Structure and transformations in amorphous paracetamol

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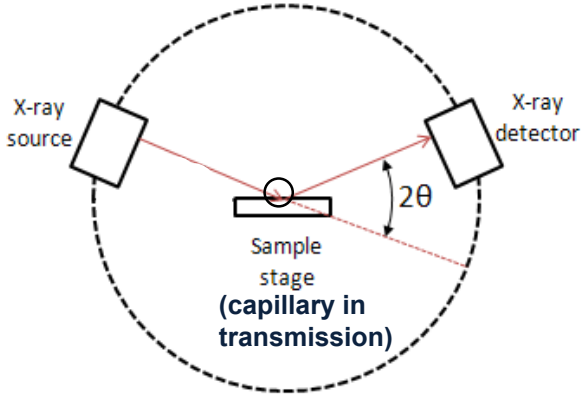
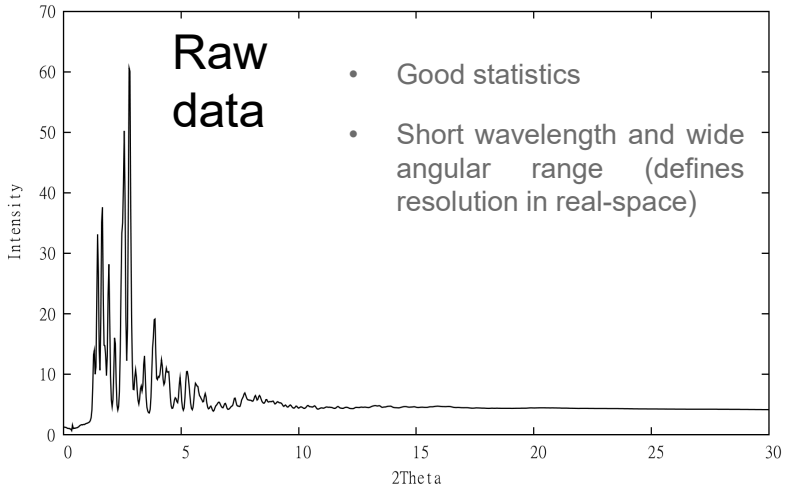
Introduction

- What structural information can be obtained from the amorphous phase using pair distribution function (PDF) analysis?
- Increasing interest in amorphous pharmaceuticals due to solubility/bioavailability advantages
- Stability/structural characterisation an issue
- Application of PDF to single component model system (paracetamol, PCM) before progression to complex formulated materials

What is the PDF?

