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Enthalpy–entropy compensation in pharmaceutical solids

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Summary

Pharmaceutical treatment of solids involves an interplay between processing operations and inherent particle parameters while stress is introduced into the crystal lattice. Concomitant energizing and disordering implies an increase of both enthalpy and entropy according to the nature and intensity of the treatment. The present work examines the extent to which small changes, δ, of enthalpy and of entropy, ΔH and ΔS, are related by the compensation principle, $\delta(\Delta H) = \beta \cdot \delta(\Delta S)$, where β is a proportionality constant having the dimensions of absolute temperature and termed the "compensation temperature". This equation may be expressed as a function of terms in free energy, ΔG, and enthalpy, ΔH, and integrated thus: $\Delta G = \Delta G_0 + (1 - T/\beta) \cdot \Delta H$, where ΔG_0 is an integration constant. The compensation relationship was tested using available literature data involving processed pharmaceutical solids, polymorphic systems and two component solids. The enthalpy change, ΔH, was determined by solution calorimetry or Van't Hoff plots and the free energy change, ΔG, by equilibrium solubility measurements or by application of the Noyes–Whitney relationship to intrinsic dissolution rates. The applicability and limitations of the compensation principle to pharmaceutical solids are discussed. The compensation temperature calculated from statistically linear plots ($r > 0.9$) of ΔG and ΔH ranged from 12 K to 175 K above the temperature of measurement and commonly ranged from 322 to 344 K. These linear relationships suggest that the factors responsible for differences in the thermodynamic quantities (ΔG, ΔH and ΔS) of a given solid drug or excipient have a common basis and may be used cautiously to predict the remaining two quantities from any one.

Introduction

Pharmaceutical treatment of solids influences inherent particle properties as a consequence of the introduction of stress into the crystal lattice. Processing alters the energy of the material (Tkacova, 1978), reflected by the enthalpy, as well as the disorder (Hüttenrauch, 1978), reflected by the entropy, and influences the crystal properties according to the nature of the treatment. The alteration of the inherent thermodynamic properties of a drug may influence its dissolution rate and bioavailability, sometimes critically (Florence et al., 1974; Burt and Mitchell, 1981; York, 1983). Changes in the energetics of solid excipients, as well as drugs, may also be responsible for the frequently observed lot-to-lot variations (Jones, 1981) and may affect the macroscopic characteristics relevant to pharmaceutical technology (Carstensen, 1980).

Subtle variations in the solid-state properties of materials serve as the macroscopic reflection of

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the intrinsic microscopic properties of component crystals. Recalling the equation, $G = H - TS$ at constant atmospheric pressure, the most stable crystalline state has minimum free energy, i.e., $dG \leq 0$, which can be brought about by either a decrease in enthalpy, H, or by an increase in entropy, S, or by a combination of both changes. At the absolute zero of temperature, T, the crystalline state is invariably the most stable since the contribution of the TS term to the overall free energy is zero. At ambient temperature, the $-TS$ term will contribute with the $+H$ term to the free energy, G, of the crystal, so the more stable form of the crystal will contain some disorder. However, the actual state of a crystalline material may not necessarily be the state at which the $+H$ term and the $-TS$ term conspire to produce a minimum G, but merely a metastable state at the expressed conditions. Lattice constituents vibrate about their equilibrium positions at which their energies of attraction and repulsion are balanced. By disturbing this equilibrium state, the potential energy increases both with increasing as well as decreasing distance between the lattice constituents. Furthermore, virtually all crystals contain lattice defects unless prepared under the most stringent conditions. The resulting disturbed structure possesses a higher energy and a higher entropy, such that the pharmaceutical properties of the material are significantly affected. The disorder in a crystal lattice that arises from inherent lattice defects may be described as a decrease in the degree of crystallinity and may be caused by the crystallization conditions (Mullin, 1972) and/or by mechanical treatment (Hüttenrauch, 1978). Thus, when lattice strain is introduced into a crystalline material, the resulting increased energy and enthalpy of the material are parallelled by an increase in disorder. The question then arises as to how these quantities are related and how they may be applied to the characterization of pharmaceutical materials.

The present work examines the extent to which the enthalpic and entropic terms are related by the compensation principle and, if appropriate, proposes that the linear enthalpy–entropy relationship be used as a diagnostic tool in the evaluation and prediction of changes in material behaviour. If the enthalpy–entropy compensation principle can be applied to the solid state, as suggested by Grant and York (1986a and b), thermodynamic factors involved in pharmaceutical operations can be easily quantitated without regard to arbitrary crystallinity scales. In the present paper, the enthalpy–entropy compensation principle has been tested using thermodynamic quantities calculated from literature data on the solution behaviour of solid drugs (a) subjected to a variety of processing conditions, (b) exhibiting polymorphism and (c) existing as molecular adducts, such as solvates. The ensuing discussion will therefore concentrate on the application of the enthalpy–entropy compensation principle in order to provide some insight into material energetics following lattice modification by means of mechanical manipulation (activation of the surfaces and the bulk), molecular spatial arrangement (polymorphism) and incorporation of foreign constituents (as in solvates, solid complexes and impure solids).

Background

The influence of pharmaceutical processing on material behaviour has been the subject of extensive pharmaceutical literature (Nakai et al., 1977; Hüttenrauch, 1978; Nakagawa et al., 1982; Kaneniwa et al., 1985). We hypothesize that this response is accompanied by changes of enthalpy and entropy which compensate each other to produce relatively minor changes in the free energy of the process under investigation.

