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

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Abstract

The modification of the physical properties of phenytoin (5,5-diphenylhydantoin; DPH) by recrystallization from methanol has been investigated as a function of the concentration of 3-butanoyloxymethyl-5,5-diphenylhydantoin (BMDPH; a potential ester prodrug of DPH) added to the crystallization medium. With increasing concentration of BMDPH in the crystallization solutions (0.5–12 g l^{-1}), there exhibited a curvilinear increase in the sorption of BMDPH (0.01–0.5 mol%) and the specific surface area of the DPH crystals; a drastic reduction in crystallization yield and a progressive change of crystal habit from needles to elongated plates. Powder X-ray diffraction studies on the samples indicated essentially the same diffraction patterns and lattice spacings for both the pure and the BMDPH-doped DPH crystals, suggesting that the doped crystals did not undergo gross structural modification. However, the enthalpy of fusion, ΔH^f, and the entropy of fusion, ΔS^f, as determined by differential scanning calorimetry, reduced by as much as 17% for the samples doped at 7 g l^{-1} BMDPH (equivalent to a sorption of 0.39 mol%), reflecting a significant upsurge in both the enthalpy and entropy of the DPH crystals. The disruption index of BMDPH, as quantitatively defined by the slope of the linear regression of ΔS^f on the ideal molar entropy of mixing, ΔS^m_{ideal}, was 73 ± 11 suggesting that the additive is capable of inducing substantial lattice disorder and disruption (about 73 times that due to simple random mixing alone) in the DPH crystals. Vigorous repeated washing of the samples with 5% methanol in water removed $\sim 25 \pm 1.3\%$ w/w of sorbed BMDPH and a negligibly small amount of DPH ($1.2 \pm 0.1\%$ w/w), suggesting the BMDPH resides mostly ($\sim 75\%$) within the crystals. The initial dissolution rate (IR) at 25 and 37°C of the various samples increased sigmoidally, reaching a maximal increment of 4–5-fold for the samples prepared at BMDPH concentrations above 5 g l^{-1} whereas the intrinsic dissolution rate, IDR (i.e. IR divided by the initial surface area), at both temperatures attained a plateauing maximum ($\sim$ 2-fold increase) for the crystals grown at and above 1 g l^{-1} BMDPH. The observed improvement of IDR is likely due to an increase in the concentration of crystal defects (both within and on the surface of the crystals) and/or to a change of crystal habit.

Keywords: Phenytoin; 3-Butanoyloxymethyl-5,5-diphenylhydantoin; Particle morphology; Crystal defects; Crystal disorder; Dissolution rate

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1. Introduction

Recent studies on phenytoin (5,5-diphenylhydantoin; DPH), an erratically absorbed antiepileptic drug, have demonstrated that doping of the drug crystals with an ester homologue of DPH during crystallization from methanol reproducibly modifies the morphology, size, density, fusion energetics, specific surface area and dissolution rate of the crystals (Chow and Hsia, 1991; Gordon and Chow, 1992). These studies have employed 3-acetoxymethyl-5,5-diphenylhydantoin (AMDPH) and 3-propanoyloxymethyl-5,5-diphenylhydantoin (PMDPH) as dopants. These dopants have been cited as potential prodrugs of DPH (Varia et al., 1984). Nearly half of the sorbed AMDPH, with a molecular size comparable to that of DPH, has been shown to reside inside the DPH crystals (Chow and Hsia, 1991), whereas PMDPH, differing from AMDPH structurally by the presence of one additional methylene group, appears to adsorb mostly ($\sim 70\%$) on the crystal surface. Whilst the effects of the two dopants are grossly similar, there are some noticeable differences which may be ascribed to the structural difference between the two additives (Gordon and Chow, 1992).

To determine the structure-effect relationship of these dopants and to formulate some selection criteria for such dopants for optimizing the physical and biological properties of pharmaceutical crystals, the present study has examined the effects of another ester prodrug homologue of DPH, namely, 3-butanoyloxymethyl-5,5-diphenylhydantoin (BMDPH), which is higher by one methylene group than PMDPH in the homologous series.

