Synchrotron X-ray Analysis of Amorphous Drugs and Drug/Polymer Dispersions

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Session Description and Objectives

- Synchrotron X-ray Pair Distribution Function (SXPDF) techniques provide valuable information about amorphous materials and dispersions.

- What is PDF?
- Why is a synchrotron needed?
- Domains of drug molecules in a dispersion
- Stability
- Latest advances

Biography and Contact Information

- Contact information:
  - At the show: booth 551
  - After the show: pam.smith@improvedpharma.com

XRD vs. PDF … global view vs. local view

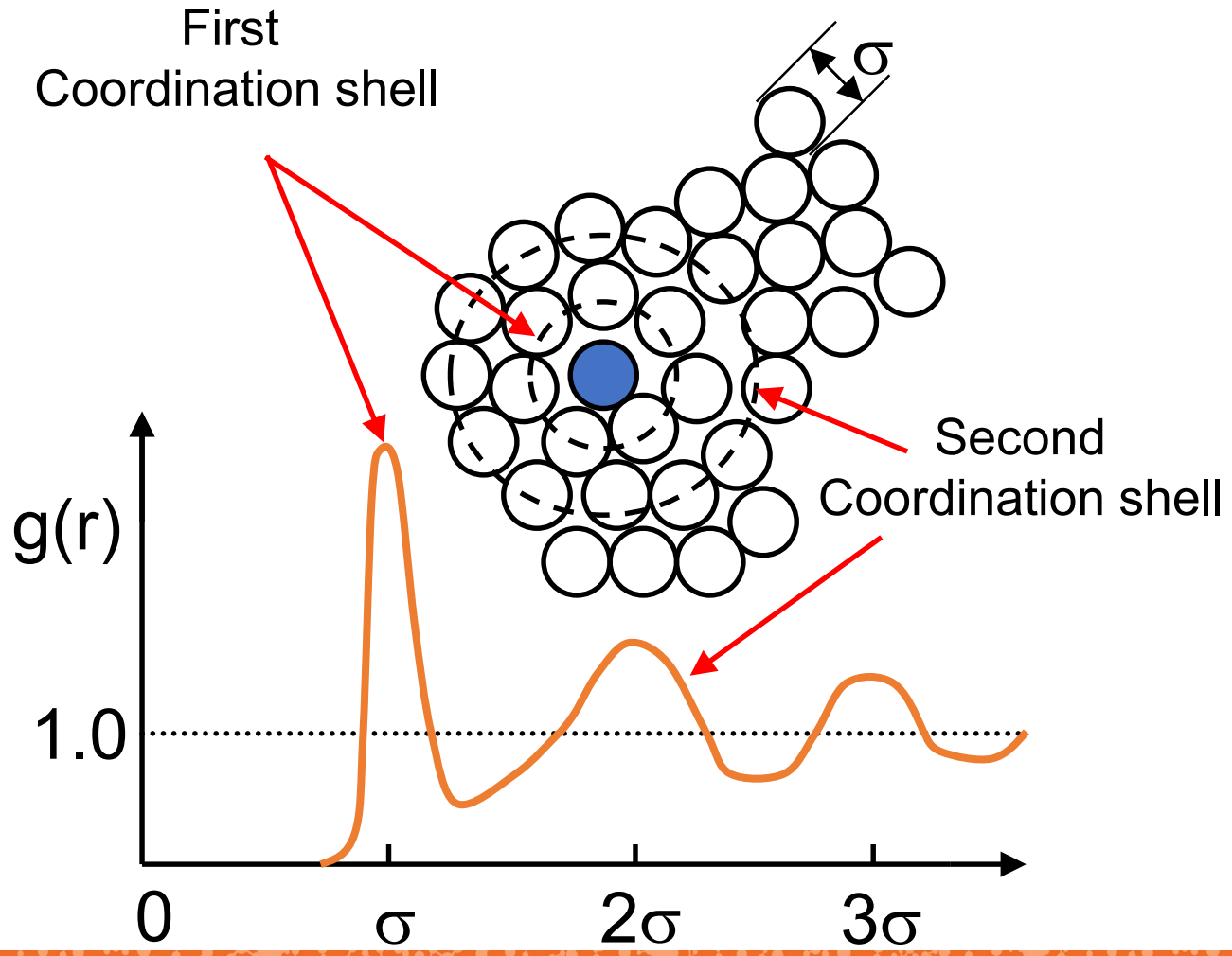
XRD (Bragg diffraction)

