DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(2), 345-354 (1987)

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

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ABSTRACT

DSC screening for drug-drug interactions of a polypharmaceutical capsule dosage form containing salicylamide, ascorbic acid, pyrilamine maleate and phenylephrine hydrochloride was performed. The results show the following:

1. Ascorbic acid is incompatible with salicylamide, pyrilamine maleate and phenylephrine hydrochloride.

2. Salicylamide is incompatible with ascorbic acid, pyrilamine maleate and phenylephrine hydrochloride.
3. Pyrilamine maleate is incompatible with ascorbic acid, salicylamide and phenylephrine hydrochloride.
4. Phenylephrine hydrochloride is incompatible with salicylamide, pyrilamine maleate and ascorbic acid.

INTRODUCTION

During the formulation of new products or the reformulation of existing products, it is advantageous to have readily available knowledge of any drug-drug or drug-excipient interactions which might affect the stability of the final dosage form.

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

In this second communication we are reporting our findings on a popular combination product containing an analgesic (salicylamide), an antihistamine (pyrilamine maleate), a decongestant (phenylephrine hydro-

chloride) and ascorbic acid as active ingredients. Since the capsule contents turned brown on storage, an instability was suspected.

The stabilization of pyrilamine maleate in combination with aspirin and ascorbic acid for cold relief was discussed[2]. The nature of the interaction was not stated but presumably the reaction took place with both aspirin and ascorbic acid. The interaction of salicylamide with pyrilamine maleate is thus possible.

Troup and Mitchner[3] characterized the acetylation of phenylephrine in the presence of aspirin. This acetylation might also occur with salicylamide.

The use of DSC in drug-drug and drug-excipient interactions was reviewed in our first communication[1] However, the interpretation of the thermal data is not always straightforward, i.e. when two substances are mixed, the purity of each is reduced and generally slightly lower melting points result. If the solid-solid interaction is extremely weak or non-existent, the reduction of the melting point is usually inconsequential. On the other hand, a large shift in melting point signifies that a strong solid-solid interaction has occurred. Nonetheless, DSC screening for compatibility does provide additional knowledge concerning possible interactions.

MATERIALS AND METHODS

Salicylamide, ascorbic acid, pyrilamine maleate and phenylephrine hydrochloride were pharmacopoeial grade.

Each of the above mentioned drugs 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 aluminum pan. The individual substances and 1:1 mixtures of each drug with one of the others, 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 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 sharp endothermic melting peak of

