International Journal of Pharmaceutics, 75 (1991) 211–218

ADONIS 037851739100318L

IJP 02508

Solid-state stability: the effect of grinding solvated excipients

W.J. Irwin and M. Iqbal

Drug Development Research Group, Pharmaceutical Sciences Institute, Aston University, Aston Triangle, Birmingham B4 7ET (U.K.)

(Received 15 November 1990)
(Modified version received 5 April 1991)
(Accepted 26 April 1991)

Key words: DSC; Grinding; Hydrate; Lactose; 4-Methoxyphenyl aminoacetate; Solid-state stability; Solvate

Summary

α-Lactose monohydrate and bropirimine acetic acid solvate were used as model excipients and 4-methoxyphenyl aminoacetate hydrochloride was used as a model labile component to study the relationship between mechanical stress on solvates and the solid-state stability of a drug component. The effect of grinding the solvates was to disrupt the integrity of the associated solvent. When samples were examined by differential scanning calorimetry this change was characterised by a broadening of the endotherm due to desolvation and a lowering of the peak maximum temperature (t_{max}) of the endothermic transition. This represents a weakening of the intermolecular forces which hold the solvent within the crystal. When 4-methoxyphenyl aminoacetate hydrochloride, a substrate which undergoes ready hydrolysis, is mixed with the solvates solid-state degradation rates, yielding 4-methoxyphenol are enhanced. The greatest effect is observed in samples where the solvate has been ground, suggesting that the enhanced lability of the solvent promotes solid-state degradation to a significant degree.

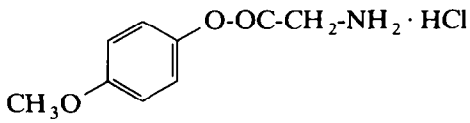
Introduction

It is well-recognised that the physical manipulation of pharmaceutical compounds may exert a substantial influence on solid-state properties. In particular, the influence of grinding on polymorphic change has been well exposed (Kaneniwa and Otsuka, 1985; Lefebvre and Guyot-Hermann, 1986; Otsuka et al., 1986) with one third of a series of thirty compounds showing such transformations on compression (Chan and Doelker, 1985). The rates of polymorphic transition have also been shown to be enhanced in the presence of various excipients (Takehashi et al., 1985a,b). Stability profiles, too, have shown themselves to be dependent upon physical history with mechanical activation, through grinding or compression, showing significant enhancement of degradation rates (Hüttenrauch et al., 1985). The effect of moisture on the physical and chemical stability of solids has been reviewed (Ahlneck and Zografi, 1990) and dehydration kinetics have been shown to follow standard solid-state degradation models (Agbada and York, 1989). The effect of grinding on hydrates has also been studied (Otsuka and Kaneniwa, 1983; Kitamura et al., 1989) and it has been shown, for example, that the rate of discoloration of cefixime trihydrate increases with the extent of grinding. Differential scanning

Correspondence: W.J. Irwin, Drug Development Research Group, Pharmaceutical Sciences Institute, Aston University, Aston Triangle, Birmingham B4 7ET, U.K.

calorimetry has been widely used in the study of the thermal properties of carbohydrates (Liskowitz et al., 1980) and its role in the elucidation of interactions, reactions, kinetics and its importance in stability predictions have been reviewed (Li Wan Po, 1986; Smith, 1986; York and Grant, 1986; Ford and Timmins, 1989).

As some earlier studies into the effect of manipulation on solid-state stability have used hydrated excipients, without consideration for the behaviour of the excipient, it is pertinent to examine the role of solvates in this regard to establish the possibility that disruption of the solvated solvent may initiate degradation rather than, or in addition to, crystal deformation of the substrate under test. To undertake this study we have examined the solid-state stability of 4-methoxyphenyl aminoacetate hydrochloride (MPAA) by means of high-performance liquid chromatography and differential scanning calorimetry. This derivative has been used as a water-soluble prodrug of 4-hydroxyanisole (4-methoxyphenol) in cancer chemotherapy. The phenolic ester nature of compound renders it unstable and it rapidly regenerates the parent phenol and glycine in aqueous solution. α-Lactose monohydrate, which has wide application as a pharmaceutical excipient, has been used as a hydrated additive while bropirimine acetic acid solvate (Alpar et al., 1986; Irwin and Iqbal, 1988) has been used as a molecule complexed with a solvent other than water.