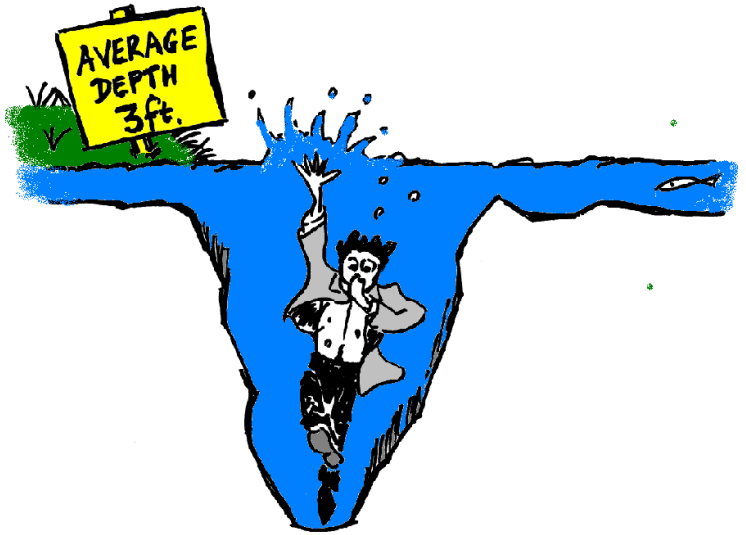
- Average structure, or global view of the structure
- Peaks in the pattern represent periodic occurrences of an atomic plane in a crystal
- There is also information between and underneath the Bragg peaks
- We can extract this additional information by mathematical methods and the right experimental techniques

PDF (atomic pair distribution function)

- Fourier transform of XRD
- 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

