

COMPATIBILITY STUDY BETWEEN NAPROXEN AND TABLET EXCIPIENTS USING DIFFERENTIAL SCANNING CALORIMETRY

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ABSTRACT

Differential scanning calorimetry (DSC) was used to investigate the physico-chemical compatibility between naproxen and a number of commonly used tablet excipients.

Interactions of naproxen with PVP, cross-linked PVP, Emcompress and the lubricants stearic acid, magnesium stearate and Precirol Ato 5 were found. Naproxen was found to be compatible with starch, Sta-Rx 1500, Primojel, Explotab, Avicel PH 101, Elcema G250, Ac-Di-Sol and Sterotex.

INTRODUCTION

In pharmaceutical work, studies of the interaction between drug and excipients in the solid state are obligatory. Excipients can effect the solid state stability of a drug either directly as a chemical reaction between the drug and the excipient(s) or, mostly

indirectly by adsorption of moisture and/or catalysis. Although a number of methods are available for routine drug-excipient interaction studies¹⁻⁵, DSC has become the screening method of choice, since it 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 stability tests, but it does represent a valuable tool in the first step of a formulation⁶.

This study was undertaken to establish the compatibility of naproxen, a potent systemic non-steroidal anti-inflammatory drug used in rheumatoid arthritis, with a number of commonly used tablet excipients. Tablet formulations typically contain diluents, binders, disintegration agents and lubricants, therefore the compatibility of naproxen with selected excipients from each group was investigated. This was achieved by comparing DSC curves of the active ingredient and each of the investigated excipients with curves for 1 : 1 mixtures of naproxen and the excipients.

EXPERIMENTAL

Materials

The following materials were used: naproxen (supplied by Twins-Propan, Johannesburg, R.S.A.); corn starch; directly compressible starch (Sta-Rx 1500®); sodium carboxymethyl starch (Primojel®, Explotab®); microcrystalline cellulose (Avicel PH 101®); microfine cellulose (Elcema G250®); a cross-linked form of sodium carboxymethyl-cellulose (Ac-Di-Sol®), magnesium stearate; stearic acid; polyvinylpyrrolidone (PVP); cross-linked polyvinylpyrrolidone;

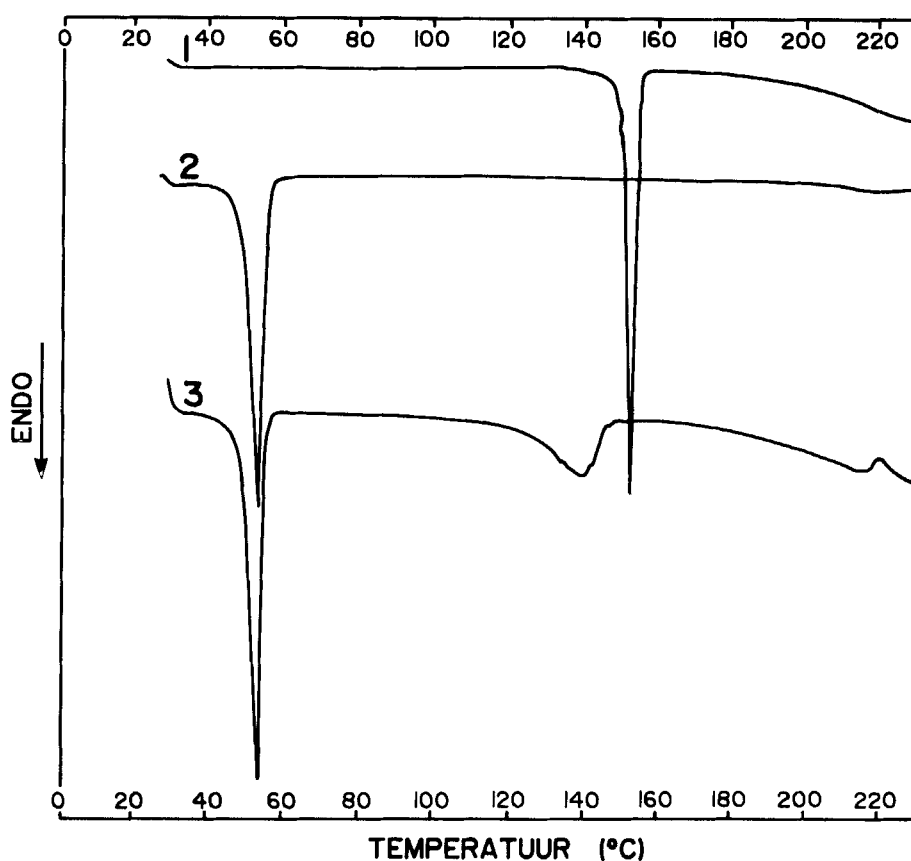


FIGURE 1

DSC thermograms of naproxen (1), stearic acid (2) and 1 : 1 physical mixture of naproxen : stearic acid (3).

hydrogenated cotton seed oil (Sterotex®); glyceryl palmito stearate (Precirol Ato 5®); dicalcium phosphate dihydrate (Emcompress®).

