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COMPATIBILITY PROBLEMS OF CHLORPROMAZINE HCl-STEARATE LUBRICANTS EXAMINED BY DIFFERENTIAL SCANNING CALORIMETRY

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Differential scanning calorimetry (DSC) was used to investigate the interactions between chlorpromazine HCl (CPZ) and stearate lubricants. The phase diagram was constructed for each CPZ-stearate system. An unknown endothermic peak at 145°C was found for the CPZ-stearate lubricants; this was affected by the grinding and heating processes. This unknown endothermic peak proved to relate to a polymorphism transition but was not an incompatibility problem. Three polymorphisms of CPZ were also determined by DSC analysis and IR spectrophotometry.

It is well known that drug-excipient interactions can exert significant influences on the physico-chemical properties, manufacture and bioavailability of a solid dosage form [1-3]. Drug-excipient compatibility testing is a practically reliable preformulation tool to select appropriate excipients for each dosage form design. Thermal methods such as differential thermal analysis (DTA) or differential scanning calorimetry (DSC) are well-developed techniques for the detection of incompatibility in drug-excipient mixture [4-6]. Since the thermal analysis used is relatively fast, easily interpreted, accurately predictive, and requires only a few test samples, it has been suggested in many studies for the routine screening of potential drug-excipient interactions in preformulation stability testing [7-10].

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Although thermal methods can not replace the classical stability program involving long-time observation, it can provide an early alert to compatibility problems and indicate the most favorable directions for the obtaining of a successful formulation. We have used DSC analysis to examine the interactions of drugs and cyclodextrins before and after grinding, freeze-drying and spray-drying processes [11-14].

Stearate lubricants are often employed to decrease the frictional forces during tablet processing. These lubricants have been shown to be incompatible with some drugs such as ibuprofen, asparatme, sodium dicloxacillin, penicillin G, ampicillin, erythromycin and cephalexin [7, 10, 15-19], due to the changes in the DSC thermograms. In our preformulation study, an unknown DSC endothermic peak was found at 145° for the physical mixture of chlorpromazine HCl (CPZ) and magnesium stearate. Thus, in the present study, we determine whether this unknown peak is related to incompatibility or to other reasons, and also examine the compatibility of the physical mixture of CPZ with a variety of stearate lubricants.

Experimental

Materials

Chlorpromazine HCl (CPZ) was purchased from Merck (Darmstadt, West Germany). Magnesium stearate, calcium stearate, aluminium stearate and stearic acid, all of reagent grade, were purchased from Nakarai Chem. Ltd. (Kyoto, Japan). All other chemicals were of reagent grade.

Preparation of physical mixtures of CPZ and stearate lubricants

CPZ and one of the aforementioned stearate lubricants were weighed out and then mixed well for 5 min with a mixer. The weight ratio was 1:0, 5:1, 2:1, 1:1, 1:2, 1:5 or 0:1. A certain amount of the mixed powders was transferred to a sample pan for DSC use.

Examination of test samples by thermal analysis and IR spectrophotometry

A differential scanning calorimeter (DSC-1090, DuPont, USA) was used to study all the test samples. The heating rate was 10 deg/min, with an open pan system in a N_2 gas flow. The instrument was calibrated with indium. The temperature and the corresponding heat flux data were stored on a floppy disk via the DSC data system.

A thermal gravimetric (TG) analysis was also carried out to study the dehydration of some samples. A sample was accurately weighed in a platinum cup. The weight loss due to dehydration was measured at a heating rate of 10 deg/min from ambient temperature up to 330°.

An IR spectrophotometer (IR-700, Jasco, Japan) was used to record the spectra of the polymorphs.