4-Methoxyphenyl aminoacetate hydrochloride (MPAA)

Experimental

Apparatus

Differential scanning calorimetry was undertaken with a Perkin-Elmer DSC-4 instrument using the Thermal Analysis Data Station (TADS) for data collection, handling and presentation. HPLC analyses were undertaken using a system constructed from an Altex 100A dual-piston reciprocating solvent-metering pump and a reversed-phase stainless-steel Shandon-type column (10 cm × 4.6 mm i.d.) packed with Hypersil-ODS (5 μm) stationary phase. Samples were introduced by means of a Rheodyne 7125 injection valve, fitted with a 20 μl loop, and detection was accomplished with a Pye LC3 variable-wavelength UV detector, fitted with an 8 μl flow cell, and operated at a wavelength of 300 nm with a sensitivity of 0.08–0.16 AUFS. The mobile phases consisted of aqueous acetonitrile (20%), adjusted to pH 2.0 with orthophosphoric acid and containing diethylamine (0.1%) as moderator, delivered at a flow rate of 1 ml min^{-1}.

Methods

Samples for thermal analysis were accurately weighed (1–4 mg) into an aluminium pan (Perkin-Elmer 219-0041), covered with an aluminium lid and crimped into position. The pan was placed in the DSC oven together with a blank, prepared in exactly the same way but without the sample. The sample and blank were continuously purged with nitrogen gas at a flow rate of 25 cm^3 min^{-1} (1.4 kg cm^{-2}) and thermograms were recorded over a temperature range of 40–250 °C with a programmed heating rate of 10 °C min^{-1}. Temperature calibration was made with an indium standard (onset temperature 156.6 °C) and temperatures are quoted as the peak maximum temperature (t_{max}).

Samples for solid-state stability were prepared by mixing the sieved fractions of MPAA and lactose monohydrate (both in the particle size range 150–212 μm) in the proportion of 10% w/w MPAA to 90% w/w lactose monohydrate. Sample 1 was produced by gentle mixing of both components in a glass vial without grinding. Sample 2 resulted from the lactose monohydrate being ground for 10 min using an agate pestle and mortar followed by gentle mixing with untreated MPAA and Sample 3 was obtained by grinding together the lactose monohydrate and MPAA for 10 min using an agate pestle and mortar. In a

similar fashion, samples of MPAA with bropirimine acetic acid solvate were prepared in a 1:1 ratio.

Each sample was separated into aliquots (20 mg for those based upon lactose and 5 mg for those containing bropirimine) contained in individual glass vials which were stored in a desiccator over a saturated solution of ammonium sulphate to provide a relative humidity of 80% at 37 °C or with lithium chloride solution at 10% relative humidity.

The samples were stored at 37 °C and at fixed time intervals vials were removed and extracted with methanol (5 ml). The contents were sonicated, filtered (0.2 μm Millipore) and samples (20 μl) were analysed by HPLC with retention times of 4 min, 4-methoxyphenyl aminoacetate hydrochloride; 5.5 min, 4-hydroxyanisole and 7 min, bropirimine. If required, samples were previously diluted 1:1 with methanol or an internal standard [2-amino-5-bromo-6-(3-fluorophenyl)-4-(3H)-pyrimidinone, ABmFPP; 0.1 mg ml^{-1}].

Results and Discussion

The ability of mechanical agitation to alter the nature of hydration is illustrated in Fig. 1 which records the effect of grinding on the thermogram of the common excipient lactose which is usually available in the α-lactose monohydrate form. The pure material is characterised by two endotherms, the lower (150.1 °C) corresponding to dehydration and the higher (217.1°C) to melting. The higher transition is followed by an irregular increase in baseline which is characteristic of thermal degradation. There are conflicting literature reports on the melting of α-lactose monohydrate and this endotherm has been quoted to occur at 212 °C (Lerk et al., 1980) or at 223 °C (Berlin et al., 1971) although the former study used open pans. Heating rates may also dramatically affect the appearance of thermograms (Itoh et al., 1978). Fig. 1 also shows that when α-lactose monohydrate was ground in a pestle and mortar, the dehydration endotherm developed a shoulder at a lower temperature. This peak became progressively larger as grinding was continued and

