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Entropy of processing: a new quantity for comparing the solid state disorder of pharmaceutical materials

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Summary

During the pharmaceutical processing of a solid (e.g. crystallization, drying, gain or loss of impurities or additives, milling, compression, heating or irradiation), defects and other imperfections develop, wander or disappear in the crystal lattice. Crystal imperfections contribute to the disorder of the crystal lattice, and entropy is here proposed as a practical and fundamental measure of this effect. The difference between the entropy of a given sample and that of the same amount of the reference material is designated the "entropy of processing (or imperfection)", ΔS^P, of the sample. Thermodynamic cycles are described for evaluating ΔS^P of a sample from differential scanning calorimetry or from solution calorimetry with solubility studies. ΔS^P may be evaluated for polymorphs, solvates (e.g. hydrates), amorphous forms, glasses, impure, or variously processed samples of a given substance. ΔS^P calculated from literature data for processed pharmaceutical solids is found to be positive with respect to a highly pure, stable, crystalline reference material and to range from 0 to 200 $J \cdot K^{-1} \cdot mol^{-1}$. Small values of ΔS^P (0–10 $J \cdot K^{-1} \cdot mol^{-1}$) are given by crystals which have been "doped" with additives or impurities in solid solution. Literature data for milled calcium gluceptate suggest that enthalpy-entropy compensation occurs and may be exploitable. ΔS^P of ground samples of chloramphenicol palmitate A or B parallels their dissolution rate and bioavailability. Data for β-lactam antibiotics and calcium gluceptate indicate that ΔS^P increases with decreasing X-ray crystallinity, purity and stability and with increasing processing stress. ΔS^P may decrease during annealing and/or storage and appears to be useful for quantifying, understanding and predicting batch-to-batch differences in pharmaceutical solids.

1. Introduction

The crystal lattice is generally recognized to be a highly ordered structure which repeats itself regularly in three dimensions. However, in actual crystals lattice imperfections abound, such as point defects (e.g. vacancies, impurity defects, interstitial occupancies), line defects (e.g. edge and screw dislocations) and plane defects (e.g. grain boundaries and crystal surfaces). Crystal lattice imperfections develop during crystallization (Mullin, 1972) and their nature and concentration (or density) are altered as a result of the stresses and strains prevailing during pharmaceutical processing operations, such as drying, sorption, milling, compression and/or temperature changes (Hüttenrauch, 1978). Impurities or additives introduce impurity defects, which have been mentioned

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above and which themselves create further crystal imperfections, such as dislocations.

Crystal lattice imperfections have been found to influence chemical reactivity (Boldyrev et al., 1979; Byrn, 1982) and dissolution rate (Burt and Mitchell, 1981) and to exert major effects in pharmaceutical formulation and processing (Hüttenrauch, 1978). Traces of additives or impurities have also been found to influence several fundamental physical properties of adipic acid and acetaminophen (Fairbrother and Grant, 1978, 1979; Chow et al., 1984, 1985a and b). These changes in crystal properties, such as habit, density, energy, entropy, surface properties and dissolution rate, are believed to be mediated by changes, usually increases, in the concentration or density of crystal defects. The nature and concentration of crystal imperfections (and impurities) 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), they frequently give rise to problems in formulation and processing and often cause lack of reproducibility and poor performance in the final product (Jones, 1981; York, 1983).

As a measure of the concentration or density of crystal imperfections, which is often expressed in terms of various empirical crystallinity scales, entropy is preferred by the authors for the following reasons. (a) Entropy, S, provides a direct quantitative measure of the disorder of the system. (b) Entropy differences, ΔS, can be measured with the help of calorimetry e.g. solution calorimetry (SC), differential scanning calorimetry (DSC) and differential thermal analysis (DTA). (c) Entropy is a thermodynamic function of the actual state of the system and is related by rigorous thermodynamic relationships to the other thermodynamic functions of state, e.g. H, G, U, A, T, p, V. (d) The present "state of the art" techniques for measuring quantitatively imperfections in crystals are of limited applicability to drugs, excipients and other organic solids, mainly because of the constraints imposed by the powder form of the materials. (e) Even when normalized to give a crystallinity scale ranging from 0% for the disordered amorphous solid state to 100% for the perfectly ordered crystal, different empirical techniques, such as density, X-ray diffraction, IR spectroscopy, NMR spectroscopy, electron microscopy, DTA, DSC, SC and kinetic studies, yield quite divergent values of crystallinity for a given sample (Hüttenrauch, 1978; Black and Lovering, 1977; Pikal et al., 1978, Suryanarayanan and Mitchell, 1985).

The usefulness of entropy for quantifying the influence of an additive or impurity (the guest substance) in solid solution on the calorimetric properties of a crystalline host substance has been explored in previous reports (York and Grant, 1985; Grant and York, 1985). We have defined, evaluated and appraised a dimensionless entropy increment ratio, named the "disruption index" (d.i.), for quantifying the influence of the guest on the difference in entropy between the more or less crystalline host and the liquid host. In practice d.i. is determined from either of the following ratios:

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

or

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

where ΔS^{f} is the entropy of fusion, ΔS^{s} is the entropy of solution and ΔS^{m}_{ideal} is the ideal entropy of mixing. The latter quantity is calculated from the analytical data for the crystals, as follows:

$$\Delta S^{m}_{ideal} = -R\sum x_j \ln x_j \quad (3)$$

where x_j is the mole fraction of a given component of the solid solution, R is the gas constant and the summation includes all the various components of the crystals. It has been recognized that Eqns. 1 and 2 are limiting laws at mole fractions of 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.

Experimental values of d.i. (York and Grant, 1985; Grant and York, 1985) may be grouped as follows:

(i) d.i. < 0, for Class (i) systems. In this case 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 has not yet been observed, is extremely unlikely, and is contrary to other experience in view of the greater orderliness of crystals than liquids and the known influence of impurity defects on the properties of solids (Reed-Hill, 1973).

(ii) d.i. = 0 for Class (ii) systems. In these cases the solid state is as sensitive as the liquid state to the disordering effect of the guest, or in the other words, the presence of guest molecules creates the same increase in entropy in the host's crystal lattice as in the liquid host. Examples include ideal solutions and regular solutions. Simple metallic systems approximate to this behaviour (York and Grant, 1985).

(iii) d.i. > 1 for Class (iii) systems. In these cases 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. The d.i. values of Class (iii) systems so far examined may be placed in the following subgroups based on their orders of magnitude:
   (a) order of magnitude about 1 for partial dehydration of cephaloridine monohydrate (Pikal et al., 1978, as interpreted by Grant and York, 1985);
   (b) order of magnitude about 10 for several organic molecules as additives in organic crystals, such as acetaminophen, DDT, griseofulvin, and phenacetin (York and Grant, 1985);
   (c) order of magnitude about 10^2 for a polymeric additive, Pluronic F68, in crystals of phenylbutazone (Al-Meshal et al., 1985);
   (d) order of magnitude about 10^2 or 10^3 for fatty acid additives in crystals of adipic acid (Grant and York, 1985).

The difference between the entropy of the solid sample under investigation and the entropy of the same amount of a reference sample, which may be a pharmacopoeial reference standard, is designated the "entropy of processing", ΔS^P or the "entropy of crystal imperfection". This quantity is evaluated in a thermodynamic cycle using either SC with solubility studies or DSC measurements. ΔS^P is a versatile quantity which may be evaluated for amorphous forms (e.g. glasses), polymorphs, solvates (e.g. hydrates), pure, impure or variously processed samples of a given substance, provided that the reference sample has been defined and characterized by appropriate measurements.

In the present report ΔS^P has been calculated from literature data for samples of processed solid drugs, as well as for crystals which have been doped with additives in solid solution. Where possible ΔS^P is related to other pharmaceutical properties. Subsequent reports will examine in more detail the relationship between ΔS^P and pharmaceutical properties and will apply the ΔS^P concept to polymorphs and solvates (e.g. hydrates).

Theoretical background

Thermodynamic cycles and "entropy of processing"

The thermodynamic treatment proposed recognizes the following realities.

(1) The samples of pharmaceutical solids, such as drugs or excipients, which are encountered in practice may be:
   (a) a modified solid of a pure substance, D, such as (i) imperfect crystals containing lattice defects, or (ii) solid particles or a glass in which virtually all the long range order has been lost, corresponding to the amorphous or vitreous state, or (iii) crystals of a polymorph in which the molecules are in an alternative state of order and/or energy of interaction, or;
   (b) a two- or multi-component system, such as a complex, an inclusion compound or a solvate, which consists of the drug or excipient, D, plus a ligand or complexing agent, A, and/or solvent, W, such as water, or;
   (c) an impure sample consisting of the major component, D, containing various impurities, A, B ... W.

(2) The thermodynamic cycles shown in Figs. 1 and 2, and the quantities represented, may be

applied not only to entropy, S, but to each of the other extensive thermodynamic state functions of the system, such as internal energy, U, enthalpy, H, Gibbs free energy, G, Helmholtz free energy, A, and volume, V. The respective thermodynamic cycles in Figs. 1 and 2 lead to the following equations in the entropy domain:

$$\Delta S^{P}_{solid} = -\Delta S^{f}_{solid} + x_D \Delta S^{f}_{D} + x_A \Delta S^{f}_{A} + x_W \Delta S^{f}_{W} + \Delta S^{m}_{liquid} \quad (4)$$

$$\Delta S^{P}_{solid} = -\Delta S^{s}_{solid} + x_D \Delta S^{s}_{D} + x_A \Delta S^{s}_{A} + x_W \Delta S^{s}_{W} + \Delta S^{m}_{solutions} \quad (5)$$