Results and discussion

The DSC curves of the pure CPZ and the physical mixture of CPZ with each stearate lubricant are shown in Fig. 1. The sample pans were not sealed because uncriped pans might give better melting peaks and baselines. Trace 1 corresponds to the thermogram of pure CPZ. Four endothermic peaks were observed for pure CPZ, at around 70°, 150°, 196° and 260°. The peak at 196° represented the melting endotherm, while that at 260° showed the thermal decomposition. The endothermic peaks at 70° and 150° will be discussed later. Trace 7 shows the thermograms of the pure lubricants: Fig. 1-A: magnesium stearate; Fig. 1-B: calcium stearate; Fig. 1-C: aluminum stearate; and Fig. 1-D: stearic acid. The endothermic peak at 196° was shifted to low temperature when CPZ was mixed with one of the stearate lubricants in increasing concentration, whereas the aluminum stearate system exhibited almost no change in peak position. Beyond a mixing ratio of 1:1, the stearic acid system did not show any endothermic peak above 120°, but its original endothermic peak at 75° still existed (Fig. 1-D). In the magnesium stearate system, however, an unknown endothermic peak appeared at 145° and was enlarged with increase of the magnesium stearate concentration (Fig. 1-A). The mean heat of melting ($n = 3$) for this peak increased from 2.3 J/g to 18.5 J/g with increasing amount of magnesium stearate. This unknown peak at 145° also appeared in the calcium stearate system, it was very small. The unknown endothermic peak at 145° may be due to a molecular interaction caused by incompatibility, a polymorphism transition or some other reason.

The phase diagrams of CPZ-stearate systems in which the temperature change at 196° is plotted *vs.* the weight fraction of the stearates, are shown in Fig. 2. The thaw point curve and peak temperature curve ran in parallel and downward with increase of the stearate concentration, with the exception of the stearic acid system. In other words, there seemed to be no interaction between CPZ and one of the stearate lubricants. Figure 3 depicts the DSC and TG curves of CPZ, magnesium stearate and their physical mix-

ture. From the TG curves, the endothermic peak at 70o for CPZ seemed to be related to the adsorbed free water since it lost weight on heating. The unchanged weight at 150° for CPZ implies that the endothermic peak at 150°

