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DSC SCREENING FOR DRUG-DRUG AND DRUG-EXCIPIENT INTERACTIONS IN POLYPHARMACEUTICALS INTENDED FOR THE ALLEVIATION OF THE SYMPTOMS OF COLDS AND FLU. I.

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ABSTRACT

DSC screening for drug-drug and drug-excipient interactions of a polypharmaceutical capsule dosage form containing acetaminophen, diphenhydramine hydrochloride, phenylephrine hydrochloride, ascorbic acid and magnesium stearate was performed. The results show the following:

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1. Diphenhydramine hydrochloride is incompatible with acetaminophen, phenylephrine hydrochloride, ascorbic acid and magnesium stearate.
2. Acetaminophen is incompatible with diphenhydramine hydrochloride, phenylephrine hydrochloride and ascorbic acid. Acetaminophen is compatible with magnesium stearate.
3. Phenylephrine hydrochloride is incompatible with diphenhydramine hydrochloride, acetaminophen, ascorbic acid and magnesium stearate.
4. Ascorbic acid is incompatible with diphenhydramine hydrochloride, acetaminophen, phenylephrine hydrochloride and magnesium stearate.

No attempt was made to determine the nature of the interactions.

INTRODUCTION

There is a tendency in some countries to combine a number of active ingredients for the purpose of alleviation of the symptoms of colds and flu. When we were confronted with problems of instability and discoloration in two different combination products in capsule form it was decided to investigate all so called cold combination products available.

In this first communication we are reporting our findings on a combination product containing acetaminophen, diphenhydramine hydrochloride, phenylephrine hydrochloride, ascorbic acid and magnesium stearate as glidant. On storage the capsule contents became brittle and turned brown.

A mixture of acetaminophen and diphenhydramine hydrochloride became sticky[1].

The influence of magnesium stearate on the browning of ascorbic acid - microcrystalline cellulose (Avicel) formulations was discussed[2].

The use of DTA in pharmacy was discussed[3] and more recently by Wollman and Braun[4].

The use of DSC in the preformulation screening of ampicillin with direct compression excipient was described[5].

Van Dooren[6] used DSC in combination with short term stress where samples are stored at 55°C for 3 weeks before performing DSC studies. He also gave a number of points to be considered when evaluating DSC thermograms.

The use of DSC to predict drug-excipient compatibility was discussed by Hardy[7] and Smith[8]. Both these authors warn against accepting that interactions thus discovered are detrimental but state that DSC

can be an invaluable tool in avoiding excipients with interaction potential.

MATERIALS AND METHODS

Diphenhydramine hydrochloride, acetaminophen, phenylephrine hydrochloride, ascorbic acid and magnesium stearate were pharmacopoeial grade.

Each of the above mentioned drugs as well as magnesium stearate were subjected to DSC. The instrumentation was a Du Pont 910 DSC system equipped with a Du Pont Series 99 Thermal Analyzer programmer. A Hewlett-Packard X-Y recorder was used.

Thermograms were obtained by heating at a constant rate of 5°C per minute and recorded at a constant chart speed of 5 cm per minute. Samples (3 - 8 mg) were measured in aluminum pans and hermetically sealed. The reference was a sealed empty aluminum pan. The individual substances and 1:1 physical mixtures of each drug with one of the other substances, prepared with mortar and pestle, were heated over a temperature range of 30 to 250°C. At least two replicates were made for each DSC thermogram.

RESULTS AND DISCUSSION

The DSC thermogram of diphenhydramine hydrochloride (trace 1 of Figure 1) shows the melting endothermic peak at 168.5°C. Magnesium stearate (trace 2 of Figure 1) shows a double peaked transition with transition temperature ranges of 92 to 103°C and 104 to 118°C. In both cases no decomposition was observed on scanning until 250°C. The DSC thermogram of the diphenhydramine hydrochloride-magnesium stearate mixture (trace 3 of Figure 1) shows four transition peaks, namely at 82 to 88°C, 88.5 to 100°C, 103.5 to 111°C and 121 to 141°C, followed immediately by a degradation reaction. Magnesium stearate alone does not seem to be degraded over the temperature range 30 to 200°C; thus it is concluded that the use of magnesium stearate as glidant should be avoided in formulations containing diphenhydramine hydrochloride.

