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An Investigation into the Erosion Behaviour of a High Drug-load (85%) Particulate System Designed for an Extended-release Matrix Tablet. Analysis of Erosion Kinetics in Conjunction with Variations in Lubrication, Porosity and Compaction Rate

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Abstract

The effects of the amounts of lubricants (magnesium stearate 0–5% and talc 0–3%) and changes in compaction rate and tablet porosity on the mechanism of drug release from high drug-load controlled-release theophylline tablets have been examined.

Drug release was satisfactorily described by a surface-erosion model that takes into account the geometry of the tablet, differential radial and axial erosion rates, and the initial burst effect ($r^2 > 0{\cdot}99$ for all formulations). The axial and radial erosion rate constants were inversely proportional to the amount of magnesium stearate in the formulation ($P < 0{\cdot}0001$). The most dramatic reductions in erosion rate occurred between 0 and 1% magnesium stearate content. For magnesium stearate concentrations $\geq 2{\cdot}5\%$ the ratio of radial to axial erosion rate constants was essentially constant at 3 (approx.); however, for formulations with magnesium stearate $\leq 1\%$ the ratio tended toward unity. Reducing matrix porosity over the range 26 to 14% resulted in reduced erosion rates. However, a threshold of 17% (approx.) porosity was identified below which further reductions in porosity resulted in only incremental changes in release rates. The rate of erosion and drug release was insensitive to changes in machine speed over the range 20 to 100 rev min^{-1}.

For highly loaded matrix tablets containing sparingly soluble drugs, such as theophylline, magnesium stearate at appropriate levels can modulate the erosion rate constants and act as an effective release-controlling excipient. Drug-release profiles are predictable and relatively robust in terms of changes in compaction rate and applied force routinely encountered in large-scale tablet manufacturing.

The phenomenon of matrix erosion and dissolution is of interest in the design of oral extended-release tablets because it provides a means of overcoming the well known disadvantages of a purely diffusion-controlled system, i.e. gradually diminishing rates of drug release and, often, incomplete drug dissolution. In particular, synchronization between diffusion and erosion fronts has been identified (depending on the geometry used) as a means of producing zero-order release (Lee 1980). Furthermore, in systems in which release is characterized purely by heterogeneous (surface) erosion, the rate of erosion and, by implication, rate of drug release, are proportional to the surface area of the system. The erosion period can, therefore, be modulated in a predictable manner with relative ease by altering the geometry (dimensions or shape, or both) of the device (Cooney 1972; Akbari et al 1998).

Another important aspect of matrix erosion is that this mechanism of drug release can be exploited in the design of extended-release matrix systems with very high drug loadings, where only a limited amount of release-controlling excipient can be added—to prevent the size of the tablet from becoming problematic. In a previous study we described an extended-release theophylline matrix tablet with high drug loading (approx. 80%). The system included only low levels of a hydrophilic cellulose ether polymer (approx. 5%), which resulted in very little swelling, and relatively high levels of magnesium stearate and talc (approx.

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3·5%). On the basis of model analysis and susceptibility to hydrodynamic stress, matrix dissolution and erosion were found to be major factors influencing drug release (Dürig & Fassihi 1997).

The objectives of the current study were to perform an in-depth kinetic analysis of this erosional process and to evaluate the quantitative effect of various lubricant levels (0–5%) and compaction variables on erosional drug release. It is known that drug release can be affected by matrix properties such as porosity and hardness. These in turn are largely a function of the compaction pressure, the nature of the compaction cycle, the punch velocity and the mechanism of consolidation of the material. For many hydroxypropylmethylcellulose-based matrix systems variations in compaction force seem to have a limited effect on drug release behaviour (Salomon et al 1979; Bettini et al 1994). However, the formulations studied in this work consist predominantly of a crystalline material with only small amounts of plastically deforming polymer. Furthermore, the matrix properties of tablets produced on commercial tableting equipment might be substantially different from those produced with the aid of a simple manually operated hydraulic press or a single-punch press, largely as a result of differences in compaction cycle and speed. These aspects and their effects on drug release from high drug-load, erodible extended-release matrices are not well documented in the literature and will be described here.

