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Thermochimica Acta 321 (1998) 59–65

thermochimica acta

Differential scanning calorimetry in compatibility testing of picotamide with pharmaceutical excipients

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Received 17 March 1997; accepted 29 September 1997

Abstract

Differential scanning calorimetry with the support of X-ray powder diffractometry was used as a screening technique for testing the compatibility of picotamide (4-methoxy-N,N′-bis(3-piridinylmethyl)-1,3-benzenedicarboxamide) in the dehydrated form with various pharmaceutical excipients for solid dosage forms. The effect of dry grinding, wet grinding (i.e. kneading) and ageing on drug-excipient blends in the 1:1 (by weight) ratio on physicochemical and chemical stability of the drug was investigated. Chemical compatibility was in general observed with exception of combinations with tartaric and ascorbic acid, where acid/base interactions induced by heating were responsible for the drug degradation evidenced by the profound modification of the thermal effects of individual components. Analogous modifications (i.e. loss of melting peak of the drug) in mixtures with polyvinylpyrrolidone were due to amorphization of picotamide with no substantial alteration of its chemical integrity. Physical compatibility was seen in the systems with microcrystalline cellulose, corn starch, hydroxypropylmethylcellulose and hydroxyethylcellulose where dehydrated picotamide was stable except under wet grinding conditions. In combinations with sodium carboxymethylcellulose, veegum and arabic gum solid-state phase transformation of dehydrated picotamide to monohydrate occurred also by simple blending, probably because of the weak interaction between excipient and the associated water. © 1998 Elsevier Science B.V.

Keywords: Picotamide; Monohydrate; Compatibility; Pharmaceutical excipients; Differential scanning calorimetry; X-ray powder diffractometry

1. Introduction

Chemical and physicochemical interactions in the solid-state between the active ingredient(s) and excipients in pharmaceutical formulations can strongly influence the stability, dissolution rate and bioavailability of solid dosage forms (tablet, capsules, granules or powders). Preformulation studies aimed at pointing out possible drug-excipient interactions are, therefore, essential to the development of fully effective solid dosage forms. Differential scanning calorimetry (DSC) is a useful technique to investigate the physicochemical compatibility between an active principle and pharmaceutical excipients [1–3]. Though DSC cannot replace chemical methods for quantitative determination of drug concentration in long-term stability tests, it gives fast and adequate data

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0040-6031/98/$ – see front matter
PII: S0040-6031(98)00440-7

to classify acceptable and unacceptable excipients through the appearance, shift, or disappearance of endothermic or exothermic peaks, as well as variations in the relevant enthalpy values, in DSC profiles of drug-excipient combinations [4–6]. In a preformulation study aimed at developing tablet dosage forms of 4-methoxy-N,N′-bis(3-piridinylmethyl)-1,3-benzenedicarboxamide (picotamide), a fibrinolytic and platelet antiaggregant agent given by mouth as monohydrate [7] (Plactidil®), DSC was used as a screening tool for the compatibility of this drug in the dehydrated state with some excipients commonly used in solid pharmaceutical dosage forms. They were corn starch, arabic gum, hydroxypropylmethylcellulose (methocel), veegum, sodium carboxymethylcellulose, microcrystalline cellulose (avicel), hydroxyethylcellulose (natrosol), polyvinylpyrrolidone K30, polyvinylpolypyrrolidone, tartaric acid and ascorbic acid. DSC curves of the drug and individual excipients were compared with those of each drug-excipient blend in the 1:1 (by weight) ratio, which was chosen to maximize the likelihood of an interaction [2,8]. The effects of intimate mixing, which was accomplished by dry grinding or by slurring with ethanol (kneading), as well as of ageing for 3 weeks at 60°C, were also investigated. X-ray powder diffraction analysis at room temperature was used to complement and support the DSC results.