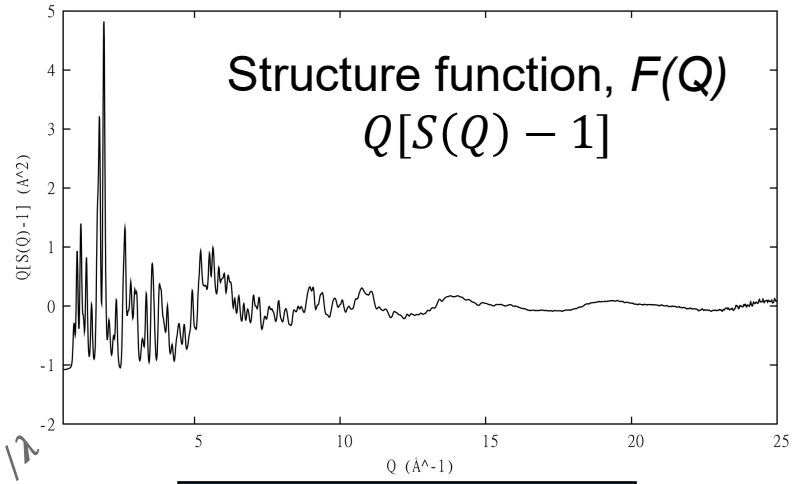




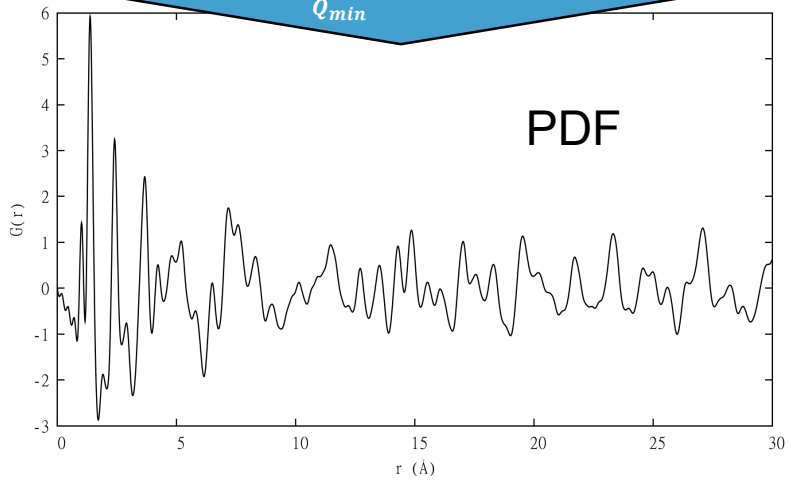
- Good statistics
- Short wavelength and wide angular range (defines resolution in real-space)

Corrections/ normalisation

$Q = 4\pi \sin\theta / \lambda$



$$G(r) = \frac{2}{\pi} \int_{Q_{min}}^{Q_{max}} F(Q)\, sin(Qr)\, dQ$$



- Essentially a histogram of interatomic distances
- Produced by Sine Fourier transform of normalised and corrected X-Ray total scattering data [1]
- Can be applied regardless of physical state
- Able to compare local packing in amorphous to known crystalline forms

[1] E. Takeshi and S. J. L. Billinge, *Underneath the Bragg Peaks - Structural Analysis of Complex Materials*, vol. 16. 2012.

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Challenges in applying PDF analysis to amorphous pharmaceuticals

- Typically poorly scattering materials
- More conformational flexibility than materials typically studied using PDF
- Data interpretation an issue
  - Local structure not as clearly defined as nicely coordinated inorganic system
- Need to begin with “model” pharmaceutical system
  - Paracetamol – minimal conformational flexibility, (until recently[2]) well-understood/characterised solid state
  - Research question: Does structure in amorphous PCM act as a template for crystallisation of Form II from the melt (at RT)?

[2] A. G. Shtukenberg *et al.*, “Melt Crystallization for Paracetamol Polymorphism,” *Cryst. Growth Des.*, vol. 19, no. 7, pp. 4070–4080, Jul. 2019.

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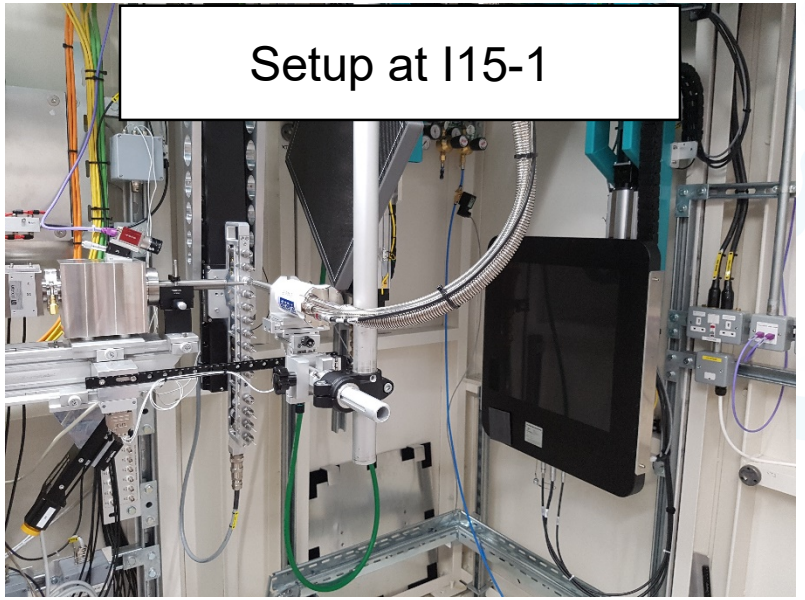
Experimental setup

- Experiment conducted at Diamond Light Source XPDF beamline I15-1
  - Dedicated PDF beamline
  - λ = 0.162 Å, Q_{max} = 35 Å^{-1}
    - High real-space resolution & flux
  - Temperature control in range -155 °C to 180°C
  - XRPD transformed to PDF using GudrunX [3]

