International Journal of Pharmaceutics, 85 (1992) 163–174

IJP 02846

Diffuse reflectance infrared Fourier transform spectroscopy for the quantitative analysis of mixtures of polymorphs

Kerry J. Hartauer [1], Erik S. Miller and J. Keith Guillory

College of Pharmacy, The University of Iowa, Iowa City, IA 52242 (USA)

(Received 10 January 1992)
(Modified version received 12 March 1992)
(Accepted 13 March 1992)

Key words: Fourier transform infrared spectroscopy; Diffuse reflectance; Polymorphism; Sulfamethoxazole; Quantitative analysis; Multicomponent analysis; Partial least-squares

Summary

Binary mixtures of sulfamethoxazole polymorphs were analyzed using diffuse reflectance infrared Fourier transform spectroscopy. A partial least-squares method was utilized for quantitative prediction from the overlapping, FT-IR spectra. The phase composition for a set of independent validation samples was predicted to within 4% of the theoretical values in all cases. The calibration model was valid over a 4 week testing period.

Introduction

Infrared spectroscopy of Nujol mulls or of potassium bromide pellets is a commonly used technique for the quantitative analysis of binary mixtures of polymorphs. In the official USP method for estimation of the proportions of polymorphs A and B of chloramphenicol palmitate in Chloramphenicol Palmitate Oral Suspension, use of a 1 in 3 mineral oil dispersion of the title compound is specified (USP, 1990). Other methods that have been employed for quantitative analysis include X-ray diffraction, solution calorimetry, and differential scanning calorimetry (DSC). A description of the advantages and shortcomings of these methods can be found in a paper by Guillory and Erb (1985).

A combination of FT-IR spectroscopy and diffuse reflectance (DRIFTS) provides an attractive alternative to traditional KBr pellet and mull techniques for the analysis of powdered samples. Prior to the introduction of FT-IR, the diffuse reflectance approach was largely ignored since the intensity of reflected radiation was too low to provide medium resolution and an adequate signal-to-noise (S/N) ratio. However, in 1978, Fuller and Griffiths (1978) constructed a diffuse reflectance cell that was the first to yield an acceptable S/N ratio at resolutions of 2–4 cm^{-1}. Subsequently, several companies have developed commercial diffuse reflectance accessories (Yang et al., 1986) with modifications to the original

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Correspondence to: J.K. Guillory, The University of Iowa, College of Pharmacy, Iowa City, IA 52242, U.S.A.

[1] *Present address:* Pharmaceutical Development and Technology, Eli Lilly and Co., Indianapolis, IN 46285, U.S.A.

optical geometry employed by Fuller and Griffiths.

The most widely accepted function that quantitatively describes diffusely reflected radiation is known as the Kubelka-Munk (K-M) equation (Kubelka and Munk, 1931). The expression is written as:

$$F(R_\infty) = \frac{(1 - R_\infty)^2}{2R_\infty} = \frac{2.303ac}{s}$$

where $F(R_\infty)$ is the Kubelka-Munk reflectance, R_∞ denotes the reflectance of the sample relative to that of a nonabsorbing standard, a represents the absorptivity, c is the concentration of analyte and s denotes a scattering coefficient. To obtain a linear relationship between the K-M intensity and concentration of analyte, the scattering coefficient must be constant and the amount of specular reflectance must be negligible, the latter being an assumption in the derivation of the K-M equation. However, both specular reflectance and scattering can be affected by particle size and sample preparation techniques. Systematic studies have been performed to evaluate the effects of particle size (Yeboah, 1983), methods for preparation of powdered samples (Hamadeh et al., 1984), presence of absorbing matrices (Brimmer and Griffiths, 1986; Olinger and Griffiths, 1988) and packing pressure (Yeboah et al., 1984) on diffuse reflectance infrared spectra. Another factor that can affect the amount of specular reflectance is the optical geometry employed as demonstrated in a series of articles published by Brimmer and co-workers (Brimmer et al. 1986; Brimmer and Griffiths, 1987, 1988). All of these studies have emphasized the need to control particle size, maintain a reproducible packing density and obtain a homogeneous mixture of the sample in a nonabsorbing matrix when attempting quantitative diffuse reflectance analysis.

