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AN INVESTIGATION INTO EVENTUAL INTERACTIONS BETWEEN CLENBUTEROL AND SOME MUCOLYTIC DRUGS BY DIFFERENTIAL SCANNING CALORIMETRY

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ABSTRACT

Differential Scanning Calorimetry was used to predict the physico-chemical compatibility between clenbuterol and some mucolytic drugs.

Mixtures of clenbuterol and ambroxol, bromhexine, tiopronin, sobrerol, eprazinone and carbocysteine were examined. Using this method, only eprazinone and carbocysteine were found to be compatible with clenbuterol.

INTRODUCTION

We previously investigated the compatibility between clenbuterol and some excipients commonly used in the manufacturing of tablets, using differential scanning calorimetry (DSC) [1].

In fact it is known that DSC is a well developed technique for drug-excipient and drug-drug compatibility testing [2-14].

In spite of some limitations [15], even though small quantities of substance are used, this method permits some predictions often comparable with the hypothesis obtained by the routine accelerated stability methods.

Presently we are investigating the thermal behaviour of physical mixtures of clenbuterol (β_2 adrenergic long-term broncodilator drug [16-21]) and some mucolytics, in order to predict eventual interactions.

DSC screening was performed for the evaluation of clenbuterol and ambroxol, bromhexine, tiopronin, sobrerol, eprazinone, and carbocysteine mixtures respectively.

EXPERIMENTAL

Materials and methods

The following substances were used: clenbuterol hydrocloride, ambroxol hydrochloride, bromhexine hydrochloride, tiopronin, carbocysteine, eprazinone dihydrochloride and sobrerol.

All the substances had a high degree of purity.

A Perkin-Elmer Model DSC-2 differential scanning calorimeter was used. Thermograms were obtained by heating at a constant heating rate of 10°C per minute. All the samples were analyzed in sealed aluminium pans, in a nitrogen atmosphere. The mixtures of the substances were prepared in a mortar, in the usual 1:1 ratio, which was the most appropriate way of proceeding even if it is far from the dosage form composition (about 1 part of clenbuterol to 1000 or more of the mucolytic).

The ΔH values were calculated by weighing a cut-out copy of the peak and comparing its area with the corresponding indium sample reference area.

Sometimes the determinations were performed at different heating rates and/or at different drug ratios (up to 1:5) to avoid eventual misinterpretations and/or to verify our predictions.

Finally, in some cases, mass spectrometry determinations were also performed to eliminate any eventual wrong interpretation of the thermograms.

A low resolution LKB 2091 mass spectrometer, connected to a PDP 11 computerized system was used. E.I. mass spectra were recorded by direct inlet system: the probe was heated by programmed temperature ranging from 15°C to 250°C, at a rate of 60°C per minute. The ion source temperature was 250°C, the electron energy was 70 eV.

RESULTS AND DISCUSSION

The thermograms of clenbuterol-ambroxol and clenbuterol--bromhexine mixtures were compared with that of the corresponding individual substances. The DSC scans of the two mucolytic drugs (Fig. 1, 2 - Traces II) were very similar, as could be expected considering their chemical structures. In fact the ambroxol thermogram showed one endothermic peak with a maximum at 245°C followed by an exothermic degradation reaction. Similarly, a degradation immediately followed the melting peak of the bromhexi-

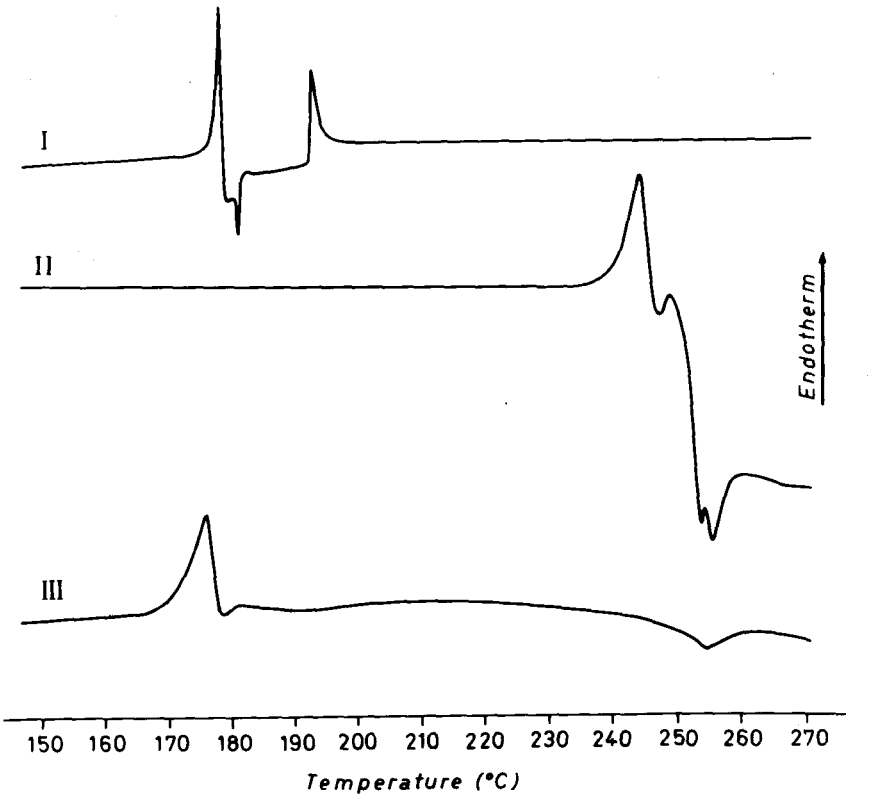

FIGURE 1

DSC thermograms of clenbuterol (I), ambroxol (II) and clenbuterol--ambroxol mixture (III).

