Synchrotron-Based Formulation Development

Wednesday, October 28, 2020

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Session Description and Objectives

- Synchrotron X-ray Pair Distribution Function (SXPDF) techniques provide information on the atom-atom distances in amorphous materials and dispersions. Not all amorphous materials are equivalent, and the PDF patterns can be used to compare the sameness of materials prepared in different ways (e.g. spray drying and melt extrusion). SXPDF can also detect neighboring drug molecules in a drug-polymer dispersion. If present, the dispersion is more likely to crystallize as compared to dispersions where no drug domains are detected.

- This presentation will introduce the viewer to the concept of SXPDF and present the latest advancements. Upon completion, the participant will be able to…
  - …understand the power of synchrotron methods and how to access this technology
  - …differentiate between intermolecular and intramolecular atom-atom interactions in a dispersion, and apply this knowledge to predicting the stability of a dispersion
  - …bridge a gap in the current drug development process by understanding how better to control the solid form in a solution

Biography and Contact Information

- Pamela A. Smith is the COO of Improved Pharma, a research and information company dedicated to improving pharmaceutical methods, formulations, and processes

- Previously at SSCI (19 years)

- Registered user of Argonne National Laboratory

- Contact information:
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XRD vs. PDF ... global vs. local view

XRD (Bragg diffraction)

- Global view of the structure

- Total x-ray structure factor, S(Q)

- No crystalline peaks, but there is also information between and underneath the Bragg peaks

- Extract this information by mathematical methods

PDF (atomic pair distribution function)

- Yields local structure, environment of the atom

- How many neighbors are there and how far away are they?