Trace 2 of Figure 2 is the thermogram of ascorbic acid showing the melting endothermic peak at 190 to 196.5°C. Decomposition started at a temperature of 217°C. The physical mixture of diphenhydramine hydrochloride-ascorbic acid (trace 3 of Figure 2) shows two broad endothermic peaks (77 to 99.5°C and 135 to 146°C) followed by an exothermic degradation reaction with an

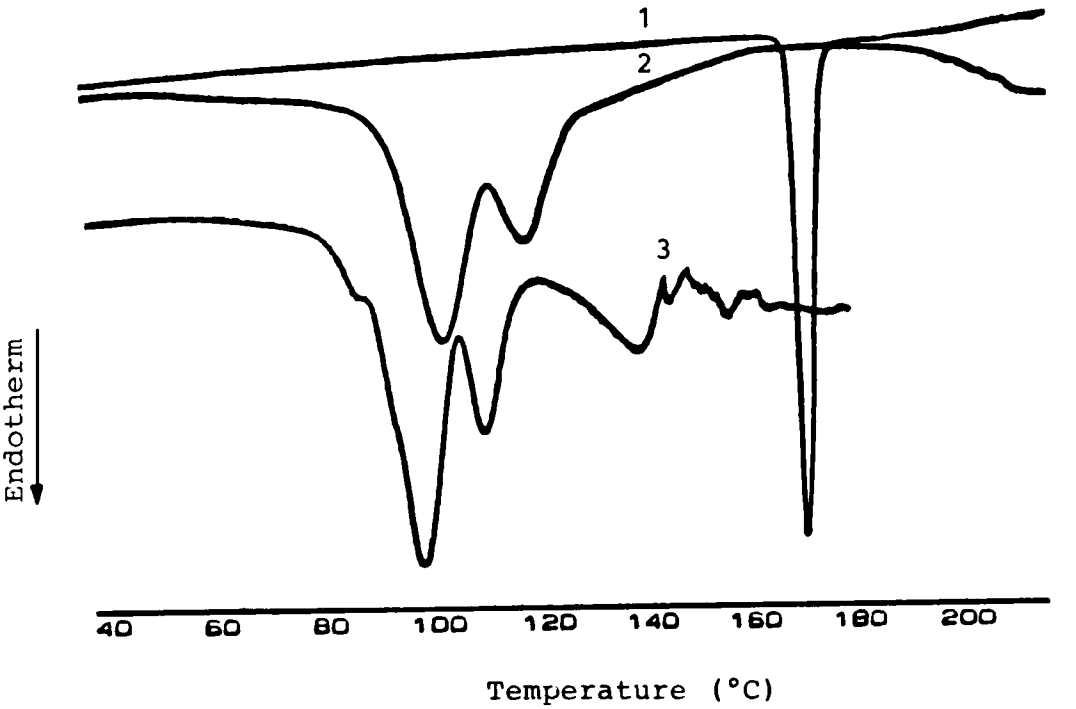

FIGURE 1

DSC thermogram of diphenhydramine hydrochloride (1), magnesium stearate (2) and 1:1 diphenhydramine hydrochloride-magnesium stearate (3).

onset temperature of 165°C, which is well below that of ascorbic acid. Diphenhydramine hydrochloride, a basic substance, should thus not be combined with the acidic ascorbic acid.

The sharp endothermic melting peak of acetaminophen at 169°C can be seen in Figure 3 (trace 2). The physical combination of diphenhydramine hydrochloride-acetaminophen (Figure 3 trace 3) shows a broad endo=

