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Quantitative determination of polymorphic impurity by X-ray powder diffractometry in an OROS® formulation

Mehdi Varasteh, Zhengyu Deng*, Helen Hwang, Yoo Joong Kim, Geoffrey B. Wong

ALZA Corporation, Department of Analytical Development, 1010 Joaquin Road, Mountain View, CA 94043, United States

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ABSTRACT

An ALZA OROS® drug delivery system was evaluated for its potential to increase drug load and reduce side effects when used with RWJ-333369 (S-2-O-carbamoyl-1-o-chlorophenyl-ethanol), a novel neuromodulatory agent initially developed by SK Bio-Pharmaceuticals and licensed by Johnson & Johnson. RWJ-333369 was found to have two crystalline polymorphs (A and B) that are enantiotropically related. Polymorph A, used in the formulation, was thermodynamically stable at room temperature. A partial polymorphic conversion in the solid state was observed at an elevated temperature of 60 °C during a two-week stability test.

The OROS® RWJ-333369 manufacturing process included milling, granulation, compression, sub-coating, membrane coating, drilling, and drying to produce a capsule-shaped OROS® tablet. The potential for polymorphic conversion during manufacturing and stability testing was evaluated using Fourier Transform Infrared Spectroscopy (FTIR), Raman Spectroscopy (Raman), and X-ray Powder Diffractometry (XRD) to detect impurities; the latter was determined to be preferred method.

Pure polymorph A and polymorph B reference materials were used for method development. Mixtures with different ratios of polymorph A and polymorph B were scanned using XRD, and the peak heights and areas were used to generate a calibration curve. OROS® RWJ-333369 formulations were spiked with polymorph B reference, and the detection limit was about 2% using the 22° 2θ diffraction angle relative peak area. Samples from different OROS® manufacturing process and stability tests were analyzed. The results indicated that polymorph A was not converted to polymorph B during manufacturing process. Polymorph B impurity was, however, detected in stability samples.

1. Introduction

Polymorphism is an important phenomenon in the drug development and manufacturing process since different polymorphs of a compound show variations in physicochemical properties such as density, morphology, solubility, dissolution rate, stability, and hygroscopicity. As a result, different polymorphs of the same drug exhibit differences in bioavailability, efficacy, and drug product performance. In order to control polymorphism in the drug development and manufacturing processes, it is critical to identify, characterize, and quantitate the presence of the various polymorphs of a pharmaceutical compound.

RWJ-333369 had previously been subjected to thermal treatment, to a precipitation test, and to crystallization tests at different temperatures using different solvents. Two crystalline polymorphs (A and B) and an amorphous form were detected in this study. Polymorphs A and B are enantiotropically related polymorphs that crystallize in different packing arrangements with the same elemental composition. Polymorph A is thermodynamically stable at room temperature and was selected for use in the RWJ-333369 controlled-release product.

An ALZA OROS® Push-Stick™ drug delivery system was evaluated for its potential as a controlled-release formulation for RWJ-333369 to increase drug load and reduce side effects (Theeuwes et al., 1990). The Push-Stick™ system is a capsule-shaped, longitudinally compressed tablet, which includes drug, cellulose acetate, magnesium stearate, poloxamer, polyethylene oxide, sodium chloride, and stearic acid (Yam et al., 2005). During the OROS® RWJ-333369 manufacturing process, jet milling/micronization, granulation, compression, sub-coating, membrane coating, drilling, and oven drying were used to produce the tablet. Processing solvents such as acetone, ethanol, and water were used during the granulation, membrane coating, and oven drying processes. During the mixing and fluid-bed granulation process, a solvent and polymeric binders were added to wet the particulate drug substance and excipients. Once the wetting

* Corresponding author. Tel.: +1 650 564 2571; fax: +1 650 564 4212.
E-mail address: rdeng@alzus.jnj.com (Z. Deng).

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granulation phase was completed, drying and milling processes were applied before blended agglomerates were longitudinally compressed into tablets. A cellulose acetate membrane was coated on the tablets, and an oven-drying process removed acetone and water. The combination of milling/micronization, granulation, solvent wetting, and drying provided a suitable environment for possible conversion of RWJ-333369 to its alternate crystalline forms. During stability studies of drug product, RWJ-333369 OROS® tablets were stored at 25 °C and 60% relative humidity and at 30 °C and 65% relative humidity chambers for an extended period. A partial polymorphic conversion in the solid state of the RWJ-333369 drug substance was observed at an elevated temperature of 60 °C during a two-week stability test. It is possible that polymorphic conversion of RWJ-333369 could take place during OROS® tablet manufacturing processes and drug product stability studies. In support of the new drug application (NDA) for RWJ-333369 (polymorph A), a quantitative assay was required for determination of polymorph B in drug substance and controlled-released OROS® drug products. Requirements for this assay included that it be suitable for a quality control environment and that: (a) polymorphic transformation did not occur during sample preparation and analysis and (b) the detection limit was ~5% (w/w) for polymorph B in drug product with polymorph A as the Active Pharmaceutical Ingredients (API).

