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RESEARCH PAPER

Thermal Analysis as a Screening Technique in Preformulation Studies of Picotamide Solid Dosage Forms

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ABSTRACT

The potential compatibilities of several commonly used pharmaceutical excipients with picotamide were evaluated using differential scanning calorimetry (DSC). The effects of aging and of mechanical treatment (blending, grinding, or kneading) of samples were also evaluated. Hot-stage microscopy (HSM) and scanning electron microscopy (SEM) were used as complementary techniques to implement and assist in interpretation of the DSC results. DSC analysis evidenced a noticeable modification of drug thermal features in the mixtures with palmitic acid, stearic acid, stearyl alcohol, polyethylene glycol (PEG) 20,000, and sorbitol, but HSM analysis showed that the DSC behavior was mainly because of the drug dissolution in the melted excipient, which allowed the presence of important solid–solid interactions to be excluded. Compatibility with Mg stearate was also found, even if sample manipulation induced the partial conversion of Mg stearate in a pseudo-polymorphic modification. Mechanical stress displayed an increased hygroscopicity of mixtures with glucose and lactose, as well as some solid–solid interactions with lactose and mannitol.

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INTRODUCTION

During the formulation of new products or the reformulation of existing products, it is advantageous to have readily available knowledge of any physical and chemical interactions between drugs and excipients which might give rise to changes in the chemical nature, stability, solubility, absorption, and therapeutic response of drugs. Differential scanning calorimetry (DSC) has been increasingly in use for quick evaluation of the possible incompatibility between the formulation components through the comparison of thermal curves of pure substances with the curve obtained from a 1:1 mixture (1–4): If the mixture curve is the superimposition of that of single components, there is no interaction and therefore no physicochemical incompatibility between drug and excipient. Problems with interpretation arise when there are differences in these curves, since this effect is not necessarily indicative of pharmaceutical incompatibility (5–8) and other analytical techniques can be necessary to substantiate DSC findings (9,10).

In the present work DSC was used to assess the compatibility of picotamide (*N,N'*-bis(3-picolyl)-4-methoxyisophtalamide), a fibrinolytic and platelet antiaggregant drug, with a number of common pharmaceutical excipients. To examine the influence of mechanical stress on the physicochemical stability of the drug, 1:1 w/w combinations of picotamide and each examined excipient were prepared in three different ways: by simple blending with a spatula, by grinding with a pestle in a mortar, and by kneading with ethanol and grinding until solvent evaporation. The effect of 3 weeks of aging at 60°C was also investigated. The 50% (by weight) ratio was initially selected to maximize the probability of observing any drug–excipient interaction. A wider range of compositions was, however, explored for those binary systems in which important modifications in the thermal behavior were detected by DSC analysis, in order to further investigate the nature of the interaction. Scanning electron microscopy (SEM) and hot-stage microscopy (HSM) were used as complementary techniques to assist in the interpretation of DSC behavior.

MATERIALS

Commercially available picotamide (PICO) was used after recrystallization from water–ethanol (8:1 v/v). The following excipients were examined: polyethylene glycol (PEG) 20,000. (Merck-Schuchardt, Munchen, Germany); palmitic acid, stearic acid, stearyl alcohol (Fluka AG, Buchs, Switzerland); and lactose, mannitol, glucose, sorbitol, and Mg stearate (Carlo Erba, Milano, Italy).

METHODS

Sample Preparation

Physical mixtures (300 mg) were prepared by gently mixing with a spatula equal weights of PICO and each of the afore-mentioned excipients, both previously sieved (75–150 μm). The blends were considered uniform when the DSC traces obtained from three separate samples taken from the same mixture were superimposable within the limit of experimental error. Coground mixtures were obtained by grinding a portion (100 mg) of each physical mixture with a pestle for approximately 10 min. Kneaded mixtures were prepared by slurrying a portion (100 mg) of each physical mixture with the minimum amount of ethanol and grinding thoroughly for about 7–10 min to obtain a paste which was dried at room temperature under vacuum up to a constant weight; the solid was sieved and the 75–150 μm sieve granulometric fraction was collected. The effect of sample storage for 3 weeks at 60°C was also evaluated.

DSC

Weighed samples (5–10 mg, Mettler M3 Microbalance, Schwerzenbach, Switzerland) of the individual components or drug–excipient combinations (75–150 μm sieve granulometric fraction) were scanned in Al pans pierced with a perforated lid at 10 K min^{-1} in the 30–200°C temperature range under static air, using a Mettler TA4000 apparatus equipped with a DSC 25 cell.

