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Increasing Application of X-Ray Powder Diffraction in the Pharmaceutical Industry

by Brian Litteer and Detlef Beckers

X-ray powder diffraction (XRPD) has recently been propelled to the forefront as an analytical tool in the pharmaceutical industry for a wide range of applications. New advances in hardware and software, specifically the development of fast X-ray detectors, have significantly reduced measurement times and improved detection limits. As a result, this well-established technique is now generating critical data for users in many areas of drug discovery, development, and manufacture.

XRPD is one technique that has the greatest potential to solve a wide variety of analytical problems and reveal structural details that were previously impossible to observe. The advantages of XRPD over other commonly used techniques include its capacity for:

- Nondestructive testing—in keeping with the emphasis on exploring the real-life properties of a sample without the need to dissolve, digest, or destroy it in order to obtain essential information
- Analysis of final dosage forms—allowing the integrity of the active pharmaceutical ingredient (API) to be determined in the final finished product
- Detection of crystalline impurities—enabling the pharmaceutical scientist to detect impurities down to 0.05%
- Detection of changes in morphology during production—ensuring the consistent processing behavior of the finished product.

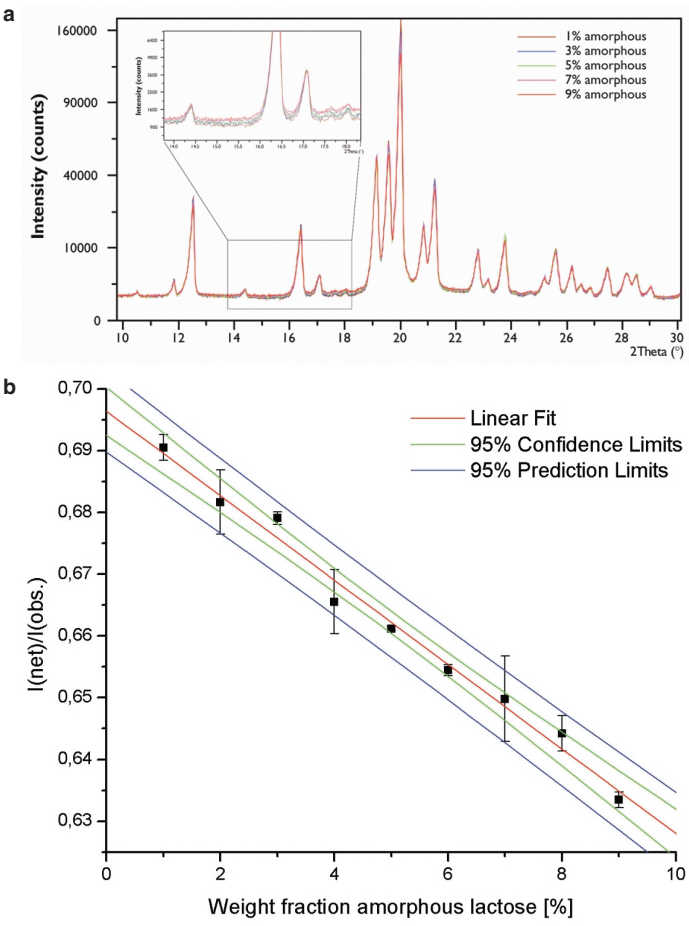

Figure 1 XRPD pattern of crystalline lactose with varying contents of amorphous lactose. The calibration curve shows the detection limit for the 0–10% amorphous phase to be about 1%.

XRPD also has the advantage of being an accepted methodology for new product registrations and patent applications; an indexed XRPD pattern or single-crystal structure is required to secure a patent. Due to the high number of polymorph phases that can often be synthesized with similar efficacy to that of a patented ingredient or drug product, issues of patent infringement and generic manufacturing are of paramount concern. Many pharmaceutical companies have consequently invested heavily in XRPD systems. Such companies are now in a position to realize the full potential of their systems for different types of analyses. Indeed, certain systems such as the X'Pert PRO MPD (PANalytical, Almelo, The Netherlands) are virtually unlimited in their capacity to adapt to new measurement techniques, made necessary because of the development of novel materials and the

