ELSEVIER

Journal of Pharmaceutical and Biomedical Analysis
25 (2001) 731–739

JOURNAL OF
PHARMACEUTICAL
AND BIOMEDICAL
ANALYSIS

www.elsevier.com/locate/jpba

A Simple Quantitative FT-IR Approach for the Study of a Polymorphic Transformation Under Crystallization Slurry Conditions☆

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Received 10 August 2000; received in revised form 15 November 2000; accepted 1 December 2000

Abstract

The pharmaceutical compound (2*R*,3*S*)-2-({(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethyl}oxy)-3-(4-fluorophenyl) morpholine hydrochloride (denoted here as Compound X), has been found to crystallize in at least two polymorphic forms. Using only two frequencies (1009 and 1058 cm^{-1}) in the infrared, a linear ($R = 0.998$) calibration plot, consisting of the ratio of the peak absorbances plotted against polymorph concentration, was constructed. This plot allowed the quantification of binary mixtures of polymorphs ranging from < 3 to ~ 100 wt% Form **II** in Form **I**. Spectra were acquired in transmission mode using mineral oil (Nujol) mull sample preparation, for reasons of compatibility with wet cake and slurry samples. The transformation of the less thermodynamically stable polymorph (Form **II**) to the more stable form (Form **I**), in stirred methyl isobutyl ketone (MIBK) slurries, was monitored spectroscopically as a function of time. Performing the experiment at various temperatures allowed the energy of activation for the process to be estimated (42 kJ/mol).

Keywords: slurry; polymorph mixture; FT-IR; quantification; transformation

1. Introduction

Polymorphs of the same chemical compound are defined by a nonequivalence in their crystal structure arrangement [1]. Polymorphs can include solvates (e.g. hydrates), but differ from amorphous solids in that they have long range molecular order. In the pharmaceutical industry, the characterization of polymorphs is of key importance, as differences in polymorphism can affect both the bulk chemical properties (shelf-life, solubility, density, etc.) and the pharmaceutical performance (bioavailability, stability, etc.) of the drug substance [2].

☆ Submitted to: Journal of Pharmaceutical and Biomedical Analysis, July 2000

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0731-7085/01/$ - see front matter
PII: S0731-7085(01)00343-0

The pharmaceutical intermediate, (2*R*,3*S*)-2-({(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethyl}oxy)-3-(4-fluorophenyl)morpholine hydrochloride (Compound X, Fig. 1), like over one-third of all organic compounds [3], exists in at least two polymorphic forms. The two crystal forms have very different physical and chemical properties, as will be discussed later.

Numerous techniques have been reported for the investigation of polymorphism. These include hot-stage microscopy [4], scanning electron microscopy [5], differential thermal analysis (DTA) [6] and differential scanning calorimetry (DSC) [7], as well as infrared (IR) [8], near-infrared (NIR) [9] and Raman [10] spectroscopies. However, only crystallographic methods (i.e. x-ray powder diffraction, XRPD [11–13], when considering the bulk of pharmaceutical compounds) can provide definitive proof of the existence of polymorphism [1]. Limitations of the XRPD approach include its susceptibility to both differences in particle size and preferred orientation [3], which, in addition to peak overlap [13], can affect the sensitivity of XRPD assays. Furthermore, XRPD does not allow any correlation of individual diffraction peaks with specific structural features. Because of these factors, much research has focused on alternative techniques for the determination of crystal form.

FT-IR spectroscopy has been at the forefront of much polymorph research. This technique is readily available in most analytical laboratories, and, in many cases, can be used to identify crystal form simply by inspection of spectral differences. For example, the incorporation of water molecules into the crystal lattice can significantly alter many molecular vibration modes relative to the anhydrous form [14], but such systems define hydrates, not necessarily polymorphs. However, more subtle spectroscopic changes can also be observed, such as those arising from tautomerism or changes in intermolecular (hydrogen) bonding [15]. Spectroscopic differences like these have resulted in the identification of absorbance bands useful for the quantitative analyses of polymorph mixtures [16].