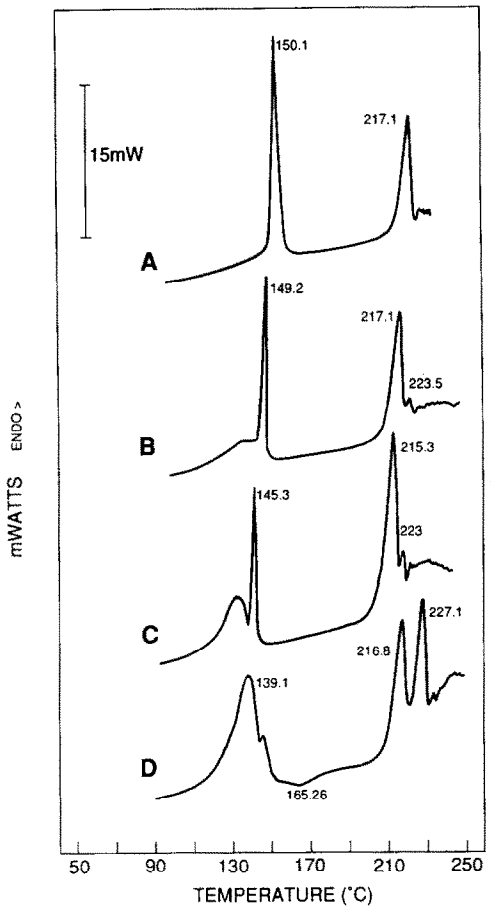


Fig. 1. DSC thermograms of α-lactose monohydrate after grinding with a pestle and mortar for various time periods. A, crystalline material; B, ground for 2 min; C, ground for 5 min; D, ground for 10 min.

indicates the disruption of the hydrate structure by mechanical manipulation. After 10 min the sharp dehydration endotherm has been replaced by a broad peak at 139.1 °C.

Similar changes in thermal behaviour have been reported previously as a result of grinding of α-lactose monohydrate (Lerk et al., 1984b), compaction and also as a function of particle size (Vromans et al., 1985a,b, 1986). Here, as particle size decreases, a broadening endotherm is observed which effectively mirrors the changes due to grinding. In each case, gradual loss of the sharp dehydration transition is seen and water-loss progressively begins at a lower temperature. It seems probable that the effects due to grinding

or compaction are largely a result of a reduction in particle size. In any event, the changes induced by grinding, illustrated in Fig. 1, indicate that disruption of the solvent binding is taking place and that the water is becoming less strongly held within the crystal lattice. Indeed, dehydration kinetics show that the rate of water-loss is linearly dependent upon the surface area of the sample (Vromans et al., 1985a, 1986). The enhanced ability of water to be mobilised by physical manipulation may free it for further interaction and may cause degradation of a susceptible parent compound (Otsuka and Kaneniwa, 1984; Takahashi et al., 1985a,b).

The development of a further endothermic peak near 223 ° C as a result of grinding was also observed. This, too, increases with mechanical treatment and is possibly due to the conversion of α-lactose monohydrate to the stable anhydrous α-lactose (Lerk et al., 1980). Anhydrous α-lactose usually contains some 13% of β-lactose (Buma and Van der Veen, 1974) which melts at 237 ° C and it is feasible that grinding, and possibly the subsequent thermal treatment during analysis, influences the position of this equilibrium to account for the appearance of the thermograms (Houminer, 1973; Fernandez-Martin et al., 1980). A third event, of variable appearance which reveals an exothermic transition is also seen to occur after 10 min grinding with a maximum near to 165 ° C. Such conversions have been discussed previously (Berlin et al., 1971; Itoh et al., 1977; Lerk et al., 1980, 1984a,b) and accounted for by tentative supposition that a new crystal structure is created — possibly the establishment of the $\alpha \leftrightharpoons \beta$ equilibrium.

