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The use of thermodynamic activation parameters and compensation analysis to model drug release from hydrophobic matrices

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Summary

Tablets have been prepared by use of combinations of indomethacin, Eudragit, lactose and magnesium stearate. The processes of granulation and direct compression have been compared. The effect of adding a surface active agent to the formulation was assessed by adding sodium lauryl sulphate to a sample of the powder mix and then preparing directly compressed and granulated formulations. Two granulated samples were prepared, one with surfactant inside and the other with surfactant outside of the granule. Dissolution profiles were monitored over an 8 h period at four temperatures (range 26–43°C). Apparent zero-order rate constants were calculated over the entire 8 h process in the case of the samples without surfactant. The samples with included surfactant did not fit a single zero-order release profile and were therefore described by two apparent zero-order rate constants, one over the first 2 h and then one over the period from 3 to 8 h. The thermodynamic activation parameters were calculated for each formulation. A linear relationship was observed between the initial entropy of activation and the percentage drug release at a fixed time. It would appear that the entropic term is a dominant factor in the drug release process(es). Enthalpy-entropy and enthalpy-free energy compensation analysis was employed to test the existence of a common mechanism of dissolution from each sample. A linear enthalpy-entropy compensation plot was obtained for each sample, the enthalpy-free energy plot (which is the more rigorous test) also indicated a common mechanism, but the correlation was not as good. Compensation analysis would seem to provide a useful method of comparing mechanism of release from different formulations.

Introduction

Sustained and controlled release oral dosage forms are now used extensively to optimise drug delivery regimes. A number of approaches exist by which the release profile of a drug from the product can be described; these include simple kinetic (zero-order or first-order) and diffusion models (e.g., Higuchi, 1963; Cobby et al., 1974; Fessi et al., 1978; Bamba et al., 1979; Gurny et al., 1982; Korsmeyer et al., 1983; Lee and Peppas, 1987).

In a recent publication (Efentakis and Buckton, 1990) we argued the case for considering the use of thermodynamic activation parameters to describe and characterise the mechanisms of drug

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release from controlled release dosage forms. This paper extends the previous work, by considering the influence of a wetting agent on the release profiles. The thermodynamic activation parameters have been calculated for a number of systems and the different results compared by use of compensation analysis. Compensation analysis looks for links between thermodynamic parameters, for example, enthalpy and entropy; a linear relationship can provide evidence of a common mechanism of action. This approach is not used widely in the pharmaceutical literature, despite the existence of an introductory review which demonstrates its potential value (Tomlinson, 1983).

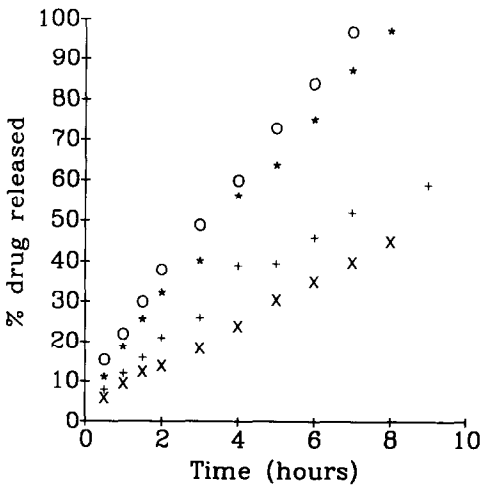

Fig. 1. Drug release (%) as a function of time from formulation A, at 26.0 (×), 31.0 (+), 37.5 (*) and 43.0 °C (○). Reproduced from Efentakis and Buckton (1990).

Materials and Methods

Sustained release tablets of indomethacin were prepared using the method and control criteria that were reported previously (Efentakis and Buckton, 1990). All formulations contained 27% w/w indomethacin (Sigma), 51.1% w/w lactose (Zaparox), 20.9% w/w Eudragit RS 100 (granule form, Rohm Pharma) and 1% w/w magnesium stearate (BDH). Formulations G_2 and G_3 also had 1% w/w sodium lauryl sulphate added, after granulation or during granulation respectively, and formulation B had 0.25% sodium lauryl sulphate (1% was found to cause very rapid drug release in directly compressed formulations and, therefore, could not be used).