2. Materials and methods

2.1. Reagents and materials

DPH used in this study was supplied by Sigma Chemical Company. BMDPH was synthesized using essentially the same procedure as reported previously (Gordon and Chow, 1992) with the following required reagents supplied by BDH Chemicals: formalin solution (37–41%), potassium carbonate, diethyl ether and butyric anhydride. The reaction product was examined for the presence of impurities by HPLC after recrystallization twice from methanol. The identity of BMDPH was verified by differential scanning calorimetry (mp 134–135°C) and solution NMR spectroscopy. Glass-distilled methanol used for HPLC and crystallization was HPLC grade from BDH Chemicals. Water was double-distilled using an all-glass apparatus. Benzene, acetonitrile (HPLC grade) and potassium dihydrogen orthophosphate used in HPLC were supplied by BDH Chemicals.

2.2. Batch crystallization from methanol

The crystallization of DPH from methanol containing BMDPH was performed according to the procedure described by Chow and Hsia (1991). A mixture of DPH (13 g) and BMDPH (0–12 g l^{-1}) in 400 ml (316.4 g) of methanol was heated under mild reflux until all the crystals had dissolved. After 30 min of equilibration at 50°C, the solution was transferred to a 500-ml three-necked, round-bottomed flask immersed in a thermostatic water bath at 30 ± 0.1°C. While being stirred at 250 ± 1 rpm, the solution was seeded with 1–2 mg of DPH seed crystals (< 75 μm) to initiate crystallization. The resulting crystals were harvested after 2 h by rapid filtration under vacuum suction and dried in a desiccator under vacuum for at least a few days prior to analysis. This drying procedure left only a negligible trace of methanol in the samples (< 1 ppm), as assayed by the GC method reported previously (Chow and Hsia, 1991).

2.3. Additive sorption determination

The sorption of BMDPH by DPH crystals was quantified by high performance liquid chromatography (HPLC) using a Hewlett Packard Series 1050 liquid chromatograph with a Hewlett Packard Series 1050 UV/visible detector and a reversed-phase Econosphere C18 5U column (4.6 × 250 mm). The mobile phase, consisting of 62% methanol and 38% 0.003 M potassium dihy-

drogen orthophosphate buffer, was eluted at a rate of 1 ml min^{-1}. The UV response at 230 nm for a series of standard mixtures containing varying amounts of BMDPH and a fixed amount of benzene as the internal standard was found to be linearly related to the concentrations of BMDPH employed. The doped crystals (35–50 mg) were dissolved in methanol, to which 150 μl of the internal standard (10% v/v benzene in methanol solution) was added before making up to final volume (10 ml). Twenty-μl samples were injected.

2.4. Surface-adsorbed additive determination

Measurement of the amount of surface-adsorbed BMDPH employed the following HPLC system and conditions: ISCO Model 2350 liquid chromatograph, ISCO V^4 UV/visible detector, ISCO Spherisorb ODS-2 column (4.6 × 250 mm), mobile phase (60% v/v acetonitrile and 40% v/v water) with a flow rate of 2 ml min^{-1} (for BMDPH analysis) or 1 ml min^{-1} (for DPH analysis). As an excellent linear correlation ($r \sim 0.996$; $n = 6$) was observed between the UV detector response at 230 nm and the amount of either BMDPH or DPH injected (via a 20-μl injection loop), inclusion of internal standard was not deemed necessary in the assay procedure.

The doped crystals (20 mg) prepared at 1, 3, 5 g l^{-1} BMDPH were repeatedly and vigorously washed with 2-ml aliquots of 5% v/v methanol in water on a vortex mixer for 2 min each. The resulting solutions were filtered through Millipore filters and 20-μl samples were injected.

2.5. Powder X-ray diffraction studies, scanning electron microscopy, differential scanning calorimetry, BET specific surface area measurement, dissolution studies

The crystals were studied for their X-ray diffraction patterns and lattice spacings, morphological features, thermal properties and surface area as reported previously (Chow and Hsia, 1991).

All the dissolution studies employed the same dissolution tester (VanderKamp 600, Van-Kel) and procedure as described previously (Chow and Hsia, 1991; Gordon and Chow, 1992) with the exception of those conducted at 200 rpm. The latter studies used an Erweka (Model DT80) Compact dissolution tester which was rigorously evaluated for reproducibility of data obtained with the Vanderkamp 600 dissolution equipment.

3. Results and discussion

3.1. Crystal yield, morphology and specific surface area

A drastic reduction in crystallization yield (from 1.83 to 0.15 g) was observed when DPH was crystallized in the presence of 2–7 g l^{-1} BMDPH (Fig. 1). This observation is in accord with previous studies (Chow and Hsia, 1991; Gordon and Chow, 1992) in which the presence of AMDPH or PMDPH in the crystallization solution has been shown to considerably retard the crystal growth of DPH. By comparison, the presence of BMDPH appears to inhibit the crystallization of DPH the most, as indicated by a much greater drop in crystallization yield at comparable concentrations of the additives in the crystallization media.

