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COMPATIBILITY STUDY BETWEEN KETOPROFEN AND TABLET EXCIPIENTS USING DIFFERENTIAL SCANNING CALORIMETRY

S.A. Botha* and A.P. Lötter
Research Institute for Industrial Pharmacy
University of Potchefstroom for C.H.E.
2520 Potchefstroom
South Africa

ABSTRACT

Differential scanning calorimetry was used to investigate the interactions between the drug ketoprofen and a number of commonly used tablet excipients. Ketoprofen was found to interact with Precirol Ato 5, magnesium stearate, Emcompress, PVP, cross-linked PVP and lactose.

INTRODUCTION

This study was undertaken to establish the compatibility of ketoprofen [2-(3-benzoylphenyl)propionic acid], a drug with analgesic, anti-inflammatory and antipyretic actions which is used in the treatment of rheumatoid arthritis and osteoarthritis, with a number of commonly used tablet and capsule excipients.

In pharmaceutical preformulation work, studies of the interaction between drug and excipients in the solid state are obligatory. Excipients can affect the solid state stability of a drug either directly as a chemical reaction between the drug and the excipient(s) or, mostly, indirectly by sorption of moisture and/or catalysis.

Since tablet formulations typically contain diluents, binders, disintegration agents and lubricants, compatibility screening must be considered with selected excipients from each group. Two methods are available for routine drug-excipient interaction studies, namely thermal analysis, both differential thermal analysis (DTA)[1-2] and differential scanning calorimetry (DSC)[3-5], and quantitative assay after an isothermal stress test[6]. DSC allows the fast evaluation of possible incompatibilities between the formulation compounds derived from appearance, shift or disappearance of peaks and/or variations in the corresponding ΔH. Thermal analysis does not replace the chemical methods for determination of the concentration of a drug in a dosage form and does not replace stability tests, but it does represent a valuable tool in the first step of a formulation[7]. Van Dooren[8] has recommended the use of DSC in combination with short time stress in order to evaluate DSC curves easier.

In this work, the compatibility of ketoprofen with a number of excipients commonly used in tablet and capsule manufacture was investigated as a preformulation study. This was achieved by comparing the DSC thermograms of ketoprofen and each of the investigated excipients with 1 : 1 mixtures of ketoprofen and excipients. Although it cannot be conclusively stated that an interaction will occur during storage at room temperature, there are often sufficient excipients available to chose only those unlikely to cause problems[9].

EXPERIMENTAL

Materials

The following materials were used: ketoprofen (supplied by Twins-Propan, Johannesburg, RSA); starch; directly compressible

starch (Sta-Rx 1500®); sodium carboxymethyl starch (Primojel®); microcrystalline cellulose (Avicel PH 101®); microfine cellulose (Elcema G250®); a cross-linked form of sodium carboxymethylcellulose (Ac-Di-Sol®); hydrogenated cotton seed oil (Sterotex®); glyceryl palmitostearate (Precirol Ato 5®); magnesium stearate; dicalcium phosphate dihydrate (Emcompress®); polyvinylpyrrolidone (PVP); cross-linked PVP; lactose.

Differential Scanning Calorimetry (DSC)

Samples (3 - 8 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 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 ketoprofen and excipients prepared by mortar and pestle, were heated over the temperature range of 30 - 250°C.

RESULTS AND DISCUSSION

The DSC thermogram of ketoprofen (trace 1 of figures 1 - 8) showed a melting endothermic peak with an onset of 88°C and a maximum peak of transition at 91°C. The excipients starch, Sta-Rx 1500, Primojel, Avicel PH 101, Elcema G250 and Ac-Di-Sol exhibited a shallow broad endotherm that was completed at 145°C. This may correspond to the volatilization of adsorbed water since it was reported that the thermal analyses of cellulose and wheat starch[10-11] showed endotherms above 100°C that were attributed to water vapor. It is probable that similar dehydration reactions occurred in

