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ERYTHROMYCIN-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 erythromycin with some of the direct compression excipients. Erythromycin was found to be compatible with Avicel PH 101, Avicel PH 105, Elcema F 150, Elcema G 250, Solka-floc BW 100, Sta-Rx 1500, Cab-O-Sil, Brownex sugar, Di-Pac, sorbitol, mannitol and granular mannitol, while incompatible with Emdex, dicalcium phosphate dihydrate, Di-Tab and Emcompress. It appears that L-(-)-leucine can be used as lubricant in formulations containing erythromycin while stearic acid and magnesium stearate cannot.

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INTRODUCTION

The authors previously used differential scanning calorimetry (DSC) as a screening technique for assessing the compatibility of aspartame[1] and cephalexin[2] with some of the direct compression excipients. El-Shattawy[3] also used DSC in preformulation stability studies on anhydrous ampicillin. The compatibilities of anhydrous ampicillin, ampicillin trihydrate and cephalexin with anhydrous dextrose and with aspartame were also investigated by the present authors[4-6].

Grant[7] reported that a precipitate was formed when erythromycin was mixed with chloramphenicol, oxytetracycline Hcl or tetracycline Hcl in 5% dextrose solution. El-Nakeeb and Yousef[8] found that erthromycin was very much less active against Staphylococcus aureus in the presence of magnesium trisilicate, sodium alginate, pectin and bentonite and less active with calamine, Aerosil, methylcellulose, carboxymethylcellulose sodium and polysorbate 80.

In this study, the authors investigated the compatibility of erythromycin with some of the direct compression excipients. This was achieved by comparing the DSC thermograms of erythromycin and each of the investigated excipients with 1:1 mixtures of erythromycin 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[9].

EXPERIMENTAL

Materials

The following materials were used: erythromycin (Sigma), Avicel PH 101 and Avicel PH 105 (FMC), Elcema F 150 and Elcema G 250 (De-

qussa), Solka-floc BW 100, Emdex and Emcompress (E. Mendell), Sta-Rx 1500 (Staley), Cab-O-Sil (Cabot), Brownex sugar and Di-Pac (Amstar), sorbital (Pfizer), mannitol and granular mannitol (ICI Americas), dicalcium phosphate dihydrate (Baker), Di-Tab (Stauffer Chemical), L-(-)-leucine (Eastman Kodak), stearic acid (Ruger Chemical) and magnesium stearate (Mallinckrodt).

Differential Scanning Calorimetry

Samples (2-8 mg) were weighed after being finely powdered and encapsulated in flat-bottomed aluminum pans with crimped-on lids. Volatile sample pans with tightly sealed lids were used for those samples containing L-(-)-leucine. 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^{o}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 erythromycin and excipients, prepared with mortar and pestel were heated over the temperature range, 30 to 300^{o}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 thermograms of erythromycin (Trace 1 of Figures 1-8) exhibit no transition when scanned over the temperature range of 30 to about 167^{o}C. At about 167^{o}C, erythromycin decomposed. Avicel PH 101, Avicel PH 105, Elcema F 150, Elcema G 250, Solka-floc BW 100, Sta-Rx 1500 and Cab-O-Sil exhibit no transition when scanned individ-