In contrast, no significant variation was observed in the thermograms of MPAA as samples were subjected to grinding for periods of up to 20 min. The melting endotherm was found within the range 148.2–151.8 ° C, small variations possibly being due to particle size differences and variable contact with the pan and heat flow properties of the solids.

To ascertain whether the observed changes in the ease of dehydration of α-lactose monohydrate can initiate or potentiate solid-state degradation reactions involving hydrolysis, mixtures of

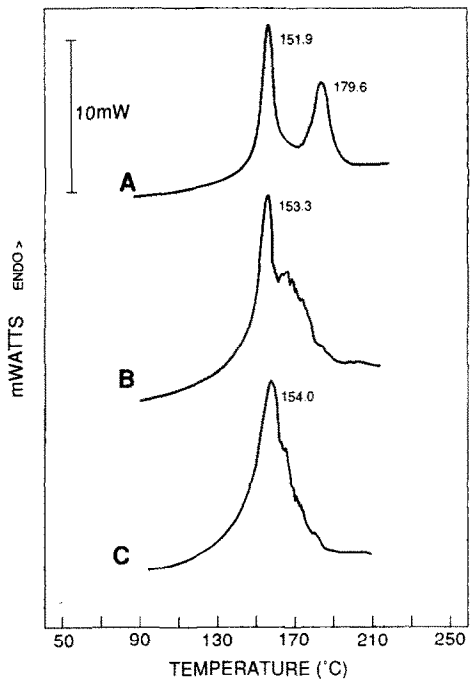


Fig. 2. DSC thermograms of 4-methoxyphenyl aminoacetate hydrochloride and α-lactose monohydrate mixtures after grinding for various periods of time. A, gentle mixing; B, ground for 1 min; C, ground for 2 min.

the excipient with 4-methoxyphenyl aminoacetate hydrochloride (MPAA) were prepared. These were obtained by gentle mixing of the two components, by grinding only the lactose monohydrate with incorporation of MPAA by gentle mixing or by grinding both components together. As shown in Fig. 2, after gentle mixing of the two components in a vial, two endothermic events are apparent. The first of these, at 151.9°C, corresponds to dehydration of α-lactose monohydrate while the second transition, at 179.6 ° C, does not correspond to any of those observed in the pure components alone. It may, however, be due to melting point depression or eutectic formation due to admixture as no indication of the endotherm originally observed at 217 ° C is now apparent. When grinding is continued for periods as short as 1 min these peaks coalesce into one broad transition and the irregular baseline thereafter indicates the possibility of a more facile thermal degradation.

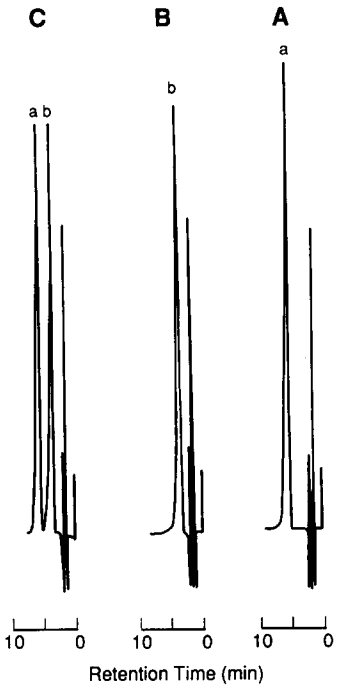


Fig. 3. High-performance liquid chromatogram of 4-methoxyphenyl aminoacetate and 4-methoxyphenol. A, 4-methoxyphenol (a); B, 4-methoxyphenyl aminoacetate (b); C, solid-state reaction mixture showing both components.

Storage of the mixtures at 37 ° C and a relative humidity of 80% initiated degradation of MPAA and the progressive appearance of 4-methoxyphenol, with the maintenance of mass balance, was observed. Fig. 3 records a typical HPLC trace of a ground mixture after storage and shows the release of 4-methoxyphenol from the prodrug during this period. This, and the observed mass balance, confirms that the degradation pathway observed in solution is also followed in the solid state, with no other products discernible. Microscopy revealed that MPAA produced thin, plate-like crystals so assessment of the kinetic profiles for degradation was undertaken using the zero-order model appropriate to a contracting slab (Acheson and Galwey, 1968; Brown et al., 1980). In such a system undergoing degradation by nucleation, overlap of possible nucleation sites occurs early in the reaction sequence with low overall extent of degradation. Under these conditions, a slab of dimensions a, b, and c undergoes a fractional degradation (α) in time (t) according to Eqn 1:

$$\alpha = \left(1 - \frac{(a - kt)(b - kt)(c - kt)}{abc}\right) \quad (1)$$

where k is the decomposition rate constant (m s^{-1}). In a slab or plate crystal, where a, $b \ggg c$, crystal edge effects may be neglected. These are described by terms containing c, apart from the slab volume term (abc), and higher powers of k. This expression then contracts to Eqn 2:

$$\alpha = \frac{kt}{c} \quad (2)$$

where c is the thickness of the slab. The extent of reaction is thus controlled by the reduction in the thickness of the crystal and which thus undergoes degradation largely by a zero-order rate process. Towards the end of the decomposition profile a

TABLE 1

Degradation rate constants for the solid-state decomposition of 4-methoxyphenyl aminoacetate hydrochloride (MPAA) under various conditions of admixture and storage with α-lactose monohydrate and bropirimine acetic acid solvate.

Conditions	Rate constant (k/c) (min^{-1}) $(\times 10^5)$
MPAA; 37°C; 10% R.H.	5.90
MPAA; 37 ° C; 80% R.H.	11.60
MPAA + α-lactose monohydrate (gently mixed); 37°C; 80% R.H.	25.50
MPAA + α-lactose monohydrate (lactose ground for 10 min then gently mixed); 37 ° C; 80% R.H.	46.70
MPAA + α-lactose monohydrate (mixture ground for 10 min); 37 ° C; 80% R.H.	50.40
MPAA + bropirimine acetic acid solvate (gently mixed); 37 ° C; 80% R.H.	18.30
MPAA + bropirimine acetic acid solvate (ground for 5 min); 37 ° C; 80% R.H.	31.00

R.H., relative humidity.

reduced rate is exhibited which is due to the variation in thicknesses of the crystals which comprise the sample.

Degradation of MPAA did, indeed, follow zero-order kinetics to over 90% decomposition (Irwin, 1990). Table 1 records rate constants, taken from the slope of the α vs time plot, and Fig. 4 illustrates the reaction profiles. It is seen that the MPAA undergoes significant degradation in the solid-state when stored at 37° C with a relative humidity of 10% ($k' = k/c = 5.9 \times 10^{-5}$ min^{-1}) and the rate of hydrolysis is substantially increased when the relative humidity is increased to 80% ($k' = 11.6 \times 10^{-5}$ min^{-1}). Gentle mixing of the two components yielded a degradation rate constant of 25.5×10^{-5} min^{-1}. In contrast, when the lactose was ground for 10 min prior to gentle mixing a degradation rate constant of 46.7×10^{-5} min^{-1} was observed. This increased rate suggests that degradation is promoted by the release of water from the hydrate. When both α-lactose monohydrate and MPAA were ground together for 10 min a further, small increase in the degradation rate constant, to 50.4×10^{-5} min^{-1}, was observed. This indicates that mobilisation of water appears to be the major influence with only a small effect due to increasing surface area of the substrate on grinding.

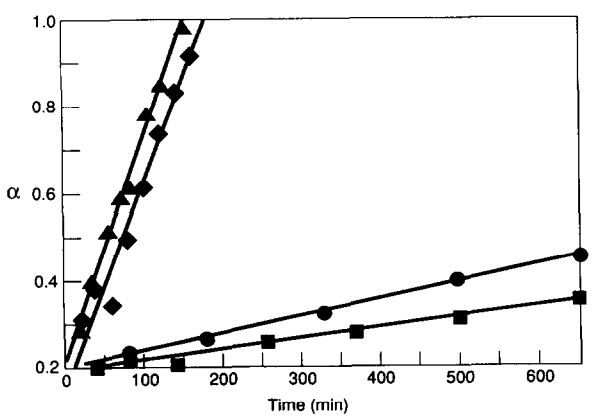


Fig. 4. Degradation profiles of 4-methoxyphenyl aminoacetate hydrochloride on admixture with α-lactose monohydrate. ■, gently mixed sample with 10% relative humidity (R.H.); ●, gently mixed sample with 80% R.H.; ♦, lactose only ground for 10 min; ▲, both MPAA and lactose ground for 10 min.