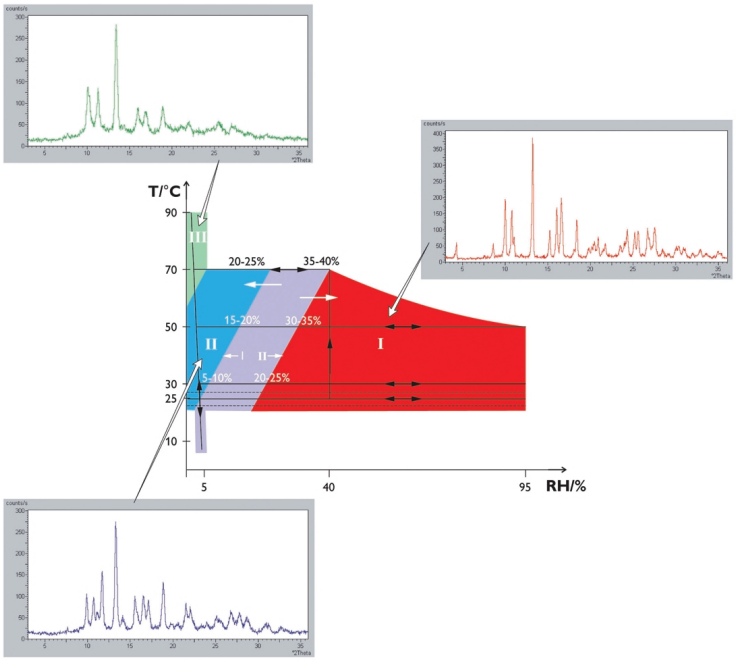

Figure 2 *Temperature–humidity phase diagram for 4-epi-oxytetracycline.*

need to answer new questions. Because it is based on factory prealigned optics and stages (the PreFIX concept), the X'Pert PRO MPD diffractometer can be quickly reconfigured from a high-end system for the crystallographic researcher to a workhorse for the laboratory technician.

Some of the many ways in which XRPD is currently being used in the pharmaceutical industry are illustrated by the following examples.

R&D applications

The most fundamental, yet crucially important, application of XRPD is in the identification or fingerprinting of crystalline phases, with different crystal structures giving rise to distinct powder diffraction patterns. The qualitative characterization of materials in this manner finds applications in many areas, including quality control and polymorph screening.

Crystallography and crystal structure determination

Although the crystal structure of a material can be determined from a general powder diffraction pattern, in most cases it is sufficient simply to identify the lattice type and dimensions of the unit cell for this new material (indexing). This form of analysis is particularly useful for characterizing alternative forms or polymorphs of registered drugs where patents are about to expire. In addition to this technique, information such as displacement parameters, coordinates of atoms within the unit cell, site occupancy, and preferred orientation can be obtained.

Phase analysis and polymorph screening

XRPD is especially valuable for distinguishing different phases or polymorphs by their unique diffraction pattern. Since the choice of polymorph can be important in relation to properties such as solubility, bioavailability, and stability, the quest to produce and characterize all accessible polymorphs of a given drug substance has become an area that attracts intense activity. Since a new crystalline form of an API could be patented as a new pharmaceutical product, the search for every polymorph of a target compound is an invaluable step toward patent protection.

Crystallinity determination

XRPD is used successfully in the determination of percent crystallinity (*Figure 1*), where the volume concentration of, for example, an amorphous filler to a crystalline active matrix is measured within a drug's dosage form. Percent crystallinity can influence a drug's processing behavior as well as its pharmacological performance.