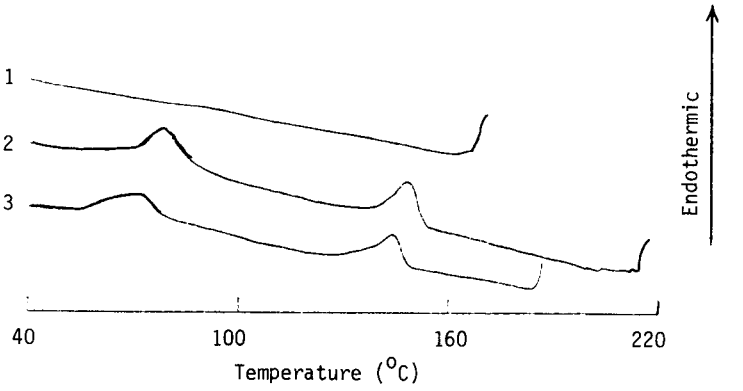

FIGURE 1

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

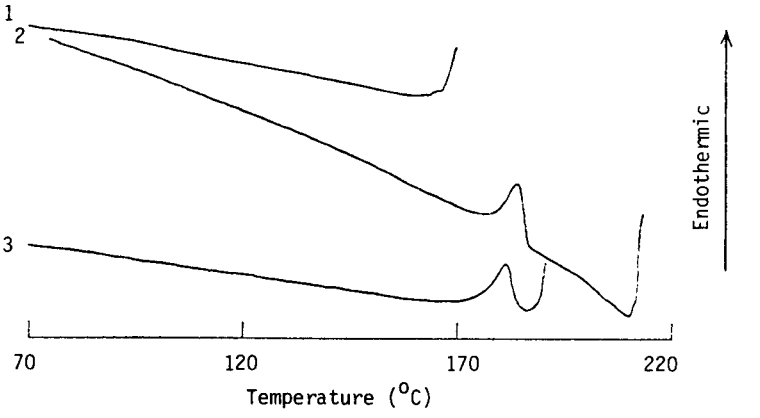

FIGURE 2

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

ually over the temperature range of 30 to 300°C. Therefore, DSC thermograms of mixtures of the excipients with erythromycin will reflect the characteristic features of the thermograms of each component if no interaction occurred. This is indeed the case as the resulting DSC thermograms showed no transition or even decomposition over the

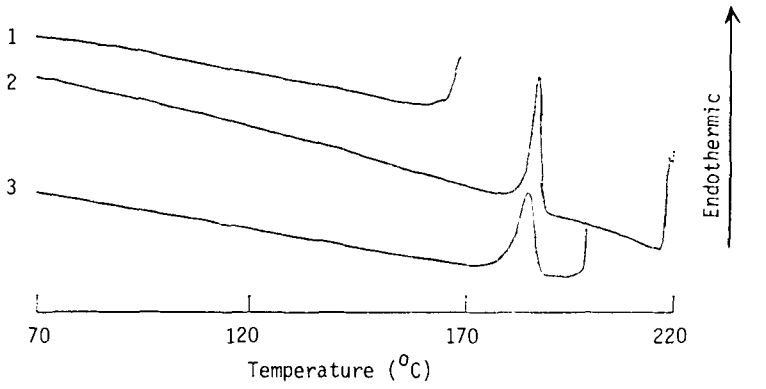

FIGURE 3
DSC thermograms of erythromycin (1), Di-Pac (2) and 1:1 erythromycin-Di-Pac mixture (3).

temperature range of 30 to 300°C, except with Sta-Rx 1500 where a decomposition was traced at 277°C. While this delay in erythromycin decomposition may be attributed to the presence of these excipients, the decomposition with Sta-Rx 1500 at 277°C may be due to the moisture content of starch[1]. The compatibility of erythromycin with starch is in agreement with the El-Nakeeb and Yousef[8] investigation.

The DSC thermogram of the erythromycin-Emdex mixture (Trace 3 of Figure 1) showed the same two endothermic peaks corresponding to Emdex (Trace 2 of Figure 1) with the transition temperature range and the maximum peak of transition shifted to lower temperatures. The enthalpy change, cal/g, of the first peak was found to be 68.46% of the predicted value calculated from the exact percentage contribution of Emdex to the total enthalpy change of the mixture first peak, while that of the second peak was found to be 82.8% of the predicted value indicating the possible incompatibility of Emdex with erythromycin under the experimental conditions.

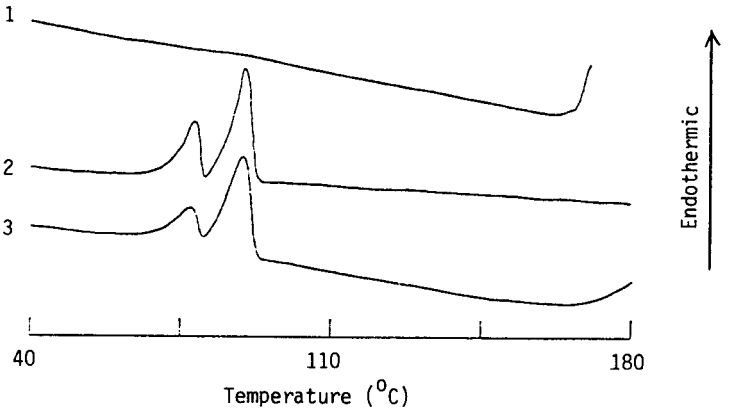

FIGURE 4

DSC thermograms of erythromycin (1), sorbitol (2) and 1:1 erythromycin-sorbital mixture (3).

