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Compatibility study between ibuproxam and pharmaceutical excipients using differential scanning calorimetry, hot-stage microscopy and scanning electron microscopy[1]

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Abstract

Differential scanning calorimetry (DSC) was used as a screening technique for assessing the compatibility of ibuproxam with some currently employed pharmaceutical excipients. The influence of processing effects (simple blending, cogrinding or kneading) on drug stability was also evaluated. On the basis of DSC results, ibuproxam was found to be compatible with corn starch, avicel and sodium carboxymethylcellulose. Some drug-excipient interaction was observed with polyethyleneglycol 4000, palmitic acid, stearic acid, Ca and Mg stearate. Actual solid-phase interactions of the drug with polyvinylpolypyrrolidone and polyvinylpirrolidone K30 were induced by mechanical treatments. Hot-stage microscopy (HSM) and scanning electron microscopy (SEM) were of help in interpreting the DSC results and excluding in all cases relevant pharmaceutical incompatibilities.

Keywords: Ibuproxam; Excipients; Compatibility; Differential scanning calorimetry; Hot-stage microscopy; Scanning electron microscopy

1. Introduction

The successful formulation of a stable and effective solid dosage form depends on careful selection of the excipients used to make administration easier or more suitable, improve patient compliance, promote release and bioavailability of the drug and protect it from degradation. It would therefore be very useful in the design of dosage forms to have readily available knowledge of potential physical and chemical interactions between drugs and excipients which might affect the chemical nature, stability, solubility and in vivo absorption of drugs. In recent years, applications of thermal analytical techniques at the preformulation stage of development of solid dosage forms have increased immensely [1–3]. In particular differential scanning calorimetry (DSC) has been proposed as a rapid method of evaluating any

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physicochemical interactions between components of the formulation and therefore selecting suitable compatible excipients. In fact it provides fast and reliable information about potential physical or chemical incompatibilities between the formulation components through the appearance, shift, or disappearance of endotherms or exotherms and/or variations in the relevant enthalpy values [4–6]. However, interpretation of DSC results is not always easy and thoughtful evaluation is necessary to avoid misinterpretation and erratic conclusion [7]. Moreover, the presence of a solid–solid interaction does not necessarily indicate pharmaceutical incompatibility [8] but it might instead be advantageous, e.g. as a more desirable form of drug delivery system [7,9]. Therefore other analytical techniques often have to be used in conjunction to adequately substantiate DSC findings [10,11].

The present study was undertaken to establish the compatibility of ibuproxam, or 2-(4-isobutylphenyl)-propiohydroxamic acid, a non-steroid anti-inflammatory drug, with a number of commonly used tablet excipients (diluents, binders, disintegration agents and lubricants). The DSC curves of the pure drug and of each of the investigated excipients were compared with those obtained from their 1:1 w/w mixtures. The 1:1 w/w ratio was selected to maximise the likelihood of observing any interaction [3,12]. In order to evaluate the effect of mechanical manipulation on the physicochemical stability of the drug, three different techniques were used to prepare drug-excipient samples: simple blending, cogrinding and kneading. When important modifications of the drug thermal profile were observed in DSC traces of mixtures, scanning electron microscopy (SEM) and hot-stage microscopy (HSM) were used as complementary techniques to assist in the interpretation of DSC results.

2. Experimental

2.1. Materials

Ibuproxam was kindly donated by Manetti and Roberts (Firenze, Italy) and used after recrystallization from ethyl acetate. The following excipients were examined: polyvinylpyrrolidone K30 (PVP K30), polyvinylpolypyrrolidone (PVPP), polyethyleneglycol 4000 (PEG 4000) (Merck-Schuchardt, Munchen, Germany); sodium carboxymethylcellulose (NaCMC) (Dow Chemical, CN); microcrystalline cellulose (Avicel PH 101), palmitic acid, stearic acid, stearyl alcohol (Fluka AG, Buchs, Switzerland); corn starch, Mg stearate, Ca 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 ibuproxam and each selected excipient were prepared in the 1:1 w/w ratio by gently blending in an agata mortar with a spatula at room temperature. Co-ground mixtures were obtained by grinding a portion of each physical mixture with a pestle for $\sim$15 min. Kneaded mixtures were prepared by slurrying a portion of each physical mixture with the minimum amount of ethanol and triturating 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. The blends were considered homogeneous when the DSC traces of three samples from the same preparation were superimposable within the limit of experimental error.

2.3. Differential scanning calorimetry

Samples of individual components as well as each drug-excipient combination were weighed (Mettler M3 Microbalance) directly in pierced Al pans (5–10 mg) and scanned in the 30–200°C temperature range under static air, with a heating rate of 10 K min^{-1}, using a Mettler TA4000 apparatus equipped with a DSC 25 cell.

2.4. Hot-stage microscopy

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 5–1 K min^{-1}.