ne, that appeared with a maximum at 254°C. The thermal behaviour of the mixtures of clenbuterol and the two substances was also very similar (Fig. 1, 2 - Traces III). The clenbuterol-ambroxol mixture showed one melting endothermic peak in a transition temperature range from 167° to 178°C, with a maximum at 175°C. The value of the corresponding enthalpy change was found to be 21 cal/g of each single component. The ΔH values related to the peaks of the individual components were 20,1 cal/g for clenbuterol and 16,1 cal/g for ambroxol.

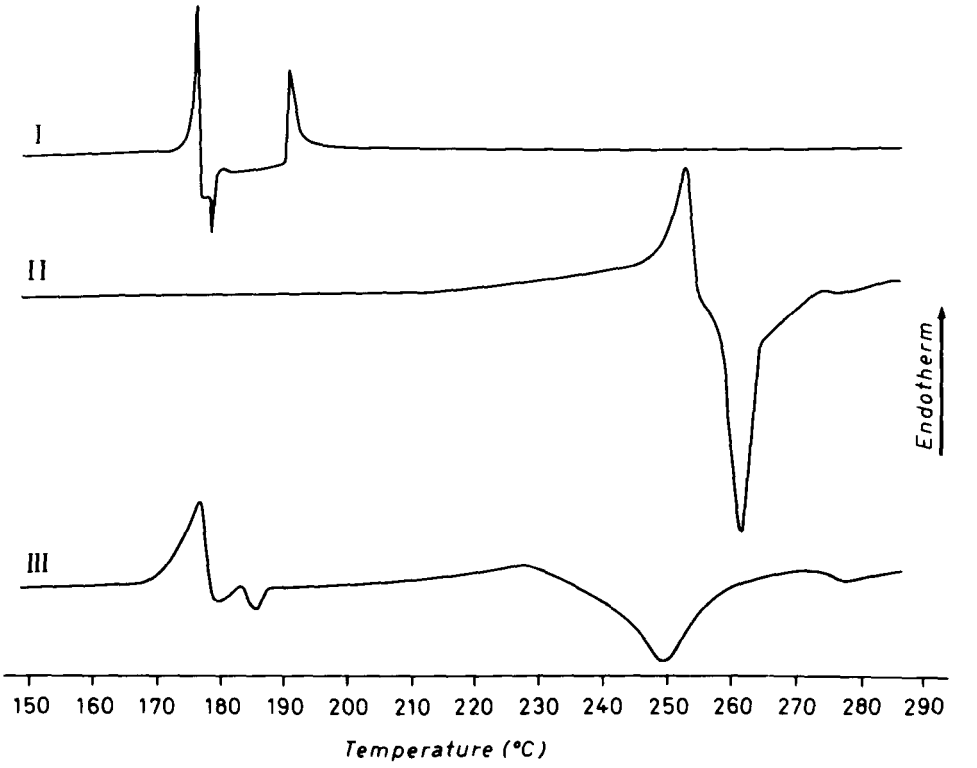

FIGURE 2

DSC thermograms of clenbuterol (I), bromhexine (II) and clenbuterol-bromhexine mixture (III).

On the other hand, the combination of clenbuterol and bromhexine had an endothermic peak with a maximum at 178°C and a transition enthalpy of 23 cal/g of each single component; the Δ H related to the bromhexine was 13,5 cal/g.

As we have previouly described [1], the values of the areas under the endothermic melting peaks should be considered approximate each time a degradation reaction immediately follows these peaks.

Nevertheless, we observed that ΔH values related to the peaks of the mixtures were very close to that of the clenbuterol melting transition. Moreover, the DSC scans of the mixtures did not modify at different heating rates and at different ratios of the components. Consequently, it seems possible to predict an interaction between the components of the mixtures, after the melting transition of the clenbuterol.

In order to confirm this assumption, mass spectra of the mixtures and of each component were carried out on the samples, after the corresponding endothermic transition processes. As Figures 3 - 7 show, comparing the mass spectra of the individual drugs and their mixture, the incompatibility predicted in our experimental conditions were confirmed. In fact the mass spectra of the clenbuterol-ambroxol mixture showed (Fig. 5), other than the signals observed in the spectra of each individual substance (for instance at m/e 114 and 264 for ambroxol, and m/e 30 and 86 for clenbuterol) (Fig. 3, 4), other signals, particularly at m/e 58 and cluster signals in high mass range between 380 and 450.

