Characterisation and prediction of stability of amorphous materials during pharmaceutical development: Pair-wise Distribution Function

Helen Blade, Steve Cosgrove, Jonathon Booth, Anne Kavanagh

PAR&D, AstraZeneca, Macclesfield, UK

May 2009

AstraZeneca
life inspiring ideas

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

Sponsored by The International Centre for Diffraction Data

PPXRD Website – www.icdd.com/ppxrd

ICDD Website - www.icdd.com

Challenges of using amorphous materials

- Increasing openness to go with amorphous drug in the formulation due to bioavailability and / or crystallinity issues
- When using an amorphous formulation within AZ we are often asked:
  - ? How physically stable is the amorphous material?
  - ? Is the material actually amorphous or is it simply nanocrystalline?
  - ? Is the formulation a true solid dispersion or is it phase separated?
- The answers all link to either the physical stability or the biopharmaceutical performance of the formulation
- We can use the PDF method to provide information

What is PDF?

PDFs are generated from the sine Fourier transformation of the normalized scattering function s(Q)

$$G(r) = \frac{2}{\pi}\int_0^\infty Q[S(Q)-1]\sin(Qr)dQ$$

Q is the magnitude scattering vector and is derived from $Q = 4\pi \sin(\theta) / \lambda$

S.J.L.Billinge and M.G.Kanatzidis, *Chem. Commun.,* **2004**, 749-760

S. Bates *et.al.*, *Pharmaceutical Research*, **2006**, 23(10) 2333-2349

S.Bates *et.al., J. Pharmaceutical Sciences*, **2007**, 96(5), 1418-1433

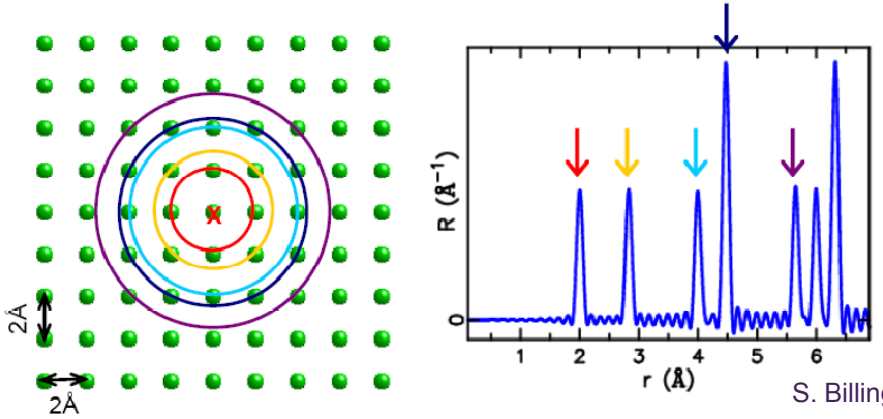
What is PDF?

PDFs are generated from the sine Fourier transformation of the normalized scattering function s(Q)

$$G(r) = \frac{2}{\pi}\int_0^\infty Q[S(Q)-1]\sin(Qr)dQ$$

Q is the magnitude scattering vector and is derived from $Q = 4\pi \sin(\theta) / \lambda$

By plotting the G(r) (i.e. the PDF) gives the probability of finding an atom at a given distance 'r' from another atom



S. Billinge. Z.Kristallogr.Suppl. **26** (2007) 17-26

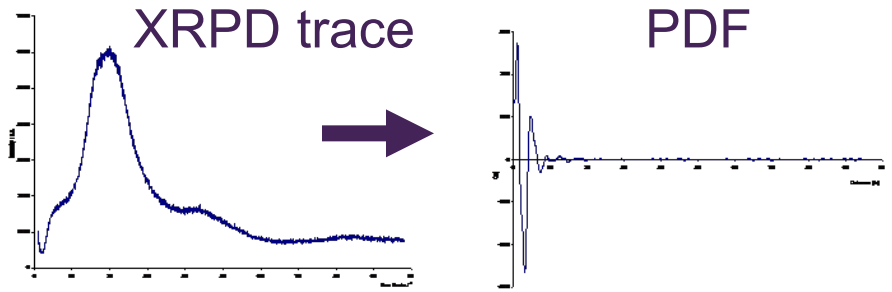
S.J.L.Billinge and M.G.Kanatzidis, *Chem. Commun.*, **2004**, 749-760

S. Bates *et.al.*, *Pharmaceutical Research*, **2006**, 23(10) 2333-2349

S.Bates *et.al., J. Pharmaceutical Sciences*, **2007**, 96(5), 1418-1433

We are using PDF as a comparative technique

- We are not using the PDF to determine any absolute structural information e.g. determining exact actual atomic distances
- It is being used as a comparative technique
- Comparing the nature and/or level of ordering present within different materials and predict their relative stability
- For example the XRPD trace of an amorphous material yields a PDF trace with no peaks past 5Å suggesting that there is no order present in the material past 5Å.



