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Physical factors influencing the aqueous dissolution rate of acetaminophen crystals doped with *p*-acetoxyacetanilide: evaluation by multiple linear regression

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Summary

A semi-empirical relationship between the aqueous intrinsic dissolution rate (J), of acetaminophen, **P**, crystals and their length-to-width ratio (l/w), uptake of *p*-acetoxyacetanilide, A (x_A), entropy of fusion (ΔS^f) and water content (x_W) has been developed by consideration of the following factors: (a) crystal anisotropy; (b) habit-related hydrodynamic conditions during dissolution; (c) crystal defects induced by A, water and/or crystallization conditions; and (d) non-stoichiometric hydrates. For the purpose of comparison, factors (a) and (b) may be represented approximately by l/w, while factors (c) and (d), which are closely related, by ΔS^f, x_A and x_W, respectively. Based on the Noyes-Whitney equation and solution thermodynamics, the following log-linear relationship is proposed:

$$\ln J = n \cdot \ln(l/w) - p \cdot \Delta S^f - q \cdot \ln x_W + r \cdot \ln x_A + s$$

where n, p, q, r and s are empirical constants. This type of equation was tested against experimental data and examined statistically by multiple linear regression analysis. About 90% of the variation in J are ascribable to l/w, ΔS^f and x_W, while the remaining 10% are due to errors and/or to other factors.

Introduction

The influence of the various crystallization conditions on the habit, water content, uptake of *p*-acetoxyacetanilide, **A**, and entropy of fusion of acetaminophen, **P**, crystals has been assessed statistically by multiple linear regression analysis (Chow and Grant, 1988a). To elucidate how the latter 4 properties govern the aqueous dissolution rate of the crystals, the respective data have also been similarly analyzed.

The objectives of the present report are:
(1) to develop a theoretical understanding of the influence of the above-mentioned physical properties on the dissolution rate;

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(2) to derive an equation linking the dissolution rate to these physical properties; and
(3) to quantify and to compare statistically the experimental influence of the various physical properties on the dissolution rate.
It is hoped that this semi-empirical approach will find application in identifying and quantifying the physical factors which control the dissolution of pharmaceutical solids.

Experimental details and data collection

The crystals were prepared and characterized as described previously (Chow et al. 1985; Chow and Grant, 1988a, b and c). The specific surface area of the crystals was determined in duplicate by the BET adsorption isotherm using nitrogen in a Quantasorb surface analyzer (Quantachrome Corp., Syosset, NY). The initial dissolution rate of the crystals (75 mg) in water at 4° C was measured in triplicate using the USP/NF dissolution apparatus 2 with paddle stirring at 50 rpm. The intrinsic dissolution rate of the crystals is given by their initial dissolution rate divided by their initial mass and by their initial surface areas. For the same reasons as those presented in the accompanying communication (Chow and Grant, 1988a), the mean values of replicate measurements were used in the present statistical analysis.

Theoretical considerations

The dissolution behaviour of single-component, single-phase, non-disintegrating pharmaceutical solids (crystals) may be described by the Noyes-Whitney (1897) equation in the following form

$$J = (\mathrm{d}m/\mathrm{d}t) \cdot 1/A = k(C_s - C) \tag{1}$$

where $\mathrm{d}m/\mathrm{d}t$ = rate of increase of the mass of solute dissolved per unit time, k = mass transfer coefficient, A = surface area of the crystals, C_s = instantaneous solubility (i.e. intrinsic solubility) at the crystal surface, C = concentration of solute dissolved at time t, and J = mass flux or intrinsic dissolution rate. Under sink conditions, i.e. $C \ll C_s$

$$J = k \cdot C_s \tag{2}$$

Eqn. 2 shows that the intrinsic dissolution rate under sink conditions gives a direct measure of intrinsic solubility. The intrinsic solubility, C_s, is a function of the surface and bulk thermodynamics of the material. If the solutions are dilute or if the differences in C_s are sufficiently small, the activity coefficient, γ, can be assumed constant; C_s is then approximately proportional to thermodynamic activity, α, of the solid, thus:

$$C_s = \alpha/\gamma \tag{3}$$

The experimental mass transfer coefficient, k, is a composite rate constant for both the transport-controlled and the surface-controlled processes (Birchumshaw and Riddiford, 1952), thus:

