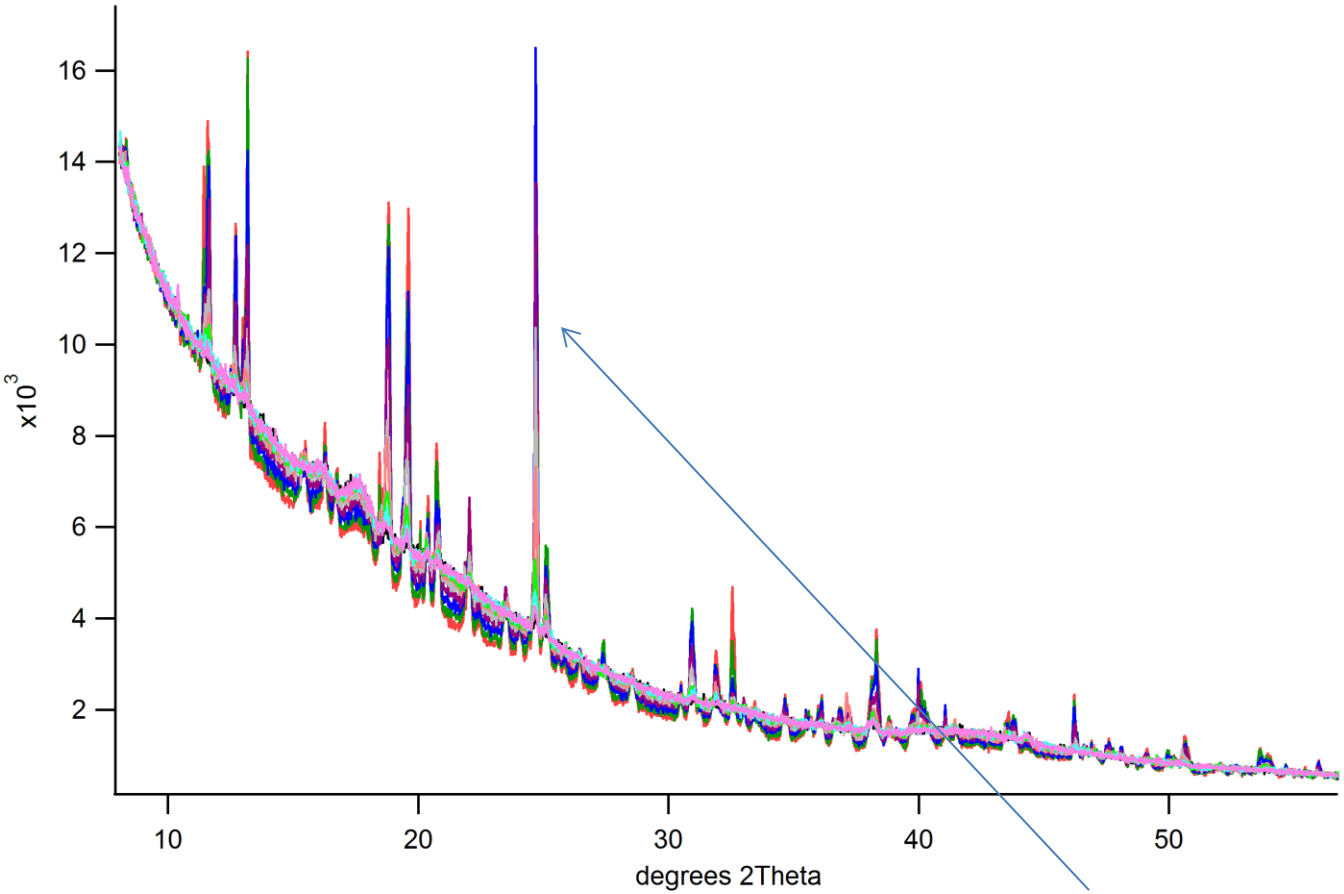
Convergent Beam Transmission Geometry
(Debye-Scherrer)

Rigaku SmartLab



Isolation cell filled and sealed in appropriate glove box environment. Provides between 15 minutes to 2 hours of stable local environment

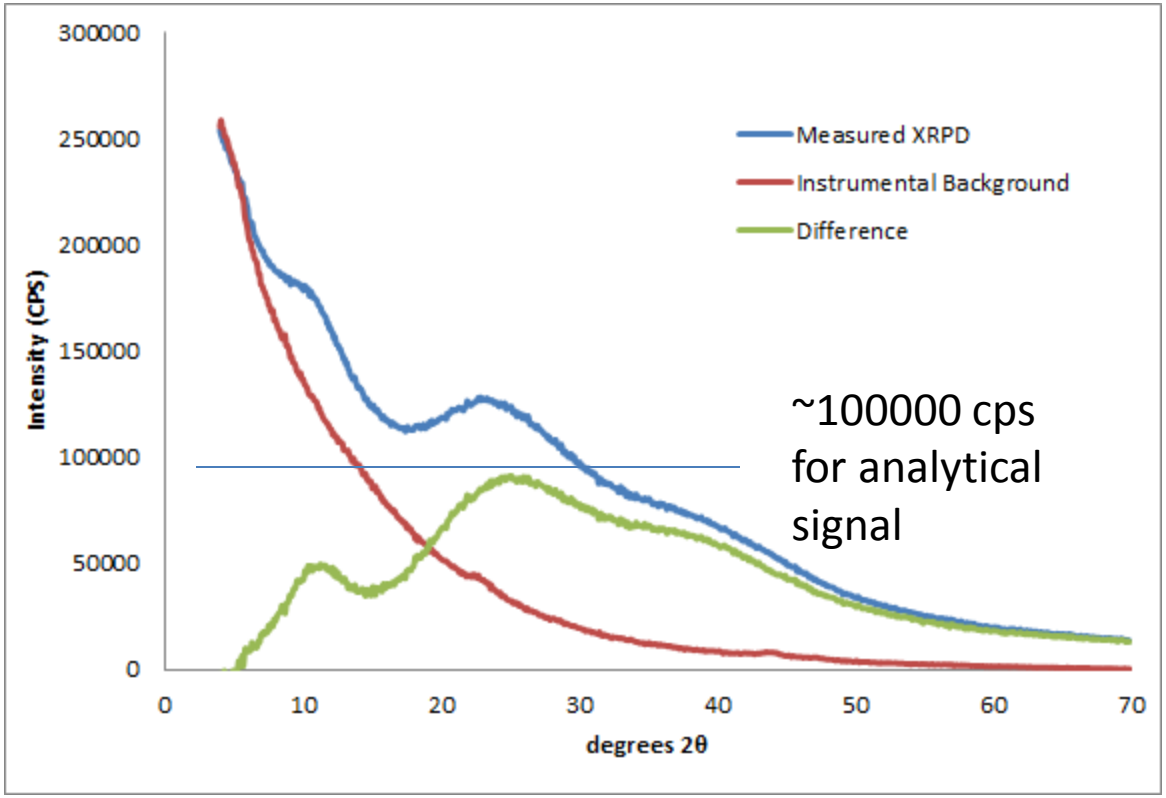
Application I: Sucrose Lyophilizates – Instrument Configuration



When measuring metastable forms, data is collected using multiple high speed loops. D'teX system allows individual scan times to be ~ 1 to 2 minutes with about 10 loops per sample

Failure of environmental cell leads to rapid re-crystallization of lyophilizates.

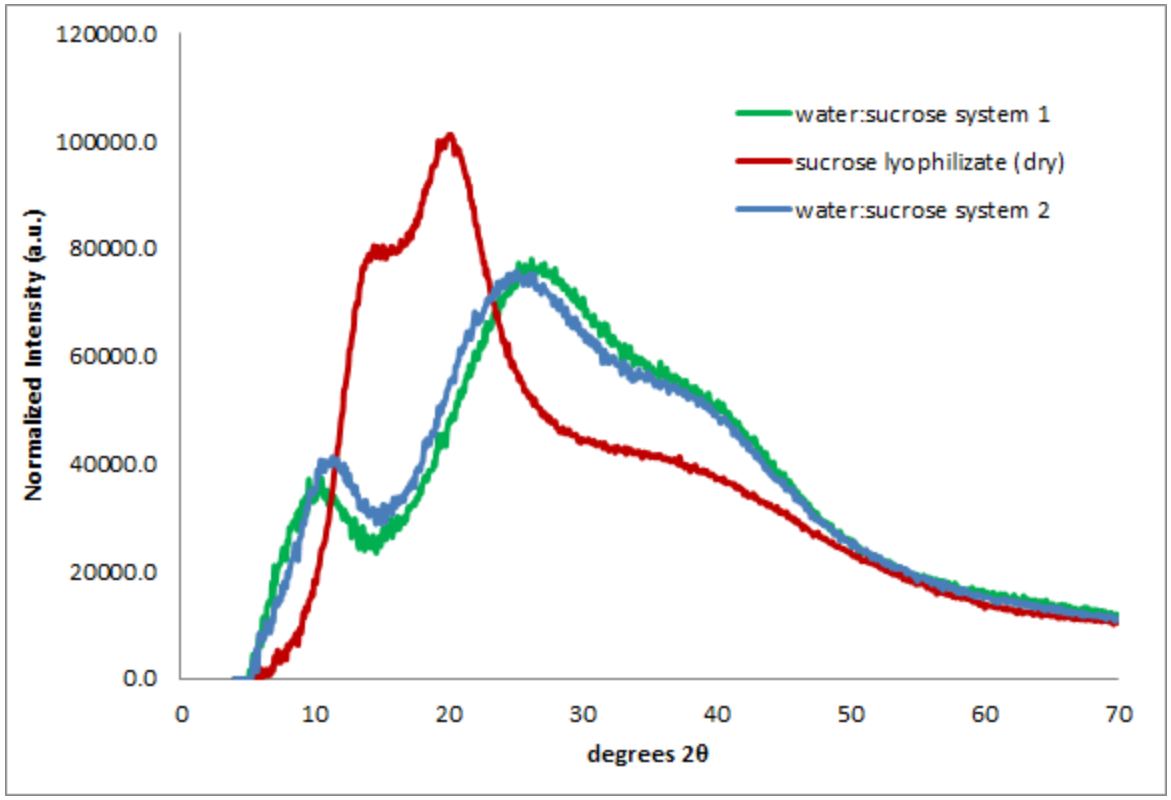
Application I: Sucrose Lyophilizates – Measured Data



For Cu k-alpha, collect data out to at least 70 degrees 2θ.

Determine instrumental background. Include scaled background into analysis. (Absorption Corrected).

