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NALIDIXIC ACID-DIRECT COMPRESSION EXCIPIENTS: PREFORMULATION STABILITY SCREENING USING DIFFERENTIAL SCANNING CALORIMETRY

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ABSTRACT

Differential scanning calorimetry was used as a screening technique for assessing the compatibility of nalidixic acid with some of the direct compression excipients. Nalidixic acid was found to be compatible with Brownex sugar, sorbitol, mannitol and granular mannitol, while incompatible with Cab-O-Sil, Di-Pac, Emdex and dicalcium phosphate dihydrate. It appears that stearic acid and L-(-)-leucine can be used as lubricants in formulations containing nalidixic acid while magnesium stearate cannot.

INTRODUCTION

El-Shattawy et al. previously used differential scanning calorimetry (DSC) as a screening technique for

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assessing the compatibility of aspartame[1,2], anhydrous ampicillin[3], cephalexin[4] and erythromycin[5] with some of the direct compression excipients. The compatibilities of anhydrous ampicillin, ampicillin trihydrate and cephalexin with anhydrous dextrose and with aspartame were also investigated by the same authors[6-8].

Fetouh[9] attributed the decrease in the dissolution rate of nalidixic acid-polyethylene glycol 4000,6000 and 20000 coprecipitates compared to that of the corresponding physical mixtures to an interaction,occurred during coprecipitation, between nalidixic acid and the polyethylene glycol polymers.

In this study, the author investigated the compatibility of nalidixic acid with some of the direct compression excipients. This was achieved by comparing the DSC thermograms of nalidixic acid and each of the investigated excipients with 1:1 mixtures of nalidixic acid and excipients. Although it cannot be conclusively stated that an interaction incompatibility will occur during storage at room temperature, there are often sufficient excipients available in a preformulation program to choose only those unlikely to cause trouble[10].

EXPERIMENTAL

Materials

The following materials were used: nalidixic acid (supplied by Memphis Chemical Company), Cab-O-Sil (Cabot), Brownex sugar and Di-Pac (Amstar), sorbitol (Pfizer), mannitol and granular mannitol (ICI Americas), Emdex

(E. Mendell), dicalcium phosphate dihydrate (Baker), stearic acid (Ruger Chemical), L-(-)-leucine (Eastman Kodak) and magnesium stearate (Mallinckrodt).

Differential Scanning Calorimetry

Samples (2-4 mg) were weighed after being finely powdered and encapsulated in volatile sample pans with tightly sealed lids. The samples were heated in an atmosphere of nitrogen and thermograms were obtained on a Perkin-Elmer DSC-1B Differential Scanning Calorimeter. Thermograms were obtained by heating at a constant heating rate of 10°C per minute, a constant range setting of 8 mcal per second and recorded at a constant chart speed of one inch per minute. The individual substances and 1:1 physical mixtures of nalidixic acid and excipients, prepared with mortar and pestle were heated over the temperature range, 30 to 330°C.

The area under the differential scanning calorimetric heating curve was measured using a K&E planimeter and the heat of transition was then calculated as described previously[1]. At least two replicates were made for each DSC thermogram.

RESULTS AND DISCUSSION

The DSC thermogram of nalidixic acid (Trace 1 of Figures 1-10) showed a melting endothermic peak with an average transition temperature range from 227-234°C and with an average maximum peak of transition at 231°C. At 300°C nalidixic acid thermograms showed an exotherm before decomposition occurred at about 316°C. The enth-

