ELSEVIER

International Journal of Pharmaceutics 119 (1995) 71–79

international journal of pharmaceutics

Utilization of differential scanning calorimetry as a screening technique to determine the compatibility of ketoprofen with excipients

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Received 6 July 1994; accepted 14 October 1994

Abstract

Differential scanning calorimetry (DSC) was used as a screening technique for assessing the compatibility of ketoprofen with some excipients currently employed in tablet or capsule formulations. The effect of sample treatment (simple blending, cogrinding, compression, kneading) was also evaluated. On the basis of DSC results, ketoprofen was found to be compatible with hydroxyethylcellulose, hydroxypropylcellulose, microcrystalline cellulose, corn starch, arabic gum, colloidal silica, veegum, lactose, glucose, sorbitol and mannitol. Some drug-excipient interaction was observed with palmitic acid, stearic acid and stearyl alcohol and eutectic formation was found with magnesium stearate. Strong solid-phase interaction with polyethylene glycol 6000, polyvinylpolypyrrolidone and even more with polyvinylpyrrolidone K30 was found.

Keywords: Ketoprofen; DSC; Compatibility; Drug-excipient interaction; Solid dosage form

1. Introduction

Interactions in dosage forms can give rise to changes in the chemical nature, solubility, absorption and therapeutic response of drugs. Therefore, during the formulation of new drugs or the reformulation of existing products, the study of the interaction between drug and excipients in the solid state is an important stage. Conventional procedures involve preparation of samples, storage under stressed conditions and analysis at set times using a suitable stability-indicating method. These procedures are very expensive and time-consuming and, generally, give indications only about chemical, and not physical, stability. In recent years it has been suggested that DSC can be a useful alternative method of predicting and/or investigating compatibility during preformulation studies (Hardy, 1982; Smith, 1982; Giron, 1986; Lachman et al., 1986; Ford, 1993). DSC in fact allows the rapid evaluation of possible interactions between the formulation components according to appearance, shift, or disappearance of endothermic or exothermic peaks and/or variations in the corresponding enthalpy (Botha and Lotter, 1990b; Lin and Han, 1992). Thermal analysis cannot replace chemical methods for determining the drug concentration and the classical long-term stability tests. How-

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SSDI 0378-5173(94)00374-2

ever, several workers (El-Shattawy et al., 1982; El-Shattawy, 1984; Gordon et al., 1984; Ciranni-Signoretti et al., 1986, 1988; Botha et al., 1987; Botha and Lotter, 1990a) have confirmed that this technique can be considered as a valuable tool in the first step of a formulation setting for the screening of candidate excipients, and good correlations were often obtained between DSC results and those of stability tests (Jacobson and Gibbs, 1973; Ager et al., 1986; Boscolo et al., 1990). Unfortunately, interpretation of the thermal data is not always plain and, to avoid misinterpretation and misleading of DSC results, it must be emphasized that the interactions observed at high temperatures may not always be relevant under room conditions (Hardy, 1982; Van Dooren and Duphar, 1983). Moreover, the presence of a solid-solid interaction does not necessarily indicate pharmaceutical incompatibility (Van Dooren and Duphar, 1983), but might instead be advantageous, e.g., as a more desirable form of drug delivery system (Hardy, 1982; Bettinetti et al., 1988).

In the present study, DSC was used to evaluate the compatibility of ketoprofen, a potent systemic non-steroidal anti-inflammatory drug, with a number of excipients commonly used in solid pharmaceutical dosage forms, such as polymers used to control drug delivery, diluents, sweeteners, binders, disintegrating agents and lubricants. The DSC curves of ketoprofen and of each of the investigated excipients were compared with their 50% mixtures. The 1:1 weight ratio was chosen because it maximises the likelihood of observing any interaction (Smith, 1982; Ford, 1993). In order to examine the effect of sample manipulation and of different surfaces of contact between drug and excipients, mixed samples for DSC studies were prepared in four different ways (physical mixture, coground mixture, compressed blend, kneaded product).