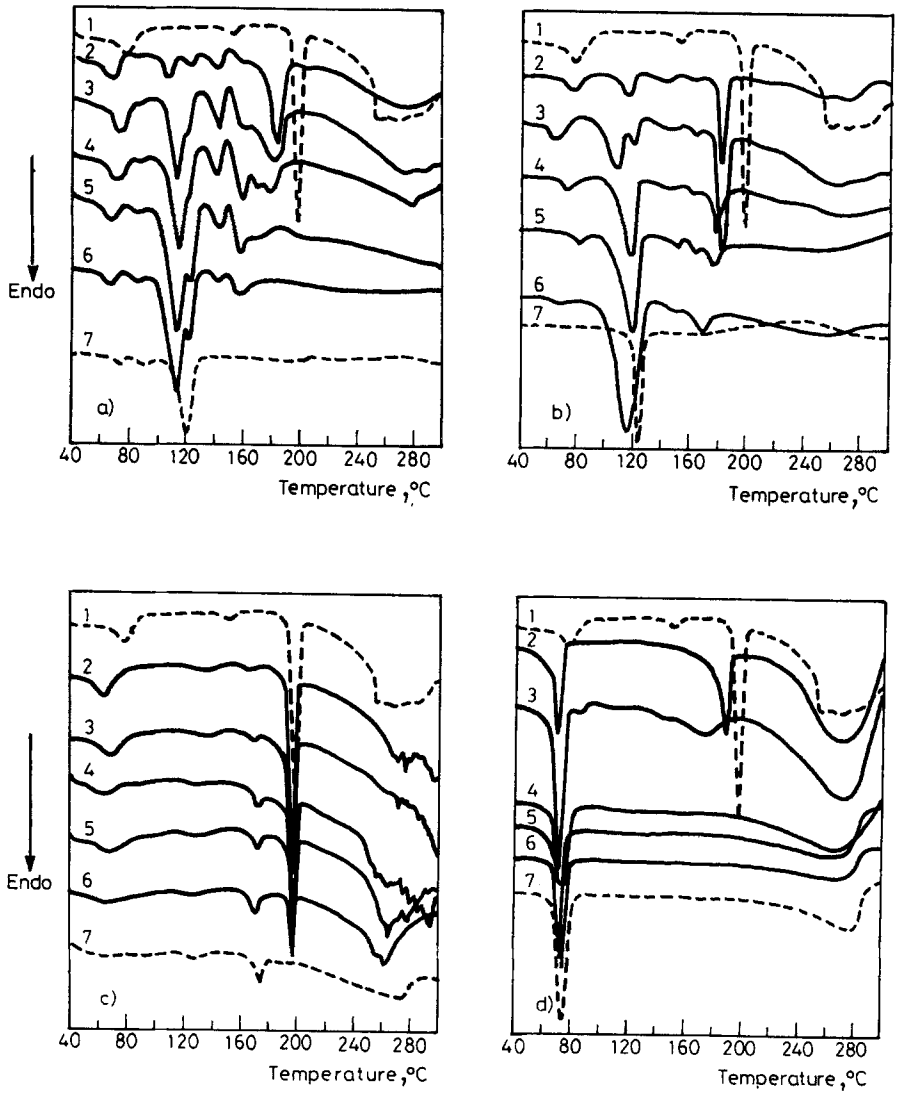


Fig. 1 DSC thermograms of chlorpromazine HCl and its physical mixtures with four stearate lubricants. Key: (a) magnesium stearate; (b) calcium stearate; (c) aluminium stearate; (d) stearic acid Traces 1 to 7 are 1:0, 5:1, 2:1, 1:1, 1::2, 1:5, 0:1 for drug: lubricant

might be connected with polymorphism. The unknown peak at 145° for the mixture was not associated with a weight loss, which implies that it is independent of the adsorbed free water, solvate or hydrate. This endothermic peak might be related to polymorphism or a molecular interaction.

