Use of Atomic Pair Distribution Function (PDF) And X-Ray Scattering Methods To Assess The Stability Of Amorphous Organic Compounds

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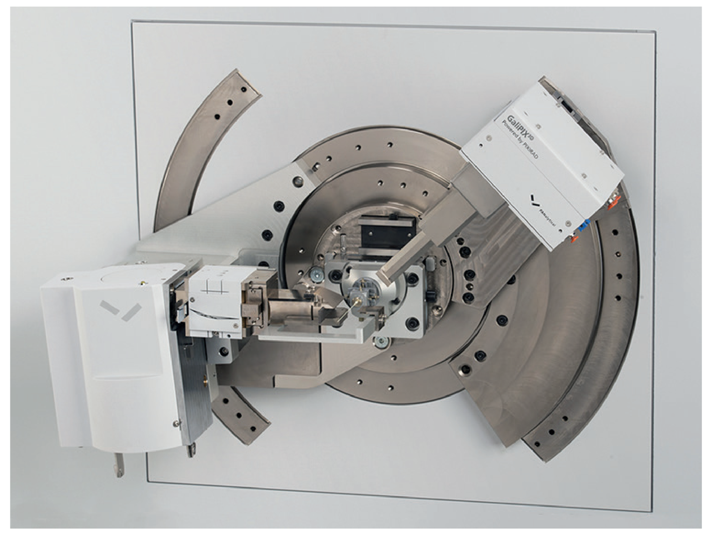
Purpose

The amorphous state is of significant interest as a possible means to enhance aqueous solubility of APIs. An important practical barrier to the development of amorphous APIs for drug products is the lack of reliable methods for structural characterization and fingerprinting. The Atomic Pair distribution function (PDF) have been suggested as an alternative approach for fingerprinting of amorphous materials and to study the short range order (i.e. inter-atomic distances) of the material. This study investigates the relative merits of an atomic Pair-wise Distribution Function (PDF) generated using conventional X-ray instrumentation and synchrotron radiation in assessing process variations in amorphous drug preparation.

Methods

PDF analyses were conducted using conventional laboratory X-ray powder diffraction (XRPD) instrumentation and compared to those obtained using high energy X-ray synchrotron data. The synchrotron data was collected to high scattering vector Q (Q > 20Å^{-1}) at Argonne National Laboratory 11-ID-B, while the conventional XRPD data was generated using a PANalytical Empyrean diffractometer with Mo or Ag source and GaliPIX^{3D} detector.



Samples

Sample set 1:
Spray dried powders (SDPs) of an amorphous API prepared with different solvent composition and process parameters (samples A-D). PDF analyses were conducted using synchrotron radiation and laboratory XRPD instrumentation.
Sample set 2:
Amorphous solid dispersions (ASDs) of Ketoconazole (KTZ) (90%) with different polymers (10%):
PAA, PHEMA, PVP
Data was collected on a PANalytical Empyrean diffractometer.