Similarly, comparing the mass spectra of the clenbuterol--bromhexine mixture (Fig. 7) and that of the individual substances (Fig. 3, 6), we noticed, in addition to the signals obtained from the individual components, other intense peaks, for example at m/e 58 and cluster signals at a high mass (m/e >380), as previously observed for ambroxol. Even if it is known that low mass fragments are not particularly characteristic, the obtained re-

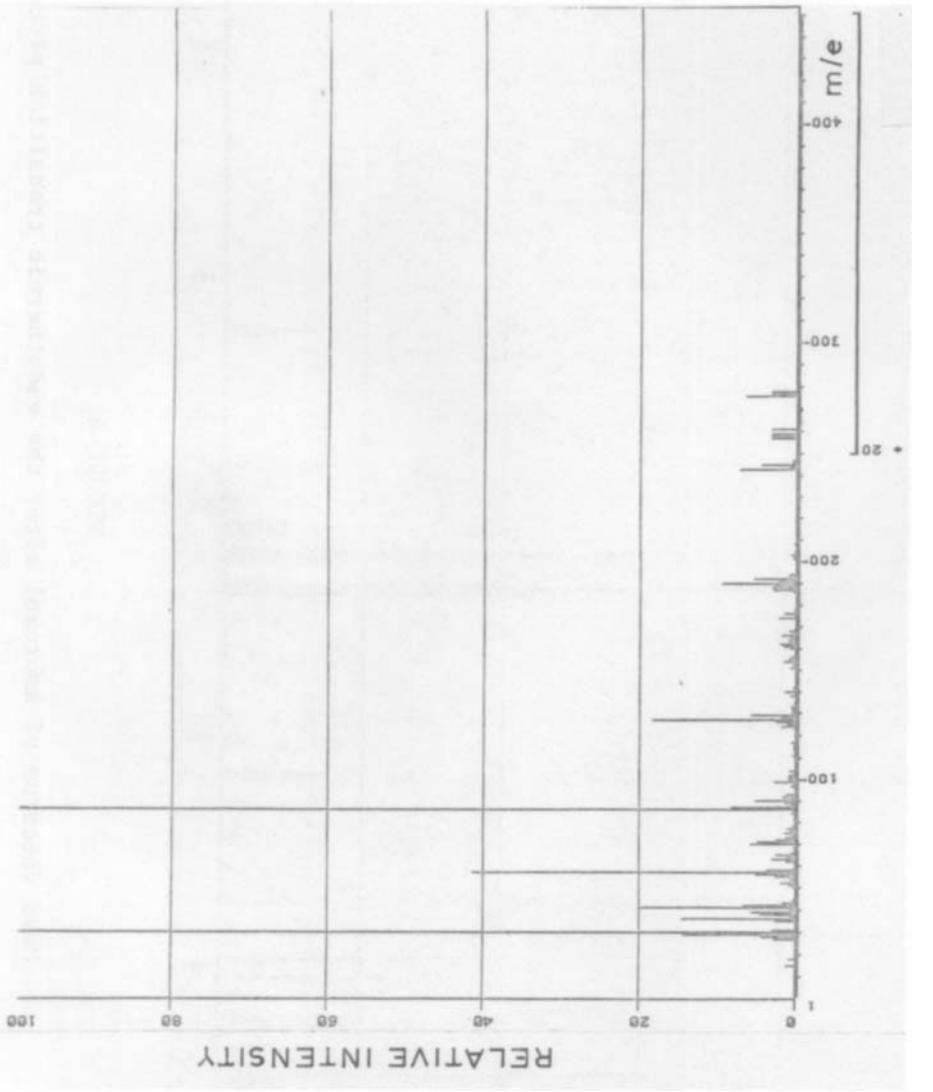

FIGURE 3

Mass spectrum of clenbuterol after the first endothermic transition process.

