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A disruption index for quantifying the solid state disorder induced by additives or impurities. I. Definition and evaluation from heat of fusion

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Summary

A dimensionless disruption index (d.i.) is proposed for quantifying the solid state disorder induced by an additive or impurity (the guest substance), when present in solid solution in the crystal lattice of a host substance at mole fractions, x_2, less than 0.05. The d.i. value is defined as the rate of change of the difference between the entropy of the solid and that of the liquid, with respect to the ideal entropy of mixing of the components of the solid, ΔS^m_{ideal}. From fundamental thermodynamic considerations d.i. is closely approximated by the slope of the plot of the entropy of fusion of the solid, ΔS^f, against ΔS^m_{ideal} for $x_2 < 0.05$. ΔS^f is given by the heat of fusion divided by the absolute melting point, while $\Delta S^m_{ideal} = -R\Sigma x_j \ln x_j$ is calculated from the analytical data of the crystals, where x_j is the mole fraction of a given component. The linear relationship was tested using the limited literature data available for 7 systems and was found to be obeyed for $x_2 < 0.05$. Values of d.i. range from zero for ideal solutions through about 10^{-1} for doping of the intermetallic compound $InCd_3$ with either of its components, (somewhat higher, 0.423, for cadmium doped with $InCd_3$), to about 10 for the doping of a stable, ordered organic crystal with an organic additive. The d.i. values for phenacetin doped with benzamide, griseofulvin + lecithin, acetaminophen + water + *p*-acetoxyacetanilide, and *pp*-DDT + *op*-DDT, are 7.94, 5.09, 6.53 and 15.1, respectively. The d.i. values

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are discussed in relation to the properties of the host and guest. The method of determining d.i. from ΔS^f is critically assessed. The d.i. values may be useful in predicting the sensitivity of the crystal lattice of a drug or excipient to the presence of traces of a given impurity in solid solution. If the presence of impurities gives rise to batch-to-batch variations, d.i. values may also be useful for quantifying the observed differences in properties between batches of materials.

Introduction

Crystal lattice imperfections, e.g. point defects and dislocations, develop during crystallization (Mullin, 1972) and have been found to exert major effects in pharmaceutical formulation and processing (Hüttenrauch, 1978). Crystal imperfections have also been shown to influence chemical reactivity (Byrn, 1982; Boldyrev et al., 1979) and dissolution rate (Burt and Mitchell, 1981). Consequently, the bioavailability of a solid may be significantly increased by the presence of a high density of lattice imperfections. Digoxin represents a classical example of a drug whose dissolution rate and bioavailability can vary between wide limits if its crystal properties are not controlled (Florence et al., 1974; Black and Lovering, 1977; Chiou and Kyle, 1979). The concentration or density of lattice imperfections is altered as a result of the stresses prevailing during processing operations, such as drying, milling and compression (for refs. see Hüttenrauch, 1978).

The presence of low concentrations of additives or impurities, in atomic, ionic or molecular form in solid solution, creates in the crystal lattice additional imperfections. This causes significant modifications to the thermodynamic properties of the crystalline state (Chow et al., 1984; Chow et al., 1985) and therefore to pharmaceutically important properties. Some of our recent work has shown that crystallization of adipic acid (Fairbrother and Grant, 1978; 1979; Chow et al., 1984) or acetaminophen (Chow et al., 1985) from water containing trace amounts of structurally related additives produces changes in crystal habit, density, crystal energy and dissolution rate as a result of uptake of the additive by the growing crystals. These changes are attributed to the increased disorder created by the incorporation of additives in solid solution in the crystal lattice.

The nature and concentration of impurities and imperfections often vary from one batch of crystals or powder to another. Batch-to-batch or lot-to-lot variations may be the rule rather than the exception (Hiestand and Smith, 1984) and frequently cause problems in formulation and processing and give rise to lack of reproducibility and poor performance in the final product (Jones, 1981; York, 1983).

Present "state of the art" techniques for examining directly and for measuring quantitatively imperfections in crystals are of limited applicability to drugs, excipients and other organic solids, primarily because of the constraints imposed by the powder form of the materials. Consequently, for practical and comparative purposes various "crystallinity" scales have been developed to provide an approximate measure of the density and influence of crystal imperfections. The near perfect, pure crystalline state possessing a minimal degree of imperfection is assigned a crystallin-

ity of 100%, while the disordered amorphous state which contains a high, and possibly maximal, degree of imperfection is assigned a crystallinity of zero. By means of physicochemical measurements on these idealized materials and on the sample under investigation, the percentage crystallinity of the sample may be estimated. The more important techniques which have been used to determine the degree of crystallinity of solids include density, X-ray diffraction, IR spectroscopy, NMR spectroscopy, electron microscopy, differential thermal analysis, solution calorimetry, and kinetic studies (Hüttenrauch, 1978; Black and Lovering, 1977; Pikal et al., 1978). Unfortunately, different techniques frequently provide quite divergent values of the crystallinity of a given sample (Pikal et al., 1978).

