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Characterization and Quantitation of Aprepitant Drug Substance Polymorphs by Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy

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In this study, we report the use of attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FT-IR) for the identification and quantitation of two polymorphs of Aprepitant, a substance P antagonist for chemotherapy-induced emesis. Mixtures of the polymorph pair were prepared by weight and ATR-FT-IR spectra of the powdered samples were obtained over the wavelength range of 700–1500 cm^{-1} . Significant spectral differences between the two polymorphs at 1140 cm^{-1} show that ATR-FT-IR can provide definitive identification of the polymorphs. To investigate the feasibility of ATR-FT-IR for quantitation of polymorphic forms of Aprepitant, a calibration plot was constructed with known mixtures of the two polymorphs by plotting the peak ratio of the second derivative of absorbance spectra against the weight percent of form II in the polymorphic mixture. Using this novel approach, 3 wt % of one crystal form could be detected in mixtures of the two polymorphs. The accuracy of ATR-FT-IR in determining polymorph purity of the drug substance was tested by comparing the results with those obtained by X-ray powder diffractometry (XRPD). Indeed, polymorphic purity results obtained by ATR-FT-IR were found to be in good agreement with the predictions made by XRPD and compared favorably with actual values in the known mixtures. The present study clearly demonstrates the potential of ATR-FT-IR as a quick, easy, and inexpensive alternative to XRPD for the determination of polymorphic identity and purity of solid drug substances. The technique is ideally suited for polymorph analysis, because it is precise, accurate, and requires minimal sample preparation.

Anticancer treatment based on cisplatin chemotherapy is associated with unpleasant and distressing side effects, such as nausea and vomiting, which reduce the quality of life and may cause patients to delay or refuse potentially curative therapy.^{1–3}

Efforts to prevent chemotherapy-induced emesis have been directed at blocking neurotransmitter receptors such as dopamine, serotonin, and substance P in the brain stem vomiting center. Aprepitant, a neurokinin-1 receptor antagonist that mediates the biological actions of substance P, is currently in clinical development for chemotherapy-induced emesis.^{4,5} In a double-blind, placebo-controlled clinical trial, Aprepitant was shown to prevent delayed emesis after treatment with cisplatin.⁴ It is known to exist in two crystal forms, hereby termed as form I and form II. Form I was determined to be thermodynamically more stable than form II, and it was selected as the desired crystal form for manufacturing.⁶

Although newer routes of drug administration are constantly being developed, solid dosage forms continue to be the most popular delivery vehicle for pharmaceutically active therapeutic agents.⁷ Physical properties of solid active ingredients can play a very important role in their processability and bioavailability. One such characteristic of the solids is polymorphism, defined as the ability of a compound to crystallize as more than one distinct crystal species.⁸ Different polymorphs of the same drug are different not only in their crystal shape and structure but also in their solubility, melting point, thermodynamic stability, density, vapor pressure, and electrical properties. It is also well-known^{8–10} that such changes in polymorphic behavior may adversely affect the pharmaceuticals' mixing and milling properties as well as their stability, suspendibility and bioavailability. Therefore, characterization of polymorphism in solid pharmaceuticals has become an important aspect of drug development and manufacturing.^{11,12}

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In the early phase of drug development, accurate identification and quantification of the desired polymorph of the drug substance is critical for the success of the program. This warrants the need for the development of an analytical technique that is capable of providing rapid qualitative and quantitative monitoring of the crystal form composition of the drug substance. Several nonspectral as well as spectral analytical methods are commonly used for the physical characterization of pharmaceutical polymorphs. Most of these techniques are based on crystallography, microscopy, thermal analysis, vibrational spectroscopy, or nuclear magnetic resonance (NMR).¹³ Some widely used nonspectral methods include differential scanning calorimetry,^{14–16} differential thermal analysis,^{17–19} and thermogravimetric analysis,^{12,20} which reveal phase transitions in solids; optical^{12,21–24}, hot-stage,²⁵ and electron²⁶ microscopy for morphological analysis; and X-ray powder diffraction (XRPD)^{27–33} for structural analysis. Alternatively, vibrational spectroscopy, such as infrared absorption^{34–37} or Raman scattering^{38,39} has been used to measure the vibrational modes of solids, which contain information about structural differences of polymorphs. Solid state NMR spectroscopy is becoming increasingly important in the study of polymorphs, because it exposes differences in the chemical environment of nuclei caused by differences in their crystal structures.^{38,40,41}

