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

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ABSTRACT

DSC screening for drug-excipient interactions of a polypharmaceutical capsule dosage form containing salicylamide, ascorbic acid, pyrilamine maleate, phenylephrine hydrochloride, lactose, colloidal silicon dioxide and sodium starch glycolate was per= formed.

The results show the following:

1. Ascorbic acid is incompatible with lactose and sodium starch glycolate.
2. Salicylamide is incompatible with lactose.
3. Pyrilamine maleate is incompatible with sodium starch glycolate.
4. Phenylephrine hydrochloride is incompatible with lactose.
5. Lactose is incompatible with ascorbic acid, salicylamide, pyrilamine maleate and phenylephrine hydrochloride.
6. Sodium starch glycolate is incompatible with ascorbic acid and pyrilamine maleate.

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

INTRODUCTION

In our first communication the DSC screening and findings of a combination product containing acetamino= phen, diphenhydramine hydrochloride, phenylephrine hydrochloride, ascorbic acid and magnesium stearate were discussed[1].

In a second communication the findings on another popular combination product containing an analgesic

(salicylamide), an antihistamine (pyrilamine maleate), a decongestant (phenylephrine hydrochloride) and ascorbic acid were reported[2]. This combination product was marketed in capsule form and on storage it was found that the capsule content turned brown. Since an instability was suspected, DSC screening for possible drug-drug, drug-excipient and excipient-excipient interactions were undertaken. In this third communication we are reporting our findings when salicylamide, ascorbic acid, pyrilamine maleate and phenylephrine hydrochloride were combined with lactose as filler and colloidal silicon dioxide (Aerosil) and sodium starch glycolate (Primojel) as other excipients.

The influence of some additives on the stability of sodium ascorbate was discussed[3]. Starch seems to have a small influence on the degradation of ascorbic acid[3]. In a study of complex formation of starches with drugs Goudah and Guth[4] found that salicylic acid forms an insoluble complex with both potato and arrowroot starch. It is thus possible that salicyl= amide can also form complexes with corn starch. The stearates have been shown to influence the stability of selected active ingredients[5, 6, 7, 8]. The browning of lactose in the presence of amines is well documented[9, 10, 11]. The question arises as to

whether the browning of the capsule contents on storage was due to lactose in the presence of amines only.

The use of DSC in drug-drug and drug-excipient interactions was reviewed in our first communication[1]

MATERIALS AND METHODS

Salicylamide, ascorbic acid, pyrilamine maleate, phenylephrine hydrochloride, lactose, colloidal silicon dioxide and sodium starch glycolate were pharmacopoeial grade.

Each of the above-mentioned drugs and excipients were subjected to DSC. The instrumentation used was a Du Pont 910 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 aluminum pan. The individual substances and 1:1 mixtures of each drug and excipient, 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 thermo= gram.

RESULTS AND DISCUSSION

The DSC thermogram of ascorbic acid (trace 1 of Figure 1) shows the melting endothermic peak at 190 to 193°C, with decomposition starting at a temperature of 217°C. The thermogram of lactose (trace 2 of Figure 1) shows an endothermic transition starting at 137°C, corresponding to dehydration of the product and sub= sequent changing into anhydrous lactose with melting points of 207.5 to 217°C and 208 to 231°C[12]. The physical mixture of ascorbic acid and lactose (trace 3 of Figure 1) shows an endothermic peak with an onset of 137°C, followed by a broad endotherm (150 to 180°C) and a third endothermic peak with an onset of 223.5°C. This change in the DSC thermogram could be due to an interaction between lactose and ascorbic acid.

The DSC thermogram of a 1:1 physical mixture of salicylamide and lactose (trace 3 of Figure 2) shows, in addition to the endothermic peak which corresponds in position to both the melting thermogram for salicylamide (trace 1 of Figure 2), as well as the first transition peak for lactose (trace 2 of Figure

