International Journal of Pharmaceutics, 39 (1987) 243–253
Elsevier

IJP 01333

A theoretical treatment of changes in energy and entropy of solids caused by additives or impurities in solid solution

Michael J. Pikal [1] and David J.W. Grant [2]

[1] *Eli Lilly and Co., Indianapolis, IN 46285 (U.S.A.) and* [2] *Faculty of Pharmacy, University of Toronto, Toronto, Ont. (Canada)*

(Received 7 May 1986)
(Modified version received 13 May 1987)
(Accepted 19 May 1987)

Key words: Thermodynamics; Free energy; Enthalpy; Entropy; Disruption index; Solid solution; Fusion; Excess entropy

---

Summary

A dimensionless entropy increment ratio, termed the "disruption index" (d.i.), has previously been defined and evaluated from heats of fusion, ΔH^{f} (*Int. J. Pharm.*, 25 (1985) 57–72), and from heats of solution, ΔH^{s} (*Int. J. Pharm.*, 28 (1986) 103–112). The d.i. quantifies the disruptive influence of an additive or impurity (the guest substance), when present at low mole fractions ($x_2 < 0.05$), in solid solution in the crystal lattice of a host substance. The present report places the thermodynamics in the previous papers on a more rigorous foundation. (1) The previously defined "enthalpy of fusion of the solid", ΔH^{f}, and "enthalpy of solution of the solid", $\Delta H^{s\theta}$, are defined in terms of the partial molar enthalpies of the two components. (2) The d.i., previously calculated from $\Delta H^{s\theta}$, is expressed in terms of the excess entropy of the solid, S^{E}. The original definition of d.i. is found to involve the assumption that the partial molar excess entropy of the guest, $\bar{S}_2^{E}$, is directly proportional to the ideal entropy of mixing. (3) The pseudo-d.i. (p.d.i.), originally defined by assuming enthalpy–entropy compensation, is expressed in terms of the excess enthalpy of the solid, H^{E}. (4) The d.i. previously calculated from ΔS^{f} is expressed in terms of $\bar{S}_2^{E}$. The d.i. derived from ΔS^{f} and that derived from $\Delta S^{s\theta}$ differ by about a unit in theory and are approximately equal when d.i. $\gg 1$; however, the experimentally observed differences express the temperature dependence of S^{E}, which is reflected in the annealing of the solid between ambient temperatures and the melting point. (5) The d.i. is compared with an alternative approach based on the limiting value of $(\partial \Delta S / \partial \Delta x_2)$ at low x_2, i.e. $(\bar{S}_2^{E})_0$. The empirical relationship between these two approaches is d.i. $= 0.035 \cdot [(\bar{S}_2^{E})_0]^{0.912}$ with $(\bar{S}_2^{E})_0$ in $\mathrm{JK^{-1}\ mol^{-1}}$ and d.i. from 10^{-1} to 4×10^{3}. It is concluded that the present rigorous thermodynamic treatment does not alter the main conclusions derived from the previous intuitive treatment but defines better the approximation inherent in the evaluation of d.i. and shows that d.i. is directly related to S^{E}.

Introduction

Virtually all pharmaceutical solids contain impurities, which are often compounds involved with the processes of synthesis, extraction, and even purification of the solid. Some impurities may be taken up by the solid from the vapour phase, such as water, others are taken up during crystal growth in solution, such as the solvent and cosolvent, if present, while others may arise in the bulk or on the surface as products of decomposition, hydrolysis or oxidation.

Sometimes a second substance, such as a solvent, cosolvent, surfactant, antioxidant or crystallization inhibitor, is deliberately added during the preparation or purification of the

---

Correspondence: D.J.W. Grant, Faculty of Pharmacy, University of Toronto, 19 Russell Street, Toronto, Ont. M5S 1A1, Canada.

0378-5173/87/$03.50 © 1987 Elsevier Science Publishers B.V. (Biomedical Division)

pharmaceutical solid for a specific purpose; such substances may be termed "additives".

When present in small proportions, e.g. less than 1 mol%, these impurities or additives may be present in solid solution within the more or less crystalline solid and can be termed "dopants", by analogy with the doping of semiconductors for electronic devices. The present paper considers the thermodynamic consequences of the formation of solid solutions in pharmaceutical solids.

The presence of a small proportion of an impurity, additive or dopant, which may collectively be termed the "guest", in atomic, ionic or molecular form in solid solution, creates impurity defects in the crystal lattice of the major component, the "host" (Boldyrev et al., 1979). Impurity defects may interact with, or give rise to, dislocations within the crystalline host. The bulk properties of the solid host are therefore altered by the presence of the guest. Molecules of the guest in the crystallization medium may be absorbed on to the surface of the host crystals and/or alter their crystal habit, while some dislocations emerge at the crystal surface; thus the surface properties of the host may be changed by the presence of the guest (Mullin, 1972). The presence of the guest may therefore change the thermodynamic properties of both the bulk and the surface of the solid host.

In previous publications of this series (York and Grant, 1985; Grant and York, 1986a), the crystal defects created by the presence of the guest molecules in solid solution are termed "imperfections" and their disruptive or disordering effect on the crystal lattice is expressed by means of a "disruption index" (d.i.). The d.i. is a dimensionless entropy increment ratio for quantifying the influence of the guest on the difference in entropy between the more or less crystalline host and either the liquid host or a dilute solution of the host. In practice d.i. is determined from either of the following ratios:

$$\text{d.i.} = -\delta(\Delta S^{\mathrm{f}})/\delta(\Delta S^{\mathrm{m}}_{\mathrm{ideal}}) \tag{1}$$

or

$$\text{d.i.} = -\delta(\Delta S^{\mathrm{s}})/\delta(\Delta S^{\mathrm{m}}_{\mathrm{ideal}}) \tag{2}$$

where δ is an operator indicating a small change in the following properties brought about by a small proportion of the guest, ΔS^{f} is the entropy of fusion, ΔS^{s} is the entropy of solution and $\Delta S^{\mathrm{m}}_{\mathrm{ideal}}$ is the ideal entropy of mixing of the guest with the host. The latter quantity is calculated from the analytical data for the crystals, as follows:

$$\Delta S^{\mathrm{m}}_{\mathrm{ideal}} = -\mathrm{R}\sum x_{\mathrm{j}} \cdot \ln x_{\mathrm{j}} \tag{3}$$

where x_{j} is the mole fraction of a given component, j, of the solid solution, R is the gas constant and the summation includes all the various components of the crystals. Eqns. 1 and 2 are limiting laws at mole fractions of the guest, x_2, not exceeding about 0.05, in solid solution in the crystal lattice of the host of mole fraction, x_1. Under these limiting conditions, the d.i. value is a property of the particular host and guest system.