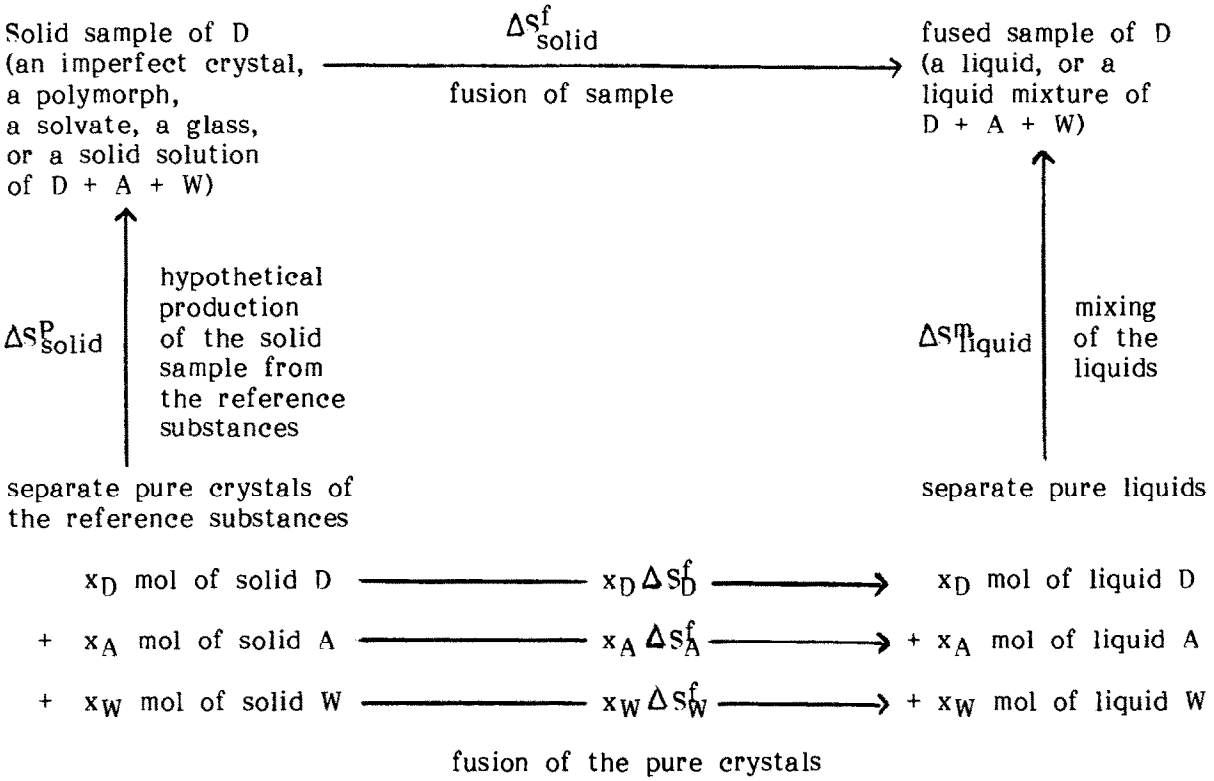
Analogous equations apply to the other thermodynamic state functions. The use of ΔS^{P}_{solid} instead of ΔS^{P} emphasizes the fact that the entropy of processing is a property of the pharmaceutical solid in question, and the two representations are used synonymously in the present work.

(3) The thermodynamic cycle may proceed via the fused or liquid states as shown in Fig. 1, or via a solution of each component in a suitable liquid solvent. L, as shown in Fig. 2, or even via the vapour or gaseous phase. The latter case is not shown because most pharmaceutical solids have very low vapour pressures. The cycle via the vapour may, however, be considered as a modification to Fig. 1 in which the individual liquids are replaced by the individual vapour states and each entropy of fusion, ΔS^{f}, is replaced by the entropy of sublimation, ΔS^{sub}.

In view of the use of the thermodynamic cycles in Figs. 1 and 2 for the evaluation of ΔS^{P}, its definition may be broadened beyond that stated in the Summary and at the end of the Introduction. The arbitrarily chosen reference sample in the previous definition is conveniently chosen to be a highly crystalline sample of the pure drug, D. Each impurity compound within the crystals, such as A or W, will increase the entropy of the solid by its own disordering effect and will also change the other thermodynamic properties (e.g. U, H, G, A, V, etc.) The most convenient reference state for each impurity is also a highly crystalline sample of that compound in the pure solid state. Thus, the "entropy (or enthalpy, etc.) of processing or of crystal imperfection", ΔS^{P}_{solid} (or ΔH^{P}_{solid} etc.), of a solid sample is the quantity on the left hand side of Figs. 1 or 2 and may be defined as the entropy change (or enthalpy change, etc.) associated with the hypothetical transition (or mixing) of the separate pure reference crystals of the individual components (present at the same mole fractions as in the sample) to produce one mole of the sample. This definition recognizes the fact that actual samples of real solids contain crystal lattice defects and impurities or additives. Similarly, the so-called pure reference crystals will also contain lattice defects but their content of impurities will usually be small and may often be negligible.

Figs. 1 and 2 as presented apply to a general case in which the solid sample consists of a solid drug, D, or excipient contaminated with two other substances, A and W. Substance A may be an additive or impurity, while substance W may be water, a solvent of crystallization or a second additive. Alternatively, D + W could constitute a drug hydrate or solvate which is contaminated with substance A, which may be an additive, a second solvent or some other impurity. The solid sample may contain lattice defects and may even be inhomogeneous. Furthermore, additional additives or impurities B, C, D, etc., may be present in the sample, and each of these will appear in Figs. 1 and 2 and will contribute an additional term, to Eqns. 4 and 5, e.g. $x_B \Delta S^{f}_{B}$ or $x_B \Delta S^{s}_{B}$.

Before applying the thermodynamic cycle in Figs. 1 and 2, it is important to ascertain whether the changes in entropy (or enthalpy etc.) refer to a defined quantity of the sample (which may contain additives or solvent, in which case the SC values refer to the respective mole fractions as is usually the case) or refer to a defined quantity of the major component, D. For example, in the analysis of heat of fusion data by York and Grant (1985) mole fractions are used (Table 1), whereas the heat of solution data of Pikal et al. (1978) refer to 1 mole of each major component, a β-lactam antibiotic (Table 3). In the latter case x_D in Fig. 2



$$\Delta S^P_{solid} = -\Delta S^f_{solid} + x_D \Delta S^f_D + x_A \Delta S^f_A + x_W \Delta S^f_W + \Delta S^m_{liquid} \quad (4)$$

Fig. 1. 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 solid 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.

and in derived equations (Eqns. 5, 7 and 9) is effectively unity, while x_W represents the ratio of the number of moles of water to the number of moles of D.

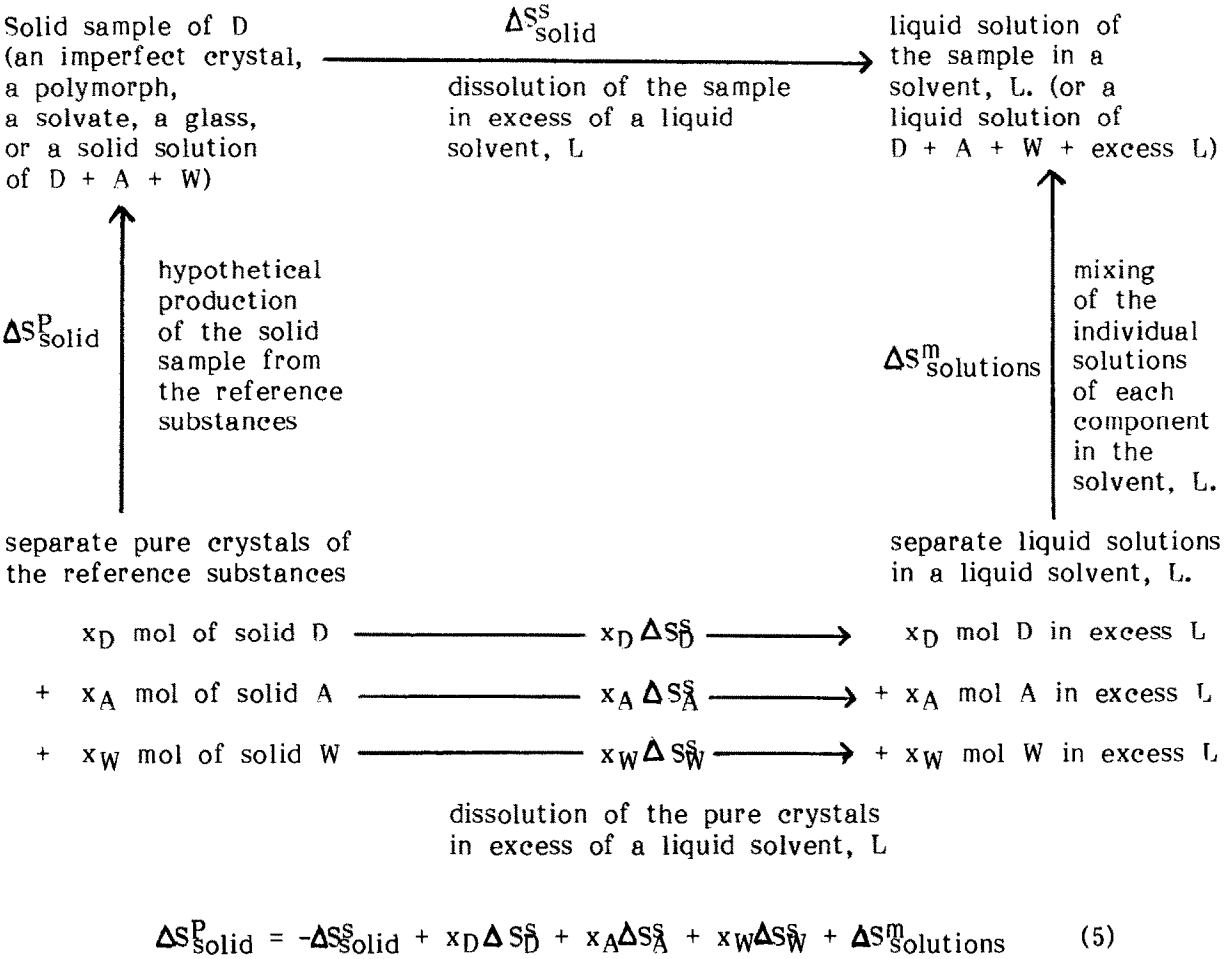
If the thermodynamic cycles shown in Figs. 1 and 2 are applied to a two-component system, such as a complex, inclusion compound, solvate or hydrate, then one of the components, say A, is omitted, in which case $x_A = 0$. Eqns. 1 and 2, respectively, are then simplified, thus:

$$\Delta S^P_{solid} = -\Delta S^f_{solid} + x_D \Delta S^f_D + x_W \Delta S^f_W + \Delta S^m_{liquid} \quad (6)$$

$$\Delta S^P_{solid} = -\Delta S^s_{solid} + x_D \Delta S^s_D + x_W \Delta S^s_W + \Delta S^m_{solutions} \quad (7)$$

where $x_D + x_W = 1$

In Fig. 1 the entropy of mixing of the pure liquid components, D, A and W, i.e. ΔS^m_{liquid} in Eqns. 4 and 6, is difficult to determine experimentally. If the orientation effects on the molecules in the liquid mixture are similar to those in the pure liquid, as expected for contaminants of crystals, it should be possible to assume that the liquids mix to produce a regular solution (Hildebrand et al., 1970). A regular solution is defined as a solution



$$\Delta S^{P}_{solid} = -\Delta S^{s}_{solid} + x_D \Delta S^{s}_{D} + x_A \Delta S^{s}_{A} + x_W \Delta S^{s}_{W} + \Delta S^{m}_{solutions} \qquad (5)$$

Fig. 2. Generalized thermodynamic cycle showing the relationships between the hypothetical stages via the solution 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 solid 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, and Gibbs free energy, G.

for which the entropy of mixing of the components is the same as that for an ideal solution, which is given by Eqn. 3.