Results Spray Dried API

Synchrotron data

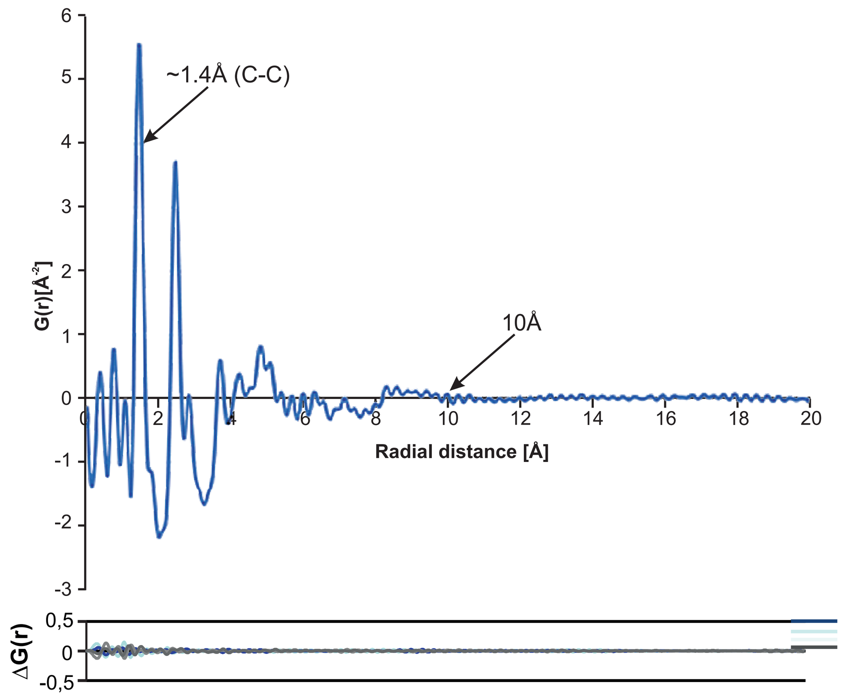


Figure 1: PDF patterns from synchrotron data

Synchrotron: The largest average deviation ΔG(r) is 0.15, and since the G(r) magnitude is around 5, the ΔG(r) is less than 3%, demonstrating analysis reproducibility.
Laboratory: The PDF plots show a highest amplitude of 5 with a maximum deviation ΔG(r) of 0.2 meaning also on this data the ΔG(r) is less than 5%.
The PDF's demonstrate that the spray dried drugs are truly amorphous (absence of nano crystalline domains) and don't possess pronounced ordering beyond ~10Å.