Eqns. 1 and 2 may be stated in the following integrated forms:

$$\Delta S^{\mathrm{f}} = \Delta S^{\mathrm{f}}_0 - (b - c) \cdot \Delta S^{\mathrm{m}}_{\mathrm{ideal}} \tag{4a}$$

$$\Delta S^{\mathrm{s}} = \Delta S^{\mathrm{s}}_0 - (b - c) \cdot \Delta S^{\mathrm{m}}_{\mathrm{ideal}} \tag{4b}$$

where ΔS^{f}_0 and ΔS^{s}_0 are the values of ΔS^{f} and ΔS^{s} respectively of a pure sample of the host substance for which $\Delta S^{\mathrm{m}}_{\mathrm{ideal}} = 0$, because no doping has taken place, and where $(b - c) =$ d.i. The constants b and c are proportionality constants defined as follows:

$$\delta(S_{\mathrm{solid}}) = b \cdot \delta(\Delta S^{\mathrm{m}}_{\mathrm{ideal}}) \tag{5a}$$

$$\delta(S_{\mathrm{liquid}}) = c \cdot \delta(\Delta S^{\mathrm{m}}_{\mathrm{ideal}}) \tag{5b}$$

where S_{solid} and S_{liquid} are the entropy of the solid and liquid host, respectively. If b and c are truly constant at low levels of the guest, whose effects are denoted by the operator δ, then ΔS^{f} and ΔS^{s} will be decreasing linear functions of $\Delta S^{\mathrm{m}}_{\mathrm{ideal}}$ as observed at $x_2 < 0.05$ (York and Grant, 1985; Grant and York, 1986a).

The "entropy of solution" of the host crystals, doped and pure, may be given by

$$T \cdot \Delta S^{\mathrm{s}\theta} = \Delta H^{\mathrm{s}} + \mathrm{R}T \cdot \ln C_{\mathrm{s}} \tag{6}$$

where δH^s is the "enthalpy of solution" of the crystals and C_s is the solubility of the host crystals in the same solvent as used for determining ΔH^s, and $-RT \cdot \ln C_s = \Delta G^{s\theta}$, the "free energy of solution".

If enthalpy-entropy compensation is assumed to occur, i.e.

$$\delta(\Delta H^s) = \beta \cdot \delta(\Delta S^s) \tag{7}$$

where β is the compensation temperature, then Eqn. 4b affords:

$$\Delta H^s = \Delta H_0^s - (b - c) \cdot \beta \cdot \Delta S_{\text{ideal}}^{\text{m}} \tag{8}$$

A pseudo-disruption index, p.d.i. $= (b' - c')$, may be defined as follows:

$$T \cdot (b' - c') = \beta \cdot (b - c) \tag{9}$$

If enthalpy-entropy compensation is appreciable, $\beta \approx T$, and the free energy term, and hence $RT \cdot \ln C_s$ in Eqn. 6, may be ignored, and p.d.i. $\approx$ d.i.

Values of d.i. determined from heats of fusion or heats of solution are summarized by Grant and York (1986b) and their orders of magnitude have thus far been found to cover the range 10^{-1}, 1, 10, 100 and 1000. The d.i. value appears to express the potential of the guest for disruption of the crystal lattice of the host or, alternatively, the sensitivity of the crystalline host to disruption by the guest molecules.

The thermodynamic relationships between x_2 and the enthalpy of fusion, ΔH^f, or enthalpy of solution, ΔH^s, in our previous treatments (cited above) are here recognized to be intuitive and simplistic and to be based on a number of unproven assumptions. Those treatments may not be sufficiently rigorous for further development of our concept of lattice disruption. In the present report, a more thorough and necessarily more complex theoretical treatment is derived, our primary objective here being to place on a more rigorous foundation the thermodynamics of our previous works (cited above). The present treatment, which is based on partial molar quantities, defines more exactly the approximations inherent in the evaluation of d.i. This more rigorous treatment, being theoretically superior to our previous treatments, may be practically superior for further understanding the origins and consequences of interbatch variation of pharmaceutical solids.

Our second objective here is to express d.i. in terms of the excess entropies of the solid and liquid (or solution) phases and to comment critically on the relative merits of the d.i. and excess entropy approaches to the quantitation of crystal lattice disruption by additives or impurities in solid solution.

Notation and Choice of Standard States

Since thermodynamic notation and definitions of standard states can becomes somewhat complex, we summarize here some of the notation used and define the choice of standard states.

Notation

Subscripts:

1 major solid component (the host)
2 minor solid component (the guest, additive, impurity or dopant)
0 limiting value of a crystal property as $x_2 \to 0$, corresponding to pure crystalline host
s saturation value

Superscripts:

s solution process
0 standard state for component in indicated phase
$\cdot$ pure liquid state
* pure crystalline solid state
α solution phase
σ solid phase
λ liquid phase
E excess quantity, with respect to the value for an ideal solution

Choice of standard states

Major solid component (1)

In solution (liquid). We choose the Henry's law standard state, which is also referred to as the hypothetical ideal 1 M solution. Denoting the activity coefficient as γ, and the chemical potential as μ, we have, $\gamma_1 \to 1$ as $C_1 \to 0$, and $[\mu_1^\alpha -$

$RT \ln C_1] \rightarrow \mu_1^{\alpha,0}$ as $C_1 \rightarrow 0$. We also note that $\mu_1^{\alpha} = \mu_1^{\alpha,0}$ when $\gamma_1 = 1$ and $C_1 = 1$. Of course, there is no real state such that the activity coefficient is unity and the concentration is 1 M. This standard state is therefore hypothetical.

In the solid. We choose pure crystalline 1 as the standard state and the activity coefficient is defined in terms of the deviation from Raoult's law, which is equivalent to: $\gamma_1 \rightarrow 1$, and $\mu_1^{\sigma} \rightarrow \mu_1^{\sigma,0}$ when the mole fraction of 1 approaches unity, $x_1 \rightarrow 1$. Since the standard state is pure crystalline 1, we have $\mu_1^{\sigma,0} = \mu_1^{*}$.