Distribution Functions





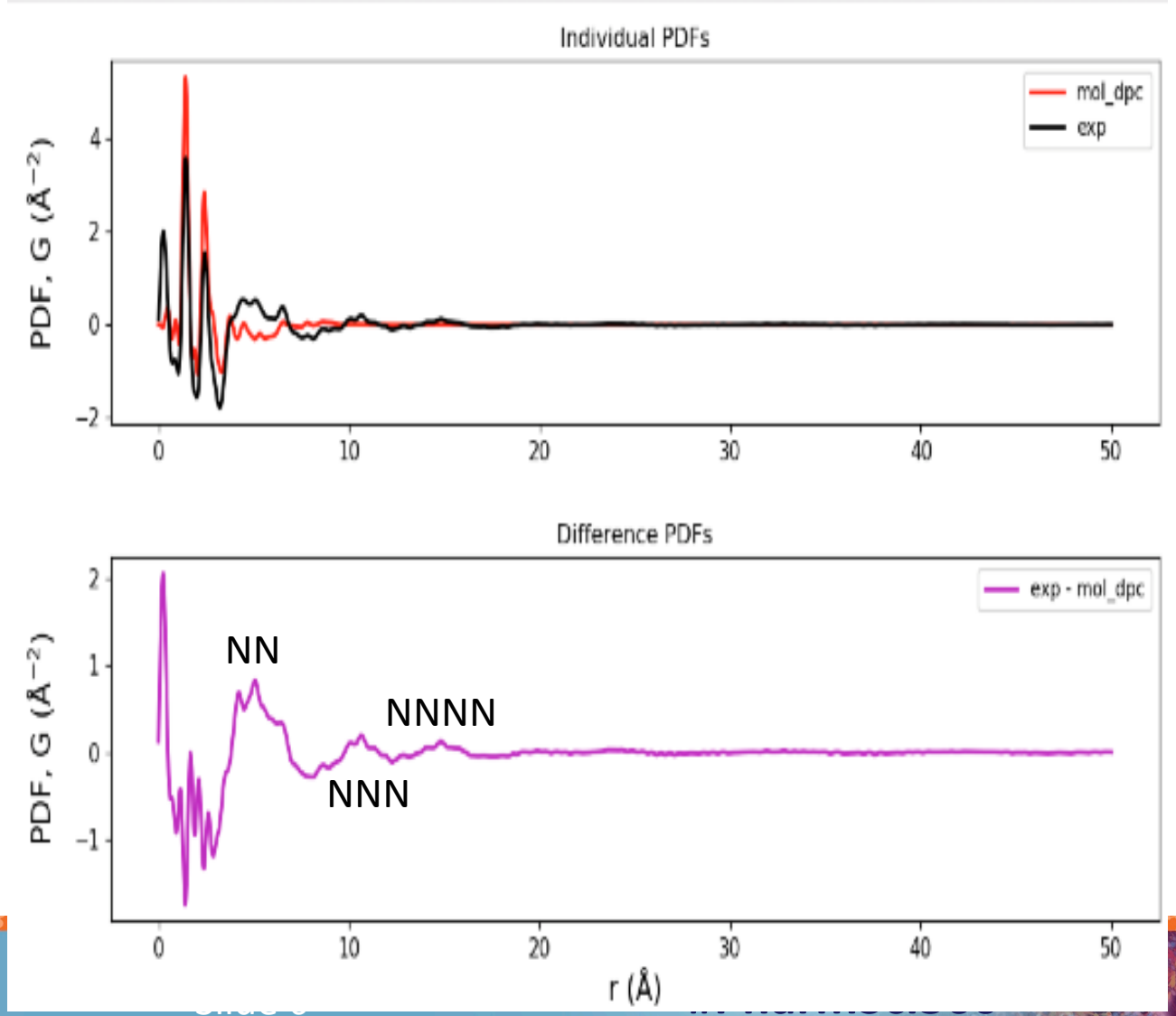
Flaw of Averages

PDF measures the AVERAGE structure
i.e. coordination number

Different Types of Interactions: Total = Intra + Inter

Intramolecular PDF:
Distances between atoms within a molecule

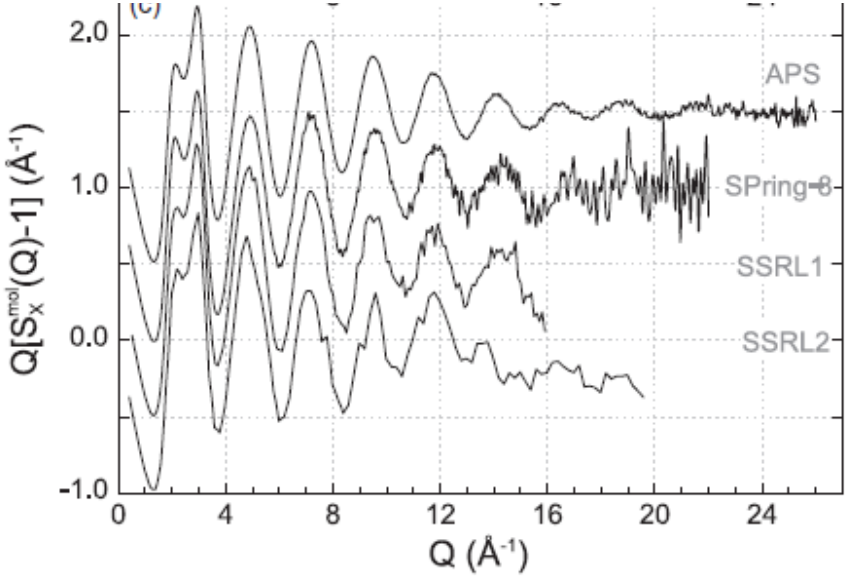
Intermolecular PDF:
Distances between atoms of neighboring molecules



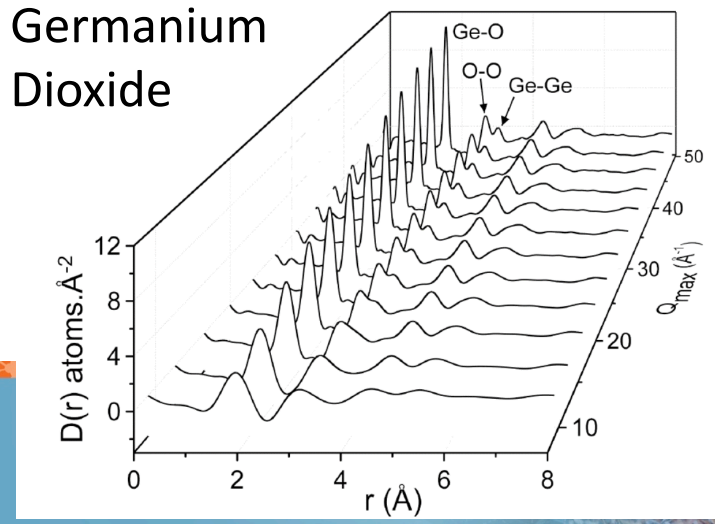
Synchrotron XRPD is required

Q_{max} affects SNR and resolution

- Data quality at large Q-values reflects the importance of using a high-energy X-ray beam
- More Q-space provides more data for the Fourier transform; leads to better quality data
- If Q_{max} is too low, resolution suffers