The quantitative analysis of spectral data has been augmented by the coupling of multivariate calibration methods and computerized FT-IR spectrometers. The partial least-squares regression method (PLS), a multivariate calibration technique for developing mathematical models from experimental data, was utilized in this work. The application of PLS to chemical data was pioneered by groups led by S. Wold and H. Martens in the late seventies. An excellent tutorial on the theory and mathematics of the PLS method has been published by Geladi and Kowalski (1986). The advantages of multivariate calibration models such as PLS include the ability to perform quantitative analyses on multicomponent mixtures with overlapping bands, calibrate using mixtures allowing the modelling of interactions between components, and use combinations of multiple numbers of wavelengths in the calibration. The PLS method has been applied in this laboratory in the simultaneous quantitation of trimethoprim and sulfamethoxazole in an intravenous pharmaceutical formulation from FT-IR/ATR spectral data (Hartauer et al., 1989).

The present investigation was undertaken to determine whether diffuse reflectance FT-IR spectroscopy could be utilized to characterize binary mixtures of polymorphs. Sulfamethoxazole was selected as the example compound because it has been studied extensively (Kuhnert-Brandstätter and Bachleitner-Hofmann, 1971; Yang and Guillory, 1972; Guillory and Erb, 1985).

Materials and Methods

Materials

Potassium chloride (Mallinckrodt, lot 6845 KAVG) was employed as the matrix for the infrared analysis. Sulfamethoxazole (Sigma, lot 76F-0018) and isopropanol (Mallinckrodt, lot 3369KBGZ) were used as received from the suppliers. Aluminum sample pans and lids (Perkin-Elmer 0219-0041) were employed for the DSC analyses.

Equipment and software

The following equipment and software were used: a Fourier transform infrared spectrometer equipped with a DTGS detector, plotter and data station (Nicolet, Model 5DXB, Nicolet Analytical Instruments, Madison, WI); PLS Quant Zeta 8 Quantitative Analysis Package (Nicolet Version 3.01, Nicolet Analytical Instruments, Madison, WI); diffuse reflectance cell (Collector Cell, Spectra-Tech, Inc., Stamford, CT); Wig-L-Bug mixer with agate mixing vial (Crescent Dental Mfg. Co., Lyons, IL); 2-inch micronizing fluid energy mill (Sturtevant, Inc., Boston, MA); analytical mill (Tekmar Co., Cincinnati, OH); differential scanning calorimeter (Model DSC-2, Perkin-Elmer Corp., Norwalk, CT); Thermal Analysis Data Station (Model 3600, Perkin-Elmer Corp., Norwalk, CT); interface and TADS-1 plotter (Perkin-Elmer Corp., Norwalk, CT); thermogravimetric analyzer (Model TGS-2, Perkin-Elmer Corp., Norwalk, CT); sample encapsulating press (DuPont Co., Wilmington, DE); automated X-ray diffractometer (Model APD 3500, Philips Electronic Instruments Co., Mahwah, NJ); scanning electron microscope (Model S-570, Hitachi Scientific Instruments, Mountain View, CA); sputter coater (Model SC500, Emscope, EM Corp., Chestnut Hill, MA); Sonic Siftor (Allen Bradley, Milwaukee, WI); 3-inch U.S. Standard Sieves (Fisher Scientific, Pittsburgh, PA); Kofler Micro Hot Stage (Model 6886A, Philadelphia, PA); microbalance, (Model 4100, Cahn Instruments, Inc., Cerritos, CA); and heated vacuum desiccator (Precision Scientific, Inc., Chicago, IL).

Analytical methods

DSC Transition temperatures and heats of transitions were determined using DSC. After initial baselines were collected, the instrument was calibrated to within better than 0.1°C on the temperature axis and 0.15 cal/g on the energy axis using ultrapure indium as a standard (theoretical m.p. = 156.6°C, $\Delta H = 6.8$ cal/g). Samples were weighed to the nearest 0.001 mg and then sealed into aluminum pans. An empty sealed pan was used as a reference for collection of thermograms. Analyses were performed under a nitrogen purge at a heating rate of 10 or 1.25°C/min.

Thermogravimetric analysis The weight loss of a sample as a function of temperature was determined by thermogravimetric analysis. Samples were placed into a platinum pan and the weight recorded to the nearest 0.0001 mg with an internal weighing mechanism. The samples were heated at a rate of 10°C/min under a nitrogen purge. Weight loss was calculated from the temperature at which the thermogram deviated from the baseline to the temperature at which a new baseline was established. The temperature axis was calibrated using data from the magnetic transitions of alumel (163°C) and nickel (354°C).

Thermal microscopy Thermal microscopic examinations of polymorphic samples were performed on a Kofler Hot Stage. Sample particles were dispersed on a microscope slide and examined neat between crossed Nicols. Alterations in birefringence and crystal shape were recorded as the sample was slowly heated through the transition temperatures.

