International Journal of Pharmaceutics, 75 (1991) 219–230

ADONIS 037851739100319Y

IJP 02509

Modification of phenytoin crystals: influence of 3-acetoxymethyl-5,5-diphenylhydantoin on solution-phase crystallization and related crystal properties

Albert H.L. Chow and Carlos K. Hsia

Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, B.C. (Canada)

(Received 2 November 1990)
(Modified version received 13 March 1991)
(Accepted 15 March 1991)

Key words: Phenytoin; 3-Acetoxymethyl-5,5-diphenylhydantoin; Crystal morphology; Particle size; True density; Fusion energetics; Crystal defect; Dissolution rate

Summary

Phenytoin (5,5-diphenylhydantoin; DPH) crystals were grown under defined conditions from glass-distilled methanol containing various concentrations of the additive, 3-acetoxymethyl-5,5-diphenylhydantoin (AMDPH; a proposed prodrug of DPH), and their physical properties characterized. The addition of 0.5–12 g l^{-1} AMDPH to the crystallization solutions at 30 °C led to an apparently sigmoidal increase in AMDPH sorption (0.034–0.5 mol%) by the crystals, a change of crystal habit from acicular prisms to long thin plates with rough surfaces, a reduction of crystallization yield, a wider density distribution, a decrease in particle size, and an increase in specific surface area. Vigorous repeated washing of the doped crystals with 5% methanol in water dislodged 51 ± 8% w/w of AMDPH and a negligible amount of DPH (1.0 ± 0.1% w/w), indicating that a substantial portion of the sorbed AMDPH is present at or near the crystal surface. Powder X-ray diffraction detected no significant changes in both the diffraction pattern and *d*-spacing values (< 0.5%), suggesting an absence of major structural changes. Thermal analysis of the doped crystals, however, revealed relatively marked decreases in the enthalpy of fusion, ΔH^f, and entropy of fusion, ΔS^f (by as much as 11%), suggesting that the sorption of AMDPH augments both the enthalpy and entropy of the crystals. The decreases in ΔS^f are 27 ± 4 times the calculated ΔS^m_{ideal} values, reflecting a substantial rise in lattice disorder and disruption due to the presence of AMDPH. The initial dissolution rate (IR) at both 25 and 37 °C increased by more than 3.5-fold for the samples prepared at 9 g l^{-1} AMDPH while the intrinsic dissolution rate, IDR (i.e. IR divided by initial surface area), at both temperatures increased by maximally 2–3-fold for the crystals grown at 5 g l^{-1} AMDPH. The enhancement of IDR is possibly associated with an increase in the density of crystal defects (on the surface and within the bulk) arising from both growth and the sorption of AMDPH, and with a positive contribution from crystal anisotropy.

Introduction

Previous studies on acetaminophen, an analgesic and antipyretic, have shown that a number

---

Correspondence: A.H.L. Chow, Faculty of Pharmaceutical Sciences, University of British Columbia, 2146 East Mall, Vancouver, B.C., V6T 1Z3, Canada.

of important pharmaceutical properties of this drug can be reproducibly altered by incorporating traces (0–0.45 mol%) of the additive, *p*-acetoxyacetanilide (both a synthetic impurity and a proposed prodrug), into its crystal lattice, during growth from aqueous solutions (Chow et al., 1985). These properties include habit (i.e. shape), size, density, enthalpy (and entropy) of fusion, surface area and dissolution rate (Chow et al., 1985; Duncan-Hewitt and Grant, 1986). To evaluate the universality of this approach for systematically modifying the pharmaceutical properties of drugs, particularly those with a solid-state related problem, similar studies have since been extended to phenytoin (5,5-diphenylhydantoin; DPH), an anticonvulsant agent used for the treatment of grand mal epileptic seizures. DPH is known to exhibit poor and/or erratic absorption in various dosage forms, whether present as the free acid or the sodium salt (Stella et al., 1975). This problem is closely associated with its low water solubility, low dissolution rate, and fairly high pK_a (~ 8.3). The poor aqueous solubility of DPH can be ascribed to its strong crystal lattice (m.p. 295 °C) resulting from strong intermolecular hydrogen bonding (Philip et al., 1984).

Similar to our previous work on acetaminophen, the present study employed a cited ester prodrug of DPH, namely, 3-acetoxymethyl-5,5-diphenylhydantoin (AMDPH), as the crystallization additive. The objectives of the present investigation are two-fold: (a) to gain a better understanding of the influence of crystallization additives on those material properties of pharmaceutical interest; and (b) to establish physicochemical principles for optimizing drug release and absorption for such problematic drugs as DPH.

Materials and Methods

Reagents and materials

DPH ($\sim$ 99%; m.p. 294–295 °C) was supplied by Sigma Chemical Co. (St. Louis, MO, U.S.A.). The sample gave one sharp peak in both DSC and HPLC. AMDPH was synthesized according to the method of Varia et al. (1984) with minor modifications and recrystallized from ethanol twice to give a white solid melting at 158–161 °C. The identity of AMDPH was determined by solution NMR spectroscopy. Methanol used for recrystallization of DPH and high-performance liquid chromatography (HPLC) was glass-distilled HPLC grade from BDH Chemicals. Cyclohexanone and isopropanol (Omnisolv) used for gas chromatography were GC grade from Sigma Chemicals and BDH Chemicals, respectively. Benzophenone (99%) and potassium dihydrogen orthophosphate used in HPLC and potassium carbonate, formalin solution (37–41%), ether and acetic anhydride used in synthesis were analytical grade supplied by BDH Chemicals. The suspending liquids, 1-bromobutane and ethylbromide, used in density measurement were supplied by Matheson, Coleman and Bell Manufacturing Chemists and Baker Chemical Co., respectively. Water used for HPLC was double-distilled in an all-glass apparatus.

Batch crystallization from methanol

DPH (13 g) and AMDPH (0–12 g l^{-1}) were dissolved in 400 ml (316.4 g) of methanol (glass-distilled HPLC grade) under mild reflux. After equilibration at 50 °C for 30 minutes, the solution was transferred to a 500 ml three-necked, round-bottomed flask immersed in a thermostatic water bath at 30 °C ± 0.1 °C. As soon as 5 min had elapsed, the supersaturated solution was seeded with 1–2 mg of DPH seed crystals (< 75 μm), and stirred at 250 ± 1 rpm for 2 h. These conditions correspond to an initial supersaturation of 6.5 g kg^{-1} at 30 °C. The crystals were then rapidly filtered off by means of suction, spread on a petri dish, air-dried for 2 days and stored in a desiccator under vacuum before use. The samples thus dried contained a barely detectable and negligible trace of methanol (1–20 ppm), as determined by GC (see below). The methanol retained by the crystals, being considerably smaller in quantity than the sorbed AMDPH, is disregarded in the discussion of this paper.

