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The role of compensation analysis in the study of wettability, solubility, disintegration and dissolution

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Summary

In the past, considerable effort has been devoted to understanding the processes of wettability, solubility and disintegration, and their respective roles in the dissolution of solid oral drug delivery systems. In this study, data from the literature that relate to each of these physical processes are considered in terms of compensation analysis. Compensation analysis is a method by which relationships between different samples, and outliers from an otherwise common trend can be investigated. The correct approach to the calculation of thermodynamic parameters, in order to avoid false correlations that are simply artifacts of the calculation method, is discussed. Compensation can be a valuable tool by which physicochemical effects can be studied, and thus is of value to aid the explanation of complex drug release studies.

Introduction

For a solid oral dosage form to be effective, it will usually be necessary for the drug to dissolve in the gastro-intestinal fluids prior to absorption. The process by which a drug dissolves from a product is termed dissolution, but in fact rather than consisting of one process, dissolution is a combination of many facets. The areas of interest are: the wettability of the product, the solubility of the drug and excipients, and perhaps disintegration of the product into smaller units. Each of these areas of interest are extremely complex and each individually form the subject of many volumes of published material. The purpose of this publication is not to consider all aspects relating to wettability, solubility, disintegration and dissolution, but to explore some aspects of the relationships between these processes and to demonstrate the potential value of compensation analysis to the development of an understanding of this field.

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Compensation analysis

A review by Tomlinson (1983) drew attention to the value of compensation analysis of pharmaceutical systems, it began "Although linear free energy relationships are familiar research tools in pharmaceutical and biochemical science, the analysis of data in terms of a further extrathermodynamic analysis, namely enthalpy-entropy compensation, is little used". Since 1983 very little has changed, and compensation analysis remains under utilised.

The extreme complexity that is inherent to many aspects of pharmaceutical science is alluded to above; the 'simple' act of dissolving a drug can involve wettability, solubility, and disintegration all of which can be divided into different mechanisms. When these three processes are considered for each of the components of a tablet, with the possibility of interactions in behaviour, it is clear that data interpretation, in terms of the mechanism of drug release and the investigation of the influence of different components of the product, will be extremely difficult. Compensation analysis allows the worker to identify systems with common mechanisms, and to identify outliers to the general relationship; it will be obvious from the examples presented below that such information is often not available from attempts to explore simple correlations from the raw experimental data.

Compensation analysis is derived from the field of extrathermodynamics, meaning that it does not form a part of classical thermodynamics, but rather looks for relationships between thermodynamic parameters.

Enthalpy-entropy compensation is simply obtained by plotting these two parameters for a range of systems, and looking for any evidence of a linear relationship. Many standard chemistry texts have treated these linear, and rarely non-linear, relationships as proof of a common causative mechanism (e.g. Laidler, 1965; Hammett, 1970), however the work of Krug et al. (1976a–c) has shown that systems without a common mechanism can result in a linear enthalpy-entropy plot simply because of artifacts in the method of calculation. If thermodynamic functions are obtained from a van't Hoff or Arrhenius relationship, then enthalpy will be calculated from the gradient of a plot of ln K (or k) as a function of $1/T$ (where K and k are equilibrium and rate constants, respectively, and T is the absolute temperature), and the entropy term will be calculated from the intercept on the y-axis. Inevitably as the gradient alters (enthalpy changes) so the intercept will alter proportionally, thus enthalpy and entropy will tend to show correlations irrespective of true commonality of mechanism. It has been shown in the literature (Krug et al., 1976a) that the greater the inaccuracy present in the measurement of enthalpy and entropy, the greater will be the correlation between these two parameters, thus, in the worst instance, a high correlation between enthalpy and entropy demonstrates nothing other than poor experimental technique. The alternative to this situation is to plot ln K (or k) as a function of $(1/T - 1/T_{mean})$, where T_{mean} is the harmonic mean temperature. In this instance, the changes in gradient (enthalpy) will not influence the intercept on the y-axis. The intercept allows the calculation of the free energy (Krug et al., 1976a). Compensation in the enthalpy-free energy domain, at the harmonic mean temperature, will be a true test of common mechanism. If a microcalorimeter is used to obtain the enthalpy, and the free energy is derived from other experiments, then there is still a problem with enthalpy-entropy plots as the entropy (S) will be obtained from the enthalpy (H) term using:

$$\Delta G = \Delta H - T\Delta S \qquad (1)$$

There are many examples in the literature where a common mechanism is claimed on the basis of an enthalpy-entropy correlation, even when no correlation exists in the enthalpy-free energy domain, for example an enthalpy-entropy plot was used to describe common mechanisms of drug protein interactions (Perrin, 1985), if the author had plotted the data in the enthalpy-free energy domain no correlation would have been observed. A similar example is for the complexation of drugs with beta-cyclodextrin (Hardee et al., 1978) where a $\Delta H/\Delta S$ correlation is quoted although no $\Delta H/\Delta G$ correlation exists.