keV
114.76
61.62
17
19.6

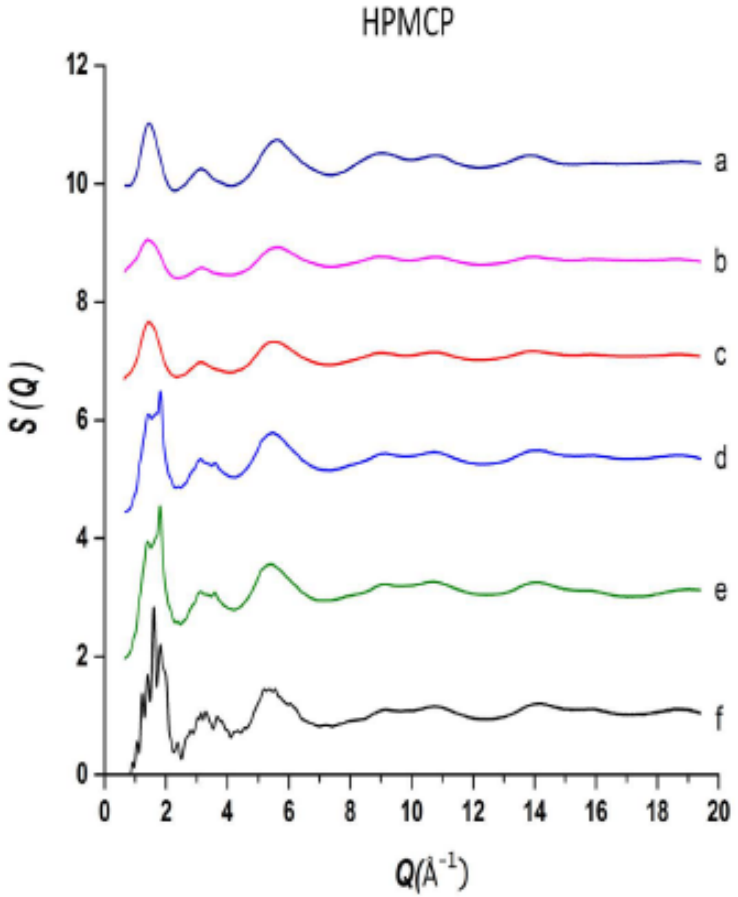


PDF of Drug/Polymer Dispersion

- Industry need
  - Amorphous forms have better solubility, but can be difficult to keep amorphous
  - Drug/polymer dispersions are one solution
  - How to know which dispersions will successfully inhibit crystallization?
- PDF
  - API molecules in close contact with each other increase the likelihood of crystallization
  - Can differentiate PDF of drug from PDF of polymer
  - PDF can determine if API domains exist
  - Lack of API domains are desired

