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Preformulation study of moisture effect on the physical stability of pyridoxal hydrochloride

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Summary

During a preformulation programme the effect of atmospheric moisture on pyridoxal HCl (PL) was investigated. A complete moisture sorption isotherm was derived for PL at 25 °C. In addition, PL samples were stored at 11 and 75% relative humidity (RH) for 2 weeks. Changes in the samples were detected by differential scanning calorimetery (DSC), infrared spectroscopy (IR) and scanning electron microscopy (SEM). DSC and IR studies provided strong evidence of two polymorphic forms of PL. In addition, DSC thermograms of the samples stored at 75% RH showed changes indicative of a partial polymorphic transformation; further, these changes in crystal habit were observed in the SEM study. The moisture sorption isotherm shows an abrupt decrease in moisture content in the region of 57–68% RH. This may correspond to the formation of the less hygroscopic, stable polymorph. PL is physically unstable at elevated levels of moisture, however, exposure to certain levels of RH may enhance its stability due to transformation of polymorphs.

The goals of the preformulation program are to establish the necessary physicochemical parameters of a drug substance, its kinetic rate profile, physical characteristics and compatibility with common excipients. Physicochemical studies are usually associated with great precision and accuracy and would include pK (if it is an acid or base), solubility, melting point and polymorphism, vapour pressures (enthalpy of vaporisation), surface characteristics and hygroscopicity. Hygroscopicity is, of course, an important characteristic of many pharmaceutical substances and it can be shown that solubility and heat of solution play an important role in what is conceived as 'hygroscopicity' (Van Campen et al., 1983a–c).

Studies of the hygroscopic nature of a solid drug are important as solids containing residual moisture exhibit significant changes in many physicochemical properties relative to their dry state (Zografi and Kontny, 1986). A possible mechanism whereby moisture can cause such changes is through the promotion of polymorphic transformations. Changes in the crystal lattice structures of drugs and excipients may also produce alterations in the solubility, chemical stabil-

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ity, physicomechanical properties and dissolution characteristics of solid dosage forms. Consequently, these changes may influence the bioavailability and therapeutic efficacy of the drug (Thoma and Serno, 1984). Furthermore, the presence of moisture is very important if a compound exhibits polymorphism, as the various crystal forms can show significant differences in hygroscopicity (Miyazaki et al., 1974; Imaizumi et al., 1980).

Thus, identification of such hygroscopic differences during preformulation is important as moisture is considered to be the most deleterious environmental factor causing instability in solid dosage forms (Monkhouse, 1984). During a preformulation investigation of pyridoxal HCl (PL), strong evidence indicative of at least two polymorphic forms of PL emerged. This evidence is presented here together with a study of the equilibrium hygroscopicity of PL and the effect of moisture on the two physical forms of PL.

PL as supplied (Fluka AG, Buchs) was examined by differential scanning calorimetry (DSC) (Mettler TA 3000 system), thermogravimetric analysis (TGA) (Dupont 9900 system) and infrared (IR) spectroscopy (Nicolet FDX spectrophotometer). To obtain DSC thermograms, samples of PL (2–5 mg) were hermetically sealed in standard aluminium pans and heated from 30 to 200 °C at a rate of 7 °C/min. Hermetic sealing is essential as this suppresses the pyrrolytic degradation which normally accompanies the melting of PL. For IR spectroscopy, PL was incorporated in a KBr pellet and analysed over the wavenumber range 400–4600 cm^{-1}. TLC was employed to ascertain whether PL decomposition had occurred during DSC scanning. Silica gel HF60 (Merck) chromatoplates, chloroform : methanol (75 : 25) as mobile phase and visualisation by UV light (254 nm) were used.