2. Experimental

2.1. Materials

Commercially available picotamide was twice recrystallized from water–ethanol 8:1 (v/v) and dried in an oven at 80°C for 24 h to obtain the dehydrated form (PICO), $T_{peak,fus}$=135.5±0.4°C, ΔH_{fus}=74.4±2.2 J g^{-1} (7 runs). The excipients examined (polyvinylpyrrolidone K30 (PVP K30)), polyvinylpolypyrrolidone (PVPXL), tartaric acid, ascorbic acid (Merck-Schuchardt, D-Munchen); hydroxypropylmethylcellulose (methocel), hydroxyethylcellulose (natrosol) (Aqualon Italia, I-Castelmaggiore); sodium carboxymethylcellulose (NaCMC), microcrystalline cellulose, (avicel) (Dow Chemical, Cincinnati, USA); veegum F (Bayer-Italia, I-Milano); arabic gum, corn starch (Carlo Erba, I-Milano)) were used as received.

2.2. Preparation of samples

Each material was sieved and the respective 75–150 μm fraction was used. Physical mixtures (300 mg) were prepared by blending equal amounts of PICO and each excipient in an agate mortar with a spatula. The blends were considered homogeneous when the DSC traces of three samples from the same preparation were superimposable within the limit of experimental error. Co-ground mixtures were obtained by triturating 100 mg of blend in the mortar with a pestle for 10 min. Kneaded mixtures were prepared by slurring 100 mg of blend with the minimum amount of ethanol (1–2 ml) and triturating as above to obtain a paste which was dried in a desiccator (over P_2O_5 at room temperature and 20 mm Hg) to a constant weight. The effect of ageing the drug-excipient blends over a period of 3 weeks at 60°C in an oven was also evaluated.

2.3. Differential scanning calorimetry

Weighed samples (5–10 mg, Mettler M3 Microbalance) of the individual components or drug-excipient combinations (75–150 μm sieve 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.

2.4. X-ray diffractometry

X-ray powder diffraction patterns were obtained with a Philips PW 1130 diffractometer (Cu Kα radiation), at a scan rate of 2° min^{-1} over the 10–40° 2θ range.

3. Results and discussion

On extended exposure to ambient conditions of relative humidity (≈50%) and temperature (≈25°C), the dehydrated form of the drug tested (PICO) (see Fig. 1, curve a) gave a solid-state phase transformation to monohydrate (PICO.H_2O) with a decrease in the aqueous solubility at 25°C from 0.11 to 0.094 mg ml^{-1} [9]. PICO.H_2O, the thermodynamically stable modification at room temperature, gave

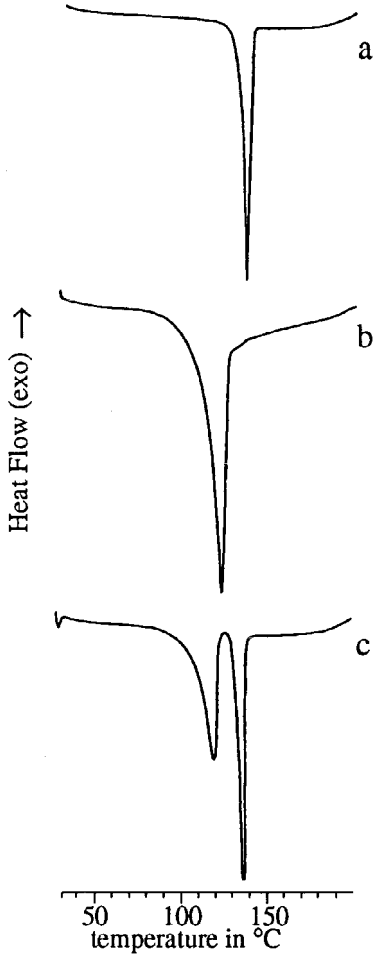

Fig. 1. DSC curves of (a) dehydrated picotamide (PICO), (b) picotamide monohydrate (PICO.H_2O) obtained from solid-state phase transition of PICO under ambient conditions of relative humidity (≈50%) and temperature (≈25°C) and (c) PICO/PICO.H_2O mixture (i.e., sample of partially transformed PICO).