Materials and Methods

Materials

Theophylline (anhydrous, USP), starch (NF), and talc (NF) were purchased from Amend (Irvington, NJ) and magnesium stearate (NF) was obtained from Mallinckrodt (St Louis, MO). Klucel (GF) (hydroxypropylcellulose NF) was donated by Hercules, Wilmington, DE.

Granulation procedure

Two batches of base granulation (batch A, 1·3 kg, and batch B, 0·8 kg) consisting of theophylline and starch (95 : 5) were prepared by wet granulation as described elsewhere (Dürig & Fassihi 1997). Sufficient hydroxypropylcellulose was then added to 100-g lots of the dried granulate and blended for 15 min in a twin-shell V-mixer (Patterson–Kelly, East Stroudsburg, PA) so that hydroxypropylcellulose constituted 4% of the final mixture. Talc (between 0 and 3% of the final granulation mix) was then added through a fine screen (80 mesh) and the mixture was blended for 5 min. This step was repeated for magnesium stearate (0 to 5% of final granulation mix). True densities of the various granulations were determined by helium pycnometry (Accu Pyc 1330, Micrometrics, Norcross, GA).

Tablet preparation

The granulations were compressed on a compaction simulator (Abacus (formerly Mand Testing) Stourbridge, UK) which has been described in detail by Celik & Marshall (1989). The tablets were compressed to four different nominal thicknesses, 2·8, 3·0, 3·2 and 3·5 mm, resulting in ''out of die'' porosities of $14 \pm 0{\cdot}5$, $17 \pm 0{\cdot}5$, $20 \pm 0{\cdot}5$ and $26 \pm 0{\cdot}5\%$. This corresponds to the ''in-die'' or ''at pressure'' porosity range of 6 to 21%. The simulated compaction cycle was that of a Manesty Betapress (double-ended compaction, varying punch velocity) at speeds of 20 and 100 rev min^{-1} (corresponding to maximum punch-tip velocities of (approx.) 50 and 250 mm s^{-1}, respectively). Standard flat-faced round tooling and a 1-cm die were used. A constant volume of granulate equivalent to 0·225 cm^3 was compressed. This resulted in compact weights (true density × 225 mg) ranging from 335 to 340 mg. Nine tablets were prepared at each thickness setting and speed.

Experimental design

A full 2^2 factorial design with four centre points and additional design points along the axes was used (Table 1). To include an estimate of the error resulting from the granulation procedure itself (rather than just blending operations), granulate from Batch B was used for two of the centre points. Batch A was used for all other runs. The design is not intended for optimization using response-surface methodology, rather the primary effects of magnesium stearate and talc and their interaction under the various compaction conditions are of interest here. The design was judged adequate for this purpose.

Drug release

Drug-release studies were performed on three tablets per batch in distilled and deionized deaerated water at 37°C with USP XXIII apparatus 1 (rotating basket; Vankel, Edison, NJ; VK6010) at 100 rev min^{-1}. Theophylline concentrations were measured every 30 min with a Hewlett–Packard (Wilmington, DE) HP 8452A diode-array spectro-

Table 1. Summary of the regression results for the erosion model.