. *X-ray diffractometry* An automated X-ray diffractometer equipped with a 2θ compensating slit and nickel filter was used to record diffraction patterns of powdered samples. The powders were pressed into sample slides and smoothed so that the surface was flush with the surface of the slide. Monochromatized CuK_α ($\lambda = 1.5418$ Å) radiation was directed onto the sample surface over a range of 2–42° (2θ). The patterns were recorded on chart paper, along with a table of 2θ values and their corresponding intensity values for peaks greater than 2.5-times the background radiation. The instrument was calibrated to within 0.02° (2θ) using the quartz peak at 26.66° (2θ).

Scanning electron microscopy (SEM) Microscopic examination of micronized potassium chloride powder and polymorphic forms of sulfamethoxazole was performed using a scanning electron microscope. The surface of the sample was sputter coated with a gold and palladium alloy and then mounted in a sample holder. Micrographs were taken at several magnifications using an accelerating voltage of 5 keV.

Preparation and characterization of polymorphic forms

Two pure polymorphic forms of sulfamethoxazole (SMZ) were prepared in 5.0 g batches. For the higher melting polymorph (form I), 5.0 g of SMZ was dissolved in 150 ml of boiling isopropanol. This was allowed to cool to room temperature while stirring and then stored overnight in a refrigerator. The resulting crystals were vacuum filtered and stored under vacuum for 24 h at 30°C (Erb, 1984). For the lower melting poly-

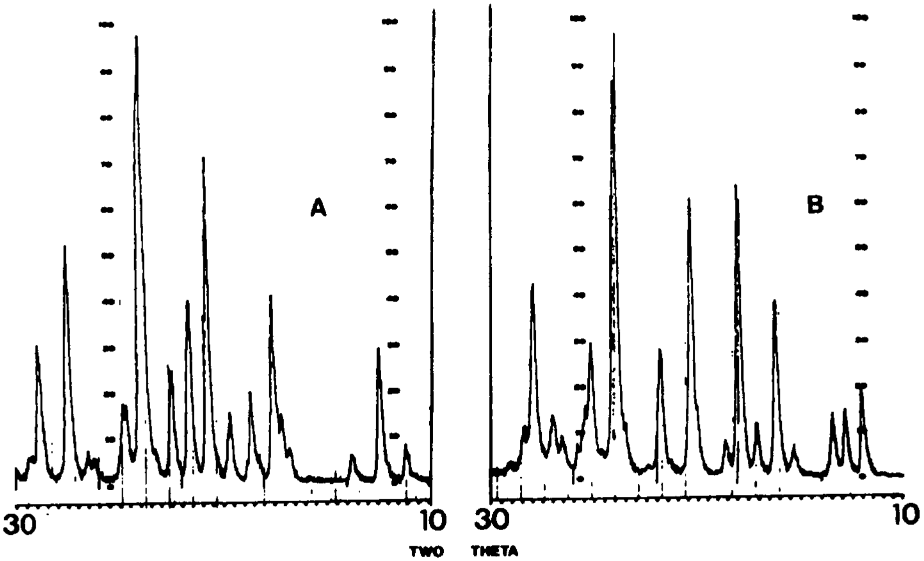

Fig. 1. X-ray diffraction patterns for (A) form I and (B) form II polymorphs of SMZ.

morph (form II), 5.0 g of SMZ was dissolved in 150 ml of boiling isopropanol. This solution was poured rapidly into 500 ml of isopropanol maintained at −10°C in a dry ice/acetone bath. The crystals formed were vacuum filtered and stored at 30°C for 24 h under vacuum.

The two polymorphs were separated into four size fractions between 4.5 and 180 μm with the Sonic Sifter and 3-inch sieves. The sized particles were stored in separate capped vials in a desiccator prior to use.