Among these techniques, XRPD provides the most direct and definitive identification of polymorphs and offers a means for

quantitative analysis of polymorphic mixtures. However, XRPD is an expensive tool not readily available in many laboratories and manufacturing sites. Furthermore, complex curve-fitting methods or whole-profile multivariate analysis may be necessary. Some other limitations of the XRPD technique are susceptibility to differences in particle size and preferred orientation as well as its inability to provide correlation of individual diffraction peaks with specific molecular features. In recent years, Fourier transform infrared (FT-IR) spectroscopy has been gaining popularity. FT-IR instruments are readily available in many laboratories and offer high resolution as well as a good signal-to-noise ratio for sensitivity. Emergence of new reflectance sampling techniques, such as diffuse reflectance^{42,43} and attenuated total reflectance (ATR)⁴⁴ promises to play a major role in the growing acceptance of FT-IR techniques for polymorph analysis. These sampling devices allow for direct measurement of IR spectra of solids in their native state, thus eliminating the need for sample pretreatment, as in the case of mineral oil or KBr pellet-sampling techniques. Therefore, reflectance sampling techniques of FT-IR appear to offer a complementary alternative to various other spectral as well as nonspectral techniques for both qualitative and quantitative analysis of pharmaceutical polymorphs. A few applications of the reflectance sample techniques for polymorph analysis have appeared in the scientific literature in the past decade. For instance, diffuse reflectance FT-IR was applied to the quantitative analysis of binary mixtures of sulfamethoxazole polymorphs.⁴⁵ Application of ATR-FT-IR has also been reported for the identification of various pharmaceutical solids⁴⁶ and most recently for quantitative analysis of mixtures of three ganciclovir polymorphs.⁴⁷ These investigations lacked a comparison of FT-IR to other techniques for polymorph analysis. Furthermore, the latter study employed a calibration model for quantification based on analysis of the raw spectral data. A recent study on polymorph analysis using near-infrared reflectance spectroscopy,⁴⁸ however, seems to suggest that the univariate method of calibration utilizing the second-derivative absorbance value at a single wavelength normalized with respect to the second-derivative value at a second (reference) wavelength may provide superior sensitivity and a more robust calibration model than the partial least-squares (PLS) model or other models based on raw data analysis by eliminating any spectral variation caused by sample particle size or intensity of FT-IR source.

In this paper, we explore the feasibility of ATR-FT-IR for use in polymorph identity and purity of Aprepitant bulk drug substance. For the two polymorphs of Aprepitant, an infrared fingerprint region was identified that contained significant spectral differences. Using the approach based on second-derivative spectral treatment, a linear calibration model was developed with several polymorph mixtures to afford the quantitative analysis of polymorphic content in bulk pharmaceuticals. The ATR-FT-IR

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results of polymorph content of Aprepitant drug substance were compared directly to those obtained with XRPD to test the predictive power of ATR-FT-IR for quantitative analysis. The effect of pressure due to the ATR sampling device on polymorph purity was also investigated to determine if pressure induces transformation of form **II** to form **I**. Finally, the ATR-FT-IR method for polymorph analysis was validated for reproducibility and precision.