Moisture sorption studies were carried out as follows; nine controlled humidity environments were created by equilibrating various saturated salt solutions in hygrostats at 25°C. Samples of PL (predried at reduced pressure over phosphorus pentoxide for 24 h) in open glass vials were equilibrated at the various relative humidity (RH) levels for 12 days. Percentage moisture content

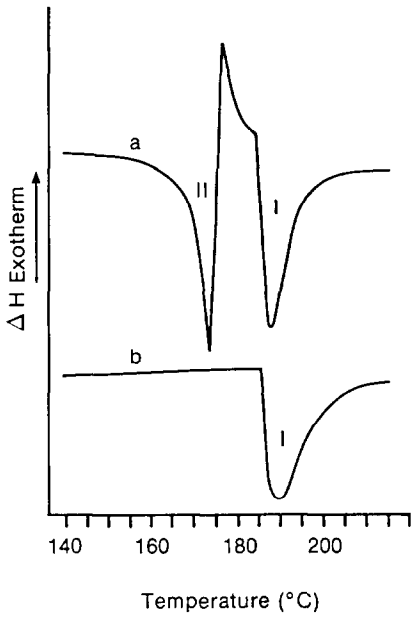

Fig. 1. DSC thermograms of PL as supplied (a) and heated to 175 °C, solidified and reheated (b).

was then measured by Karl Fischer titration (Mettler DL 18 titrator). Additional samples were stored at 11 and 75% RH at 25 and 40°C, respectively, and analyzed by DSC as described above. The samples were also studied for surface characterisation by SEM (Jeol JSM 840 scanning electron microscope).

Fig. 1a shows the DSC thermogram of PL (as supplied). An additional sample of PL was heated to 175 °C, its approximate exothermic peak temperature, and then solidified by cooling. Upon reheating of the solidified sample, only one peak corresponding to the second endothermic peak of the initial thermogram (Fig. 1a) appeared (Fig. 1b). Such thermograms are characteristic of monotropic polymorphic transformations involving the melting of the metastable form II (endothermic) and crystallisation of the stable form I from the melt (Giron-Forest, 1984). The second endothermic peak in Fig. 1 indicates the melting of form I. Decomposition reactions and oxidation could be discounted as causes of the exothermic peak. This was confirmed by TLC analysis of samples heated to 175 °C in hermetically sealed pans indicating no decomposition products.

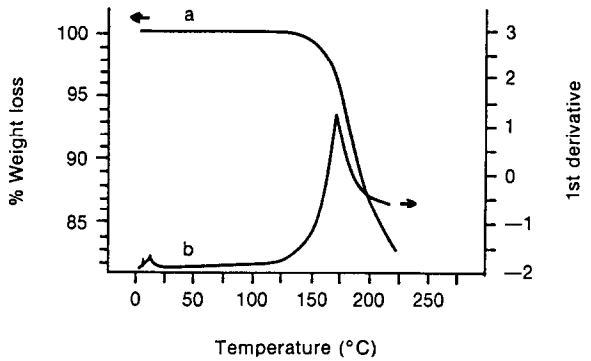

Fig. 2. (a) TGA and (b) first derivative DTGA trace of PL.

Transformations of this nature have also been previously reported for sulphamethoxypyridazine (Maury et al., 1985), carbamazepine (Krahn and Mielck, 1987) and a dibenzoxazepine compound (Gibbs et al., 1976). The presence of pseudopolymorphism was ruled out as no weight loss indicative of desolvation occurred before melting as illustrated by TGA analysis (Fig. 2). The rapid weight loss coinciding with melting can be attributed to the pyrrolytic decomposition accompanying the melting process, in agreement with published reports (Windholz et al., 1983). Slight differences between PL (as supplied) and heated and resolidified PL (form I) can also be discerned from the IR spectra (see Fig. 3).