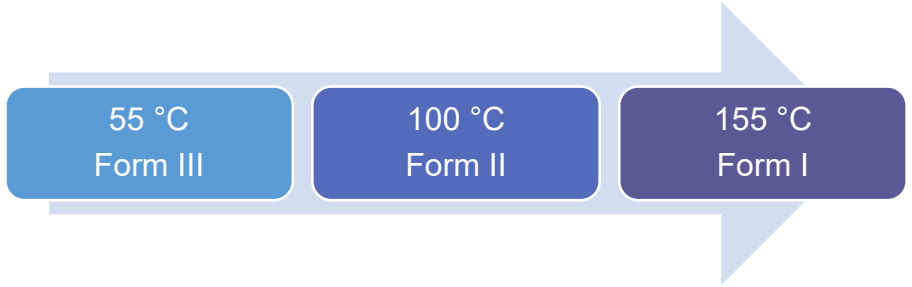


Setup at I15-1

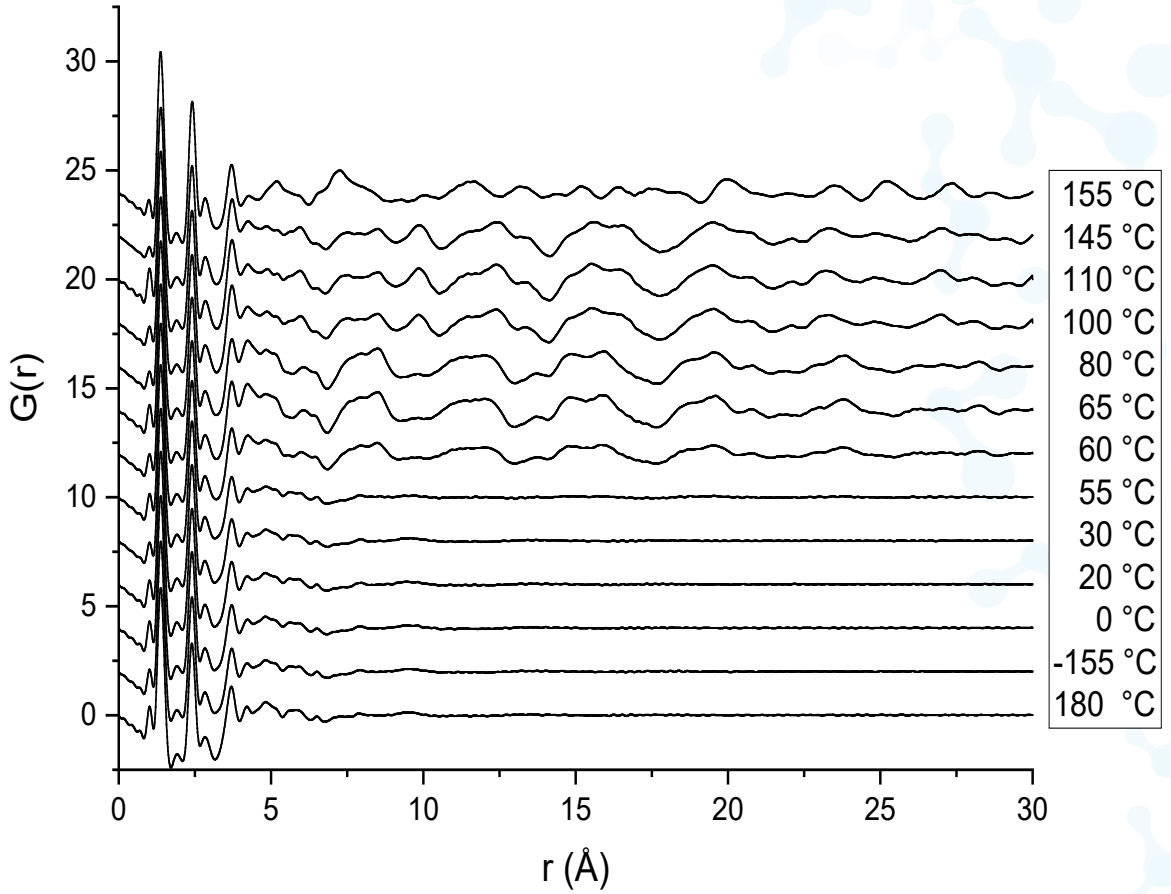
[3] A. K. Soper and E. R. Barney, "Extracting the pair distribution function from white-beam X-ray total scattering data," *J. Appl. Crystallogr.*, vol. 44, no. 4, pp. 714–726, Aug. 2011.

