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# AN INVESTIGATION INTO SOME PHARMACEUTICAL INTERACTIONS BY DIFFERENTIAL SCANNING CALORIMETRY

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## ABSTRACT

Differential scanning calorimetry has been used to investigate the interactions between the drugs indomethacin and chlorpropamide with some tablet excipients, and also between the excipients themselves. Chlorpropamide was found to interact with both sodium starch glycolate and magnesium stearate, indomethacin with magnesium stearate and the tablet binder polyethylene glycol 6000 with microfine cellulose.

## INTRODUCTION

Thermal analysis is now a well developed technique used in the detection of incompatibilities in drug excipient mixtures. Jacobson and Reier (1) have used differential thermal analysis to identify stearic acid as the inactivating component in a formulation containing sodium dicloxacillin and other excipients. Incompatibility was also shown between stearic acid with both

potassium penicillin G and sodium oxacillin monohydrate. Lee and Hersey (2) reported preformulation stability testing using differential thermal analysis, and showed magnesium stearate to be incompatible with oxytetracycline dihydrate and hydrochloride.

The technique of thermal analysis seems well suited to detect incompatibilities in granules prepared by fusion techniques. Wells et al (3) and Ford (4) have granulated chlorpropamide-urea solid dispersions by in situ fusion techniques. A similar fusion technique (5) has been used to formulate indomethacin-polyethylene glycol 6000 solid dispersions. Although decomposition has been observed in these formulations, the underlying causes have not been investigated. This paper outlines the possible interactions between the drugs and excipients used in the previous solid dispersion formulation studies (3,4,5).

## MATERIALS

The following were used:- chlorpropamide B.P., indomethacin B.P., urea, polyethylene glycol 6000 (PEG 6000), calcium hydrogen phosphate anhydrate, microfine cellulose (Elcema G250, Degussa), sodium starch glycolate (Explotab, Mendell Co. Inc.) and magnesium stearate.

## METHODS

A Perkin-Elmer Model DSC-1B differential scanning calorimeter was used for thermal analysis. Aluminium sample pans and pan lids were used for all samples, the lids being crimped into position. Samples (5-15 mg) were run from 300-450$^{o}$K at a scanning rate of 4$^{o}$C min$^{-1}$, in a nitrogen atmosphere. Temperatures were determined after calibration with an indium standard. Samples used were either the materials as supplied or their mixtures (1:1) prepared by gentle trituration in a glass mortar and pestle.

## RESULTS AND DISCUSSION

The thermograms of the chlorpropamide-urea and indomethacin-PEG 6000 solid dispersions have been described in detail elsewhere (6,7). Chlorpropamide displayed two melting endotherms corresponding to melting points of 124° and 128.5°C, whilst urea showed a single melting endotherm at 132°C. Indomethacin showed a single melting endotherm at 159°C whilst PEG 6000 gave a single, broader endotherm with an initial melting point of 59° and a peak endotherm temperature of 61°C.

Anhydrous calcium hydrogen phosphate displayed a gradual endothermic shift in base line without any transition being apparent. Elcema G250 showed a shallow, broad endotherm that was completed at ∿ 143 C (Figure 1). This may correspond to the volatilization of adsorbed water since Kilzer (8) reported that regardless of the source of cellulose, the thermal analysis curve showed some common features including an endotherm above 100°C that was attributed to volatilization of adsorbed water.

The Explotab thermogram was more complicated (Figure 1B). Again a broad endotherm was present (peak at 116°C), followed by a sharper endotherm at 159°C. Morita (9) considered that endotherms in the thermograms of wheat starch at 145° and 275°C were due to selective dehydration, and it is probable that similar dehydration reactions occurred in sodium starch glycolate.

Magnesium stearate (Figure 1C) presented 4 discernible peaks at 81°, 95°, 107° and 116°C. Jacobson and Reier (1) showed that magnesium stearate has an endotherm at 125°C. However, Pacor and Spier (10) using D.S.C. of some fatty acid soaps, found peaks corresponding to transitions in the solid state and it is therefore possible that the peaks in the magnesium stearate thermogram corresponded to changes from an ordered crystalline state through liquid crystalline phases of various orders. Giron (11) however has shown that DSC curves of magnesium stearate displayed differences due to the solvents retained. The thermogram (Figure 1C) may similarly be due to retained solvent.

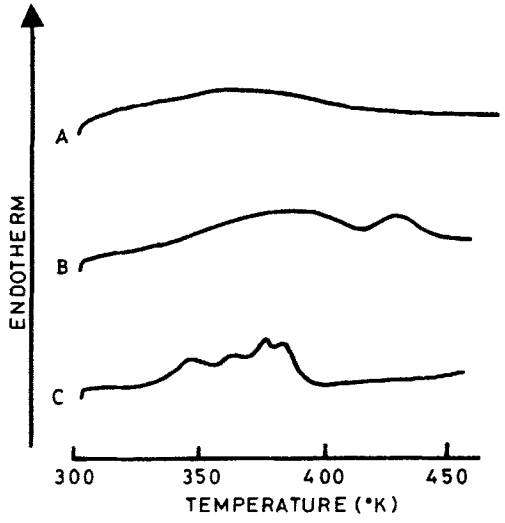


FIGURE 1

D.S.C. thermograms of (A) microfine cellulose, (b) sodium starch glycolate and (C) magnesium stearate.

Thermograms of chlorpropamide-calcium hydrogen phosphate and chlorpropamide-microfine cellulose showed the combined thermal characteristics of each without alteration to the position of endotherms. This indicates their probable compatibility.