Residual methanol content determination

The amount of residual methanol in the dried crystals was determined by GC employing a

Hewlett Packard series 5830A gas chromatograph, a capillary column (HP Ultra 2 cross-linked 5% phenylmethyl silicone; 25 m × 0.32 mm i.d.), a split injection mode (ratio of 30 : 1) and a flame ionization detector. Cyclohexanone was used as the crystals' solvent and isopropanol as the internal standard. Two stock solutions (A and B) containing methanol (100 ppm) and isopropanol (50 ppm), respectively, in cyclohexanone were prepared. A calibration curve was constructed using solutions (1–40 ppm methanol, 5 ppm isopropanol) prepared by diluting 0.01–0.4 ml of A with 0.1 ml of B to a final volume of 1 ml with cyclohexanone. For the analysis, the crystals (0.05 g) and 0.1 ml of B were dissolved and made up to a final volume of 1 ml with cyclohexanone. 2-μl samples were injected. The GC operating conditions were as follows: injection temperature 160 °C; column temperature initially set at 60 °C for 4.2 min, then increased to 130 °C at a rate of 30 °C min^{-1}; detector temperature 250 °C; carrier gas (helium UHP) flow 1 ml min^{-1}; hydrogen UHP flow 30 ml min^{-1}; air flow 240 ml min^{-1}; auxiliary gas (helium) flow 30 ml min^{-1}; head pressure 7 p.s.i.

Additive sorption determination

The sorption of AMDPH by DPH crystals was determined by HPLC using an isocratic HPLC system (Hewlett Packard HP 1050), a variable-wavelength detector (Hewlett Packard HP 1050), an area integrator (Hewlett Packard HP 3396A), a micropore reversed-phase ODS-Hypersil C-18 column (2.1 × 100 mm), a mobile phase composed of 52% 0.003 M potassium dihydrogen orthophosphate buffer and 48% methanol eluted at a rate of 0.5 ml min^{-1}. The doped crystals (10–15 mg) were dissolved in methanol, to which 100 μl of benzophenone solution (1 μg μl^{-1}) as the internal standard were added prior to making up to final volume (10 ml). 5-μl (0.003–0.045 μg AMDPH + 0.05 μg benzophenone) samples were injected. The retention times of DPH, AMDPH and benzophenone were 2.05, 5.98 and 9.91 min, respectively. Calibration plots were obtained using different amounts of AMDPH and a fixed amount of benzophenone as the internal standard. The UV detector response at 230 nm was linearly related to the peak area ratio of AMDPH to benzophenone over the concentration range employed.

Surface-adsorbed additive determination

The amount of surface-adsorbed additive was determined by HPLC employing the same analytical conditions as described above. The crystals (0.02 g) grown at various concentrations of AMDPH were repeatedly and vigorously washed four times by vortexing each time with 2 ml of 5% methanol in water for 2 min. 1 ml of the filtered supernatant of each washing with 100 μl benzophenone solution (1 μg μl^{-1}) were diluted to 10 ml with methanol. 5-μl samples were analyzed as before.

Particle size distribution

The particle size distribution of the DPH samples was determined using a Brinkman laser-based optical particle size analyzer (Model 2010) equipped with a built-in, charged coupled device microscopic video camera for image analysis. The crystals (0.05 g) were suspended in 2 ml of 1-bromobutane in a quartz magnetic stirring cell. A pulsed light source (strobe) 'froze' the particle motion to give a 'still life' picture on a TV screen. The specific length and specific width (defined by the equations below) were then obtained for each frozen particle image by means of an IBM PC computer with specialized software for analysis of particle size data.

Specific length

$$= \left(\text{perimeter} + \sqrt{\text{perimeter}^2 - \text{area} \times 16}\right)/4 \tag{1}$$

Specific width

$$= \left(\text{perimeter} - \sqrt{\text{perimeter}^2 - \text{area} \times 16}\right)/4 \tag{2}$$

Powder X-ray diffraction studies

The crystals were subjected to X-ray diffraction in a Rigaku Geigerflex X-ray diffractometer using CuK$_\alpha$ X-rays and a nickel filter. The DPH samples (0.05 g) and lithium fluoride (0.01 g) as the internal standard were triturated gently in a mortar by means of a pestle before being packed into a glass sample holder. The samples were scanned from $2\theta = 5$ to 55° at a speed of 5° per min. The data was collected and analyzed by a data processing computer unit (D/Max-B Control).

Scanning electron microscopy

The samples were coated with gold and their habits and surface features studied using a Hitachi S-570 scanning electron microscope.

Differential scanning calorimetry

The enthalpy of fusion, ΔH^{f}, and melting point, T_{m}, of the DPH crystals (1–2 mg) were determined in hermetically sealed aluminum pans heated at a rate of 10°C min^{-1} in a Dupont 910 Series 99 differential scanning calorimeter using nitrogen as the purge gas and indium as the calorimetric standard. Sealed pans were used to prevent sublimation of DPH.

From the single endotherm, T_{m} of the crystals was taken as the temperature at the point of intersection of the leading line of steepest slope and the base line. ΔH^{f} was calculated from the peak area which was determined by cutting and weighing. The precision of this procedure was 0.5–1.5%, as determined by six repeated measurements of the melting peak of the indium standard.