Variable temperature data collection

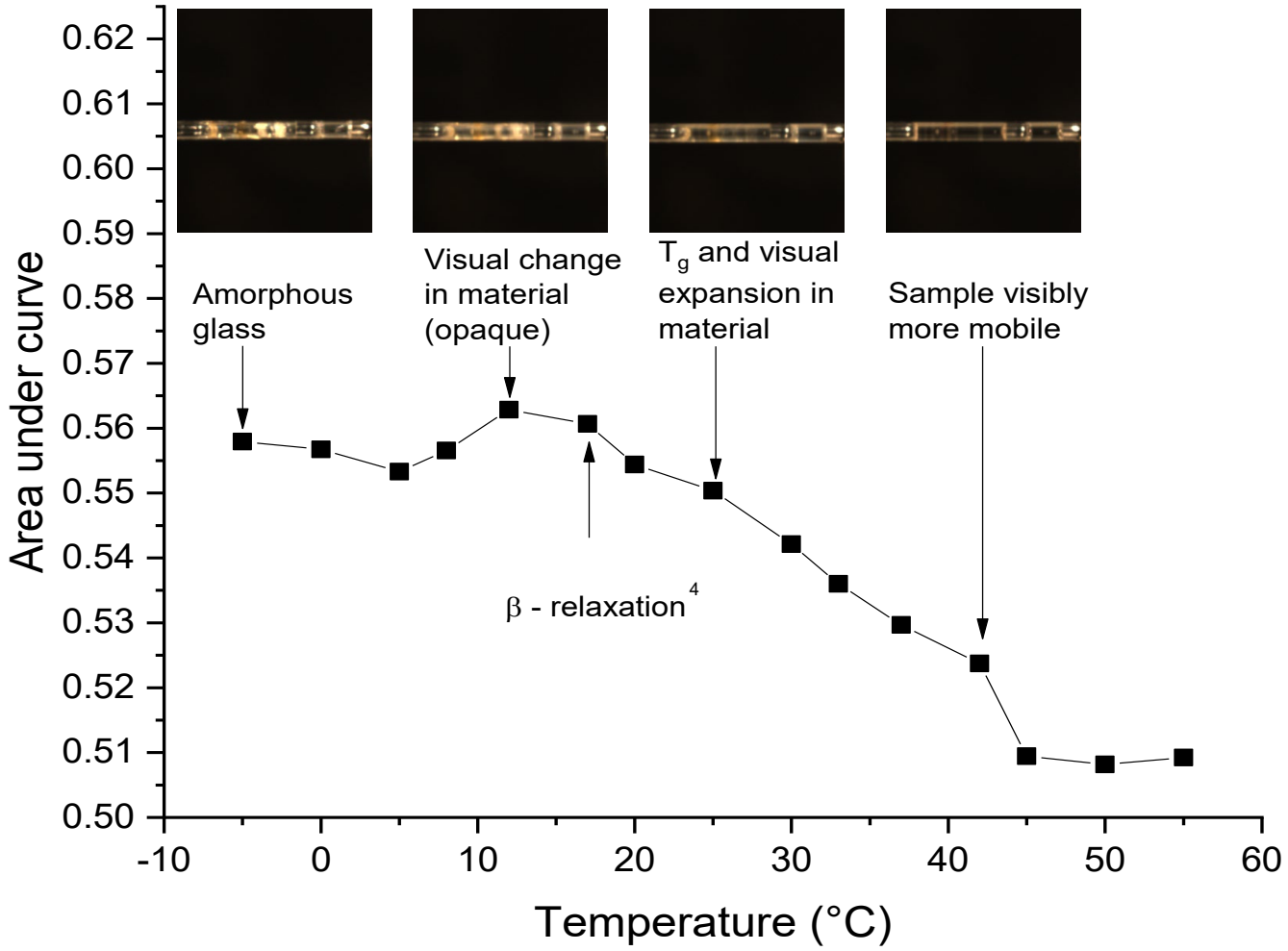
- Minimal visual changes between liquid (melt) and amorphous solid, and above and below T_g
- Crystallisation pathway:



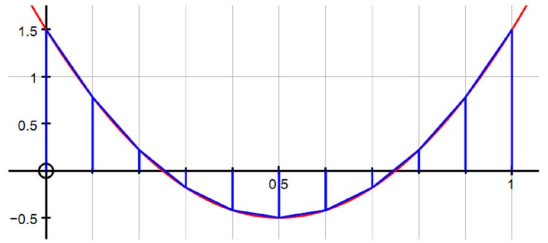
- Further investigation necessary to extract information from amorphous data



Variable temperature data collection



- PDF curve area plotted as function of temp using Trapezoidal method:

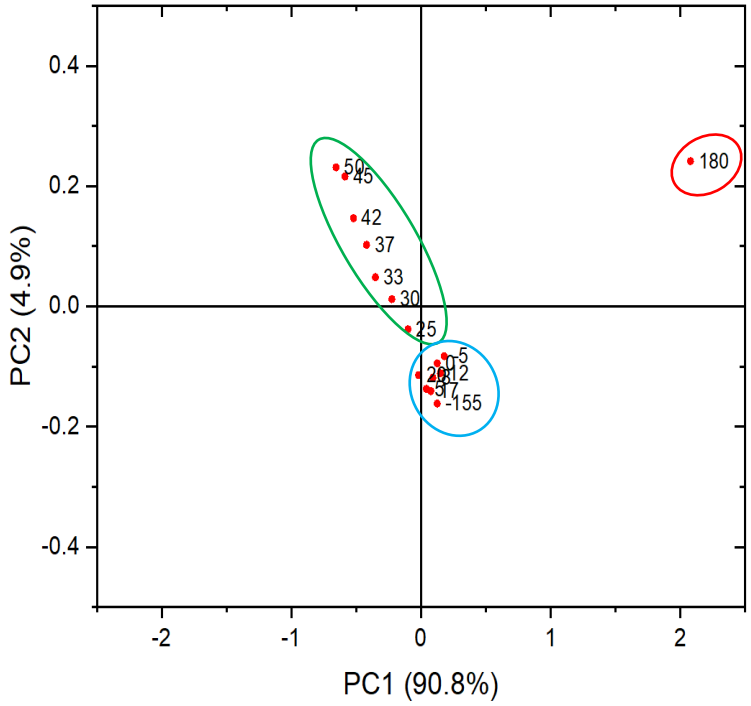


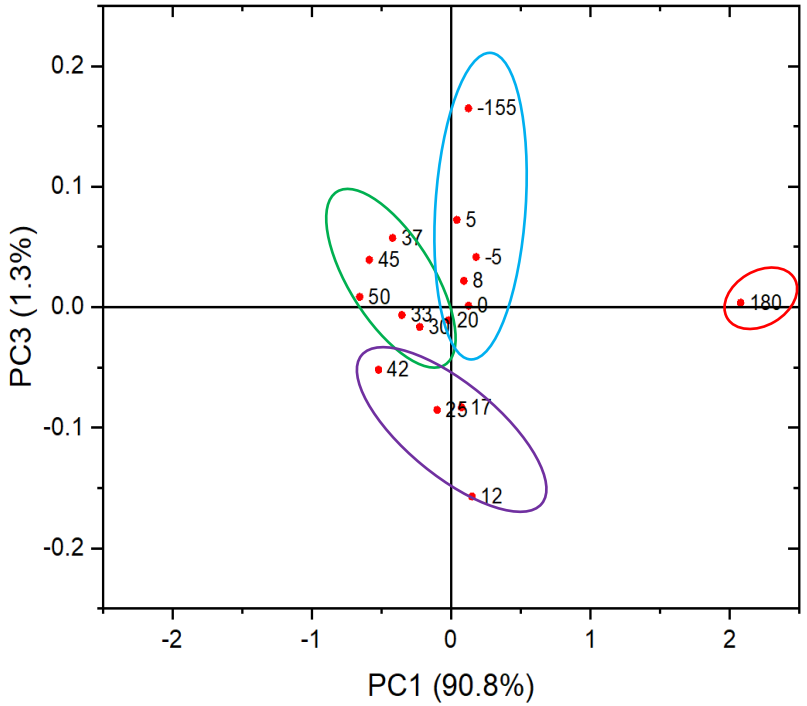
- PDF shows sensitivity to potential changes in local ordering
- "Plateau" before crystallisation
  - potential for PDF to assess physical stability