The Food and Drug Administration (FDA) drug substance guideline states that appropriate analytical procedure should be used to detect polymorphic forms of drug substance (ICH, 1999). Further, it is the applicant's responsibility to control the crystal form of drug substances and drug products. In order to control polymorphism during manufacturing processes and stability studies of drug substances and products, analytical methods must identify and quantitate different crystal forms. It is essential that these methods measure very small amounts of polymorphic content accurately. Many techniques have been used to determine polymorphic composition of active pharmaceutical polymorphs in crystalline drug substances and drug products (Byrn et al., 1995; Brittain, 1999). Diffuse reflectance infrared spectroscopy (IR) and X-ray powder diffractometry (XRD) have been used to identify two different hydrated forms of cefepime.2HC (Bugay et al., 1996). An IR quantitative assay was established with a minimum quantifiable level of 1.0% (w/w) and a detection limit of 0.3% (w/w) dihydrate in monohydrate materials. The XRD assay achieved a minimum quantifiable level of 2.5% (w/w) and a detection limit of 0.75% (w/w). Near-infrared spectroscopy (NIR) was used for quantitation of polymorphs during the drying phase of wet granulation process (Davis et al., 2004). Solid-state nuclear magnetic resonance spectroscopy (NMR) was used to identify two polymorphs of clarithromycin (Tozuka et al., 2002). Areas from well-separated peaks of ^{13}C spectra for the two polymorphs were the basis for quantitative analysis of polymorphic composition. Fourier-transform Raman (FT-Raman) Spectroscopy has a relatively low detection limit compared to XRD (Kontoyannis et al., 1997). A variety of analytical techniques for characterization the solid forms of pharmaceuticals have been reviewed recently (Stephenson et al., 2001). Each technique has advantages and drawbacks for quantitative analysis in terms of sample preparation, measurement time, and sensitivity. Small sample sizes, non-destructive sample preparation, rapid analysis with the new generation X-ray detector and unique XRD patterns with improved detection limits make XRD the preferred technique for the analysis of polymorphic composition in mixtures. Quantitative determination of the polymorphic composition of chlorpropamide in intact compacted tablets using parallel-beam XRD has been reported (Cao et al., 2002). The integrated intensity ratio of a selected peak for each crystal form was used for quantitation of each polymorph. Excellent linear correlation was observed for both polymorphs. Preferred orientation effect has also been investigated for the quantitative analysis of mannitol polymorphs by XRD (Roberts et al., 2002). Rotation and reduction of the particle size range to <125 μm halved the limits of detection and quantitation to 1% and 3.6%, respectively. In addition, a novel powder sample preparation method has been used to improve the sensitivity and accuracy of quantitative analysis for polymorphic mixtures by XRD (Okumura and Otsuka, 2005). α and γ forms of indomethacin were micronized in a jet mill to remove anisotropy and attain a nearly equal grain size of less than 10 μm. The micronization of analyte powder reduced the effects of powder inhomogeneity and preferred orientation on the peak intensity. The micronized powder was physically mixed at various ratios in a vibrating mill containing a rubber ball. Using precise standard mixtures, the detection and quantitation limits were calculated to be 0.57% and 1.73%, respectively, yielding superior sensitivity and accuracy compared to mixtures prepared using an agate mortar. A synchrotron XRD method has also been developed for highly sensitive quantification analysis of crystallinity in substantially amorphous pharmaceuticals (Nunes et al., 2005). High-intensity X-ray allows discernment of subtle changes in the lattice order of materials. The estimated limit of detection of crystalline sucrose in an amorphous matrix was 0.2% (w/w) compared to the reported value of ~1% (w/w) using conventional XRD.

The purpose of this study was to establish a reliable analytical method to determine lower detection and quantitation limits for the polymorphic composition of RWJ-333369 during OROS® formulation development and manufacturing processes. Pure polymorph A and B reference materials were used for method development. Raw drug, granulated, and compressed core samples were used to develop independent quantitative calibration curves for polymorphic impurity concentrations. FTIR, Raman, and XRD methods for quantitative analysis of RWJ-333369 in drug substance were evaluated. XRD was found to be the preferred method to monitor possible form conversion. Mixtures with different ratios of polymorph A and polymorph B were studied to generate a calibration curve. These reference samples were ground into a powder form and sieved to produce a material with a uniform particle size distribution. Reference samples were mixed with low-weight percentages of polymorph B to make several different calibration sets. Multiple scans of each calibration sample were taken. Scans were fitted using peak search application, and pertinent peak parameters were used to develop calibration models. The XRD scan peak height and area were calculated for the calibration curves. Peak height and area ratios were varied to find a parameter set with the highest correlation and the lowest root mean square deviation. Models were also used to test for presence of polymorph B in stability sample prepared followed ICH guideline (ICH, 2003).

2. Experimental

2.1. Materials

A micronized RWJ-333369 lot used in the formulation and manufacturing process was the reference material for polymorph A. Reproducibility of signal was confirmed with two other lots with 5–15 μm particles of polymorph A. An additional lot of raw material of polymorph A was milled and sieved into target particle sizes of 80, 50, and 20 μm to evaluate the effect of particle size on XRD peak intensities. Reference polymorph B raw material was obtained in the form of needle-like crystals from. The major excipients used were polyethylene oxide, poloxamer and magnesium stearate. Products of drug granulation, placebo granulation, and isolated drug layer from core tablets at various stages of the manufacturing process were evaluated in this study. The drug load in the systems under study was substantial (~70% by weight).

2.2. Sample preparation

Although reference materials were not ground before testing with FTIR and Raman spectra, XRD profiling requires fine particles for reproducible patterns that are free from preferred orientation effects. In sample preparation for XRD, each polymorph was weighed directly into a mortar and ground. Core and granulation samples were also ground and sieved before being spiked with ground polymorph B to make calibration mixtures. Each mixture was ground for 10 min to ensure uniform distribution, and the entire amount of the mixture was transferred onto a zero-background sample holder using a spatula and flattened into a disc with a 15-mm diameter.