Tomlinson (1983) has provided an excellent review of enthalpy–entropy compensation in solution systems relevant to the biological and pharmaceutical sciences. The particular type of mutual compensation of enthalpy and entropy, which is our major concern here, is that in which the enthalpy change in an isothermal process is linearily related to the entropy change thus:

$$\delta(\Delta H) = \beta \cdot \delta(\Delta S) \qquad (1)$$

Since this relationship is not a direct consequence of thermodynamic laws, it is termed an "extra-thermodynamic relationship" (Leffler, 1955). This type of compensation is well-known

among physical organic chemists engaged in the study of chemical rate processes and equilibria in solution where the systematic variation of solvent environment demonstrate the compensation effects. Some examples of extrathermodynamic analysis include the linear free energy relationships of physical organic chemistry (e.g., the Brønsted, Hammett and Taft relationships), and the quantitative structure–activity relationships of medicinal chemistry (e.g. Hansch analysis). A survey of the variety of chemical, physical and biological systems to which enthalpy–entropy compensation has been found to apply (Tomlinson, 1983) suggests that there may be at least some justification in applying this extrathermodynamic relationship to systems in the solid state in which the independent variable is the degree of crystal lattice disruption. The frequency with which compensation phenomena appears in the solid state is less well-known but, as will be demonstrated, may be sufficiently great to warrant more thorough investigation.

In principle, the quantities ΔH and ΔS for a rate or equilibrium process are each functions of the temperature thus:

$$\frac{\partial(\Delta H)}{\partial T} = \Delta C_p \tag{2}$$

$$\frac{\partial(\Delta S)}{\partial T} = \frac{\Delta C_p}{T} \tag{3}$$

These equations are linked through ΔC_p which expresses the automatically compensated portion of ΔH and ΔS. However, we recognize that portions of ΔH and ΔS may not compensate each other.

The parameter β is a constant with the dimensions of absolute temperature (referred to as the compensation temperature), and like some other constants in physical chemistry, will have a different value when the temperature of the system is altered. When the value of β is equivalent to the temperature of measurement, total compensation will be observed and ΔG will have a constant value independent of the treatment. Actual examples of compensation relationships usually show some deviations which result from perturbations by one or more additional interaction mechanisms of lesser importance. Where deviations are significant, these perturbations then command a more dominant involvement in the interaction mechanisms.

The expression of the enthalpy–entropy compensation relationship in its simplest form (Eqn. 1) allows the derivation of 3 integrated equations (Eqns. 4, 6 and 7). Integration of Eqn. 1 yields:

$$\Delta H = \Delta H_0 + \beta \cdot \Delta S \tag{4}$$

Sequential substitution of the ΔH and ΔS terms into the classical Gibbs expression:

$$\delta(\Delta G) = \delta(\Delta H) - T \cdot \delta(\Delta S) \tag{5}$$

where δ denotes a small change in the system undergoing a process, followed by integration yields the remaining two equations:

$$\Delta G = \Delta G_0 + (\beta - T)\Delta S \tag{6}$$

$$\Delta G = \Delta G_0 + (1 - T/\beta)\Delta H \tag{7}$$

Both ΔH_0 and ΔG_0 are integration constants and represent the value of the left side of the respective equation when the independent variable of the equation is zero. The researcher thus has 3 possible planes (ΔH–ΔS, ΔG–ΔS, ΔG–ΔH) in which to plot the experimental data. If ΔS is calculated from ΔH and ΔG values, as is usually the case, and enthalpy–entropy compensation is tested using Eqn. 4, the errors in measurement of ΔH are proportional to those in measurement of ΔS. In this case deviant values of ΔH may be a linear function of deviant values of ΔS even if Eqn. 1 is not obeyed. Krug et al. (1976), in their discussion of the fundamental statistical problems associated with the determination of extrathermodynamic factors, concluded that any observed distribution of data points along straight lines in the ΔH–ΔS plane is more often a result of the propagation of measurement errors than of real variations in energetics. The same arguments would apply if enthalpy–entropy compensation is tested by Eqn. 6 in the ΔG–ΔS plane. For these reasons, when the measured variables are ΔG and ΔH, the examination of the thermodynamic varia-

bles should be performed in the ΔG–ΔH plane at the harmonic mean of the temperature(s) of measurement(s) (Eqn. 7) in order to provide unbiased estimates of the constants, β and ΔG_0. Throughout the tables, values of β are stated in K with the 95% confidence limit and the standard deviation (S.D.), while in the text and figure legends S.D. is stated with β in K.

Approach to data analysis

General introduction

There are few examples in the pharmaceutical literature for which sufficient thermodynamic data exist to test the principle of enthalpy–entropy compensation. However, in some cases the general trend of these values is sufficient to illustrate the existence of the compensation phenomenon. Small changes, δ, in the thermodynamics of a solid (i.e., G_{solid}, H_{solid}, S_{solid}) are expressed most conveniently in terms of the corresponding small changes for the process; solid → dilute solution, (i.e., ΔG^s, ΔH^s, ΔS^s). Thus, if the solution is dilute, $\delta(\Delta G^s) = \delta(G_{solid})$, $\delta(\Delta H^s) = \delta(H_{solid})$ and $\delta(\Delta S^s) = \delta(S_{solid})$ (Grant and York, 1986a). Since the principle of enthalpy–entropy compensation is tested using linear regression, relative values of ΔG and ΔH may be used in place of absolute values, as will be noted where appropriate in the discussion.