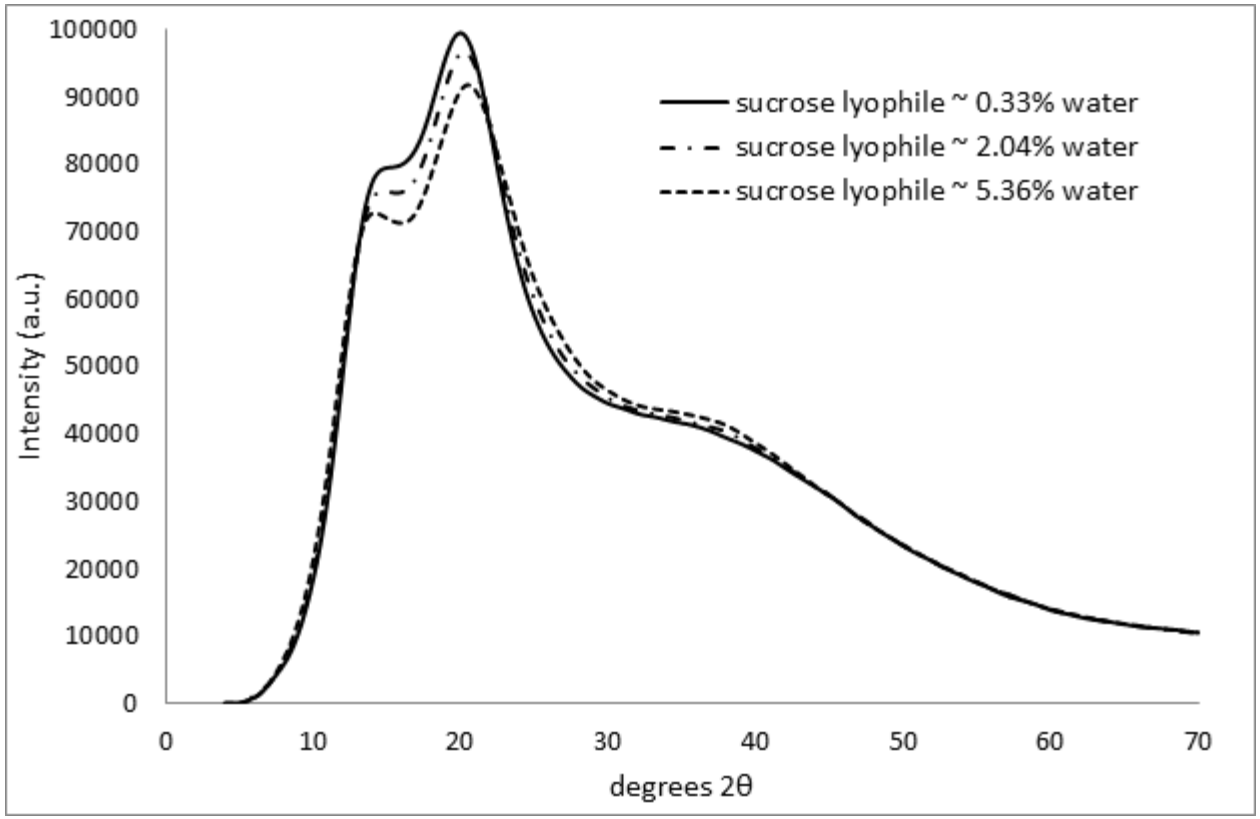
Application I: Sucrose Lyophilizates – Normalizing Procedure 1



Analytical Data Scaled to common integrated intensity and asymptotic high angle response.

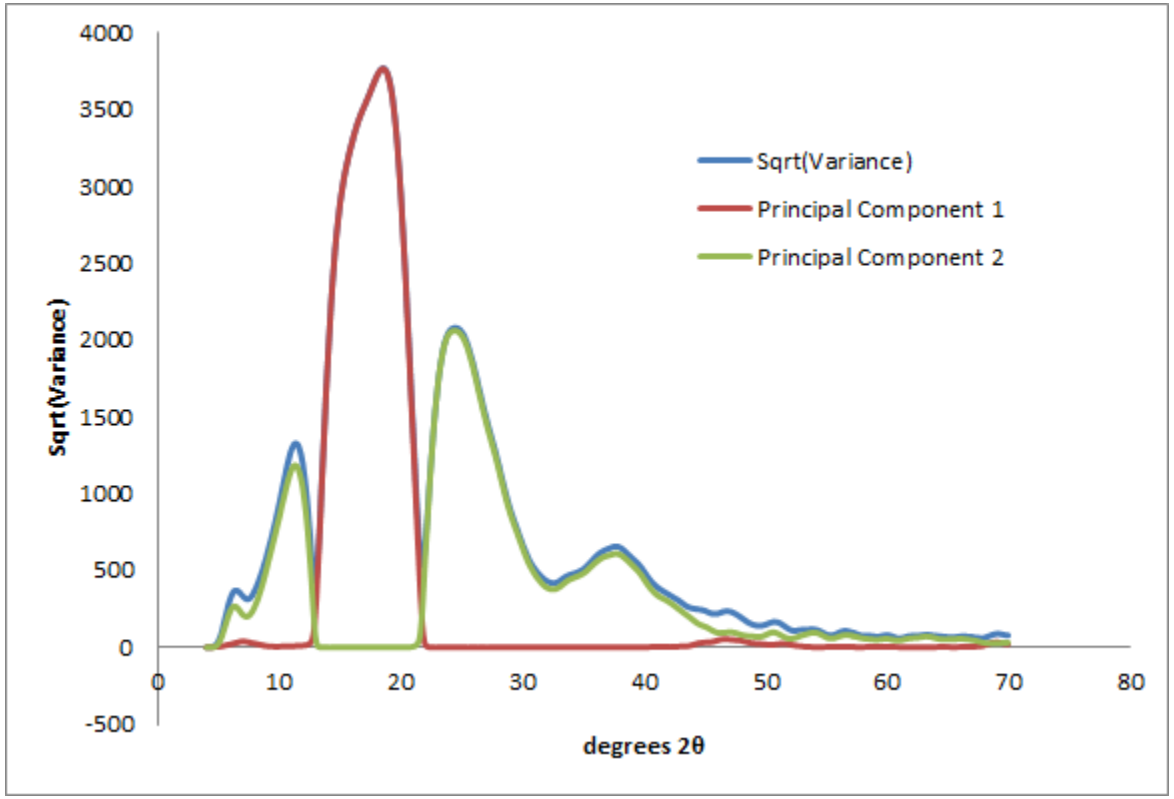
Assumes organic molecular system!

Application I: Sucrose Lyophilizates – Normalizing Procedure 1



With appropriate normalization of the analytical signal – variance in the data is significant and meaningful.

Application I: Sucrose Lyophilizates – Variance Analysis



Variance across 11 lyophilizates with water content ranging from 0.13% w/w to 5.4% w/w described by two orthogonal principal components

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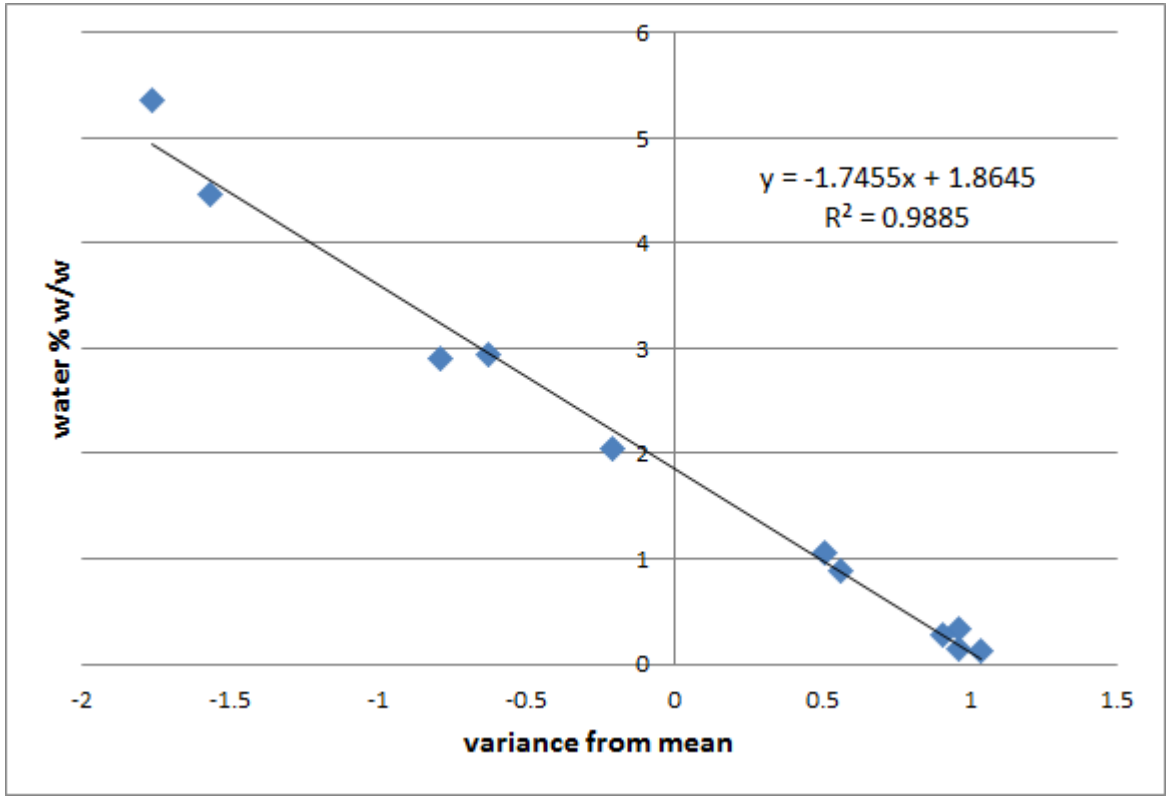
Application I: Sucrose Lyophilizates – Variance from Mean



Variance from mean for each of the lyophilizates is linearly correlated to water content over full range from 0.13% w/w to 5.4% w/w

