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Predicting the dissolution rate of ibuprofen-acidic excipient compressed mixtures in reactive media

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Summary

Acid excipients suppressed the dissolution rate of ibuprofen from mixed discs causing the drug's dissolution profile to curve positively while the excipient profile curved negatively. The release of ibuprofen into a buffered medium from compressed discs containing adipic acid, succinic acid, L-(+)-tartaric acid or citric acid monohydrate indicated that the extent of suppression and curvature depends on the proportion of excipient in the disc, its pK_a and solubility. Good predictions for the solubility of ibuprofen in acid excipient solutions were made using EQUIL®. A modified non-interacting model which uses these solubility predictions to calculate limiting rates gave the most accurate predictions in the case of the less soluble excipients.

Introduction

Previous studies (Ramtoola and Corrigan, 1987, 1988) have examined the dissolution characteristics of compressed discs containing an acid drug and an acid excipient in buffer. The excipient decreased the dissolution rate of the drug and in some cases drug dissolution profiles showed positive curvature. Prediction of the limiting dissolution rate required the effects of varying concentrations of acid excipients on drug solubility to be measured experimentally.

In this study, we directed our efforts toward the following objectives: (i) to examine how a range of acidic excipients affect both the solubility and dissolution rate profiles of ibuprofen; (ii) to compare experimentally determined solubilities of ibuprofen in solutions of the acid excipients in buffered medium with theoretical predictions obtained using EQUIL® (1990); and (iii) to use these solubility predictions to estimate the limiting dissolution rate of ibuprofen from compressed mixtures of varying composition and compare these rates to those obtained experimentally.

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Materials and Methods

Materials

B.P. grade Ibuprofen was used. All excipients and other chemicals used were of analytical grade.

Methods

Solubility determinations

Solubilities were determined, at 37°C, by the sealed ampoule method (Mooney et al., 1981). Mutually saturated solubilities were determined by placing an excess of both ibuprofen and the excipient in 10 ml of phosphate buffer pH 7.35 in a conical flask which was then shaken for 72 h in a water-bath maintained at 37°C.

Dissolution studies

Dissolution profiles were determined by the static disc method from compressed discs mounted in paraffin wax as previously described (Corrigan and Timoney, 1975). All powders used were below 180 μm in size. In the case of mixed discs the powders were mixed in an agate mortar before compression.

Analysis

Solubility studies UV analysis (Shimadzu UV 160 and Hewlett Packard HP8452A) was used for samples containing only one component (i.e., either ibuprofen or acid excipient). Acid excipient concentrations in samples from mutual saturation solubility studies were determined by UV spectroscopy (either single or multicomponent analysis depending on the $E_{1\%}$ of the excipient). Ibuprofen concentrations in the presence of acid excipients were determined by HPLC using a Spherisorb C8 5 μm, 250 × 4.6 mm column, a mobile phase of methanol-1% H_3PO_4 (70:30, v/v) run at ambient temperature with a flow rate of 0.8 ml/min and absorbance detection at 220 nm.

Dissolution studies Samples from the dissolution of pure component discs were analysed by UV spectroscopy, while those from mixed discs were analysed by HPLC or UV multicomponent spectroscopy (second-derivative spectroscopy – maximum likelihood). The method used for each component of the disc depended on the ratio of acid excipient to ibuprofen in the disc and the magnitude of their $E_{1\%}$ values.

When ibuprofen was analysed by HPLC the conditions were as previously described. When the acid excipients were analysed by HPLC the analysis was performed using 0.25 M H_3PO_4 as the mobile phase run at 0.8 ml/min and ambient temperature through a Spherisorb C8 5 μm 250 × 4.6 mm column with absorbance detection of the effluent at 210 nm. In the case of adipic acid, however, the mobile phase used was methanol-1% H_3PO_4 (50:50, v/v).

