Application Report XRD 36

X-ray Powder Diffraction (XRPD) in Pharma

- Amorphous Content Determination and Degree of Crystallinity

The D8 ADVANCE is a versatile diffractometer that provides exceptional data quality. In this report, we describe the characterization of a crystalline organic phase blended with varying amounts of microcrystalline cellulose (MCC). Excellent linearity is achieved for blends across the compositional gradient and detection of crystalline API is possible as low as 0.2 wt%

Amorphous phases are frequently used within the pharmaceutical industry – examples include lyophilized/ freeze-dried active pharmaceutical ingredients (API) as well as binders and excipients used as bulking aids (e.g., microcrystalline cellulose and modified starches). XRPD is the premier analytical technique for measuring degree of crystallinity due to its nondestructive nature and speed in data collection.[1]

While the limit of detection (LOD) for crystalline phases is material-specific, LOD is frequently given as 1-2 wt% for laboratory diffractometers.[2-3] Achieving low LOD requires excellent signal-to-noise and low instrument background – this is accomplished through use of the LYNXEYE XE-T detector and Motorized Air-Scatter Screen (MASS).

Data were collected using a D8 ADVANCE diffractometer configured with copper (Cu) radiation (40 kV, 40 mA), motorized divergence slits (0.2 mm), rotation stage, 4.0 degree axial soller slits, MASS, and LYNXEYE XE-T detector. The MASS provides significant improvements to low angle data quality by removing unwanted signal from air scatter. The LYNXEYE XE-T provides a significant gain in intensity by eliminating the need for Ni-filter or secondary monochromator.

Acetaminophen (Spectrum) was crushed to a fine powder prior to use. Microcrystalline cellulose (Vivapur 101, JRS Pharma) was used as received without additional processing. Samples were weighed as individual gram-scale batches and then dry vortexed to evenly disperse the crystalline phase. Diffraction specimens were prepared in triplicate using low background silicon wafer mounts with a small circular cavity (15 mm diameter x 0.5 mm depth). Diffraction data are shown in **Figure 1** for samples with the following degrees of crystallinity: 0, 0.2, 0.5, 1, 5, 10, 25, 50, 75, 90, 95, 99, 100 wt%. The broad features for the amorphous MCC phase are gradually replaced by sharp diffraction peaks with increasing acetaminophen content. A zoomed in region for the pure cellulose, 0.2 wt%, and 0.5 wt% samples is shown in the inset of **Figure 1**. For the crystalline phase, limit of quantification (LOQ) and limit of detection (LOD) can be defined with signal-to-noise ratios of 10:1 and 3:1, respectively, which correspond to 0.5 wt% (LOQ) and 0.2 wt% (LOD).

Percent crystallinity values were calculated using whole pattern fitting with the software package DIFFRAC.TOPAS – representative data are shown in **Figure 2**. This sample had a nominal degree of crystallinity of 5 wt% and a calculated value of 4.6 wt%. The fitting model was applied to all diffractograms to calculate degree of crystallinity. Plotted values are shown in **Figure 3** and demonstrate a high degree of precision and linearity.

Low levels of amorphous material can also similarly be detected. As shown in **Figure 4**, MCC concentrations as low as 1 wt% are detectable by comparing background shapes and total intensity for the cellulose phase.

References

1. Byrn, S. R.; Zografi, G.; Chen, X. *Solid-State Properties of Pharmaceutical Materials;* John Wiley & Sons: Hoboken, NJ; 2017; p 340.
2. Surana, R. and Suryanarayanan, R. *Powder Diffraction*, 2000, *15*, 2.
3. Crowley, K.J. and Zografi, G. *J. Pharma. Sci.* 2002, *91*, 492.

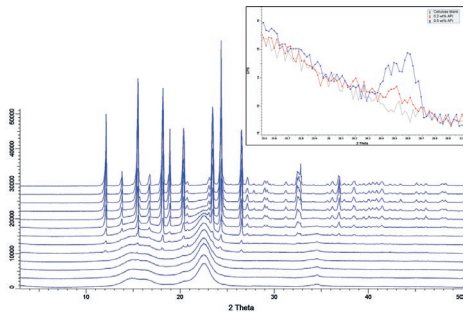

Figure 1. Waterfall plot of diffraction data for each composition of acetaminophen and MCC. Bottom scan is 100 % amorphous and top scan is 100 % crystalline. (inset) Zoomed in region for pure MCC, 0.2 wt%, and 0.5 wt% acetaminophen.

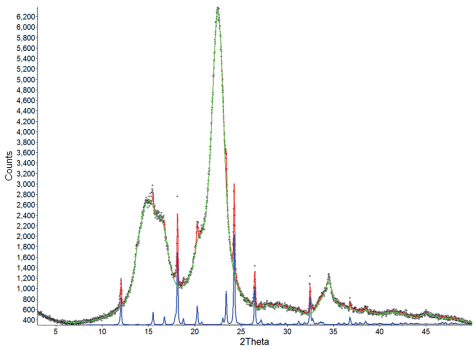

Figure 2. Whole pattern fitting for the sample with 5 wt% crystallinity. Raw data is shown as black data points. Fitted data is shown in red. The contributions from amorphous and crystalline phases are shown in green and blue, respectively.

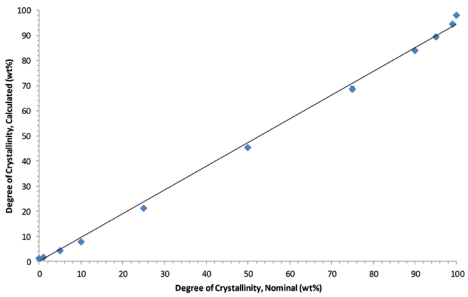

Figure 3. Comparison between nominal and calculated values for degree of crystallinity. Averages and standard deviations (shown as error bars) were calculated for specimens prepared in triplicate.

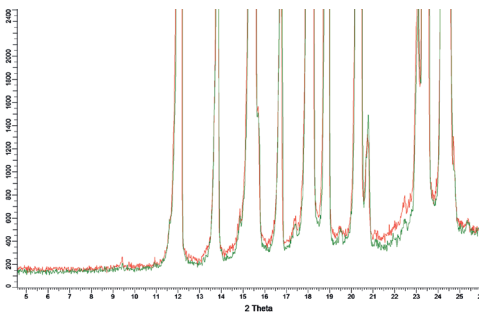

Figure 4. Diffraction data for pure API (green scan) and sample with 1 wt% amorphous (red scan). The increased baseline intensity is due to the broad scatter from the small amounts of cellulose in the sample.

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