Further understanding and quantification of crystal imperfections are evidently required. In this presentation a simplistic working hypothesis based on changes in entropy is developed, which enables the disruptive effect of additives or impurities on the crystal lattice structure to be evaluated. The model is then tested using data available in the literature for a number of disparate systems. Since entropy provides a quantitative measure of the state of disorder in a system, entropy would seem to provide a useful measure of the disruptive influence of imperfections in crystals. A dimensionless "disruption index" is derived and evaluated for quantifying the disorder induced by a given additive or impurity when present in solid solution in the crystal lattice.

Theoretical background

Imperfections, such as point defects and dislocations, in the lattice of a crystal cause regions of misfit and disorder in the three-dimensional arrangement of the molecules. The internal energy, U_{solid}, and the entropy, S_{solid}, of the solid phase are therefore larger than the corresponding values of the pure, perfect crystal. The application of mechanical, radiative or thermal stress to the crystal will further increase the lattice strain and density of imperfections, thereby further increasing U_{solid} and S_{solid}. The incorporation of traces of additives or impurities into the crystal lattice, such that a solid solution is formed, will introduce impurity defects and attendant dislocations which further increase the lattice strain and therefore cause additional increases in U_{solid} and S_{solid}. During the fusion process, the observed changes in internal energy, ΔU^f, enthalpy, ΔH^f, and entropy, ΔS^f, of the imperfect, defective, dislocated, strained, and/or impure crystals will be less than for the perfect crystals, because the state and structure of the former crystals are tending towards the more energetic and disordered liquid state.

For the fusion process, which is indicated by the superscript f, the molar thermodynamic quantities at constant atmospheric pressure, p, and at constant absolute temperature, T, are related as follows:

$$\Delta U^f = U_{liquid} - U_{solid} \tag{1}$$

$$\Delta H^f = H_{liquid} - H_{solid} \tag{2}$$

$$\Delta S^f = S_{liquid} - S_{solid} \tag{3}$$

$$\Delta V^f = V_{liquid} - V_{solid} \tag{4}$$

$$\Delta H^f = \Delta U^f + p\Delta V^f \tag{5}$$

where V is the molar volume and the subscripts indicate the receptive phases. At the melting point, T_m, fusion is reversible, so the free energy of fusion, ΔG^f, is zero, and therefore:

$$\Delta S^f = \Delta H^f / T_m \tag{6}$$

Since the additives in the crystals cause proportional changes in density which are an order of magnitude less than the proportional changes in ΔH^f (Chow et al., 1984), then V_{solid} and ΔV^f can be considered virtually constant. Thus, a change in enthalpy directly reflects a change in internal energy (Eqn. 5) and a change in entropy (Eqn. 6) for a crystalline material. As mentioned at the end of the introduction, we wish to focus attention on the entropy changes of the crystals, when considering lattice imperfections, particularly those created by additives or impurities.

For purposes of comparison, the reference entropy change in the solid (or liquid) state is defined in terms of that for a hypothetical ideal solid (or liquid) solution. The ideal partial molar entropy, $\bar{S}_j$, of a component substance, j, in an ideal solution is given by:

$$\bar{S}_j = -Rx_j \ln x_j \tag{7}$$

and therefore depends only on its mole fraction, x_j. R is the universal gas constant, 8.3143 $J \cdot K^{-1} \cdot mol^{-1}$. For a system containing two or more component substances, the ideal molar entropy of mixing is the sum of the individual partial molar entropies, thus:

$$\Delta S^m_{ideal} = \Sigma \bar{S}_j = -R\Sigma x_j \ln x_j \tag{8}$$

ΔS^m_{ideal} represents the change in entropy (i.e. disorder) associated with the substitution of an additive into the host's crystal lattice (or into the liquid host) so as to give an ideal solid (or liquid) solution. Since ΔS^m_{ideal} depends only on the mole fraction, x_j, of each individual component, it merely represents the disorder created by simple mixing or dilution and excludes any disorder resulting from lattice disruption in the solid or preferential orientation in the liquid. Since the x_j values must each be less than unity in a mixture or solution, the individual $\bar{S}_j$ values and ΔS^m_{ideal} are positive quantities. These concepts are often applied to liquid mixtures or liquid solutions, and there is no reason in principle why they may not be applied to solids under the appropriate circumstances. Use of the above ideal entropies does not imply any assumptions about the changes in internal energy or enthalpy in mixing, ΔU^m and ΔH^m, respectively. The latter quantities may not have the ideal values of zero

assumed for ideal solutions on account of differences in the nature and strength of the intermolecular interactions between like and unlike molecules. For example, the concept of regular solutions, which has been developed by Hildebrand, Scatchard and co-workers (see Hildebrand et al., 1970) to account for the liquid solubility of certain non-electrolytes, assumes that ΔS^m is equal to the ideal value (Eqn. 8) while the ΔU^m and ΔH^m may exceed the ideal values of zero.