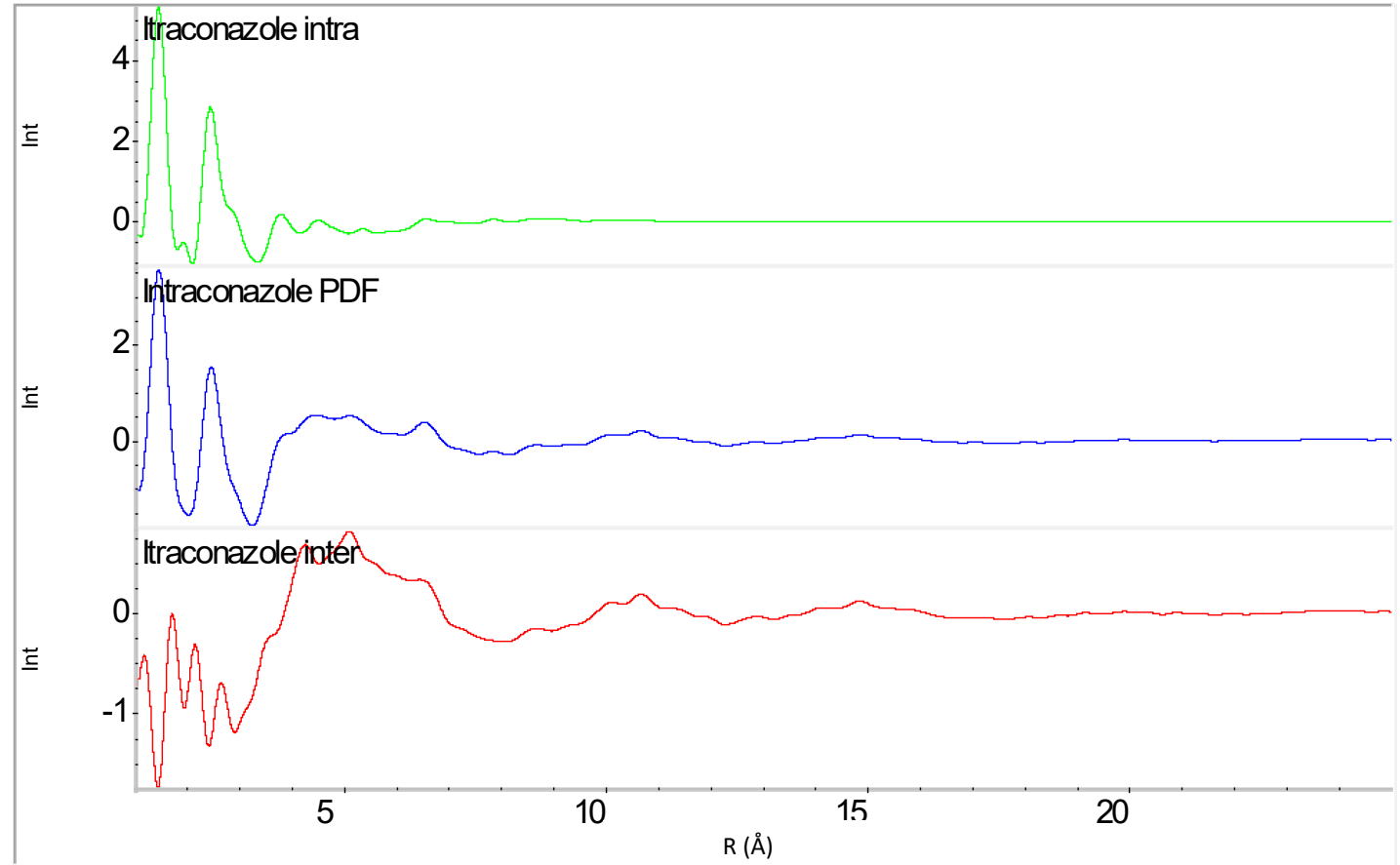- Determines the distribution of distances between pairs of atoms
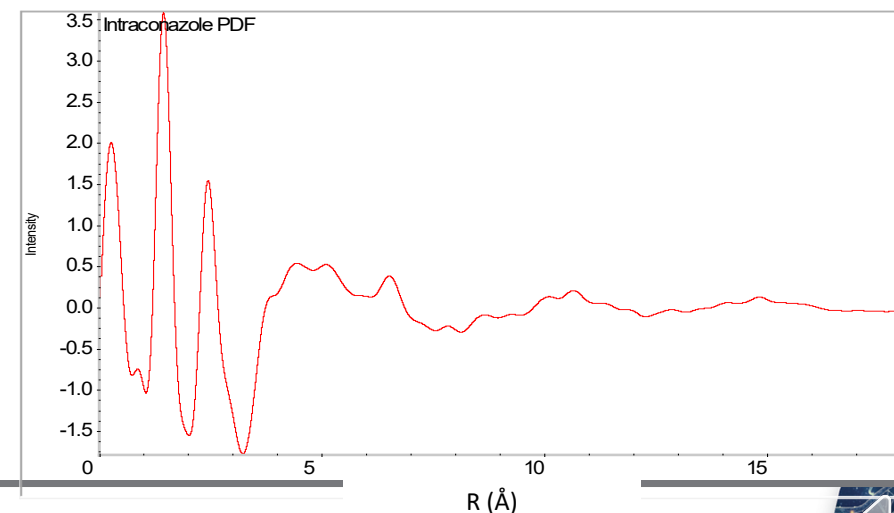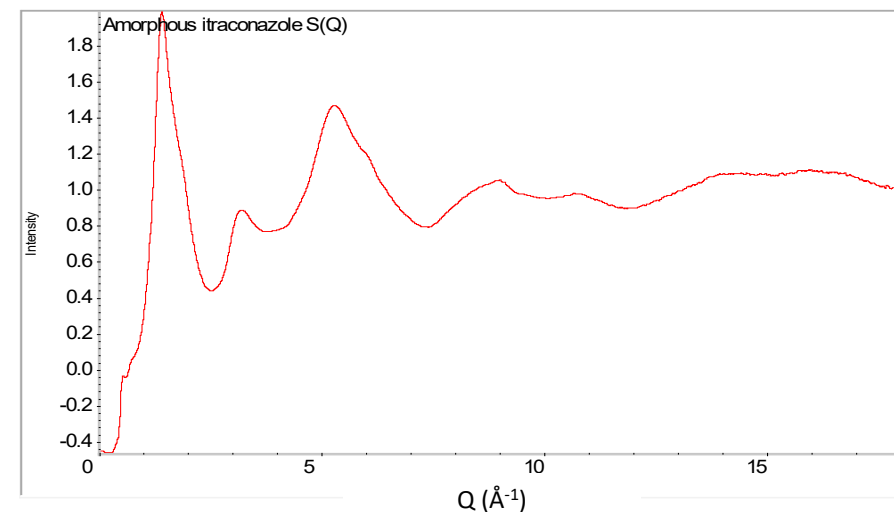
Total PDF = Intramolecular + Intermolecular

Intramolecular PDF:
Distances between
atoms within a molecule

Total PDF:
Distances between all
atoms in the sample

Intermolecular PDF:
Distances between
atoms of neighboring
molecules

Applications

- Detection of domains of API molecules
- Prediction of relative stability of different formulations
- Detection of low amounts of crystalline material
- Detection of hydration of amorphous forms prior to crystallization
- Sameness determination of different amorphous preparations (shown previously, AAPS 2015)
- Lab model for spray drying via acoustic levitation (shown previously, AAPS 2019)

