DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 16(14), 2125-2133 (1990)



# COMPATIBILITY STUDY BETWEEN DOXYLAMINE SUCCINATE WITH OTHER DRUGS AND EXCIPIENTS USING DIFFERENTIAL SCANNING CALORIMETRY

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## ABSTRACT

Differential scanning calorimetry was used to investigate the interactions between doxylamine succinate and a number of drugs and excipients. Doxylamine succinate was found to be compatible with mannitol, Aerosil®, calcium salts, starches, Ac-Di-Sol®, Primojel® and Avicel®. Doxylamine succinate was found to be incompatible with acetominophen, dextromethorphan hydrobromide, codeine phosphate, pseudoephedrine hydrochloride, magnesium stearate, stearic acid, P.V.P. and lactose.

## INTRODUCTION

Doxylamine succinate [NN-Dimethyl-2-[1-phenyl-1-(pyrid-2-yl)-ethoxy] ethylamine succinate® an antihistamine is used in combination with other drugs for the treatment of headaches and colds. It is combined with acetaminophen, caffeine and codeine phosphate for headaches and with dextromethorphan hydrobromide, pseudoephedrine hydrochloride, acetaminophen, caffeine and codeine phosphate in cold preparations.

This study was undertaken to establish the compatibility of Doxylamine succinate with the abovementioned drugs and a number of commonly used excipients by DSC in order to derive a stable combination of doxylamine succinate with drugs and excipients. DSC allows the fast evaluation of possible incompatibilities between substances in a formulation, by looking at appearance, shift or disappearance of peaks and/or variations in the corresponding $\Delta H$[1] During the DSC study the thermograms of 1 to 1 mixtures of doxylamine succinate with the drugs or excipients were compared with that of doxylamine succinate and that of the drug or excipient in question. Although it cannot be conclusively stated that an interaction will occur during storage at room temperature there are often enough other drugs or excipients available to use in choosing only those unlikely to cause problems[2].

## EXPERIMENTAL

### Materials

The following materials were used: doxylamine succinate; starch; directly compressable starch (Sta Rx 1500®); sodium carboxymethyl starch (Primojel®); microcrystalline cellulose (Avicel pH 101®); cross linked sodium carboxymethyl cellulose (Ac-Di-Sol®); colloidal silicon dioxide (Aerosil®); lactose; mannitol; calcium carbonate; dicalcium phosphate; calcium phosphate; calcium sulphate; polyvinylpyrrolidone (PVP); acetominophen; caffeine; codeine phosphate; dextromethorphan hydrobromide; pseudoephedrine hydrochloride.

### Differential Scanning Calorimetry

Samples (3 - 9 mg) were measured (Sartorius 4503 microbalance) and hermetically sealed in flat bottomed aluminum pans. These samples were heated in an atmosphere of nitrogen and thermograms were obtained with a Du Pont 910 DSC system equipped with a Du Pont Series 99 Thermal Analyzer programmer. A Hewlett-Packard X-Y recorder was used. The instrument was

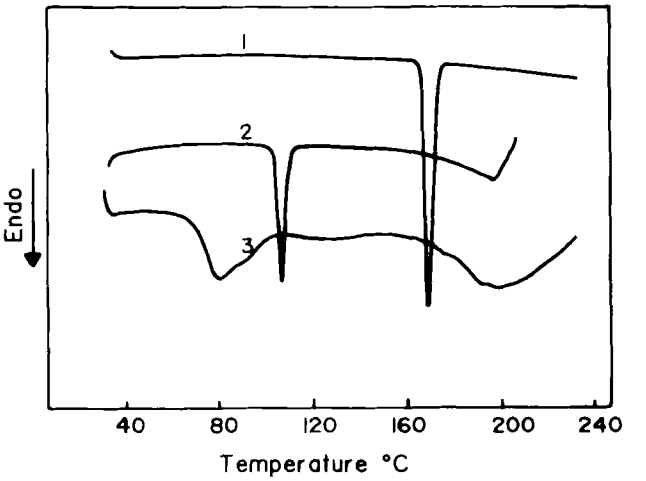


FIGURE 1

DSC thermograms of acetaminophen (1), doxylamine succinate (2) and their physical mixture (3).

calibrated with an indium standard. Thermograms were obtained by heating at a constant rate of 5°C per minute and recorded at a constant chart speed of 10 mm per minute. The individual substances, as well as 1:1 physical mixtures of doxylamine succinate and drugs and excipients prepared by mortar and pestle, were heated over the temperature range of 30 - 240°C.