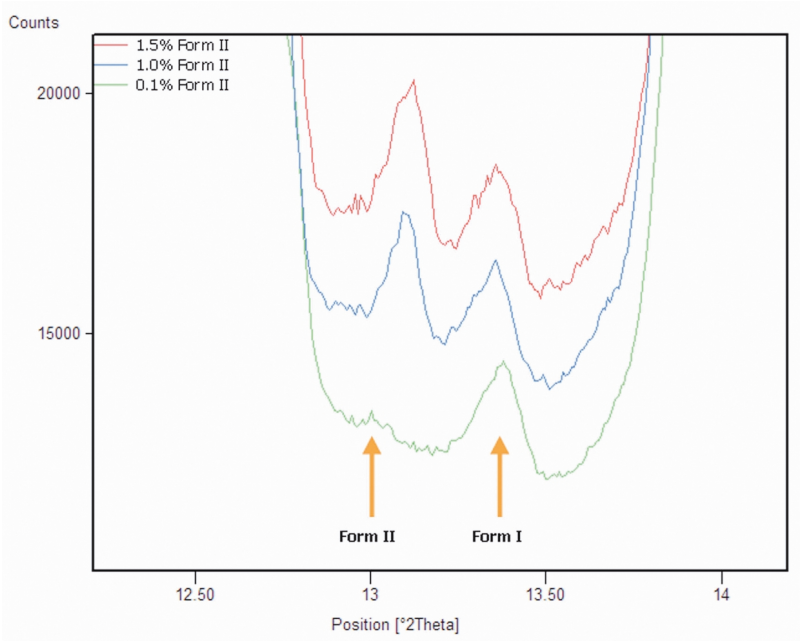

Figure 3 *Measurement of mixtures of two azithromycin forms with different concentrations showing a detection limit for Form II of around 0.1%.*

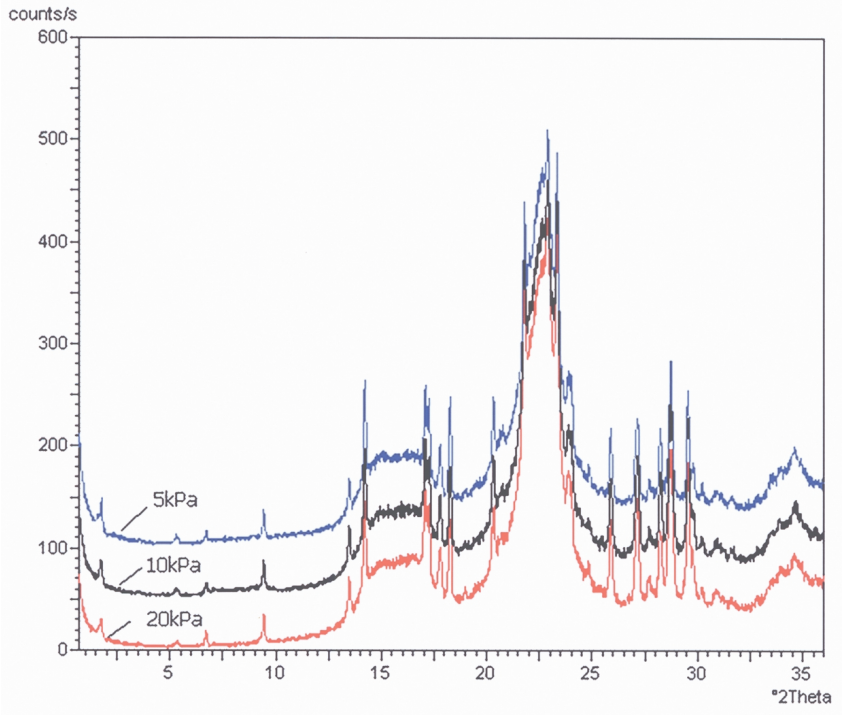

Figure 4 *Monitoring the influence of tableting pressure on the properties of finished tablets. By determining the range of pressure associated with stable structural parameters, it was possible to assign the optimal pressure for the drug's target dissolution rate.*

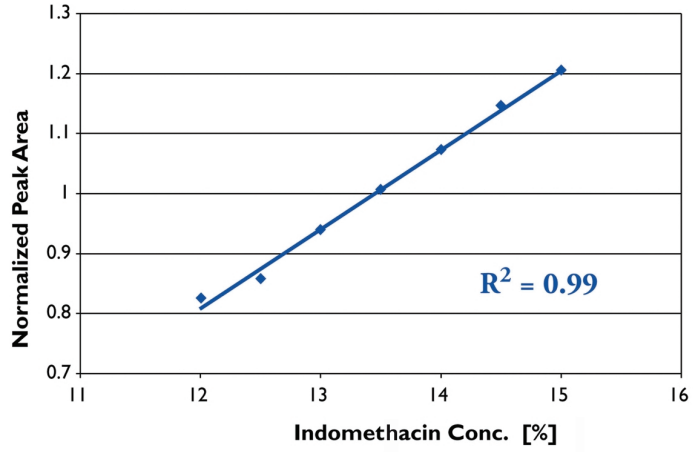

Figure 5 *Calibration line for the API quantification in finished indomethacin tablets. A methodology was developed that allowed an API content determination within ±0.5 accuracy (a significantly higher degree of accuracy than that which is legally required in most countries).*

Compatibility studies

The nondestructive nature of XRPD makes it an ideal tool for systematic drug–excipient compatibility studies in preformulation. Careful selection of the excipients along with the systematic evaluation of drug–excipient interactions is essential to achieve consistent release and bioavailability and to avoid unexpected formulation stability problems in later stages of formulation development.