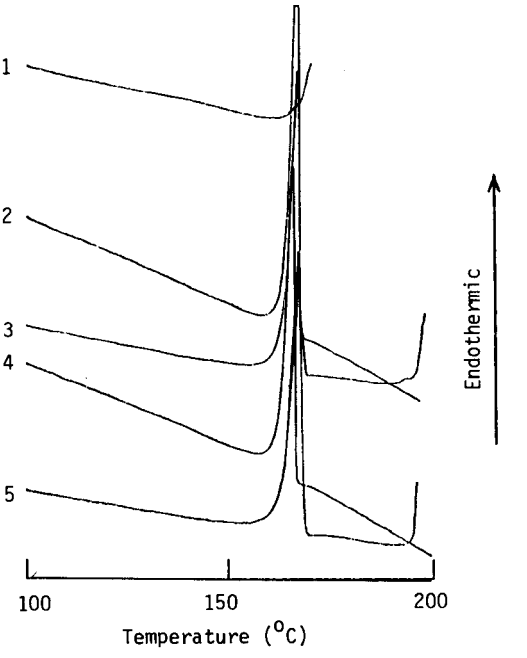

FIGURE 5

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

The DSC thermogram of erythromycin-Brownex sugar mixture (Trace 3 of Figure 2) showed an endothermic peak corresponding to the melting transition of Brownex sugar (Trace 2 of Figure 2) followed by the mixture decomposition. The enthalpy change, cal/g, of the mixture transition was found to be 91.02% of the predicted value calculated from the exact percentage contribution of Brownex sugar to the total enthalpy change of the mixture indicating no incompatibility of Brownex sugar with erythromycin under these conditions.

Trace 3 of Figure 3 is the thermogram of erythromycin-Di-Pac mixture which shows an endothermic peak corresponding to the melting transition of Di-Pac (Trace 2 of Figure 3) with some change in peak's height-to-width ratio. This change in peak's height-to-width ratio which can be attributed to the possible differences in the mixture sample geometry[10], did not alter the enthalpy change, cal/g, of the mixture which was found to be quantitatively identical to the predicted value indicating no incompatibility under these conditions.

The thermograms of the erythromycin-sorbitol mixture (Trace 3 of Figure 4), erythromycin-mannitol mixture (Trace 3 of Figure 5) and erythromycin-granular mannitol mixture (Trace 5 of Figure 5) combined the features characteristic of the thermograms of each component. 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.

The DSC thermogram of dicalcium phosphate dihydrate (Trace 2 of Figure 6) showed a broadened transiton corresponding to the loss of water of crystallization followed by a melting endothermic peak with a transition temperature range from 172-202^{o}C and with a maximum peak of transition at 191^{o}C. No decomposition of dicalcium

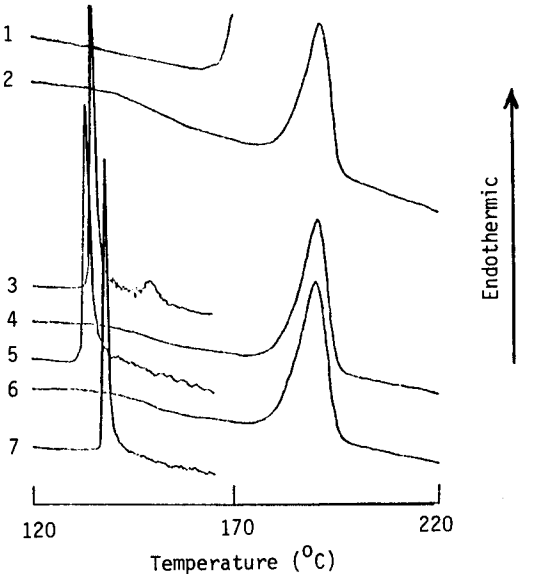

FIGURE 6

DSC thermograms of erythromycin (1), dicalcium phosphate dihydrate (2), 1:1 erythromycin-dicalcium phosphate dihydrate mixture (3), Di-Tab (4), 1:1 erythromycin-Di-Tab mixture (5), Emcompress (6) and 1:1 erythromycin-Emcompress mixture (7).

