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COMMUNICATION

A COMPARISON OF DIFFUSE REFLECTANCE FT-IR SPECTROSCOPY AND DSC IN THE CHARACTERIZATION OF A DRUG-EXCIPIENT INTERACTION

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ABSTRACT

Differential scanning calorimetry (DSC) and diffuse reflectance Fourier transform infrared spectroscopy (FT-IR) were employed for the characterization of the well-known interaction between aminophylline and lactose. Brown discoloration appears in samples containing 1:5 (w/w) mixtures of aminophylline and lactose following three weeks of storage at 60°C. DSC thermograms can be used to predict that such an interaction will occur, but provide little insight into the nature of the interaction. Using FT-IR, it was possible to show that the discoloration is due to a chemical reaction between ethylenediamine and lactose.

INTRODUCTION

An important consideration in the development of a stable and effective solid dosage form is the possibility that a physical or chemical interaction may occur between the active medicinal agent and excipients that might be present in the

formulation. It has been recommended[1] that differential scanning calorimetry (DSC) be employed for the routine screening of excipients for compatibility, with confirmation by thin layer chromatography.

It is generally assumed that, if there are no interactions between drug and excipient, the thermal properties of the physical mixture will be roughly equivalent to the sum of the properties of the individual components. Interactions will be indicated by large changes in melting point, changes in peak shape and area and/or by the appearance of a peak not present in the separate components.

Recently, the efficiency and predictive value of excipient compatibility studies have come into question[2]. Based on drug-excipient compatibility tests, excipients may be eliminated that would perform satisfactorily, or excipients chosen which may present difficulties in the final dosage form. Both scenarios were demonstrated in an investigation of DSC as a compatibility predictor for fenretinide[3]. The DSC method has received specific criticism that it subjects drug and excipient to elevated temperatures that are unrealistically high. In addition, in order to detect interactions, frequently ratios of drug to excipient must be used that are not likely to be encountered in practice. Furthermore, DSC thermograms do not provide information about the nature of the interaction, they only indicate the likelihood of an interaction.

Monkhouse[4] used diffuse reflectance spectroscopy (DRS) in the UV-visible range as a routine screening procedure in investigating interactions between hydrochlorthiazide and excipients. Earlier work using this technique is described in a review article dealing with drug-excipient interactions[5].

While UV spectroscopy provides useful information about the structure of molecules, infrared spectroscopy is, in comparison, potentially more valuable. Peaks in the infrared spectrum can often be identified as arising from the stretching or bending vibrations of a particular functional group. Consequently, the disappearance of a peak in the infrared spectrum, or the appearance of new peaks, should provide clear-cut evidence of a chemical interaction.

It has been reported that a yellow or brown color develops when aminophylline is mixed with lactose[6]. The purpose of this study was to examine this interaction using DSC and diffuse reflectance FT-IR spectroscopy, and to compare the usefulness of the two techniques.

EXPERIMENTAL

Materials

Aminophylline, theophylline, ethylenediamine, and alpha-lactose monohydrate were all obtained from Sigma. Potassium chloride was purchased from Mallinckrodt.

Equipment and methods

DSC thermograms were obtained at a heating rate of 10°C/min under a nitrogen purge on the Perkin-Elmer Model DSC-2, equipped with a Model 3600 Thermal Analysis Data Station. Following linearization of the baseline, 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 (Alfa) as a standard (theoretical m.p. 156.6°C, $\Delta H_f = 6.80$ cal/g). Samples were weighed to the nearest 0.001 mg (Cahn Model 4100 Electrobalance), and sealed in aluminum pans using a sample encapsulating press (DuPont).

Samples containing single components included aminophylline (100 mg), theophylline (100 mg), alpha-lactose monohydrate (500 mg) and ethylenediamine (2 mL). The mixture samples included alpha-lactose monohydrate in a 5:1 w/w ratio with each of the three other compounds, to approximate the ratio of drug to excipient in a final dosage form.