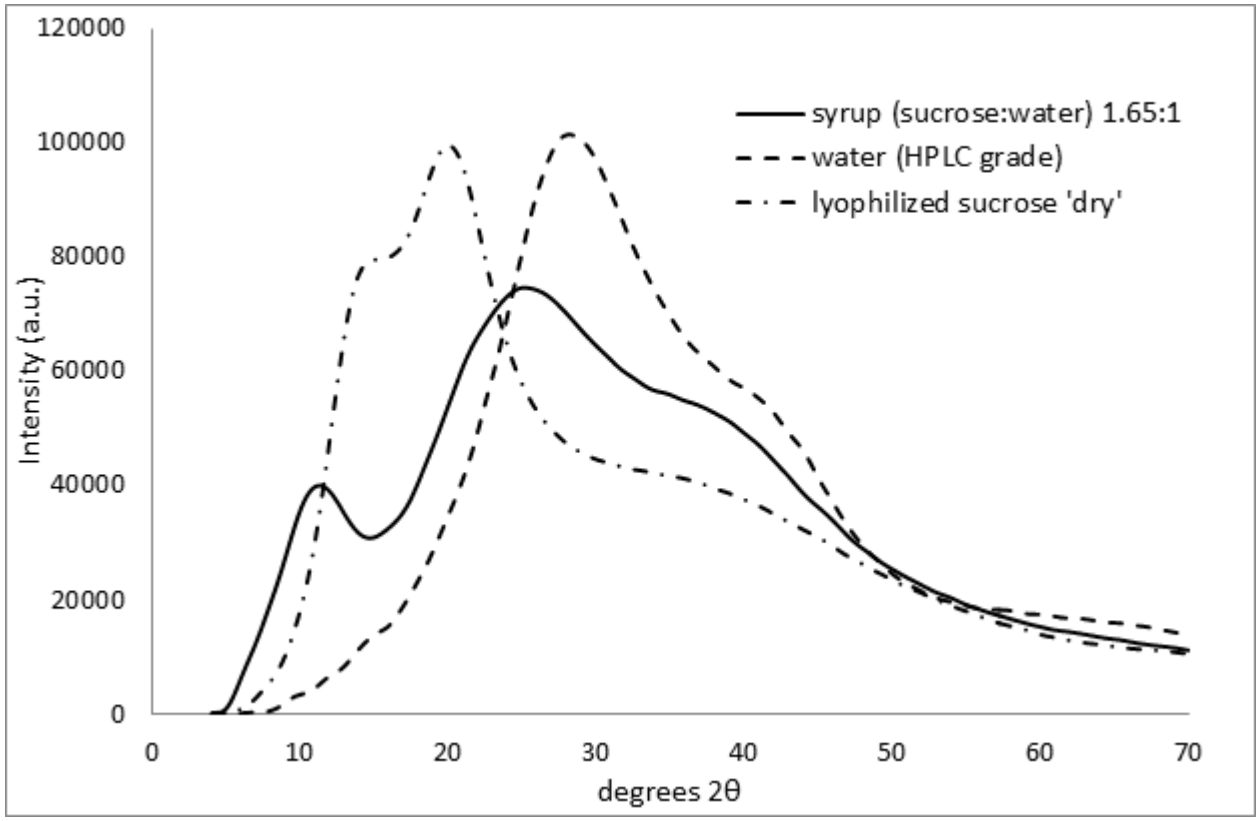
Application I: Sucrose Lyophilizates – Variance linear correlation

- The measured powder patterns when self-consistently normalized show significant variance that is linearly correlated to residual water content.
- Variance can be directly used for quantitative analysis.
- Variance measure is linear with residual water content down to levels below 0.2% w/w

Application I: Sucrose Lyophilizates – Local Structure Analysis

- In addition to variance, non-crystalline powder patterns will contain information on local molecular order including the occurrence of miscibility.
- Molecular modeling or reference samples can be used to generate reference powder patterns for known systems.
- Total Pattern Fitting of analytical data using reference patterns can provide a useful characterization tool for local order.

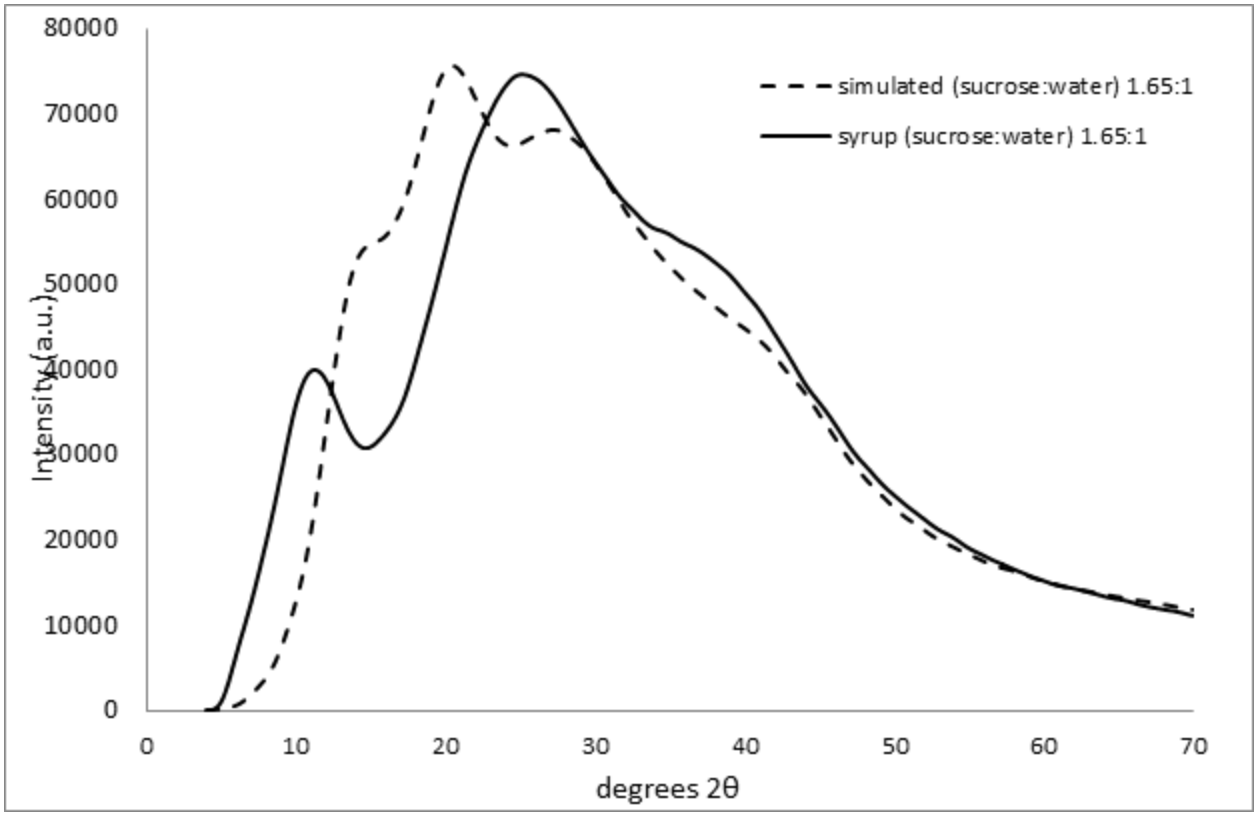
Application I: Sucrose Lyophilizates – Bound and Free Water: Miscibility



Miscibility can occur between molecules in non-crystalline systems giving solid/liquid solutions.
Solid solutions scatter X-rays as a combined molecular system

Note unique features in powder pattern for solid/liquid solution.

Application I: Sucrose Lyophilizates – Bound and Free Water: Miscibility



Due to the locally mixed molecular order, a powder pattern measured on a miscible system can not be described in terms of reference powder patterns for each constituent.

A linear combination of water and lyophilized sucrose reference powder patterns do not describe measured powder for solid/liquid solution

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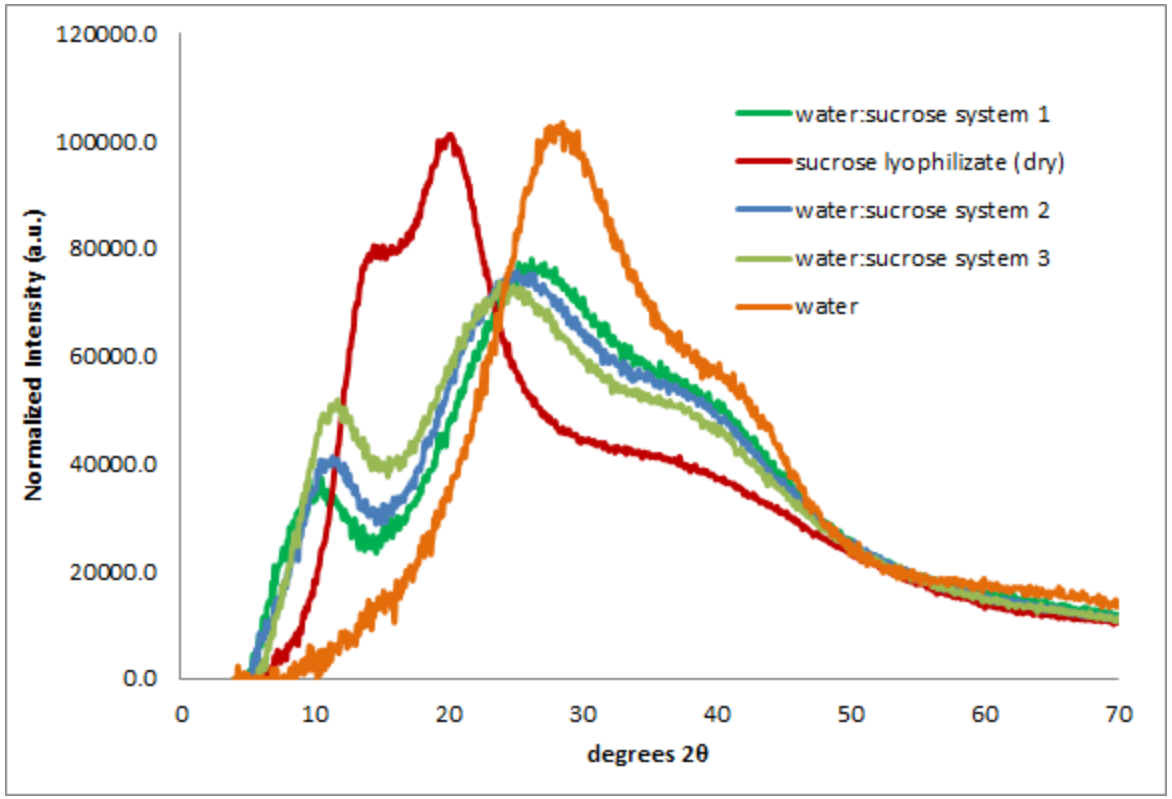
Application I: Sucrose Lyophilizates – Full Pattern Fitting



Series of sucrose:water solid/liquid solutions made and used to generate reference XRPD patterns to test for miscibility. Combined with free water and dry lyophilized sucrose reference patterns for full pattern fitting

Pattern fitting performed w.r.t. the measured lyophilizate data using a predominantly positive minimization.