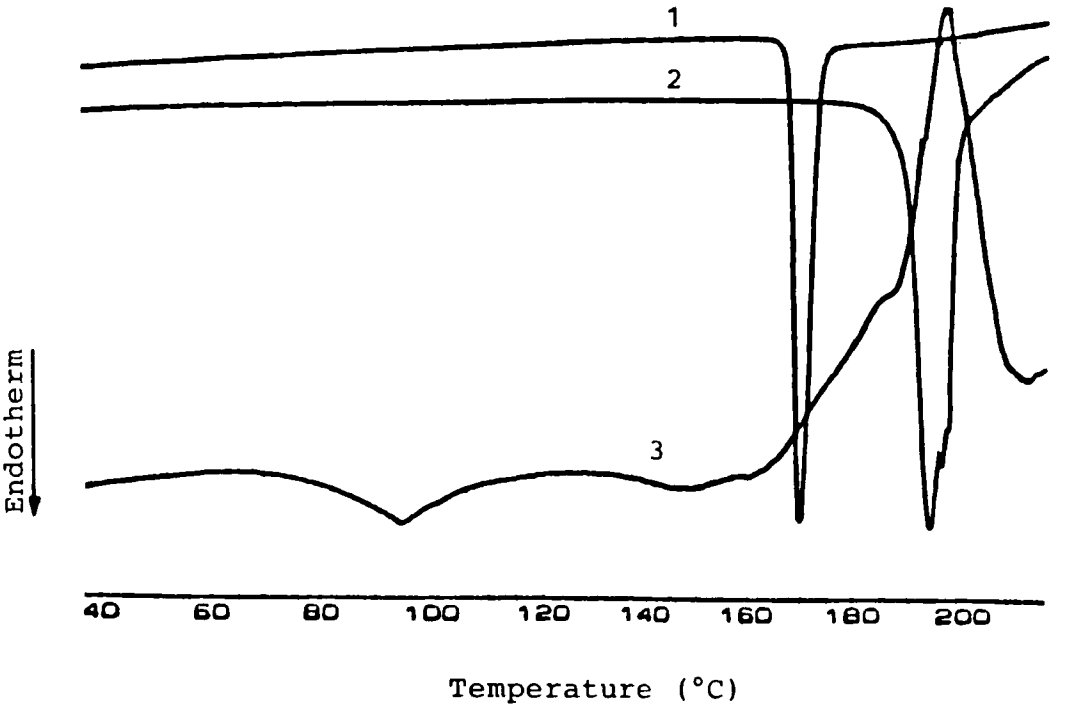

FIGURE 2

DSC thermogram of diphenhydramine hydrochloride (1), ascorbic acid (2) and 1:1 diphenhydramine hydro= chloride-ascorbic acid (3).

thermic peak at a temperature of 70 to 87.5°C, well below that of acetaminophen (169°C) and diphenhydramine hydrochloride (168.5°C). This peak is not due to an interaction with breakdown products but could well be the eutectic mixture described by Maeda and Mori[1] as a stickiness. Until the real nature of this interaction is elucidated, a combination of these drugs in a dosage form should be avoided.

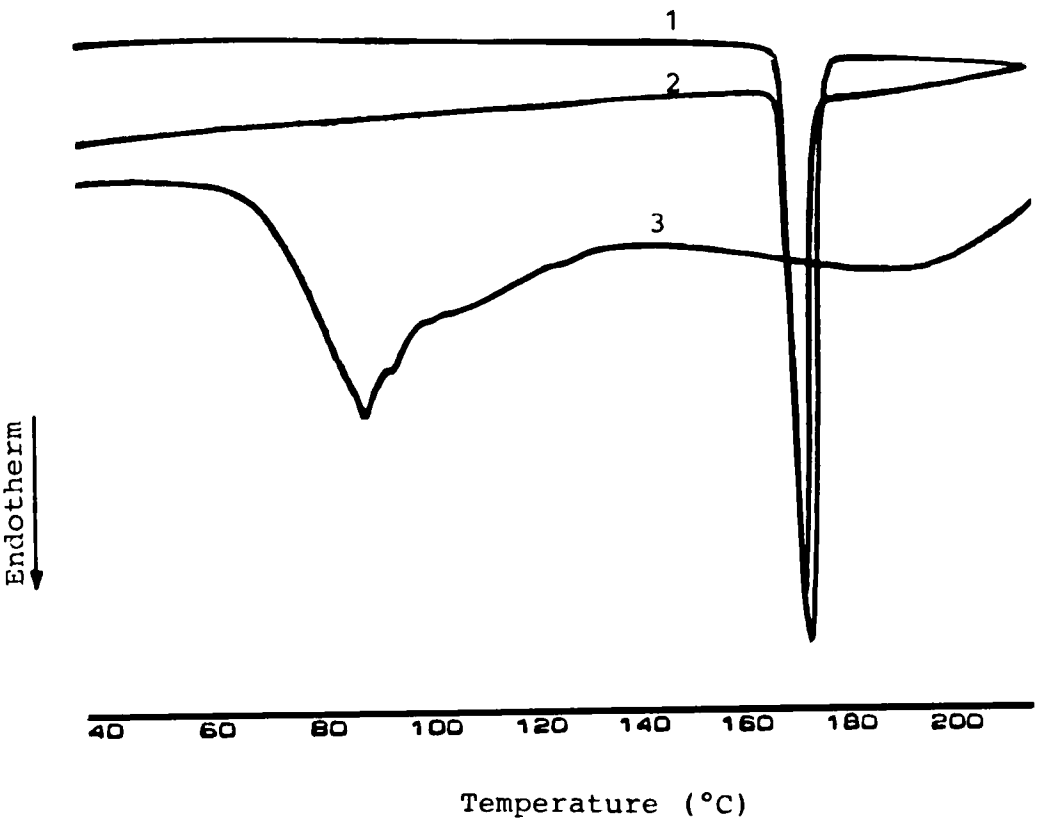

FIGURE 3

DSC thermogram of diphenhydramine hydrochloride (1), acetaminophen (2) and 1:1 diphenhydramine hydro= chloride-acetaminophen mixture (3).