In Fig. 2 the entropy of mixing of the individual liquid solutions of each component, D, A and W, in a solvent, L, i.e. $\Delta S^{m}_{solutions}$ in Eqns. 5 and 7, may also be difficult to determine experimentally. If the individual liquid solutions are dilute, the partial molar entropy of each component, D, A and W (and of the solvent, L), will be small and may be neglected. This means that the liquid solutions in solvent L are so dilute that the major entropy changes in Fig. 2 are ΔS^{s}_{solid} and the $x\Delta S^{s}$ terms, so that very little additional disorder remains to be created on mixing the dilute liquid solutions. Thus, if the liquid solutions in solvent L are dilute, $\Delta S^{s}_{solutions}$ may be neglected.

If the thermodynamic cycles shown in Figs. 1 and 2 are applied to a modified solid of a pure substance, e.g. (i) pure imperfect crystals, (ii) a

pure polymorph, or (iii) a pure amorphous form, then $x_A = 0$, $x_W = 0$, $x_D = 1$ and no mixing takes place, so that $\Delta S^m_{liquid} = 0$ and $\Delta S^m_{solutions} = 0$. Eqns. 4 and 5, respectively, are then simplified, thus:

$$\Delta S^P_{solid} = -\Delta S^f_{solid} + \Delta S^f_D \quad (8)$$

$$\Delta S^P_{solid} = -\Delta S^s_{solid} + \Delta S^s_D \quad (9)$$

Determination of ΔS^P_{solid} by means of the fusion cycle in Fig. 1

The individual entropies of fusion, i.e. ΔS^f_{solid}, ΔS^f_D, ΔS^f_A and ΔS^f_W, in Fig. 1 and in Eqns. 4, 6 and 8 may each be readily determined by DSC or DTA, by means of relationship

$$\Delta S^f = \Delta H^f / T_m \quad (10)$$

where ΔH^f is the enthalpy of fusion at the melting point, T_m. The thermodynamic cycle in Fig. 1 and Eqns. 4, 6 and 8 assume conditions of constant temperature and constant pressure. Usually, differences in pressure will not significantly change the thermodynamic quantities in Fig. 1. To prevent their sublimation, volatile substances are normally encapsulated in a volatile sample pan; in this case, the influence of increased pressure on ΔH^f, T_m and ΔS^f, which is usually small, is far less serious than the errors introduced by sublimation or evaporation of the sample. Differences in temperature will generally exert greater influences on ΔH^f and ΔS^f than will pressure, because temperature directly influences thermal motion. In practice this may not be a serious problem in the scheme shown in Fig. 1, because the most influential terms, namely ΔS^f_{solid} and $x_D \Delta S^f_D$ in Eqns. 4, 6 and 8, are often measured at temperatures within a few degrees of each other. The other ΔS^f terms, namely $x_A \Delta S^f_A$ and $x_W \Delta S^f_W$, may be measured at quite different temperatures than ΔS^f_{solid} and $x_D \Delta S^f_D$, which introduce errors in ΔS^f_A and ΔS^f_W, but the influences of $x_A \Delta S^f_A$ and $x_W \Delta S^f_W$ are reduced by the relatively smaller magnitudes of x_A and x_W. It should be emphasized that the errors resulting from temperature differences may be more serious when ΔS^P_{solid} is determined for one polymorph relative to another using Eqn. 8 or for a complex or solvate relative to the parent uncomplexed or unsolvated form using Eqn. 6.

If the solid sample under investigation is totally amorphous or, in other words, exhibits zero crystallinity, it will not give a fusion peak in DSC or DTA, i.e. $\Delta S^f = 0$, in which case Eqn. 8 simplifies further to $\Delta S^P_{solid} = \Delta S^f_D$. This expresses the fact that the disorder in the sample is the same as that in the fused crystalline form of D so that the entropy of the sample exceeds that of crystalline D by an amount equal to the entropy of fusion. For a pure totally amorphous sample with zero crystallinity dissolving in a liquid solvent, L, ΔS^s_{solid} in Eqn. 9 is the same as that for the liquid, which expresses the fact that the entropy of the sample exceeds that of crystalline D by the same amount as the entropy of the liquid exceeds that of crystalline D, i.e. $\Delta S_{solid} = \Delta S_{liquid}$.

If the solid under consideration is a polymorph of the reference substance D, it may undergo a polymorphic transition while being heated in DSC or DTA. If the product of the transition approximates to the reference sample, the transition enthalpy ΔH^t at the transition temperature T_t will approximate to the enthalpy difference between the sample and the reference, i.e. $\Delta H^t_{solid} \approx \Delta H^P_{solid}$, so the corresponding entropy difference will be $\Delta S^P_{solid} \approx \Delta H^t_{solid}/T_t$. Whether or not the product of the polymorphic transition approximates to the reference sample, it may be possible to employ a rapid heating mode, so that the sample melts before the molecules have time to rearrange into a different polymorphic lattice and Eqn. 8 can be employed.

Two disadvantages of measurements of $\Delta S^f (= \Delta H^f/T_m)$ using DSC and DTA for the determination of ΔS^P_{solid} are as follows: (a) on increasing the temperature, the increasing thermal motion may change the molecular disorder of the solid sample by processes similar to annealing; and (b) thermolabile materials or substances which decompose near the melting point will undergo chemical reactions which will usually lead to uninterpretable enthalpy changes, in which case ΔH^f and T_m will be unreliable. For adipic acid crystals doped with fatty acids, the former case (a) is found to apply, since d.i. determined by DSC is found to be appreciably smaller than that determined by solu-

tion calorimetry (Grant and York, 1985). For these reasons, the isothermal cycle via solutions in a liquid solvent, L, represented by Fig. 2 and Eqns. 5, 7 and 9, may be preferable.

Determination of ΔS^{P}_{solid} by means of the solution cycle in Fig. 2

The thermodynamic cycle in Fig. 2 and Eqns. 5, 7 and 9 employs constant temperature and constant pressure conditions. Differences in pressure will not usually present a significant problem, since it is practicable to choose a liquid solvent, L, which gives solutions of low volatility. Differences of temperature are eliminated by the favoured use of isothermal conditions when studying the physical chemistry of solutions. The individual entropies of solution, i.e. ΔS^{s}_{solid}, ΔS^{s}_{D}, ΔS^{s}_{A} and ΔS^{s}_{W}, in Fig. 2 and Eqns. 5, 7 and 9 may each be determined from the corresponding calorimetric enthalpy of solution, ΔH^{s}, by appropriate substitution into the equation

$$\Delta S = (\Delta H - \Delta G)/T \qquad (11)$$

Grant and York (1985) defined ΔG^{s}, the Gibbs free energy of transfer (or solution) of one mole of the major solute component (the host) from the solid to the solution standard state, thus:

$$\Delta G^{s} = -RT \ln C^{s}\gamma^{s} \approx -RT \ln C^{s} \qquad (12)$$

where C^{s} is the solubility (molarity or molality) of the major component in the solvent, which should be sufficiently low that the activity coefficient of the dissolved solute, $\gamma^{s} \approx 1$. For this purpose, the solution standard state of the dissolved host corresponds to unit (molar or molal) concentration which is assumed to behave ideally. Substitution of Eqn. 12 into Eqn. 11 leads to

$$\Delta S^{s} = \Delta H^{s}/T + R \ln C^{s} \qquad (13)$$

The determination of ΔS^{s} of each solid may best proceed from measurements of ΔH^{s} and solubility C^{s} in a suitable liquid solvent, L, at a single defined temperature, T, e.g. 25 or 37°C. The value of C^{s} for an unstable polymorph, solvate or amorphous form may be determined by means of a dynamic technique (Higuchi et al., 1963). However, in certain cases, especially with imperfect or doped crystals, C^{s} may be difficult to determine directly. Thus, after the dissolved concentration during dissolution has reached the solubility of the stable phase, processes of crystallization will lead to reductions in ΔG^{s} and C^{s} towards those of the stable solid. For example, dehydrated calcium gluceptate which had been milled for longer than 2 h dissolved in water to produce an unstable solution from which solid was rapidly precipitated (Suryanarayanan and Mitchell, 1985). Two approaches to this problem have been proposed by Grant and York (1985). The first suggestion is to measure the initial dissolution rate per unit surface area (intrinsic dissolution rate) which is proportional to C^{s} according to the equation of Noyes and Whitney (1897). The second approach is to employ calorimetric enthalpy changes instead of entropy changes and to utilize Eqns. 5, 7 and 9 as their enthalpy analogues. Eqn. 5 is then expressed as:

$$\Delta H^{P}_{solid} = -\Delta H^{s}_{solid} + x_{D}\Delta H^{s}_{D} + x_{A}\Delta H^{s}_{A} + x_{W}\Delta H^{s}_{W} + \Delta H^{m}_{solutions} \qquad (14)$$

If, D, A and W are either similar compounds or are present in dilute solution, their mixing will proceed ideally, unperturbed by changes of molecular environment, so that $\Delta H^{m}_{solutions} = 0$. The use of enthalpy changes in place of entropy change amounts to assuming that enthalpy-entropy compensation is occurring, which is to be considered in a subsequent section.

