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Synchrotron X-Ray Diffraction and Pair Distribution Function Analysis of Drug/Polymer Dispersions: A Comparison of Subtraction Techniques to Isolate Intra- and Intermolecular Interactions

Pamela Smith[a], Stephen R. Byrn[a], Gabriel L.B. de Araujo[b], Chris J. Benmore[c]

a) Improved Pharma, b) Department of Pharmacy, University of Sao Paulo, c) X-ray Science Division, Advanced Photon Source, Argonne National Laboratory

CONTACT INFORMATION: pam.smith@improvedpharma.com

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PURPOSE

The pair distribution function (PDF) of an amorphous dispersion represents the sum of all atom-atom contacts in that dispersion. Difference pair distribution functions are obtained by subtracting the PDFs of the intramolecular drug and polymer contributions from the overall dispersion PDF. This approach provides important information on the structure of the dispersion and the presence or absence of domains of drug in that dispersion. The overall aim of this study is to compare results from a new subtraction approach to results obtained in published studies. Specifically, intramolecular and intermolecular reference PDF curves created with xINTERPDF[1,2] from amorphous G(r) experimental data will be compared to those fit to S(Q) experimental data using XISF[3] and methodology described previously[4]. The ultimate goal is to compare these two approaches and illustrate their consistency.

METHODS

Data collected from various spray-dried dispersions (1:3, 1:1, 3:1) of lapatinib/polymer[5] or flubendazole/polymer[6] were used in this study. Intramolecular and intermolecular PDF curves and the subtraction results obtained in those publications via the S(Q) files were used as-is as the basis for comparison. To evaluate an alternative approach, the data collected previously were imported into PDFgetX2[7] and G(r) files were created. These files, along with the molecular structure (in xyz format) for lapatinib were loaded into xINTERPDF, and the intramolecular and intermolecular PDFs for amorphous lapatinib were extracted. Using Excel, the extracted intramolecular PDF was subtracted from the experimental G(r) data files, as were the polymer PDFs. The subtraction results were then compared to the previous results.

Secondly, to investigate the impact of data input for the molecular structure file, indomethacin was used as a test-case. Both alpha and gamma crystal structures were used in xINTERPDF, and the resulting calculated intramolecular and intermolecular indomethacin files were compared.

RESULTS

The xINTERPDF subtraction results for the lapatinib/HPMC-E3 dispersions are displayed in Figure 1. The top trace in the figure represents the intermolecular PDF for pure lapatinib. The large, broad peak ~4.3 Å represents a nearest-neighbor (NN) interaction between two lapatinib molecules. Another smaller peak ~8.4 Å represents a next-nearest-neighbor (NNN) interaction, indicating the presence of clusters of lapatinib molecules. These two peaks can be detected in all three lapatinib/HPMC-E3 dispersions; therefore, these dispersions contain clusters of lapatinib molecules.

The xINTERPDF subtraction results for the lapatinib/HPMCP dispersions are displayed in Figure 2. As before, the top trace in the figure represents the intermolecular PDF for pure lapatinib. The intensity of the broad peak ~4.3 Å is not as strong in the lapatinib/HPMCP dispersion subtractions, compared to the lapatinib/HPMC-E3 results. In fact, the NN and NNN peaks are almost completely absent for the 1:3 lapatinib/HPMCP dispersion subtraction result. These results suggest that the 1:3 lapatinib/HPMCP sample does not contain clusters of lapatinib molecules. If so, then this dispersion should be more stable than the others. In fact, a stress test with direct exposure was carried out under 40 °C/75% RH, and the 1:3 lapatinib/HPMCP dispersion sample remained amorphous whereas the other dispersions crystallized[5]. Therefore, the presence of lapatinib domains in a drug/polymer dispersion can be used as an indicator for stability. These results are equivalent to those obtained previously.

Lastly, an interesting observation was made when using xINTERPDF to derive the intramolecular and intermolecular PDFs for indomethacin. Indomethacin can be present in the alpha or gamma form. The G(r) file for amorphous indomethacin was imported into xINTERPDF, and two different sets of intramolecular and intermolecular PDF curves were extracted: one using the molecular structure of the alpha form and the other using the molecular structure of the gamma form. The calculated intramolecular PDFs are displayed in Figure 3, along with the experimental PDF of amorphous indomethacin. Interestingly, using different crystalline structure inputs for indomethacin resulted in different calculated intramolecular PDFs, most notably between 4 and 7 angstroms.

CONCLUSIONS

xINTERPDF is a viable and acceptable program for creating intramolecular and intermolecular PDF patterns. The program was successfully used on a variety of previously analyzed spray-dried drug/polymer dispersions, and subtractions were performed yielding equivalent results as before. Evidence of intermolecular lapatinib interactions indicating the presence of lapatinib domains were found in many of the dispersions, which led to a decrease in stability and subsequent crystallization. The same drug/polymer dispersion (the 1:3 lapatinib/HPMCP sample) was found to contain essentially no lapatinib domains, no matter which data analysis approach was used.

Secondly, the impact of reference data used as inputs into the xINTERPDF program was examined for indomethacin with respect to selecting the proper molecular structure for PDF calculations. The results obtained from using the crystal structure file for alpha versus gamma indomethacin yielded significantly different results. Therefore, this type of PDF analysis could be very helpful in determining which conformation or mixture of conformations are present in the amorphous phase.