Determination of ΔG

In order to discern whether a material has undergone activation as a result of stress incurred during pharmaceutical processing, we equate ΔG in Eqn. 7 with ΔG^s, the free energy of solution, which is given by:

$$\Delta G^s = -RT \ln \alpha \tag{8}$$

where α is the activity of the solid state which is related to the mole fraction, x, by the activity coefficient, γ, thus:

$$\alpha = \gamma \cdot x^s \tag{9}$$

In dilute solutions the solute molecules are surrounded most of the time by solvent molecules in their immediate vicinity. Therefore, in sufficiently dilute solution molality and molarity are proportional to the mole fraction, and α in Eqn. 8 may be replaced by the corresponding concentration term. By an appropriate choice of standard state (Grant and York, 1986a), Eqn. 8 can be written as follows:

$$\Delta G^s = -RT \ln c^s \tag{10}$$

where c^s may here be determined either as the instantaneous solubility (Suryanarayanan and Mitchell, 1985) or as the dynamic solubility (Simonelli et al., 1976) of a particular solute. The conditions of determination of c^s must be such that recrystallization, which accompanies dissolution near equilibrium, exerts negligible influences.

If the solubility cannot be determined, the Noyes–Whitney (1897) relationship indicates that, under sink conditions, the intrinsic dissolution rate, J, is proportional to solubility, and may be used in its place:

$$J = \frac{dm}{dt} \cdot \frac{1}{A} = k \cdot c^s \tag{11}$$

where dm/dt is the initial dissolution rate, A is the surface area of the solid, c^s is the equilibrium solubility of the solute at the temperature of the experiment and k is the dissolution rate constant or mass transfer coefficient. Provided that fixed hydrodynamic conditions are maintained, c^s can be accurately determined from the initial dissolution rate thereby avoiding the complexities associated with the changing surfaces of dissolving particles, i.e., recrystallization.

If, for example, c^s is proportional to some quantity Q, which may be the ratio of c^s of the solid to that of a reference solid or polymorph or an intrinsic dissolution rate in the Noyes–Whitney equation, we can write:

$$c^s = k \cdot Q \tag{12}$$

and then:

$$\Delta G^s = -RT \ln Q - RT \ln k \tag{13}$$

$$= -RT \ln Q + K \tag{14}$$

which provides a means of determining the relative value of ΔG^s for the solid of interest.

Determination of ΔH

Solubility–temperature plots of pharmaceutical solids in a given solvent can provide thermodynamic data for the solution process. The familiar van't Hoff isochore may be expressed in exact form at constant pressure as:

$$\left(\frac{\partial \ln \alpha_2^{sat}}{\partial T}\right)_P = \frac{\Delta H_2^s}{RT^2} \tag{15}$$

where α_2^{sat} is the activity of the solute at saturation with respect to a suitable standard state at absolute temperature T, R is the gas constant and ΔH_2^s is the actual differential enthalpy of solution of the solute which may not be independent of temperature. The following equation for ΔH_2^s is often sufficient to allow for the influence of temperature:

$$\Delta H_2^s = a' + b' \cdot T \tag{16}$$

where a' is a constant and b' is the change in molar heat capacity of the solute, ΔC_{p2}, at constant pressure. Gill et al. (1976) have suggested that the introduction of higher polynomial orders of T (e.g., $c'T^2 \cdot d'T^3$, etc.) in this expression is unnecessary. Substituting Eqn. 16 into Eqn. 15 and integrating yields:

$$\ln \alpha_2 = -\frac{a'}{R} \cdot \frac{1}{T} + \frac{b'}{R} \cdot \ln T + \text{constant}' \tag{17}$$

Hollenbeck (1980) has noted that, in practice, the apparent partial molar enthalpy of solution, ΔH_2^{s*}, defined by the following approximation:

$$\left(\frac{\partial \ln x_2}{\partial T}\right)_P = \frac{\Delta H_2^{s*}}{RT^2} \tag{18}$$

is composed of two factors: the actual differential heat of solution and a function characterizing the extent of deviation from ideal behaviour, thus:

$$\Delta H_2^{s*} = \Delta H_2^s \left(\frac{\partial \ln x_2}{\partial \ln a_2}\right)_T \tag{19}$$

Thus ΔH_2^{s*} is only equivalent to ΔH_2^s when the partial differential coefficient in Eqn. 19 is equal to unity. By analogy with Eqn. 16;

$$\Delta H_2^{s*} = a + b \cdot T \tag{20}$$

where $b = \Delta C_{p2}^*$, the change in the apparent molar heat capacity of the solute. Substituting Eqn. 20 into Eqn. 18 and integrating affords the following non-linear relationship between $\ln x_2$ and temperature, the utility of which has recently been emphasized by Grant et al. (1984):

$$\ln x_2 = -\frac{a}{R} \cdot \frac{1}{T} + \frac{b}{R} \cdot \ln T + \text{constant} \tag{21}$$

Multiple linear regression analysis is used to quantify the variation of solubility, x_2, with absolute temperature, T, and to evaluate a, b and constant. If the partial molar enthalpy of solution may be assumed to be independent of temperature, i.e. if $\Delta C_{p2}^* \approx 0$, the following simple Van't Hoff equation results:

$$\ln x_2 = \frac{-\Delta H_2^{s*}}{R} \cdot \frac{1}{T} + \text{constant} \tag{22}$$

The fact that linear plots of $\ln x_2$ vs $1/T$ are often obtained indicates that $\partial \ln x_2 / \partial \ln \alpha_2$ and ΔH_2^s are constant within experimental error over the temperature range of the experiment and thus $b' = 0$. The use of Eqns. 21 and 22 (e.g., Van't Hoff plots) permits the determination of the apparent ΔH_2^s of the less soluble component of a multiple component system since solubility determinations can be performed specifically for the least soluble solute. This approach assumes that solubility is independent of interactions in solution and depends solely on the state of the solid phase.

