Application Note XRD 612

High-Throughput Screening with the D8 DISCOVER™ HTS Diffraction Solution

- High Speed Powder X-ray Diffraction for the Pharmaceutical Industry

Well-plates are commonly used in the development of pharmaceutical products, for example in crystallization studies or during polymorph screening. Powder X-ray diffraction (PXRD) provides a wealth of information for these studies such as phase identification and quantification of crystalline and amorphous parts, as well as crystallite size determination. Bruker's D8 DISCOVER HTS system has been specifically developed to address the challenges of well-plate screening: small sample quantities, high sample throughput and 21 CFR Part 11 compliance. Pair the high-throughput screening instrument with our powerful cluster-analysis software, and you get a solution ready to measure and analyze thousands of samples a week, accelerating drug development and improving the quality of pharmaceutical products.

Introduction

High-throughput screening (HTS) in the pharmaceutical industry has challenging requirements: thousands of samples have to be measured within a short time frame, operation should be possible 24/7, the large amount of data needs to be managed from the measurement to the analysis and the entire process should be 21 CFR Part 11 compliant [1]. And of course, the data quality should not suffer under these constraints!

HTS X-ray diffractometers operate in either reflection or transmission geometry. In reflection geometry, variations in sample amounts can lead to large peak shifts in the data as well as other sample related effects, like peak broadening. Measuring in transmission geometry largely overcomes these problems but often suffers from other data quality issues, such as high background and lower intensities.

Materials and Methods

The D8 DISCOVER HTS allows for polymorph screening by delivering high-intensity low-background data. The system is equipped with a focusing X-ray optic, a multiple-position well-plate changer, a magnetically mounted beamstop and the LYNXEYE XE-T fast linear detector.

Data were collected on a 96 position well plate in transmission geometry with a measurement time of 2.5 minutes/ well. This equates to 240 min/ plate and to approximately 600 datasets/ day. The datasets are of Rietveld quality with R_{obs} ranging from 4 – 6 %, with a representative dataset shown in figure 1. Data collection can be easily started from the well plate measurement tab by just selecting the wells and a measurement file. Different types of well plates can be predefined, with variable number of rows and columns.

Cluster Analysis

While visual inspection of PDF patterns can be useful to qualitatively compare a small number of datasets, the manual analysis of each individual dataset would be very time-intensive and costly. Analysis can be sped up considerably through the use of computer algorithms. Cluster analysis programs such as PolySNAP [2], as implemented in DIFFRAC.EVA [3], partition datasets based on their similarity using statistical methods and can handle thousands of datasets in a single run. The results from cluster analysis not only show which samples are similar (i.e. the same polymorph), but also highlight any unusual data/outliers, which could be then be investigated in more detail. The data is typically presented in the form of dendrograms

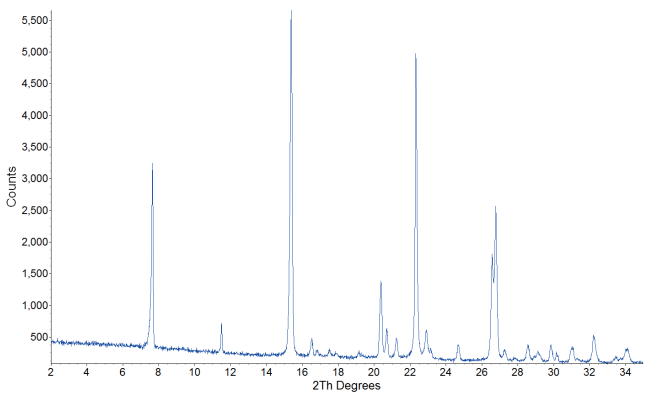

Figure 1 Representative dataset from a 2.5 min scan of a single well-plate. Note the low background and good S/N.

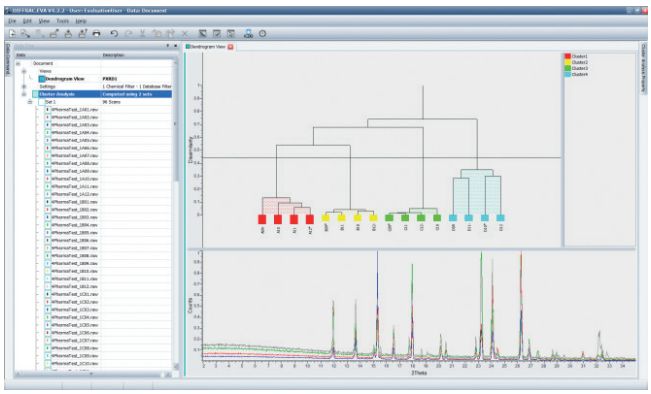

Figure 2 Dendrogram View in DIFFRAC.EVA illustrating the results of clustering. Individual scans can be selected from the dendrogram to be displayed for quick inspection.