In the chlorpropamide-sodium starch glycolate thermogram (Figure 2A) the sodium starch glycolate exotherm at 159°C was lost, and the initial peak endotherm of chlorpropamide was lowered to 118°C with loss of the second endotherm. Although a lowering in exotherm temperatures may occur in the presence of an impurity (12), this lack of a secondary endotherm indicated compatibility.

The chlorpropamide-magnesium stearate thermogram (Figure 2B) contained no endotherms corresponding to chlorpropamide fusion. The number of endotherms attributable to the lubricant decreased to three at 74°, 92° and 102°C. Hentze and Voege (13) showed

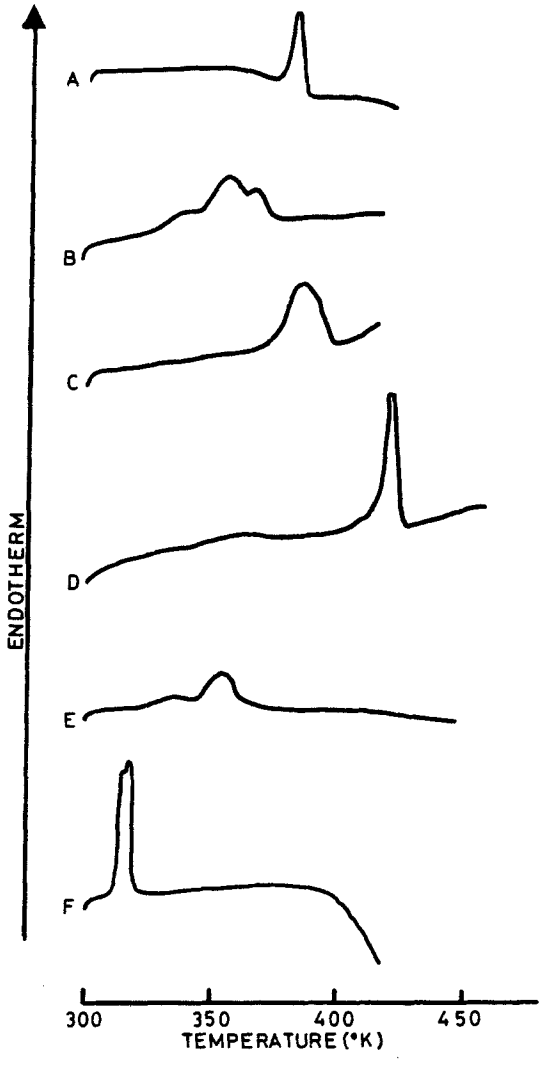


FIGURE 2

D.S.C. thermograms of mixtures (1:1) of (A) chlorpropamide-sodium starch glycolate, (b) chlorpropamide-magnesium stearate, (C) urea-sodium starch glycolate, (D) indomethacin-sodium starch glycolate, (E) indomethacin-magnesium stearate and (F) PEG 6000-sodium starch glycolate.

that drug endotherms were lost on thermal analysis in the presence of magnesium stearate when their mixtures were incompatible.

The microfine cellulose-urea, calcium hydrogen phosphate-urea, and magnesium stearate-urea thermograms showed the characteristics of the individual materials indicating compatibility. However urea appeared incompatible with sodium starch glycolate (Figure 2C). Only one, very broad endotherm was obtained with a peak at 118°C.

The indomethacin-calcium hydrogen phosphate and indomethacin-microfine cellulose thermograms displayed the elements characteristic of each component indicating lack of interaction.

The indomethacin-sodium starch glycolate thermogram showed no conclusive evidence of interaction. The second endotherm of the starch derivative (159°C) overlapped the endotherm of indomethacin (159°C) and the combined endotherm possessed a peak temperature of 157°C (Figure 2D).

With indomethacin-magnesium stearate only two endotherm maxima were obtained (Figure 2E) at 71° and 88°C. No melting endotherm was detected corresponding to indomethacin. Indomethacin in tablets was found to decompose during storage (5) and this may be attributed to this interaction between magnesium stearate and indomethacin.

In each of the thermograms containing PEG 6000 and excipients, a double melting endotherm of PEG 6000 was observed. This was probably due to the grinding undertaken to obtain a homogenous mix. Beech et al (14) have reported a double melting endotherm for PEG 6000 which was dependent on the preparative technique used.

The combined thermograms of PEG 6000 with calcium hydrogen phosphate, sodium starch glycolate, and magnesium stearate showed a reduction in the size of the endotherms of the excipients although a reduction in their transition temperatures did not occur. The effects probably do not correspond to incompatibility;

the fusion of PEG 6000 would result in a liquid probably masking the thermal characteristics of the other excipients. The thermogram of PEG 6000-microfine cellulose (Figure 2F) showed a remarkable exothermic decrease commencing at $\sim 130^{\circ}C$ and probably corresponded to a breakdown in integrity between the two materials. Decomposition, identifiable by charring, occurred in PEG 6000-microfine cellulose mixture when maintained at $100^{\circ}C$ for 1 h.

Slight differences in the thermograms of the other mixed tablet excipients were considered not to be indicative of incompatibility.

## CONCLUSIONS

Although this work was initiated as a preformulation stability exercise in the formulation of tablets containing solid dispersions, the interactions between the following pairs of materials might result in decomposition during stability storage:- chlorpropamide-sodium starch glycolate; chlorpropamide-magnesium stearate; urea-sodium starch glycolate; indomethacin-magnesium stearate and PEG 6000-microfine cellulose.

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