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Assessment of wettability and its relationship to the intrinsic dissolution rate of doped phenytoin crystals

Albert H.L. Chow[a,*], Carlos K. Hsia[b], John D. Gordon[b], Janet W.M. Young[b], Eva I. Vargha-Butler[c]

[a]*Department of Pharmacy, Faculty of Medicine, Chinese University of Hong Kong, Shatin, N.T., Hong Kong*
[b]*Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, B.C., Canada*
[c]*College of Pharmacy, Dalhousie University, Halifax, Nova Scotia, Canada*

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Abstract

It has been inferred previously that the changes in intrinsic dissolution rate (i.e., initial dissolution rate divided by the initial surface area; IDR) observed for phenytoin (5,5-diphenylhydantoin; DPH) crystals doped with traces of 3-acetoxymethyl-DPH (AMDPH), 3-propanoyloxymethyl-DPH (PMDPH) or 3-butanoyloxymethyl-DPH (BMDPH) are possibly linked to the following key factors: (a) crystal habit; (b) crystal imperfections; and (c) 'poisoning' of the active dissolution sites by the adsorbed dopants. To elucidate how these factors could have affected the observed IDR and to determine the relative contributions of these factors, the surface tensions of the pure and doped DPH crystals and of the three dopants were assessed using a previously established technique based on the change in sedimentation volume of particles in selected wetting liquid systems. In addition, the contact angles were measured for droplets of the wetting liquids on DPH compacts made from compressed DPH crystals (both pure and doped) and on dopant films formed from acetone solutions. With all the three dopants, a statistically significant positive correlation ($r = 0.777$; $n = 12$ (mean values); $p < 0.05$) existed between the surface tensions of the various DPH samples and the corresponding IDRs, suggesting that the observed increases in IDR may be attributable to the increases in wettability and vice versa. The estimated surface tensions of PMDPH (42.9 ± 0.8 mN m^{-1}; $n = 6$) and AMDPH (44.1 ± 1.1 mN m^{-1}; $n = 7$) were comparable to that of the pure recrystallized DPH sample (42.4 ± 1.5 mN m^{-1}; $n = 13$) whereas that of BMDPH (50.9 ± 2.0 mN m^{-1}; $n = 10$) was significantly higher, reflecting similar wettabilities for the pure recrystallized DPH, AMDPH and PMDPH but significantly higher wettability for BMDPH. Complementary contact angle measurements also afforded values consistent with the observed wettabilities, i.e., high but similar contact angles for the pure DPH samples ($\theta_{\text{water}} = 65.8 \pm 1.1°$; $n = 20$), AMDPH ($\theta_{\text{water}} = 68.5 \pm 0.8°$; $n = 52$) and PMDPH ($\theta_{\text{water}} = 66.5 \pm 1.2°$; $n = 50$); and low contact angle for BMDPH ($\theta_{\text{water}} = 45.0 \pm 1.7°$; $n = 66$). Whilst the relatively good wettability of adsorbed BMDPH appears to be 'directly' responsible, at least in part, for the observed increases in IDR, the possibilities remain that the improved wettability of doped DPH crystals, particularly that observed with AMDPH as dopant, may be a result of a dopant-mediated augmentation of the density of structural defects at the crystal surface and/or of a habit-related increase in the areas of the relatively polar crystal faces.

Keywords: Phenytoin; Additive sorption; Crystal habit; Crystal defects; Wettability; Surface tension; Intrinsic dissolution rate

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* Department of Pharmacy, Faculty of Medicine, Chinese University of Hong Kong, Shatin, New Territories, Hong Kong.