To ensure the identity and purity of the SMZ

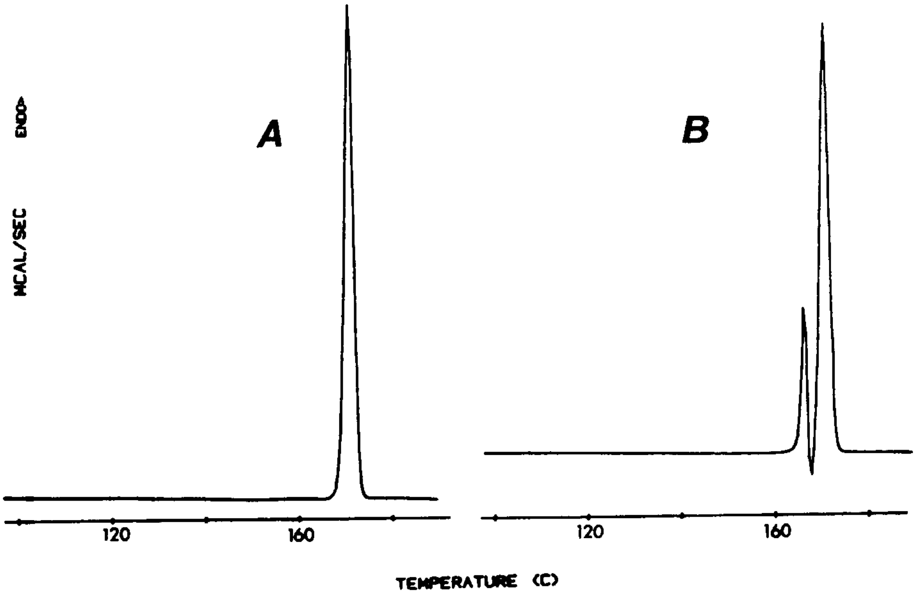

Fig. 2. DSC thermograms (10°C/min) of (A) form I and (B) form II SMZ polymorphs.

polymorphs for use in the quantitative diffuse reflectance studies, the individual polymorphic forms were analyzed by X-ray crystallography, thermal methods, hot stage microscopy and scanning electron microscopy.

Results and Discussion

The X-ray diffraction patterns, 10–30° (2θ), of the two polymorphs are presented in Fig. 1. The dissimilarity of the two patterns is indicative of two different crystalline forms, while the sharpness of the diffraction peaks denotes a high degree of crystallinity for both polymorphs.

The melting behavior of the higher melting (form II) and lower melting polymorphs is displayed in Fig. 2. The thermogram for form I reveals a single endotherm at 169°C, corresponding to its melting. Two endotherms, at 164 and 169°C, are observed in the thermogram for form II. When the data are collected at a slower heating rate of 1.25°C/min for form II (Fig. 3), the thermogram is resolved into an endotherm, followed by an exotherm, and a larger endotherm. This corresponds to melting of form II, the recrystallization of the melt into form I, and the subsequent melting of these crystals. Trituration of the polymorphs results in no change in the DSC traces for the two polymorphs. The TG analysis shows both polymorphs to be devoid of solvent, with no weight loss from 30 to 120°C.

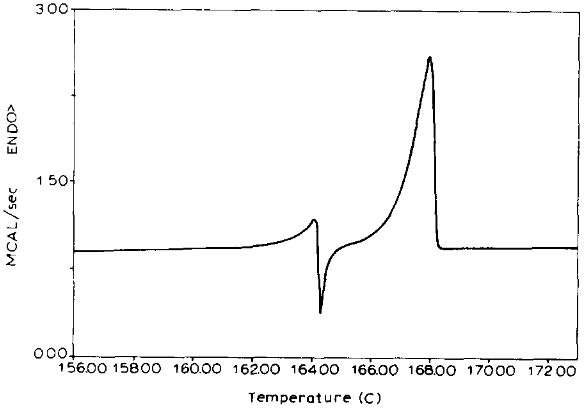

Fig. 3. DSC thermogram (1.25°C/min) for the form II polymorph of SMZ.

SEM photomicrographs of form I and form II crystals in Figs 4 and 5, respectively, reveal the crystal habit of form I to be rod-like, while form II crystals are plates. The homogeneity with respect to the crystal habit seen in the SEM micrographs is further evidence of the purity of the polymorphs. When observed by means of a hot stage microscope, the birefringent form I crystals melt uniformly at approx. 166°C. The form II crystals undergo a simultaneous melting and recrystallization at approx. 163°C, with subsequent melting at 166°C.

Quantitative analysis of SMZ polymorphic mixtures using DRIFTS

For the calibration and unknown samples, both forms I and II were ground in an agate vial for 3 min to obtain smaller and more uniform particles. If grinding of the material caused a crystalline or amorphous conversion, it would be necessary to employ sieving to obtain appropriately sized particles. In this case, analysis of the ground polymorphs by X-ray and DSC indicated there were no crystalline conversions.

In the diffuse reflectance sampling procedure for the polymorphic mixture varying amounts of forms I and II were weighed to make a total of 4.8 mg of SMZ. This was added to an agate mixing vial along with 295.2 mg of micronized KCl powder, to give a total sample weight of 300 mg with 1.6% total SMZ. The contents of the agate vial were then mixed for 30 s in the Wig-L-Bug mixer and the entire contents poured into the macro sample cup. The powder in the cup was leveled with a microscope slide and a 2 kg weight placed on top of this to provide for a constant packing pressure. The height of the sample cup in the Collector Cell was adjusted for each sample for maximal throughput. After a 5 min purging time, 300 co-added scans were collected at 4 cm^{-1} resolution and a detector gain of 1. The spectra of calibration mixtures were all collected in duplicate, with the sample cup being removed and repacked prior to the second collection. All spectra were stored on floppy disks for later analysis.