Density measurement

The density of the crystals was measured using the flotation method described by Duncan-Hewitt and Grant (1986) with modifications. The suspending fluid consisted of 94.3% 1-bromobutane and 5.7% ethylbromide saturated with DPH. About 100 crystals were suspended in 5 ml of the liquid in a tightly capped test tube. The tube was equilibrated in a large beaker containing water being circulated through an external thermostatic water bath (±0.01°C). The bath was initially kept at a temperature at which all the crystals floated on the liquid. The temperature of the liquid was then successively raised to give three crystal density end-points, namely, the upper end of the density range (D_{U}) the mid-point (median) density (D_{M}) and the lower end of the density range (D_{L}). D_{U} corresponded to the temperature at which the first few crystals started sinking or remained suspended in the middle of the liquid. D_{M} was determined by the temperature at which about half of the crystals sank midway or to the bottom of the liquid. D_{L} was marked by the temperature at which all the crystals either stayed suspended throughout or settled at the bottom of the liquid. The three density-defining temperatures were measured using a digital platinum resistance thermometer. A calibration plot of density vs temperature of the liquid was constructed using a digital density meter (PAAR DMA 45) and employed for calculating the density range and median density of the DPH crystals.

Specific surface area measurement

The specific surface area of DPH crystals was determined by krypton adsorption at 0.0322, 0.075 and 0.1093% in helium using the B.E.T. triple-point gas adsorption isotherm and a Quantasorb (Quantachrome Corp., Syosset, NY) surface area analyzer (Chow et al., 1985). Prior to measurement, the samples were outgassed by repeated adsorption (at 77 K) and desorption (at 298 K) of krypton until a constant desorption response was attained. Calibration was performed immediately following each desorption measurement by injecting a volume of pure nitrogen equivalent to within ±10% of the volume of krypton adsorbed.

Dissolution studies

The dissolution rate of 20 mg of DPH crystals in water at 25 and 37°C was determined in an automated six-spindle dissolution tester (Vanderkamp 600, VanKel, Edison, NJ) employing the USP/NFXVI (1985) dissolution Method 2 with paddle stirring at 100 or 200 rpm. The crystals were added at zero time to 900 ml of degassed distilled water containing hydrochloric acid (0.001 M) and Brij 30 (1:112500 v/v). Triplicate samples of 2.4 ml were withdrawn by means of an automated sample collector (Vanderkamp EDS-10) at selected time intervals and the concentrations of DPH in the samples were determined by UV spectrophotometry at 230 nm using a diode array spectrophotometer (Hewlett Packard HP8452-A). The mass of DPH dissolved was calculated from the concentration after correcting for the change in volume of the dissolution medium.

Results and Discussion

Crystal morphology and particle size distribution

DPH was crystallized under defined conditions from methanol (glass-distilled HPLC grade) containing various concentrations (0–12 g l^{-1}) of the additive, AMDPH. In the absence of AMDPH, acicular prisms with smooth faces were obtained (Fig. 1). Raising the concentration of AMDPH in the solutions above 5 g l^{-1} yielded long thin plates with relatively rough surfaces, as shown by scanning electron microscopy (Fig. 1). The extent of habit thinning and surface roughness was found to depend on the AMDPH concentration. Examination of particle size revealed a reduction in the size of the crystals as a function of the AMDPH concentration (Fig. 2). However, two-dimensional image analysis on the samples did not show any significant changes in the length-to-width ratio, suggesting that growth of DPH is preferentially inhibited along the crystallographic axis on the third dimension, probably by adsorption of the additive onto the corresponding faces, thereby giving rise to a long thin platy habit. The inhibitory effect of AMDPH on crystal growth is further demonstrated by a concentration dependent reduction in crystal yield harvested 2 h after seeding (Fig. 3). The observed changes in crystal habit were not mediated through a change in the initial supersaturation of the solutions, since the concentrations of AMDPH employed did not appear to affect significantly the equilibrium solubility of DPH at 30 °C.

Specific surface area

Increasing the concentration of AMDPH in the solutions beyond 3 g l^{-1} (Fig. 4) caused a progressive increase in the specific surface area (SSA) of the crystals up to approx. 0.5 m^2 g^{-1}. The increases in SSA appear to result from a combination of three factors, namely, the reduction in particle size, the thinning of the crystal habit, and the increase in surface roughness.

Additive sorption

The sorption of AMDPH by the crystals at 30 °C displayed an approximately sigmoidal increase with increasing concentration of AMDPH in the solutions, plateauing at approx. 0.5 mol% from 9 g l^{-1} AMDPH onwards (Fig. 5). A substantial portion of the sorbed AMDPH appeared to reside on or near the surface of the DPH crystals prepared at 0.5–5 g l^{-1} AMDPH in solutions, since vigorous repeated washing of the crystals with 5% methanol in water (four times) removed a total of $51 \pm 8\%$ w/w of AMDPH and $1.0 \pm 0.1\%$ w/w of DPH. (In these latter studies, very little or no AMDPH could be detected in the fourth wash for the various doped crystal samples, thus the number of washing was limited to four.) In contrast, the crystals grown at higher concentrations of AMDPH (9–12 g l^{-1}) yielded $30 \pm 3\%$ w/w AMDPH and $1.1 \pm 0.1\%$ w/w DPH in solutions when subjected to the same washing treatment. The lower percent by weight of surface-adsorbed AMDPH of these samples corresponds to the higher AMDPH sorption by the crystals. The above findings accord with the previous studies on acetaminophen in that the dopant sorption by the drug crystals assumes a constant level above a certain dopant concentration in solutions (Chow et al., 1985), but differs in that a substantial amount of the sorbed dopant is located at or near the surface of the drug crystals. This difference in sorption behaviour between the two crystallization systems likely stems from the requirement of employing much higher concentrations of AMDPH in solutions to effect habit modification and a trace incorporation of AMDPH into the DPH crystals which substantially enhance the interaction of AMDPH with the crystal surface. This requirement may be explained in terms of a stronger interaction between the DPH molecules themselves, or to a stronger interaction between the additive and the solvent molecules, or to both. Further studies are