Table 1
Thermal parameters of ibuproxam and selected excipients

Sample	T_{peak} (°C)	T_{onset} (°C)	$\Delta_{fus}H$ (J g^{-1})	$\Delta_{dehyd}H$ (J g^{-1})
Ibuproxam	130.1	126.0	125	—
Corn starch	107.4	59.0	—	246
Avicel	115.7	72.0	—	147
NaCMC	101.0	56.8	—	293
Stearic acid	69.2	63.8	206	—
Palmitic acid	63.0	62.1	187	—
Stearyl alcohol	63.0	56.2	191	—
PEG 4000	61.0	56.3	175	—
Mg stearate	96.6	85.5	203	—
Ca stearate	123.2	111.4	186	—
PVP K30	105.6	66.8	—	329
PVPP	106.7	68.3	—	303

2.5. Scanning electron microscopy

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

3. Results and discussion

Thermal parameters calculated from DSC curves of individual components and drug-excipient combinations are presented in Tables 1 and 2, respectively. Figs. 1–3 and 6 illustrate selected thermograms of the various systems investigated. The DSC thermal curve of ibuproxam (trace 1 of these figures) showed a sharp endothermic peak at its melting point, followed by an intense exothermal effect attributable to the drug decomposition process. At a scan rate of 10 K min^{-1}, the observed melting peak temperature was 130.1 ($\pm$ 0.3)°C (T_{onset} = 126.0 ($\pm$ 0.4)°C) with an apparent heat of fusion of 125 ($\pm$ 5) J g^{-1}. The exothermal effect was peaked at 165.8 ($\pm$ 0.6)°C with a relevant enthalpy value of 530 ($\pm$ 10) J g^{-1}. Trace 2 of these figures indicates the DSC thermograms of different excipients. Traces 3, 4 and 5 are the thermograms of 1:1 physical mixture, coground mixture and kneaded product of ibuproxam with each excipient, respectively.

The excipients corn starch, Avicel and NaCMC (Fig. 1) all exhibited a shallow broad endothermic effect in the 80–130°C range due to the polymer dehydration. Mixed systems of ibuproxam with each of these excipients, regardless of the method of sample preparation, exhibited the characteristic thermal profile of the drug, suggesting that no problems of compatibility should occur. Some changes in peak shape and height-to-width ratio or slight reduction of temperature of drug melting endotherm were sometimes observed but they can be ascribed to the mixing of the components [8,13]. Moreover, the enthalpy values of this series of hydrate mixed samples should be considered as approximate due to the partial overlapping of the endothermic drug melting peak to the polymer dehydration process.

The DSC curve of PEG 4000, palmitic acid, stearyl alcohol, stearic acid, Ca stearate (Figs. 2 and 3) all presented a single sharp endothermic peak due to excipient melting, typical of crystalline anhydrous substances. On the other hand, the melting endotherm of Mg stearate (Fig. 3) was followed by a small shoulder at a higher temperature, probably due to the presence of the corresponding palmitate salt impurity [14]. Curves of their 1:1 w/w combinations with ibuproxam showed a probable solid–solid interaction. In fact, though the endothermal effect due to drug melting was always evident, a noticeable downward shift of peak temperature by more than 15°C was observed [3], with a concomitant reduction of peak size and enthalpy per unit mass of ibuproxam. On the other hand, no particular

Table 2
Thermal parameters of ibuproxam in binary mixtures with excipients

Excipient	3]Peak temp. (°C)			Onset temp. (°C)			Enthalpy (J g^{-1})		
	Phys. mix	Ground mix	Knead. mix	Phys. mix	Ground mix	Knead. mix	Phys. mix	Ground mix	Knead mix
Corn starch	129.1	129.1	129.3	122.2	123.4	124.0	107	122	89
Avicel	130.9	129.9	131.1	125.0	124.8	125.3	110	116	125
NaCMC	125.9	123.8	124.3	117.4	116.2	119.1	47	40	28
Stearic acid	111.7	113.0	111.3	94.6	96.6	94.1	117	117	101
Palmitic acid	109.8	110.0	111.0	92.0	92.8	94.4	100	83	88
Stearyl alcohol	113.4	110.4	113.0	94.7	92.7	95.2	71	57	52
PEG 4000	111.4	107.8	106.8	87.2	86.6	85.4	39	28	26
Mg stearate	113.0	110.5	97.4	n.d.	n.d.	90.7	12	15	14
Ca stearate	103.1	n.d.	102.5	77.2	n.d.	75.5	n.d.	n.d.	n.d.
PVP K30	136.3	n.d.	n.d.	129.1	n.d.	n.d.	41	n.d.	n.d.
PVPP	130.6	129.1	n.d.	126.3	n.d.	n.d.	69	n.d.	n.d.

n.d., not exactly determinable.

