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Quantification of olanzapine polymorphs using powder X-ray diffraction technique

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Abstract

Accurate quantification of crystalline phases present in drug materials is becoming increasingly important, due to stringent regulatory concerns about polymorph characterization and control in drug substances and products. In the present study, a quantification method for polymorphic forms of olanzapine (OLZ) has been developed using powder X-ray diffraction (PXRD). Preferred orientation has been reported to be the major source of error in PXRD analysis, therefore, prior to development of a quantification method, pure polymorphic forms (I and II) of different size ranges were analyzed. Preferred orientation effect was found to decrease on using sieve fraction BSS # 120/240 for form I. In order to obtain good peak resolution in optimum time, the step time and step size were varied so as to optimize the scan rate. Among the five combinations selected, step size of 0.05° with step time of 5 s demonstrated identification of four characteristic peaks of form I in form II in 62 min. A calibration curve was constructed in the range of 0–100% (w/w) using the characteristic peak of form I at 18.48° 2θ (I/I_0 78.8%). The PXRD assay was reproducible and precise and displayed a LOD of 0.40% (w/w) and LOQ of 1.22% (w/w). Validation results showed excellent correlation between actual and predicted concentrations with R^2 0.9999.

Keywords: Olanzapine; Powder X-ray diffraction; Quantitative analysis of polymorphs; Preferred orientation; Polymorphism

1. Introduction

Pharmaceuticals may exist in various solid forms featuring different physical and chemical properties. Probable differences in the bioavailability of these polymorphic forms have provoked imposition of stringent regulatory requirements on identification and specification of polymorphs for a particular drug substance as part of the quality assurance process [1]. The International Conference on Harmonization (ICH) Q6A guidelines provide guidance on when and how polymorphic forms should be monitored and controlled [2]. For stability concerns the most stable form is normally employed in the formulation. However, the metastable polymorphic form may be inadvertently generated due to the stress produced by temperature, mechanical treatment and moisture during processing or storage of the drug product [3]. Contamination by these polymorphic impurities can adversely influence both the stability and performance of the final product. It has thus become imperative to develop accurate quantification methods for such low level physical impurities of separate crystalline phase, in pharmaceuticals. Moreover, USFDA regulations require development of validated methods for analysis of proportion of forms throughout the retest period and shelf life of the drug substance and product [4].

Multitude of analytical techniques like infrared (mid- and near-IR), FT-Raman, solid-state NMR spectroscopy, thermal methods, and powder X-ray diffraction (PXRD) have been reported to be used for determination of polymorphic content in mixtures or amorphous content in crystalline materials, to levels as low as 1% [5]. However, advantages like uniqueness of X-ray powder pattern of compounds, non-destructive nature, simplicity and measurement at room temperature of both the drug substance and product, make PXRD the most preferred and extensively used technique for quantification of polymor-

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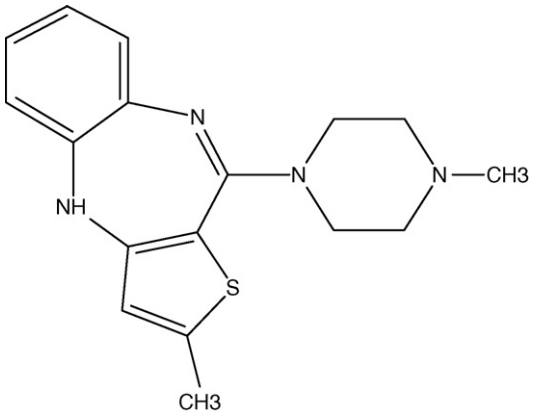

Fig. 1. Chemical structure of OLZ.

phic mixtures. One of the critical factors in developing any assay for solid-state forms is the generation of authentic and validated calibration curve, which reproduces actual material that will be assayed in future [6]. This requires an accurate measurement of intensity, height and area of diffraction lines, but these decisive parameters are strongly influenced by potential source of errors due to inherent nature of the sample, instrument and sample preparation parameters [7]. The latter two parameters can be optimized in order to minimize the errors associated with measurement of vital outputs. Various sample preparation parameters like type of sample holder, rotation of sample, particle size, powder packing, and preferred orientation effects, have been demonstrated to be critical [8]. This study focuses on dual objectives of (i) optimization of sample preparation and instrument parameters and (ii) development of an accurate, precise and reproducible PXRD quantification method for polymorphic forms of olanzapine (OLZ), an antipsychotic drug.

