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COMPATIBILITY STUDY BETWEEN CLENBUTEROL AND TABLET EXCIPIENTS USING DIFFERENTIAL SCANNING CALORIMETRY

E. Ciranni Signoretti, A. Dell'Utri,
A. De Salvo, L. Donini

Drug Chemistry Laboratory
Istituto Superiore di Sanità
Viale Regina Elena, 299 - 00161 Roma (ITALY)

ABSTRACT

In order to improve the formulation of clenbuterol, the physico-chemical compatibility between this drug and various excipients commonly used in manufacturing of tablets, was studied by Differential Scanning Calorimetry (DSC).

Using this method, clenbuterol was found to be compatible with talc, stearic acid, magnesium stearate and titanium dioxide, whereas an incompatibility was shown with maize starch, pregelatinized starch, sodium starch glicollate, polyvinylpyrrolidone, avicel PH 101 and lactose.

INTRODUCTION

Clenbuterol (4-amino-3,5-dichloro-α-[[(1,1-dimethylethyl)] amino] methyl benzenemethanol) is a β_2 adre

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nergic long-term highly active broncodilator, used orally in chronic asthmatic desease [1-6].

Since this compound, due to its chemical structure, is liable to degradation and its content in each oral dose is very small, we decided to study the stability of its pharmaceutical formulations, with specific attention given to possible interactions with some excipients commonly used in the manufacturing of tablets.

This work, aiming at improving formulations, originates from previous stability studies by different authors on various formulations of drugs like antibiotics, edulcorants, etc [7-16].

In preformulation studies, to know any possible incompatibility is obviously important, ever since it has been shown that certain interactions can change the bioavailability of a product, for example by alteration of its partition coefficient between the aqueous and lipidic phase [17].

DSC allows the fast evaluation of possible incompatibilities between the formulation components, derived from appearance, shift or disappearance of peaks and/or variations in the corresponding ΔH.

The physico-chemical effects observed with DSC may not result in alterations during room temperature storage. Therefore, considerations and limitations relevant to the routine accelerated stability studies fit the present case.

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EXPERIMENTAL

Materials

- Clenbuterol hydrochloryde (Resfar);
- talc (U.S.P.);
- magnesium stearate (U.S.P.);
- stearic acid (Carlo Erba);
- titanium dioxide (Merck);
- sodium starch glicollate (Primojel, Tunnel Avebe Starches Ldt. U.K.);
- maize starch (B.P.);
- pregelatinized starch (Laing National Ldt. U.K.);
- polyvinylpyrrolidone (U.S.P.);
- avicel PH 101 (U.S.P.);
- lactose (U.S.P.).

Methods

A differential scanning calorimeter (Perkin-Elmer DSC-2) was used.

All the samples were encapsulated in flat bottomed alluminum pans. Samples (1-5 mg) were triturated in mortar, then heated in a temperature range of 30--350 ^{o}C, with a heating rate of 5 ^{o}C per minute, in a nitrogen atmosphere.

The transition enthalpies (ΔH) were calculated by weighing the area of each peak and comparing it with an indium sample reference.

Mixtures of excipient and drug, in the range 1:1 to 1:10, were examined.

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The thermogram interpretation of single clenbuterol and mixture with titanium dioxide was done by mass spectrometry. A low resolution mass PDP 11 computer system using an LKB 2091 spectrometer was used. The spectra were obtained through direct insertion probe. The ion source temperature was 250 ^{o}C. The probe was heated by programming temperature from 15 ^{o}C to 250 ^{o}C, at 60 ^{o}C per minute rate.

RESULTS AND DISCUSSION

Figure 1 shows the thermogram of clenbuterol. The first endothermic peak represents the melting of this substance in a transition temperature range of 172-180 ^{o}C, with a maximum at 177 ^{o}C. The calculated enthalpy was 20.1 cal/g, although this value should be considered as approximate, due to the difficulty of exactly evaluating the endothermic melting peak, being this one immediately followed by the peak due to the alteration process. The same limitation applies to all other experimental thermograms, from which this Δ H value is derived. This alteration is confirmed by comparing mass spectra carried out on the substance after the first and the second endothermic transition process respectively (Fig. 2 and Fig. 3). A process of polymerization of the clenbuterol (molecular cluster ions: 274-280) is noted by observing the presence of characteristic cluster signals in the mass range between 200 to 600. In particular, the m/e values from 540 to 546 are probably due to a dimer formation.