Closely associated with the decrease in crystallization yield was a progressive habit change from

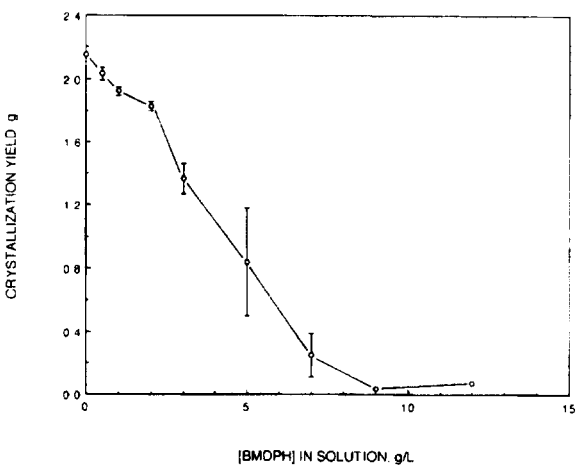

Fig. 1. Yields of DPH crystals grown from methanol in the presence of various concentrations of BMDPH. Each data point represents the mean of two to three separate batches.

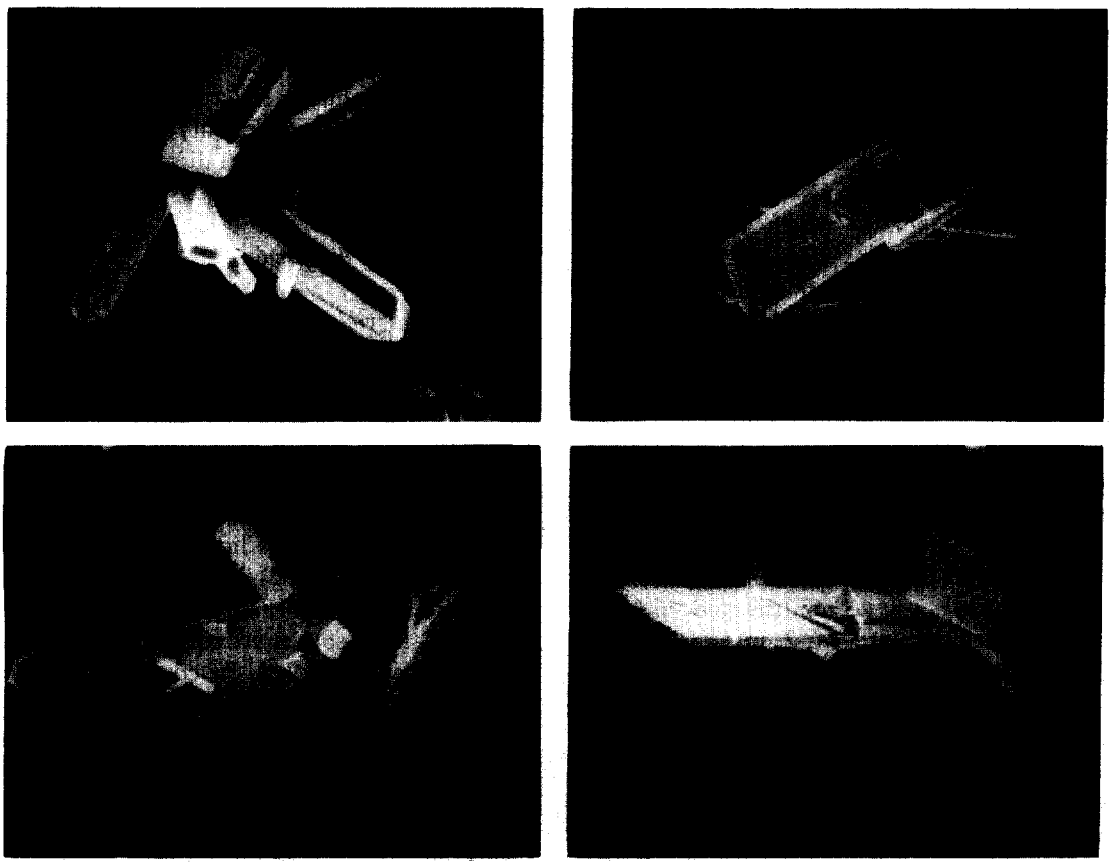

Fig. 2. Scanning electron photomicrographs of DPH crystallized from methanol in the presence of 0 (upper left), 1 (upper right), 3 (lower left) and 7 (lower right) g l^{-1} BMDPH.