$$k = k_s \cdot k_t/(k_s + k_t) \tag{4}$$

where k_s = rate constant of the surface reaction, and k_t = rate constant of the transport process. The constant, k, has been shown to depend on the intensity of agitation, on the temperature, on the size and shape of the particles, on the hydrodynamics of the apparatus and on the diffusivity of the dissolved material.
(a) For a predominantly transport-controlled process, i.e. $k_s \gg k_t$, Eqn. 2 becomes the Nernst (1904) and Brunner (1905) equation defined under sink conditions, thus:

$$J = k_t \cdot C_s = D \cdot C_s/h \tag{5}$$

where D = diffusivity of the solute in solution, and h = thickness of the diffusion layer.
(b) For an essentially surface-controlled mechanism, i.e. $k_s \ll k_t$, Eqn. 2 assumes the form:

$$J = k_s \cdot C_s \tag{6}$$

The logarithm of k_s is a negative linear function of the free energy of activation for the dissolution process, divided by the absolute temperature and the gas constant, as in reaction kinetics.
(c) For a mixed surface-controlled and transport-controlled dissolution process, the intrinsic dissolution rate under sink conditions may be expressed by substituting Eqn. 4 into Eqn. 2.

For further development of the theory, it is convenient to express the equations under (a), (b) and (c) in their logarithmic form, thus:

$$\ln J = \ln k + \ln C_s \qquad (7)$$

Crystal anisotropy and habit-related hydrodynamics of dissolution

As discussed previously (Chow et al., 1985; Chow and Grant, 1988a, b and c), the influence of the length-to-width ratio of the crystals may be mediated by crystal anisotropy (Case 1) or by changes in the boundary conditions around the particles during dissolution (Case 2) or by both (Case 3).

Case 1. For a predominantly surface-controlled dissolution process. $k \approx k_s$, where k_s has been defined for Eqn. 6.

Quantitation of the polarity of the polar surfaces or the degree of anisotropy of crystals often proves difficult, particularly for powders. If the morphology (i.e. shape) of the particles is relatively uniform, as observed for the **P** crystals in our previous studies (Chow et al., 1985; Chow and Grant, 1988 a, b and c), a relatively simple parameter of the crystals may be used to define crystal anisotropy. For this purpose, the length-to-width ratio may be useful, since the acicular habit of the crystals approximates to that of a cylindrical rod or a rectangular parallelepiped. The length-to-width ratio for either geometry is approximately proportional to the area of the surfaces along the axis of elongation or growth propagation, divided by that at right angles to the axis. The former surfaces, being the ones whose growth is inhibited the most, probably predominate as the crystals continue to grow preferentially at their extremities. These surfaces may also be the polar faces which would dissolve faster in water, as suggested earlier (Chow et al., 1985). In summary, the higher the length-to-width ratio, l/w, the lower will be the free energy of activation for dissolution and therefore the greater will be the mass transfer coefficient, k. The relationship between k and l/w may therefore be stated as follows:

$$k \propto (l/w)^m$$

$$\text{i.e. } k = k_1 \cdot (l/w)^m \qquad (8)$$

where k_1 is a proportionality constant and m is a positive constant.

Case 2. For an essentially diffusion-controlled dissolution process. $k \approx k_t \approx D/h$, where k_t, D and h have been defined for Eqn. 5.

With constant agitation and at constant temperature, the diffusivity, D, of the drug molecules may be assumed constant. Thus, an increase in k with an increase in l/w must be due to a decrease in h. The following empirical expression may describe this relationship:

$$k \propto h^{-1} \propto (l/w)^n$$

$$\text{i.e. } k = k_2 \cdot (l/w)^n \qquad (9)$$

where k_2 is a proportionality constant and n is a positive constant.

Case 3. For a "mixed" transport and surface-determined dissolution process. Eqn. 4 is employed. Three special subcases can be considered:

(a) when $k_s = k_t$, $k = k_s/2 = k_t/2$, so that

$$k = (k_1/2) \cdot (l/w)^m = (k_2/2) \cdot (l/w)^n \qquad (10)$$

(b) when $k_s \neq k_t$ and $m > n$

$$k = k_1 \cdot k_2 \cdot (l/w)^m / \left[k_1 \cdot (l/w)^{m-n} + k_2\right] \qquad (11)$$