EXPERIMENTAL SECTION

Instrumentation. *Attenuated Total Reflectance (ATR) Fourier Transform Infrared Spectroscopy.* A Nicolet Nexus-670 FT-IR (Nicolet Instrument Co., Madison, WI) equipped with a DTGS detector was employed for all experiments. A Golden Gate Diamond ATR sampling accessory (Specac Inc., Technology Court, Smyrna, Georgia, USA) was employed for ATR-FT-IR experiments. Each sample was placed on the ATR sampling device and aligned according to the manufacturer's recommendation. In all experiments, a torque of 20 cNm was applied by the Golden Gate Diamond ATR sampling device, except in studies when the effect of pressure (directly proportional to torque) on polymorphic content was examined. Nitrogen purge was maintained throughout during data acquisition. Each spectrum represents 32 co-added scans measured at a spectral resolution of 2 cm^{-1} in the $4000\text{--}600\text{ cm}^{-1}$ range with an aperture of 36. Spectral data were acquired with Omnic E.S.P software version 5.1 (Nicolet Instrument Co.). The Unscrambler software from Camo, Version 7.5 (Corvallis, OR) was employed for data analysis.

X-ray Powder Diffractometry (XRPD). A Phillips APD XRG 3100 X-ray powder diffractometer (Amsterdam, Netherlands) equipped with a Philips PW 3710 MPD controller was utilized for all XRPD experiments. Each sample was placed evenly on a slide and scanned at a rate of $0.01^\circ/\text{s}$. The X-ray generator produced copper $K\alpha$ radiation at an accelerating potential of 45 kV with 40 mA filament emission. Patterns were collected in continuous-scan mode from 2 to 40° (2θ) for initial surveys and in a step-scan mode from 20 to 22° (2θ) for final analysis.

Solid-State Nuclear Magnetic Resonance (NMR). A Bruker DSX-400 NMR instrument (Billerica, MA) was used in the study. All solid-state NMR spectra were obtained in 9.4-T magnetic field strength using a Bruker double-resonance CPMAS probe spinning at 15.0 kHz for $^1\text{H}/^{13}\text{C}$ and a CRAMPS probe spinning at 15.0 kHz for ^{19}F . The ^{13}C and ^{19}F resonance frequencies are 100.63 and 376.49 MHz , respectively, at this magnetic field strength. The $^1\text{H}/^{13}\text{C}$ CPMAS NMR experiments were performed with a relaxation delay of 5 s and dwell time of $14.3\text{ }\mu\text{s}$ using 10 Hz of line broadening. All ^{13}C spectra were obtained using a standard CPMAS pulse sequence and referenced to the carbonyl carbon of glycine (176.03 ppm). The ^{19}F experiments were performed with a relaxation delay of 3 s , dwell time $5\text{ }\mu\text{s}$, echo delay of 0.00002 s , and line broadening of 100 Hz . The reference standard for the ^{19}F was Teflon (-122 ppm). The ^{19}F chemical shifts associated with form **I** are -61.6 , -63.6 , and -111.7 ppm , and those for form **II** are -61.6 , -62.8 , and -111.7 ppm . The ^{13}C chemical shifts associated with CF_3 groups resonate in the region of $125\text{--}132\text{ ppm}$ for both polymorphs.

Materials. The structure of Aprepitant is shown in Figure 1. The two polymorphs, form **I** and form **II**, were synthesized and isolated at Merck Research Laboratories (Merck & Co., Inc., Rahway, NJ). Each polymorph was further analyzed by reversed-

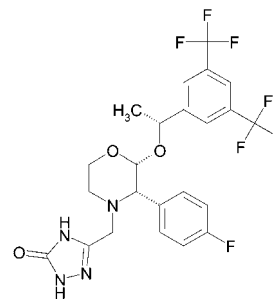


Figure 1. Structure of Aprepitant.

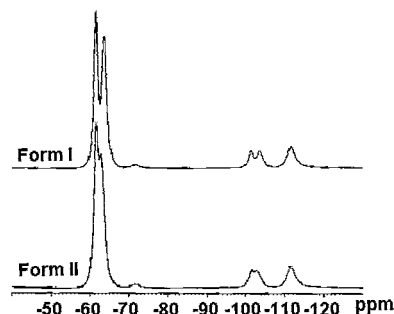


Figure 2. ^{19}F MAS (a) and ^{13}C CPMAS (b) NMR spectra of Aprepitant polymorph forms **I** and **II**.

phase HPLC and determined to contain $<1\%$ of other process related impurities.