OLZ, chemically (2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-b]) (Fig. 1) [9], can crystallize in more than 25 crystalline forms of which seven are pharmaceutically relevant [10]. Form II is designated as the most stable anhydrous polymorphic form and is used in the dosage form. On the other hand form I is metastable and unsuitable for commercial use as it discolors in the presence of air and such a color change during storage can be particularly tormenting for psychotic patients [11]. Polymorphic forms I and II, the most commonly occurring forms, show very minor differences in their diffractograms and hence, there is a need to develop a sensitive method for quantification. A quantification method has been developed using PXRD, validated and checked for assay errors.

2. Experimental section

2.1. Materials

OLZ form I and form II were gifted by Jubilant Organosys, Uttar Pradesh (India). Potassium bromide (FTIR grade) was purchased from Aldrich Chemical Company Ltd., Milwaukee (USA). All materials were used as received with out any further purification.

2.2. Methods

2.2.1. Solid-state characterization of OLZ polymorphs

2.2.1.1. Microscopy. The particle characteristics of OLZ were assessed by optical microscopy using Leica DMLP polarized light microscope (Leica Microsystems Wetzlar GmbH, Wetzlar, Germany). Photomicrographs were acquired using Leica DC 300 camera and analyzed using Leica IM 50 (Version 1.20) software.

2.2.1.2. Thermal analysis.

- *Hot stage microscopy (HSM).* Thermal transitions in OLZ polymorphs were studied using Leica LMW Hot stage and Leica DMLP polarized microscope. The samples were heated on the hot stage and observed under normal and polarized light.
- *Differential scanning calorimetry (DSC).* DSC analysis was performed using a Mettler Toledo 821e DSC (Mettler Toledo, Switzerland) operating with Version 5.1 of Star^e software using (4–6 mg) sample in aluminium pans with pierced lids at heating rate of 10 °C min^{-1} and nitrogen purge at 80 ml min^{-1}.
- *Thermogravimetric analysis (TGA).* The mass loss of the sample as a function of temperature was determined using a Mettler Toledo 851e TGA/SDTA (Mettler Toledo, Switzerland). OLZ form I and II were placed in open alumina crucibles and heated at a rate of 10 °C min^{-1} under a nitrogen purge (20 ml min^{-1}).

2.2.1.3. Fourier transform infrared spectroscopy (FTIR). The FTIR spectra OLZ form I and II were recorded on a FTIR multiscope spectrophotometer (Perkin Elmer, UK) equipped with spectrum v3.02 software using KBr pellet method. The spectrum for each sample (an average of 16 co-added scans) was recorded over the 450–4000 cm^{-1} spectral region with a resolution of 4 cm^{-1}.

2.2.1.4. Powder X-ray diffraction (PXRD). PXRD patterns of samples were recorded at room temperature on Bruker's D8 Advance diffractometer (Karlsruhe, West Germany) Cu Kα radiation (1.54 Å), at 40 kV, 40 mA passing through nickel filter with divergence slit (0.5°), antiscattering slit (0.5°), and receiving slit (1 mm). The diffractometer was equipped with a 2θ compensating slit, and was calibrated for accuracy of peak positions with silicon pellet. Samples were subjected to X-ray powder diffraction analysis in continuous mode with a step size of 0.01° and step time of 1 s over an angular range of 3–40° 2θ. Five hundred milligrams powder mixture was loaded in a 25 mm holder made of poly methyl methacrylate (PMMA) and pressed by a clean glass slide to ensure coplanarity of the powder surface with the surface of the holder. The sample holder was rotated in a plane parallel to its surface at 30 rpm during the measurements. Obtained diffractograms were analyzed with DIFFRAC^{plus} EVA (ver. 9.0) diffraction software.

Table 1
Different step time and step size for optimization of scan rate

Combination	Step time (s)	Step size (°)	Scan rate (° 2θ/min)	Recording time (min)	No. of identifiable peaks
A	0.5	0.025	3	12.33	1
B	0.5	0.0125	1.5	24.67	1
C	1	0.0125	0.75	49.33	2
D	5	0.05	0.6	61.66	4
E	5	0.0125	0.15	246.66	4

2.2.2. Optimization of sample preparation and instrumental parameters

For optimization of sample parameters, all studies were carried for both forms of OLZ with each sample analyzed for six consecutive runs and average values of area and height were taken. Background was subtracted from each diffractogram to nullify the affect of sample holder.