Amount of magnesium stearate (%)	Amount of talc (%)	Erosion rate constants ($mg\,mm^{-2}\,h^{-1}$)		k_a/k_b	Burst effect (%)	Correlation coefficient	(Sum of weighted square residuals/degrees of freedom)$^{0.5}$	Degrees of freedom
		Radial (k_a)	Axial (k_b)					
Porosity 14%								
0	0	0·676	0·588	1·150	0·00	0·9998	0·815	4
0	1·5	0·778	0·672	1·150	0·00	0·9998	0·452	3
0	3	1·199	0·653	1·830	0·00	0·9999	0·537	2
1	0	0·417	0·418	0·998	0·00	0·9998	0·855	2
2·5	0	0·366	0·121	3·023	5·80	0·9987	0·273	19
2·5	1·5	0·349	0·116	3·003	6·43	0·9994	1·015	17
2·5	1·5	0·343	0·114	3·000	8·19	0·9988	1·496	15
2·5	1·5	0·250	0·083	2·994	7·07	0·9991	1·594	24
2·5	1·5	0·264	0·088	3·000	8·19	0·9986	1·416	19
5	0	0·200	0·068	2·956	11·25	0·9971	2·391	13
5	3	0·214	0·071	3·010	10·01	0·9976	2·013	24
Porosity 17%								
0	0	1·17	0·614	1·900	1·06	0·9993	1·756	3
0	1·5	0·796	0·718	1·109	0·48	0·9998	0·928	3
0	3	0·856	0·693	1·230	1·23	0·9995	1·090	3
1	0	0·484	0·471	1·030	1·88	0·9999	0·358	5
2·5[a]	0	–	–	–	–	–	–	–
2·5	1·5	0·338	0·116	2·920	4·15	0·9995	1·189	15
2·5	1·5	0·334	0·115	2·904	7·23	0·9985	1·961	16
2·5	1·5	0·240	0·083	2·895	10·47	0·9986	1·380	19
2·5	1·5	0·249	0·086	2·895	15·21	0·9985	1·360	16
5	0	0·218	0·075	2·904	11·28	0·9979	2·070	24
5	3	0·229	0·079	2·903	8·73	0·9986	1·507	21
Porosity 20%								
0	0	1·239	0·448	2·765	3·49	0·9997	1·219	3
0[a]	1·5	–	–	–	–	–	–	–
0[a]	3	–	–	–	–	–	–	–
1	0	0·641	0·543	1·179	0·00	0·9990	1·714	7
2·5	0	0·361	0·295	1·220	1·65	0·9996	0·891	12
2·5	1·5	0·430	0·156	2·763	3·65	0·9997	0·934	13
2·5	1·5	0·434	0·157	2·756	6·18	0·9997	0·742	10
2·5	1·5	0·296	0·109	2·715	6·11	0·9990	1·616	18
2·5	1·5	0·290	0·110	2·636	6·20	0·9990	1·590	17
5	0	0·246	0·093	2·758	9·25	0·9983	1·761	20
5	3	0·294	0·105	2·800	6·38	0·9991	1·305	17

[a]No regression analysis was performed owing to insufficient data points.

photometer equipped with automatic sampling. Erosion studies were performed with the same apparatus and under the same conditions. At each time point three tablets were removed from the dissolution medium and dried under vacuum at 70°C for 24 h, which was sufficient to achieve constant weight. The extent of tablet erosion was then determined gravimetrically.

Results and Discussion

Erosion model

Katzhendler et al (1997) recently derived a general model for drug release from surface-erodible tablet matrices:

$$M_t/M_\infty = 1 - (1 - k_a t/c_0 a_0)^2(1 - 2k_b t/c_0 b_0) \quad (1)$$

where M_t and M_∞ are, respectively, the amount of drug released after time t and the total amount of drug released when the device is exhausted. k_a and k_b are the radial and axial erosion rate constants and a_0 and b_0 the initial tablet radius and height. c_0 is the uniform initial concentration of the drug in the tablet matrix. The assumption is made that erosion is the rate-limiting step, with neither time-dependent diffusion processes nor matrix swelling having a significant impact on drug release. With regard to the formulations used in this study a minor modification was made to equation 1 to accommodate the burst effect expected with the high drug loading (83–91%) during initial wetting and rapid surface dissolution before the hydration of the system reaches equilibrium. Therefore the equation used in our work takes the form:

$$M_t/M_\infty = 1 - (1 - k_a t/c_0 a_0)^2(1 - 2k_b t/c_0 b_0) + B \quad (2)$$

where B provides an estimate of the burst effect. The drug-release data were fitted to equation 2 by use of a non-linear regression program (WinNonlin, Scientific Consulting, Cary, NC) employing the Gauss–Newton–Levenberg algorithm. No weighting factor was applied.