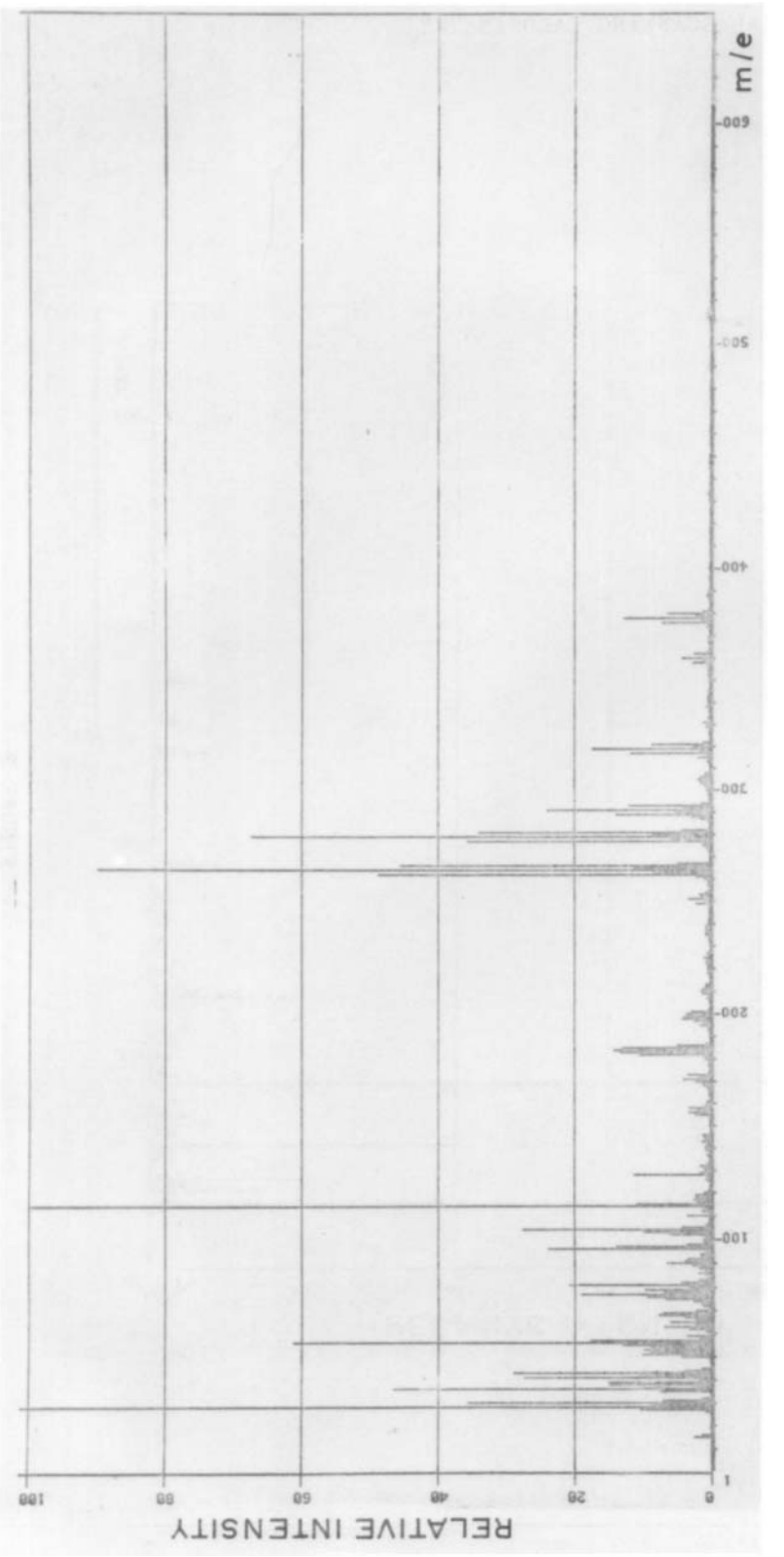

FIGURE 4

Mass spectrum of ambroxol after the endothermic transition process.