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1. Introduction

Previous studies in our laboratories have demonstrated that doping of phenytoin (5,5-diphenylhydantoin; DPH) crystals by recrystallization from methanol with one of the following three dopants: 3-acetoxymethyl-DPH (AMDPH), 3-propanoyloxymethyl-DPH (PMDPH) and 3-butanoyloxymethyl-DPH (BMDPH), consistently exhibited an increase in dopant sorption; a change in crystal habit from acicular prisms to long thin plates; a decrease in the enthalpy and entropy of fusion; and an enhancement of the intrinsic dissolution rate (i.e., initial dissolution rate divided by the initial surface area) of the crystals (Chow and Hsia, 1991; Gordon and Chow, 1992; Chow et al., 1995). Since significant differences in dissolution rate are still observed after correction for the contribution due to surface area, the following possible contributing factors for the observed changes have been suggested, as based on the changes observed in other related physical properties: (a) crystal habit, which governs the hydrodynamic conditions during dissolution and the areas of the relatively polar, rapid-dissolving crystal faces; (b) crystal defects, which depend on the dopant sorption and the crystallization conditions; and (c) 'poisoning' of the high energy dissolution sites by the adsorbed dopant (Chow and Hsia, 1991; Gordon and Chow, 1992; Chow et al., 1995). To elucidate the roles of these factors in the dissolution mechanisms of doped DPH crystals and to evaluate their relative significance, the present study has investigated the surface tensions of the various crystal samples using an established technique based on the change in sedimentation volume of particles in selected dispersing liquid mixtures. Complementary studies have also been conducted on the measurement of contact angles for droplets of suitable wetting liquids with compacts made from compressed DPH crystals.

2. Theory

It has been shown earlier (Neumann et al., 1982) that a strong correlation exists between the van der Waals type of particle interactions and particle surface tensions. It has also been established that the van der Waals interactions between unlike solid particles dispersed in a liquid may be repulsive as well as attractive, but thermodynamic considerations showed that when like particles are suspended in a liquid medium, they can only attract each other with zero or no interaction being the limiting case (Omenyi et al., 1981). The interaction between the dispersed like particles is governed by the free energy of cohesion, ΔF^{coh}, which can be expressed as

$$\Delta F^{coh} = -2\gamma_{SL}$$

where γ_{SL} is the particle/liquid interfacial tension. Since solid/liquid interfacial tensions are always positive or zero, it follows that $\Delta \mathrm{F}^{\mathrm{coh}}$ is either negative or zero. This implies that there will always be (at least in the absence of electrostatic forces) an attraction between like particles suspended in a liquid. The limiting case is when there is no van der Waals interaction ($\gamma_{\mathrm{SL}} = 0$) i.e. when the surface tension of the suspending liquid, γ_{LV}, is equal to the particle surface tension, γ_{SV}. Under this limiting condition, when the particles sediment, their sedimentation volume, $\mathrm{V}_{\mathrm{sed}}$, should theoretically reach a minimum value. This suggests that the particle surface tension can be estimated by determining the surface tension of the liquid medium, at which an extremum in the $\mathrm{V}_{\mathrm{sed}}$ occurs, i.e., where $\gamma_{\mathrm{LV}} = \gamma_{\mathrm{SV}}$.

To test this hypothesis, sedimentation experiments were performed on model polymer particles of known surface tension in binary liquid mixtures as dispersing media (Vargha-Butler et al., 1985a). In order to control and vary the surface tension of the suspending media in these experiments, the binary liquid mixtures were selected such that one of the pure liquids had a lower and the other a higher surface tension than that of the particles. The experimental results obtained for hydrophobic polymers dispersed in non-polar solvent mixtures appeared to support the above hypothesis, as did the theoretical considerations and calculations performed by Smith et al. (1986). The limiting case where the van der Waals interactions between particles become zero had also been illustrated for hypothetical particles having a surface tension $\gamma_{\mathrm{SV}} = 20$ mN m^{-1} by plotting the ΔF^{coh}

against the surface tension of the suspending liquid, γ_{LV}. This plot displayed a minimum in ΔF^{coh} at $\gamma_{LV} = 20$ mN m^{-1}, which is consistent with the theoretical prediction that a minimum in the V_{sed} should occur when $\gamma_{SL} = 0$, and $\gamma_{LV} = \gamma_{SV}$ (Smith et al., 1986).

Since the magnitude of the attractive forces acting between like particles is expected to affect particle aggregation/agglomeration, there might be at least two possible patterns of behaviour in particle sedimentation, depending on whether or not the early stages of sedimentation are accompanied by agglomeration of particles.