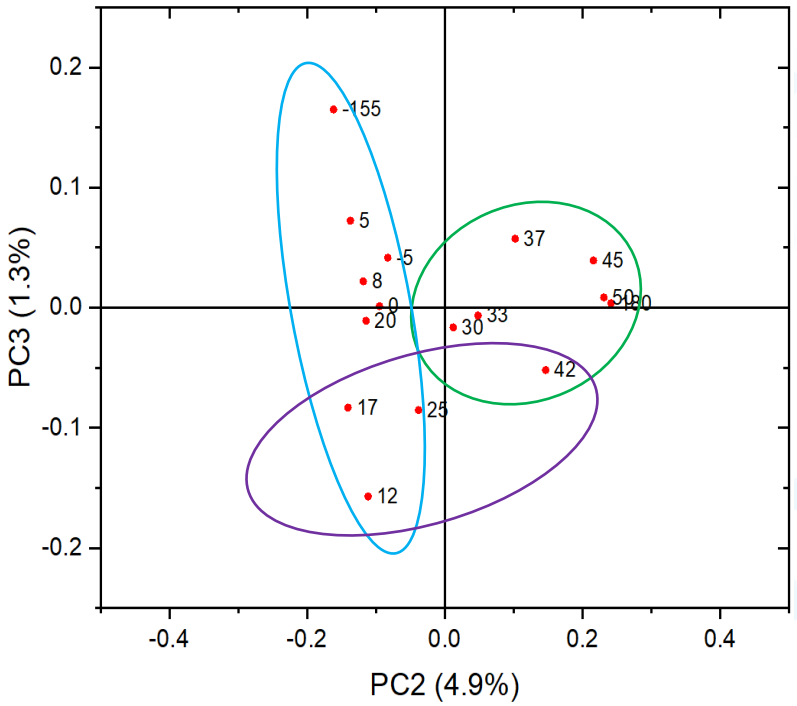
[4] J. Sibik, K. Löbmann, T. Rades, and J. A. Zeitler, "Predicting Crystallization of Amorphous Drugs with Terahertz Spectroscopy," *Mol. Pharm.*, vol. 12, no. 8, pp. 3062–3068, Aug. 2015.

Principal component analysis of amorphous PDFs

- Clustering of datasets above and below T_g
- Correlation between temperatures where physical changes are observed in the material
- Liquid/melt consistently an outlier