Minor solid component (2)

In solution (liquid). Again, we choose the Henry's law standard state for the solute in the solution phase, which for component 2 becomes: $\gamma_2 \rightarrow 1$ as $C_2 \rightarrow 0$, and $[\mu_2^{\alpha} - RT \ln C_2] \rightarrow \mu_2^{\alpha,0}$ as $C_2 \rightarrow 0$.

In the solid. For the "impurity" component, we choose the standard state as pure liquid 2 and use the deviation from Raoult's law to define the activity coefficient. Thus, $\gamma_2 \rightarrow 1$ as $x_2 \rightarrow 1$, and $\mu_2^{\sigma} \rightarrow \mu_2^{\sigma,0}$ when $x_2 = 1$. Since the standard state is the pure liquid, $\mu_2^{\sigma,0} = \mu_2^{\cdot}$. Since component 2 is, by definition, a low-level impurity in the solid phase, it might seem more reasonable to define the standard state and activity coefficient in term of Henry's law. However, an objective of the present work is to express the disruption index in term of the excess entropy of mixing, and for this purpose, the pure components are more consistent choices for the standard states. Although liquid 2, rather than solid 2, is chosen for the standard state, it should be emphasized that from a pure thermodynamics point of view, the choice of standard state is arbitrary and the essential features of this analysis do not depend on the exact choice.

Thermodynamic Changes on Solution

This section defines more clearly the enthalpy and Gibbs free energy changes which occur on dissolution of a two component solid. The intent is to place the thermodynamics of the previous works (York and Grant, 1985; Grant and York, 1986a) on a more rigorous foundation. We consider a solid sample consisting of one mole ($n_1 = 1$) of a major component (subscript 1) and n_2 moles of an impurity component (subscript 2) which dissolves in a solvent. If the final solution is sufficiently dilute such that the heat of dilution to infinite dilution is negligible, this solution is equivalent (from an enthalpy point of view) to the solution standard state for both solid components. Thus, the heat of solution to infinite dilution, ΔH^{s}, is given in partial molar enthalpies, $\overline{H}_i$, as

$$\Delta H^{s} = n_1\left(\overline{H}_1^{\alpha,0} - \overline{H}_1^{\sigma}\right) + n_2\left(\overline{H}_2^{\alpha,0} - \overline{H}_2^{\sigma}\right) \qquad (10)$$

where $\overline{H}_i^{\alpha,0}$ (for $i = 1,2$) are partial molar enthalpies in the solution standard state, and $\overline{H}_i^{\sigma}$ are partial molar enthalpies in the solid phase. Since $n_1 = 1$ and $n_2 \ll 1$, ΔH^{s} is *approximately* the heat of transfer of 1 mol of component 1 from the solid to the solution standard state. Previous work (Grant and York, 1986a) defined an entropy change, denoted $\Delta S^{s\theta}$, as

$$\Delta S^{s\theta} = \Delta H^{s}/T + R \ln C_s \qquad (11)$$

where R is the gas constant and C_s is the solubility of component 1 when solid containing both components 1 and 2 is in equilibrium with the solution. It should be noted that equilibrium for component 1 does not necessarily demand equilibrium for component 2 (the impurity), particularly when using the dissolution rate method for evaluating solubility (cited above). However, expressing $RT \ln C_s$ (a free energy term) in terms of the component chemical potentials only demands phase equilibrium for component 1. The chemical potential of component 1 in the solution phase is

$$\mu_1^{\alpha} = \mu_1^{\alpha,0} + RT \ln C_s\gamma_s \qquad (12)$$

while the chemical potential of component 1 in the solid phase is

$$\mu_1^{\sigma} = \mu_1^{\sigma,0} + RT \ln a_1^{\sigma} \qquad (13)$$

where a_1^{σ} is the activity of component 1 in the solid phase, which is equal to the product of the mole fraction of 1 and the activity coefficient of 1 in the solid. Using the phase equilibrium condition, $\mu_1^\alpha = \mu_1^\sigma$, choosing the standard states outlined earlier, and assuming the saturated solution is sufficiently dilute so the activity coefficient γ_s is approximately unity, we have

$$-\mathrm{R}T \ln C_s = \left(\mu_1^{\alpha,0} - \mu_1^*\right) - \mathrm{R}T \ln a_1^\sigma \tag{14}$$

where the chemical potential term in parenthesis is the standard-state free energy change for dissolution of the major component (transfer from the pure crystalline solid to the Henry's law solution standard state). We note that, while the assumption of $\gamma_s = 1$ may be a good approximation, the corresponding assumption for the solid is evidently not generally valid. The data (Grant and York, 1986a) indicate that the solubility, C_s, is significantly changed (increased or decreased, depending on the system) by levels of impurity of the order of 0.1 mol%. Here, the mole fraction of component 1 is essentially unity so nearly all of the change in C_s is due to deviation of the activity coefficient from unity.

Combination of Eqns. 10, 11, 13, and 14 yields

$$\Delta S^{s\theta} = n_1\left(\bar{S}_1^{\alpha,0} - \bar{S}_1^\sigma\right) + n_2\left(\bar{S}_2^{\alpha,0} - \bar{S}_2^\sigma\right) + n_2\left(\mu_2^{\alpha,0} - \mu_2^\sigma\right)/T \tag{15}$$

Note that $\Delta S^{s\theta}$ as defined by Grant and York is not exactly a pure entropy change. The extra chemical potential term in μ_2 is related to the solubility of component 2 when the mixed solid is in equilibrium with the solution phase. From the phase equilibrium condition, $\mu_2^\alpha = \mu_2^\sigma$, it follows that

$$\mu_2^{\alpha,0} - \mu_2^\sigma = -\mathrm{R}T \ln(C_s)_2 \tag{16}$$

where $(C_s)_2$ is the solubility of component 2. Substitution of Eqn. 16 for the chemical potential term in Eqn. 15 yields

$$\Delta S^{s\theta} + n_2\mathrm{R} \ln(C_s)_2 = n_1\left(\bar{S}_1^{\alpha,0} - \bar{S}_1^\sigma\right) + n_2\left(\bar{S}_2^{\alpha,0} - \bar{S}_2^\sigma\right) \tag{17}$$

The right-hand side of Eqn. 17 is obviously a pure entropy term and represents the entropy of solution of a solid containing n_1 moles of component 1 ($n_1 = 1$) and n_2 moles of component 2, where the solution states are the respective standard states. However, solubility data for the guest species in the mixed solid are not available and indeed would be difficult to obtain. Thus, the implicit assumption by Grant and York that $\Delta S^{s\theta}$ is a pure entropy quantity is equivalent to the assumption that the absolute value of "$n_2 \ln(C_s)_2$" is small and specifically is much less than the absolute value of "$\ln C_s$".