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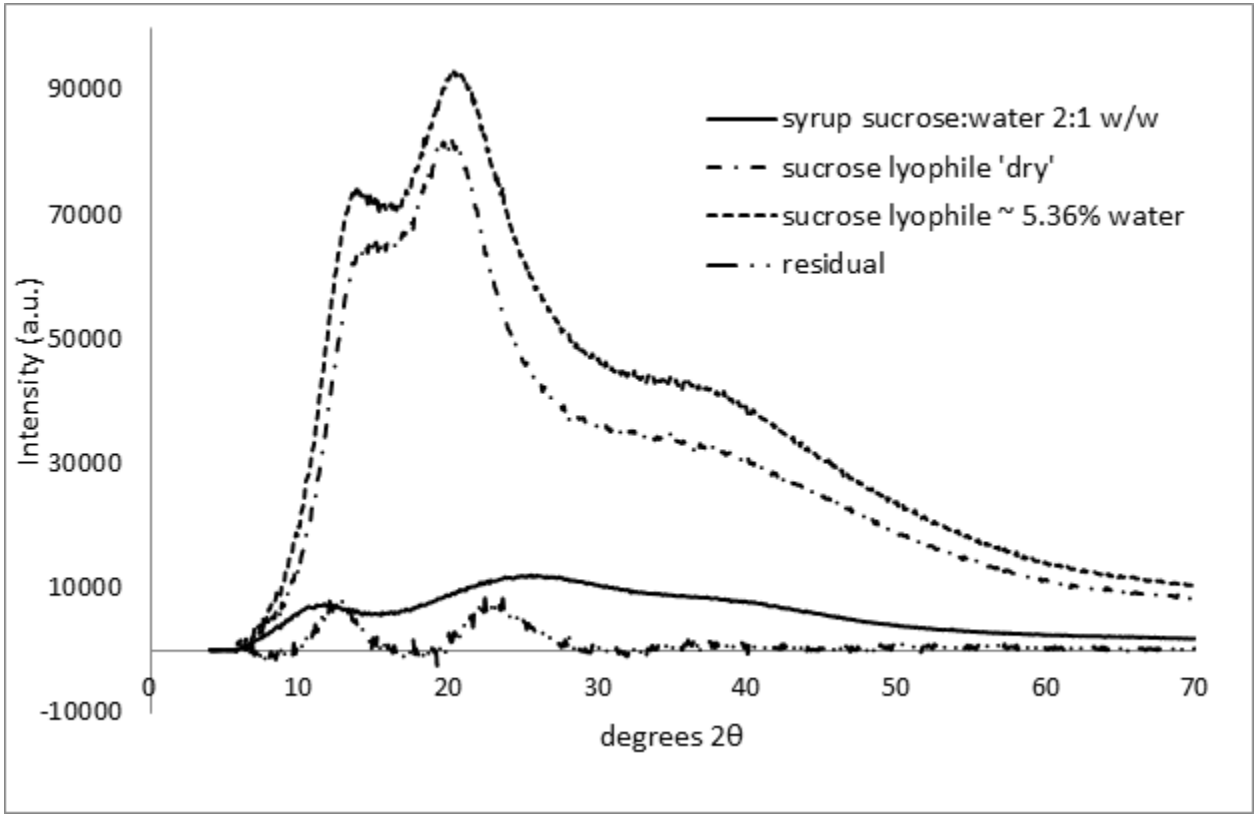
Application I: Sucrose Lyophilizates – Predominantly Positive (PP) Minimization



Reference powder patterns combined and fit to analytical data using scale factors.

PP minimization is method of choice when reference patterns do not describe 100% of analytical response

Residual from PP minimization will be essentially positive and correspond to real unknown components in analytical response.

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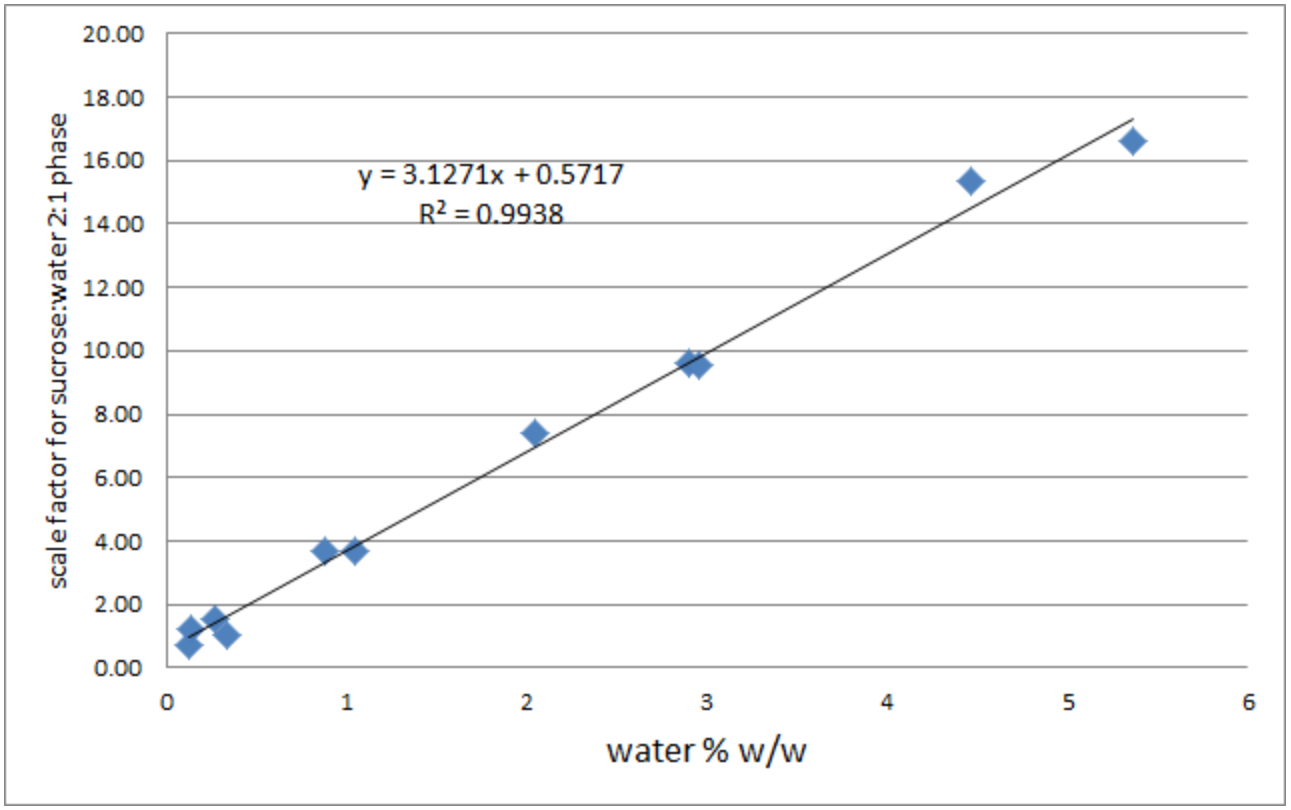
Application I: Sucrose Lyophilizates – Sucrose:Water 2:1 w/w system



Only Sucrose:Water 2:1 w/w system returned self-consistent scale factors.

Scale Factor linearly correlated with residual water w/w% with R factor of ~0.994.

Suggests residual water is intimately bound with sucrose forming a 2:1 w/w sucrose:water solid/liquid solution.

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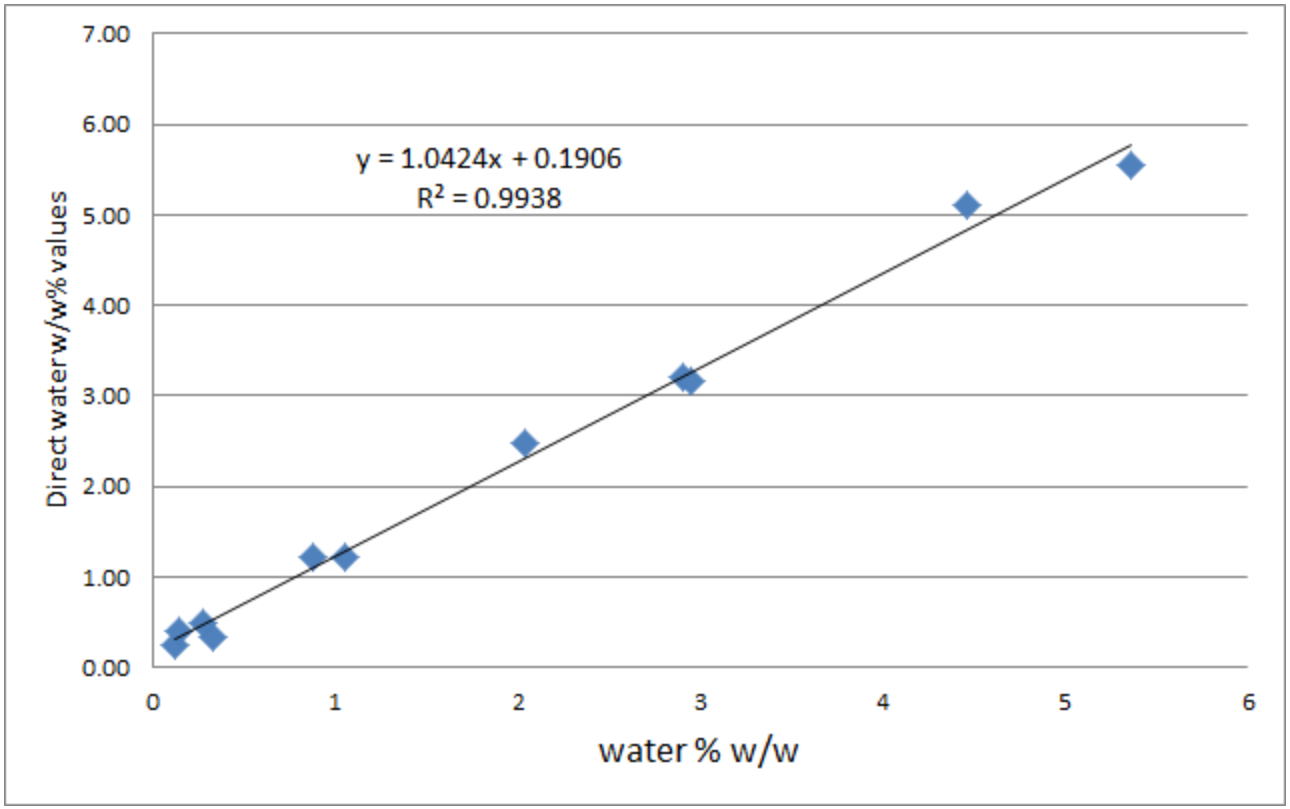
Application I: Sucrose Lyophilizates – Absolute water w/w% Quantification



Scale Factor for 2:1 system can be converted to absolute water w/w values by scaling for incoherent atomic form factor per unit mass for water and sucrose.

Water scatters about 1.16x more X-rays per unit mass than sucrose according to incoherent sum of atomic form factors. (Use like I/Ic correction).

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Application I: Sucrose Lyophilizates – General Observations

- Consistent normalization of analytical data allows variance to be used for system characterization.
- Full pattern fitting with reference patterns can be used to study miscibility: free verses bound.
- Knowledge of molecular environment (matrix) along with incoherent atomic form factor can be used to extract absolute quantitative numbers.
  - No need for standards (Vainshtein's law)

Application II: Processed materials – Defects and Amorphous Formation

- Whenever crystalline materials are processed or exposed to an energetic environment, defects and/or amorphous material may be produced.