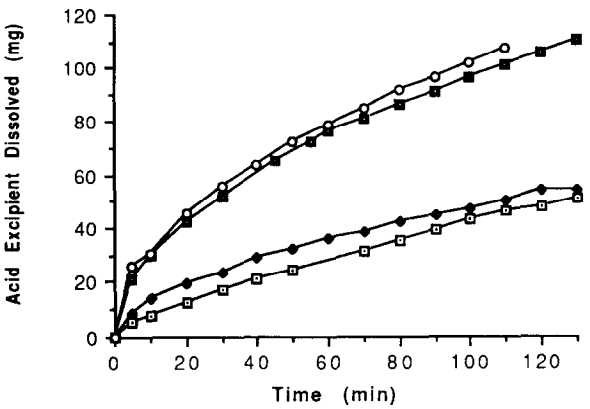

Fig. 1. Dissolution profiles of acid excipients from 40:60 ibuprofen/acid excipient compressed discs. (⊡——⊡) Adipic acid/ibuprofen, (♦——♦) succinic acid/ibuprofen, (■——■) tartaric acid/ibuprofen, (○——○) citric acid/ibuprofen.

Results and Discussion

Dissolution studies of compressed discs

Compressed discs were made from ibuprofen and one of four different acids (adipic acid, succinic acid, L-(+)-tartaric acid and citric acid monohydrate) in a number of different weight ratios. Dissolution profiles for both components of the discs were determined in phosphate buffer pH 7.35 at 37°C. In all cases the weight fractions were such that ibuprofen formed the surface layer of the disc and hence, as expected from theory (Higuchi et al., 1965), the excipient dissolution profiles show a downward curvature (Fig. 1).

The dissolution rate of ibuprofen was shown to be decreased in the presence of acid excipients (Fig. 2) and suppression of dissolution was increased with increasing concentration of acid excipient in the disc (Fig. 3).

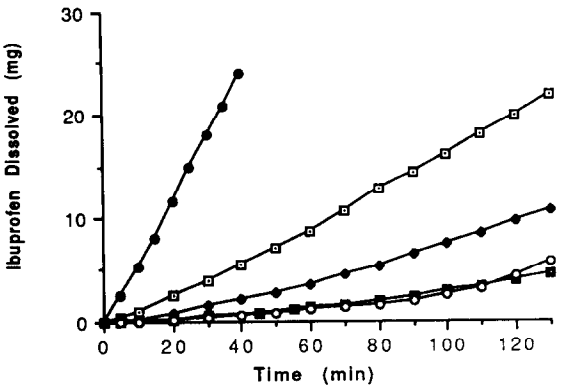

Fig. 2. Dissolution profiles of ibuprofen from 40:60 ibuprofen/acid excipient compressed discs. (⊡——⊡) Adipic acid/ibuprofen, (♦——♦) succinic acid/ibuprofen, (■——■) tartaric acid/ibuprofen, (○——○) citric acid/ibuprofen, (●——●) ibuprofen alone.

Dissolution profiles, rather than being linear, as predicted by the simple non-interacting model for polyphase mixtures (Higuchi et al., 1965), show positive curvature in all cases. This positive curvature can be attributed to the recession of the acid excipient from the surface of the disc, leading to a rise in pH at the surface-liquid interface which in turn leads to an increase in the solubility and the dissolution rate of the surface component, i.e., ibuprofen.

Limiting rates (calculated in general from the mean rates at the last two or three time intervals)

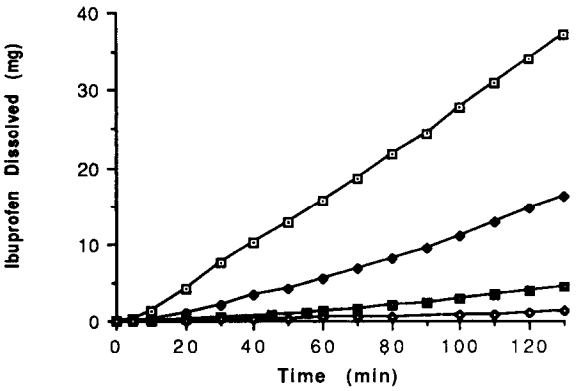

Fig. 3. Dissolution profiles of ibuprofen from ibuprofen/L-(+)-tartaric acid compressed discs. Ratio of ibuprofen to tartaric acid: (⊡——⊡) 60:40, (♦——♦) 50:50, (■——■) 40:60, (◇——◇) 30:70.