Phenylephrine hydrochloride exhibits a sharp melting endotherm at 141°C, with no decomposition apparent up to a temperature of 250°C (trace 2 Figure 4). The DSC thermogram of the diphenhydramine hydro= chloride-phenylephrine hydrochloride combination shows a single broad endotherm ranging from 92.5 to 110°C

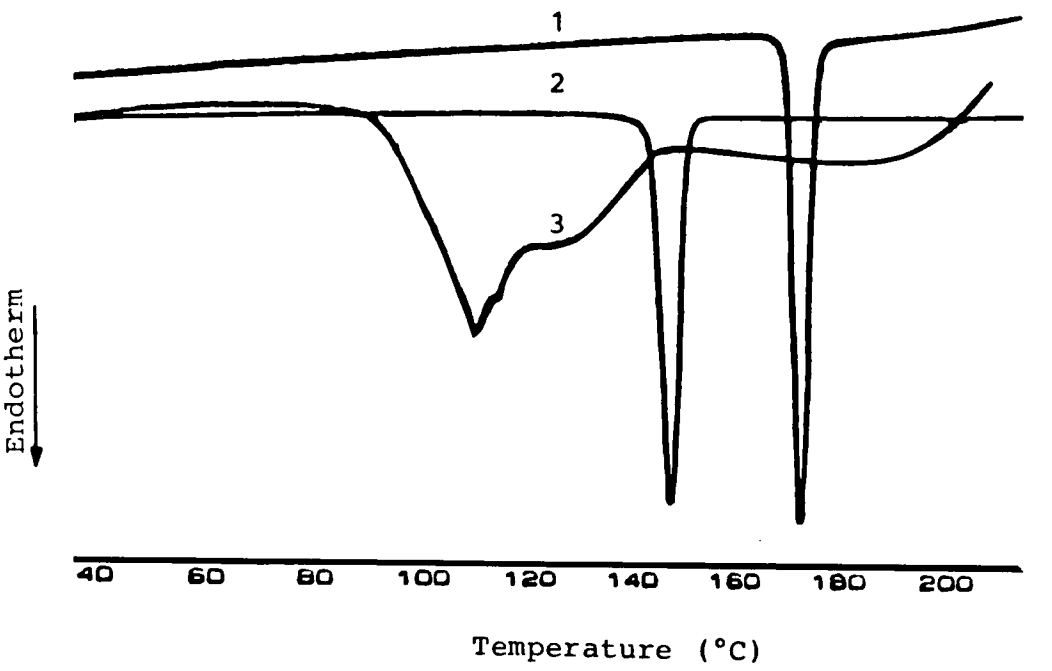

FIGURE 4

DSC thermogram of diphenhydramine hydrochloride (1), phenylephrine hydrochloride (2) and 1:1 diphenhydramine hydrochloride-phenylephrine hydrochloride (3).

(trace 3 of Figure 4), which can be indicative of an interaction.

The DSC thermogram of acetaminophen (trace 1 of Figure 5) shows a sharp endothermic melting peak with an onset temperature of 169°C. Acetaminophen, in combination with magnesium stearate (trace 3 of Figure 5) shows, apart from the magnesium stearate transition peak (91 to 100°C), no extra peak. Thus, magnesium