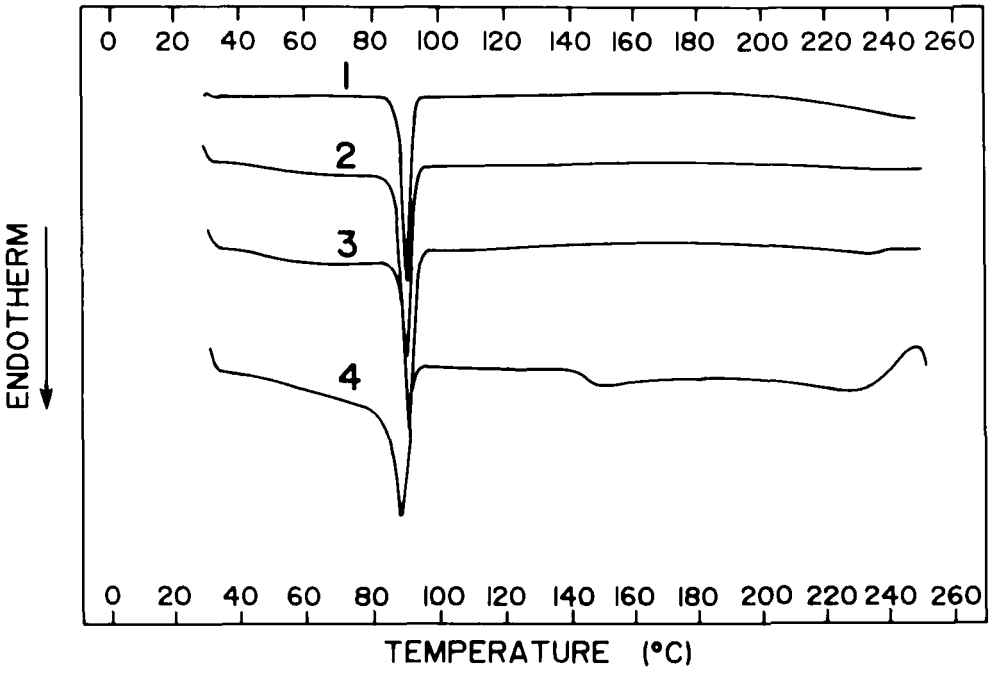

FIGURE 1
DSC thermograms of ketoprofen (1), physical mixtures of ketoprofen - Avicel PH 101 (2), ketoprofen - Elcema G250 (3) and ketoprofen - Primojel (4).

Primojel and Ac-Di-Sol. If no interaction occurred, the DSC thermograms of mixtures of these excipients with ketoprofen will reflect the combined characteristic features of ketoprofen and the excipient. This is indeed the case as showed in trace 2 - 4 of fig. 1, illustrating the thermograms of 1 : 1 physical mixtures of ketoprofen with Avicel PH 101, Elcema G250 and Primojel respectively. Similar thermograms were obtained with 1 : 1 mixtures of ketoprofen and starch, Sta-Rx 1500 and Ac-Di-Sol. As expected, some changes in peak shape and height-to-width ratios were found, because of possible differences in the mixture sample geometry[12]

The thermogram of ketoprofen : Sterotex physical mixture (trace 3, fig.2) combined the features characteristic of the