## RESULTS AND DISCUSSION

No shifts or minor ones in peak positions between single and 1:1 mixtures were found for combinations of doxylamine succinate with mannitol, Aerosil®, calcium salts, starches, Ac-Di-Sol®, Primojel® and Avicel®. These substances were therefore regarded as compatible with doxylamine succinate.

In figure 1 the thermograms of acetaminophen (1) and Doxylamine succinate (2) are compared to that of the 1:1 physical mixture (3). It is clear in thermogram 3 that the endotherms of

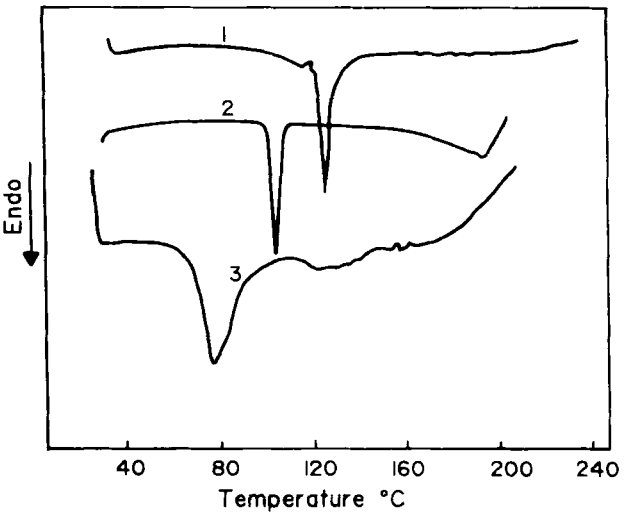


FIGURE 2

DSC thermograms of dextromethorphan hydrobromide (1), doxylamine succinate (2) and their physical mixture (3).



both drugs had disappeared. Two broad endotherms at 70 - 100°C and 170 - 240°C appeared. It is concluded that these two drugs should not be used in combination with each other.

In figure 2 dextromethorphan hydrobromide (1), doxylamine succinate (2) and their 1:1 mixture (3) are compared. A new broad endotherm appeared from 60 to 100°C with the disappearance of the endotherms of both drugs. These two drugs might also interact in combination.

In figure 3 codeine phosphate (1), doxylamine succinate (2) and their 1:1 physical mixture (3) are compared. Both endotherms of codeine phosphate disappeared in thermogram 3 whilst the doxylamine endotherm was shifted to a lower temperature with broadening and tailing. These two drugs should be avoided in combination.

In figure 4 pseudoephedrine hydrochloride (1), doxylamine succinate (2) and their 1:1 physical mixture (3) are compared.

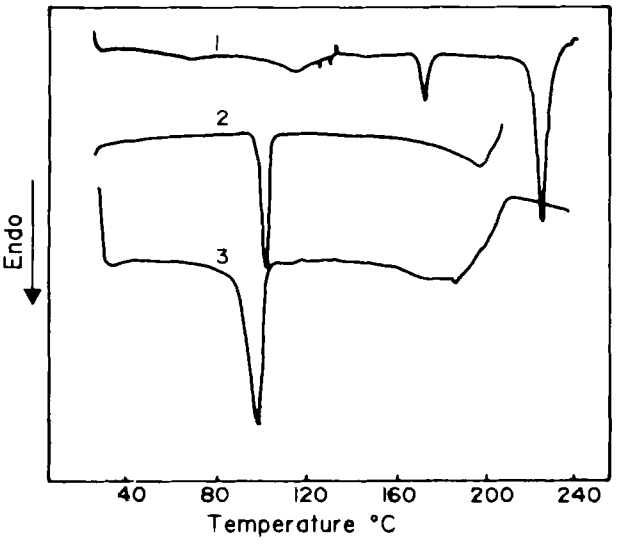


FIGURE 3

DSC thermograms of codeine phosphate (1), doxylamine succinate (2) and their physical mixture (3).