If there is agglomeration at finite values of the free energy of cohesion (caused by the van der Waals attraction between like particles) (case 1) then this agglomeration should cease when ΔF^{coh} approaches zero. Since irregularly shaped particles, when aggregated, do not pack well, the V_{sed} of the particles will decrease with decreasing aggregation; at $\Delta F^{coh} = 0$, a minimum V_{sed} would be expected.

Conversely, when there is initially no agglomeration at finite values of attractive forces (case 2), then zero free energy of cohesion might imply the attainment of the lowest degree of close packing of the sediment and hence a maximum V_{sed}.

Minima as well as maxima in the V_{sed} have indeed been observed when V_{sed} was plotted as a function of the surface tension of the dispersing liquid mixtures for polymer powders (Vargha-Butler et al., 1985a; Vargha-Butler et al., 1987) for coal fines (Vargha-Butler et al., 1985b; Vargha-Butler et al., 1985c), for drug powders (Vargha-Butler et al., 1991) and for liposomes (Vargha-Butler et al., 1989; Vargha-Butler et al., 1991). However, when particle sedimentation was investigated in different liquid combinations, it was observed that the positions of the minima and maxima obtained were very similar for the same polymer (Vargha-Butler et al., 1985a; Vargha-Butler et al., 1987) or drug powder (Vargha-Butler et al., 1991), indicating the estimated surface tension is independent of the type of extremum.

Although the reason for the occurrence of the two types of extremum is not fully understood, the fact that both types of extremum are located at similar surface tensions for the same particles reflects the reliability of the procedure regardless of the type of extremum. The accuracy of surface tensions of various particles previously determined by the sedimentation technique has also been confirmed by other methods (Vargha-Butler et al., 1985a; Vargha-Butler et al., 1985c).

3. Materials and Methods

3.1. Reagents and Materials

All solvents used, including 1-propanol, 1,2-propanediol, 1,3-propanediol, ethylene glycol, 1-octanol, formamide were of spectroscopically pure grade and supplied by Aldrich Chemicals. The water employed for surface characterization was Nanopure® grade, organic-free distilled water.

The various crystal samples of DPH doped with AMDPH, PMDPH or BMDPH and the three dopants were prepared as reported previously (Chow and Hsia, 1991; Gordon and Chow, 1992; Chow et al., 1995).

3.2. Equilibrium solubility measurements of dopants

The equilibrium solubilities at 30°C of AMDPH, PMDPH and BMDPH in methanol were measured using the HPLC procedures developed previously (Chow and Hsia, 1991; Gordon and Chow, 1992; Chow et al., 1995).

3.3. Sedimentation volume method

Equal masses (0.020–0.050 g, depending on the volume of the sediment obtained) of various DPH crystal samples or dopant powders were weighed into Eppendorf micro-centrifuge tubes. The samples were then suspended in 0.1 to 0.2 ml of binary liquid mixtures (at 25°C) selected from the following: 1-propanol/water, 1,2-propanediol/water, 1-propanol/ethylene glycol and 1-octanol/1,3-propanediol. Different proportions of the liquids were used to yield mixtures of different surface tensions. The liquids were chosen so that they covered a range of surface tensions including the surface tension of the particles being investigated. The suspensions were agitated for 5 min using a vortex mixer. In order to achieve complete displacement of air from the surface of the particles and to break up aggregates, the samples were left for 24 h, then agitated again for 5 min.

Each dispersion was then quantitatively transferred by means of Pasteur pipettes into graduated Wintrobe sedimentation tubes with a 1 ml total volume. The appropriate liquid mixture was used to fill the tubes to a volume of 1 ml. The tubes were then sealed, shaken for approximately 10 min so that the particles were evenly suspended in the liquid column. The reading of the sedimentation volume was taken every day until no further change in V_{sed} occurred. Each sample was studied in different liquid mixtures. The measurements were repeated at least six times. The standard deviation and the population mean were calculated from the sample mean. The errors shown in Fig. 1 and Table 1 are the 95% confidence limits.

3.4. *Sample preparation for contact angle measurement*

Contact angle measurements were performed on compacts made from compressed DPH crystals (pure and doped) and on a thin film of each dopant formed (from a 2% solution in acetone) on an extremely clean glass substrate. Prior to compact preparation or film formation, the samples were kept at room temperature (25°C) and at a relative humidity of 52%.