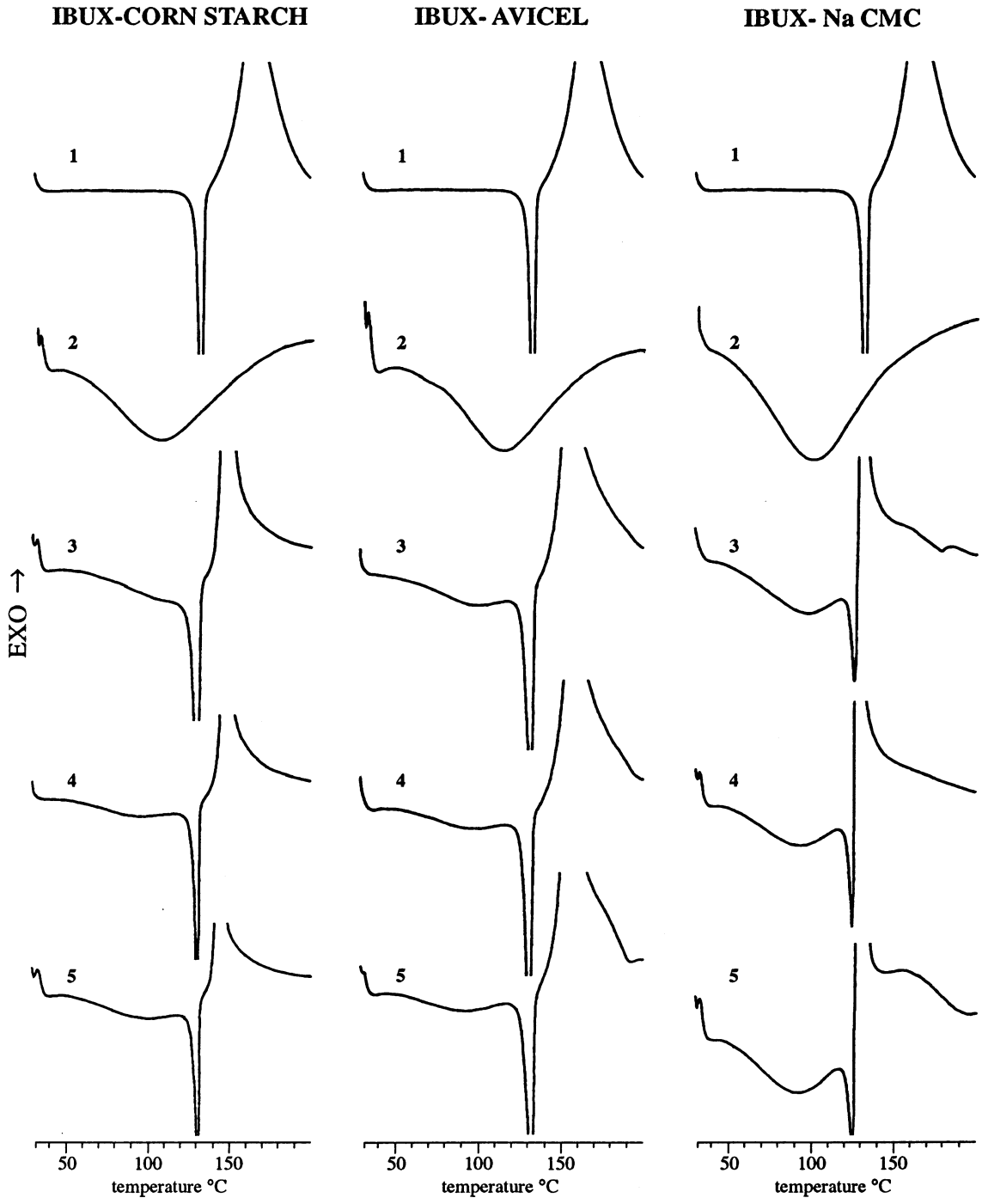

Fig. 1. DSC curves of ibuproxam (IBUX) and its 1:1 w/w mixed systems with excipients: (1) IBUX; (2) excipient; (3) physical mixture; (4) coground mixture; (5) kneaded mixture.