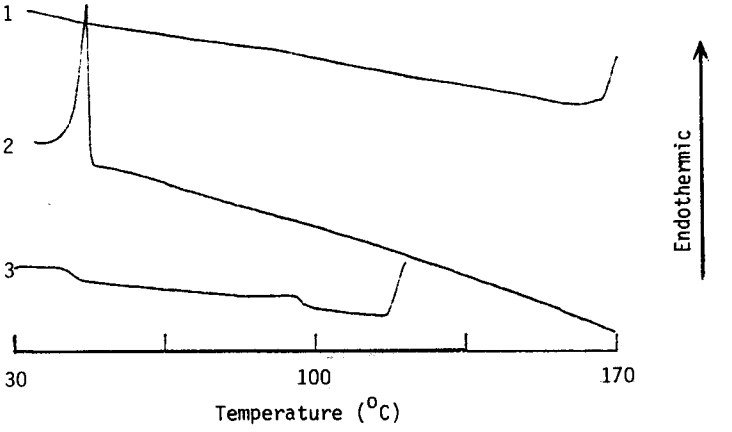

FIGURE 7

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

phosphate dihydrate was traced on scanning until 300°C. Trace 3 of Figure 6 is the thermogram of erythromycin-dicalcium phosphate dihydrate mixture which shows a sharp peak with a maximum peak of transition at 135°C. Before the down curve of this peak returned to the program line, decomposition occurred at about 137°C. This marked change in the thermal behavior of the mixture and its decomposition at markedly lower temperature than those of the pure respective original components indicated the possible incompatibility of dicalcium phosphate dihydrate with erythromycin under the experimental conditions. The thermal behavior of Di-Tab and Emcompress alone and in physical mixtures with erythromycin was found to be more or less the same as with dicalcium phosphate dihydrate, being chemically the same, and is illustrated in Figure 6 (Traces 4-7).

L-(-)-leucine exhibited no transition when scanned over the temperature range of 30 to 285°C; after that a sublimation endotherm begins. Therefore, the DSC thermogram of erythromycin-leucine mixture will reflect the characteristic features of the thermograms of each component if no interaction occurred. This is indeed the case as the DSC thermogram of the mixture showed no transition over the temperature range of 30 to about 240°C; after that decomposition occurred.

Trace 3 of Figure 7 is the thermogram of erythromycin-stearic acid mixture. The endotherm characteristic of stearic acid (Trace 2 of Figure 7) has been obliterated and a rapid decomposition at about 117°C occurred, i. e., the decomposition occurred at a temperature markedly lower than those of the pure respective original components. This change in the thermal behavior of the mixture was expected as erythromycin readily forms salts with inorganic and

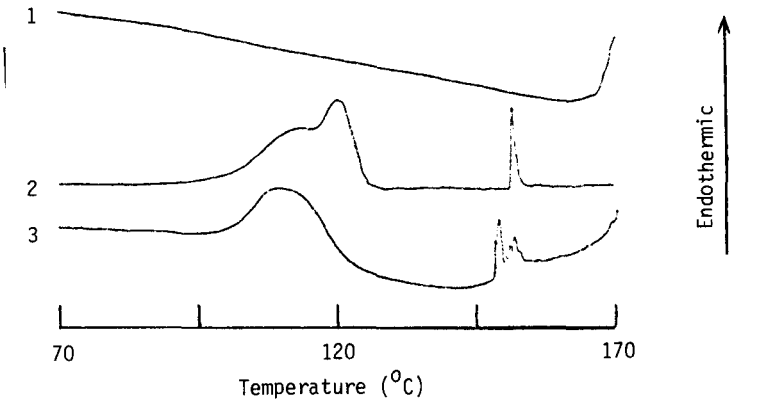

FIGURE 8

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

organic acids, and also forms esters[11]. While erythromycin stearate releases active erythromycin in the duodenum[11], the possible interaction of stearic acid with erythromycin during tableting or storage must be guarded against to avoid the effect of water released from the interaction.

Trace 3 of Figure 8 is the thermogram of erythromycin-magensium stearate mixture which shows rapid decomposition occurred at about 150°C, immediately after the second endotherm of magnesium stearate. The enthalpy change, cal/g, of the mixture was found to be 66.06% of the predicted value indicating the possible incompatibility of magnesium stearate with erythromycin under the experimental conditions.

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