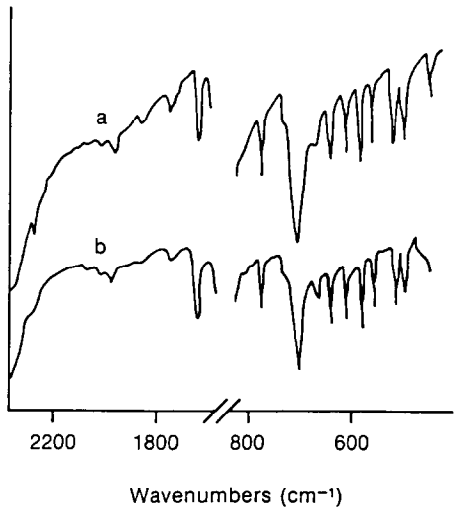

Fig. 3. IR spectra of PL as supplied (a) and resolidified PL (b).

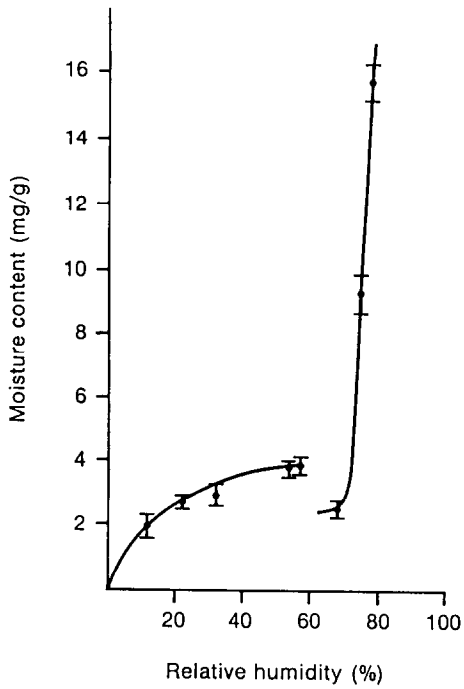

Fig. 4. Moisture sorption isotherm of PL at 25 °C. ($n = 3$, $P < 0.1$).

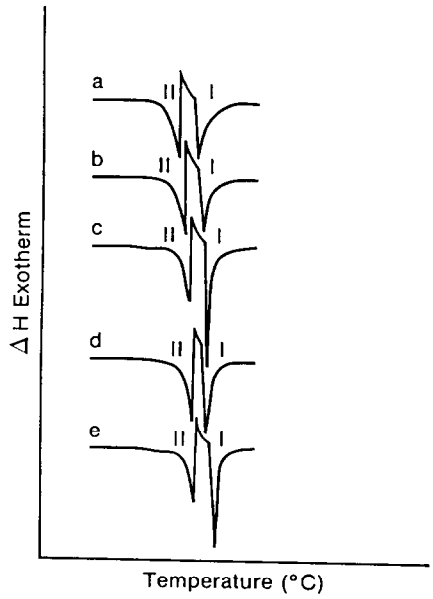

Fig. 5. DSC traces of PL (a) as supplied; (b) stored at 25°C, 11% RH; (c) stored at 25 °C, 75% RH; (d) stored at 55°C, 11% RH and (e) stored at 55°C, 75% RH. Peak temperatures and ratio of the enthalpies for these traces are presented in Table 1.