In the lactose/ethylenediamine mixture, ten microliters of ethylenediamine (8.5 mg) was pipetted onto the lactose (42.6 mg) and mixed with a spatula. The other mixtures, each weighing a total of 600 mg, were prepared in a Wig-L-Bug mixer. Initially, the samples were analyzed by DSC and diffuse reflectance. For storage the samples were filled into 5 mL amber serum vials, and then sealed by hand with butyl rubber stoppers. The vials were submerged in a 60°C water bath for three weeks and then removed for immediate analysis by diffuse reflectance.

Infrared spectra were obtained using the Nicolet Model 5DXB spectrometer, equipped with a DTGS detector and diffuse reflectance cell (Collector Cell, Spectra Tech, Inc.) The cell was previously aligned on a removable baseplate to ensure optimal throughput. Spectra were the result of 300 co-added scans at a resolution of 4 cm^{-1} and a detector gain of 1. Spectra were ratioed to the background spectrum of potassium chloride powder, which previously had been milled and sieved to a particle size of less than 44 μm. Mixtures of each sample (1-6%) were

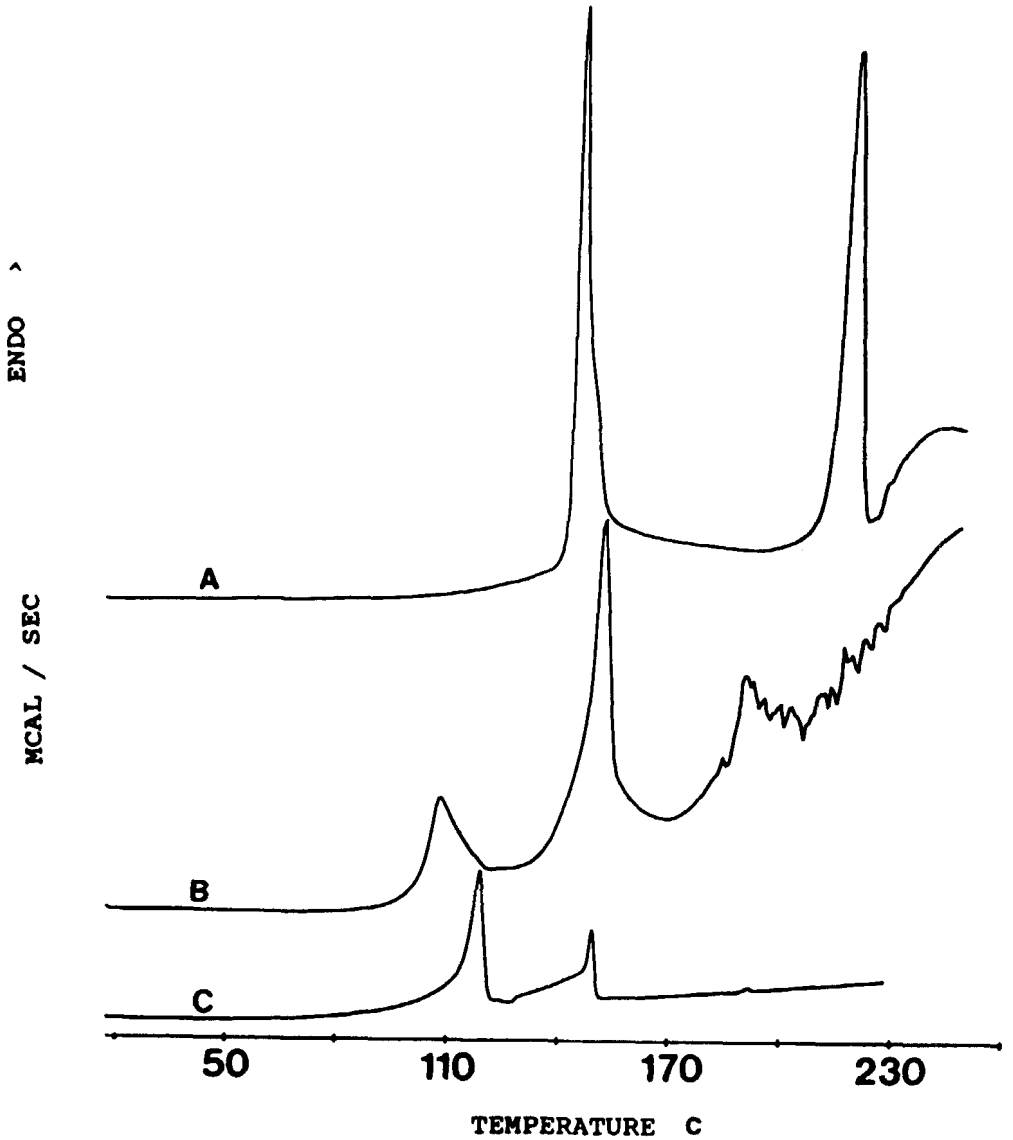

Figure 1

DSC thermogram of (A) α-lactose monohydrate, (B) a 1:5 weight ratio mixture of aminophylline and α-lactose monohydrate, and (C) aminophylline.

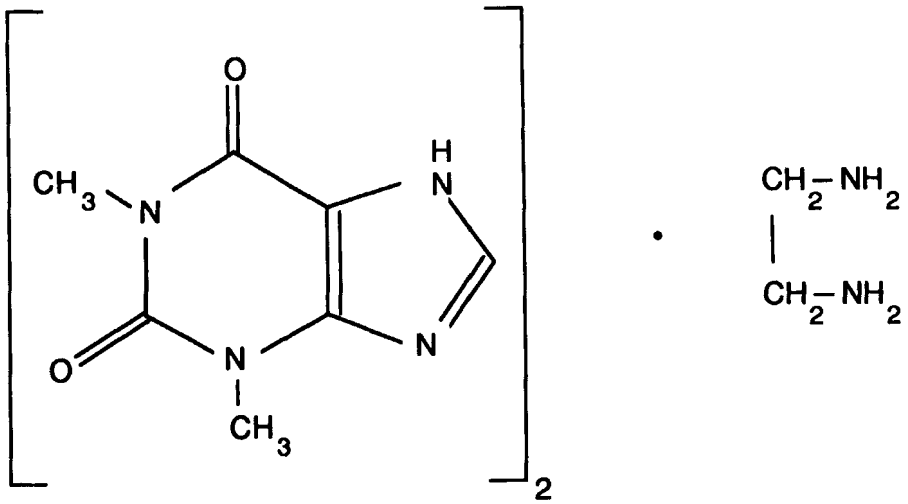

Figure 2

Chemical structure of aminophylline.

prepared in KCl using the Wig-L-Bug mixer, filled into the macro sample cup (4 mm x 2 mm) of the Collector Cell and leveled with a spatula. The height of the sample cup in the Collector Cell was adjusted to optimize energy throughput. A 5 minute purge was allowed prior to the collection of all spectra to equilibrate water and $C0_2$ vapors.

RESULTS AND DISCUSSION

Thermograms of the individual components, aminophylline and lactose, as well as a mixture consisting of a 1:5 ratio of aminophylline to lactose are shown in Figure 1. Van Dooren and Duphar[7] have proposed that if the DSC trace of a combination is a simple superposition of the individual components' traces, an incompatibility is highly unlikely. The appearance of extra-thermal effects in the DSC trace or the disappearance of one of the component peaks is an indication of an incompatibility. The DSC thermogram for the mixture of the two components lacks the 219°C thermogram that is present in the thermogram of lactose alone. An interaction between these two components was confirmed when the mixture of

aminophylline and lactose exhibited brown discoloration after storage at 60°C for three weeks.

Although in this case the DSC thermogram correctly predicts an interaction, it provides little insight into the nature of the interaction. The diffuse reflectance spectra, on the other hand, provide information that is useful in elucidating the nature of the interaction.