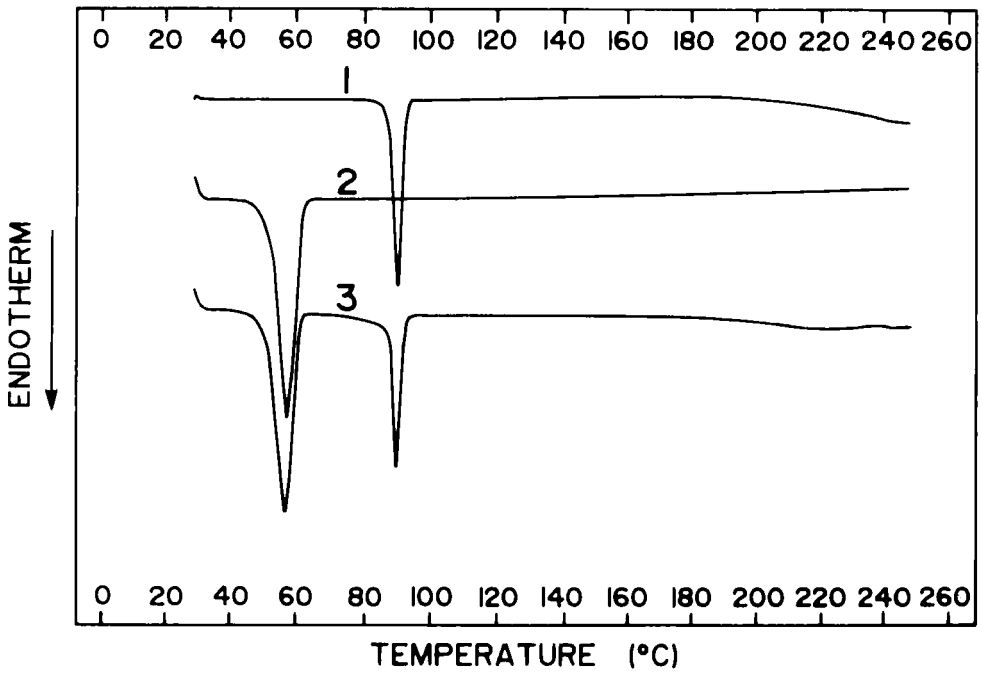

FIGURE 2
DSC thermograms of ketoprofen (1), Sterotex (2) and a physical mixture of ketoprofen - Sterotex (3).

thermograms of each component indicating that no reaction occurred.

On the other hand, the thermogram of ketoprofen : Precirol Ato 5 (trace 3, fig. 3) showed a downward shift of the ketoprofen melting endotherm to a temperature of 77 - 96°C; also, the size of the peak was appreciably smaller than expected. A large shift in melting point signifies that a strong solid-solid interaction has occurred, although it does not necessarily indicate an incompatibility.

The thermogram of magnesium stearate (trace 2, fig. 4) showed transition endotherms with onsets of 110°C and 150°C, the latter small. Müller[13], using DTA/TG, examined two crystalline forms of magnesium stearate; each with a number of transition

