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The use of thermal analysis in the assessment of crystal disruption

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Abstract

The highly ordered crystal lattice of small organic molecules, such as drugs, contains defects resulting from the crystallization process. Pharmaceutical processing and impurities introduce further defects which cause partial disruption of the crystalline order decreasing the crystallinity and increasing the crystal energy, enthalpy, entropy and free energy. As a result, the intrinsic dissolution rate increases and other solid state properties, including the compaction (tableting) behavior, are changed, thereby accounting for interbatch variations. Differential scanning calorimetry (DSC) or differential thermal analysis (DTA) are used to measure the enthalpy of fusion at the melting point and hence the entropy of fusion. The negative slope of the plot of the entropy of fusion against the ideal entropy of mixing of a guest impurity in solid solution in the host solid affords the disruption index (d.i.) resulting from the presence of the guest. The significance and magnitude of d.i. are discussed. The change in the entropy of fusion resulting from the processing of the solid is used to calculate the entropy of processing, ΔS^p, which is related to changes in various pharmaceutical properties. The uses of d.i. and ΔS^p are illustrated using a variety of pharmaceutical examples.

Keywords: Bioavailability; Crystal defect; Disruption index; DSC; DTA; Entropy of processing

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1. Pharmaceutical implications of crystal disruption

The crystal lattice is generally regarded as a highly ordered structure which repeats itself in three dimensions. However, even the most carefully prepared and grown crystals, such as those of many drug substances, inevitably contain defects, i.e. imperfections, and residual impurities [1]. Crystal lattice imperfections, e.g. point defects, dislocations (Fig. 1) and inclusions, develop during crystallization [3] and have been extensively discussed by Wright [1]. The nature and concentration of crystal defects are altered as a result of the stresses prevailing during many pharmaceutical processing operations, such as drying, milling, sorption and compression. The imperfections may develop, wander, change their nature and/or disappear in the crystal lattice during processing [2,4]. Crystal imperfections have been shown to influence the reactivity [5,6], dissolution rate [7] and possibly the bioavailability of drug substances. Digoxin represents a classical example for which certain crystal properties, especially crystallline disorder, were found to significantly alter the dissolution rate and bioavailability of the drug substance [8–10].

Virtually all crystalline drug substances contain impurities which are incorporated into the crystal lattice during crystallization, or which are taken up by the crystal from the vapor phase, e.g. water. The impurity, a guest molecule, by virtue of its different shape and electronic structure, interacts with the neighboring host molecules in a way which is different from the interaction between a host molecule and the surrounding host molecules. Thus, the host molecules surrounding the impurity molecule possess energies and occupy positions which are different from those of the host molecules surrounding a host molecule in a normal host lattice to extents which depend on the difference between the shape of electronic structure of the impurity molecule and the host molecule [1]. Thus, the incorporation of the impurity leads to a decrease in the overall symmetry of the crystal [11] which has

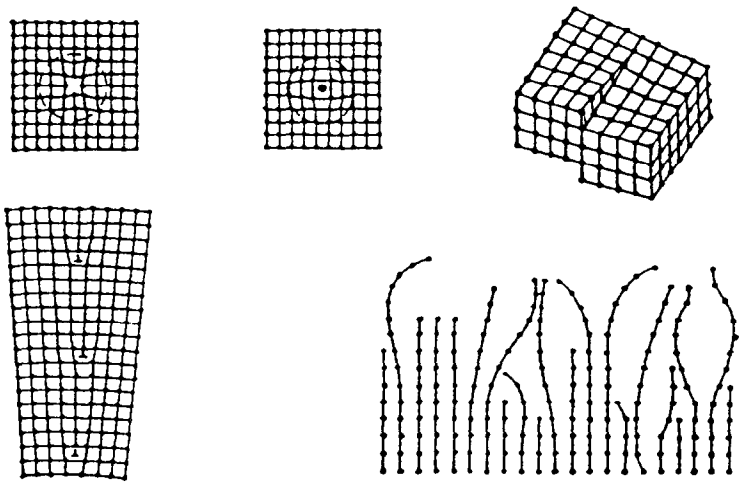


Fig. 1. Crystal line defects of various dimensionalities (reproduced from Ref. [2], with permission).

been demonstrated in organic solids by Weisinger-Lewin et al. [12] using neutron diffraction.

Even in a crystal of 99.9% purity, one molecule in ten in any given direction is likely to be an impurity molecule [1], perturbing the crystalline order of the lattice and increasing the lattice strain. As a result of the incorporation of an impurity, the increase in enthalpy of the solid itself due to the increased lattice strain may be partially offset by an increase in entropy, corresponding to the accompanying disorder, so that the corresponding increase in Gibbs free energy may not be large. However, because equilibrium properties such as metastable solubility and solid reaction rates are exponential functions of Gibbs free energy, and because crystal disruption can arise relatively easily from the incorporation of impurity molecules and from the development of crystal imperfections, major effects on the physicochemical properties of solids may result.