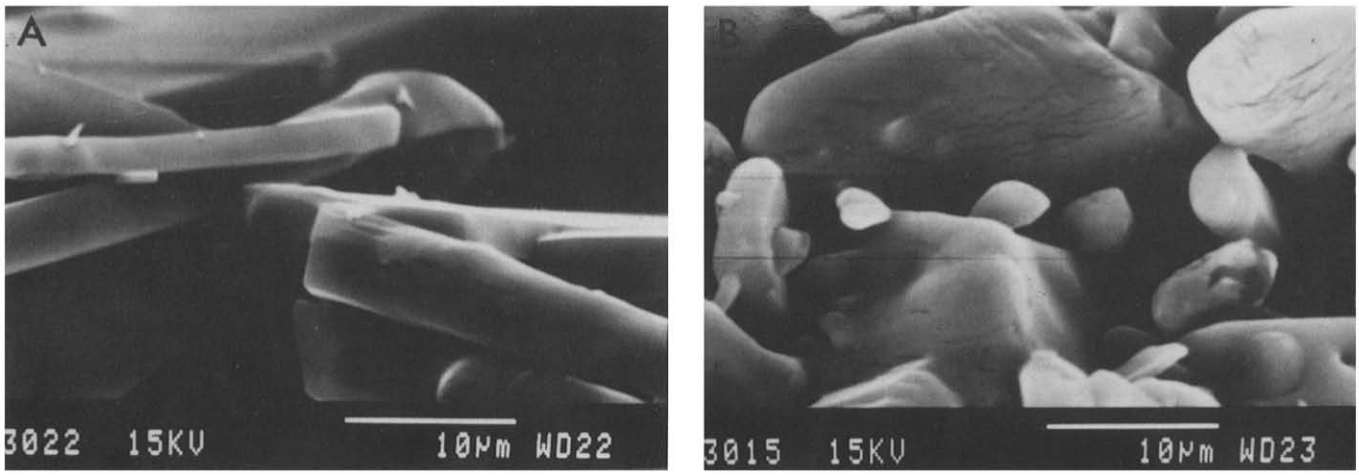

Fig. 6. Electron micrographs of PL: (A) stored at 11% RH and (B) 75% RH for 2 weeks demonstrating changes in crystal habit.

The results of moisture sorption isotherm studies were interesting and showed a discontinuity between 60 and 68% RH (Fig. 4). The sorption isotherms were subjected to repeated analysis to evaluate method performance, which was found to be acceptable. The coefficient of variation of the assay procedure was 3.6%. Isotherms of this nature have previously been reported for amorphous systems which transform into energetically more stable, less hygroscopic, crystalline systems when exposed to moisture (Makower and Dye, 1956; Umprayn and Mendes, 1987). Although hygroscopicity is highly order dependent (Huttenrauch, 1977), even small changes in crystal structure can lead to significant differences in hygroscopicity. This has been exemplified by the marked differences in hygroscopicity of the polymorphs of indomethacin (Imaizumi et al., 1980) and chlortetracycline (Miyazaki et al., 1974). It should be noted that metastable polymorphs have energetically unstable molecular arrangements and can therefore be regarded as activated systems relative to their stable form. Consequently, metastable polymorphs can be expected to be more hygroscopic.

In the present report, a moisture-induced transition from the predominantly metastable state (II) to a more stable, less hygroscopic form is evident from the DSC thermograms and electron micrographs of PL stored at 75% RH (Figs 5 and

TABLE 1

Peak temperatures (T, in °C) and enthalpies (ΔH, in J/g) of PL obtained from the DSC thermograms under various storage conditions

Sample	Storage conditions	Peak II		Peak I		$\Delta H_{II}/\Delta H_I$ [a]
		T	ΔH	T	ΔH	
a	No storage	170.3	87.8	185.0	91.2	0.96
b	25°C, 11% RH, 14 days	171.7	81.6	184.6	88.1	0.93
c	25 °C, 75% RH, 14 days	172.3	75.9	185.2	94.4	0.80
d	40°C, 11% RH, 14 days	172.2	78.1	182.4	76.6	1.01
e	40°C, 75% RH, 14 days	172.3	72.1	187.3	91.2	0.79

[a] The ratio of the enthalpies of melting corresponding to the two endothermic peak areas (I and II).

6; and Table 1). A marked change in the ratio of the two endothermic peak areas (I and II) which correspond to the enthalpies of melting of the metastable form II and the stable form I is observed (see Fig. 5 and Table 1). The decrease in the melting peak of the metastable form suggests a partial conversion to the stable polymorph. This correlates well with the observed moisture sorption isotherm (Fig. 4) and scanning electron micrographs, where partial conversion to thin, plate-like crystals with large faces and well defined edges is evident at 75% RH (Fig. 6).

