International Journal of Pharmaceutics, 79 (1992) 171–181

IJP 02632

Modification of phenytoin crystals. II. Influence of 3-propanoyloxymethyl-5,5-diphenylhydantoin on solution-phase crystallization and related crystal properties

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(Received 11 June 1991)
(Modified version received 30 August 1991)
(Accepted 4 September 1991)

Key words: Phenytoin; 3-Propanoyloxymethyl-5,5-diphenylhydantoin; Crystal size; Crystal morphology; Crystal defects; Crystal disorder; Dissolution rate

Summary

The effects of crystallizing phenytoin (5,5-diphenylhydantoin; DPH) from methanol under defined conditions in the presence of various concentrations of the additive, 3-propanoyloxymethyl-5,5-diphenylhydantoin (PMDPH; a cited prodrug of DPH) were investigated. An increase in the concentrations of PMDPH (from 0.5 to 11 g l^{-1}) in the crystallization solutions at 30 °C brought about a linear increase in PMDPH sorption (0.03–0.57 mol%) by the DPH crystals, a morphological change of the crystals from needles to elongated plates, a drop in crystallization yield, a decrease in particle size and an increase in specific surface area of the crystals. Vigorous multiple washing of the doped crystals with methanol/water (5:95) detached approx. 70 ± 2% w/w of PMDPH and a negligible amount of DPH (1.0 ± 0.1% w/w), indicating that the sorbed dopant is predominantly located at or close to the crystal surface. While powder X-ray diffraction studies on the doped and pure crystals presented no significant differences in both their diffraction patterns and lattice spacings, the enthalpy of fusion, ΔH^f, and entropy of fusion, ΔS^f, of the crystals, as determined by differential scanning calorimetry, were lowered with increasing sorption of PMDPH (by as much as 8% at 0.57 mol% of sorbed PMDPH), suggesting that the sorption of PMDPH raises both the enthalpy and entropy of the crystals. The disruption index of PMDPH, as estimated from the negative slope of the linear regression of ΔS^f on the ideal molar entropy of mixing, ΔS^m_{ideal}, is 19 ± 2, implying an introduction of considerable disorder and disruption (about 19-times that expected from pure random mixing alone) in the crystal lattice of DPH by the presence of PMDPH. Determination of the aqueous dissolution rate of the various samples at 25 and 37 °C afforded an upward trend in initial dissolution rate (IR) as a function of the PMDPH sorption, with the largest increase at 0.36 mol% of PMDPH (~ 3.3-times those of the pure, undoped crystals). The intrinsic dissolution rate, IDR (i.e. IR divided by initial surface area), of the crystals at both temperatures also displayed a rise, but peaked at 0.16 mol% of sorbed PMDPH (corresponding to ~ 1.7-fold increase). The observed increases in IDR are probably mediated through increases in the concentration of crystal defects arising from the sorption of PMDPH, and to a much lesser extent, through changes in crystal habit.

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Introduction

In recent years, it has been reported that doping of pharmaceutical crystals with a structurally

related additive during crystallization from solutions consistently modifies such physical properties of the crystals as the habit, size, energy, true density, surface area and dissolution rate. (Fairbrother and Grant, 1978, 1979; Chow et al., 1984, 1985).

Most recently, Chow and Hsia (1991) further demonstrated that the same properties of the problematic antiepileptic drug, phenytoin (5,5-diphenylhydantoin; DPH) could be similarly altered by crystallizing the drug from methanol in the presence of the additive, 3-acetoxymethyl-5,5-diphenylhydantoin (AMDPH). AMDPH is an acetyl ester derivative of DPH, and has been cited as a potential prodrug of DPH (Varia et al., 1984). In addition to being structurally akin to DPH, AMDPH is not appreciably greater in molecular size than DPH, which makes possible, from the thermodynamic standpoint, the incorporation of AMDPH into the crystal lattice of DPH. As pointed out by Kitaigorodsky (1973), the formation of solid solutions or mixed crystals in organics can normally occur by substitution. For such molecular substitution to occur, the host (drug) and the guest (dopant) molecules need to be similar in both size and shape. Thus, for a series of homologous dopants related to the drug by structure, there exists a certain molecular size limit for these dopants beyond which their incorporation into the crystals would not be energetically feasible.

To investigate how the molecular sizes of the ester homologues of DPH influence their incorporation into DPH crystals and the resulting crystal properties, studies similar to those described above (Chow and Hsia, 1991) have been applied to another additive higher in the ester homologous series, viz. 3-propanoyloxymethyl-5,5-diphenylhydantoin (PMDPH). PMDPH, also cited as a potential prodrug of DPH, differs from AMDPH in possessing an additional methylene group in its ester side chain (Varia et al., 1984). The specific objectives of the present study are: (1) to compare the effects of PMDPH with those of AMDPH on the physical properties of DPH crystals; and (2) to establish some general guidelines for the selection of homologous additives for doping drug crystals.