2.2.2.1. Effect of particle size on preferred orientation. OLZ form I was passed through different sieves (passed through BSS # 80 and collected on BSS #120 [#80/120], passed through BSS # 120 and collected on BSS # 240 [# 120/240], and passed through BSS # 240) and the sieve fractions were collected. The sieved fractions were mounted on sample holder and recordings were made with rotation of sample holder. Sieving of samples was performed in a humidity controlled environment at 30% RH (±5% RH). Form II was used as received.

For optimization of instrumental parameters 5% (w/w) physical mixtures of OLZ form I in form II was used.

2.2.2.2. Optimization of scan rate. Table 1 enlists the step size and step time varied in order to alter the scan rate of sample.

2.2.3. Preparation of calibration curve

OLZ form I was passed through BSS #120 and collected on BSS # 240 (# 120/240) and form II was used as received. OLZ form I was physically mixed in various ratios (0, 0.1, 0.2, 0.4, 0.6, 0.8, 1, 2, 4, 6, 8, 10, 20, 40, 60, 80, and 100%, w/w) with form II by geometric mixing in a controlled environment (25 ± 2 °C; 30 ± 5% RH). Samples were made in triplicate and accurately weighed 500 mg powder mixtures were loaded on sample holder. A graph was plotted between average area and % w/w of form I. Limit of detection (LOD) and limit of quantitation (LOQ) were determined with the help of this calibration curve.

2.2.4. Validation of analytical method

The analytical method developed for quantification of OLZ form I in form II was checked for validation parameters like linearity, accuracy, precision, ruggedness, LOD, and LOQ (Table 2).

2.2.5. Estimation of assay error

In order to determine errors coupled with PXRD assay, single mixture (5% (w/w) of form I) was prepared to explore the parameters described in Table 2 and % relative standard deviation (R.S.D.) was calculated.

Table 2
Validation and assay errors associated with quantitative analysis using PXRD

Validation parameters	Measurement description
Accuracy	Accuracy of the calibration curve was determined by independently examining nine different concentration (0.3, 0.5, 0.7, 3, 5, 7, 30, 50, and 70%) samples, in triplicate
Precision	Precision depicts the repeatability of the X-ray measurement. The repeatability of measurement of the diffraction peak area for refills of sample into holder ($n = 6$) was investigated for 0.1, 1, 10, and 100% (w/w) of form I
LOD and LOQ	The LOD and LOQ of the quantitative method were calculated using Eqs. (1) and (2) respectively, as recommended in the ICH guidelines [12]. These values were determined from data obtained in the range of 0–100% (w/w) of form I: $\mathrm{LOD} = 3.3\sigma/S$ (1) $\mathrm{LOQ} = 10\sigma/S$ (2) where σ is the standard deviation of the blank and S is the slope of calibration curve
Error category	**Measurement description**
Instrument reproducibility	Reproducibility of the instrument was investigated by placing a single sample (5%, w/w) in the PXRD instrument and acquiring six data sets without removing the sample from the sample holder and instrument
Intra-day reproducibility	Variability of the instrument responses during a typical working day was investigated by using a single sample and acquiring six diffraction patterns over 8 h period
Inter-day reproducibility	Variability in instrument response was investigated for 6 days. A single sample was placed in the instrument and X-ray profile was recorded each day
Sample positioning	Effect of variation in position of sample holder within the instrument was examined by using a single sample and randomly repositioning the holder at six different positions
Sample packing	Variation due to crystal orientation was assessed by re-packing the sample six times and acquiring the diffraction profile after each packing

3. Results and discussion

3.1. Solid-state characterization of polymorphs

Qualitative analysis of polymorphs was performed using microscopy, FTIR, DSC, TGA, HSM, and PXRD. Both forms of OLZ showed different morphology when observed under the microscope. Form I was found to exist as large lath-shaped crystals while in case of form II, crystals were plate shaped. The DSC curve of form I exhibited melting endotherm at 180.3–184.3 °C, which was followed by a recrystallization exotherm at 184.2–188.3 °C, and finally melted at 193.7–198.1 °C, as form II. Form II on the other hand, showed only a single melting endotherm at 193.6–198.4 °C. OLZ form I and II were found to be anhydrous as they exhibited no weight loss due to desolvation during TGA. In both forms, mass loss takes place after melting peak, and these results were concordant to previously reported study [13]. Similar pattern was observed under HSM where form I showed melting at 179 °C and recrystallization into plate-shaped crystals at 186 °C that finally melted at 193 °C. Form II directly melted at a temperature of about 195 °C. The region of 1500–1000 cm^{-1} is important in case of FTIR for identification of form II that showed unique $–CH_2$ band at 1470 cm^{-1}.