Data analysis and discussion

Solid solutions

Solid solutions (and solvates) are single phase systems consisting of two or more components, D, A, W, etc., in which case an equation of the type Eqns. 4–7 may be applied. Table 1 presents data which were abstracted from the literature and analyzed according to Fig. 1 and Eqn. 4 or 6, depending on whether or not W is present.

For the intermetallic, host and guest, systems

TABLE 1

APPLICATION OF THE FUSION CYCLE IN FIG. 1 TO DOPED CRYSTALS; VALUES OF THE INDIVIDUAL ENTROPY TERMS IN EQN. 4.

Mole fractions			Entropy terms, J K^{-1} mol^{-1}					
x_D	x_A	x_W	$-\Delta S^f_{solid}$	$x_D \Delta S^f_D$	$x_A \Delta S^f_A$	$x_W \Delta S^f_W$	ΔS^m_{liquid}	ΔS^P_{solid}
Host, D = $InCd_3$ Guest, A = Cd (Data from Rosina, 1974)								
1.00	0	–	−8.23	8.23	0	–	0	0
0.98	0.02	–	−8.16	8.07	0.21	–	0.81	0.92
0.96	0.04	–	−8.12	7.90	0.41	–	1.40	1.59
0.92	0.08	–	−8.02	7.57	0.82	–	2.32	2.69
0.88	0.12	–	−7.90	7.24	1.23	–	3.05	3.63
0.84	0.16	–	−7.80	6.91	1.64	–	3.66	4.41
0.80	0.20	–	−7.74	6.58	2.06	–	4.16	5.06
Host, D = $InCd_3$ Guest, A = In (Data from Rosina, 1974)								
1.00	0	–	−8.23	8.23	0	–	0	0
0.99	0.01	–	−8.15	8.15	0.08	–	0.68	0.75
0.96	0.04	–	−8.10	7.90	0.31	–	1.37	1.48
0.94	0.06	–	−8.08	7.74	0.46	–	2.00	2.11
0.90	0.10	–	−8.05	7.41	0.76	–	2.78	2.90
Host, D = Cd Guest, A = $InCd_3$ (Data from Rosina, 1974)								
1.00	0	–	−10.28	10.28	0	–	0	0
0.98	0.02	–	−9.89	10.27	0.16	–	0.81	1.16
0.96	0.04	–	−9.64	9.87	0.33	–	1.40	1.96
0.92	0.08	–	−9.21	9.46	0.66	–	2.32	3.22
0.88	0.12	–	−8.88	9.05	0.99	–	3.05	4.20
0.84	0.16	–	−8.68	8.64	1.32	–	3.66	4.93
0.80	0.20	–	−8.39	8.22	1.65	–	4.53	6.02
Host, D = phenacetin Guest, A = benzamide (Data from Marti, 1972)								
1.0000	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 Venkataram and Rogers, 1984)								
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 = acetaminophen Guest, A = p-acetoxyacetanilide Guest, W = water (Data from Chow, A.H.-L. et al., 1985a)								
1.0000	0	0	−68.00	68.00	0	0	0	0
0.9586	0	0.0414	−58.80	65.18	0	0.91	1.43	8.73
0.9708	0.0003	0.0289	−61.00	66.01	0.02	0.64	1.11	6.81
0.9789	0.0009	0.0202	−62.17	66.57	0.06	0.45	0.88	5.75
0.9853	0.0018	0.0129	−63.20	67.00	0.13	0.28	0.68	4.89
0.9824	0.0021	0.0155	−63.57	66.80	0.15	0.34	0.79	4.49
0.9728	0.0031	0.0241	−60.97	66.15	0.22	0.53	1.12	7.02
0.9746	0.0037	0.0217	−60.17	66.27	0.26	0.48	1.07	7.89
0.9744	0.0044	0.0212	−60.55	66.26	0.31	0.47	1.09	7.62

TABLE 1 (continued)

Mole fractions			Entropy terms, J K^{-1} mol^{-1}					
x_D	x_A	x_W	$-\Delta S^f_{solid}$	$x_D\Delta S^f_D$	$x_A\Delta S^f_A$	$x_W\Delta S^f_W$	ΔS^m_{liquid}	ΔS^P_{solid}
Host, D = pp-*DDT Guest, A* = op-*DDT (Data from Plato and Glasgow, 1969)*								
Data treatment I: *op*-DDT treated as a single molecular species								
1.0000	0	–	−68.83	68.83	0	–	0	0
0.9994	0.0006	–	−68.83	68.79	0.05	–	0.04	0.05
0.9966	0.0034	–	−66.67	68.40	0.27	–	0.19	2.39
0.9942	0.0058	–	−64.50	68.43	0.46	–	0.30	4.69
Data treatment II: *op*-DDT treated as a racemic mixture (the R and S being A and W, respectively)								
1.0000	0	0	−68.83	68.83	0	0	0	0
0.9994	0.0003	0.0003	−68.83	68.79	0.02	0.02	0.05	0.05
0.9966	0.0017	0.0017	−66.67	68.60	0.13	0.13	0.21	2.40
0.9942	0.0029	0.0029	−64.50	68.43	0.23	0.23	0.33	4.72

[a] Two solid phases (Venkataram and Rogers, 1984).

($InCd_3 + Cd$, $InCd_3 + In$, and $Cd + InCd_3$, respectively) ΔS^P_{solid} is only slightly larger than ΔS^m_{solid}, the difference being not more than about 40%. In these cases, $(x_D\Delta S^f_D + x_A\Delta S^f_A)$ is only slightly larger than ΔS^f_{solid}, so that ΔS^m_{ideal} is the major contributor to ΔS^P_{solid} (Table 1). This means that ideal mixing of the components, D and A, is the major contributor to ΔS^P and little additional disorder is created in the crystal lattice of the host by the guest. In these examples, the "disruption index" has the values 0.075, 0.115 and 0.423, which are the smallest recorded, being close to the value zero for systems belonging to Class (ii), (York and Grant, 1985).

For the organic, host + guest, systems (phenacetin + benzamide, griseofulvin + lecithin, acetaminophen + *p*-acetoxyacetanilide + water, and *pp*-DDT + *op*-DDT), ΔS^P_{solid} is larger than ΔS^m_{ideal} by factors ranging from about 4 to 16. In these cases, $(x_D\Delta S^f_D + x_A\Delta S^f_A)$ is appreciably larger than ΔS^f_{solid}, and this difference is the major contributor to ΔS^P_{solid} (Table 1). This difference represents the total disorder created by A within the crystal lattice of D and is evidently much larger than ΔS^m_{ideal}. This indicates that the presence of A within the crystal lattice of D creates additional disorder over and above the ideal value that is attributable only to simple molecular substitution or dilution. This additional disorder arises from crystal defects that result from distortion of the lattice by the presence of molecules of A which possess shapes, sizes and intermolecular interactions different from those of D. The impurity defects create additional point defects and dislocations, such that the overall influence of A on the disorder of the crystal lattice of D is magnified. In these examples, the "disruption index" has values ranging from 5 to 15 or more, appropriate for Class (iii) systems (York and Grant, 1985).

The system, acetaminophen + *p*-acetoxyacetanilide + water (Chow et al., 1985a) is an example of a three component system (D + A + W) and is also a member of the organic Class (iii) systems mentioned above. In this case, however, the third species, water (= W) contributes an additional term $x_W\Delta S^f_W$, which is in fact greater than $x_A\Delta S^f_A$, because of its greater mole fraction in the crystal lattice of D (Table 1). Here, A + W conspire together to create more disorder in the crystal lattice of D than can be accounted for by ideal mixing. Table 1 shows that the lattice disruption is brought about by relatively small mole fractions of A and W, such that $x_A\Delta S^f_A$ and $x_W\Delta S^f_W$ in Eqn. 4 are very small, while $(x_D\Delta S^f_D - \Delta S^f_{solid})$ is the major contributor to ΔS^P_{solid}.

The present treatment illustrates the value of the scheme shown in Fig. 1 for elucidating the relative influence of various factors in accounting for the overall disruption of the crystal lattice,

which is measured by the entropy of processing, ΔS^P_{solid}.

Processed pharmaceutical solids

Yamamoto et al. (1977) compared physical and biological properties of solid chloramphenicol palmitate, forms A and B, which had been ground and/or blended with microcrystalline cellulose. Table 2 shows the measured values of ΔH^f and T_m and values of ΔS^P derived from Eqn. 8, taking pure, untreated crystals of polymorph A as the reference state, D. In the first place, ΔS^P is greater for the less stable, more energetic and more disordered form B than for A. Grinding with a mortar and pestle appreciably increases ΔS^P of both polymorphs, A and B, as expected. Simple blending with microcrystalline cellulose increases ΔS^P by smaller increments. (Cellulose undergoes no phase changes in DSC under the conditions of measurements.) Grinding a mixture of either polymorph with the cellulose greatly increase ΔS^P, as expected. For all treatments the resulting increases in ΔS^P are smaller for the thermodynamically less stable, more energetic and higher entropy form, B. The temperatures of the measured heats of fusion are sufficiently close to validate comparison of the ΔS^P values. Yamamoto et al. (1977) found that the ground mixture for each polymorph was amorphous in X-ray diffraction.

We hypothesize: (a) that the derived ΔS^P values reflect the extent of disorder and hence the degree of activation of the solids at ca. 350–365 K (i.e. 77–92°C) and (b) that the rank order is unchanged on lowering the temperature to 310 K (37°C). Hence we may predict that the rate of dissolution and the rate of intestinal absorption follow the same rank order as ΔS^P. Yamamoto et al. (1977), subjected four of the eight systems in Table 2 to these kinetic studies at 37°C. They observed the following rank order in dissolution profile, initial rate and cumulative extent of urinary excretion after intestinal absorption, and initial rate of enzymatic hydrolysis: form B ground mixture > form A ground mixture > form B pure crystals > form A pure crystals. This rank order is the same as that for ΔS^P, in agreement with the prediction. We note that grinding the crystals of the stable polymorph A can increase their enthalpy and entropy to values above those for the unprocessed metastable polymorph B. (However, chloramphenicol palmitate B when ground without excipient in an agate centrifugal ball mill for longer than 140 min is converted to form A, whereas form C is first transformed to form B which is later converted to form A; Kaneniwa and Otsuka, 1985.)

