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Thermochimica Acta 285 (1996) 337–345

thermochimica acta

Application of differential scanning calorimetry to the study of drug–excipient compatibility

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Received 27 July 1995; accepted 9 February 1996

Abstract

Differential scanning calorimetry (DSC) has been used to investigate drug–excipient interactions and, in consequence, their compatibility. In particular, binary mixtures of nefazodone with magnesium stearate and lactose, and fosinopril with the same excipients were prepared and analysed, after proper conditioning.

The thermoanalytical results were compared with those obtained by spectroscopic (UV, IR) and chromatographic (HPLC) analysis. We believe that changes in DSC runs cannot always be a sufficient condition to prove that some interaction occurs between drug and excipient during storage at room temperature.

Some data on the spectroscopic characteristics of nefazodone and fosinopril drugs and their thermal behaviour are also reported.

Keywords: DSC; Nefazodone; Fosinopril; Compatibility

1. Introduction

Thermal analysis has been applied in the pharmaceutical industry for both from a basic research standpoint and from the perspectives of practical problem solving (e.g. quality control, characterization of components, etc.).

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PII: S0040-6031(96)02904-8

Recent reviews have highlighted the application of differential scanning calorimetry (DSC) and a related technique, differential thermal analysis (DTA), for the rapid evaluation of the compatibility of drug substances with excipients [1–8]. In general, judgment is expressed on the basis of the modifications observed in DSC runs of the active substance in the absence and in the presence of the tested excipient.

Although some authors acknowledge that the presence of a physical or chemical interaction does not necessarily indicate incompatibility, they all agree that a change observed in DSC curves is unambiguous proof of interaction between drug and excipient.

The aim of our study is to investigate this problem because it is our belief that the change in DSC curves, carried out by increasing the temperature, cannot be a sufficient condition to prove that some interaction will occur between drug and excipient during storage at room temperature.

In our experiments we studied the possible interactions between nefazodone, a new synthetic drug with antidepressant activity [9, 10] and fosinopril, the first member of a new chemical class of angiotensin-converting enzyme inhibitors [11, 12], with lactose and magnesium stearate, two excipients usually employed in pharmaceuticals. Each of the above mentioned substances was subjected to spectroscopic and thermoanalytical characterization and their mixtures, after proper conditioning, were analysed by DSC, HPLC, UV and IR to try to correlate any change in DSC runs with some chemical modification of the drug in the blend.

2. Experimental

2.1. Materials

Nefazodone, [2-[3-[4-(3-chlorophenyl)-1-piperazinyl]-propyl]-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one] hydrochloride (BMY 13754-1) and fosinopril, [(2a,4b)-4-cyclohexyl-1-[[[2-methyl-1-(1-oxopropoxy)propoxy]-(4-phenylbutyl)-phosphynyl]-acetyl]-L-proline] sodium salt (SQ28555), were a gift from Bristol–Myers–Squibb (Anagni, Italy). Lactose monohydrate and magnesium stearate were USP grade [13].

2.2. Preparation of physical mixtures

Homogeneous 1:1 (*w*/*w*) binary mixtures of nefazodone with lactose monohydrate and magnesium stearate as well as those of fosinopril with the same excipients were prepared by mechanical shaking and stored in stoppered flasks at 25°C and 35°C. A sample of each mixture was analysed every two weeks.

2.3. Apparatus

Spectral data were obtained using a model 320 Perkin–Elmer UV–visible spectrophotometer and a model 1760 Perkin–Elmer FTIR.

HPLC analyses were performed using a model 8110 Spectra Physics chromatograph with UV detector. The experimental conditions were those proposed by Franc et al. for nefazodone [14] and by Kirschbaum et al. for fosinopril determination [15].

The thermal measurements were carried out using a Perkin–Elmer TGS-2 thermal analyser and a DSC-4 differential scanning calorimeter equipped with a data station. TG and DSC runs were made on samples of about 1 mg, heating rate 10°C min^{-1}, in a stream of nitrogen (flow rate 50 mL min^{-1}).