The effects of crystal disruption on the pharmaceutical properties have been well documented [2,13–23]. Crystal disruption due to various unit operations, such as milling, crystallization, has been found to dramatically alter the pharmaceutically important physicochemical properties such as dissolution rate and compaction behavior (see, for example, Refs. [16,18,19,23,24]). The process-induced changes in the solid state properties often result in the batch-to-batch or lot-to-lot variations in the performance of pharmaceutical solid dosage forms, such as tablets and capsules.

2. Quantitation of solid state disorder in pharmaceutical solids

Many drugs and excipients exist as powders, whose particles are often micronized with poorly developed crystal faces. Therefore, many "state-of-the-art" techniques for the characterization and quantification of crystal defects, such as X-ray topography, electron microscopy and positron annhilation, are of limited use in routine quantitation of crystal disruption induced by pharmaceutical processing operations. As a result arbitrary crystallinity scales have been developed by pharmaceutical scientists to provide an approximate measure of the concentration and influence of the crystal imperfections [2,19]. The most crystalline solid phase obtainable is arbitrarily assigned a crystallinity of 100%, while the least crystalline (amorphous) solid phase, which contains the highest degree of crystal disruption, is assigned a crystallinity of zero. By means of a suitable physicochemical measurement on each of these reference materials and on the sample under investigation, the percentage degree of crystallinity of the sample may be estimated.

A variety of physicochemical techniques, including IR spectroscopy, X-ray diffraction, true density, NMR spectroscopy, solution calorimetry, differential scanning calorimetry (DSC), and differential thermal analysis (DTA) are each reported to be useful in determining the percentage crystallinity of various pharmaceuticals [2,9,15,19,25,26]. Unfortunately, different techniques often provide different values for the degree of crystallinity of a given sample [15,25] because they utilize different principles to characterize the solid state disorder.

3. Quantitative evaluation of crystal disruption using thermal analysis

Chemists and molecular crystallographers have used thermal analysis to characterize the solid state disoder in a molecular crystal by measuring heat capacity as a function of temperature (see, for example, Refs. [27,28]). Uvarov and Hairetdinov [29] utilized thermal analysis to estimate the concentration of point defects in solids, including a limited number of molecular crystals. Although thermal analysis was used to study the structural disorder in molecular crystals (see Ref. [1] for more details), no specific reference was made by Uvarov and Hairetdinov [29] to the quantitation of the disorder introduced by the incorporation of an impurity as a solid solution in a crystalline host.

In the pharmaceutical field, thermal analysis has been used to detect small changes in the enthalpy of fusion ΔH^f, melting point T_m, and entropy of fusion, ΔS^f ($\Delta H^f/T_m$) of a crystalline host produced by the impurity or guest in solid solution [16–18,23,30,31]. Fig. 2 shows the change in the enthalpy of fusion of a model drug, (RS)-(−)-ephedrinium 2-naphthalenesulfonate, as a function of the mole fraction of the opposite enantiomer, (SR)-(+)-ephedrinium 2-naphthalenesulfonate, in the crystals. With increasing mole fraction of the enantiomeric impurity in the crystals, the ΔH^f decreased to a minimum indicating disruption of the crystal lattice and an increase in the lattice strain. At higher concentration of the impurity in the crystals, ΔH^f increased, suggesting a relaxation of the lattice strain. Similar changes in ΔH^f were also observed when adipic acid was crystallized

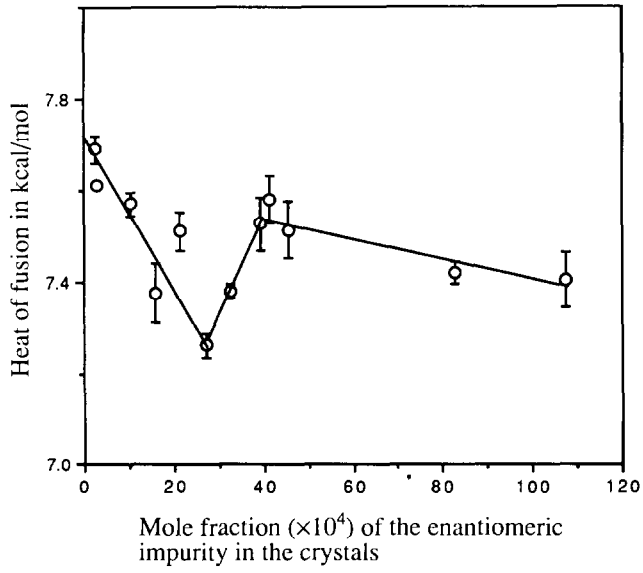


Fig. 2. Plot of the heat of fusion of (−)-ephedrinium 2-naphthalenesulfonate vs. the mole fraction of the enantiomeric impurity in the crystals. The vertical bars represent standard deviations ($n = 3$) (reproduced from Ref. [23], with permission).