In recent literature, the quantification of mixtures of polymorphs of drug substances has been accomplished using both Diffuse Reflectance Infrared Fourier Transform (DRIFT) [17–20] and Attenuated Total Reflectance FT-IR (ATR FT-IR) spectroscopies [2], with detection limits (strongly system dependent) in the range of 2–7% w/w [2,18]. While these techniques may be suitable for the solid-state analysis of bulk drugs and even tablets [18], the ability to characterize polymorph composition during crystallization is very attractive. The identification/quantification of undesirable polymorphs at this stage can allow for remedial action to be taken, in-process. For instance, seeding the batch with the desired crystal form (at an appropriate temperature, in the case of enantiotropic polymorphs) can often produce the desired crystal form, and thus affect polymorph purity and overall product yield. Unlike the DRIFT approach (using KBr), the use of mulls, in a transmission geometry, allows infrared spectra of the 'wet' (slurry/wet cake) solid samples to be acquired, with better sensitivity than ATR FT-IR. Furthermore, the sample preparation is relatively fast and simple, and avoids high pressure sample compression which can induce polymorphic changes [2].

In this work, a calibration curve was constructed for binary mixtures of Compound X polymorphs, using only an absorbance ratio of two characteristic IR frequency bands (samples prepared as Nujol mulls for reasons mentioned above). The calibration curve was applied to a kinetic investigation of the transformation of the less stable polymorph of Compound X (Form **II**) to the more stable form (Form **I**), in methyl isobutyl ketone (MIBK) slurries. The progress of the transformation was monitored (with the aid of the calibration curve) at various temperatures to determine the activation energy barrier for the process. The experimental conditions were selected to mimic those of a typical crystallization, prior to isolation of the product. This is a markedly different approach from many previous investigations of polymorph transformation [21] and interconversion [22], involving elevated temperatures to initiate these processes in solid samples.

2. Experimental

2.1. Materials

Forms **I** and **II** of Compound X (HCl salt) were produced by Merck & Co., Inc.. Both forms had a chemical purity in excess of 99.5%, as determined by HPLC. The solvent 4-methyl-2-pentanone (methyl isobutyl ketone, MIBK) was used as obtained from the manufacturer (Pride-Union Carbide, lot number 25340).

2.2. Differential Scanning Calorimetry (DSC)

DSC was performed using a Pyris 1 instrument with closed pans, at a heating rate of 10°C/min.

2.3. Solubility Studies

The solubilities of both polymorphic forms of Compound X, in MIBK, were obtained using an HPLC weight percent assay. Excess solids were agitated with MIBK in sealed ampoules held in a thermostat bath at 25°C. After equilibration, the ampoules were centrifuged, opened, and the supernatant filtered through cotton wool. The filtrate was quantitatively diluted (100-fold) for concentration analysis by HPLC (YMC ODSAQ column, injection volume = 20 μl, flow rate = 1.2 ml/min and detector set to 220 nm). With a mobile phase composition of 55/45 (v/v) methanol/0.1% (v/v) phosphoric acid (isocratic), the approximate retention time for Compound X was 3 min. XRPD analysis was carried out on the remaining solids immediately after filtration, to ensure no polymorph transformation had occurred.

2.4. Solid State ^{13}C NMR

The characterization of the two polymorphs by solid-state nuclear magnetic resonance (NMR) was performed using a Bruker DSX 400WB NMR system, operating at 100.6 MHz for ^{13}C and 400.1 MHz for ^{1}H. A Bruker MAS 400WB BL7 double-resonance probe with a spinning module housing and a 7 mm zirconia rotor with Kel-f end caps were utilized in the data acquisition. Solid-state ^{13}C NMR spectra were acquired using cross polarization (CP), magic-angle spinning (MAS) and high-power (~ 59 kHz) decoupling, with variable-amplitude cross-polarization and total sideband suppression (TOSS). Proton and carbon 90° pulse widths were 4.25 μs, with a contact time of 2.0 ms. The samples were spun at 7.0 kHz and a total of 176 scans were collected for the Form **I** spectrum, while 174 scans were collected for the Form **II** spectrum. A line broadening of 10 Hz was applied to the spectra before the Fourier transform was performed. Chemical shifts were observed on the TMS scale, using the carbonyl carbon of glycine (176.03 ppm) as a secondary reference.