acicular prisms to long thin plates (Fig. 2) and an increase in specific surface area (from 0.2 to 0.44 m^2 g^{-1}) of the crystals (Fig. 3). These effects are grossly similar to those of AMDPH and PMDPH reported previously (Chow and Hsia, 1991; Gordon and Chow, 1992). As with PMDPH, the habit thinning effect of BMDPH was not apparent until its concentration approached 3 g l^{-1}. However, AMDPH began to exert such an effect only at higher concentrations (≥ 5 g l^{-1}). As far as habit modification is concerned, the relative effectiveness of the three additives, as measured by their respective threshold concentrations, appears to follow this order: BMDPH > PMDPH > AMDPH.

The observed changes in crystallization yield and crystal habit with AMDPH, PMDPH and BMDPH are indicative of the ability of adsorbed additive to inhibit the crystal growth of DPH. Since the presence of any of these additives did not affect the equilibrium solubility of DPH at 30°C, the perceived modifications in crystal morphology were not a result of a change in the initial supersaturation of the solutions (Chow and Hsia, 1991; Gordon and Chow, 1992) and must therefore be related to the selective adsorption of these additives on to certain crystallographic faces. However, alterations in crystal habit could also be mediated through a change in the interfacial tension brought about by the adsorbed additive at the solid-solvent interface. Studies on the surface energetics of the modified DPH crystals are nearing completion, and will be reported in another paper.

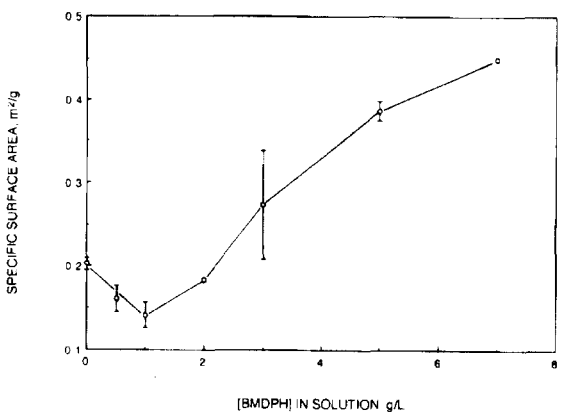

Fig. 3. Specific surface areas of DPH crystallized from methanol in the presence of various concentrations of BMDPH. Each data point represents the mean value of two separate pooled batches.

3.2. Sorption of BMDPH

The sorption of BMDPH (0–0.5 mol%) by DPH crystals, as analyzed by HPLC, increased curvilinearly with increasing concentration of BMDPH (0–12 g l^{-1}) in the crystallization solutions (Fig. 4; Table 1). Vigorous repeated washing for four times with 5% methanol in water of the samples crystallized at 1, 3 and 5 g l^{-1} (2.8, 8.5 and 14.2 mmol l^{-1}) BMDPH cleared away in total 23.9 ± 2, 24.9 ± 1 and 26.4 ± 1% w/w of the adsorbed BMDPH, respectively, but only an insignificantly small quantity of DPH (1.2 ± 0.1% w/w). This suggests that most of the BMDPH (~75% w/w) resides within the crystals. As shown in the previous studies (Chow and Hsia, 1991; Gordon and Chow, 1992), subjecting the crystals doped with comparable concentrations of AMDPH or PMDPH to similar washing treatment resulted in the removal of 51 ± 8% w/w AMDPH or 70 ± 2% PMDPH together with 1.0 ± 0.1% w/w DPH. The considerably lower percentage of surface adsorption observed with BMDPH is indicative of more extensive and possibly stronger interactions of the additive with the host (DPH) molecules in the crystal lattice. The reason why the presence of a longer side chain in the BMDPH molecule would favour a higher proportion of BMDPH being incorporated into the DPH crystals remains obscure.

