with its standard deviation. The mean values for x_{10} and x_{90} must not deviate by more than 5 per cent from the certified range of values. Below 10 μm, these values must be doubled.

Although the use of materials consisting of spherical particles is preferable, non-spherical particles may also be employed. Preferably, these particles have certified or typical values from laser diffraction analyses performed according to an agreed, detailed operating procedure. The use of reference values from methods other than laser diffraction may cause a significant bias. The reason for this bias is that the different principles inherent in the various methods may lead to different sphere-equivalent diameters for the same non-spherical particle.

In addition to the certified reference materials mentioned above, product samples of typical composition and particle-size distribution for a specified class of products can also be used, provided their particle-size distribution has proven to be stable over time. The results must comply with previously determined data, with the same precision and bias as for the certified reference material.

Verification of the system. In addition to the calibration, the performance of the apparatus must be verified at regular time intervals or as frequently as appropriate. This can be undertaken using any suitable material as mentioned in the previous paragraph.

The verification of the system is based on the concept that the equipment, electronics, software and analytical operations constitute an integral system, which can be evaluated as an entity. Thus the entire measurement procedure is examined, including sample collection, sample dispersion, sample transport through the measuring zone, and the measurement and deconvolution procedure. It is essential that the total operational procedure is fully described.

In general, unless otherwise specified in the individual monograph, the response of a laser diffraction instrument is considered to meet the requirements if the x_{50} value does not deviate by more than 10 per cent from the range of values of the reference material, i.e. the mean value together with its standard deviation. If optionally the values at the sides of the distribution are evaluated (e.g. x_{10} and x_{90}), then these values must not deviate by more than 15 per cent from the certified range of values. Below 10 μm, these values must be doubled.

01/2008:20933

2.9.33. CHARACTERISATION OF CRYSTALLINE AND PARTIALLY CRYSTALLINE SOLIDS BY X-RAY POWDER DIFFRACTION (XRPD)

Every crystalline phase of a given substance produces a characteristic X-ray diffraction pattern.

Diffraction patterns can be obtained from a randomly oriented crystalline powder composed of crystallites or crystal fragments of finite size. Essentially 3 types of information can be derived from a powder diffraction pattern: angular position of diffraction lines (depending on geometry and size of the unit cell); intensities of diffraction lines (depending mainly on atom type and arrangement, and particle orientation within the sample); and diffraction line profiles (depending on instrumental resolution, crystallite size, strain and specimen thickness).

Experiments giving angular positions and intensities of lines can be used for applications such as qualitative phase analysis (for example, identification of crystalline phases) and quantitative phase analysis of crystalline materials. An estimate of the amorphous and crystalline fractions(6) can also be made.

In addition, analysis of line-profile broadening can also allow the determination of crystallite size (size of coherently scattering domains) and micro-strain.

The X-ray powder diffraction (XRPD) method provides an advantage over other means of analysis in that it is usually non-destructive in nature (specimen preparation is usually limited to grinding to ensure a randomly oriented sample). XRPD investigations can also be carried out under *in situ* conditions on specimens exposed to non-ambient conditions, such as low or high temperature and humidity.

PRINCIPLE

X-ray diffraction results from the interaction between X-rays and electron clouds of atoms. Depending on the atomic arrangement, interferences arise from the scattered X-rays. These interferences are constructive when the path difference between 2 diffracted X-ray waves differs by an integral number of wavelengths. This selective condition is described by the Bragg equation, also called Bragg's law (see Figure 2.9.33.-1):

$$2d_{\mathrm{hkl}}\sin\theta_{\mathrm{hkl}} = \mathrm{n}\lambda$$

The wavelength λ of the X-rays is of the same order of magnitude as the distance between successive crystal lattice planes, or d_{hkl} (also called 'd-spacings'). θ_{hkl} is the angle between the incident ray and the family of lattice planes, and $\sin\theta_{\mathrm{hkl}}$ is inversely proportional to the distance between successive crystal planes or d-spacings.

The direction and spacing of the planes with reference to the unit cell axes are defined by the Miller indices {*hkl*}. These indices are the reciprocals, reduced to the next-lower integer, of the intercepts that a plane makes with the unit cell axes. The unit cell dimensions are given by the spacings *a*, *b* and *c* and the angles between them, α, β, and γ.

The interplanar spacing for a specified set of parallel *hkl* planes is denoted by d_{hkl}. Each such family of planes may show higher orders of diffraction where the *d* values for the related families of planes n*h*, n*k*, n*l* are diminished by the factor 1/n (n being an integer: 2,3,4, etc.).

Every set of planes throughout a crystal has a corresponding Bragg diffraction angle, θ_{hkl}, associated with it (for a specific wavelength λ).