Samples (3 - 8mg) were measured and hermetically sealed in flat-bottomed aluminium pans. Samples of individual substances, as well as 1 : 1 physical mixtures of naproxen and excipients prepared by grinding in a mortar and pestle, were heated over the temperature range of 30 - 200°C in an atmosphere of nitrogen at a

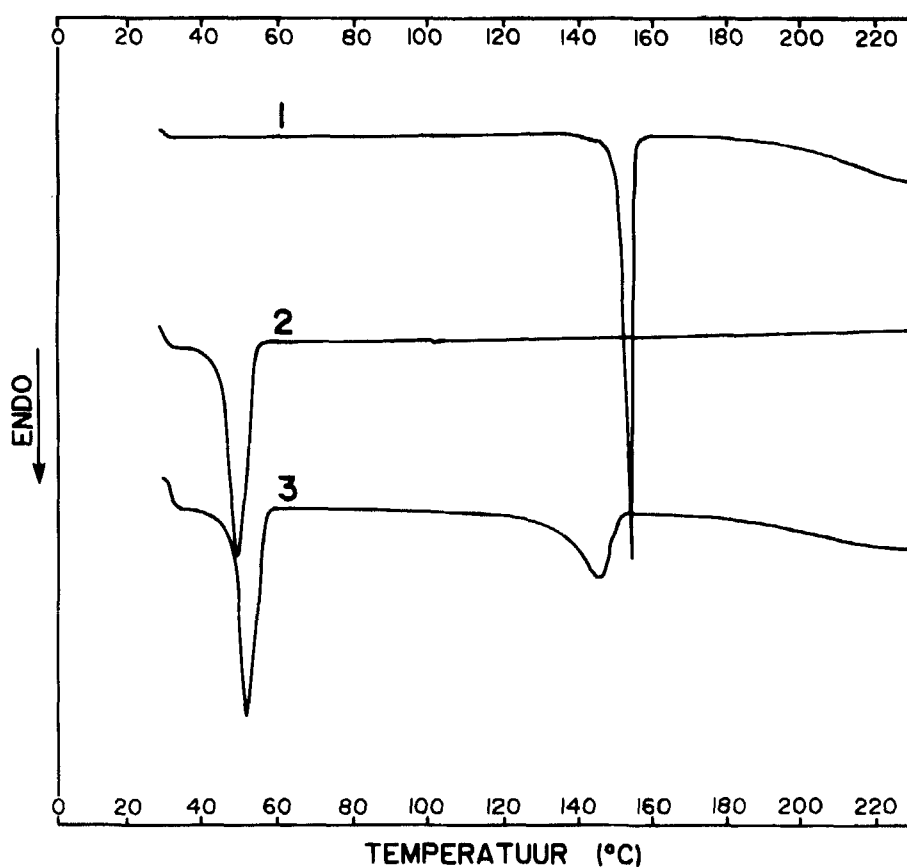


FIGURE 2

DSC thermograms of naproxen (1), Precirol Ato 5 (2) and 1 : 1 physical mixture of naproxen : Precirol Ato 5 (3).

constant rate of 5°C per minute in 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. The DSC curves of naproxen and each of the investigated excipients with 1 : 1 mixtures of naproxen and excipients were compared.