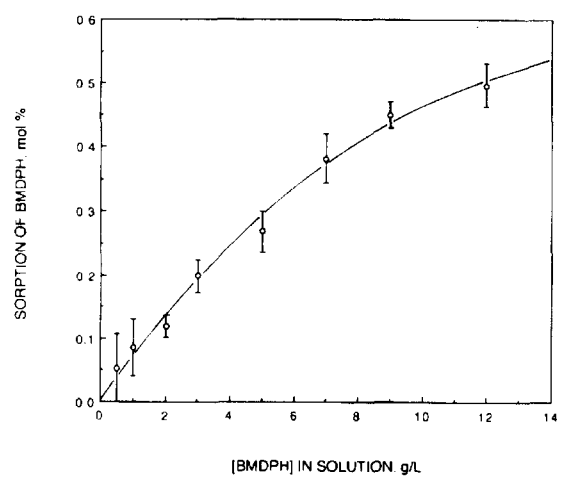

Fig. 4. Sorption of BMDPH by DPH crystals grown from methanol in the presence of various concentrations of BMDPH. The error bars at 0.5–7 g l^{-1} and 9–12 g l^{-1} BMDPH depict the standard deviations of seven to 14 and two to three determinations, respectively.

3.3. Powder X-ray diffraction and thermal analysis

Powder X-ray diffraction studies on the doped and undoped crystals afforded essentially the same diffraction pattern and *d*-spacing values, suggesting that the presence of BMDPH did not induce any gross crystalline changes.

Thermal analysis of the samples indicated a negligible decrease (< 0.2%) in the melting point but a significant reduction in the enthalpy of fusion, ΔH^f, and the entropy of fusion, ΔS^f, by up to 17% for the samples grown at 7 g l^{-1} BMDPH (equivalent to a BMDPH sorption of 0.39 mol%). This indicates that doping with BMDPH enhances the enthalpy and entropy of the crystals (Fig. 5; Table 1).

As established previously on a semi-empirical basis (Chow et al., 1985; York and Grant, 1985; Pikal and Grant, 1987; Chow and Hsia, 1991; Gordon and Chow, 1992), the degree of disorder and disruption induced by an incorporated additive within a crystal may be assessed in terms of the disruption index (d.i.), which is quantitatively defined by the negative slope of the linear regression of ΔS^f on the ideal molar entropy of mixing,

Table 1
Mole fraction sorption (x_B) of BMDPH, 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 0–7 g l^{-1} BMDPH together with 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 B = 3-butanoyloxymethyl-5,5-diphenylhydantoin and D = 5,5-diphenylhydantoin

[BMDPH]	x_B	$T_m \pm$ S.D.	$\Delta H^f \pm$ S.D.	$\Delta S^f \pm$ S.D.	$\bar{S}_B$	$\bar{S}_D$	ΔS^m_{ideal}
(g l^{-1})	(x 10^4)	(K)	(kJ mol^{-1})		(J K^{-1} mol^{-1})		
0	0	568.3 ± 0.4	34.2 ± 0.8	60.1 ± 1.5	0	0	0
0.5	5.2	568.2 ± 0.2	33.5 ± 1.4	59.0 ± 2.5	0.0072	0.0010	0.0082
1.0	8.6	568.2 ± 0.3	32.0 ± 1.8	56.2 ± 3.2	0.0175	0.0029	0.0204
2.0	12.0	567.9 ± 0.3	30.4 ± 1.9	53.6 ± 3.3	0.0470	0.0100	0.0570
3.0	19.9	567.9 ± 0.3	31.4 ± 0.7	55.3 ± 1.2	0.0643	0.0148	0.0791
5.0	26.9	567.5 ± 0.3	29.0 ± 1.9	51.1 ± 3.3	0.0901	0.0232	0.1133
7.0	38.1	567.2 ± 0.4	28.3 ± 0.9	49.8 ± 1.5	0.0960	0.0252	0.1212

ΔS^m_{ideal}. Calculated from the crystal compositions, the ΔS^m_{ideal} value represents the entropy change resulting from simple random mixing of two (or more) closely alike chemical species, as in an ideal solution; and serves essentially as a reference thermodynamic property for comparing and evaluating lattice disorder and disruption. Applying the same thermodynamic treatment to the present data, the disruption index of BMDPH was estimated to be 73 ± 11, suggesting that about 73 times more disorder and disruption in the crystal lattice of DPH were generated by the incorporation of BMDPH than by simple random mixing or dilution of DPH with BMDPH (Fig. 6).