HSM

HSM assays were performed using an Olympus BH-2 microscope fitted with a Mettler FP-82 hot stage. A small amount of sample was placed on the sample stage and heated in the 30–200°C temperature range at a rate of 1–5 K min^{-1}.

SEM

SEM analysis was carried out using a Philips (The Netherlands) XL-30 scanning electron microscope. Prior to examination, samples were gold sputter-coated to render them electrically conductive.

RESULTS AND DISCUSSION

Figures 1, 5, and 6 illustrate selected thermograms of the various systems investigated. The DSC thermal curve of PICO (trace I of these figures) showed a single sharp endothermic peak at its melting point. At a scan rate of 10 K min^{-1}, the observed peak temperature was 135.3 ± 0.2°C and the apparent heat of fusion was 75.6 ± 2.5 J/g (the values are the mean of five separate determinations). Trace 2 of the figures indicates the DSC thermograms of different excipients. Traces 3, 4, and 5 are the thermal curves of 1:1 w/w physical mixture, coground mixture, and kneaded product of PICO with each excipient. Trace 6 represents the thermal curves of aged physical mixtures. Thermal parameters of the pure components are collected in Table 1 and those of PICO after mixing with excipients are collected in Table 2.

The thermal curves of stearyl alcohol, palmitic acid, stearic acid, and PEG 20,000 (Fig. 1) all gave a sharp endothermic peak, typical of crystalline anhydrous sub-