Materials and Methods

Reagents and materials

The sources and grades of the reagents used, including DPH, glass-distilled methanol, glass-distilled cyclohexanone, isopropanol, potassium dihydrogen orthophosphate, potassium carbonate, formalin solution (37–41%) and diethyl ether, were reported previously (Chow and Hsia, 1991). Water used in HPLC was double-distilled in an all-glass apparatus. Toluene and propionic anhydride were analytical grade supplied by BDH Chemicals.

PMDPH was synthesized according to the method of Varia et al. (1984) with modifications. The synthetic intermediate, 3-hydroxymethyl-5,5-diphenylhydantoin (30 g), was suspended in an excess of propionic anhydride (100 ml) with the aid of stirring. Following acidification with concentrated sulfuric acid (0.4 ml), the suspension was continuously stirred for an additional 15 min. The resulting solid was filtered, washed with diethyl ether (100 ml), recrystallized twice from methanol, and checked for purity by HPLC. The identity of the reaction product was determined by differential scanning calorimetry (m.p. 172–174 °C) and solution NMR spectroscopy.

Batch crystallization from methanol

The crystals were grown as previously described (Chow and Hsia, 1991) from a supersaturated methanolic solution of DPH at 30 °C (σ = 6.5 g kg^{-1}) in the presence of 0–11 g l^{-1} PMDPH. After crystallization had proceeded for 2 h, the crystals were rapidly filtered off by means of suction, spread on a petri dish and stored in a desiccator for at least 3 days before characterization. The dried crystals were analyzed for their residual methanol contents using a previously developed GC procedure (Chow and Hsia, 1991). The GC analysis indicates that the various dried samples of DPH contain a negligible trace of methanol (7–16 ppm), which is small compared with the amount of PMDPH present.

Additive sorption determination

The sorption of PMDPH by DPH crystals was determined by high-performance liquid chro-

matography (HPLC) using a Hewlett Packard Series 1050 liquid chromatograph with UV detection at 230 nm, a micropore reversed-phase ODS-Hypersil column (2.1 × 100 mm), a mobile phase composed of 52% 0.003 M potassium orthophosphate buffer/48% methanol, and a flow rate of 0.5 ml min^{-1}. The linearity of the UV response at 230 nm was checked using solutions (10 ml) of varying amounts of DPH (4–20 μg) and a fixed amount of toluene (100 μl of a 3% v/v toluene in methanol stock solution) as the internal standard. The doped crystals (20–30 mg) were dissolved in a few milliliters of methanol, to which 100 μl of the 3% v/v toluene stock solution was added before making up to a final volume of 10 ml. 5-μl samples were injected.

Surface-adsorbed additive determination

HPLC utilizing the same analytical conditions as those described above was used to determine the amount of additive adsorbed on to the crystal surface of DPH. The crystals (20 mg) grown in the presence of 3, 5 and 7 g l^{-1} PMDPH were repeatedly washed by vortex mixing with four 2-ml aliquots of 5% methanol in water for 2 min each. The resulting supernatants were filtered through Millipore filters. For the HPLC analysis, 50 μl of the toluene stock solution (described above) were added to 0.9-ml aliquots of the filtered supernatants. 10-μl samples were analyzed for both DPH and PMDPH contents.

Particle size analysis, scanning electron microscopy, specific surface area determination, powder X-ray diffraction, differential scanning calorimetry, dissolution studies

The crystal samples were subjected to particle size analysis, powder X-ray diffraction, morphological analysis, specific surface area measurement, thermal analysis and dissolution rate determination as reported previously (Chow and Hsia, 1991).

The particle size distribution of the DPH samples was examined using a Brinkman laser-based optical particle size analyzer (Model 2010) equipped with a charge-coupled device microscopic video camera for image analysis. The crystals (0.05 g) were suspended in 2 ml of 1-bromobutane in a quartz cell using a magnetic stirrer bar. The specific lengths and specific widths of the crystals were determined from particle images 'frozen' by a pulsed light technique and 'captured' by an IBM PS2 computer equipped with the PSA 2010 software supplied by Brinkman.

The crystal samples were gold-coated before being examined in a Hitachi S-570 scanning electron microscope.

The specific surface area of the DPH crystals was determined using a B.E.T. triple-point gas adsorption technique with krypton as adsorbate, on a Quantasorb (Quantachrome Corp., NJ, U.S.A.) surface area analyzer.

Powder X-ray diffraction studies were conducted on the DPH crystals (~ 50 mg packed in a glass sample holder) using CuK_α X-rays with a nickel filter. The samples were scanned from $2\theta = 5$ to 55° at a speed of 5° min^{-1}.

The enthalpy of fusion, ΔH^f, and melting point, T_m, of the DPH samples (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 thermal analyzer using nitrogen as the purge gas and indium as the calorimetric standard. The melting point was taken as the temperature at the point of intersection of the leading line of the steepest slope and the baseline. The enthalpy of fusion was calculated from the peak area which was determined by means of an integration routine on an Apple II plus computer interfaced with the thermal analyzer.