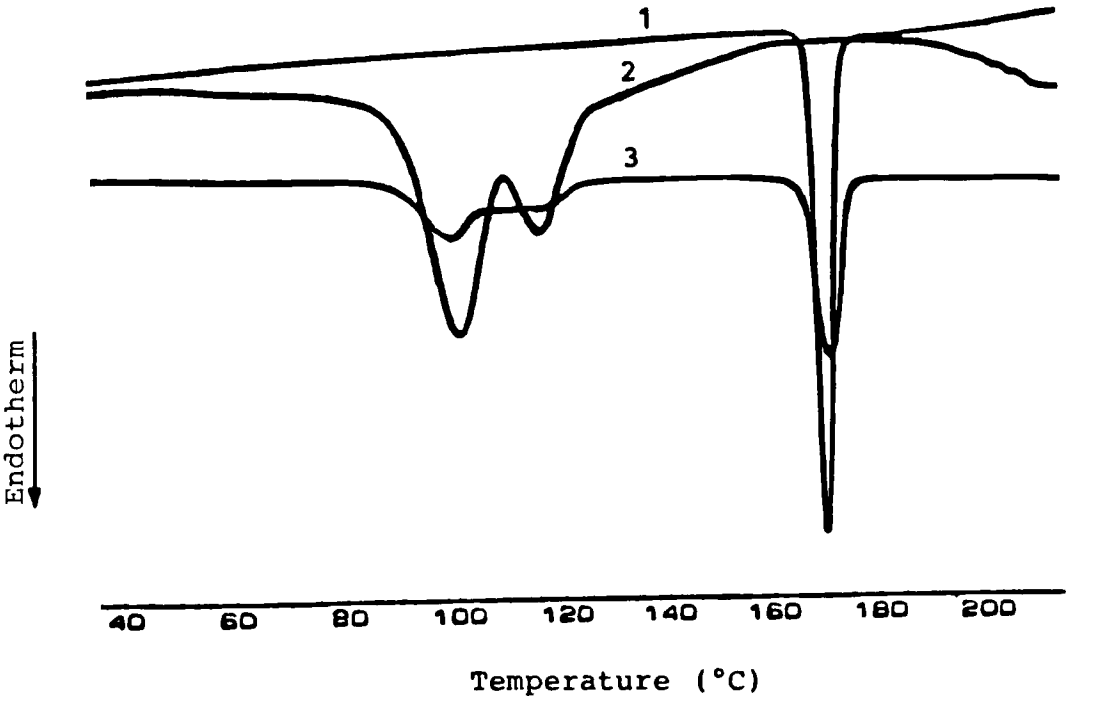

FIGURE 5

DSC thermogram of acetaminophen (1), magnesium stearate (2) and 1:1 acetaminophen-magnesium stearate mixture (3).

stearate can be used in combination with acetaminophen in formulations.

Acetaminophen in a mixture with ascorbic acid (trace 3 of Figure 6) shows two melting peaks, namely at 151 to 155°C and at 161 to 167°C. Since the melting transitions of acetaminophen and ascorbic acid are at 169°C and at 190 to 196°C, respectively, and since interaction due to degradation products can be

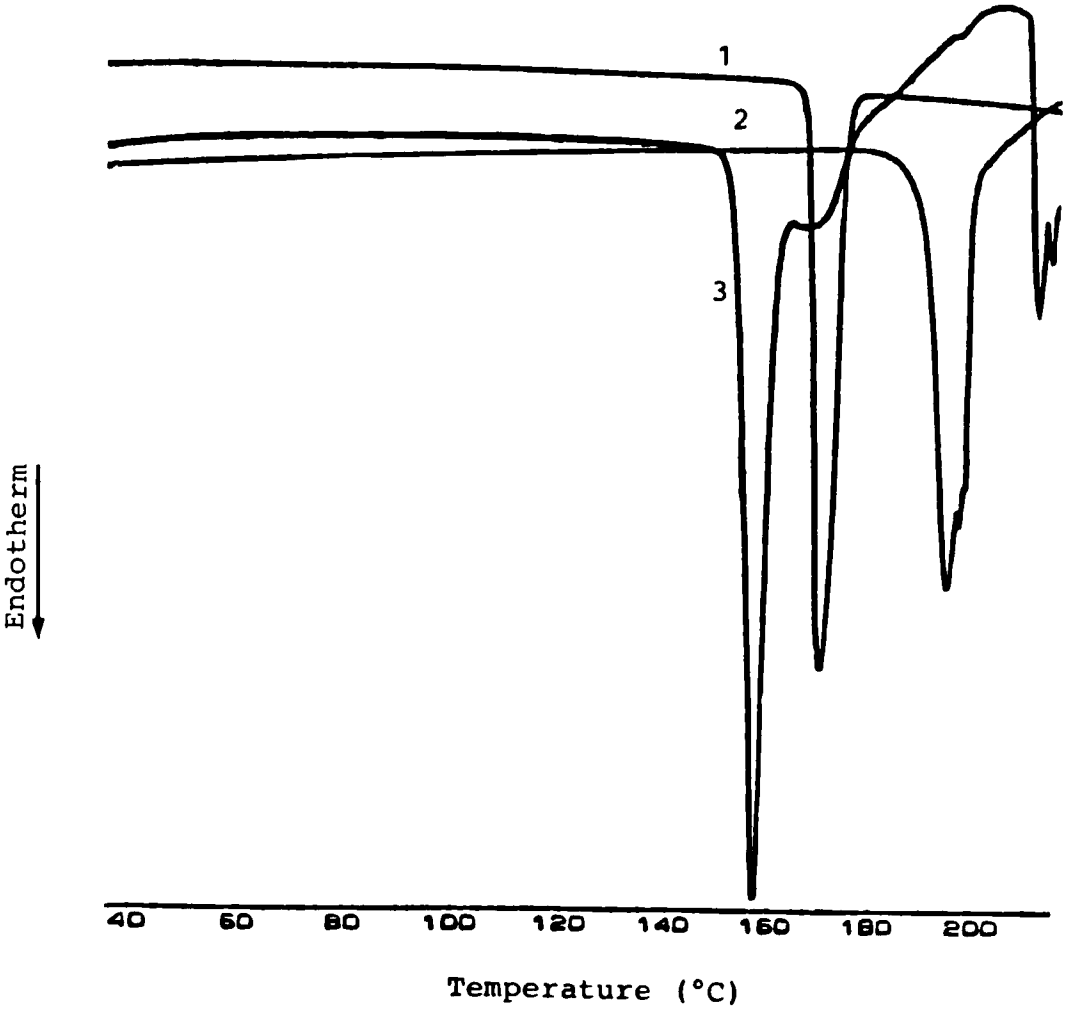

FIGURE 6

DSC thermogram of acetaminophen (1), ascorbic acid (2) and 1:1 acetaminophen-ascorbic acid (3).

ruled out, it seems as if a combination of acetamino= phen and ascorbic acid could lead to an interaction.