In an ideal surface-eroding system drug is released into the surrounding media as the erosion boundary moves toward the core centre. The release kinetics should therefore equal the erosion rate or rate of mass loss of the matrix. As erosion occurs from the surface only, the matrix should retain its shape and integrity and the matrix material itself does not change with time as the device undergoes erosion. It is therefore possible to predict the fraction of matrix eroded, m_t/m_0, at any time, t, on the basis of initial mass (m_0), initial drug concentration (c_0), initial dimensions of the tablet (a_0 and b_0) and the applicable erosion rate constants (k_a and k_b), which can be determined from the dissolution data:

$$m_t = v_t m_0/v_0 \text{ and } m_t/m_0 = a^2 b/a_0^2 b_0 \qquad (3)$$

where v_t and v_0 are, respectively, the tablet volume at time t and the initial volume and a ($=a_0-(k_a t/c_0)$) and b ($=(2k_b t/c_0)$) are the radius and height at any time t.

The change in matrix mass predicted on the basis of the erosion rate constants derived from fitting equation 2 to a typical set of dissolution data and the actual fractional change measured in erosion studies is shown in Figure 1. It is apparent there is relatively good agreement between the behaviour predicted by the heterogeneous erosion model and the changes observed.

It is also evident from Figure 2 and the regression results in Table 1 that the model provides a good fit over the entire range of formulations tested in this study. Furthermore, visual confirmation of the progressive erosion and complete disappearance of the tablets at the end of the test period and previously observed dependence on stirring rate (Dürig & Fassihi 1997) support the adoption of this erosion model.

Effect of magnesium stearate and talc

The effect on the release kinetics of varying the amounts of magnesium stearate and talc at different matrix porosities is depicted in Figures 2 and 3 . A general trend of reduced dissolution rate with increasing amounts of magnesium stearate is apparent. Talc seems to have a negligible effect on the release process, although when the tablets contained no magnesium stearate release was occasionally increased slightly by the presence of talc.

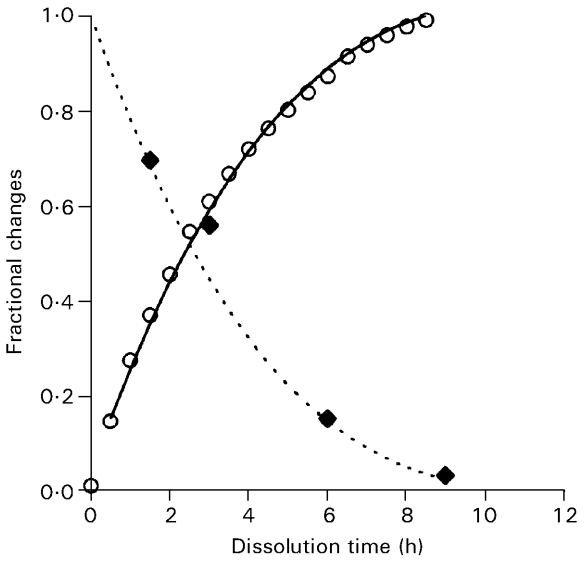

Figure 1. Actual and predicted dissolution and erosion profiles for a typical formulation (drug load 87%, magnesium stearate 2·5%, talc 1·5%, porosity 17%, compaction speed 100 rev min^{-1}): ○, observed fraction of drug released; —, predicted fraction of drug released; - -, predicted fraction of mass remaining; ◆, observed fraction of mass remaining.