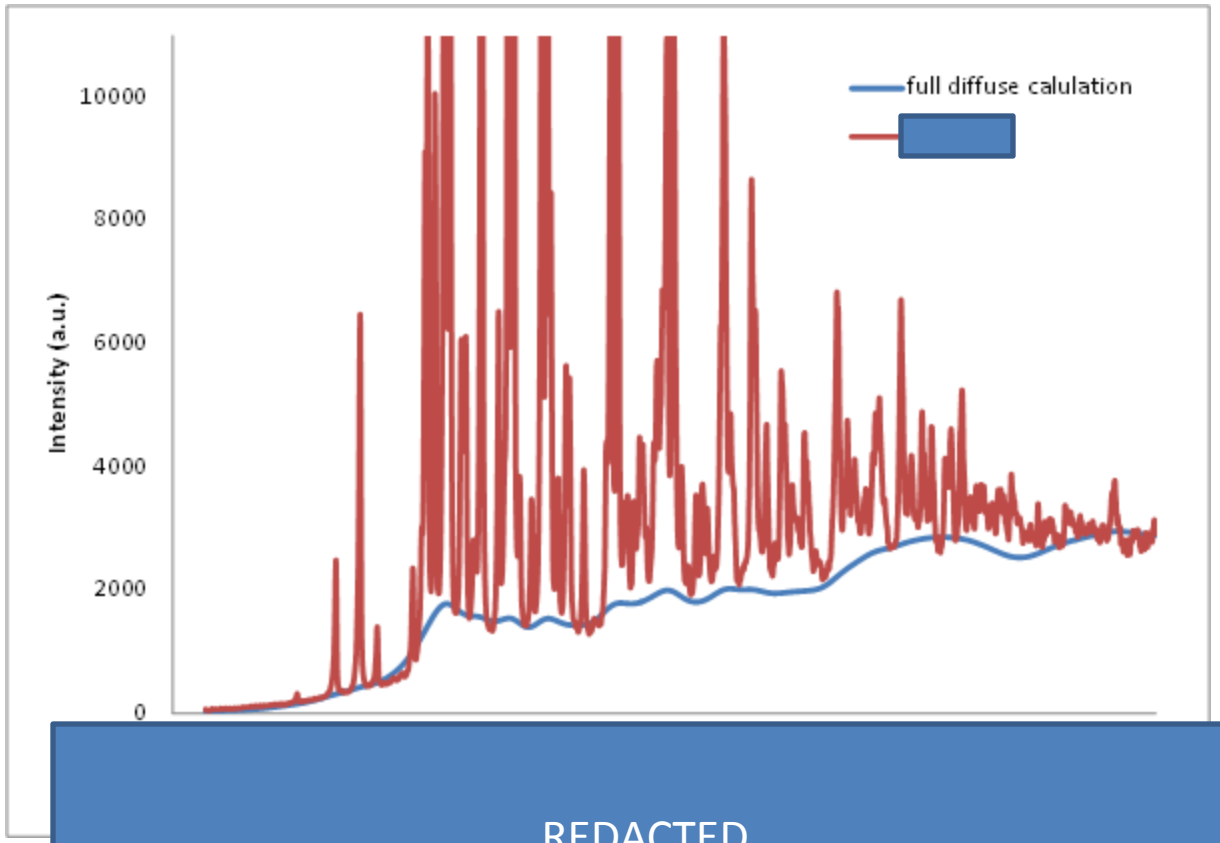
- Characterization of non-crystalline diffraction profile for processed materials can yield information on the types of disorder formed.

- Can help in optimizing processing conditions.

Sources of Diffuse X-ray Scattering in a Measured Powder Pattern

- Non-crystalline Material
- Mesophases
- Local Disorder in a Mean Crystal Structure
- Thermal Vibration in a Crystalline Lattice
- Compton Scattering
- Instrumental Contributions
  - Air Scatter
  - Brehmstrallung
- **Be Careful!**

Application II: Processed materials – Example Total Diffraction Analysis



REDACTED

Predominantly Positive fitting was used with variables:

1.) % amorphous
2.) % defects
3.) defect strain field
4.) RMS thermal vibration

Application II: Processed materials – Milling induced disordered

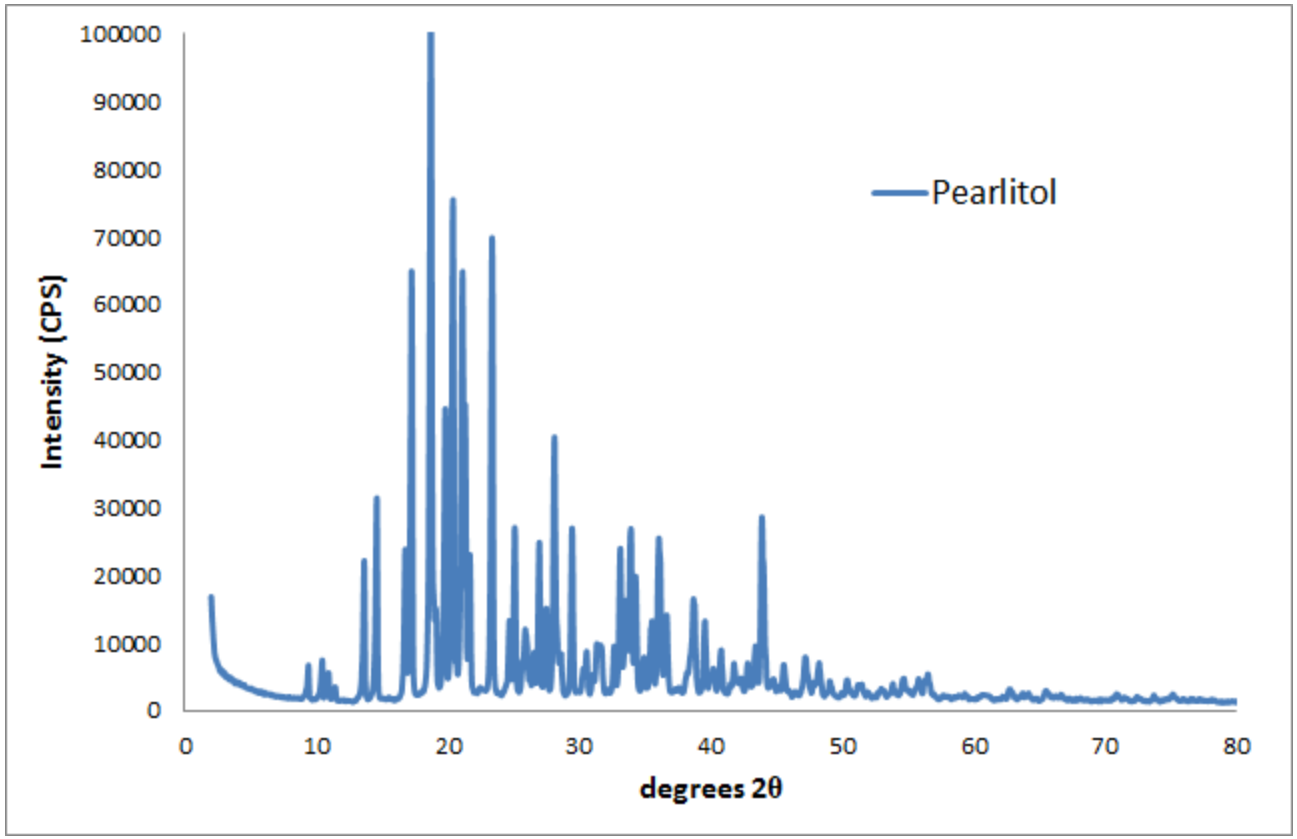
Column1	Unmilled	Fresh Milled	Annealed
%Amorphous	REDACTED		
%defects			
Strain Field (Å)			

Milling induces both amorphous and defect diffuse X-ray scattering profiles. Annealing removes the amorphous component but the defect contribution remains.

Application II: Processed materials – Analytical Procedure

- Normalize analytical response to Electron Units
  - Correct for instrumental LP and optical shadow
  - Normalize to Compton and Incoherent Atomic Form Factor
- Include sample and instrumental diffuse components (TDS, Brehmstrallung etc..)
- Estimate defect scattering profile
- Use PP minimization for all components.

Application II: Processed materials – Analytical Procedure



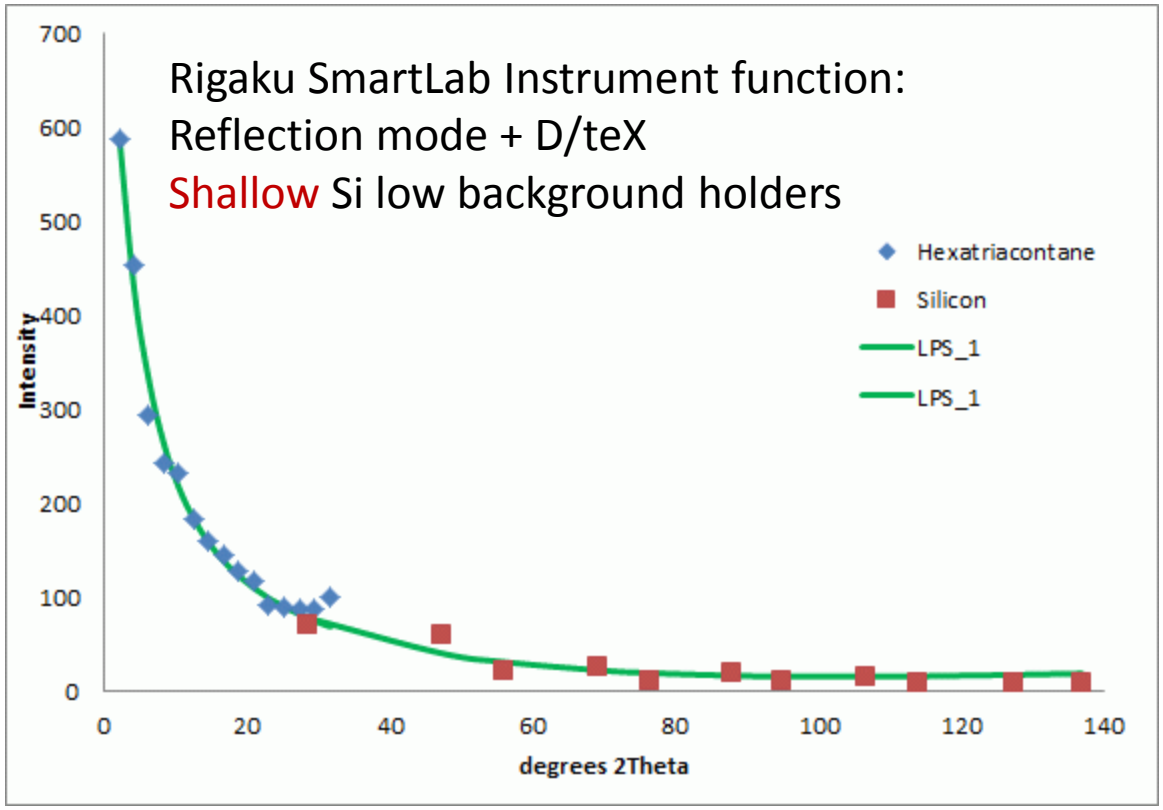
Pearlitol used as a reference material:
1.) Mixed 50:50 mannitol system.
2.) Little propensity for PO
3.) No stable amorphous form
4.) Low defect concentration
5.) 'Small' particle size
6.) Functions as a close to ideal material.

Application II: Processed materials – Normalizing Procedure 2: LP factor

Instrumental intensity function:

- Lorentz Factor
  ~ sin(θ)^(-Y)
- Polarization Factor
  ~[1+cos(2θ)^2]/2
- Optical shadow factor
  ~[1+atan(Z*(Q-2π/X))/1.5]/2

Measuring a standard material with known structure factors allows removal of the atomic form factor contribution.
Remaining intensity variation is due to instrument response for the sample holder being used.