a DSC endothermal effect at 123.0±2.4°C with an associated dehydration enthalpy of 156±13 J g^{-1} (7 runs) and can be restored easily to PICO by heating in an oven at 80°C for 24 h (see Fig. 1, curve b). The 'dehydrated hydrate' [10] PICO retains the X-ray diffraction pattern of the hydrate from which it was derived (Fig. 2), so that the nature of a 'pseudopolymorphic hydrate' for PICO.H_2O according to the classification of Byrn [11] can be assumed. Except for tartaric acid and ascorbic acid, all other excipients examined exhibited a shallow, broad DSC endothermic effect in the 70–140°C temperature range due to

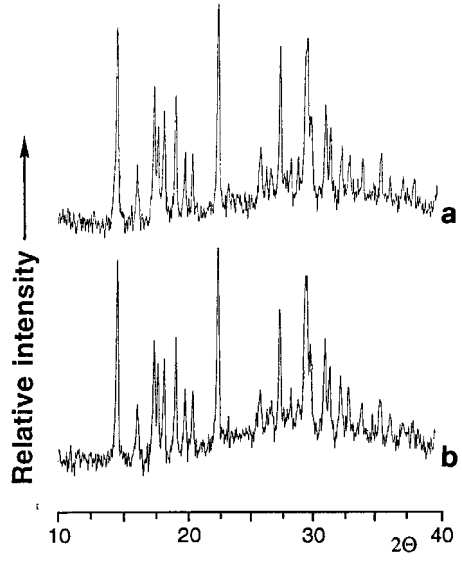

Fig. 2. X-ray diffraction patterns of (a) dehydrated picotamide (PICO) and (b) picotamide monohydrate (PICO.H_2O) obtained from solid-state phase transition of PICO under ambient conditions of relative humidity (≈50%) and temperature (≈25°C).

water loss (Table 1). Thermal parameters calculated from DSC curves of individual components and drug-excipient combinations, that is from freshly prepared and aged blends and dry ground and kneaded (i.e. wet ground) mixtures, are presented in Tables 1 and 2, respectively. The anhydrous state of the drug was maintained by blending and dry grinding with avicel (Fig. 3(a)), corn starch, methocel or natrosol, indicat-

Table 1
Thermal parameters of dehydrated picotamide (PICO) and excipients tested

Sample	T_{peak} (°C)	T_{onset} (°C)	$\Delta_{fus}H$ (J g^{-1})	$\Delta_{dehyd}H$ (J g^{-1})
PICO	135.3	130.7	75.6	–
Corn starch	107.4	59.0	–	246.5
Arabic gum	102.2	54.7	–	267.4
Methocel	99.7	61.8	–	101.0
Veegum	130.7	60.8	–	121.4
NaCMC	101.0	56.8	–	293.4
Avicel	115.7	72.0	–	267.4
Natrosol	107.7	65.1	–	137.8
PVP K30	105.6	66.8	–	329.6
PVP XL	106.7	68.3	–	303.2
Tartaric acid	171.9	169.9	215.4	–
Ascorbic acid	192.0	190.4	210.3	–

Table 2
Thermal parameters of picotamide (PICO) in binary mixtures with the excipients tested

Excipient	Peak temperature (°C)				Onset temperature (°C)				Enthalpy (J g^{-1})			
	Physical mixture		Ground mixture	Kneaded mixture	Physical mixture		Ground mixture	Kneaded mixture	Physical mixture		Ground mixture	Kneaded mixture
	Fresh	Aged			Fresh	Aged			Fresh	Aged		
Corn starch	132.2	135.5	133.0	119.6	124.7	126.5	126.6	94.4	79	82	64	94
Arabic gum	123.8	122.0	124.0	123.7	114.4	113.7	114.2	113.9	104	99	90	96
Methocel	135.3	135.5	135.0	119.9	127.2	128.3	126.4	97.8	69	71	59	93
Veegum	121.8	121.9	120.9	122.1	105.8	107.7	105.2	108.3	82	91	52	57
NaCMC	128.5	125.6	121.7	125.8	118.1	118.0	113.5	115.8	68	76	83	67
Avicel	135.2	134.1	134.0	118.1	128.9	110.6	126.9	99.8	49	56	54	66
Natrosol	134.2	132.4	126.3	118.5	104.9	102.7	100.3	103.6	58	65	59	83
PVP K30	133.6	135.0	–	–	125.9	128.9	–	–	72	74	–	–
PVP XL	134.5	134.7	124.0	119.6	128.3	126.9	97.0	96.5	77	62	–	70
Tartaric acid	117.4	–	–	–	101.2	–	–	–	58	–	–	–
Ascorbic acid	130.0	–	–	–	112.5	–	–	–	70	–	–	–