in the presence of trace quantities of fatty acid impurities [16,39], suggesting a common underlying mechanism of lattice disruption in the organic solid state. It was hypothesized that, at higher concentrations of the impurity, crystal defects may interact with each other during heating in a DSC resulting in an overall increase in ΔH^f [23]. Duddu et al. [23] observed that the T_m ($\approx$446.4 K) and the mole fraction of water (8×10^{-4}) in the crystals of (RS)-(−)-ephedrinium 2-naphthalene-sulfonate did not change as a function of the concentration of the opposite enantiomer. Because T_m remained constant, the change in ΔS^f ($=\Delta H^f/T_m$) was found to be parallel to the change in ΔH^f [23]. Note that $\Delta H = \Delta H_{liquid} - \Delta H_{solid}$ and $\Delta S^f = S_{liquid} - S_{solid}$.

Entropy provides a measure of the state of disorder in a system. Therefore attempts were made to quantitate crystal disruption by calorimetrically measuring the changes in the entropy of fusion or entropy of solution. Specifically, a dimensionless disruption index (d.i.) and a quantity termed entropy of processing (ΔS^p) were developed, evaluated and reported to be useful in quantifying the crystal disruption [4,32–34]. The remainder of this article highlights the utility of thermal analysis in the assessment of crystal disruption using the concepts of disruption index and entropy of processing.

3.1. Disruption index

This dimensionless index was derived to quantify the disorder induced by a given impurity when present in solid solution in a crystal lattice. As discussed earlier, the incorporation of a trace quantity of additive into the crystal lattice of a host introduces strain into the lattice arising from the crystal imperfections. As a result, during the fusion process, the increase in enthalpy, internal energy and entropy of the impure and strained crystal (termed a doped crystal) will each be less than that of the pure crystal.

Mixing of the additive or impurity with the host to form a solid solution of a liquid solution will increase the entropy of the solid or liquid states. When the mole fraction of the guest is small ($x_2 < 0.05$), York and Grant [32] assumed that the changes in the entropies are proportional to the ideal entropies of mixing. Thus

$$\delta(S_{solid}) = b\delta(\Delta S^m_{ideal}) \quad (1)$$

$$\delta(S_{liquid}) = c\delta(\Delta S^m_{ideal}) \quad (2)$$

and subtracting Eq. (2) from Eq. (1) gives

$$\delta(S_{solid}) - \delta(S_{liquid}) = (b - c)\delta(\Delta S^m_{ideal}) \quad (3)$$

where b and c are constants which represent the sensitivity of the disordering of the host solid and liquid, respectively, to simple mixing with the guest for which the entropy of mixing is represented by $\Delta S^m_{ideal} = -R \Sigma x_j \ln x_j$, where x is the mole fraction of the jth component in the mixture. The quantity $(b - c)$ represents 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 and is termed the disruption index.

By definition, entropy of fusion $\Delta S^f = S_{liquid} - S_{solid} = \Delta H^f/T_m$, and because $\delta(\Delta S^f) = \delta(S_{solid}) - \delta(S_{liquid})$, it follows from Eq. (3) that

$$\delta(\Delta S^f) = -(b - c)\delta(\Delta S^m_{ideal}) \quad (4)$$

Integration of Eq. (4) yields

$$\Delta S^f = \Delta S^f_0 - (b - c)\Delta S^m_{ideal} \quad (5)$$

The disruption index (d.i. $= b - c$) compares the disorder created in the crystalline host with that created in the liquid host by simple mixing with the guest molecules. Mixtures of liquid organic compounds often give entropies of mixing which are close to ideal, as in the case of regular solutions [35,36]. Thus, to a first approximation, $c \approx 1$ in Eq. (2). Furthermore, with very rare exceptions for which the molecules of the guest and the host have very similar charge, shape and size, the value of b is always greater than that of c, resulting in a positive value for d.i. $= b - c$ (for a detailed discussion see Ref. [32]). A positive value for d.i. suggests that the guest molecule creates more disorder in the host crystal lattice than in the liquid host.

The availability of versatile differential scanning calorimeters and sensitive analytical methods permits accurate measurements of the entropy of fusion of the crystalline host and the mole fraction of the guest in the host, respectively. In practice, the entropy of fusion of each sample of the pure and the doped crystals is accurately determined from the enthalpy of fusion and the melting point. Doped crystals, washed free from the adsorbed impurity, are analyzed using a suitable analytical method, such as high performance liquid chromatography (HPLC), to determine the mole fraction of the incorporated impurity or additive (the guest). Water as an impurity may be determined by Karl–Fischer titrimetry, gas chromatography or thermal gravimetric analysis (TGA), if sufficiently sensitive. According to Eq. (5), and as shown in Fig. 3, the slope of a plot of the entropy of fusion of the host versus the ideal entropy of mixing of the guest with the host, calculated from the measured mole fraction values, yields the negative value of d.i. $(b - c)$, when the mole fraction of the guest is small, typically less than 0.05.