2. Materials and methods

2.1. Materials

Ketoprofen was obtained from Sigma Chemical Co. (St. Louis, USA). The following excipients were examined: polyvinylpyrrolidone K30 (PVP K30), polyvinylpolypyrrolidone (PVPP), polyethylene glycol 6000 (PEG 6000) (Merck-Schuchardt, München, Germany); hydroxyethylcellulose (Natrosol) (Eigenmann and Veronelli, Milano, Italy); hydroxypropylmethylcellulose (Methocel) (Dow Chemical, Cincinnati, USA); microcrystalline cellulose (Avicel PH 101), palmitic acid, stearic acid, stearyl alcohol (Fluka AG, Buchs, Switzerland); colloidal silica (Aerosil 200) (Serva Fenbiochemica, Heidelberg, Germany); Veegum F (Bayer-Italia, Milano, Italy); lactose, glucose, mannitol, sorbitol, corn starch, arabic gum, magnesium stearate (Carlo Erba, Milano, Italy).

2.2. Preparation of samples

Each material was sieved and the respective 75–150 μm granulometric fraction was selected.

Physical mixtures of ketoprofen and each excipient were prepared in a 1:1 w/w ratio by gently mixing in an agate mortar with a spatula at room temperature. Coground mixtures were obtained by grinding a portion of each physical mixture with a pestle for approx. 10 min. Compressed blends were prepared by compressing a portion of each physical mixture with a laboratory hydraulic press for IR spectroscopy KBr discs at a force of about 3 tonne for 2 min; the discs obtained were then broken up and sieved, the 75–150 μm granulometric fraction being collected. Kneaded mixtures were prepared by slurrying a portion of each physical mixture with ethanol and grinding thoroughly to obtain a paste which was dried under vacuum at room temperature up to a constant weight; the solid was sieved and the 75–150 μm granulometric fraction was collected.

Uniformity of the physical mixtures was verified by comparing thermograms obtained from three samples all taken from the same mixture.

2.3. DSC

Samples of individual substances as well as mixed systems of ketoprofen and excipients were weighed (Mettler M3 Microbalance) directly in pierced aluminium pans (5–10 mg) and scanned

between 30 and 200°C at a heating rate of 10 K min^{-1} under static air, using a Mettler TA4000 apparatus equipped with a DSC 25 cell.

3. Results and discussion

Fig. 1–4 illustrate selected thermograms of the various systems investigated. The DSC thermal curve of ketoprofen (trace 1 of Fig. 1–4) showed a single sharp endothermic peak at its melting point. At a scan rate of 10 K min^{-1}, the observed peak temperature was 95.8 ± 0.2°C and the apparent heat of fusion was 199.4 ± 0.7 J/g. Trace 2 of Fig. 1–4 indicates the DSC thermograms of different excipients. Traces 3–6 are the thermograms of the 1:1 physical mixture, coground mixture, compressed blend and kneaded product of ketoprofen with each excipient. The values of the melting peak temperature and enthalpy of ketoprofen after mixing with excipients are collected in Table 1.

The excipients corn starch, arabic gum, Avicel, Natrosol and Methocel (Fig. 1) all exhibited a shallow broad endothermic effect in the 80–130°C range, due to the evaporation of water. The combination of ketoprofen with each of these excipients, regardless of the method of sample preparation, reflected the characteristic features of the drug melting, suggesting that no problem of compatibility should occur. Some modifications of ketoprofen melting peak, such as changes in area, shape or peak temperature were found, but they arose simply from mixing the components (Watson et al., 1964; Van Dooren and Duphar, 1983). A reduction in enthalpy of the overall thermal effect per unit mass of ketoprofen was generally observed when the surface of contact between drug and excipient was increased by grinding or compression, or kneading. However, the enthalpy values relative to this series of hydrate mixed samples should be considered as approximate, due to the difficulty of exactly evaluating the endothermic drug melting peak, since this partially overlapped the polymer dehydration process. Analogous results were obtained using Veegum and Aerosil 200 (not shown).