For the pure and doped DPH crystals, each sample (0.2 g) was compressed into a compact using a Carver Laboratory Press with a custom-made, highly polished die of 12 mm diameter. The die was carefully cleaned with distilled water, rinsed with acetone and dried prior to the compact formation. A pressure of 4014 kg cm^{-2} was applied for 2 min.

3.5. *Contact angle (θ) measurements*

The contact angle, θ, of distilled water and those of the other selected liquids were determined by means of the sessile drop method using a Rame-Hart type contact angle goniometer Model NRL-100. The experimental apparatus consisted of a horizontal stage positioned in an environmental chamber, a source of illumination (from behind the drop) and a telescope equipped with a goniometer eyepiece. A droplet of the selected liquid was placed on the surface of the specimen using a 2-ml micrometer syringe (Gilmont® Instrument Inc.). For each liquid a separate syringe and needle were used and both were very carefully cleaned prior to the measurement.

Employing water and formamide as wetting liquids, advancing contact angles were measured on drug compacts and on dopant films (within 30 s) after the liquid drop was positioned on the surface, readings being taken on both sides of the droplet to check the drop symmetry. The size of the drop was initially set at 0.02 ml and was increased twice by adding more liquid. The measurements were performed at 25°C and at constant relative humidity. The arithmetic mean of the contact angles was calculated from the 18 to 42 (or more) data points obtained for a given surface (individual drug compact or dopant film) with each liquid. The standard deviation and the population mean were calculated from the sample mean assuming a t distribution. The errors presented in Fig. 1 and in Table 1 are the 95% confidence limits.

4. Results and discussion

The surface tensions of the pure DPH crystals and three doped DPH samples for each dopant were determined and plotted against the dopant concentration in the crystallization media (Fig. 1). These data together with the contact angles measured on drug compacts and dopant films as well as the surface tensions of the three dopants are given in Table 1.

With increasing concentration of AMDPH in the crystallization solutions, the surface tension of the DPH crystals increased up to a maximum at 5 g l^{-1} and decreased thereafter (Fig. 1). Similar and somewhat less significant changes were observed with PMDPH as dopant. However, with BMDPH in the crystallization media, the surface tension of the crystals exhibited a gradual rise between 0 and 5 g l^{-1} BMDPH, and a sharp rise at higher concentrations, indicating the crystal surfaces became more wettable or 'hydrophilic' (Fig. 1). As expected theoretically from the inverse relationship between contact angle and surface tension, the contact angles measured on DPH compacts made from compressed crystals showed the reverse trends, thus further substantiating the observed changes in wettability (Table 1).

As observed in the previous studies (Chow and Hsia, 1991; Gordon and Chow, 1992; Chow et al., 1995), the initial dissolution rates (DR) of doped DPH crystals consistently displayed an increasing trend as a function of the concentrations of dopants in the crystallization media. To account for the effect of surface area, the initial dissolution rate data were normalized by the initial surface area, SA, data (i.e., DR/SA) to yield the intrinsic dissolution rate (IDR). For each dopant, the IDRs were found to increase and then decrease or plateau with an increase in dopant concentration in the solutions, indicating that factors other than surface area are responsible for the changes in IDR. These changes in IDR appeared to parallel those in the surface tension observed in the present study. Indeed, a statistically significant positive correlation between the surface tensions and the IDRs of the crystals was obtained ($r = 0.777$; $n = 12$ (mean values); $P < 0.05$; Fig. 2), suggesting that wettability or surface free energy may play a major role in the dissolution mechanisms of the doped DPH crystals. Although the causes for the observed 'rise and fall (or levelling)'

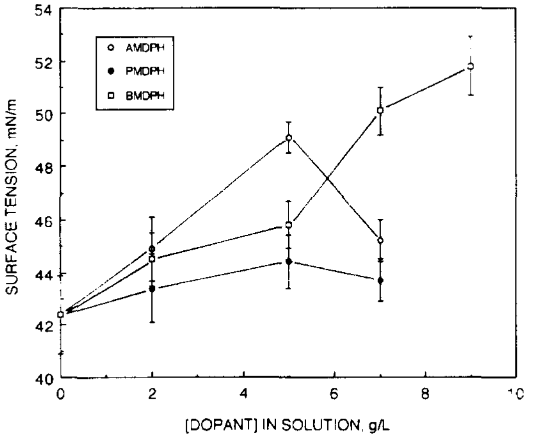

Fig. 1. Plot of the surface tensions of DPH crystals at 25°C versus the concentrations of dopants in crystallization media. The vertical bars depict the 95% confidence limits of six to 13 determinations.