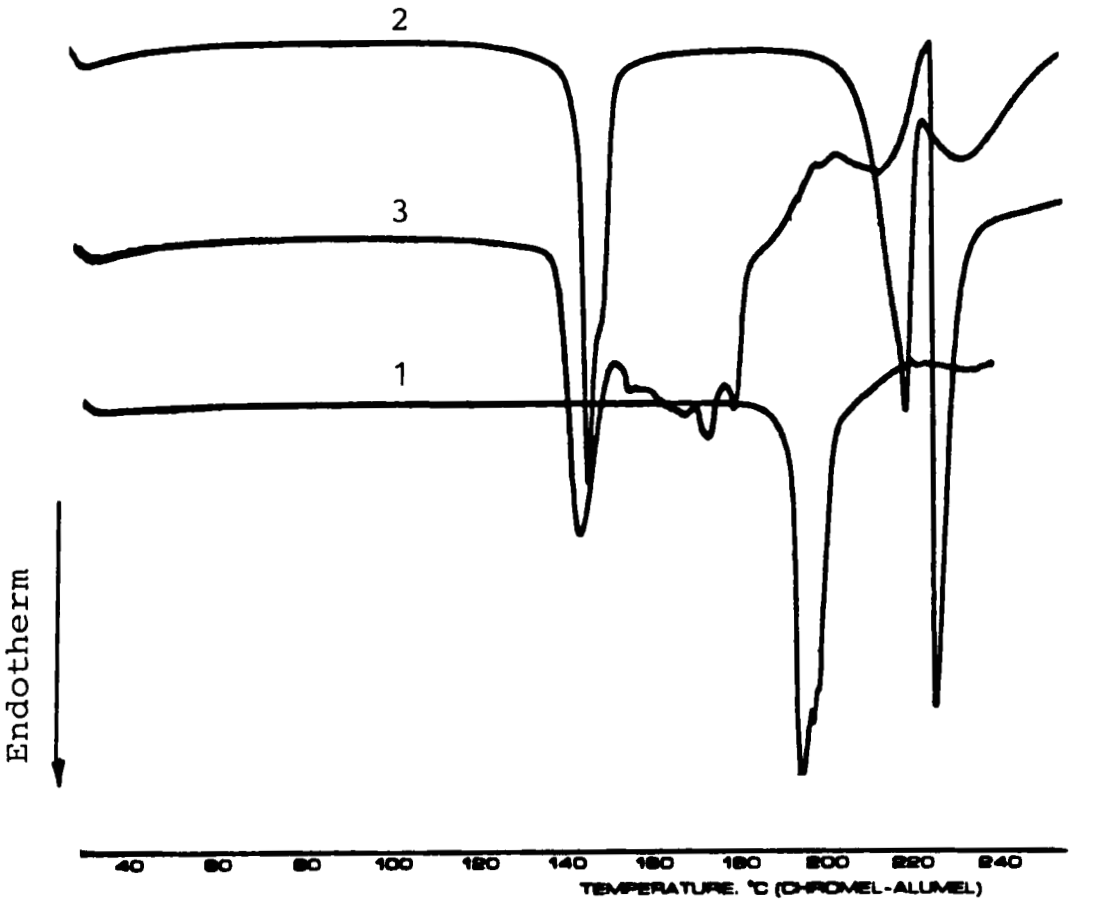

FIGURE 1

DSC thermograms of ascorbic acid (1), lactose (2) and 1:1 physical mixture of ascorbic acid and lactose (3).

2), an extra endotherm with an onset of 127°C and a maximum of 130°C. The third endotherm of the physical mixture of salicylamide and lactose with an onset of 185°C differs in position from that of pure lactose which has endothermic peaks with onsets of 137, 207.5

