Physical Characterization of Picotamide Monohydrate and Anhydrous Picotamide

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Abstract □ Picotamide is an antiplatelet agent given by mouth as monohydrate (PICOW) (Plactidil) in thrombo-embolic disorders. This study deals with physical characterization of PICOW recrystallized from various solvents and the respective dehydration products using X-ray powder diffractometry (XRD), infrared spectroscopy (IR), and thermal analytical techniques (differential scanning calorimetry, DSC; thermogravimetric analysis, TGA; simultaneous TGA/DSC; hot stage microscopy, HSM). Monophasic and biphasic DSC and TGA profiles of water loss were recorded under open conditions for PICOW samples which showed the same monoclinic crystal structure. Biphasic profiles became monophasic for gently ground samples which were, however, structurally identical to the intact samples. Morphological factors, the various degree of "perfection" of the PICOW crystal lattice, and/or cluster aggregation of PICOW crystals were assumed to be responsible for the differing dehydration patterns. Polymorphism in anhydrous picotamide, i.e., nucleation of crystal forms A, mp 135.5 ± 0.4 °C, and B, mp 152.9 ± 0.3 °C after dehydration of PICOW, was detected by DSC and HSM. The dehydration product of PICOW under isothermal conditions (115 °C, 20 mmHg), PICOA, was mainly composed of the lower melting polymorph A (fusion enthalpy 74.4 ± 2.2 J g^{-1}), which gradually reverted to the starting hydrate by storing in an ambient atmosphere. Dissolution tests of PICOW and PICOA in water at 37 °C as both powders and compressed disks reflected to some extent the higher solubility of the metastable form (by 24% at 37 °C) in terms of both higher dissolution efficiency and percent of active ingredient dissolved (by 28%) and intrinsic dissolution rate (by 32%).

Introduction

Picotamide (4-methoxy-*N*,*N*′-bis(3-pyridinylmethyl)-1,3-benzenedicarboxamide, Figure 1) is an antiplatelet agent sharing a dual anti-thromboxane activity (i.e., inhibition of thromboxane A2 synthase and thromboxane A2 receptor antagonism) which in the second half of the 1990s has been widely studied from the pharmacological and clinical point of views mainly in Italy.[1] Picotamide is given by mouth in thrombo-embolic disorders as monohydrate (PICOW), the active ingredient present in commercial dosage forms (Plactidil). The crystal structure of PICOW has been determined since 1986,[2] but the solid-state properties of this drug[3] and some of its binary systems with pharmaceutical excipients[4,5] have been investigated only recently.

Although all picotamide samples recrystallized by precipitation from various solvents showed the same physicochemical properties as PICOW, different DSC dehydration profiles and dehydration products were obtained depending on the recrystallizing solvent of the tested PICOW sample.[3] The same anhydrous crystal form, hereafter reported as PICOA, was however obtained by dehydration under isothermal conditions (115 °C, 20 mmHg) of PICOW, whatever the recrystallization solvent of the sample.

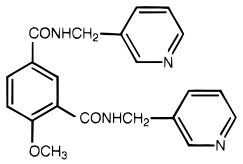

Figure 1—Molecular structure of picotamide.

The thermodynamic differences between a drug hydrate and its anhydrous counterpart necessitate detailed studies on their phase stability. The change in thermodynamic activity of the drug due to hydration/dehydration alters pharmaceutically important properties such as physical and chemical stability, as well as solubility and dissolution rate.[6–8] The effect of mechanical treatments, i.e., grinding, also deserve attention in this respect,[9] particularly because of the possible dependence of the dehydration mechanism on the particle size.[10,11]

The present study deals with the physical characterization of PICOW and PICOA by X-ray powder diffractometry (XRD), mid- and near-infrared (IR) spectroscopy, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), simultaneous TGA-DSC, and hot-stage microscopy (HSM). Thermal dehydration of intact and ground samples of PICOW from different recrystallization solvents and rehydration of PICOA under controlled conditions of relative humidity (RH) and temperature were investigated. The aqueous solubilities of PICOW and PICOA as a function of temperature (20−45 °C), as well as their dissolution rates in water at 37 °C as both powders and compressed disks, were also determined.

Experimental Section

Materials—Commercially available PICOW (Manetti & Roberts, Firenze, Italy) was used. The product was recrystallized from water−ethanol 8:1 (v/v) and subsequently dried in a desiccator over P_2O_5 at room temperature (see Table 1). PICOA was prepared by drying PICOW from water−ethanol 8:1 (v/v) under reduced pressure (over P_2O_5 in a drying pistol, 20 mmHg) in a hot air oven at 115 °C for 1 h and storing over P_2O_5 in a desiccator (see Table 1). Solvents of analytical reagent grade and bi-distilled water were used.