As shown in Tables 1 and 2, a variety of host–guest systems were characterized using the concept of disruption index. For doping of the intermetallic compound $InCd_3$ with either of its components, the d.i. was calculated to be on the order of 0.1, only slightly larger than the value of zero expected for an ideal solid solution consisting of metal atoms cadmium (Cd) and indium (In) of similar size and at neighboring positions in the periodic table. A slightly larger value (0.42) was observed when cadmium was doped with $InCd_3$, a complex molecular species which is significantly larger in size than the host, cadmium.

The d.i. value ranged from 5 to approximately 800 for various organic systems studied (Table 2). For a given host such as adipic acid, increasing the molecular size (especially the chain length) of the guest, such as from octanoic acid to oleic acid, produces an appreciably higher degree of lattice disruption. In the majority of cases, the d.i. values were found to be on the order of 5 to 25, suggesting that the disorder produced by the guest is several orders of magnitude more than that explained by

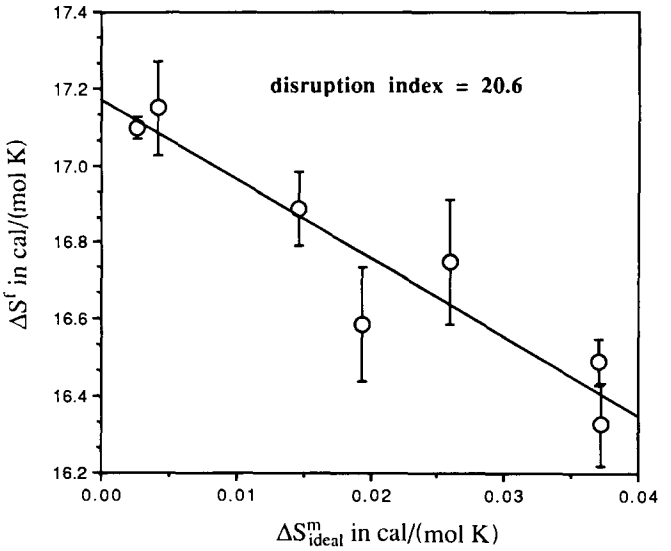


Fig. 3. Plot of the entropy of fusion of (−)-ephedrinium 2-naphthalenesulfonate vs. the ideal entropy of mixing of (−)-ephedrinium 2-naphthalenesulfonate with the enantiomeric impurity ($r = 0.938$); the vertical bars represent standard deviations ($n = 3$) (reproduced from Ref. [23], with permission).

Table 1
The use of thermal analysis in the assessment of crystal disruption induced by an impurity or additive, when present as a solid solution in the crystal lattice of the host (metallic systems) [a]

Host	Guest	Maximum decrease in ΔS^f/%	ΔS^m_{ideal} corresponding to maximum decrease in ΔS^f/ (J mol^{-1} K^{-1})	d.i.
1 $InCd_3$	Cd	5.95	4.53	0.12
2 $InCd_3$	In	2.19	2.78	0.08
3 Cd	$InCd_3$	18.38	4.53	0.42

Reproduced from Ref. [32], with permission.
[a] Original data from Ref. [37].

simple random mixing of the host with the guest. Significantly, enantiomeric and other stereoisomeric guests produce a high degree of disruption of the crystal lattice of the host (d.i. of the order of 20), which indicates that differences in the spatial orientation of the atoms or groups are powerful disruptors of organic crystal lattices.

Based on a more rigorous thermodynamic treatment, Pikal and Grant [34] described d.i. in terms of the limiting partial molar excess entropy of the guest, $(\bar{S}_2^E)_0$. Following from this model, the entropy of fusion can be expressed by the following quadratic equation in x_2, the mole fraction of the additive.

$$\Delta S^f = \Delta S_0^f - (\bar{S}_2^E)_0 x_2 + K x_2^2 \quad (6)$$

Table 2
The use of thermal analysis in the assessment of crystal disruption induced by an impurity or additive, when present as a solid solution in the crystal lattice of the host (organic systems)