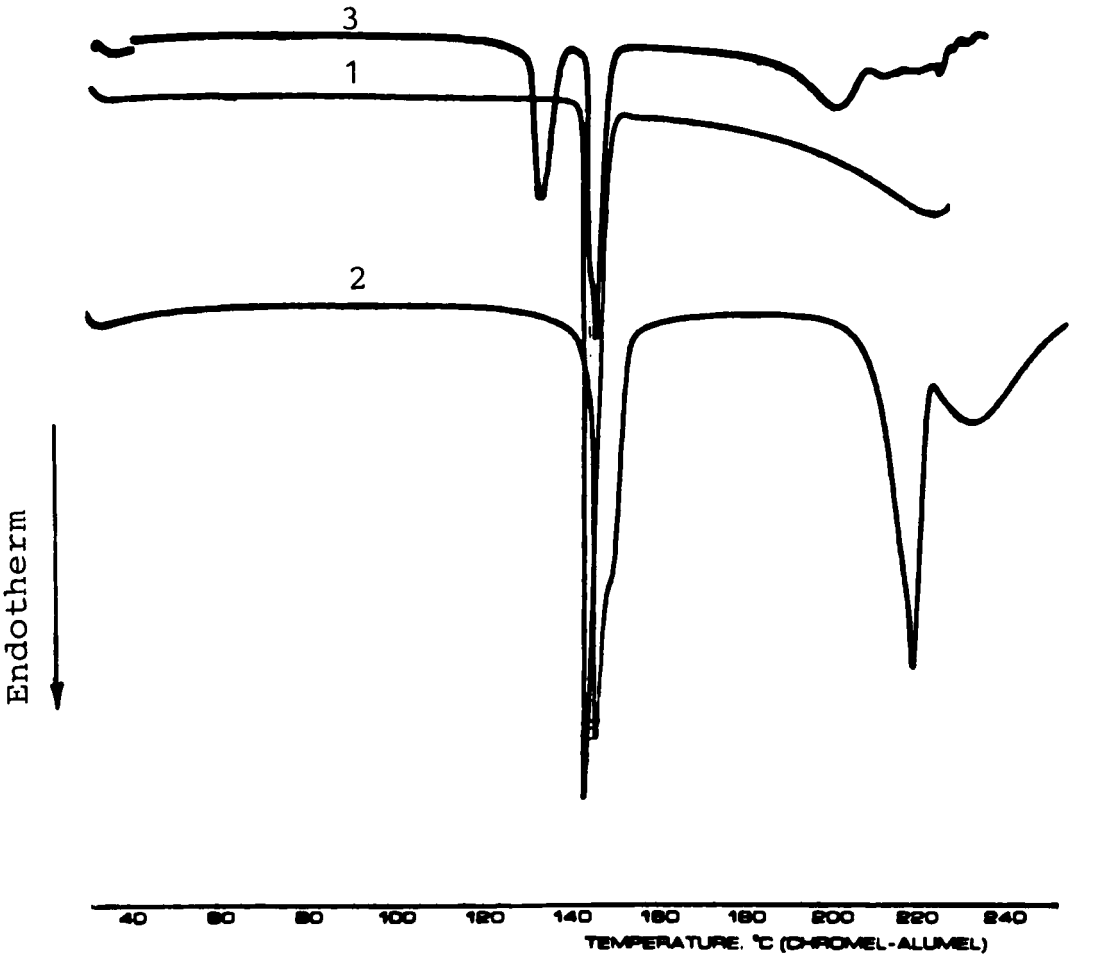

FIGURE 2

DSC thermograms of salicylamide (1), lactose (2) and 1:1 physical mixture of salicylamide and lactose (3).

and 208°C. This result was expected, since it is well known that lactose forms brown coloured Schiff bases in the presence of amines.

The DSC thermogram of a 1:1 physical mixture of pyrilamine maleate and lactose shows and endothermic

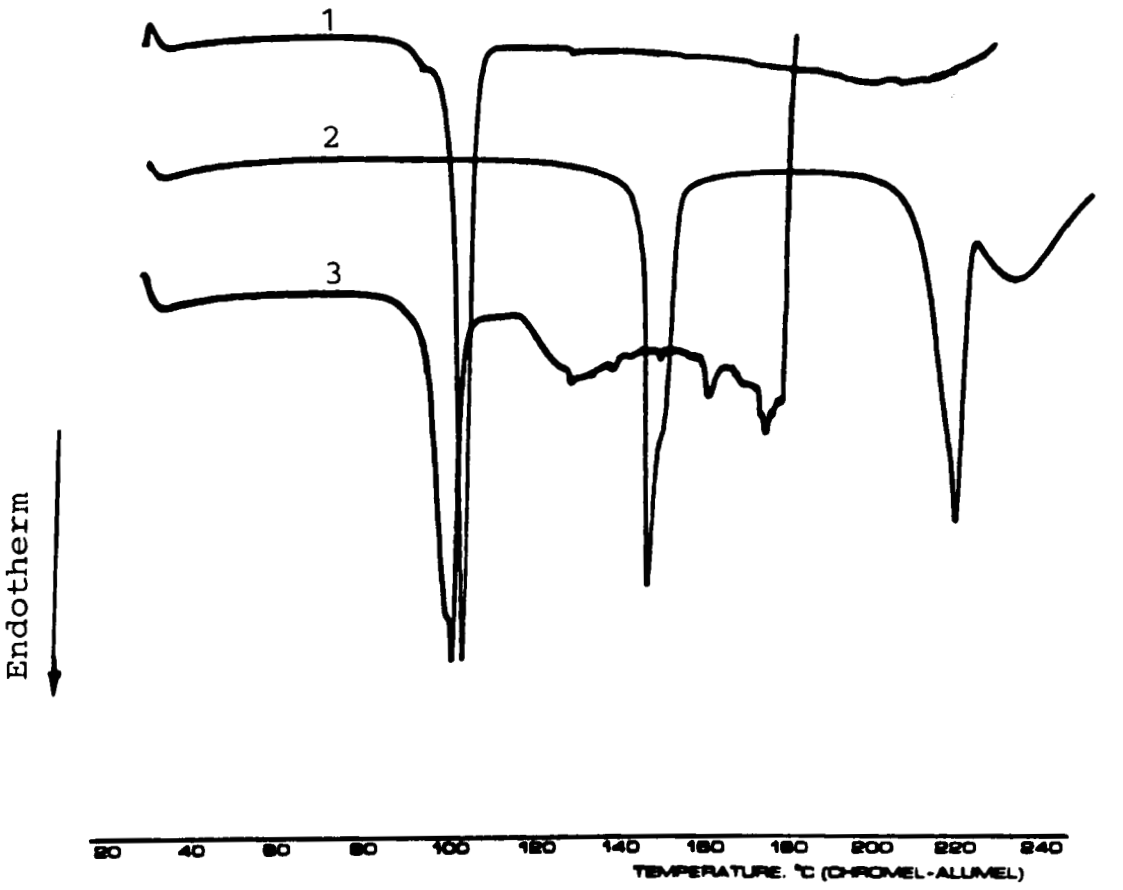

FIGURE 3

DSC thermograms of pyrilamine maleate (1), lactose (2) and 1:1 physical mixture of pyrilamine maleate and lactose (3).

peak with an onset of 94°C (trace 3 of Figure 3). This peak differs slightly in position from that of pyrilamine maleate (trace 1 of Figure 3; 99.5°C) as well as being somewhat broader. The most strikingly different feature of this thermogram is the onset of

degradation at a temperature of 125°C, while none of the single components showed degradation at tempera= tures below 250°C. Although the detrimental effect arising from the combination of lactose and primary and secondary amines is well-documented, the question arises as to whether this effect is restricted to primary and secondary amines, since pyrilamine maleate has two tertiary amine functions.