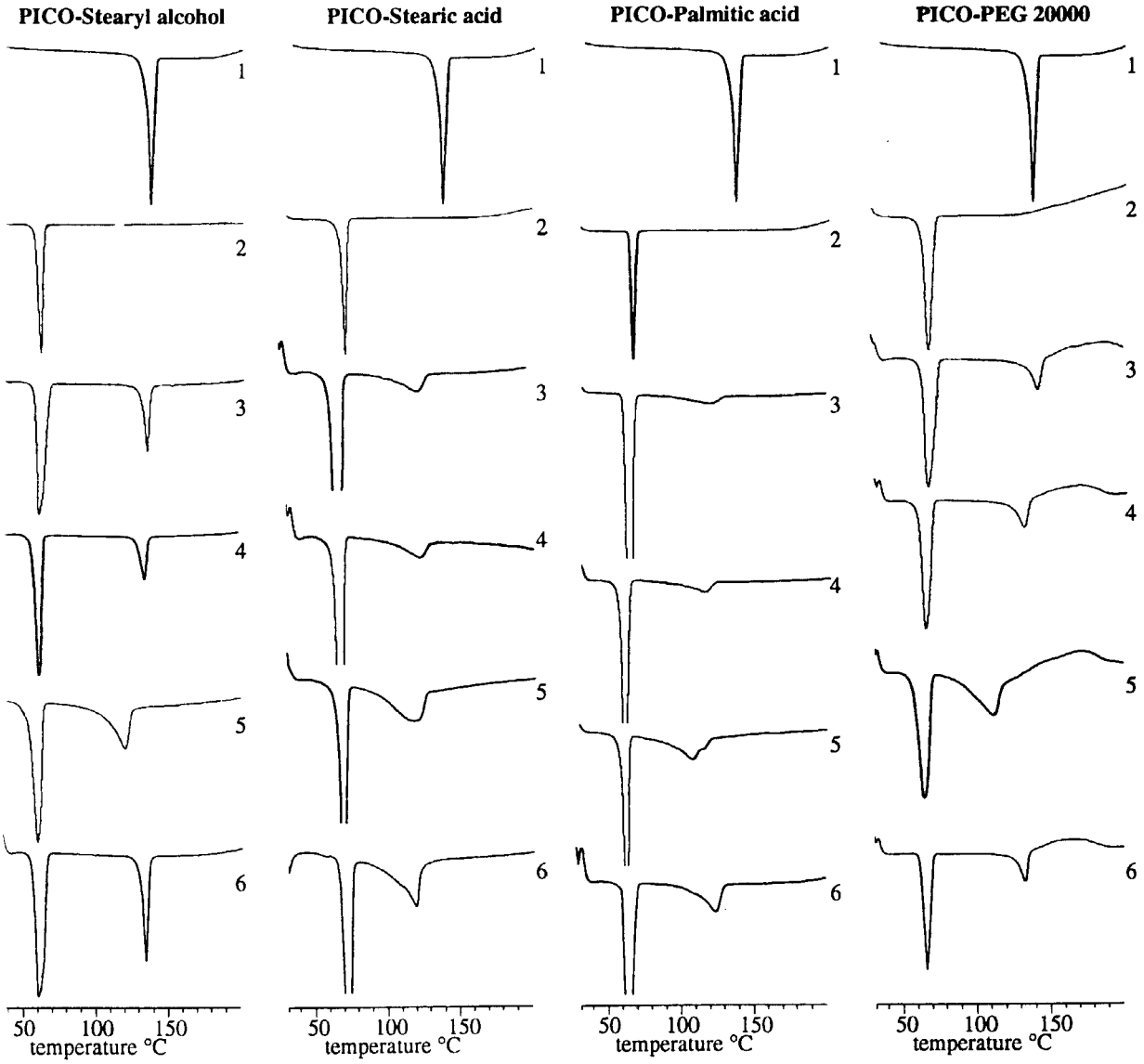

Figure 1. DSC curves of picotamide (PICO) and the 1:1 w/w mixed systems with excipients. Key: 1, PICO; 2, excipient; 3, physical mixture; 4, coground mixture; 5, kneaded mixture; 6, aged physical mixture.

stances. In their 1:1 w/w combinations with PICO, the characteristic endotherms of the drug and excipient were always present, and no extrathermal effects were observed, either after sample manipulation or aging. However, dramatic broadening and reduction in both peak size and enthalpy per unit mass of PICO were found, and for palmitic and stearic acids were accompanied by an appreciable downward shift of drug peak temperature, which could be indicative of some drug–excipient solid–solid interaction. Instead, HSM analysis showed that this effect was mainly because of the partial dissolution of the drug in the melted excipient (Fig. 2). The modification of drug thermal behavior was more or less intense, depending on the different degree of drug solubility in the melted component and, for the same excipient, on the mechanical treatment sustained by the sample. SEM analysis showed that both the drug and excipient particles preserved their morphology and the drug particles appeared uniformly and finely dispersed as crystalline microaggregates on the surface of excipient particles (Fig. 3). This phenomenon was consistent with the findings of HSM analysis and could concur to cause the observed reduction of apparent heats of fusion of the drug in these mixtures.

Typical equilibrium phase diagrams, constructed using peak melting points and HSM data, are shown in Fig. 4. They revealed no evidence of the presence of eutectics or solid solutions and were all of the monotectic type, the monotectic species being the pure drug. This indicates that the melts are miscible, but that there is a negligible interaction in the solid state. Thus, compatibility of PICO with these lubricant agents could be expected, also owing to the severe conditions of the test. The excipient was in fact present in the mixture in equal weight ratio with the drug, whereas the concentrations of lubricant commonly used in pharmaceutical formulations are generally very low.

A particular behavior pattern was observed for mixed systems with Mg stearate [Fig. 5(a)]. The thermogram of the excipient showed an endothermal peak at 96°C followed by a small shoulder at a higher temperature. The DSC curve of the physical mixture was the simple superimposition of those of the pure components, and the thermal curves of coground and kneaded systems, as well as of aged physical mixture, showed the appearance

Table 1

Thermal Parameters of Picotamide (PICO) and Selected Excipients

Sample	T_{peak} (°C)	T_{onset} (°C)	$\Delta_{fus}H$ (J/g)
PICO	135.3	130.7	75.6
Stearic acid	69.2	63.8	206.1
Palmitic acid	63.0	62.1	187.1
Stearyl alcohol	63.0	56.2	191.4
PEG 20,000	64.6	59.9	168.4
Mg stearate	96.6	85.5	202.6
Glucose	160.9	156.2	182.9
Lactose	142.9	140.0	138.9
Mannitol	166.1	163.7	265.9
Sorbitol	98.1	91.1	148.4