2.3. Instrumentation

2.3.1. FTIR and Raman

The FTIR spectrum of each polymorph was obtained with a PerkinElmer Spectrum 2000 spectrometer (PerkinElmer Life and Analytical Sciences, Inc., Waltham, MA, USA). A small amount of reference material was placed on the Si crystal of a micro-ATR accessory (SplitPea™, Harrick Scientific Products, Inc., Pleasantville, NY, USA), and FTIR-ATR spectra were obtained using a liquid-N_2-cooled MCT detector with 32 scans and 4 cm^{-1} resolution. Raman spectra of the two polymorphs were obtained using a LabRAM Infinity Raman microscope system (HORIBA Jobin Yvon Inc., Edison, NJ, USA) equipped with a holographic notch filter and Peltier-cooled CCD detector. The sample was irradiated with a frequency-doubled Nd:YAG laser at 532 nm, and the Raman signal was collected using a 50× objective and holographic grating through a 100 μm slit and accumulated for 30 s.

2.3.2. X-ray powder diffractometry

Samples were weighed out using a Mettler Toledo AG245 analytical balance (Mettler Toledo Inc., OH, USA). A PANalytical X'Pert PRO PW3040-Pro X-ray diffractometer (PANalytical, Almelo, The Netherlands) equipped with an X'celerator™ detector was used to obtain patterns. Measurements at elevated temperatures were made with the Anton Paar TTK 450 hot temperature stage and the TCU 100 temperature controller unit (Anton Paar GmbH, Graz, Austria). With the X-ray generator set at 45 kV and 40 mA, a copper anode was used to produce a divergent beam with an average Kα wavelength of 1.541874 Å. The range of 4–45° 2θ with a step size of 0.017° 2θ and a count time of 10.16 s per step was used for the measurements. The room temperature measurements were conducted on a spinner stage operating at a rotational speed of one revolution per 2 s. Using a programmable divergence slit and a programmable receiving slit, a spot of 11.5 mm from about the center was irradiated with the source and the central 10 mm of the sample was observed by the detector. Calibration mixtures were targeted to be 25 mg, so a similar mass of material was used in all the measurements. X'Pert Highscore™ data analysis software version 1.0d (PANalytical, Almelo, The Netherlands) was used to find peak parameters.

3. Results and discussion

3.1. Characterization of the reference polymorphs

3.1.1. Spectral differences of two polymorphs

A prerequisite for polymorphic composition analysis is to have distinguishable spectral profiles for each polymorph. Figs. 1–3, respectively, show FTIR, Raman spectra, and XRD patterns of the two polymorphs of the RWJ-333369 active pharmaceutical ingredient (API). Two polymorphs of RWJ-333369 showed similar, but not identical FTIR spectra with measurable differences in peak position, relative intensity, and line width for some corresponding peaks from form A and B. Apparently, the largest difference between the two polymorphic forms in FTIR was two peaks at 764.4 and 755.9 cm^{-1} for polymorph A versus a single peak at 758.2 cm^{-1} for B. All of these corresponding pairs of peaks showed some degree of overlap. Two polymorphs of RWJ-333369 also showed slightly different Raman spectral patterns as shown in Fig. 2, with a peak at 1128 cm^{-1} for A versus a broad peak at 1115 cm^{-1} for B being the biggest difference. Any of the corresponding pairs of peaks in form A and B did not show clear separation in Raman spectrum.

Among the three techniques employed, XRD provided most distinct pattern differences between two polymorphs. Although many of the diffraction peaks were common in both polymorphs in Fig. 3, the peak position, relative intensity, and peak width were different. There are also a few unique peaks for each polymorphs. A strong diffraction peak in polymorph B appeared at 22.2° 2θ, while polymorph A lacked any diffraction at that position. Other less intense characteristic peaks near 19.3° 2θ and 30.7° 2θ appeared also only for polymorph B, while the peaks at 21.0 2θ and 26.1 2θ are unique for form A without much interference from polymorph B. Based

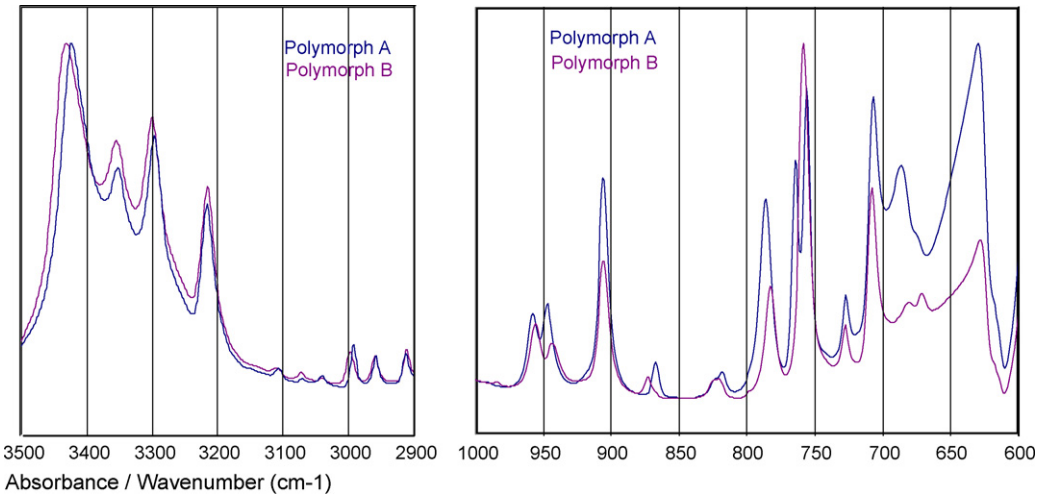

Fig. 1. FTIR spectra of two polymorphic forms of RWJ-333369.