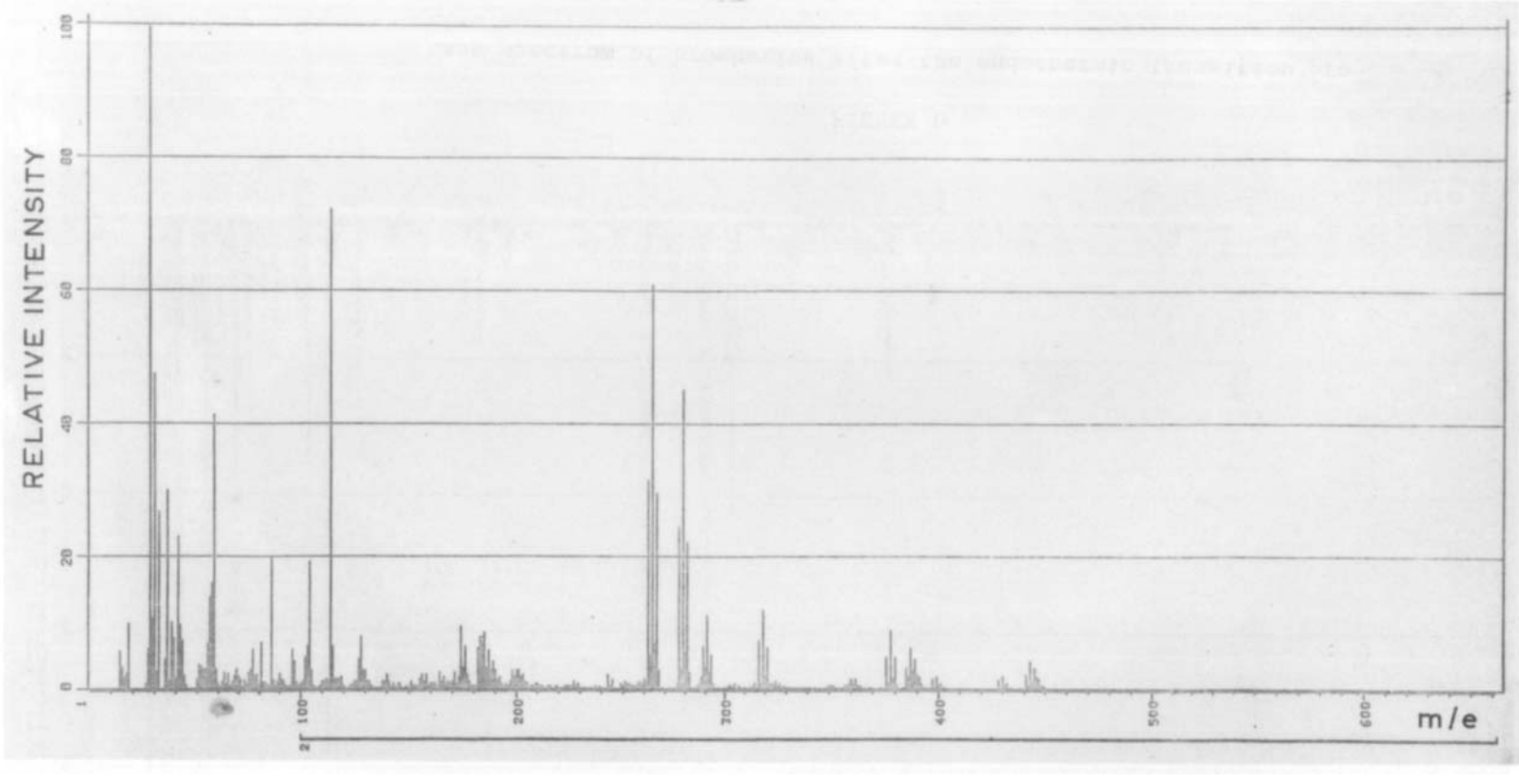

FIGURE 5

Mass spectrum of clenbuterol-ambroxol mixture after the endothermic transition process.

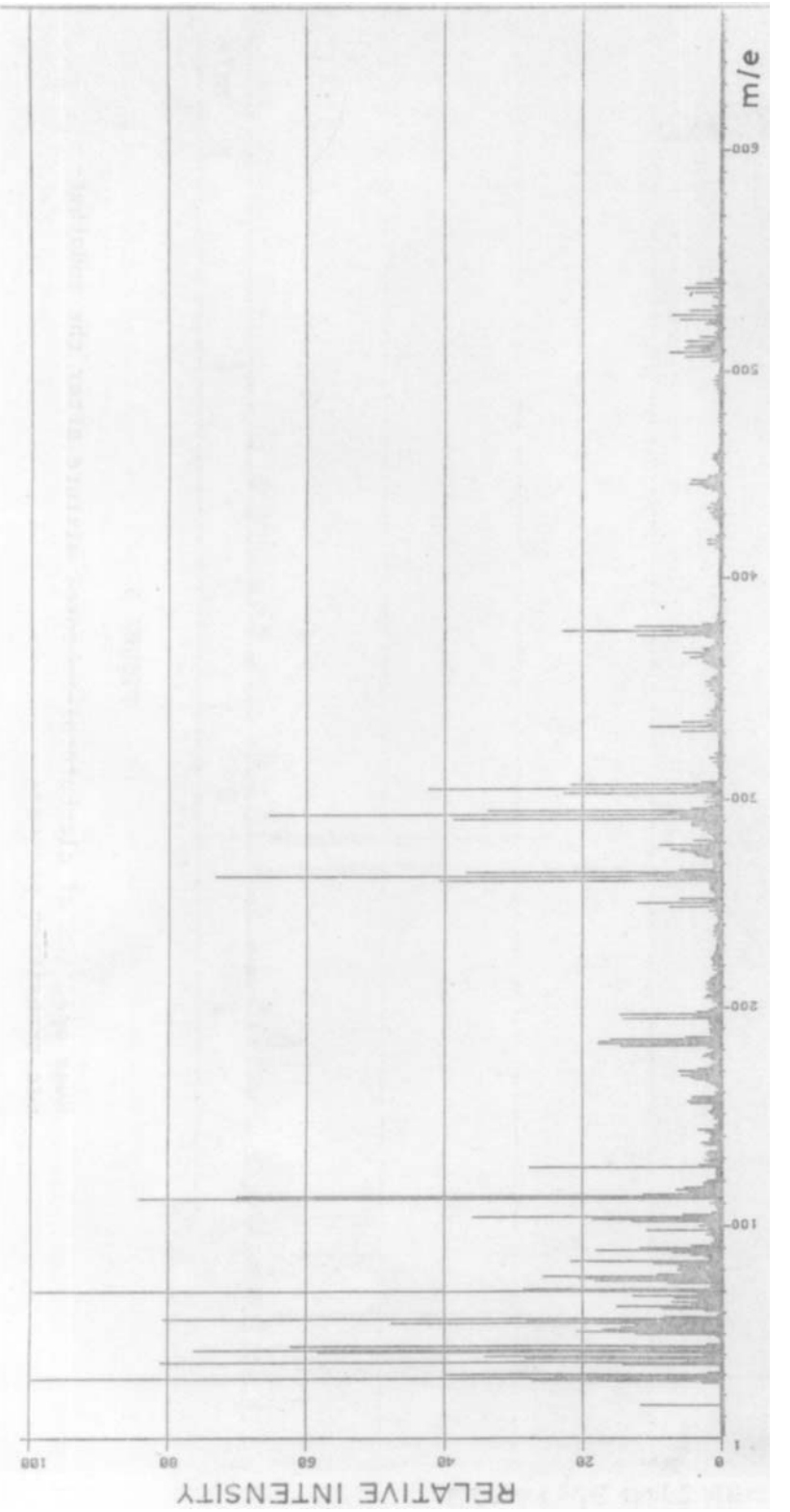

FIGURE 6

Mass spectrum of bromhexine after the endothermic transition process.