The dissolution-time profile of DPH crystals (20 mg) was determined in water at 25 and 37 °C using an automated six-spindle dissolution tester (Vanderkamp 600, VanKel) and the USP/NFXVI (1985) dissolution Method 2 with paddle stirring at 100 or 200 rpm. The dissolution medium consisted of 900 ml of degassed distilled water containing hydrochloric acid (0.001 M) and Brij 30 (1 in 112 500 v/v). Samples were withdrawn by an automated sample collector (Vanderkamp EDS-10) at selected time intervals and analyzed by UV spectrophotometry at 230 nm using a diode array spectrophotometer (Hewlett Packard HP8452A).

Results and Discussion

Crystal morphology, particle size distribution, specific surface area

In the absence of PMDPH, DPH crystallized from methanol in the form of acicular prisms. The presence of 3 g l^{-1} (8.9 mmol l^{-1}) or more of PMDPH in the crystallization media caused the DPH crystals to develop into long, thin plates (Fig. 1), the extent of which depended on the PMDPH concentration. Concomitant with the habit thinning of DPH crystals was a slight decrease in mean particle size and an increase in specific surface area of the crystals (Fig. 2). However, the length-to-width ratios of the crystals, as measured by two-dimensional image analysis, revealed no significant changes, suggesting that the additive selectively inhibits growth of the DPH crystals along the crystallographic axis on the third dimension, probably, by adsorbing on to the corresponding faces. The latter view is supported by an attendant reduction in crystallization yield collected at 2 h (Fig. 3). The observed change in crystallization yield was not associated with a change in the initial supersaturation of the crystallization solutions, since the solubility of DPH in methanol at 30 °C was not significantly altered by the presence of PMDPH (0.5–7 g l^{-1}), thus substantiating the ability of adsorbed PMDPH to retard the crystal growth of DPH. While all these effects are grossly similar to those of AMDPH (Chow and Hsia, 1991), there appear to be two major differences. Firstly, AMDPH exerted no noticeable effects on both the crystallization yield and the crystal habit of DPH until its concentration in solutions reached 5 g l^{-1} (15.4 mmol l^{-1}) (Chow and Hsia, 1991). Secondly, the rough surfaces seen on the AMDPH-doped DPH crystals did not appear to develop to the same extent on the crystals treated with PMDPH at the concentrations studied. Thus, it would seem that AMDPH is less potent than PMDPH as a habit modifier of the DPH crystals, but more disruptive than PMDPH in terms of inducing 'roughness' or structural defects on the crystal surface of DPH.

Sorption of PMDPH

The sorption of PMDPH by DPH crystals, as determined by HPLC, increased linearly with increasing concentrations (0–11 g l^{-1}) of PMDPH in the crystallization media (Fig. 4). Subjection of the doped crystals prepared at 3, 5, and 7 g l^{-1} (8.7, 14.8, and 20.7 mmol l^{-1}) PMDPH to vigorous repeated washing with 5% methanol in water four times dislodged cumulatively 69 ± 2, 72 ± 2 and $50 \pm 2\%$ w/w of the sorbed PMDPH, respectively, but only $1.0 \pm 0.1\%$ w/w of DPH for each sample. This indicates that an appreciable portion of the sorbed additive is situated at or close to the crystal surface. It has been shown previously that similar washing treatment applied to AMDPH-doped crystals removes $51 \pm 8\%$ w/w of the sorbed AMDPH for DPH crystals grown in the presence of 0.5–5 g l^{-1} or 1.5–15.4 mmol l^{-1} AMDPH (Chow and Hsia, 1991). In terms of proportion by weight, there appears to be more PMDPH than AMDPH adsorbed to the crystal surface of DPH at comparable concentrations of the two additives in solutions. The difference ($\sim 20\%$) in surface adsorption observed between the two additives appears unrelated to the difference in surface area of the resulting crystals, since the latter difference is insignificantly small. All these observations, coupled with the lower threshold concentration (3 g l^{-1}) of PMDPH for habit modification, suggest that addition of a methylene group to the side chain of an ester derivative of DPH considerably enhances its interaction with the crystal surface of DPH.

Powder X-ray diffraction and thermal analysis

Powder X-ray diffraction analysis of the DPH samples revealed no significant changes in either the diffraction pattern or d-spacing values ($< 0.5\%$) between the various samples, indicating that PMDPH did not promote gross crystalline modification such as polymorphism.

Differential scanning calorimetric studies revealed that the sorption of PMDPH slightly altered the melting point, T_m, of the crystals, but significantly reduced both the enthalpy of fusion, ΔH^f, and entropy of fusion, ΔS^f, of the crystals, by as much as 8% for the samples prepared at 11 g l^{-1} PMDPH (Fig. 5; Table 1). This suggests that the presence of PMDPH raises the enthalpy and entropy of the crystals.