Formulations A and B were directly compressed from powder mixtures (Turbula T2C, Bachofern, Basel, 15 min mixing time), by hand filling into a Manesty F3 tabletting machine.

Formulations G_1, G_2 and G_3 were all granulated (see Efentakis and Buckton, 1990), the only difference being that, as explained above, formulation G_1 had no surfactant present, G_2 had surfactant added after the granulation process (i.e. outside of the granules) and G_3 had the surfactant added during granulation (i.e. inside the granules). The rationale for these variations was to see if the position of the surfactant had any significant effect on the drug release mechanism.

Dissolution experiments were undertaken in a USP apparatus (paddle, 100 rpm), using 750 ml of pH 7.4 phosphate buffer (USP). The experiments were carried out at 26.0, 31.0, 37.5 and 43.0 °C. Samples, which were taken periodically over an 8 h period, were filtered and analyzed using a UV spectrophotometer (318 nm). Results are averages of six determinations, which showed high reproducibility.

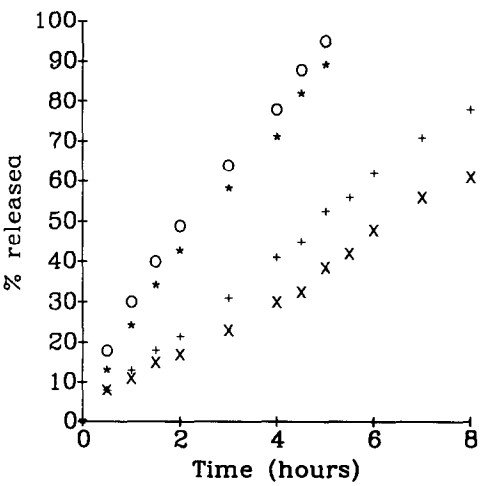

Fig. 2. Drug release (%) as a function of time, from formulation B, at 26.0 (×), 31.0 (+), 37.5 (*) and 43.0 °C (○).

Results

Figs 1–5 show the dissolution results for each of the five formulations at each of the four temperatures. In order to calculate the thermodynamic activation parameters, it is necessary to obtain rate constants for the dissolution process (es). The formulations which contain no surfactant have already been ascribed zero-order rate constants (Efentakis and Buckton, 1990). The formulations that have surfactant included do not fit simple kinetic profiles. Attempts to fit either simple zero- or first-order kinetics were unsuccessful, however, if the process is treated as two stages it is possible to calculate an apparent zero-order rate constant for 0.5–2 h and another apparent zero-order rate constant for the period from 3 to 8 h. The formulations without surfactant present can be seen to exhibit a small deflection in their release profiles after about two hours, at the highest temperature (Figs 1 and 2). The apparent rate constants are presented in Table 1.

The thermodynamic parameters of activation can be calculated from a plot of ln k (k = rate constant) as a function of the reciprocal of absolute temperature (T). The enthalpy and entropy terms can be calculated from the gradient and intercept of such a plot (Atkins, 1988). Consequently, the Gibbs function can be calculated.

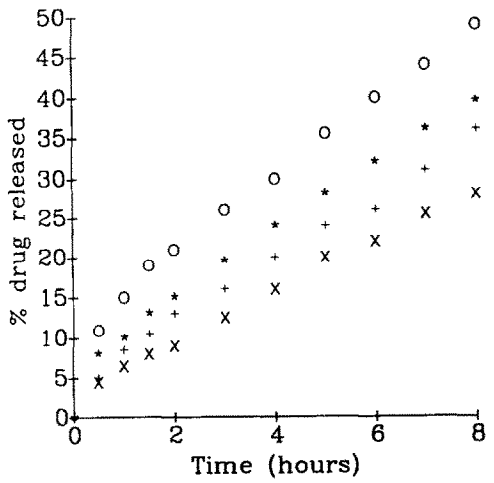

Fig. 3. Drug release (%) as a function of time, from formulation G_1 at 26.0 (×), 31.0 (+), 37.5 (*) and 43.0 °C (○). Reproduced from Efentakis and Buckton (1990).