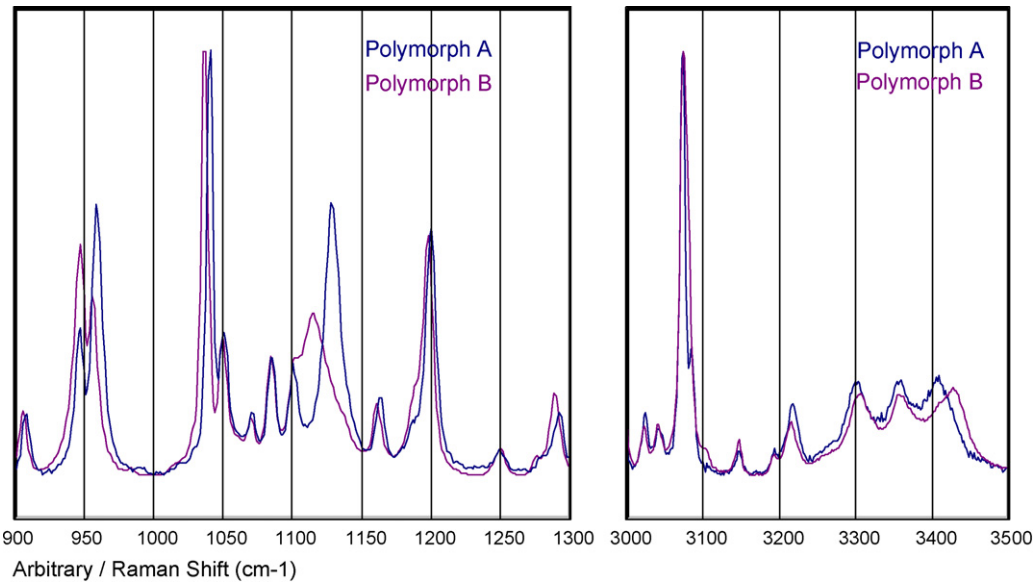

Fig. 2. Raman spectra of two polymorphic forms of RWJ-333369.

on the comparison, XRD was chosen for determining polymorphic impurity in RWJ-333369 OROS® formulations and stability samples of OROS® drug products.

In this study, some of the unique XRD peaks were used for distinguishing two forms and detecting the presence of polymorph B, both in drug substance as well as in formulations containing excipients. Among these peaks, 22.2° 2θ of polymorph B was mainly used for quantification of polymorph B. Amorphous portion of the API and the consequent amorphous halo in XRD pattern were insignificant, and therefore a consistent baseline correction was applied independent of the amount of spiked polymorph B.

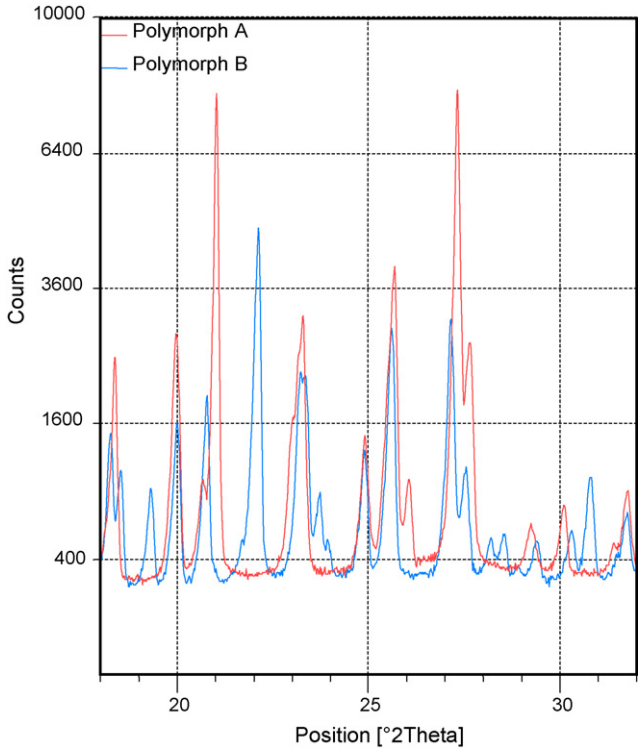

Fig. 3. XRD pattern comparison shows two polymorphic forms of RWJ-333369.