Preparation of PICOW Samples—Recrystallized samples were prepared by precipitation of PICOW from different recrystallization solvents following the procedures described in ref 3. Ground samples were prepared by manually grinding 500 mg of

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Table 1—Elemental Analysis and Water Content of Picotamide Monohydrate (PICOW) from Water–Ethanol 8:1 (v/v) and Anhydrous Picotamide (PICOA)

sample	elemental analysis (% w/w) found (calcd)	water content (% w/w)[a] KFT[b]	TGA[c]
PICOW	C 63.78(63.95)		
$C_{21}H_{20}N_4O_3 \cdot H_2O$	H 5.69(5.62)	4.96 (0.23)	4.84 (0.21)
	N 14.01(14.20)		
PICOA	C 67.24(67.01)		
$C_{21}H_{20}N_4O_3$	H 5.46(5.36)		
	N 14.81(14.88)		

[a] Calculated for the monohydrate 4.57% (w/w). [b] Karl-Fischer titrimetry, standard deviation in parentheses ($n = 6$). [c] Thermogravimetric analysis in open pans (mass loss over the temperature range of the DSC dehydration endotherm), standard deviation in parentheses ($n = 6$).

material with pestle and mortar. Rehydrated samples were prepared by storing PICOA (≈2 g samples spread on Petri dishes) in a desiccator at room temperature (22 °C) kept at a relative humidity (RH) of 45% or ≈100% by equilibrating over a saturated solution of KNO_2 or pure water, respectively. Samples (5−10 mg) were taken out at appropriate intervals and checked for water content by DSC and TGA (see below).

X-ray Diffractometry (XRD)—Powder X-ray diffraction patterns were taken at ambient temperature and atmosphere with a computer-controlled Philips PW 1800/10 apparatus equipped with a specific PC-APD software. Wavelengths: Cu $K_{\alpha,1} = 1.54060$ Å, Cu $K_{\alpha,2} = 1.54439$ Å. Scan range: 2−50° 2θ. Scan speed: 0.02° 2θ s^{-1}. Monochromator: graphite crystal.

Infrared (IR) Spectroscopy—Mid-IR (400−4000 cm^{-1}) spectra were recorded by the Nujol mull method using a double beam Perkin-Elmer 983 IR spectrophotometer. Near-IR (4500−10000 cm^{-1}) spectra (NIR) were recorded directly on powder samples (75−150 μm sieve granulometric fraction) by using an optical head linked to the NIR reflectance analyzer (Infraprover II Technicon Model No. 450 RP) by optical fibers.

Karl Fischer Titrimetry (KFT)—The amount of water in the PICOW samples was determined with a Mettler DL40GP Memo titrator apparatus. Samples (80−90 mg) were quickly transferred to the titration vessel containing anhydrous methanol and titrated using Hydranal Composite 5 (Riedel-de Haen, Milano, Italy).

Differential Scanning Calorimetry (DSC)—Temperature and enthalpy values were measured with a METTLER STAR^e system equipped with a DSC821^e Module on 3−5 mg (Mettler M3 Microbalance) samples in uncovered aluminum pans under static air. An uncovered empty pan was used as reference. The heating rate was 5 K min^{-1} over the 30−180 °C temperature range.

Thermogravimetric Analysis (TGA)—Mass losses were recorded with a Mettler TA 4000 apparatus equipped with a TG 50 cell at the heating rate of 5 K min^{-1} on 7−10 mg samples in open alumina crucibles in the 30−180 °C temperature range under static air.

Simultaneous TGA-DSC—Simultaneous recording of mass loss and enthalpy change was carried out with a METTLER STAR^e system equipped with a TGA/SDTA851^e Module and calibrated with indium on 2.5−3.5 mg samples in a platinum crucible under nitrogen gas flow (150 mL min^{-1}). The heating rate was 10 K min^{-1} over the 40−200 °C temperature range.

Hot-Stage Microscopy (HSM)—Microscopic observation of the thermal events was carried out under a Reichert polarized light microscope equipped with a Mettler FP82HT/FP80 system at a heating rate of 10 K min^{-1} which was reduced to 5 K min^{-1} in the regions of the DSC peaks. Images were transferred via a Panasonic WV-CP100E CCTV camera to a Panasonic WC-CH110A video monitor.

Solubility Measurements—Excess amounts (50 mg) of PICOW or PICOA powder (75−150 μm sieve granulometric fraction) were added to 30 mL of nonbuffered water (pH ≈ 6) in sealed 50 mL glass containers, which were electromagnetically stirred at a constant temperature (20, 25, 32, 37, 45 °C ± 0.2 °C). At suitable time intervals aliquots were withdrawn, filtered (pore size 0.45 μm), suitably diluted with water, and spectrophotometrically assayed for drug concentration at $\lambda = 254.4$ nm (Perkin-Elmer 552S Spectrophotometer). Residual solid material was identified