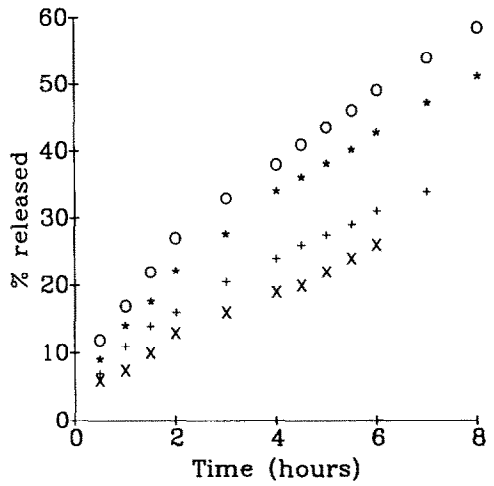

Fig. 4. Drug release (%) as a function of time, from formulation G_2 at 26.0 (×), 31.0 (+), 37.5 (*) and 43.0 °C (○).

The thermodynamic parameters for activation for the samples with no surfactant present have been calculated before (Efentakis and Buckton, 1990) and are shown in Table 2 (N.B. the notation in the previous paper is not consistent with the current work, formulations B and G from Efentakis and Buckton (1990) are referred to as formulations A and G_1, respectively, in this work).

The samples in which surfactant was included all produced reasonable fits to a plot of ln k as a function of $1/T$ (Figs 6–8), when the data were treated as two sequential processes.

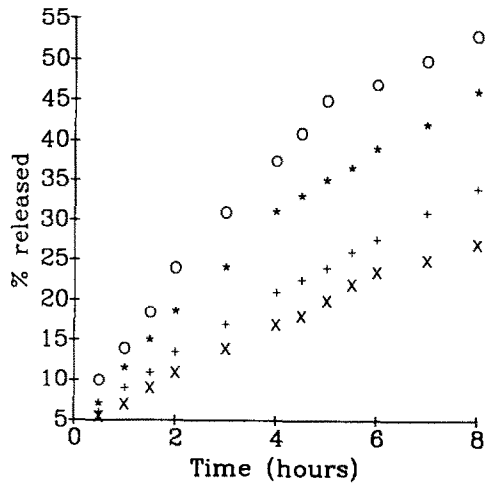

Fig. 5. Drug release (%) as a function of time, from formulation G_3 at 26.0 (×), 31.0 (+), 37.5 (*) and 43.0 °C (○).

TABLE 1

Apparent zero-order rate constant for drug release at 37.5 °C

Formulation	Rate constants ($\times 10^3$) (s^{-1})		
	0.5–8 h	0.5–2 h	3–8 h
A	3.14	–	–
B	–	5.47	4.30
G_1	1.18	–	–
G_2	–	2.36	1.27
G_3	–	2.11	1.15

Correlation coefficients for % drug released as a function of time, as used to calculate the apparent rate constants were in the region of 0.99 (or above) for each system.

TABLE 2

Thermodynamic parameters for activation calculated for T = 310 K

Formulation	$\Delta H^{\ddagger}$ (kJ/mol)	$\Delta G^{\ddagger}$ (kJ/mol)	$\Delta S^{\ddagger}$ (J/mol per K)	r
A (0.5–8 h)	40.7	102.5	−199.5	0.977
B (0.5–2 h)	60.2	101.0	−131.7	0.975
B (3–8 h)	41.5	101.1	−192.4	0.995
G_1 (0.5–8 h)	16.1	104.3	−284.5	0.985
G_2 (0.5–2 h)	33.1	102.7	−224.8	0.995
G_2 (3–8 h)	20.8	104.3	−269.4	0.974
G_3 (0.5–2 h)	42.3	103.1	−196.2	0.995
G_3 (3–8 h)	19.3	104.6	−275.1	0.995

r = correlation coefficient for the plot of ln k as a function of $1/T$.