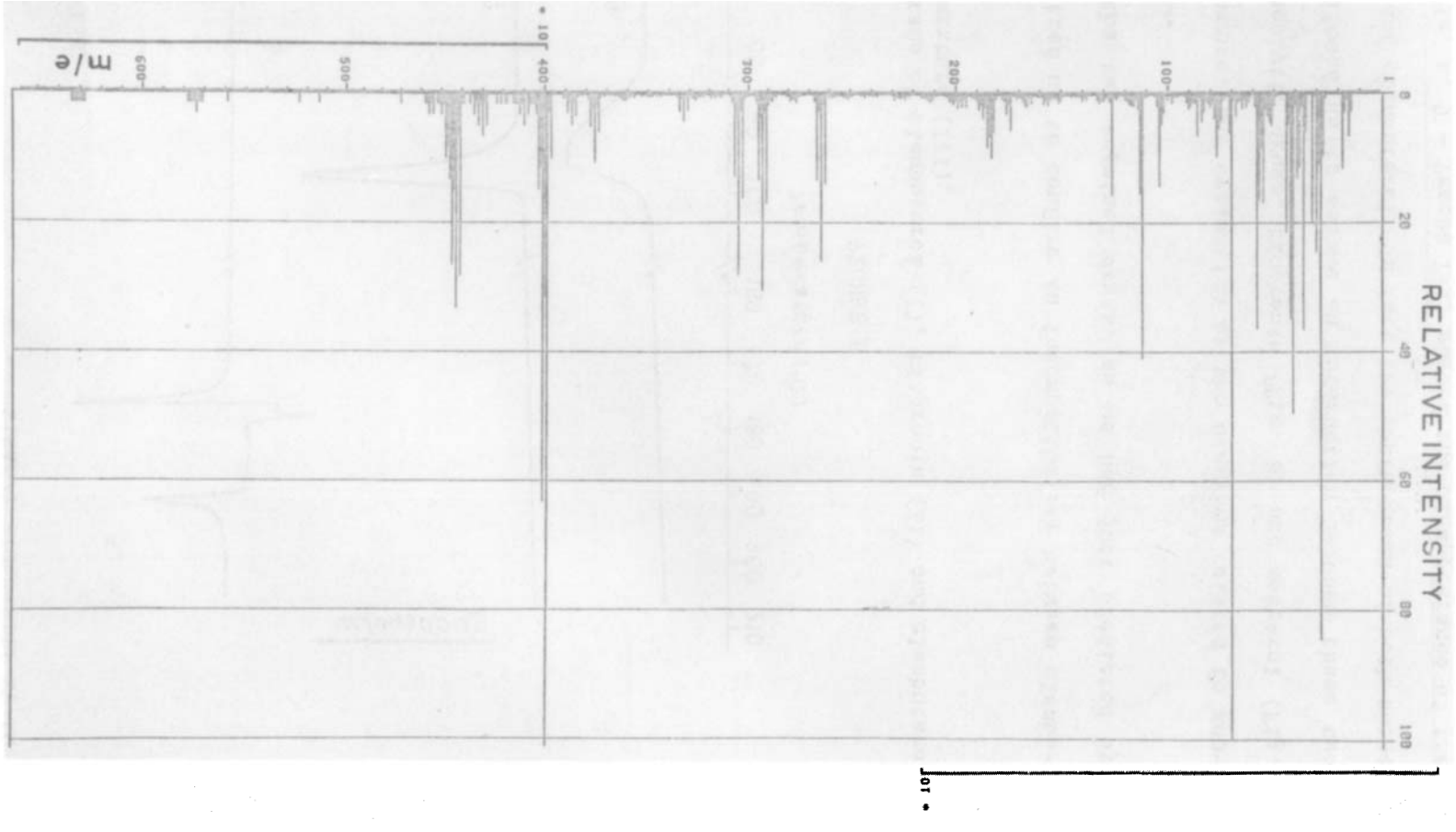

FIGURE 7

Mass spectrum of clenbuterol-bromhexine mixture after the endothermic transition process.