3. Results and discussion

3.1. Spectral data and thermal behaviour of the drugs

Fig. 1 shows the UV spectra of nefazodone, in 95% ethanolic solution, and fosinopril, in aqueous solution. The nefazodone spectrum exhibits two maxima at 211.5 nm [$\varepsilon = (3.65 \pm 0.02) \times 10^4$ L mol^{-1} cm^{-1}] and 253.5 nm [$\varepsilon = (1.26 \pm 0.02) \times 10^4$ L mol^{-1} cm^{-1}], whereas fosinopril spectrum exhibits only one maximum at 206 nm [$\varepsilon = (1.67 \pm 0.02) \times 10^4$ L mol^{-1} cm^{-1}].

The infrared spectra of the drugs are reported in Fig. 2.

TG in a dynamic nitrogen atmosphere (Fig. 3a) shows that nefazodone is stable up to about 175°C and then decomposes in two separate steps, the first of which, correspond-

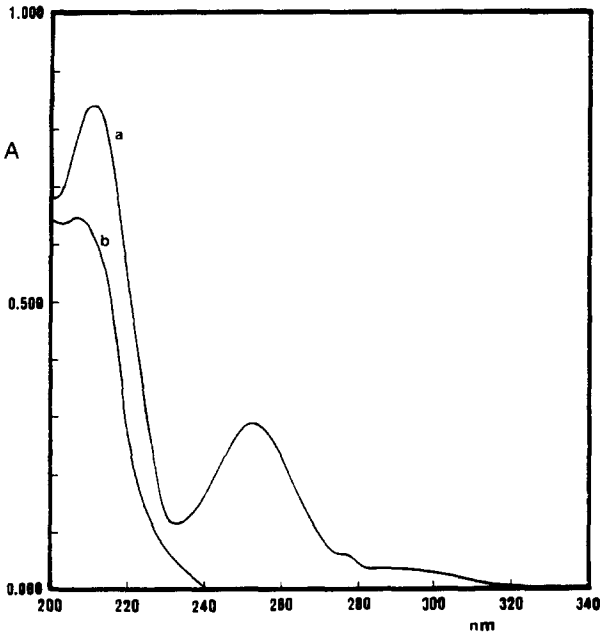

Fig. 1. UV absorption spectra of nefazodone in 95% ethanol (a) and fosinopril in aqueous solution (b).