One would normally expect a Gibbs free energy term to be related more directly than an entropy term or an enthalpy term to the above rate processes. If, however, enthalpy–entropy compensation is occurring in closely-related organic solid phases, e.g. chloramphenicol palmitate, then

TABLE 2

APPLICATION OF THE FUSION CYCLE IN FIG. 1 TO CRYSTALS OF CHLORAMPHENICOL PALMITATE WHICH HAVE BEEN GROUND AND/OR BLENDED WITH MICROCRYSTALLINE CELLULOSE

The values of the individual enthalpy terms in the entha!py analogue of Eqn. 9 are shown. The data are from Yamamoto et al., 1977.

	Chloramphenicol palmitate, form A					Chloramphenicol palmitate, form B				
	T_m (K)	ΔH^f_{solid} ($kJ \cdot mol^{-1}$)	ΔS^f_{solid}	ΔS^f_D ($J \cdot K^{-1} \cdot mol^{-1}$)	ΔS^P_{solid}	T_m (K)	ΔH^f_{solid} ($kJ \cdot mol^{-1}$)	ΔS^f_{solid}	ΔS^f_D ($J \cdot K^{-1} \cdot mol^{-1}$)	ΔS^P_{solid}
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

[a] Prepared by trituration with a mortar and pestle for 30 min.

[b] Prepared by geometrical dilution using a spatula.

[c] Prepared by grinding the simple blend for 6 h with an alumina vibrational ball mill.

parallel changes in ΔH and ΔS will necessarily be associated with parallel but smaller changes in ΔG. Some experimental evidence for this is presented in the next section.

Pikal et al. (1978) applied solution calorimetry to solid β-lactam antibiotics which had been partially amorphized. Their data are analyzed in the remainder of this section. Since the liquid solvent, L, used for the solution calorimetry was the same as the residual or solvating solvent, W, in the sample, ΔH^s_W, ΔG^s_W and ΔS^s_W, are all effectively zero, because they represent the solution of W in W. If the heats of solution or other thermodynamic quantities refer to infinite dilution, $\Delta H^m_{solutions} = 0$, since the solutes are so dilute that they cannot interact with each other. Thus, for solvates containing only D and W and no other impurity or additive, A, Eqn. 5 reduces to Eqn. 9.

This simple additivity concept is the basis of the calorimetric method of determining crystallinity as applied by Pikal et al. (1978). Crystallinity expressed as a percentage using the present notation is given by:

$$\text{Crystallinity}\ (\%) = \frac{\Delta H^s_{solid} - \Delta H^s_{am}}{\Delta H^s_D - \Delta H^s_{am}} \times 100 \qquad (15)$$

$$= \frac{\Delta H^P_{am} - \Delta H^P_{solid}}{\Delta H^P_{am}} \times 100 \qquad (16)$$

where ΔH^s_{am} is the measured enthalpy of solution of the amorphous form which by definition has zero crystallinity and ΔH^s_D is the enthalpy of solution of the reference sample which is assigned a crystallinity of 100%. ΔH^P_{am} is the enthalpy of processing of the amorphous form. The choice of the appropriate materials for the amorphous and

TABLE 3

APPLICATION OF THE SOLUTION CYCLE IN FIG. 5 TO PARTIALLY AMORPHIZED CRYSTALS: VALUES OF THE INDIVIDUAL TERMS IN THE ENTHALPY ANALOGUE OF EQN. 9

Data for β-lactam antibiotics from Pikal et al., 1978.

Sample number	$-\Delta H^s_{solid}$	$x_D \Delta H^s_D$	ΔH^P_{solid}	$\Delta H^P_{solid}/T$
	(kJ · mol^{-1})			(J · K^{-1} · mol^{-1})
Cefazolin sodium. D = Sample 1 [a]				
1	−32.6	+32.6	0	0
2	−18.4	+32.6	14.2	48
3	+5.9	+32.6	38.5	129
4	+8.4	+32.6	41.0	138
5	+14.6	+32.6	47.3	159
5a	−3.3	+32.6	29.3	98
6	+13.4	+32.6	46.0	154
7	+18.8	+32.6	51.5	173
8	+22.6	+32.6	55.2	185
Cefamandole nafate. D = Sample 9 [a]				
9	−8.0	+8.0	0	0
10	−6.2	+8.0	1.8	6
11	+4.2	+8.0	12.2	41
12	+14.2	+8.0	22.3	75
13	+18.4	+8.0	26.4	89
Cefamandole sodium. D = Sample 14 [a]				
14	−1.1	+1.1	0	0
15	+7.7	+1.1	8.8	29
16	+13.0	+1.1	14.1	47
17	+22.2	+1.1	23.3	78
Cephalothin sodium. D = Sample 18 [a]				
18	−7.95	6.15	−1.80	−6.0
19	−6.99	6.15	−0.84	−2.8
20	−6.15	6.15	0	0
21	−5.02	6.15	1.13	3.8
22	+17.15	6.15	23.30	78.2
25	−5.82	6.15	0.33	1.1
26	−4.81	6.15	1.34	4.5
27	−1.34	6.15	4.81	16.1
28	+3.51	6.15	9.67	32.4
29	+5.44	6.15	11.59	38.9
Penicillin G potassium. D = Sample 23 [a]				
23	+1.3	−1.3	0	0
24	+23.0	−1.3	21.3	71

[a] D is the reference drug sample.

100% crystalline forms is unfortunately quite arbitrary and this is a major drawback of crystallinity scales.

Table 3 presents values of ΔH^P_{solid} calculated from Eqn. 9. Although the choice of reference sample, D, is arbitrary, it is easy to recalculate ΔH^P_{solid}, if an alternative reference sample is selected. Since solubility and dissolution rate data were not available, ΔG^s could not be calculated. Values of $\Delta H^P_{solid}/T$ are presented in Table 3 instead of ΔS^P_{solid}, which, as mentioned above, is equivalent to assuming that enthalpy–entropy compensation is occurring.

In the remainder of this section the relationships between the values of $\Delta H^P/T$ in Table 3 and the published information on the processing history of the samples (Pikal et al., 1978) are examined for each compound in turn. These examples show that $\Delta H^P/T$ increases with increasing processing stress, with decreasing crystallinity and with decreasing hydration but decreases on crystallization of an amorphous form, for example by annealing. The degree of crystallinity was assessed by X-ray powder diffraction and by birefringence under the optical microscope. Amorphous forms invariably have relatively large positive values of $\Delta H^P/T$, and may be prepared by spray-drying or freeze-drying a solution of the drug, the latter giving the higher value. $\Delta H^P/T$ appears to provide a measure of the energy and the entropy of the solid sample.

Cefazolin sodium. Sample 1 in Table 3 is the crystalline pentahydrate (α-form) which, since it was prepared by recrystallization from aqueous ethanol, appears to be the more stable form in the presence of water and is therefore chosen to represent the reference material, D. Sample 2 is the crystalline monohydrate which was prepared by partial dehydration of a suspension of the α-form in anhydrous ethanol. Sample 5a is a weakly crystalline (i.e. poorly crystallized) form of the monohydrate, while samples 3–8 are materials of varying crystallinity containing only traces of water. Table 3 shows that $\Delta H^P/T$ increases in the order: crystalline pentahydrate (sample 1) < crystalline monohydrate (sample 2) < weakly crystalline monohydrate (sample 5a) < weakly crystalline anhydrates (samples 3–6) < amorphous anhydrate (sample 7, spray-dried) < amorphous anhydrate (sample 8, freeze-dried). This rank order is that of the reactivity towards water and is the reverse of that for stability in aqueous solution.

Cefamandole nafate. Samples 9 and 10 are both crystalline γ-forms crystallized as one lot. Since sample 10 was subjected to a greater processing stress in vacuum-drying (50°C for 24 h which gave an amorphous coat) than sample 9 (25°C for 24 h and 40°C for 24 h), $\Delta H^P/T$ is greater for sample 10. Sample 11 is a weakly crystalline α-form prepared by precipitation from acetone followed by vacuum-drying. Samples 12 and 13 are respectively spray-dried and freeze-dried amorphous forms. With decreasing crystallinity, $\Delta H^P/T$ increases in the predicted rank order: sample 9 < sample 10 < sample 11 < sample 12 < sample 13.

Cefamandole sodium. In accordance with the above behaviour for cefazolin sodium, $\Delta H^P/T$ increases in the rank order: crystalline monohydrate (sample 14) < crystalline anhydrate (sample 15, vacuum dehydrated 14) < amorphous anhydrate (sample 16, spray-dried) < amorphous anhydrate (sample 17, freeze-dried).

Penicillin G potassium. Following the above pattern, the amorphous freeze-dried sample 24 exhibits a higher $\Delta H^P/T$ value than the crystalline sample 23.

Cephalothin sodium. In practice, the material chosen to be the reference sample, D, is likely to be a crystalline vacuum-dried commercial sample, which in the case of cephalothin sodium is sample 20 in Table 3. On this basis, however, samples 18 and 19, which are commercial samples that were recrystallized four times by salting out, display reduced, i.e. negative, values of $\Delta H^P/T$, reflecting an increase in crystallinity. Pikal et al. (1978) attributed the thermodynamic differences between samples 18–20 to differences in crystal perfection, i.e. point defects and dislocations. Sample 21 was prepared by vigorous mortar grinding of sample 20, a process which stressed the material decreasing its crystallinity and concomitantly increasing $\Delta H^P/T$. The production of the amorphous form (sample 22) by the freeze-drying of a 20% aqueous solution is accompanied by a large increase in $\Delta H^P/T$.