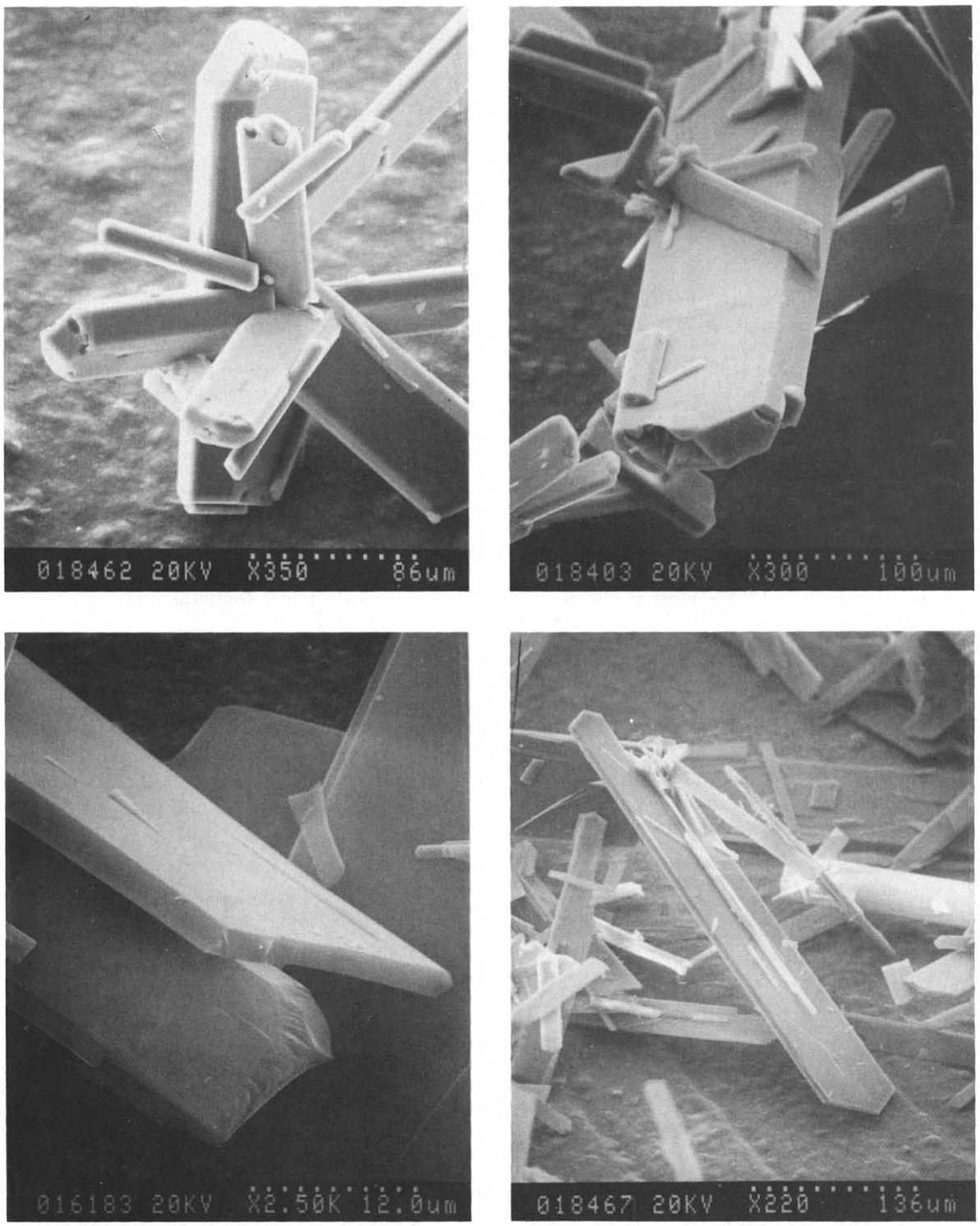

Fig. 1. Scanning electron photomicrographs of DPH crystallized from methanol in the presence of the following concentrations of PMDPH: upper left, 0 g l^{-1}; upper right, 1 g l^{-1}; lower left, 5 g l^{-1}; lower right, 7 g l^{-1}.

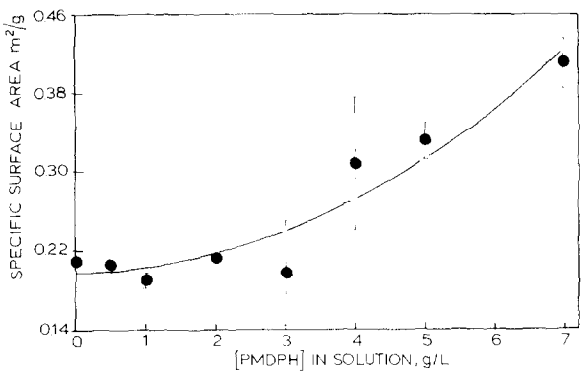

Fig. 2. Specific surface areas of DPH crystallized from methanol containing various concentrations of PMDPH. Each data point is the mean value of two separate batches.