3.1.2. Transformation of polymorph A to polymorph B

A temperature increase of 10 °C per minute was used to heat treat the samples. Diffraction patterns were collected at each step after a 10 min wait time. The sample temperature was cooled to below 50 °C within 10 min after being at maximum temperature. Experiments verified partial polymorphic conversion to polymorph B after the polymorph A reference sample was heated at approximately 100 °C for the API and 70 °C for the blend. Fig. 4 shows significant conversion detected from XRD profiles at 120 °C, but no increase in the amorphous halo was observed. The melting point of polymorph A is known to be lower than the melting point of polymorph B, and both are close to 130 °C. After 10 min at 130 °C, only the polymorph B pattern remained during the in-situ scan. This was

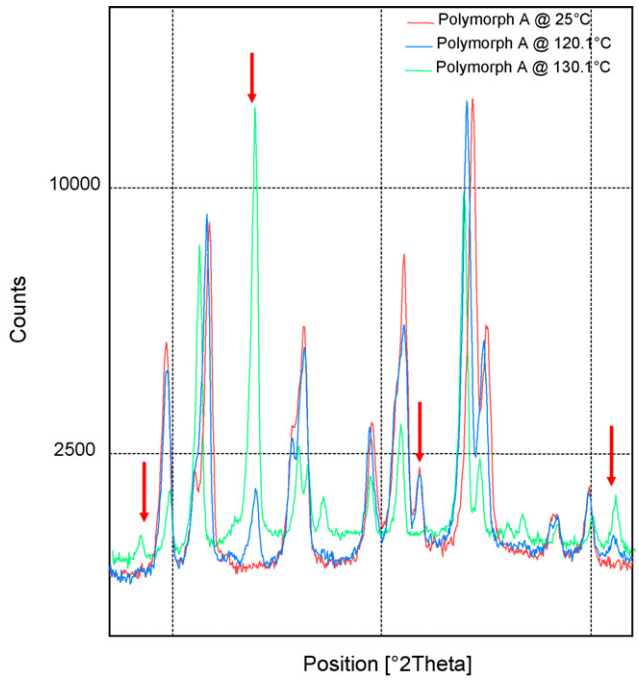

Fig. 4. RWJ-333369 polymorph A reference sample item heated to show conversion to polymorph B at high temperature.

confirmed by the missing polymorph A signature peak near 26.0° 2θ in the profile. The forced conversion resulted in a decrease in crystallinity at 130 °C, as depicted by the change in the background halo. After the sample was cooled, it was a powder. It did not appear to have melted and recrystallized, but a solid-state conversion had taken place.

Additional XRD profiles were taken after the sample was allowed to cool to room temperature. When the temperature exceeded 135 °C (beyond the melting point of both polymorphs), the resulting room-temperature profile was only an amorphous halo, and the sample appeared melted and recrystallized into amorphous. If the sample was heated to 132 °C and cooled to room temperature, the room-temperature scan of the sample showed only polymorph B. Following heating at 125 °C, the room-temperature profile showed a mixture of the two patterns.

3.2. Quantitation

3.2.1. Determination of peak analysis parameters

Mixtures of the two polymorphs were readily quantifiable using the 22° 2θ peak as shown in Fig. 5. There were two useful quantitation parameters from collected XRD profiles. First, a linear relationship was demonstrated for the peak height of polymorph B versus the weight percentage of impurity. In addition to the calibration of absolute peak intensity, the relative intensity of the peak at approximately 22° 2θ was used to quantify the presence of impurity. An investigation of the linear performance from different sets of parameters was used to compare the height of the peak near 22° 2θ to the following: the absolute maximum peak, the 23° 2θ intensity, the sum of the intensities between 18° and 30° 2θ, the net sum of all peak intensities between 4° and 45° 2θ, and the total number of counts in the scan.

The second parameter employed to quantify impurity levels was peak area. This parameter was more useful than peak height when considering multi-component systems like granulation mixtures or tablet cores. Plating uniformly distributed components from a

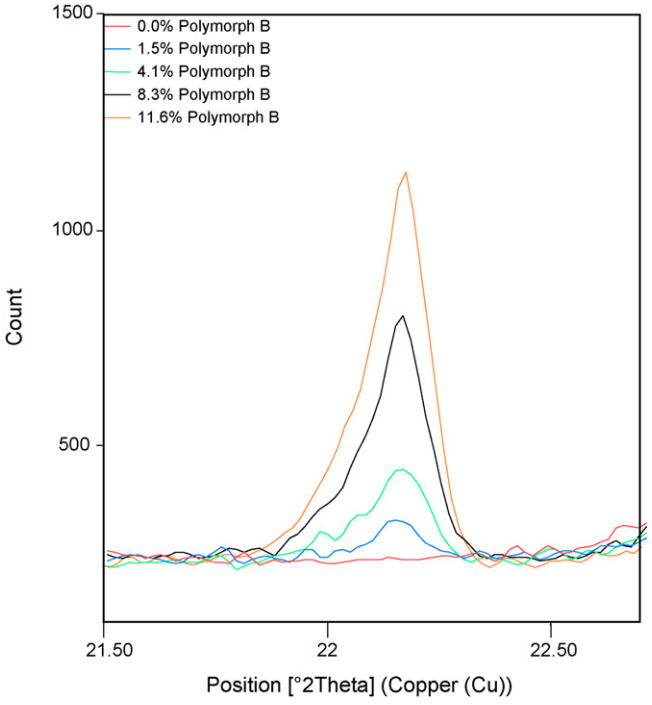

Fig. 5. Polymorph B peak from scans of API calibration samples spiked with different weight percentages of polymorph B.

complex mixture with consistent reproducibility was difficult to achieve, and the small variations in the amount of each component present were observed using normal XRD measurements. As a result, the use of a single observed value, such as peak height, to correlate the impurity response led to larger variance. Improved results were obtained using the area parameter, because the response of the impurity was averaged over a wider range of angles, and the influences of excipient interference and changes in their concentrations were reduced.