Ex 1: Predicting stability of dispersions
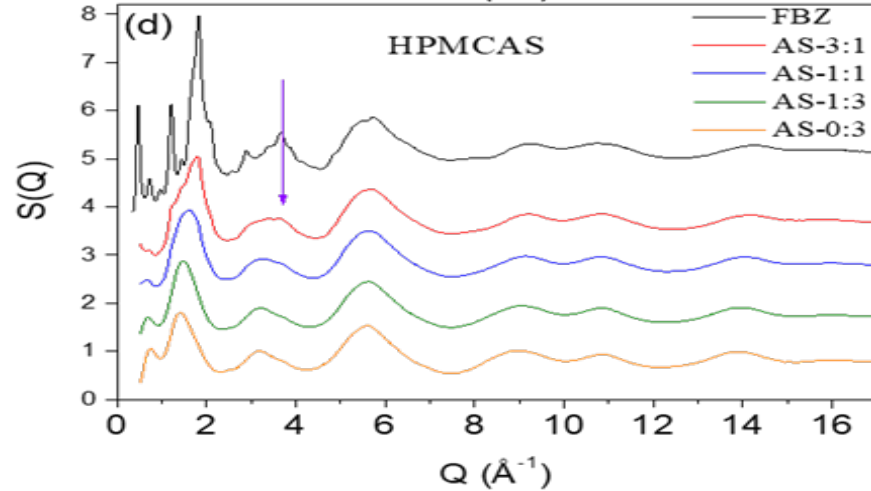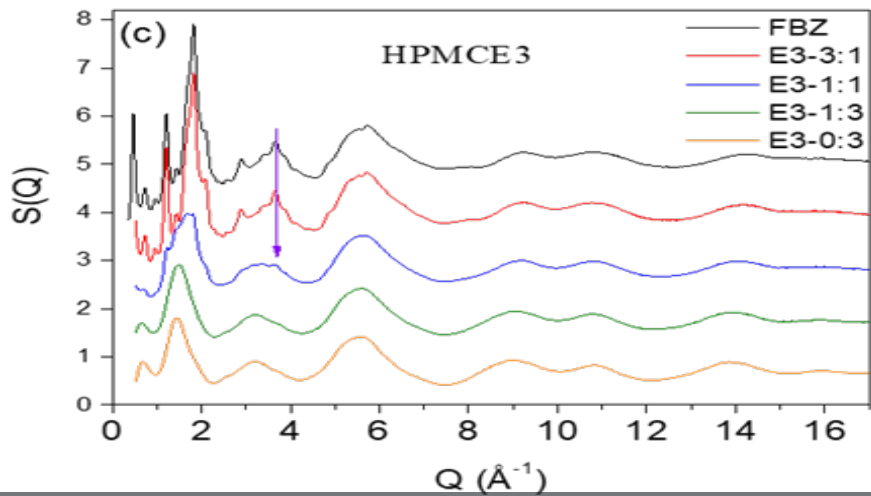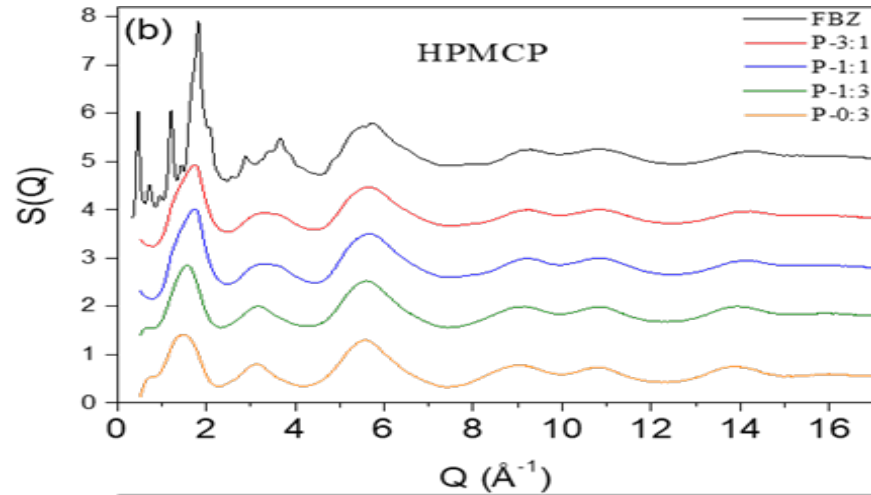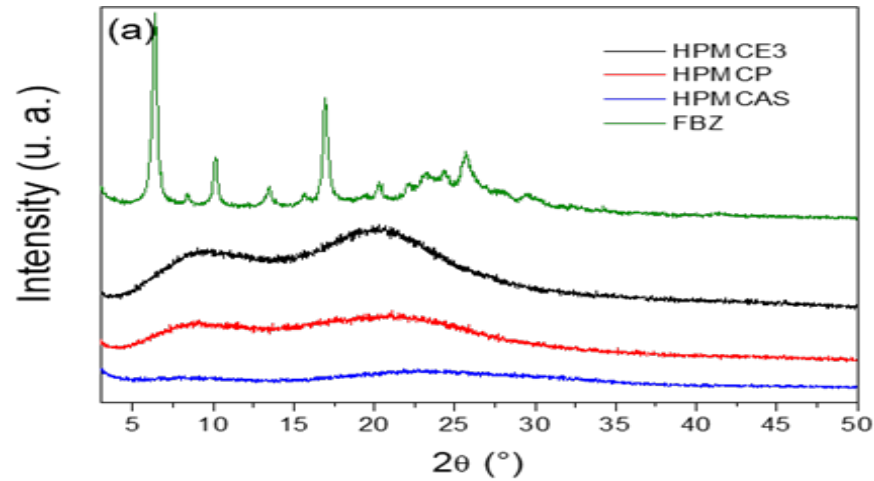
Amorphous dispersions of flubendazole in hydroxypropyl