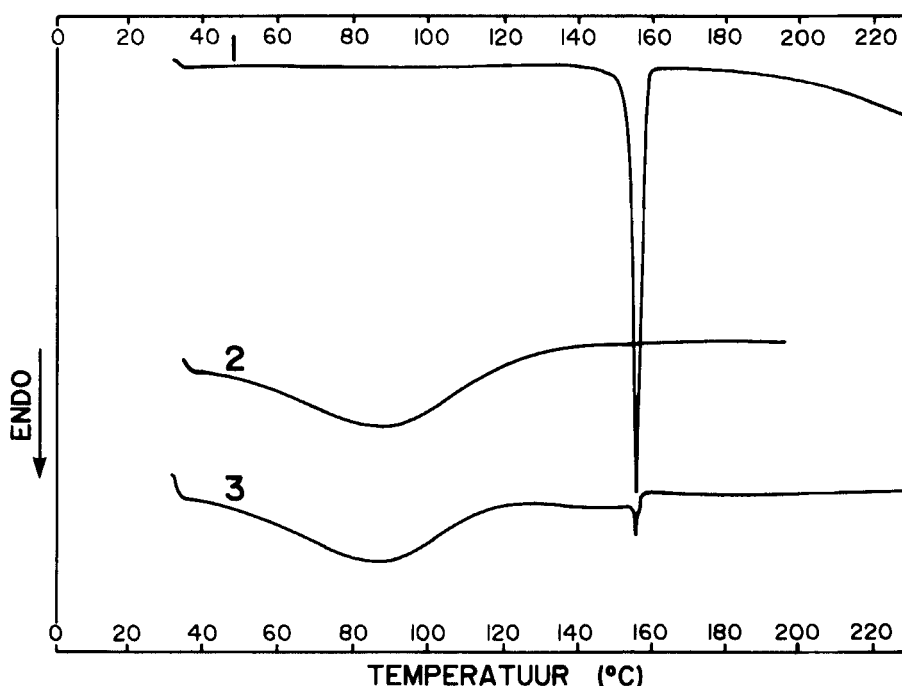


FIGURE 3

DSC thermograms of naproxen (1), PVP cross-linked (2) and 1 : 1 physical mixture of naproxen : PVP cross-linked (3).

RESULTS AND DISCUSSION

The DSC trace of naproxen (trace 1 of fig. 1 - 6) shows a sharp melting endotherm with an onset of 152°C and a maximum occurring at 155°C.

The excipients corn starch, Sta-Rx 1500®, Primojel®, Explotab®, Avicel PH 101®, Elcema G-250® and Ac-Di-Sol® all exhibit a shallow broad endotherm that is completed at 145°C. This might correspond to the volatilization of adsorbed water, since it was reported that the thermal analysis of cellulose⁷ and wheat starch⁸ showed endotherms above 100°C that were attributed to water va-

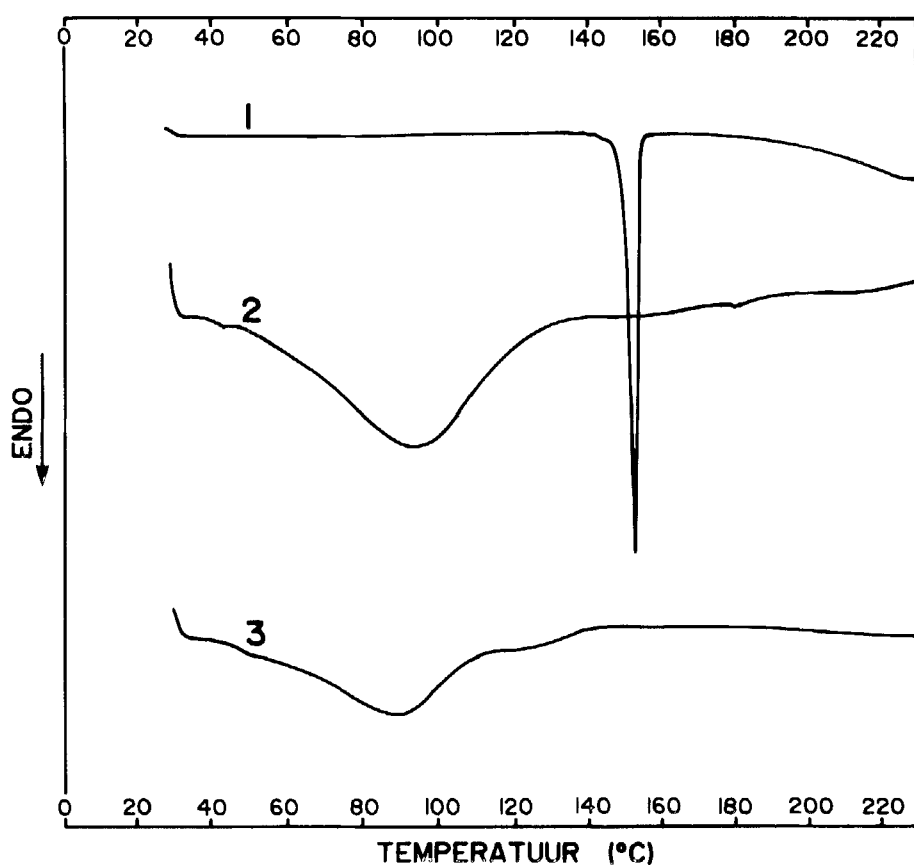


FIGURE 4

DSC thermograms of naproxen (1), PVP (2) and 1 : 1 physical mixture of naproxen : PVP (3).

por. It is probable that similar dehydration reactions occur in Primojel, Explotab and Ac-Di-Sol. The combination of naproxen with each of these excipients exhibit the characteristic features of naproxen, indicating compatibility. As expected, some changes in peak shape and height-to-width ratio can be seen because of possible differences in the mixture sample geometry⁹.