Ketoprofen was also found to be compatible

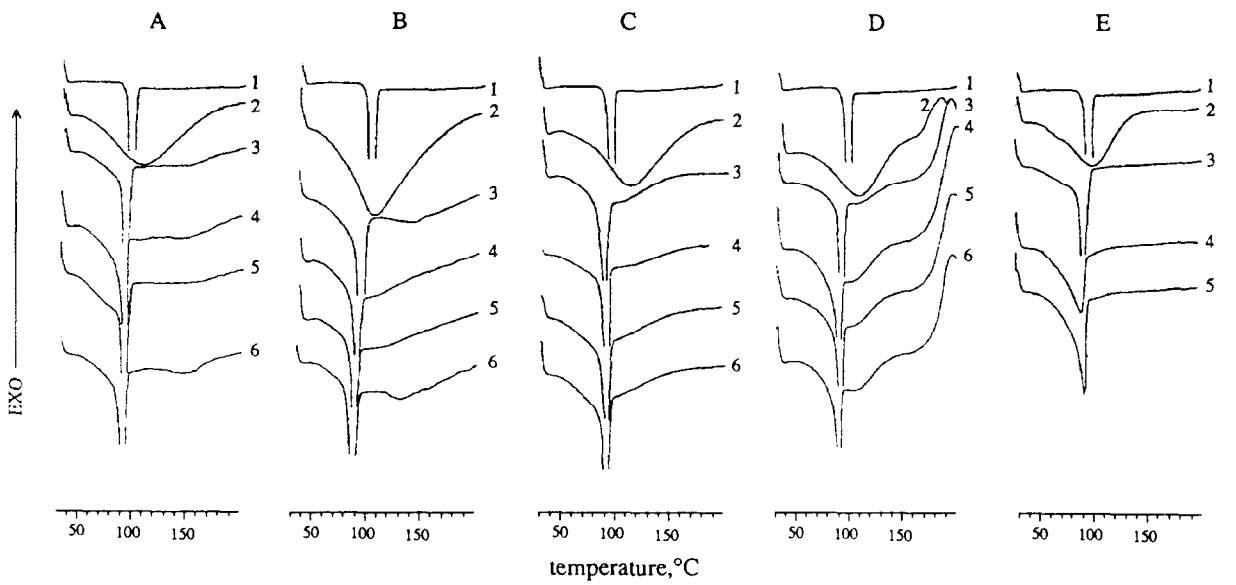

Fig. 1. DSC curves of ketoprofen and 1:1 w/w mixed systems of ketoprofen with (A) corn starch, (B) arabic gum, (C) Avicel, (D) Natrosol, and (E) Methocel. 1, ketoprofen; 2, excipient; 3, physical mixture; 4, coground mixture; 5, compressed blend; 6, kneaded mixture.

with glucose, lactose, mannitol and sorbitol, as may be deduced from the thermograms in Fig. 2. The thermal curves of glucose, lactose and mannitol (Fig. 2A–C) gave a sharp endothermic peak, respectively, at 160.9°C ($\Delta_{fus}H$ = 182.9 J/g), 142.9 ($\Delta_{fus}H$ = 138.9) and 166.1°C ($\Delta_{fus}H$ = 265.8). In their 1:1 w/w combinations with ketoprofen, the characteristic endotherm of the drug was always present. This was followed by the endothermic effect due to the melting of the excipient, indicating the absence of incompatibility, although, in the case of glucose and particularly of lactose, some downward shift and broadening of the excipient melting peak were found. No extra thermal peaks indicating possible incompatibility were observed in ketoprofen-lactose mixtures, in contrast with the observations of Botha and Lotter (1989). Sorbitol (Fig. 2D) melted in the region of ketoprofen (at about 98°C), and its 1:1 w/w mixture with the drug gave a single peak at 97°C. Even when the drug/excipient ratio was changed (e.g., 3:7 or 7:3 w/w) a single peak was always observed, at about constant temperature (96–98°C). This effect was clearly due to the insufficient power of resolution of the analytical technique under these experimental conditions. In fact, thermograms obtained by heating at a lower scan rate (2 K min^{-1}) revealed two distinct peaks, at 93.3 and 96.2°C, attributable to drug and excipient melting, respectively (see window at the top of Fig. 2D). Thus, in this case as well, no interaction was observed. Furthermore, no important effects on either the temperature of drug melting peak, or the enthalpy value per unit mass of ketoprofen due to the sample treatment were seen, confirming the absence of incompatibility.