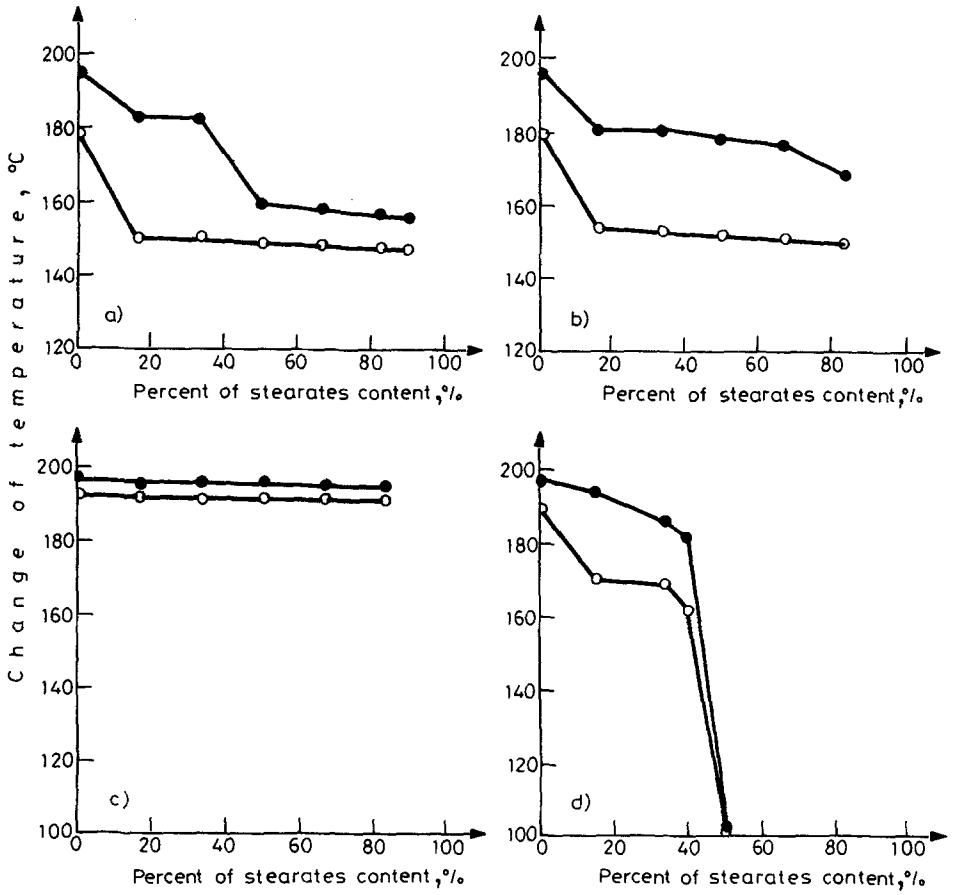


Fig. 2 Phase diagram of chlorpromazine HCl-stearate lubricant system. Key: see Fig. 1. Full point: peak temperature curve Empty point: thaw point curve

In this study, grinding and heating processes were used to examine the unknown peak at 145°, because both are supposed to be able to improve the inclusion complex formation between acetaminophem and β-cyclodextrin [20-21]. Figure 4 shows the effect of grinding on the DSC curves of CPZ and the CPZ-magnesium stearate mixture. The endothermic peak at 150° for

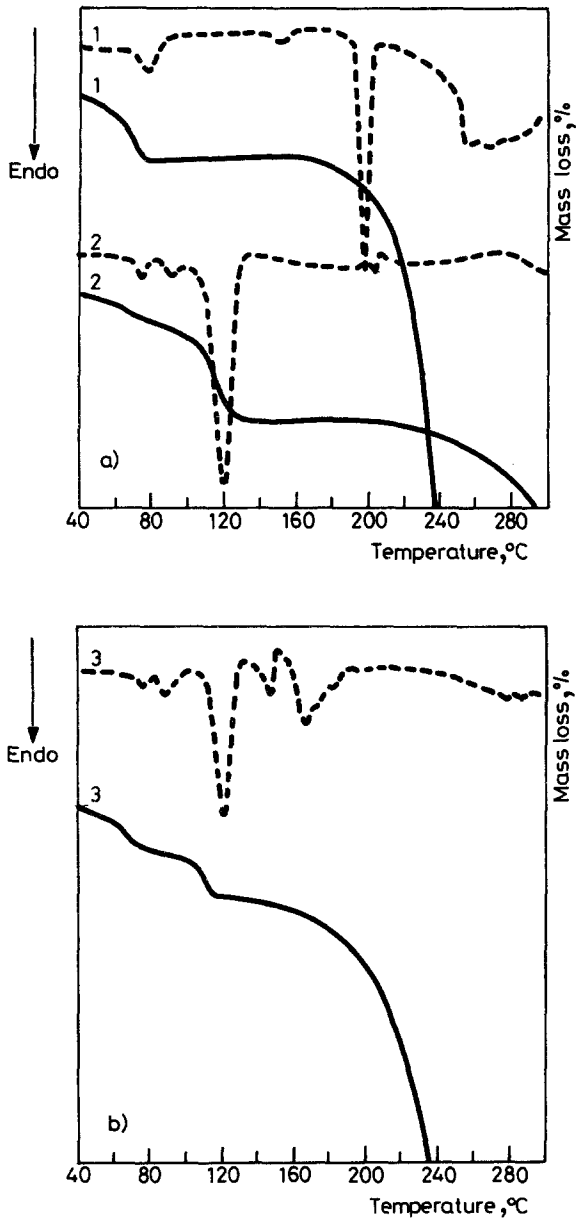


Fig. 3 DSC thermograms and TG curves of chlorpromazine HCl, magnesium stearate and their physical mixture. Key: Tracer 1; chlorpromazine HCl Tracer 2; magnesium strearate Tracer 3; physical mixture