Discussion

It has been noted (Efentakis and Buckton, 1990) that the thermodynamic activation parameters offer a method by which the drug release from a hydrophobic matrix can be described and quantified. When considering a directly compressed and a granulated system (Efentakis and Buckton, 1990) it was observed that the thermodynamic functions suggested a disfavoured process; this is in line with the sustained release effect.

The values for the Gibbs function are very similar for each system studied in this work (Table 2), showing a total variation of between 101.0 and 104.6 kJ/mol. The dissolution process will, therefore, be dominated by the relative magnitude of the enthalpic and entropic factors.

A trend exists whereby the product with the fastest dissolution rate (B) has the lowest entropic hindrance (−131.7 J/mol per K), and that as the entropic hindrance rises the dissolution rate slows. Due to the complexity of having two apparent rate constants to describe the release from most of the formulations, the relationship between drug release and the entropic factor can best be demonstrated by relating the percentage drug released at 6 h (arbitrary assessment of dissolution rate) to the initial entropy of activation (Fig. 9). Despite the fact that Fig. 9 is obviously a simplistic representation of the relationship (as the changes in the

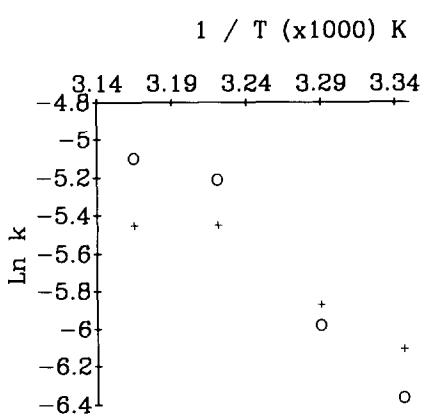

Fig. 6. Natural logarithm of the apparent zero-order rate constant as a function of $1/T$ for formulation B (0.5–2 h (○) and 3–8 h (+)).

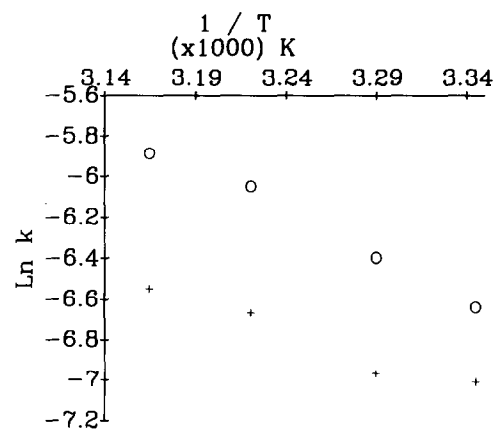

Fig. 7. Natural logarithm of the apparent zero-order rate constant as a function of $1/T$ for formulation G_2 (0.5–2 h (○) and 3–8 h (+)).

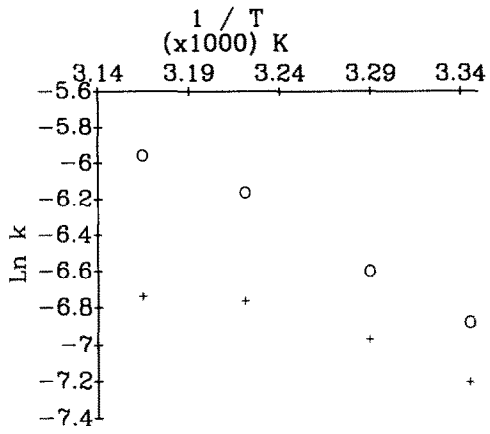

Fig. 8. Natural logarithm of the apparent zero-order rate constant as a function of $1/T$ for formulation G_3 (0.5–2 h (○) and 3–8 h (+)).

entropic factor over the entire process are not considered), it is indicative of a strong relationship between the entropy of activation and the dissolution process. (N.B. the relationship shown in Fig. 9 is not altered if the percentage released after 2 h is considered, i.e. before the rate change).

