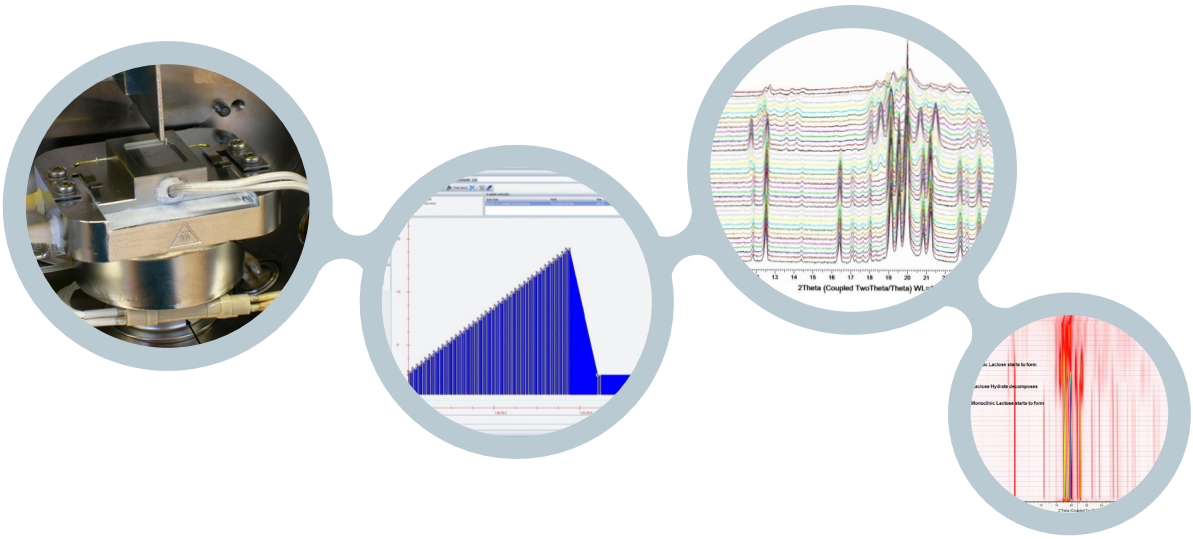

Lab Report XRD 75

Non-Ambient X-Ray Powder Diffraction (XRPD) for Pharmaceutical Samples

Summary

XRPD measurements at non-ambient conditions are frequently required for characterization of polymorphic phase transitions or to study the effect of non-ambient conditions on the stability of pharmaceutical compounds. The D8 ADVANCE with TWIN/TWIN, fast LYNXEYE XE 1D detector, and a fully integrated, software controlled, temperature/humidity stage is the ideal setup to collect and analyze this data. DIFFRAC.POLYSNAP can be used for cluster/similarity analysis of large datasets to automatically identify the phase transitions and give the most representative pattern for each phase for additional analysis. DIFFRAC.EVA can be used to identify crystalline phases using search/match and further determine critical transition temperatures with flexible data visualization options. DIFFRAC.TOPAS allows quantitative Rietveld analysis on a large set of multi-range scans to give quantitative phase abundances, lattice parameters and microstructural changes as a function of temperature.

D8 ADVANCE with TWIN/TWIN setup

Introduction

This lab report describes how to collect powder X-ray diffraction data on pharmaceutical samples using various measurement conditions in a non-ambient temperature stage. Lactose Hydrate was selected as a typical pharmaceutical excipient that is also commonly used in dairy based food applications. The benefits of different measurement geometries and the effect of different measurement conditions on data quality and the various capabilities and display options of the DIFFRAC.EVA and DIFFRAC.TOPAS software packages are demonstrated.

Instrumental Setup and Data Collection

The data were acquired using a D8 ADVANCE system equipped with a copper X-ray tube, LYNXEYE XE detector and an Anton Paar CHC+ stage, which can be used as a "dry" temperature stage, with elevated humidity levels up to 90°C, or with a cooling option.