methyl cellulose: formulation stability assisted through pair distribution function analysis, VDN Bezzon, FF Ferreira, PA Smith, CJ Benmore, SR Byrn, GLB de Araujo, in press (2020)
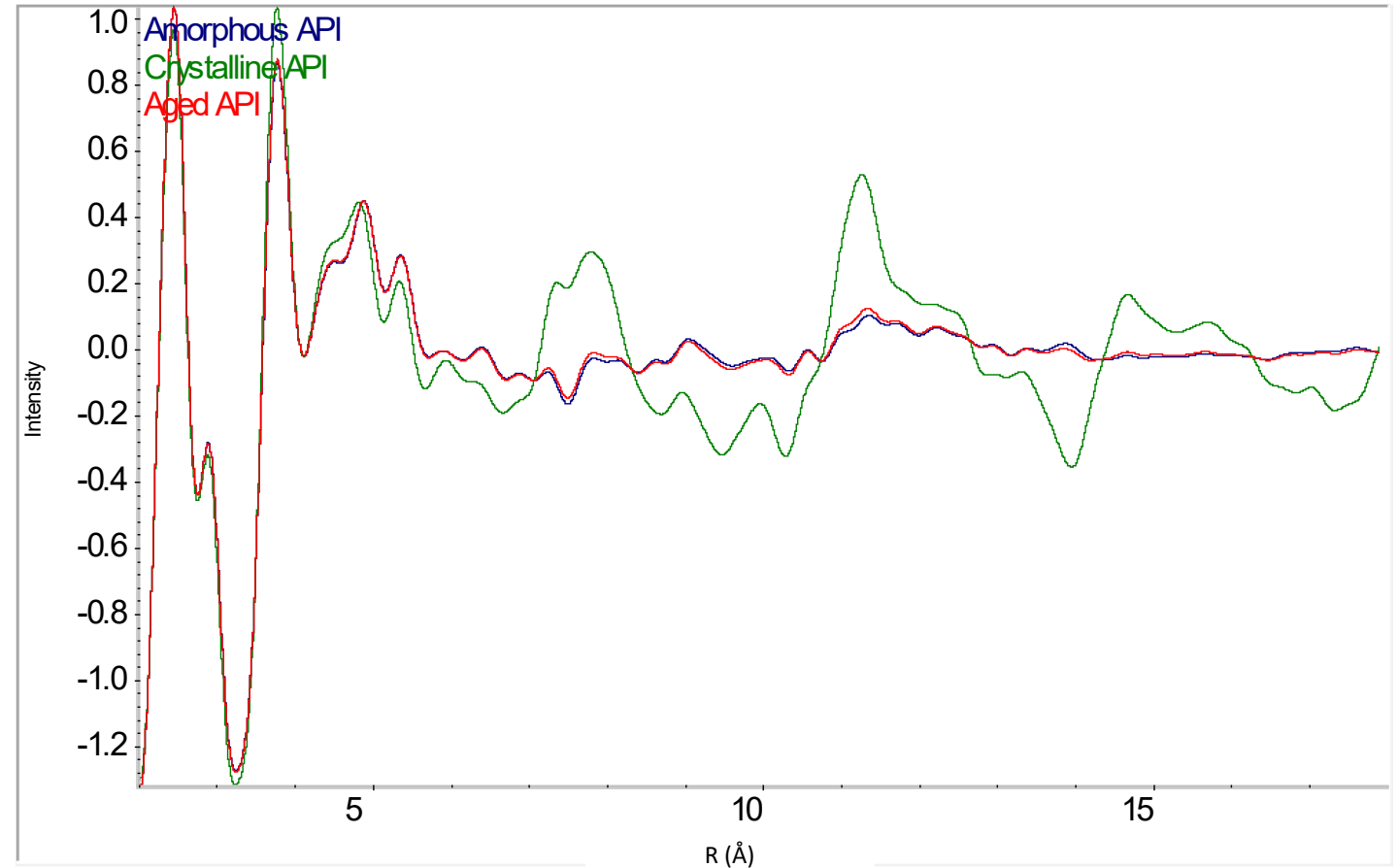
Ex 1: Predicting stability of dispersions