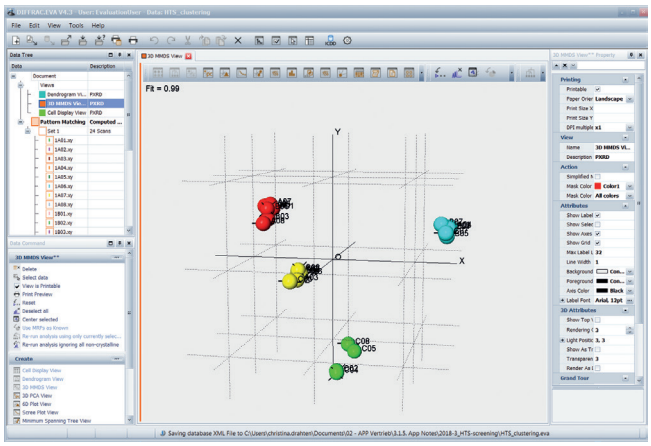

Figure 3 In the 3D MMDS View, each sphere represents one dataset. Similar datasets appear close to each other, dissimilar datasets are further apart.

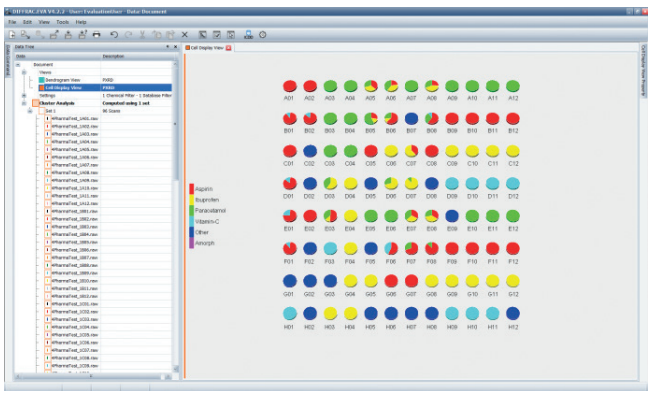

Figure 4 Cell Display with respect to known references in DIFFRAC.EVA, showing the compositions of the individual wells. The coloring is with respect to reference datasets of pure compounds.

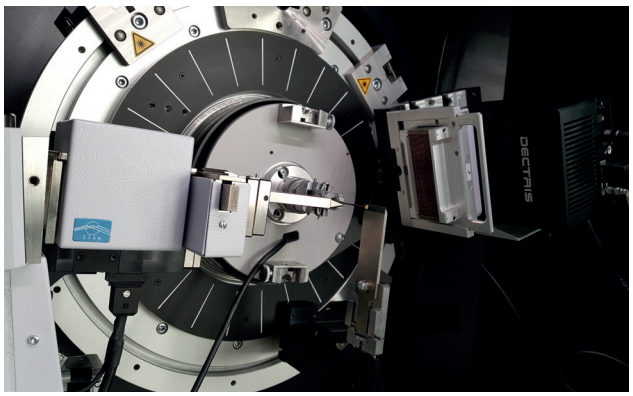

Figure 5 Capillary stage mounted in the center of the goniometer. Shown also is a UBC scatter guard to minimize air-scattering and the EIGER2 R 500K detector with panoramic Soller slits in 2θ optimized mode.

(figure 2) or as 3D MMDS views (figure 3), in which the similarity of two datasets is represented as the distance between two spheres. In addition to clustering, datasets from individual well-plates can also be compared to known references, for example those of different polymorphs of an API. The reference patterns are then scaled to the measured data to give a semi-quantitative result, which can be presented in a "Cell Display View", shown in figure 4.

Modularity

In addition to screening a large number of samples, it is sometimes necessary to characterize a polymorph in more detail and analyze its structure. On the D8 DISCOVER, changing the configuration from the high-throughput set-up to e.g. a Debye-Scherrer configuration dedicated to structural analysis takes only minutes: the capillary stage (figure 5) is mounted with a bayonet fixture at the goniometer center and requires no additional alignment.