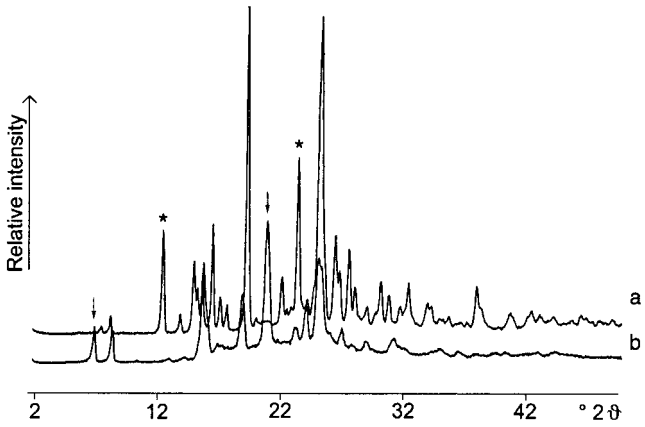

Figure 2—XRD patterns of (a) picotamide monohydrate (PICOW) from water–ethanol 8:1 (v/v) and (b) anhydrous picotamide (PICOA). Characteristic diffraction peaks of PICOW at 12.6° and 23.6° (2θ) (stars) and of PICO A at 7.1° and 21.2° (2θ) (arrows) are indicated.

postequilibrium by DSC and IR analysis. Plateau values of dissolved concentration of the metastable PICOA form, before declining toward the corresponding plateau value of the stable PICOW form, were assumed as the equilibrium solubility. Tests were performed in triplicate and averaged.

Dissolution Tests—Dispersed amount experiments were performed in nonbuffered water (pH ≈ 6) at 37 ± 0.2 °C by adding 45 mg of PICOW or PICOA powder (75−150 μm sieve granulometric fraction) to 75 mL of water in a 150 mL beaker (nonsink conditions). A glass three-blade propeller (19 mm diameter) was immersed in the beaker 25 mm from the bottom and rotated at 100 ± 1 rpm. In the rotating disk method, tablets (1.3 cm in diameter) were prepared by compressing 300 mg of powders using a Perkin-Elmer hydraulic press for KBr disks for IR spectroscopy, at a force of 1.5 t cm^{-2} for 10 min which yielded tablets with a surface area of 1.33 cm^2 which would not disintegrate during the test. No lubricant was used. No detectable PICOW dehydration or PICOA hydration associated with compression was found in the disks by IR, DSC, and TGA analysis of powder samples taken by gently scratching the disk surface with a blade. The tablets were inserted into a stainless steel holder, so that only one face was exposed to the dissolution medium. The holder was then connected to a stirring motor, centrally immersed in a 150 mL beaker containing 100 mL of nonbuffered water (pH ≈ 6) at 37 ± 0.2 °C and rotated at 100 ± 1 rpm. In both methods, suitable aliquots were withdrawn with a filter-syringe (pore size 0.45 μm) at the specified times and assayed for drug content as in Solubility Measurements. A correction was calculated for the cumulative dilution caused by replacement of the sample with equal volume of original medium. Each test was repeated four times (coefficient of variation, CV < 3% and < 7% for dispersed amount and rotating disk experiments, respectively).

Results and Discussion

Physicochemical Properties of the Solid Phases—PICOW and PICOA (see Table 1 for elemental analysis and water stoichiometry) were characterized with data from XRD, IR, conventional and simultaneous DSC and TGA, and HSM. The XRD pattern of PICOW corresponding to the theoretical powder pattern assessed from crystal structure data[3] was obtained using a ground sample (Figure 2). Actually, using an intact sample, a strong enhancement of the diffracted intensities of some peaks probably due to preferred orientation effects[12] was observed.[3] A distinctly different XRD pattern was recorded for PICOA, which shows characteristic reflections at 7.1° and 21.2° (2θ) which are useful for identification purposes and an apparent lower crystallinity than that of the parent hydrate.

The IR spectra of PICOW and PICOA are presented in Figure 3. In the O−H stretching region of PICOW, crystal-