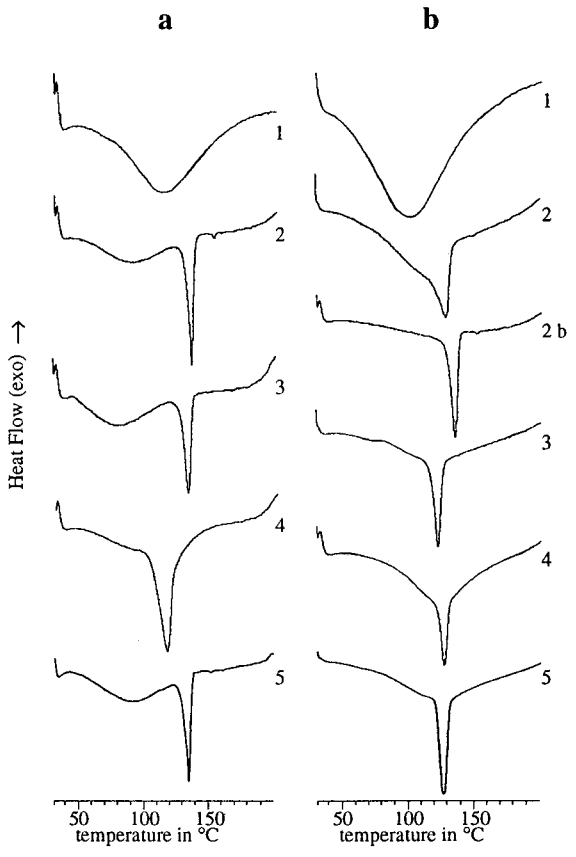

Fig. 3. DSC curves of 1:1 (by weight) dehydrated picotamide (PICO)/avicel (a) and PICO/sodium carboxymethylcellulose (NaCMC) (b) combinations. Key: 1, excipient; 2, blend; 2b, blend kept at 100°C for 10 min in an oven; 3, cogroud mixture; 4, kneaded mixture; 5, aged blend. Curves (a) representative for the systems of PICO with corn starch, hydroxypropylmethylcellulose (methocel) and hydroxyethylcellulose (natrosol); curves (b) representative for the systems of PICO with veegum and arabic gum.