Multilinear regression and analysis of variance were used to determine the significance of these observations and to characterize the relationship between the erosion rate constants (k_a and k_b) and

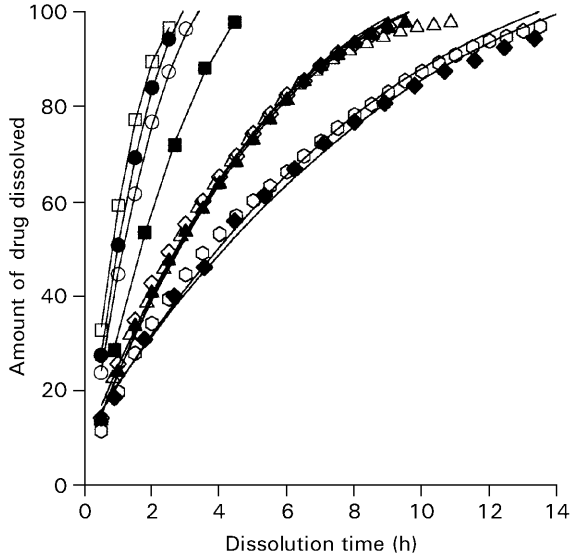

Figure 2. Dissolution profiles for batches compressed at 20 rev min^{-1} to 14% porosity containing different amounts of magnesium stearate and talc: ○, 0% magnesium stearate, 0% talc; ●, 0% magnesium stearate, 1·5% talc; □, 0% magnesium stearate, 3% talc; ■, 1% magnesium stearate, 0% talc; △, 2·5% magnesium stearate, 0% talc; ▲, 2·5% magnesium stearate, 1·5% talc, batch 1; ◇, 2·5% magnesium stearate, 1·5% talc, batch 2; ◆, 5% magnesium stearate, 0% talc; ⬡, 5% magnesium stearate, 3% talc. The solid lines represent the predicted profiles.

the amounts of magnesium stearate and talc. The polynomial models obtained by multilinear regression revealed significant curvature and lack of fit. Further indicators that the equations were inappropriate included systematic patterns in the residual plots, unexplained outliers and deviations from the linear normal plot of the residuals. The inverse transformation ($Y' = 1/Y$) was therefore used as for variance-stabilizing transformation of the erosion rate data. This enabled the underlying assumptions of the analysis of variance to be satisfied. The resultant models were found to be highly significant ($P < 0.0001$) without significant lack of fit (see Table 2). The final equations in terms of actual uncoded factors for batches compressed to 14% porosity at 20 rev min^{-1} are (see Figure 3 for graphical interpretation):

$$1/k_a = 1.26 + 0.71 \times MS \quad (4)$$

$$1/k_b = 1.25 + 2.63 \times MS \quad (5)$$

where MS is the amount (%) of magnesium stearate. Post-analysis of variance effects analysis (Table 3) shows that the effect of magnesium stearate is highly significant ($P < 0.0001$). No significant interaction effect between magnesium stearate and talc or significant primary effect for talc could be determined. Similar inverse relationships between the erosion rate constants and amount of magnesium stearate were found for tablets compressed to 17 and 20% porosity (Figure 3).