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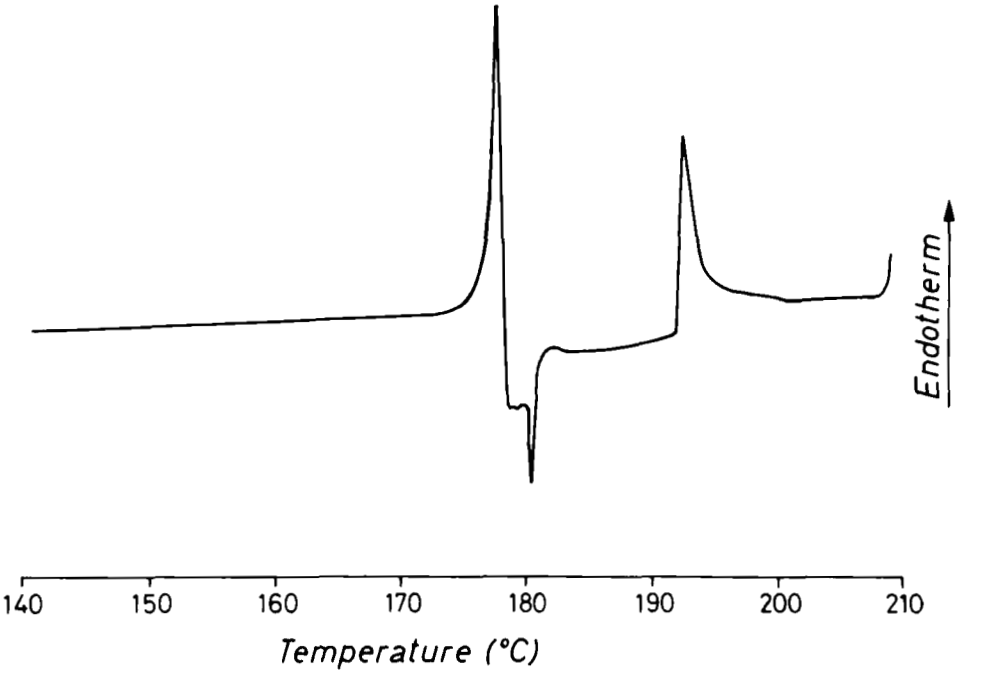

Figure 1

DSC thermogram of clenbuterol

As previously pointed out, the mixtures were prepared with various excipients and different ratios of clenbuterol, but this variation of parameter did not substantially cause modifications of the final results, other than some small changes in the maximum peak values. Therefore only the thermograms of 1:1 mixtures are shown.

Clenbuterol was found to be compatible with talc, stearic acid, magnesium stearate and titanium dioxide. On the contrary, it was found incompatible with the other excipients examined.

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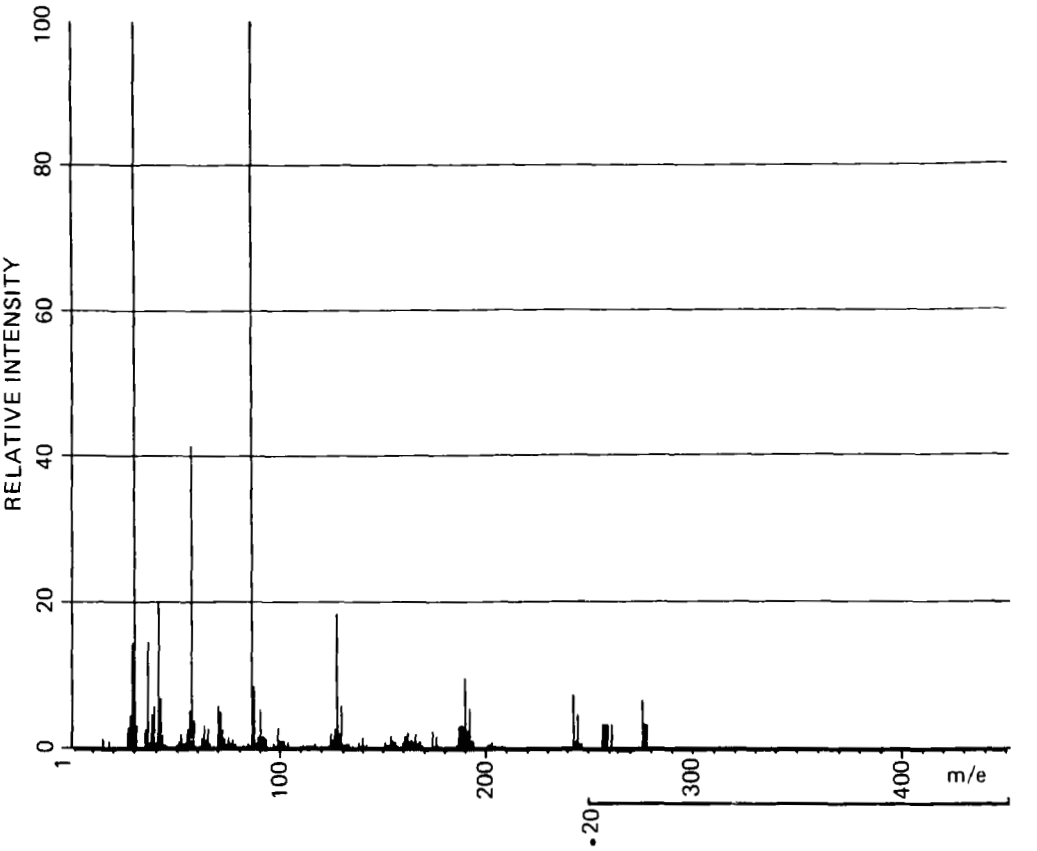

Figure 2

Mass spectrum of clenbuterol after the first endothermic transition process

Thermoanalysis of talc shows no transition in the examined temperature range. When mixed with clenbuterol, it exhibits the typical feature of this drug, without alteration of the transition enthalpy of clenbuterol (20.1 cal/g).