The DSC thermogram of the phenylephrine hydro= chloride-acetaminophen mixture (trace 3 of Figure 7) shows a single endothermic peak at a temperature of 111.5 to 118.5°C, well below that of the individual ingredients (141°C and 169°C, respectively). This interaction could be due to the combination of a basic and an acidic component.

Phenylephrine hydrochloride in combination with magnesium stearate (trace 3 of Figure 8) shows basically the same DSC pattern as the two individual components, apart from a broadening in the second transition melting peak of magnesium stearate and a very obvious reduction in the size of the phenylephrine hydrochloride melting peak. The occurence of a possible interaction between phenylephrine hydro= chloride and the glidant magnesium stearate should thus be considered in formulations utilizing this excipient.

The DSC thermogram of the phenylephrine hydro= chloride-ascorbic acid mixture (trace 3 of Figure 9) shows a broad endotherm with a transition onset of 109.5°C, well below the melting temperature of phenylephrine hydrochloride (141°C) and ascorbic acid

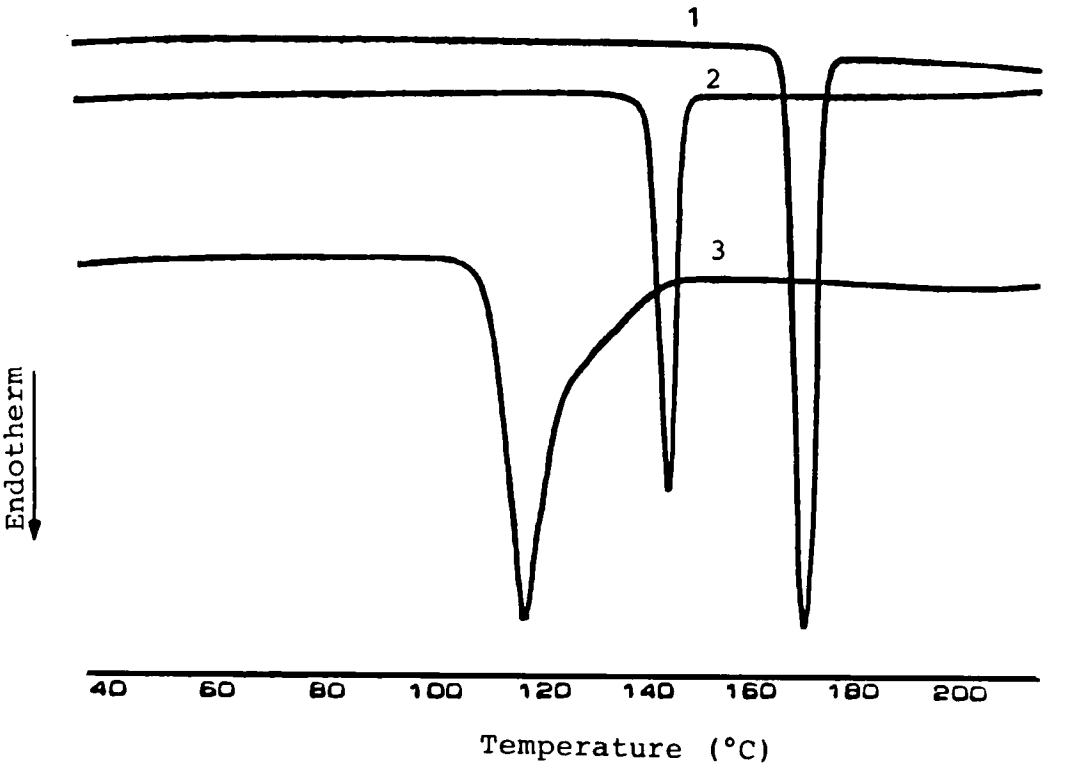

FIGURE 7

DSC thermogram of acetaminophen (1), phenylephrine hydrochloride (2) and 1:1 acetaminophen-phenylephrine hydrochloride (3).

(190 to 193°C). Degradation immediately followed the second transition peak. An interaction between the basic phenylephrine hydrochloride and the acid could be the cause of the change in the thermogram.