Results and Discussion

Wettability and solubility

The importance of wettability and surface energy cannot be overstated. As all interactions occur at interfaces, it can reasonably be assumed that the behaviour of surfaces will play a vital role in all aspects of the preparation and use of products. Recent publications have demonstrated that surface energies can be used to predict the spreading of binders over powders during granulation

(e.g. Rowe, 1989), and indeed the properties of the tablets that are produced (e.g. the friability etc.) (Rowe, 1990). It is well known that the adhesion of film coatings onto tablets is related to surface energies, as is the ease of dispersion of powders in liquids, and the tendency of powders to aggregate in suspension (Young and Buckton, 1990). In this work only the role of wettability as a forerunner to solubility will be considered.

It is accepted that the dissolution rate of a drug is directly proportional to its solubility (e.g. Valvani and Yalkowsky, 1980), furthermore, the Noyes Whitney equation:

$$dm/dt = bA(C_s - C) \quad (2)$$

[where the dissolution rate, expressed as the mass (m) of drug transferred in time t, is related to the surface area (A), the concentration of drug at time t (C), the concentration of drug required to saturate the media (C_s) and a constant (b)] demonstrates that the dissolution rate is directly proportional to the effective surface area of the product. The surface area will be determined by many factors, including wettability. It is not possible for a drug to dissolve unless it is at least partially wetted, as zero wetting will, by definition, result in no drug in contact with the fluid, i.e. $A = 0$.

It is often assumed that if a drug is insoluble it will be poorly wetted and vice versa. This is not the case, for example $CaHPO_4$ is insoluble but hydrophilic (Carmella et al., 1988). In similar vane, solubility (and by extension wettability) is often regarded as a simple function of chain length; the relationships are not this simple. To demonstrate this point, the solubilities of the alkyl *p*-aminobenzoates (Yalkowsky et al., 1972) show that a break in the relationship between length of the carbon side chain and aqueous solubility occurs at about 4 carbons. The wettability of such systems is further complicated as it is a function of chemical composition at the powder surface, and the past history of the sample, e.g. milling, etc. (see Buckton et al. (1988) for an example of how milling affects the surface energies of a powder).

The relationship between wettability and dissolution rate has been investigated in a number of publications (e.g. Lippold and Ohm, 1986), but, this is a complex field of study and simple relationships between these parameters are often difficult to obtain.

Relationships between wettability and solubility can, however, be investigated by use of compensation analysis. Using the extrathermodynamic approach, it is possible to investigate common mechanisms for wettability, common mechanisms for solubility and then, by comparison, investigate any relationships that exist between these two physical properties. Although this approach has not been explored in the pharmaceutical literature, it is possible to draw on published data to demonstrate how it could be of value.

The thermodynamic parameters of wetting can be assessed by vapour sorption, either by recording uptake in a vacuum microbalance at different temperatures (the isosteric method, e.g. Buckton et al. (1986)) or by comparison of uptake data from isothermal work using a vacuum microbalance and a microcalorimeter (Buckton and Beezer, 1988). The solution thermodynamics can be obtained by determining equilibrium solubilities at different temperatures and then using a van't Hoff operator. The thermodynamics of adsorption obtained from microcalorimetric (Buckton and Beezer, 1988) and isosteric (Buckton et al., 1986) experiments for a series of substituted barbiturates all have near identical values of ΔG (Table 1), even if the thermodynamic functions are calculated at the harmonic mean temperature. This means that despite the severe reservations that are noted above, compensation must be studied in the enthalpy-entropy domain. The goodness of fit ($r = 0.999$) for the enthalpy-entropy plot for the isosteric thermodynamic adsorption parameters, is of no great significance (Buckton and Beezer, 1989), however, the important factor is the ranking of the compounds on the compensation plot, i.e. the most hydrophilic is butobarbitone, then phenobarbitone, pentobarbitone and amylobarbitone.