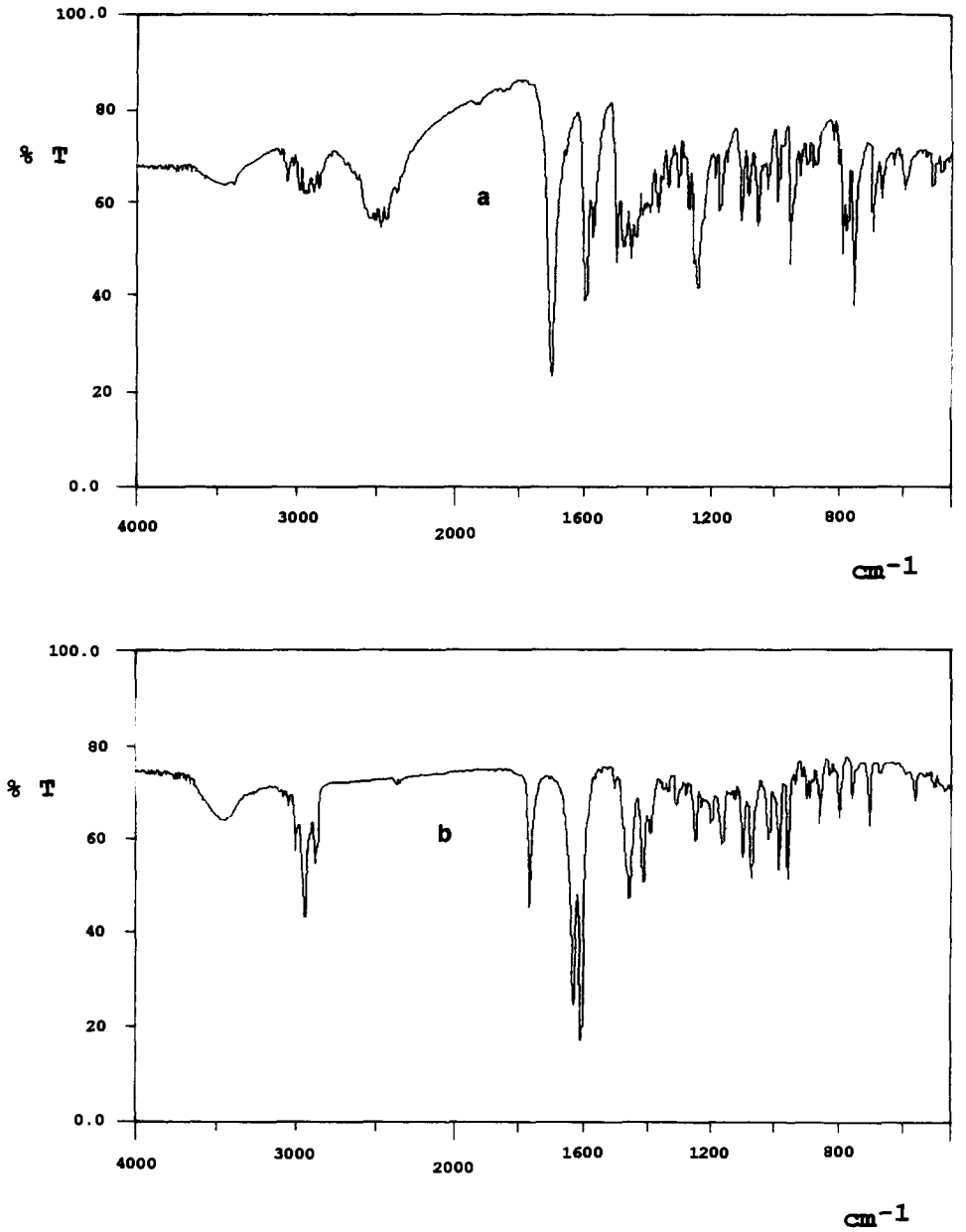

Fig. 2. IR spectra (KBr disk) of nefazodone (a) and fosinopril (b).

ing to about 7.5% mass loss, involves the elimination of one HCl molecule (calc. 7.20%) as proved by the analysis of the evolved gas. The second decomposition process begins at about 230°C and is complete at 360°C with a maximum rate at 350°C; the last residue is completely eliminated at about 600°C.