A combination of magnesium stearate and ascorbic acid (trace 3 of Figure 10) has a single transition peak at 81.5 to 92°C and an exothermic peak at 165°C.

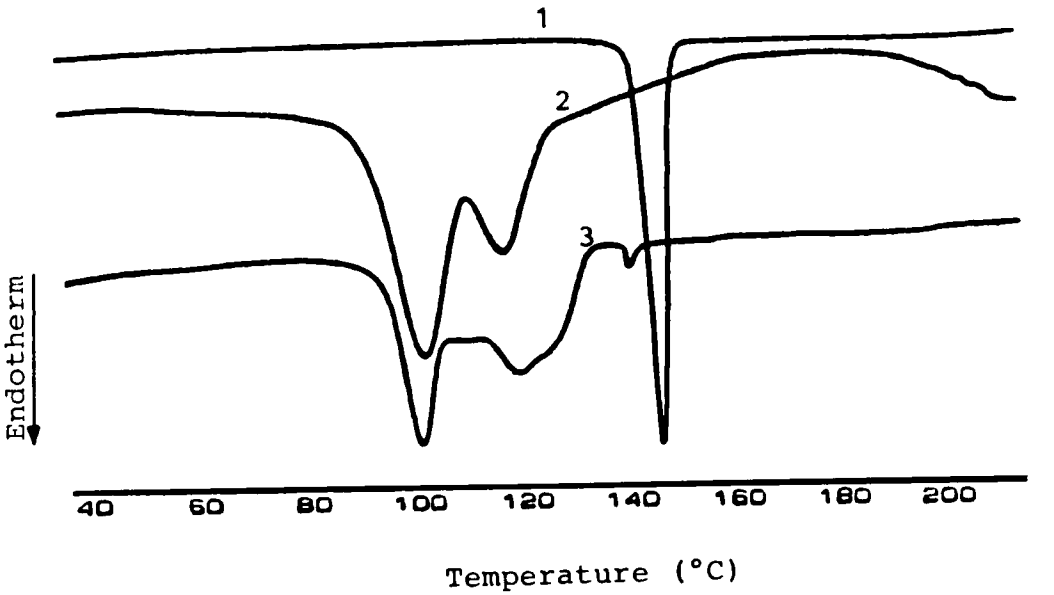

FIGURE 8

DSC thermogram of phenylephrine hydrochloride (1), magnesium stearate (2) and 1:1 phenylephrine hydrochloride-magnesium stearate (3).

Interaction with breakdown products can be ruled out. This is further proof of the interaction described by Wortz[2].

No attempt was made during this study to determine the nature of the interactions, namely chemical, physical, eutectic or complex formation.

It is also accepted that in a number of cases where 1:1 mixtures were made this is a much higher ratio than would ever be used in practice. This to