A powder specimen is assumed to be polycrystalline so that at any angle θ_{hkl} there are always crystallites in an orientation allowing diffraction according to Bragg's law(7). For a given X-ray wavelength, the positions of the diffraction peaks (also referred to as 'lines', 'reflections' or 'Bragg reflections') are characteristic of the crystal lattice (d-spacings), their theoretical intensities depend on the crystallographic unit cell content (nature and positions of atoms), and the line profiles on the perfection and extent of the crystal lattice. Under these conditions the diffraction peak has a finite

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(6) There are many other applications of the X-ray powder diffraction technique that can be applied to crystalline pharmaceutical substances such as: determination of crystal structures, refinement of crystal structures, determination of crystallographic purity of crystalline phases, characterisation of crystallographic texture, etc. These applications are not described in this chapter.

(7) An 'ideal' powder for diffraction experiments consists of a large number of small, randomly oriented spherical crystallites (coherently diffracting crystalline domains). If this number is sufficiently large, there are always enough crystallites in any diffracting orientation to give reproducible diffraction patterns. To obtain a precise measurement of the intensity of diffracted X-rays, it is recommended that the crystallite size be small, i.e. typically 10 μm or less, depending on the characteristics of the specimen (X-ray absorption, shape, etc.) and the diffraction geometry.

intensity arising from atomic arrangement, type of atoms, thermal motion and structural imperfections, as well as from instrument characteristics.

The main characteristics of diffraction line profiles are 2θ position, peak height, peak area and shape (characterised by, for example, peak width or asymmetry, analytical function, empirical representation). An example of the type of powder patterns obtained for 5 different solid phases of a substance(8) are shown in Figure 2.9.33.-2.

In addition to the diffraction peaks, an X-ray diffraction experiment also generates a more-or-less uniform background, upon which the peaks are superimposed. Besides specimen preparation, other factors contribute to the background, for instance the sample holder, diffuse scattering from air and equipment, other instrumental parameters such as detector noise, general radiation from the X-ray tube, etc. The peak to background ratio can be increased by minimising background and by choosing prolonged exposure times.

APPARATUS

Instrument set-up. X-ray diffraction experiments are usually performed using powder diffractometers or powder cameras.

A powder diffractometer generally comprises 5 main parts: an X-ray source; incident beam optics, which may perform monochromatisation, filtering, collimation and/or focusing of the beam; a goniometer; diffraction beam optics, which may perform monochromatisation, filtering, collimation and focusing or parallelising of the beam; and a detector. Data collection and data processing systems are also required and are generally included in current diffraction measurement equipment.

Depending on the type of analysis to be performed (phase identification, quantitative analysis, lattice parameters determination, etc.), different XRPD instrument configurations and performance levels are required. The simplest instruments used to measure powder patterns are powder cameras. Of the various camera types available, there are 3 commonly employed instruments: the Debye-Scherrer, the Gandolfi and the Guinier focusing cameras. Replacement of photographic film as the detection method by photon detectors has led to the design of diffractometers in which the geometric arrangement of the optics is not truly focusing but parafocusing, such as in the Bragg-Brentano geometry. The Bragg-Brentano parafocusing configuration is currently the most widely used and is therefore briefly described here.

A given instrument may provide a horizontal or vertical $\theta/2\theta$ geometry or a vertical θ/θ geometry. For both geometries, the incident X-ray beam forms an angle θ with the specimen plane and the diffracted X-ray beam forms an angle 2θ with the direction of the incident X-ray beam (an angle θ with the specimen plane). The basic geometric arrangement is represented in Figure 2.9.33.-3. The divergent beam of radiation from the X-ray tube (the so-called 'primary beam') passes through the parallel plate collimators and a divergence slit assembly and illuminates the flat surface of the specimen. All the rays diffracted by suitably oriented crystallites in the specimen at an angle 2θ converge to a line at the receiving slit. A second set of parallel plate collimators and a scatter slit may be placed either behind or before the receiving slit. The axes of the line focus and of the receiving slit are at equal distances from the axis of the goniometer. The X-ray quanta are counted by a radiation detector, usually a scintillation counter, a sealed-gas proportional counter, or a position-sensitive or solid-state detector. The receiving slit assembly and the detector are coupled together and move tangentially to the focusing circle. For $\theta/2\theta$ scans the goniometer rotates the specimen about the same axis as that of the detector, but at half the rotational speed, in a $\theta/2\theta$ motion. The surface of the specimen thus remains tangential to the focusing circle. The parallel plate collimator limits the axial divergence of the beam and hence partially controls the shape of the diffracted line profile.