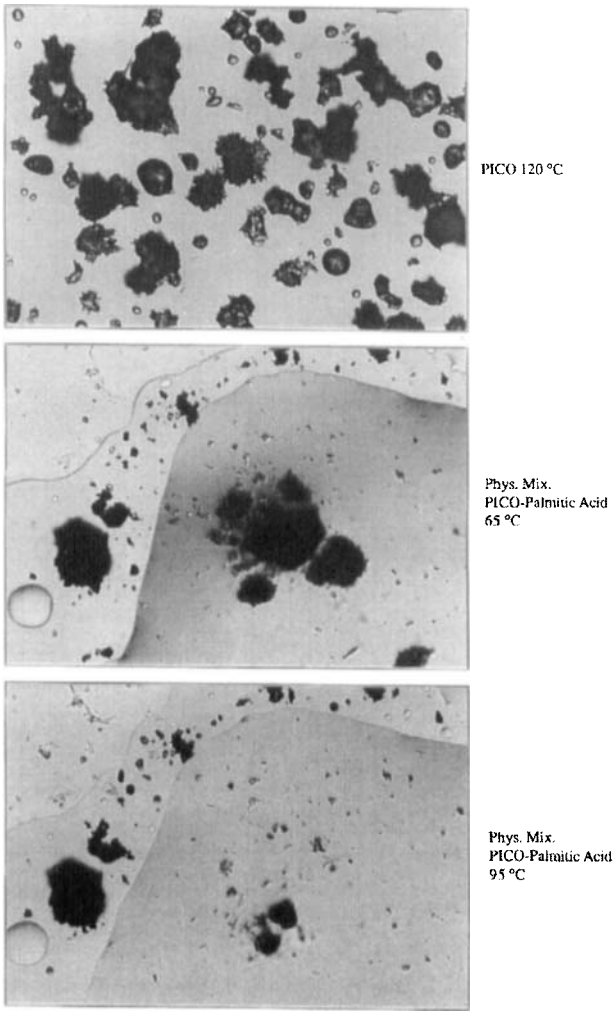

Figure 2. Photomicrographs of crystals of picotamide (PICO) (at 120°C) and the 1:1 w/w physical mixture with palmitic acid (at 65 and 95°C) taken during HSM analysis.

Table 2

Thermal Parameters of Picotamide (PICO) in Binary Mixtures with Excipients

	Peak Temperature (°C)				Onset Temperature (°C)				Enthalpy (J/g)			
Excipient	Physical Mix	Ground Mix	Kneaded Mix	Aged Physical Mix	Physical Mix	Ground Mix	Kneaded Mix	Aged Physical Mix	Physical Mix	Ground Mix	Kneaded Mix	Aged Physical Mix
Stearic acid	125.8	121.5	103.8	118.4	103.8	97.4	91.5	101.9	22.6	19.8	24.2	56.1
Palmitic acid	119.8	114.8	108.1	124.8	87.1	86.4	83.2	104.4	24.4	19.8	44.3	26.3
Stearyl alcohol	133.7	133.1	120.2	133.6	127.8	126.0	101.3	127.7	58.2	56.9	67.2	61.5
PEG 20,000	132.0	130.4	111.0	131.8	123.2	120.4	83.2	124.6	23.7	32.1	57.8	41.4
Mg stearate	135.4	133.8	135.1	134.9	128.9	127.6	128.5	127.6	73.6	66.0	35.7	65.1
Glucose	133.4	119.9	109.9	132.9	127.5	113.5	97.2	127.2	68.0	57.0	66.1	73.6
Sorbitol	110.3	106.7	102.8	111.4	102.7	90.8	–	92.0	57.4	27.3	–	28.8
Lactose	133.9	121.2	115.9	133.8	128.2	114.1	99.2	127.8	71.4	64.0	74.9	76.1
Mannitol	132.6	127.8	112.3	132.7	127.2	121.4	101.3	127.1	74.0	61.5	65.9	75.9