The structure of aminophylline is shown in Figure 2. It is a hydrogen-bonded complex consisting of two theophylline molecules and an ethylenediamine molecule. The diffuse reflectance spectra of a 1% dispersion of aminophylline in KCl obtained initially and after storage are shown in Figure 3. The fingerprint regions of the two spectra match up identically, and there is no indication of degradation of the aminophylline under the storage conditions. The spectra of 5% lactose in KCl both before and after storage are shown in Figure 4.

All peaks in both spectra coincide, again showing no change of the individual components under storage conditions. The peak at *ca.* 1656 cm^{-1} in the spectrum of lactose is due to water of crystallization[8]. Spectra from the mixture of the two components in a 1:5 weight ratio are shown in Figure 5. As was mentioned previously, the mixture developed a brown discoloration upon storage, and many differences are apparent between the two spectra through the spectral region displayed. The most striking difference is apparent in the double bond region from 1800 cm^{-1} to 1500 cm^{-1}. The spectrum of the pre-storage mixture contains a broad peak from *ca.* 1725 cm^{-1} to 1580 cm^{-1}, which is a composite of vibrations from the hydrogen bonded carbonyl groups of aminophylline, as well as the water of crystallization of lactose. In the spectrum of the post-storage sample, this same region now contains two relatively sharp bands with maxima at 1715 cm^{-1} and 1667 cm^{-1}.

These two peaks at 1715 cm^{-1} and 1667 cm^{-1} in the post-storage sample match up well with the absorption peaks from the two carbonyl groups in theophylline. This assignment is supported by Figure 6, which shows the similarity in this spectral region between the post-storage mixture and pure theophylline. This spectral information led to the hypothesis that the ethylenediamine is liberated from the complex in the vapor state and reacts with the lactose through a Schiff base intermediate, resulting in the brown discoloration of the sample. The fact that the mixture contains only 1:5 parts by weight of