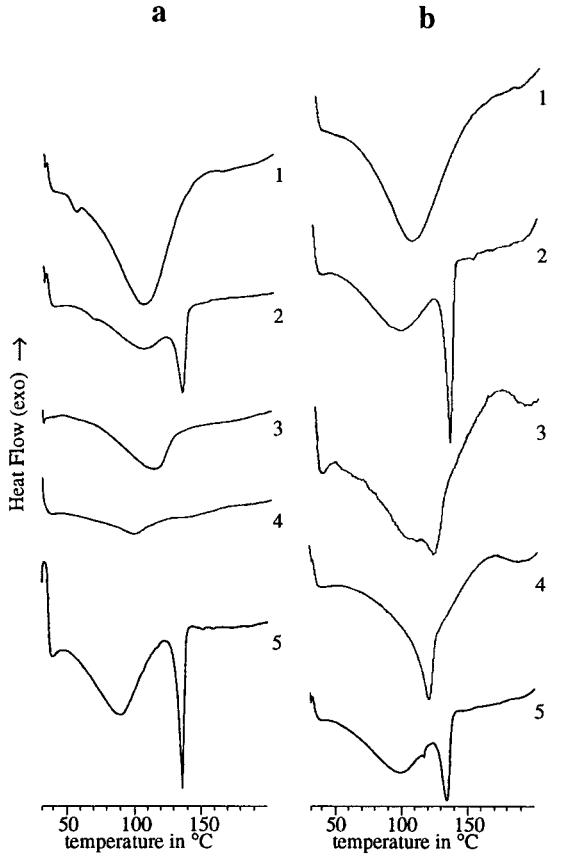

Fig. 4. DSC curves of 1:1 (by weight) dehydrated picotamide (PICO)/PVP K30 (a) and PICO/PVP-XL (b) combinations. Key: 1, excipient; 2, blend; 3, coground mixture; 4, kneaded mixture; 5, aged blend.

ing compatibility of PICO with these excipients. Wet conditions, i.e. kneading, were necessary to bring about the solid-state transformation to PICO.H_2O. In the systems with NaCMC (Fig. 3(b)), veegum and arabic gum, instead, hydration of the drug occurred simply by blending. It can be attributable to the mobility of water bound to these excipients as reflected by the onset temperature of water loss which for NaCMC, for example, was distinctly lower than for avicel (Table 1). Phase transformation to PICO.H_2O was reversible because of the easy conversion to PICO by heating at 100°C for 10 min (Fig. 3(b), curve 2b).

In freshly prepared and aged blends with polyvinylpyrrolidone, PICO remained in the anhydrous state, whilst in ground mixtures distinct interactions were revealed by DSC (Fig. 4). In particular in the combination with PVP-XL, the dehydration peak of PICO.H_2O at about 124°C emerged (Fig. 4(b)) indicating hydration of the drug which probably occurred with the same mechanism assumed for avicel. In the combination with PVP K30, instead, a profound modification of thermal effects with loss of the PICO melting endotherm was seen (Fig. 4(a)). X-ray powder diffraction patterns of the PICO-PVP K30 ground mixtures kept at room temperature or at higher temperatures (100, 110, 120°C) for 10 min revealed the presence, respectively, of crystalline or amorphous PICO (Fig. 5). This demonstrated the role of heating

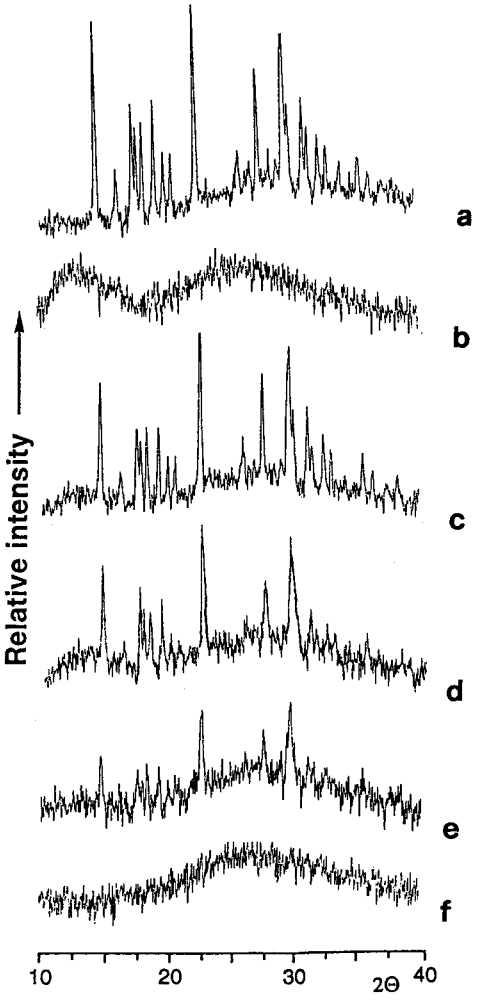

Fig. 5. X-ray diffraction patterns of dehydrated picotamide (PICO) and 1:1 w/w mixed systems of PICO with PVP K30. Key: PICO (a); PVP K30 (b); physical mixture (c); coground mixture (d); PICO-PVP K30 coground mixture after 10 min heating at 100°C (e) and 120°C (f).