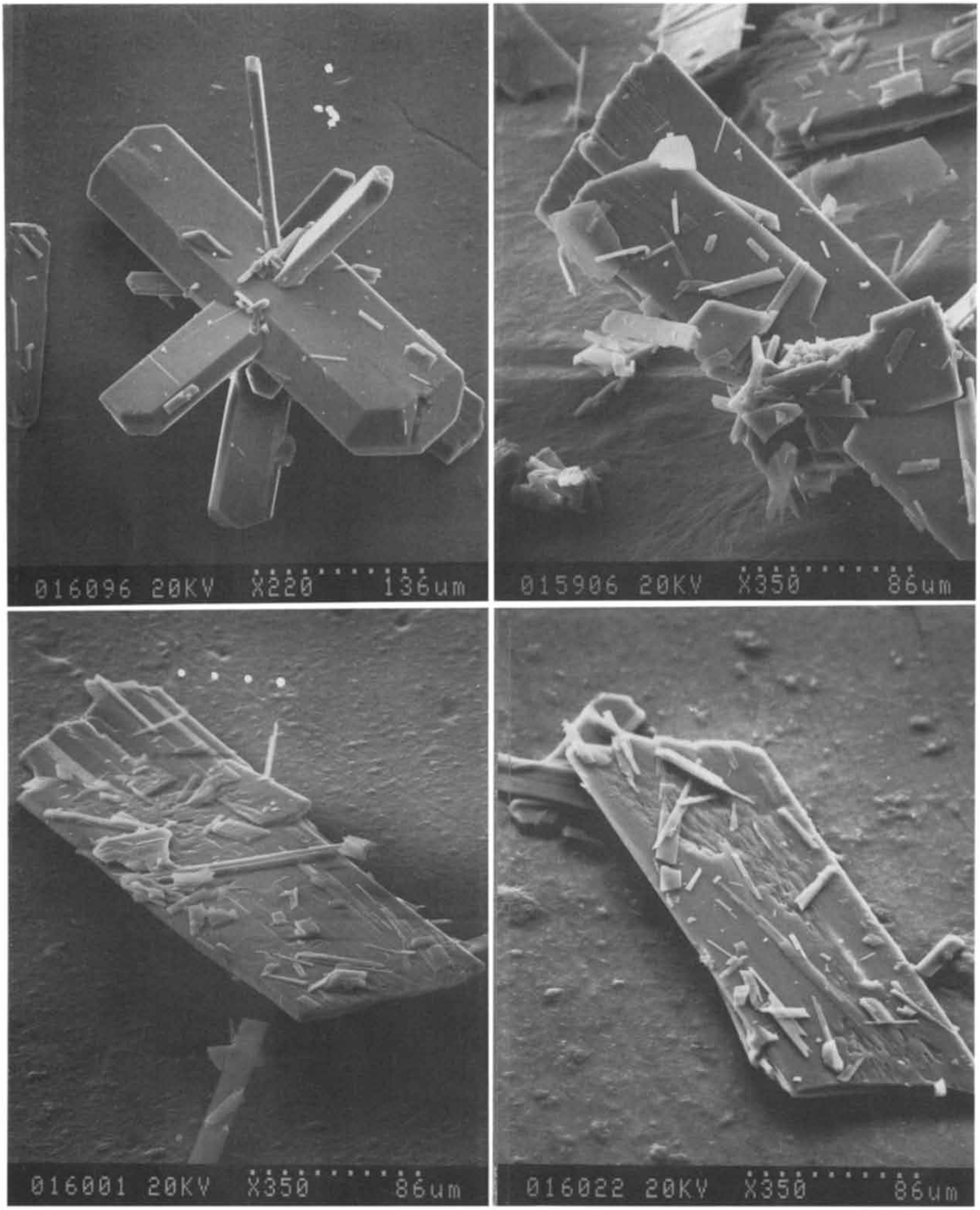

Fig. 1. Scanning electron photomicrographs of DPH crystals grown from methanol containing the following concentrations of AMDPH: upper left, 0 g/l; upper right, 5 g/l; lower left, 9 g/l; lower right, 12 g/l.

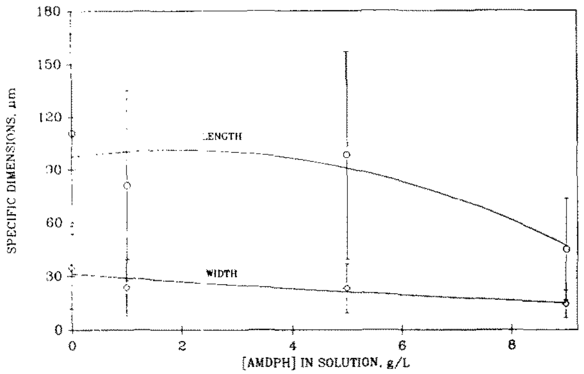

Fig. 2. Specific lengths and specific widths of DPH crystals grown from methanol containing various concentrations of AMDPH. Each vertical bar represents the standard deviation of 40 measurements.

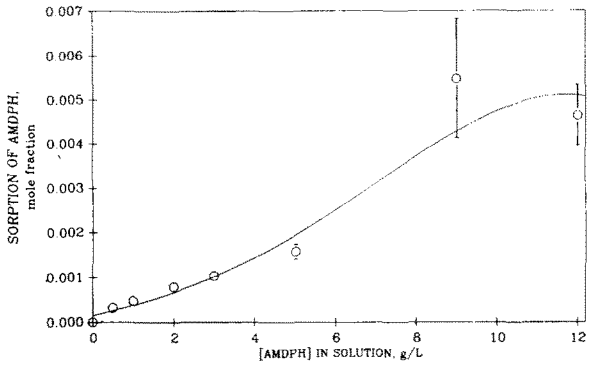

Fig. 5. Sorption of AMDPH by DPH crystals grown from methanol in the presence of various concentrations of AMDPH. The vertical bars represent the standard deviations of five determinations.

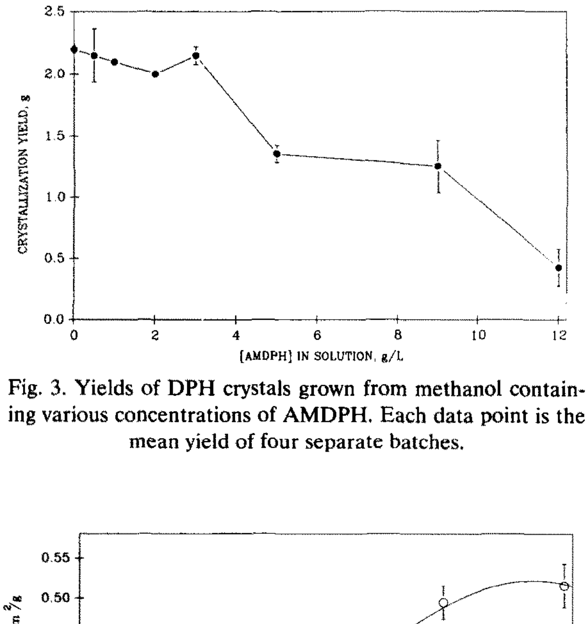

Fig. 3. Yields of DPH crystals grown from methanol containing various concentrations of AMDPH. Each data point is the mean yield of four separate batches.