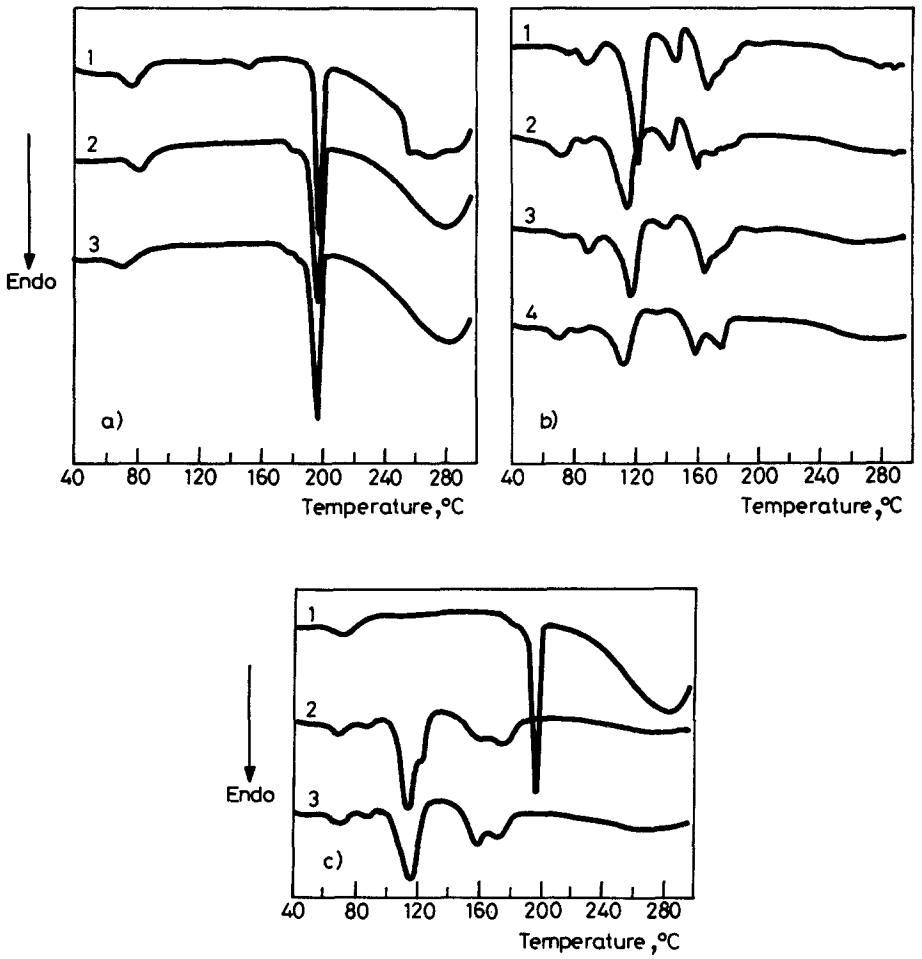


Fig. 4 Grinding effect on the DSC curves of chlorpromazine HCl and chlorpromazine HCl-magnesium stearate mixture. Key: (a) chlorpromazine HCl Tracer 1: original Tracers 2 and 3: grinding for 2 min and 5 min; (b) physical mixture Tracer 1: original Tracers 2 to 4: grinding for 2, 10, 20 min; (c) physical mixture Tracer 1: chlorpromazine grinding for 10 min Tracer 2: mixture of (sample of tracer 1+magnesium strearate) Tracer 3: mixture of (sample of tracer 1+magnesium strearate) grinding for 10 min

CPZ disappeared when CPZ was ground for 2 min or 5 min (Fig. 4-A). Likewise, the unknown peak at 145° for the mixture decreased and gradually disappeared with increase of the grinding time (Fig. 4-B). The physical mixture of ground CPZ and magnesium stearate exhibited the same DSC curve as the ground physical mixture of CPZ and magnesium stearate did after