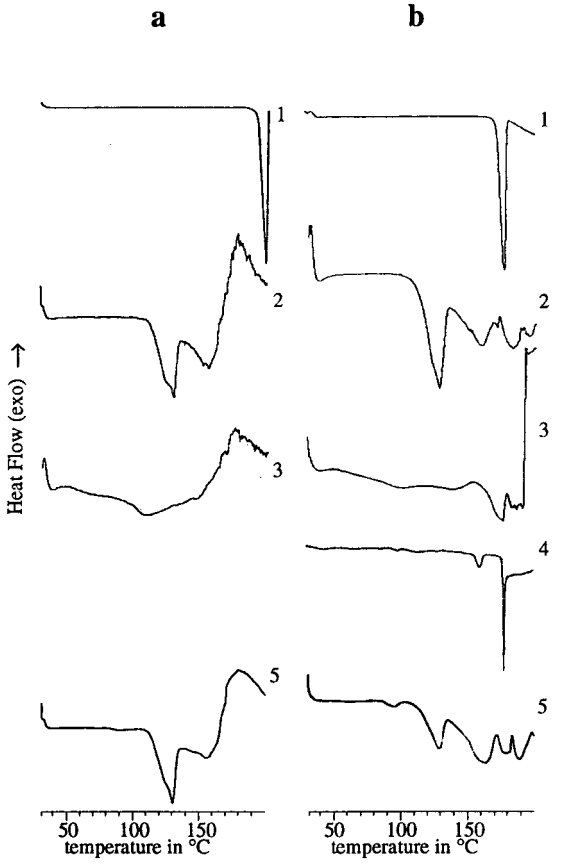

Fig. 6. DSC curves of 1:1 (by weight) dehydrated picotamide (PICO)/ascorbic acid (a) and PICO/tartaric acid (b) combinations. Key: 1, excipient; 2, blend; 3, coground mixture; 4, kneaded mixture; 5, aged blend.

in promoting the amorphization of PICO dispersed within the amorphous polymer. Such an effect has been already described for other drugs such as naproxen [12] and ketoprofen [13]. Since the chemical integrity of the drug in the combinations with PVP was not adversely affected, these interactions are not detrimental from pharmaceutical point of view [14] despite the dramatic alteration of the thermal behaviour pointed out by DSC. In the presence of acid excipients, drug stability seemed to be seriously affected, when the marked broadening and downshift of thermal effects of individual components, followed by exothermic or endothermic decomposition, present even in DSC traces of freshly prepared blends, is considered (Fig. 6). Acid–base interactions were probably responsible for excipient incompatibility. The salt formation with tartaric acid (pK_a 2.99–4.34) is in fact known [15] and it can be analogously hypothesized with ascorbic acid (pK_a 4.2). X-ray diffraction showed, however, the absence of significant interactions at room temperature not only in freshly prepared blends but also in both aged and mechanically treated samples (Fig. 7). Heating was then the driving force of the decomposition process between PICO and the partner of acidic character.