For analysis, spectra were first leveled to zero absorbance units and then converted to K-M units on the ordinate axis using the K-M conversion program that is resident on the Nicolet software. The PLS software program was utilized in the calibration and prediction of unknowns. However, it was necessary to change the flags in the file for each spectrum from K-M units to absorbance units, since the PLS program would not accept the K-M format. The absolute values of the ordinate scale were still those of K-M units.

Fig. 6 is a full spectral display of the mid-infrared region for forms I and II, both as 1.6% dispersions in KCl. Spectral differences and band

Fig. 4. An SEM photomicrograph of form I SMZ crystals. Bar = 150 μm.

overlap are apparent in the high-frequency range from 3600 to 2800 cm^{-1}, as well as in an expanded view of the fingerprint region (Fig. 7).

Spectral effects of sample preparation

The development of a reproducible sample preparation technique is essential when attempting quantitative diffuse reflectance. A total sample weight of 300 mg was selected, as this allowed the entire contents of each mixture to be filled into the sample cup. Several types of mixing vials including agate, glass, Teflon and polyethylene were tried in the Wig-L-Bug mixer. While the glass, Teflon and polyethylene all showed notice-

Fig. 5. An SEM photomicrograph of form II SMZ crystals. Bar = 150 μm.

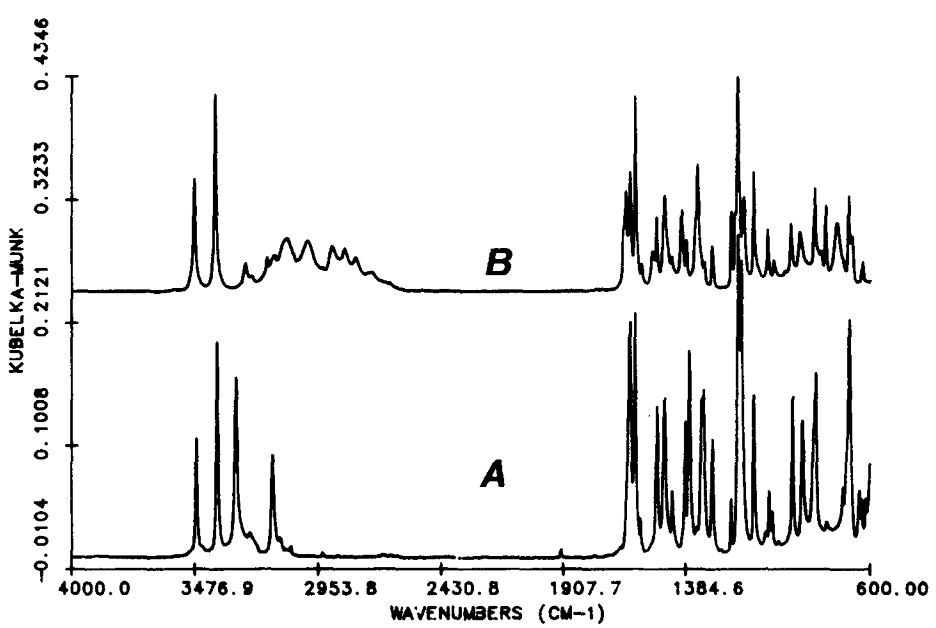

Fig. 6. Diffuse reflectance spectra of (A) 1.6% form I SMZ polymorph in KCl and (B) 1.6% form II polymorph in KCl.

able sticking of the powder mixture to the walls of the vial, no sticking was observed upon emptying mixtures from the agate vial.

As mentioned in the Introduction, particle size of both the nonabsorbing matrix and sample can influence the diffuse reflectance infrared spec-