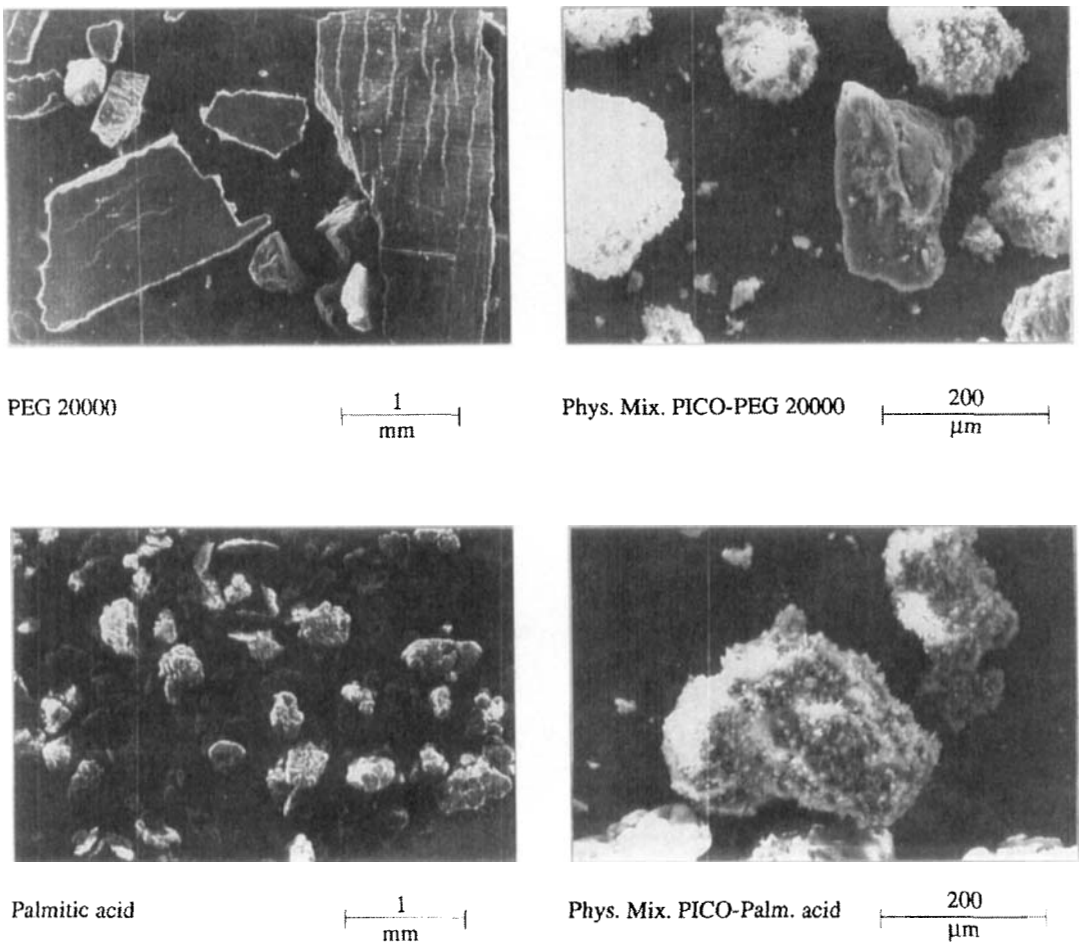

Figure 3. Scanning electron micrographs of palmitic acid and PEG 20,000 and the 1:1 w/w physical mixtures with picotamide (PICO).

of an additional endothermal effect, falling between the excipient and drug melting peaks. It was, however, demonstrated that this effect was not the result of a drug–excipient interaction, but of the partial conversion of Mg stearate, during the grinding process, in a pseudo-polymorphic form. In fact, depending on the preparation conditions, this can appear in several hydrate forms, with different fusion temperatures (11). A modification of the Mg stearate DSC curve as a function of the grinding was observed (Fig. 5(b)], with a progressive downward shift and reduction until disappearance of the peak initially present at 96°C. A similar phenomenon was observed for the coground mixture heated 10 min at 110°C and then rapidly cooled to ambient conditions, where only the Mg stearate form melting at 120°C was present [Fig. 5(a), trace 4b].

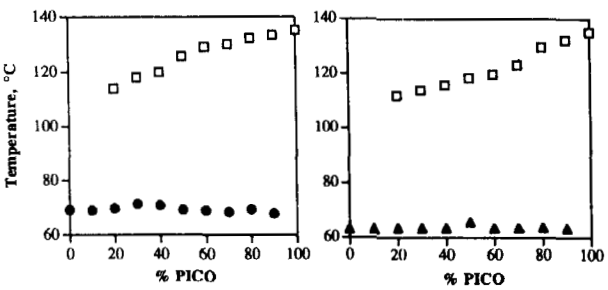

Figure 4. Phase diagrams of picotamide (PICO) (□) in mixtures with stearic acid (●) or palmitic acid (▲).

The thermal curves of mannitol, glucose, lactose, and sorbitol (Fig. 6) gave a sharp endothermal peak due to the excipient melting. In the combinations of mannitol with PICO, the endothermal effect caused by the drug melting was always present, but a progressive downward