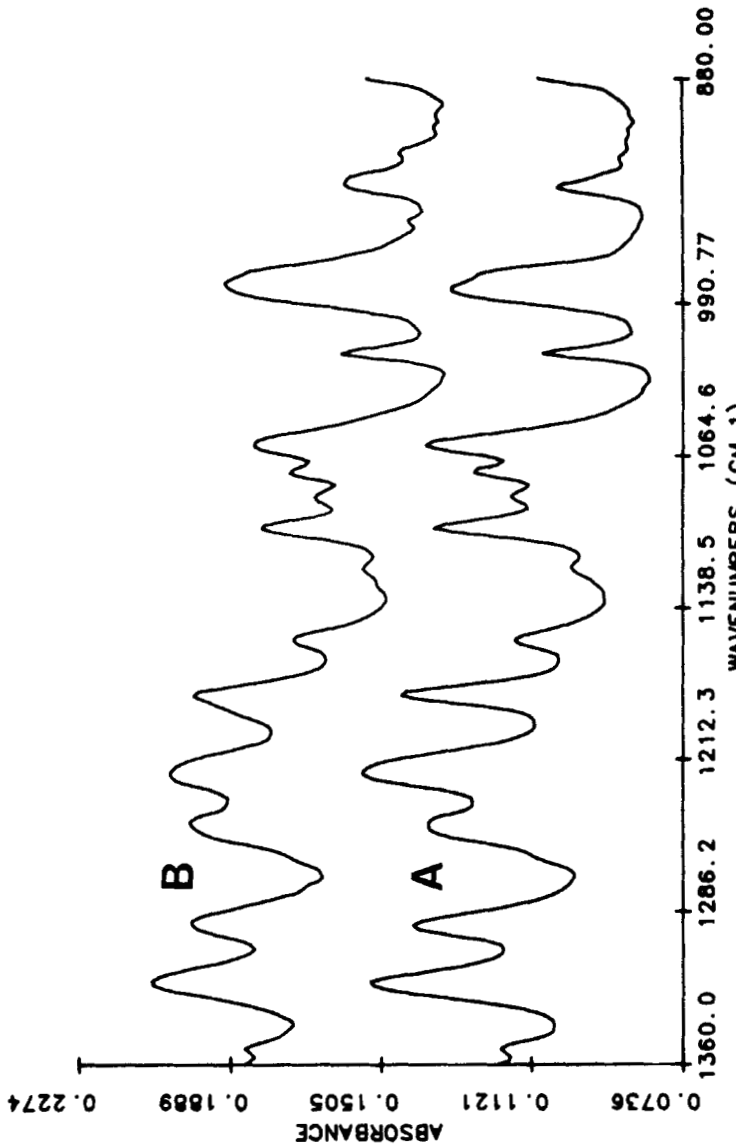

Figure 3

Diffuse reflectance spectra of 1% aminophylline in KCl both (A) before and (B) after storage at 60°C for three weeks.

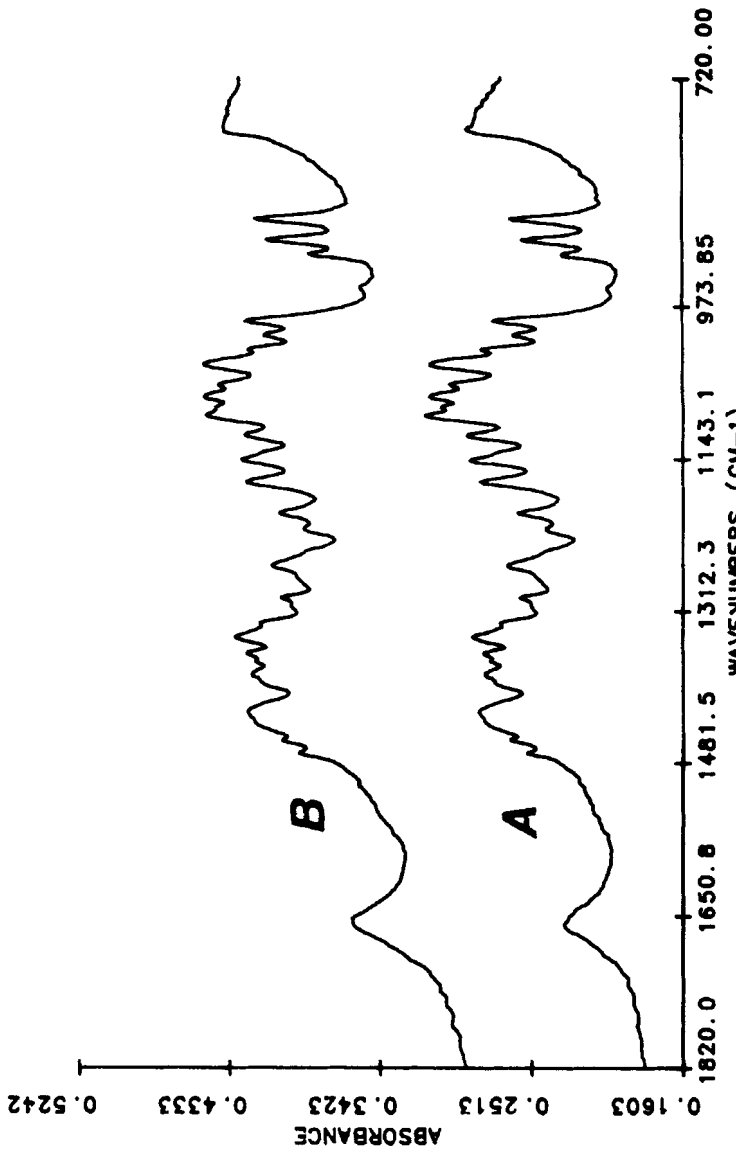

Figure 4

Diffuse reflectance spectra of 5% α-lactose monohydrate in KCl both (A) before and (B) after storage at 60°C for three weeks.