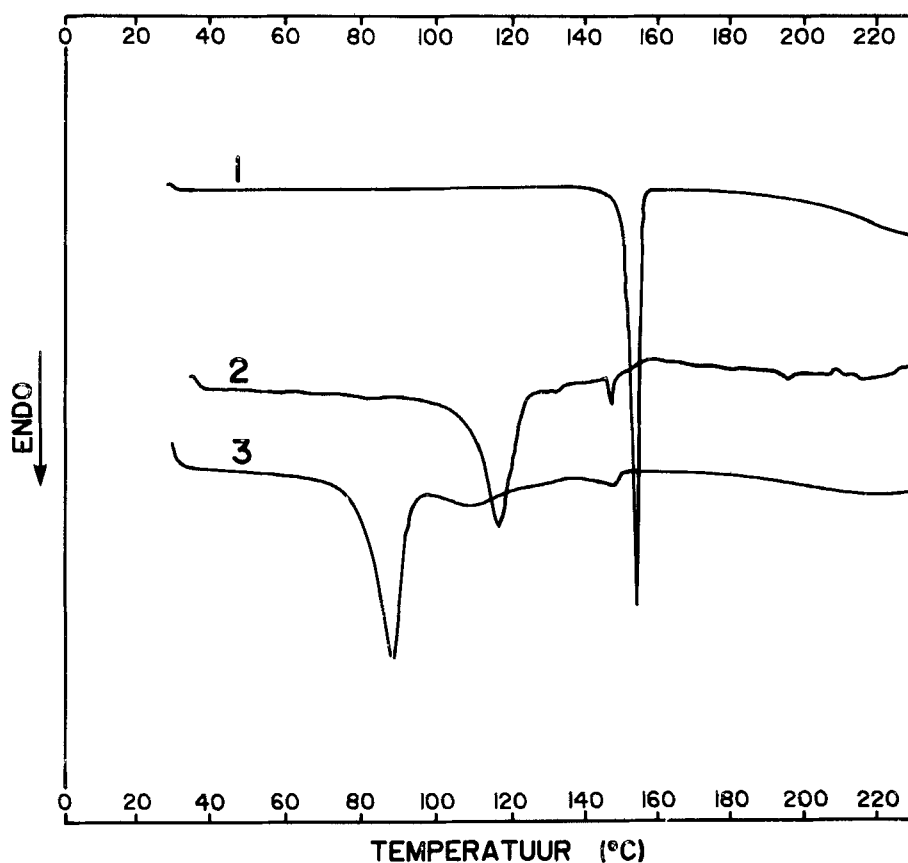


FIGURE 5

DSC thermograms of naproxen (1), Mg-stearate (2) and 1 : 1 physical mixture of naproxen : Mg-stearate (3).

The trace of naproxen : Sterotex® also combines the features characteristic of the curves of each component, indicating compatibility.

When two substances are mixed, the purity of each may be reduced and generally slightly lower melting endotherms result. If the solid-solid interaction is extremely weak or non-existent, the reduction of the melting point is usually inconsequential. On the