The PXRD pattern (Fig. 2) of each polymorphic form shows unique peaks that can be used for their identification and quantification. The *d* values and 2θ values of form I and II corresponded well with values reported in US patent 5,736,541 [14], and showed no evidence of contamination by other polymorphic forms. Both forms show intense peaks indicating their crystalline nature.

In earlier reported studies on quantification of polymorphic forms of drugs, using PXRD, the highest intensity peak ($I/I_0 = 100\%$) has been used for estimation of polymorphic content in mixtures [8,15–18]. However, in case of OLZ form I, the highest peak was overlapping with peak of form II at 8.79° 2θ. Apart from the 18.48° peak ($I/I_0 = 78.8\%$), other characteristics peaks at 10.91° ($I/I_0 = 10.4\%$), 12.99° ($I/I_0 = 17.6\%$), 14.01° ($I/I_0 = 6.6\%$), and 19.38° 2θ ($I/I_0 = 14.3\%$) are of low intensity and area. Hence, the sample and instrument parameters need to be critically studied for identification of form I in low concentrations in mixtures.

3.2. Optimization of sample preparation and instrumental parameters

The optimization of sample preparation parameters was performed by studying the effect of sample parameters on area, height, and resolution, on ten most intense peaks (though may not be characteristic). Large variations and fluctuations of up to 31% in relative standard deviation (R.S.D. have been reported in the literature in the PXRD data [8]). In earlier reported studies, higher variation has been observed in peak shape and height with change in particle size, whereas area was less variant [8,18–21].