Figure 1: Comparison of intermolecular differential pair distribution functions of lapatinib/HPMC-E3 dispersions (top to bottom: pure lapatinib, 3:1 lapatinib/HPMC-E3, 1:1 lapatinib/HPMC-E3, 1:3 lapatinib/HPMC-E3)

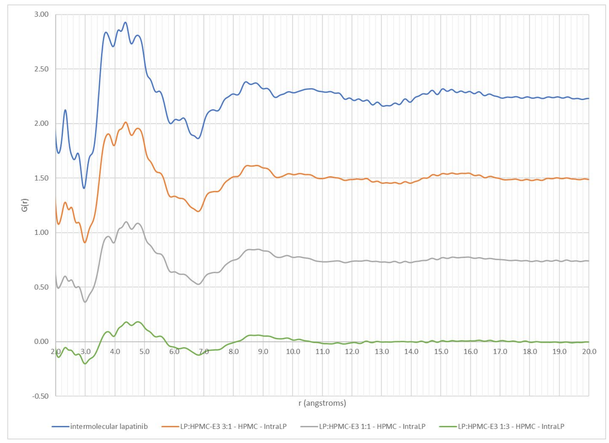


Figure 2: Comparison of intermolecular differential pair distribution functions of lapatinib/HPMCP dispersions (top to bottom: pure lapatinib, 3:1 lapatinib/HPMCP, 1:1 lapatinib/HPMCP, 1:3 lapatinib/HPMCP)

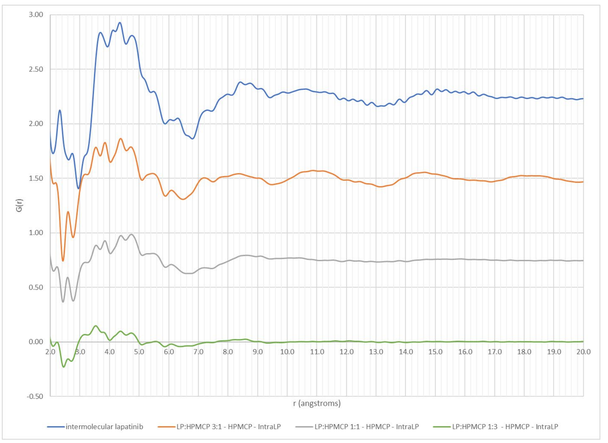
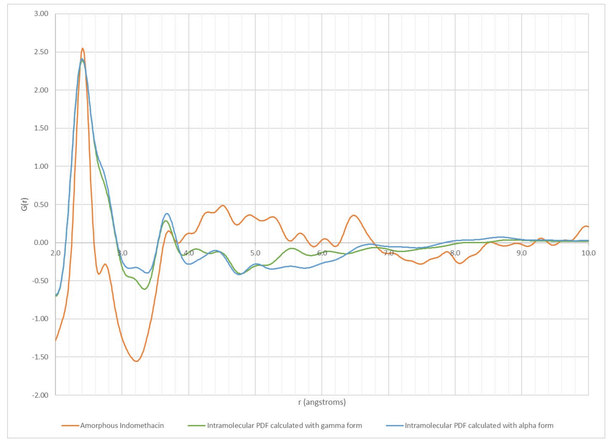


Figure 3: Intramolecular pair distribution functions of indomethacin created in xINTERPDF using either the gamma or the alpha form compared to the experimental pair distribution function of amorphous indomethacin



SUMMARY	3:1 dispersion	1:1 dispersion	1:3 dispersion
Lapatinib/HPMC-E3	Lapatinib clusters detected	Lapatinib clusters detected	Lapatinib clusters detected
Lapatinib/HPMCP	Lapatinib clusters detected	Lapatinib clusters detected	No lapatinib clusters; most stable dispersion

REFERENCES

1. Shi, C, xINTERPDF, a graphical user interface for analyzing intermolecular pair distribution functions of organic compounds from X-ray total scattering data. *J. Appl. Crystallogr*, **51**, 1498-1499 (2018).
2. Juhas, P, Farrow, C. L., Yang, X., Knox, K. R., Billinge, S. J. L. Complex modeling: a strategy and software program for combining multiple information sources to solve ill posed structure and nanostructure inverse problems, *Acta Crystallogr A*. **71**, 562-568 (2015).
3. Mou, Q., Benmore, C. J., Yarger, J. L. X-ray Intermolecular Structure Factor (XISF): separation of intra-and intermolecular interactions from total X-ray scattering data. *J. Appl. Crystallogr*. **48**, 950-952 (2015).
4. Benmore, C. J. *et al.* Structural Characterization and Aging of Glassy Pharmaceuticals made Using Acoustic Levitation. *J. Pharm. Sci.* **102**, 1290–1300 (2013).
5. de Araujo, G. L. B., Benmore, C. J. & Byrn, S. R. Local Structure of Ion Pair Interaction in Lapatinib Amorphous Dispersions characterized by Synchrotron X-Ray diffraction and Pair Distribution Function Analysis. *Sci. Rep.* **7**, 46367 (2017).
6. De Araujo, G.L.B., Hydroxypropyl methylcellulose derivatives of Amorphous flubendazole dispersions: formulation stability assisted through pair distribution function analysis, in press (2019).
7. Qiu, X., Thompson, J.W., Billinge, S.J.L. PDFgetX2: A GUI driven program to obtain the pair distribution function from X-ray powder diffraction data. *J. Appl. Crystallogr.* **37**, 678 (2004).

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