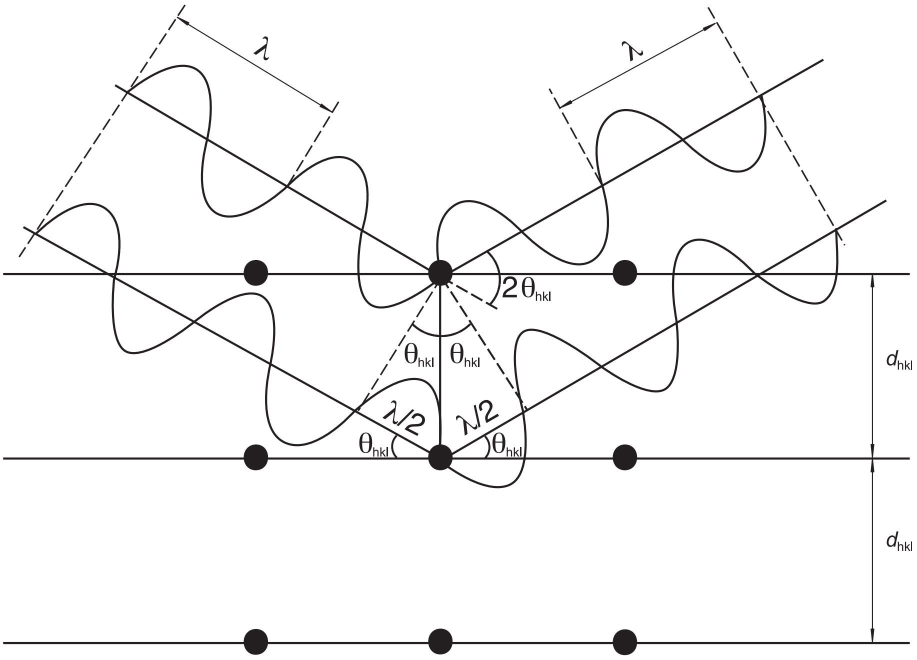

Figure 2.9.33.-1. – *Diffraction of X-rays by a crystal according to Bragg's law*

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(8) These diffraction patterns were collected on a Siemens D500 diffractometer (Bragg-Brentano geometry) using a pure monochromatic CuKα1 radiation ($\lambda = 0.1540598$ nm) selected with an incident-beam curved-crystal germanium monochromator with asymmetric focusing (short focal distance 124 mm, long focal distance 216 mm). Detection of signal was achieved using a scintillation detector. To reduce the effect of transparency of the specimens, a thin layer of powder was deposited on an oriented single crystal silicon wafer. The alignment of the diffractometer was checked by means of the OOI reflections of fluorophlogopite mica (NIST SRM 675). The zero error was estimated as less than 0.01° (2θ). The instrumental resolution function of the set-up exhibits a shallow minimum of 0.065° (2θ) at about 40° (2θ) and has twice this value at 130° (2θ). For each phase, the diffraction pattern was scanned with the same step length of 0.02° (2θ), but with different fixed counting times [form A: 30 s; form B: 48 s; form C: 48 s; form D: 40 s; amorphous phase: 10 s].