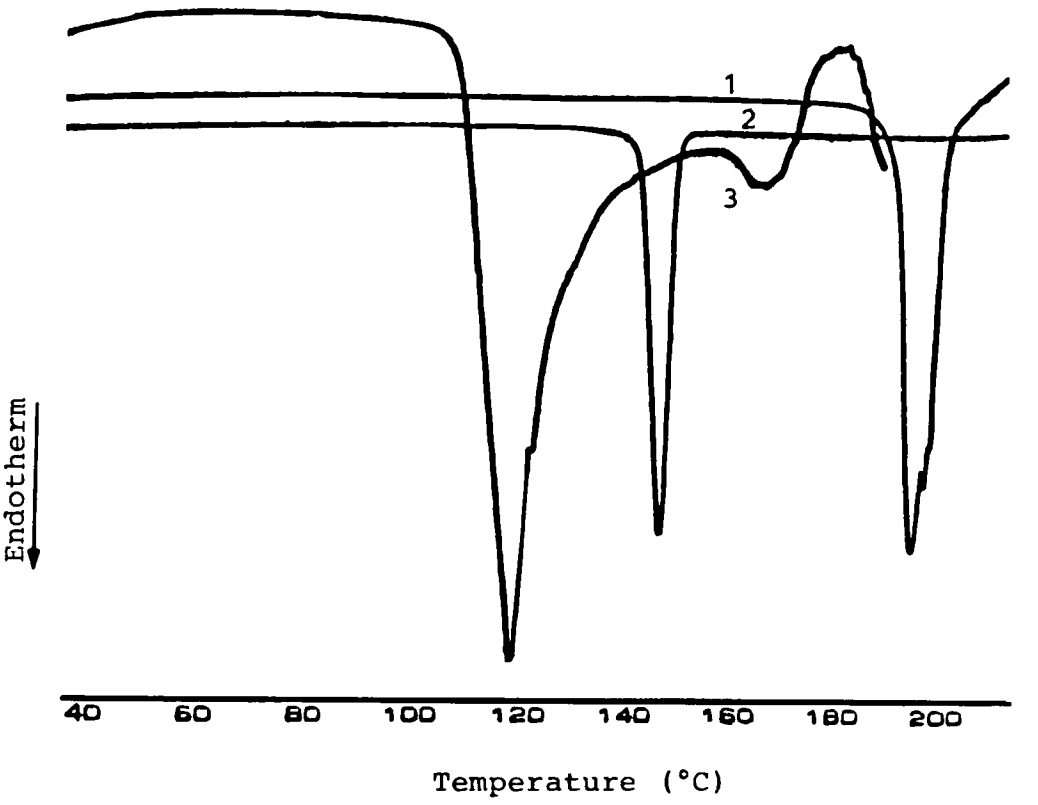

FIGURE 9

DSC thermogram of ascorbic acid (1), phenylephrine hydrochloride (2) and 1:1 ascorbic acid-phenylephrine hydrochloride mixture (3).

our mind does not however minimize the value of the results.

Our conclusion is that for the specific combination dosage form in question only the combination of acetaminophen and magnesium stearate seems to be compatible and the combination of the five ingredients should be avoided in one dosage form.

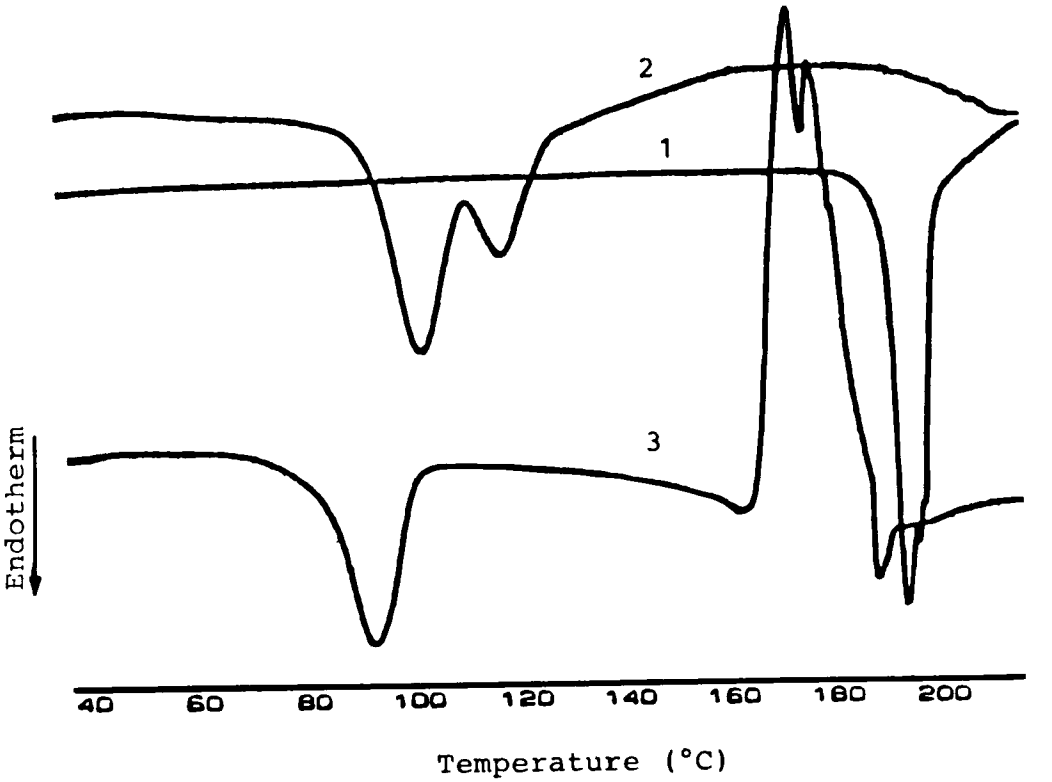

FIGURE 10

DSC thermogram of ascorbic acid (1), magnesium stearate (2) and 1:1 ascorbic acid-magnesium stearate mixture (3).

The results could of course be used for the individual drugs and can be summarized as follows:

1. Diphenhydramine hydrochloride is incompatible with acetaminophen, phenylephrine hydrochloride, ascorbic acid and magnesium stearate.
2. Acetaminophen is incompatible with diphenhydramine hydrochloride, phenylephrine hydrochloride and

ascorbic acid. However, acetaminophen is compatible with magnesium stearate.

3. Phenylephrine hydrochloride is incompatible with diphenhydramine hydrochloride, acetaminophen, ascorbic acid and magnesium stearate.
4. Ascorbic acid is incompatible with diphenhydramine hydrochloride, acetaminophen, phenylephrine hydrochloride and magnesium stearate.

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