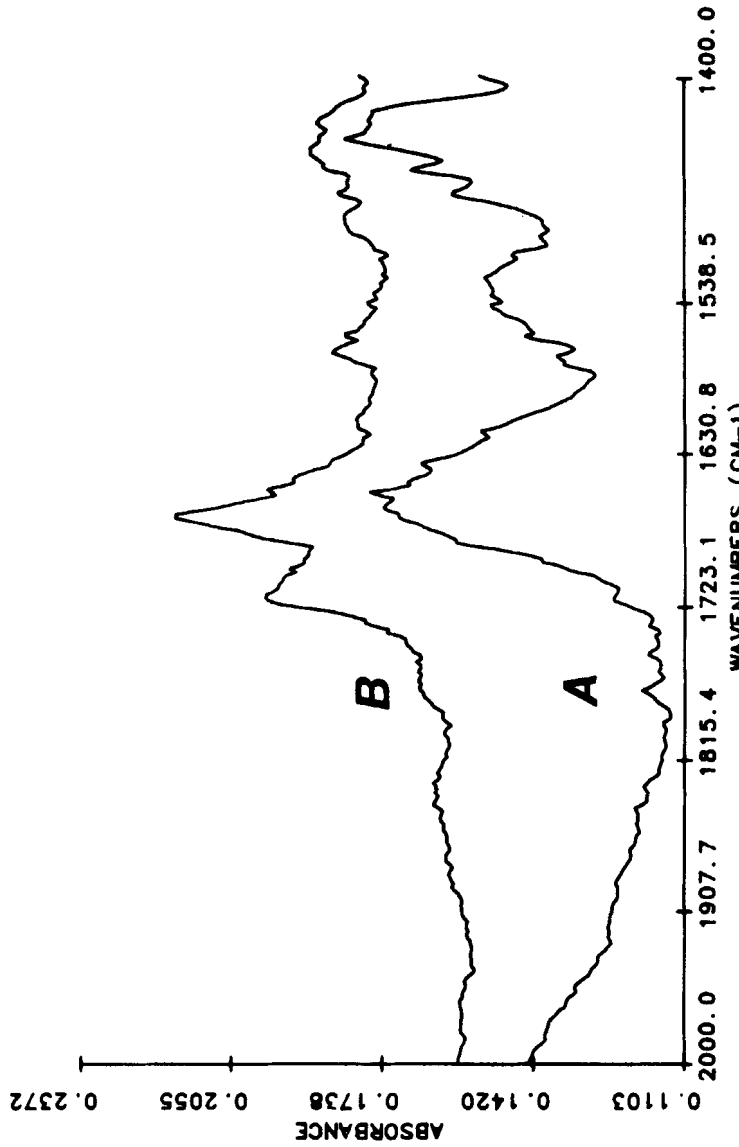

Figure 5

Diffuse reflectance spectra of a 1:5 weight ratio mixture of aminophylline and α-lactose monohydrate both (A) before and (B) after storage at 60°C for three weeks.