This was also observed in the case of magnesium stearate where the thermogram of the mixture shows the

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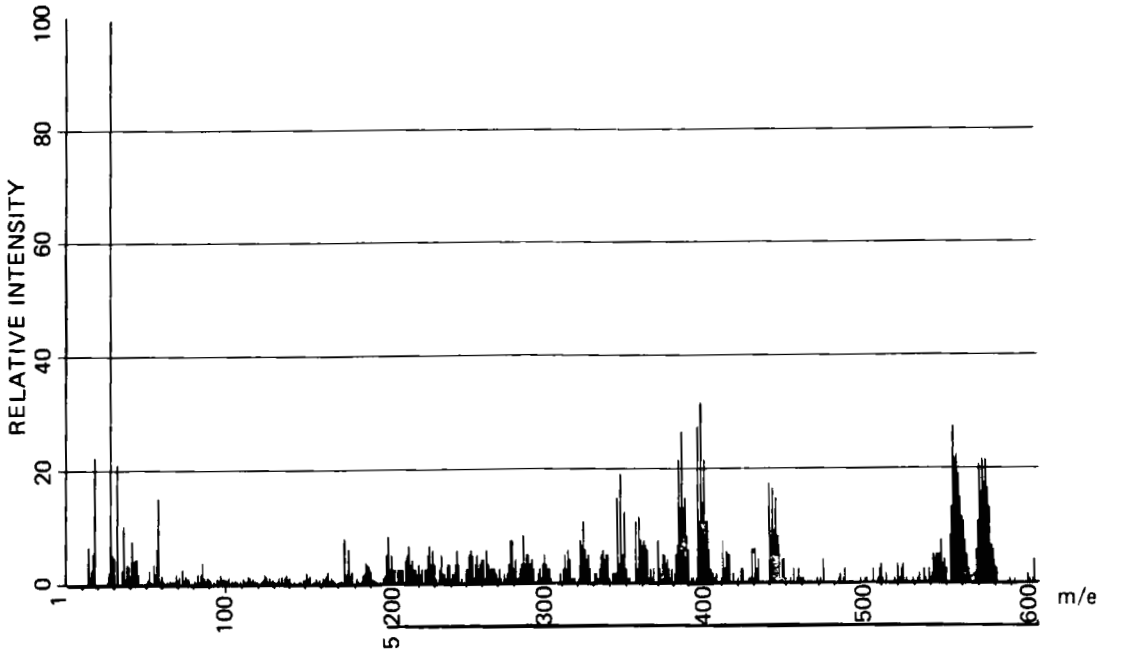

Figure 3

Mass spectrum of clenbuterol after the second endothermic transition process

same feature as the single components. The magnesium stearate thermogram shows an endothermic peak at 116 °C, which, as already stated by other authors, could be related to changes in the ordered cristalline states, through liquid cristalline phases of various order, or to possible retained solvents [8, 20, 21]. In Fig. 4 the thermograms of clenbuterol-talc and clenbuterol-magnesium stearate mixtures are shown.

No incompatibility was noticed either between clenbuterol and stearic acid, as seen in Fig. 5, even if,

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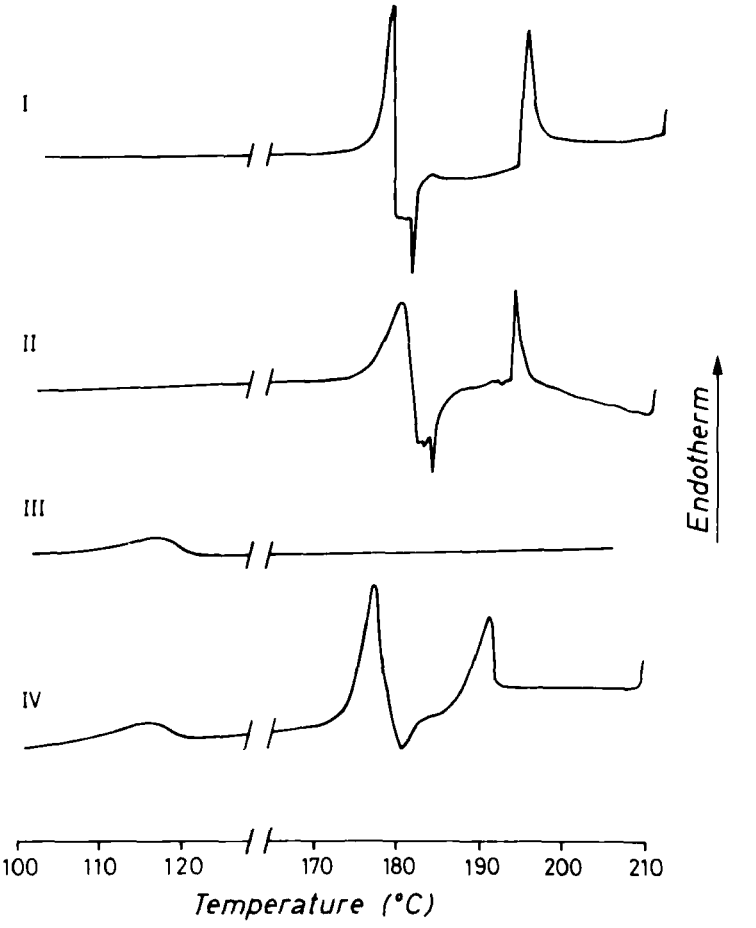