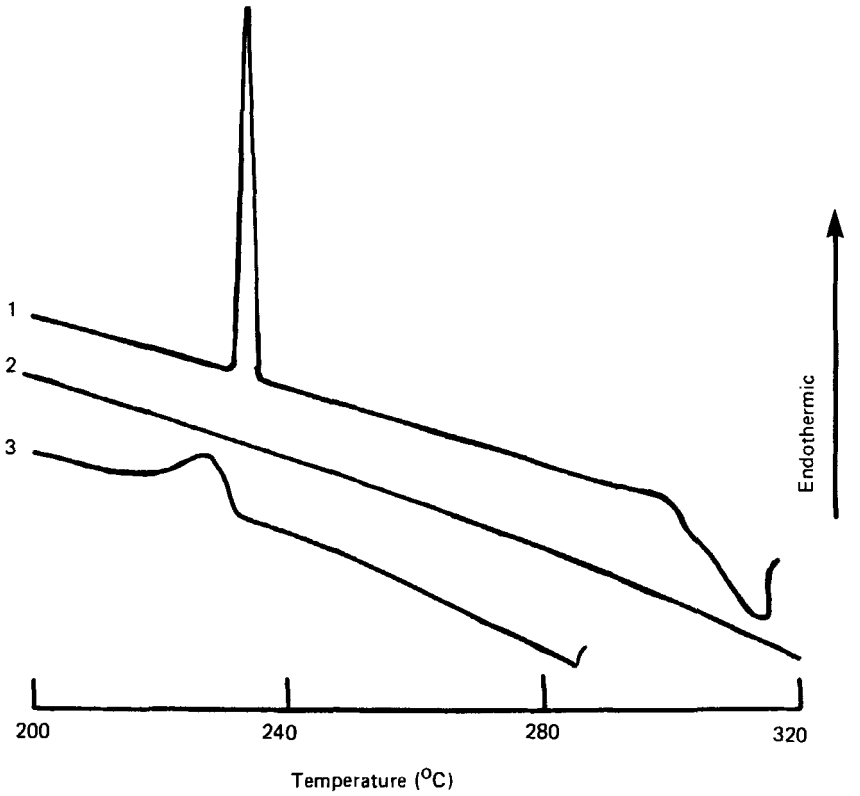

FIGURE 1

DSC thermograms of nalidixic acid (1),Cab-O-Sil (2) and 1:1 nalidixic acid-Cab-O-Sil mixture (3).

alpy change (cal/g) of the melting transition of nalidixic acid was taken as a base fore assessing its stability in this work. This is because a DSC peak area is a true electrical energy measurement, the magnitude of which does not depend on any of the thermal constants of the sample or apparatus[11].

Cab-O-Sil exhibits no transition when scanned over the temperature range of 30 to 350°C[1]. The DSC thermogram of the nalidixic acid-Cab-O-Sil mixture (Trace 3 of Figure 1) showed the endothermic peak corresponding to