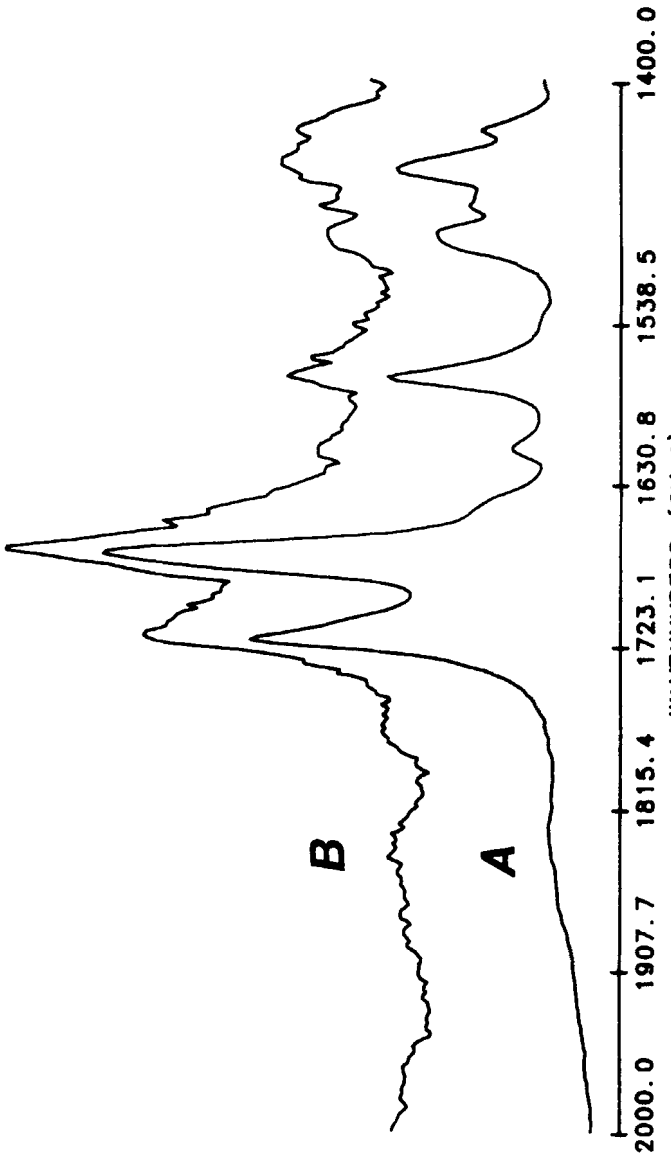

Figure 6

Diffuse reflectance spectra of (A) 1% theophylline in KCl and (B) post-storage mixture of aminophylline and α-lactose monohydrate.

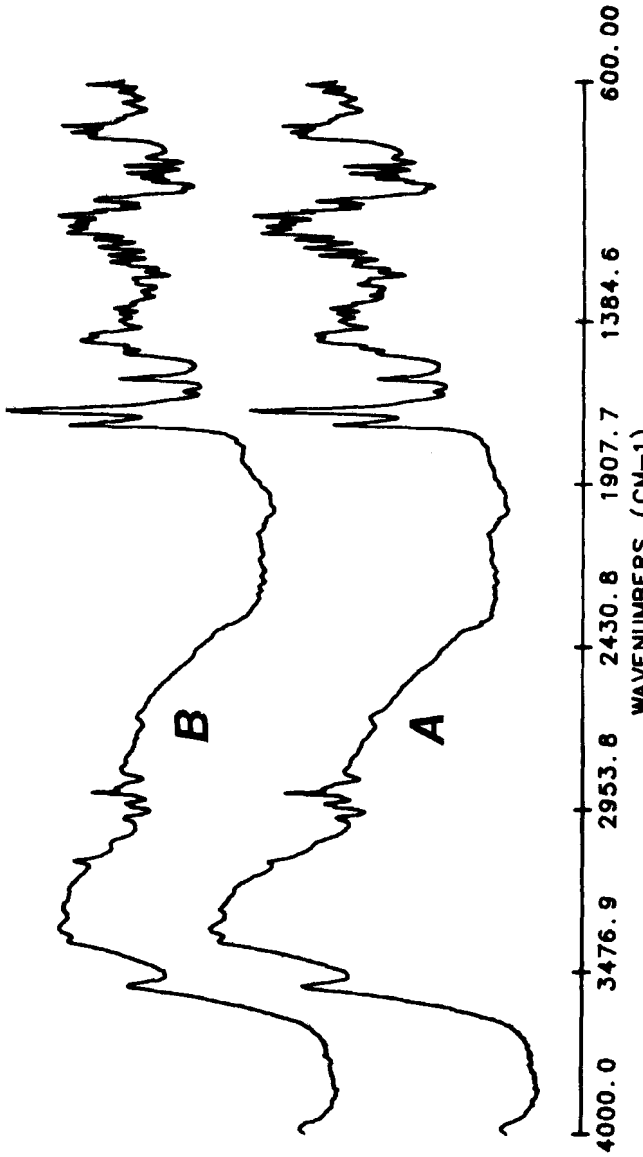

Figure 7

Diffuse reflectance spectra of a 1:5 weight ratio mixture of theophylline and α-lactose monohydrate both (A) before and (B) after storage at 60°C for three weeks.