- The 3:1 flubendazole:HPMC-E3 shows domains (ordered three-dimensional intermolecular arrangements) and eventually crystallized
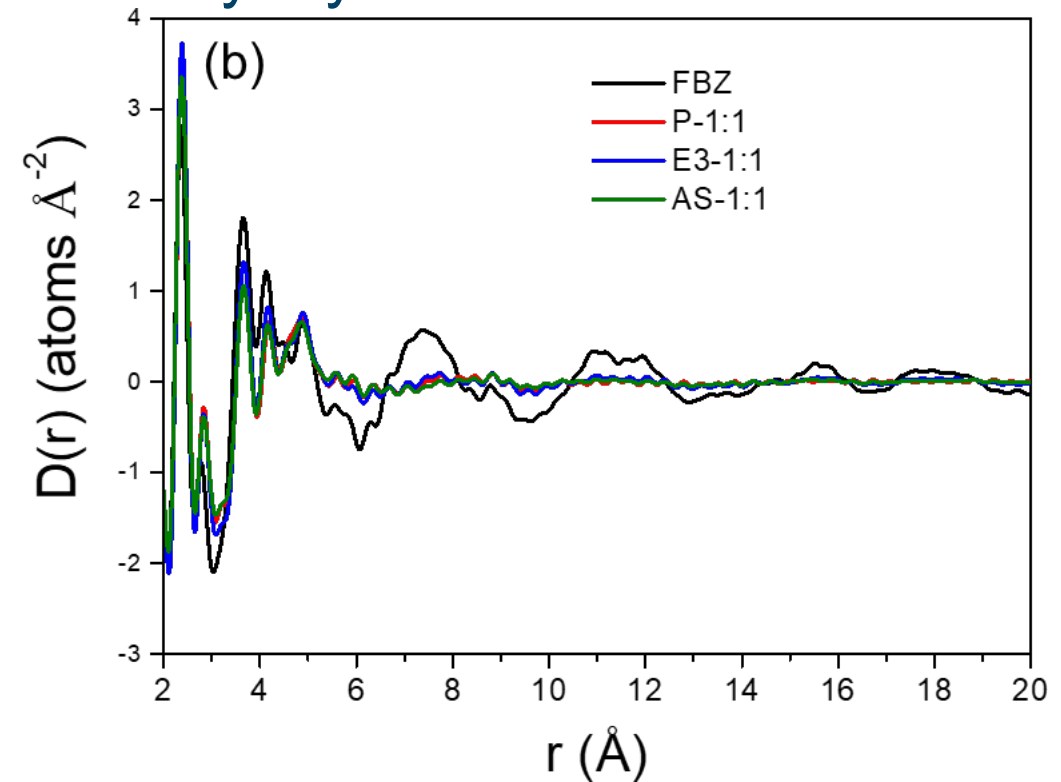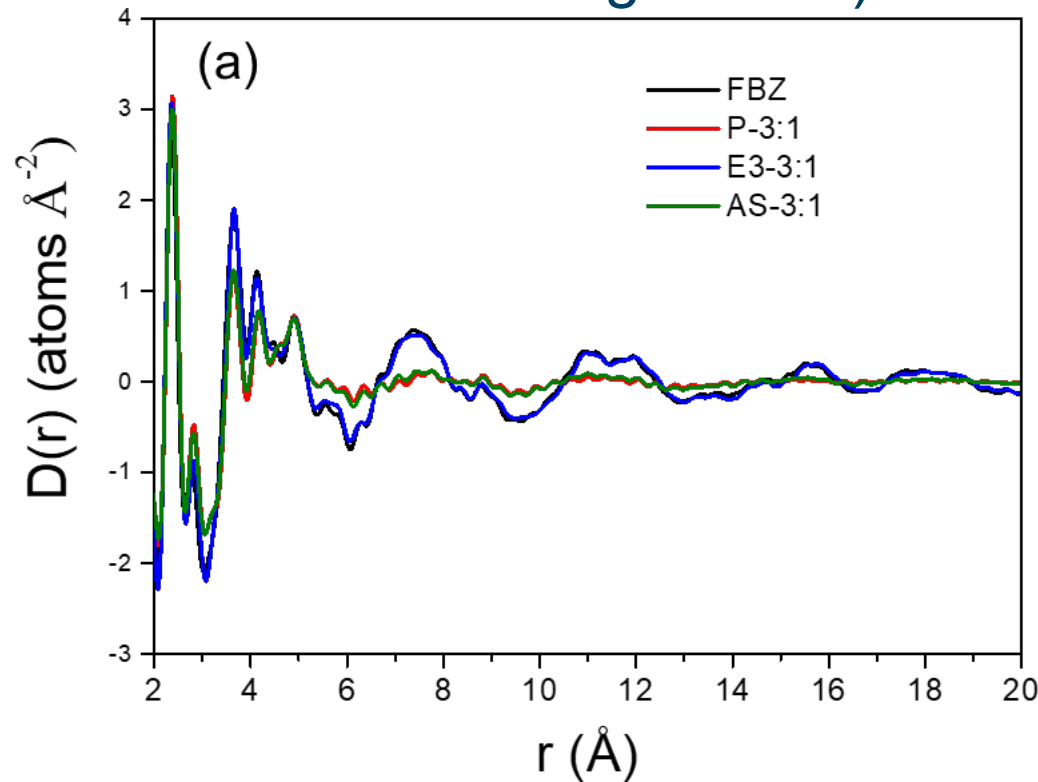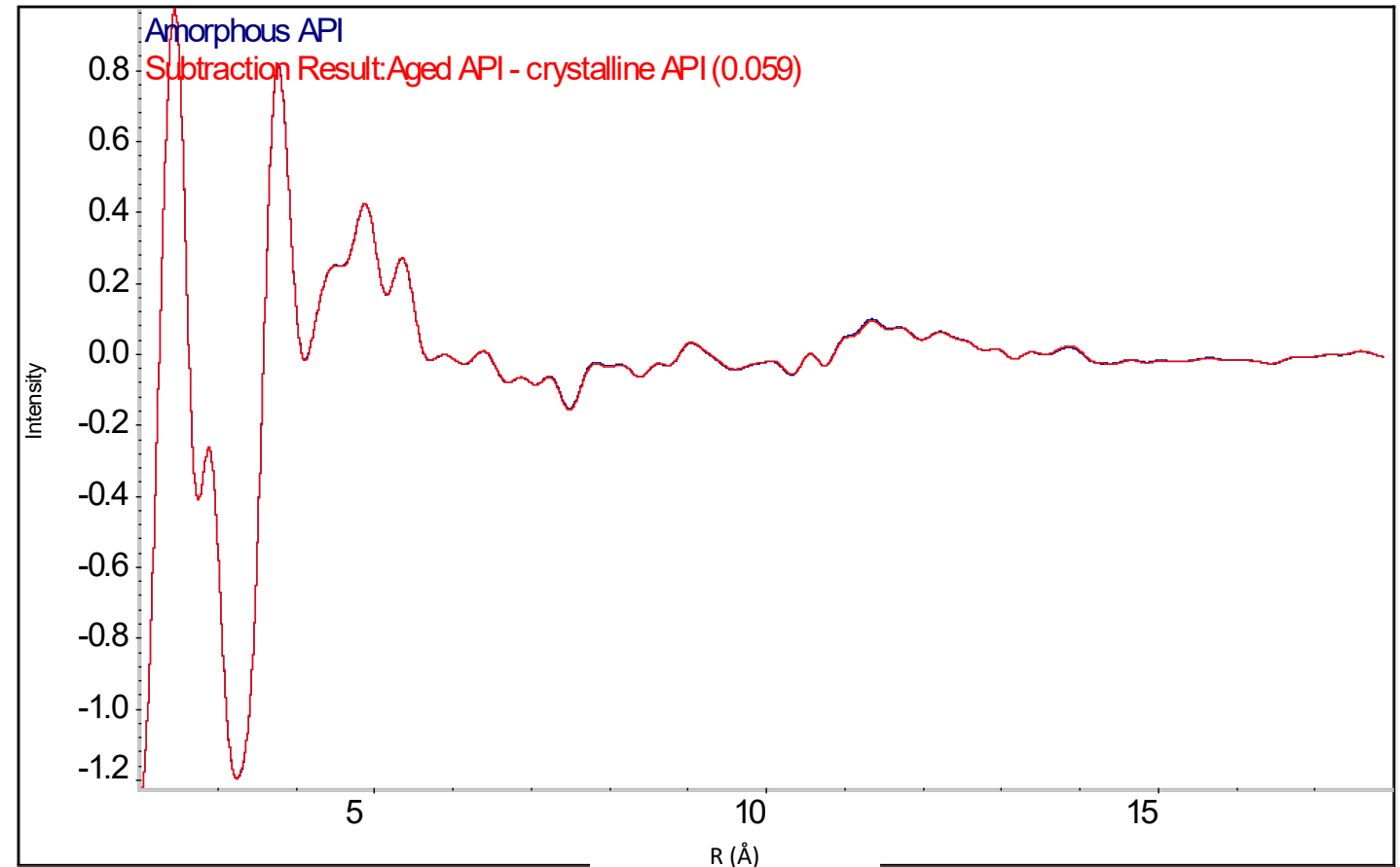
Ex 2: Quantifying amount of crystalline API