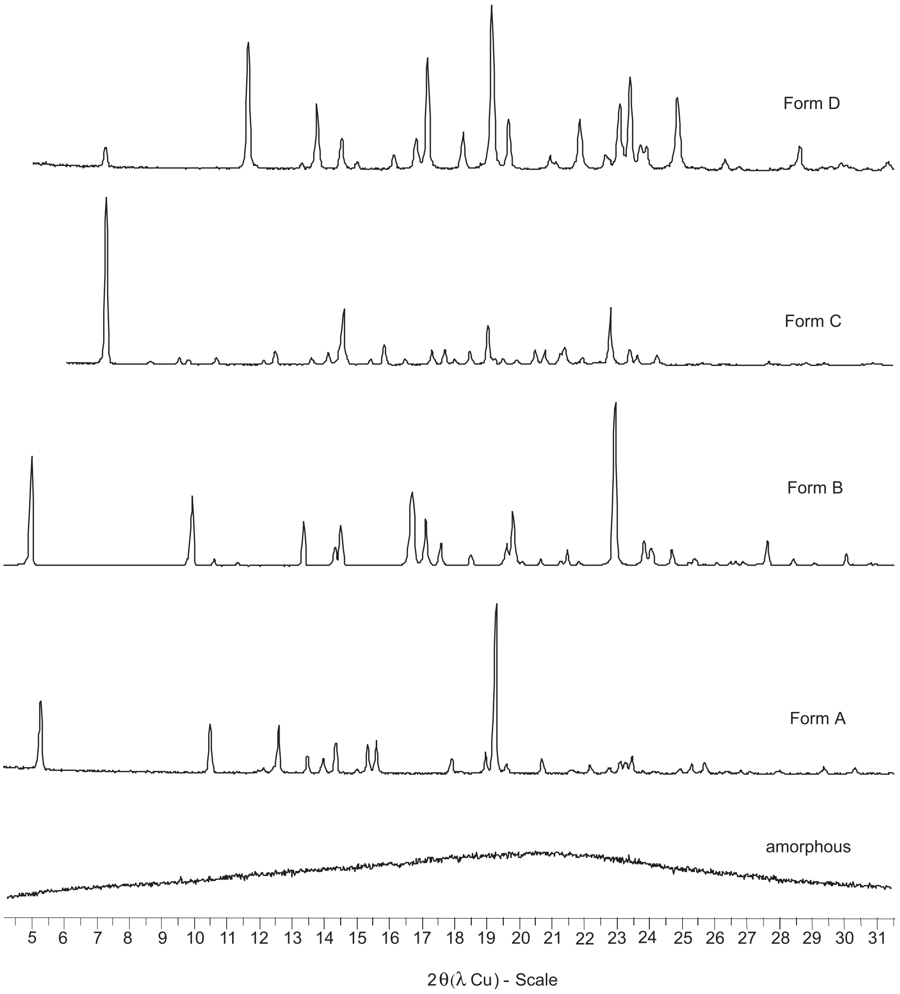


Figure 2.9.33.-2. – *X-ray powder patterns collected for 5 different solid phases of a substance (the intensities are normalised)*

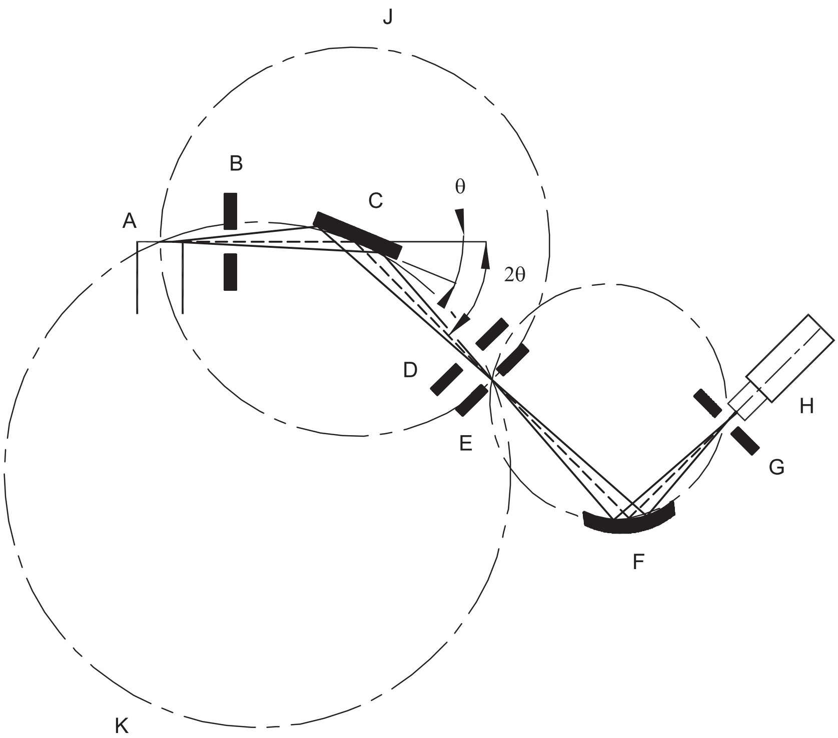
A Bragg-Brentano diffractometer may also be used in transmission mode. The advantage with this technology is to lessen the effects due to preferred orientation. A capillary of about 0.5-2 mm thickness can also be used for small sample amounts.

X-ray radiation. In the laboratory, X-rays are obtained by bombarding a metal anode with electrons emitted by the thermionic effect and accelerated in a strong electric field (using a high-voltage generator). Most of the kinetic energy of the electrons is converted to heat, which limits the power of the tubes and requires efficient anode cooling. A 20- to 30-fold increase in brilliance can be obtained using rotating anodes and by using X-ray optics. Alternatively, X-ray photons may be produced in a large-scale facility (synchrotron).

The spectrum emitted by an X-ray tube operating at sufficient voltage consists of a continuous background of polychromatic radiation and additional characteristic radiation that depends on the type of anode. Only this characteristic radiation is used in X-ray diffraction experiments. The principal radiation sources utilised for X-ray diffraction are vacuum tubes utilising copper, molybdenum, iron, cobalt or chromium as anodes; copper, molybdenum or cobalt X-rays are employed most commonly for organic substances (the use of cobalt anodes can be especially preferred to separate distinct X-ray lines). The choice of radiation to be used depends on the absorption characteristics of the specimen and possible fluorescence by atoms present in the specimen. The wavelengths used in powder diffraction generally correspond to the K_α radiation from the anode. Consequently, it is advantageous to make the X-ray beam 'monochromatic' by eliminating all the other components of the emission spectrum. This can be partly obtained using K_β filters, i.e. metal filters selected as having an absorption edge between the K_α and K_β wavelengths emitted by the tube.

