

Mechanistic Evaluation of Binary Effects of Magnesium Stearate and Talc as Dissolution Retardants at 85% Drug Loading in an Experimental Extended-Release Formulation

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Abstract □ The feasibility of producing extended-release matrix tablets with high drug loadings (80–90% w/w) containing a binary combination of magnesium stearate (MS) and talc (T) at different levels as major dissolution retardants was investigated. Matrix tablets were prepared from a granulation containing theophylline, starch, hydroxypropylcellulose, and varying amounts of MS and T. Using a 3² factorial design, the effect of MS and T levels on the physical properties and drug release characteristics of the tablets was evaluated. Response surface analysis showed that the binary combination of MS and T at levels >3% adversely affected both tensile strength and friability. A parabolic relationship was observed for the increase in time required for the release of 50% of the theophylline (*t*_{50%}) with increased MS levels. Moreover, as the proportion of MS and T was increased, the release profiles became more linear. A combination of 3% MS and T provided both near zero-order release kinetics as well as a coherent matrix structure. Based on model fitting, a release mechanism combining diffusion and matrix erosion/dissolution is proposed. It may be concluded that in the development of controlled-release systems, the binary combination of MS and T at levels exceeding those conventionally used for lubrication can be employed as an inexpensive, low bulk dissolution retardant for formulations with high drug loading.

Introduction

The reduction in drug dissolution rate associated with the presence of hydrophobic lubricants, especially magnesium stearate (MS), is well documented.^{1–4} The work of Rednick and Tucker⁵ represents one of the earlier attempts to apply this phenomenon to the controlled release of drugs from solid oral dosage forms. In their study, they describe a formulation for compressed boluses suitable for sustained drug delivery in ruminants, with levels of 1–3.5% MS as dissolution retardant. However, high levels of MS concentration may adversely influence powder flow and cause undesirable and unpredictable changes in tablet properties, such as decreased tensile strength and increased friability.^{6,7} Therefore, MS has not found widespread acceptance as a dissolution retardant.

More recently, combinations of MS and talc (T) as dissolution retardants have been investigated by Fassihi et al.⁸ These workers studied the feasibility of using higher than conventionally accepted levels of MS and T as dissolution retardants in a directly compressible matrix that contained dicalcium phosphate, methacrylate polymers, and ethyl cellulose as major formulation components and theophylline as a model drug. In another study, dexchlorpheniramine was used as an example of a highly water soluble drug in a similar matrix.⁹ It would appear from the two studies that in certain combinations, MS and T can interact in a suitably chosen matrix system to achieve dissolution retardation while simultaneously counteracting any softening/weakening of the ma-

trix structure that is frequently cited as an adverse effect resulting from the presence of excessive levels of MS in tablet formulations. In both studies, the effect of MS and T on release kinetics and shape of release profile has not been investigated in any depth. Neither was any attempt made to achieve any specific release characteristics. Furthermore the formulations included relatively large amounts of additional dissolution retarding excipients.

One of the attractive aspects of using MS and T as dissolution retardants would conceivably be in controlled-release formulations where high drug loading capacity is essential. Examples of drugs administered in sustained/controlled-release formulations with relatively high doses of active drug include theophylline, lithium carbonate, procainamide, verapamil, and diltiazem. Recent reports on the development of a sustained-release formulation of zidovudine (AZT) provide an additional example.¹⁰ Depending on the loading dose, the sheer physical size of the tablet may be problematic when large amounts of excipients have to be used as release-controlling agents. Therefore, addition of as little as possible volume of such excipients becomes a necessity. One way of overcoming such problems is drug particle coating with polymers or highly hydrophobic agents. For example, the hydrophobic nature of MS and its coating actions when blended in powders or the use of MS combined with T (i.e., binary hydrophobic blend) may present an alternative, inexpensive, low bulk, dissolution-retarding system.

To investigate this possibility, theophylline was chosen as a model drug suitable for sustained delivery where high drug loading is essential. Depending on whether 12- or 24-h dosing intervals are used, typical adult therapeutic doses range from 300 to 600 mg for this drug. The objective was to study the feasibility of producing an extended-release tablet formulation with high drug loading capacity (+/- 90%, w/w), with MS and T blends as retardants and a minimum use of additional excipients. To achieve this objective, a factorial design and response surface methodology were used to evaluate the effect of varying the levels of MS and T on the mechanical strength and the release characteristics of the matrices. The response surface plots were then used to identify a formulation with desirable mechanical strength and release characteristics.

Experimental Section

Materials and Equipment—To prepare the tablets, anhydrous theophylline BP (Holpro Analytics, Johannesburg, South Africa), hydroxypropylcellulose (Klucel GF; Aqualon, Düsseldorf, Germany), starch BP (Holpro Analytics, Johannesburg, South Africa), magnesium stearate BP (Fluka, Buchs, Switzerland), and talc (SAAR Chem, Krugersdorp, South Africa) were used as received. All dry mixing was performed with a perspex cube mixer (Erweka AR400, Heusenstamm, Germany). For wet massing, a planetary mixer (Bear, USA) was employed. An oscillating sieve granulator (Erweka AR400, Heusenstamm, Germany) with a 1-mm stainless steel sieve was employed for granulation. Granules were tray dried in a convection-type oven under controlled conditions (Memmert, Schwabach, Ger-

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Table 1—Transformed Factor Levels (MS and T) and Values for the Various Response Variables