The heat of solution of the solid to infinite dilution (here equal to the differential heat of solution of the solid) can be used to express ΔH values in Eqn. 7. Calorimetry usually provides a more accurate estimation of enthalpy change than temperature dependence of solubility. However, the calorimetric heat of solution represents the sum of the heats of solution of all the components present in the material and thus is better suited to solids of high purity. In fact, solution calorimetry has been used to compare the enthalpies (~

energies) of pharmaceutically processed solids with those of the untreated material (Pikal et al., 1978).

If the transition enthalpy, ΔH^t, is available instead of the enthalpy of solution, ΔH^s, we may use the following relationship to calculate the enthalpy of solution of the form of interest (subscript 2):

$$\Delta H^t = \Delta H_2^s - \Delta H_1^s \quad (23)$$

where ΔH_1^s is the enthalpy of solution of the reference solid or polymorph which may be treated as another constant K':

$$\Delta H_2^s = \Delta H^t + K' \quad (24)$$

In this fashion the relative value of ΔH_2^s may be calculated.

Analysis of available literature data

Processing of pharmaceutical solids

General introduction

The application of a mechanical force to a powder bed may bring about processes of friction, deformation, fracture and plastic flow. These phenomena in turn lead to displacements or increases in lattice defects. During fracture, the newly formed surfaces generally exhibit increased structural defects and the activation of the material increases with increasing applied stress or degree of subdivision (Lee and Mersey, 1977; Hüttenrauch, 1978; Zunino et al., 1984). The mechanical activation and lattice disruption of solids may be quantitated through the use of arbitrary crystallinity scales (Black and Lovering, 1977; Hüttenrauch, 1978; Nakai et al., 1982; Otsuka et al., 1983; Suryanarayanan and Mitchell, 1985) or entropy of processing, ΔS^p (Grant and York, 1986b). Such scales which quantitate mechanical activation and lattice disruption are useful for characterizing a particular material in pharmaceutical applications.

Recently, however, Hüttenrauch et al. (1985) employed the theory of absolute reaction rates to quantitate mechanical activation and lattice disruption. Lattice-strained material was prepared by trituration of vitamin D_2 with lactose for various lengths of time. Hüttenrauch et al. (1985), using Eyring's relationship and assuming a unimolecular mechanism, attributed the increased rate of decomposition to an increase in free energy as a result of mechanical activation of the solid. The method, however, is limited in its applicability since, not only must some readily measurable chemical rate process be available, but mechanical activation arising from multimolecular mechanisms is disregarded.

Milling

By exploiting an equilibrium property of the material such as solubility in order to determine free energy changes, Grant and York (1986a) showed that the principle of enthalpy–entropy compensation applies to dehydrated calcium gluceptate which had been milled for various lengths of time (Suryanarayanan and Mitchell, 1985). Eqn. 7 expresses the relationship between ΔG^s (Eqn. 10) and ΔH^s (from solution calorimetry) where $r = 0.996$, $T = 295.14$ K and $\beta = 329.5 \pm 2.5$ K.

Spray-drying

Although the spray drying of drug powders is a widely used technique in the pharmaceutical industry, debate still persists about the actual mechanism responsible for the observed increase in dissolution rate. Increased dissolution rates of poorly soluble drugs often result from coprocessing the drug with a polymer (Bates, 1969; Chiou and Riegelman, 1969; Corrigan et al., 1980). This has been attributed to the formation of the higher-energy amorphous form of the drug (Simonelli et al., 1969; Corrigan and Holohan, 1984) illustrated in Fig. 1. Corrigan and Holohan (1984) investigated spray-dried hydroflumethiazide-povidone systems and found that, in contrast to simple mechanical mixtures of polymer and drug, spray-dried systems were amorphous on examination by X-ray powder diffraction. The influence of dissolved povidone on the solubility of hydroflumethiazide was negligible based on the solubility of mechanical mixtures of drug and polymer. Thus, the application of Eqns. 10 and 22

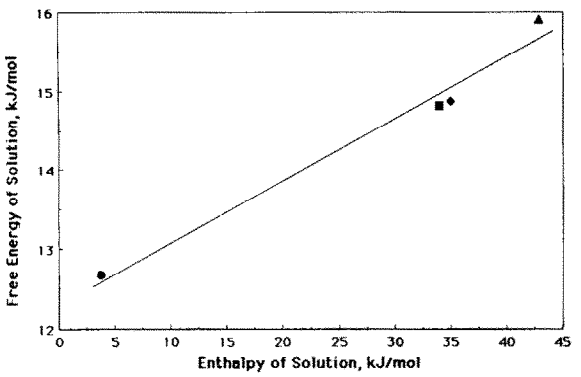

Fig. 1. Compensation relationship between free energy of solution, ΔG^s, (Eqn. 10) and enthalpy of solution, ΔH^s, (Eqn. 22) for processed hydroflumethiazide samples; $r = 0.989$, $T = 310.2$ K, $\beta = 336.6 \pm 0.1$ K and $\Delta G_0 = 12.30$ kJ·mol^{-1}. ▲, Crystalline drug; ◆, spray-dried drug; ■, spray-dried drug with 1% povidone; ●, spray-dried drug with 20% povidone (original data from Corrigan and Holohan, 1984).

to the published solubility data provides a means of determining ΔG^s and ΔH^s of the drug component. From the slope of the curve in Fig. 1, the resulting of the drug component. From the slope compensation temperature is only 27 K above experimental conditions indicating a considerable compensatory effect.