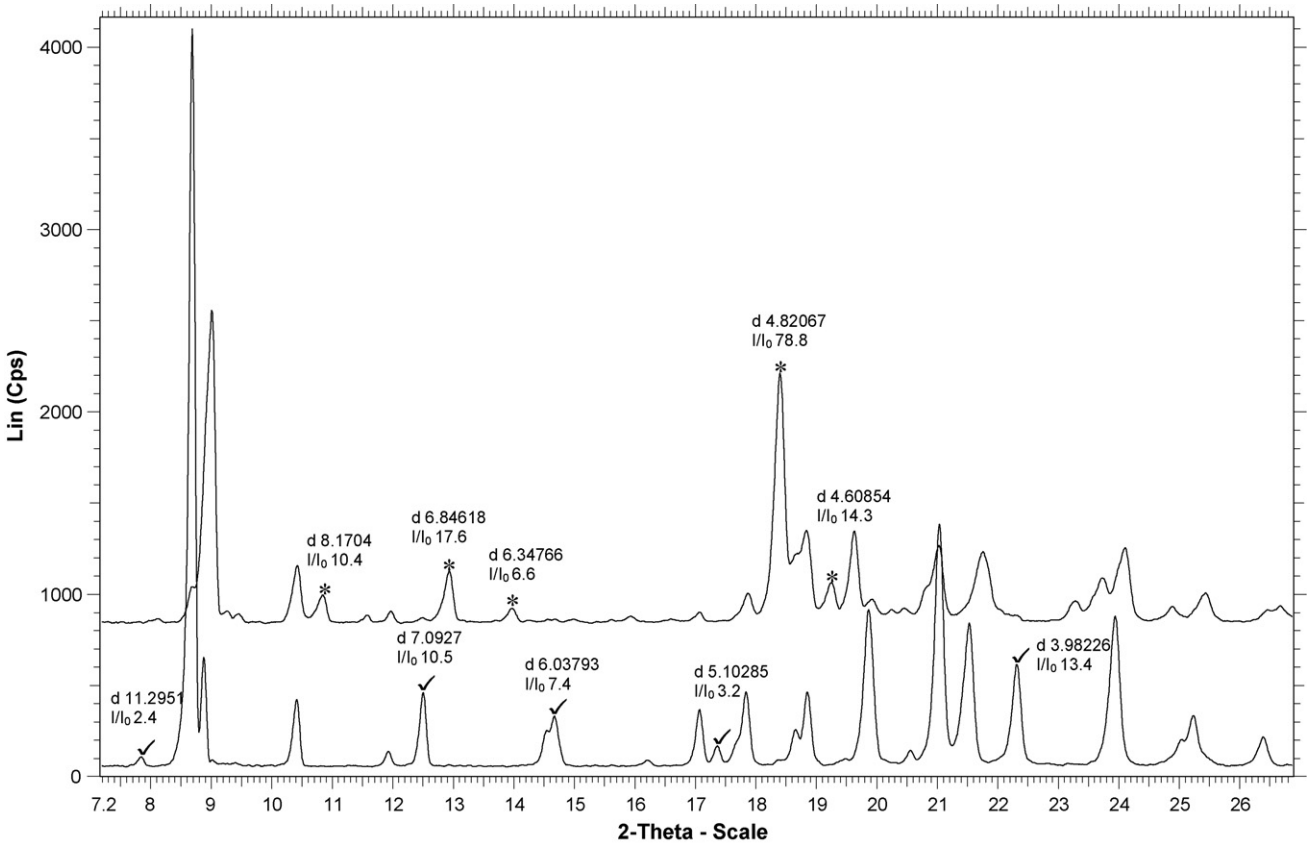

Fig. 2. Background subtracted and smoothened PXRD patterns of OLZ polymorphs (a) form I, (b) form II, "*" shows the characteristic peaks in form I and "√" shows characteristic peaks of form II.

Similar results were observed when the % R.S.D. was calculated by considering the height and area of peaks. % R.S.D. of 10–28% and 8–17% (form I) and 9–22% and 1–10% (form II) was observed by analyzing height and area, respectively. Hence, for further studies, peak area was considered for analysis of results.

Error due to preferred orientation is the most widely studied parameter in PXRD. Packing of powder sample in the holder can lead to preferred orientation because of non-random distribution of crystal orientations [18]. Crystallographic orientation of particles can affect intensity up to 100%, and the consequence is more pronounced for acicular and irregular shaped crystals [8]. Form I was found to exhibit lath-shaped crystals and particle size distribution of 5–125 μm whereas form II was platy in nature with smaller crystals (3–35 μm). Diffraction data of sieved and unsieved samples showed differences in peak area in form I of OLZ. Peak areas were 1–41% higher for BSS # 120/240 sieve fraction in comparison to BSS # 80/120 for form I (Table 3). Further sieving could not be performed on form II, due to development of electrostatic charges. Particle size plays a major role in preferred orientation [16] and use of smaller particles (∼10 μm) has been reported to aid in minimizing preferred orientation of the particles [17]. OLZ form II with smaller size, exhibited higher area and lesser % R.S.D. (1–10% for as received sample) in comparison to form I (0.87–18.55% for sieve fraction BSS # 120/240). The results of peak area for form I were subjected to ANOVA analysis to understand the effect of particle size within the same sieve fraction and Student–Newman–Keuls method was applied for analysis of data of different sieve fractions. One way ANOVA exemplified that the difference in the median values among different samples of the same sieve fractions of forms I was not high enough to exclude the possibility that the difference is due to random sampling variability, hence, does not show statistically significant difference. On the other hand, Student–Newman–Keuls test illustrated that the difference in the median values of different sieve fraction groups is greater than would be expected by chance ($P = <0.001$), hence, there is a statistically significant difference between different sieve fractions for form I. Student–Newman–Keuls test is a multiple comparison non-parametric test applied for a pair wise comparison of every combination of group pairs. It helps to identify whether all groups are different from one another, or some groups are not significantly different. Therefore, it was concluded that changes in particle size had an effect on peak area, thus, sieve fraction BSS # 120/240 was used for further studies of form I.