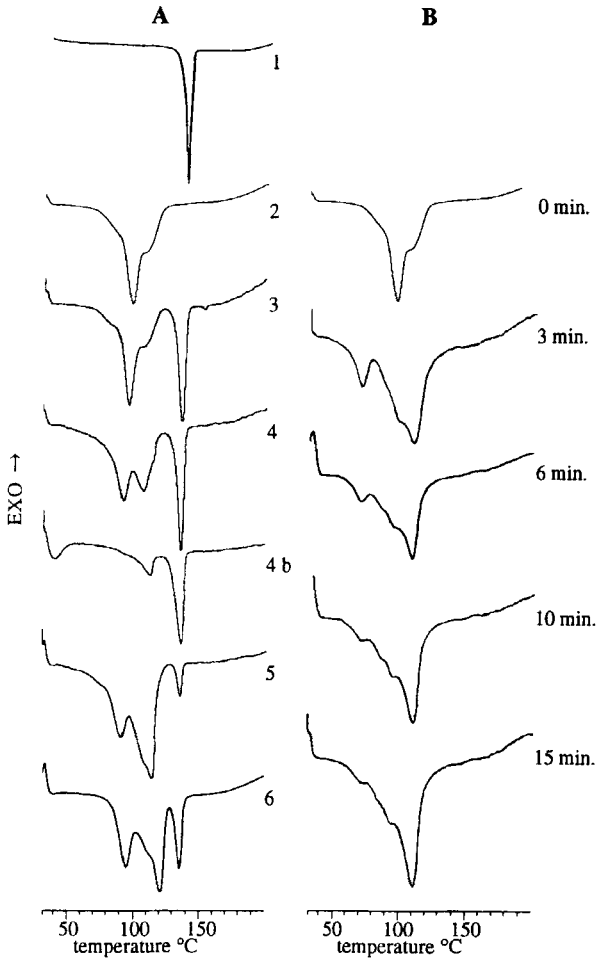

Figure 5. (a) DSC curves of picotamide (PICO) and the 1:1 w/w mixed systems with Mg stearate. Key: 1, PICO; 2, excipient; 3, physical mixture; 4, coground mixture; 4b: coground 10 min heated at 110°C; 5, kneaded mixture; 6, aged physical mixture; (b) effect of grinding time on the thermal curve of Mg stearate.

shift of peak temperature was observed when the mixture passed from physical mixture to the coground state and was even more pronounced in the kneaded system, with a concomitant broadening and reduction of peak size. The results indicated that some solid–solid interaction had occurred as a consequence of sample mechanical treatment. A similar and even more accentuated behavior was observed for mixtures of PICO with sorbitol, but HSM analysis showed that, in this case, the effect was mainly attributable to the partial dissolution of the drug in the melted excipient (Fig. 7). On the other hand, SEM analysis showed, as for the mixtures with lubricants, the formation of a fine dispersion of microcrystalline drug adsorbed on the excipient surface (Fig. 8), a phenomenon particularly evident in the mechanically treated systems in which sample cogrinding or kneading resulted in an increase in surface area available and in a much higher extent of intimate contact between drug and excipient. The equilibrium phase diagram (Fig. 9) revealed no evidence of the presence of eutectic or solid solution and was of the monotectic type, with the pure drug as monotectic species, indicating miscibility of the melts, but negligible interaction between components in the solid state.

The thermal curve of 1:1 w/w physical mixture of glucose with PICO showed the characteristic endotherm of drug followed by the endothermal effect caused by the melting of the excipient, indicating the presumable absence of incompatibility. Instead, coground and kneaded systems showed the unexpected appearance of a third broad endothermal effect at lower temperature (around 80–100°C) together with a significant downward shift of drug melting peak. The extrathermal effect, which appeared also in the aged physical mixture, was simply a result of the evaporation of water adsorbed during the mixture treatment or aging. In fact, as is shown in Fig. 6 (trace 4b), the extrathermal effect disappeared after sample dehydration. Nevertheless, the observed phenomenon cannot be overlooked, because it indicates increased hygroscopicity of the sample as a consequence of the mechanical treatment and might cause problems during processing or storage. Although the thermal curve of 1:1 w/w physical mixture of lactose with PICO was the superimposition of those of single components, significant variations of DSC trace were observed as a consequence of sample grinding. In fact, in addition to the appearance of a new broad endothermal effect at about 100°C (which appeared also in the aged physical mixture and, as already observed for glucose mixture, disappeared after sample dehydration), clear changes in both the drug and excipient endothermal peaks (downward shift of the melting peak and appearance of a shoulder for the former; drastic reduction of peak size and fusion enthalpy for the latter) were evident, indicative of some solid–solid interactions and therefore potential incompatibility.