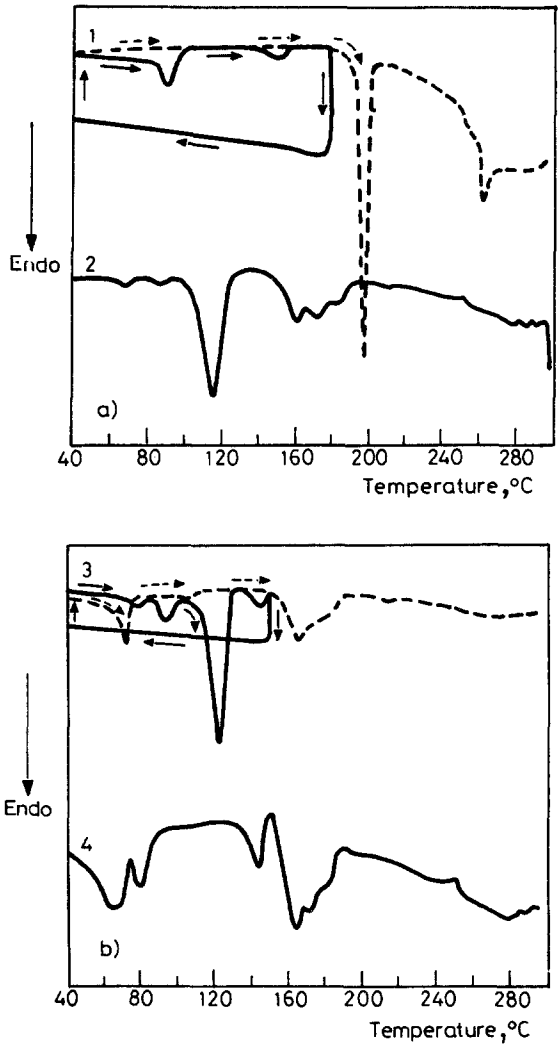


Fig. 5 Heating effect on the DSC curves of chlorpromazine HCl and chlorpromazine HCl-magnesium strearate mixture Key: Tracer 1: chlorpromazine HCl Tracer 2: mixture of chlorpromazine HCl and preheated magnesium strearate Tracer 3: physical mixture Tracer 4: mixture of 180°C preheated chlorpromazine HCl and magnesium strearate

grinding for 10 min (Fig. 4-C), but no unknown peak appeared at 145°. Apparently, the unknown peak at 145° is related to the polymorphism transition, which was not caused by the interaction of CPZ and magnesium stearate.

When CPZ was first heated to 180°, cooled to 40° and again heated to 300°, the DSC curve was simplified as shown in Fig. 5. The peaks at 70° and 150° for CPZ both disappeared, but the peaks at 196° and 260° remained (Trace 1 in Fig. 5-A). The unknown peak at 145° for the mixture also disappeared when CPZ was preheated to 180° (Trace 2). This was confirmed by the 150°-preheated physical mixture of CPZ and magnesium stearate, as shown in Trace 3 in Fig. 5-B. However, the unknown peak at 145° still existed for the physical mixture of CPZ and 150°-preheated magnesium stearate (Trace 4). These results demonstrate that the unknown peak was also influenced by the heating process, suggesting that the unknown peak at 145° for the physical mixture of CPZ and magnesium stearate was significantly correlated with the temperature shift from 150° to 145° by the polymorphism transition in the presence of magnesium stearate. No interaction occurred.