Compared with the dopants, AMDPH (d.i. = 27 ± 4) and PMDPH (d.i. = 19 ± 2), studied previously (Chow and Hsia, 1991; Gordon and Chow, 1992), BMDPH has a considerably higher d.i. (73 ± 11), implying that the strong crystal lattice of DPH is much more sensitive to disruption by doping with BMDPH than with either AMDPH or PMDPH. This particularly high lattice disruption potential of BMDPH may

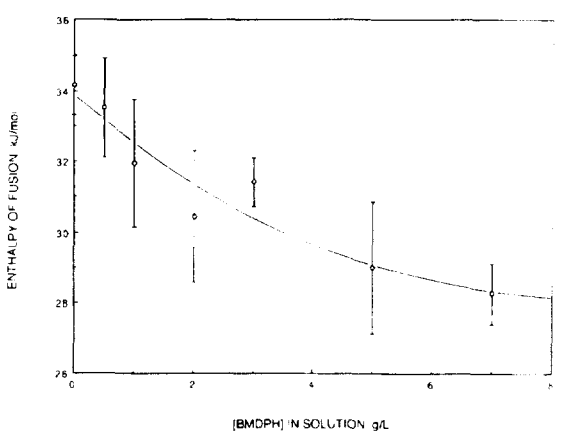

Fig. 5. Enthalpies of fusion, ΔH^f, of DPH crystals grown from methanol in the presence of various concentrations of BMDPH. The error bars represent the standard deviations of six determinations.

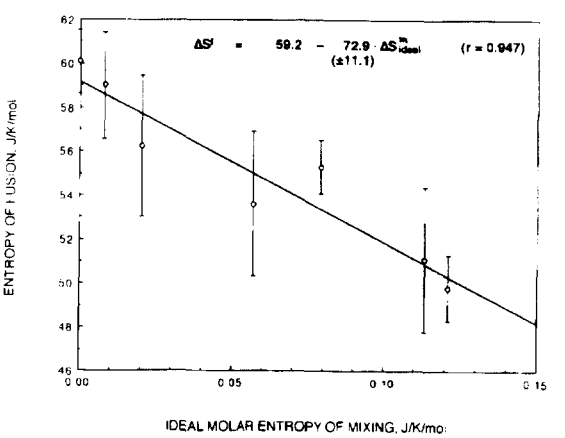

Fig. 6. Linear regression plot of the entropy of fusion, ΔS^f, versus the ideal molar entropy of mixing, ΔS^m_{ideal}, for DPH crystals grown from methanol in the presence of various concentrations of BMDPH. The error bars represent the standard deviations of six determinations.

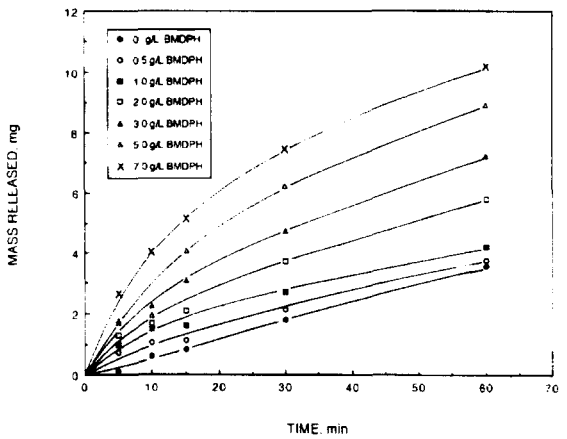

Fig. 7. Dissolution-time profiles at 25°C of DPH crystals grown from methanol containing various concentrations of BMDPH.

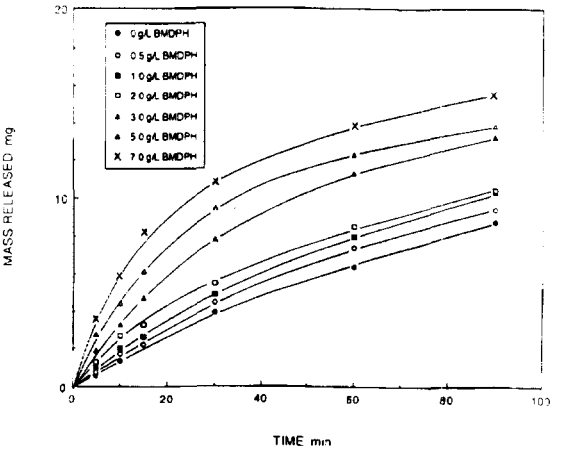

Fig. 8. Dissolution-time profiles at 37°C of DPH crystals grown from methanol containing various concentrations of BMDPH

be attributed to its larger molecular size which creates more intense lattice strain and distortion and/or to the presence of a larger amount of BMDPH within the crystals, as shown by the crystal washing studies.