Data acquisition

Experimental

- Standard XRPD diffractometer in reflection mode can be used
- The software PDFgetX2* is then used to generate the PDFs
- The XRPD pattern includes scattering due to the both the sample and the sample environment i.e air scatter, sample holder...

* X. Qiu, J. W. Thompson, and S. J. L. Billinge, PDFgetX2: A GUI driven program to obtain the pair distribution function from X-ray powder diffraction data, (2004) **Copyright © International Union of Crystallography** *J. Appl. Cryst.* **37**, 678-678

Experimental

- Key to generating real PDFs is the reduction of any scatter not due to the sample
  - Reduce scatter from sample holder – for example use a modified holder which has reduced background
  - Reduce air scatter – data are collected with the sample chamber under vacuum or a light gas e.g. argon
- This reduces the need to correct for background scatter within the software and so reduces the risk of generating false PDFs

How are AZ using PDF during the drug development process?

Case Studies

Pharmaceutical and Analytical R&D **PAR&D**

Some of the questions we are regularly asked within AZ:

- ? How physically stable is the amorphous material?
- ? Is the material actually amorphous or is it simply nanocrystalline?
- ? Is the formulation a true solid dispersion or is it phase separated?

➢ The answers all link to either the physical stability (i.e. shelf life) or the biopharmaceutical performance of the formulation

Some of the questions we are regularly asked within AZ:

? How physically stable is the amorphous material?

? Is the material actually amorphous or is it simply nanocrystalline?

? Is the formulation a true solid dispersion or is it phase separated?

➢ The answers all link to either the physical stability (i.e. shelf life) or the biopharmaceutical performance of the formulation

How physically stable is the amorphous formulation?

Theory

- Peaks in the PDF trace indicates at what particular atomic distance there are two pairs of atoms
- Relative intensity in the PDF directly relates to the number of these pairs of atoms
- The point at which there are no more peaks present in the PDF trace can be considered as the extent of the long range ordering within the material
- Used to rank the physical stability of the material

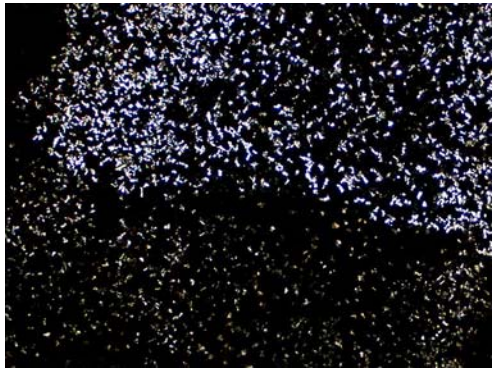
How physically stable is the amorphous formulation?