Preparation of Standards and Polymorph Mixtures. Known amounts of the two pure polymorphs were weighed separately on a Mettler analytical balance (Hightstown, NJ) to an accuracy of 0.01 mg and mixed together to prepare a set of standards for the development of the calibration models for ATR-FT-IR and XRPD. For instance, 5.00 mg of form **II** was mixed with 95.00 mg of form **I** to prepare a calibration standard containing 5 wt \% form **II**. The mixture was ground in a mortar and thoroughly agitated for 5 min to ensure mixing uniformity. The total weights were kept consistent for each set of samples at $\sim 100\text{ mg}$. Calibration standards containing $2, 4, 5, 6, 8, 10, 12, 14, 15, 16, 18, 20, 30, 35, 40, 60$ and 80 wt \% of form **II** were prepared in this manner. A test group of polymorphic mixtures containing varying ratios of the two crystal forms was also prepared for polymorph analysis and comparison study. All samples, that is, the pure components, calibration standards, and test mixtures, were stored in amber bottles sealed with Teflon-lined caps and kept at room temperature.

RESULTS AND DISCUSSION

The two Aprepitant polymorphs were characterized by solid-state NMR and solubility studies. The ^{19}F MAS NMR spectra of the two forms in Figure 2 displayed a significant difference in the chemical shift due to one CF_3 group, whereas the remaining two ^{19}F environments were found to be similar for both forms. Solubility studies were carried out with both polymorphs to determine the thermodynamically more stable form. The solubilities of the two forms under equilibrium conditions were measured in a $2:1$ (v/v) methanol/water system at 0°C . No conversion of the solids was observed under these conditions after 18 h of agitation. Form **I** was found to be less soluble in the methanol/water system than form **II**, indicating that form **I** is the thermo-

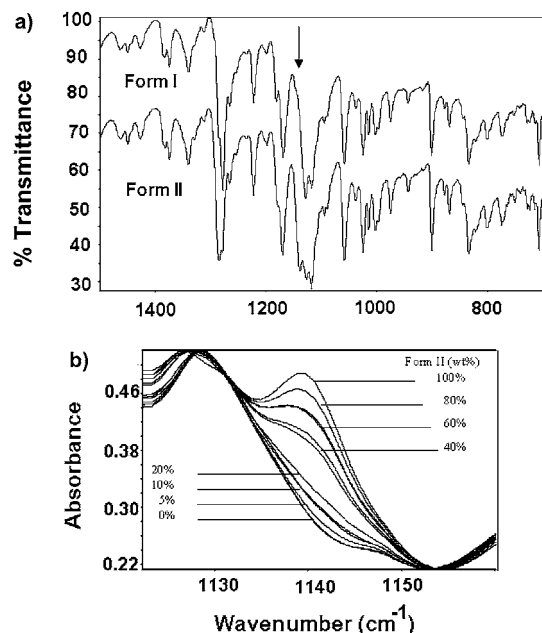


Figure 3. (a) Stacked ATR-FT-IR transmittance spectra of Aprepitant forms **I** and **II** and (b) overlaid ATR-FT-IR absorbance spectra of Aprepitant polymorph mixtures containing 0, 5, 10, 20, 40, 60, 80, and 100 wt % of form **II**.

dynamically more stable form at 0 °C. This finding is further supported by the observation using XRPD that form **II** completely converts to form **I** when recrystallized out of a solution of acetonitrile or when heated to 230 °C under nitrogen. Under ambient conditions, form **I** is the most stable polymorph, and pure samples of form **I** can be stored for long periods of time without undergoing conversion.