The system was also equipped with TWIN/TWIN optics allowing a completely software-controlled switch between Bragg-Brentano geometry with either fixed or variable slits or true parallel beam geometry with a Goebel mirror and an equatorial Soller slit on the diffracted beam side. For powder samples where a flat sample surface can be prepared, Bragg-Brentano geometry is advantageous because the LYNXEYE XE detector can be used in 1D mode, resulting in much shorter measurement times and better counting statistics. For parallel beam geometry the Goebel mirror option of the primary TWIN optic is used in combination with the equatorial Soller slit of the secondary TWIN optic. True parallel beam geometry eliminates sample height errors due to thermal expansion and can be advantageous for applications where very accurate peak positions are required to determine an unknown unit cell of a single phase sample.

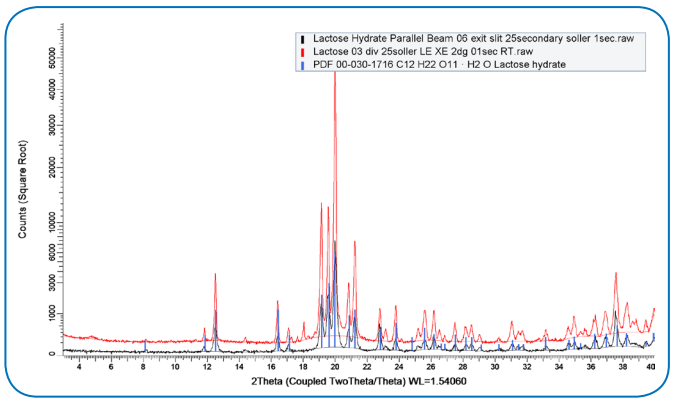

Figure 1: Comparison of Bragg-Brentano (red) (0.1s/step) and Parallel Beam (black) geometry scans (1s/step) of Lactose Hydrate.

A comparison between a scan collected in Bragg-Brentano geometry and Parallel Beam Geometry is shown in Figure 1.

The Bragg-Brentano geometry option with a divergence slit of 0.3° and 2.5° Soller slits was used to collect many temperatures scans with good counting statistics and excellent peak resolution. The sample area of the CHC stage is shown in Figure 2.

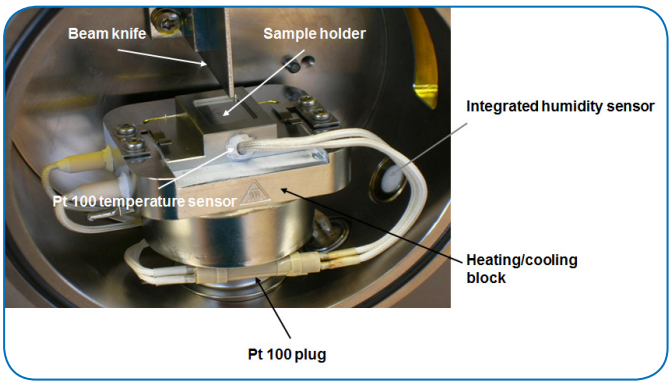

Figure 2: Sample area of the Anton Paar CHC non-ambient stage

The built-in knife edge of the non-ambient stage was set to approximately 1mm above the sample to minimize excessive air-scatter at low angles due to the proximity of the direct X-ray beam. For the same reason the opening of the position sensitive detector was reduced to 2° to be able to collect data starting at 3° 2theta and avoid scanning the low angle side of the detector through the direct beam. Initially, the correct stage height should be determined by running a standard with known peak positions in Bragg-Brentano geometry in which diffraction peaks are shifted unless the stage is at the proper height.

In this study of α-Lactose Monohydrate, fixed slits were used to keep the diffraction volume constant, which is advantageous for quantitative analysis. The sample was loaded without any further sample preparation and the sample surface was flattened using a glass slide. DIFFRAC.WIZARD was set up to collect data in dry mode without the humidity sensor and in 5° temperature increments between room temperature and 250°C. Data was collected with a method using 0.016° steps and 0.1s/step resulting in measurement times of approximately 4 minutes for a scan range between 3 and 40° 2theta. The sample stage was heated up with a rate of 5°/min and a delay of 60 s was added for every temperature step before the measurement was started.