Table 1

Contact angles and surface tensions of various DPH crystal samples (pure and doped) and dopants (AMDPH, PMDPH, BMDPH)

Sample	Contact angle at 25°C		Surface tension at 25°C from V_{sed}
	Mean θ_{water} (°)	Mean $\theta_{formamide}$(°)	γ_{SV} (mN/m)
Pure DPH	65.8 ± 1.1 ($n = 20$)	47.5 ± 1.5 ($n = 20$)	42.4 ± 1.5 ($n = 13$)
DPH doped with AMDPH at			
2 g/l	62.9 ± 1.4 ($n = 26$)	46.9 ± 0.6 ($n = 14$)	44.9 ± 1.2 ($n = 7$)
5 g/l	51.1 ± 2.0 ($n = 15$)	36.6 ± 2.4 ($n = 10$)	49.1 ± 0.6 ($n = 6$)
7 g/l	60.6 ± 1.2 ($n = 26$)	44.6 ± 1.2 ($n = 14$)	45.2 ± 0.8 ($n = 7$)
DPH doped with PMDPH at			
2 g/l	62.4 ± 0.7 ($n = 21$)	46.4 ± 1.1 ($n = 16$)	43.4 ± 1.3 ($n = 6$)
5 g/l	60.9 ± 1.8 ($n = 26$)	44.6 ± 1.3 ($n = 14$)	44.4 ± 1.0 ($n = 8$)
7 g/l	62.6 ± 0.9 ($n = 18$)	43.8 ± 0.7 ($n = 20$)	43.7 ± 0.8 ($n = 8$)
DPH doped with BMDPH at			
2 g/l	63.5 ± 1.3 ($n = 16$)	44.9 ± 0.8 ($n = 16$)	44.5 ± 1.0 ($n = 7$)
5 g/l	63.4 ± 1.4 ($n = 16$)	43.1 ± 1.2 ($n = 16$)	45.8 ± 0.9 ($n = 8$)
7 g/l	57.1 ± 1.0 ($n = 38$)	37.3 ± 1.0 ($n = 26$)	50.1 ± 0.9 ($n = 8$)
9 g/l	–	–	51.8 ± 1.1 ($n = 9$)
Dopants:			
AMDPH	68.5 ± 0.8 ($n = 52$)	52.1 ± 1.8 ($n = 44$)	44.1 ± 1.1 ($n = 7$)
PMDPH	66.5 ± 1.2 ($n = 50$)	50.1 ± 1.7 ($n = 46$)	42.9 ± 0.8 ($n = 6$)
BMDPH	45.0 ± 1.7 ($n = 66$)	33.2 ± 1.5 ($n = 80$)	50.9 ± 2.0 ($n = 10$)

Errors shown are the 95% Confidence limits.

trends in IDR have not been fully elucidated, several possible key contributing factors can be identified, based on the changes observed in other related physical properties (e.g., crystal morphology, surface features, enthalpy and entropy of fusion). These factors are: (a) crystal habit, which is closely associated with the hydrodynamic conditions during dissolution and the relative abundance of the polar (rapid-dissolving) and non-polar (slow-dissolving) crystal faces; (b) crystal defects (both in the bulk and on the surface) which may arise from growth or be mediated through surface-adsorbed and incorporated dopants; (c) 'poisoning' (blocking) of the active dissolution sites by adsorbed dopants. Since these factors probably overlap with each other in terms of their influence on the surface energetics of the crystals, assessment of their relative contributions may prove difficult.