Alternatively, Eqn. 15 may be written in a pseudo-pure entropy form by using the enthalpy–entropy compensation principle (Eqn. 7), where β is a constant of the same order of magnitude as the absolute temperature, T (Grant and York, 1986a; Vachon and Grant, 1987). This principle implies that ΔG is small compared to $T \cdot \Delta S$. In terms of β, the chemical potential difference in Eqn. 15 may be written in the form,

$$\mu_2^{\alpha,0} - \mu_2^\sigma = (\beta - T)\left(\bar{S}_2^{\alpha,0} - \bar{S}_2^\sigma\right) \tag{18}$$

We now define the deviation from perfect compensation ($\beta = 1$) by the quantity ϕ, where

$$\phi = \beta/T - 1 \tag{19}$$

and write Eqn. 15 in the form

$$\Delta S^{s\theta} = n_1\left(\bar{S}_1^{\alpha,0} - \bar{S}_1^\sigma\right) + n_2\left(\bar{S}_2^{\alpha,0} - \bar{S}_2^\sigma\right)(1 + \phi) \tag{20}$$

The deviation parameter, ϕ, may be either positive or negative, but according to the compensation principle, will be small in magnitude compared to unity. Clearly, if $\phi \approx 0$, $\Delta S^{s\theta}$ reduces to the "entropy of solution of the solid", and the Grant and York treatment is therefore also equivalent to the assumption of perfect compensation for the change involving transfer of component 2 from the solid to the solution standard state.

Disruption Index from Heat of Solution

Since the non-ideal character of a system is commonly expressed in terms of the excess thermodynamic functions (Guggenheim, 1967; Kaufman and Nesor, 1975), we will develop the relationship between the d.i. and the excess entropy of the solid. For this purpose, we now express the partial molar entropies in terms of the excess entropy. Consider mixing n_1 mol of crystalline component 1 and n_2 mol of liquid component 2 to form the mixed solid. The entropy of the solid may be written,

$$S^{\sigma} = n_1\bar{S}_1^{*} + n_2\bar{S}_2^{\bullet} - n_1\mathrm{R}\ln x_1 - n_2\mathrm{R}\ln x_2 + S^{\mathrm{E}} \tag{21}$$

where the first two terms in Eqn. 21 define the reference entropy for the mixing process (pure components), the next two terms (in mole fraction, x_{i}) represent the ideal entropy of mixing, and S^{E} is the excess entropy of the mixed solid. The partial molar entropy of the i^{th} component in the solid, defined by $\bar{S}_{\mathrm{i}}^{\sigma} = (\partial S^{\sigma}/\partial n_{\mathrm{i}})_{\mathrm{T,P,nj}}$, is then evaluated by differentiation of Eqn. 21 with the results

$$\bar{S}_1^{\sigma} = \bar{S}_1^{*} - \mathrm{R}\ln x_1 + \bar{S}_1^{\mathrm{E}} \tag{22}$$

$$\bar{S}_2^{\sigma} = \bar{S}_2^{\bullet} - \mathrm{R}\ln x_2 + \bar{S}_2^{\mathrm{E}} \tag{23}$$

where $\bar{S}_{\mathrm{i}}^{\mathrm{E}}$ is the partial molar excess entropy of the i^{th} component. The excess entropy of the solid is given in terms of the partial molar excess entropies, thus:

$$S^{\mathrm{E}} = n_1\bar{S}_1^{\mathrm{E}} + n_2\bar{S}_2^{\mathrm{E}} \tag{24}$$

Combining Eqn. 20 and Eqns. 22–24 with $n_1 = 1$, gives

$$\Delta S^{\mathrm{s}\theta} = \Delta S_0^{\mathrm{s}\theta} + (1+\phi)\left(\bar{S}_2^{\alpha,0} - \bar{S}_2^{\bullet}\right)n_2 - \left\{\Delta S_{\mathrm{ideal}}^{m} - [\mathrm{R}\phi n_2 \ln x_2] + \left(S^{\mathrm{E}} + \phi n_2\bar{S}_2^{\mathrm{E}}\right)\right\} \tag{25}$$

where $\Delta S_0^{\mathrm{s}\theta}$ is the entropy of solution of one mole of pure crystalline 1,

$$\Delta S_0^{\mathrm{s}\theta} = \bar{S}_1^{\alpha,0} - \bar{S}_1^{*} \tag{26}$$

and $\Delta S_{\mathrm{ideal}}^{\mathrm{m}}$ is the ideal entropy of mixing one mole of crystalline 1 and n_2 moles of liquid 2,

$$\Delta S_{\mathrm{ideal}}^{\mathrm{m}} = R[-\ln x_1 - n_2 \ln x_2] \approx \mathrm{R}n_2(1 - \ln x_2),\ x_2 \ll 1 \tag{27}$$

With $\phi \approx 0$, the terms in curved brackets, { }, in Eqn. 25 represent the entropy of mixing. The Grant and York treatment is equivalent to assuming that this entropy of mixing is proportional to the ideal entropy of mixing. While the ideal entropy of mixing does appear explicitly in Eqn. 25, it is by no means obvious that the *excess* entropy has the same x_2 dependence as does the ideal entropy of mixing (Eqn. 27). While both the excess entropy and the ideal entropy of mixing are zero when x_2 is zero and both will increase as x_2 increases from zero, there is no obvious theoretical basis for a direct proportion between the excess entropy and the ideal entropy of mixing. We will return to this point later, but for the present will accept the proportional relationship as an empirical observation justified only by the fact that plots of $\Delta S^{\mathrm{s}\theta}$ vs. $\Delta S_{\mathrm{ideal}}^{\mathrm{m}}$ are linear over a far greater range of x_2 than are corresponding plots using any other simple function of x_2 in place of $\Delta S_{\mathrm{ideal}}^{\mathrm{m}}$. Thus, we write the Grant and York assumption in mathematical form as

$$S^{\mathrm{E}} + \phi n_2\bar{S}_2^{\mathrm{E}} = b_{\mathrm{E}}\Delta S_{\mathrm{ideal}}^{\mathrm{m}} \tag{28}$$

where b_{E} is a constant for a given host/guest system.