The benefit of capillary geometry for structure analysis is that the peak intensities are accurate, since preferred orientation effects are minimized and geometry corrections are known. The data measured in this geometry is of Rietveld refinement quality (figure 6).

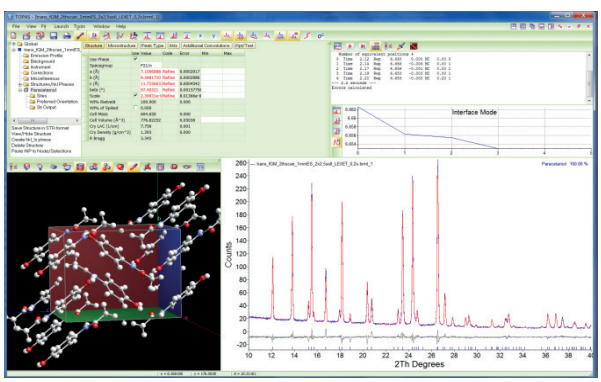

Figure 6 Rietveld fit and crystal structure to data of a paracetamol powder sample measured in capillary transmission (Debye-Scherrer) with a Cu-Goebel mirror.

Figure 7 D8 DISCOVER HTS with IμS microfocus source and VÅNTEC-500 2D detector for enhanced performance.

The system's performance and sample-throughput could be improved further using an IμS microfocus source and Montel optic together with a three-position well-plate changer and a large 2-dimensional detector, such as the VÅNTEC-500 or the EIGER2 R 500K (figure 7).

Summary

With the D8 DISCOVER™ HTS system we deliver a unique multi-purpose X-ray diffractometer platform that can be configured to meet customers' analytical requirements:

- High intensity optics shorten scan times,
- UBC collimator and beamstop reduce air scattering and improve background,
- Optional well-plate changer for highest sample throughput,
- Dedicated software interface makes starting measurements even easier,
- Snap-lock and bayonet systems allow fast and reproducible changing of configuration.

Combining the D8 DISCOVER™ HTS with powerful clustering algorithms implemented in our DIFFRAC.EVA software, or our DIFFRAC.TOPAS Rietveld software, will boost the capabilities of any lab working in formulation- and drug-development.

21 CFR Part 11 compliance

Diffraction data can be acquired and analyzed in cGxP/ 21 CFR Part11 regulated environments with the DIFFRAC.SUITE PART11 solution, which includes the MEASUREMENT.CENTER, DIFFRAC.EVA and DIFFRAC.DQUANT software packages. Our Part 11 solution offers all tools required to make compliant work safer, easier and faster: Multi-user environments with secure system log-ins, automatic audit trail generation and tamper proof data files provide and guarantee authenticity, integrity and confidentiality of electronic records and signatures.

A white paper detailing BRUKER AXS 21 CFR Part 11 policy as well as the implementation of the 21 CFR Part11 requirements in DIFFRAC.SUITE Part11 is available on request [1].

References

[1] Bruker AXS, (2016). White Paper DiFFRAC.SUITE 21 CFR Part 11 Policy (Document number DOC-M88-EXX241)

[2] Barr, G., Dong, W., Gilmore, C.J, J. (2009). Appl. Cryst., 42, 965-974.

[3] Bruker AXS, (2016). DIFFFRAC. EVA, Bruker AXS, 2010-2017, Version 4.2 (Computer Software).

[4] https://www.alcaminow.com/blog/scientist-spotlight-april-2017

Testimonial

"As innovators in early-phase pharmaceutical development, Alcami requires fast screening on minimal amounts of material, to obtain a broad overview of the polymorphic behavior and be decisive about which crystalline form to take forward. The implementation of the Bruker D8 DISCOVER HTS™ x-ray powder diffraction system in our unique solid state development workflow considerably accelerated our high resolution, high-throughput analytical capabilities. We identify, characterize, and report hundreds of unique forms daily with the use of this integrated 96 well-plate screening platform. The D8 DISCOVER HTS allows us to select the single phase, pure form with optimal physical and chemical properties and implement it into the manufacturing process within a few days. Alcami's Center of Excellence for Solid State Chemistry houses this crucial form selection system."– Edwin Aret, Ph.D., Principal Scientist Solid State Chemistry at Alcami.

Figure 7 Instrument configuration at Alcami [4].

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