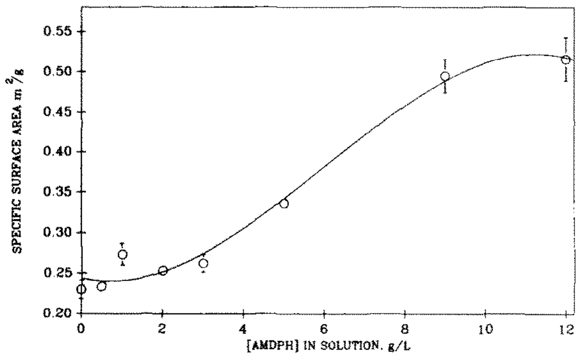

Fig. 4. Specific surface areas of DPH recrystallized from methanol containing various concentrations of AMDPH. Each data point is the mean value of duplicate determinations.

currently underway to determine the distribution of AMDPH within the crystals.

Powder X-ray diffraction, fusion thermodynamic properties and true density

Powder X-ray diffraction studies on the crystals did not detect any significant differences in either the diffraction pattern or the *d*-spacing values (< 0.5%) between the doped and undoped samples, indicating that gross crystalline changes, e.g. polymorphism, did not occur. However, thermal analysis showed that while the melting points of the doped crystals exhibited a negligible decrease (< 0.2%), the enthalpy of fusion, ΔH^{f}, and entropy of fusion, ΔS^{f}, were reduced by as much as 11% when the concentration of AMDPH in the solutions was raised from 0.5 to 12 g l^{-1} (corresponding to a sorption of 0.034–0.5 mol%) (Fig. 6 and Table 1). This suggests that the presence of traces of AMDPH significantly augments both the enthalpy and entropy of the crystals. The decreases in ΔS^{f} are 27 ± 4 times the ideal molar entropy of mixing, $\Delta S^{\mathrm{m}}_{\mathrm{ideal}}$, as determined by the negative slope or 'disruption index' (d.i.) obtained from the linear regression of ΔS^{f} on $\Delta S^{\mathrm{m}}_{\mathrm{ideal}}$ (Chow et al., 1985; York and Grant, 1985; Pikal and Grant, 1987). Fig. 7 shows the regression plot of ΔS^{f} vs $\Delta S^{\mathrm{m}}_{\mathrm{ideal}}$ based on the following derived semi-empirical equation.

$$\Delta S^{\mathrm{f}} = \Delta S^{\mathrm{f}}_{0} - b \cdot \Delta S^{\mathrm{m}}_{\mathrm{ideal}} \qquad (3)$$

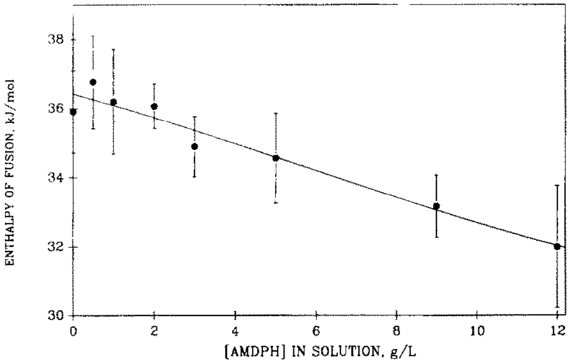

Fig. 6. Enthalpies of fusion of DPH crystals grown from methanol containing various concentrations of AMDPH. The vertical bars represent the standard deviations of five to seven determinations.

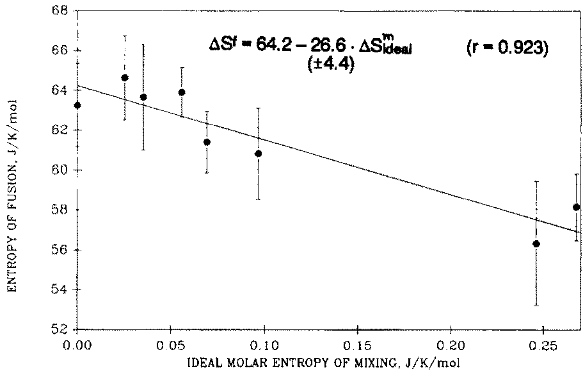

Fig. 7. Linear regression plot of the entropy of fusion, ΔS^{f}, vs the ideal molar entropy of mixing, $\Delta S^{\mathrm{m}}_{\mathrm{ideal}}$, for DPH crystals grown from methanol containing various concentrations of AMDPH. The vertical bars represent the standard deviations of five to seven determinations.

where the slope, b, is the disruption index (d.i.); the intercept, $\Delta S^{\mathrm{f}}_{0}$, is the hypothetical entropy of fusion of uncontaminated, perfect DPH crystals, for which $\Delta S^{\mathrm{m}}_{\mathrm{ideal}} = 0$, if impurity defects are the only, or at least the predominant, defects present. The $\Delta S^{\mathrm{m}}_{\mathrm{ideal}}$ value is calculated from the equation

$$\Delta S^{\mathrm{m}}_{\mathrm{ideal}} = -R \cdot (x_{\mathrm{A}} \ln x_{\mathrm{A}} + x_{\mathrm{D}} \ln x_{\mathrm{D}}) \qquad (4)$$

where R is the universal gas constant, x_{A} and x_{D} are the mole fractions of AMDPH and DPH in the crystals, respectively. This thermodynamic quantity considers only the disorder created in the lattice by simple random mixing or dilution of the host (i.e. DPH) with the guest (i.e. AMDPH) molecules, as in an ideal solution, and disregards any disorder resulting from lattice disruption (or defects) in the solid or preferential orientation of molecules in the liquid. The use of $\Delta S^{\mathrm{m}}_{\mathrm{ideal}}$ here neither assumes nor implies the formation of an ideal solid solution; this quantity simply serves as an 'ideal' reference parameter for quantifying and comparing lattice disorder. (In the present study, the entropy of mixing of AMDPH with DPH is probably not equal to the $\Delta S^{\mathrm{m}}_{\mathrm{ideal}}$ since the distribution of AMDPH in the crystals appears nonuniform or nonrandom with a signifi-