Figure 4

DSC thermograms of clenbuterol (I), clenbuterol - talc mixture (II), magnesium stearate (III) and clenbuterol - magnesium stearate mixture (IV)

in the mixture, the clenbuterol peak is shifted towards a lower temperature. In this mixture the first enthalpy change was found to be 39.0 cal/g and the second one 21.4 cal/g. These values are quantitatively identical to those calculated for individual clenbuterol and stearic acid.

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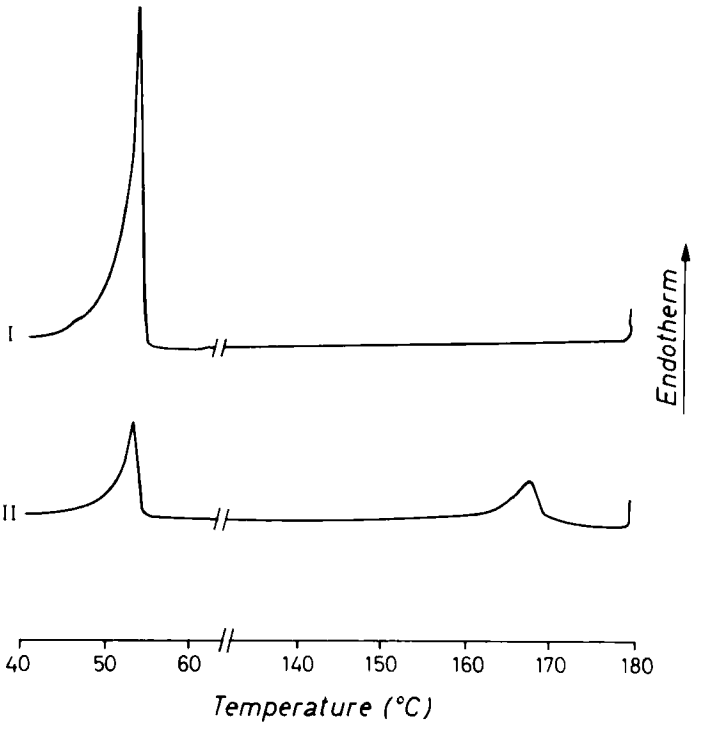

Figure 5

DSC thermograms of stearic acid (I) and clenbuterol - stearic acid mixture (II)

Moreover, the disappearance of phenomena observed after the melting of clenbuterol could be regarded as due to the possible formation of a salt with the stearic acid.

The mixture obtained with titanium dioxide, which exhibits no transition in the temperature range of 30--350 ^{o}C, gives the thermogram shown in Fig. 6, from

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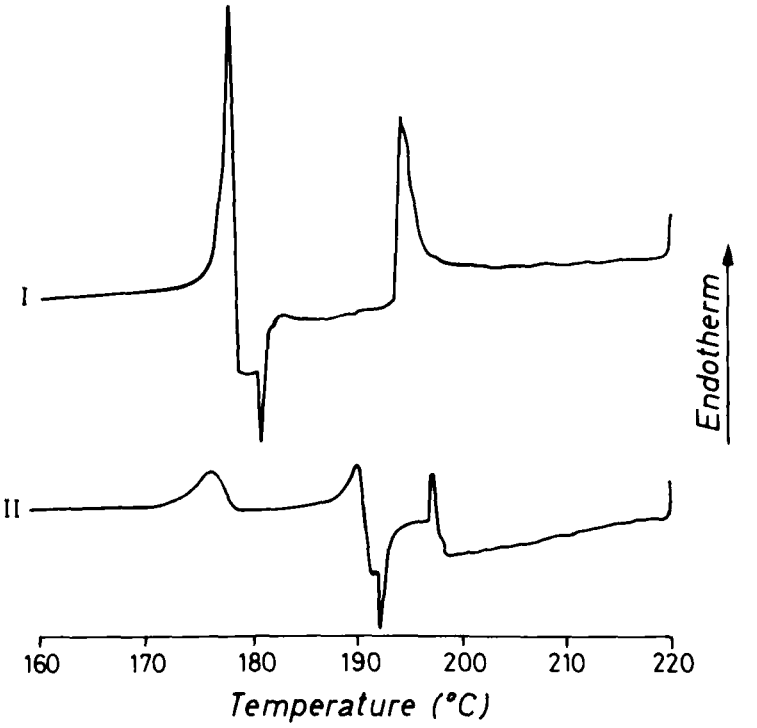