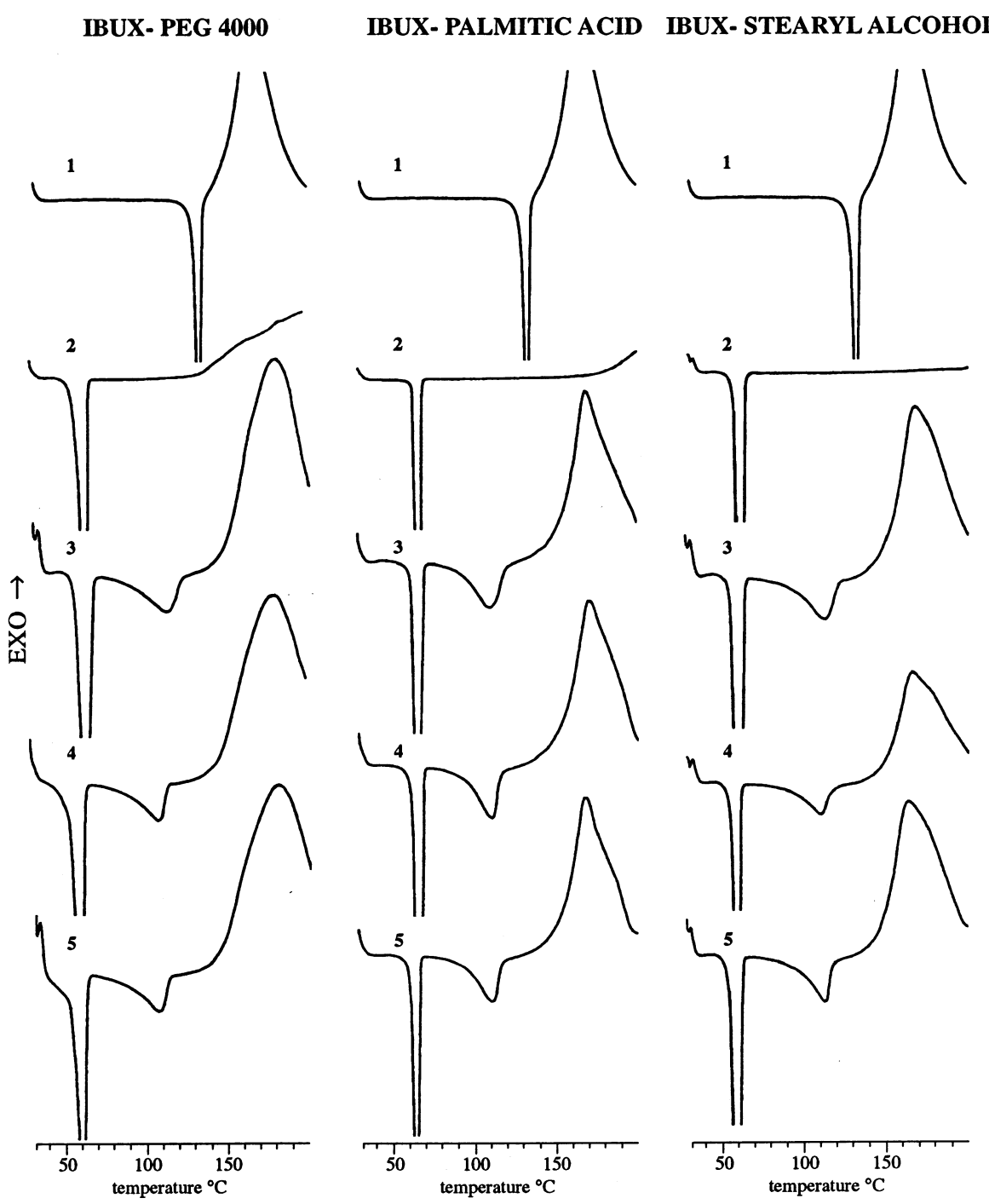

Fig. 2. DSC curves of ibuproxam (IBUX) and its 1:1 w/w mixed systems with excipients: (1) IBUX; (2) excipient; (3) physical mixture; (4) coground mixture; (5) kneaded mixture.

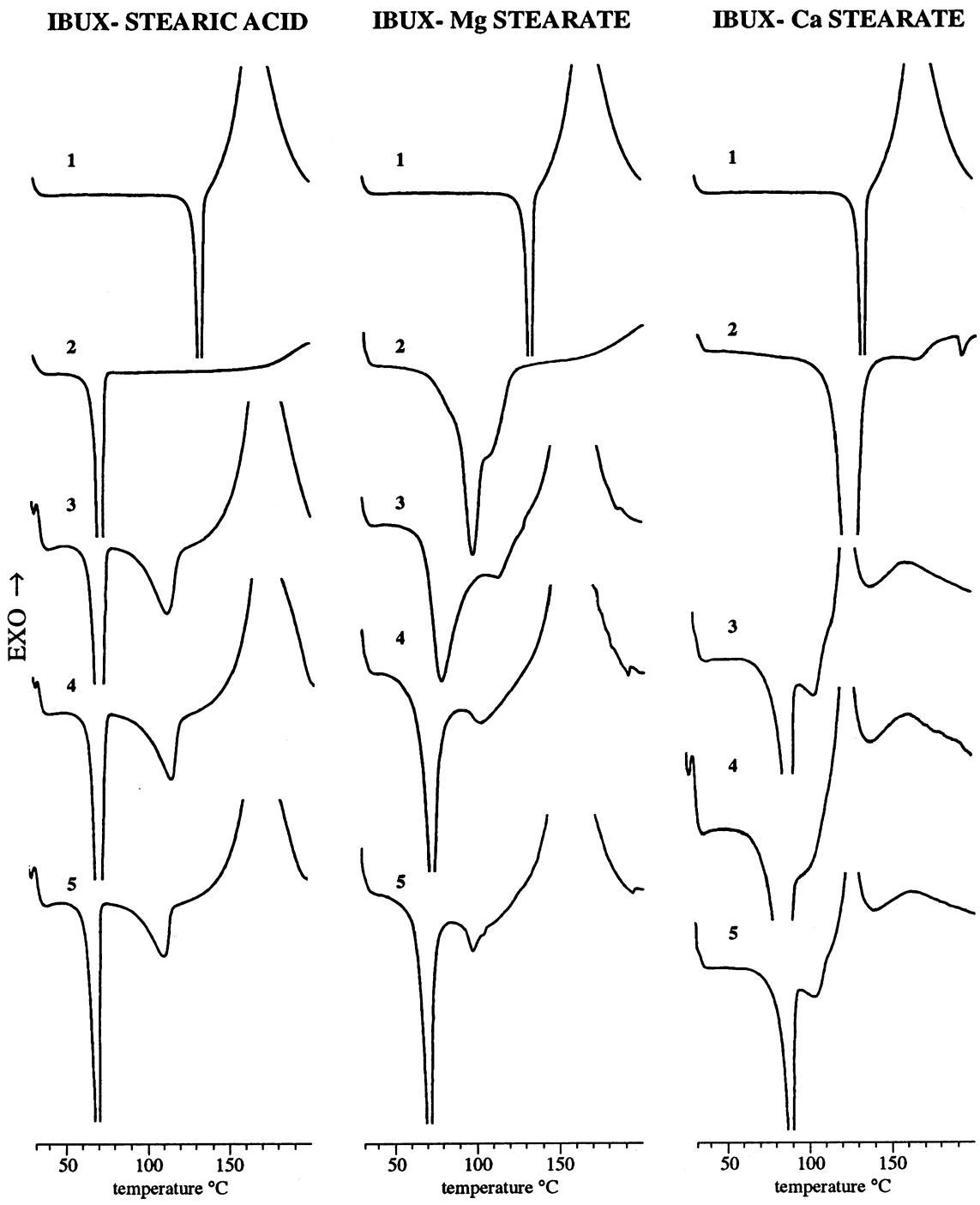

Fig. 3. DSC curves of ibuproxam (IBUX) and its 1:1 w/w mixed systems with excipients: (1) IBUX; (2) excipient; (3) physical mixture; (4) coground mixture; (5) kneaded mixture.