TABLE 1

Initial and limiting dissolution rates for ibuprofen from ibuprofen / succinic acid mixed discs of varying weight fraction ratios

Dissolution rate (mg/cm^2 per min)	Ibuprofen : succinic acid			
	50:50	40:60	30:70	20:80
Initial	0.0802	0.0192	0.0104	0.00323
Limiting	0.1767	0.0810	0.0594	0.04113
Ratio (L:I)	2.2032	4.2188	5.7115	12.7337

were in all cases greater than initial rates (calculated from the mean rates at 5 and 10 min). The difference between initial and limiting dissolution rates produced over the sampling time increases with increasing weight fraction of excipient in the disc (Table 1). A similar trend was seen for all excipients used.

In Table 2 we have compared the limiting to initial dissolution rates for ibuprofen from 50:50 ibuprofen : acidic excipient discs. The results indicate that the magnitude of suppression of dissolution rate and degree of curvature depend on the solubility and pK_a of the excipient (Table 3). The greater the solubility and/or the lower the pK_a values, the greater the suppression and curvature seen over the sampling time period.

Solubility studies and predictions

The solubility of ibuprofen was determined in a range of both buffered and unbuffered media of different pH values, at 37°C. Ibuprofen solubility (C_s) was plotted against final pH. By fitting the plot obtained to Eqn 1, the intrinsic solubility of ibuprofen (C_0) was determined to be 0.064 mg/ml and the pK_a to be 4.39.

TABLE 2

Initial and limiting dissolution rates of ibuprofen from 50:50 ibuprofen : acidic excipient discs

Dissolution rate (mg/cm^2 per min)	Acidic excipient			
	Adipic acid	Succinic acid	Tartaric acid	Citric acid
Initial	0.1668	0.0802	0.0188	0.0126
Limiting	0.2261	0.1767	0.1338	0.0775
Ratio (L:I)	1.3555	2.2032	7.1170	6.1508

TABLE 3

The pK_a values and saturated solubilities of acids

Acid	pK_{a1} [a]	pK_{a2} [a]	pK_{a3} [a]	Solubility [b] (mg/ml)
Adipic acid	4.418	5.412	–	49.4
Succinic acid	4.207	5.635	–	134.6
L-(+)-Tartaric acid	2.930	4.230	–	875.3
Citric acid (monohydrate)	3.128	4.761	6.396	972.0
Ibuprofen	4.39	–	–	6.3

[a] Measured in water at 25°C (Dean, 1985; Merck Index, 1989; except ibuprofen – see section entitled Solubility studies and predictions).

[b] Measured in phosphate buffer pH 7.35 in the presence of excess ibuprofen.

$$C_s = C_0 \cdot (1 + 10^{(pH - pK_a)}) \quad (1)$$

Solubility predictions

By employing the values obtained for the intrinsic solubility and pK_a of ibuprofen, the pK_a values for the various acid excipients as listed in Table 3, and using as input a series of equilibrium reactions of the type shown below for the various species in solution, solubility predictions could be made for ibuprofen (Ibu) in phosphate buffer pH 7.35, in the presence of varying concentrations of acid excipients (E) using EQUIL®.

$$\text{H-Ibu} \Leftrightarrow \text{H}^+ + \text{Ibu}^-$$

$$\text{H3-E}\ ^{a} \Leftrightarrow \text{H}^+ + \text{H2-E}^-$$

$$\text{H2-E}^- \Leftrightarrow \text{H}^+ + \text{H-E}^{2-}$$

$$\text{H-E}^{2-} \Leftrightarrow \text{H}^+ + \text{E}^{3-}$$

$$\text{H}_3\text{PO}_4 \Leftrightarrow \text{H}^+ + \text{H}_2\text{PO}_4^-$$

$$\text{H}_2\text{PO}_4^- \Leftrightarrow \text{H}^+ + \text{HPO}_4^{2-}$$

$$\text{HPO}_4^{2-} \Leftrightarrow \text{H}^+ + \text{PO}_4^{3-}$$

$$\text{H}_2\text{O} \Leftrightarrow \text{H}^+ + \text{OH}^-$$

([a] Reaction exists for tricarboxylic acid only, i.e., citric acid.)

EQUIL® is a program for solving solution equilibrium problems, based on an equilibrium algebra compiler. When a set of equilibrium relationships are used as input to the compiler the mass balance relationships are constructed, and the routine identifies which chemical species concentrations can be readily calculated from others (i.e., which are independent variables) and which cannot (dependent variables). The nonlinear system of equations which is then generated during the compilation phase of the program's routine is solved by a modification of the method of Powell (1970). This method is essentially a hybrid between the steep descent and Gauss-Newton methods for solving nonlinear equations.