Table 3
Effect of particle size on average area ($n = 6$) of 10 most intense peaks of OLZ form I

I/I_0	° 2θ	Area of peaks (cps × 2θ)			
		As received sample	BSS # 80/120	BSS #120/240	BSS #240
100.00	9.15	347	389	421	394
24.60	10.62	62	73	86	81
14.30	11.12	36	40	50	48
18.80	13.13	61	66	73	66
88.80	18.64	291	310	336	325
39.70	19.09	148	179	187	184
35.30	19.87	123	115	124	123
35.70	21.25	143	162	168	143
27.70	21.99	144	188	188	184
29.90	24.35	128	139	155	153

The instrument parameters have been optimized in the polymorphic mixture (5%, w/w) and finally these optimized parameters have been used in the quantification of form I in the mixture. The degree of precision in the measurement of the decisive parameters (area, height, and intensity) determines the accuracy of quantitative PXRD. Several instrumental parameters have been reported to critically affect the area of diffraction peaks. Among these parameters, scan rate and chopper increment have a direct impact on the counting statistics [7]. As observed from Table 1, at slower scan rates the number of identifiable characteristic peaks of form I in the mixture increased. In combination A (scan rate of 3° 2θ/min) only one peak was identified at 18.48°, while in combination D and E (scan rate of 0.6 and 0.15° 2θ/min, respectively) maximum four peaks of form I at 2θ 10.91, 12.99,18.48, and 19.38° were identified (Fig. 3). The peak at 14.01° 2θ, a very low intensity peak ($I/I_0 = 6.6\%$) was not observed in any of the combinations. Data obtained at a higher scan rate usually resolves fewer peaks than data obtained at lower scan rates because as the scan rate increases recording time reduces and *vice versa*. Similarly, the accuracy of *d*-spacing measurement and resolution of peaks at higher scan rate, of the minor phase was significantly less, even for strong peaks. Lower scan rates, increase the number of identifiable peaks and peak resolution but also significantly increase the experimental time. Therefore, final experimental protocol should keep a balance between the peak resolution and recording time. Scan rate of 0.6° 2θ/min with about 62 min recording time was the fastest offering resolution of maximum peaks and was thus selected for further experiments.

3.3. Quantitative method development

Out of the four characteristic peaks of OLZ form I at 10.91, 12.99, 18.48, and 19.38° 2θ, peak at 18.48° 2θ (I/I_0 78.8%) was selected for quantification of form I in binary mixtures. The difference was radically interpretable at this 2θ with the change in concentration. The other three low intensity peaks exhibited low R^2 values (less than 0.934) and were thus not used for quantification. Also, these peaks were not traceable below a 5% (w/w) concentration of form I in the mixture.

The peak at 18.48° 2θ was integrated from 18.25° to 18.60° 2θ and this area monitors the level of form I in the samples. The calibration curve (Fig. 4) covering a wide range (0–100%, w/w) of form I showed good linearity over the entire concentration range and exhibited a regression line equation of $y = 2.7219x + 8.5708$ with a high correlation coefficient of 0.9986.

3.4. Validation of the analytical method

Any analytical method before being successfully utilized for quantification needs to be validated [12]. The method developed was found to be linear in the range 0–100% with LOD and LOQ