Results

Phase identification was performed using DIFFRAC.EVA software and using the ICDD database. An overlay of a room temperature scan and a scan taken at 170°C is shown in Figure 3 with identified phases displayed as colored stick patterns.

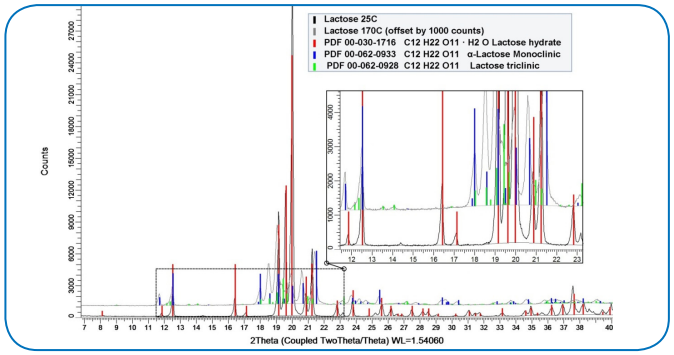

Figure 3: The room temperature scan of Lactose shows pure Lactose hydrate. The data collected at 170°C was offset for clarity and consists of a mixture of a monoclinic and triclinic form of Lactose.

The magnified insert clearly shows that the room temperature Lactose Hydrate form was completely dehydrated at 170°C and two forms of Lactose, monoclinic and triclinic, have formed. The temperature scan data can be plotted in DIFFRAC.EVA using various display options such as the waterfall display (Figure 4) where the individual scans can be offset by equal amounts in the y-direction.

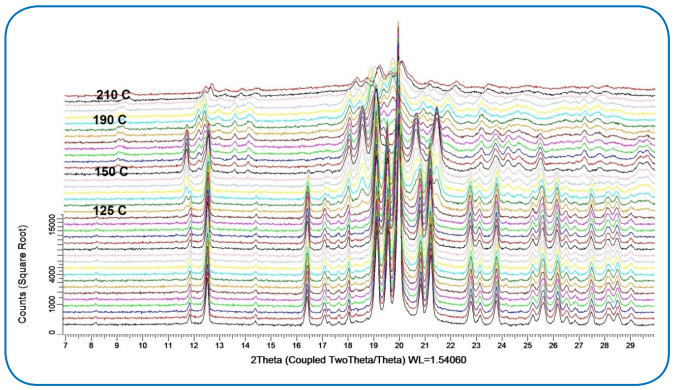

Figure 4: Waterfall display of Lactose hydrate temperature scans.

Two-dimensional plots where the temperature is displayed on the y-axis and intensities are displayed in customizable colors are ideal for visualizing phase transitions (Figure 5).

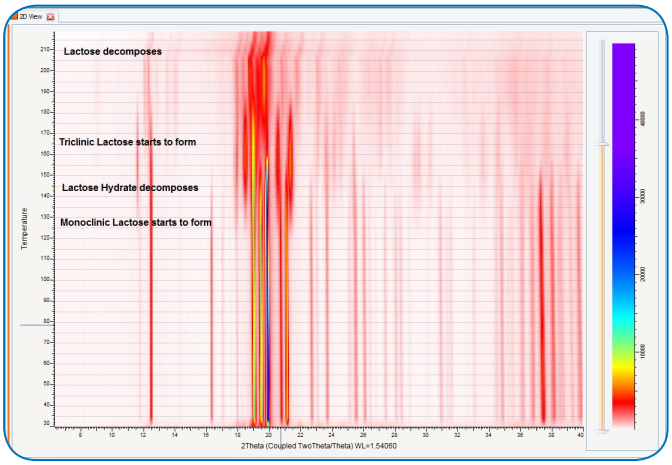

Figure 5: 2D plot in DIFFRAC.EVA of Lactose Hydrate temperature scans.

Every thin blue grid line in the plot represents a temperature where data was collected. The additional peaks occurring at approximately 120°C represent the monoclinic Lactose form that starts to form as Lactose Hydrate starts to loose water. Lactose Hydrate completely disappeared between 145°C to 150°C and a triclinic Lactose forms at approximately 170°C. The triclinic Lactose form has similar unit cell size and similar a, b and c parameters but is slightly distorted.