Lapatinib Drug/Polymer Dispersion Study

Comparison of measurement X-ray factors



Pure polymer

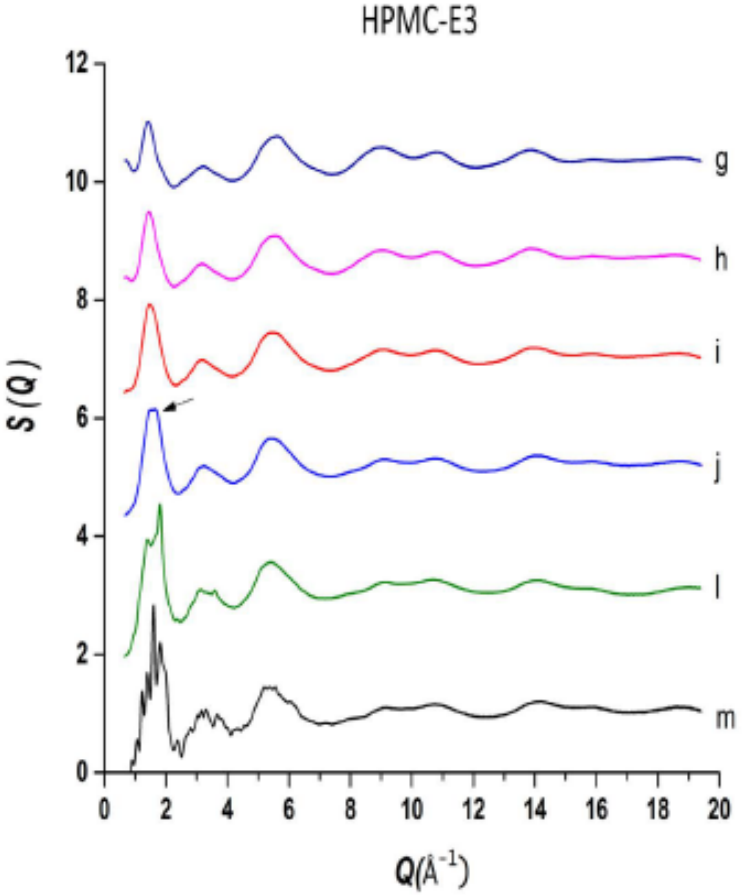
1:3 API/Polymer

1:1 API/Polymer

3:1 API/Polymer

Pure amorphous API

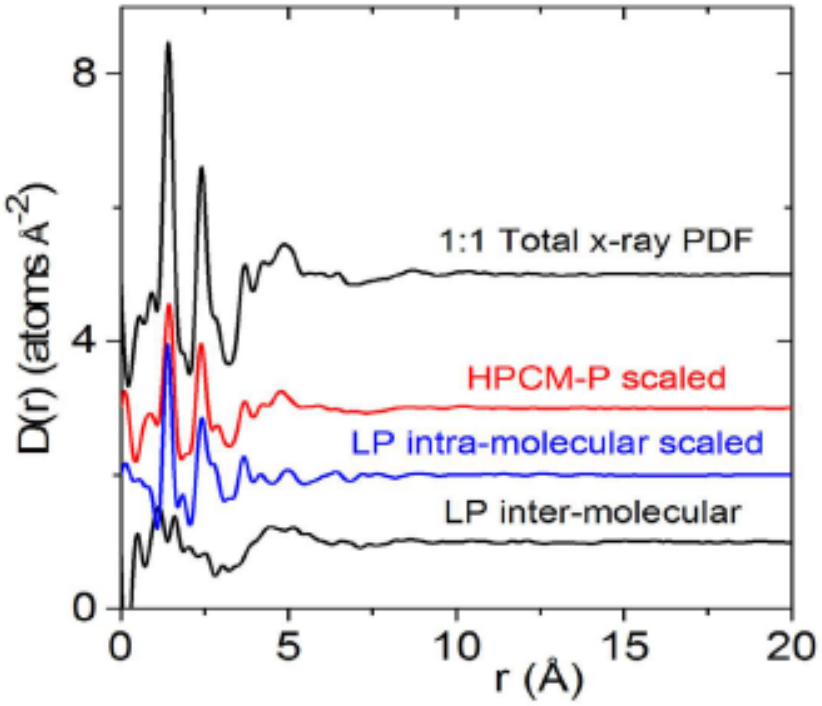
Pure crystalline API

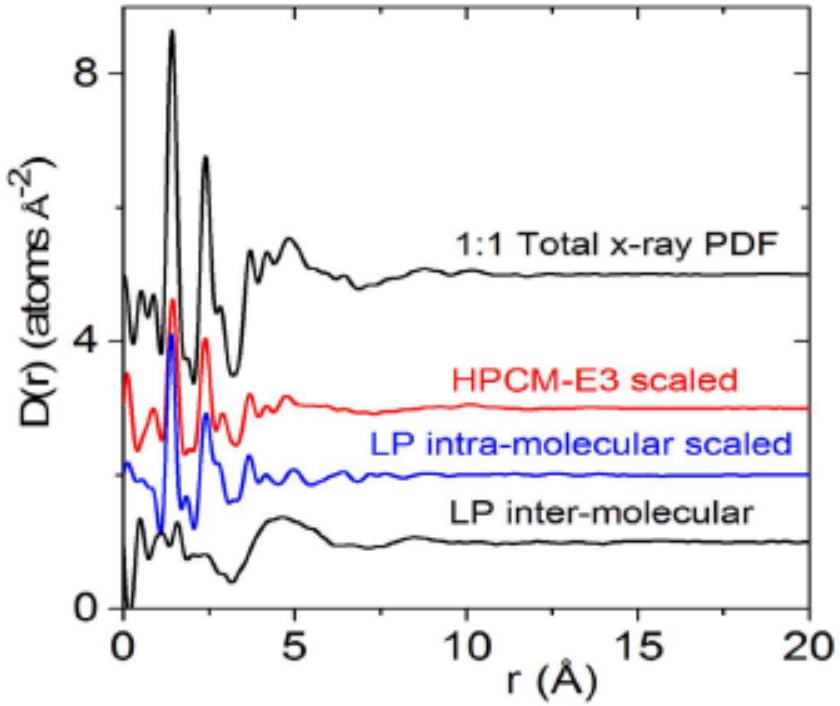