Host	Guest(s)	Maximum decrease in ΔS^f/%	ΔS^m_{ideal} corresponding to maximum decrease in ΔS^f/ (J mol^{-1} K^{-1})	d.i.
1 Griseofulvin (from Ref. [17])	Lecithin	19.02	4.69	5.1
2 Acetaminophen (from Ref. [18])	Water/ *p*-acetoxyacetanilide	4.27	1.09	6.5
3 Phenacetin (from Ref. [30])	Benzamide	16.87	2.74	7.9
4 pp-DDT (from Ref. [31])	op-DDT [a]	6.29	0.33	15.1
5 pp-DDT (from Ref. [31])	op-DDT [b]	6.29	0.30	16.9
6 Phenytoin (from Ref. [38])	3-Propanoyloxymethyl-5,5-diphenylhydantoin	7.85	0.29	18.8
7 (RS)-(−)-Ephedrinium 2-naphthalenesulfonate (from Ref. [23])	(SR)-(+)-Ephedrinium-2-naphthalenesulfonate	5.20	0.04	20.6
8 (SS)-(+)-Pseudoephedrinium salicylate (from Ref. [39])	(RR)-(−)-Pseudo-ephedrinium salicylate	4.30	0.04	24.7
9 Adipic acid [c]	Hexanoic acid	9.12	0.27	24.7
10 Phenytoin (from Ref. [21])	3-Acetoxymethyl-5,5-diphenylhydantoin	11.05	0.25	26.6
11 Adipic acid [c]	Octanoic acid	4.48	0.05	75.2
12 Adipic acid [c]	Undecanoic acid	17.75	0.02	834.0
13 Adipic acid [c]	Oleic acid	6.30	0.006	841.0

[a] op-DDT is treated as a racemic mixture. [b] op-DDT is treated as a single enantiomer. [c] Reproduced from Ref. [32]; original data from Refs. [16] and [40].

At low mole fractions (i.e. when x_2 is small) ΔS^f is a linear function of x_2. Then, a comparison of Eqs. (5) and (6) shows a direct proportionality between excess entropy and the ideal entropy of mixing. Thus, this more exact approach, although it does not alter the thermodynamic treatment underlying the concept of disruption index, highlighted the underlying assumptions, the most important being the direct proportionality between the excess entropy of the solid and the ideal entropy of mixing. Pikal and Grant [34] also demonstrated excellent correlation between the disruption index, calculated using Eq. (5), and the partial molar excess entropy of the guest, $(\bar{S}_2^E)_0$ (Fig. 4). This relationship suggests that both approaches are equivalent, d.i. being preferred from a practical viewpoint, and partial molar entropy from a theoretical perspective.

A common criticism of the use of thermal analysis (DSC or DTA) to evaluate crystal disruption is the effect of heating the sample on the nature and density of

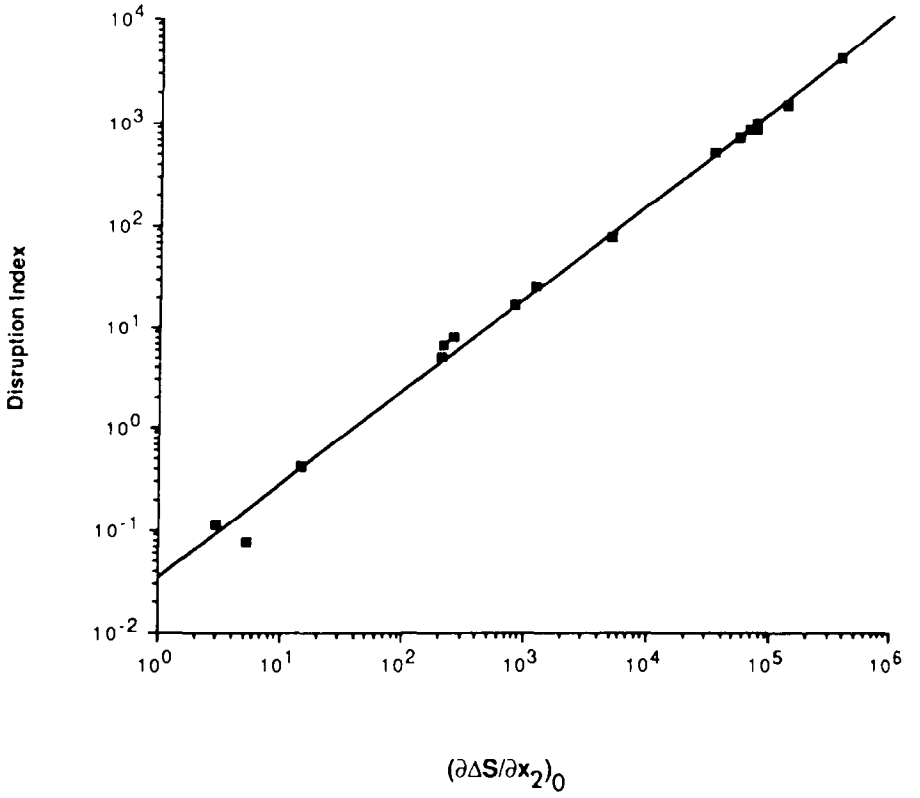


Fig. 4. Correlation between experimental values of d.i. (logarithmic scale) and the calculated limiting partial molar excess entropy of the guest $(\partial\Delta S/\partial\Delta x_2)_0$ (logarithmic scale) (reproduced from Ref. [34], with permission).