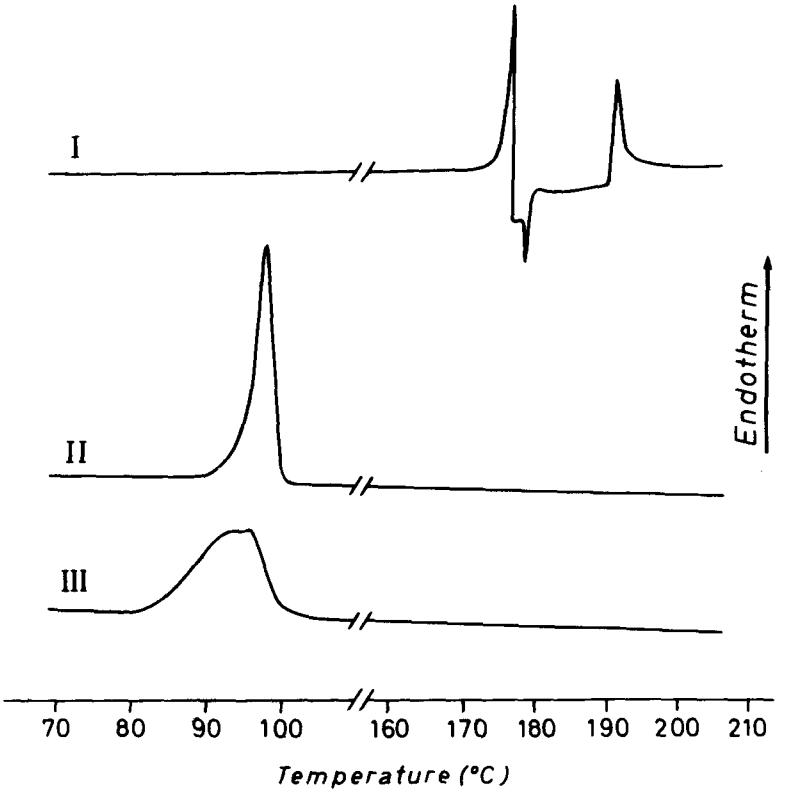

FIGURE 8

DSC thermograms of clenbuterol (I), tiopronin (II) and clenbuterol--tiopronin mixture (III).

sults permitted us to confirm an incompatibility between clenbuterol and the two examined drugs, as we had just predicted by means of DSC.

Furthermore, the evaluation of the diagrams related to another two mucolytic drugs, tiopronin (Fig. 8) and sobrerol (Fig. 9), also allowed us to assume an interaction between these two substances and clenbuterol. In fact the thermograms of both these mixtures (Fig. 8, 9 - Traces III) showed the disappearance of the

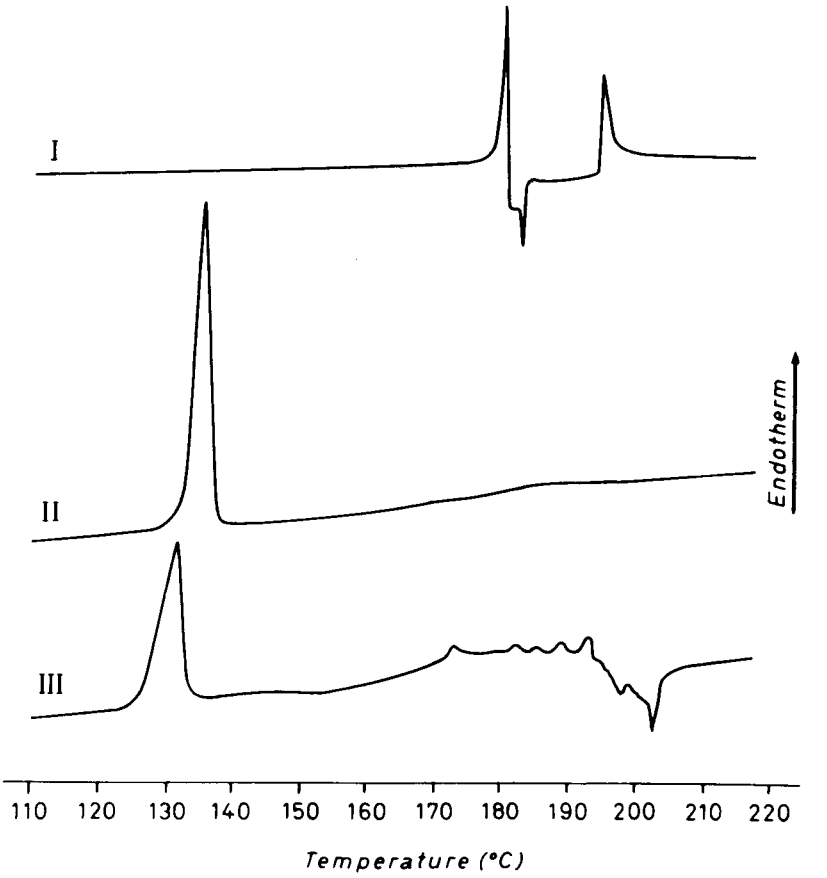

FIGURE 9

DSC thermograms of clenbuterol (I), sobrerol (II) and clenbuterol--sobrerol mixture (III).

melting transition peak of clenbuterol and one endothermic peak with ΔH values similar to those of the individual substances. Finally no significant difference was noted in DSC scans when the mixtures were prepared with various ratios of the individual components. Therefore, also in this case, an interaction between the components of the mixtures could occur after the melting transition of clenbuterol.