Figure 6

DSC thermograms of clenbuterol (I) and clenbuterol-titanium dioxide mixture (II)

which a compatibility between the two substances could be derived. Nevertheless, a mass spectrometric analysis was carried out to confirm this assumption. It was performed on the mixtures both after the first endothermic peak and after the last transition appearing in the diagram. As is shown in Fig. 7, the mass spectrum of the mixture after the first transition corresponds to

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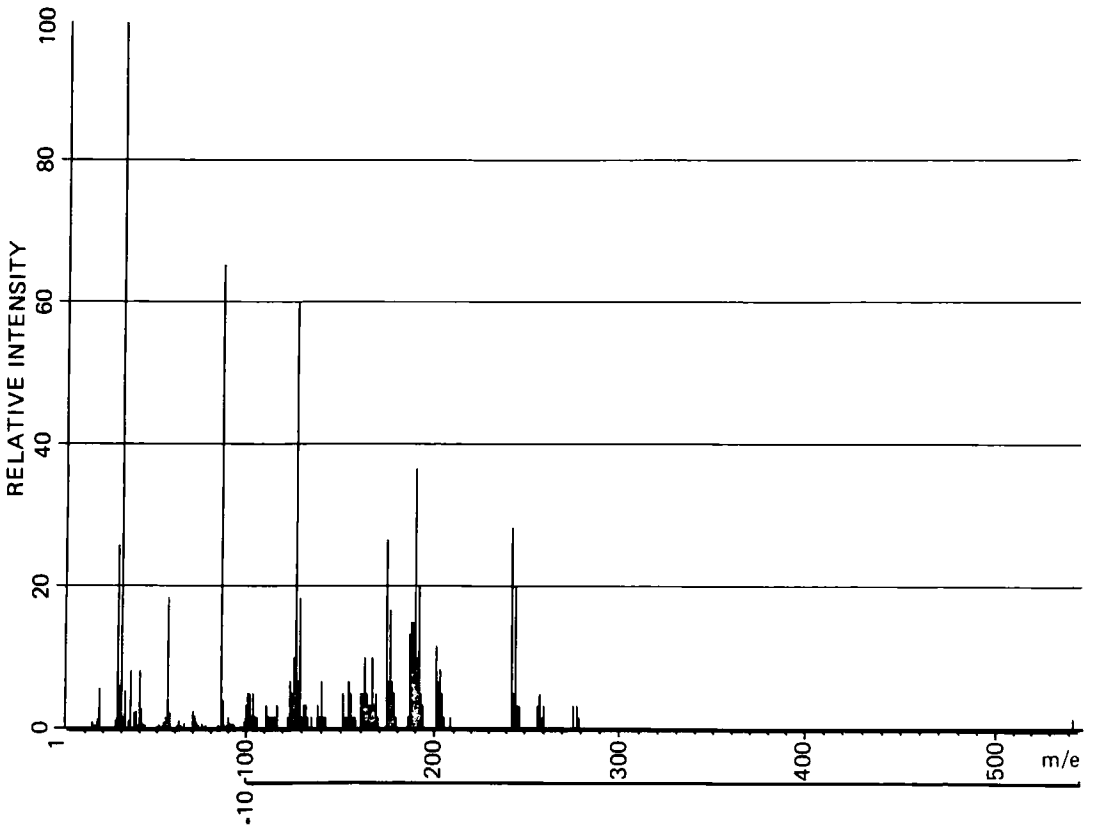

Figure 7

Mass spectrum of clenbuterol - titanium dioxide mixture after the first endothermic transition process

that of melted clenbuterol (Fig. 2). On the other hand, the second one (Fig. 8) corresponds to the spectrum of polymerized clenbuterol (Fig. 3). It confirms the assumption of a compatibility between the two substances.

Also the sodium starch glicollate, which exhibits an endothermic peak at the same temperature as the mel