(c) when $k_s \neq k_t$ but $m = n$

$$k = k_1 \cdot k_2 \cdot (l/w)^m / (k_1 + k_2)$$

$$= k_1 \cdot k_2 \cdot (l/w)^n / (k_1 + k_2) \qquad (12)$$

In each of the above cases, Eqns. 8–12 indicate that ln k is a linear function of $\ln(l/w)$, e.g.

$$\ln k = \ln(\text{constant}) + (m \text{ or } n) \cdot \ln(\text{l/w}) \qquad (13)$$

Hydrates

Shefter and Higuchi (1963) showed that the aqueous dissolution rate increases with decreasing stoichiometric water in the crystals (i.e. anhydrate > hydrate). Similar arguments may be applied to the dissolution rates of non-stoichiometric hydrates in the present work. The tendency of **P** to form (non-stoichiometric) hydrates suggests that the incorporation of water into the crystals of **P** reduces the thermodynamic activity, α, with respect to an aqueous solution of **P**. Thus, the overall relationship between the solubility, activity and the water content can be stated as

$$C_s \propto \alpha \propto (x_W)^{-p},$$

$$\text{i.e. } C_s = k_3 \cdot \alpha = k_4 \cdot (x_W)^{-p} \tag{14}$$

where k_3 and k_4 are proportionality constants, p is a positive constant and x_W is the mole fraction of water in the crystals. Eqn. 14 may be stated in the following logarithmic form:

$$\ln C_s = \ln k_3 + \ln \alpha = \ln k_4 - p \cdot \ln x_W \tag{15}$$

Crystal imperfections

Since crystal defects represent regions of molecular misfit and misalignment and of unbalanced intermolecular forces, their presence within the crystal lattice is expected to increase the internal energy, enthalpy and entropy of the system. Thus, thermodynamic properties such as the enthalpy of fusion, ΔH^f, melting point, T_m, and the entropy of fusion, ΔS^f, may afford a measure of crystal imperfection. The inverse relationship (Chow et al., 1984) between intrinsic dissolution rate and ΔH^f, ΔS^f, or T_m of the crystals can be explained by the following thermodynamic equations (Hildebrand and Scott, 1962):

$$\ln \alpha = -(\Delta H^f/R) \cdot (1/T - 1/T_m) \tag{16}$$

$$= -\Delta S^f \cdot (1/R) \cdot (T_m/T - 1) \tag{17}$$

The hypothetical pure supercooled liquid is here chosen as the standard state of unit activity. R is the universal gas constant and T is the absolute temperature. According to Eqns. 16 and 17, α of the solid (or crystal) should be inversely related to ΔH^f, ΔS^f or T_m, which signify the energetic and entropic states of the crystal and hence reflect the density of lattice imperfections. Since the intrinsic dissolution rate under sink conditions is proportional to C_s, which is approximately proportional to α (Eqn. 3), it can be similarly related to the above thermodynamic properties. This treatment assumes that:

(a) ΔH^f is independent of temperature, i.e. the change in heat capacity, ΔC_p, on melting is ignored;

(b) the interaction of the supercooled liquid with water is relatively insensitive to the presence of trace additives or impurities; and

(c) the intrinsic dissolution rate is proportional to α or C_s, i.e. the mass transfer coefficient, k, is assumed to be independent of crystal imperfections.

The last assumption may be violated by possible variation in hydrodynamics during dissolution and by the known influence of crystal anisotropy on the intrinsic rate constant (Burt and Mitchell, 1979, 1980).

If the change in T_m due to crystal defects is much smaller than that in ΔS^f, as deduced by Chow et al. (1984), Eqn. 17 will approximate to

$$\ln \alpha \approx -q \cdot \Delta S^f \tag{18}$$

where q is a proportionality constant.

As discussed by Chow et al. (1985), impurity defects within the crystal lattice are higher energy sites of higher thermodynamic activity which promotes more rapid dissolution of the crystals. Since C_s is approximately proportional to thermodynamic activity (Eqn. 3), which is directly related to the amount of impurity incorporated, an equation analogous to Eqn. 15 can be written, thus:

$$\ln C_s = \ln k_5 + \ln \alpha = \ln k_6 + r \cdot \ln x_A \tag{19}$$

where k_5 and k_6 are proportionality constants, r is a positive constant and x_A is the mole fraction of **A** in the crystals.