- Residual crystallinity of lapatinib can be seen in several samples, including the “pure” amorphous API

Lapatinib Drug/Polymer Dispersion Study

Total PDF curves and intra/inter PDF curves



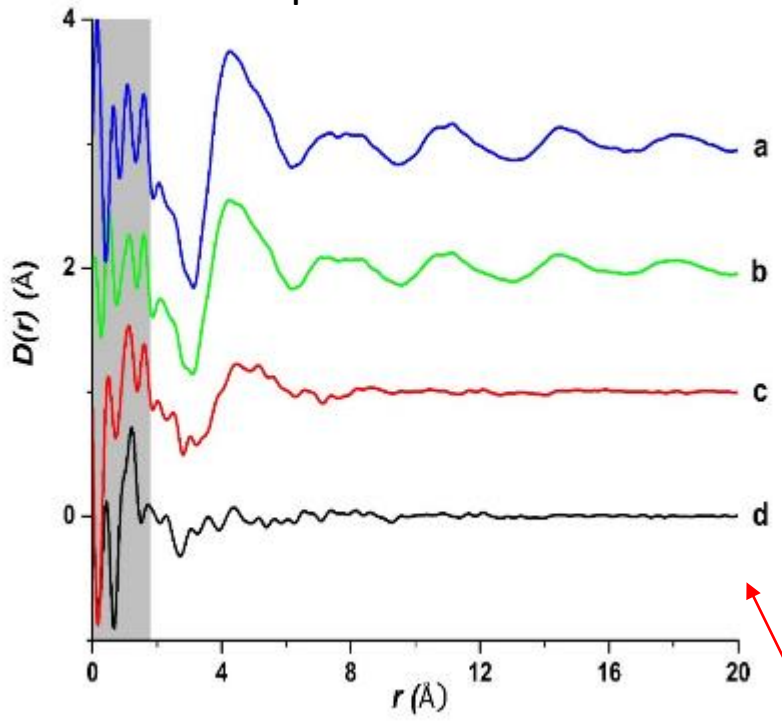


- Separate the total PDF curve into separate components
- Subtract components to reveal differences