The DSC thermogram of a physical combination of phenylephrine hydrochloride - lactose (trace 3 of Figure 4) shows that the combination of lactose (trace 2 of Figure 4) and phenylephrine hydrochloride (trace 1 of Figure 4) which has a secondary amine function, is incompatible. It can thus be concluded from this study that lactose is incompatible not only with primary amines, but also with secondary and tertiary amines.

The thermogram of sodium starch glycolate (trace 2 of Figure 5) shows a broad endothermic peak, ranging from 87 to 162°C, due to the presence of adsorbed water. The physical mixture of ascorbic acid and sodium starch glycolate (trace 3 of Figure 5) shows, apart from the endothermic peak, an exotherm with an onset of 169°C. It is concluded that this combination should best be avoided.

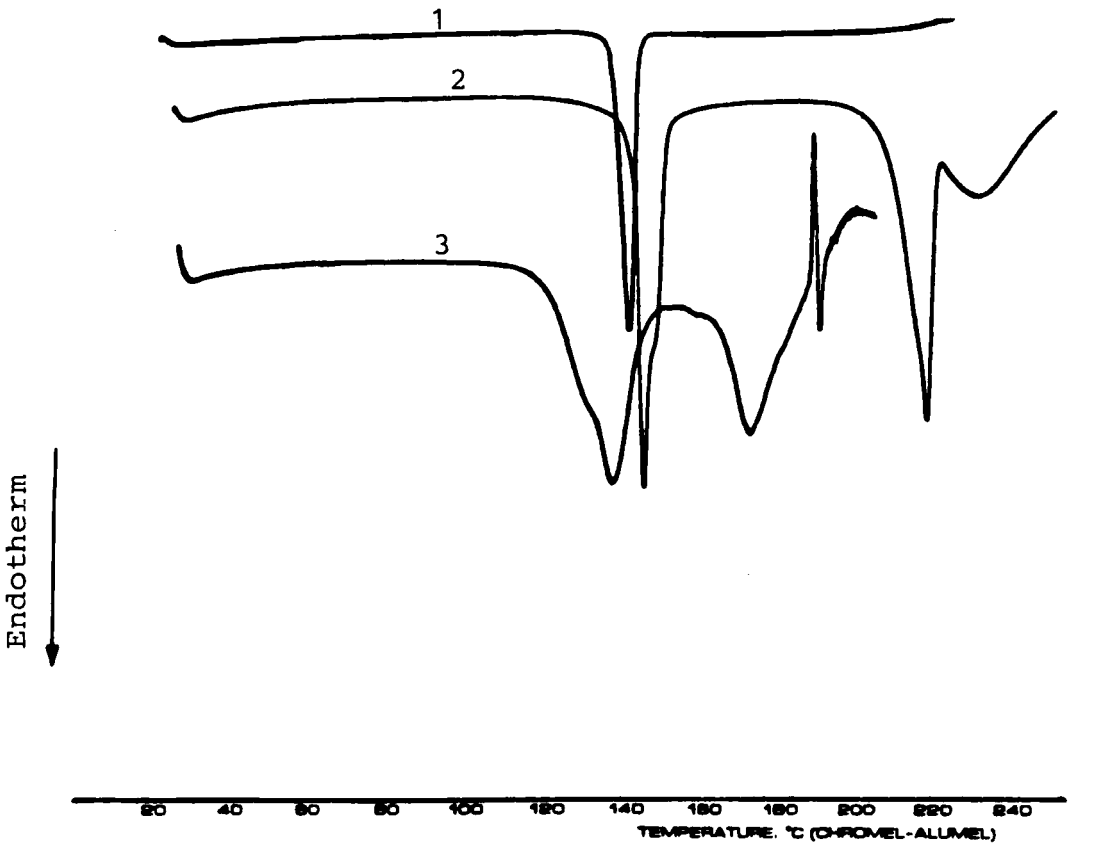

FIGURE 4

The DSC thermograms of phenylephrine HCl (1), lactose (2) and 1:1 physical mixture of phenylephrine HCl and lactose (3).