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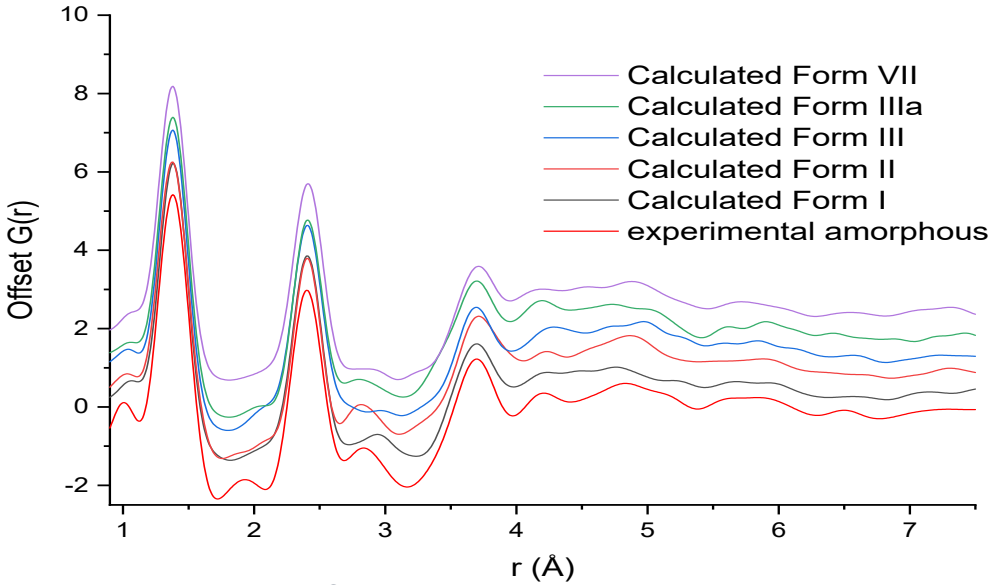
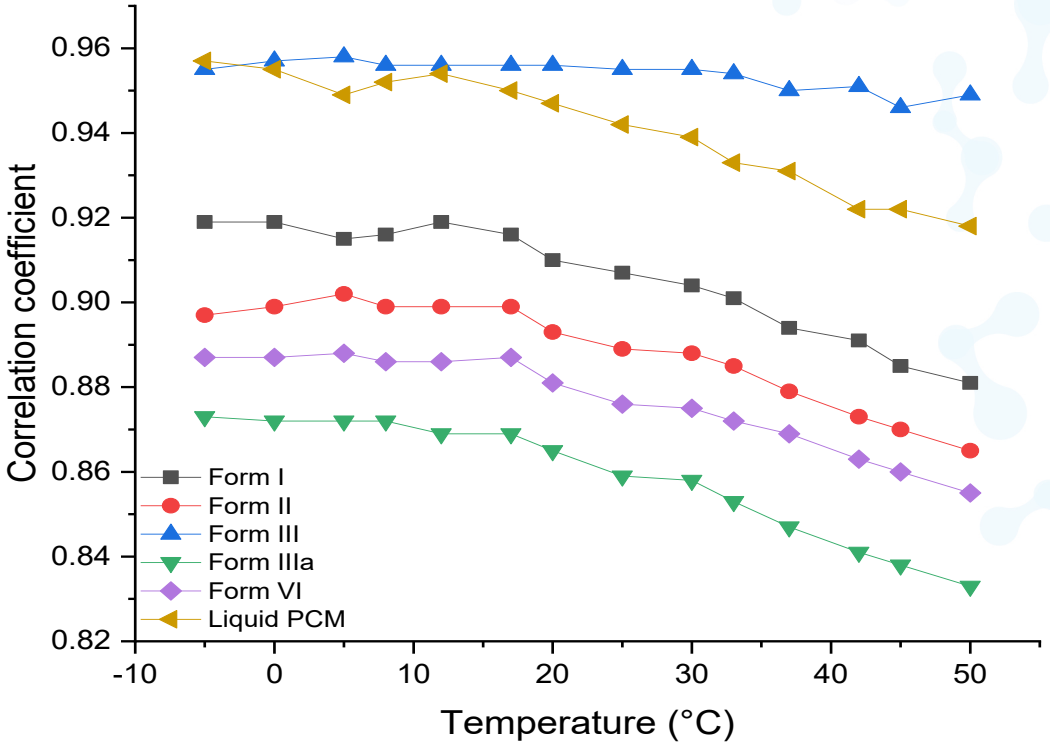
Comparison to calculated PDFs of known forms



- PDFs calculated from crystal structures using TOPAS academic V6 [5]
- Similarity of experimental and calculated PDFs assessed using correlation coefficients (CC) [6]
- PDF of amorphous form most similar to melt and metastable Form III



- CC decreases significantly with temperature in most cases
- CC with Form III, however, remains largely consistent

[5] A. A. Coelho, "TOPAS and TOPAS-Academic: An optimization program integrating computer algebra and crystallographic objects written in C++: An," *J. Appl. Crystallogr.*, vol. 51, no. 1, pp. 210–218, Feb. 2018.
[6] G. Barr, W. Dong, and C. J. Gilmore, "PolySNAP: A computer program for analysing high-throughput powder diffraction data," *J. Appl. Crystallogr.*, vol. 37, no. 4, pp. 658–664, Aug. 2004.

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Conclusions

- Local structure of amorphous paracetamol most similar to that of Form III
  - Does not appear to influence Form II crystallisation at RT
  - Form III crystallisation thermodynamically driven
  - Possible that molecules pack such that the energy change between amorphous and next high energy form is minimized
- PCA demonstrates the sensitivity of PDF to physical transitions in the material (T_g, T_β etc.)
- PDF demonstrated as having potential to assess physical stability using the Trapezoidal integration method

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Current developments

- Use of molecular dynamics to generate structural models of amorphous pharmaceuticals for comparison to PDF data
- PDF analysis of other model compounds
- Application of PDF in solubility determination in drug-polymer systems

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