The solution thermodynamics for some substituted barbiturates have been recalculated from published data (Wang and Paruta, 1984a,b) at the harmonic mean temperature (Table 2). Fig. 1 shows the enthalpy-free energy compensation plot. A reasonable correlation exists, with the

TABLE 1

The thermodynamic functions of adsorption of water onto selected barbiturates [isosteric data (subscript iso) from Buckton et al, (1986) and calorimetric data (subscript cal) from Buckton and Beezer (1988)]

Powder	$\Delta_{ads}G$ (kJ/mol)	$\Delta_{ads}H_{cal}$ (kJ/mol)	$\Delta_{ads}H_{iso}$ (kJ/mol)	$\Delta_{ads}S_{cal}$ (J/mol per K)	$\Delta_{ads}S_{iso}$ (J/mol per K)
Amylobarbitone	38.4	−25.2	−66.8	−214.4	−353.0
Pentobarbitone	38.4	−12.7	−67.5	−171.5	−355.4
Phenobarbitone	38.6	−8.1	−65.2	−156.7	−348.3
Butobarbitone	38.4	−4.5	−61.4	−144.0	−334.9

possible exceptions of phenobarbitone and vinbarbitone (5-ethyl-5(1-methyl-1-butenyl)barbituric acid) which are the only structures which have unsaturated bonds (the ring structure in phenobarbitone and a double bond in vinbarbitone). The results would suggest that the structure of the molecule (presence of unsaturated bonds) affects the solution mechanism. When compared with the data for wettability, the solubility results reveal that phenobarbitone is displaced in the ranking of the compounds (Fig. 1), suggesting that the mechanisms for wettability and solubility are not the same. It is reasonable that the wettability and solubility of a powder will vary independently, solubility will be a function of the molecular structure of the compound (size, shape, area, functional groups etc.), the binding energy within the crystal and the solid/liquid interaction; wettability will relate to the exposed regions of the surface of the crystal, thus the chemical structure will affect the results, but not all functional groups will play a part in this surface phenomena, as some may be fully internalised. The surface of a solid is also altered by physical treatment, e.g. crystallisation procedure and milling (see Buckton et al., 1988), thus further complicating any relationship between solubility and wettability.

Compensation analysis offers scope for the investigation of these complex relationships, particularly in cases where the free energy of the wetting process varies sufficiently to allow the more reliable enthalpy-free energy compensation plot.

TABLE 2

Solution thermodynamics at the pK_a for substituted barbituric acids, calculated at the harmonic mean temperature from the data of Wang and Paruta (1984b)

Powder	ΔH (kJ/mol)	ΔG (kJ/mol)	ΔS (J/mol per K)
Barbitone	14.8	91.4	−250.7
Butobarbitone	13.9	93.3	−259.9
Metharbitone	18.3	94.3	−248.8
Probarbital	20.9	95.4	−243.9
Phenobarbitone	28.7	96.0	−220.2
Pentobarbitone	23.7	96.7	−238.9
Secbutabarbitone	25.2	96.4	−233.0
Vinbarbitone	42.9	96.7	−176.1
Amylobarbitone	25.6	97.8	−236.2
Thiopentone	40.6	103.6	−212.6

Disintegration

Disintegration can play an important role in the dissolution, and hence bioavailability, of a tabletted product. Indeed, the disintegration of a

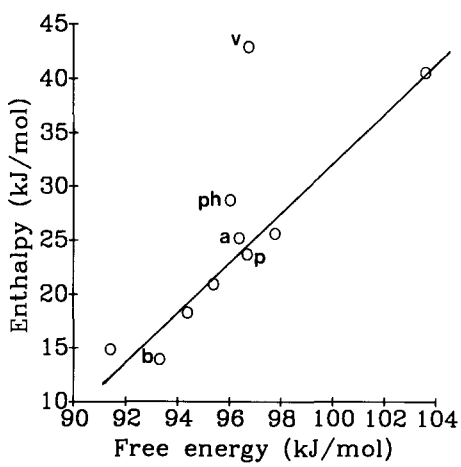

Fig. 1. Free energy-enthalpy compensation plot for the solution thermodynamics of substituted barbituric acids. ph, phenobarbitone; v, vinbarbitone; a, amylobarbitone; b, butobarbitone; p, pentobarbitone.

product can be the rate limiting step in the dissolution and absorption process (Caramella et al., 1988). The disintegration process has been modelled as a combination of detachment of particles from the solvent/tablet interface and the diffusion of detached molecules away from the interface into bulk solution (the interfacial and diffusional models respectively) (e.g. Caramella et al., 1988). Thus the wettability of the product is inextricably linked to not only the dissolution, but also the disintegration process.