The thermal behaviour of PVP K30 was very similar to that of PVPP (Fig. 3A and B), apart from the presence of a glass transition at about 60°C, and was typical of a hygroscopic amorphous substance, with a large endothermic effect in the 90–120°C range due to polymer dehydration. However, their 1:1 w/w mixed systems with ketoprofen showed a different thermal behaviour. In

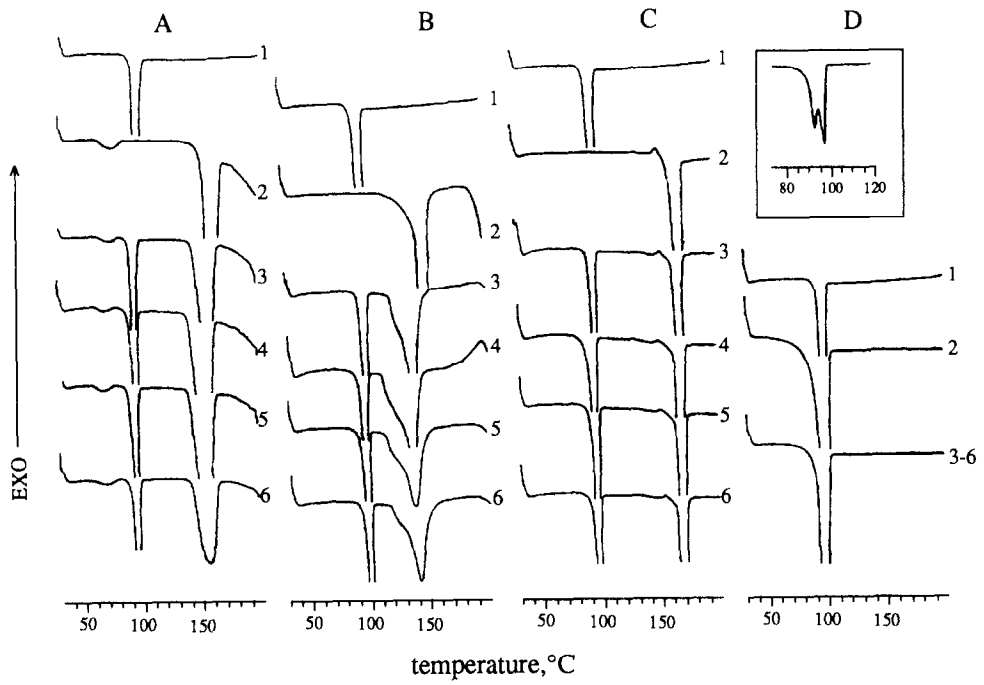

Fig. 2. DSC curves of ketoprofen and 1:1 w/w mixed systems of ketoprofen with (A) glucose, (B) lactose, (C) mannitol and (D) sorbitol. 1, ketoprofen; 2, excipient; 3, physical mixture; 4, coground mixture; 5, compressed blend; 6, kneaded mixture (window: thermogram of ketoprofen-sorbitol physical mixture recorded at a scan rate of 2 K/min).

the case of PVPP, the drug-polymer physical mixtures demonstrated a broadening of the ketoprofen endothermic peak together with a shift to a lower temperature. Interestingly, the DSC profile was profoundly influenced by the sample treatment; in fact, as a consequence of compression, and particularly of grinding or kneading, a progressive downward shift, broadening and flattening of the drug melting peak was observed, up to its complete disappearance. This behaviour, which resembles that already described for other drugs such as naproxen (Bettinetti et al., 1988), ibuprofen (Najib et al., 1986), and ketoprofen itself (Botha and Lotter, 1989), indicates that a strong solid-solid interaction has occurred. However it does not necessarily indicate pharmaceutical incompatibility, but could be explained by the formation of crystalline microaggregates of the drug and their considerable dispersion within the amorphous polymeric matrix (Bettinetti et al., 1991), with a positive effect on drug hydrosolubility (Bettinetti and Mura, 1994). Probably the sample treatment, by reducing the drug crystal dimensions and by increasing the drug-polymer contact surface, favours a more complete drug dispersion in the polymeric matrix and then a greater interaction. In the case of the mixed systems containing PVP K30, the disappearance of the drug melting peak occurred even in the simple blend. Moreover, the sample treatment caused a further marked modification of the thermal behaviour; in fact, heat absorption appeared at a higher temperature, followed by a discontinuous return to baseline. Furthermore, poor reproducibility of the DSC profile was found by comparing thermograms obtained from a same mixed system. These phenomena indicate a very strong solid-phase interaction and cannot be attributed, as in the case of PVPP, to a simple drug amorphization. The more intense interaction observed in the presence of PVP K30 as compared with PVPP could be attributed to the greater ease of the drug in penetrating and diffusing in the polymeric mass (Mura et al., 1992).