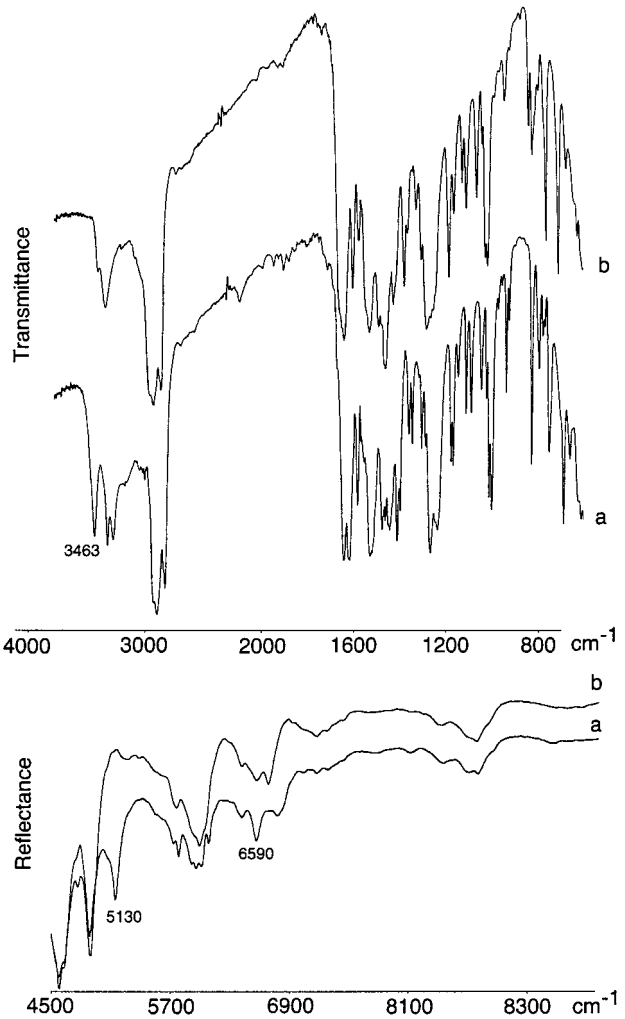

Figure 3—IR spectra of (a) picotamide monohydrate (PICOW) from water–ethanol 8:1 (v/v) and (b) anhydrous picotamide (PICOA) in the 4000–700 and 4500–9900 cm^{-1} range. Characteristic absorption bands of water at 3463 cm^{-1}, 5130 cm^{-1}, and 6590 cm^{-1} are indicated.

line water shows a sharp high-frequency (3463 cm^{-1}) absorption band[13] which suggests the presence of "tightly bound" water in the crystal lattice.[14] The number and strength of hydrogen bonds involving the water molecules regularly arranged through the crystal[2] confirm this hypothesis. Other differences at the level of the 3354−3304 (assignable to the N−H amide stretching) and 1658−1632 cm^{-1} (assignable to the amide carbonyl group) doublets in the anhydrous and hydrated structures can be attributed to the absence and presence of lattice water within the hydrogen bond patterns. The NIR absorption bands at 5130 and 6590 cm^{-1} are also characteristic of crystalline water[15,16] and permit discrimination between the anhydrous and hydrated picotamide forms.

The thermal behavior of PICOW obtained by recrystallization from water−ethanol 8:1 (v/v), ethyl acetate, or benzene and of PICOA is depicted in Figures 4−6. The negative DSC peak for endotherms between 60 and 130 °C (enthalpy change 189 ± 5 J g^{-1}) of the intact PICOW sample from water−ethanol 8:1 (v/v) (Figure 4a) was reflected by the negative derivative TGA peak for mass loss over the same temperature range (Figure 5a). The relevant mass loss of 4.84 ± 0.21% (w/w) was confirmed by simultaneous TGA/DSC (Figure 6) and corresponded to a monohydrate stoichiometry (see Table 1). Moderate grinding did not substantially alter the water content and the dehydration enthalpy of the sample, whereas it decreased (by 3−4