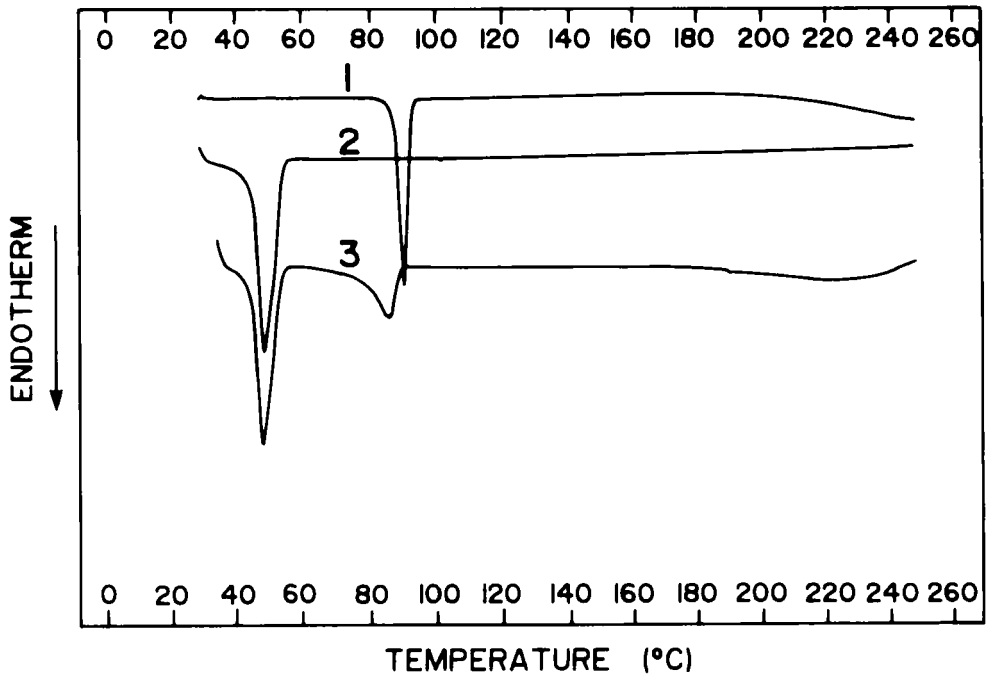

FIGURE 3
DSC thermograms of ketoprofen (1), Precirol Ato 5 (2) and a physical mixture of ketoprofen - Precirol Ato 5 (3).

temperatures. The needle form had endothermic transition peaks at 59, 81, 116, 150°C and a degradation exotherm at 183°C, while magnesium stearate plates exhibited endothermic transition temperatures at 60, 76, 104, 170°C and a degradation exotherm at 200°C. The endotherm of magnesium stearate at 110°C was very small in the thermogram obtained by the mixture ketoprofen : magnesium stearate (trace 3, fig. 4). Also, the characteristic endotherm due to ketoprofen was absent and an endotherm at a much lower temperature (59 - 65°C) was obtained. Extra thermal effects in a thermogram before the peak of the lower melting component might be indicative of an incompatibility, this also applies when one of the component peaks disappears completely[8]. Stearates

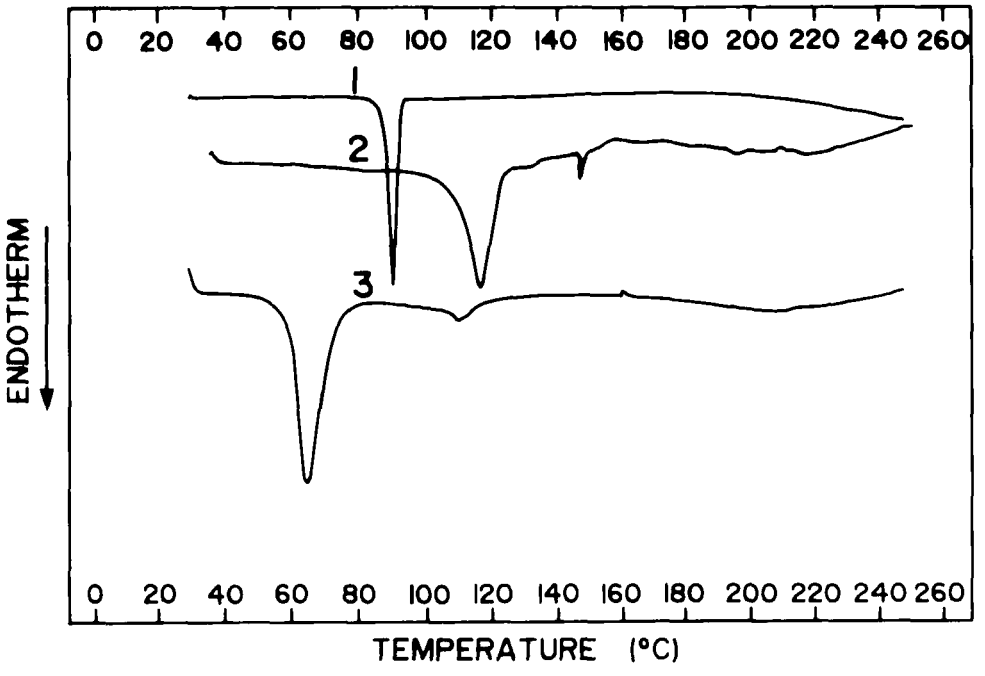

FIGURE 4
DSC thermograms of ketoprofen (1), magnesium stearate (2) and a physical mixture of ketoprofen - magnesium stearate (3).

were shown to be incompatible with cephalexin[14], anhydrous ampicillin[15], erythromycin[16], nalidixic acid[17], chlorpropamide and indomethacin[18].