- Good specificity between amorphous and crystalline PDF curves

- Is the aged API different from the amorphous API?

Ex 2: Quantifying amount of crystalline API

- The crystalline PDF was subtracted from the aged PDF until it matched the amorphous PDF

- Subtraction factor = 0.059, therefore the aged sample contains 5.9% crystalline API

Ex 2: Quantifying amount of crystalline API

- Double-checking the results
- If there is 5.9% crystalline in the aged sample, then the remainder (94.1%) must be amorphous
- The amorphous PDF was subtracted from the aged PDF (subtraction factor = 0.941)
- Excellent correlation with crystalline PDF
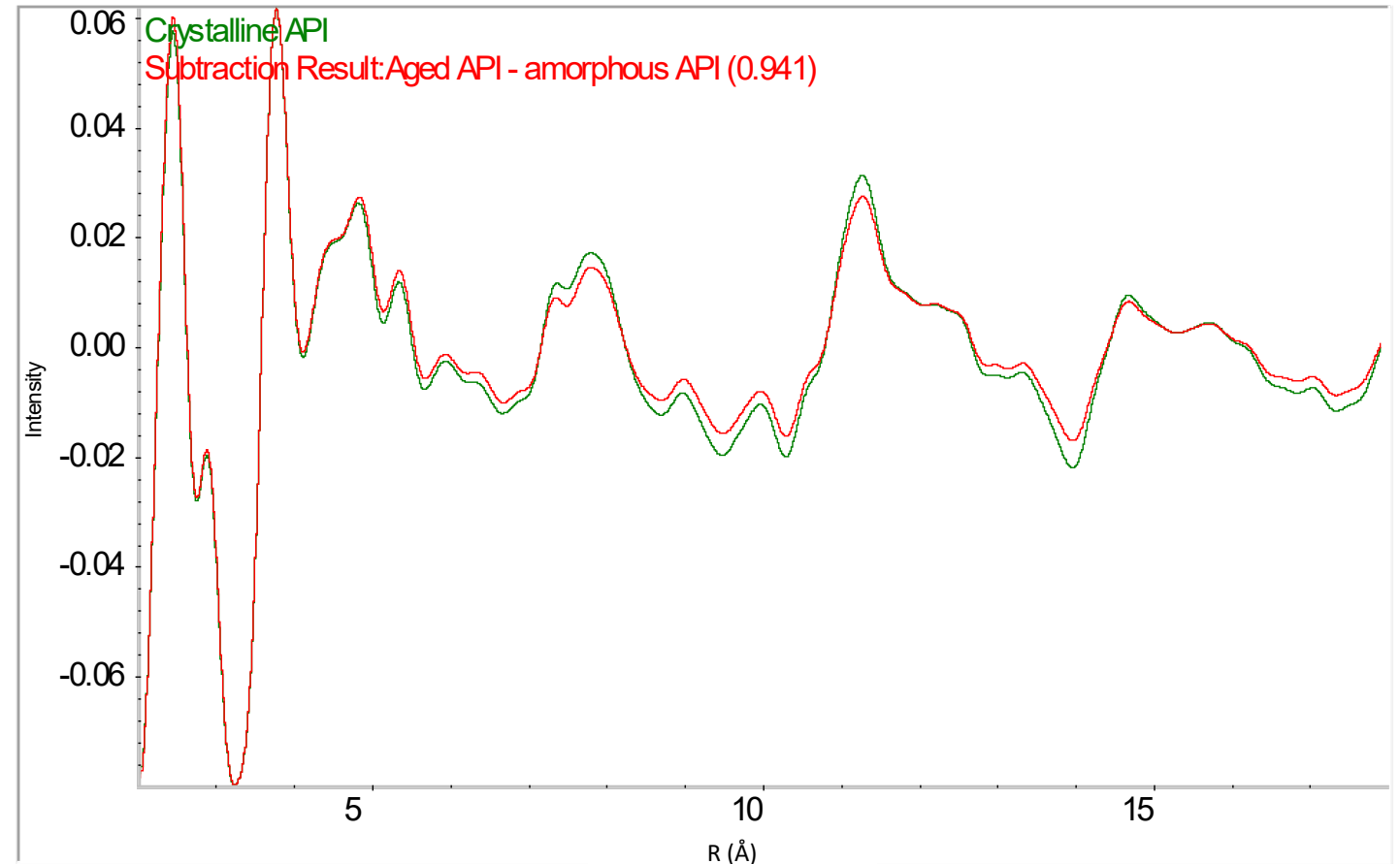
Ex 3: Detecting hydration of amorphous API