The right-hand side of Eqns. 7, 13, 15 and 19, when multiplied by $-RT$, are seen to represent Gibbs free energy terms. If these terms are truly independent of each other, they can be added in a linear fashion to afford a linear free energy relationship (Wells, 1968), thus:

$$\ln J = n \cdot \ln(l/w) - p \cdot \ln x_W - q \cdot \Delta S^f + r \cdot \ln x_A + s \tag{20}$$

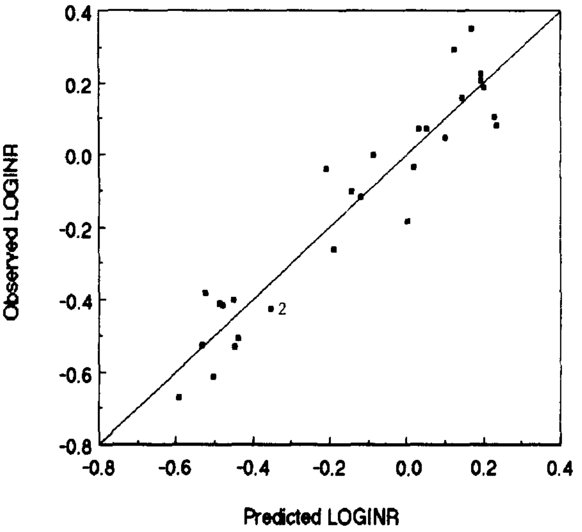

Fig. 1. Plot of the logarithm of the observed intrinsic dissolution rate (observed LOGINR) against LOGINR predicted from Eqn. 21 in Table 1. The point nearest the digit 2 represents two virtually coincident pairs of values.

where n, p, q, r, s are the respective regression coefficients.

Data Analysis by Multiple Linear Regression

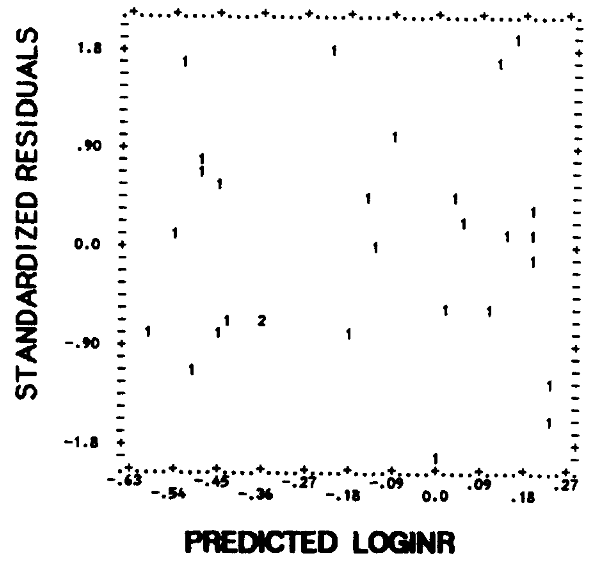

Fig. 2. Standardized residuals plotted against the predicted LOGINR for the linear regression of LOGINR on ENTFUS, LOGLWR and LOGWAT, represented by Eqn. 21 in Table 1. The number 2 represents the position of two virtually coincident points.

Based on these considerations, the data on dissolution and on the related physical properties were fitted to Eqn. 20 by the least-squares regression method using the BMDP2R and BMDP9R programmes (BMDP manual, 1983), as described by Chow and Grant (1988a). However, unlike the data treatment detailed by Chow and Grant (1988a), the present analysis does not warrant consideration of the interaction regressors since the development of Eqn. 20 is guided mainly by theoretical rather than by statistical arguments. The abbreviated variables used in the computation are listed as follows:

LOGLWR	the natural logarithm of the length-to-width ratio of the crystals
LOGWAT	the natural logarithm of the mole fraction of water in the crystals
LOGPAA	the natural logarithm of the mole fraction of A in the crystals
ENTFUS	entropy of fusion of the crystals, $J \cdot K^{-1} \cdot mol^{-1}$
LOGINR	the natural logarithm of intrinsic dissolution rate of the crystals, $g \cdot min^{-1} \cdot m^{-2}$

TABLE 1

Parameters and statistics for the linear regression of LOGINR on ENTFUS, LOGLWR and LOGWAT

Variable	Regression coefficient	Standard error	Standardized coefficient	t-Statistic	Tolerance
Intercept	1.63	0.751		2.16 *	
ENTFUS	−0.0618	0.0164	−0.632	−3.77 *	0.1462
LOGLWR	0.188	0.0234	0.695	8.02 *	0.5475
LOGWAT	−0.426	0.0655	−0.980	−6.50 *	0.1808

RMS = 0.0105; $R^2 = 0.897$; d.f. $= n - 4$, where $n = 29$.