The results presented in Fig. 9 may lead to the conclusion that the drug release is entropically controlled, and that the mechanism is identical for the directly compressed and granulated formulations, with or without surface active agent. Although it is fair to assume a dominant entropic effect, this would be a simplistic conclusion with regard to mechanism. Indeed it would not provide an explanation for the fact that Fig. 9 does not form a perfect straight line.

A valuable approach to the study of mechanism is that of compensation analysis. Derived from the field of extrathermodynamics, compensation analysis looks for relationships between thermodynamic parameters. A linear relationship provides evidence for a common causative mechanism. This approach can be of value in demonstrating a common mechanism, and also in indicating the existence of members which do not conform to the otherwise common mechanism.

Fig. 10 shows an enthalpy-entropy compensation plot for the activation process, all the results from Table 2 being included. The fit to a straight line for this type of compensation plot is extremely good, and can lead to the view that a common mechanism of release exists for each formulation, irrespective of the method of production (i.e. direct compression or granulation) or the presence or absence of surface-active agents.

Tomlinson (1983) and others have criticised the use of plots of enthalpy as a function of entropy. The problem is that systems which have no common causative mechanism will tend to show compensation simply because the entropy was calculated directly from the enthalpy. In order to have a test which is not open to a false correlation due to a statistical artefact, it is necessary to carry out the compensation in the enthalpy-free energy co-

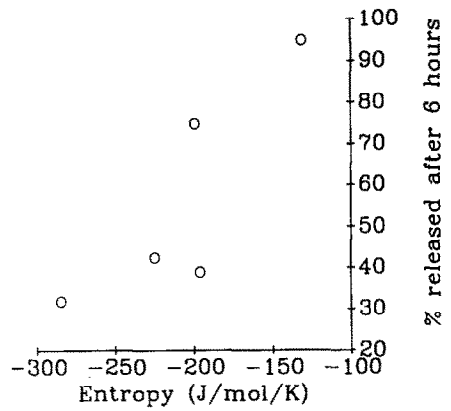

Fig. 9. The initial entropy of activation for the dissolution process as a function of the % drug released after 8 h.

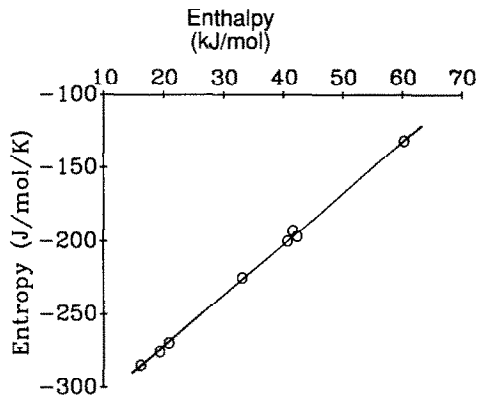

Fig. 10. Enthalpy-entropy compensation plot (data from Table 2).

TABLE 3

Thermodynamic parameters for activation calculated at the mean experimental temperature

Formulation	$\Delta H^{\ddagger}$ (kJ/mol)	$\Delta G^{\ddagger}$ (kJ/mol)	$\Delta S^{\ddagger}$ (J/mol per K)
A (0.5–8 h)	40.6	90.9	−163.6
B (0.5–2 h)	60.2	89.8	−96.3
B (3–8 h)	41.5	89.8	−157.1
G_1 (0.5–8 h)	16.1	92.7	−249.2
G_2 (0.5–2 h)	33.1	91.3	−189.1
G_2 (3–8 h)	20.8	92.7	−301.6
G_3 (0.5–2 h)	42.3	91.7	−160.7
G_3 (3–8 h)	19.3	93.0	−239.8

ordinates. Krug et al. (1976a,b) have demonstrated that the extrapolation to the y axis of a plot of ln k as a function of $(1/T)$ will yield a value for the entropy term which must be correlated with the enthalpy term (derived from the gradient), since the value of the gradient will determine the intercept. If, however, the Gibbs function is calculated at the harmonic mean of the experimental temperatures, the value will be independent of the gradient, thus any correlation between enthalpy and free energy values determined at the mean experimental temperature will be a true reflection of the existence of a common mechanism. The values in Table 3 are the thermodynamic parameters for activation calculated at the mean experimental temperature as described by Krug et al. (1976a).