Example – Bicalutamide solid dispersions

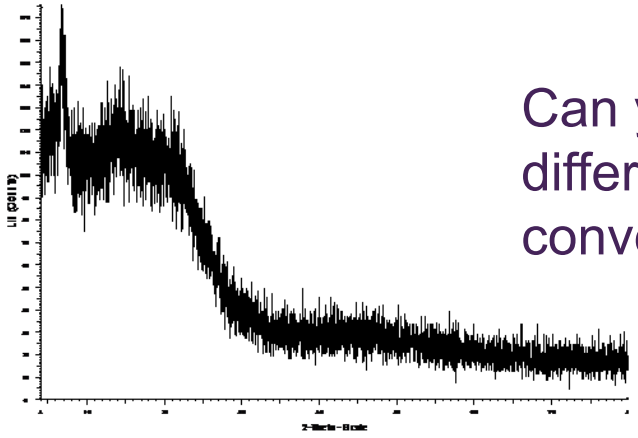
Bicalutamide:PVPVA

SD slides after 15 days at 40/75

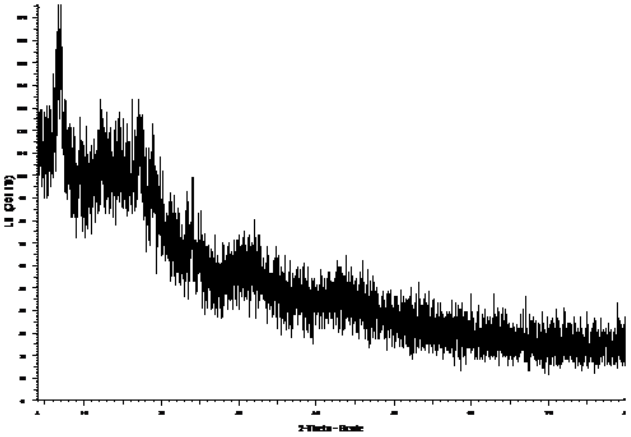
PVPVA SD is more stable than the Eudragit SD



Bicalutamide:Eudragit



Can you see any difference by conventional XRPD?



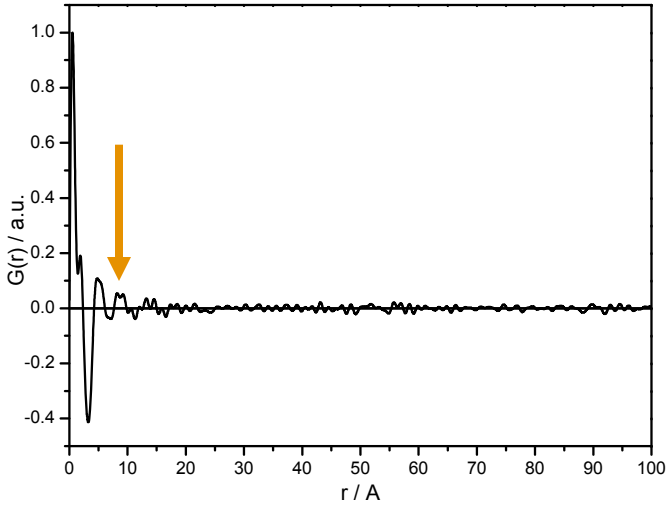
Pharmaceutical and Analytical R&D **PAR&D**

How physically stable is the amorphous formulation?

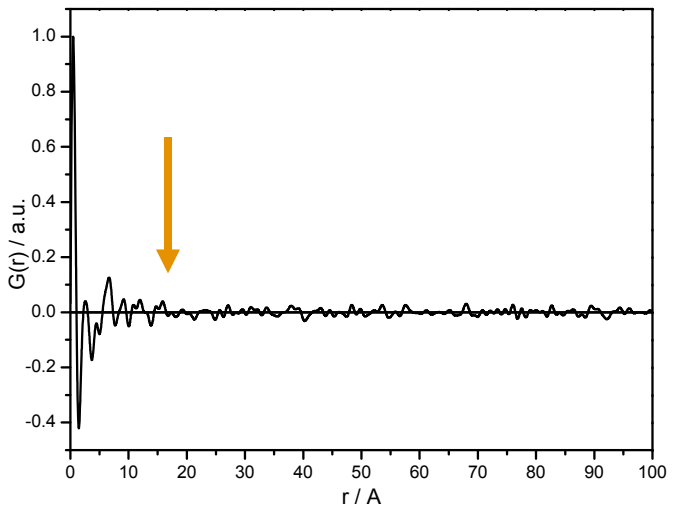
Example – Bicalutamide solid dispersions

- PDF data compares well with the stability data
- PVPVA SD exhibits no peaks past 10Å – stable formulation
- Eudragit SD exhibits peaks out to 20Å – unstable formulation that will recrystallise on storage

Bicalutamide:PVPVA



Bicalutamide:Eudragit



Some of the questions we are regularly asked within AZ:

? How physically stable is the amorphous material?

? Is the material actually amorphous or is it simply nanocrystalline?

? Is the formulation a true solid dispersion or is it phase separated?