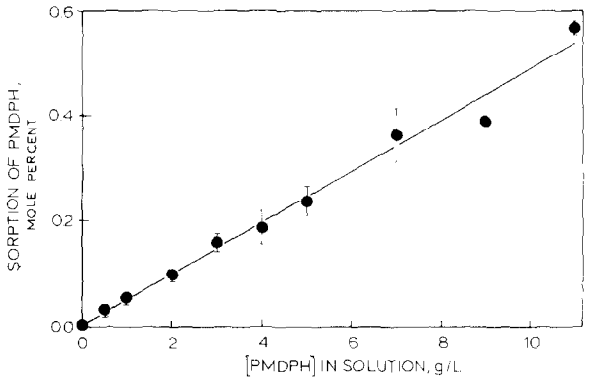

Fig. 4. Sorption of PMDPH by DPH crystals grown from methanol containing various concentrations of PMDPH. The vertical bars depict the standard deviations of quadruplicate determinations.

To evaluate the extent of lattice disruption or disorder induced by PMDPH, the observed ΔS^{f} values were regressed against the ideal molar entropy of mixing, ΔS^{m}_{ideal}, values calculated from the crystal compositions, yielding a slope of 19 ± 2 (Fig. 6). According to the previously established basis for this semi-empirical thermodynamic approach (Chow et al., 1985; York and Grant, 1985; Pikal and Grant, 1987; Chow and Hsia, 1991), the value of this slope or of the so-called disruption index indicates that the presence of PMDPH causes about 19-times more disorder and disruption in the crystal lattice of DPH than would be expected from pure random mixing or dilution of the DPH with PMDPH alone, as in an ideal solution. As has been stressed previously (Chow et al., 1985; York and Grant, 1985; Chow and Hsia, 1991), the ΔS^{m}_{ideal} value, which is used as a thermodynamic reference quantity for assessing lattice disorder or disruption, only reflects the entropy change brought about by random mixing of two closely similar chemical species. Any deviation from this ideal value in a particular situation could indicate a nonrandom or nonuniform distribution of the minor component in the major component, as observed in the present case, or a dissimilarity between the two components in terms of bonding strength and molecular volume. Since a substantial amount of the additive has been found on the surface and since the incorpo-

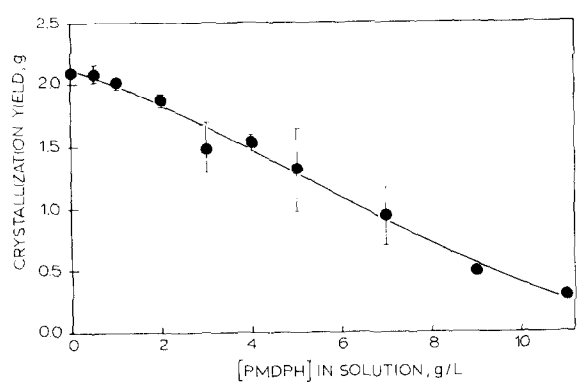

Fig. 3. Yields of DPH crystallized from methanol containing various concentrations of PMDPH. The vertical bars represent the standard deviations of four separate batches.

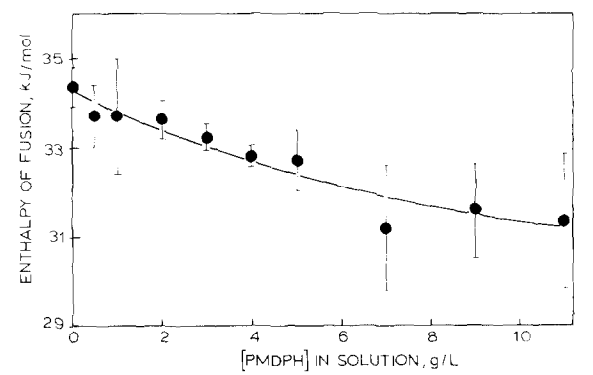

Fig. 5. Enthalpies of fusion, ΔH^{f}, of DPH crystals grown from methanol in the presence of various concentrations of PMDPH. The vertical bars represent the standard deviations of 6–10 determinations.

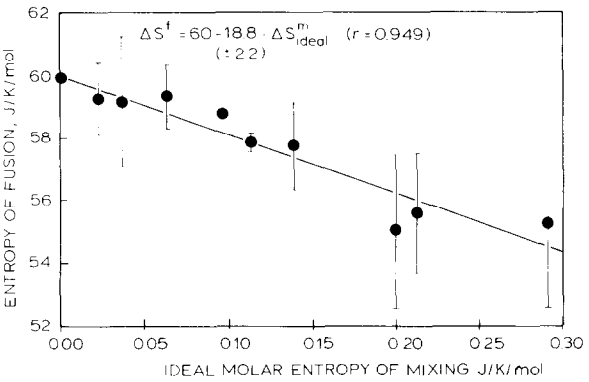

Fig. 6. Linear regression plot of the entropy of fusion, ΔS^f, against the ideal molar entropy of mixing, ΔS^m_{ideal}, for DPH crystals grown from methanol in the presence of various concentrations of PMDPH. The vertical bars depict the standard deviations of 6–10 determinations.

rated additive is likely not uniformly distributed throughout the DPH crystals, the ΔS^m_{ideal} value probably does not reflect the actual entropy change in the additive sorption process. Nonetheless, the relatively large magnitude of the calculated disruption index indicates that the strong crystal lattice of DPH is sensitive to the presence of traces of PMDPH. The disruptive potential of the additives is likely due to their ability to disrupt the close molecular packing arrangement and/or the hydrogen bonding pattern within the DPH crystal lattice.

