APPLICATION NOTE

X-Ray Powder Diffraction — A powerful tool in pharmaceutical analysis

BY DETLEF BECKERS

Within the pharmaceutical industry, X-ray powder diffraction (XRPD) is an accepted methodology as part of new product registrations and patent applications. Indeed, an indexed XRPD pattern or single crystal structure is required to secure a patent. As a result, many pharmaceutical companies have invested heavily in XRPD systems.

However, the role of XRPD is by no means limited to issues of patent protection. Recent advances in hardware and software technology, specifically the development of fast X-ray detectors, have significantly reduced measurement times and improved detection limits. This means XRPD can now generate valuable data in many areas of drug discovery, development and manufacture. Many companies are already realising the benefits, while others are only now beginning to appreciate the technique's potential.

The suitability of XRPD for such a wide range of applications is largely due to the many different types of analysis that can be carried out on a single diffractometer. Flexible systems (such as PANalytical's X'Pert PRO MPD) enable the addition of appropriate modules so that the diffractometer can be quickly and easily reconfigured, from a high-end system for the crystallographic researcher to a 'work-horse' for high throughput routine applications.

The growing role of XRPD also owes much to a number of key characteristics — the non-destructive nature of the technique, its ability to detect crystalline impurities (in some cases down to 0.05%), the capability to analyse final dosage forms and its utility in the detection of changes in morphology during production. This article focuses on these last two, illustrating firstly how the application of the technique to the analysis of final dosage forms allows the integrity of the active pharmaceutical ingredient (API) to be determined in the finished product. Secondly, it examines how the ability to detect morphological changes during production helps ensure consistent behaviour of the finished product. The examples discussed are all based on the use of a PANalytical X'Pert PRO MPD system (*Figure 1*).

Analysis of final dosage forms

Using XRPD, it is possible to analyse the actual percentages of an active ingredient in the final dosage form of a drug, together with the percentages of any crystalline or amorphous excipients used. In this particular example, different shapes of Indometacin tablets as well as different Indometacin particle sizes were tested. Different diffraction geometries and/or data collection strategies were used to find the right combination for optimal results. Three different optical configurations were tested (*Figure 2*).

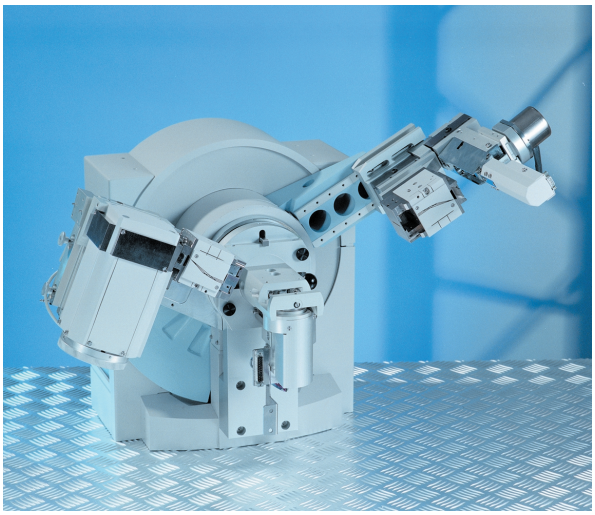

Figure 1 The X'Pert PRO MPD X-ray diffraction system in parallel beam mirror-mirror geometry.

Both flat and curved Indometacin tablets of approximately 10 mm diameter and 4 mm thickness and with mean Indometacin particle sizes of 20 µm and 3 µm, were investigated. Of the various non-active excipients, only lactose and magnesium stearate showed crystalline diffraction patterns; the others (cornstarch, PVP, PVP-CL and SiO_2) were amorphous.

For all the tablet morphologies studied, a methodology was developed that allowed an API content determination with better than ± 0.5% accuracy — a significantly higher degree of accuracy than is legally required in most countries for this type of tablet. For example, in the case of curved tablets with small Indometacin particles, the most accurate results were achieved using the mirror-mirror geometry. *Figure 3* shows the calibration line generated with this set-up. By exchanging the mirror on the diffracted beam side with PANalytical's Real Time Multiple