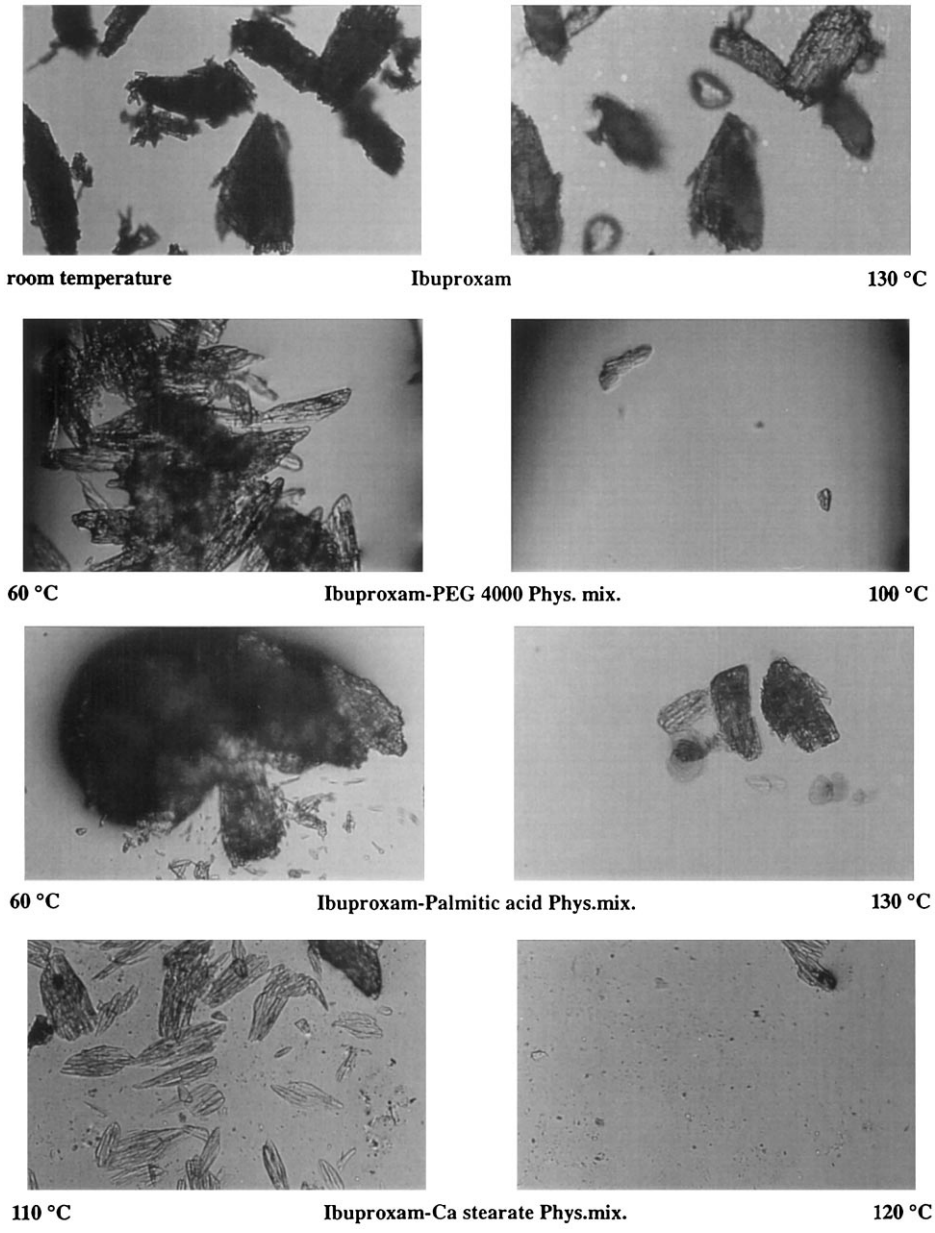

Fig. 4. Photomicrographs of crystals of ibuproxam and its 1:1 w/w physical mixtures with PEG 4000, palmitic acid and Ca stearate taken during HSM analysis.

effects due to the sample manipulation were observed.

HSM analysis showed that the phenomenon observed in DSC analysis was mainly due to the partial dissolution of the drug in the melted excipient (Fig. 4). The modification of drug thermal profile was more or less marked, depending on both the excipient melting temperature and the 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 main-