CONCLUSIONS

The results confirmed the utility of thermal analysis, and particularly of DSC, at the earliest stages of

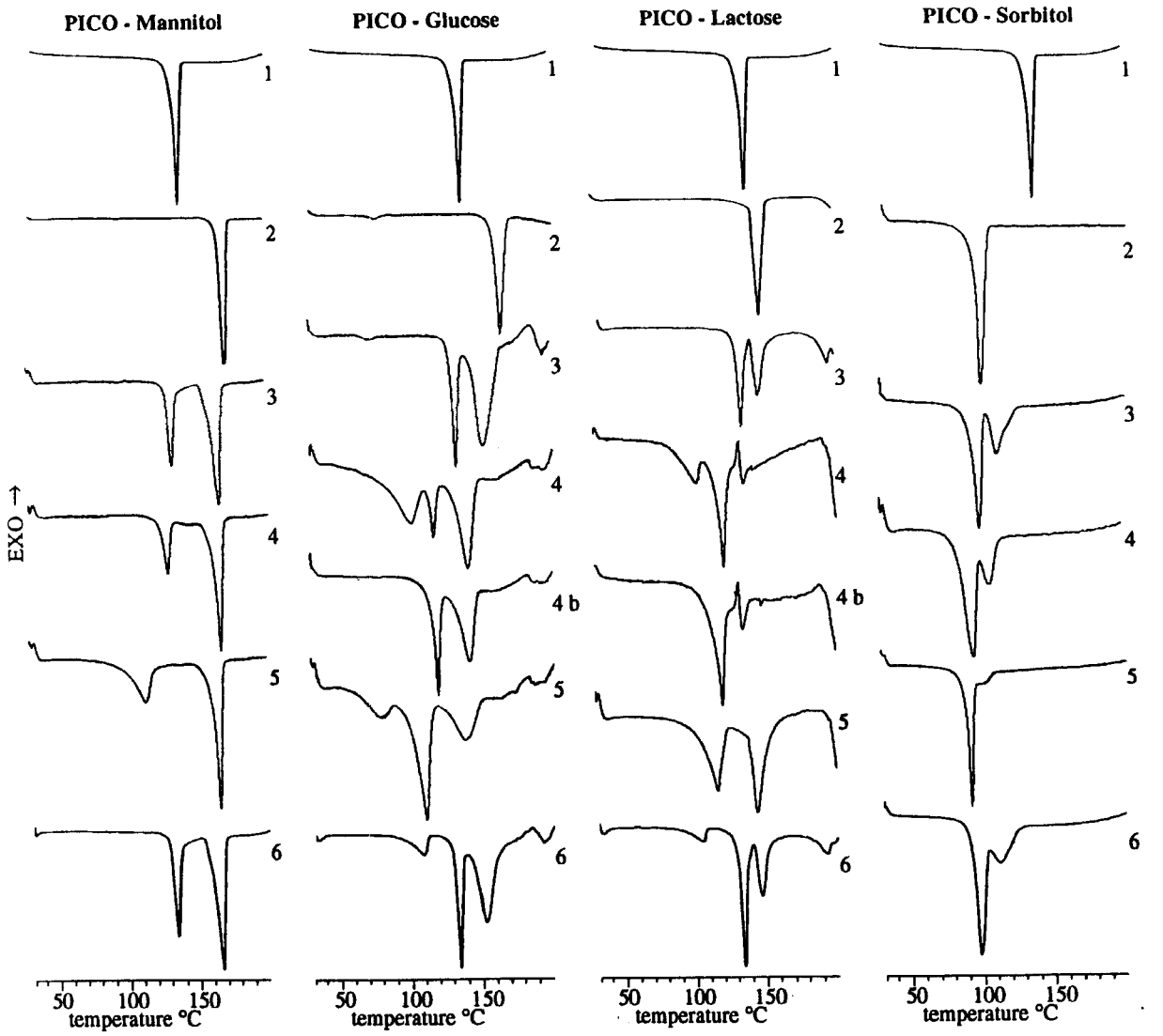

Figure 6. DSC curves of picotamide (PICO) and the 1:1 w/w mixed systems with excipients. Key: 1, PICO; 2, excipient; 3, physical mixture; 4, coground mixture; 4b, coground mixture dehydrated; 5, kneaded mixture; 6, aged physical mixture.