Eqn. 25 contains the standard molar entropy of solution of pure liquid 2, $\bar{S}_2^{\alpha,0} - \bar{S}_2^{\bullet}$, which may be evaluated from the solubility of liquid 2, $C_{\mathrm{s}}^{\bullet}$, and the heat of solution of liquid 2, $\Delta H^{\mathrm{s}^{\bullet}}$, using the relationship

$$\bar{S}_2^{\alpha,0} - \bar{S}_2^{\bullet} = \Delta H^{\mathrm{s}^{\bullet}}/T + \mathrm{R}\ln C_{\mathrm{s}}^{\bullet} \tag{29}$$

Representative data (Table 1) indicate that the entropy of solution of liquid 2 is of the same order of magnitude as the gas constant, R. Therefore, the term, $(1+\phi)(\bar{S}_2^{\alpha,0} - \bar{S}_2^{\bullet})n_2$, in Eqn. 25 is of magnitude $\mathrm{R}n_2$ and is a small term for low levels of guest. Retaining the term in ϕ would include a term of order, $\mathrm{R}n_2\phi$, which is *very* small. Conse-

TABLE 1

Thermodynamic aqueous solution properties at 298.15 K for various liquid fatty acids used to dope adipic acid crystals

$C_s^{\cdot}$ [a] (M)	$\Delta H^{s\cdot}$ [b] (kJ/mol)	$\Delta S^{s\cdot}$ [c] (J/mol K)	$b-c$ [d]	x_2 [e]	c [f]	c' [g]
Hexanoic acid				5.0×10^{-2} [h]	-0.27	0.35
				1.0×10^{-2}	-0.19	0.25
8.53×10^{-2}	3.46	-8.85	505	8.3×10^{-4} [i]	-0.13	0.17
				1.0×10^{-4}	-0.10	0.14
				1.0×10^{-6}	-0.07	0.09
Octanoic acid				5.0×10^{-2} [h]	-0.30	1.02
				1.0×10^{-2}	-0.21	0.73
5.07×10^{-3}	10.15	-9.90	950	2.4×10^{-4} [i]	-0.13	0.44
				1.0×10^{-4}	-0.12	0.40
				1.0×10^{-6}	-0.08	0.28
Undecanoic acid				5.0×10^{-2} [h]	-1.02	0.86
				1.0×10^{-2}	-0.72	0.61
5.56×10^{-4}	8.50	-33.8	693	2.2×10^{-4} [i]	-0.43	0.36
				1.0×10^{-4}	-0.40	0.34
				1.0×10^{-6}	-0.27	0.23

[a] $C_s^{\cdot}$ = molar solubility in water at 298.15 K interpolated from the Van't Hoff plot of the solubility of the liquid at various temperatures (Singleton, 1960); density values of water from Weast and Astle (1982).

[b] $\Delta H^{s\cdot}=\overline{H}_2^{\alpha,0}-\overline{H}_2^{\cdot}$, calculated from the slope of the above Van't Hoff plot.

[c] $\Delta S^{s\cdot}=\overline{S}_2^{\alpha,0}-\overline{S}_2^{\cdot}$, calculated from the above using Eqn. 29.

[d] d.i. $=b-c=-\delta(\Delta S^{s\theta})/\delta(\Delta S^{m}_{\text{ideal}})$, from Grant and York (1986a) using Eqn. 29.

[e] x_2 = mole fraction of fatty acid in the adipic acid crystals.

[f] Defined approximately by York and Grant (1985) and by Grant and York (1986a).

[g] Calculated from $\Delta H^{s\cdot}$ and x_2 using Eqn. 38.

[h] The upper limit for the theoretical analysis (York and Grant, 1985; Grant and York, 1986a).

[i] Analytical value of x_2 corresponding to measured changes in thermodynamic properties (Chow et al., 1984).

quently, we use the approximation, $\phi \approx 0$, in the entropy of solution term.

The ideal entropy of mixing is also a relatively small contribution to Eqn. 25, being less than 0.06R for $n_2 < 0.01$. Most of the decrease in $\Delta S^{s\theta}$ arises from the excess entropy terms when the disruption index is significantly greater than unity. Since the term, $-\mathrm{R}\ n_2 \ln x_2$ is less than the ideal entropy of mixing, and we assume $\phi \ll 1$, the term in square brackets, [ ], in Eqn. 25 is very small and may be taken as zero with no significant loss in accuracy.

Using the $\phi \approx 0$ approximation as indicated above, the small x_2 approximation for $\Delta S^{m}_{\text{ideal}}$ (Eqn. 27), and Eqn. 28 for the excess entropy terms, we may write Eqn. 25 in the form,

$$\Delta S^{s\theta}=\Delta S_0^{s\theta}-\left[(1+b_{\mathrm{E}})-\left(\overline{S}_2^{\alpha,0}-\overline{S}_2^{\cdot}\right)/\mathrm{R}(1-\ln x_2)\right]\Delta S^{m}_{\text{ideal}} \tag{30}$$

In the Grant and York treatment, the d.i. is defined in terms of the difference between a constant, b, reflecting the entropy increase of the solid caused by the guest, and a constant, c, reflecting introduction of the guest into the solution

$$\Delta S^{s\theta}=\Delta S_0^{s\theta}-[b-c]\Delta S^{m}_{\text{ideal}} \tag{31}$$

where the disruption index is defined as, d.i. = $[b-c]$. Comparison of Eqn. 30 and Eqn. 31 leads to the identifications, $b=(b_{\mathrm{E}}+1)$, and

$$c=\left(\overline{S}_2^{\alpha,0}-\overline{S}_2^{\cdot}\right)/\mathrm{R}(1-\ln x_2) \tag{32}$$

Clearly, the parameter, c, is not really a constant. However, the x_2 dependence is modest over the range of x_2 studied in a given application (Grant and York, 1986a) and most important, the values of c are extremely small (Table 1), so it makes little practical difference if they are constant or variable as long as the disruption index is significantly greater than unity. Experimental values of d.i. determined from Eqn. 31 are greater than 500.