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Application II: Processed materials – Normalizing Procedure 2: LP factor

From fundamental Kinematic diffraction theory, there are a number of absolute diffraction 'constants' that can be directly calculated for any material:

1.) Coherent Atomic Form Factor ~

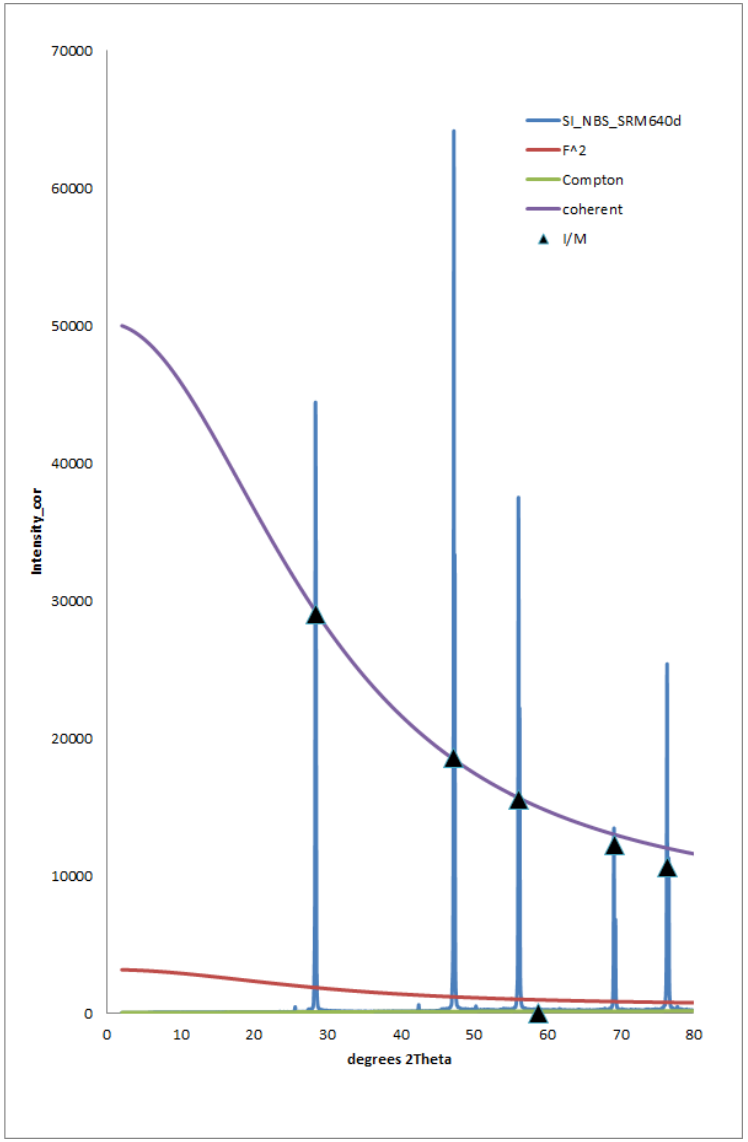
$$\sim \left| \sum_i f(Q)_i \right|^2$$

2.) Incoherent Atomic Form Factor ~

$$\sim \sum_i |f(Q)|_i^2$$

3.) Compton Scattering

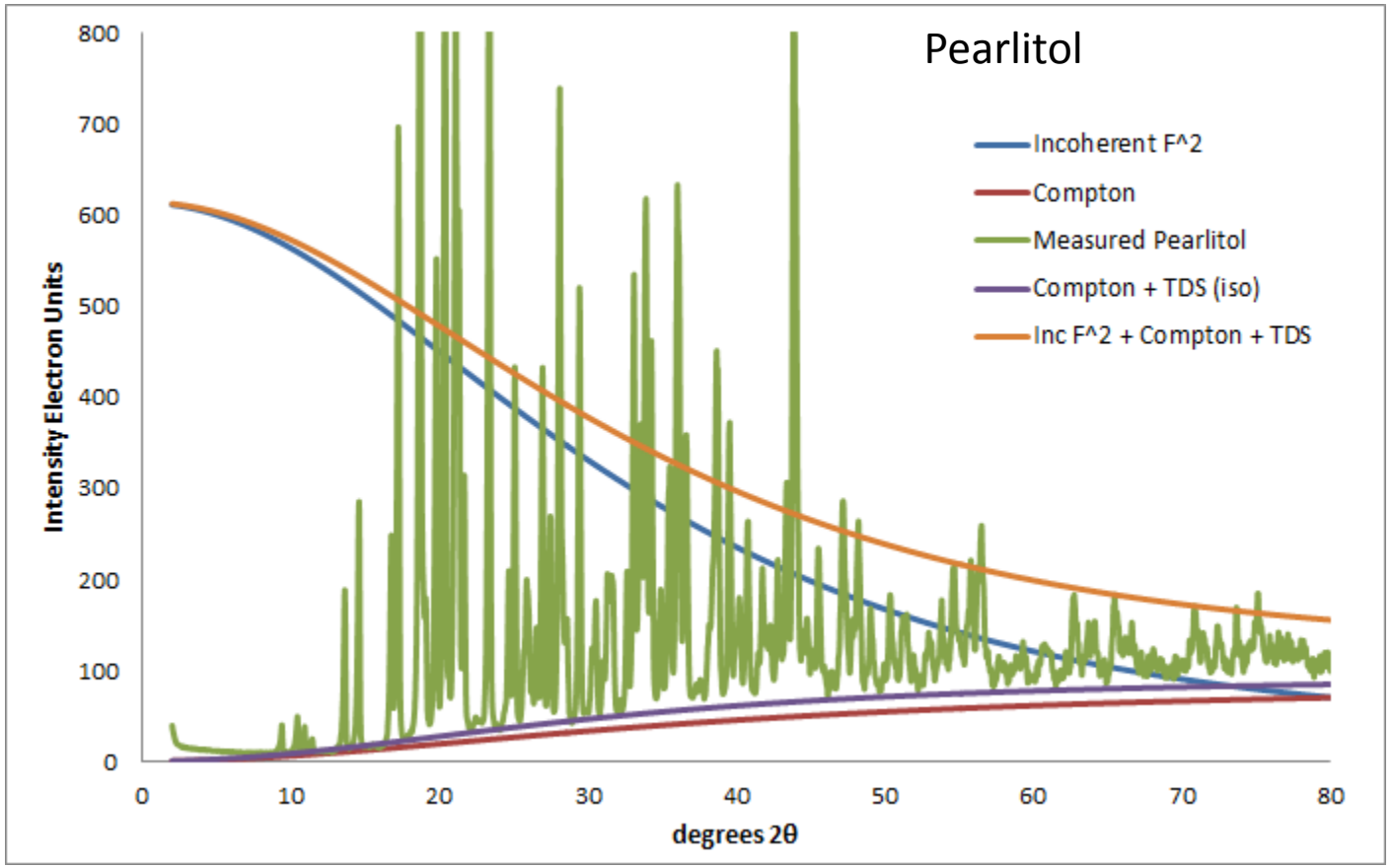
$$\sim\sim\sim \sum_i |f(0) - f(Q)|_i$$



Application II: Processed materials – Normalizing Procedure 2: Scale to EU

Data Scaled to give asymptotic convergence to calculated atomic scattering parameters at high Q (2Theta).

Forces data to an absolute Electron Units scale independent of instrument used or experimental technique



TDS derived from simple isotropic independent atom model. RMS deviation ~ 0.11Å

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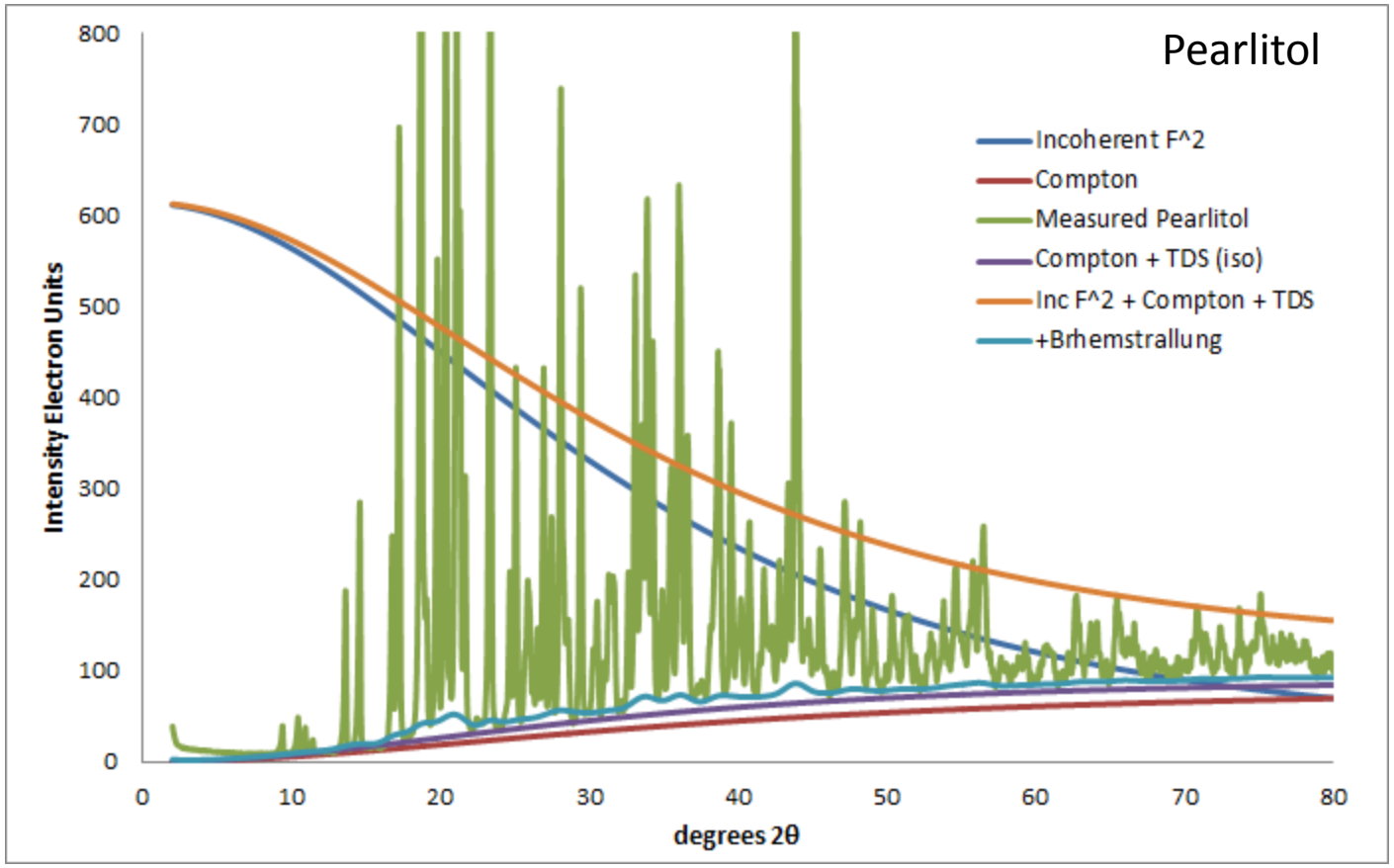
Application II: Processed materials – Diffuse Components: Brehmstrallung

Brehmstrallung radiation is a continuous source of X-ray's from the X-ray tube.