2.5. X-ray powder diffraction

XRPD was performed using a Philips APD XRG 3100 X-ray generator (producing Cu K-alpha radiation) and a Philips PW 3710 MPD controller. The analyses used an accelerating potential of 45 kV and a current of 40 mA. Samples were scanned from 2 to 40° (2 δ) with a continuous scan of 475 s duration.

Samples were ground thoroughly in a mortar before analysis. The sample slide was filled with the ground material and spread flat. Mixtures of Forms **I** and **II** were prepared by combining weighed amounts of each solid, grinding in a mortar for 3 min, transferring the solids into a second mortar, and grinding thoroughly a second time.

2.6. FT-IR Instrumentation

Infrared spectra were recorded using a Nexus 670 spectrometer (Nicolet) equipped with a DTGS detector, using 32 co-added scans acquired at 4 cm^{-1} resolution in the 4000 to 600 cm^{-1} range. A PC running Omnic E.S.P. software (version 5.1) was used to capture the spectra. A dry air purge was employed during all data acquisition.

2.7. FT-IR Calibration Curve

To construct the calibration curve, the absorbance of the peak at the analytical frequency (1009 cm^{-1}) was divided by that of the reference peak (1058 cm^{-1}), and the ratio plotted against

the concentration of Form **II**. Standard samples were prepared as 100 mg mixtures of the two polymorphs, in various mass ratios: 0.00, 2.19, 5.17, 10.1, 20.3, 28.6, 50.3, 73.6 and 100% w/w of Form **II** in Form **I**. To each ground (mortar and pestle) mixture of solids was added 10 drops of mineral (Nujol) oil and the sample ground thoroughly a second time, producing an opaque white paste. Approximately 2 to 3 drops of the paste were loaded onto NaCl windows for spectral acquisition (background spectra taken periodically). Four spectra, each consisting of 32 co-added scans, were collected at each concentration (fresh samples loaded for each spectrum). The spectra were optimized for sensitivity in the fingerprint region using relatively high sample loadings, the Nujol peak at 1460 cm^{-1} giving $< 15\%$ T. Robustness was incorporated into the calibration curve by purposely varying the sample loadings on the NaCl windows.

2.8. Polymorph Transformation Study

Slurries containing 2.31 g of Form **II** (of Compound **X**) in 10.0 ml of MIBK were stirred at a constant rate (ca. 400 rpm, using a mechanical mixer) inside a thermostat bath (containing 50/50 propylene glycol/water) maintained at a constant temperature of either -5, 10, 15 or 20°C for the duration of the reaction. At each temperature, infrared spectra were acquired periodically until the slurry contained only Form **I** crystals (by inspection of the spectra). Removing the excess solvent from the slurry samples was achieved using 0.45 μm disposable PTFE filters (Whatman), allowing spectra to be acquired on the 'wet' solids as Nujol mulls. Drawing samples, removing the excess MIBK and acquiring the spectra was performed as rapidly as possible (maximum sampling turnaround time of ca. 7 min) to minimize variations in the data from polymorph transformation while on the wet filter. The calibration curve (described above) was used to relate the concentration of Form **II** in the slurry as a function of time.

3. Results and Discussion

3.1. Characterization of the Polymorph Species

Compound X (Fig. 1), of interest to the pharmaceutical industry, was found to crystallize in at least two forms. A visual comparison of the X-ray diffraction patterns (data not shown) demonstrated that Form **II** is easily distinguishable from Form **I**. It was found that a unique reflection at approximately 20.8° (2 δ, Form **II**) could be used to detect the presence of Form **II** (in Form **I**) at the 20% w/w level. Solid state ^{13}C NMR spectra (not shown) of the two forms showed several clearly shifted ^{13}C peaks, a phenomenon common to different polymorphic forms of the same compound [3,8]. Both forms appeared to possess the same number of molecules in the asymmetric unit cell, however, as no peak splittings were observed.