Polymorph Identity and Content by ATR-FT-IR. Examination of techniques based on infrared spectroscopy for potential use in polymorph analysis appears to be particularly promising in light of recent studies^{34,37,45,47} and owing to the ubiquitous nature of such techniques. The FT-IR method utilizing mineral oil may not be an ideal technique for quantitative polymorph analysis, because it introduces unnecessary spectral interference associated with mineral oil as well as variation due to sample concentration. Even the alternative sample pretreatment approach of KBr pellet formation may subject the sample to high pressures, which raises an important concern about the possibility of mechanical-stress- or chemical-reactivity-induced polymorphic changes.⁴⁹ The recent emergence of reflectance sampling techniques, which allow for direct measurement of infrared spectra of solids, appears to have successfully addressed most of these concerns. For this reason, the Golden Gate attenuated total reflectance accessory was considered in this study for qualitative and quantitative analysis of Aprepitant polymorphs as an advancement over mineral oil and KBr-based IR techniques.

Since the ¹⁹F MAS NMR analysis of the two Aprepitant polymorphs showed a significant shift of a CF₃ group from form **I** to form **II**, ATR-FT-IR spectral data were obtained in the 1100–1400 cm^{−1} region where the C–F stretch vibrations are observed. Figure 3a illustrates an ATR-FT-IR transmittance spectra of the

two polymorphs in the frequency range of 700–1500 cm^{−1}. Indeed, the form **II** spectrum exhibits an additional vibrational band at 1140 cm^{−1} that clearly distinguishes it from form **I**, indicating that ATR-FT-IR can provide definitive identification of the two polymorphs. In combination with ¹⁹F MAS NMR data, the presence of an additional band at 1140 cm^{−1} suggests a different spatial arrangement of a CF₃ group in form **II** polymorph. The ATR-FT-IR method is precise and reproducible with 7.0% RSD of peak height at 1129 cm^{−1} based on four absorbance spectra of form **I** polymorph obtained over a period of 7 days.

To investigate the potential of the ATR-FT-IR technique for quantitative polymorph analysis, several calibration standards containing 0, 5, 10, 15, 20, 40, 60, 80, and 100 wt % of form **II** in mixtures of form **I** and form **II** were analyzed. Figure 3b illustrates the ATR-FT-IR absorbance spectra thus obtained. The spectra show that the band at 1140 cm^{−1} increases in intensity as the weight percent of form **II** increases from 0 to 100% in the polymorph mixture. By plotting the absorbance at 1140 cm^{−1} against the weight percent of form **II** in the polymorph mixture, a linear calibration plot was obtained with a correlation coefficient (*r*²) of 0.9779 and a standard deviation of 6.0 wt %. Another statistical approach, based on partial least-squares (PLS), was adopted to analyze the raw absorbance data. The PLS calibration models were employed in two spectral regions around 1140 cm^{−1}, that is, 1101–1160 and 1135–1160 cm^{−1}. The results indicated that the standard errors of cross-validation were 7.3 and 8.5 wt % form **II**, respectively, with three or more factors.

Additional data analyses were carried out to investigate if the accuracy of quantitative measurement of form **II** in the Aprepitant polymorph mixture could be further enhanced. The PLS regressions were built with second-derivative spectra on three spectral regions around 1140 cm^{−1}, that is, 900–2000, 1135–1160, and 1101–1160 cm^{−1}. The second derivative of the spectra was obtained with eight data points and fitted to a polynomial of second order. Results obtained with these models indicated that the standard errors of cross-validation were over 7.4 wt % form **II** with three or more factors. Thus, the PLS analysis on second-derivative spectra did not yield better results in terms of linearity, accuracy, or robustness than did the direct analysis or the PLS regression of the raw absorbance data. Apparently, additional spectral information other than the peak of 1140 cm^{−1} does not add any analytical merit to the quantitation of form **II**, since the only spectral change related to form **II** in this region is at 1140 cm^{−1}.