Activity coefficient (γ) calculations were performed using the Davies equation (Eqn 2) which provides qualitatively correct behaviour at high ionic strengths, unlike the more commonly used Debye-Huckel method.

$$\ln(\gamma) = -Az^2\left(\frac{\sqrt{\mu}}{1+\sqrt{\mu}} - 0.2\mu\right) \quad (2)$$

where $A = 1.825(10^6 \cdot \ln(10)/(\varepsilon T)^{3/2})$, ε denotes the dielectric constant, T is temperature (K), z represents the charge on ionic species and μ is the ionic strength.

These predicted solubilities of drug in buffer containing increasing concentrations of acid excipients were compared to experimentally determined values. A nonlinear relationship was seen to exist between ibuprofen solubility and acid excipient concentration. The plots obtained were of the form shown in Fig. 4 for ibuprofen solubility in solutions of adipic acid.

The best straight line fits of plots of experimental against predicted values were obtained by the least-squares method. The slopes and r values obtained indicate the good correlation as shown in Table 4.

Dissolution rate predictions

The two-component non-interacting model (Higuchi et al., 1965) was modified to account for the suppressing effect of the acid excipient on

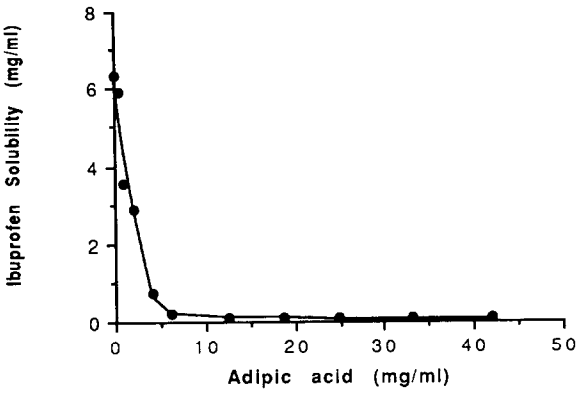

Fig. 4. Ibuprofen solubility in phosphate buffer solutions of adipic acid. (———) Predicted, (●) experimental.

ibuprofen solubility at the disc surface so that the decreased limiting dissolution rates could be predicted.

In order to simplify the iterative calculation (Ramtoola and Corrigan, 1987) of the steady-state surface concentration of excipient during drug dissolution, the relationships between drug solubility and acid excipient concentration were approximated by an empirical relationship of the form:

$$C_{\text{Ibu}} = X(C_{\text{ae}})^{-Y} \tag{3}$$

where C_{Ibu} represents the solubility of ibuprofen and C_{ae} is acid excipient concentration. An initial estimate for the limiting rate for the surface component of the disc, i.e., ibuprofen, is obtained from Eqn 4:

$$G_{\text{Ibu}} = \frac{D_{\text{Ibu}} \cdot C_{\text{Ibu}(h=0)}}{h} \tag{4}$$

TABLE 4

Correlation of experimental and predicted results for ibuprofen solubility in solutions of acid excipients in buffered medium

Acid excipient	Slope	r values [a]
Adipic acid	0.996	0.9897
Succinic acid	1.027	0.9996
Tartaric acid	1.011	0.9998
Citric acid (monohydrate)	1.012	0.9999

[a] r, correlation coefficient.

where G_{Ibu} denotes the dissolution rate of ibuprofen per unit surface area, D_{Ibu} is the diffusion coefficient, h corresponds to the diffusion layer thickness and $C_{\text{Ibu}(h=0)}$ is the solubility at the interface. $C_{\text{Ibu}(h=0)}$ is initially the solubility of ibuprofen in the presence of a saturated solution of excipient. The limiting rate of the excipient (i.e., the receding component) is then obtained from Eqn 5:

$$G_{\text{ae}} = G_{\text{Ibu}} \cdot \frac{N_{\text{ae}}}{N_{\text{Ibu}}} \tag{5}$$

where G_{ae} is the dissolution rate per unit surface area of the acid excipient and $N_{\text{ae}}/N_{\text{Ibu}}$ represents the relative proportions of the two components in the disc. The recession of the excipient from the surface leads to a decrease in concentration of acid excipient at the disc surface-liquid interface which in turn causes the solubility of ibuprofen at the surface to increase. The surface concentration of excipient was estimated from:

$$C_{\text{ae}(h=0)} = G_{\text{Ibu}} \cdot h \cdot \frac{N_{\text{ae}}}{D_{\text{ae}} \cdot N_{\text{Ibu}}} \tag{6}$$