In case the resulting phases are not known or are not available in the search database, DIFFRAC.POLYSNAP provides the added ability to cluster a large number of data ranges and group them by similarities. Numerous display options are available and typically the critical temperature regions, where phase changes are occurring can be readily identified. The dendogram plot in Figure 6 illustrates how the various phase regions were automatically identified by the software.

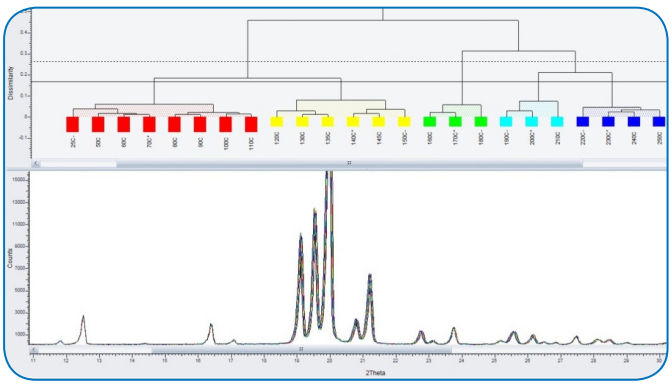

Figure 6: DIFFRAC.POLYSNAP for cluster analysis and automatically grouping scans by similarity.

Since all the crystal structures of the phase mixture were available in the ICDD database the scans could also be used for quantitative Rietveld analysis using DIFFRAC.TOPAS in which refined lattice parameters for each phase, average crystallite sizes as well as quantitative analysis of the phase mixtures can be performed for each temperature range.

An example scan collected at 170°C with the two Lactose phases quantified and individually calculated phase traces displayed is shown in Figure 7.

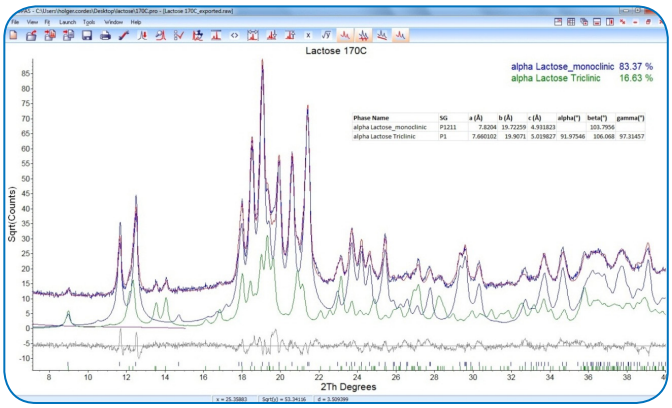

Figure 7: Quantitative Rietveld analysis in DIFFRAC.TOPAS using the Lactose Hydrate scan collected at 170°C. The blue curve shows the measured data, the red curve shows the calculated pattern. Individual traces of both Lactose forms are also shown.

The scan was scaled as Square root (counts) to highlight some of the minor peaks. In DIFFRAC.TOPAS these multi-range temperature scans can be fitted either simultaneously or sequentially and the resulting quantitative results can be plotted as a function of temperature (Figure 8).

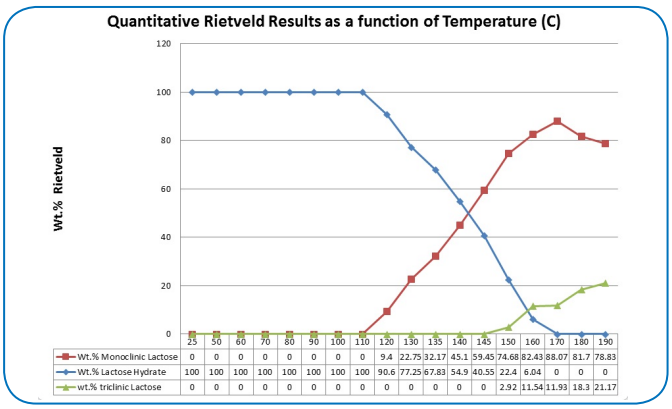

Figure 8: wt.% of each Lactose phase as a function of temperature

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