crystal imperfections induced by the impurity. It is likely that the heating mode of DSC or DTA eliminates an appreciable proportion of crystal imperfections by processes similar to annealing [33]. As an alternative approach, Grant and York [33] extended the value of d.i. by measuring the entropy of solution at a constant temperature, rather than entropy of fusion as shown in Eq. (5). This approach requires measurement of solubility (or intrinsic dissolution rate) to evaluate the free energy of solution and solution calorimetry to evaluate the enthalpy of solution. The entropy of solution is then calculated at constant temperature from $\Delta S = (\Delta H - \Delta G)/T$. For further details, the reader is encouraged to consult Ref. [33]. When d.i. is significantly greater than unity, the variation in d.i. obtained from solution thermodynamic data and the fusion data reflects the temperature dependence of excess entropy [34].

3.2. *Entropy of processing*

While the concept of disruption index (d.i.) was developed to quantify the solid state disorder induced by an impurity, the concept of entropy of processing (ΔS^p)

was developed to compare the solid state disorder arising from any processing stresses applied to pharmaceutical solids [4]. Examples of these stresses include milling, drying, crystallization, and also incorporation or loss of additives or impurities. The entropy of processing ΔS^p is defined as the difference between the entropy of a given sample and that of a same quantity of a reference sample. Thus ΔS^p may be evaluated not only for processed solids, but also for amorphous forms, polymorphs, solvates and impure solids. Thus, ΔS^p is a versatile quantity for quantitating the disorder of any pharmaceutical solid with respect to a defined reference material of the same major component. As in the case of disruption index, ΔS^p can be evaluated either from the entropy of fusion data, using thermal analysis, or from the solution thermodynamic data using solution calorimetry and solubility studies. The discussion in this paper will be restricted to the evaluation of ΔS^p using thermal analysis. Details concerning the evaluation of ΔS^p using solution thermodynamics have been provided by Grant and York [4].

The generalized thermodynamic cycle which describes the evaluation of ΔS^p for a solid sample under investigation is shown in Fig. 5. The entropy of processing ΔS^p is given by

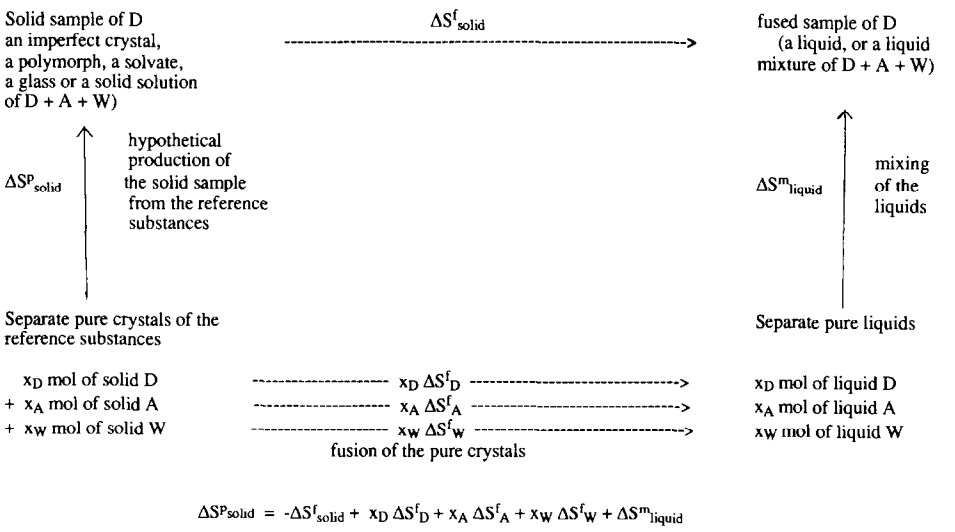
$$\Delta S^p = -\Delta S^f_{solid} + x_D \Delta S^f_D + x_A \Delta S^f_A + x_W \Delta S^f_W + \Delta S^m_{liquid} \quad (7)$$

Fig. 5 represents a general case in which the solid sample under investigation consists of the major component D, which may be a solid drug or excipient (any inert material used in compounding the drug) doped or contaminated with two other substances, A (an additive) and W (water). The solid sample may contain lattice defects and may even be inhomogeneous. ΔS^f_D is the entropy of fusion of an arbitrarily chosen reference sample with which the sample under investigation is being compared. Eq. (7) is general and can be applied to a variety of situations, as mentioned earlier. For example, when applied to a two component system, such as a crystalline material containing an additive A, but without water, then $x_W = 0$. Thus, Eq. (7) reduces to

$$\Delta S^p = -\Delta S^f_{solid} + x_D \Delta S^f_D + x_A \Delta S^f_A + \Delta S^m_{liquid} \quad (8)$$

In Eq. (7), the entropies of fusion of various components D, A and W can be accurately determined using a differential scanning calorimeter. The mole fractions of D, A and W can also be accurately determined by various analytical techniques. However, the value of ΔS^m_{liquid} is difficult to measure experimentally. Therefore, as discussed in connection with the d.i. (under Eq. (5)), it is satisfactory to assume that $\Delta S^m_{liquid} = \Delta S^m_{ideal}$ because many organic liquids mix to produce regular solutions and exhibit entropies of mixing which are approximately equal to the ideal entropy of mixing [36].