Mixing of the additive or impurity (the guest substance) with the main component (the host substance) to form a solid solution or a liquid solution will change the entropy of the solid and the liquid states, respectively. If the mole fraction of the guest is small (i.e. $x_2 < 0.05$), the small changes, δ, in each of these entropies may be proportional to the ideal entropy of mixing, thus:

$$\delta(S_{solid}) = b \cdot \delta(\Delta S^m_{ideal}) \tag{9}$$

$$\delta(S_{liquid}) = c \cdot \delta(\Delta S^m_{ideal}) \tag{10}$$

Subtracting Eqn. 10 from Eqn. 9, we obtain

$$\delta(S_{solid}) - \delta(S_{liquid}) = (b - c) \cdot \delta(\Delta S^m_{ideal}) \tag{11}$$

where b and c are positive, dimensionless proportionality constants which represent the sensitivity of the disordering of the host solid and liquid to simple mixing or dilution with a guest substance, for which mixing is represented by ΔS^m_{ideal}. The quantity $(b - c)$ represents the difference between the sensitivity of the entropy of the solid to contamination and that of the liquid, and is designated the "disruption index" (d.i.) by analogy with other dimensionless indices (e.g. bonding index, BI, brittle fracture index, BFI, and strain index, SI; Hiestand and Smith, 1984). The lower case notation for disruption index is proposed to provide flexibility of definition and nomenclature. If, for example, values of d.i. are found always to be positive, as expected, and to range over several powers of 10, it may be preferable to redefine the disruption index as log $(b - c)$ and to abbreviate it to DI, such that DI = log (d.i.).

From the rules of differentiation, the left hand side of Eqn. 11 may be expressed thus:

$$\delta(S_{solid}) - \delta(S_{liquid}) = \delta(S_{solid} - S_{liquid}) \tag{12}$$

Comparison of Eqn. 12 with Eqn. 3 shows that

$$-\delta(\Delta S^f) = \delta(S_{solid}) - \delta(S_{liquid}) \tag{13}$$

Comparison of Eqn. 13 with Eqn. 11 indicates that

$$\delta(\Delta S^f) = -(b - c) \cdot \delta(\Delta S^m_{ideal}) \tag{14}$$

This equation may be stated in the following integrated form:

$$\Delta S^f = \Delta S_0^f - (b - c) \cdot \Delta S_{ideal}^m \quad (15)$$

Eqns. 14 and 15 are supported by experimental data as will be seen (e.g. Chow et al., 1985) at $x_j < 0.05$. The intercept, ΔS_0^f, represents the entropy of fusion of the pure sample of the host substance, for which $\Delta S_{ideal}^m = 0$, because no doping of the host lattice has taken place.

The d.i. value ($= b - c$) compares the disorder created in the solid host with that created in the liquid host by simple mixing with the guest molecules. Mixtures of liquid organic compounds often given entropies of mixing which are close to ideal, as in the case of regular solutions (Hildebrand and Scott, 1950; Hildebrand et al., 1970), or in other words, S_{liquid} increases by an amount equal to that for ΔS_{ideal}^m, meaning that $c = 1$ in Eqn. 11. The regular solution concept presupposes that the intermolecular interactions are simply London dispersion forces and excludes specific interactions and specific orientation effects, such as hydrogen bonding. To a first approximation, it may often be satisfactory to assume that $c \approx 1$ for mixtures of organic compounds whose molecules have similar structure and similar chemical groups and for mixtures of metals of similar chemical nature and atomic volume. The assumption that $c \approx 1$ is probably quite accurate when the guest molecules are in dilute solution in the liquid host, i.e. for $x_2 < 0.05$, as in the examples to be discussed.

According to the present definition, the value of d.i. ($= b - c$) depends on the relative magnitude of b and c, for which the following three broad classes may be distinguished: (i) $b < c$, i.e. d.i. is negative; (ii) $b = c$, i.e. d.i. $= 0$; (iii) $b > c$, i.e. d.i. is positive.