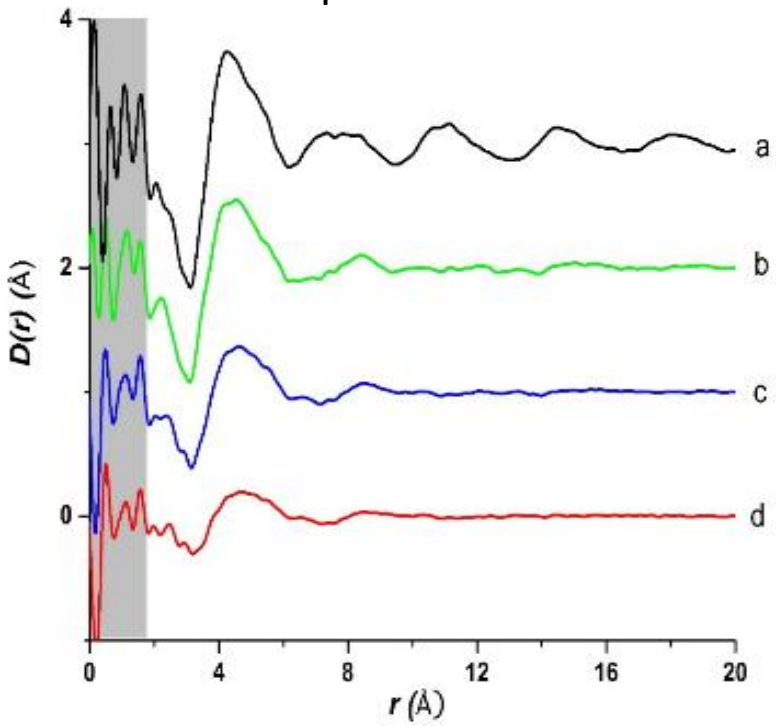
Lapatinib Drug/Polymer Dispersion Study

Differential PDF curves

HPMCP dispersions



HPMC-E3 dispersions

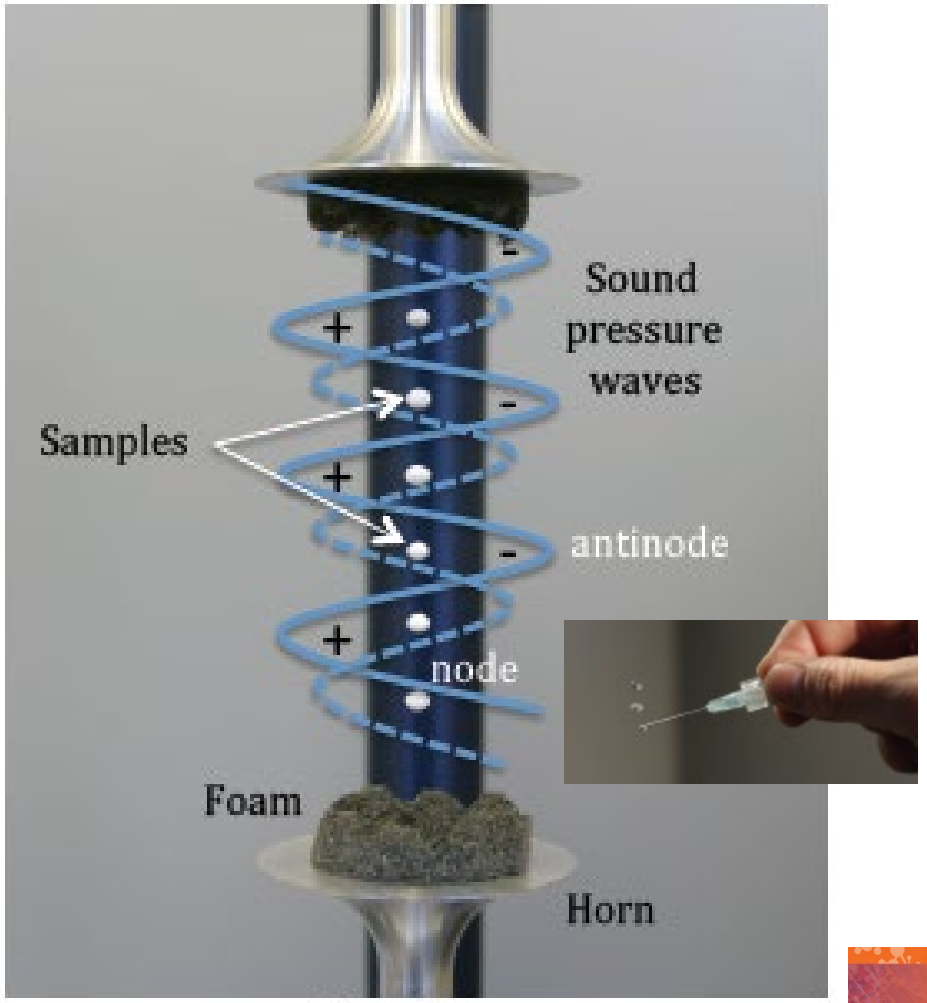


- The only dispersion lacking intermolecular API interactions (no NN API domains)
- The only dispersion that remained amorphous after stress testing at 40 ˚C/75% RH

Latest Advances

Collaboration with Materials Development Inc. through Phase 2 SBIR

- Lab on a drop with acoustic levitation
  - Lab model for spray drying
    - Suspend a droplet in the sample beam and obtain patterns as the drop evaporates, leaving amorphous material behind
  - Vitrification by container-less melting
    - Obtain hard-to-get amorphous materials
  - Drug/polymer dispersion screen
    - Quickly screen several different formulations on an extremely small scale



References

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Questions

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