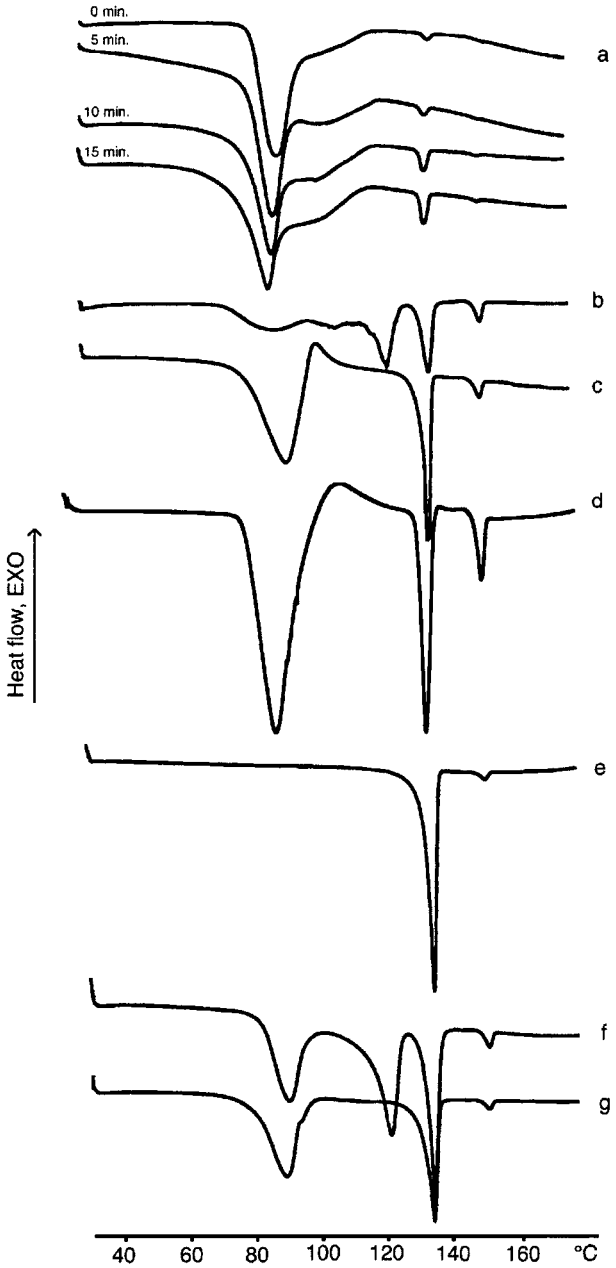

Figure 4—DSC curves of picotamide monohydrate (PICOW) and anhydrous picotamide (PICOA). Key: (a) PICOW from water–ethanol 8:1 (v/v) (grinding time on the curves); (b) PICOW from ethyl acetate, intact sample; (c) PICOW from ethyl acetate, ground sample; (d) PICOW from benzene, intact sample; (e) PICOA by isothermal dehydration (115 °C, 20 mmHg) of an intact sample of PICOW from water-ethanol 8:1 (v/v); (f) PICOW by rehydration of PICOA in an ambient atmosphere (RH ≈ 45%), intact sample; (g) PICOW by rehydration of PICOA at RH ≈ 45%, ground sample.

°C) the onset and peak temperatures of the DSC dehydration endotherm (see Figure 4a) possibly by reducing the particle size and changing the surface feature of the crystals.[17] A parallel increase in the enthalpy change of the small endothermal effect at ≈136 °C was evident. This effect was attributable to melting of the anhydrous crystal form A of picotamide (see later).

A thermal behavior similar to that depicted in Figures 4a and 5a was recorded for PICOW samples recrystallized from water, methanol, ethanol, and *n*-propanol.[3] Different DSC and TGA profiles in both the dehydration and post-dehydration stages were instead observed for PICOW recrystallized from ethyl acetate (Figures 4b and 5b) and from benzene (Figures 4d and 5d). The distinct crystal-

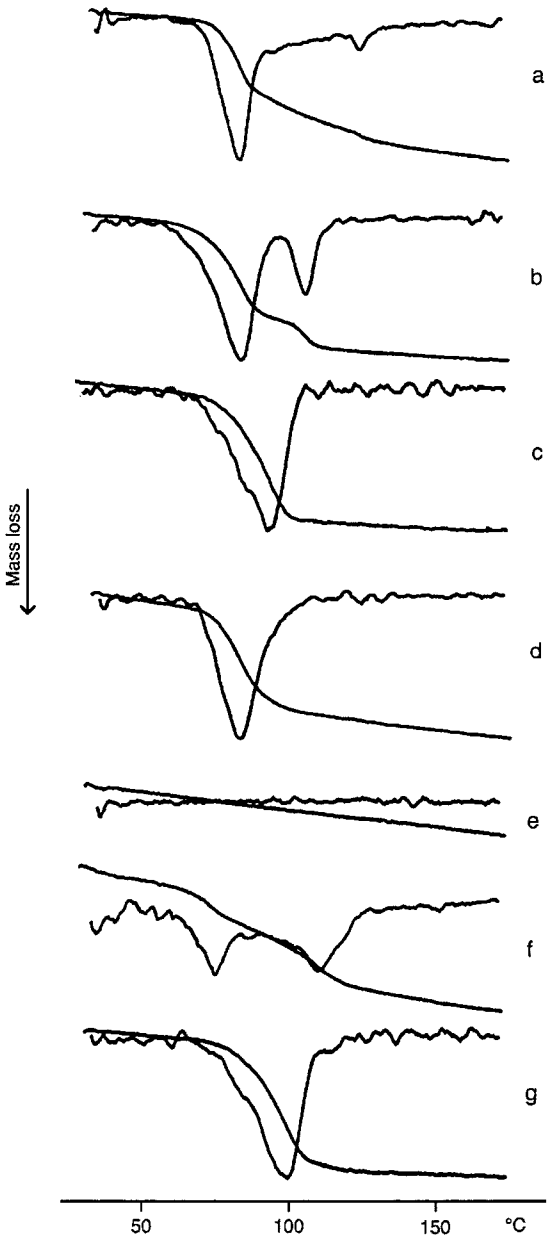

Figure 5—TGA curves of picotamide monohydrate (PICOW) and anhydrous picotamide (PICOA). Key: (a) PICOW from water–ethanol 8:1 (v/v), intact sample; (b) PICOW from ethyl acetate, intact sample; (c) PICOW from ethyl acetate, ground sample; (d) PICOW from benzene, intact sample; (e) PICOA by isothermal dehydration (115 °C, 20 mmHg) of (a); (f) PICOW by rehydration of PICOA in an ambient atmosphere (RH ≈ 45%), intact sample; (g) PICOW by rehydration of PICOA at RH ≈ 45%, ground sample.

lization of the lower-melting crystal form A (mp 135.5 ± 0.4 °C, fusion enthalpy 62 ± 10 J g^{-1}; $n = 8$) and the higher-melting crystal form B (mp 152.9 ± 0.3 °C, fusion enthalpy 14 ± 3 J g^{-1}; $n = 8$) of anydrous picotamide can be seen by the small exothermal effects at 115 °C and 138 °C in the sample recrystallized from benzene (Figure 4d).