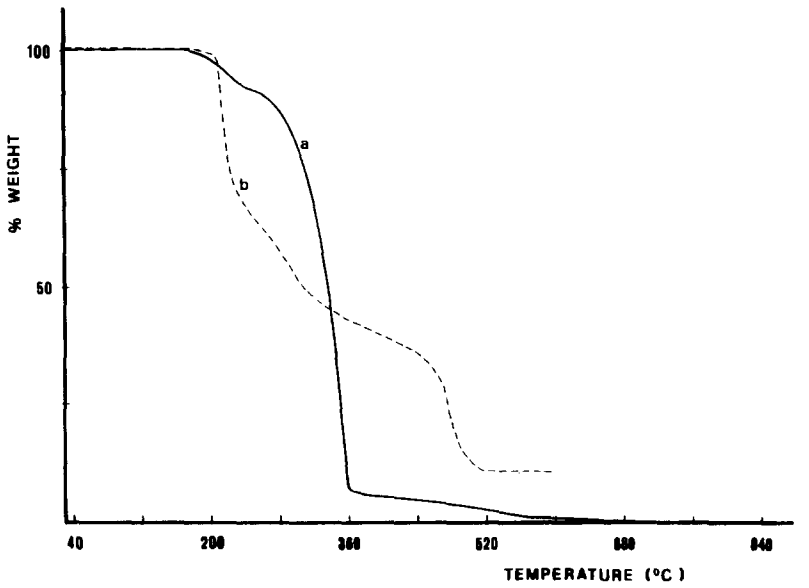

Fig. 3. TG curves in a nitrogen atmosphere of nefazodone (a) and fosinopril (b); heating rate 10°C min^{-1}.

DSC (Fig. 4a) shows a sharp endothermic peak from 175 to 192°C (maximum temperature T_m = 188°C; enthalpy change ΔH = 112–120 J g^{-1}). The event is irreversible and involves the release of the HCl molecule and the contemporaneous melting of the resulting compound. In fact, after stopping the temperature increase at 190°C and cooling the sample, the next DSC run exhibits a new endothermic peak at T_m = 144°C (ΔH = 45 J g^{-1}). The broad peak which begins at about 230°C corresponds to the complete decomposition of nefazodone.

The thermal decomposition of fosinopril occurs with a three-step process in the temperature range 200–550°C (Fig. 3b) and gives a final residue that consists mainly of $(NaPO_3)_x$ (calc. 17.41%, found 16.1%). The DSC curve (Fig. 4b) shows two partly overlapping peaks (190–202°C); the first, endothermic, corresponds to the melting of fosinopril, the other, exothermic, is connected with its first decomposition step. The correctness of this statement is supported by the results of our experiments: DSC runs on the residues obtained by stopping the temperature increase just before or after the occurring exothermic process are not modified except in the first case.

According to the thermogram, the water-content of lactose monohydrate is evolved at temperatures up to 160°C. The water-free compound is stable up to about 220°C, then it decomposes: the DSC curve (Fig. 5a) shows a first endothermic peak (T_m = 148°C) corresponding to the dehydration reaction; a small exothermic process occurs in the temperature range 171–181°C, probably connected with a thermal internal transition because it is not associated with a weight variation. Finally, a new endothermic peak occurs (T_m = 217°C) corresponding to the melting of the compound and the contemporaneous thermal decomposition.

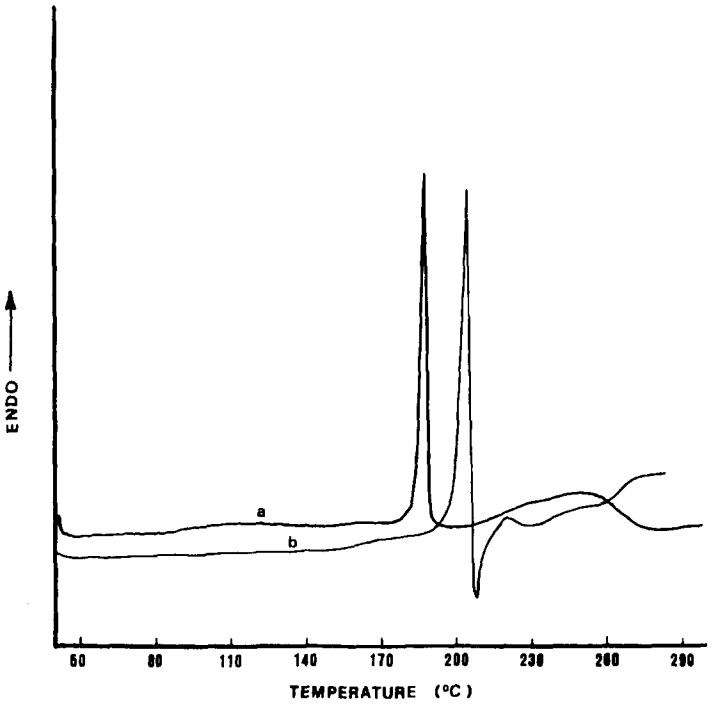

Fig. 4. DSC curves in a nitrogen atmosphere of nefazodone (a) and fosinopril (b); heating rate 10°C min^{-1}.