Such a filter is usually inserted between the X-ray tube and the specimen. Another, more-and-more-commonly used way to obtain a monochromatic X-ray beam is via a large monochromator crystal (usually referred to as a 'monochromator'). This crystal is placed before or behind the specimen and diffracts the different characteristic peaks of the X-ray beam (i.e. K_α and K_β) at different angles, so that only one of them may be selected to enter into the detector. It is even possible to separate $K_{\alpha1}$ and $K_{\alpha2}$ radiations by using a specialised monochromator. Unfortunately, the gain in getting a monochromatic beam by using a filter or a monochromator is counteracted by a loss in intensity. Another way of separating K_α and K_β wavelengths is by using curved X-rays mirrors that can simultaneously monochromate and focus or parallelise the X-ray beam.

RADIATION PROTECTION. Exposure of any part of the human body to X-rays can be injurious to health. It is therefore essential that whenever X-ray equipment is used, adequate precautions are taken to protect the operator and any other person in the vicinity. Recommended practice for radiation protection as well as limits for the levels of X-radiation exposure are those established by national legislation in each country. If there are no official



A. X-ray tube
B. divergence slit
C. sample
D. anti-diffusion slit
E. receiving slit
F. monochromator
G. detector receiving slit
H. detector
J. diffractometer circle
K. focusing circle

Figure 2.9.33.-3. – *Geometric arrangement of the Bragg-Brentano parafocusing geometry*

regulations or recommendations in a country, the latest recommendations of the International Commission on Radiological Protection should be applied.

SPECIMEN PREPARATION AND MOUNTING

The preparation of the powdered material and mounting of the specimen in a suitable holder are critical steps in many analytical methods, and are particularly so for X-ray powder diffraction analysis, since they can greatly affect the quality of the data to be collected(9). The main sources of error due to specimen preparation and mounting are briefly discussed here for instruments in Bragg-Brentano parafocusing geometry.

SPECIMEN PREPARATION

In general, the morphology of many crystalline particles tends to give a specimen that exhibits some degree of preferred orientation in the specimen holder. This is particularly evident for needle-like or plate-like crystals when size reduction yields finer needles or platelets. Preferred orientation in the specimen influences the intensities of various reflections, so that some are more intense and others are less intense, compared to what would be expected from a completely random specimen. Several techniques can be employed to improve randomness in the orientation of crystallites (and therefore to minimise preferred orientation), but further reduction of particle size is often the best and simplest approach. The optimum number of crystallites depends on the diffractometer geometry, the required resolution and the specimen attenuation of the X-ray beam. In some cases, particle sizes as large as 50 μm will provide satisfactory results in phase identification. For quantitative XRPD analysis, it is often recommended that the specimen have coherent domains (crystallites) with a size less than 10 μm. However, excessive milling (crystallite sizes less than approximately 0.5 μm) may cause line broadening and significant changes to the sample itself such as:

- specimen contamination by particles abraded from the milling instruments (mortar, pestle, balls, etc.);
- reduced degree of crystallinity;
- solid-state transition to another polymorph;
- chemical decomposition;
- introduction of internal stress;
- solid-state reactions.

Therefore, it is advisable to compare the diffraction pattern of the non-ground specimen with that corresponding to a specimen of smaller particle size (e.g. a milled specimen). If the X-ray powder pattern obtained is of adequate quality considering its intended use, then grinding may not be required.

It should be noted that if a sample contains more than one phase and if sieving is used to isolate particles to a specific size, the initial composition may be altered.

SPECIMEN MOUNTING

Effect of specimen displacement. A specimen surface that is offset by *D* with reference to the diffractometer rotation axis causes systematic errors that are very difficult to avoid entirely, resulting in absolute $D\cdot\cos\theta$ shifts(10) in 2θ positions (typically of the order of 0.01° in 2θ at low angles ($\cos\theta \simeq 1$) for a displacement D = 15 μm) and asymmetric broadening of the profile towards low 2θ values. Use of an appropriate internal standard allows the detection and correction of this effect simultaneously with that arising from specimen transparency. This is by far the largest source of errors in data collected on well-aligned diffractometers.

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(9) Similarly, changes in the specimen can occur during data collection in the case of a non-equilibrium specimen (temperature, humidity).

(10) Note that a goniometer zero alignment shift would result in constant shift on all observed 2θ-line positions, in other words, the whole diffraction pattern is in this case translated by an offset of Z° in 2θ.

Effect of specimen thickness and transparency. When the XRPD method in reflection mode is applied, it is often preferable to work with specimens of 'infinite thickness'. This means that, for a given mass attenuation and bulk density of the specimen and a given range of diffraction angles, the diffracted intensity from the back of the specimen is negligible. For quantitative analysis, to ensure that the diffracted intensity is at least 99.9 per cent of the maximum attainable by increasing the specimen thickness *t*, the thickness must be at least:

$$t = 3.45 \sin\theta / \mu'\rho'$$

- μ' = mass attenuation coefficient (often referred to as the mass absorption coefficient);
- ρ' = bulk density of the specimen.