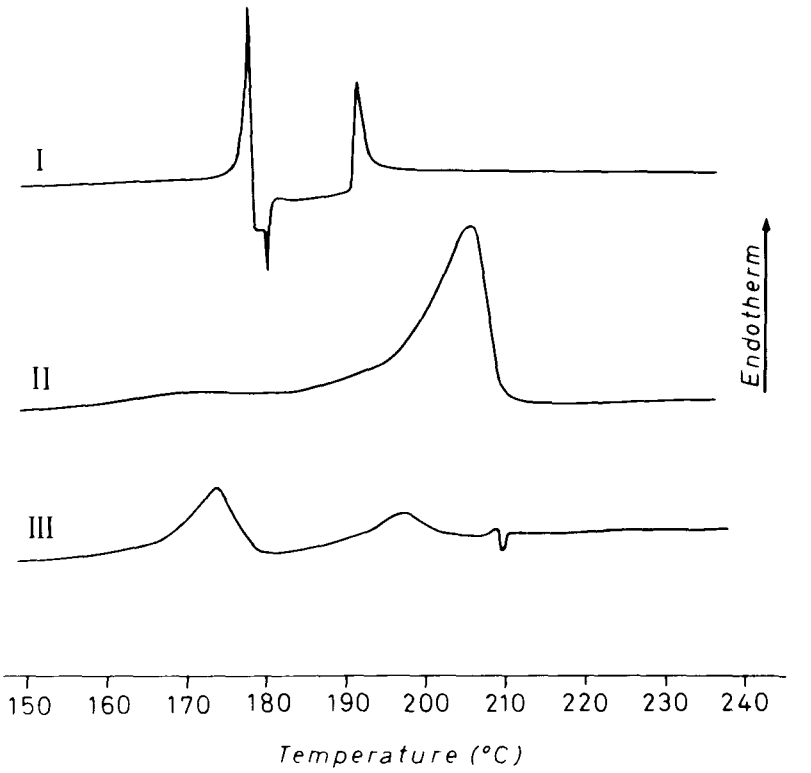

FIGURE 10

DSC thermograms of clenbuterol (I), eprazinone (II) and clenbuterol--eprazinone mixture (III).

Trace II of Figure 10 is the thermogram of eprazinone showing the melting endothermic peak with a maximum at 204°C.

The mixture of this drug with clenbuterol (Fig. 10, trace III) showed two endothermic peaks with maxima at 174° and 197°C. The transition temperature (174°C) and the ΔH (20,8 cal/g) values of the first peak were very similar to the correspondent ones obtained from clenbuterol (177°C; 20,1 cal/g). On the other hand, the transition temperature of the endothermic peak of e-

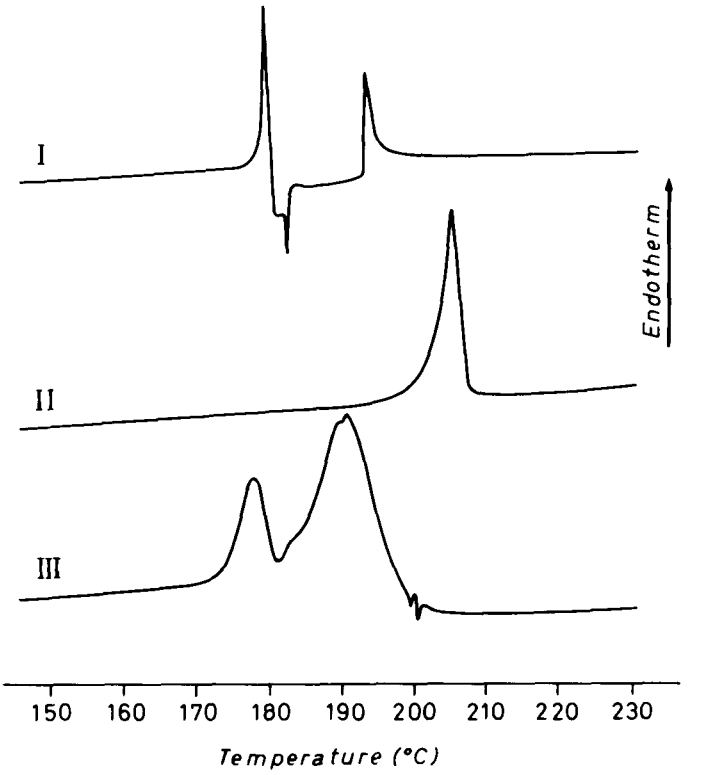

FIGURE 11

DSC thermograms of clenbuterol (I), carbocysteine (II) and clenbuterol-carbocysteine mixture (III).

prazinone (204°C) was similar to that obtained from the second endothermic peak of the mixture (197°C). In addition, the mixtures prepared with different ratios of the two drugs showed thermograms with the same values of transition temperature and enthalpy changes. Nevertheless, the ratios of the two peak areas were different, in accordance with the ratios of each individual component. Therefore, a compatibility between the two drugs could be assumed.

Finally, Fig. 11 shows the thermograms of clenbuterol and carbocysteine and their mixture. This last diagram (Fig. 11 - Trace III) exhibited two endothermic peaks, the first one at a very similar temperature to the clenbuterol melting point, the second one at a lower temperature than the carbocysteine melting peak. As with eprazinone, also in this case the DSC scans obtained from different mixtures, prepared with various ratios of the two individual components, showed the same values of transition temperature, but different ratios of the two peak areas in accordance with the composition of the mixtures. The method used to calculate the enthalpy changes was not suitable for evaluating those of the two endothermic peaks of the mixture, because they were not well separated from each other. Therefore, even if the ΔH values were not available, the obtained results allowed us to predict a possible compatibility between clenbuterol and carbocysteine.

CONCLUSIONS

DSC screening allowed us to predict a compatibility of clenbuterol with only two of the six mucolytic drugs examined. Eprazinone and carbocysteine did not seem to present any interaction with clenbuterol by means of the DSC method.

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