- Dry amorphous indomethacin exposed to 80% RH at room temp

- Growth of a peak at 4.4Å describes the formation of the metastable partially hydrated amorphous form prior to crystallization (plateaus at ~10 hours)
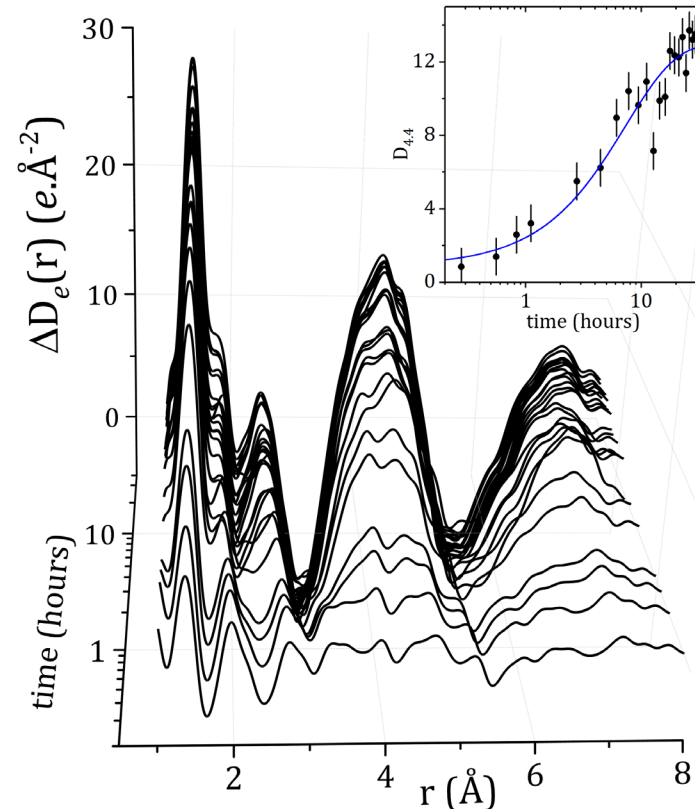
The insert shows the changes in height of the peak at r=4.4Å as a function of time with the uptake of water.

A high energy x-ray diffraction study of the hydration of amorphous Indomethacin, CJ Benmore, SR Byrn, PA Smith, F Gozzo, C Shi, D Smith, SR Byrn, JKR Weber, in press (2020)

Process

- Collect data at a synchrotron using an area detector (.tif files)

- Use Fit2D to convert .tif image files to .chi files

- Use PDFgetX2 to convert .chi files to S(Q) and G(r) files

- Use xINTERPDF to extract intramolecular and intermolecular PDF curves from an amorphous reference API curve

- Use Excel or Omnic to compare data files

- Use Omnic for subtractions
  - Dispersions
  - Polymers
  - Crystalline API
  - Amorphous API
    - Intramolecular API
    - Intermolecular API

References

- A P Hammersley, *ESRF Internal Report*, **ESRF97HA02T**, "FIT2D: An Introduction and Overview", (1997).

- *PDFgetX2: a GUI driven program to obtain the pair distribution function from X-ray powder diffraction data.* X. Qiu, J.W. Thompson, S.J.L. Billinge. J. Appl. Cryst. **37**, 678-678 (2004).

- *xINTERPDF: a graphical user interface for analyzing intermolecular pair distribution functions of organic compounds from X-ray total scattering data.* C. Shi. J. Appl. Cryst. **51(Pt 5)**, 1498-1499 (2018).

- *Local Structure of Drug Interactions in Amorphous Solid Dispersions characterized by Synchrotron X-Ray diffraction and Pair Distribution Function Analysis.* G. Lima Barros de Araujo, C.J. Benmore and S.R. Byrn, Scientific Reports 7 (2017) 46367.

Acknowledgments

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Questions

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