The characteristic melting endotherm of ketoprofen can be seen in a combination of ketoprofen with Emcompress (trace 3, fig. 5), but the characteristic melting endotherm of Emcompress (176 - 187°C; trace 2, fig. 5) had been obliterated. An extra endotherm could be seen at a temperature of 98 - 103°C, indicating a possible incompatibility of ketoprofen with Emcompress.

Trace 2 of fig. 6 is the thermogram of PVP, showing a broad endotherm (53 - 96°C) due to adsorbed water. In the thermogram of a physical mixture of ketoprofen-PVP (trace 3, fig. 6), the

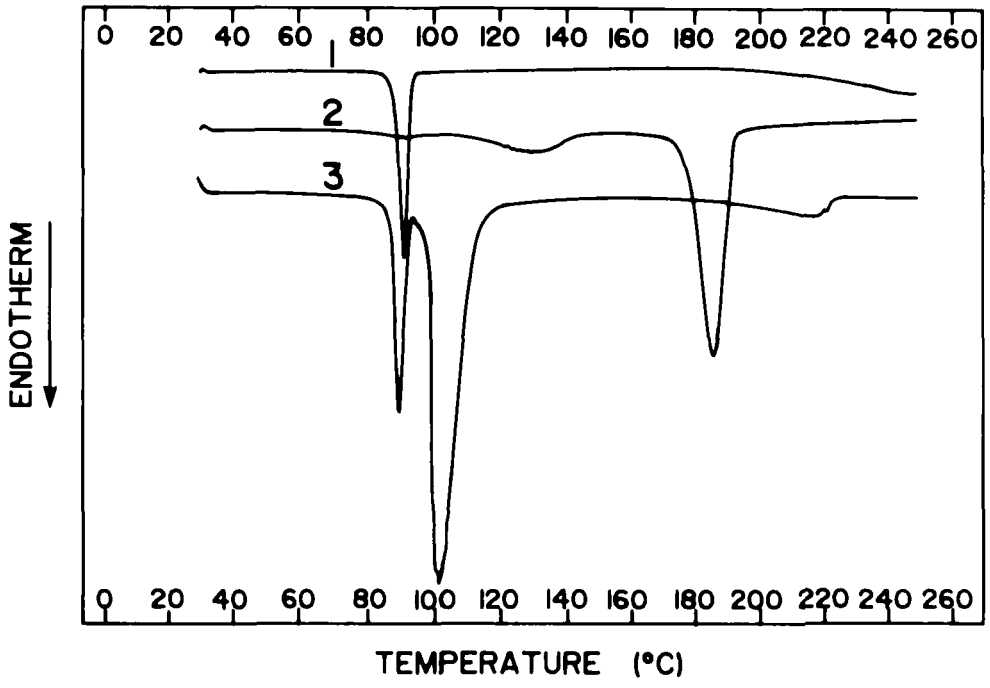

FIGURE 5
DSC thermograms of ketoprofen (1), Emcompress (2) and a physical mixture of ketoprofen - Emcompress (3).