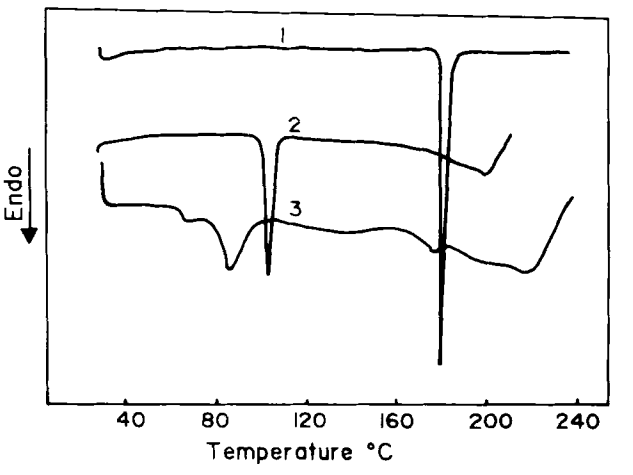


FIGURE 4

DSC thermograms of pseudoephedrine hydrochloride (1), doxylamine succinate (2) and their physical mixture (3).

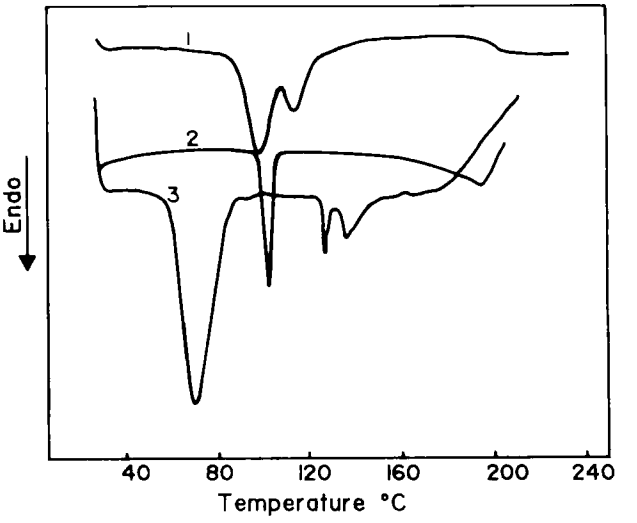


FIGURE 5

DSC thermograms of magnesium stearate (1), doxylamine succinate (2) and their physical mixture (3).



The endotherm of pseudoephedrine in the mixture was shifted to a lower temperature and is very much smaller than expected. The endotherm of doxylamine succinate in the mixture was also shifted to a lower temperature and is very much broader. This combination should also best be avoided.

In figure 5 magnesium stearate (1), doxylamine succinate (2) and their 1:1 physical mixture (3) are compared. The endotherms of magnesium stearate were shifted to higher temperatures and became much smaller than expected. The endotherms of doxylamine succinate was shifted to a lower temperature but became much larger and broader than expected. Magnesium stearate should best be avoided as an excipient for doxylamine succinate tablets.

In figure 6 stearic acid (1), doxylamine succinate (2) and their 1:1 physical mixture (3) are compared. The stearic acid endotherm shifted to a lower temperature and become much larger and broader than expected. The endotherm of doxylamine succinate was also

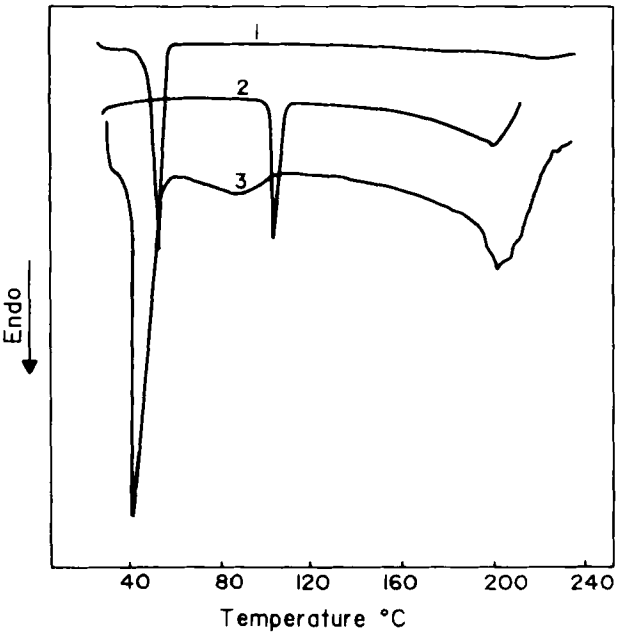


FIGURE 6

DSC thermograms of stearic acid (1), doxylamine succinate (2) and their physical mixture (3).