μ' is additive for the mass attenuation coefficients of the individual elements that constitute the material. It is independent of the physical state of the material.

For specimens with low attenuation (such as organic materials where the linear absorption coefficients are very small), the diffracted intensity appears to originate from a position below the surface resulting in line shifts and changes in line widths. This effect, referred to as the transparency effect, is large for thick specimens with low attenuation and can lead to angular errors of as much as a tenth of a degree. For such specimens, a precise measurement of line positions can be carried out on a specimen that is as thin as possible, but which still gives acceptable diffraction intensities. It is advisable to use a non-diffracting substrate (zero background holder), for example a plate of single crystalline silicon cut parallel to the 510 lattice planes(11). One advantage of the transmission mode is that problems with sample height and specimen transparency are less important.

The use of an appropriate internal standard allows the detection and correction of this effect simultaneously with that arising from specimen displacement.

DIFFRACTOMETER ALIGNMENT

Goniometers and the corresponding incident and diffracted X-ray beam optics have many mechanical parts that need adjustment. The degree of alignment or misalignment directly influences the quality of the results of an XRPD investigation. Therefore, the different components of the diffractometer must be carefully adjusted (optical and mechanical systems, etc.) to adequately minimise systematic errors, while optimising the intensities received by the detector. The search for maximum intensity and maximum resolution is always antagonistic when aligning a diffractometer. Hence, the best compromise must be sought whilst performing the alignment procedure. There are many different configurations and each supplier's equipment requires specific alignment procedures.

CALIBRATION, PERFORMANCE TESTING AND MONITORING OF DIFFRACTOMETERS

To establish the magnitude of potential errors in the diffractometer, a calibration curve, using a proper calibrant, whether internal or external, can be prepared after the alignment of the diffractometer for each of the following:

- angular calibration;
- intensity calibration;
- line shape calibration.

The calibration is usually performed using certified reference standards (choice is dependent on type of analysis). The overall diffractometer performance should be tested and monitored periodically using working standards and/or reference standards (depending on the type of analysis).

QUALITATIVE PHASE ANALYSIS (IDENTIFICATION OF PHASES)

The identification of the phase composition of an unknown sample by XRPD is usually based on the visual or computer-assisted comparison of a portion of its X-ray powder pattern to the experimental or calculated pattern of a reference material. Ideally, these reference patterns are collected on well-characterised single-phase specimens. This approach makes it possible in most cases to identify a crystalline substance by its 2θ diffraction angles or d-spacings and by its relative intensities. The computer-aided comparison of the diffraction pattern of the unknown sample to the comparison data can be based either on a more-or-less extended 2θ-range of the whole diffraction pattern or on a set of reduced data derived from the pattern. For example, the list of d-spacings and normalised intensities I_{norm}, a so-called (d, I_{norm})-list extracted from the pattern, is the crystallographic fingerprint of the material, and can be compared to (d, I_{norm})-lists of single-phase samples compiled in databases.

For most organic crystals, when using Cu K_α radiation, it is appropriate to record the diffraction pattern in a 2θ-range from as near 0° as possible to at least 40°. The agreement in the 2θ-diffraction angles between specimen and reference is within 0.1° for the same crystal form, while relative intensities between specimen and reference may vary considerably due to preferred orientation effects. For other types of samples (e.g. inorganic salts), it may be necessary to extend the 2θ-region scanned to well beyond 40°. It is generally sufficient to scan past the 10 strongest reflections identified in single phase X-ray powder diffraction database files.

It is sometimes difficult or even impossible to identify phases in the following cases:

- non-crystallised or amorphous substances;
- the components to be identified are present in low mass fractions of the analyte amounts (generally less than 10 per cent *m/m*);
- pronounced preferred orientation effects;
- the phase has not been filed in the database used;
- formation of solid solutions;
- presence of disordered structures that alter the unit cell;
- the specimen comprises too many phases;
- presence of lattice deformations;
- structural similarity of different phases.

QUANTITATIVE PHASE ANALYSIS

If the sample under investigation is a mixture of 2 or more known phases, of which not more than 1 is amorphous, the percentage (by volume or by mass) of each crystalline phase and of the amorphous phase can, in many cases, be determined. Quantitative phase analysis can be based on the integrated intensities, on the peak heights of several individual diffraction lines(12), or on the full pattern. These integrated intensities, peak heights or full-pattern data points are compared to the corresponding values of reference materials. These reference materials shall be single-phase

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(11) In the case of a thin specimen with low attenuation, accurate measurements of line positions can be made with focusing diffractometer configurations in either transmission or reflection geometry. Accurate measurements of line positions on specimens with low attenuation are preferably made using diffractometers with parallel beam optics. This helps to reduce the effects of specimen thickness.