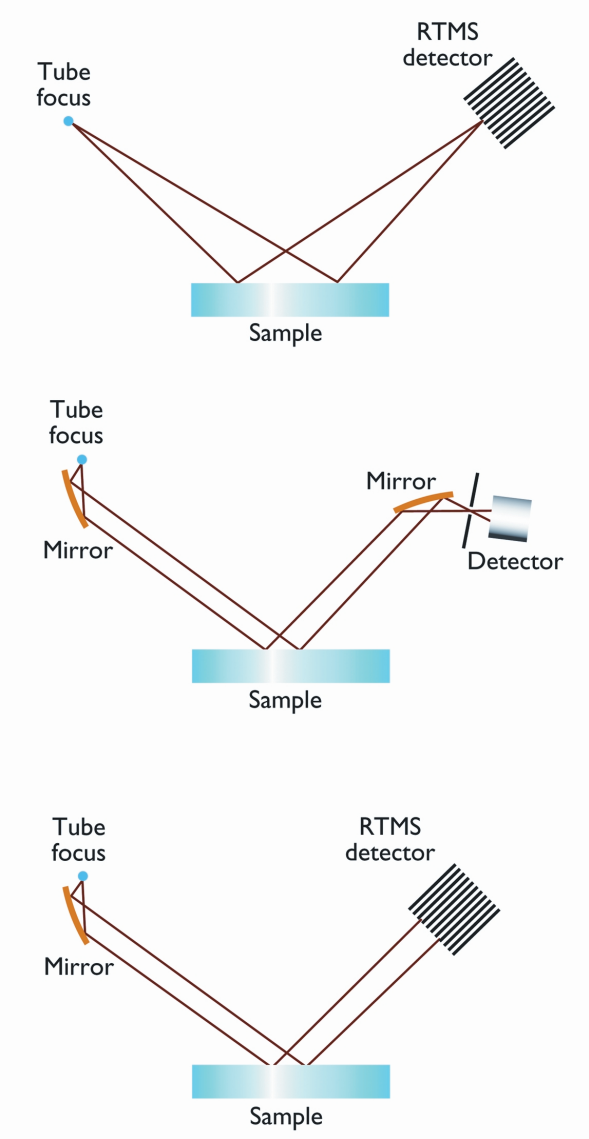

Figure 2 Schematic representations of the different optical configurations used: (a) Bragg-Brentano geometry; (b) Mirror-Mirror geometry; (c) Mirror-X'Celerator geometry.

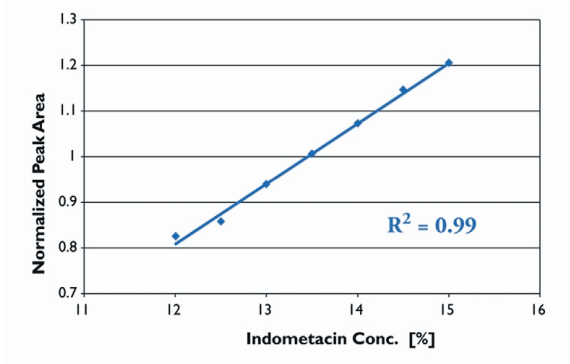

Figure 3 Calibration line of the mirror-mirror measurements on curved tablets with 3 µm Indometacin mean particle size.

Table 1 The best geometries and data collection strategies for the different tablet morphologies studied.

Tablet Shape	Indometacin Particle Size	Best Geometry & Data Collection Strategy
Flat	3 µm	Bragg-Brentano geometry and single reflection area determination
Flat	20 µm	Mirror-mirror geometry and Rietveld refinement of the data
Curved	3 µm	Mirror-RTMS detector geometry and single reflection area determination
Curved	20 µm	Mirror-mirror geometry and Rietveld refinement of the data

Strip (RTMS) X'Celerator detector, measurements become significantly faster (less than a minute) with only slightly less accuracy.

Taking the data collection time into account, the best geometries and data collection strategies for the different tablet morphologies studied are summarised in *Table 1*. For most of the morphologies, the XRD measurements showed better accuracy than comparative UV measurements.

Detecting changes in morphology

Any change in the crystal morphology of active ingredients or excipients can influence a drug's bioavailability. Stability profiles, particularly with respect to the environmental conditions likely to be experienced during production and storage, are essential for the complete analysis of pharmaceutical compounds. XRPD is particularly good for the systematic analysis of stability issues because it allows *in situ* measurements under defined environmental conditions. By fitting the X'Pert PRO MPD system with PANalytical's PreFIX Temperature Controlled Humidity Chamber, X-ray diffraction can be carried out with simultaneous control of both temperature and humidity.

In the following example, the stability of magnesium stearate (a lubricant widely used in pharmaceutical tablets) is

investigated. As magnesium stearate is always also on the surface of the tablet, any change in its morphology, resulting from changes in temperature or humidity, can have a serious impact on the production process or on the storage conditions for a drug.

Commercially available magnesium stearate was analysed under various ambient conditions using the X'Pert PRO MPD fitted with its PreFIX Temperature Controlled Humidity Chamber, to cycle the relative humidity from low to high values at constant temperature and to change the temperature under dry conditions. Before each measurement, a stabilisation time of approximately 90 minutes was allowed to enable the formation of an equilibrium state. Results were compared with those determined by conventional thermogravimetric analyses (TGA) and by differential scanning calorimetry (DSC).

Both TGA and DSC identified two phase transitions in dry nitrogen atmosphere — the first stage of mass loss was at approximately 75°C and the second at approximately 100°C. X-ray diffraction identified the same two transitions but because of its capacity for *in situ* measurements at different relative humidities, it also allowed (by varying the relative humidity at different temperatures) the identification of two additional forms, each with absolutely reproducible and stable conditions. In general, it appeared that the form present under certain conditions depended on the previous treatment and process history. The exact conditions for the phase transitions observed could not be determined by other methods.

Conclusion

The complexity of modern drug formulations demands a multi-disciplinary approach to their development. XRPD allows *in situ* characterisation of the entire formulation, correlating the physicochemical and crystallographic structure to the observed stability and drug release profiles. XRPD is proving to be a powerful technique for pharmaceutical analyses, with the potential to solve many analytical problems and unambiguously reveal structural details.

Author's details and contact information

Dr Detlef Beckers is Market Segment Manager, Pharmaceuticals XRD, at PANalytical BV, Lelyweg 1, 7602 EA, PO Box 13, 7600 AA Almelo, The Netherlands; Tel: +31 546 534444;
www.panalytical.com