The physical mixture of salicylamide and sodium starch glycolate (trace 3 of Figure 6), shows a double-peaked melting peak with onsets of 139 and 142°C, while salicylamide has a single melting peak with an onset of 140°C (trace 1 of Figure 6). Although the possibility of an interaction cannot altogether

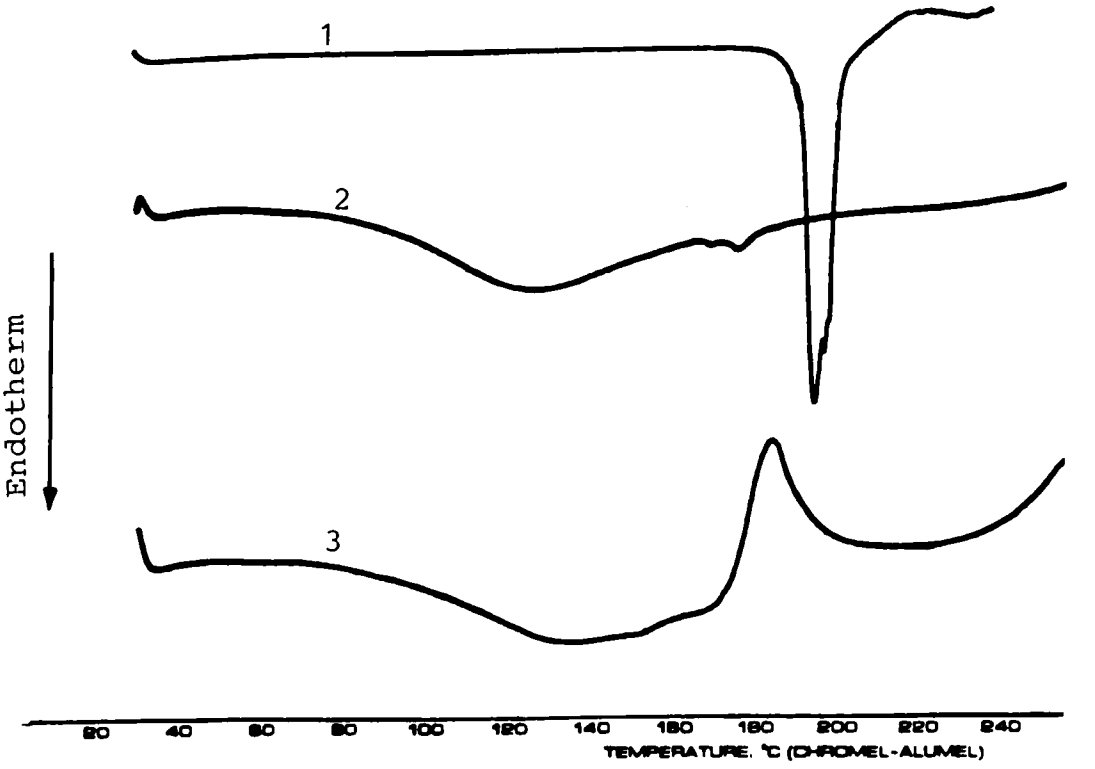

FIGURE 5

DSC thermograms of ascorbic acid (1), sodium starch glycolate (2) and 1:1 physical mixture of ascorbic acid and sodium starch glycolate (3).

be excluded, it seems as if sodium starch glycolate can be used as an excipient in pharmaceutical formulations containing salicylamide.

The DSC thermogram of a physical combination of pyrilamine maleate and sodium starch glycolate is substantially different from that of the single components. The mixture has two broad endothermic peaks, at 60 to