The sequence of thermal events in Figure 4d was confirmed by HSM. Upon heating at 10 K min^{-1} from 25 to 100 °C and then reducing the heating rate to 5 K min^{-1} on a microscope stage, water evolution started at 110 °C and the newly formed small prismatic crystals melted at 136 °C. Upon further heating very few needle crystals were formed, which then melted at 153 °C.

XRD patterns of all recrystallized picotamide samples matched the theoretical XRD pattern of the monohydrate,[2,3] indicating that no difference existed in the fundamental

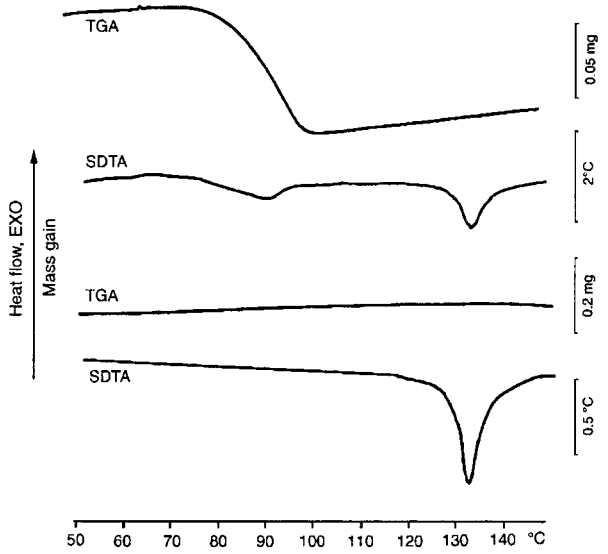

Figure 6—Simultaneous TGA-DSC curves over the 50–150 °C temperature range of picotamide monohydrate (PICOW) from water–ethanol 8:1 (v/v) (upper curves) and anhydrous picotamide (PICOA) (lower curves).

crystal lattice of the PICOW samples examined.[18] IR spectra also show that these samples were structurally identical. Therefore, the biphasic DSC dehydration profile recorded for the intact sample from ethyl acetate (Figure 4b) and reflected by the dTGA curve (Figure 5b) can be attributed to different crystal size and shape or various degrees of "perfection" of a common lattice structure of the tested samples.[19,20] Implications of the morphology of a pharmaceutical solid on the bulk properties of the material have been reported for furosemide,[21] nitrofurantoin,[22] and diclofenac/*N*-(2-hydroxyethyl)pyrrolidine salt.[23] Surface characteristics, adsorbed or occluded impurities and crystal defects which prevent the perfect alignment of molecules in the crystal lattice as well as nuclei of anhydrous polymorphs formed, may also affect the kinetics of solid-state transitions,[23] in particular dehydration. Actually, a highly strained or stressed lattice structure loses water more easily than a regular one. Cluster aggregation of PICOW crystals grown in ethyl acetate solution may also be responsible for the observed thermal behavior. Samples from ethyl acetate, which had been gently ground to ensure homogeneity of the polycrystalline material with no apparent alteration of the XRD pattern of the intact samples, showed indeed a monophasic dehydration pattern in both DSC (Figure 4c) and dTGA (Figure 5c) curves.

As can be seen in Figures 4e and 5e, the product of isothermal dehydration at 115 °C and 20 mmHg of PICOW from water−ethanol 8:1 (v/v) was almost totally composed of the lower-melting crystal form A, with enthalpy of fusion 74.4 ± 2.2 J g^{-1} ($n = 7$). Simultaneous TGA/DSC confirmed that no mass loss was associated with the endothermal effect at ≈136 °C (Figure 6). By storing at a RH of 45% or ≈100% and room temperature (22 °C), PICOA transformed to PICOW, as confirmed by DSC, TGA, and IR spectroscopy. Transformation to monohydrate was rather fast (within 48 h) at ≈100% RH and rather slow (within 3 months) at 45% RH. PICOW samples obtained by rehydration of PICOA in an ambient atmosphere (RH ≈ 45%) show biphasic dehydration patterns similar to those recorded for intact PICOW samples recrystallized from ethyl acetate (see Figures 4b and 5b). The couple of DSC endotherms centered at 91 °C (dehydration enthalpy 56.2 J g^{-1}) and 122 °C (dehydration enthalpy 60.4 J g^{-1}) in Figure 4f was reflected by a two-step TGA mass loss of 1.9% (w/w) and 2.5% (w/w) in Figure 5f. Thermal analysis of gently ground samples of rehydrated PICOA showed that

Table 2—Equilibrium Solubilities of Picotamide Monohydrate (PICOW) from Water–Ethanol 8:1 (v/v) and Anhydrous Picotamide (PICOA) in Water at Various Temperatures

temperature (°C)	equilibrium solubility (μg/mL)[a]	
	PICOW	PICOA
20	88(8)	158(13)
25	123(9)	207(16)
32	172(12)	249(17)
37	234(14)	289(18)
45	328(13)	368(18)

[a] Standard deviation in parentheses ($n = 3$).