3.2.2. Preparation of the calibration curve

The peak height at each impurity concentration was measured six times after redistribution of the sample between measurements. The average of these measurements was used for quantitation after pre-treatment. For example, isolated peak height was normalized using the maximum peak intensity in the scan, giving values from 0 to 1 before averaging. The ratio of impurity peak height to other peak heights was also a valuable parameter for calibration. Another means of reducing inconsistencies was to use the peaks that were not strongly influenced by particle size and associated with polymorph A as an internal reference standard to measure impurity concentrations. This approximation was valid based on the assumption that there were only relatively small changes in polymorph A concentration. Overall, binary mixtures of different forms of pure API were more readily correlated using peak height as a variable.

The area calculations were not as straight-forward, because the full-width of peak at the half maximum (FWHM) value varied from peak to peak over the given scan range. Other challenges, such as determination of the background contribution, needed to be resolved in order to study granulations or compressed cores. In addition, peak overlap in the formulation made the isolation of peak area difficult at many of the reflections. To avoid bias when calculating peak area, an automated software method that accounted for the entire pattern was used to find peak parameters. Consequently, for complex mixtures like granulations and cores, peak area parameters had slightly better impurity correlation than those using peak heights.

3.2.3. Estimation of assay errors and sources of error

Many researchers believe the greatest source of error when performing XRD quantitative analyses arises during sample preparation. Indeed, the reproducibility of the method relies heavily on correct preparation of samples and calibration sets. The meticulous preparation and consistent technique used in this study ensured proper blending of the spiked component in the calibration set. A secondary means of verifying concentrations and uniform distributions of polymorphic impurity in calibration samples is vital in confirming correct sample preparation.

Plating the entire calibration sample ensured the total amount of spiked impurity was captured in the measurement and confirmed the sample contents. Weight measurements using a five-point scale (±0.01 mg) were considered adequate. For a 30-mg sample, a spike contribution of 1.5 mg was incorporated to prepare a 5% impurity level standard. For a method to be globally applicable, lot-to-lot variations and instrumental variations such as source intensity and stability must be accounted for during calibration curve development. Our rapid X-ray detector allowed spike measurements were performed in a single day to minimize this sort of shift or drift of instrumentation. A total of six sets of patterns obtained during normal generator operation were collected over several days.

3.2.4. Particle size effect on quantitation

Particle size studies on polymorph A revealed peak parameter dependence for strong reflections at 21.0° 2θ and 27.3° 2θ.

Significant variations were observed at these angles for samples with target mean particle size of 20, 50, and 80 μm. These variation issues would have been more apparent in the calibration set if micron milling had not controlled particle size of the API. The angles were not excluded since the calibration set was made from a single micronized lot. Chemometric methods may be able to exclude this source of discrepancy if required. Alternatively, sieving the sample may help to reduce variations caused by particle size.

3.2.5. Excipient interference on quantitation

The probability of finding a peak without excipient interference for quantification decreased as the number of components that were combined together in the formulation increased. Three of the excipients were amorphous, so their addition to mixture resulted in a small upward shift in the baseline. Two other excipients had reflections close to the signature polymorph B peak near 22° 2θ but, at a fraction of a percent, the concentration of these components was not significant enough to alter the collected patterns. The final two components had weak shoulder reflections in the region of interest. Of these two, the excipient with the greatest amount of interference was polyethylene oxide. Fortunately, the average particle size of polyethylene oxide was known to be greater than 75 μm. Hence, passing the sample through a 200-mesh sieve to eliminate particles larger than 75 μm reduced this interference as shown in Fig. 6. The API particle size was small enough to easily pass through this sieve. In addition, the sieving process made the collected patterns smoother as the particle size distribution became more uniform.

3.2.6. Determination of polymorph purity in API

With the strong polymorph B signature peak near 22° 2θ, the purity of polymorph A (up to 98%) was discernible by visual inspection of the collected pattern. Multi-variant regression methods may be used to improve determination of exact levels of impurity; peaks at 12.8° 2θ, 19.4° 2θ, and 30.8° 2θ were other unique indicators of polymorph B. A good quantitation method requires sample particle size control for all measurements. Sieving the reference polymorph A sample before spiking it improved the curve reproducibility by lessening the preferred orientation effects exhibited by larger particles.

Because the response standard deviation increased as the impurity weight percentage increased, based on counting statistics a weight factor inversely proportional to the spike percentage was applied to emphasize data points at lower concentrations. After applying the weight factor, the ratio between the root mean square error and calibration slope was reduced by a factor of two, validating the assumption that more emphasis should be placed on lower concentration responses. In fact, when a response peak rapidly grows with an increase in the spike percentage, the Poisson distribution—in which the standard deviation equals the square root of the number of counts—applies. Hence, the standard deviation difference between 11.6% impurity at 1308 counts and 2.4% impurity at 319 counts was 32 versus 18, nearly double. As a result, measurements taken at lower concentrations were more precise.