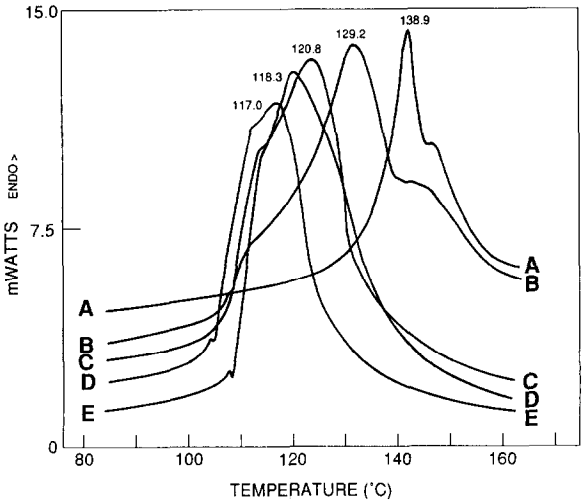


Fig. 5. DSC thermograms of bropirimine acetic acid solvate after grinding for various periods of time. A, crystalline material; B, ground for 1 min; C, ground for 3 min; D, ground for 4 min; E, ground for 5 min.

To explore this effect further and to determine whether solvates other than hydrates may promote degradation reactions, the influence of grinding on bropirimine acetic acid solvate was also studied. Thermograms of bropirimine have previously been reported and show an excipient-dependent degradation exotherm (Irwin and Iqbal, 1988). The thermogram of the acetic acid solvate additionally shows a desolvation endotherm near 140° C; substantially higher than the boiling point of acetic acid (118° C). As recorded in Fig. 5, the original sharp endotherm undergoes successive broadening with a concomitant drop in the peak maximum temperature when the sample is ground with a pestle and mortar. Over a 5 min period the initial peak is replaced by a much broader peak at 118.3°C. This parallels the behaviour of α-lactose monohydrate and indicates that the solvent becomes less tightly held as grinding progresses. In contrast, when bropirimine acetic acid solvate and MPAA were gently mixed without grinding the individual peaks corresponding to either pure MPAA or the desolvation endotherm were not evident but, as shown in Fig. 6, were replaced by a broader, shouldered peak whose maximum was lower than those of either pure component alone. With grinding this

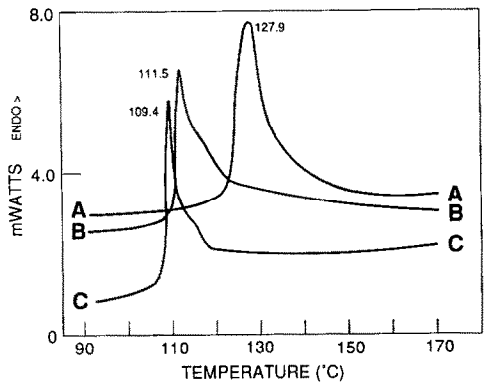


Fig. 6. DSC thermograms of 4-methoxyphenyl aminoacetate hydrochloride and bropirimine acetic acid solvate after grinding for various time periods. A, gentle mixing; B, ground for 2 min; C, ground for 3 min.

endotherm became progressively shifted to lower temperatures and resembled that of the ground solvate in general shape but at a lower temperature (109.4 °C).

To assess the stability implications of these changes, mixtures of bropirimine acetic acid solvate and MPAA were prepared under various conditions. Table 1 records the rate constants for the degradation of these samples. As was observed for the MPAA-lactose systems the addition of bropirimine acetic acid solvate induced a small increase in the solid-state degradation rate when the solvate was gently folded in to the MPAA. When the solvate and MPAA were ground together for 5 min prior to degradation a further substantial increase in the rate of decomposition was observed. The heightened lability of the acetic acid in these samples clearly contributes to the enhanced degradation rates. Moreover, the stability profiles parallel the changes in the DSC thermograms and show that this technique can expose potential threats to stability induced by grinding. Although reports exist on the effect of mechanical manipulation on the integrity of drug substances these usually relate to the effect of stress on polymorphic changes (Chan and Doelker, 1985; Kaneniwa and Otsuka, 1985; Takahashi et al., 1985a,b; Otsuka et al., 1986) or the degradation of the parent compound. Where physical interactions have been observed there has usually been no attempt made to evaluate the cause (Botha et al., 1987). Experiments performed here show that the degradation of hydrolytically labile substances may be promoted by admixture with solvated excipients when subjected to mechanical stress and such manipulation may compromise the integrity of the formulation.