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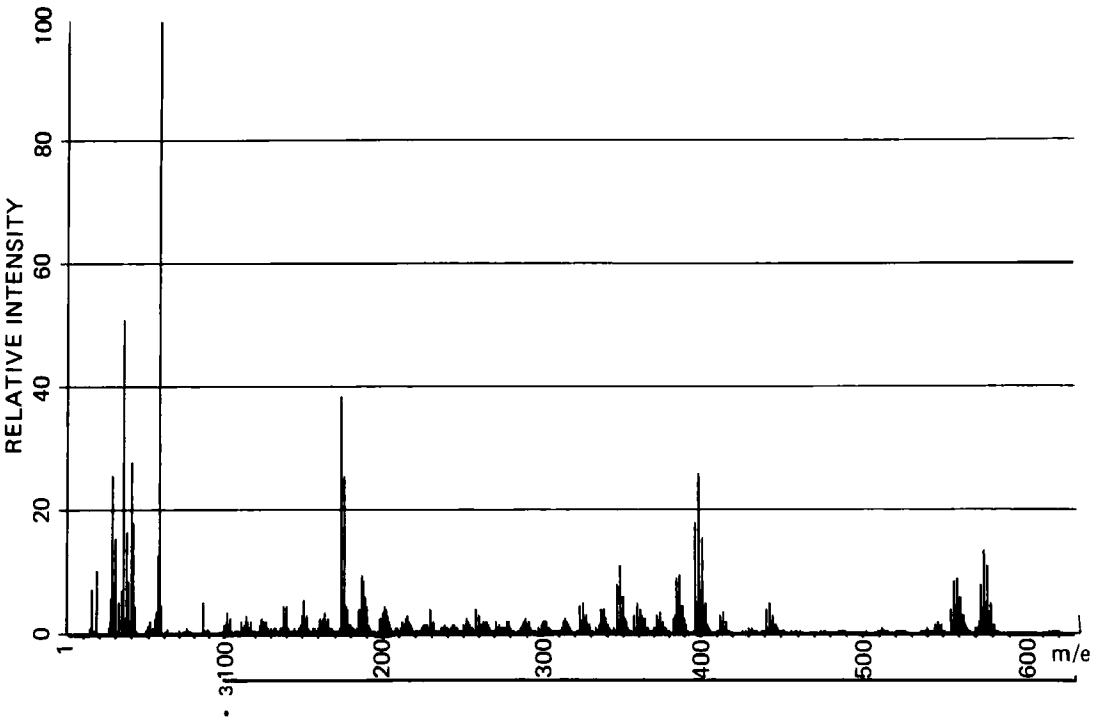

Figure 8

Mass spectrum of clenbuterol - titanium dioxide mixture after the second endothermic transition process

ting peak of clenbuterol, does not interact with this substance. This appears from the transition enthalpy (104.8 cal/g) which is the sum of the transition enthalpy of the single substances (20.1 cal/g and 80.0 cal/g respectively) (Fig. 9).

In Fig. 10, 11, 12, 13 the thermograms of starch, pregelatinized starch, polyvinylpyrrolidone, avicel PH

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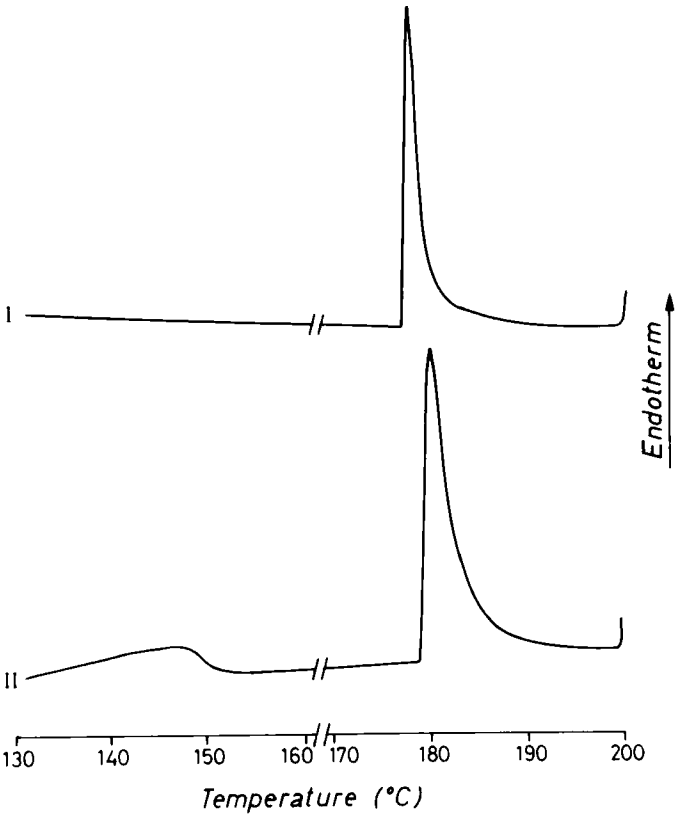

Figure 9

DSC thermograms of sodium starch glicollate (I) and clenbuterol - sodium starch glicollate mixture (II)

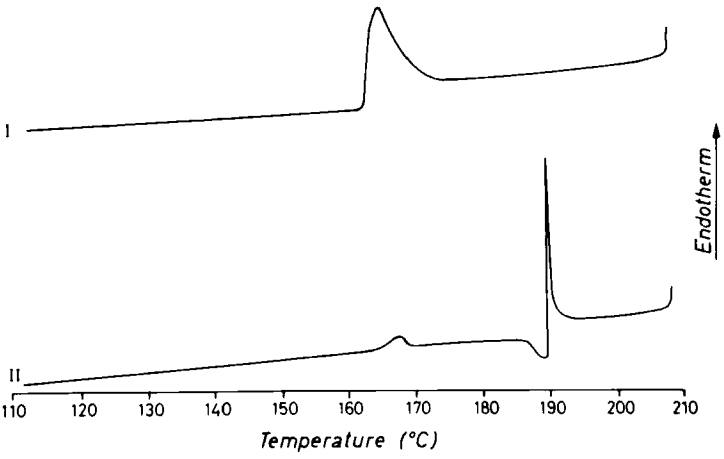

Figure 10

DSC thermograms of maize starch (I) and clenbuterol - maize starch mixture (II)