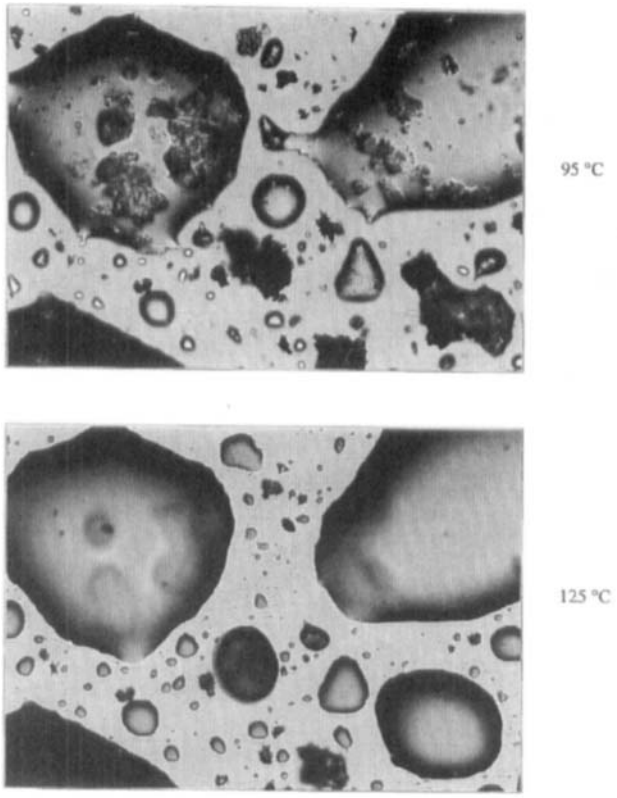

Figure 7. Photomicrographs of 1:1 w/w coground mixture of picotamide (PICO) and sorbitol at 95 and 125°C taken during HSM analysis.

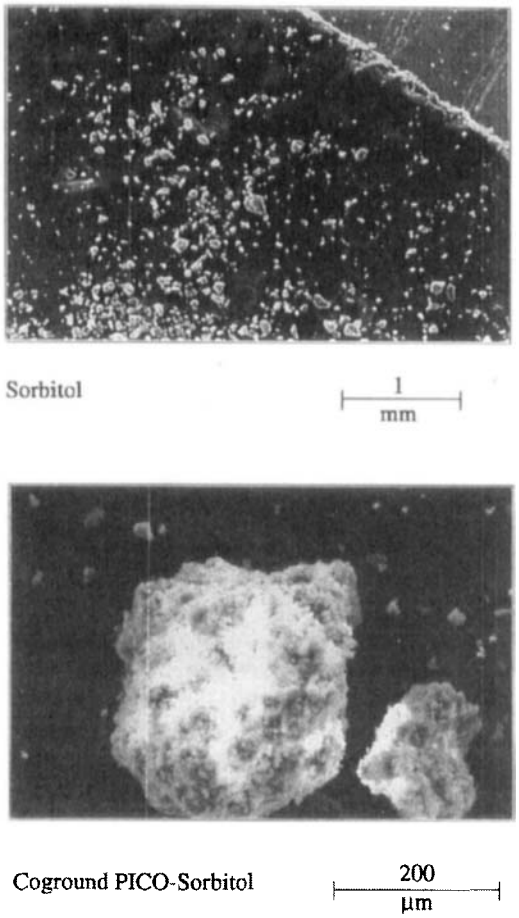

Figure 8. Scanning electron micrographs of sorbitol and the 1:1 w/w coground mixture with picotamide (PICO).

preformulation studies as a useful tool for the screening of a wide range of candidate excipients, allowing a rapid evaluation of possible drug–excipient interactions. However, it was shown that a careful evaluation of any modification of DSC trace is necessary to avoid misinterpretations and use of misleading DSC results, and consequently erratic conclusions. In fact, in spite of noticeable modification of PICO thermal features in its mixed systems with lubricants, a more in depth investigation extended to various drug–excipient ratios and supported by HSM and SEM analysis, allowed the exclusion of incompatibility, at least at the drug–excipient ratios commonly used in pharmaceutical formulations. Moreover, the importance of the different mechanical treatment sustained by the sample, and then of different surface contacts between drug and excipient, in the likelihood of any possible interaction, was demonstrated. In fact, cogrinding or kneading of drug–excipient mixtures revealed, for example, an increased hygroscopicity of

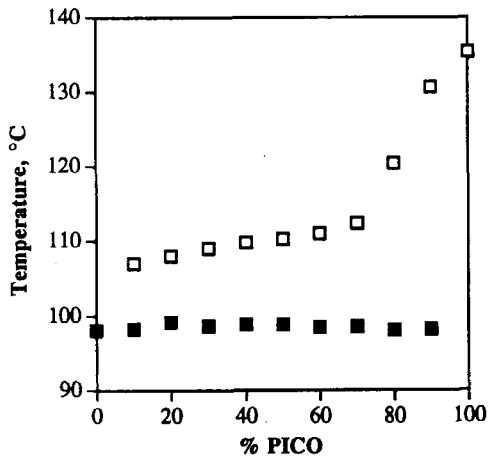

Figure 9. Phase diagrams of picotamide (PICO) (□) sorbitol, (■) system.

mixtures with glucose and lactose in addition to some solid–solid interactions with lactose and mannitol, warning against their use; all these phenomena were not detectable in simply blended mixtures or became detectable only after their aging.

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