3.4. Dissolution studies

The initial dissolution rates of the various crystal samples were calculated using data collected during the first 15 min of each dissolution run. The calculation assumes that sink conditions held during this time period.

The rate and extent of DPH dissolved at 25 and 37°C increased sigmoidally with increasing concentration of BMDPH in the crystallization medium, attaining about 4.6 times those of the pure DPH crystals, for the samples prepared at 7 g l^{-1} (corresponding to a BMDPH sorption of 0.39 mol%) (Figs. 7–9). To adjust the dissolution rate for the contribution due to changes in surface area, the intrinsic dissolution rate (i.e. the initial dissolution rate divided by the initial surface area; IDR) of the samples was calculated. The IDR at both 25 and 37°C assumed an essentially constant maximum (~ 2-fold increase) for the crystals prepared at and above 1 g l^{-1} BMDPH (Fig. 10), indicating that factors other than surface area are responsible for the changes in the IDR. These factors possibly encompass crystal anisotropy, shape-related hydrodynamic variations during dissolution, crystal defects engendered by adsorbed or incorporated dopants, and 'poisoning' (blocking) of the high energy sites for dissolution by adsorbed dopants (Chow et al., 1985; Chow and Grant, 1989; Chow and Hsia, 1991; Gordon and Chow, 1992). The significant upsurge in the concentration of crystal defects, as reflected by the

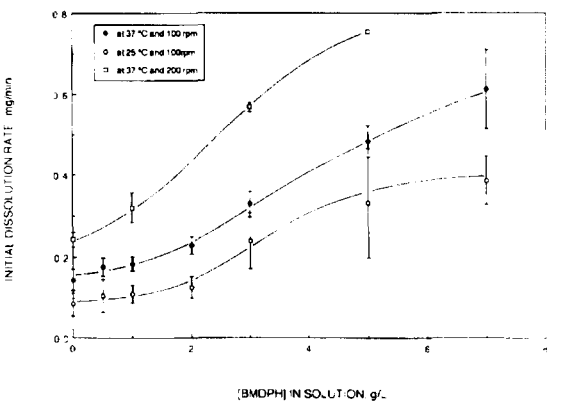

Fig. 9. Initial dissolution rates at 25 and 37°C and at 100 (and 200) rpm for DPH crystals grown from methanol containing various concentrations of BMDPH. The error bars for the data at 37°C and 200 rpm represent the standard deviations of two to three determinations. The error bars for the data at 25 and 37°C (100 rpm) depict the standard deviations of three to four and six to seven determinations, respectively.

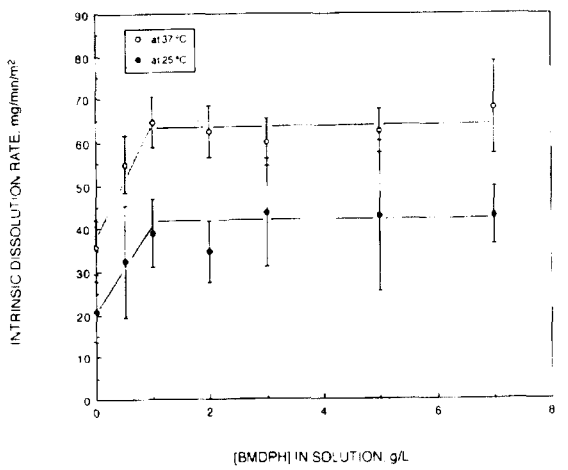

Fig. 10. Intrinsic dissolution rates at 25 and 37°C and at 100 rpm for DPH crystals grown from methanol containing various concentrations of BMDPH. The error bars for the curves at 25 and 37°C represent the standard deviations of three to four and six to seven determinations, respectively.

relatively high disruption index (73 ± 11), may have contributed to the initial rise in IDR within 0–1 g l^{-1} BMDPH at both 25 and 37°C, while further increases in IDR for the crystals prepared at higher concentrations may have been offset by the opposing effect of 'poisoning' of the active sites for dissolution by the adsorbed dopant, thus accounting for the observed plateauing of IDR. Habit thinning, which was more apparent for the crystals grown at 3–7 g l^{-1} BMDPH, appeared to have relatively little effect on the IDR.