The DSC curve of PEG 6000 (Fig. 3C) exhibited a single sharp endothermic effect corre-

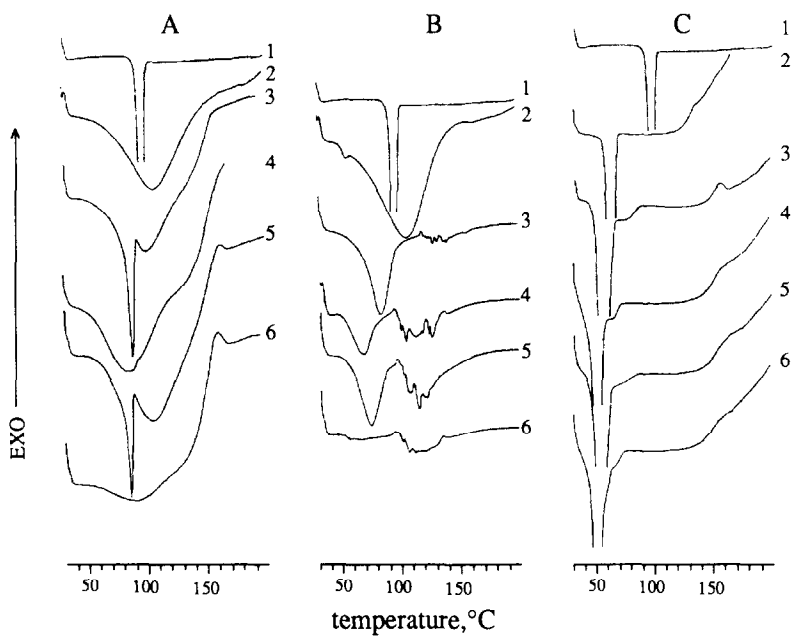

Fig. 3. DSC curves of ketoprofen and 1:1 w/w mixed systems of ketoprofen with (A) PVPP, (B) PVP K30 and (C) PEG 6000. 1, ketoprofen; 2, excipient; 3, physical mixture; 4, coground mixture; 5, compressed blend; 6, kneaded mixture.

sponding to the melting of the polymer (T_{fus} = 61.0°C and $\Delta_{fus}H$ = 198 J/g). In the thermograms of 1:1 w/w drug-excipient mixed systems, the characteristic melting endotherm of ketoprofen was absent and a single endothermic peak, corresponding to the melting of the polymer, was in all cases observed. The disappearance of the drug melting peak is certainly indicative of a strong interaction, but not necessarily of incompatibility. In fact, a similar effect was observed for other drugs, such as naproxen (Mura et al., 1993), diflunisal (Najib and Suleiman, 1989) or piroxicam (Fernandez et al., 1992) in mixtures with various PEGs, and was attributed to drug dissolution in the melted polymer.

The DSC curves of palmitic acid, stearic acid and stearyl alcohol (Fig. 4A–C) showed a sharp endothermic peak due to the excipient melting at 69.1°C ($\Delta_{fus}H$ = 187.1 J/g), 59.2°C ($\Delta_{fus}H$ = 206.1 J/g) and 63.0°C ($\Delta_{fus}H$ = 191.4 J/g), respectively. The curves for their 1:1 w/w combinations with ketoprofen showed a probable drug-excipient interaction. In fact, even if the endothermic peak due to the drug melting was always present, it was lowered by more than 10°C. Moreover, this effect was coupled to a significant reduction of peak size and enthalpy per unit mass of ketoprofen, and became more evident when passing from physical mixtures to kneaded, coground and compressed systems. On the other hand, as regards the drug melting temperature, no particular effects due to sample manipulation were observed.