In conclusion, there are strong indications that PL exists in at least two polymorphic forms. Transformation to the stable form can be achieved by melting and resolidification and appears to be monotropic. However, the less hygroscopic form can also be induced by exposure to elevated moisture levels. The stable polymorphic form of PL is of interest as its lower hygroscopicity may enhance its chemical stability, while the concurrent expected decrease in its solubility is unlikely to be significant as PL is highly water soluble.

References

Gibbs, I., Heald, A., Jacobson, H., Wadke, D. and Weliky, I,. Physical characterization and activity in vivo of polymorphic form of 7-chloro-5,11-dihydrodibenz[b,e][1,4]oxazepine-5-carboxamide, a potential tricyclic antidepressant. *J. Pharm. Sci.*, 65 (1976) 1380–1385.

Giron-Forest, D., Anwendung der thermischem Analyse in der Pharmazie. *Pharm. Ind.*, 46 (1984) 851–859.

Huttenrauch, R., Abhaerigigkeit der Hygroskopizitaet von der Kristalinitaet. *Pharmazie*, 32 (1977) 240–241.

Imaizumi, H., Nambu, N. and Nagar, T., Stability and several physical properties of amorphous and crystalline forms of Indomethacin. *Chem. Pharm. Bull.*, 28 (1980) 2565–2569.

Krahn, F.V. and Mielck J.B., Relations between several polymorphic forms and the dihydrate of carbamazepine. *Pharm. Acta Helv.*, 62 (1987) 247–254.

Makower, B. and Dye, W.B., Equilibrium moisture content and crystallization of amorphous sucrose and glucose. *J. Agric Food Chem.*, 4 (1956) 72–81.

Maury, L., Rambaud, J., Pauvert, B., Berge, G., Audran, M. and Lasserre, Y., Etude physico-chimique de sulfamides. IV. Le sulfamethoxypyridazine. *Pharm. Acta Helv.*, 60 (1985) 22–27.

Miyazaki, S., Arita, T., Hori, R. and Ito, K., Effect of polymorphism on the dissolution behaviour and gastro-intestinal absorption of chlorotetracycline HCl. *Chem. Pharm. Bull.*, 22 (1974) 638–642.

Monkhouse, D.C., Stability aspects of preformulation and formulation of solid pharmaceuticals. *Drug Dev. Ind. Pharm.*, 10 (1984) 1373–1412.

Thoma, K. and Serno, P., Physikalische Instabilitaet von Arzneimitteln als Folge von polymorphen Veraenderungen der Kristallstruktur. *Deutsche Apoth. Ztg.*, 43 (1984) 2162–2170.

Umprayn, K. and Mendes, R.W., Hygroscopicity and moisture adsorption kinetics of pharmaceutical solids: a review. *Drug Dev. Ind. Pharm.*, 13 (1987) 653–693.

Van Campen, L., Amidon, G.L. and Zografi, G., Moisture sorption kinetics for water soluble substances. I: Theoretical considerations of heat transport control. *J. Pharm. Sci.*, 72 (1983a) 1381–1387.

Van Campen, L., Amidon, G.L. and Zografi, G., Moisture sorption kinetics for water-soluble substances. II: Experimental verification of heat tranport control. *J. Pharm. Sci.*, 72 (1983b) 1388–1393.

Van Campen, L., Amidon, G.L. and Zografi, G., Moisture sorption kinetics for water-soluble substances. III: Theoretical and experimental studies in air. *J. Pharm. Sci.*, 72 (1983c) 1394–1398.

Windholz, M., Budavari, S., Blumetti, R.F. and Otterbein, E.S., *The Merck Index*, 10th Edn, Merck & Co. Inc., Rahway, NJ, 1983, p. 7882.

Zografi, G. and Kontny, M.J., The interactions of water with cellulose- and starch-derived pharmaceutical excipients. *Pharm. Res.*, 3 (1986) 187–192.