Manufacturing and production

The ability of XRPD to detect and quantify the presence of any polymorphic contamination, the level of crystallographic changes, and the active ingredient in the final dosage form allows the technique to be used to monitor and improve production efficiency and cost. Once the active ingredient of a pharmaceutical product is in its final dosage form, the morphology parameters measured by X-ray diffraction can be related directly to the final drug performance.

Control of ingredients

XRPD is well suited for monitoring the crystal morphology of active ingredients or the excipients (*Figure 3*). This is important because any change in the morphology of fillers or in the crystalline state of active ingredients in the final product, as a result of the manufacturing process, can influence a drug's bioavailability.

With the X'Celerator (PANalytical), the lower limit of detection for minority phases has been reduced considerably, in some cases even down to 0.05%.

Stability studies

In situ powder diffraction studies carried out as a function of temperature and/or relative humidity can provide a direct means of characterizing the stability of a pharmaceutical compound and the occurrence of hydration/dehydration processes (*Figure 2*). Such nonambient diffraction experiments can be performed at any stage of the drug development process.

Process control

The ability of XRPD to determine structural parameters, together with its capacity for nondestructive analysis, makes it useful in diverse applications. One such example is the use of XRPD in determining the optimal range of tableting pressure. This allows manufacturers to track the crystallographic structure of an API to ensure that the finished tablet achieves its target dissolution rate (*Figure 4*).

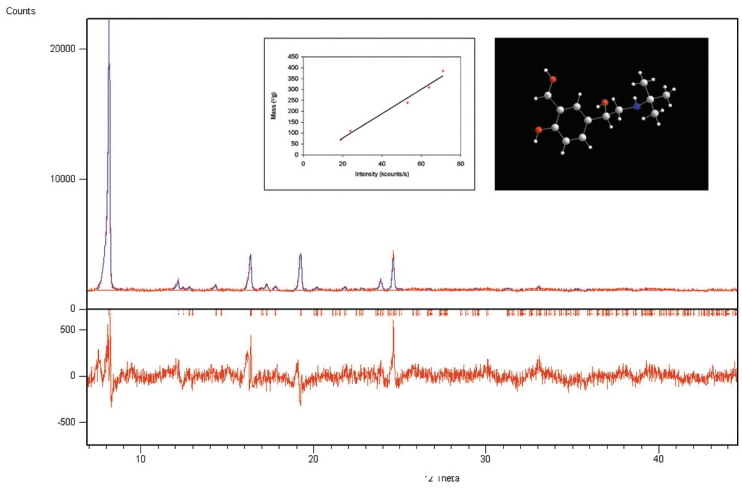

Figure 6 Identification and quantification of Salbutamol® (GlaxoSmithKline, Middlesex, U.K.) delivered by a pressurized metered dose inhaler.

Batch/dosage uniformity

Because XRPD allows materials to be investigated directly under the conditions in which they are used in specific applications, it is valuable for monitoring batch/dosage uniformity. It is possible to analyze the actual percentages of individual active ingredients in the final dosage form of a drug in situ (*Figure 5*), together with the percentage of any amorphous or crystalline packing ingredients used. XRPD can even be used to identify and quantify the small amounts of crystalline aerosol drug delivered by a pressurized metered dose inhaler. For the example shown in *Figure 6*, high-quality data were obtained without any special sample preparation method or equipment.

Conclusion

The level of complexity seen in today's drug formulations requires a multidisciplinary approach to their development. One of the great strengths of XRPD lies in its capacity for in situ characterization of the entire formulation, correlating the physicochemical and crystallographic structure to the observed stability and drug release profiles. It is also proving to be of great value for polymorph screening, nonambient analysis, and indexing. It is not surprising, therefore, that this powerful technique is fast becoming a key analytical tool utilized throughout the pharmaceutical industry.

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