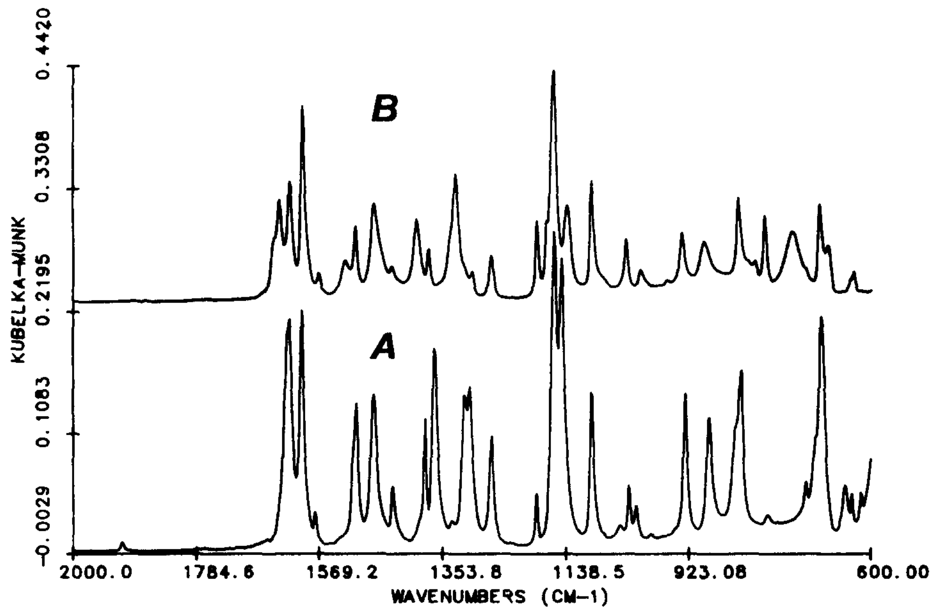

Fig. 7. Diffuse reflectance spectra in the fingerprint region of (A) 1.6% form I SMZ and (B) 1.6% form II SMZ.

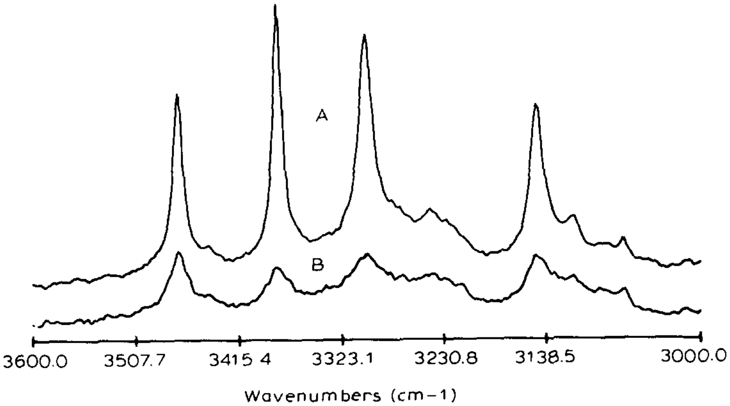

Fig. 8. Diffuse reflectance spectra of 1% dispersions of form I SMZ polymorph in KCl where the SMZ particles were (A) ground and (B) sieved to a 63–75 μm size range.

trum. In order to minimize unwanted specular reflectance, micronized KCl was used as the non-absorbing matrix. SEM analysis of the micronized KCl showed it to be uniformly sized in the particle size range of 1–10 μm. The effect of varying the particle size of the SMZ polymorphs is illustrated in Fig. 8, where the spectra of two 1.0% dispersions of form I in KCl are shown. In one case, the polymorph had been ground previously and in the other a particle size range of 63–75 μm was employed. Significantly sharper and more intense peaks are seen in the case where the polymorph was ground. This observation can be explained by a combination of two factors resulting from the reduction in particle size. One is the decrease in specular reflectance, i.e., that radiation which is reflected from the surface of the powder bed without ever having passed through a particle (Brimmer et al., 1986). In addition, the smaller particle size allows closer packing of the powder and a subsequent reduction in the scattering coefficient (Yeboah, 1983; Hamadeh et al., 1984).

The effect of sample packing was studied with four repetitive spectra collected for two separate samples of form II (approx. 1.4%). For one of the

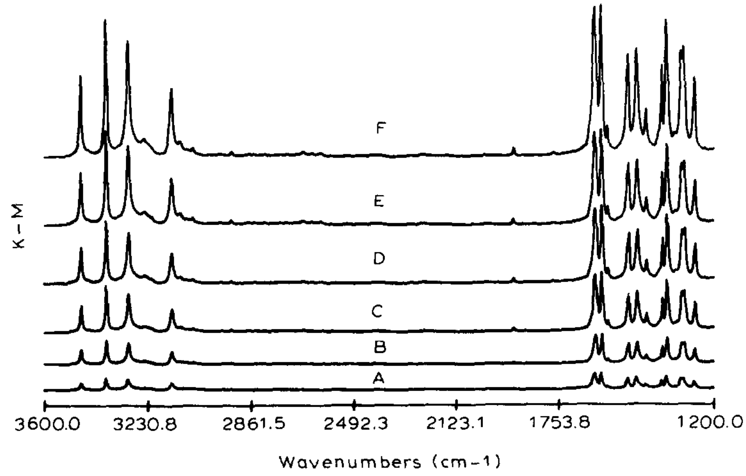

Fig. 9. Diffuse reflectance spectra of form I SMZ dispersed in KCl at the following concentrations: (A) 0.140%, (B) 0.263%, (C) 0.400%, (D) 0.542%, (E) 0.837%, and (F) 1.194%.