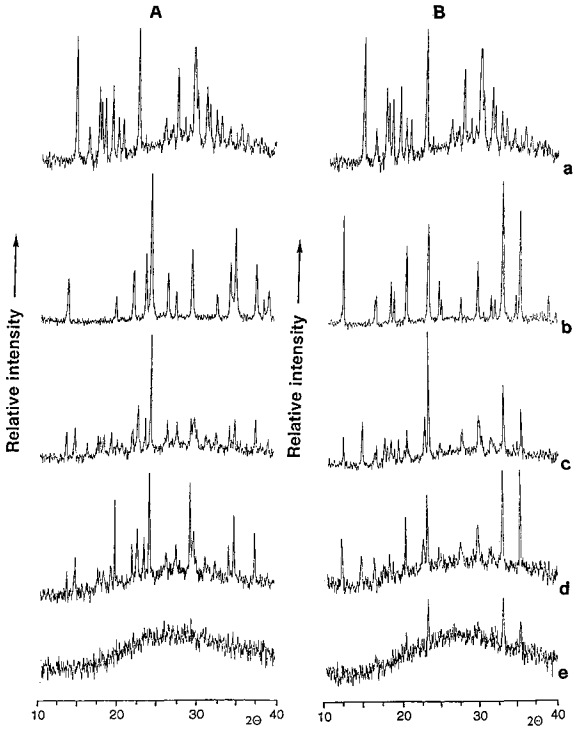

Fig. 7. X-ray diffraction patterns of dehydrated picotamide (PICO) and 1:1 w/w mixed systems of PICO with tartaric acid (A) and ascorbic acid (B). Key: PICO (a); excipient (b); physical mixture (c); coground mixture (d); coground mixture after 10 min heating at 120°C (e).

Transformation of powder PICO-ascorbic acid mixtures into rubbery non-pulverisable masses can, therefore, be ascribed to physical incompatibility rather than to salt formation.

4. Conclusions

The results demonstrated the suitability of DSC as a quick screening tool of candidate excipients at the early stages of a formulation design. Although thermal effects recorded at elevated temperatures must be interpreted cautiously and may not be always relevant at ambient conditions, DSC provides useful indications of the potential problems, so that an excipient can be rejected, or if it is considered indispensable, the nature of interactions with the active ingredient can be investigated in depth.

In the case of PICO, compatibility with various cellulose derivatives, corn starch, veegum and arabic gum was demonstrated, as well as a facile transformation of dehydrated PICO to monohydrate in some mixtures. On the other hand, drug stability was strongly affected by the presence of tartaric and ascorbic acids, as reflected by the profound modifications of thermal profiles in the respective mixtures. The marked interaction in ground mixtures with PVP resulting in loss of melting endotherm of PICO, was due to a heating-induced drug amorphization rather than to chemical degradation, as confirmed by the X-ray diffraction patterns. X-ray powder diffractometry is, therefore, a valuable technique to support the DSC results in preformulation studies.

Acknowledgements

This work was supported by a grant from Istituto Superiore di Sanità – Roma (Progetto proprietà chimico-fisiche dei medicamenti e loro sicurezza d'uso).

References

[1] D. Giron, J. Pharm. Biomed. Anal. 4 (1986) 755.
[2] J.L. Ford, Acta Symposium on Pharmacy and Thermal Analysis, Freiburg, 1993, 2 pp.
[3] S. Venkataram, M. Khohlokwane, S.H. Wallis, Drug Dev. Ind. Pharm. 21 (1995) 847.
[4] S.A. Botha, A.P. Lotter, Drug Dev. Ind. Pharm. 16 (1990) 673.
[5] S.Y. Lin, R.Y. Han, Pharmazie 47 (1992) 266.
[6] D.C. Monkhouse, A. Maderich, Drug Dev. Ind. Pharm. 15 (1989) 2115.
[7] E. Foresti, L. Riva di Sanseverino, P. Sabatino, Acta Crystallogr. C42 (1986) 220.
[8] A. Smith, Anal. Proc. 19 (1982) 559.
[9] G. Orzalesi, I. Volpato, Patent no. 48494A/80, Italy, 1980.
[10] G.P. Bettinetti, A. La Manna, Boll. Chim. Farm. 134 (1995) 352.
[11] S. Byrn, R. Pfeiffer, M. Ganey, C. Hoiberg, G. Poochikian, Pharm. Res. 12 (1995) 945.
[12] G.P. Bettinetti, P. Mura, A. Liguori, G. Bramanti, F. Giordano, Farmaco Ed. Pr. 43 (1988) 331.
[13] S.A. Botha, A.P. Lotter, Drug Dev. Ind. Pharm. 15 (1989) 415.
[14] G.P. Bettinetti, P. Mura, Drug Dev. Ind. Pharm. 20 (1994) 1353.
[15] Martindale, in: J.E.F. Reynolds (Ed.), The Extra Pharmacopeia, 31st ed., Royal Pharmaceutical Society, London, 1996.