TG of magnesium stearate shows a 3.5% weight loss which begins at 50°C and is complete near 120°C; it is connected with dehydration process as proved by the endothermic peak in the DSC curve in a nearly identical temperature range (Fig. 5b).

Upon further heating, a slow weight loss beings at about 220°C and continues up to about 360°C, where it speeds up suddenly; at 520°C the decomposition is complete ($T_m = 418$°C).

3.2. Study of drug–excipient interaction

DSC runs of nefazodone–magnesium stearate mixtures combine the features of the thermograms of each component; this indicates that no interaction occurred. In contrast, some modifications are observed in the thermal properties of all the other systems.

In the trace of nefazodone–lactose (Fig. 6), apart from the endothermic peak at 148°C connected with lactose dehydration, the other two endothermic peaks, corresponding to HCl release and melting processes, occur in a changed temperature range compared with thermograms of each component ($T_m = 175$°C and 201°C). The sharp endothermic melting peak of fosinopril at about 200°C disappears in the 1:1 (*w/w*) mixture with magnesium stearate and a new exothermic peak ($T_m = 175$°C) is revealed, (Fig. 7a). With lactose, the thermogram exhibits only a large jagged endothermic peak

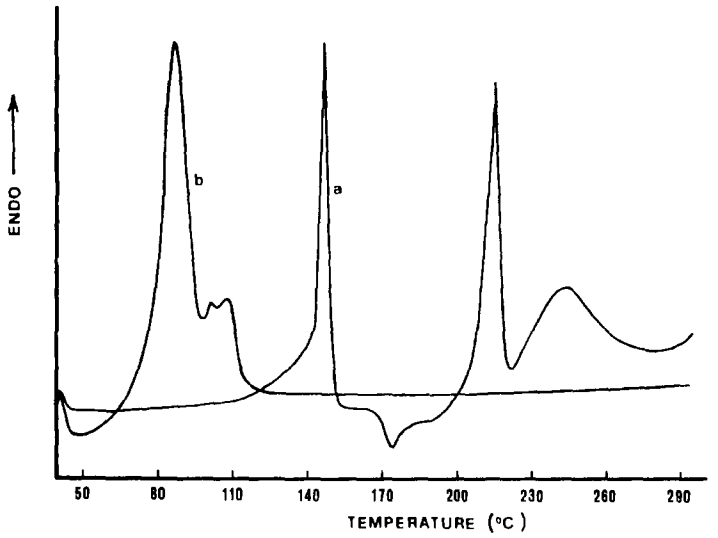

Fig. 5. DSC curves in a nitrogen atmosphere of lactose monohydrate (a) and magnesium stearate (b); heating rate 10°C min^{-1}.