It has been shown in previous studies that the dopant, AMDPH, has a disruption index of 27 ± 4 when retained by the DPH crystals (Chow and Hsia, 1991). Comparison of this value with that obtained for PMDPH (19 ± 2) indicates that AMDPH is capable of generating more intense lattice disruption than PMDPH. However, this latter inference must be viewed with caution in view of the higher proportion of AMDPH being present within the DPH crystals (Chow and Hsia, 1991), as determined by the crystal washing technique described above. Furthermore, the difference in lattice disruption ability between the two additives, as suggested by the relative magnitude of the disruption indices, is barely significant statistically on account of the fairly large variability in the measured ΔS^f values.

Dissolution studies

As with previous studies (Chow and Hsia, 1991), the data collected within the first 15 min of each dissolution run were used to calculate the initial rate of dissolution under sink conditions. The concentrations of DPH released into solution during this time period were found to be no more than 20% of the equilibrium solubility of DPH at the stated temperature, thus conforming to the criterion of 'sink conditions'.

The crystals displayed progressive increases in both the initial rate and extent of dissolution at

TABLE 1

Mole fraction sorption (x_P) of PMDPH, 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 0–11 g l^{-1} PMDPH, and calculated ideal partial molar entropies ($\bar{S}_j = -Rx_j \ln x_j$), and ideal molar entropies of mixing ($\Delta S^m_{ideal} = \Sigma \bar{S}_j$) of the components in the crystals, where P = 3-propanoyloxymethyl-5,5-diphenylhydantoin and D = 5,5-diphenylhydantoin

[PMDPH] (g l^{-1})	x_P ($\times 10^4$)	$T_m \pm$ S.D. (K)	$\Delta H^f \pm$ S.D. (kJ mol^{-1})	$\Delta S^f \pm$ S.D.	$\bar{S}_P$ (J K^{-1} mol^{-1})	$\bar{S}_D$	ΔS^m_{ideal}
0	0	568.6 ± 0.1	34.4 ± 0.4	59.9 ± 0.1	0	0	0
0.5	3.0	568.4 ± 0.5	33.7 ± 0.7	59.2 ± 1.2	0.0202	0.0025	0.0227
1.0	5.2	568.4 ± 0.2	33.7 ± 1.3	59.2 ± 2.1	0.0324	0.0043	0.0367
2.0	9.6	568.4 ± 0.2	33.6 ± 0.4	59.3 ± 1.0	0.0554	0.0080	0.0634
3.0	15.6	568.5 ± 0.5	33.2 ± 0.3	58.7 ± 0.1	0.0838	0.0130	0.0968
4.0	18.7	567.9 ± 0.3	32.8 ± 0.2	57.8 ± 0.3	0.0976	0.0155	0.1131
5.0	23.7	568.2 ± 0.3	32.7 ± 0.7	57.7 ± 1.4	0.1190	0.0196	0.1386
7.0	36.2	567.4 ± 0.7	31.2 ± 1.4	55.0 ± 2.5	0.1695	0.0301	0.1996
9.0	38.9	568.0 ± 0.2	31.6 ± 1.1	55.6 ± 1.9	0.1794	0.0323	0.2117
11.0	56.7	567.4 ± 0.2	31.3 ± 1.5	55.2 ± 2.7	0.2436	0.0470	0.2906

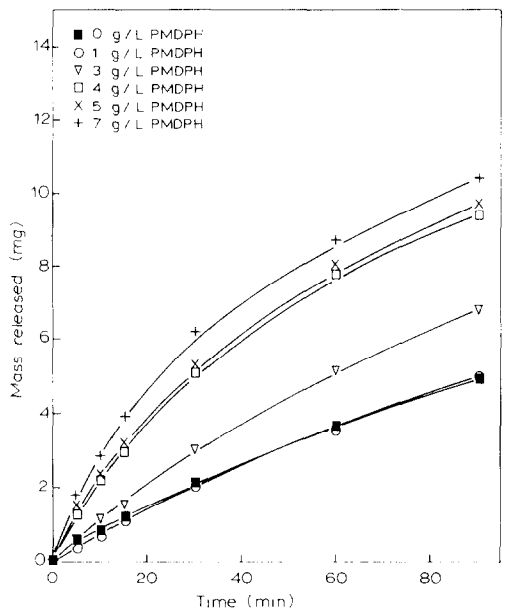

Fig. 7. Dissolution-time profiles at 25 °C of DPH crystals grown from methanol containing various concentrations of PMDPH.