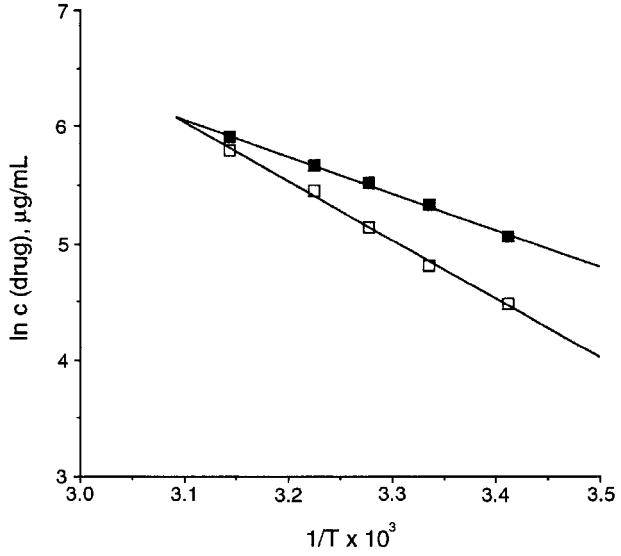

Figure 7—Van't Hoff plot from the solubility data (Table 2) of picotamide monohydrate (PICOW) from water–ethanol 8:1 (v/v) (□) and anhydrous picotamide (PICOA) (■).

the split DSC endotherms and dTGA peaks gathered in a single thermal effect with an associated enthalpy change (121.5 J g^{-1}) and mass loss (4.9% (w/w)) nearly equal to the sum of those of the single effects (Figures 4g and 5g). The monophasic dehydration pattern of ground samples, which show the same XRD pattern (i.e., structural arrangement) as the intact ones, confirms that external factors such as morphology, surface characteristics, cluster aggregation, etc., are responsible for the observed thermal behavior.

Solubility and Dissolution Properties of the Solid Phases—The equilibrium solubilities of PICOW and PICOA in water as a function of temperature are given in Table 2. The solubility of the stable hydrated form was calculated from the plateau value of dissolved concentration at each temperature. The maximum concentrations of dissolved PICOA at each temperature also gave plateau values, which were maintained for about 1 h (at 45 °C) to about 4 h (at 20 °C) before declining toward the corresponding equilibrium solubility values of PICOW due to phase transition. A crystalline anhydrous to hydrate phase change has been reported for theophylline, which is rapidly transformed to monohydrate in contact with water where simultaneous dissolution and hydrate formation occurs.[24,25] At 45 °C the solubility level of PICOW (i.e., complete transformation of the metastable phase, as confirmed by DSC and IR analysis of the residual solid material) was reached in >4 h. This behavior suggested that the maximum dissolved concentration of PICOA can be assumed as its equilibrium solubility.[26] The metastable to stable solubility ratios of 1.1−1.8 over the range of temperatures tested (Table 2) were typical of anhydrous−hydrate drug systems[27] and confirmed this hypothesis. By plotting the solubility data according to the van't Hoff equation,[26] a good linearity was observed (Figure 7). The least squares linear regression gave a slope of $(-4.90 \pm 0.16) \times 10^3$, an intercept of 21.2 ± 0.5 and a coefficient of determination of 0.997 for the stable PICOW form, and a slope of $(-3.0 \pm 0.2) \times 10^3$, an intercept of 15.4 ± 0.6 and a coefficient of determination of 0.988 for the metastable PICOA form. The transition temperature at which PICOW and PICOA have equal solubilities, free energies, and stabilities was 50 ± 6 °C.

Table 3—Dissolution Efficiency (DE),[a] Percent of Active Ingredient Dissolved (DP),[b] and Intrinsic Dissolution Rate Constants (IDR)[c] of Picotamide Monohydrate (PICOW) from Water–Ethanol 8:1 (v/v) and Anhydrous Picotamide (PICOA) in Water at 37 °C (standard deviations in parentheses refer to last decimal digit).[d]

sample	DE			DP			IDR
	10 min	30 min	60 min	10 min	30 min	60 min	
PICOW	12.6(3)	17.3(4)	19.8(5)	17.5(4)	21.5(5)	23.0(4)	1.26(8)
PICOA	15.9(4)	22.4(6)	25.4(7)	22.7(6)	27.6(8)	29.2(8)	1.66(9)

[a] Area under the dissolution curve with $t = 10$, 30, and 60 min (measured using the trapezoidal rule) expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time (see Figure 8). [b] Calculated at $t = 10$, 30, and 60 min. [c] K_i, mg cm^{-2} h^{-1}. [d] Each value is the average of four determinations.