The solubility of ibuprofen was then recalculated (giving a new value for $G_{\text{Ibu}(h=0)}$) from the known relationship between solubility and acid excipient concentration.

Thus, we proceed in an iterative manner until steady-state limiting dissolution rates are reached. D_{Ibu}, the diffusion coefficient of ibuprofen, was calculated from the dissolution profile of ibuprofen in phosphate buffer pH 7.35 to be 4.595×10^{-4} cm^2/min; h, the diffusion layer thickness, was taken to be 62×10^{-4} cm as previously determined (Corrigan and Timoney, 1978); D_{ae}, the dissolution coefficient of the acid excipient was calculated from the Stokes-Einstein equation (Flynn et al., 1974) with D_{Ibu} as the reference diffusion coefficient. This equation predicts that D is proportional to $M^{-1/3}$, where M is the molecular weight of the diffusing molecule.

Predicted limiting rates were compared to those obtained from experimental data. The best correlation between predicted values and experi-

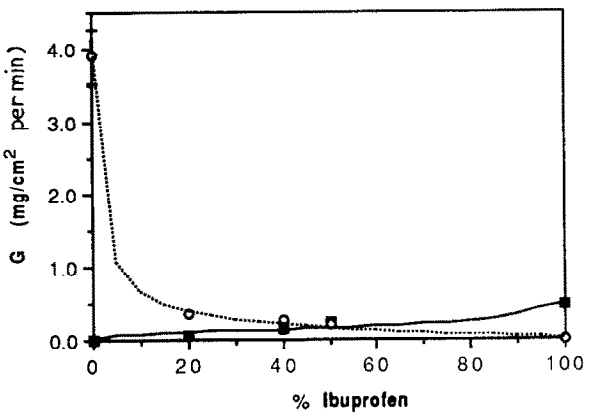

Fig. 5. Limiting dissolution rates (G) of ibuprofen and adipic acid from mixed ibuprofen/adipic acid compressed discs. (■) $G_{\text{Ibuprofen}}$ (experimental), (———) $G_{\text{Ibuprofen}}$ (predicted); (○) $G_{\text{Adipic acid}}$ (experimental), (· · · · · ·) $G_{\text{Adipic acid}}$ (predicted).

mental results is seen in the case of discs where ibuprofen was compressed with the less soluble acids, i.e., adipic and succinic acids (Figs 5 and 6).

For the more soluble acid excipients (e.g., citric acid; Fig. 7), predicted and experimental rates differ greatly when the percentage by weight of excipient in the disc is equal to or exceeds 60%. At this weight fraction there is a 2.5–3-fold difference between experimental and predicted rates for ibuprofen and the deviation increases with increasing proportion of acid excipient in the

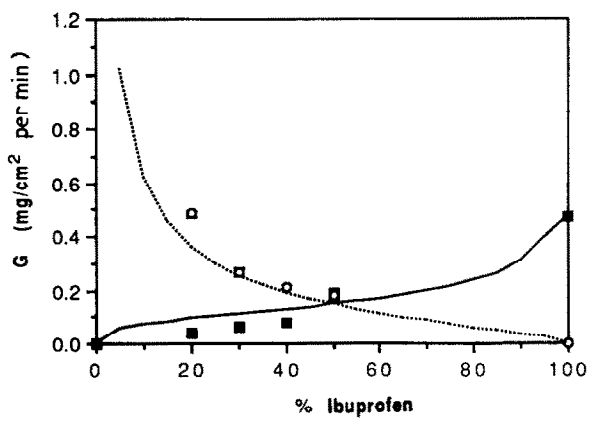

Fig. 6. Limiting dissolution rates (G) of ibuprofen and succinic acid from mixed ibuprofen/succinic acid compressed discs. (■) $G_{\text{Ibuprofen}}$ (experimental), (———) $G_{\text{Ibuprofen}}$ (predicted); (○) $G_{\text{Succinic acid}}$ (experimental), (· · · · · ·) $G_{\text{Succinic acid}}$ (predicted).