Fig. 1 illustrates the predictive capability of enthalpy–entropy compensation plots. Although Corrigan and Holohan (1984) performed solubility studies on systems containing 1, 5, 10, 15, 20, 25 and 30% povidone in the solid drug, the temperature dependence of solubility was studied only with 1 and 20% povidone in the solid. Nevertheless, the linearity of Fig. 1 permits the interpolation of ΔH as in Table 1 and hence the calculation of ΔS (from both ΔH and ΔG) for the remaining polymer systems. It should be emphasized that predictions based on enthalpy–entropy compensation should be viewed with extreme caution.

Co-precipitation

Simonelli et al. (1976) demonstrated that the apparent solubility of higher-energy forms of a drug was increased. Since the higher-energy forms are unstable thermodynamically, the determination of the apparent solubility may not be practical. By adding the polymer, povidone, as a crystallization inhibitor, the system is kinetically stabilized allowing an increase in solubility. The linear plot of the solubility of coprecipitated sulphathiazole at 17 °C vs polymer concentration was extrapolated to 0% polymer in order to provide the apparent solubility of the drug in water in the absence of povidone. This was repeated at 27 °C and 47 °C and a Van't Hoff plot was constructed from which ΔH^s was determined accord-

TABLE 1

Thermodynamic parameters of hydroflumethiazide–povidone spray-dried systems (original data from Corrigan and Holohan, 1984)

Solid form	Povidone (% w/w)	c^s [a] (mmol · litre^{-1})	ΔG^s [b]	ΔH^s [c]	ΔH^s_{pred} [d]
			(kJ · mol^{-1})		
Crystalline drug	0	2.08	15.9	43.0	46.5
Spray-dried drug with povidone	0	3.12	14.9	35.0	33.1
	1	3.19	14.8	34.0	32.3
	5	4.44	14.0	–	21.4
	10	4.94	13.7	–	17.9
	15	5.75	13.3	–	12.8
	20	7.35	12.7	3.8	4.7
	25	8.45	12.3	–	0.1
	30	8.19	12.4	–	1.1
				$r = 0.989$ $P \leqslant 0.025$, Eqn. 7	

[a] c^s = Apparent solubility determined in 0.1 N HCl at 37 °C.
[b] ΔG^s = Free energy of solution in 0.1 N HCl at 37 °C (Eqn. 10).
[c] ΔH^s = Enthalpy of solution in 0.1 N HCl at 37 °C (Eqn. 22).
[d] ΔH^s_{pred} = Enthalpy of solution in 0.1 N HCl predicted from Fig. 1 and Eqn. 7.

ing to Eqn. 22. The use of such solubility–temperature plots may in certain cases be complicated by the presence and dissolution of other possible solid phases, i.e., different crystal forms. The authors concluded, however, that the presence of any chemical barriers plays an insignificant role as evidenced by the linearity of the corresponding Van't Hoff plots. The free energy changes for the various forms of sulphathiazole were calculated relative to that of crystalline form I from the ratios of their respective solubilities according to Eqn. 14, where the constant, K, was assigned to the ΔG^s of form I.

Presentation of the data in the free energy–enthalpy domain in Fig. 2 indicates that the sulphathiazole-povidone coprecipitate (1 : 2 by weight) is not only significantly more energetic than the pure amorphous form but also lies on the regression line formed by the other 3 crystal forms. Since Simonelli et al. (1976) confirmed the solubility of sulphathiazole in water increased with increasing polymer concentration, the determination of the apparent sulphathiazole solubility at 0% polymer for other drug–polymer ratios would provide ΔG^s for these systems. Thus the drug–polymer ratio providing the highest drug concentration in solution can be selected by applying the enthalpy–entropy compensation principle. The presence of polymer will change the molecular environment, (i.e., γ in Eqn. 9), of the dissolved solute, thereby influencing the activity of the dissolved solute and hence ΔG^s, however calculated; and this will become more serious the higher the concentration of polymer in solution.

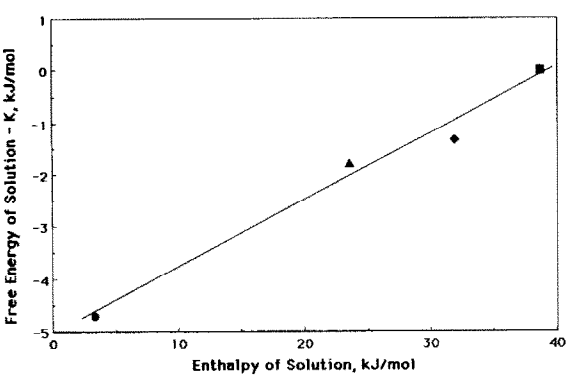

Fig. 2. Compensation relationship between free energy of solution, ΔG^s, (Eqns. 10 and 14) and enthalpy of solution, ΔH^s (Eqn. 22), for processed sulphathiazole–povidone coprecipitates; $r = 0.992$, $T = 300.2$ K, $\beta = 344.4 \pm 8.3$ K and $\Delta G_0 = -5.09$ kJ·mol^{-1}. ■, Polymorph I; ◆, polymorph II; ▲, glass; ●, drug–povidone coprecipitate (1 : 2 w/w) (original data from Simonelli et al., 1976).

Enthalpy–entropy compensation among polymorphic forms

General introduction

Polymorphic changes in pharmaceutical solids exert major effects in pharmaceutical formulation and processing (Haleblian, 1975) as well as bioavailability (Mullins and Macek, 1960). Polymorphic transitions may occur during tabletting (Nikolics et al., 1980) probably because the activated states required for phase transformations can be induced by mechanical treatment (Hüttenrauch, 1978). The pharmaceutical significance of variations in the thermodynamic properties of different crystal forms of a given drug has been investigated by Higuchi et al. (1963). The free energies of the various polymorphs of a drug determine the stability and bioavailability. Thus, any relationship between ΔG and ΔH (Eqn. 7) may be of value in understanding the factors determining the differences in activities among polymorphs and in the characterization and selection of the most suitable crystalline form for processing and bioavailability. Compounds having more than two polymorphs are required to test for linearity, as predicted by enthalpy–entropy compensation.