* Significant at the 5% level.

$$\text{LOGINR} = 0.188(\text{LOGLWR}) - 0.426(\text{LOGWAT}) - 0.0618(\text{ENTFUS}) + 1.63 \qquad (21)$$

Regression analysis (Table 1) using the FS-BE procedure retains only the variables, LOGLWR, LOGWAT and ENTFUS in Eqn. 20, when expressed in its numerical form (Eqn. 21, Table 1), LOGPAA being insignificant in the presence of the preceding 3 variables. This is to be expected since PAAUPT is heavily correlated with LWR (Chow and Grant, 1988a) which appears to exert a predominant influence on the dissolution rate. In addition, water is present in much larger amounts than A in the crystals, and may also mask the potential effects of A on the dissolution rate (Chow et al., 1985; Chow and Grant, 1988b and c). The last two points probably explain why the involvement of A in modifying the dissolution rate of the crystals cannot be statistically demonstrated.

Fig. 1 shows the relationship between the logarithm of the observed intrinsic dissolution rate (observed LOGINR) and LOGINR predicted from Eqn. 21 (in Table 1) and therefore conforming to semi-empirical Eqn. 20. The relatively low standard errors of the predicted values (Table 1) suggest that the regression parameters are acceptable. The signs of the regression coefficients for the various predictor variables (i.e. the direction of changes) accord with those expected from theoretical considerations. The residual analysis is also satisfactory. The standardized residuals, ϵ, are randomly distributed about $\epsilon = 0$, within a narrow horizontal band and exhibit no discernable systematic pattern (Fig. 2). No unusually high residuals can be detected. Thus, Eqn. 21 in Table 1 sufficiently defines the proposed relationship. According to the *t*-statistic, the relative importance of the various factors in controlling the intrinsic dissolution rate of the crystals decreases in the order: LOGLWR > LOGWAT > ENTFUS. On the other hand, the sensitivity of LOGINR to changes in the various factors, based on the absolute values of the standardized regression coefficients, follows the order: LOGWAT > LOGLWR > ENTFUS. Since the 3 factors are

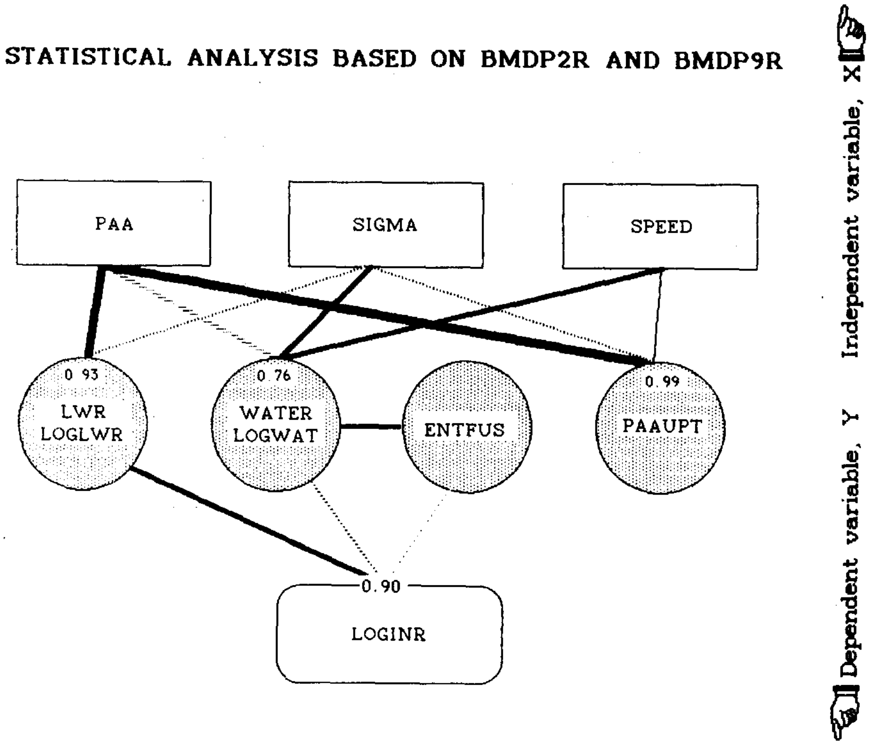

Fig. 3. Flow chart summarizing the interrelationships between the conditions of crystallization and the various pharmaceutical properties of acetaminophen. The intensity of the line represents the strength of the relationship. The numerical values represent the multiple R^2.