(12) If the crystal structures of all components are known, the Rietveld method can be used to quantify them with good accuracy. If the crystal structures of the components are not known, the Pawley method or Partial Least Squares (PLS) method can be used.

or a mixture of known phases. The difficulties encountered during quantitative analysis are due to specimen preparation (the accuracy and precision of the results require in particular homogeneity of all phases and a suitable particle size distribution in each phase) and to matrix effects.

MATRIX EFFECTS

Matrix-effects corrections consist of eliminating or estimating the absorption phenomenon, except in the case of mixtures of polymorphic samples in which all phases have the same absorption coefficients. However, it should be noted that in the case of organic systems, such effects are rather limited, hence corrections can in many such cases be neglected.

POLYMORPHIC SAMPLES

For a sample composed of 2 polymorphic phases *a* and *b*, the following relationship can be written for the fraction F_a of phase *a*:

$$F_a = \frac{1}{1 + K\,(I_b/I_a)}$$

The fraction is derived by measuring the intensity ratio between the 2 phases, knowing the value of the constant *K*. *K* is the ratio of the absolute intensities of the 2 pure polymorphic phases I_{oa}/I_{ob}. Its value can be determined by measuring standard samples.

METHODS USING A STANDARD

The most commonly used methods for quantitative analysis are:

- the ‘external standard method’;
- the ‘internal standard method’;
- the ‘spiking method’ (often also called the ‘standard addition method’).

The ‘external standard method’ is the most general method and consists of comparing the X-ray diffraction pattern of the mixture, or the respective line intensities, with those measured in a reference mixture or with the theoretical intensities of a structural model, if it is fully known.

To limit errors due to matrix effects, an internal reference material with crystallite size and X-ray absorption coefficient comparable to those of the components of the sample, and with a diffraction pattern that does not overlap at all that of the sample to be analysed, can be used. A known quantity of this reference material is added to the sample to be analysed and to each of the reference mixtures. Under these conditions, a linear relationship between line intensity and concentration exists. This application, called the ‘internal standard method’, requires a precise measurement of diffraction intensities.

In the ‘spiking method’ (or ‘standard addition method’), some of the pure phase *a* is added to the mixture containing the unknown concentration of *a*. Multiple additions are made to prepare an intensity-versus-concentration plot in which the negative *x* intercept is the concentration of the phase *a* in the original sample.

ESTIMATE OF THE AMORPHOUS AND CRYSTALLINE FRACTIONS

In a mixture of crystalline and amorphous phases, the crystalline and amorphous fractions can be estimated in several ways. The choice of the method used depends on the nature of the sample:

- if the sample consists of crystalline fractions and an amorphous fraction of different chemical compositions, the amounts of each of the individual crystalline phases may be estimated using appropriate standard substances as described above; the amorphous fraction is then deduced indirectly by subtraction;
- if the sample consists of one amorphous and one crystalline fraction, either as a 1-phase or a 2-phase mixture, with the same elemental composition, the amount of the crystalline phase (‘the degree of crystallinity’) can be estimated by measuring 3 areas of the diffractogram:

A = total area of the peaks arising from diffraction from the crystalline fraction of the sample;

B = total area below area A;

C = background area (due to air scattering, fluorescence, equipment, etc).

When these areas have been measured, the degree of crystallinity can be roughly estimated using the following formula:

$$\%\ \text{crystallinity} = 100A/(A + B - C)$$

It is noteworthy that this method does not yield absolute degree-of-crystallinity values and hence is generally used for comparative purposes only.

More sophisticated methods are also available, such as the Ruland method.

OBTAINING STRUCTURAL INFORMATION FROM XRPD PATTERN

Powder X-ray diffraction has been an important standard tool for many decades for identifying and characterising crystalline materials. Recent developments in XRPD methods also allow some relevant structural information to be extracted from accurate XRPD data, as briefly described below.

Determination of lattice parameters. In an X-ray powder diffraction pattern, each line can be associated with a d-spacing and the Miller indices {*hkl*} of the corresponding family or families of planes, if the unit cell of the lattice is known (crystal system, Bravais lattice, approximate lattice parameters). The d-spacings measured from the diffractogram are related to the lattice parameters by geometric relations involving the Miller indices of the planes considered. If the material studied consists of crystalline phases for which the corresponding lattice parameters are approximately known, the lattice parameters can be refined by a least squares method using the whole powder pattern or a list of indexed d-spacings.

If the material studied consists of an unknown crystalline phase, the determination of the lattice parameters requires *ab initio* indexing of the XRPD pattern. This results in Miller indices being attributed to each line of the observed diffractogram. It can be accomplished by comparison with a reference pattern or by automatic indexing programs. Whether the mathematical solution found by an automatic indexing program is the true crystallographic unit cell or only a ‘pseudo-cell’ depends on the completeness and uncertainty of the experimental data and on the size and symmetry of the unit cell.