Table 3 presents three examples of the data abstracted from the literature and analyzed according to Eq. (8). Table 3 shows that ΔS^p is much greater than ΔS^m_{liquid}. Furthermore, $(x_D \Delta S^f_D + x_A \Delta S^f_A)$ is appreciably larger than ΔS^f_{solid}, and this difference is the major contributor to ΔS^p. This difference represents the total disruption produced by the guest within the crystal lattice of the host and is evidently much larger than the ideal entropy of mixing. The crystal lattice disruption presumably



$$\Delta S^{p}_{solid} = -\Delta S^{f}_{solid} + x_D \Delta S^{f}_{D} + x_A \Delta S^{f}_{A} + x_W \Delta S^{f}_{W} + \Delta S^{m}_{liquid}$$

Fig. 5. Generalized thermodynamic cycle showing the relationships between the hypothetical stages via the liquid phases and the associated entropy changes involved in the production of one mole of a given solid sample of a drug D, or excipient from its individual pure components D, A and W, which may be pure reference substances. A is an additive, impurity, ligand or complexing agent and W is another component, such as water or a solvent of crystallization. A and/or W may be absent or present in stoichiometric or non-stoichiometric proportions. An analogous cycle and equation may be applied to the other extensive thermodynamic state functions, such as internal energy U, enthalpy H, Gibbs free energy G, and volume V. Reproduced from Ref. [4], with permission.

arises from increased density of crystal defects and subsequent distortion of the crystal lattice.

When the crystal lattice of a material is disrupted simply by processing without the incorporation of any additive, then both x_D and x_W are equal to zero and ΔS^p reduces to the difference between the entropies of fusion of the reference and the sample under investigation. Similarly, the difference between the entropy of fusion of the stable and the unstable polymorphs provides the ΔS^p value for the unstable polymorph with respect to the thermodynamically stable polymorph.

Table 4 presents the applicability and evaluation of ΔS^p for polymorphs and processed solid forms of chloramphenicol [4,41]. The ΔS^p values for various samples were calculated from the data of Yamamoto et al. [41]. For this purpose the stable, pure and unprocessed polymorph A was selected as the reference state D. The ΔS^p value is greater for the less stable, and hence more energetic, polymorph B. While simple blending with microcrystalline cellulose and trituration with a mortar and pestle increases ΔS^p by small amounts, grinding in a vibration mill significantly increases the ΔS^p values of both polymorphs. For all treatments the resulting changes in ΔS^p are smaller for the less stable polymorph B. As mentioned by Grant and York [4] the temperatures of measurement of the heats of fusion are sufficiently close to validate comparison of the ΔS^p values. Although some measurements were carried out on mixtures of the drug and microcrystalline cellulose,

Table 3
Typical examples illustrating the calculation and the applicability of the entropy of processing for describing the crystal disruption produced by an additive, or guest, present as a solid solution in a host

Mole fractions		Entropy terms/(J mol^{-1} K^{-1})				
x_D	x_A	$-\Delta S^f_{solid}$	$x_D \Delta S^f_D$	$x_D \Delta S^f_A$	ΔS^m_{liquid}	ΔS^p_{solid}
Host, D = phenacetin; Guest, A = benzamide (data from Ref. [30])						
1.000	0	−80.85	80.85	0	0	0
0.9853	0.0147	−75.42	79.66	0.72	0.64	5.60
0.9728	0.0272	−72.67	78.65	1.33	1.04	8.35
0.9478	0.0522	−71.98	76.63	2.55	1.70	8.90
0.8978	0.1022	−67.99	72.59	4.98	2.74	12.32
Host, D = griseofulvin; Guest, A = lecithin (data from Ref. [17])						
1.000	0	−84.69	84.69	0	0	0
0.975	0.025	−78.97	82.57	3.56	0.97	8.13
0.948	0.052	−75.97	80.29	7.40	1.70	13.42 [a]
0.887	0.113	−69.54	75.12	16.07	2.94	24.59 [a]
0.749	0.251	−68.58	63.43	35.70	4.69	35.24 [a]
Host, D = (RS)-(−)-ephedrinium 2-naphthalenesulfonate; Guest, A = (SR)-(+)-ephedrinium 2-naphthalenesulfonate (data from Ref. [23])						
1.000	0	−71.90	71.90	0	0	0
0.9997	2.6×10^{-4}	−71.69	71.88	0.02	0.02	0.23
0.9997	3.0×10^{-4}	−71.43	71.87	0.02	0.02	0.48
0.9989	11.0×10^{-4}	−70.60	71.82	0.08	0.07	1.37
0.9984	16.0×10^{-4}	−69.30	71.78	0.12	0.10	2.70
0.9979	21.0×10^{-4}	−70.01	71.74	0.15	0.13	2.01
0.9972	28.0×10^{-4}	−68.25	71.69	0.20	0.16	3.80
0.9968	32.0×10^{-4}	−68.92	71.66	0.23	0.18	3.15

Part of the table is reproduced from Ref. [4], with permission.
[a] Two solid phases [17].