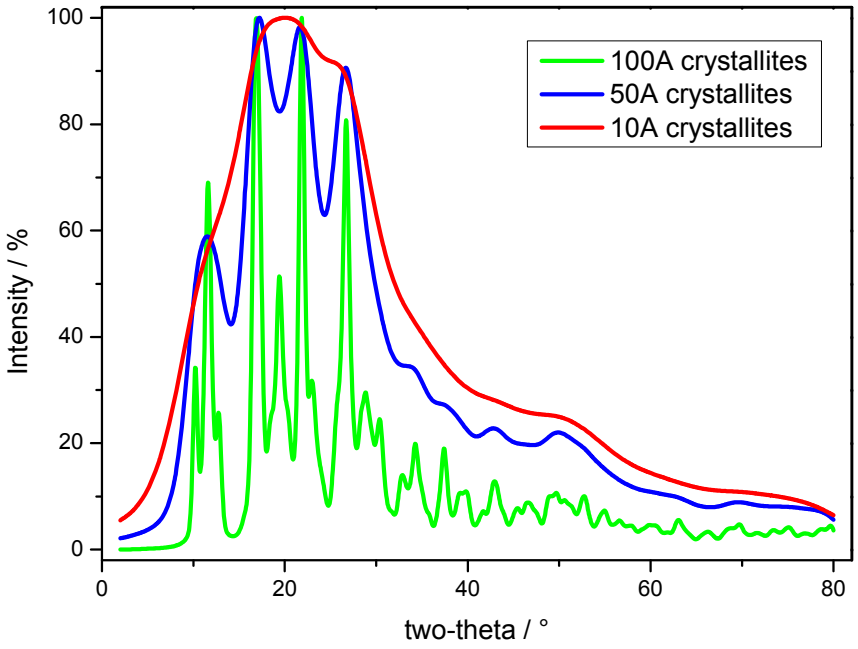
➢ The answers all link to either the physical stability (i.e. shelf life) or the biopharmaceutical performance of the formulation

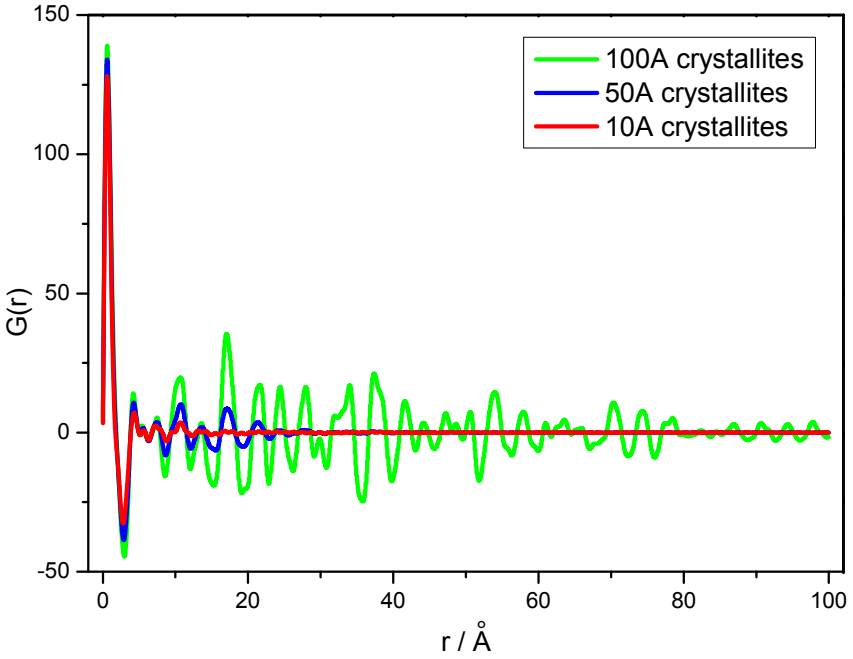
Amorphous or nanocrystalline?

- Nanoparticles appear amorphous by X-ray diffraction
- PDF is sensitive enough to detect the degree of ordering that is present within the small particle.
- Amorphous versus nanocrystalline has a direct impact on physical stability as a nanocrystalline material may ripen on storage

Amorphous or nanocrystalline?

- XRPD patterns simulated with different sized crystallites
- The PDFs were then generated from each





- The PDF differentiates between amorphous and nanocrystalline material

Some of the questions we are regularly asked within AZ:

? How physically stable is the amorphous material?

? Is the material actually amorphous or is it simply nanocrystalline?

? Is the formulation a true solid dispersion or is it phase separated?