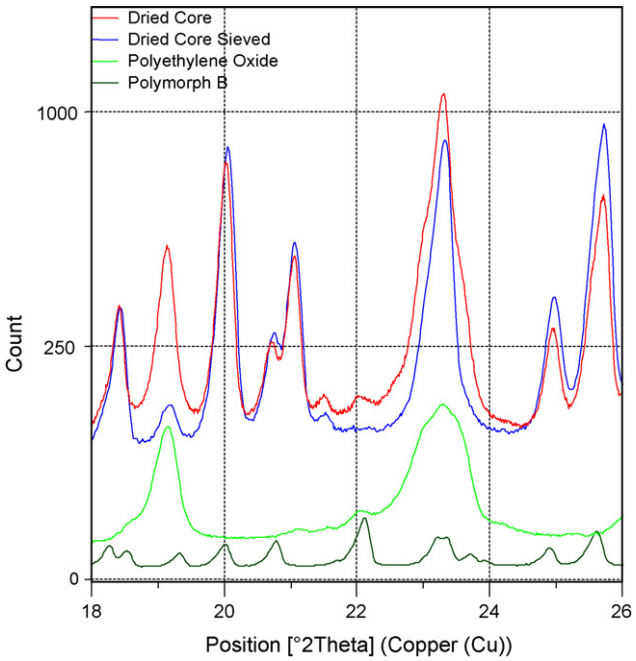

Fig. 6. XRD profile of drug layer isolated from compressed core before and after sieving compared to reference polymorph B and to polyethylene oxide.

Table 1 shows the fit resulting from application of different parameters on the same data set of API mixtures. In this case study, calibration curves developed using the peak height parameters were more robust than those using peak area parameters. The method that used the ratio of the 22.2° 2θ to the sum of peak parameters between 18° and 30° 2θ had the best performance among the regressions. Nearly all of the strong reflections were captured in this range.

3.2.7. Determination of polymorph purity in OROS formulation and stability samples

There were five calibration samples made with the granulation. Correlations derived from height parameters were slightly better than those derived from area parameters for the granulation calibration curve. The method correlating the relative intensity of 22.2° 2θ had the lowest limits of detection and quantification among the granulation sample set as shown in Fig. 7.

Since the investigation calls for the detection of minute amounts of polymorph B, it was determined to emphasize low-spike concentrations (to 12%) of polymorph B. In evaluating the core calibration samples, such a set would be able to detect conversion of polymorph A during manufacturing or stability testing. After practice with calibration samples comprised of API, granulation, and even

Table 1
Summary of fit and parameter estimates results from linearly fit model of RWJ-333369 API calibration samples peak area vs. percentage spiked.

	22° 2θ		22° 2θ:23° 2θ		22° 2θ:18–30° 2θ		22° 2θ: net peaks		22° 2θ: total counts	
	Area	Height	Area	Height	Area	Height	Area	Height	Area	Height
RSquare	0.95	0.98	0.95	0.96	0.98	0.98	0.97	0.98	0.96	0.97
Root mean square error	5.24	0.47	1.45	1.66	9.38	9.95	7.33	7.06	4.88	0.60
Intercept	−4.8	−1.0	0.1	−1.1	−14.6	−18.8	−10.1	−13.2	−5.5	−1.1
Slope	8.6	1.3	2.3	3.3	24.0	28.9	16.6	20.1	8.5	1.3
Detection limit	2.0	1.2	2.1	1.7	1.3	1.1	1.5	1.2	1.9	1.6
Quantitation limit	6.1	3.6	6.2	5.1	3.9	3.4	4.4	3.5	5.7	4.7

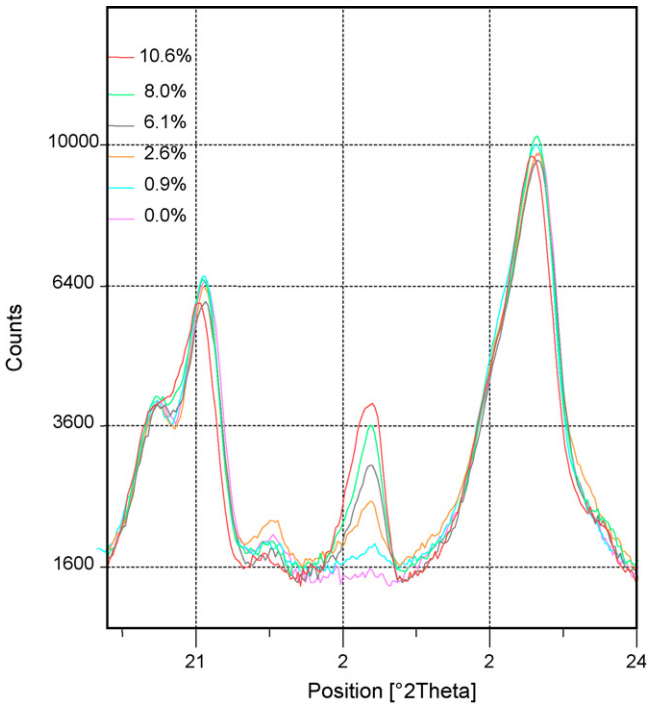

Fig. 7. XRD profile behavior of drug layer that was isolated from compressed core, ground, sieved, and spiked with various percentages of polymorph B.

some non-sieved-cores, the sample-preparation technique proved successful with optimal execution for the sieved-core sample set. The lowest detection limit for polymorph B content based on sieved-core sample calibration curve performance was found using the area parameter ratio comparison of 22.2° 2θ to 23° 2θ as shown in Fig. 8. This detection limit was calculated to be 0.6% for the core calibration curve. Core samples taken from the drug layer after compression, sub-coating, and the coating and drying processes were all tested; no visible impurity peak was observed in any of these samples.