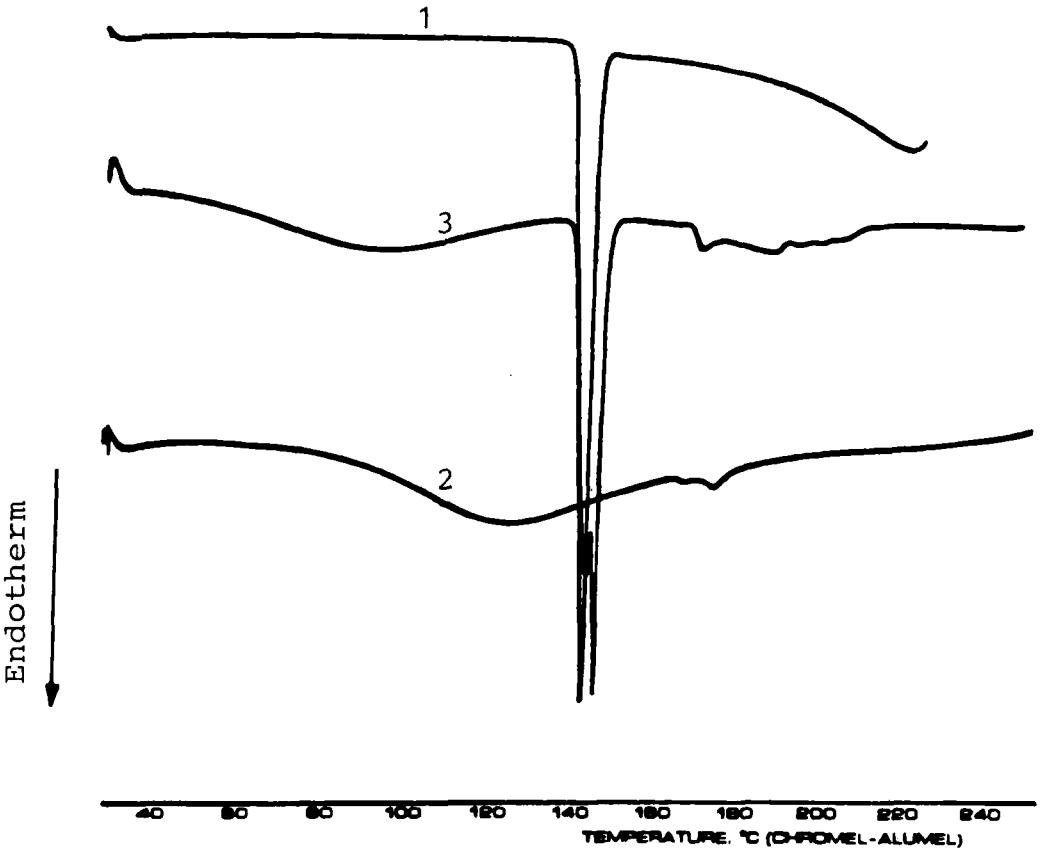

FIGURE 6

DSC thermograms of salicylamide (1), sodium starch glycolate (2) and 1:1 physical mixture of salicylamide and sodium starch glycolate (3).

77°C and 124 to 135°C (trace 3 of Figure 7) while pyrilamine maleate alone had a sharp melting endotherm at 99.5 to 102°C (trace 1 of Figure 7). Thus, there is a possibility of an interaction between pyrilamine maleate and sodium starch glycolate.

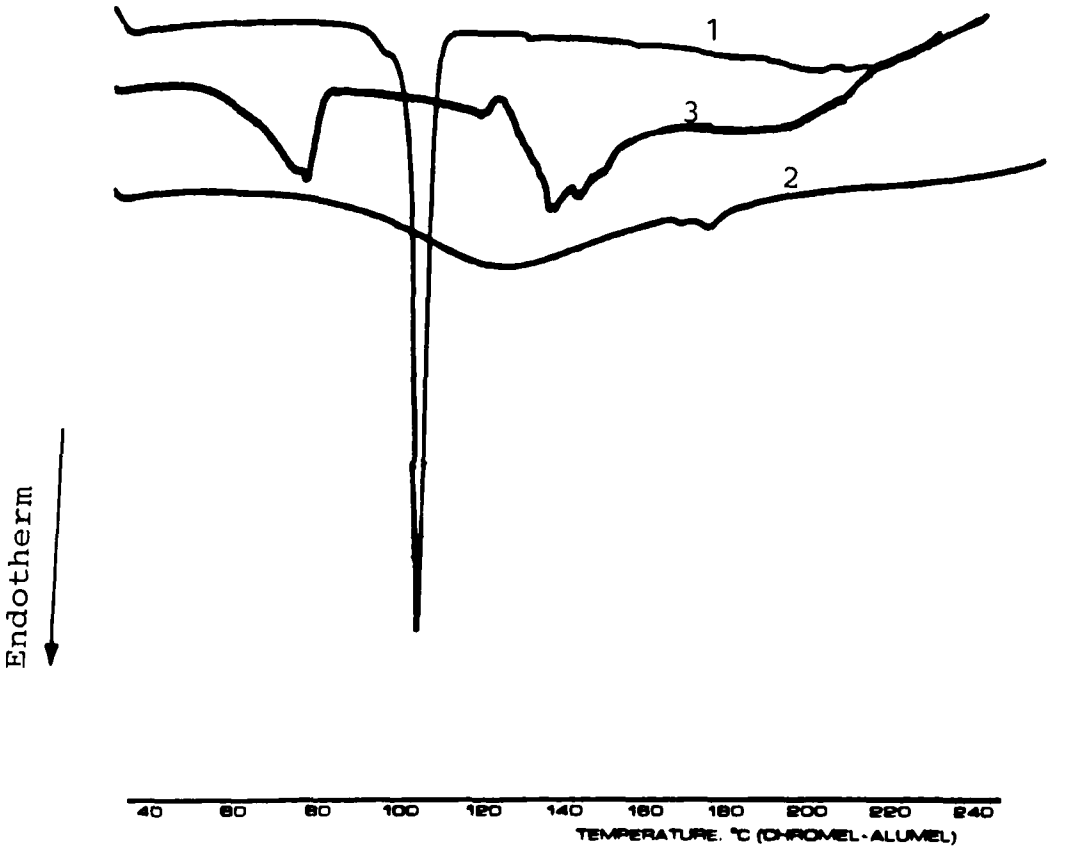

FIGURE 7

DSC thermograms of pyrilamine maleate (1), sodium starch glycolate (2) and 1:1 physical mixture of pyrilamine maleate and sodium starch glycolate (3).