Acknowledgements

We are grateful to Aston University, for the award of a Postgraduate Research Scholarship to M.I., and to Dr R.J. Griffin for the preparation of a sample of 4-methoxyphenyl aminoacetate hydrochloride.

References

Acheson, R.J. and Galwey, A.K., Thermal decomposition of salts of mellitic acid. IV. Silver mellitate. *J. Chem. Soc. A*, (1968) 942–946.

Agbada, C.O. and York, P., Dehydration kinetics of theophylline monohydrate under isothermal conditions. *J. Pharm. Pharmacol.*, 41 (1989) 65P.

Ahlneck, C. and Zografi, G., The molecular basis of moisture effects on the physical and chemical stability of drugs in the solid state. *Int. J. Pharm.*, 62 (1990) 87–95.

Alpar, H.O., Whitmarsh, S.J., Ismail, H., Irwin, W.J., Slack, J.A., Belaid, K.A. and Stevens, M.F.G., Formulation studies on 2-amino-5-bromo-6-phenyl-4(3H)-pyrimidinone (ABPP), an interferon inducer, anti-cancerogenic agent. *Drug Devel. Ind. Pharm.*, 12 (1986) 1795–1811.

Berlin, E., Kliman, P.G., Anderson, B.A. and Pallansch, M.J., Calorimetric measurement of the heat of desorption of water vapor from amorphous and crystalline lactose. *Thermochim. Acta*, 2 (1971) 143–152.

Botha, S.A., DuPreez, J.L. and Lotter, A.P., DSC screening for drug-drug and drug-excipient interaction in polypharmaceuticals intended for the alleviation of the symptoms of colds and flu. *Drug Devel. Ind. Pharm.*, 13 (1987) 1197–1215.

Brown, W.E., Dollimore, D. and Galwey, A.K., Reactions in the solid phase. In Bamford, C.H. and Tipper, C.F.H. (Eds), *Comprehensive Chemical Kinetics*, Vol. 22, Elsevier, Amsterdam, 1980.

Buma, T.J. and Van der Veen, H.K.C., Accurate specific optical rotations of lactose and their dependence on temperature. *Netherlands Milk Dairy J.*, 28 (1974) 175–185.

Chan, H.K. and Doelker, E., Polymorphic transformations of some drugs under compression. *Drug Devel. Ind. Pharm.*, 11 (1985) 315–332.

Fernandez-Martin, F., Morais, F. and Ohano, A., Thermal

behaviour of lactose. *Proc. 2nd Int. Congr. Food Process. Eng.*, Helsinki, 1979, 1980, pp. 523–529.

Ford, J.L. and Timmins, P., *Pharmaceutical Thermal Analysis: Techniques and Applications*, Ellis Horwood, Chichester, 1989.

Houminer, Y., Thermal degradation of carbohydrates. In Birch, G.E. and Green, L.F. (Eds), Molecular Structure and Function of Food Carbohydrates, Ind. Univ. Coop. Symp., Wiley, New York, 1973, pp. 133–154.

Hüttenrauch, R., Fricke, S. and Zielke, P., Mechanical activation of pharmaceutical systems. *Pharm. Res.*, 2 (1985) 302–306.

Irwin, W.J., *Kinetics of Drug Decomposition: BASIC Computer Solutions*, Elsevier, Amsterdam, 1990, pp. 25–31,167–174.

Irwin, W.J. and Iqbal, M., Thermal stability of bropirimine. *Int. J. Pharm.*, 41 (1988) 41–48.

Itoh, T., Satoh, M. and Adachi, S., Differential thermal analysis of α-lactose hydrate. *J. Dairy Sci.*, 60 (1977) 1230–1235.