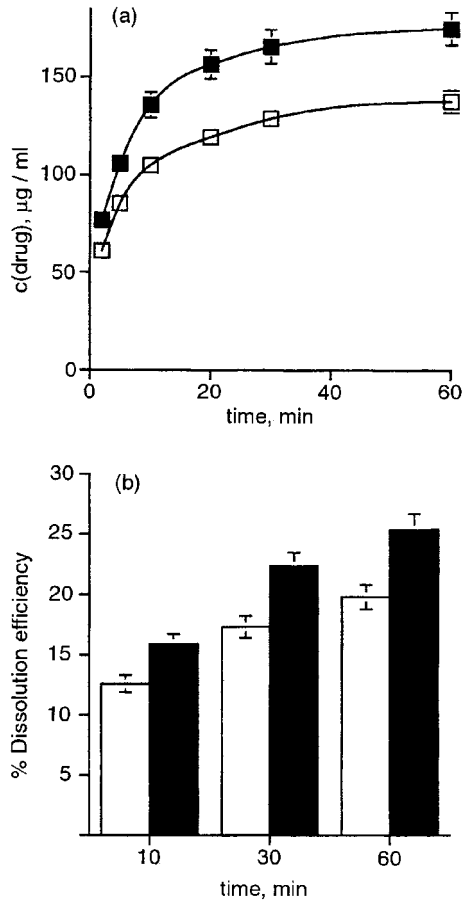

Figure 8—Dispersed amount curves in water at 37 °C (a) and dissolution efficiency (b) of picotamide monohydrate (PICOW) from water–ethanol 8:1 (v/v) (□) and anhydrous picotamide (PICOA) (■). Error bars indicate standard deviation ($n = 4$).

Dispersed amount experiments revealed statistically significant differences ($P < 0.01$) between PICOA and PICOW in terms of both dissolution efficiency at 10, 30, and 60 min and percent of drug dissolved at the same

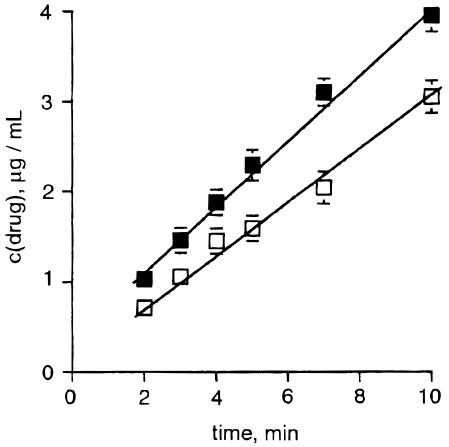

Figure 9—Intrinsic dissolution rates in water at 37 °C of picotamide monohydrate (PICOW) from water-ethanol 8:1 (v/v) (□) and anhydrous picotamide (PICOA) (■). Error bars indicate standard deviation ($n = 4$).

times, in accordance with the solubility data (Table 3 and Figure 8). The metastable to stable dissolution efficiency ratios and percent of drug dissolved ratios (≈1.3 at each time point) reflect to some extent the metastable to stable solubility ratio (1.24 at 37 °C). The higher thermodynamic activity and lower crystallinity (see Figure 2) of PICOA probably concur to its higher dissolution efficiency (by 28%) compared to PICOW. The dissolution rate data in water at 37 °C using nondisintegrating disks of PICOA or PICOW were in agreement with those obtained from powder samples (Table 3 and Figure 9). The metastable anhydrous form shows a better performance also in terms of intrinsic dissolution rate, which results higher than that of the stable hydrated form by 32%.

Conclusions

PICOW, the most stable picotamide form in water and organic solvent as well as under ambient atmosphere, is the raw material of choice for the preparation of commercial tablets (Plactidil). The dehydration of PICOW under open DSC and TGA conditions follows a monophasic or biphasic pattern, depending on the history of the sample (recrystallization solvent, rehydration conditions, intact or ground specimen, etc.). Morphological factors, various degrees of "perfection" of a common lattice structure, and/or cluster aggregation may be responsible for the distinct thermal behavior of the same hydrate phase and for the nature of the dehydration products (amorphous or polymorphic crystal forms A and B).

Total or partial dehydration of PICOW can occur in pharmaceutical processes where aqueous wetting and drying are involved. The subsequent in situ rehydration of PICOA, which depends on numerous factors (temperature, water vapor pressure, excipients in the formulation, etc.), is also possible. The careful characterization of the solid state is necessary so that the behavior of the material can be predictable and reproducible.

PICOA, the metastable picotamide anhydrous form, due to its physical stability in an ambient atmosphere and compatibility with pharmaceutical excipients, could be a promising modification to improve the dissolution rate of the active principle in solid dosage forms because of its higher solubility reached in water before recrystallizing to the less soluble hydrate. A study of possible implications on bioavailability will be the subject of future work.

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