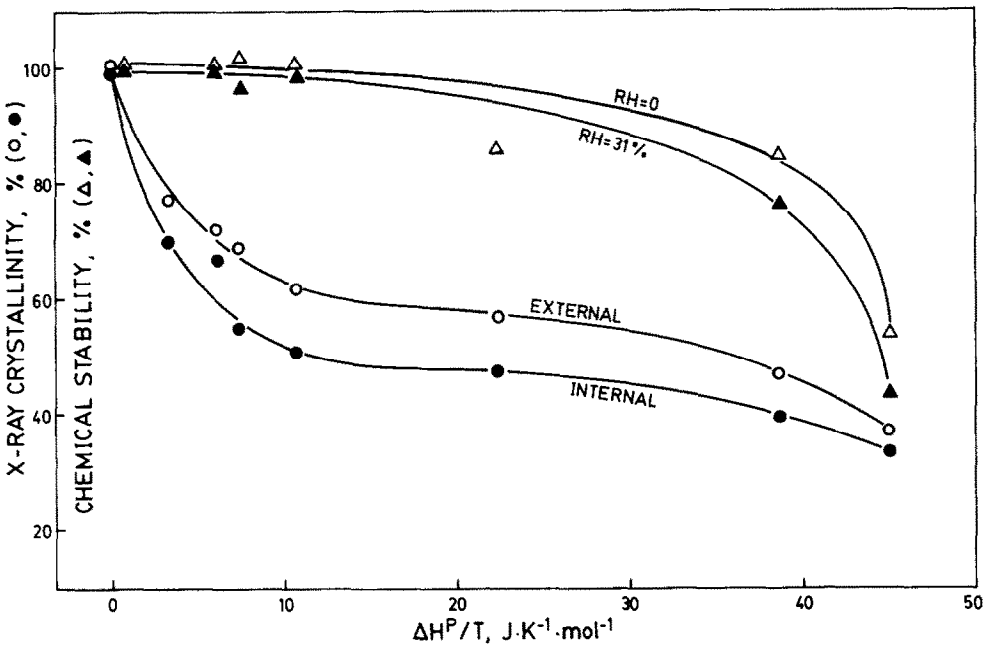


Fig. 3. Influence of crystallization and drying processes on the properties of solid cephalothin sodium samples. (a) Relationships between $\Delta H^P/T$ and X-ray crystallinity; X%, determined by an external method (○) and an internal method (●). (b) Relationships between $\Delta H^P/T$ and chemical stability of the solid at 50°C under relative humidities of 0% (△) and 31% (▲). (Data from Pikal et al., 1978.)

When the amorphous sample 22 was allowed to anneal at −5°C for 3–18 h, partially crystalline samples (26–28) were produced. The process of annealing with crystallization was marked by a decrease in $\Delta H^P/T$ and by an increase in birefringence. The fraction of the birefringent, i.e. crystalline, material decreased with increasing $\Delta H^P/T$. During 24 months storage of sample 26 at 25°C, ΔH^s_{solid} increased from 1.15 to 1.46 kcal · mol^{-1} (Pikal et al., 1978) which corresponds to a decrease in $\Delta H^P/T$ from 4.5 to 0.1 J · K^{-1} · mol^{-1}. On further ageing sample 26 at 50°C for 2 months, no further change was observed. Samples 25 and 29 are partially crystalline materials which were prepared by spray-drying an aqueous solution. Sample 25 was initially poorly crystallized with $\Delta H^s = -0.06$ kcal · mol^{-1}, corresponding to $\Delta H^P/T = 21.5$ J · K^{-1} · mol^{-1}, but when allowed to anneal at ambient temperature for 2 months, afforded essentially crystalline material consisting of virtually 100% birefringent beads with a low value of $\Delta H^P/T = 1.1$ J · K^{-1} · mol^{-1}, as reported in Table 3.

Fig. 3 shows the relationship between $\Delta H^P/T$ and the intensity ratio of an X-ray diffraction peak of crystallized and variously dried samples of cephalothin sodium measured at a defined value of 2θ and expressed as degree of crystallinity, X, on a scale from 0 to 100%. The relationship is not linear, perhaps because ΔG^P is not considered. However, Fig. 3 clearly shows that $\Delta H^P/T$, which had been altered mainly by drying, increases with decreasing X-ray crystallinity. Fig. 3 also shows that the stability at 50°C at 0 and 31% relative humidity decreased when $\Delta H^P/T$, increased beyond 11 J · K^{-1} · mol^{-1}. Fig. 4 emphasizes dependence of chemical decomposition on $\Delta H^P/T$, which had been changed by ageing of amorphous freeze-dried cephalosporins. By definition, $\Delta H^P = 0$ at zero time. Chemical decomposition is here expressed as f mole percent of the free 3′-side chain in cefamandole nafate, thus:

$$f = (0.250 \pm 0.075)\Delta H^P/T + 0.777,$$
$$r = 0.830,\ n = 7,\ s/\text{mean } f = 0.299 \qquad (17)$$

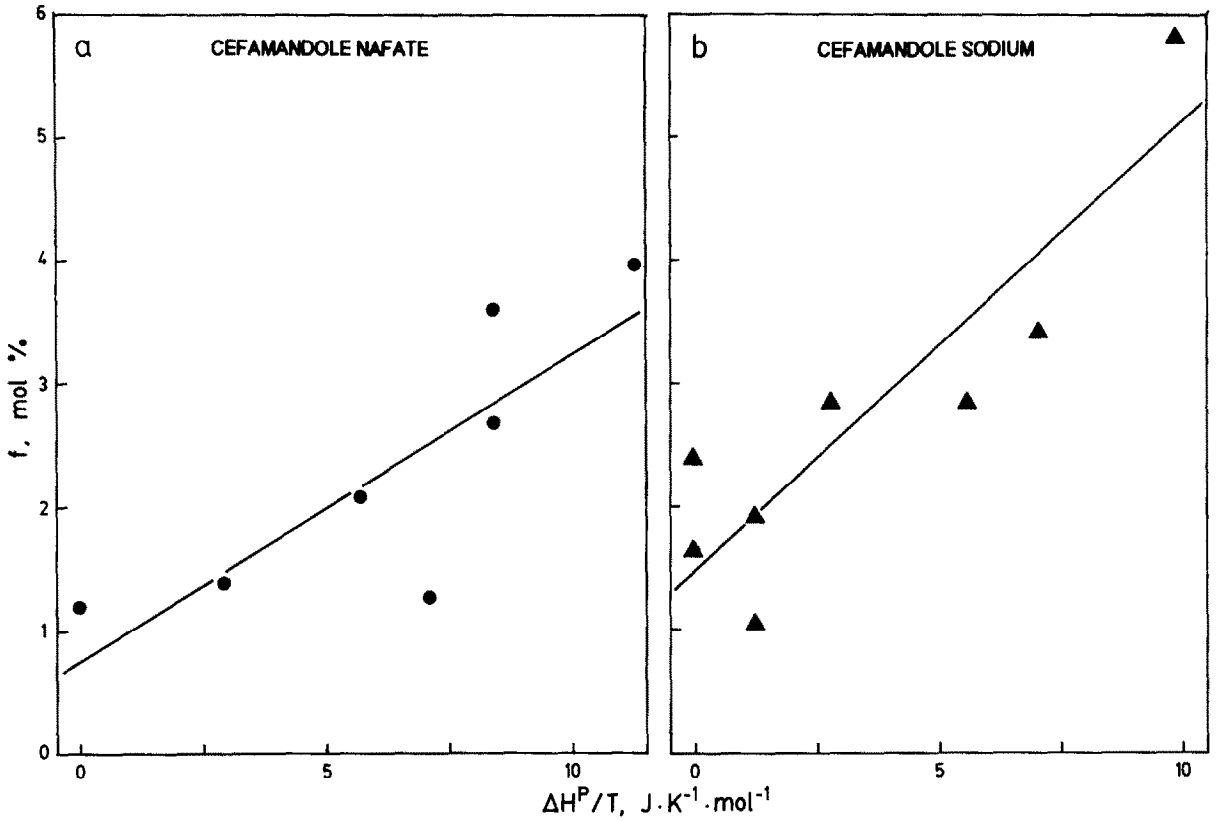


Fig. 4. Influence of ageing from 0 to 6 months at various temperatures on the decomposition and $\Delta H^P/T$ of cefamandole nafate (a, ●) and cefamandole sodium (b, ▲). The extent of decomposition is expressed as f mol percent of free 3'-side chain. (Data from Pikal et al., 1978.)

and in cefamandole sodium, thus:

$$f = (0.371 \pm 0.075)\Delta H^P/T + 1.492,$$
$$r = 0.895,\ n = 7,\ s/\text{mean } f = 0.250 \qquad (18)$$

where s is the residual (ordinate) standard deviation, f represents the ordinate values and s/mean f is a dimensionless residual standard deviation normalized to the ordinate values. (Analogous representations based on the appropriate ordinate values are applied to subsequent linear regressions, i.e. Eqns. 24, 25.) The poor quality of these correlations (Fig. 4) may arise from the variability of the water content which is not known exactly, but which probably exerts a significant influence on ΔS^P (e.g. acetaminophen, Table 1, Chow et al., 1985a). In our calculations of $\Delta H^P/T$, the water content, x_w, was assumed constant so that its influence would cancel enabling the enthalpy analogue of Eqn. 9 to be employed. However, $\Delta H^P/T$ correlates well with the water absorption by solid samples of cephalothin sodium at 31% relative humidity at 25°C. This is illustrated by Fig. 6 in Pikal et al. (1978). The abscissa in this plot is "percent crystallinity (calorimetric)", c, which is related to $\Delta H^P/T$ by definition, thus:

$$c = 100 - 1.19 \cdot \Delta H^P/T(J \cdot K^{-1} \cdot mol^{-1}) \qquad (19)$$

so that, when $\Delta H^P/T = 0$, c = 100% and when $\Delta H^P/T = 84.1\ J \cdot K^{-1} \cdot mol^{-1}$, c = 0%.