(i) $b < c$, i.e. the presence of the guest molecules creates less disorder (entropy) in the host's crystal lattice than in the liquid host, so that d.i. is negative. This is extremely unlikely, because it would imply that the crystalline state is less sensitive to traces of foreign molecules than the liquid state. This is contrary to experience in view of the greater orderliness of crystals than liquids and the known enormous influence of impurity defects on the properties of solids, such as metals (Reed-Hill, 1973).

(ii) $b = c$, i.e. the presence of the guest molecules creates the same increase in entropy in the host's crystal lattice as in the liquid host, so that d.i. $= 0$. An example of this behaviour is the formation of an ideal or regular solution in both the solid state (i.e. $b = 1$ in Eqn. 9) and the liquid state (i.e. $c = 1$ in Eqn. 10). Systems giving this behaviour include closely-packed spherical host molecules, interacting equally with their nearest neighbours, doped by guest molecules of similar size, shape and chemical nature. Such systems will give a continuous range of solid solutions, which will behave ideally at the extremities of the the composition range, and will also give ideal liquid solutions. Examples include certain metallic systems, e.g. gold + silver, cobalt + nickel, and mixtures of salts for which one or more types of ion have identical charge and similar sizes, e.g. sodium chloride + silver chloride (Glasstone, 1946).

(iii) $b > c$, i.e. the presence of the guest molecules creates more disorder (entropy) in

the host's crystal lattice than in the liquid host, so that d.i. is positive. This is probably the most common behaviour, since the crystalline state, being intrinsically more ordered than the liquid state, is more sensitive to the presence of guest molecules. Impurity defects are known to exert enormous influences on the properties of solids, such as metals (Reed-Hill, 1973). Evidence is accumulating that this is also true for the doping of organic crystals, such as adipic acid (Chow et al., 1984) and acetaminophen (Chow et al., 1985). Many organic compounds crystallize to form ordered lattices whose structure is governed by directional intermolecular interactions, as a result of hydrogen bonding, or by the nature of the molecular symmetry. The incorporation of guest molecules, which undergo intermolecular interactions of a different type or which possess symmetry properties, shapes and sizes different from those of the host molecules, are likely to create more disorder in the host lattice than expected from simple mixing or dilution in the liquid. Guest + host systems of this type will only form solid solutions over a limited range of composition and are expected to give d.i. > 0. These considerations suggest that d.i. will increase with increasing disparity in molecular size, shape and interactions of the guest and the host. Thus, d.i. is likely to be large for a stable lattice doped with an additive of dissimilar molecular size, shape, melting point and solubility (in a defined polar and/or non-polar solvent).

In crystal lattices which already possess considerable disorder, the addition of small concentrations of a structurally related additive will increase the disorder by an amount of about the same magnitude as in the liquid state. For such systems, therefore, b will be only slightly larger than c, i.e. d.i. will be a small positive quantity. Examples would include those solid state molecular compounds, solid state complexes or intermetallic compounds which tend to decompose into their molecular components at temperatures approaching the melting point. Such a system may be recognized by an incongruent melting point or by a congruent melting point with a broad, shallow maximum in the temperature–composition phase-equilibrium diagrams. Under the conditions used to determine ΔH^f, i.e. in the region of the melting point, the solid lattice will contain a significant concentration of relatively free, unbound component molecules from the molecular complex or relatively free, unbound metal atoms from the intermetallic compound. This discussion suggests that d.i. will decrease with decreasing thermal stability of the solid state and with decreasing differences in molecular size, shape and interactions. The d.i. will probably approach zero for components which exhibit similar crystal structures, melting points and solubilities (in a defined polar and/or non-polar solvent).

Analysis of data

A literature survey has revealed a scarcity of published values of ΔH^f and T_m for crystalline solids containing known amounts of additives in solid solution. We recognize the fact that these studies have utilized different experimental conditions and different equipment and were motivated by different objectives. From the limited data available on 7 systems, Table 1 gives values of mole fraction of the host,

TABLE 1

PUBLISHED VALUES OF MOLE FRACTIONS, x_j, MELTING POINT, T_m, AND ENTHALPY OF FUSION ΔH^f, OF DOPED CRYSTALS AND THE CALCULATED MOLAR ENTROPY OF FUSION, ΔS^f, AND IDEAL MOLAR ENTROPY OF MIXING, ΔS^m_{ideal}, OF THE COMPONENTS IN THE CRYSTALS