Yamamoto et al. [41] reported that microcrystalline cellulose undergoes no phase change in DSC under the conditions of measurement. The ground mixtures of each polymorph exhibited X-ray diffraction patterns characteristic of amorphous solids, suggesting that large changes in ΔS^p values are indicative of extensive lattice disruption and subsequent amorphization of chloramphenicol palmitate polymorphs.

If one assumes that the ΔS^p truly reflects the extent of disruption of the crystal lattice at about 350–365 K and that the rank order of the extent of disruption remains unchanged on lowering the temperature to 310 K (i.e. 37°C) then the data in Table 4 predicts that the dissolution rate and the rate of intestinal absorption would follow the same rank order as ΔS^p. Indeed, Yamamoto et al. [41] found that, for systems investigated in Table 4, the dissolution rate, the initial rate and cumulative extent of urinary excretion after intestinal absorption and the initial rate of enzymatic hydrolysis, all followed the rank order: form B ground mixture > form A ground mixture > form B pure crystal > form A pure crystal, in parallel with the ΔS^p values in Table 4.

Table 4
Calculation and applicability of entropy of processing to the polymorphs and processed solid forms of chloramphenicol palmitate

	Chloramphenicol palamitate, form A					Chloramphenicol palamitate, form B				
	T_m/ K	ΔH^f_{solid}/ (kJ mol^{-1})	ΔS^f_{solid}/ (J mol^{-1} K^{-1})	ΔS^f_D/ (J mol^{-1} K^{-1})	ΔS^p_{solid}/ (J mol^{-1} K^{-1})	T_m/ K	ΔH^f_{solid}/ (kJ mol^{-1})	ΔS^f_{solid}/ (J mol^{-1} K^{-1})	ΔS^f_D/ (J mol^{-1} K^{-1})	ΔS^p_{solid}/ (J mol^{-1} K^{-1})
Pure crystal	364.7	66.11	181.3	181.3	0	360.2	45.61	126.6	181.3	54.7
Pestle ground [a]	361.7	53.97	149.2	181.3	32.0	357.2	42.26	118.3	181.3	63.0
Simple blend [b]	364.7	58.16	159.5	181.3	21.8	358.7	45.61	127.2	181.3	54.1
Ground mix [c]	355.2	19.66	55.4	181.3	125.9	350.7	18.83	53.7	181.3	127.6

Reproduced from Ref. [4] (original data from Ref. [41]) with permission.

[a] Prepared by trituration with a mortar and pestle for 30 min. [b] Prepared by geometric dilution using a spatula. [c] Prepared by grinding the simple blend for 6 h with an alumina vibrational ball mill.

A better correlation of the above rate processes may be expected with a Gibbs free energy term rather than an entropy term ΔS^p. If, however, enthalpy–entropy compensation [42] is occurring in closely-related organic solid phases, e.g. chloramphenicol palmitate, then parallel changes in entropy and enthalpy will necessarily be associated with parallel but smaller changes in Gibbs free energy ΔG. In such an event, measurements of the enthalpy of fusion or enthalpy of solution can also be utilized to quantitate the solid state disorder in pharmaceutical solids [4,15]. The applicability of enthalpy–entropy compensation to pharmaceuticals has been reviewed by Vachon and Grant [42] and by Buckton [43].

4. Conclusions

In summary, thermal analytical techniques, e.g. differential scanning calorimetry and differential thermal analysis, are valuable tools in the assessment of crystal disruption resulting from various processing stresses, such as the uptake of additives or impurities (doping), milling, crystallization and drying. Quantitatively, the disruption of a (host) crystal produced by an additive or impurity (the guest) can be evaluated as the d.i., which is a measure of the rate of change of the difference between the entropy of solid and that of the liquid with respect to the ideal entropy of mixing of the host with the guest. Furthermore, the overall disorder for processed samples, including polymorphs, glasses and impure samples, can be quantitatively evaluated using the entropy of processing ΔS^p, which is defined as the difference between the entropy of the sample and that of a standard reference material. The ultimate goal of these measurements is to offer the pharmaceutical scientist a means of quantitating and understanding the batch-to-batch variability of various physicochemical properties of the drug substances, and subsequently the variability in their dissolution rate and bioavailability.

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