ΔS^P (Table 2) and $\Delta H^P/T$ (Table 3) of phar-

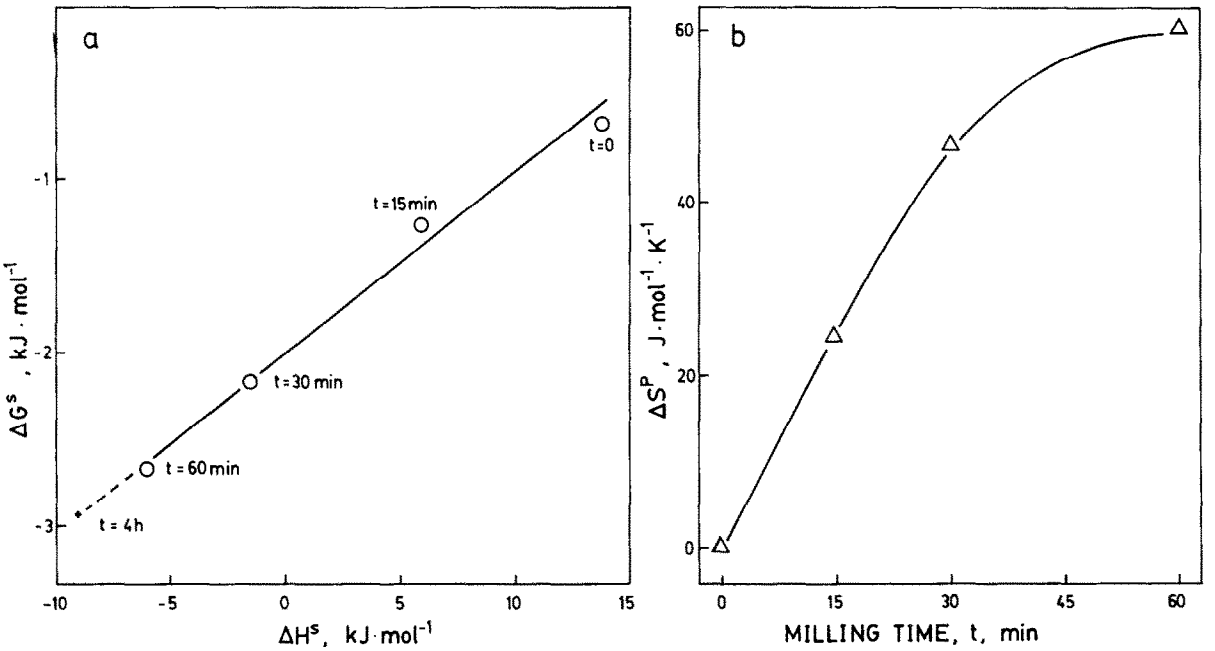


Fig. 5. Effect of milling for various times, t, on the following thermodynamic properties of dehydrated calcium gluceptate crystals: (a) the Gibbs free energy of solution, $\Delta G^s = -RT \cdot \ln(\text{molal solubility})$, and the enthalpy of aqueous solution, ΔH^s, (○) at 22°C; (b) the entropy of processing, ΔS^P, (△). (Data from Suryanarayanan and Mitchell, 1985.) After milling for 4 h, point + in (a) indicates that $\Delta G^s = -2.944$ kJ · mol^{-1}, corresponding to a solubility of 3.32 mol · kg^{-1} at 22°C, and $\Delta S^P = 69.7$ kJ · mol^{-1}, extrapolated from the measured value of $\Delta H^s = -9.13$ kJ · mol^{-1}. Extrapolation using (b) is not possible.

maceutical solids which have been subjected to processes, such as grinding, milling, freeze-drying, spray-drying and vacuum dehydration, range from 0 to 200 J · K^{-1} · mol^{-1}. These values are about one order of magnitude larger than ΔS^P of doped crystals (i.e. solid solutions, Table 1), suggesting that normal pharmaceutical processing exerts a much greater disruptive influence on the crystal lattice than doping with additives or impurities. The factors influencing $\Delta S^P \approx \Delta H^P/T$ (Table 3) of various β-lactam antibiotics, from Pikal et al. (1978) as discussed above, show that the effects of processing on the concentration of crystal imperfections may be transitory. In other words, the solid particles may pass from states of higher energy and entropy to states of lower energy and entropy on storage and/or annealing. We have seen that the approach described in the present work can detect this effect. The influence of small amounts of additives or impurities introduced as solid solutions into the crystals during crystallization appear to be more permanent, though smaller, presumably as a result of the lower energy and entropy of the state which has been created.

Enthalpy–entropy compensation and ΔS^P for ground dehydrated calcium gluceptate

An excellent account of enthalpy-entropy compensation has been provided by Tomlinson (1983). This extrathermodynamic relationship states that

$$\delta(\Delta H) = \beta \cdot \delta(\Delta S) \qquad (20)$$

where δ denotes the difference between a variable and defined system (e.g. the partial disruption of a defined crystal lattice) which is undergoing a process (e.g. dissolution) involving a change in enthalpy and entropy. β is a proportionality constant possessing the dimensions of absolute temperature and known as the isoequilibrium (or isokinetic) temperature or compensation temperature. Eqn. 20 may be converted to the enthalpy -

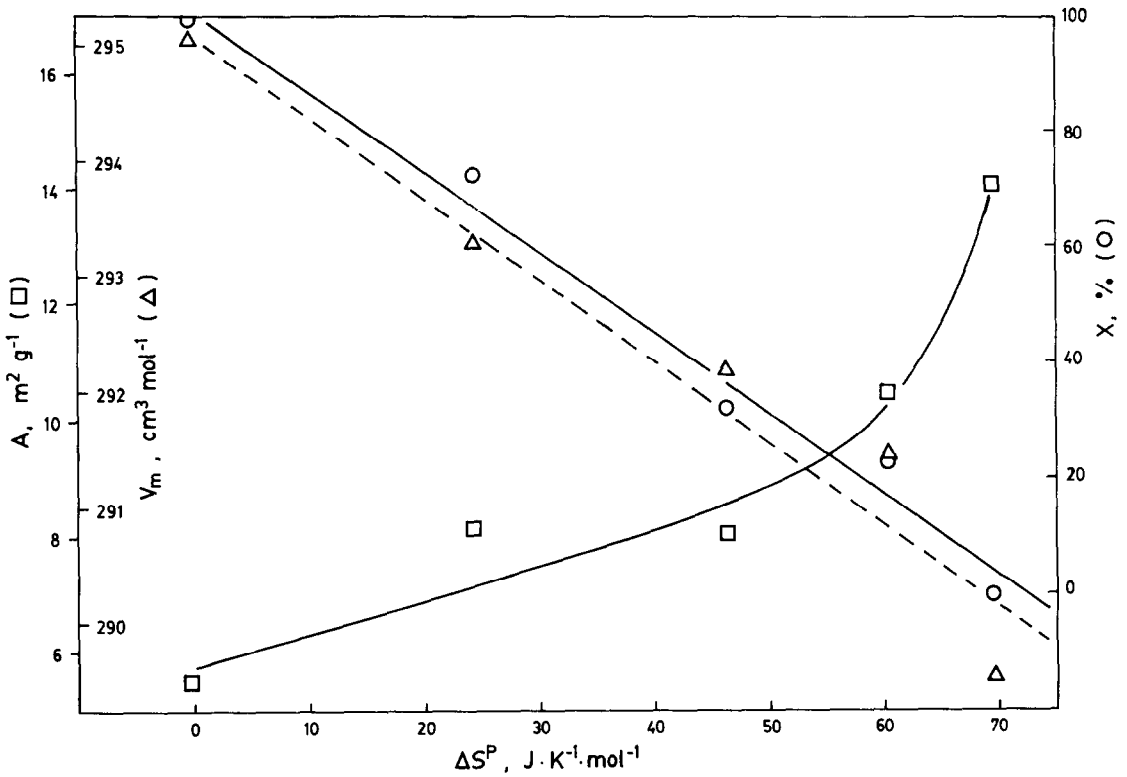


Fig. 6. Relationship between entropy of processing, ΔS^P, of dehydrated calcium gluceptate crystals, which have been milled for various times (Fig. 3), and the following properties of the crystals: X-ray crystallinity, X, ○———○; molar volume, V_m, Δ---Δ; specific surface area, A, □———□. (Data from Suryanarayanan and Mitchell, 1985.)

Gibbs free energy domain by means of Eqn. 11 in its derivative form. The result is:

$$\delta(\Delta G) = (1 - T/\beta) \cdot \delta(\Delta H) \qquad (21)$$

which may be stated in the following integrated form:

$$\Delta G = \Delta G_0 + (1 - T/\beta) \cdot \Delta H \qquad (22)$$

where ΔG_0 is a constant, which represents the value of ΔG when $\Delta H = 0$. To test Eqns. 21 and 22 in solid pharmaceutics requires both accurate ΔH values, preferably from calorimetry, and accurate ΔG values, from an equilibrium property, such as solubility. In view of these simultaneous requirements and in view of the difficulty of determining intrinsic solubilities of unstable solid phases, enthalpy–entropy compensation is difficult to test experimentally in solid pharmaceutics. Recently, however, Suryanarayanan and Mitchell (1985) have obtained valuable data, which, when suitably plotted according to Eqn. 21, supports the compensation principle, although only four points are available. The solid employed was dehydrated calcium gluceptate which had been milled for various lengths of time and which is so soluble in water that its instantaneous solubility can be determined rapidly in that solvent. We equate ΔG in Eqns. 21 and 22 with ΔG^s, which is given by Eqn. 12, where C^s is the instantaneous molal solubility of the solid in water. We equate ΔH in Eqns. 21 and 22 with ΔH^s, the enthalpy of solution of the solid in water. Fig. 5a depicts the linear relationship predicted by Eqn. 22, for which $r = 0.996$, s/mean $\Delta G = 0.060$ and in which $\Delta G_0 = -1.99$ kJ · mol^{-1}, $T = 295.14$ K and $\beta = 329.5 \pm 2.5$ K. This corresponds to a compensation temperature of 56.5°C, which, being only 34.3°C above the

temperature of measurement, indicates a considerable compensatory effect. In other words, $\delta(\Delta G^s) \ll \delta(\Delta H^s)$, so that $\Delta H^s/T \approx \Delta S^s$ and $\Delta H^P/T \approx \Delta S^P$.

The practical value of enthalpy–entropy compensation resides in its predictive capability. Thus, C^s may be predicted from the measured value of ΔH^s and vice versa. For example, after milling dehydrated calcium gluceptate for longer than 2 h, the solution was so unstable that C^s could not be measured (Suryanarayanan and Mitchell, 1985), as mentioned above. Since, however, these workers had measured $\Delta H^s (= -9.13\ kJ \cdot mol^{-1}$ after a milling time of 4 h), we predict from the linear regression (Eqn. 22, Fig. 5a) that $\Delta G^s = -2.944\ kJ \cdot mol^{-1}$, corresponding to $C^s = 3.32\ mol \cdot kg^{-1}$ at 22°C after milling for 4 h. We note that extrapolation in the time domain (Fig. 5b) would be most unwise without further evidence, but extrapolation in the ΔG^s and ΔH^s domain is evidently short, probably linear and apparently reasonable.