Host crystal	Additive(s)	Mole fractions			T_m (K)	ΔH^f (kJ·mol^{-1})	ΔS^f (J·K^{-1}·mol^{-1})	ΔS^m_{ideal} (J·K^{-1}·mol^{-1})
		x_1	x_2	x_3				
$InCd_3$	Cadmium	1.00	0.00		513.15	4.22	8.23	0.000
		0.98	0.02		514.15	4.20	8.16	0.811
(Rosina, 1974)		0.96	0.04		515.15	4.18	8.12	1.397
		0.92	0.08		517.15	4.15	8.02	2.318
		0.88	0.12		519.15	4.10	7.90	3.050
		0.84	0.16		521.15	4.07	7.80	3.656
		0.80	0.20		523.15	4.05	7.74	4.531
$InCd_3$	Indium	1.00	0.00		513.15	4.22	8.23	0.000
		0.99	0.01		511.15	4.17	8.15	0.676
(Rosina, 1974)		0.96	0.04		507.15	4.11	8.10	1.369
		0.94	0.06		503.15	4.06	8.08	1.999
		0.90	0.10		497.15	4.00	8.05	2.775
Cadmium	$InCd_3$	1.00	0.00		594.15	6.11	10.28	0.000
		0.98	0.02		592.15	5.86	9.89	0.811
(Rosina, 1974)		0.96	0.04		590.15	5.69	9.64	1.397
		0.92	0.08		586.15	5.40	9.21	2.318
		0.88	0.12		581.65	5.17	8.88	3.050
		0.84	0.16		578.65	5.02	8.68	3.656
		0.80	0.20		573.65	4.81	8.39	4.531

		$\times 10^2$	$\times 10^2$					
Phenacetin	Benzamide	100.00	0.00		406.75	32.89	80.85	0.000
		98.53	1.47		406.65	30.67	75.42	0.637
(Marti, 1972)		97.28	2.72		405.35	29.46	72.67	1.038
		94.78	5.22		404.55	29.12	71.98	1.703
		89.78	10.22		402.15	27.34	67.99	2.743
		$\times 10^1$	$\times 10^1$					
Griseofulvin	Lecithin	10.00	0.00		494.95	41.92	84.69	0.000
		9.75	0.25		492.15	38.87	78.97	0.972
(Venkataram and Rogers, 1985)		9.48	0.52		490.15	37.24	75.97	1.699
		8.87	1.13		490.55	34.12	69.54	2.936
		7.49	2.51		488.45	33.50	68.58	4.685
		$\times 10^2$	$\times 10^4$	$\times 10^2$				
Acetaminophen	*p*-Acetoxyacetanilide (x_2)	95.86	0.00	4.14	439.1	25.82	58.8	1.433
Water (x_3)		97.08	2.71	2.89	441.6	26.94	61.0	1.108
		97.89	8.76	2.02	441.2	27.43	62.2	0.880
(Chow et al., 1985)		98.53	18.00	1.29	441.9	27.93	63.2	0.683
		98.24	21.44	1.55	441.9	28.09	63.6	0.791
		97.28	31.13	2.41	441.2	26.90	61.0	1.118
		97.46	37.16	2.17	441.1	26.54	60.2	1.073
		97.44	43.90	2.12	440.3	26.66	60.5	1.086
		$\times 10^2$	$\times 10^2$					
pp-DDT	*op*-DDT [a]	99.94	0.06		382.98	26.36	68.83	0.042
		99.66	0.34		382.81	25.52	66.67	0.189
(Plato and Glasgow, 1969)		99.42	0.58		382.70	24.69	64.50	0.296
		$\times 10^2$	$\times 10^2$	$\times 10^2$				
pp-DDT	*op*-DDT [b]	99.94	0.03	0.03	382.98	26.36	68.83	0.045
		99.66	0.17	0.17	382.81	25.52	66.67	0.208
(Plato and Glasgow, 1969)		99.42	0.29	0.29	382.70	24.69	64.50	0.330

[a] *op*-DDT is here treated as a single molecular species.

[b] *op*-DDT is here treated as a racemic mixture (equimolecular mixture of the R-form and the S-form).