Itoh, T., Katoh, M. and Adachi, S., Improved method for the preparation of crystalline β-lactose and observations on melting point. *J. Dairy Res.*, 45 (1978) 363–371.

Kaneniwa, N. and Otsuka, M., Effect of grinding on the transformation of polymorphs of chloramphenicol palmitate. *Chem. Pharm. Bull. Tokyo*, 33 (1985) 1660–1668.

Kitamura, S., Miyamae, A., Koda, S. and Morimoto, Y., Effect of grinding on the solid-state stability of cefixime trihydrate. *Int. J. Pharm.*, 56 (1989) 125–134.

Lefebvre, C. and Guyot-Hermann, A.M., Polymorphic transitions of carbamazepine during grinding and compression. *Drug Devel. Ind. Pharm.*, 12 (1986) 1913–1927.

Lerk, C.F., Buma, T.J. and Andreae, A.C., The effect of mechanical treatment on the properties of lactose as observed by differential scanning calorimetry. *Netherlands Milk Dairy J.*, 34 (1980) 69–73.

Lerk, C.F., Andreae, A.C., De Boer, A.H., De Hoog, P., Kussendrager, K. and Van Leverink, J., Alterations of α-lactose during differential scanning calorimetry. *J. Pharm. Sci.*, 73 (1984a) 856–857.

Lerk, C.F., Andreae, A.C., De Boer, A.H., De Hoog, P., Kussendrager, K. and Van Leverink, J., Transitions of lactoses by mechanical and thermal treatment. *J. Pharm. Sci.*, 73 (1984b) 857–859.

Liskowitz, J.W., Weill, C.E. and Carroll, B., Thermal behaviour of some reducing sugars. *Carbohydr. Res.*, 79 (1980) 23–28.

Li Wan Po, A., Application of differential scanning calorimetry in the prediction of solid state stability of drugs. *Anal. Proc.*, 23 (1986) 391–393.

Otsuka, M. and Kaneniwa, N., Effect of grinding on the degree of crystallinity of cephalexin powder. *Chem. Pharm. Bull. Tokyo*, 31 (1983) 4489–4495.

Otsuka, M., Matsumoto, T. and Kaneniwa, N., Effect of environmental temperature on polymorphic solid-state transformation of indomethacin during grinding. *Chem. Pharm. Bull. Tokyo*, 34 (1986) 1784–1793.

Smith, A., Studies in polymorphism and hydration. *Anal. Proc.*, 23 (1986) 388–389.

Takehashi, Y., Nakashima, K., Nakagawa, H. and Sugimoto, I., Effects of grinding and drying on the solid-state stability of ampicillin trihydrate. *Chem. Pharm. Bull. Tokyo*, 32 (1985a) 4963–4970.

Takehashi, Y., Nakashima, K., Ishihara, T., Nakagawa, H. and Sugimoto, I., Polymorphisms of fostedil: Characterisation and polymorphic change by mechanical treatments. *Drug Devel. Ind. Pharm.*, 11 (1985b) 1543–1563.

Vromans, H., De Boer, A.H., Bolhuis, G.K., Lerk, C.F. and Kussendrager, K.D., Studies on tabletting properties of lactose. Part 1. The effect of initial particle size on binding properties and dehydration of characteristics of lactose. *Acta Pharm Suec.*, 22 (1985a) 163–172.

Vromans, H., De Boer, A.H., Bolhuis, G.K., Lerk, C.F., Kussendrager, K.D. and Bosch, H., Studies on tabletting properties of lactose. Part 2. Consolidation and compaction of different types of crystalline lactose. *Pharm. Weekbl. Sci. Ed.*, 22 (1985b) 103–172.

Vromans, H., De Boer, A.H., Bolhuis, G.K., and Lerk, C.F., Studies on tabletting properties of lactose; The effect of initial particle size on binding properties and dehydration of characteristics of α-lactose monohydrate. *Drug Devel. Ind. Pharm.*, 12 (1986) 163–172.

York P. and Grant, D.J.W., Solid state disorder of drugs and excipients. *Anal. Proc.*, 23 (1986) 396–397.