It has been shown in the previous studies that an increase in the rate of agitation of the dissolution medium increased the initial dissolution rate of the PMDPH-doped crystals while having no significant effect on the dissolution of AMDPH-doped samples (Chow and Hsia, 1991; Gordon and Chow, 1992). In the present study, it was demonstrated that doubling the rate of stirring (i.e. from 100 to 200 rpm) of the dissolution medium at 37°C nearly doubled the initial dissolution rate (Fig. 9). All these observations suggest that under similar experimental conditions, the dissolution of both PMDPH-doped and BMDPH-doped crystals is both transport-and surface-reaction controlled whereas that of AMDPH-treated samples is predominantly governed by the surface properties of the crystals (Bircumshaw and Riddiford, 1952).

Similar to the cases with AMDPH and PMDPH, maximal dissolution rates of BMDPH-doped samples were attained at intermediate dopant concentrations.

4. Conclusions

DPH crystals grown from methanol in the presence of increasing added concentrations (0.5–12 g l^{-1}) of the dopant, BMDPH, display a curvilinear increase in the BMDPH sorption (0.03–0.5 mol%); a progressive change in crystal morphology from needles to long thin plates; an increase in the specific surface area; a decrease in both the enthalpy and entropy of fusion; and an increase in the initial rate and extent of dissolution.

Both BMDPH and PMDPH exert a habit thinning effect on DPH crystals at a threshold concentration of 3 g l^{-1}, whereas similar habit changes are produced by AMDPH only at higher concentrations (≤ 5 g l^{-1}). Thus AMDPH appears to be the least potent habit modifier of DPH crystals.

As suggested by the crystal washing studies, there appears to be a considerably higher proportion of BMDPH than either AMDPH or PMDPH being incorporated into the DPH crystals under essentially identical crystallization conditions. The reason why the larger molecular size of BMDPH would result in a larger percentage of it being incorporated remains unclear.

As with AMDPH and PMDPH, the sorption of BMDPH lowers the enthalpy of fusion, ΔH^f, and entropy of fusion, ΔS^f, of the crystals, and thereby increases the enthalpy and entropy of the crystals. However, the latter dopant, with a disruption index (73 ± 11) substantially higher (about 2.5 times) than those of AMDPH (27 ± 4) and PMDPH (19 ± 2), is capable of generating much more intense lattice disruption, which is consistent with the presence of a larger amount of BMDPH within the crystals.

As observed for AMDPH and PMDPH, the changes in dissolution rate of the BMDPH-doped crystals cannot be entirely explicated by changes in their surface area, and may involve the follow-

ing factors: (a) crystal habit which governs the dissolution hydrodynamics and the relative abundance of the polar (rapid-dissolving) and non-polar (slow-dissolving) crystal faces; (b) crystal defects which depend on the extent of dopant sorption and the crystallization conditions; and (c) 'poisoning' of the active dissolution sites by adsorbed dopants.

Maximal dissolution rates of the DPH crystals are attained and maintained at intermediate concentrations for all the three dopants with BMDPH-doped crystals being able to reach the maximum rate at concentrations as low as 1 g l^{-1}. As with PMDPH, the dissolution of BMDPH-doped crystals appears to be a mixed transport and surface-reaction process while that of AMDPH-doped samples is rate-limited by the surface properties of the crystals.

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References

Bircumshaw, L.L. and Riddiford, A.C., Transport control in heterogeneous reactions. *Q. Rev. Chem. Soc.*, 6 (1952) 157–185.

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) 238–258.

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.

Chow, A.H.L. and Hsia, C.K., Modification of phenytoin crystals: influence of 3-acetoxymethyl-5,5-diphenylhydantoin on solution-phase crystallization and related properties. *Int. J. Pharm.*, 75 (1991) 219–230.

Gordon, J.D. and Chow, A.H.L. Modification of phenytoin crystals. II. Influence of 3-propanoyloxymethyl-5,5-diphenylhydantoin on solution-phase crystallization and related properties. *Int. J. Pharm.*, 79 (1992) 171–181.

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.

Varia, S.A., Schuller, S., Sloan, K.B. and Stella, V.J., Phenytoin prodrugs III: Water-soluble prodrugs for oral and/or parental 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. 1. Definition and evaluation from heat of fusion. *Int. J. Pharm.*, 25 (1985) 57–72.