Better correlation was achieved by taking the second derivative of the absorbance spectra and normalizing the band intensity at 1140 cm^{−1} against an appropriately selected reference band. This approach offered to enhance the accuracy of quantitation by eliminating baseline effects, any variation caused by sample particle size, or intensity of the FT-IR source, as observed in previous studies.⁴⁵ Although, the second derivative may add spectral noise, this effect was not observed with peak ratio approach. Figure 4 illustrates the second derivative of ATR-FT-IR spectra for various polymorph mixtures in the 1110–1290 cm^{−1} region. As seen, spectral differences between the two polymorphs are significantly enhanced at 1140 cm^{−1} by taking the second derivative. The band at 1272 cm^{−1} was chosen as the reference, since it yielded the best calibration curve when the band intensity at 1140 cm^{−1} was normalized by the band intensity at 1272 cm^{−1}

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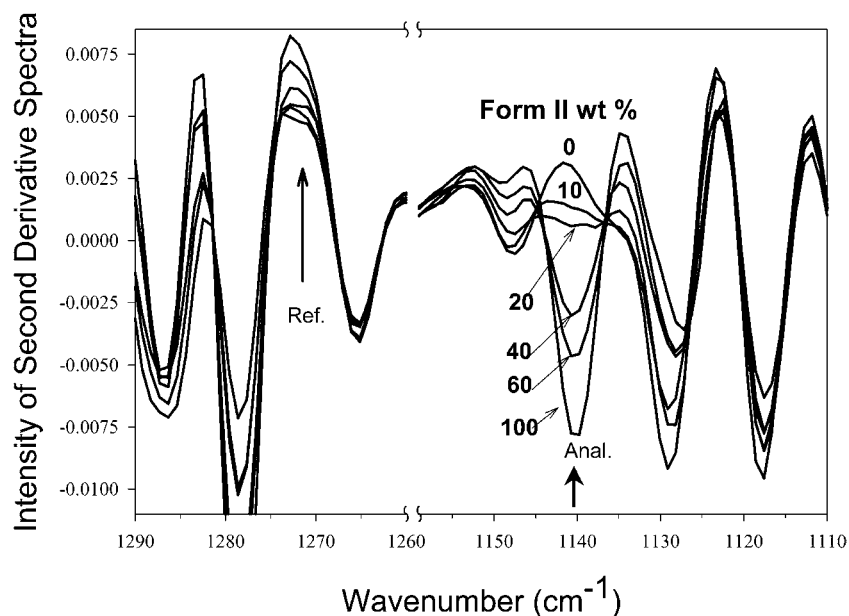


Figure 4. Overlaid second derivative ATR-FT-IR absorbance spectra of Aprepitant polymorph mixtures containing 0, 10, 20, 40, 60, and 100 wt % of form II showing both analytical (1140 cm^{-1}) and reference (1272 cm^{-1}) frequencies.

and this ratio was plotted against form II weight percent in the polymorph mixtures. Each data point on this plot represented the average of three replicate measurements. The calibration plot exhibited good linearity over the entire concentration range studied. Indeed, a much better regression coefficient (r^2) of 0.9971 with a slope of 0.02242 (± 0.00046) and y -intercept of -0.3046 (± 0.023) was achieved using the peak ratio approach on second-derivative spectra. The standard deviation of the method was determined to be 2.1 wt %.

The peak ratio calibration plot based on the second-derivative spectral treatment was employed to investigate the predictive power of ATR-FT-IR in quantitative polymorph analysis. The test mixtures containing 5, 10, 15, 20, 80 and 100 wt % of form II were analyzed in at least duplicate by ATR-FT-IR, and the results are tabulated in Table 1 along with the mean and percent RSD. As seen, weight percent form II values predicted by ATR-FT-IR are in good agreement with actual values, clearly demonstrating the strength of ATR-FT-IR in determining the polymorphic composition of bulk drug substance. The ATR-FT-IR method is also precise and reproducible, as determined by the relatively low percent RSD for weight percent values. The limit of detection (LOD) for this method was calculated by using three times the standard deviation in the intercept as the minimum detectable signal. It was estimated as 3.1 wt % form II in a mixture of form I and II. To confirm the LOD estimated from the calibration plot, three polymorph mixtures containing 3 wt % of form II were prepared according to the procedure describe in the Experimental Section and analyzed by ATR-FT-IR in triplicate. Indeed, the method was able to detect such a low level of form II in the mixtures (2.1 wt % \pm 1.3).