Chloramphenicol palmitate polymorphs

Table 2 presents the correlation for the 3 polymorphs of chloramphenicol palmitate. Aguiar and Zelmer (1969) concluded that large differences in the free energy of these polymorphs may significantly affect the absorption and resulting blood levels for this drug. Since the various polymorphs of chloramphenicol palmitate were found to revert to polymorph A in a solution of 35% t-butanol in water, the maximum concentration obtained in the dissolution-time profile of crystals of each polymorph was assumed to approximate to its true solubility. Van't Hoff plots were then con-

TABLE 2

Values of the enthalpy of solution, ΔH^s, and the free energy of solution, ΔG^s, at temperature, T, and the compensation temperature, β, from Eqn. 7, for polymorphs of chloramphenicol palmitate (original data from Aguiar and Zelmer, 1969) and metolazone (original data from Burger, 1975)

Crystal form	T (K)	ΔH^s	ΔG^s	β (K)	S.D. (K)	95% Confidence limits (K)	r
		($kJ \cdot mol^{-1}$)					
Chloramphenicol palmitate							
Polymorph A	303.2	91.2 [a]	K [c]				
Polymorph B	303.2	64.4 [a]	$K - 3.24$ [c]				
Polymorph C	303.2	72.0 [a]	$K - 1.95$ [c]				
				343.4	5.8	14	0.992
Metolazone							
Polymorph I	298.2	K' [b]	K [d]				
Polymorph II	298.2	$K' - 4.79$ [b]	$K - 1.20$ [d]				
Polymorph III	298.2	$K' - 2.04$ [b]	$K - 0.36$ [d]				
				399.5	18	45	0.990

[a] Enthalpy of solution in 35% *t*-butanol in water (Eqn. 22).
[b] Enthalpy of solution in *n*-butanol (Eqn. 21 and 24).
[c] Free energy of solution in 35% *t*-butanol in water (Eqn. 14).
[d] Free energy of solution in *n*-butanol (Eqns. 11–14).

structed for the three polymorphic forms from which ΔH^s was calculated according to Eqn. 22. Aguiar and Zelmer (1969) calculated the free energy differences between the polymorphs in question and that of polymorph A from the respective solubilities while the actual free energy of solution for polymorph A is represented by some constant K according to Eqn. 14. The calculation of the thermodynamic parameters is based on the assumption that Henry's law is obeyed, i.e., the differences in free energy are independent of the solvent used (Higuchi et al., 1963). Table 2 shows the linear relationship for the 3 polymorphs from which the compensation temperature is 343.4 ± 5.8 K at 30 °C.

Metolazone polymorphs

From the dissolution data of Burger (1975), Table 2 illustrates the existence of enthalpy–entropy compensation among the polymorphs of metolazone. Since in this case an equilibrium between the solvent and solid forms of the drug could not be established, initial dissolution rates, dm/dt, were assumed to be proportional to the solubility according to Eqn. 11. The dissolution technique used a compressed disc of known surface area, the preparation of which may have caused some change in the thermodynamic properties of the solid. A more reliable method would have been the use of the intrinsic dissolution rate, J, of the untreated solid. Since the Van't Hoff plots are not linear, the data were fitted to Eqn. 21 which provided ΔH_2^s*.

Thus, the possibility of conversion of polymorph II or III to the more stable polymorph I during pharmaceutical processing conditions can be monitored by determining either the enthalpy of solution or the dissolution profile of the sample.

Sulphanilamide polymorphs

The isolation of several polymorphs of a compound can be a difficult task, owing to the possibility of polymorphic transitions. Fig. 3 presents data calculated using Eqns. 10 and 22 from measurements of Guillory and Lin (1976) on the individual aqueous solubilities at 37 °C of 4 polymorphs of anhydrous sulphanilamide. Form α departs appreciably from the linearity exhibited by the other 3 forms which illustrates the partial conversion to the monohydrate that can occur at 38 °C. The low value of the compensation temper-

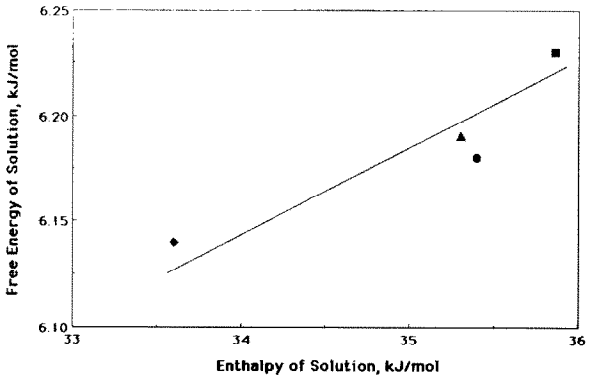

Fig. 3. Compensation relationship between free energy of solution, ΔG^s, (Eqn. 10) and enthalpy of solution, ΔH^s, (Eqn. 22) for polymorphs of sulphanilamide; $r = 0.921$, $T = 310.2$ K, $\beta = 322.2 \pm 1.4$ K and $\Delta G_0 = 4.98$ kJ·mol^{-1}. ■, Polymorph δ; ●, polymorph α; ▲, polymorph β; ◆, polymorph γ (original data from Guillory and Lin, 1976).