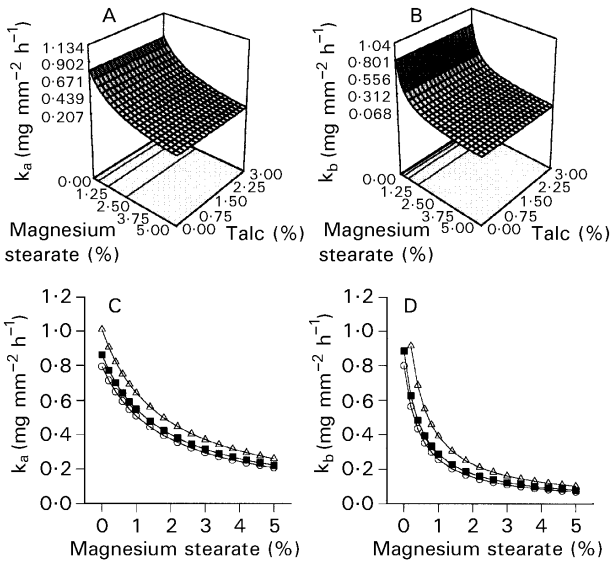

Figure 3. A and B. Three-dimensional plots of predicted relationships between k_a and k_b and amounts of magnesium stearate and talc for tablets compressed to 14% porosity at 20 rev min^{-1}. C and D. Predicted relationships between k_a and k_b and amount of magnesium stearate at ○ 14%, ■ 17% and △ 20% porosity. C. ○ $1/k_a = 1.26 + 0.71 \times MS$, where MS represents the amount of magnesium stearate (model $P < 0.0001$, lack of fit (LOF) $P = 0.872$); ■ $1/k_a = 1.16 + 0.67 \times MS$ (model $P < 0.0001$, LOF $P = 0.961$); △ $1/k_a = 0.99 + 0.57 \times MS$ (model $P = 0.0024$, LOF $P = 0.791$); D. ○ $1/k_b = 1.25 + 2.63 \times MS$ (model $P < 0.0001$, LOF $P = 0.945$); ■ $1/k_b = 1.13 + 2.34 \times MS$ (model $P < 0.0001$, LOF $P = 0.982$); △ $1/k_b = 0.73 + 1.82 \times MS$ (model $P = 0.0026$, LOF $P = 0.479$).

Although reductions in drug dissolution rates associated with hydrophobic lubricants such as magnesium stearate are well documented for immediate-release tablets (Hussain et al 1992), the use of elevated levels of magnesium stearate as an inexpensive dissolution retardant has not found widespread acceptance, because high levels ($> 2\%$) of magnesium stearate frequently result in unpredictable and deleterious changes in tablet tensile strength and powder flow. However, the current formulation was relatively lubricant-insensitive, retaining 60% (approx. 1 MPa) of the tensile strength of unlubricated tablets on addition of 5% magnesium stearate.

In general, dissolution rate retardation in the presence of magnesium stearate has been attributed to the formation of a hydrophobic film on the surface of the host particle. These hydrophobic barriers might effectively result in reduced wettability and reduced host particle surface area available for dissolution (Hussain et al 1992). The observed inverse relationship between magnesium stearate levels and erosion rate and the dramatic reductions in erosion rate between 0 and 1% magnesium stearate could, therefore, be attributed to the initially rapid decreases in effective surface area and wettability on addition of magnesium stearate, because of its extremely large surface area and high spreadability, which results in efficient hydrophobic film formation. However, upon continued addition of magnesium stearate further reductions in drug release are more gradual because of the diminishing host surface area available.

It was further observed that magnesium stearate influenced the balance between radial and axial erosion rates. The ratio of radial to axial erosion rates (k_a/k_b) (Table 1) is essentially constant at (approx.) 3 for formulations containing magnesium stearate $\geq 2.5\%$. On the other hand for formulations with low levels of magnesium stearate ($\leq 1\%$), k_a/k_b tends toward unity. Observed values of k_a/k_b and theoretical values calculated from equations 4 and 5 are shown in Figure 4. In general, the axial (single- or double-ended) compaction of particulate systems results in anisotropic compacts in respect of such matrix characteristics as porosity, density distribution, bonding and mechanical strength (Kandeil et al 1977; Nyström & Karehill 1995). It is therefore reasonable to assume that for certain formulations the anisotropicity in matrix char-

Table 2. Analysis of variance multiple regression models used to characterize the radial and axial erosion rate constants at 14% porosity.

Source	Sum of squares	Degrees of freedom	Mean value	*F* value	*P* value
Response radial erosion rate constant					
Model	16·86	1	16·86	85·12	< 0·0001
Curvature	0·32	1	0·32	1·62	0·2387
Residual	1·58	8	0·2		
Lack of Fit	0·55	5	0·11	0·32	0·8727
Pure Error	1·03	3	0·34		
Corrected total	18·77	10	R^2adj[a] = 0·9033		RMSE[b] = 0·45
Response axial erosion rate constant					
Model	240	1	240·1	158·32	< 0·0001
Curvature	13·75	1	13·75	9·07	0·0168
Residual	12·13	8	1·52		
Lack of Fit	2·97	5	0·59	0·19	0·945
Pure Error	9·16	3	3·05		
Total correlation	265·99	10	R^2adj[a] = 0·9459		RMSE[b] = 1·23

[a]Adjusted correlation coefficient. [b]Root mean square error.