TABLE 1

Mole fraction sorption (x_A) of AMDPH, melting points (T_m), molar enthalpies of fusion (ΔH^f), molar entropies of fusion ($\Delta S^f = \Delta H^f / T_m$) of DPH crystals grown from methanol at 0–12 g l^{-1} AMDPH, and calculated ideal partial molar entropies ($\bar{S}_j = -Rx_j \ln x_j$), ideal molar entropies of mixing ($\Delta S^m_{ideal} = \Sigma \bar{S}_j$) of the components in the crystals, where A = 3-acetoxymethyl-5,5-diphenylhydantoin, D = 5,5-diphenylhydantoin

[AMDPH] (g l^{-1})	x_{A} ($\times 10^4$)	$T_{\mathrm{m}} \pm$ S.D. (K)	$\Delta H^{\mathrm{f}} \pm$ S.D. (kJ mol^{-1})	$\Delta S^{\mathrm{f}} \pm$ S.D.	$\bar{S}_{\mathrm{A}}$	$\bar{S}_{\mathrm{D}}$	$\Delta S^{\mathrm{m}}_{\mathrm{ideal}}$
					(J K^{-1} mol^{-1})		
0	0	568.1 ± 0.3	35.9 ± 0.8	63.3 ± 1.4	0	0	0
0.5	3.4	568.2 ± 0.3	36.7 ± 1.2	64.6 ± 2.1	0.0226	0.0028	0.0254
1.0	4.9	568.4 ± 0.2	36.2 ± 1.5	63.7 ± 2.7	0.0312	0.0041	0.0353
2.0	8.3	568.4 ± 0.2	36.2 ± 0.7	63.7 ± 1.2	0.0489	0.0069	0.0558
3.0	10.6	568.2 ± 0.4	34.9 ± 0.9	61.4 ± 1.5	0.0604	0.0088	0.0692
5.0	15.6	568.0 ± 0.4	34.6 ± 1.3	60.8 ± 2.3	0.0837	0.0130	0.0967
9.0	51.4	567.5 ± 0.4	33.2 ± 0.9	58.4 ± 1.6	0.2251	0.0426	0.2677
12.0	46.5	567.8 ± 0.4	31.9 ± 1.4	56.3 ± 2.5	0.2077	0.0386	0.2463

cant portion located at or near the crystal surface.) Accordingly, the larger the decrease in ΔS^{f} (which depicts the entropy excess of a doped defective crystal above that of the pure perfect crystal) with respect to the $\Delta S^{\mathrm{m}}_{\mathrm{ideal}}$ (which represents the entropy contribution purely from random mixing of similar chemical species), the greater is the extent of lattice disorder or disruption induced by the additive. In the present situation, a disruption index of 27 (±4) observed for AMDPH would imply the creation of considerable disorder and disruption in the crystal lattice of DPH (about 27 times that expected from pure random mixing alone) by the sorbed AMDPH. The disruptive influence of AMDPH on DPH crystals is approx. 4 times that of *p*-acetoxyacetanilide and water on acetaminophen crystals, as estimated by comparing the disruption indices determined for both cases, indicating that the particularly strong crystal lattice of DPH is much more sensitive to doping.

Density measurement by the flotation method indicated that the doped crystals had a wider particle density distribution (range ~ 1.270–1.298 g cm^{-3}) than the undoped samples (range ~ 1.270–1.283 g cm^{-3}) with identical or almost identical values at the lower end and higher values at the upper end (Fig. 8). The median particle density (defined here as the density on or below which roughly 50% by number of the particles fall) tended to increase (from 1.2744 to 1.2916 g cm^{-3}) with increasing AMDPH concentration from 0 to 5 g l^{-1} and to decrease thereafter to a constant level (1.2784 g cm^{-3}). This suggests that within a certain concentration range, AMDPH promotes the formation of less defective crystals, as expected from its retardation of crystal growth which tends to deter the occurrence of defects arising from growth. At higher concentrations, however, the reduction in growth-mediated defects may be offset by an increase in additive-mediated defects, thus accounting for the decrease in median particle density. Although the trend in median particle density appears to be inconsistent with that of the enthalpy of fusion, the inconsistency may be reconciled by the supposition that the more defective crystals, though fewer in number, are mostly the larger particles which weigh more and hence exert a predominant influence on ΔH^{f} which is quantified on a weight or mole basis.

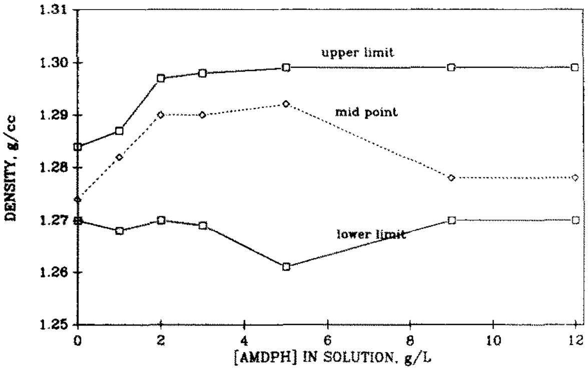

Fig. 8. Particle densities of DPH crystals grown from methanol containing various concentrations of AMDPH. The upper and lower data points at each concentration denote the upper and lower limits of the density range while the midpoint represents the median density. Each data point is the mean value of duplicate determinations.

Dissolution studies

The regression slope calculated from the dissolution-time profile within the first 0–15 min was taken as the initial dissolution rate, assuming dissolution occurred essentially under sink conditions during this time period.