Although the sorption of each dopant (AMDPH, PMDPH or BMDPH) by the DPH crystals was shown to be comparable in magnitude under essentially identical crystallization conditions, the extents of their adsorption on the crystal surface were distinctly different with PMDPH being the most extensively adsorbed and BMDPH the least (Chow and Hsia, 1991; Gordon and Chow, 1992; Chow et al., 1995). This difference in surface adsorption appeared to be negatively correlated with the equilibrium solubilities of the three dopants in methanol at 30°C ($r = -0.969$; $n = 9$; $P < 0.05$; Fig. 3), indicating that a lower solubility in methanol (as was observed for PMDPH) favours interaction with the solid surface and discourages interaction with the solvent phase and vice versa. Interestingly, the equilibrium solubilities of these homologous dopants also showed a strong negative correlation with the melting points ($r = -0.999$; $n = 3$ (mean values); $P < 0.05$; Fig. 4), suggesting that the solubilities in methanol are determined by the strength of solute-solute interactions in the solid phase, as revealed by the melting points. Thus the relatively strong solute-solute interactions in PMDPH, as reflected by the relatively high melting point (172–174°C), are responsible for its low solubility in methanol. The converse is true for BMDPH.

Whilst the significance of surface adsorption of these dopants in governing the dissolution behaviour of doped DPH crystals is not entirely clear, it is quite possible that the observed surface

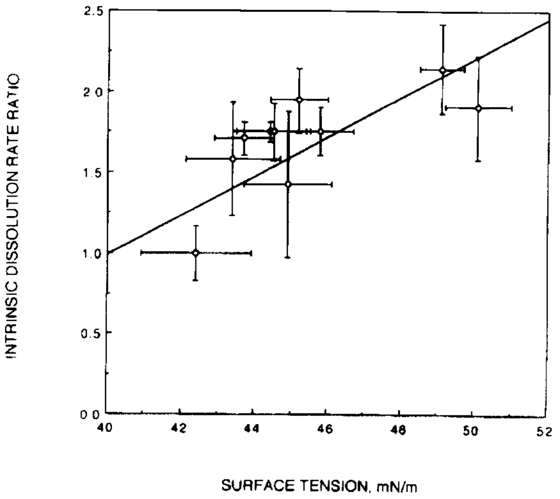

Fig. 2. Plot of the intrinsic dissolution rate ratios at 37°C versus the surface tensions of DPH crystals at 25°C. The intrinsic dissolution rate ratio is calculated by dividing the intrinsic dissolution rate of each sample (both pure and doped) by the intrinsic dissolution rate of the pure (undoped) crystals. The vertical and horizontal bars represent the 95% confidence limits of four to six and six to 13 determinations, respectively.

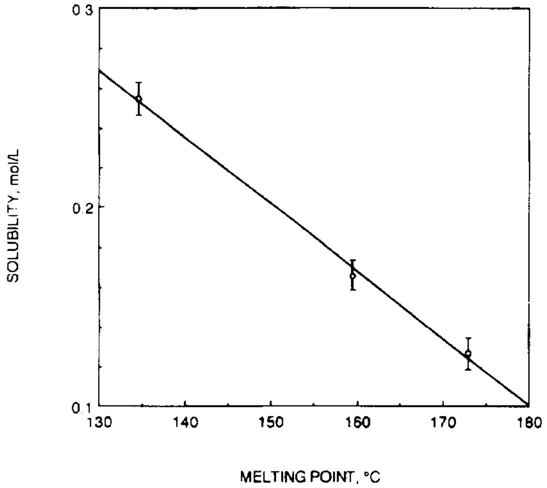

Fig. 3. Plot of the equilibrium solubilities in methanol at 30°C versus the melting points of dopants. The vertical bars represent the standard deviations of eight determinations.