TABLE 1

Reproducibility of band intensities for form II SMZ polymorph

	Band Intensity	
	At 3477.1 cm^{-1}	At 1596.9 cm^{-1}
Not repacked	0.1575 ± 0.0007	0.2179 ± 0.0003
Repacked	0.1570 ± 0.0034	0.2099 ± 0.0033

Note: All values are average ± S.D. of four absorbance measurements.

samples, the sample cup was not repacked between successive spectra. In the second case, the sample was emptied and repacked into the sample cup between each spectrum. The calculated averages and standard deviations at two of the band maxima in both samples are shown in Table 1. The increase in standard deviation due to repacking the sample further emphasizes the need for a consistent sample preparation method.

Linearity of individual polymorphs

To examine the linear response of K-M intensities, samples containing increasing concentrations of each polymorph in KCl were separately examined. Fig. 9 illustrates the spectra for increasing concentrations of form I dispersed in KCl. Baseline corrected K-M intensities were obtained at various absorption bands and regressed versus concentration. The linear plot obtained for the NH_2 stretching band of form I at 3468.2 cm^{-1} is shown in Fig. 10. Table 2 lists the K-M values and linear regression analysis for two bands studied in the spectra of each polymorph. In all these bands, good linear relationships are observed between K-M intensity and concentration. However, a similar plot for the most intense band (1160 cm^{-1}) in the spectrum of form II shows a falling off of K-M intensities from the linear extrapolation of concentration values less than 1.0% (Fig. 11). This is most likely due to specular reflectance, as specular reflectance increases with the magnitude of the absorption coefficient at any given wavelength. The nonlinearity of this spectral band precludes its elimination from spectral regions used in the quantitative analysis of binary mixtures.

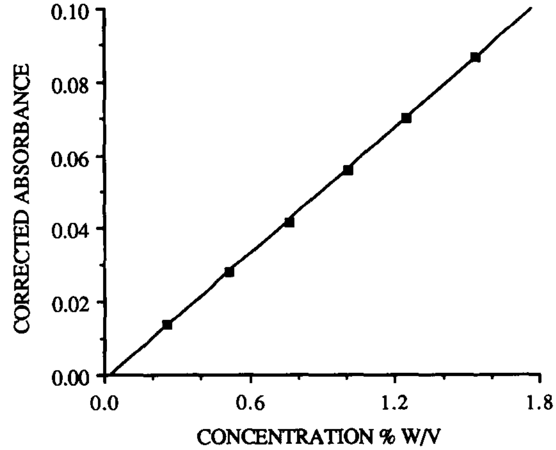

Fig. 10. Linear response plot of K-M intensity at 3468 cm^{-1} vs concentration.

TABLE 2

K-M intensity vs concentration at band maxima for SMZ polymorphs

Form I			Form II		
Conc. (% in KCl)	3468 cm^{-1} (K-M intensity)	1597 cm^{-1} (K-M intensity)	Conc. (% in KCl)	3476 cm^{-1} (K-M intensity)	1597 cm^{-1} (K-M intensity)
0.140	0.0097	0.0236	0.128	0.0092	0.0244
0.263	0.0204	0.0428	0.267	0.0209	0.0403
0.400	0.0357	0.0815	0.539	0.0487	0.1030
0.542	0.0505	0.1066	0.800	0.0626	0.1156
0.837	0.0730	0.1312	1.060	0.0998	0.1765
1.194	0.1140	0.2099	1.603	0.1259	0.1965
Correlation coefficient	0.998	0.990		0.990	0.965

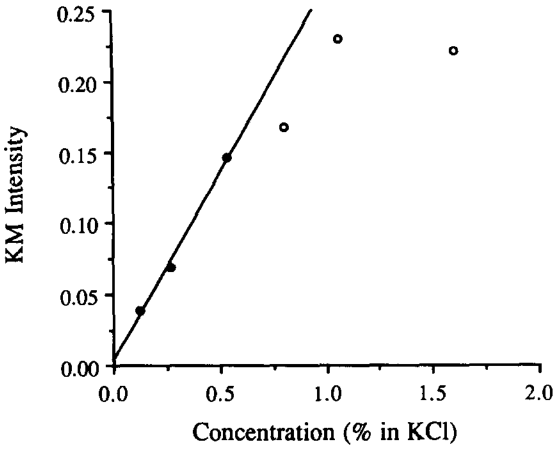

Fig. 11. Linear response plot of K-M intensity at 1160 cm^{-1} vs concentration.