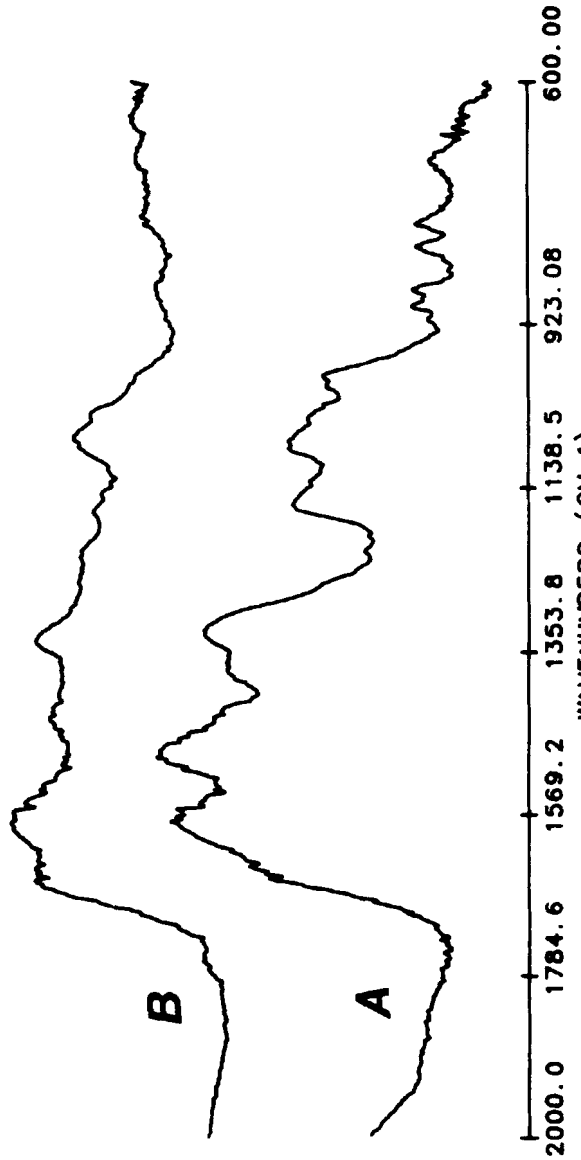

Figure 8

Diffuse reflectance spectra of a 1:5 weight ratio mixture of ethylenediamine and α-lactose monohydrate both (A) before and (B) after storage at 60°C for three weeks.

aminophylline, which itself is only 12% by weight ethylenediamine supports the principle spectral contributions arising from theophylline and lactose.

As a further test of this hypothesis, ethylenediamine and theophylline were mixed separately with lactose, and subjected to the same storage conditions. The pre-storage and post-storage spectra for the theophylline/lactose mixture are shown in Figure 7. The full spectra of the two samples are superimposable, and visual inspection shows no brown discoloration of the post-storage mixture. On the other hand, a blackish-green colored product formed in the ethylenediamine/lactose mixture. Although the degradation product was not identified from the infrared spectrum, its spectrum is markedly different from that of the pre-storage sample (Figure 8).

CONCLUSION

While DSC correctly predicted a drug-excipient incompatibility between aminophylline and lactose, it provided little insight into the interaction. Diffuse reflectance spectroscopy provided additional evidence useful in interpreting the drug-excipient interaction. The recent development of diffuse reflectance environmental chambers, from which the diffuse reflectance spectrum of a sample can be obtained *in situ* under different temperature and pressure conditions, should further enhance the utility of diffuse reflectance spectroscopy as an auxiliary or first-line approach to the determination of physico-chemical interactions between drugs and excipients.

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