Pseudo-disruption Index

The p.d.i. (Grant and York, 1986a) is defined in terms of the variation in the heat of solution with level of guest species. Eqn. 10 gives the heat of solution in terms of partial molar enthalpies. Expressing the partial molar enthalpies of components 1 and 2 in the solid phase in terms of the standard state molar enthalpies and the partial molar excess enthalpies,

$$\overline{H}_1^\sigma = \overline{H}_1^* + \overline{H}_1^{\mathrm{E}} \tag{33}$$

$$\overline{H}_2^\sigma = \overline{H}_2^\bullet + \overline{H}_2^{\mathrm{E}} \tag{34}$$

Eqn. 10, with $n_1 = 1$, becomes

$$\Delta H^{\mathrm{s}} = \Delta H_0^{\mathrm{s}} + (\Delta H^{\mathrm{s}\bullet}) n_2 - H^{\mathrm{E}} \tag{35}$$

where $\Delta H^{\mathrm{s}\bullet} = (\overline{H}_2^{\alpha,0} - \overline{H}_2^\bullet)$ is the heat of solution of pure liquid 2, $\Delta H_0^{\mathrm{s}} = (\overline{H}_1^{\alpha,0} - \overline{H}_1^*)$ is the molar heat of solution of pure crystalline 1, and $H^{\mathrm{E}} = (\overline{H}_1^{\mathrm{E}} + n_2 \overline{H}_2^{\mathrm{E}})$ is the excess enthalpy of the solid. The Grant and York analysis is equivalent to the assumption

$$H^{\mathrm{E}} = b'(T\Delta S_{\mathrm{ideal}}^{\mathrm{m}}) \tag{36}$$

Substitution of Eqn. 36 for H^{E}, and use of Eqn. 27 to eliminate n_2, allows Eqn. 35 to be written in the form

$$\Delta H^{\mathrm{S}} = \Delta H_0^{\mathrm{s}} - [b' - c'] T\Delta S_{\mathrm{ideal}}^{\mathrm{m}} \tag{37}$$

where p.d.i. $= [b' - c']$, and c' is given by

$$c' = (\Delta H^{\mathrm{s}\bullet}/\mathrm{R}T)/(1 - \ln x_2) \tag{38}$$

Again, the parameter c' is not a true constant, but values of c' (Table 1) are small.

Disruption Index from Heat of Fusion

The heat of fusion of a solid consisting of 1 mol of component 1 and n_2 moles of component 2 may be expressed in terms of the partial molar enthalpies in the liquid (λ) and solid (σ) phases,

$$\Delta H^{\mathrm{f}} = n_1(\overline{H}_1^\lambda - \overline{H}_1^\sigma) + n_2(\overline{H}_2^\lambda - \overline{H}_2^\sigma) \tag{39}$$

with $n_1 = 1$. The corresponding Gibbs free energy change is

$$\Delta G^{\mathrm{f}} = n_1(\mu_1^\lambda - \mu_1^\sigma) + n_2(\mu_2^\lambda - \mu_2^\sigma) \tag{40}$$

where phase equilibrium for the major component demands, $\mu_1^\lambda = \mu_1^\sigma$, but since one does not necessarily have equilibrium with respect to compound 2 in the fusion experiment, we do not assume $\mu_2^\lambda = \mu_2^\sigma$. York and Grant (1985) define the quantity, $\Delta S^{\mathrm{f}} = \Delta H^{\mathrm{f}}/T$. If one assumes phase equilibrium for component 2, ΔS^{f} is the entropy of fusion. Here, we assume phase equilibrium only with respect to component 1 and assume the enthalpy–entropy compensation principle for transfer of component 2 from the solid to the melt. By a treatment analogous to that used in developing Eqn. 20, we write

$$\Delta S^{\mathrm{f}} = n_1(\overline{S}_1^\lambda - \overline{S}_1^\sigma) + n_2(1 + \phi_{\mathrm{f}})(\overline{S}_2^\lambda - \overline{S}_2^\sigma) \tag{41}$$

where ϕ_{f} measures the deviation from perfect compensation in transfer of component 2 from the solid to the melt.

We now consider expression of the partial molar entropies in the liquid state in terms of mole fraction and excess entropy. We choose the pure liquid as the standard state for both components. For the usual regular solution model, which assumes random mixing, the excess entropy, S^{E}, is zero (Fowler and Guggenheim, 1939). Lifting the restriction of random mixing gives a more complex free energy expression (Fowler and Guggenheim, 1939) from which the excess entropy can be calculated. Our calculations indicate that the excess entropy is proportional to x_2^2 at small x_2, and while it is no longer identically zero, calculated values using realistic values of the interaction energy parameter are still very small in the range of x_2 of interest to this research. Consequently, we assume the excess entropy of the melt may be taken as zero. The partial molar entropy of the i^{th} component in the liquid phase may then be written

$$\bar{S}_{\mathrm{i}}^{\lambda} = \bar{S}_{\mathrm{i}}^{\cdot} - \mathrm{R} \ln x_{\mathrm{i}} \tag{42}$$

Combination of Eqns. 22–24, 41 and 42 then gives, with $n_1 = 1$

$$\Delta S^{\mathrm{f}} = \Delta S_0^{\mathrm{f}} - \left[S^{\mathrm{E}} + \phi_{\mathrm{f}} n_2 \bar{S}_2^{\mathrm{E}} \right] \tag{43}$$

where $\Delta S_0^{\mathrm{f}} = (\bar{S}_1^{\cdot} - \bar{S}_1^{*})$ is the entropy of fusion of pure crystalline 1.

With the assumed relationship between the excess entropy terms and the ideal entropy of mixing given by Eqn. 28, the d.i., as determined from heat of fusion data is, d.i. $= b_{\mathrm{E}}$. Note that the disruption index, as determined from solution thermodynamics data, given by the term in square brackets, [ ], in Eqn. 30 is not simply b_{E}. However, assuming for the moment that the values of b_{E} are the same for both methods of determining d.i., the difference between the solution derived d.i. and the fusion derived d.i. is of the order of unity. Thus, the difference between the definitions of d.i. is of no practical consequence as long as the d.i. is significantly greater than unity. However, the values of b_{E} cannot be expected to be identical. First, the definitions are not identical unless ϕ and ϕ_{f} are identical. This difference should not result in sizable differences in the b_{E} values as long as we are correct in assuming both ϕ and ϕ_{f} are small. More important, b_{E}, being an entropy-related property, is likely to be temperature dependent. Not only is the entropy of an equilibrium state temperature dependent through the ratio of the heat capacity to the absolute temperature, but a significant component of the excess entropy in the solid could be a result of non-equilibrium states of high energy and high entropy which may convert to states of lower free energy, enthalpy, and entropy as higher temperatures speed the rate of conversion. This type of equilibration, or annealing, of metastable states during a heat of fusion experiment was postulated by Grant and York (1986a) to rationalize the much lower d.i. values determined from heat of fusion data as compared to the corresponding d.i. obtained from solution thermodynamics data.