TABLE 3

Parameters of PLS calibration model for SMZ polymorphic mixtures

Parameter	Form I polymorph	Form II polymorph
Spectral regions [a] (cm^{-1})	3520–2680 1680–1300	3520–2680 1680–1300
Number of factors	4	4
% concentration explained [b]	98.67	98.58

[a] Only used absorbance values ≤ 1.5 in these regions.

[b] Cumulative effect of factors in describing variance for concentration set of each component.

PLS analysis of binary mixtures

The PLS model consists of an optimal number of factors or loading vectors (Haaland and Thomas, 1988) to represent the complexity of the system without overfitting the data. The calibration information for the optimal PLS model developed for the quantitation of the binary mixtures is given in Table 3. The combination of two spectral regions and four factors utilized in the model, could account for more than 98% of the variation in the concentrations of the calibration samples. Actual vs calculated concentration values (% in KCl) for forms I and II in the calibration mixtures are plotted in Fig. 12. The model provided for good agreement between the actual and predicted values for the calibration samples, with the average absolute errors being 0.006 (% in KCl) and 0.004 (% in KCl) for form I and form II, respectively. However, a more rigorous test would employ an independent set of unknowns. Table 4 contains the predicted values and absolute errors for the unknown samples. To allow for easier interpretation of the predictive ability of the method, the concentration of each polymorph is expressed as % of total SMZ. The statistics included in the data for unknowns (nos 3–5) represent the average of three measurements collected over a 4 week time period. The magnitudes of the standard deviations of these measurements confirm the validity of the calibration model over this testing period. The agreement of the predicted values with the theoretical values demonstrates that, when careful attention is paid to experimental details, diffuse reflectance can be

TABLE 4

Predictive ability of PLS model for SMZ polymorphic mixture

Number	Form I			Form II		
		(% of total SMZ)			(% of total SMZ)	
	Calculated	Actual	Absolute error	Calculated	Actual	Absolute error
1	37.33	37.06	−0.27	62.77	62.94	0.14
2	65.25	61.29	−3.96	35.29	38.71	3.42
3	47.96 ± 0.52	49.98	2.02	51.75 ± 0.54	50.02	−1.73
4	19.76 ± 0.72	18.89	−0.87	80.25 ± 0.23	81.11	0.86
5	79.14 ± 2.58	80.29	1.15	20.43 ± 2.74	19.71	−0.72

Note: Data for unknowns (nos 3–5) are the average of four measurements.

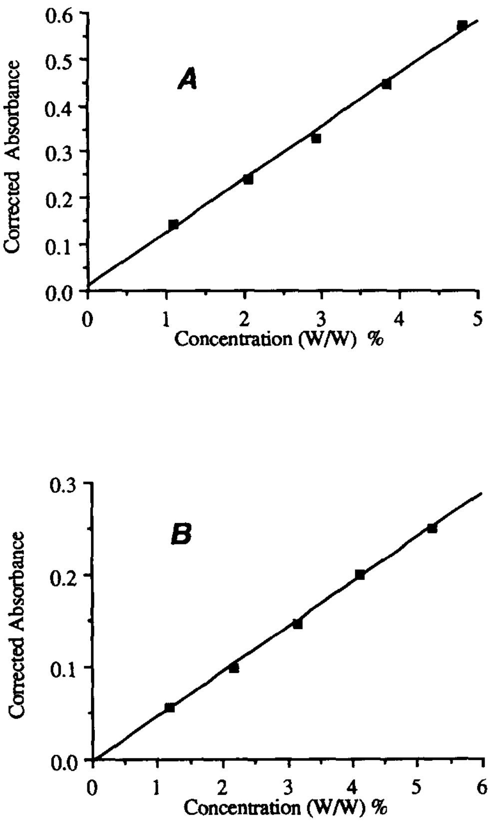

Fig. 12. Actual vs calculated concentration values (% in KCl) for (A) form I and (B) form II SMZ polymorphs in calibration mixtures.

useful as a quantitative technique for characterizing polymorphs.

Acknowledgements

This work was supported in part by fellowships awarded to K.J.H. by the United States Pharmacopeial Convention and the American Foundation for Pharmaceutical Education.

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