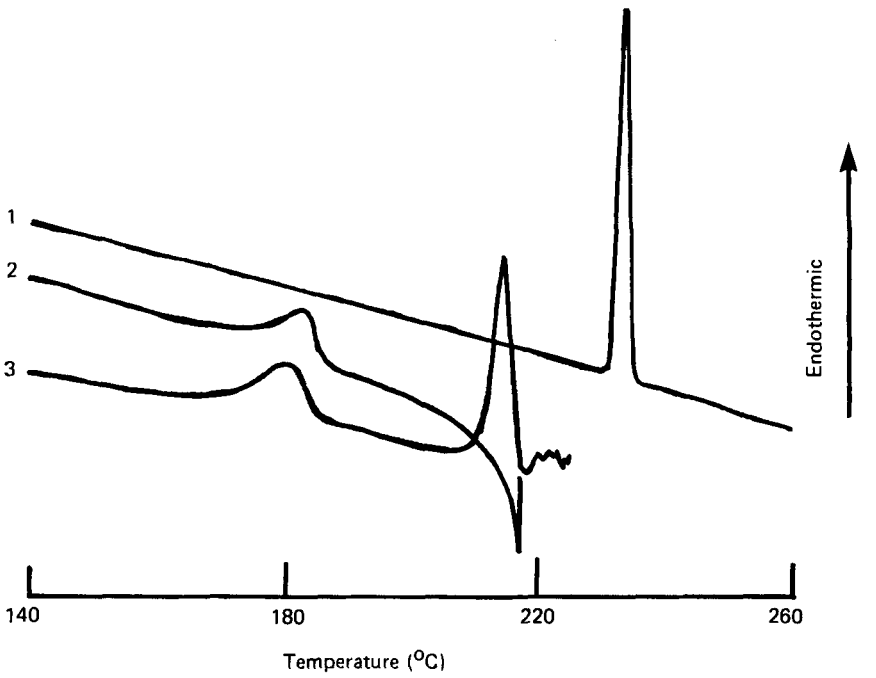

FIGURE 2

DSC thermograms of nalidixic acid (1), Brownex sugar (2) and 1:1 nalidixic acid-Brownex sugar mixture (3).

nalidixic acid with some change in peak's shape and with the transition temperature range and the maximum peak of transition shifted to lower temperatures. The enthalpy change, cal/g, of the mixture was found to be 69.96% of the predicted value calculated from the exact percentage contribution of nalidixic acid to the total enthalpy change of the mixture indicating the possible incompatibility of Cab-O-Sil with nalidixic acid under the experimental conditions. The decomposition of nalidixic acid-Cab-O-Sil mixture was found to be at about 285°C, i.e.,

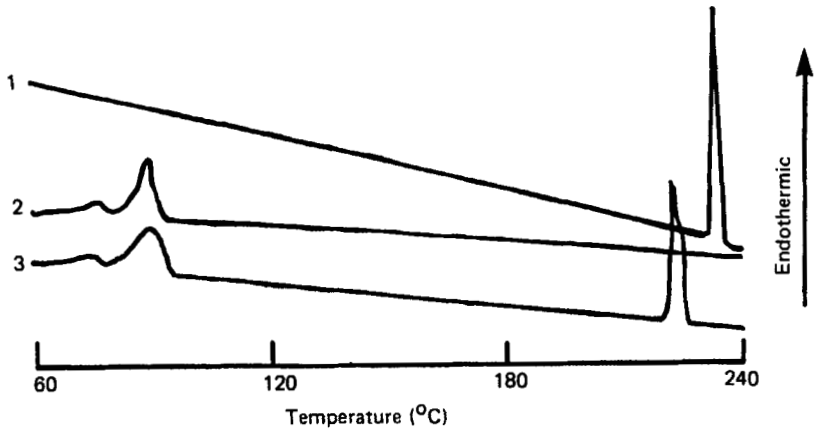

FIGURE 3

DSC thermograms of nalidixic acid (1), sorbitol (2) and 1:1 nalidixic acid-sorbitol mixture (3).