The initial rate and amount of DPH dissolved at 37 °C displayed an increase attaining a peak maximum (~ 3.8 fold of the control) for the crystals grown at 9 g l^{-1} AMDPH (Figs. 9 and 10). In contrast, the initial rate and extent of dissolution at 25 °C exhibited a progressive increase up to approx. 6.6 times those of the undoped crystals at 12 g l^{-1} AMDPH (Figs 10 and 11). The intrinsic dissolution rate (i.e. the initial dissolution rate divided by the initial surface area; IDR) at 37 °C exhibited a peak maximum (~ 2.1-fold increase) for the crystals prepared at 5 g l^{-1} AMDPH, whereas the IDR at 25 °C increased by as much as 3-fold and levelled off beyond 5 g l^{-1} AMDPH (Fig. 12). Since significant differences in dissolution rate of the crystals still exist after adjusting for the contribution due to surface area, factors other than surface area must be responsible. The factors most likely involved in the present situa-

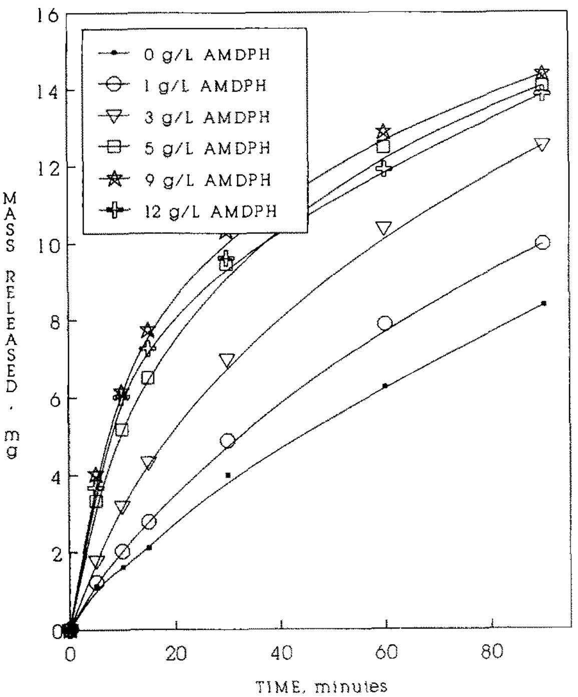

Fig. 9. Dissolution-time profiles at 37 °C of DPH crystals grown from methanol containing various concentrations of AMDPH.

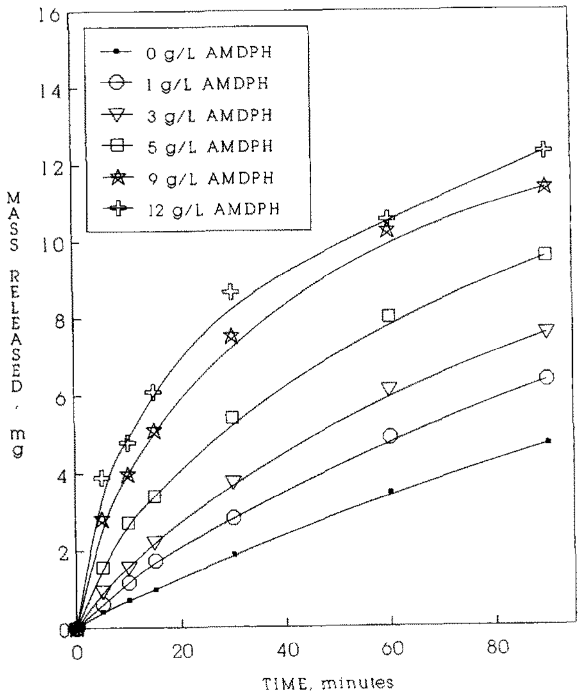

Fig. 11. Dissolution-time profiles at 25 °C of DPH crystals grown from methanol containing various concentrations of AMDPH.

tion are the following: (a) crystal anisotropy, which refers here to the presence of crystal faces exhibiting different polarities and hence different dissolution rates and is habit-dependent (Burt and Mitchell, 1980); (b) hydrodynamic conditions during dissolution, which is also habit-dependent; and (c) crystal defects (both on the surface and within the bulk) induced by AMDPH and crystallization conditions (Burt and Mitchell, 1981; Chow and Grant, 1988a,b, 1989; Chow et al., 1985). The initial increases in IDR at both 25 and 37 °C

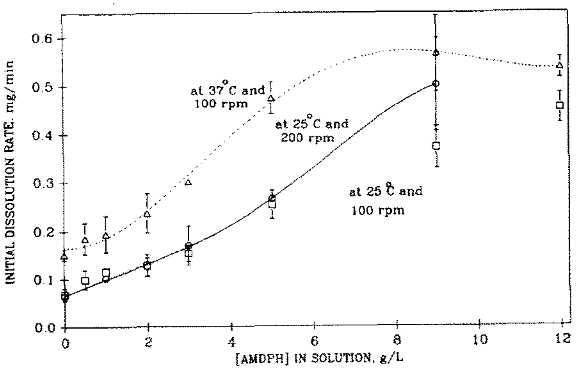

Fig. 10. Initial dissolution rates at 25 and 37 °C and at 100 and 200 rpm of DPH crystals grown from methanol containing various concentrations of AMDPH. The vertical bars depict the standard deviations of quadruplicate determinations.

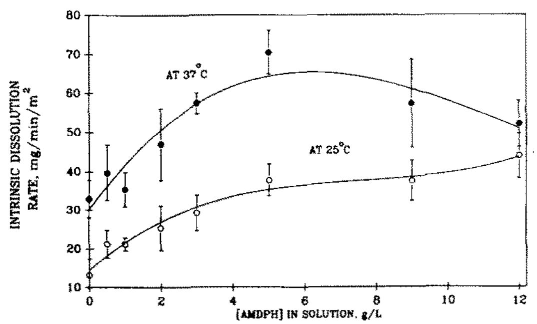

Fig. 12. Intrinsic dissolution rates at both 25 and 37 °C of DPH crystals grown from methanol containing various concentrations of AMDPH. The vertical bars depict the standard deviations of quadruplicate determinations.

within 0.5–5 g l^{-1} AMDPH may be attributable to increases in the density of crystal defects (generated by both sorbed AMDPH and growth), to increases in the relative area of the more polar faces, and to more favourable hydrodynamic conditions for dissolution. However, the contributions from crystal anisotropy and from dissolution hydrodynamics in particular appear relatively minor, since the change of habit was not apparent until the AMDPH concentration in the crystallization media exceeded 5 g l^{-1} and since the initial dissolution rates of all the crystal samples at 25 ° C were virtually unaffected by an increase of stirring speed from 100 to 200 rpm (Fig. 10). On the other hand, the subsequent decreases at 37 ° C and plateauing at 25 ° C of IDR (from 5 g l^{-1} AMDPH onwards) may be ascribed to 'poisoning' of the active sites for dissolution by adsorbed AMDPH (Piccolo and Tawashi, 1970, 1971a,b) and/or to the entrapment of air pockets within 'cracks' or 'pits' on the crystal surface which interfered with the dissolution. This latter difference in the trend of IDR between 25 and 37 ° C is indicative of a temperature dependence of the various factors affecting the dissolution process of doped DPH crystals. Although both additives, AMDPH and *p*-acetoxyacetanilide, are similar in their effects on the dissolution rate of their respective doped drug crystals (Chow et al., 1985), they may not act by exactly identical mechanisms since the effects of *p*-acetoxyacetanilide on the dissolution of acetaminophen crystals appear to mediate mostly through crystal anisotropy and/or shape-related dissolution hydrodynamics (Chan and Grant, 1989; Chow and Grant, 1989).