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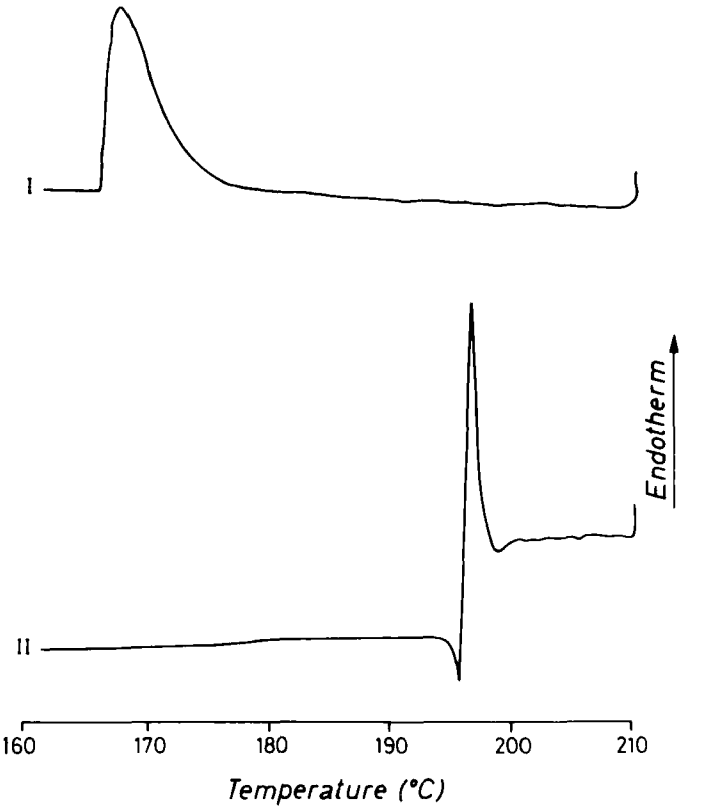

Figure 11

DSC thermograms of pregelatinized starch (I) and clenbuterol - pregelatinized starch mixture (II)

101 and 1:1 mixtures of clenbuterol with these excipients are shown. From the evaluation of these diagrams, the disappearance of the melting transition peak of clenbuterol allows us to identify a possible interaction between the drug and the four excipients examined.

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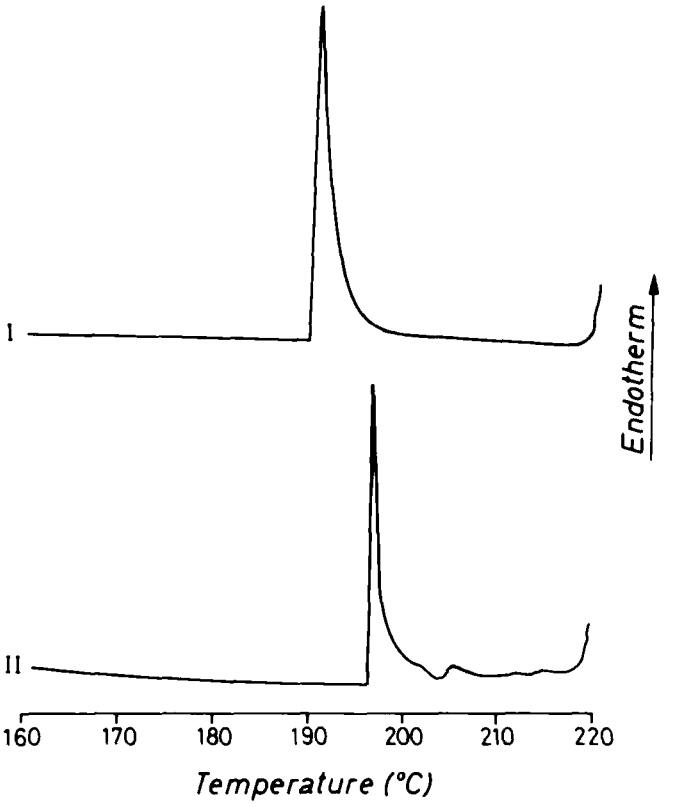

Figure 12

DSC thermograms of polyvinylpyrrolidone (I) and clenbuterol - polyvinylpyrrolidone mixture (II)

Finally, an incompatibility can also be assumed in the case of clenbuterol-lactose mixture, since the Δ H related to the peak with a maximum at 177 ^{o}C is of 63.0 cal/g for the mixture, being 20.1 cal/g for clenbuterol and 12.2 cal/g for lactose (Fig. 14).