correlated with each other to some extent (i.e. the information that they provide overlaps), it is not possible to estimate the relative contribution of the individual factors to the dissolution rate. However, if the variables were to be entered into the equation in their order of significance, it can be readily seen that the accountability of the equation for LOGINR, as determined by the multiple R^2, would be raised in successive increments of 67% for LOGLWR, 17% when including LOGWAT, and 6% when also including ENTFUS. Only 90% of the total variation in LOGINR can be explained by LOGLWR, LOGWAT and ENTFUS; the remaining 10% of the variation are due to experimental errors and/or to other less important factors that were not investigated.

Fig. 3 presents a flow chart summarizing the interrelationship between the conditions of crystallization and the various pharmaceutical properties of the crystals.

Conclusions

To account for the observed variation in intrinsic dissolution rate of the **P** crystals, 4 well-documented key factors have been proposed: viz. (a) crystal anisotropy; (b) habit-related hydrodynamic conditions during dissolution; (c) crystal defects generated by the additive, water and/or crystallization conditions; and (d) non-stoichiometric hydrates. For the purpose of comparison, factors (a) and (b) may be expressed approximately by the length-to-width ratio of the crystals while factors (c) and (d), which are mutually related, may be represented by the entropy of fusion and the water content of the crystals, respectively. The relative significance of these factors in controlling the dissolution rate, as determined by multiple linear regression analysis, follows the order: (a) and (b) > (d) > (c). About 90% of the total variation in the intrinsic dissolution rate of **P** crystals are attributable to these factors while the remaining 10% of variation are due to errors and/or to other potential factors that have not been quantified, e.g. poisoning of active sites for dissolution by the adsorbed additive molecules.

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References

Bircumshaw, L.L. and Riddiford, A.C., Transport control in heterogeneous reactions. *Q. Rev. Chem. Soc.*, 6 (1952) 157–185.

BMDP Statistical Software Manual, University of California Press, Berkeley, CA, U.S.A. 1983.

Brunner, E., Zur Kenntnis der Auflösungsgeschwindigkeit des Zinks. *Z. Phys. Chem.*, 51 (1905) 95–105.

Burt, H.M. and Mitchell, A.G., Dissolution anisotropy in nickel α-hexahydrate crystals. *Int. J. Pharm.*, 3 (1979) 261–274.

Burt, H.M. and Mitchell, A.G., Effect of habit modification on dissolution rate. *Int. J. Pharm.*, 5 (1980) 239–251.

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

Chow, A.H.-L. and Grant, D.J.W., Influence of crystallization conditions on the physical properties of acetaminophen crystals: evaluation by multiple linear regression. *Int. J. Pharm.* (1988a) in press.

Chow, A.H.-L. and Grant, D.J.W., Modification of acetaminophen crystals. II. Influence of stirring rate during solution-phase growth on crystal properties in the presence and absence of *p*-acetoxyacetanilide. *Int. J. Pharm.*, 41 (1988b) 29–39.

Chow, A.H.-L. and Grant, D.J.W., Modification of acetaminophen crystals. III. Influence of initial supersaturation during solution-phase growth on crystal properties in the presence and absence of *p*-acetoxyacetanilide. *Int. J. Pharm.*, 42 (1988c) 123–133.

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.

Hildebrand, J.H. and Scott, R.L., *Regular solutions*, Prentice Hall, Englewood Cliffs, NJ, U.S.A., 1962, pp. 19–23.

Nernst, W., Theorie der Reaktionsgeschwindigkeit in heterogenen Systemen. *Z. Phys. Chem.*, 47 (1904) 52–55.

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.

Shefter, E. and Higuchi, T., Dissolution behaviour of crystalline solvates and nonsolvated forms of some pharmaceuticals. *J. Pharm. Sci.*, 52 (1963) 781–791.

Wells, P.R., *Linear Free Energy Relationships*, Academic, London, 1968, pp. 1–7.