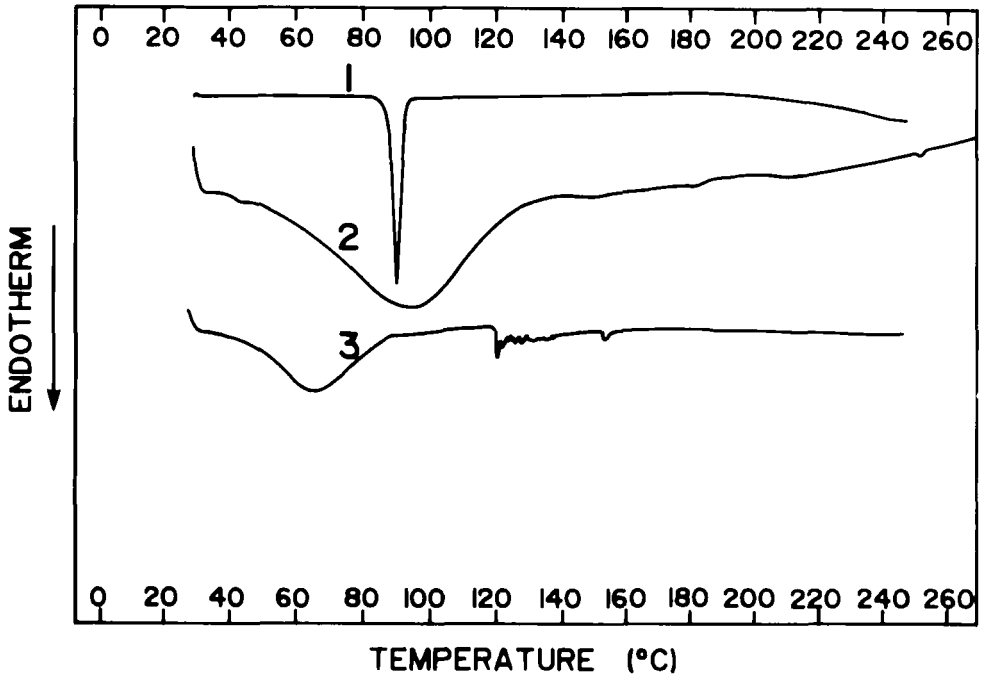

FIGURE 6
DSC thermograms of ketoprofen (1), PVP (2) and a physical mixture of ketoprofen - PVP (3).

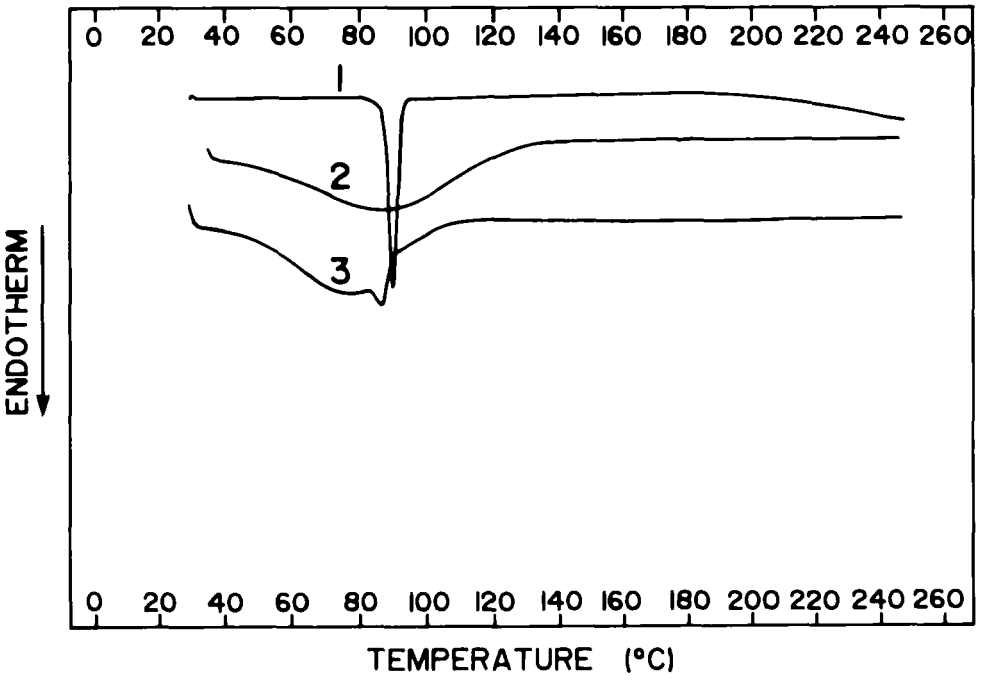

FIGURE 7
DSC thermograms of ketoprofen (1), cross-linked PVP (2) and a physical mixture of ketoprofen - cross-linked PVP (3).

characteristic melting endotherm of ketoprofen was absent, which can be indicative of an interaction.