Since the ATR sampling device applies pressure on the sample, an experiment was conducted to determine the critical pressure that induces polymorph transformation. The sampling device torque was varied from 20 cNm to 100 cNm, and the spectrum of the pure form II polymorph was obtained at each pressure. Figure 5 illustrates the effect of pressure on the spectrum of form II

Table 1. Accuracy and Reproducibility of ATR-FT-IR in Quantitative Measurement of Form II

actual wt %	calc wt %
100	97
	105
	107
	103
	94
	(mean = 101)
	(% RSD = 5)
80	75
	82
	79
	(mean = 79)
	(% RSD = 4)
20	19
	20
	19
	(mean = 19)
	(% RSD = 3)
15	17
	20
	16
	(mean = 18)
	(% RSD = 12)
10	9
	11
	9
	(mean = 10)
	(% RSD = 12)
5	2
	3
	(mean = 3)
	(% RSD = 28)

polymorph. It is seen that the band at 1140 cm^{-1} decreases in intensity with an increase in pressure. Using the peak ratio calibration plot based on the second derivative of the absorbance spectra, the form II purity at 20, 40, 70, 80, and 100 cNm was determined to be 96, 81, 74, 71 and 68 wt %, respectively, indicating that an increase in pressure results in transformation of form II

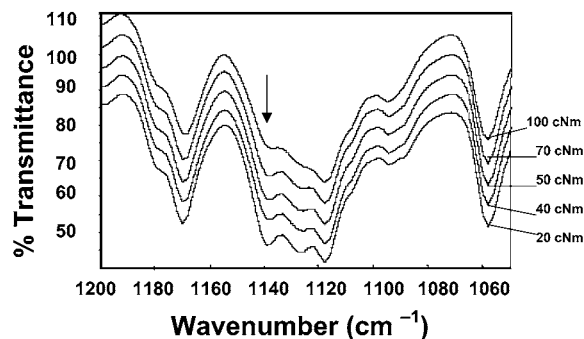


Figure 5. Effect of ATR sampling device pressure on FT-IR transmittance spectra of form II polymorph.

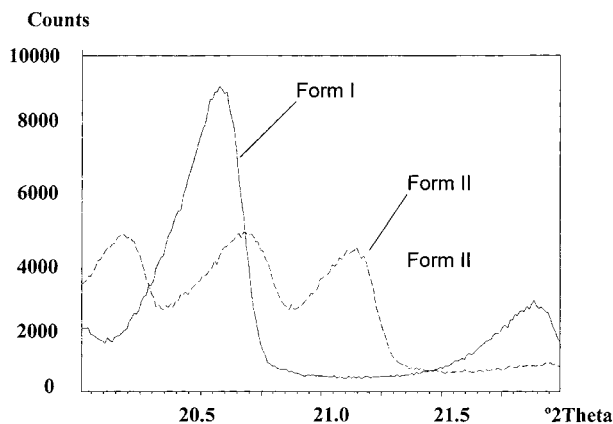


Figure 6. X-ray powder diffraction patterns for Aprepitant polymorphs.

to form I. Results from this investigation justified the selection of a torque of 20 cNm for polymorph analysis to ensure minimal interference from sampling device pressure.

Comparison of ATR-FT-IR and XRPD. To validate the ATR-FT-IR method, an XRPD method was developed for Aprepitant polymorph analysis. The diffraction patterns were obtained for the two polymorphs to identify any differences that could be used to unambiguously distinguish them. Figure 6 illustrates the X-ray powder diffraction patterns of the two polymorphs in the 20–22° (2 θ) region. It is seen that both form I and form II have distinguishing characteristics, which can be used for their identification. In the region from 20.9° to 21.3° in particular, form II exhibits an intensity peak with maximum at ~21.1° (2 θ), whereas form I shows no diffraction peak. This region in the XRPD pattern was chosen for quantification of form II. A set of calibration standards containing 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 and 30 wt % of form II in the polymorph mixture was used in order to build a calibration model for the purpose of quantitation by XRPD. XRPD patterns were obtained for all the standards, and the maximum peak intensity was determined in the range of 21.08–21.17°. This value was plotted against the weight percent of form II in the polymorphic mixture. The calibration plot was found to be linear, with a correlation coefficient (r^2) of 0.9719.