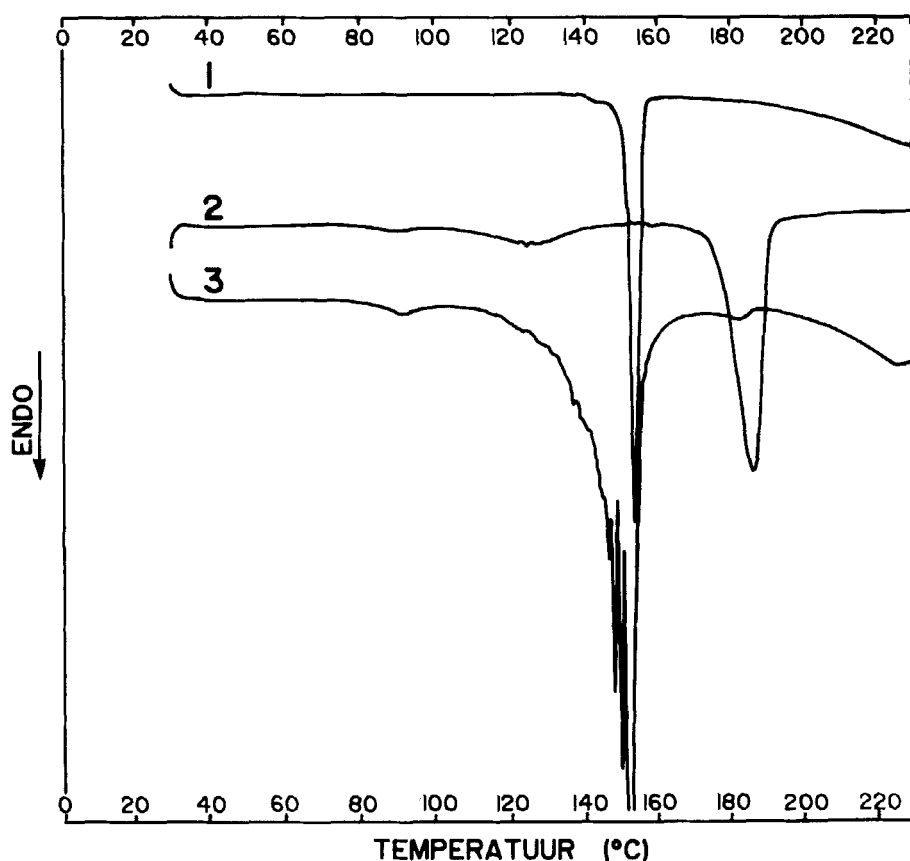


FIGURE 6

DSC thermograms of naproxen (1), Emcompress (2) and 1 : 1 physical mixture of naproxen : Emcompress (3).

other hand, any large shift in melting point signifies that a strong solid-solid interaction has occurred, although it does not necessarily indicate an incompatibility.

In the trace of a naproxen : stearic acid mixture (trace 3; fig. 1) the characteristic endotherm of stearic acid (49 - 55°C) can be seen, as well as a lowered naproxen endothermic peak at a temperature of 124 - 141°C. This peak is also smaller than antic-

ipated and could be indicative of an interaction. A number of incompatibilities between stearic acid and drug components have already been reported¹⁰⁻¹³.

The combination naproxen : Precirol Ato 50 (trace 3; fig. 2) shows not only a lowered naproxen endotherm, namely at 135 - 146°C, but also a smaller peak than anticipated. This result might be indicative of an interaction.

The curve of cross-linked PVP (trace 2, fig. 3) shows a broad endotherm (30 - 140°C) due to the volatilization of adsorbed water. The combination naproxen : cross-linked PVP shows, apart from the water endotherm, a small endotherm with an onset temperature of 153°C (trace 3; fig. 3). This peak is much smaller than anticipated and could be indicative of an interaction.

Trace 2 of fig. 4 is the curve of PVP, showing a broad adsorbed water endotherm (12% of water as determined by Karl Fischer titration method) over the temperature range of 53 - 96°C. A mixture of naproxen : PVP shows, apart from the water endotherm, a very slight endotherm with a maximum at 125°C. The disappearance of one of the component peaks in a mixture might be indicative of an incompatibility³.

The DSC curve of magnesium stearate shows a broad melting endotherm at 110 - 118°C (trace 2, fig. 5) while the combination of naproxen : magnesium stearate shows an endothermic peak with an onset of 81°C and also two small endotherms with onsets of 85°C and 140°C (trace 3, fig. 5). Extra thermal effects in a thermogram before the peak of the lower melting component might be indicative of an incompatibility³.

Dicalcium phosphate dihydrate (Emcompress®) shows a melting endotherm with an onset of 176°C and a maximum at 187°C (trace 3, fig. 6). The combination of naproxen : dicalcium phosphate dihydrate shows a complicated endotherm which could be indicative of an incompatibility, sine the combination of an alkaline vehicle, such as dicalcium phosphate with an acidic component (pK_a 4,7) is contra-indicated¹⁴.

CONCLUSIONS

DSC studies of naproxen in combination with a number of commonly used tablet excipients reveal no interaction between naproxen and following excipients, namely corn starch, Sta-Rx 1500, Primojel, Explotab, Avicel PH 101, Elcema G250, Ac-Di-Sol and Sterotex.

Although it cannot be conclusively stated that an interaction will occur during storage at room temperature if naproxen is used in combination with stearic acid, Precirol Ato 5, cross-linked PVP, PVP, magnesium stearate or Emcompress, there are sufficient excipients available to choose only those unlikely to cause problems.

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