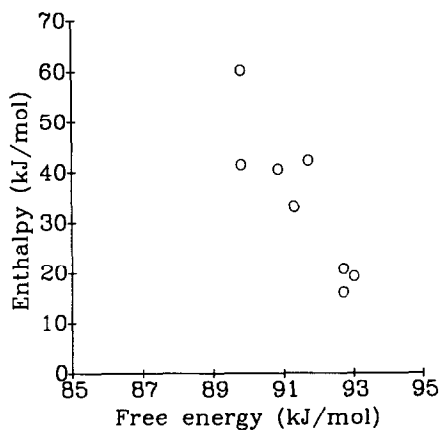

Fig. 11. Free energy-enthalpy compensation plot, for data calculated at the mean experimental temperature.

Fig. 11 shows a free energy-enthalpy compensation plot. The thermodynamic parameters that were calculated for body temperature (Table 2) that are used in Fig. 10 are open to the artefact of self-correlation, however, this is not true for Fig. 11 (see above). The slight deviation from the straight line (Fig. 11) indicates the possibility that the mechanism of release may alter slightly between the different formulations studied. However, the deviations from a straight line are marginal, and further work would be necessary to confirm the existence of varying mechanisms.

It is important to draw distinction between rate and mechanism. Granulation clearly results in a reduced rate of drug release compared to direct compression, and addition of surface-active agent results in an increased rate of release. Despite changes in rate, the mechanism can be the same.

Conclusion

It is possible to study the mechanism of drug release from a controlled release oral dosage form, by use of the thermodynamic parameters of activation.

Compensation analysis provides a useful method by which the mechanism of release from different formulations, and from the same formulations at different stages in their release profile (i.e. 0–2 and 3–8 h), can be compared.

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References

Atkins, P.W., *Physical Chemistry*, 3rd Edn., Oxford University Press, Oxford, 1988, pp. 700–750.

Bamba, M., Puisieux, F., Marty, J.P. and Carstensen, J.T., Release mechanisms in gel forming sustained release preparations. *Int. J. Pharm.*, 2 (1979) 307–315.

Cobby, J., Mayersohn, M. and Walker, G.C., Influence of shape factors on kinetics of drug release from matrix tablets. I: Theoretical. *J. Pharm. Sci.*, 63 (1974) 725–732.

Efentakis, M. and Buckton, G., Modelling of drug release from hydrophobic matrices by use of thermodynamic activation parameters. *Int. J. Pharm.*, 60 (1990) 229–234.

Fessi, H., Marty, J.P., Puisieux, F. and Carstensen, J.T., The Higuchi square root equation applied to matrices with high content of soluble drug substance. *Int. J. Pharm.*, 1 (1978) 265–274.

Gurny, R., Doelker, E. and Peppas, N.A., Modelling of sustained release of water-soluble drugs from porous hydrophobic polymers. *Biomaterials*, 3 (1982) 27–32.

Higuchi, T., Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J. Pharm. Sci.*, 52 (1963) 1145–1149.

Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P. and Peppas, N.A., Mechanism of solute release from porous hydrophilic polymers. *Int. J. Pharm.*, 15 (1983) 25–35.

Krug, R.R., Hunter, W.G. and Grieger, R.A., Enthalpy-entropy compensation. 1. Some fundamental statistical problems associated with analysis of van 't Hoff and Arrhenius data. *J. Phys. Chem.*, 80 (1976a) 2335–2341.

Krug, R.R., Hunter, W.G. and Geiger, R.A., Enthalpy-entropy compensation. 2. Separation of the chemical from the statistical effect. *J. Phys. Chem.*, 80 (1976b) 2341–2351.

Lee, P.I. and Peppas, N.A., Prediction of polymer dissolution in swellable controlled release systems. *J. Cont. Release*, 6 (1987) 207–215.

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