Peppas et al. (1989) have demonstrated that the expansion rate constant for the disintegration of a tablet, can be used to ascertain whether the disintegration is predominantly of the interfacial or diffusional mechanism. The approach is based on the Arrhenius expression, using an expansion for two processes:

$$k = k_0 \exp[-E_1/RT_d]\exp[-E_2/RT_d] \quad (3)$$

where k is the rate constant for disintegration, k_0 is a pre-exponential constant, T_d is the disintegration time, and E_1 and E_2 are the activation energies for the two processes. For the diffusional process, the Williams Landel Ferry equation can be applied (see Peppas et al. (1989)):

$$E_1 = 4135T_d/(51.6+T_d-T_g) \quad (4)$$

where T_g is the glass transition temperature for the product. The interfacial process is based on the Avrami equation (see Peppas et al. (1989)):

$$E_2 = 4L\sigma_s\sigma_c T_g/\Delta H_m(T_d-T_g) \quad (5)$$

where σ_s and σ_c are the surface free energies of the peripheral area and the end plane of a tablet with thickness L. ΔH_m is the enthalpy of formation for a tablet of known thickness and molar composition.

This erudite data interpretation involves certain complex processes, e.g. measurement of T_g values for the components of the tablet. It is possible that the two mechanisms (i.e. interfacial and diffusional) can be distinguished by use of compensation analysis. Peppas et al. (1989) have demonstrated that of their four formulations, those containing

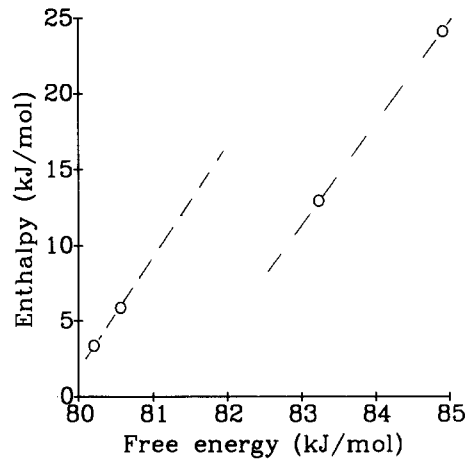

Fig. 2. Free energy-enthalpy compensation plot for the disintegration of four different tablet formulations, two of which have been shown to disintegrate by an interfacial and two by a diffusional mechanism (after Peppas et al. (1989)).

polyplasdone XL and Ac-di-sol disintegrated predominantly by the interfacial, and those containing Primojel and Avicel PH-101 disintegrated predominantly by the diffusional mechanism. If the natural logarithm of the expansion constants for the disintegration of these products is plotted as a function of $(1/T-1/T_{mean})$ then the thermodynamic functions can be determined (as described by Krug et al. (1976b)). The enthalpy-free energy compensation plot (Fig. 2) can be represented as two different processes (albeit with only two points on each line). It should be possible for any other formulation that is prepared to be tested for a dominant interfacial or diffusional disintegration mechanism, by its fit to one of these lines, without the need to measure glass transition temperatures etc.

As discussed in the preceding section, it would be interesting to compare compensation plots for the same compounds for the different processes i.e. wettability, solubility and disintegration.

Dissolution

It has been noted above that dissolution is in fact a composite process consisting of all or some of the following: wetting, disintegration, diffusion, solution. Many approaches have been used in attempts to characterise the process(es) by which drug is release from solid oral dosage forms

and, in particular, controlled/sustained release systems. Higuchi (1963) derived a relationship which identified the presence of a diffusional mechanism, and many other workers have developed this, or similar themes, over the past 27 years (e.g. Cobby et al., 1974; Fessi et al., 1978; Bamba et al., 1979; Gurny et al., 1982; Korsmeyer et al., 1983; Lee and Peppas, 1987). Dissolution is a complex study, but compensation analysis can be used to identify products with similar, and indeed dissimilar release mechanisms. Due to the complex range of processes, it is possible, but not proven, that a large number of dissolution mechanisms may exist for products with different formulations and methods of manufacture.

In recent publications (Buckton and Efentakis, 1990; Buckton et al., 1990), compensation analysis has been utilised to investigate mechanisms of dissolution from controlled release dosage forms. Controlled release products containing indomethacin as a model drug, were prepared using a matrix of Eudragit RS, with lactose and magnesium stearate as the diluent and lubricant. Tablets were prepared by direct compression of powder mixes, with the addition of sodium lauryl sulphate (0, 0.25 or 1% w/w), also the polymer was dissolved in an organic solvent and used to form a granulation prior to tabletting. For the granulated product, the surfactant was added either in the granulating fluid or as a mix just prior to tabletting. Dissolution experiments were undertaken at four different temperatures and the thermodynamic activation parameters were calculated from an Arrhenius plot (cf. Krug et al., 1976a). All formulations showed pseudo-zero order release, but with certain formulations there was a change in rate during the dissolution process. For ease of comparison the results for the initial release only are presented in Table 3.