Will be modified by the choice of X-ray optics and detector.

Typically contributes about 7.5% of Crystalline Bragg intensity to measured data



Very little unexplained diffuse X-ray scattering:

→ Low defect concentration

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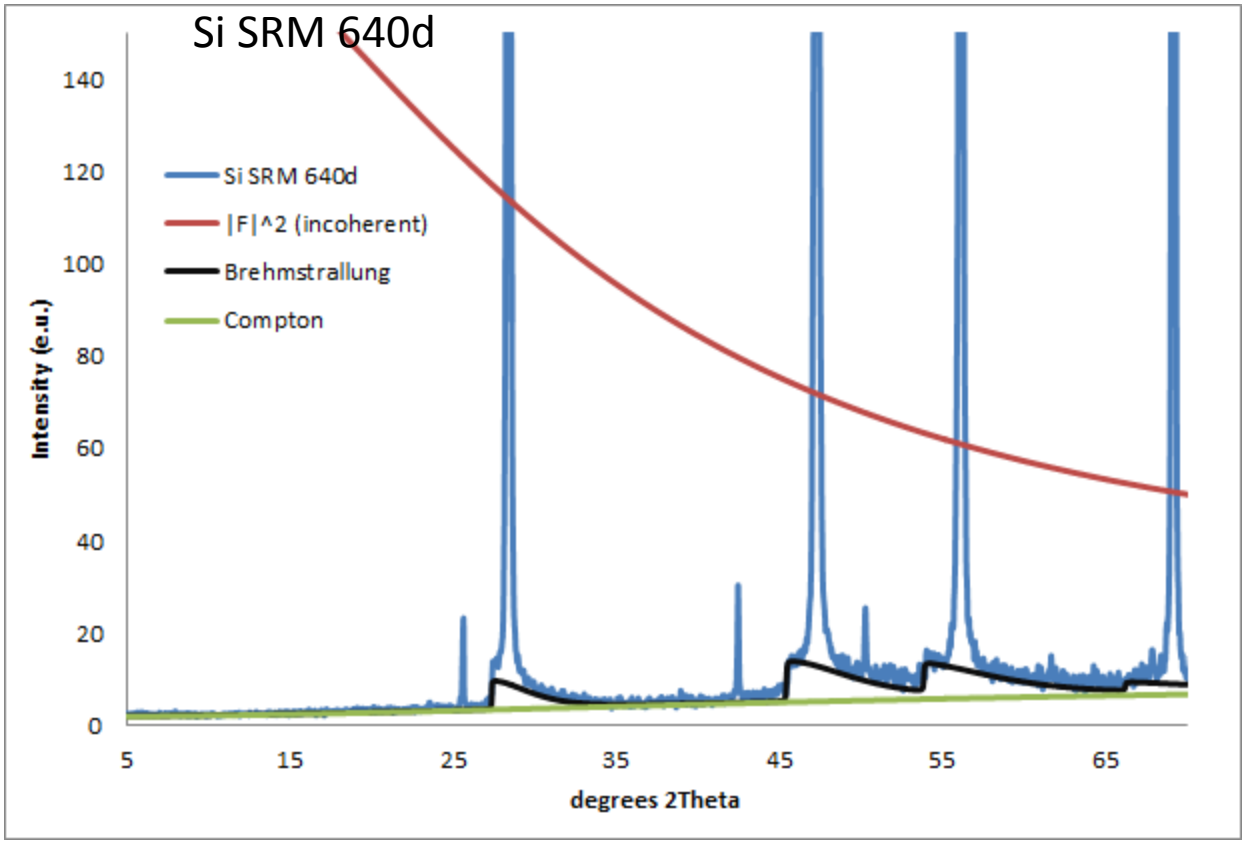
Application II: Processed materials – Diffuse Components: Brehmstrallung

Brehmstrallung calculation demonstrated for Si reference standard.

We use beta filter in the X-ray optics with no monochromator → step in diffuse profile that helps identify the Brehmstrallung



Very little unexplained diffuse X-ray scattering:
→ Low defect concentration

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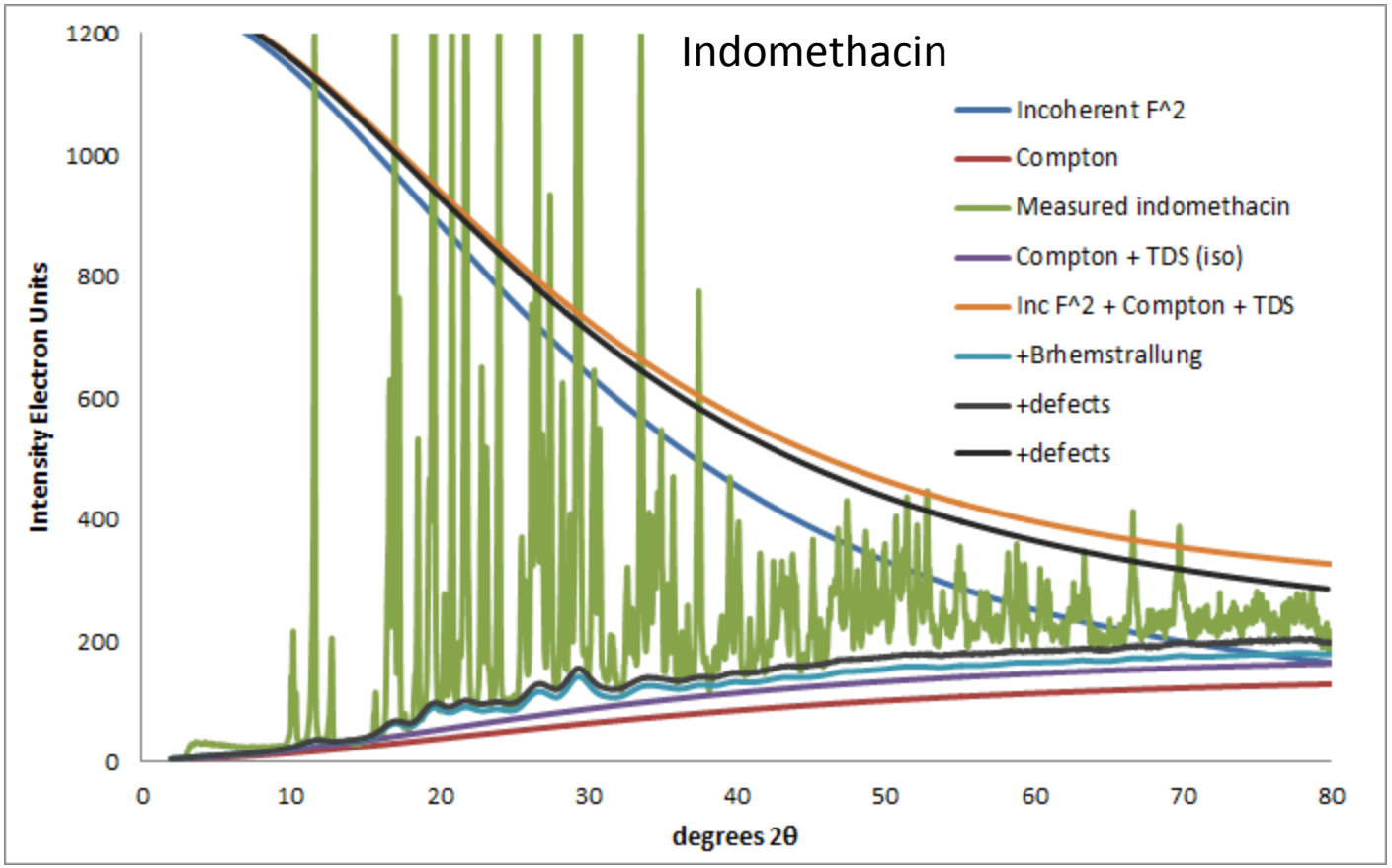
Application II: Processed materials – Defect Modeling

Diffuse defect profile can be calculated using Debye-Einstein theory (J.M. Cowley). Requires single crystal structure.
Can be estimated from measured data if no structure available.
PP minimization of all components gives defect contribution ~7%



Significant unexplained diffuse X-ray scattering:
→ can be modeled using point defect theory.

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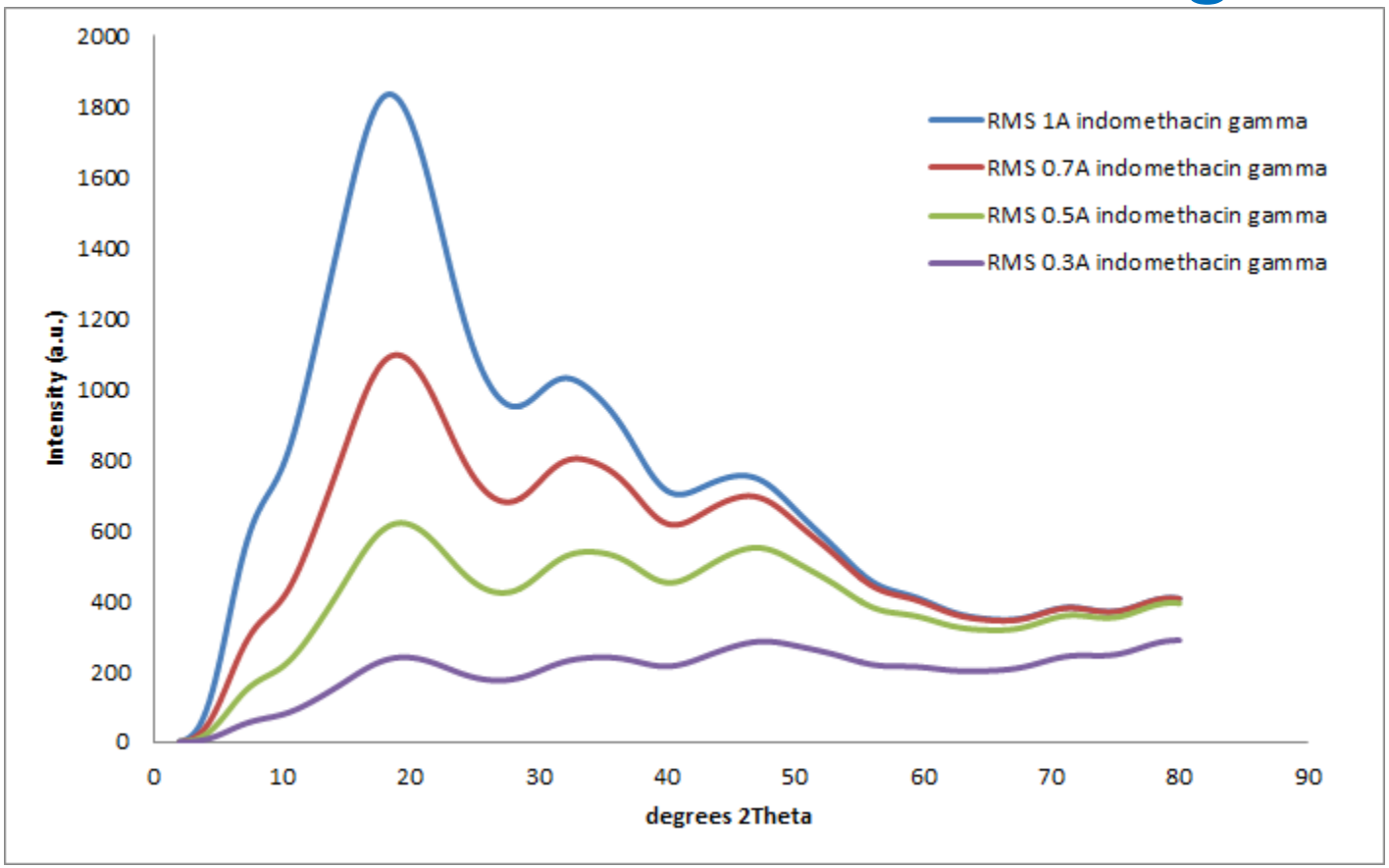
Application II: Processed materials – Defect Modeling



$$defect \sim SF * (1 - e^{-(Q\,\Delta)^2/2})\,|F(Q)|^2$$

$$\Delta = RMS\ strain\ field\ (\dot{A})$$

The defect scattering contribution from the Debye Einstein theory has 2 variables:
1.) % defects
2.) RMS strain field

Modeling of crystalline indomethacin gives an estimated strain field of about 0.11A. Similar to TDS RMS value for thermal vibration.