The predictive power of XRPD was tested by analyzing several test mixtures of Aprepitant polymorphs containing known amounts of form II and comparing the results predicted from the linear calibration model with the actual weight percent values. Table 2 lists the replicate results of form II in each mixture predicted by using the linear calibration plot, along with mean values and

Table 2. Accuracy and Reproducibility of XRPD in Quantitative Measurement of Form II

actual wt %	predicted wt %
5	6 5 5 (mean = 5) (% RSD = 11)
10	11 11 10 (mean = 11) (% RSD = 5)
15	17 19 18 (mean = 18) (% RSD = 6)
25	26 22 (mean = 24) (% RSD = 12)

Table 3. Comparison of ATR-FT-IR and X-ray Results for Polymorph Mixtures of Aprepitant

actual wt % of form II	predicted wt% by XRPD ^a	predicted wt% by ATR-FT-IR ^a
0	0	0
5	6	7
8	8	10
10	11	13
15	17	15

^a Data represents average of three measurements.

percent RSD. It is seen that the predicted XRPD values are in close agreement with the actual weight percent values with the mean of absolute difference being small, indicating that the XRPD linear calibration model is accurate for quantitative polymorph analysis in the region of 0–30 wt % form II. Furthermore, the low percent RSD values indicate that the XRPD method is precise and reproducible. The XRPD calibration plot is expected to be linear also in the higher concentration range. Since the focus of this investigation was primarily to detect low levels of form II in mixtures of the two polymorphs, it was deemed adequate for the purpose of quantification to build the XRPD calibration model in the 0–30 wt % form II region only.

To test the accuracy of ATR-FT-IR in determining the polymorphic content of the drug substance, a study was undertaken that aimed at comparing the results of this method to those obtained by XRPD. In this endeavor, several test mixtures were analyzed in triplicate by both ATR-FT-IR and XRPD, and their respective calibration models were adopted to determine the polymorphic purity of the mixtures. The form II weight percent results thus attained using the two techniques are listed in Table 3. As seen, the results obtained by the two disparate techniques are comparable to each other and in good agreement with the actual weight percent values. In particular, a polymorph mixture containing 5 wt % of form II was analyzed with considerable accuracy by both methods within experimental error. It is concluded that ATR-FT-IR is a powerful technique for both

polymorph identity and content analysis and can be used as a replacement for XRPD for Aprepitant polymorph analysis.

CONCLUSIONS

An ATR-FT-IR method was successfully developed to determine the identity and purity of Aprepitant polymorphs, and its performance in quantitative analysis was compared with that of a well-established technique based on XRPD. The results obtained in this study clearly demonstrate the potential strength of the ATR-FT-IR technique, using the peak ratio second-derivative spectral treatment approach, in qualitative and quantitative analysis of pharmaceutical polymorphs. The technique is comparable to XRPD in terms of precision, reproducibility, and sensitivity, and affords a fast, convenient, and inexpensive means for polymorph analysis. Furthermore, it provides an attractive alternative to traditional disk and mull techniques for the analysis of powdered samples by requiring no sample pretreatment, thereby offering great advantage when normal transmission IR could not be used because of spectral interference by mull or because of concerns for phase transformation. Notwithstanding these strengths, the

ATR-FT-IR technique may not be applicable to some pharmaceutical compounds. Distinct spectral differences between pharmaceutical polymorphs due to differences in spacial arrangement of atoms are essential for the successful employment of this technique for accurate polymorph analysis. When such differences are insignificant, techniques utilizing other modes of detection or differences in resonance frequencies, such as Raman spectroscopy or solid-state NMR, may become the better choices for polymorph analysis.

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