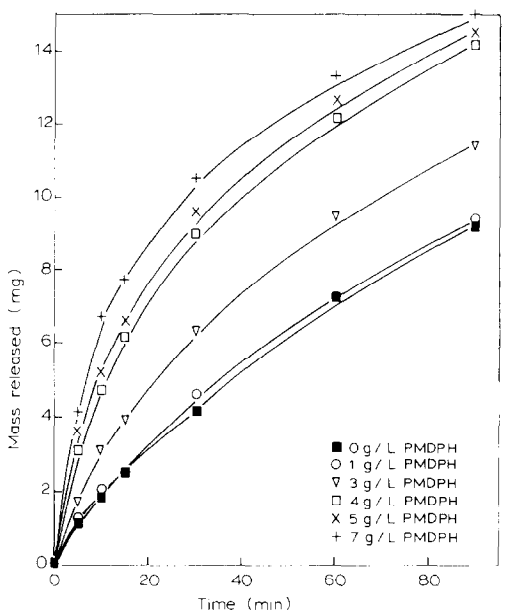

Fig. 8. Dissolution-time profiles at 37 °C of DPH crystals grown from methanol containing various concentrations of PMDPH.

25 and 37 °C when grown from solutions with increasing concentrations of PMDPH, up to 3.3-times those of the pure, undoped crystals at 7 g l^{-1} (corresponding to a PMDPH sorption of 0.36 mol%) (Figs 7–9). The change in specific surface area also followed a similar trend (Fig. 2), with the result that the intrinsic dissolution rate (i.e. the initial dissolution rate divided by the initial surface area, IDR) at both 25 and 37 °C attained a maximum (~ 1.7-fold increase) for the DPH crystals grown at 3 g l^{-1} PMDPH (equivalent to a PMDPH sorption of 0.16 mol%) (Fig. 10). The significant differences observed in IDR indicate that factors other than surface area must also be influencing the observed dissolution rates. As discussed previously (Chow and Hsia, 1991), these factors possibly involve: (a) crystal anisotropy (Burt and Mitchell, 1980); (b) dissolution hydrodynamics; and (c) crystal defects at the surface and within the bulk of the crystals induced by both PMDPH and growth (Burt and Mitchell, 1981; Chow et al., 1985; Chow and Grant, 1989). In the present situation, increases in the concentration of crystal defects (induced by both crystallization conditions and sorbed PMDPH), as suggested by a relatively high disruption index, may be largely responsible for the observed increases in IDR at both 25 and 37 °C for the crystals prepared with 1–3 g l^{-1} PMDPH, whereas the plateauing in IDR seen with the crystals grown at higher concentrations of PMDPH may be linked

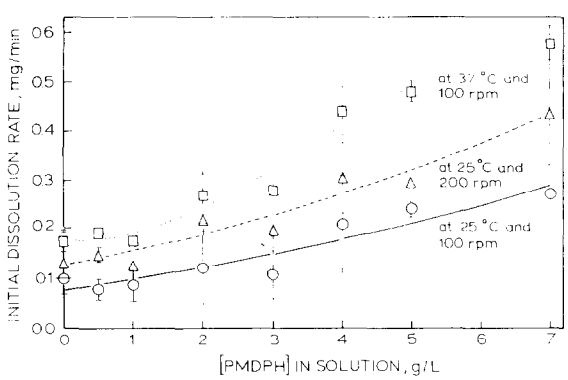

Fig. 9. Initial dissolution rates at 25 and 37 °C and at 100 and 200 rpm of DPH crystals grown from methanol containing various concentrations of PMDPH. The vertical bars represent the standard deviations of six determinations.

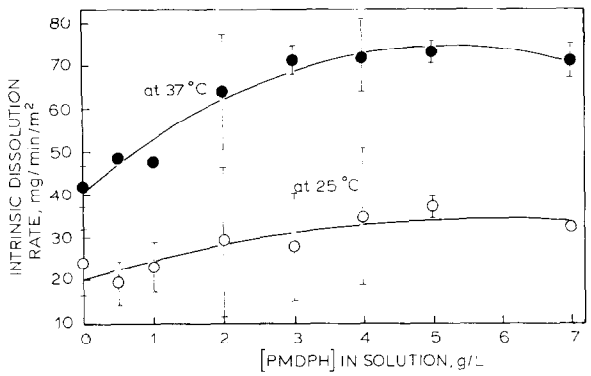

Fig. 10. Intrinsic dissolution rates at both 25 and 37 °C and at 100 rpm of DPH crystals grown from methanol containing various concentrations of PMDPH. The vertical bars depict the standard deviations of six determinations.

to the mounting influence of two opposing factors, namely, 'poisoning' of the active sites for dissolution in the crystals by adsorbed PMDPH (Piccolo and Tawashi, 1970,1971a,b) and the relatively poor wettability of adsorbed PMDPH. Although crystal anisotropy and shape-related dissolution hydrodynamics can both influence the dissolution behaviour of the crystals, their impacts, if any, appear relatively insignificant for the samples prepared at low dopant concentrations (1–3 g l^{-1}), because these samples showed very little changes in their specific surface area and habit in spite of the significant increases being seen in their IDRs.