Solubility studies in MIBK at 25°C demonstrated a lower solubility for Form **I** (3.6 mg/g solution) than for Form **II** (12.2 mg/g). Since no differences in X-ray diffraction patterns were observed for the 'wet' versus dry solids, these solubilities can be considered to be the equilibrium solubilities of the polymorphs. (In addition, the X-ray data demonstrated that no solvates were formed.) From the solubility differences, it is evident that Form **I** is more thermodynamically stable than Form **II**. These results were supported by DSC data. DSC scans exhibited single endotherms for both polymorphs, Form **I** having an onset temperature of 200.3°C (peak: 203.8°C, 27.1 J/g) and Form **II** having an onset temperature of 163.1°C (peak: 171.1°C, 21.8 J/g). For Form I, the higher melting point (also note the 2.5 kJ/mol greater enthalpy of fusion) supports the observation that it is the more stable of the two crystal forms.

3.2. Quantification of Polymorphs by IR Spectroscopy

Infrared spectroscopy, a technique common to most analytical laboratories, can often be used to quickly distinguish polymorphs of the same compound. IR spectroscopy has the added advantage over XRPD in being able to provide information

on intermolecular bonding and the disposition of functional groups in the crystals. In the case that the spectroscopic differences between the crystal forms are sufficiently large, quantification of polymorph mixtures may be possible. An application of interest for the quantification of polymorphs lies in the process stages prior to isolation of the drug substance (i.e. crystallization slurries), where, unfortunately, many analytical techniques find limited applicability. However, Nujol mull sample preparation, coupled with FT-IR (transmission mode) spectroscopy, lends itself to the analysis of such 'wet' samples.

For each polymorph of Compound X, there exist several bands in the IR fingerprint region which impart differences to the spectra of the two crystal forms (note that the Nujol peaks at ca. 1376 and 1459 cm^{-1} obscure only a small portion of this region). For instance, the strong C–O–C ether stretches, split into two (ca. 1130 and 1174 cm^{-1}, not shown) by the presence of the 'branching' methyl group [23] in the molecule, are sensitive to the changes in crystal structure. Most notable, however, are the differences in the medium-to-weak absorption bands in the region 1000 to 1250 cm^{-1}, originating from C–N stretches coupled with the stretching modes of the adjacent bonds in the molecule. Two such bands are of interest here for quantitation purposes (see Fig. 2).

The calibration plot shown in Fig. 3 utilizes only two IR bands for simplicity. While the band at the analytical frequency (1009 cm^{-1}) monitors the level of Form **II** in the sample, the reference peak (at 1058 cm^{-1}), common to both polymorphs, acts as an internal standard. The reference band remains essentially constant, irrespective of crystal form (in mulls of fixed concentration with similar path length), thus serving to minimize matrix effects caused by differences in sample loading and crystal form composition. The high degree of linearity in the calibration curve relies on the absorbance of the

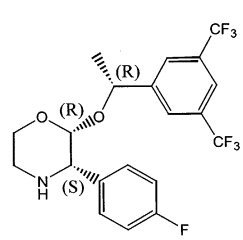

Fig. 1. Structure of (2*R*,3*S*)-2-({(1*R*)-1-[3,5-bis(trifluoromethyl) phenyl]ethyl}oxy)-3-(4-fluorophenyl)morpholine, shown as the free base.