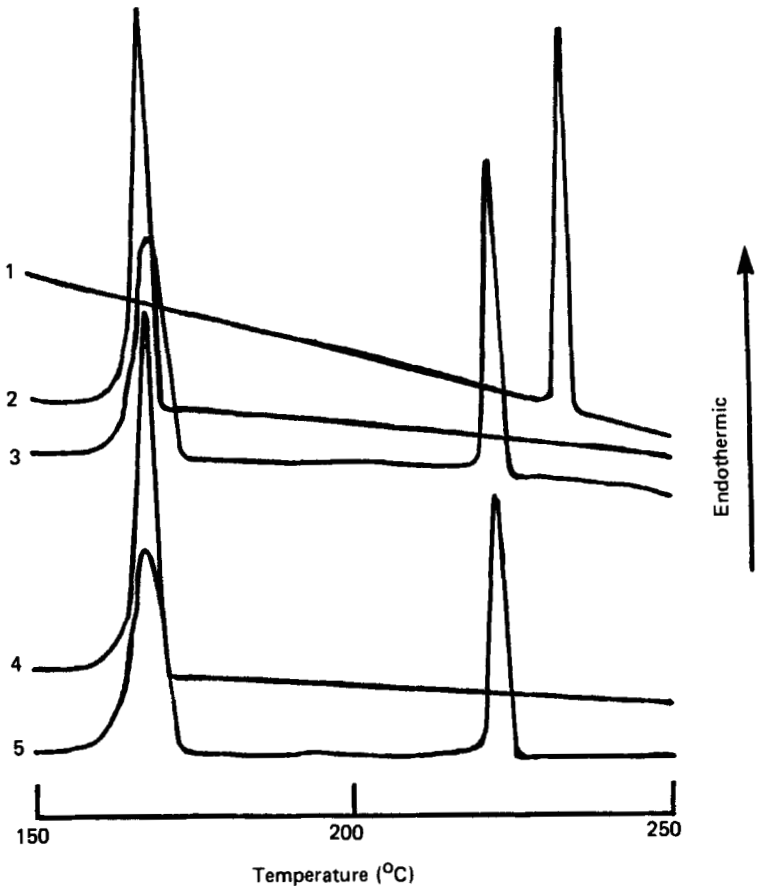

FIGURE 4

DSC thermograms of nalidixic acid (1), mannitol (2), 1:1 nalidixic acid-mannitol mixture (3), granular mannitol (4) and 1:1 nalidixic acid-granular mannitol mixture (5).

markedly lower than those of the pure respective original components, again indicated the possible incompatibility.

The DSC thermograms of the nalidixic acid-Brownex sugar mixture (Trace 3 of Figure 2), nalidixic acid-sorbitol mixture (Trace 3 of Figure 3), nalidixic acid-mannitol mixture (Trace 3 of Figure 4) and nalidixic acid-granular mannitol mixture (Trace 5 of Figure 4) combined the features characteristic of the thermograms of each component, but with a shift to lower temperatures as regards the peaks characteristic to nalidixic acid. The enthalpy change, cal/g, of the transitions of these mixtures was found to be quantitatively identical to the predicted values indicating no incompatibility under these conditions. Some change in peak's shape and height-to-width ratio was expected because of possible differences in the mixtures sample geometry[12,13].

The DSC thermogram of Di-Pac (Trace 2 of Figure 5) showed a melting endothermic peak followed by an exotherm before decomposition occurred. Trace 3 of Figure 5 is the thermogram of nalidixic acid-Di-Pac mixture which shows three transitions corresponding to the melting endotherm of Di-Pac, the melting endotherm of nalidixic acid and the Di-Pac exotherm respectively, but with the transition temperatures shifted to lower temperatures. The enthalpy change, cal/g, of the mixture transition corresponding to the Di-Pac endotherm, was found to be 82.50% of the predicted value, while that corresponding to nalidixic acid was found to be 81.86% of the predicted value indicating the possible incompatibility of Di-Pac with nalidixic acid

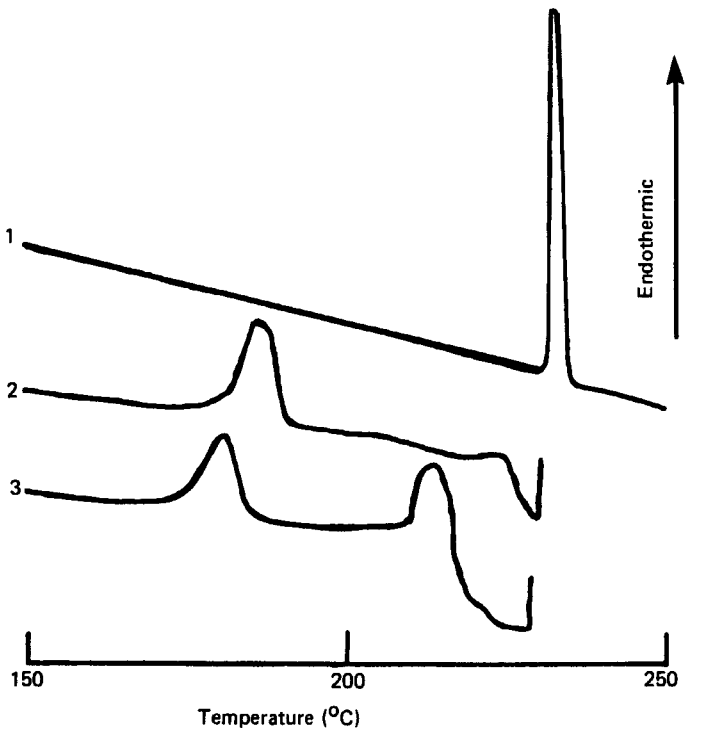

FIGURE 5

DSC thermograms of nalidixic acid (1), Di-Pac (2) and 1:1 nalidixic acid-Di-Pac mixture (3).