Laboratory data

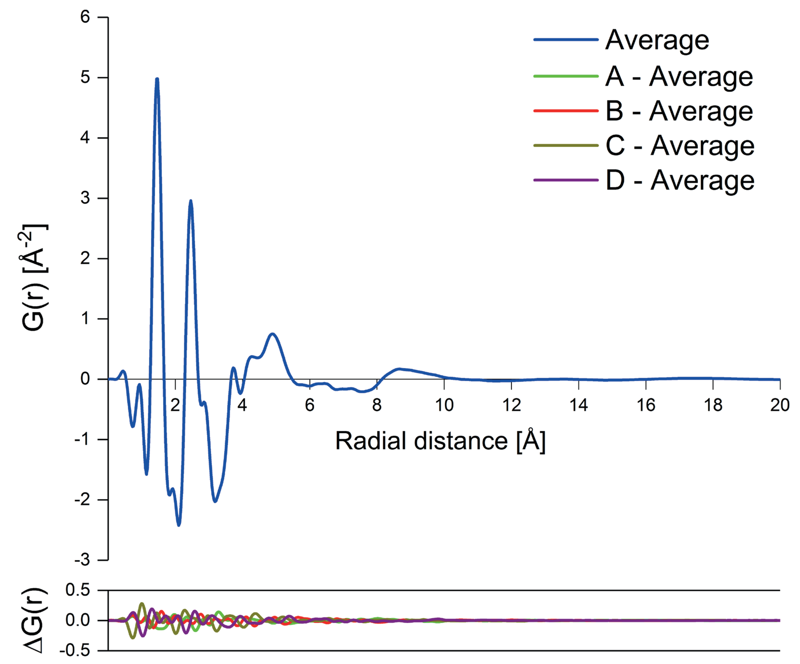


Figure 2: PDF patterns from laboratory data measured up to Q = 17 Å^{-1}

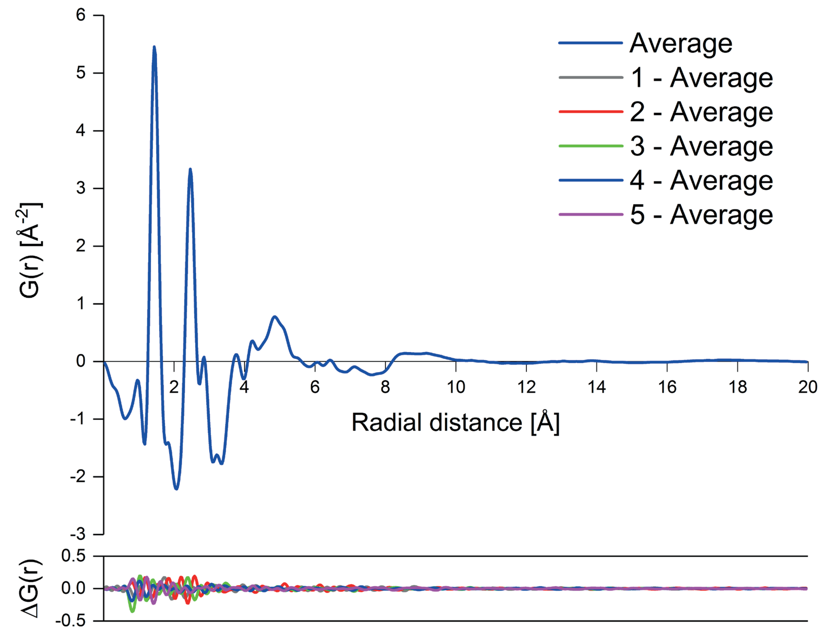


Figure 3: Reproducibility tests (5 sample preparations): PDF patterns from laboratory data measured up to Q = 19.4 Å^{-1}