The thermogram of cross-linked PVP also showed a broad endotherm due to adsorbed water (trace 2, fig. 7). A small endothermic transition at a temperature of 75 - 88°C was found in the thermogram of a physical mixture of ketoprofen : cross-linked PVP (trace 3, fig. 7) which is indicative of an interaction.

The thermogram of lactose showed two large endothermic transitions at 137 - 144°C and 207.5 - 217°C, followed by a third smaller endotherm (trace 2, fig. 8). The ketoprofen : lactose combination showed, apart from the characteristic ketoprofen endotherm, also endotherms at 126 - 133°C and 204 - 210°C as well

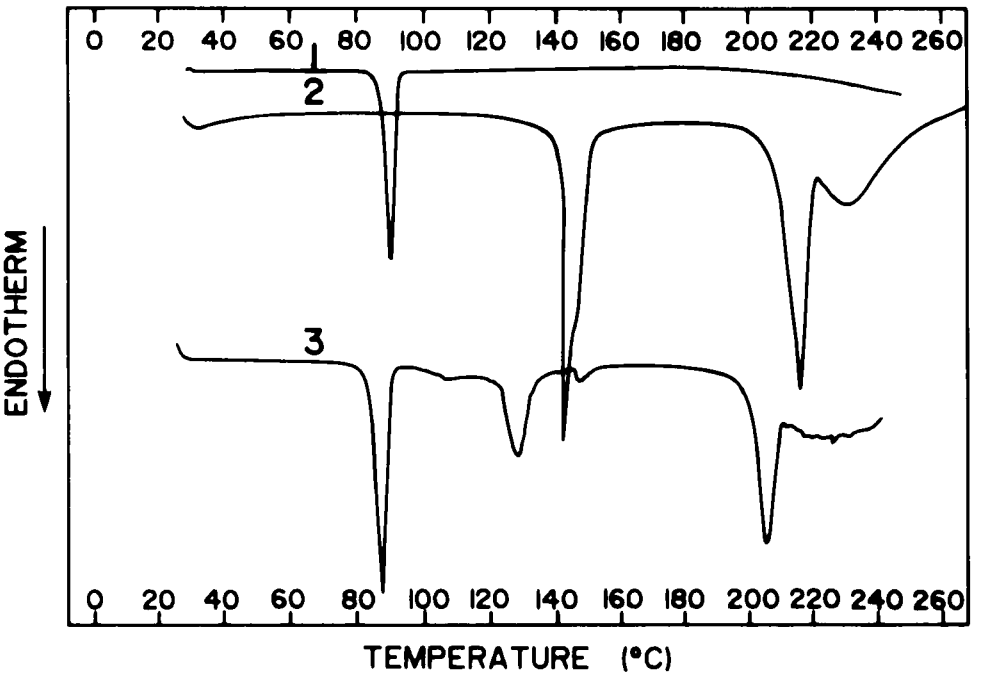

FIGURE 8
DSC thermograms of ketoprofen (1), lactose (2) and a physical mixture of ketoprofen - lactose (3).

as a smaller endotherm at 150 - 151°C. If characteristic new peaks can be seen in thermograms of drug-excipient mixtures, it can be inferred that an interaction is occurring between the compounds and is likely to result in a chemical incompatibility[19]

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

CONCLUSIONS

In the preformulation stability screening in order to formulate a ketoprofen dosage form, it was found that ketoprofen was com-

patible with starch, Sta-Rx 1500, Primojel, Avicel PH 101, Elcema G250 and Ac-Di-Sol. Interactions between ketoprofen and the following excipients might result in decomposition during stability storage : Precirol Ato 5; magnesium stearate; Emcompress; PVP; cross-linked PVP and lactose.

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