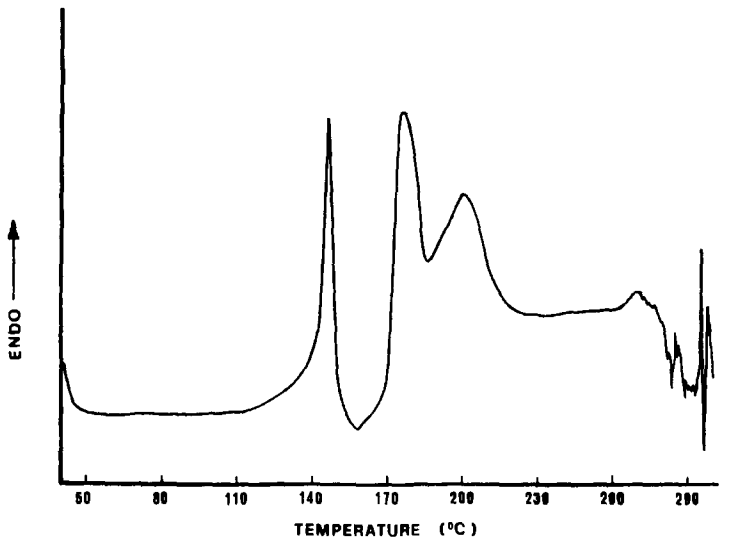

Fig. 6. DSC curve in a nitrogen atmosphere of a nefazodone–lactose monohydrate 1:1 (w/w) mixture; heating rate 10°C min^{-1}.

(T_m = 193°C) instead of the endothermic and exothermic processes connected with melting and decomposition reactions of the components (Fig. 7b).

None of the mixtures stored at 25°C and 35°C for up to two months showed significant differences in the calorimetric traces in comparison with those described above.

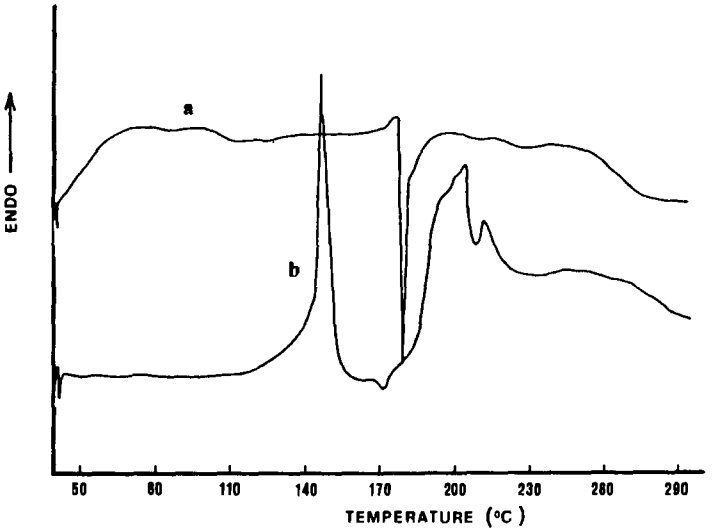

Fig. 7. DSC curves in a nitrogen atmosphere of fosinopril–magnesium stearate (a) and fosinopril–lactose monohydrate (b) 1:1 (*w*/*w*) mixtures; heating rate 10°C min^{-1}.

On the basis of these results it should seem fosinopril is incompatible with both magnesium stearate and lactose, while nefazodone is incompatible with the latter excipient only.

To verify if this conclusion is right, we carried out further experiments determining the content of the drugs in each mixture by UV and HPLC methods and compared their IR spectra with those computed by adding the spectrum of the drug to that of the excipient. All these results demonstrated that no interaction occurred between the drug and the excipient considered.

4. Conclusions

Taking into account the results of the chemical and spectroscopic analyses, the interpretation of DSC curves must be revised.

The modifications observed in the thermal properties of the analysed mixtures must be due to some interaction between drug and excipient induced solely by the temperture increase and not preexistent in the mixtures stored in the usual conditions.

In particular it is fairly probable that a physical or a chemical transformation (e.g. melting) of one component can produce a different environment in which the behaviour of the other species is modified. It is possible, also, that the interaction between drug and excipient is so slow at room temperature that it is negligible but, on increasing the temperature, the kinetics of the reaction increase and the physico-chemical properties of the components are changed.

To sum up, we have reason to believe that DSC gives useful information concerning the interaction between drug and excipient, and by consequence on their compatibility, in these cases:

(1) DSC runs of the mixture combine the features of the thermograms of each component (no interaction);

(2) a new peak appears at temperature lower than that connected with the first chemical or physical transformation of either component (interaction); and

(3) a calorimetric trace of the mixture stored for some time shows significant differences in comparison with that of newly prepared mixture (interaction).

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