TABLE 3

The thermodynamic parameters of activation for the dissolution of Eudragit/indomethacin/lactose matrix tablets, calculated at the harmonic mean experimental temperature

Formulation	$\Delta H^{\ddagger}$ (kJ/mol)	$\Delta G^{\ddagger}$ (kJ/mol)	$\Delta S^{\ddagger}$ (J/mol per K)
DC	40.6	90.9	−163.6
$DC_{0.25}$	60.2	89.8	− 96.3
DC_1	76.4	6.5	− 32.8
G	16.1	92.7	−249.2
$G_{0.25A}$	23.0	91.8	−224.0
$G_{0.25B}$	38.1	92.6	−177.3
G_{1A}	33.1	91.3	−189.1
G_{1B}	42.3	91.7	−160.7

DC, directly compressed mixture; G, granulated product; Subscripts: % w/w of added sodium lauryl sulphate which was added either (A) after granulation as a mix, or (B) before granulation in the granulating fluid.

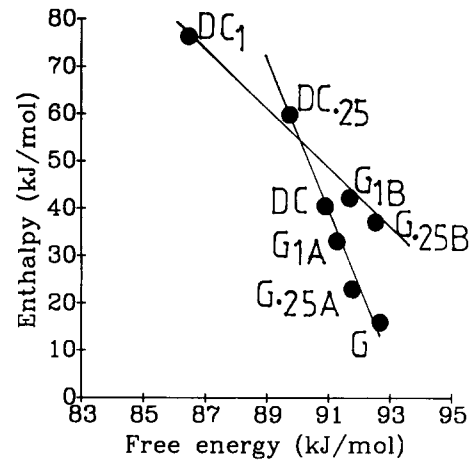

Fig. 3. Free energy-enthalpy compensation plot for the dissolution of indomethacin tablets prepared with differing amounts of surfactant and by direct compression or granulation (key: see Table 3).

Fig. 3 shows the free energy-entropy compensation plot for the dissolution of the indomethacin formulations. A possible interpretation (see Buckton et al., 1990) is that two mechanisms exist, one for products in which the polymer is not disrupted (those without added surfactant, and those which were granulated prior to adding the surfactant) and the other for products in which the Eudragit structure is compromised (i.e. those in which the surfactant is included in the granulating fluid and the directly compressed products with added surfactant, particularly when the concentration is high).

From these initial results it would appear that compensation analysis has a valuable application in studies of dissolution mechanism.

Conclusions

From both a fundamental and practical view point, there is considerable interest in the processes of wettability, solubility, disintegration and dissolution. It would be valuable to assess the relative importance of these different processes on the release of drug from delivery systems. Despite many valuable publications in this field of study, there is still a lack of understanding as to how and why various factors will influence drug release from a solid dosage form. The factors of importance are the composition of the product i.e. the effects of different drugs and excipients, and the method of production (including granulation and direct compression).

Thermodynamic parameters offer a valuable tool by which the investigator can explore mechanism. The use of extrathermodynamics, in the form of free energy-enthalpy compensation analysis, allows the study of the effects of physicochemical structure on various phenomena. From the limited data in the literature, it can be seen that it is possible to investigate wettability, solubility, disintegration and dissolution by this approach. Indeed it is also possible to consider partitioning, e.g. liquid/liquid and liposome/water systems, biological membrane permeation, and receptor and enzyme interactions (for further details the reader is directed to the excellent review by Tomlinson, 1983). The ultimate extension of this approach is that the action of drugs, for which it is not unusual to describe structure activity and linear free energy relationships, can be presented in the form of compensation analysis; a published example of this is the interaction of nystatin with *Saccharomyces cerevisiae* (Beezer, 1984). An integrated approach by which thermodynamic parameters are obtained for as many of the different processes as possible, could prove extremely valuable in determining the relative contributions and importance of different physical aspects to drug release, and indeed drug action.

By way of caution, it should be stated that although compensation analysis shows common mechanism and the existence of outliers, it does not demonstrate that the behaviour can be attributed to any one particular phenomenon, thus other supportive approaches will often be necessary. Furthermore, it is preferable to obtain thermodynamic data by calorimetric means, rather than through a van't Hoff operator, as this improves the accuracy and, with regard to mechanism, the reliability of the data (e.g. see Schroder, 1984; Buckton and Beezer, 1988).

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