Results Solid Dispersions

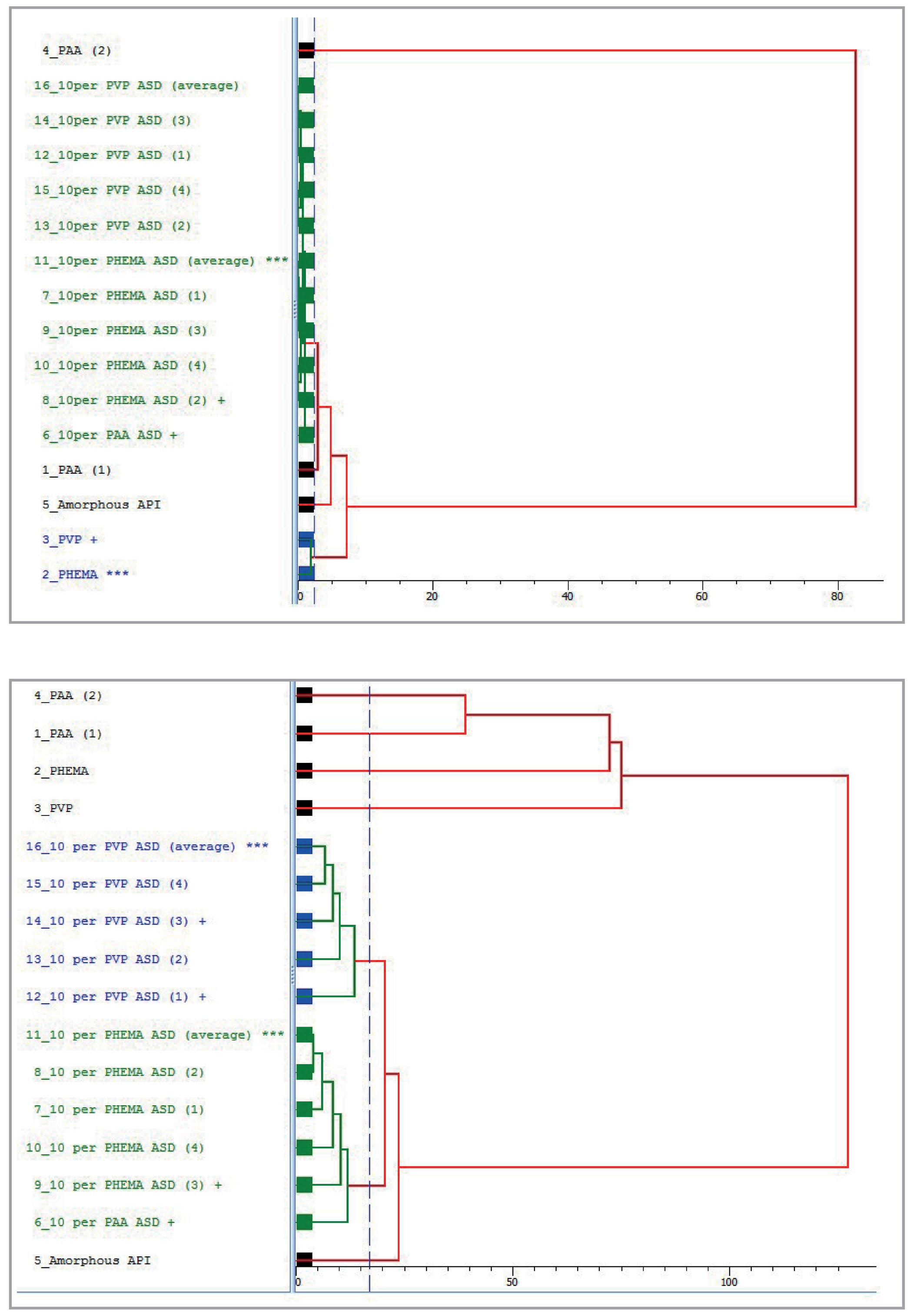


Figure 4: Comparison of cluster analysis Dendograms of XRD patterns vs. PDF patterns from the ASDs, the amorphous API and the polymers in sample set 2: Differences (dissimilarities) of the PDF patterns are larger than the differences of the raw data (polymers, ASDs, API). PDF patterns also show a clear clustering of the repeated measurements. This demonstrates that the PDFs of amorphous compounds are more suited for finger printing than the raw XRD data patterns.

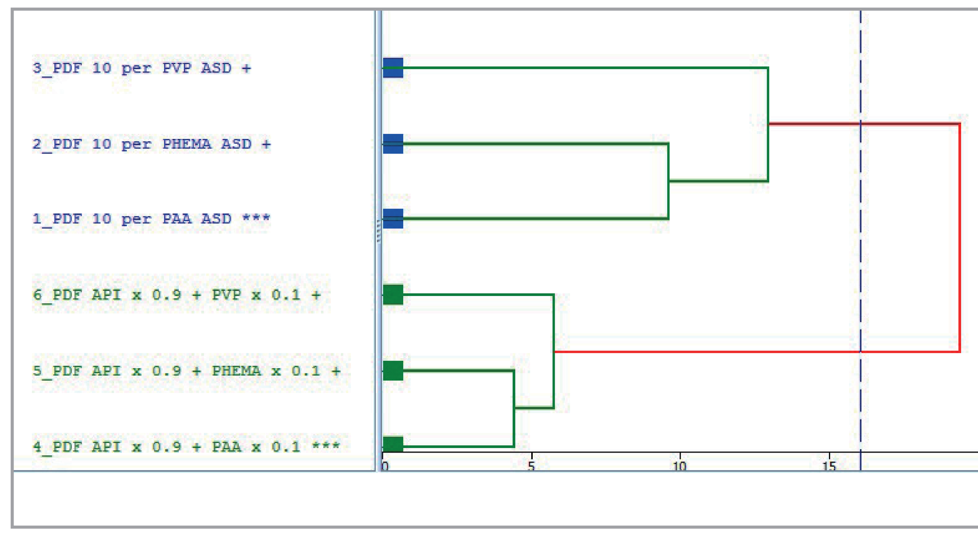


Figure 5: Comparison of the PDF patterns of the ASDs with the PDF patterns of the calculated compound mixtures (API + polymer). The clustering indicates structural changes of the ASDs which may be related to the observed higher stability against re-crystallization

Conclusion

PDF analysis was used to confirm the comparability of the amorphous drug prepared by different spray drying processes and gave insight to their degree of molecular order which can be impactful to their physical stability. The cluster analysis of PDF patterns in addition shows that PDF patterns can reliably be used for fingerprinting of amorphous drugs and drug compounds.

Compared to previous studies, the use of recently developed detector technology optimized for hard radiation on laboratory X-ray diffractometers and improved software algorithms allowed to minimize artifacts or fluctuations in the PDF arising from statistical noise, resulting in more reliable data. This development enables us to study amorphous and nanocrystalline drug materials reliably in the laboratory.

Acknowledgement: Sample set 2 courtesy of Raj Suryanarayanan, Pinal Mistry, University of Minnesota, Minneapolis