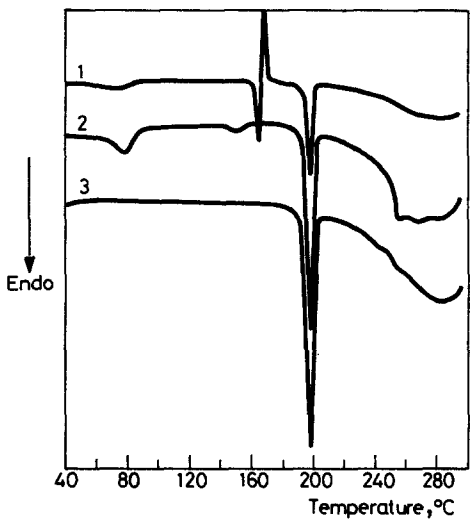
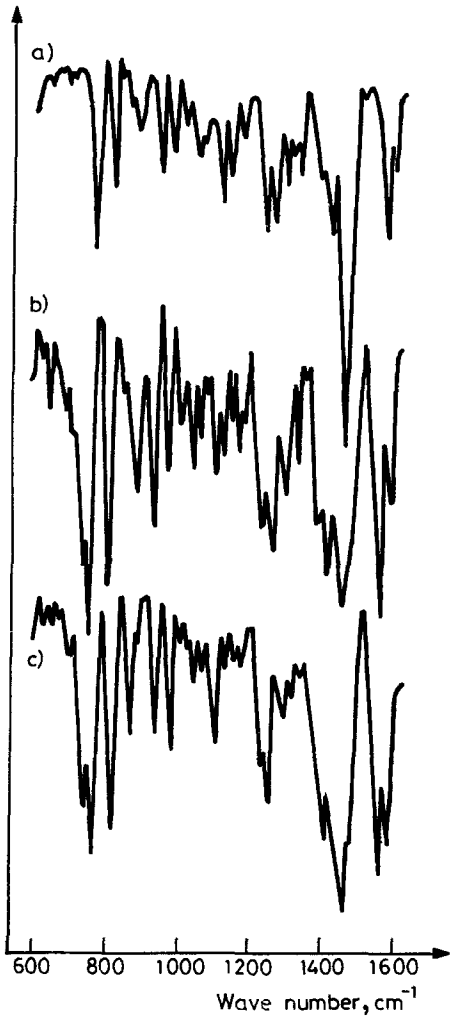


Fig. 6 DSC thermograms of three polymorphs of chlorpromazine HCl Key: Tracer 1: polymorph I Tracer 2: polymorph II Tracer 3: polymorph III

The existence of polymorphism for CPZ has been suggested [22], but is not clear. We used methanol-chloroform (1:1), benzene-ethanol (1:1) and chloroform to recrystallize the CPZ, and obtained three polymorphs: polymorph I, II and III, respectively, as indicated by the DSC curves and IR spectra (Figs 6 and 7). Two metastable (polymorph I and II) and one stable



(a) 1594 cm^{-1}	(b) 1592 cm^{-1}	(c) 1592 cm^{-1}
1568	1566	1566
1458	1456	1458
1412	1410	1408
1386	1380	-
-	-	1338
1328	1328	-
-	1306	-
1284	1284	1284
1252	1250	1246
1230	1230	-
-	-	1170
1162	1162	-
-	1142	1142
1128	1126	1126
1104	1100	1096
-	-	1054
1040	1036	1036
1006	1006	1010
-	990	990
966	966	968
934	930	926
878	872	-
854	-	850
804	804	802
752	750	748
734	732	730
678	678	678
-	632	628
586	584	584
-	544	550
-	514	518
484	482	482
446	448	448

Fig. 7 IR sprectra of three polymorphs of chlorpromazine HCl Key: Tracer a: polymorph I Tracer b: polymorph II Tracer c: polymorph III

(polymorph III) polymorphs were found. The CPZ used in this study was in a metastable form (polymorph II), which allowed the unknown peak at 145° to occur when magnesium stearate was also present. The DSC curves of the physical mixtures of each polymorph with magnesium stearate are shown in