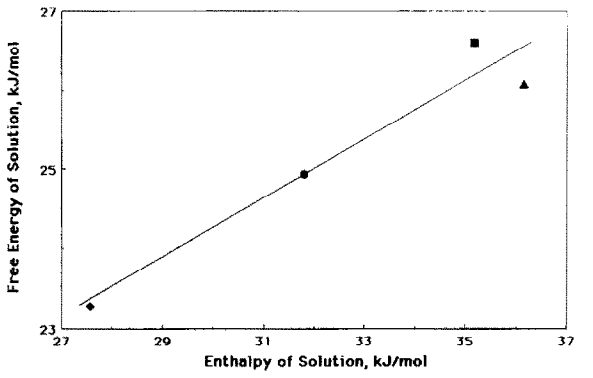

Fig. 4. Compensation relationship between free energy of solution, ΔG^s, (Eqn. 12) and enthalpy of solution, ΔH^s, (Eqn. 22) for polymorphs of acetohexamide; $r = 0.967$, $T = 303.2$ K, $\beta = 478.1 \pm 46$ K, $\Delta G_0 = 13.27$ kJ·mol^{-1}. ■, Polymorph I; ▲, polymorph III; ●, polymorph IV; ◆, polymorph V (original data from Graf et al., 1984).

ature, 322.2 ± 1.4 K, indicates extensive compensation. Guillory and Lin (1976) note that during the determination of aqueous solubility, sizeable amounts of the crystals remain in their original metastable forms in contact with water although partial conversion of the polymorphs to their hydrates does occur. The incorporation of solvent molecules into the crystal lattice may introduce an extra variable into the disruptive influence that might be reflected in the measured thermodynamic parameters, thus explaining this deviation of the α form from the enthalpy–entropy compensation line.

Acetohexamide polymorphs

Peak solubility data measured in 0.1 N HCl at 30 °C by Graf et al. (1984) for the 4 polymorphs of acetohexamide enabled both the enthalpy and the free energy of solution to be calculated by applying Eqns. 10 and 22 respectively as shown in Fig. 4. The 4 crystal forms of acetohexamide appeared to behave as two separate polymorphic systems; forms I and IV as a monotropic system and III and V as an enantiotropic system. The high value for the compensation temperature (478.1 ± 46.3 K) as compared to the other polymorphic systems discussed may be related in part to the canonical forms available to the sulphonylurea moiety in acetohexamide. These forms could give rise to different resonance hybrids with different conformations and propensity for hydrogen bonding in the solid state. The net effect results in the superposition of intramolecular chemical changes on the usual physical changes in the lattice, leading to a more complex interplay of thermodynamic factors contributing to the overall energetics of the solid.

Incorporation of foreign constituents

General introduction

The crystal lattice presents a highly ordered and structured system within which the addition of foreign constituents creates additional disorder over and above that attributable to inherent point defects and dislocations. This additional disorder is a result of the distortion of the crystal lattice by the presence of foreign constituents which possess different molecular shapes and intermolecular interactions from those of the host substance. Although not considered in detail, solvates are extreme situations of this nature for which a new crystal lattice is created and may not therefore be expected to exhibit simple enthalpy–entropy compensation effects.

The allowances provided by pharmacopoeias in

establishing purity of drugs recognize the reality that therapeutic agents are impure materials. Thus the presence of foreign constituents in solid and liquid drugs is the rule rather than the exception and for impure solids can be characterized as (a) a solid solution of a precursor of synthesis in the drug crystals; (b) molecular adducts or solid complexes resulting from interaction of the drug with solvent molecules and other complexing agents; and (c) two-phase systems. The complexity of these systems hinders the determination of thermodynamic parameters solely for the drug molecule. If, however, the solvent used in determining the solubility of these materials (e.g., water) is the same as the foreign molecule then calorimetry or Van't Hoff approaches may be applied in determining the enthalpy of solution. On the other hand, if the solvent is different from the foreign molecule, ΔG^s of the foreign molecules must be subtracted from ΔG_2^s of the solid. Furthermore, the use of calorimetric measurements would require that the portion of the solution enthalpy contributed by the foreign molecules be subtracted from the total enthalpy of solution; in these cases Van't Hoff approaches would be more suitable.

Succinylsulphathiazole hydrates

Shefter and Higuchi (1963) investigated the dissolution behaviour of crystalline hydrate and anhydrous forms of succinylsulphathiazole and confirmed that the aqueous concentration of a drug attainable in solution with a hydrate may be less than that for the stable anhydrate. Recalculated data using Eqns. 10 and 22 are presented in Table 3 and show a linear compensation effect for the anhydrate and the two polymorphs of the monohydrate.

Cephalexin hydrates

The solubility data in water obtained by Otsuka and Kaneniwa (1982) for hydrates of cephalexin, recalculated in Table 3, show a lack of linearity between ΔG^s and ΔH^s and thus indicate that non-compensating thermodynamic terms are required to describe the system. These hydrates differ in the co-ordination number (not necessarily stoichiometric) of solvating water molecules.