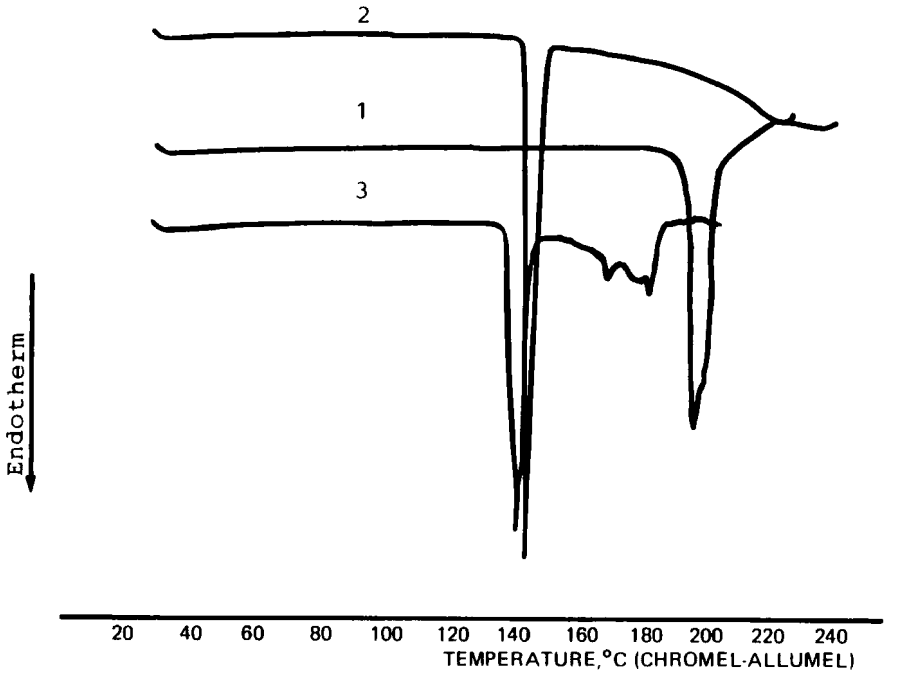

FIGURE 1

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

salicylamide at 140°C can be seen in trace 2 of Figure 1, with no decomposition up to 250°C. The physical 1:1 mixture of ascorbic acid and salicylamide (trace 3 of Figure 1) shows a single endothermic peak with an onset of 135°C, followed by two small endothermic peaks (onsets of 165 and 177°C). Thus, the combination of ascorbic acid and salicylamide should be avoided.

Trace 2 of Figure 2 is the thermogram of pyril= amine maleate showing the melting endothermic peak at

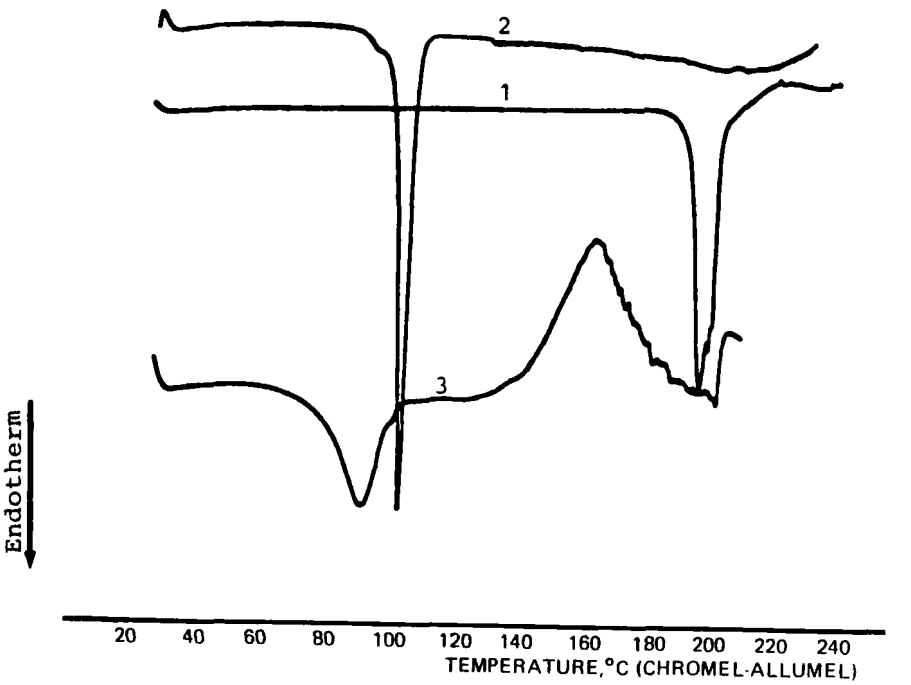

FIGURE 2

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

99.5 to 102°C. The physical mixture of ascorbic acid-pyrilamine maleate (trace 3 of Figure 2) shows a broad endotherm, ranging from 77.5 to 91°C, followed by an exotherm with an onset of 136°C. Since neither ascorbic acid, nor pyrilamine maleate shows a degradation exotherm at temperatures below 200°C, it can be concluded that the acidic ascorbic acid is incompatible with basic pyrilamine maleate.