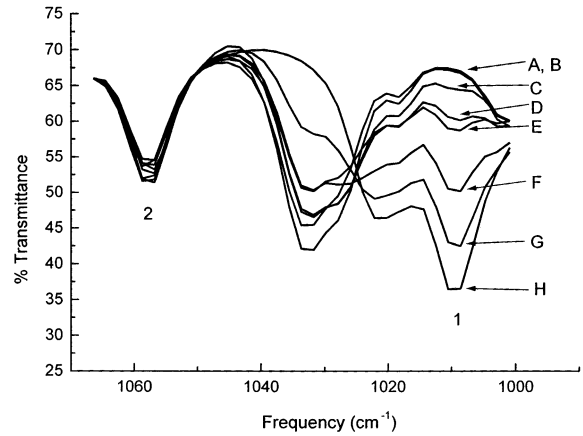

Fig. 2. Overlaid FT-IR spectra (in the region of interest) of various concentrations of the two crystal forms, showing both the analytical (1) and reference (2) frequencies. A to H represent 0, 2.2, 10, 20, 29, 50, 74 and 100% w/w mixtures of Form **II** in Form **I**.

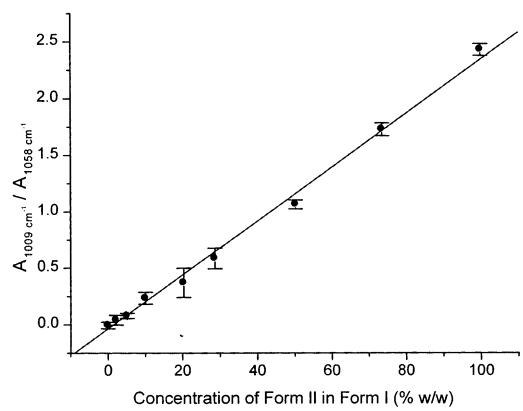

Fig. 3. Calibration curve established by plotting the ration of peak absorbances at 1009 and 1058 cm^{-1}, versus the concentration of Form **II** in Form **I**. Each data point represents the mean (error bars are the standard deviation) of four replicate measurements. The linear regression fit has $R = 0.998$, with a slope of 0.00238 ($\pm$0.0006) and y-intercept of -0.04 ($\pm$0.02).

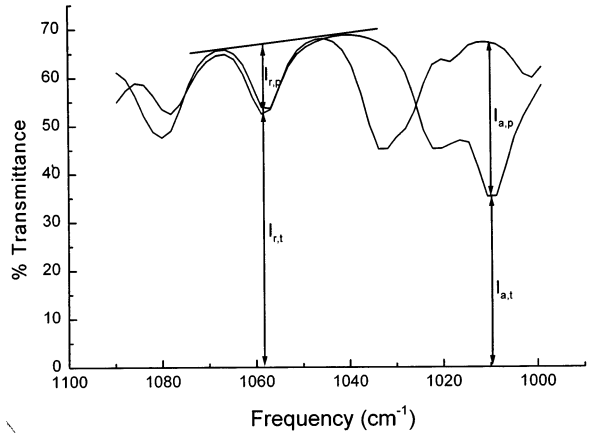

Fig. 4. Overlaid FT-IR spectra of pure Forms **I** and **II**, demonstrating the procedure for the measurement of the peak ratios for the calibration plot. See text for details.

analytical band obeying the Beer-Lambert Law, with the absorbance of the reference band being independent of the relative polymorph concentration. The fit of the data using only the two frequencies to characterize the differences between the crystal forms was found to be comparable to more sophisticated multivariate techniques.

Fig. 4 graphically demonstrates the procedure for the measurement of the absorbance ratio in the construction of the calibration curve, using overlaid transmission spectra. This ratio was calculated using the equation:

$$A_{\mathbf{1009}\mathrm{cm}^{-1}}/A_{\mathbf{1058}\mathrm{cm}^{-1}} = -\log[(I_{a,t})(I_{r,p}+I_{r,t})/(I_{r,t})(I_{a,p}+I_{a,t})] \quad (1)$$

where $I_{a,p}$ is the intensity (in transmission mode) of the analytical peak, $I_{r,p}$ the intensity of the reference peak, $I_{a,t}$ the transmitted intensity at the analytical frequency and $I_{r,t}$ the transmitted intensity at the reference frequency. While the baseline for the analytical peak was determined using a spectrum of pure Form **I** (since the peak is present only in Form **II**), the baseline for the reference peak was estimated from the tangential line shown in the figure.