It has been demonstrated previously that the dissolution rates of the DPH crystals doped with AMDPH are not significantly affected by a change of stirring speed of the dissolution media from 100 to 200 rpm (Chow and Hsia, 1991). In the present study with PMDPH as the dopant, such a change of dissolution conditions increased the initial dissolution rates of the various crystal samples at 25 °C to roughly the same extent such that the trends in dissolution rate at both stirring speeds almost paralleled each other (Fig. 9), reflecting an active involvement of transport-mediated dissolution mechanism under those stated conditions (Birchumshaw and Riddiford, 1952). The latter is further demonstrated by a steady climb in the IDR at 25 °C of the crystals prepared at 0, 1 and 5 g l^{-1} PMDPH when the stirring speed of the dissolution media was raised stepwise from 50 to 250 rpm (Fig. 11).

The present findings are similar to those previously obtained for AMDPH (Chow and Hsia, 1991) in many respects. Both additives yield samples which exhibit maximal dissolution rates at intermediate concentrations of the additives in solutions with decreases (or plateauing) in rate at higher concentrations. While these results may indicate that both additives behave in a similar fashion at higher concentrations towards the dissolution process of DPH (i.e. they both can poison the active dissolution sites), the mechanisms involved may be different since the initial dissolution rates of the AMDPH-doped crystals showed no significant changes upon raising the stirring speed of the dissolution media from 100 to 200 rpm. The latter observations suggest that the dissolution rates of the AMDPH-doped samples are probably governed by the surface properties of the DPH crystals rather than by the diffusion of solute away from the crystal surface, whereas the dissolution of the PMDPH-doped samples is likely controlled by both transport (diffusion) and surface reaction under the same conditions, as demonstrated by a gradual rise in dissolution rate with increasing stirring speed (Fig. 11).

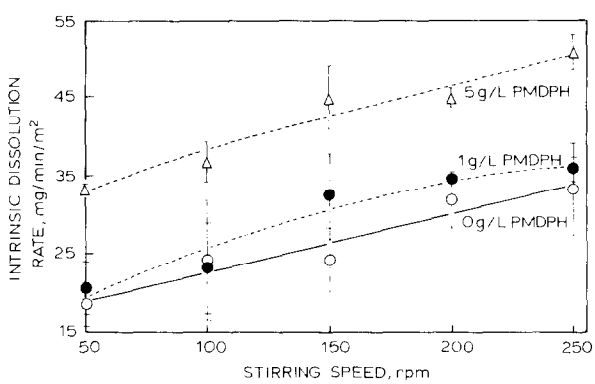

Fig. 11. Effect of stirring speed on the intrinsic dissolution rate of DPH crystals grown from methanol containing 0, 1 and 5 g l^{-1} of PMDPH. The vertical bars represent the standard deviations of six determinations.

Conclusions

The following conclusions can be reached:

(1) Growth of DPH crystals from methanol containing various concentrations of the additive, PMDPH, results in a linear rise in the sorption of PMDPH (0.03–0.57 mol%) as well as changes in the habit, particle size, specific surface area, fusion energetics and dissolution rate of the crystals.

(2) Unlike AMDPH, PMDPH tends to adsorb predominantly on the surface of the DPH crystals.

(3) As with AMDPH, the sorption of PMDPH reduces both the enthalpy of fusion, ΔH^f, and entropy of fusion, ΔS^f, of the crystals, corresponding to an increase in enthalpy and entropy of the crystals. The presence of PMDPH generates marginally less lattice disorder and disruption in the DPH crystals than does the presence of AMDPH, as determined by comparison of the disruption indices (i.e. the negative slopes of ΔS^f vs ΔS^m_{ideal}) of the two additives (Chow and Hsia, 1991).

(4) As with previous studies employing AMDPH as the crystallization additive (Chow and Hsia, 1991), the observed changes in dissolution rate cannot be explained entirely in terms of the changes in surface area. The following factors probably play roles of differing significance: (a) defects on the surface and within the bulk of the crystals (induced by PMDPH and/or crystallization conditions); (b) crystal anisotropy; and (c) dissolution hydrodynamics. Though similar in many aspects towards the dissolution behaviour of DPH, both AMDPH and PMDPH probably do not act via the same mechanism. The dissolution of AMDPH-treated crystals appears to be rate-limited by the surface properties of the crystals while the dissolution of the PMDPH-doped samples seems to be both transport- and surface-determined under the same experimental conditions.

(5) Like AMDPH, PMDPH possesses the ability to reproducibly modulate and enhance the intrinsic dissolution rate of DPH crystals.

(6) The present studies clearly demonstrate that a minor change in the structure of a homologous crystallization additive could significantly influence its interaction with the drug in the solid state and the resulting physicochemical properties.

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. The authors gratefully acknowledge the technical assistance of Drs Wayne Riggs and Andras Szeitz with the gas chromatographic analysis described in the present work. Thanks are also due to the British Columbia Health Care Research Foundation (Grants 87-2-042, 88-2-069) and the Medical Research Council of Canada (Grant MA 10514) for operating grants for A.H.L.C. and to Berlex Laboratories for a graduate scholarship for J.D.G.

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