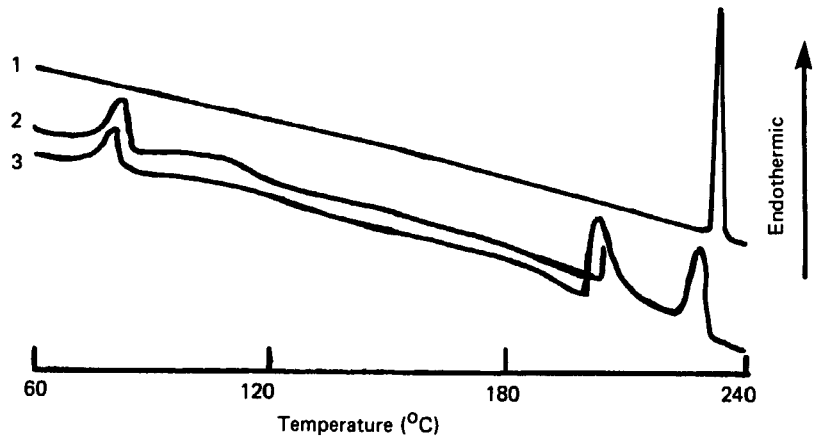

FIGURE 6

DSC thermograms of nalidixic acid (1), Emdex (2) and 1:1 nalidixic acid-Emdex mixture (3).

under the experimental conditions.

Trace 2 of Figure 6 is the thermogram of Emdex, which shows two endothermic peaks followed by decomposition at about 205°C. Trace 3 of Figure 6 is the thermogram of nalidixic acid-Emdex mixture. Four transitions were observed corresponding to the first peak of Emdex, the second peak of Emdex, the Emdex decomposition and the nalidixic acid peak respectively, but with the transition temperatures of the peak characteristic to nalidixic acid shifted to lower temperatures. The enthalpy change, cal/g, corresponding to the first peak of Emdex, the seconed peak of Emdex and the peak of nalidixic acid, was found to be 81.46, 86.31 and 84.71%, respectively, of the predicted values indicating the possible incompatibility of Emdex with nalidixic acid under the experimental conditions.

The DSC thermogram of dicalcium phosphate dihydrate (Trace 2 of Figure 7) showed a broadened transition corresponding to the loss of water of crystallization followed by a melting endothermic peak. Trace 3 of Figure 7 is the thermogram of nalidixic acid-dicalcium phosphate dihydrate mixture. Three transitions were observed corresponding to the loss of dicalcium phosphate dihydrate water of crystallization, the dicalcium phosphate dihydrate endotherm and the nalidixic acid peak respectively, but with the temperatures of transition of the peak characteristic to nalidixic acid shifted to higher temperatures. The enthalpy change, cal/g, of the mixture transition corresponding to the dicalcium phosphate dihydrate peak,was found