The thermogram of magnesium stearate (Fig. 4D) showed an endothermic peak at 96°C, coinciding with the ketoprofen melting peak and followed by a small shoulder at a higher temperature, probably due to the presence of the corre-

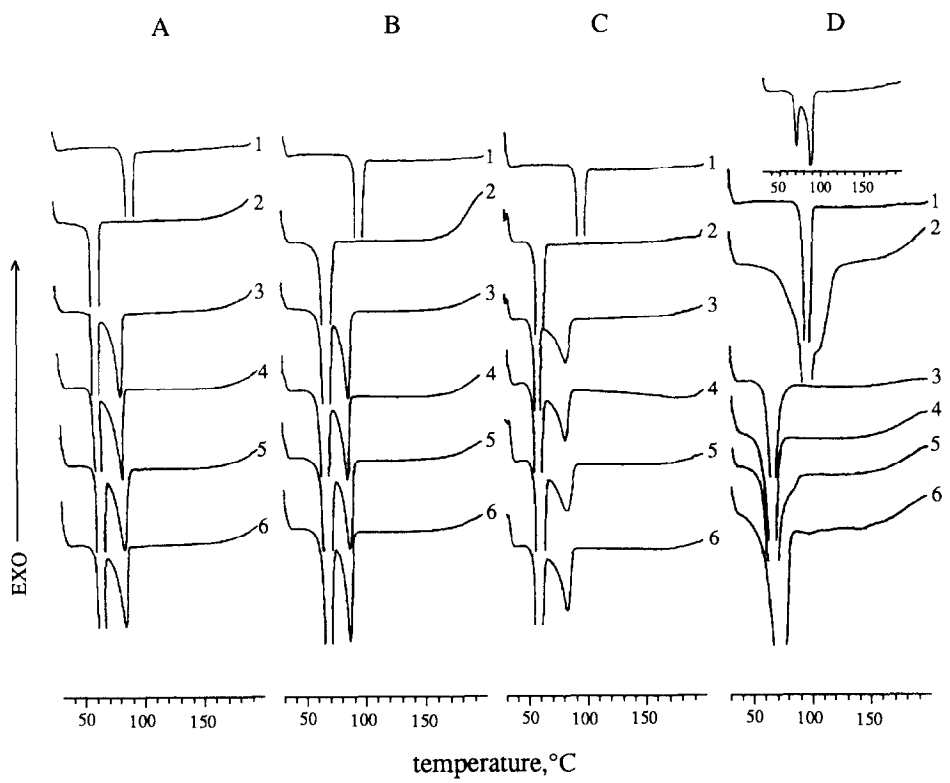

Fig. 4. DSC curves of ketoprofen and 1:1 w/w mixed systems of ketoprofen with (A) palmitic acid, (B) stearic acid, (C) stearyl alcohol and (D) Mg stearate. 1, ketoprofen; 2, excipient; 3, physical mixture; 4, coground mixture; 5, compressed blend; 6, kneaded mixture (inset: 8:2 w/w ketoprofen-Mg stearate physical mixture).

Table 1
Peak temperature and enthalpy values of ketoprofen after co-mixing with excipients

Excipient	Peak temperature (°C)				Enthalpy (J/g)			
	Physical mixture	Ground mixture	Compressed mixture	Kneaded mixture	Physical mixture	Ground mixture	Compressed mixture	Kneaded mixture
Corn starch	92.6	89.9	93.2	91.8	102.8	104.6	102.4	93.0
Arabic gum	90.9	87.7	87.1	87.3	119.6	79.7	86.0	100.0
Natrosol	91.4	89.4	90.3	89.4	93.6	77.7	79.0	66.6
Methocel	93.5	90.5	92.0	– [a]	92.5	77.2	83.3	– [a]
Avicel	92.8	90.4	92.0	92.3	104.0	85.8	88.3	99.4
Veegum	93.6	92.1	92.7	93.1	89.8	65.2	81.7	72.7
Aerosil	95.1	93.4	94.5	– [a]	84.1	73.5	67.4	– [a]
Lactose	95.7	93.3	95.3	95.6	82.4	81.4	94.0	94.1
Glucose	95.4	93.7	95.2	95.2	97.8	86.5	88.5	93.6
Mannitol	95.6	93.6	94.9	95.2	101.7	86.8	95.0	97.2
Sorbitol	94.8	93.3	93.8	93.1	n.v. [b]	n.v. [b]	n.v. [b]	n.v. [b]
PVP K30	–	–	–	–	–	–	–	–
PVPP	88.0	–	85.2	–	85.8	–	61.0	–
PEG 6000	–	–	–	–	–	–	–	–
Palmitic acid	85.3	84.3	84.6	84.6	78.1	62.8	53.1	63.4
Stearic acid	87.6	86.6	87.9	87.5	57.6	49.3	45.7	55.1
Stearyl alcohol	82.1	82.4	84.1	84.0	53.2	43.7	38.9	54.6
Mg stearate [c]	68.8	65.7	66.4	70.3	94.5	79.2	87.2	107.7