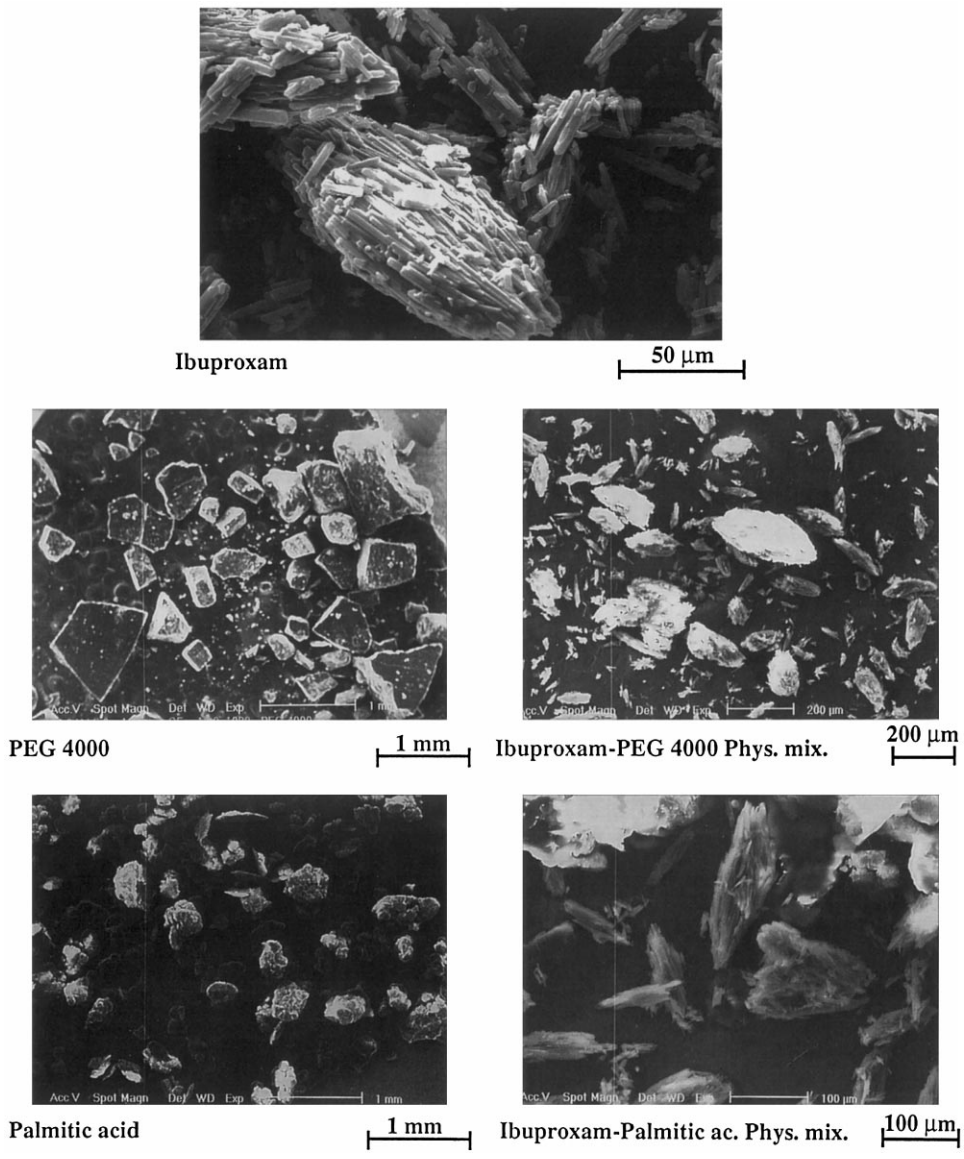

Fig. 5. Scanning electron micrographs of PEG 4000 and palmitic acid and their 1:1 w/w physical mixtures with ibuproxam.

tained their morphology and the drug crystals appeared uniformly and finely dispersed on the surface of excipient particles (Fig. 5). This phenomenon was consistent with the findings of HSM analysis and could concur to explain the observed reduction of apparent heats of fusion of the drug found for these mixtures. Thus compatibility of ibuproxam with this series of lubricants can be reasonably expected, also considering that lubricants are generally present in pharmaceutical formulations at concentrations of only 0.5–2% w/w.

The thermal behaviour of PVP K30 was very similar to that of PVPP (Fig. 6), 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 the water evaporation.