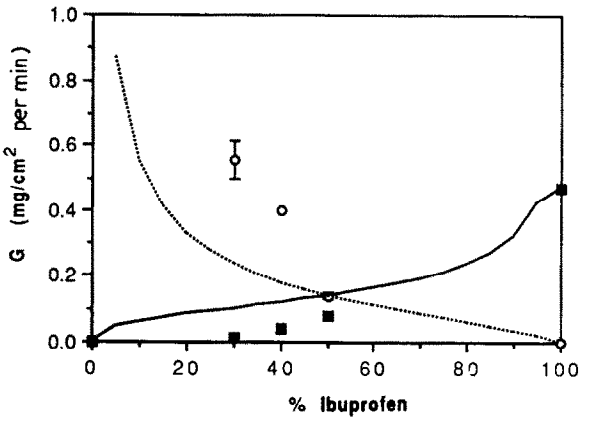

Fig. 7. Limiting dissolution rates (G) of ibuprofen and citric acid monohydrate from mixed ibuprofen/citric acid monohydrate compressed discs. (■) $G_{\text{Ibuprofen}}$ (experimental), (———) $G_{\text{Ibuprofen}}$ (predicted); (○) $G_{\text{Citric acid}}$ (experimental), (· · · · · ·) $G_{\text{Citric acid}}$ (predicted).

disc. The predicted rates for the excipient tend to be higher than obtained experimentally in the case of the more soluble acids.

The reason for the poor prediction may be due to the fact that, in the case where there is a large difference in solubilities between the two components of the disc, we effectively have a matrix of the less soluble component (ibuprofen in this case), through which the more soluble component diffuses. The difference in solubilities and dissolution rates between the two components of the disc is such that, theoretical limiting rates, although they may be correct given an infinitely thick disc, will only be approached but never reached in a compressed disc of finite thickness over a limited time period.

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References

Corrigan, O.I. and Timoney, R.F., The influence of polyvinylpyrrolidone on the dissolution properties of hy-

droflumethiazide. *J. Pharm. Pharmacol.,* 27 (1975) 759–764.

Corrigan, O.I. and Timoney, R.F., Towards standardizing agitation conditions in the beaker dissolution method. *Int. J. Pharm.,* 1 (1978) 299–302.

Dean, J.A., *Lange's Handbook of Chemistry,* 13th Edn, McGraw-Hill, New York, 1985, pp. 5.18–5.60.

EQUIL® (Ver. 2.0), Micromath Scientific Software, UT, 1990.

Flynn, G.L., Yalkowsky, S.H. and Roseman, T.J., Mass transport phenomena and models: Theoretical concepts. *J. Pharm. Sci.,* 63 (1974) 479–510.

Higuchi, W.I., Mir, N.A. and Desai, S.J., Dissolution rates of polyphase mixtures. *J. Pharm. Sci.,* 54 (1965) 1405–1410.

Merck Index, 11th Edn, Merck & Co. Inc., Rahway, NJ, 1989, p. 1433.

Mooney, K.G., Mintun, M.A., Himmelstein, K.J. and Stella, V.J., Dissolution kinetics of carboxylic acids I: effect of pH under unbuffered conditions. *J. Pharm. Sci.,* 70 (1981) 13–22.

Powell, M.J.D., A Fortran subroutine for solving systems of nonlinear algebraic equations. In Rabinowitz, P. (Ed.), *Numerical Methods for Nonlinear Algebraic Equations,* Gordon & Breach, New York, Chap. 7, 1970, pp. 114–161.

Ramtoola, Z. and Corrigan, O.I., Dissolution characteristics of benzoic and salicylic acid mixtures in reactive media. *Drug Dev. Ind. Pharm.,* 13 (1987) 1703–1720.

Ramtoola, Z. and Corrigan, O.I., Effect of agitation on the dissolution rate of indomethacin and indomethacin-citric acid compressed discs. *Drug Dev. Ind. Pharm.,* 14 (1988) 2241–2253.