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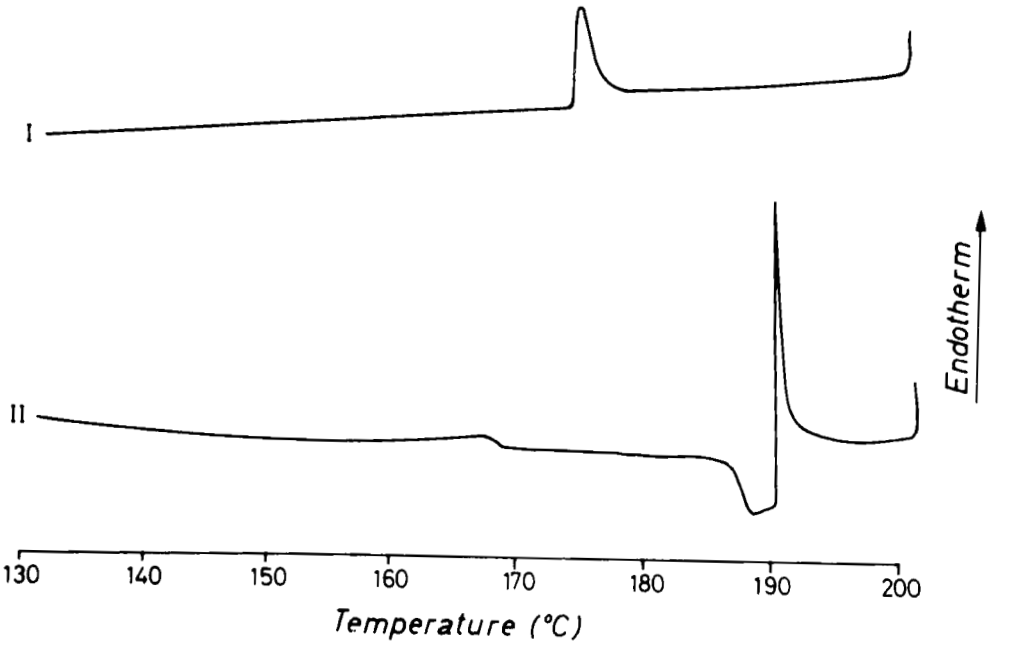

Figure 13

DSC thermograms of avicel PH 101 (I) and clenbuterol-avicel PH 101 mixture (II)

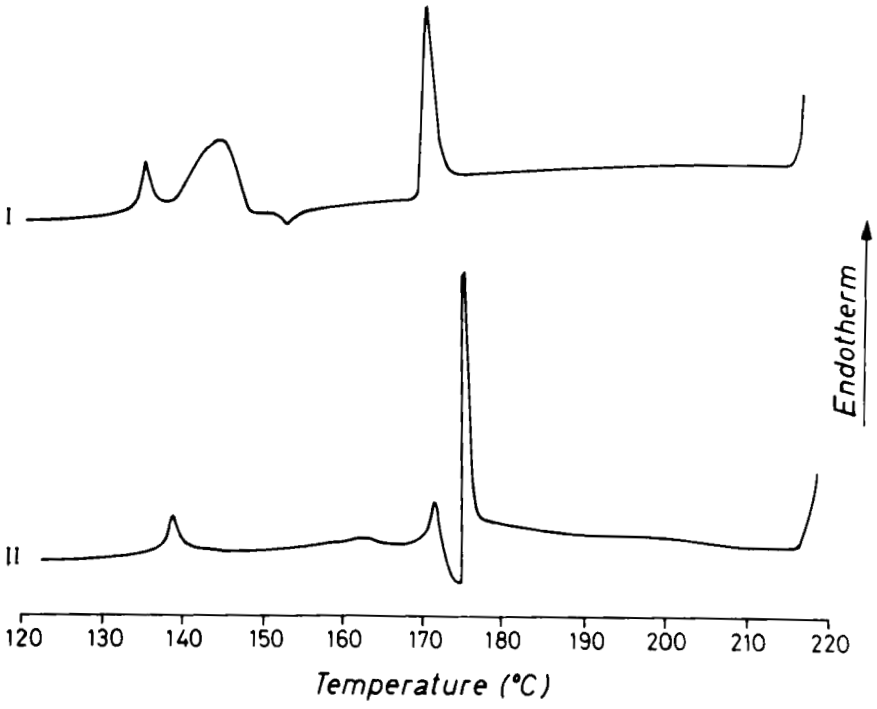

Figure 14

DSC thermograms of lactose (I) and clenbuterol - lactose mixture (II)

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CONCLUSIONS

The incompatibility between clenbuterol and five of the ten excipients examined (starch, pregelatinized starch, polyvinylpyrrolidone, avicel PH 101 and lactose) was derived by DSC. Thus, this technique could be usefully employed to optimize the clenbuterol formulations, leading to better storage stability.

ACKNOWLEDGEMENTS

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