Structure solution. In general, the determination of crystal structures is performed from X-ray diffraction data obtained using single crystals. However, when substances cannot be prepared in the appropriate pure crystallographic form, this conventional approach cannot be employed. Recent developments based on high-resolution X-ray diffraction techniques using powders have led to significant progress in crystal structure determination. Crystal structures can sometimes be determined from sufficiently well-resolved powder diffraction data by applying trial and error, Patterson methods and/or direct methods. However, crystal structure analysis of organic crystals is a challenging task, since the lattice parameters are comparatively large, the symmetry is low and the scattering properties are normally very low. For any given crystalline form of a substance, knowledge of the crystal structure allows the calculation of the corresponding XRPD pattern, thereby providing a 'preferred-orientation-free' reference XRPD pattern, which can then be used for batch comparisons.

Refinement of crystal structures. Refinement of crystal structures consists of minimising the difference between the intensities of the experimental diffraction pattern of a crystalline substance and the intensities calculated from a structural model sufficiently close to the true structure. The minimisation is carried out using a least squares method (or other procedure) to refine the structural parameters of the model (unit cell dimensions, atom co-ordinates, site occupancies) and the atomic displacement parameters, until a satisfactory agreement between calculated and observed intensities is obtained. This application requires accurate diffraction data (intensity and position), containing sufficient information to estimate the structural parameters concerned. Structure refinement is most often carried out by Rietveld-type methods, but the integrated intensity method can also be applied.

01/2008:20936

2.9.36. POWDER FLOW

The widespread use of powders in the pharmaceutical industry has generated a variety of methods for characterising powder flow. Not surprisingly, scores of references appear in the pharmaceutical literature, attempting to correlate the various measures of powder flow to manufacturing properties. The development of such a variety of test methods was inevitable; powder behavior is multifaceted and thus complicates the effort to characterise powder flow.

The purpose of this chapter is to review the methods for characterising powder flow that have appeared most frequently in the pharmaceutical literature. In addition, while it is clear that no single and simple test method can adequately characterise the flow properties of pharmaceutical powders, this chapter proposes the standardisation of test methods that may be valuable during pharmaceutical development.

4 commonly reported methods for testing powder flow are:

- angle of repose,
- compressibility index or Hausner ratio,
- flow rate through an orifice,
- shear cell.

In addition, numerous variations of each of these basic methods are available. Given the number of test methods and variations, standardising the test methodology, where possible, would be advantageous.

With this goal in mind, the most frequently used methods are discussed below. Important experimental considerations are identified and recommendations are made regarding standardisation of the methods. In general, any method of measuring powder flow must be practical, useful, reproducible and sensitive, and must yield meaningful results. It bears repeating that no simple powder flow method will adequately or completely characterise the wide range of flow properties experienced in the pharmaceutical industry. An appropriate strategy may well be the use of multiple standardised test methods to characterise the various aspects of powder flow as needed by the pharmaceutical scientist.

ANGLE OF REPOSE

The angle of repose has been used in several branches of science to characterise the flow properties of solids. Angle of repose is a characteristic related to interparticulate friction, or resistance to movement between particles. Angle of repose test results are reported to be very dependent upon the method used. Experimental difficulties arise due to segregation of material and consolidation or aeration of the powder as the cone is formed. Despite its difficulties, the method continues to be used in the pharmaceutical industry, and a number of examples demonstrating its value in predicting manufacturing problems appear in the literature.

The angle of repose is the constant, three-dimensional angle (relative to the horizontal base) assumed by a cone-like pile of material formed by any of several different methods, described briefly below.

Basic methods for angle of repose

A variety of angle of repose test methods are described in the literature. The most common methods for determining the static angle of repose can be classified based on 2 important experimental variables:

- the height of the 'funnel' through which the powder passes may be fixed relative to the base, or the height may be varied as the pile forms;
- the base upon which the pile forms may be of fixed diameter or the diameter of the powder cone may be allowed to vary as the pile forms.

Variations in angle of repose methods

Variations of the above methods have also been used to some extent in the pharmaceutical literature:

- *drained angle of repose*: this is determined by allowing an excess quantity of material positioned above a fixed diameter base to "drain" from the container. Formation of a cone of powder on the fixed diameter base allows determination of the drained angle of repose;
- *dynamic angle of repose*: this is determined by filling a cylinder (with a clear, flat cover on one end) and rotating it at a specified speed. The dynamic angle of repose is the angle (relative to the horizontal) formed by the flowing powder. The internal angle of kinetic friction is defined by the plane separating those particles sliding down the top layer of the powder and those particles that are rotating with the drum (with roughened surface).

General scale of flowability for angle of repose

While there is some variation in the qualitative description of powder flow using the angle of repose, much of the pharmaceutical literature appears to be consistent with the classification by Carr(1), which is shown in Table 2.9.36.-1. There are examples in the literature of formulations with an angle of repose in the range of 40-50 degrees that manufactured satisfactorily. When the angle of repose exceeds 50 degrees, the flow is rarely acceptable for manufacturing purposes.