M1430-06-31

Feasibility of Synchrotron XRD for the Analysis of Mixture Sub-samples

Ruba Alajlouni[a], Pamela Smith[a], Saul Lapidus[b]

[a]Improved Pharma LLC, [b]Argonne National Laboratory

CONTACT INFORMATION: Ruba.Alajlouni@improvedpharma.com

PURPOSE

X-ray diffraction analysis (XRD) is the gold standard for identifying solid-state forms of pharmaceutical powders. From form screening tests to quantifying components in mixtures, XRD has been used reliably for crystalline samples, but not without limitations. Generating reliable XRD data starts with preparing good samples, especially in the case of mixtures. The quality of mixing is essential since it is not always possible to analyze the entire sample at once.

The purpose of this study is to demonstrate that synchrotron XRD (SXRD) can be effectively utilized to manage the risk of sub-sampling a large sample volume. We used geometric mixing with the "coning and quartering" technique and conducted the analysis on sub-samples of the mixtures. The power of SXRD was further highlighted by comparing results with conventional laboratory instrument (LXRD).

METHOD(S)

1. Three binary mixtures of Caffeine (Caff) in Acetaminophen (APAP) were prepared at concentrations of 0.84%, 5% and 10%.
   - Pure samples of Caff and APAP were used to established specificity of Caff in the mixtures.
2. Sub-samples were analyzed using both conventional LXRD and SXRD.
   - LXRD: sub-samples were analyzed using a zero-background holder in a Bragg-Brentano geometry generating a pattern.
   - SXRD: sub-samples were packed into polyimide capillaries and tested by both a point and an area detector. Data collected from multiple spots on each capillary (sub-sample) generating a pattern per spot.
3. SXDR calibration curves were constructed using Caff peak at 11.97° 2θ.

RESULT(S)

- SXRD was able to detect Caff at the lowest-concentration. By contrast, no Caff peaks were observed at that concentration using LXRD (Fig 1).
- SXRD data shows variations within each sub-sample (i.e., spots in each capillary).
- While SXRD data shows variations within each sub-sample (i.e., spots in each capillary), averaging the patterns of individual spots eliminated the variation between sub-samples of each preparation. For LXRD, the variation between sub-samples of the 5 and 10% mixtures were apparent in both the intensity of peak height and shape, while allowing the detection of only the most intense Caff peaks.

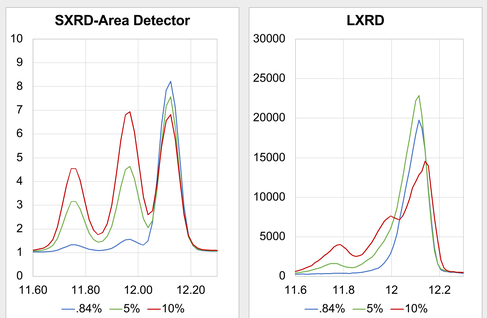
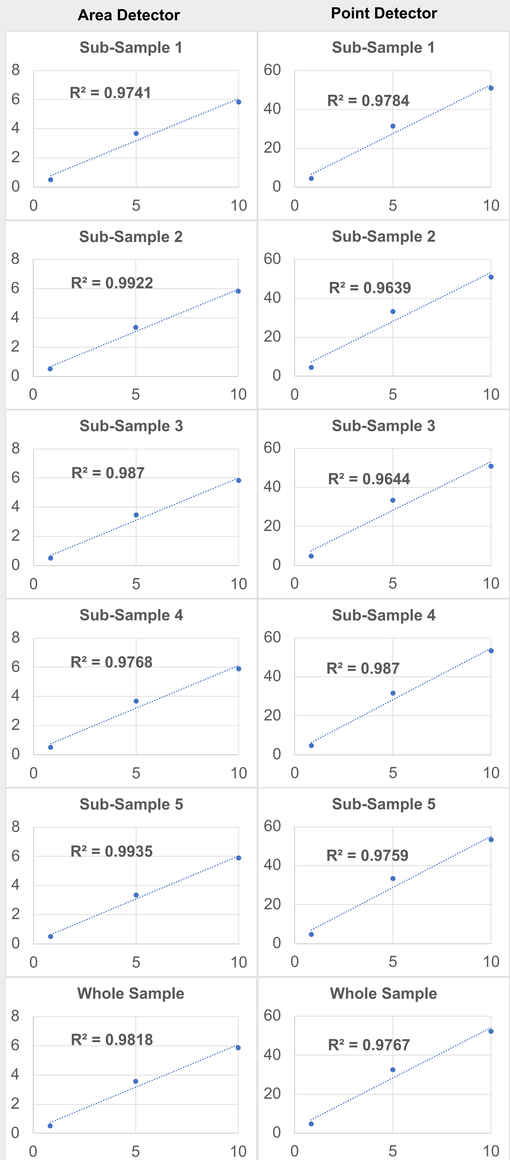


***Fig 1**. Pattern comparison of Caff In APAP mixtures at three concentrations collected with synchrotron and laboratory x-ray diffractions techniques (range 11.6-12.2° 2θ)*



- Data from both the SXRD point and area detectors produced calibration curves with R^2 values as high as 0.99. When calibration curves of different pairing of sub-samples were created, resulting R^2 values ranged from 0.96-0.99 for the point detector data and 0.97-0.99 for the area detector data (Fig 2). Similar R^2 was achieved for the whole sample (0.98).
- Given the essentially equivalent R^2 values obtained, the choice between using a point versus an area detector for data collection relies on the sample being analyzed and the experimental objectives.
- Both area and point SXRD detectors generated highly reliable data. However, data still varies between both detectors in quality (intensity and shape) of the produced patterns and required pre-processing. The precision of peak intensity and shape produced by the point detector makes it a better option for quantification purposes, whereas the area detector is most appropriate for qualitative purposes and samples with grainy/broad peaked components.

***Fig 2.** Generated calibration curves of SXRD area and point detector data for sub-samples (top 1-5 sub-samples) and for the whole sample (bottom curves).*

CONCLUSION

- SXRD offers better sensitivity and resolution of diffraction peaks than conventional LXRD because of high flux, tunable wavelength, and better alignment of the synchrotron ray, which improves the identification of minor components.
- Our data show that with the proper sample preparation procedure, a single capillary (i.e., a sub-sample) is sufficient to generate high quality and reliable data from a mixture using SXRD, unlike LXRD.
- However, it is critical that multiple spots on the same capillary are scanned, and the data averaged to create a pattern that represents the entire capillary.
- Lastly, different detectors for SXRD analysis can be used for different purposes depending on the sample to be tested and the experimental objective.