tension of the doped crystals could just simply be that of the surface-adsorbed dopant if the whole crystal surface was assumed to be completely covered with the dopant molecules. However, this has not been proven to be the case since the surface tensions of the dopants did not exactly correspond to the surface tensions of the respective doped samples, which were mostly higher than the former. In addition, the surface tension of BMDPH (50.9 ± 2.0 mN m^{-1}; $n = 10$) was significantly higher than that of the pure undoped DPH sample (42.4 ± 1.5 mN m^{-1}; $n = 13$) while those of AMDPH (44.1 ± 1.1 mN m^{-1}; $n = 7$) and PMDPH (42.9 ± 0.8 mN m^{-1}; $n = 6$) were comparable to the latter (Table 1). This reveals that BMDPH is the most wettable dopant of all the three whereas AMDPH and PMDPH have lower, but similar wettabilities to the pure recrystallized DPH. Complementary contact angle measurements also yielded values in agreement with the observed wettabilities (Table 1), i.e., low contact angle for BMDPH ($\theta_{\text{water}} = 45.0 \pm 1.7°$; $n = 66$), and high but similar contact angles for the pure DPH samples ($\theta_{\text{water}} = 65.8 \pm 1.1°$; $n = 20$), AMDPH ($\theta_{\text{water}} = 68.5 \pm 0.8°$; $n = 52$) and PMDPH ($\theta_{\text{water}} = 66.5 \pm 1.2°$; $n = 50$). Two possible explanations for the observed variations in wettability can be postulated. Firstly, the changes in surface tension may simply be the result of the differences in the degree of surface coverage or adsorption by the dopants. This may be the case with BMDPH where the highest surface tension for the crystals attained (51.8 ± 1.1 mN m^{-1}; $n = 9$) approximated the surface tension of BMDPH (50.9 ± 2.0 mN m^{-1}; $n = 10$), corresponding to maximum surface coverage of the dopant (Table 1). Secondly, the interactions of the dopants with the crystal surface may be stereospecific; the dopant molecules may have assumed certain orientations at the crystal surface with their polar groups mostly in contact with the external environment. This could perhaps explain the particularly high surface tension (49.1 ± 0.6 mN m^{-1}; $n = 6$) or wettability of the DPH crystals doped at 5 g l^{-1} AMDPH in solutions (Table 1). However, since the habit changes of the DPH crystals engendered by the three dopants closely resemble each other, it can be argued that the mode of surface adsorption of these dopants should be quite similar if not identical. If this were indeed the case, then one would not expect such a significant variation in surface tension among the various doped samples. Thus, although the relatively good wettability of adsorbed BMDPH appears to account for, to some extent, the enhanced dissolution rate of DPH, the possibilities remain that the improved wettability and hence dissolution rate of modified DPH crystals (particularly those doped with AMDPH) may be attributed to a dopant-induced augmentation of the structural defects at the crystal surface and/or to a habit-dependent increase in the areas of the relatively polar faces.

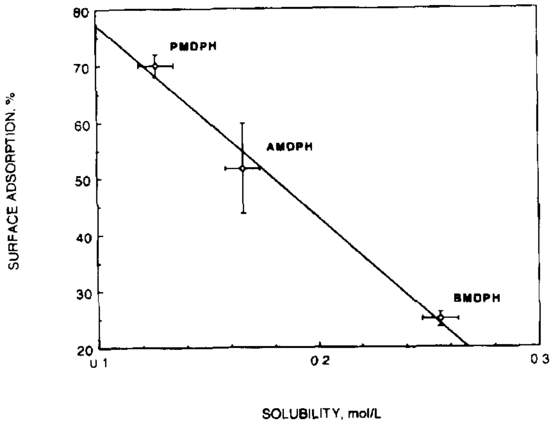

Fig. 4. Plot of the percent surface adsorption versus the equilibrium solubilities of dopants at 30°C. The vertical bars represent the standard deviations of three determinations.

5. Conclusions

The present study clearly lends support to the significant roles of the previously identified factors in the dissolution mechanisms of doped DPH crystals: viz. (a) crystal habit; (b) crystal imperfections; and (c) 'poisoning' of the active sites for dissolution by adsorbed dopants. However, since these factors can all influence the surface energetics and consequently the dissolution rate of the crystals to various extents, it is difficult to assess their relative contributions solely on the basis of the measured surface tensions. Nevertheless, the fact that the dissolution rate correlates well with the surface tensions strongly suggests that the concentration of surface defects and possibly the areas of the relatively polar faces are likely to be important determinants of the dissolution behaviour of doped DPH crystals.

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