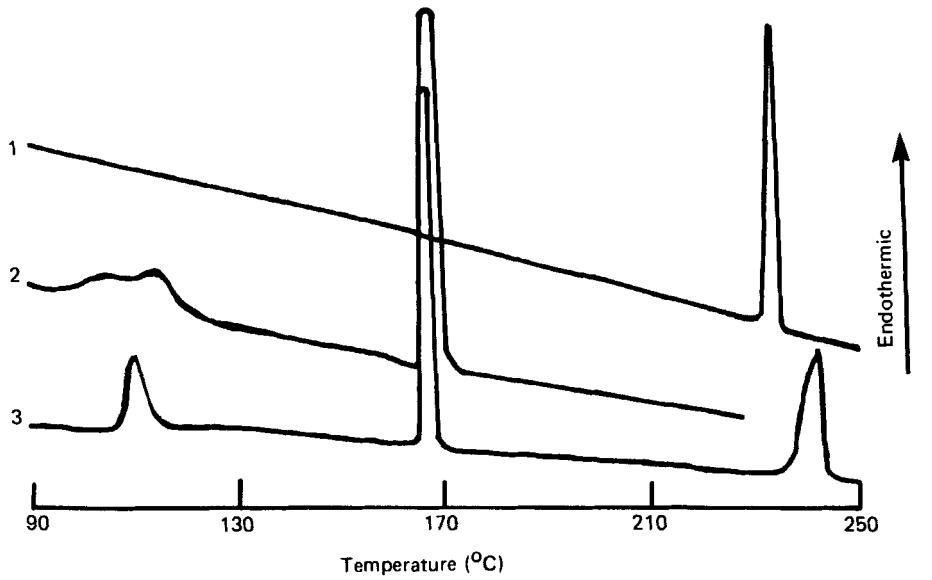

FIGURE 7

DSC thermograms of nalidixic acid (1), dicalcium phosphate dihydrate (2) and 1:1 nalidixic acid-dicalcium phosphate dihydrate mixture(3).

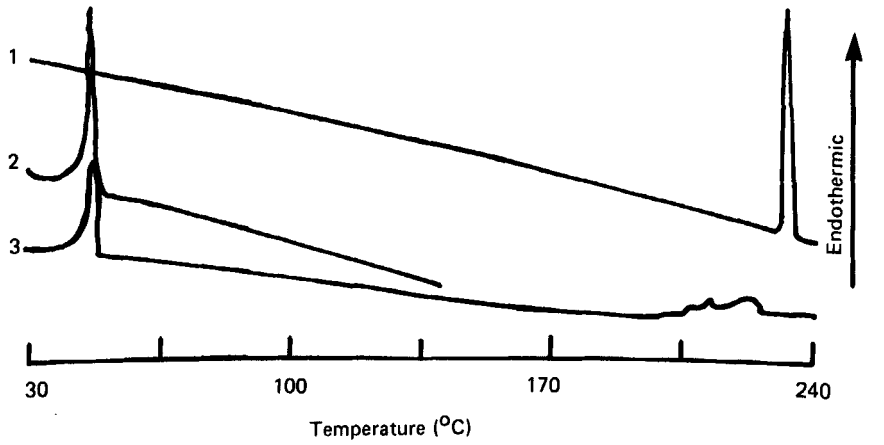

FIGURE 8

DSC thermograms of nalidixic acid,2 mg (1), stearic acid, 2 mg (2) and 1:1 nalidixic acid-stearic acid mixture, 2 mg (3).

to be 65.99% of the predicted value, while that corresponding to nalidixic acid was found to be 84.22% of the predicted value indicating the possible incompatibility of dicalcium phosphate dihydrate with nalidixic acid under the experimental conditions. This possible incompatibility was expected as the combination of an alkaline vehicle, such as dicalcium phosphate dihydrate, with an acidic active ingredient such as nalidixic acid is obviously contra-indicated[14].

Trace 3 of Figure 8 is the thermogram of nalidixic acid-stearic acid mixture which combined the features characteristic of the thermograms of each component, but with the peak characteristic to nalidixic acid broadened and shifted to lower temperatures. This change in nalidixic acid peak's characteristics which can be attributed to the possible differences in the mixture sample geometry[12,13], did not alter the enthalpy change, cal/g, of the mixture which was found to be quantitatively identical to the predicted value indicating the possible use of stearic acid as a lubricant in formulations containing nalidixic acid.