TABLE 2

DISRUPTION INDEX, d.i., FOR DOPED CRYSTALS AND THE STATISTICS OF LINEAR REGRESSION BETWEEN THE ENTROPY OF FUSION, ΔS^f, AND THE IDEAL ENTROPY OF MIXING, ΔS^m_{ideal}, ACCORDING TO EQN. 15

System	Host crystal	Additive(s)	d.i. = − slope = b − c	No. points in analysis (n)	Correlation coefficient ($-r$)	Residual standard deviation (σ)	Standard error of the slope	Intercept (z)	$\frac{(z-\Delta S_0^f)}{\Delta S_0^f} \cdot 100$ [c]
1.	$InCd_3$	Cadmium	0.115	7	0.9916	0.027	0.007	8.26	−0.30
2.	$InCd_3$	Indium	0.075	4	0.9696	0.020	0.013	8.22	−0.17
3.	Cadmium	$InCd_3$	0.423	7	0.9976	0.052	0.013	10.23	−0.45
4.	Phenacetin	Benzamide	7.939	3	0.9984	0.332	0.45	80.75	−0.13
5.	Griseofulvin	Lecithin	5.091	4	0.9985	0.429	0.20	84.43	−0.31
6.	Acetaminophen	*p*-Acetoxyacetanilide + Water	6.53	8	0.9554	0.513	0.83	68.00	–
7.	*pp*-DDT	*op*-DDT [a]	16.85	3	0.9959	0.277	1.53	69.63	–
	pp-DDT	*op*-DDT [b]	15.09	3	0.9963	0.263	1.30	69.60	–

[a] *op*-DDT is here treated as a single molecular species.

[b] *op*-DDT is here treated as a racemic mixture (equimolecular mixture of the R-form and the S-form).

[c] ΔS_0^f is here the measured value of ΔS^f for the pure host, while z is the value predicted from the linear regression, as the intercept in Eqn. 15.

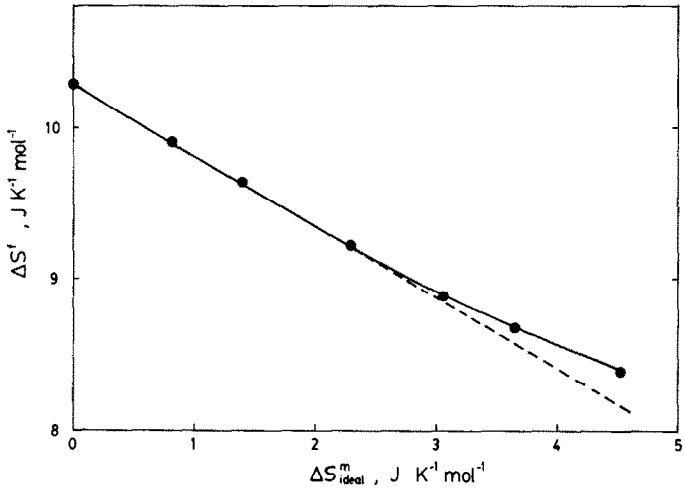

Fig. 1. Correlation between the molar entropy of fusion, ΔS^f, at the melting point, of cadmium doped with the intermetallic compound, $InCd_3$, and the ideal molar entropy of mixing, ΔS^m_{ideal}, of the components of the solid solution. The dotted line represents the hypothetical linear relationship obeyed at $InCd_3$ mole fractions less than 0.10. The data were provided by Rosina (1974).

x_1, and of the additives(s), x_2, x_3, etc., T_m and ΔH^f, together with calculated values of ΔS^f (from Eqn. 6) and of ΔS^m_{ideal} (from Eqn. 8). Figs. 1 and 2 show representative plots of ΔS^f against ΔS^m_{ideal} for Cd + $InCd_3$ and for griseofulvin + lecithin, respec-

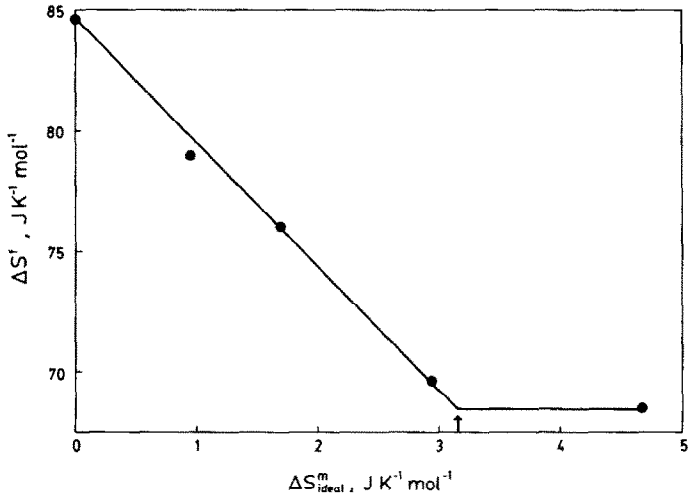

Fig. 2. Correlation between the molar entropy of fusion, ΔS^f, at the melting point, of griseofulvin coprecipitated with lecithin and the ideal molar entropy of mixing, ΔS^m_{ideal}, of the components of the solid solution. ↑ indicates the approximate limit of linearity, which corresponds to mole fraction 0.125 of lecithin. The data were provided by Venkataram and Rogers (1984).

tively, according to Eqn. 15. Table 2 lists the statistical parameters for the linear regression analysis of each system according to Eqn. 15, together with the calculated values of d.i. (i.e. b–c).