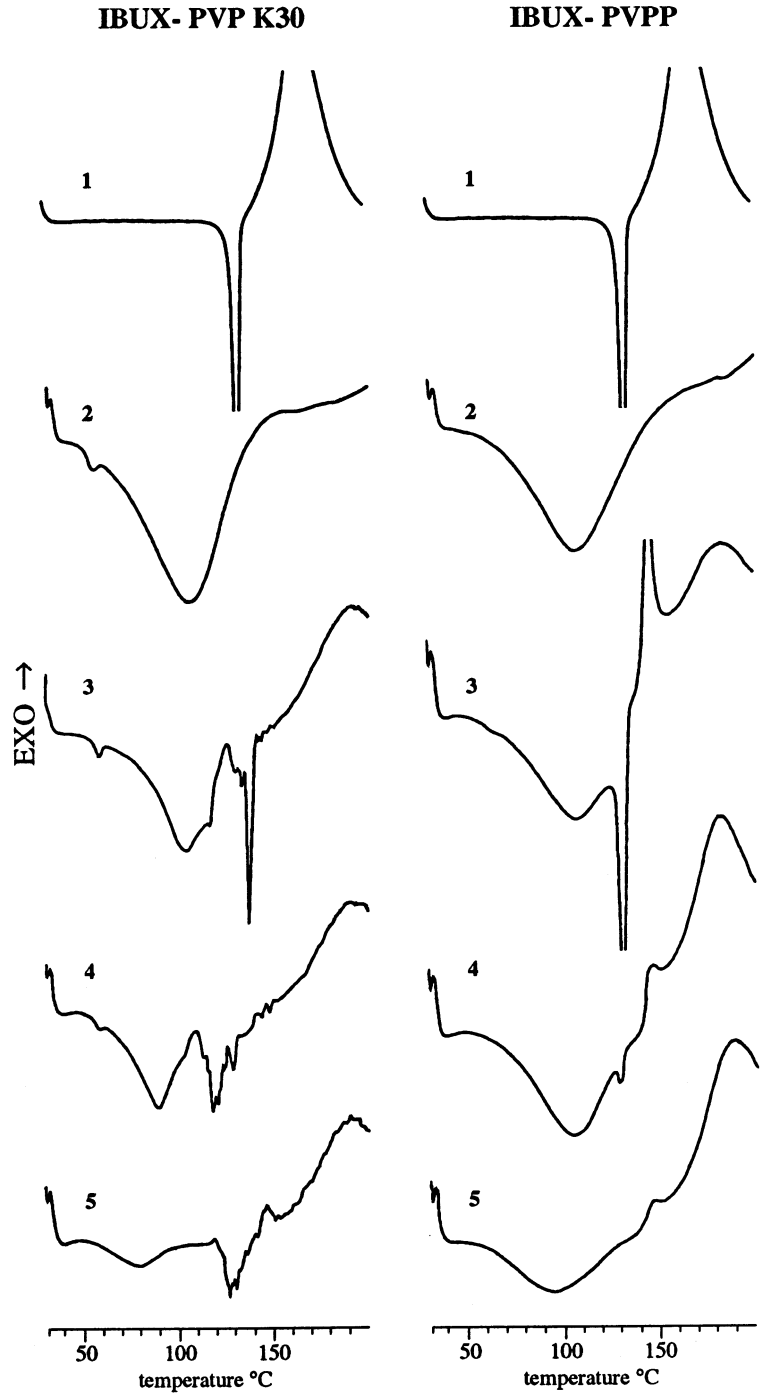

Fig. 6. DSC curves of ibuproxam (IBUX) and its 1:1 w/w mixed systems with PVPK30 and PVPP: (1) Ibuproxam; (2) excipient; (3) physical mixture; (4) coground mixture; (5) kneaded mixture.

The DSC profile of their 1:1 w/w mixed systems with ibuproxam was profoundly influenced by the sample treatment. Interestingly, a different thermal behaviour was observed for the two series of samples. In the case of binary systems with PVPP, the typical drug melting profile was present in the physical mixture, indicating the absence of drug–excipient interaction and therefore compatibility; however, as a consequence of grinding, a dramatic reduction of the drug fusion endotherm was observed, up to its complete disappearance in the kneaded product. This behaviour, which resembles that already described for other drugs such as ketoprofen [6], naproxen [4,9] and ibuprofen [15], indicates that a strong solid–solid interaction has occurred. However it does not necessarily indicate a pharmaceutical incompatibility, but could be attributed to the formation of crystalline microaggregates of the drug and their high dispersion within the amorphous polymeric matrix [16]. This phenomenon, responsible for the particular drug thermal behavior, could even give rise to an improvement of the drug dissolution properties [17]. In mixed systems containing PVP K30, the drug thermal profile appeared considerably modified even in the simple blend, indicating a greater aptitude of this polymer for interacting with the drug. Moreover, the mechanical treatment of the sample caused further deep changes in the drug DSC trace. In fact, in addition to a downward shift, a significant broadening and disfigurement of its endothermal peak was observed. On the other hand no decomposition products of ibuproxam were found (TLC analysis, benzene-cyclohexane-ethyl acetate 5:5:1 v/v) in its blends, ground or kneaded mixtures with both PVPP or PVP K30, in demonstration of drug chemical stability in these binary systems.

SEM analysis (Fig. 7) showed the important role played in the drug–polymer physical interaction by size, shape and roughness of the polymer particles. In particular, in the case of PVPP, where the polymer microspheres present a characteristic popcorn-like structure and appear to be melted into large porous agglomerates, the ibuproxam particles can both adhere to the surface and fill the empty spaces between agglomerates. On the contrary in the case of PVP K30, the drug particles can not only adhere to microspheric particles of the polymer, but also penetrate into the interior of microspheres through openings or fissures. The drug–polymer interaction is favoured by the temperature increase (as it occurs during DSC analysis), owing to the positive influence on the diffusional process: the drug crystals, inserted into the cavities or sticking to the surface of polymer particles can easily be dispersed as crystallites in the amorphous polymeric matrix. 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. HSM analysis showed that the water present in PVP particles emerged in the temperature range from 70 to 120°C, causing ibuproxam crystals to spread out into the softened PVP matrix with a concomitant comminution, phenomenon which further concurs to explain DSC results. The more intense interaction observed in the presence of PVP K30, as compared with PVPP, could be attributed to the lesser difficulty of the drug to penetrate and diffuse into the polymeric mass [18]. It can be concluded that the modification of the melting peak of the drug constitutes the phenomenology of the solid-state interaction between the drug and the polymer and does not represent a pharmaceutical incompatibility.

4. Conclusions

The results obtained confirm that DSC could usefully be employed at preformulation stage as an useful tool for a rapid screening of several candidate excipients, in order to optimise the drug formulation. However it was demonstrated that a careful evaluation of DSC traces is necessary to avoid misinterpretation of the results of such rapid-scan analyses, indicating incompatibilities which may not actually exist. In fact, in spite of noticeable modification of ibuproxam thermal profile in its mixtures with various lubricants, a further and more in-depth investigation by HSM and SEM analysis made it possible to reasonably exclude pharmaceutical incompatibility, at least