The physical mixture of pyrilamine maleate-salicylamide (trace 3 of Figure 3) shows a single

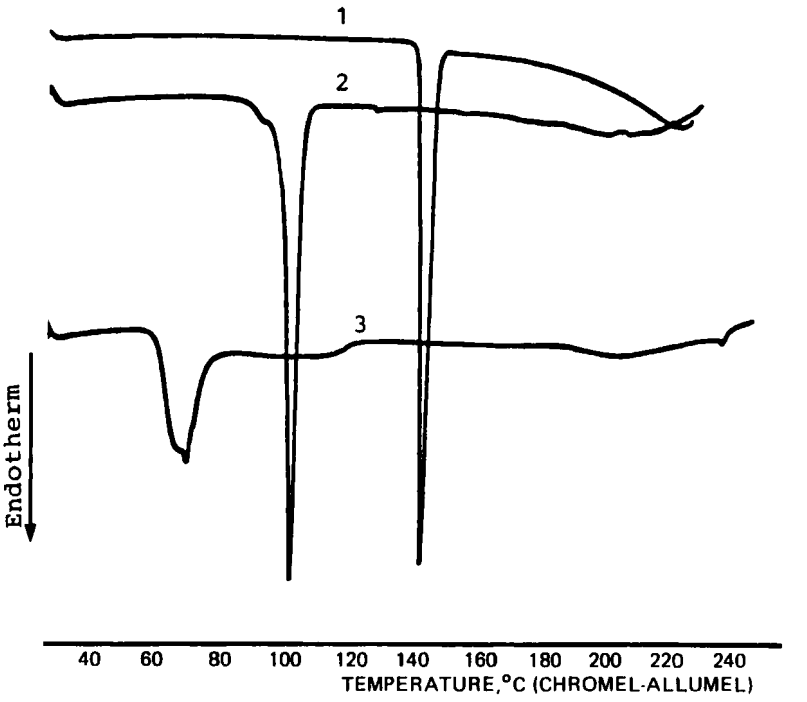

FIGURE 3

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

broad endotherm (62 to 71°C), which does not correspond in position to either pure salicylamide (trace 1 of Figure 3; onset 140°C) or pure pyrilamine maleate (trace 2 of Figure 3; onset 99.5°C) leading one to conclude that there might be a possibility of an interaction between pyrilamine maleate and salicylamide.

The DSC thermogram of phenylephrine HCl shows a sharp endothermic melting peak from 141.5 to 144°C (trace 1 of Figure 4). The 1:1 physical mixture of

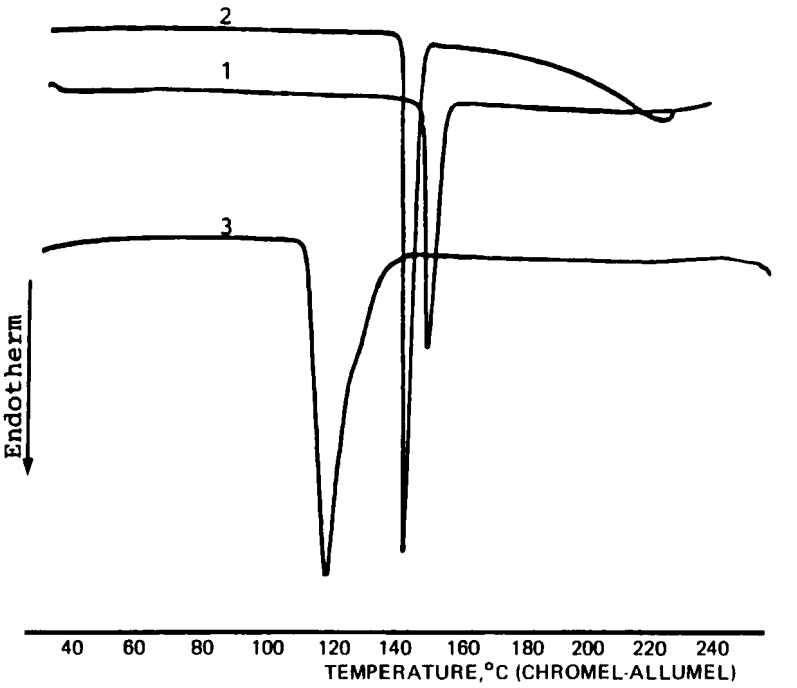

FIGURE 4

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

phenylephrine HCl-salicylamide shows a broad endotherm with an onset of 114°C (trace 3 of Figure 4), which could be related to the acetylation of the secondary amine function[3].