Table 3. Post-analysis of variance effects analysis for regression models used to characterize the radial and axial erosion rate constants at 14% porosity.

Factor	Coefficient estimate	Degrees of freedom	Standard error	*t*	*P* value
Response radial erosion rate constant					
Intercept	3·03	1	0·17		
Magnesium stearate (%)	1·77	1	0·20	8·90	< 0·0001
Response axial erosion rate constant					
Intercept	7·83	1	0·48		
Magnesium stearate (%)	6·58	1	0·55	11·93	< 0·0001

acteristics might manifest itself in differential axial and radial erosion rates. The large k_a/k_b values obtained for formulations containing magnesium stearate ≥2·5% might be attributed to this effect.

Effect of porosity and compaction rate

In general terms increases in compaction force result in increases in apparent density and thus a reduction in matrix porosity. The exact nature of the pressure–density relationship is highly material-dependent and also depends on experimental factors such as compression speed and size and shape of the tooling (York 1979). In this study comparisons between tablets prepared at different levels of force are made in terms of matrix porosity (1 − D, where D is the relative density of the matrix). The influence of porosity on the erosion rate constants and the dissolution rate of the formulations studied here is illustrated in Figures 3C, D and 5 . A general trend of faster release at higher levels of porosity is evident.

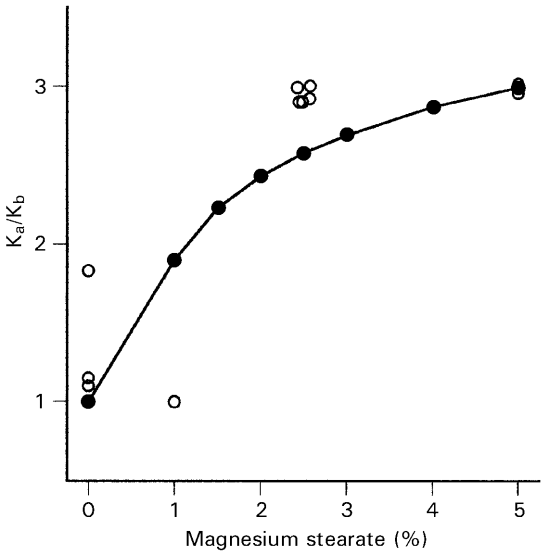

Figure 4. Observed (○) and predicted (●) relationship between k_a/k_b and amount of magnesium stearate for all batches used in this study. Data points are means from three tablets. Tablets were compressed to 14% porosity at 20 rev min^{-1}.