Excess Entropy and Disruption: a Simple Model

The relationship between excess entropy and disruption may be illustrated by the following simplified model. For the present, we restrict our discussion to very low levels of guest (component 2). Assume that the presence of a guest molecule disrupts the structure of z host molecules such that the z host molecules are changed from the crystalline state to a more disordered state. To be specific for the purposes of this discussion, we will suppose that this disordered state is the amorphous state. The amorphous state would be the liquid state if the temperature were the melting temperature or a supercooled liquid, perhaps a glass, if the temperature were below the melting point. Thus, the introduction of n_2 moles of guest molecules would result in a crystalline to amorphous transition of $n_2 z$ moles of host molecules plus a change in environment for the guest molecules from the pure liquid state to a solution state where the guest is surrounded by host molecules. Assuming this solution state behaves as a regular solution, the excess entropy due to the change in environment is zero. Thus, the excess entropy is the increase in entropy due to the disruption of structure of the $n_2 z$ host molecules

$$S^{\mathrm{E}} = z n_2 \left(\bar{S}_1^{\cdot} - \bar{S}_1^{*} \right) \tag{44}$$

where $\bar{S}_1^{\cdot}$ and $\bar{S}_1^{*}$ are the molar entropies of pure 1 in the amorphous and crystalline states, respectively, at the temperature of interest. Thus, the excess entropy is directly proportional to the mole fraction of guest, and the partial molar excess entropies become $\bar{S}_1^{\mathrm{E}} = 0$, and $\bar{S}_2^{\mathrm{E}} = \mathrm{z}(\bar{S}_1^{\cdot} - \bar{S}_1^{*})$.

The entropy change, $(\bar{S}_1^{\cdot} - \bar{S}_1^{*})$, is related to the entropy of fusion of crystalline 1 by the relationship

$$\bar{S}_1^{\cdot} - \bar{S}_1^{*} = \Delta S^{\mathrm{f}} - \int_T^{T_{\mathrm{m}}} \left[\Delta C_{\mathrm{p}} / T \right] \mathrm{d}T \tag{45}$$

where ΔC_p is the molar heat capacity difference between liquid and crystalline solid, $\bar{C}_p^{\cdot} - \bar{C}_p^{*}$.

Note that in this model, the excess entropy is proportional to n_2 (or x_2 since x_2 is small). However, as x_2 increases and overlap of disruption zones begins to occur, one would expect $\bar{S}_2^E$ (and therefore S^E) to decrease. $\bar{S}_1^E$ will also then assume positive values as determined by the Gibbs–Duhem equation, $n_1 d\bar{S}_1^E + n_2 d\bar{S}_2^E = 0$. The net result is that both S^E and $n_2\bar{S}_2^E$ may be expressed as power series in x_2, with the leading term being $(\bar{S}_2^E)_0 x_2 = z(\bar{S}_1^{\cdot} - \bar{S}_1^{*})x_2$, and the second order term being negative. Thus, in this model, the expressions for ΔS^f and $\Delta S^{s\theta}$ are

$$\Delta S^f = \Delta S_0^f - (\bar{S}_2^E)_0 x_2 + \mathrm{K} x_2^2 \tag{46}$$

$$\Delta S^{s\theta} = \Delta S_0^{s\theta} - \Delta S_{\mathrm{ideal}}^{m} - \left[(\bar{S}_2^{\alpha,0} - \bar{S}_2^{\cdot}) + (\bar{S}_2^E)_0 \right] x_2 + K x_2^2 \tag{47}$$

where K is a positive constant. In those systems for which $\Delta S^{s\theta}$ data are available, neither $\Delta S_{\mathrm{ideal}}^{m}$ nor $(\bar{S}_2^{\alpha,0} - \bar{S}_2^{\cdot})x_2$ contributes significantly to $\Delta S^{s\theta}$ (Grant and York, 1986a). Thus, the limiting slopes of plots of either ΔS^f or $\Delta S^{s\theta}$ vs x_2, denoted $(\partial \Delta S/\partial x_2)_0$, give directly the value of $(\bar{S}_2^E)_0$ at the respective temperature.

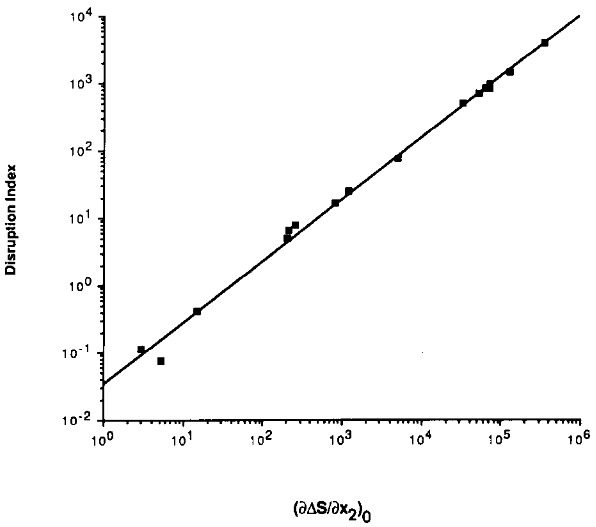

Fig. 1. Correlation between experimental values of the d.i. (logarithmic scale) and the calculated limiting partial molar excess entropy of the guest, $(\partial \Delta S/\partial \Delta x_2)_0$ (logarithmic scale). The data were provided by York and Grant (1985) and Grant and York (1986a).