Discussion

Whilst in some cases a strictly linear function (Eqns. 14 or 15) is obeyed by only dilute solid solutions (e.g. $x_2 < 0.1$ in Figs. 1 and 2), the calculated statistical parameters for all the sets of data examined in Table 2 support the decreasing linear relationship between ΔS^f and ΔS^m_{ideal}, i.e. $b > c$, as in case (iii) above. Thus, analysis of available data from both metallic and organic solid solutions supports the concept that additives incorporated into crystal lattices at low concentrations produce more disorder than in the liquid state, which is reflected in positive values of d.i. ($= b - c$). The calculated values of d.i. span a 200-fold range from 0.075 to 15.

The Cd + In system can be regarded as a eutectic system with complete solid solubility at Cd and a partial solubility at the In side with the existence of an intermolecular compound, $InCd_3$ (Rosina, 1974). The flatness of the temperature–composition phase-equilibrium diagram in the region of the intermetallic compound (Betteridge, 1938; Wilson and Wick, 1937) indicates that $InCd_3$ is relativelly unstable near its melting point and is therefore somewhat disordered, presumably because of the decomposition equilibrium:

$$InCd_3 = In + 3Cd \qquad (16)$$

Addition of small amounts of Cd or In to $InCd_3$ (according to Systems 1 and 2), respectively, in Tables 1 and 2) shifts this equilibrium to the left in favour of the formation of $InCd_3$ and increased stability and order. This explains why the d.i. values for Systems 1 and 2 (0.115 and 0.075, respectively) are only slightly larger than the value of the zero expected for an ideal solid solution consisting of metal atoms of similar size (atomic volumes, $cm^3 \cdot mol^{-1} = 13.0$ for Cd, 15.7 for In; Weast et al., 1982) and at neighbouring positions in the periodic table. The addition of small amounts of $InCd_3$ to Cd, however, results in a significantly greater d.i. value (0.423 for System 3 in Table 2). In this case the ability of the added In atoms to exchange partners with neighbouring Cd atoms may not be effective enough to counteract the disorder created by adding a larger, complex molecular species to the atomic lattice of cadmium.

Systems 4 and 5 in Tables 1 and 2 give plots of ΔS^f against ΔS^m_{ideal}, which are linear up to mole fraction 0.03 of benzamide in phenacetin and 0.12 of lecithin in griseofulvin (Fig. 2), but which diverge from linearity at higher mole fractions of each additive. At first sight, these limits of linearity might either correspond to the solid solubility limit of the guest molecules in the host lattice or might otherwise indicate that Eqn. 15 is a limiting law generally applicable to dopant levels not exceeding a few mole percent. However, the linearity of Fig. 2 extends beyond the solid solubility limit of lecithin mole fraction $\leqslant 0.05$, indicated by the phase diagram

of Venkataram and Rogers (1984); this suggests the influence of additional factors which are capable of cancelling the expected deviations from linearity. The d.i. values for phenacetin + benzamide and griseofulvin + lecithin (7.94 and 5.09, respectively) indicate 8-fold and 5-fold increases in crystal lattice disorder induced by the additive as compared with mixing or dilution in the liquid state. These higher values of d.i. can readily be explained by the proposed model, since somewhat dissimilar guest molecules are being incorporated into the relatively ordered crystal lattice of the host, each of which has relatively large values of ΔH^f and ΔS^f (Table 1). Furthermore, griseofulvin crystals have a high melting point (220°C, Windholz, 1983) as well as a highly ordered arrangement of molecules (Malmros et. al., 1977; Cheng et al., 1979). In addition, the shape of each guest molecule is appreciably different from that of the corresponding host molecule and the intermolecular interactions, such as hydrogen bonding and dipolar groups, of each guest molecule have a nature and arrangement which are different from those of the corresponding host molecule (Windholz et al., 1983). Furthermore, lecithin is a phospholipid and consists of very flexible molecules, while griseofulvin molecules contain rigid ring structures.