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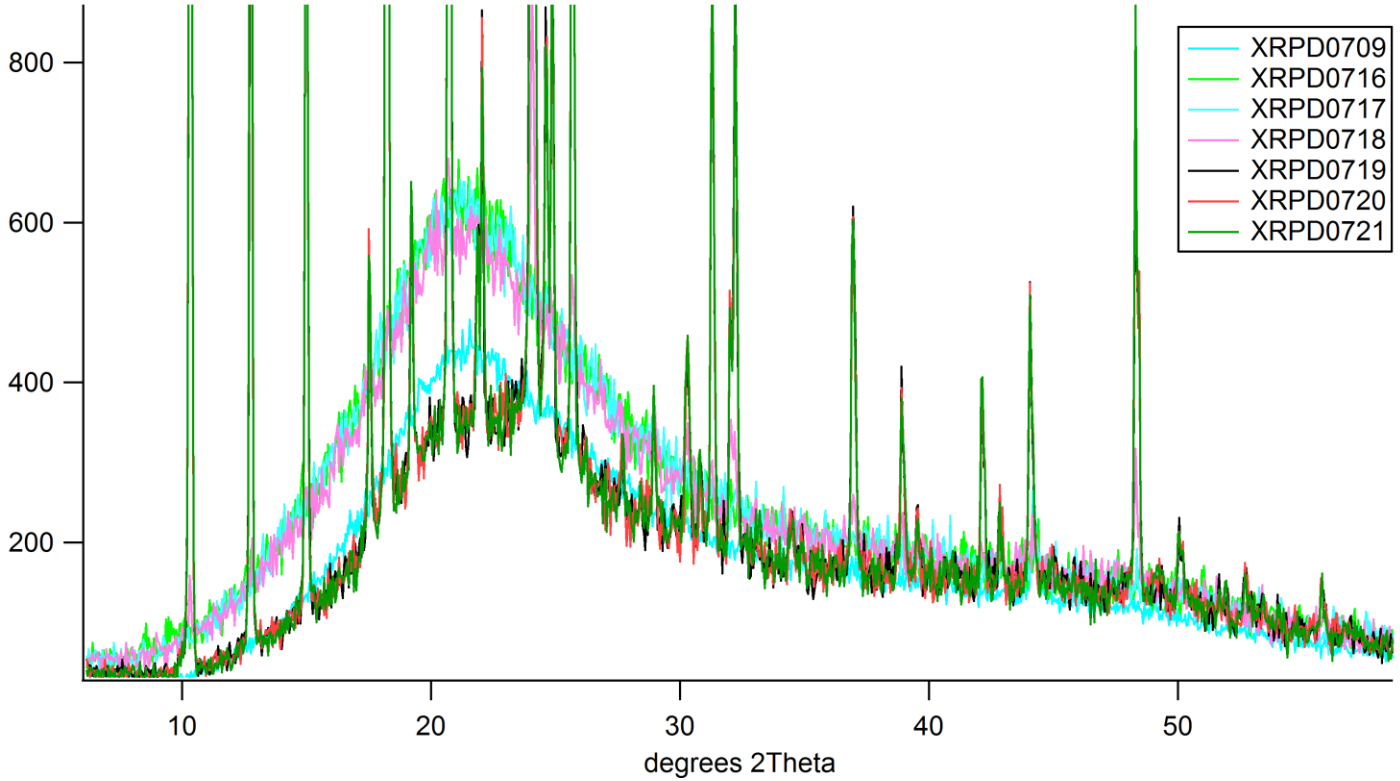
Application II: Processed materials – Cluster Analysis and Chemometrics



Dynamic powder patterns showing recrystallization of acetaminophen glass

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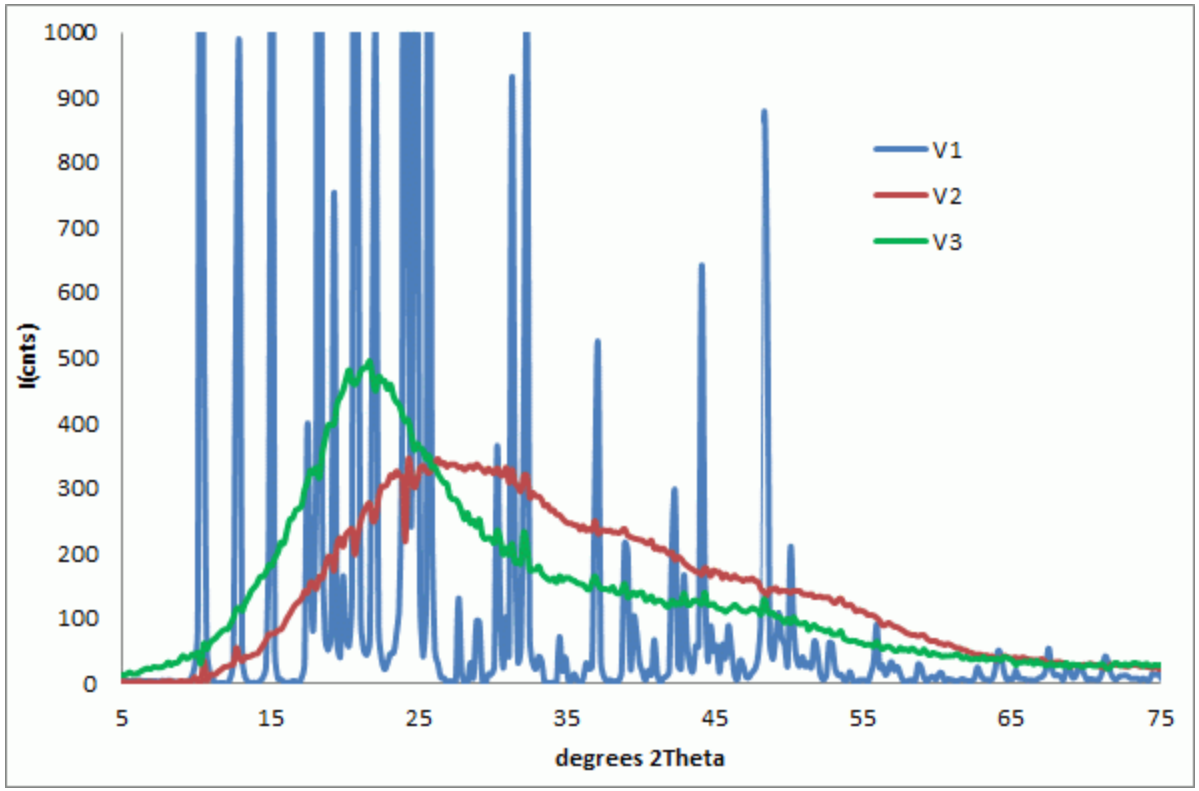
Application II: Processed materials – Cluster Analysis and Chemometrics



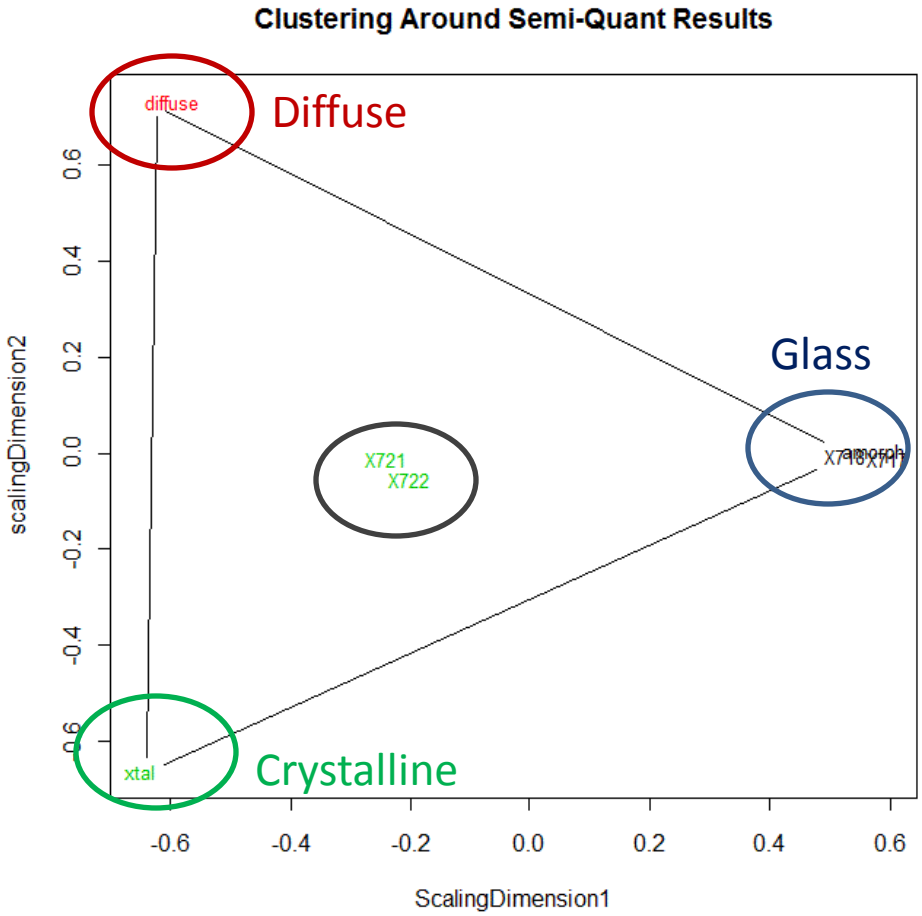
Principal Component Analysis identifies 3 distinct components associated with acetaminophen re-crystallization.

1.) V1 = Crystalline

2.) V3 = Glass

3.) V2 = Diffuse?

Application II: Processed materials – Cluster Analysis and Chemometrics



Cluster analysis based upon principal components can be used to visually represented the stability and recrystallization process for non-crystalline systems