Conclusions

The findings of the present study can be summarized as follows.

(1) Crystallization of DPH from methanol in the presence of various concentrations of the additive, AMDPH, leads to an approximately sigmoidal increase in additive sorption of 0.034–0.5 mol% by the crystals, and to concomitant changes in the habit, surface features, size distribution, density distribution, specific surface area, fusion energetics, dissolution rate of the crystals.

(2) The sorption of AMDPH (guest) by the DPH (host) crystals reduces both their ΔH^{f} and ΔS^{f}, reflecting an augmentation of both the enthalpy and entropy of the crystals. The extent of lattice disorder and disruption in DPH crystals engendered by the presence of AMDPH, as determined by the negative slope of ΔS^{f} against $\Delta S^{\mathrm{m}}_{\mathrm{ideal}}$, is substantially higher than that brought about by *p*-acetoxyacetanilide and water in the acetaminophen host crystals (Chow et al., 1985), indicating that the strong crystal lattice of DPH is particularly sensitive to doping with a structurally related additive.

(3) The changes in dissolution rate cannot be accounted for solely by the changes in surface area, and likely also involve the complex interplay of these factors: (a) structural defects within and on the surface of the crystals (induced by both AMDPH and growth); and (b) crystal anisotropy.

(4) The ability of AMDPH to systematically control and enhance (by 2–3 fold) the intrinsic dissolution rate of DPH crystals may find applications in the design and formulation of a more consistent and more bioavailable solid dosage form for DPH.

(5) The present findings are in close agreement with those reported for acetaminophen (Chow et al., 1985), and further demonstrate the feasibility of using traces of a structurally related additive to control the physicochemical properties of pharmaceutical crystals.

Acknowledgements

This work was presented at the Fifth Annual Meeting of the American Association of Pharmaceutical Scientists in Las Vegas, NV, U.S.A., on November 4–8, 1990. We thank Drs Wayne Riggs and Andras Szeitz for assistance with the gas chromatographic analysis of methanol. We also thank the Medical Research Council of Canada

(Grant MA 10514) and the British Columbia Health Care Research Foundation (Grants 87-2-042, 88-2-069) for financial support.

References

Burt, H.M. and Mitchell, A.G., Effect of habit modification on dissolution rate. *Int. J. Pharm.*, 5 (1980) 239–251.

Burt, H.M. and Mitchell, A.G., Crystal defects and dissolution. *Int. J. Pharm.*, 9 (1981) 137–152.

Chan, H.-K. and Grant, D.J.W., Influence of compaction on the intrinsic dissolution rate of modified acetaminophen and adipic acid crystals. *Int. J. Pharm.*, 57 (1989) 117–124.

Chow, A.H.-L., Chow P.K.K., Wang, Z. and Grant, D.J.W., Modification of acetaminophen crystals: influence of growth in aqueous solutions containing *p*-acetoxyacetanilide on crystal properties. *Int. J. Pharm.*, 24 (1985) 239–258.

Chow, A.H.-L. and Grant, D.J.W., Modification of acetaminophen crystals. II. Influence of stirring rate during solution-phase growth on crystal properties in the presence and absence of *p*-acetoxyacetanilide. *Int. J. Pharm.*, 41 (1988a) 29–39.

Chow, A.H.-L. and Grant, D.J.W., Modification of acetaminophen crystals. III. Influence of initial supersaturation during solution-phase growth on crystal properties in the presence and absence of *p*-acetoxyacetanilide. *Int. J. Pharm.*, 42 (1988b) 123–133.

Chow, A.H.-L. and Grant, D.J.W., Physical factors influencing the aqueous dissolution rate of acetaminophen crystals doped with *p*-acetoxyacetanilide: evaluation by multiple linear regression. *Int. J. Pharm.*, 51 (1989) 129–135.

Duncan-Hewitt, W.C. and Grant, D.J.W., True density and thermal expansivity of pharmaceutical solids: comparison of methods and assessment of crystallinity. *Int. J. Pharm.*, 28 (1986) 75–84.

Philip, J., Holcomb, I.J. and Fusari, S.A., Phenytoin. In Florey, K. (Ed.), *Analytical Profiles of Drug Substances*, Academic Press, Orlando, FL, 1984, vol. 13, pp. 417–445.

Piccolo, J. and Tawashi, R., Inhibited dissolution of drug crystals by a certified water soluble dye. *J. Pharm. Sci.*, 59 (1970) 56–59.

Piccolo, J. and Tawashi, R., Inhibited dissolution of drug crystals by certified water-soluble dyes. II. *J. Pharm. Sci.*, 60 (1971a) 59–63.

Piccolo, J. and Tawashi, R., Inhibited dissolution of drug crystals by certified water-soluble dyes. II. *J. Pharm. Sci.*, 60 (1971b) 1818–1820.

Pikal, M.J. and Grant, D.J.W., A theoretical treatment of changes in energy and entropy of solids caused by additives or impurities in solid solution. *Int. J. Pharm.*, 39 (1987) 243–253.

Stella, V., Higuchi, T, Hussain A. and Truelove, J., The chemistry of a novel 5,5-diphenylhydantoin prodrug. In Higuchi, T. and Stella, V. (Eds), *Prodrugs as Novel Drug Delivery Systems*, American Chemical Society Symposium Series 14, 1975, pp. 154–183.

USP XXI/NF XVI, The United States Pharmacopeial Convention, Rockville, MD 1985, pp. 1242–1244.

Varia, S.A., Schuller, S., Sloan, K.B. and Stella, V.J., Phenytoin prodrugs III: Water-soluble prodrugs for oral and/or parenteral use. *J. Pharm. Sci.*, 73 (1984) 1068–1073.

York, P. and Grant, D.J.W., A disruption index for quantifying the solid state disorder induced by additives or impurities. I. Definition and evaluation from heat of fusion. *Int. J. Pharm.*, 25 (1985) 57–72.