[a] Gummy mass not pulverizable.
[b] n.v., not valuable data.
[c] Data referred to eutectic compound.

sponding palmitate salt impurity. The DSC curves of 1:1 w/w drug-excipient mixed systems displayed a single endothermic peak at a much lower temperature (around 66–70°C) in comparison with the melting points of the pure components. A similar effect was observed by Botha and Lotter (1989) and was considered indicative of general incompatibility. The formation of a simple eutectic mixture between magnesium stearate and ketoprofen may be reasonably hypothesized. In order to confirm this supposition, DSC runs were performed on a series of physical mixtures at various drug/excipient ratios (from 1:9 to 9:1 w/w). At different ratios from 1:1 w/w, two distinct endothermic peaks appeared (see, for example, the inset at the top of Fig. 4D, for the 8:2 w/w drug/excipient ratio). The first peak occurred at about constant temperature (between 68.8 and 70.4°C), and was attributed to the eutectic melting. The second peak, at higher temperature, gradually shifted to the lower peak, as the percent composition of the mixture approached the eutectic composition (50% w/w), and was then ascribed to the melting of the excess component. The phase diagram (Fig. 5) was constructed by plotting the melting temperature of the two components vs the ketoprofen weight fraction. Generally, eutectic behaviour does not mean pharmaceutical incompatibility, even if it cannot always be overlooked, since it might cause difficulties with a given composition during processing (Giron, 1986; Botha and Lotter, 1990a,b).

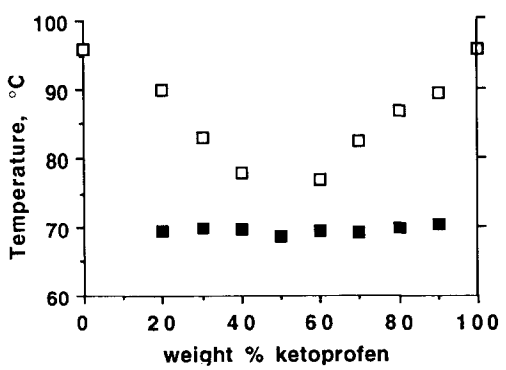

Fig. 5. Phase diagram of the ketoprofen-Mg stearate system.

4. Conclusion

The results confirmed the utility of DSC as a rapid and convenient method of screening candidate excipients during preformulation studies, because it permits the rapid ascertainment of excipient compatibility or demonstration of drug-excipient interaction or incompatibility. Even if the occurrence of a physical or chemical interaction under the test conditions does not necessarily mean that there is definite incompatibility, the technique provides useful indications of potential problems, so that an excipient can be avoided, or, if it is considered particularly important, the nature of the interaction can be further investigated.

No definite cases of pharmaceutical incompatibility were found in this study. Compatibility of ketoprofen with the subsequently tested excipients, glucose, lactose, mannitol, sorbitol, cellulose derivatives, clays derivatives, arabic gum and corn starch can certainly be expected, since the thermal features of the drug in the mixed systems remained more or less constant. Some drug-excipient interaction was found with stearates, and eutectic formation was demonstrated with magnesium stearate. A strong interaction occurred with PEG 6000, PVPP and particularly PVP K30. In all these cases, further studies will be performed, also with other analytical techniques, in order to gain insight into the nature of the interaction and to establish an actual pharmaceutical incompatibility.

Acknowledgements

Financial support from the MURST is gratefully acknowledged.

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