The calibration plot exhibits good linearity over nearly the entire concentration range studied, with an estimated limit of quantitation (LOQ) of ca. 2.7% w/w Form **II** in Form **I**. The LOQ was calculated using twice the standard deviation in the intercept as the minimum detectable signal.

3.3. Polymorph Transformation

Kinetic studies investigating polymorph transformation have been performed by others, using techniques such as DSC and FT-IR, on heated solid samples [24,25]. The work presented here parallels these investigations, but focuses on slurries. The progress of the conversion of Form **II** to Form **I**, at various temperatures, was followed spectroscopically with the aid of the calibration plot in Fig. 3.

At each temperature, a plot of the concentration of Form **II** as a function of time (for example, see Fig. 5 Inset) yielded a sigmoidal curve. Each reaction profile had an induction period (similar to that observed by others for different systems [25,26]), followed by an 'acceleratory' and, finally, a 'decay' period. The induction period, which is thought to describe the formation of Form **I** nuclei at the surface cracks or strain lines of the Form **II** crystals, ranged from ca. 200 min at -5°C to less than 20 min at 20°C. The

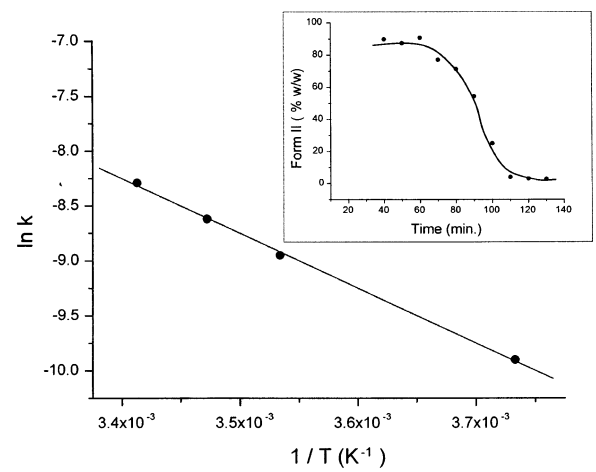

Fig. 5. Arrhenius plot for the polymorph transformation from Form **II** to Form **I**, in stirred MIBK slurries. The linear regression fit has a slope of -5000 K (± 100) and intercept of 8.7 (± 0.5). *Inset*: Reaction profile for the transformation followed as a function of time, at 10°C.

subsequent 'acceleratory' period (well described by an autocatalytic expression [26]), reflects a three-dimensional growth of the nuclei, proceeding relatively unhindered at the early stages of the transformation while there are abundant reaction centers available. The 'decay' period is caused by a limitation in the number of centers from which crystal growth (branching) can occur in the latter stages of the transformation, as the abundance of Form **I** crystals increases and concentration of Form **II** diminishes.

Extracting rate constants from the data in the manner described by Matsuda et al. [25] (using the Avrami-Erofe'ev equation [27–29]) or Gunning et al. [24] (using an equation derived from earlier work by Prout and Tompkins [26]) was complicated by limited precision in the data points and/or too few points collected, especially at the higher temperatures. The scatter in the data can be partially attributed to matrix variations (i.e. amount of MIBK) among the 'wet' samples pulled from the slurries. Additional error arises from the fact that the standard samples used to construct the calibration curve did not contain the solvent, unlike the analytical samples. The likelihood of quantification being affected by the formation of 'metastable' polymorphs during the transformation process is thought to be low, as none of these species were observed by DSC and no evidence for their existence was provided by FT-IR. Nevertheless, from the sigmoidal reaction profiles, it was possible to obtain a good estimate of the midpoint of the reaction. Prout and Tompkins [26] demonstrated that an equation of the type:

$$\exp[-k(t-t_{\frac{1}{2}})] = x/(1-x) \quad (2)$$

(where k is the rate constant for the process, x is the mole fraction of Form **II** at time t, and $t_{\frac{1}{2}}$ is the time required for 50% conversion), can adequately describe the sigmoidal shape of these curves beyond the induction period. Even though we are interested in the case where x approaches 0.5 (as $t \rightarrow t_{\frac{1}{2}}$), if, in Eq. (2), the exponential term is small, (i.e. $x \rightarrow 0$ as $t \rightarrow \infty$), the equation reduces to:

$$x = \exp(-kt + c) \quad (3)$$

where c is a constant, equal to the product of k and $t_{\frac{1}{2}}$. Eq. (3) may be reduced further to:

$$x = c' \exp(-\mathrm{kt}) \quad (4)$$

where c' is a new constant, equal to $\exp(-c)$. Note that Eq. (4) has the form of a first order reaction. The reaction rate constant can thus be estimated (within reasonable uncertainty) from the time required for the conversion to reach 50% completion, using the relation:

$$k = (\ln 2)/(t_{\frac{1}{2}}) \quad (5)$$

where the data point of interest (corresponding to the midpoint of the transformation) may be easily estimated from the reaction profile.

An Arrhenius plot [30], consisting of the natural logarithm of the reaction rates (k) plotted against their corresponding reciprocal temperatures ($1/T$, where T is in K), is shown in Fig. 5. The linearity of the regression fit is given by $R = 0.999$, and the activation energy extracted from the slope of the line is ca. 42 kJ/mol (believed to be accurate to within 15%). This value is of the same order of magnitude as the activation energy obtained by others, for the solid state transformations of different compounds [25]. Note that the solvent in these slurry systems is thought to play a significant role in accelerating the polymorph transformation, since dry, solid Form **II** has been found to be stable at room temperature for at least 6 months (stored in a dark screw-cap glass bottle). Matsuda et al. [25] showed that increased humidity levels alone can shorten the induction period for polymorph transformation in solid phenylbutazone, the water serving as a catalyst for nucleation (note that Compound **X** is non-hygroscopic).

A survey of the literature uncovered a previously reported quantitative FT-IR assay, involving Nujol mull sample preparation, for the investigation of polymorph interconversion in aqueous suspensions of sulphamethoxydiazine [31,32]. In support of our observations, it was found that the polymorph transformation (in this case, a measure of the drug substance stability when stored as a suspension) occurred significantly faster in the presence of water than in the dry solid.

4. Conclusions

A simple approach for the quantification of mixtures of polymorphs of (2*R*,3*S*)-2-({(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethyl}oxy)-3-(4-fluorophenyl)morpholine hydrochloride (Compound X), monitoring only two IR frequencies in the fingerprint region, was developed. The calibration curve constructed was linear, with sufficient precision to allow quantification of less than 3% w/w Form **II** in Form **I**. The Nujol mull sample preparation scheme, coupled with transmission mode FT-IR spectroscopy, provided good sensitivity for quantitation as well as compatibility with the analysis of slurry samples.

An application of this technique was demonstrated by studying the transformation of Form **II** to Form **I** crystals of Compound X, in MIBK slurries, as a function of temperature. The investigation provided a reasonable estimate for the activation energy of the process, carried out under typical crystallization conditions. The presence of solvent was found to increase the rate of the transformation reaction, consistent with observations by others. Previously, the transformations of many polymorph species were performed using DSC or 'hot stage' microscopies, on dry solid samples, which do not adequately reflect process conditions.

5. Future Directions

The on-line determination of polymorphic form, eliminating the need for sample withdrawal and preparation, is attractive for the study of crystallization slurries. The analytical performance (precision) of an on-line technique can be superior to an off-line method, as the sample matrix effects are often averaged out (this includes both the solvent effects and issues associated with the mixing of powders of different morphologies [1]). Using near infrared (NIR) spectroscopy (the probe placed directly into a mixture of powders of the two polymorphs), our preliminary results have shown that the quantification of the two crystal forms of Compound X can be accomplished with near comparable sensitivity to the IR method described here (using factor analysis on second-derivative background-corrected spectra, in the C–H overtone region). In addition, data collection can be performed significantly faster, allowing higher temperature processes to be studied.

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