The physical mixture of ascorbic acid-colloidal silicon dioxide (trace 3 of Figure 8) shows no signi= ficant differences compared to that of the individual substances (trace 1 and 2 of Figure 8). One can there= fore conclude that these two substances can be used together in pharmaceutical dosage forms. Although an

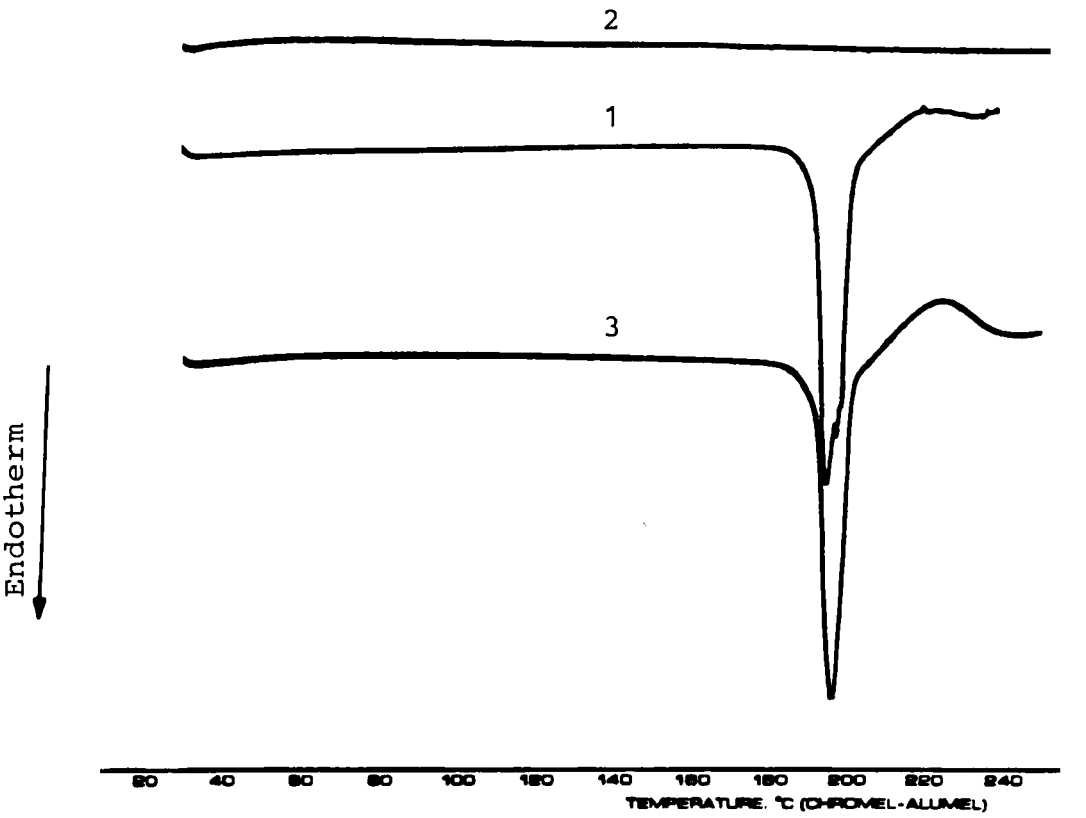

FIGURE 8

DSC thermograms of ascorbic acid (1), colloidal silicon dioxide (2) and 1:1 physical mixture of ascorbic acid and colloidal silicon dioxide (3).

interaction of silicic acid and ascorbic acid[13] as well as a decrease in ascorbic stability in the presence of hydrated sodium silico aluminate[14] were reported, it seems as if this interaction does not exist in mixtures of ascorbic acid and colloidal silicon dioxide

The physical mixture of lactose and sodium starch glycolate shows that the first endothermic peak (trace