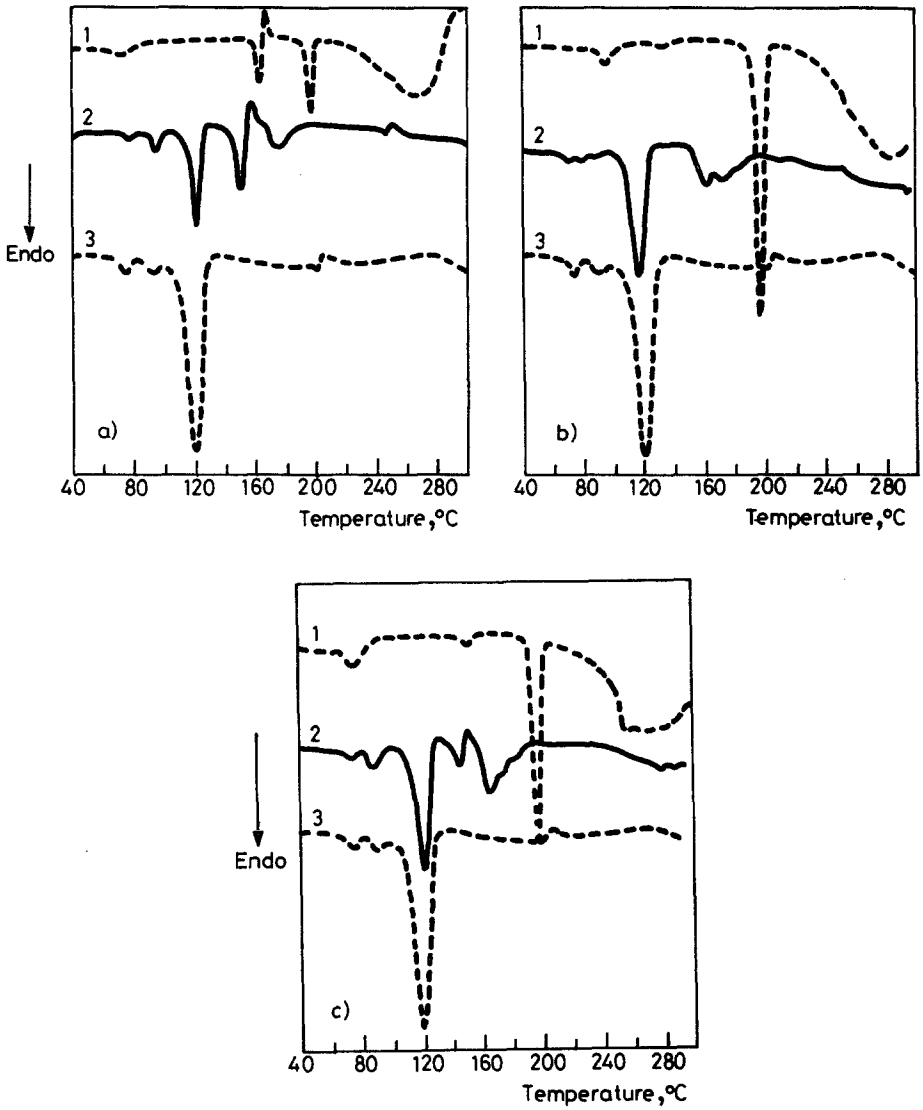


Fig.8 DSC thermograms of each polymorph of chlorpromazine HCl, magnesium stearate and their physical mixture Key: (a) polymorph I-magnesium stearate system; (b) polymorph II-magnesium stearate system; (c) polymorph III-magnesium stearate system Tracer 1: each polymorph Tracer 2: physical mixture Tracer 3:magnesium stearate

Fig. 8. The unknown endothermic peak at 145° appeared for the physical mixture of metastable CPZ and magnesium stearate, but was not found for the stable CPZ-magnesium stearate mixture.

To summarize, an unknown endothermic peak observed in DSC curves in preformulation studies must be considered carefully to determine whether it is related to incompatibility or polymorphism transition.

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Zusammenfassung — Mittels DSC wurden die Wechselwirkungen zwischen ChlorpromazinHCl (CPZ) und Stearatgleitmitteln untersucht. Für jedes CPZ-Stearat-System wurde das Phasendiagramm erstellt. Bei CPZ-Stearatgleitmitteln ergab sich bei 145°C ein unbekannter endothermer Peak, der durch Zerkleinerungs- und Erhitzungsprozesse beeinflußt wurde. Dieser unbekannte endotherme Peak scheint einer polymorphen Umwandlung zu entsprechen, stellte jedoch kein Inkompatibilitätsproblem dar. Weiterhin wurden mittels DSC und IR-Spektroskopie drei Polymorphien von CPZ festgestellt.