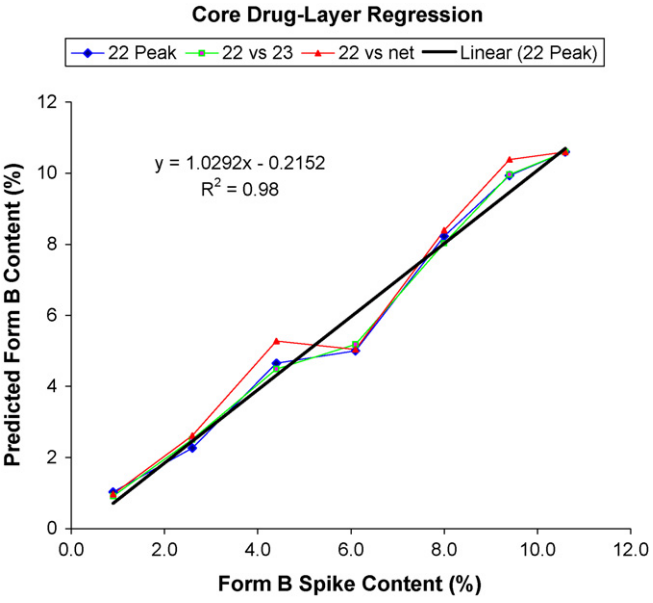

Fig. 8. Compressed core's calibration curve comparison of three methods with plotting response as a function of weight percentage spike.

Table 2
Summary of fit and parameter estimates results from linearly fit model of granulation calibration samples peak area vs. percentage spiked and from linearly fit model of core calibration samples peak area vs. percentage spiked.

Core	22° 2θ		22°:23° 2θ		22°:17–26° 2θ	
	Area	Height	Area	Height	Area	Height
RSquare	0.98	0.97	0.99	0.98	0.98	0.98
Root mean square error	6.42	0.68	0.32	0.71	0.1	0.13
Detection limit (%)	0.8	1.1	0.6	1	1	1
Quantitation limit (%)	2.5	3.2	1.8	3.1	2.9	2.9
Granulation	22° 2θ		22°:23° 2θ		22°:17–26° 2θ	
	Area	Height	Area	Height	Area	Height
RSquare	0.92	0.96	0.92	0.93	0.93	0.95
Root mean square error	1.83	15.02	1.88	1.29	0.34	0.22
Detection limit (%)	1.8	1.3	1.8	1.6	1.7	1.4
Quantitation limit (%)	5.4	4	5.5	5	5.2	4.1

3.2.8. Evaluation of limit of detection and limit of quantitation

The detection and quantitation limits were calculated using ICH guidelines with consideration of both background response and blank response to determine the noise level. The results are provided in Table 2. The limited number of samples from the granulation set increased the quantitation limit to between 4 and 5% with the height parameter having the greatest correlation value.

The core samples comprised a more complete sample set for calibration curve development. The area parameter had better correlation and a lower quantitation limit compared to the height parameter when considering the core samples. A calibration curve developed from a ratio of the signature polymorph B peak to a nearby, strong, and reproducible peak at 23° two theta had a quantitation limit below 2%. The correlation value for this curve was over 99%, and it was used to investigate the effects of the manufacturing process as well as stability storage on the API. Again, the processing did not shown any indications that a transformation had taken place. However, the results of the calibration curve on the stability samples after two years did indicate the presence of

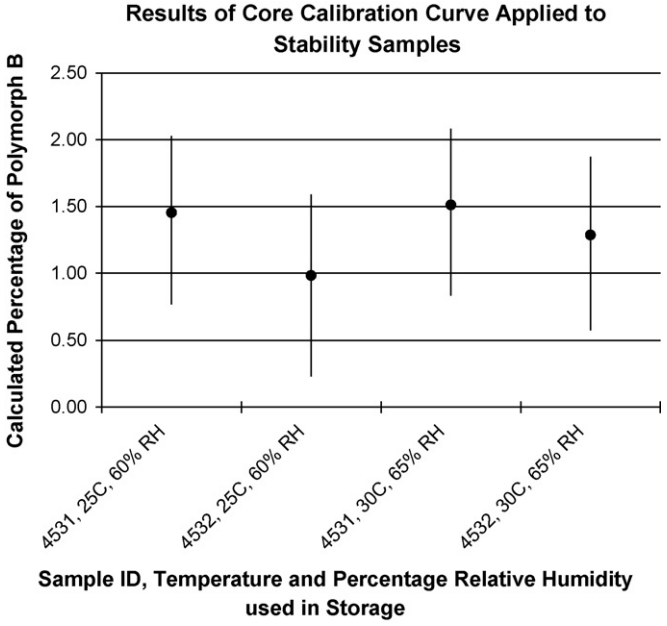

Fig. 9. Results of core calibration curve applied to stability samples.

polymorph B as shown in Fig. 9. The pattern comparison before and after sieving the pulverized tablet revealed that the interference from the excipient had been removed. Overlay of the pattern with spiked curves gathered from the calibration set have the signature peak for the stability samples in the range between 0.9% and 2.1%, matching well with the predicted value from the curve of about $1.5 \pm 0.6\%$.

4. Conclusions

Powder X-ray diffraction can potentially be a viable method to monitor crystal form stability of the active pharmaceutical ingredient in tablet formulations. Here, it has been shown that XRD measurements of the molecule under study were able to detect polymorphic transformation down to less than 1%. Careful and consistent sample preparation was vital in developing a robust calibration curve for quantitation. Particle size control was used to segregate excipients that interfered with important method parameters and statistical methods were applied to focus on impurity concentrations less than 12%. This study proved that the OROS manufacturing process did not cause any change in the crystal form of the drug and that X-ray diffractometery can be used as a convenient and effective test to monitor polymorphic form stability in drug product.

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