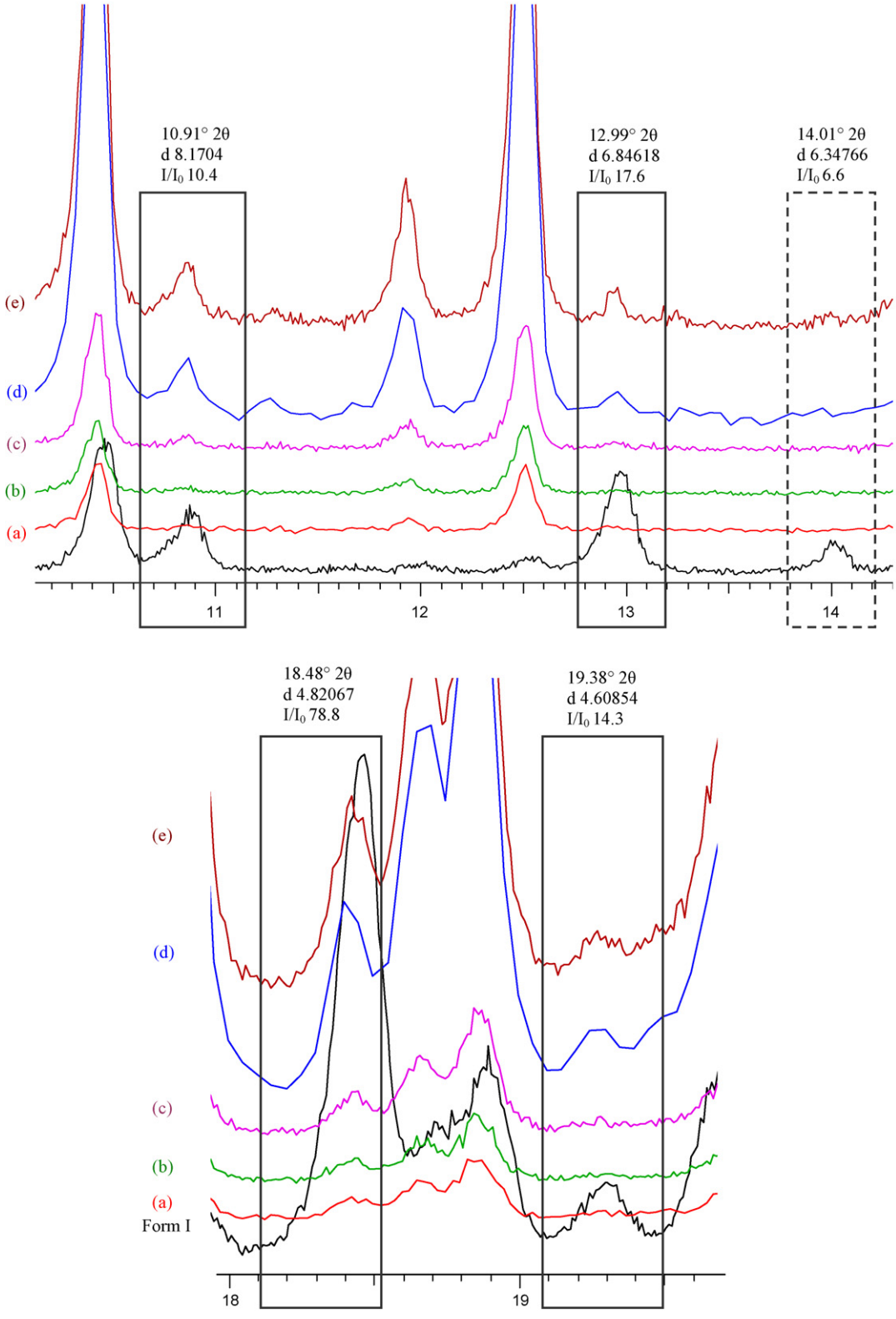

Fig. 3. Effect of scan rate on X-ray diffractogram of 5% (w/w) of form I. Scan rate shown in the figure are (a) 3° 2θ/min, (b) 1.5° 2θ/min and (c) 0.75° 2θ/min (d) 0.6° 2θ/min, and (e) 0.15° 2θ/min. The solid line boxes depict the identifiable peaks and the dotted box shows the peak that was not detected in 5% (w/w) mixture.

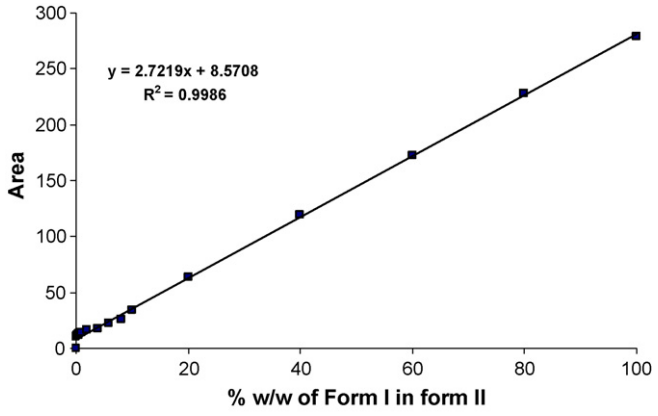

Fig. 4. Calibration curve for determination of OLZ polymorphic form I in form II by PXRD.

calculated to be 0.40 and 1.22%, respectively. The method was found to be precise with % R.S.D. between 3 and 5% and accurate with recovery in the range of 97–102%. The actual versus predicted content (%, w/w) of form I was plotted (Fig. 5), and a linear curve with R^2 value of 0.9999, fitted slope of 1.005 and a small intercept of −0.0587 was obtained. This further indicated that the method developed was rugged. Validation data is summarized in Table 4. Although the validation results show excellent correlation between input and calculated concentration, assay errors can be introduced by a combination of sample positioning, sample packing, inter-day and intra-day variability.