With the treatment described above, disruption is described in terms of the limiting partial molar excess entropy of component 2, $(\bar{S}_2^E)_0$. Specification of this quantity as, $(\bar{S}_2^E)_0 = z(\bar{S}_1^{\cdot} - \bar{S}_1^{*})$, is useful but is not essential to the basic features of the analysis. It should be emphasized that, according to this analysis, plots of ΔS^f or $\Delta S^{s\theta}$ are linear in x_2 for very small x_2, but *not linear* in $\Delta S_{\mathrm{ideal}}^{m}$ as the disruption index approach assumes. $\Delta S_{\mathrm{ideal}}^{m}$ is clearly not linear in x_2, nor is $\Delta S_{\mathrm{ideal}}^{m}$ proportional to a power series in x_2. From an empirical point of view, the data (York and Grant, 1985; Grant and York, 1986a) are fit equally well by a quadratic in x_2 or a linear expression in $\Delta S_{\mathrm{ideal}}^{m}$. Since the quadratic fit demands an additional adjustable parameter, there is somewhat more statistical uncertainty associated with $(\bar{S}_2^E)_0$ than with the disruption index for the same data set. Using the available data (references above) numerical values of $(\bar{S}_2^E)_0$ were calculated by $(\bar{S}_2^E)_0 = (\partial \Delta S/\partial x_2)_0$, and compared with the reported d.i. data. This comparison (Fig. 1) demonstrates an excellent correlation between the two measures of disruption, although as expected, $(\bar{S}_2^E)_0$ and d.i. are not exactly proportional. Rather, we find

$$\text{d.i.} = 0.035\left[(\bar{S}_2^E)_0 \right]^{p}, \quad p = 0.912 \tag{48}$$

with a correlation coefficient of 0.9974. Thus, the ratio of $(\bar{S}_2^E)_0$ to d.i. varies from about 28 J K^{-1} mol^{-1} at d.i. ≈ 0.1 to about 10 J K^{-1} mol^{-1} at d.i. ≈ 3000. This ratio has an order of magnitude similar to that of the gas constant, R. Variation in this ratio is a reflection of variation in the ratio of $\Delta S_{\mathrm{ideal}}^{m}$ to x_2 over the range of x_2 used to evaluate the d.i. and $(\bar{S}_2^E)_0$. Both ratios vary by about a factor of 3 over the data sets examined. When the d.i. is small, larger levels of guest are used to evaluate the thermodynamic changes, and thus, the mean value of the $\Delta S_{\mathrm{ideal}}^{m}$ to x^2 ratio is smaller than for a guest/host system giving large values of d.i.

We note that d.i. is dimensionless, unlike $(\bar{S}_2^E)_0$, which has the same dimension as the gas constant, R. Therefore, $(\bar{S}_2^E)_0$ may be converted to a dimensionless index, which may term the "excess entropy index" (e.e.i.), by dividing by R, thus, e.e.i. = $(\bar{S}_2^E)_0/R$.

The natural question at this point is: which method of analysis, d.i. or $(\bar{S}_2^E)_0$, is best? From the point of view of numerical analysis, the d.i. approach is superior since only two adjustable parameters are required to fit the data. One can argue that the proportionality between excess entropy and ideal entropy of mixing has considerable experimental support, and may, therefore, have a theoretical foundation. However, the physical origin of the proportionality constant, b_E, remains obscure. From a physical perspective, the $(\bar{S}_2^E)_0$ approach has an advantage since the mathematical form for the x_2 dependence of ΔS^f (or $\Delta S^{s\theta}$) is rationalized in terms of a simple physical model and the parameter of interest, $(\bar{S}_2^E)_0$, may be given a more specific interpretation. Thus, it is not obvious which approach is best. It must be emphasized that, while d.i. and $(\bar{S}_2^E)_0$ are not exactly proportional, the two measures of disruption are highly correlated (Eqn. 48), and over modest ranges of d.i., approximate proportionality is maintained. Consequently, in a practical sense, the two approaches are equivalent, and the question of which method of analysis is best is not critical. Either method may be used to compare quantitatively the effect of guest species on the entropy of host crystals.

Conclusions

The rigorous thermodynamic treatment developed in this report does not alter the main conclusions derived from the intuitive treatment presented in previous papers (York and Grant, 1985; Grant and York, 1986a). However, the analysis given in this report better defines the approximations inherent in the evaluation of the d.i. and shows that the d.i. is related to the excess entropy of the solid. Definition of the d.i. involves the assumption that the excess entropy of the solid is directly proportional to the ideal entropy of mixing. An alternate approach based upon a direct proportion between excess entropy and mole fraction of guest at very low levels of guest is, from a practical point of view, equivalent to the d.i. approach. Provided the d.i. is significantly greater than unity, the definitions of d.i. from solution thermodynamics data and from heat of fusion data are equivalent, and experimentally observed differences in d.i. derived from the two types of data reflect temperature dependence of the excess entropy.

Acknowledgement

D.J.W.G. acknowledges support from the Medical Research Council of Canada (Operating Grant MT-7835).

References

Boldyrev, V.V., Bulens, M. and Delmon, B., *The Control of the Reactivity of Solids, Studies in Surface Science and Catalysis, Vol. 2,* Elsevier, Amsterdam, 1979.

Chow, K.Y., Go, J., Mehdizadeh, M. and Grant, D.J.W., Modification of adipic acid crystals: influence of growth in the presence of fatty acid additives on crystal properties. *Int. J. Pharm.,* 20 (1984) 3–24.

Fowler, R.H. and Guggenheim, E.A., *Statistical Thermodynamics,* Cambridge University Press, London, 1939, pp. 319–376.

Grant, D.J.W. and York, P., A disruption index for quantifying the solid state disorder induced by additives or impurities. II. Evaluation from heat of solution. *Int. J. Pharm.*, 28 (1986a) 103–112.

Grant, D.J.W. and York, P., Entropy of processing: a new quantity for comparing the solid state disorder of pharmaceutical materials. *Int. J. Pharm.*, 30 (1986b) 161–180.

Guggenheim, E.A., *Thermodynamics*, North Holland, Amsterdam, 1967, pp. 170–219.

Kaufman, L. and Nesor, H., Relation of the thermochemistry and phase diagrams of condensed systems. In N.B. Hannay (Ed.), *Treatise on Solid State Chemistry, Vol. 5, Changes of State*, Plenum, New York, 1975, pp. 179–232.

Mullin, J.W., *Crystallization*, Butterworth, London, 1972, pp. 156, 157.

Singleton, W.S., Solution properties. In K.S. Markley (Ed.), *Fatty Acids — Part I*, 2nd edn., Interscience, New York, NY, 1960, pp. 609–678.

Vachon, M.G. and Grant, D.J.W., Enthalpy–entropy compensation in pharmaceutical solids. *Int. J. Pharm.,* in press.

Weast, R.C. and Astle, M.J., *CRC Handbook of Chemistry and Physics*, 63rd edn., CRC, Boca Raton, FL, 1982, p. F-11.

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