The d.i. for doped acetaminophen (System 6, Table 2) has a value of 6.53 similar to those of Systems 4 and 5, discussed above. Chow et al. (1985) have highlighted the interplay between two additives, water and *p*-acetoxyacetanilide, both of which exert a disruptive effect on the crystal lattice. The lower correlation coefficient and slightly higher residual standard deviation probably reflect the greater complexity of lattice disruption. In this case, increasing incorporation of *p*-acetoxyacetanilide molecules into the acetaminophen lattice parallels slower crystal growth and leads to increasing rejection of the water molecules which are incorporated during rapid crystal growth. Above a certain mole fraction value (0.0015) of *p*-acetoxyacetanilide in the crystals, water molecules are readmitted and further disrupt the crystal lattice of acetaminophen. The 6.5-fold greater disordering of this lattice by the combined effects of water and *p*-acetoxyacetanilide, compared with simple random substitution, mixing and dilution in the liquid state, is indicated by d.i. = 6.53 (Table 2). The stable, ordered nature of the crystal lattice of acetaminophen is indicated by appreciable ΔH^f and ΔS^f values (Table 1), by hydrogen bonding propensity at the phenolic and amide groups and by single crystal X-ray crystallography (Haisa et al., 1974). Lattice disruption may occur because the small water molecule can actively participate in hydrogen bonding at each type of group, while the larger *p*-acetoxyacetanilide molecule possesses an ester group instead of the phenolic hydroxyl group of acetaminophen. A corollary of this study is that small non-stoichiometric proportions of water incorporated into the crystal lattice during crystallization may exert analogous disruptive effects on the crystal lattice order of other materials and thereby account for certain batch-to-batch variations.

The highest observed value of d.i., 15 or 17, is given by System 7 (Table 2) in which the symmetrical, achiral molecule, 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (*pp*-DDT) is doped with small amounts of the asymmetric, isomeric molecule, 1,1,1-trichloro-2,-(2-chlorophenyl)-2-(4-chlorophenyl)ethane (*op*-DDT), as the additive. While the isomers have identical or very similar molecular

weights and molecular sizes, they have different molecular shapes, symmetry and molecular packing. The melting point of *op*-DDT (76°C) is much lower than that of *pp*-DDT (110°C) (Buckingham and Donaghy, 1982) indicating that it packs less well into the crystal lattice, presumably on account of its lower molecular symmetry. Although *op*-DDT has a chiral centre, the literature for the *pp*-DDT + *op*-DDT system (Plato and Glasgow, 1969) does not indicate whether a single enantiomer or the racemic mixture was used as the dopant of the *pp*-DDT crystals. Accordingly, the mole fractions and the ΔS^m_{ideal} values (System 7, Table 1) and the d.i. value with the statistics of linear regression between ΔS^f and ΔS^m_{ideal} (System 7, Table 2) were calculated assuming either: (a) that a single enantiomer was used; or (b) that the racemic mixture was used. It is particularly interesting that the d.i. value is only 10% smaller for assumption (b) than for (a), while the intercept, the correlation coefficient and the statistics of linear regression are very similar. In view of the greater availability and lower cost of the racemic mixture, it is unlikely that a pure enantiomer of *op*-DDT was used as a dopant, so (b) is probably the more appropriate assumption in Tables 1 and 2. If this is the case, a possible explanation for the high d.i. value of 15 may be the presence of point defects and dislocations of different properties arising from the introduction of two different molecules related by mirror image into the crystal lattice.

The present procedure of quantifying the disruption of the crystal lattice of a host substance by small concentrations of an additive or impurity involves the determination of ΔS^f ($= \Delta H^f/T_m$). The following are two disadvantages of this procedure. (a) The closely related techniques, differential thermal analysis (DTA) and differential scanning calorimetry (DSC), which are the most convenient methods for determining ΔS^f, may change the order of the crystal lattice by increasing thermal motion and/or by annealing the solid during the heating process. These effects may be reduced by the use of a rapid heating mode. (b) The measurement of ΔS^f for thermo-labile materials or for substances which decompose near the melting point will be liable to appreciable errors, reducing the reliability of d.i. values. However, for such materials it may be possible to determine the entropy of solution, ΔS^s, of the crystals in a suitable solvent at a suitable temperature and to employ ΔS^s in place of ΔS^f in Eqns. 13–15. This alternative method of evaluating d.i. will be considered in a subsequent communication.

The d.i. values for the doping of solid drugs, and other organic crystals, with organic compounds are found to lie between 5 and 15 for the limited number of systems examined, suggesting appreciable lattice disruption. Since virtually all the pharmaceutically significant properties of a solid drug depend to some extent on the lattice disorder, crystallinity and the concentration of crystal defects, d.i. may be useful in accounting for and predicting certain batch-to-batch variations. In general, d.i. values may be useful in predicting the sensitivity of the crystal lattice of a drug or excipient to the presence of traces of a given impurity in solid solution. The relationships between d.i. and the pharmaceutically important physicochemical and physico-technical properties of solids will be examined in later reports.

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