The entropy of processing, ΔS^P, of treated or processed crystals of a drug, whose composition or state of solvation is constant, may be calculated from Eqn. 9 into which Eqn. 13 has been substituted, thus:

$$\Delta S^P_{solid} = -(\Delta H^s_{solid}/T + R \ln C^s_{solid}) + (\Delta H^s_D/T + R \ln C^s_D) \quad (23)$$

where ΔH^s_{solid} and ΔH^s_D are the enthalpy of solution of the solid in question and of the reference material, D, respectively and where C^s_{solid} and C^s_D are the respective intrinsic solubilities. The temperature (absolute value T) should be constant and identical for all measurements. We have applied Eqn. 23 to the data of Suryanarayanan and Mitchell (1985) for milled dehydrated calcium gluceptate crystals, the reference material, D, being the unmilled crystals. The calculated values of ΔS^P are plotted against the time of milling in Fig. 5b. The slope tends to decrease with increasing time suggesting a progressively diminishing influence on lattice disruption; this may be attributed to the progressively competing influence of the aggregation of the increasingly activated particles (Hüttenrauch, 1978).

Since ΔS^P expresses the disorder which is created by processing in the crystal lattice, ΔS^P must be related fundamentally to other physical properties and processing variables. These relationships are currently under investigation. In the meantime we have plotted in Fig. 6 various physical properties of milled dehydrated calcium gluceptate crystals, considered above, against our derived values of ΔS^P. From the data of Suryanarayanan and Mitchell (1985) we have selected the following properties and examined their linear regressions against ΔS^P: (a) the intensity ratio of an X-ray diffraction peak measured at a defined value of 2θ and expressed as degree of crystallinity, X, on a scale from 0 to 100%.

$$X = 102.2 - (1.401 \pm 0.113) \cdot \Delta S^P\ (J \cdot K^{-1} \cdot mol^{-1})$$
$$r = -0.990,\ s/\text{mean } X = 0.139 \quad (24)$$

(b) The molar volume, V_m = molecular weight/density, of the anhydrous crystals,

$$V_m\ (cm^3 \cdot mol^{-1}) = 295.2 - (0.06973 \pm 0.00982) \cdot \Delta S^P\ (J \cdot K^{-1} \cdot mol^{-1})$$
$$r = -0.972,\ s/\text{mean } V_m = 0.00189 \quad (25)$$

When one considers the experimental uncertainties in the X-ray powder diffraction measurements and in the accurate measurement of densities of solids, the quality of these linear fits is remarkably good. Eqn. 24 demonstrates that ΔS^P actually reflects the disorder created by the milling process in the crystals, since it correlates strongly with decreasing intensity of a defined X-ray diffraction peak relative to a defined crystalline standard. Eqn. 25 demonstrates the ΔS^P, which is the molar thermodynamic capacity factor complementary to temperature as the intensity factor, correlates with V_m, which is the molar thermodynamic capacity factor complementary to pressure as the intensity factor. The correlation expressed by Eqn. 25 is rather worse than that expressed by Eqn. 24, because lattice expansion and contraction, which are measured by density and expressed here as V_m, tend to be rather insensitive to milling

(Hüttenrauch, 1978) and to other forms of lattice disruption (Chow et al., 1984, 1985a, 1985b). The ratios, surface area/mass (A in Fig. 6), mass/surface area, surface area/volume and volume/surface area, do not correlate well with ΔS^P. This probably reflects the fact that the particles of the milled solid calcium gluceptate are sufficiently large that the bulk properties rather than the surface properties exert the major influence on the crystalline disorder as measured by ΔS^P.

Further studies are in progress to assess the value of ΔS^P for the quantitation and prediction of batch-to-batch differences in pharmaceutical solids, on the one hand, and for the correlation of these differences with dissolution behaviour, bioavailability and the physico-technical properties of powders and tablets, on the other hand.

Conclusions

(1) The entropy of processing, ΔS^P, (i.e. the entropy of crystal imperfection) of a solid sample is defined as the difference between the entropy of the sample and that of the same amount of a conveniently chosen reference material.

(2) ΔS^P may be evaluated by applying thermodynamic cycles *either* (a) to entropies of fusion determined by DSC *or* (b) to entropies of solution determined from calorimetric heats of solution and free energies of solution (derived from solubility or dissolution studies).

(3) ΔS^P can, in principle, be evaluated for processed samples, amorphous forms, glasses, polymorphs (single component systems), solvates, hydrated and doped or impure samples (multiple component systems).

(4) ΔS^P of the processed pharmaceutical solids thus far examined ranges from 0 to 200 $J \cdot K^{-1} \cdot mol^{-1}$. For crystals which have been doped with additives or impurities in solid solution ΔS^P ranges from 0 to about 10 $J \cdot K^{-1} \cdot mol^{-1}$. The presence of a second phase further increases ΔS^P.

(5) ΔS^P of chloramphenicol palmitate polymorphs A and B increases after appropriate pharmaceutical processing. The rank order of ΔS^P of the samples is the same as that for the dissolution profile, rate of absorption (urinary excretion) and rate of hydrolysis).

(6) ΔS^P of dehydrated calcium gluceptate crystals increases non-linearly with time of milling but increases linearly with decreasing X-ray crystallinity and decreasing molar volume.

(7) Milled samples of dehydrated calcium gluceptate crystals exhibit enthalpy–entropy compensation with a compensation temperature of 330 K. Enthalpy–entropy compensation may, in principle, be used to predict experimentally inaccessible instantaneous solubilities and ΔS^P, and may justify the rough approximation $\Delta S^P \approx \Delta H^P/T$.

(8) $\Delta H^P/T$ of variously dried and/or aged samples of β-lactam antibiotics increases with decreasing X-ray crystallinity and chemical stability and with increasing water absorption.

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References

Al-Meshal, M., York, P. and Grant, D.J.W., Disruptive effects of surfactant molecules incorporated into phenylbutazone crystals. J. Pharm. Pharmacol., 37 Suppl. (1985) 58P.

Black, D.B. and Lovering, E.G., Estimation of the degree of crystallinity in digoxin by X-ray and infrared methods. J. Pharm. Pharmacol., 29 (1977) 684–687.

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, The Netherlands, 1979.

Burt, H.M. and Mitchell, A.G., Crystal defects and dissolution rate. Int. J. Pharm., 9 (1981) 137–152.

Byrn, S.R., Solid State Chemistry of Drugs, Academic Press, New York, N.Y., 1982.

Chow, A.H.-L., Chow, P.K.K., Wang Zhongshan, and D.J.W. Grant, Modification of acetaminophen crystals: influence of growth in aqueous solutions containing *p*-acetoxyacetanilide on crystal properties. Int. J. Pharm., 24 (1985a) 239–258.

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.

Chow, K.Y., Go, J., Wang Zhongshan, Mehdizadeh, M. and Grant, D.J.W., Modification of adipic acid crystals. II.

Influence of growth in the presence of oleic acid on crystal properties. Int. J. Pharm., 25 (1985b) 41–55.

Fairbrother, J.E. and Grant, D.J.W., The crystal habit modification of a tablet lubricant, adipic acid. J. Pharm. Pharmacol., 30 Suppl. (1978) 19P.

Fairbrother, J.E. and Grant, D.J.W., Crystal engineering studies with an excipient material (adipic acid). J. Pharm. Pharmacol., 31 Suppl. (1978) 27P.

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 (1986) 103–112.

Hiestand, E.N. and Smith, D.P., Indices of tableting performance. Powder Technol., 38 (1984) 145–159.

Higuchi, W.I., Lau, P.K., Higuchi, T. and Shell, J.W., Polymorphsm and drug availability. Solubility relationships in the methylprednisolone system. J. Pharm. Sci., 52 (1963) 150–153.

Hildebrand, J.H., Prausnitz, J.M. and Scott, R.L., Regular and Related Solutions, Van Nostrand Reinhold, New York, 1970.

Hüttenrauch, R., Molekulargalenik als Grundlage moderner Arzneiformung. Acta Pharm. Technol., APV Informationsdienst, Suppl. 6 (1978) 55–127.

Jones, T.M., The physico-technical properties of starting materials used in tablet formulation. Int. J. Pharm. Tech. Prod. Mfr., 2 (1981) 17–24.

Kaneniwa, N. and Otsuka, M., Effect of grinding on the transformations of polymorphs of chloramphenicol palmitate. Chem. Pharm. Bull., 33 (1985) 1660–1668.

Marti, E.E., Purity determination by differential scanning calorimetry. Thermochim. Acta, 5 (1972) 173–220.

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

Noyes, A.A. and Whitney, W.R., The rate of solution of solid substances in their own solutions, J. Am. Chem. Soc., 19 (1897) 930–934.

Pikal, M.J., Lukes, A.L., Lang, J.E. and Gaines, K., Quantitative crystallinity determinations of β-lactam antibiotics by solution calorimetry: correlations with stability, J. Pharm. Sci., 67 (1978) 767–773.

Plato, C. and Glasgow, A.R. Differential scanning calorimetry as a general method for determining the purity and heat of fusion of high purity organic chemicals—application to 95 compounds. J. Anal. Chem., 41 (1969) 330–336.

Reed-Hill, R.E., Physical Metallurgy Principles, 2nd Edn., Van Nostrand, New York, NY, 1973.

Rosina, A., Calorimetric measurements in the Cd-In system. Therm. Anal. Vol. 1. Proc. 4th Int. Conf. Therm. Anal., Budapest, 1974, pp. 811–824.

Suryanarayanan, R. and Mitchell, A.G., Evaluation of two concepts of crystallinity using calcium gluceptate as a model compound. Int. J. Pharm., 24 (1985) 1–17.

Tomlinson, E., Enthalpy–entropy compensation analysis of pharmaceutical, biochemical and biological systems. Int. J. Pharm., 13 (1983) 115–144.

Venkataram, S. and Rogers, J.A., Characteristics of drug–phospholipid coprecipitates. J. Pharm. Sci., 73 (1984) 757–761.

Yamamoto, K., Matsuda, S., Nakano, M., Arita, T. and Nakai, Y., Physicochemical properties and intestinal absorption of a ground mixture of chloramphenicol palmitate with microcrystalline cellulose. Yakugaku Zasshi, 97 (1977) 367–372.

York, P., Solid state properties of powders in the formulation and processing of solid dosage forms. Int. J. Pharm., 14 (1983) 1–28.

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.