Discussion

This report suggests a possible application of enthalpy–entropy compensation and perhaps other linear free energy analyses of pharmaceutical materials. Increasingly thorough investigation of thermodynamic changes of processed drug entities should facilitate this. It is reasonable to expect

TABLE 3

Aqueous solution thermodynamic parameters for solvates of succinylsulphathiazole (original data from Shefter and Higuchi, 1963) and cephalexin (original data from Otsuka and Kaneniwa, 1982)

Crystal form	T (K)	ΔH^s [a]	ΔG^s [b]	β [c] (K)	S.D. (K)	95% Confidence limits (K)	r
		($kJ \cdot mol^{-1}$)					
Succinylsulphathiazole							
Anhydrate	298.2	14.3	16.8				
Monohydrate I	298.2	50.2	20.4				
Monohydrate II	298.2	49.4	19.3				
				325.8	8.9	46	0.957
Cephalexin							
Anhydrate	293.2	0.21	8.69				
Monohydrate	293.2	0.08	9.18				
Dihydrate	293.2	0.35	8.97	168.3	–	–	0.407

[a] ΔH^s = Enthalpy of solution in water (Eqn. 22).
[b] ΔG^s = Free energy of solution in water (Eqn. 10).
[c] β = Compensation temperature (Eqn. 7).

that whenever a crystal lattice is stressed, externally via mechanical treatment or internally via the incorporation of foreign constituents, an increase in disorder (reflected in ΔS) is obtained as well as an increase in internal energy (reflected in enthalpy increase, ΔH) which express the thermodynamic changes resulting from lattice disruption. When, however, the compositions of the systems being manipulated depart appreciably from the pure drug substance, the free energy–enthalpy plots appear to depart from linearity. This may arise from the replacement of simple interactions between like molecules by those between dissimilar molecules thereby introducing new entropy and enthalpy terms.

Inherent errors in the estimation of the enthalpy of solution from the slopes of Van't Hoff plots of the literature data may have also contributed to the departure from linearity in the compensatory plots. Since measurement errors are randomly distributed when presenting thermodynamic data in the free energy–enthalpy plane, it is prudent to determine these quantities independently. Solution calorimetry is then the method of choice for enthalpic determinations. Likewise the change in the free energy of solution can be determined by applying the Noyes–Whitney relationship (Eqn. 11) and can be directly related to the instantaneous solubility. Work is currently under way in our laboratory to test the applicability of this approach.

Although speculation on the physicochemical meaning of the compensation temperature, β, has been criticized (Krug et al., 1976), the fact that a straight line is obtained in a ΔG vs ΔH plot indicates a common element is responsible for its existence. Unlike solution studies of compensation behaviour where values for β can range far from the temperature of measurement (Leffler, 1955), the compensation temperatures of the solid sys-

TABLE 4

Summary of systems displaying enthalpy–entropy compensation

Systems	Main component	Other component	Nature of lattice differences	Data available and treatment	T [a] (K)	β [b] (K)	S.D. (K)	95% Confidence limits (K)	$\beta - T$ (K)
Processed solids									
Milling	Calcium gluceptate	None	Disruption	Solubility, Calorimetry	295	330	2.5	4.0	35
Spray-drying	Hydroflumethiazide	Povidone	Disruption	Solubility, Van't Hoff	310	337	0.1	0.2	27
Co-precipitation	Sulphathiazole	Povidone	Disruption	Solubility, Van't Hoff	300	344	8.3	13	44
Polymorphs									
	Chloramphenicol palmitate	None	Structure	Solubility, Van't Hoff	303	343	5.8	14	40
	Metolazone	None	Structure	Dissolution, Van't Hoff	298	399	18	45	101
	Sulphanilamide	None	Structure	Solubility, Van't Hoff	310	322	1.4	2.2	12
	Acetohexamide	None	Structure	Solubility, Van't Hoff	303	478	46	74	175
Hydrates									
	Succinyl–sulphathiazole	Water	Solvation	Solubility, Van't Hoff	298	326	8.9	46	28
	Cephalexin	Water	Solvation	Solubility, Van't Hoff	293	no discernible compensation			

[a] Temperature of measurement.

[b] Compensation temperature (Eqn. 7).

tems considered in this paper are often quite close to ambient conditions. If the temperatures of measurement, T, and compensation, β, are close, the sensitivity of ΔG will be small and may be either indiscernible or subject to large errors. Indeed, Franks (1975, referring to aqueous mixtures) stated that the free energy term is not a very discriminating function and thus may conceal more than it reveals.

The examples of compensation relationships discussed (Table 4) give correlation coefficients of 0.90 or better, the exception being cephalexin hydrates. When lattice disruption as a result of pharmaceutical processing of a solid fails to exhibit a linear behaviour in the ΔG–ΔH plane, two explanations are proposed. One is that the physical changes have been studied at the compensation temperature and are therefore not evident. The other is that the mechanism does not involve a simple principal factor but rather numerous and random perturbating mechanisms. On the other hand, a high correlation coefficient does not always mean that the relationship is a single interaction mechanism, since if β values happen to be equal, two mechanisms would result in a single straight line. The fact that β is positive for all the solid state modifications presented here is theoretically expected. For each modification of interactions between lattice constituents, the minimum internal energy and entropy existing when certain specific geometrical conditions are satisfied no longer prevails. These conditions constitute an increase in lattice strain with correspondingly extra degrees of freedom and mean that the increase in energy will be accompanied by some increase in entropy. If energizing and disordering of the crystal lattice are indeed linearily related, then any one of the quantities, ΔG, ΔH and ΔS for the process, solid → solution, can predict the remaining two quantities.

Conclusion

Recognizing that induced lattice disruptions are thermodynamically unstable, the use of thermodynamics to express material alteration during pharmaceutical processing warrants further development. Since disorder of a lattice structure can be quantitated in terms of entropy and since the accompanying increases in lattice energies can be quantitated in terms of enthalpy, a relationship between these quantities has a predictive capability. Literature data presented here indicate that enthalpy–entropy compensation may occur in a number of situations in pharmaceutical processing and formulation. Comminution, spray-drying and polymer coprocessing of pharmaceutical powders evidently cause changes in material behaviour, the magnitude of which can be predicted from analysis of free energy–enthalpy plots. Polymorphic transitions also appear to exhibit compensation phenomena. Cephalexin hydrates do not display simple compensation phenomena, but follow a more complex behaviour, perhaps involving significant contributions from drug–water and drug–drug interactions.

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