➢ The answers all link to either the physical stability (i.e. shelf life) or the biopharmaceutical performance of the formulation

Solid dispersion or phase separated?

Theory – shape of the PDF trace

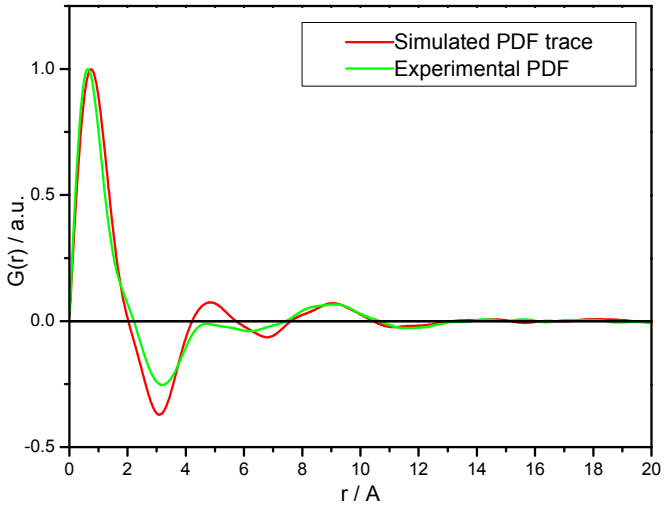
- Take PDF traces of the formulation components
- Linear combination at the correct ratio to give a simulated PDF trace for a physical mix of the formulation
- Compare the simulated and observed PDFs
- If they **match** the material is a physical mix, suggesting that there are no interactions between the API and the polymer, and so the API would not be stabilised in the amorphous state.
- If they **do not match** the material is truly dispersed and the formulation is likely to be more stable as the API is interacting with the polymer matrix.

Newman A, Engers D, Bates S, Ivanisevic I, Kelly R C, Zografi G; *J. Pharm. Sciences,* 97 (11), **2008**, 4840

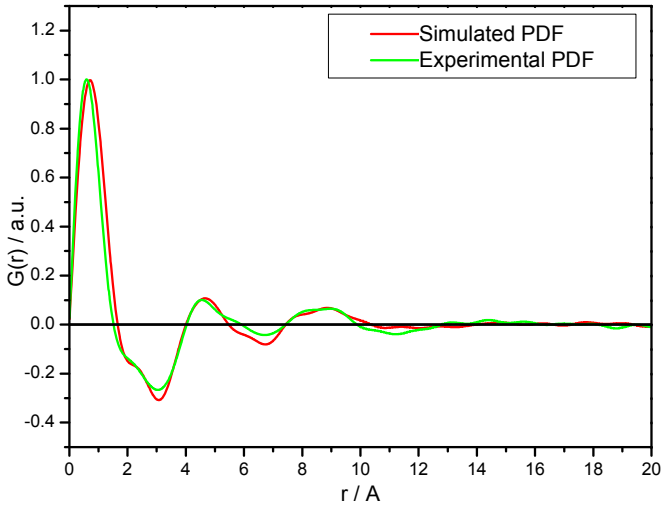
Solid dispersion or phase separated?

Example: Felodipine Copovidone formulation

- Two solid dispersions with different drug loading levels
- PDF indicates that the 5% loaded solid dispersion is miscible – when this material is exposed to water it remains amorphous
- PDF of the 50% loaded material indicates that it is phase separated – when this material is exposed to water it recrystallises



5% felodipine – 95% copovidone



50% felodipine – 50% copovidone

Where does PDF fit into the drug development process?

- Ranking the physical stability of amorphous materials
  - Traditional approach is to use accelerated stability
    - E.g. Storage at 40^{o}C at 75% relative humidity
    - This can typically take a month
    - These are stress conditions – could give false negative results
  - ➢ PDF can predict the stability in a one-off analysis at the initial time point (i.e. time = 0)
  - ➢ Allowing for quicker decisions to made
- ➢ Helping to improve the understanding of each amorphous material speed up the overall drug development process

Summary

- PDF can be used to help AZ answer:
  - ? How physically stable is the amorphous material?
  - ? Is the material actually amorphous or is it simply nanocrystalline?
  - ? Is the formulation a true solid dispersion or is it phase separated?
- PDF can provide a ranking of physical stability at the point of preparation, negating the need for stability studies
- Helps to speed up the overall drug development process

Any Questions?