The combination of phenylephrine HCl and pyrilamine maleate in a 1:1 ratio has a DSC thermogram with peak onsets of 72°C and 124°C, (trace 3 of Figure 5) which do not correspond to the melting endotherms of pure phenylephrine HCl (trace 1 of Figure 5; 141.5°C) or pure pyrilamine maleate (trace 2 of Figure 5, 99.5°C).

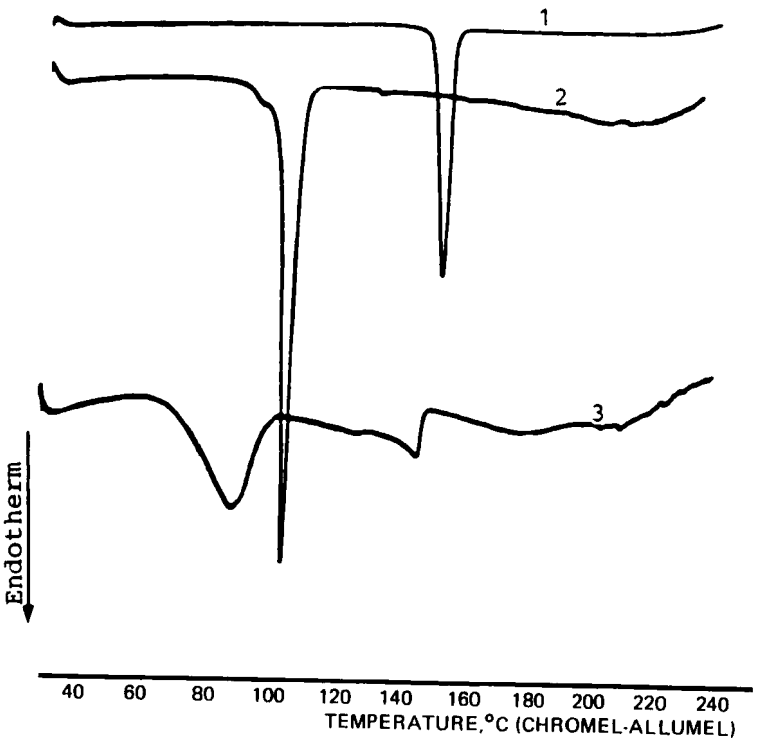

FIGURE 5

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

The combination of phenylephrine HCl and pyrilamine maleate in a dosage form could lead to an instability.

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 this is a higher ratio than would ever be used in practise. However, to our

mind this does not minimize the value of the results.

Our conclusion is that for the specific combination dosage form in question none of the active components seems to be compatible with one another and the combination of salicylamide, ascorbic acid, pyrilamine maleate and phenylephrine hydrochloride should be avoided in one dosage form.

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

1. Ascorbic acid is incompatible with salicylamide, pyrilamine maleate, as well as with phenylephrine hydrochloride[1].
2. Salicylamide is incompatible with ascorbic acid, pyrilamine maleate and phenylephrine hydrochloride.
3. Pyrilamine maleate is incompatible with ascorbic acid, salicylamide and phenylephrine hydrochloride.
4. Phenylephrine hydrochloride is incompatible with salicylamide, pyrilamine maleate and ascorbic acid[1].

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2. S. Siegel, R.H. Reiner, T.A. Zelinskie and E.J. Hanus, J. Pharm. Sci., 51, 1068 (1962).
3. A.E. Troup and H. Mitchner, J. Pharm. Sci., 53, 375 (1964).