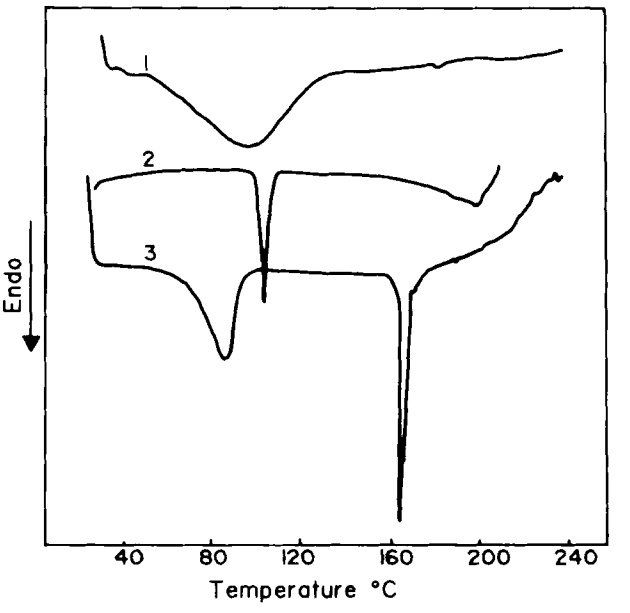


FIGURE 7

DSC thermograms of PVP (1), doxylamine succinate (2) and their physical mixture (3).

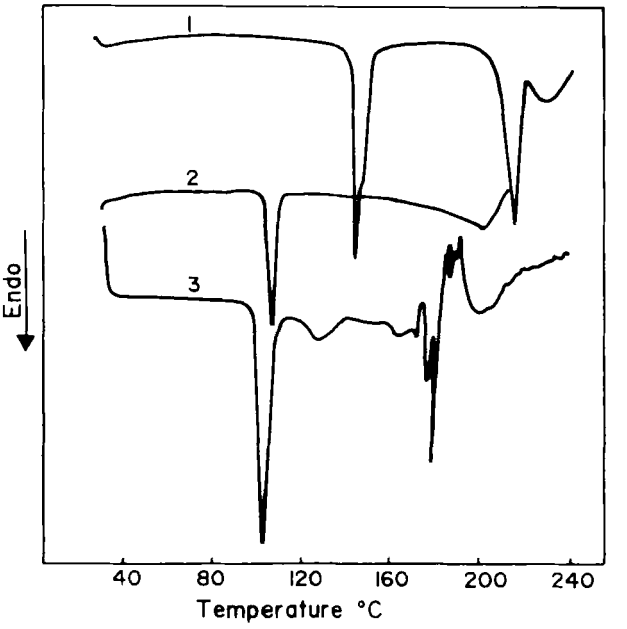


FIGURE 8

DSC thermograms of lactose (1), doxylamine succinate (2) and their physical mixture (3).



shifted to a lower temperature and became much smaller and very broad. It nearly disappeared. Stearic acid should be avoided as lubricant for doxylamine succinate.

In figure 7 PVP (1), doxylamine succinate (2) and their physical 1:1 mixture (3) are compared. The PVP endotherm due to absorbed moisture is much smaller or disappeared in thermogram 3. The thermogram at a lower temperature may be due in part to a shift to a lower temperature of doxylamine's endotherm or due to the lesser amount of moisture from the PVP drug mixture. The extra peak at 170°C is most probably a complex between PVP and doxylamine succinate. Before this combination is used one will have to make sure that complexation does not lead to a less soluble drug.

In figure 8 lactose (1), doxylamine succinate (2) and their 1:1 physical mixtures (3) are compared. The endotherm of

doxylamine was shifted to a lower temperature but become much larger and broader than expected. The lactose peaks also shifted to lower temperatures and became broader (peak 1) or smaller (peak 2). It seems as if some of the lactose interacted with doxylamine succinate to give a larger peak (peak 1 of thermogram 3). This type of interaction of amine with lactose was previously described[3].

No attempt was made during this study to determine the nature of the interactions, whether it is chemical or physical interactions or eutectic or complex formation. Some of the interactions may be useful to effect better solubility and others may be used to effect sustained release. Before using the combination it must however be stressed that the nature of the interaction be investigated beforehand.

## CONCLUSIONS

During this preformulation stability screening of doxylamine succinate it was found that doxylamine was compatible with mannitol, Aerosil®, calcium salts, starches, Ac-Di-Sol®, Primojel® and Avicel®. Interactions between doxylamine and the following drugs and excipients might result in decomposition during stability storage: acetaminophen, dextromethorphan hydrobromide, codeine phosphate, pseudoephedrine hydrochloride, magnesium stearate, stearic acid, PVP and lactose.

## REFERENCES

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3. R.N. Duvall, K.T. Koshy and J.W. Pyles, **J. Pharm. Sci., 54**, 607 (1965).