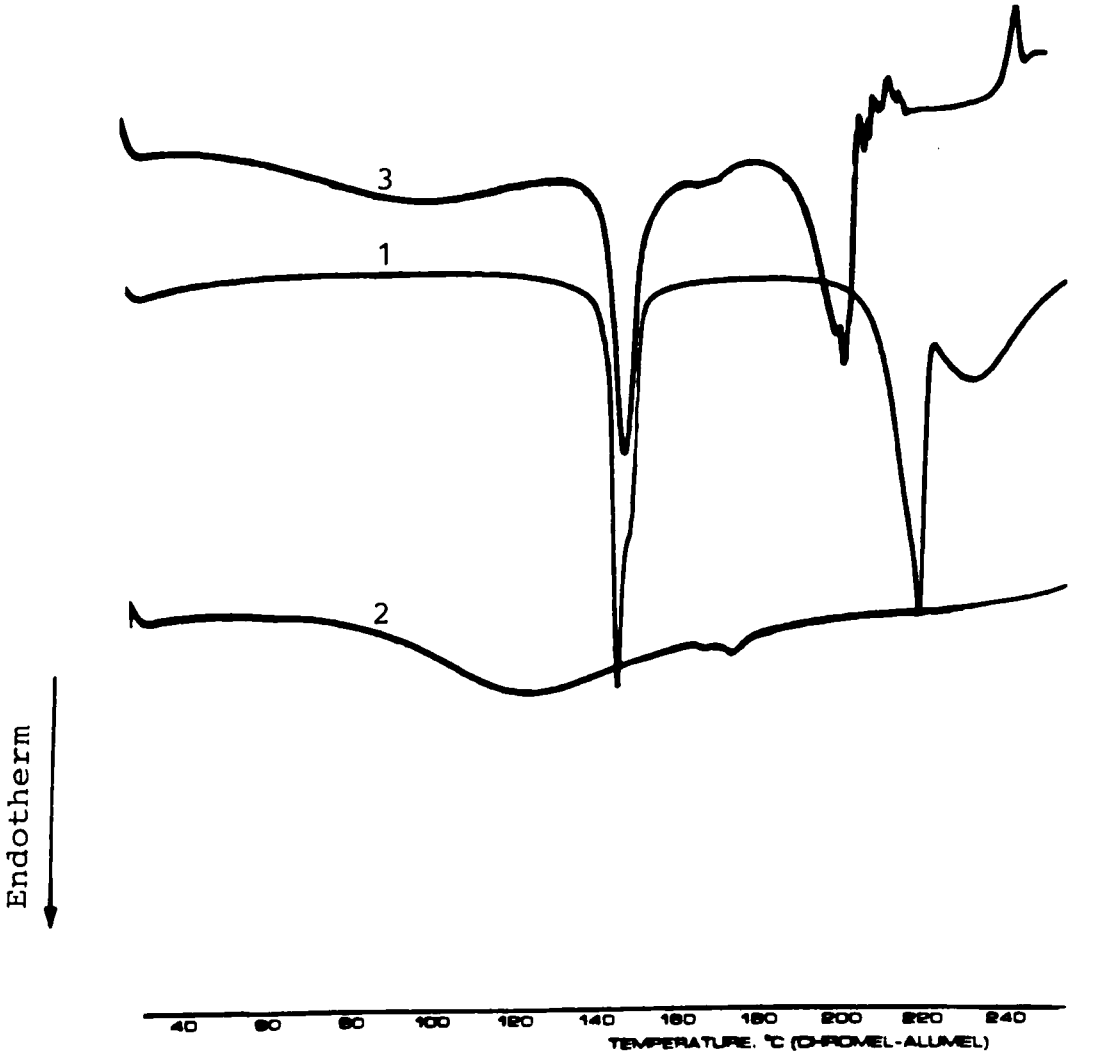

FIGURE 9

The DSC thermograms of lactose (1), sodium starch glycolate (2) and 1:1 physical mixture of lactose and sodium starch glycolate (3).

3 of Figure 9) corresponds in position to that of pure lactose (trace 1 of Figure 9), but the second endothermic peak (trace 3 of Figure 9; 191 to 200°C) is different in position to that of pure lactose (trace 1 of Figure 9; 207.5 to 217°C). Also, the second endotherm of the mixture is immediately followed by a degradation reaction. In the pure substances, no degradation was detectable up to a temperature of 250°C. The combination of lactose and sodium starch glycolate as excipients in dosage forms should thus be avoided.

The combinations of phenylephrine hydrochloride and sodium starch glycolate and phenylephrine hydrochloride, pyrilamine maleate or salicylamide with colloidal silicon dioxide show, apart from a slight broadening in the endothermic melting peak as compared to that of the single substance, no change in position of the endothermic peak. It can be concluded that these drug-excipient combinations can be used in pharmaceutical dosage forms.

The combinations of colloidal silicon dioxide and sodium starch glycolate and colloidal silicon dioxide and lactose are not significantly different from that of the individual components. Thus, colloidal silicon dioxide and sodium starch glycolate or colloidal

silicon dioxide and lactose can be combined in dosage forms as excipients.

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

It is also accepted that in a number of cases where 1:1 mixtures were made that this is a higher ratio than would ever be used in practice, however, to our mind this does not minimize the value of the results.

The results can be summarized as follows:

1. Lactose is incompatible with ascorbic acid, salicylamide, pyrilamine maleate and phenylephrine hydrochloride.
2. Sodium starch glycolate is incompatible with ascorbic acid and pyrilamine maleate.
3. Ascorbic acid is compatible with colloidal silicon dioxide.
4. Salicylamide is compatible with colloidal silicon dioxide and sodium starch glycolate.
5. Phenylephrine hydrochloride is compatible with colloidal silicon dioxide and sodium starch glycolate.

6. Lactose is compatible with colloidal silicon dioxide and sodium starch glycolate.
7. Sodium starch glycolate is compatible with salicyl= amide, phenylephrine hydrochloride, lactose and colloidal silicon dioxide.
8. Colloidal silicon dioxide is compatible with ascorbic acid, salicylamide, phenylephrine hydro= chloride, lactose and sodium starch glycolate.

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