L-(-)-leucine exhibited no transition when scanned over the temperature range of 30 to 285°C; after that a sublimation endotherm begins[2]. Therefore, the DSC thermogram of nalidixic acid-leucine mixture will reflect the characteristic features of the thermograms of each component if no interaction occurred. This indeed the case as seen in Figure 9. The energy of transition, cal/g, was

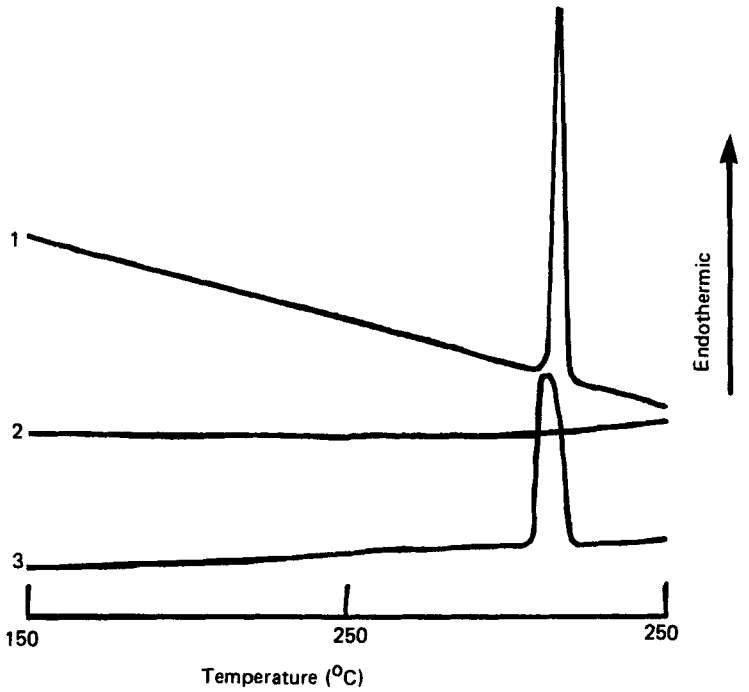

FIGURE 9

DSC thermograms of nalidixic acid (1),L-(-)-leucine (2) and 1:1 nalidixic acid-L-(-)-leucine mixture(3).

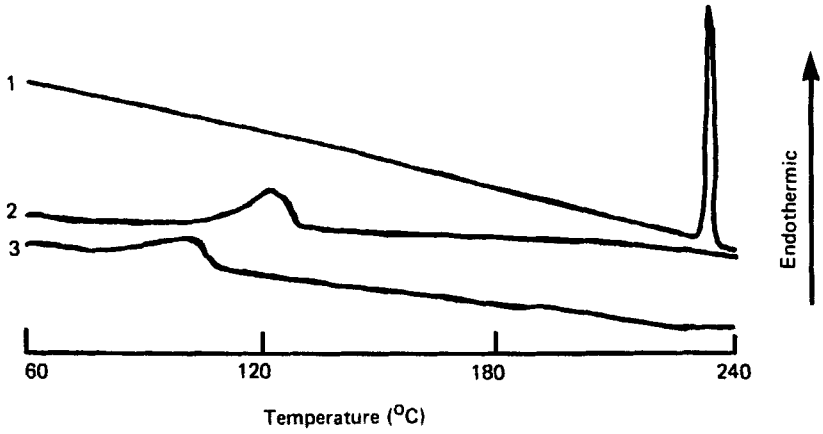

FIGURE 10

DSC thermograms of nalidixic acid (1), magnesium stearate (2) and 1:1 nalidixic acid-magnesium stearate mixture (3).

found to be 92.96% of the predicted value indicating the possible use of L-(-)-leucine as a lubricant in formulations containing nalidixic acid.

Trace 3 of Figure 10 is the thermogram of nalidixic acid-magnesium stearate mixture. A shift to lower temperatures did occur for the peak characteristic to magnesium stearate while the endothermic peak characteristic to nalidixic acid has been obliterated. This marked change in the thermal behavior of the mixture indicated the possible incompatibility of magnesium stearate with nalidixic acid under the experimental conditions.

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