3.5. Estimation of assay error

The instrument reproducibility of about 2.9% was observed when the same sample was consecutively measured with out disturbance. The inter-day variation observed was 7.8% in comparison to 2.1% intra-day variation. However, it should be borne in mind that the day-to-day error for which the sample was removed daily from the instrument is a composite including variability resulting from sample re-positioning and possibly from sample disturbance on re-analysis. The effect of position

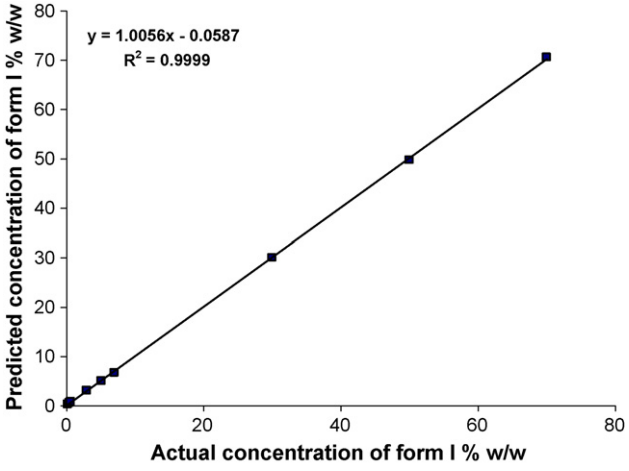

Fig. 5. Correlation curve of observed vs. theoretical percentage of form I in form II, obtained using peak areas in PXRD.

Table 4
Validation parameters and assay error evaluation for 0–100% (w/w) calibration curve of OLZ form I

Validation parameters	Validation data
Recovery (%)	97–102
Precision (% R.S.D.)	3–5
R^2 of correlation curve	0.9999
Slope of correlation curve	1.005
Intercept of correlation curve	−0.0587
LOD (%)	0.40
LOQ (%)	1.22
Instrument reproducibility (% R.S.D.)	2.9
Inter-day variability (% R.S.D.)	7.8
Intra-day reproducibility (% R.S.D.)	2.1
Sample positioning (% R.S.D.)	7.6
Sample packing (% R.S.D.)	14
Overall assay error (% R.S.D.)	5.2

of sample holder in the PXRD autosampler was determined, and the variation observed due to sample position was 7.6%. Variation due to crystal orientation was investigated by re-packing a single sample six times and recording the diffraction pattern after each preparation. Re-packing the same sample led to variation of 14%. Based on the PXRD diffraction response, an overall R.S.D. of 5.2% was determined for the PXRD assay. These overall R.S.D. is actually a combination of errors introduced into the assay by all factors such as instrument reproducibility, inter- and intra-day variation, sample positioning, and sample packing. The assay error obtained for the method was lower than the previous reported studies by Bugay et al. (R.S.D. 7.8%) [22] and Campbell et al. (R.S.D. 6.2%) [8].

From the potential errors investigated in this study, control of parameters such as sample packing appears critical to the accuracy of the data obtained. Generally, parameters involving the response of the instrument with no sample disturbance (instrument and intra-day variability) gave relatively small R.S.D. values (around 2%) indicating good reproducibility of the technique.

4. Conclusion

A quantitative PXRD method has been developed to determine the amount of form I OLZ in form II. In order to minimize the errors associated with quantification and to obtain an accurate method, the sample preparation and instrument parameters were previously optimized. Particle size and scan rate of the experiment was found to significantly affect the number of identifiable peaks and their areas. Preferred orientation influenced by particle size profoundly affected the peak area and sieve fraction BSS #120/240 demonstrated a significant increase in peak area. Lower scan rates increased the number of detectable peaks in the 5% mixture of form I in form II. However, a balance between the recording time and peak resolution was made by selecting a scan rate of 0.6° 2θ/min, which led to identification of four out of five characteristic peaks of form I in 5% mixture. Increase in area aids in development of a rugged and precise method, especially at lower concentrations. The quantification method developed was found to be linear in the range of 0–100% (w/w) with LOD

as low as 0.40% and LOQ of 1.22%. The overall assay error (5.2%), a combination of errors introduced by factors such as instrument reproducibility, inter- and intra-day variation, sample positioning, and sample packing was found to be lower than the previous reported studies on quantification by PXRD, probably due to prior optimization of instrument and sample preparation parameters. Through this method it would be possible to quantify the polymorphic mixture of OLZ in bulk drug samples. It would be of great interest to further develop quantification method for polymorphic mixtures in the dosage form.

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