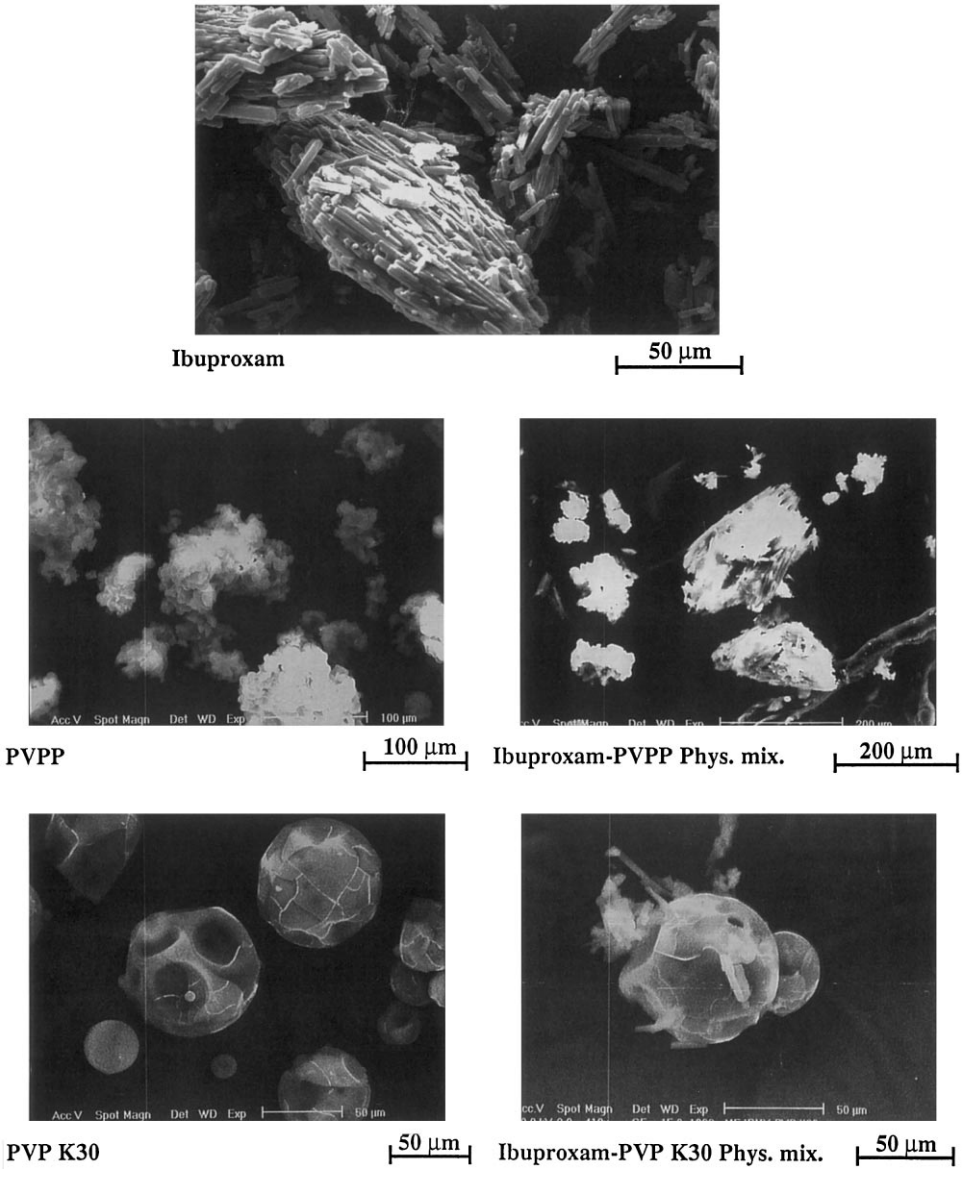

Fig. 7. Scanning electron micrographs of PVPP and PVP K30 and their 1:1 w/w physical mixtures with ibuproxam.

with the lubricant concentrations currently used in solid dosage forms. Finally the importance of sample mechanical treatment in the likelihood of possible solid–solid interactions should be underlined. Cogrinding or kneading may cause (as for systems with PVPP) or emphasize (as for systems with PVP K30) drug–excipient solid–solid interactions not visible or not clearly evident in simple blends. Also in this case HSM and SEM analysis helped to interpret DSC results and allowed for ruling out the hypothesis of pharmaceutical incompatibility.

Acknowledgements

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References

[1] J.L. Ford, P. Timmins, in: M.H. Rubinstein (Ed.), Pharmaceutical Thermal Analysis, Ellis Horwood, Chichester, 1989, pp. 201–237.
[2] D. Giron, J. Pharm. Biomed. Anal. 4 (1986) 755–770.
[3] J.L. Ford, Symposium on Pharmacy and Thermal Analysis, Freiburg, 1993, p. 2.
[4] S.A. Botha, A.P. Lotter, Drug Dev. Ind. Pharm. 16 (1990) 673–683.
[5] S.Y. Lin, R.Y. Han, Pharmazie 47 (1992) 266–268.
[6] P. Mura, A. Manderioli, G. Bramanti, S. Furlanetto, S. Pinzauti, Int. J. Pharm. 119 (1994) 71–79.
[7] M.J. Hardy, Anal. Proc. 19 (1982) 556–557.
[8] A.A. Van Dooren, B.V. Duphar, Drug Dev. Ind. Pharm. 9 (1983) 43–55.
[9] G.P. Bettinetti, P. Mura, A. Liguori, G. Bramanti, F. Giordano, Farmaco Ed. Prat. 43 (1988) 331–343.
[10] P. Mura, G.P. Bettinetti, M.T. Faucci, A. Manderioli, P.L. Parrini, Thermochim. Acta (in press).
[11] M.A. Holgado, M. Fernàndez-Arevalo, J.M. Ginés, I. Caraballo, A.M. Rabasco, Pharmazie 50 (1995) 195–198.
[12] A. Smith, Anal. Proc. 19 (1982) 559–561.
[13] E.S. Watson, M.J. O'Neill, J. Justin, N. Brenner, Anal. Chem. 36 (1964) 1233–1238.
[14] R.E. Gordon, C.L. Van Koevering, D.J. Reits, Int. J. Pharm. 21 (1984) 99–105.
[15] M.N. Najib, M.S. Suleiman, A. Malakh, Int. J. Pharm. 32 (1986) 229–236.
[16] G.P. Bettinetti, P. Mura, F. Giordano, M. Setti, Thermochim. Acta 199 (1991) 165–171.
[17] G.P. Bettinetti, P. Mura, Drug Dev. Ind. Pharm. 20 (1994) 1353–1366.
[18] P. Mura, G.P. Bettinetti, F. Melani, A. Manderioli, 17th Congr. Naz. Soc. Chim. Ital., Genova, 1992, p.231.