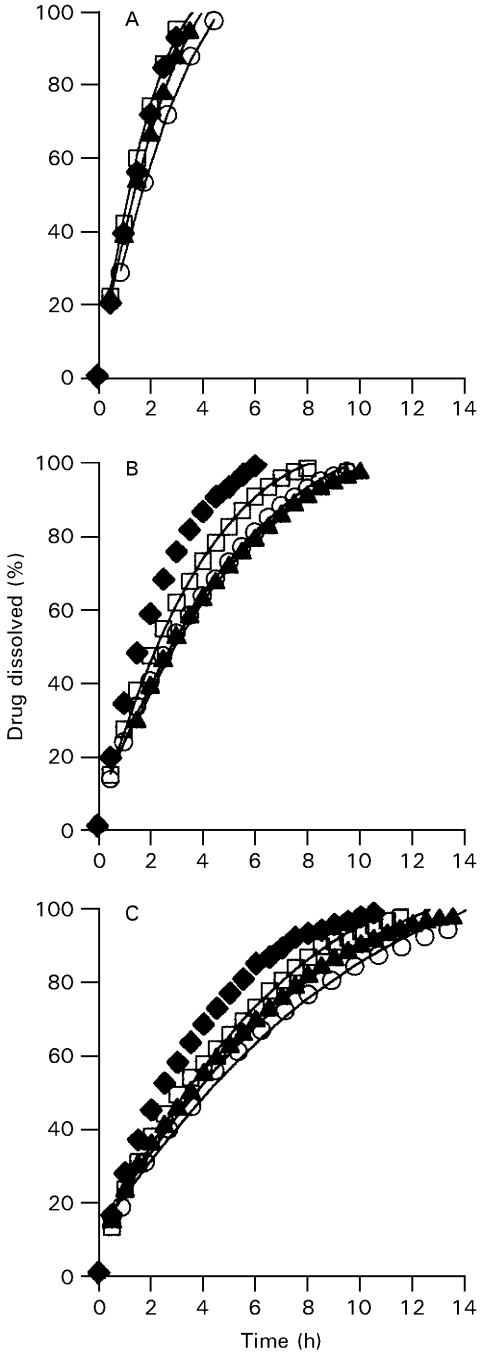

Figure 5. Dissolution profiles for tablets compressed at four different porosities (○ 14%, ▲ 17%, □ 20% and ◆ 26%) containing 1% magnesium stearate and 0% talc (A), 2·5% magnesium stearate and 1·5% talc (B), and 5% magnesium stearate and 0% talc (C).

In terms of the surface erosion and dissolution model the trend toward reduced erosion rates seen with reduced porosity and larger compression force can be attributed to the reduced surface area available for dissolution and the reduced wettability and water ingress as a result of the reduced pore structure. However, as illustrated by the small differences between the dissolution profiles and rate constants for tablets with 14 and 17% porosity, there seems to be a threshold for applied pressure and porosity achieved beyond which further densification results in only incremental changes in release. The relationship between drug release and applied pressure might be related to the relative contributions of simultaneously occurring mechanisms of consolidation which are known to affect tablet surface area. These would include particle fragmentation which results in creation of new surface area, increased interparticulate contact (which might lead to bonding) and the flattening of particle asperities resulting in asperity melting and smoothing of particle surfaces, both of which result in reduced surface area (Higuchi et al 1953; Armstrong 1995).

In some formulations changing the rate of production of a tablet press or changing from one type of press to another, which might involve a change in compression speed, can affect the quality of the resulting tablets (Armstrong 1989). This is of particular importance during scale up and it is generally believed that formulations with low compression speed sensitivity are likely to be more robust and easier to scale up. Although many studies indicate a tendency toward production of weaker tablets at higher punch velocities, the effect of changes in speed and compression time on drug-dissolution behaviour seems to have received less attention. Formulations compressed to the same nominal thicknesses at 20 and 100 rev min^{-1} yielded superimposable dissolution profiles. This insensitivity to time-dependent changes in compression might well be attributed to the relatively brittle nature of the granules.

Conclusion

For the formulation system investigated in this study drug release can be described by a surface-erosion model. In this regard magnesium stearate was found to be the critical erosion-controlling excipient, with erosion rates being inversely proportional to the amount of magnesium stearate in the formulation. This was attributed to the surface-covering ability and hydrophobic film formation associated with magnesium stearate. The retarding effect of magnesium stearate on drug release was especially dramatic over the range 0 to 1%. Furthermore, magnesium stearate was found to affect the balance between axial and radial erosion rates. Talc was found to have no significant effect on erosion kinetics. With regard to compaction variables the formulations showed some robustness. Changes in compaction force resulting in ‘‘out of

die'' porosities in the range 14 to 17% (corresponding to ''in-die'' porosity changes in the range 6 to 10%) and changes in machine speed from 20 to 100 rev min^{-1} did not result in materially different release kinetics. However at porosities exceeding the above range more rapid erosion should be expected.

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