Run no.	Factor Levels		Response Variables ^a						
	%MS	%T	S _T (Nm ⁻²)	Fr (%)	D _T (g/mL)	Cl	t ₅₀ (h)	n	H (mm)
1	2	0	1.215	0.215	0.541	17.62	3.100	0.659	4.045
2	4	0	1.361	0.247	0.534	15.58	6.260	0.940	4.055
3	0	4	0.821	0.288	0.552	16.79	2.460	0.630	4.060
4	4	4	1.081	0.331	0.567	18.36	5.630	1.220	4.070
5	4	2	1.345	0.261	0.556	17.62	6.890	1.180	4.040
6	0	2	0.842	0.222	0.529	16.92	2.150	0.690	4.055
7	0	0	0.302	0.313	0.495	11.11	1.834	0.650	4.460
8	2	2	1.115	0.179	0.537	16.58	3.100	0.750	4.055
9	2	4	1.107	0.247	0.561	13.45	3.410	0.790	4.050

^a S_T, tensile strength; Fr, friability; D_T, tapped density; Cl, Carr's index; t₅₀, time for 50% drug release, n, release exponent; H, tablet thickness.

many). Tablets were compressed on a single punch press (Manesty F3, Liverpool, U.K.) fitted with 8.5-mm punches and die. A USP XXII dissolution apparatus was used in the release studies (Calveva FST, Cambridge, U.K.). A Beckman DU650 UV spectrophotometer (Fullerton, CA) was used to measure the amount of drug released. The mechanical strength of the tablets was assessed with a model PTB311 motorized diametral compression tester (Pharmatest, Hainburg, Germany) and a Roche-type friabilator (Erweka, Heusenstamm, Germany).

Software—Statgraphics Version 5 (Statistical Graphics Corporation, Rockville, MD) was used for all data analysis. This analysis includes generating the experimental design, fitting a polynomial model to the data, calculating the model parameters, testing the fit, and plotting response surfaces. The program was also used to fit various kinetic models to the drug release data by nonlinear regression with the Marquardt algorithm.

Preparation of Tablet Matrices—A standard granulation mix consisting of theophylline, starch, and hydroxypropylcellulose (90:6:4 respectively) was prepared. Starch and theophylline were sieved and blended in the cube mixer for 15 min. The mixture was then transferred to a planetary mixer and sufficient water was added to form a coherent wet mass. The wet mass was then passed through a 1-mm sieve on an oscillating granulator. The granules were then tray dried in a convection oven for 40 min at 70 °C. Hydroxypropylcellulose was then added to the granulation and blended for 15 min in the cube mixer. The appropriate amount of T was then added to 20 g of granulation through a fine screen (600 μm) and blended into the mixture for 5 min. The same was repeated for MS. Depending on the levels of MS and T used, the final mix for compression varied between 20 and 21.7 g (i.e., the standard granulation constituted between 92 and 100% of final compression mix). The granulation mixtures were compressed on a single punch press keeping the compression force (160 ± 5 MPa) and tablet weight (250 mg) constant for all batches.

Experimental Design—A randomized 3² factorial design was chosen to study the relationship between the amount of MS and T in the formulation and the resulting tablet properties. The transformed levels of MS and T and various response variables are depicted in Table 1. The levels of MS and T were chosen after the evaluation of basic preliminary studies and the earlier results obtained by Fassih *et al.*^{8,9}

Evaluation of Formulation Characteristics—Tensile Strength—Using the diametral compression test, the crushing force (F) was determined with the diametral compression tester. Simultaneously, tablet thickness (H) and diameter (D) were also determined with the device. For each batch, 10 tablets that failed in tension were used to calculate the average radial tensile strength (S_T) according to the method of Fell and Newton¹¹ with the following equation:

$$\text{Tensile Strength} = 2F/\pi DH \quad (1)$$

Friability—Ten tablets, accurately weighed, were placed in the plastic drum of the friabilator and subjected to 100 rotations.

Friability was then calculated as the percent decrease in weight after dedusting.

Granulation Packing Properties—The bulk density (D_b) of the different formulations was determined from an accurately weighed 10-g sample that was poured through a funnel into a graduated 50-mL cylinder. Tapped density (D_t) was then determined by manually tapping the samples 150 times over a height of ~3 cm at a rate of 2 taps/s. This procedure achieved a constant volume for all granulations. Carr's compressibility index (CI) was then calculated as follows:

$$CI = \{(D_t - D_b)/D_t\} \times 100\% \quad (2)$$

Drug Release Studies—Three tablets per run were evaluated with the USPXXII apparatus II (paddle apparatus). Deaerated double-distilled water (1000 mL) that was preheated and maintained at 37 °C was used as dissolution medium. The standard paddle speed was 75 rpm. Additional studies were carried out on selected formulations at 50, 100, and 150 rpm. Samples (2 mL) were drawn three times in the first hour and then hourly thereafter and replaced with fresh dissolution medium. Theophylline concentrations were then determined spectrophotometrically at 270.5 nm.

Data Analysis—The release profiles were characterized by determining t_{50%} (time in hours required for the release of 50% of the theophylline) and the release exponent (n) in a modified version of the Korsmeyer-Peppas equation as described by Lindner and Lippold¹²:

$$Q = kt^n + b \quad (3)$$

where Q corresponds to the fraction of the loading dose released at time t, k is a kinetic constant, exponent n indicates the general operating release mechanism, and b corresponds to the y-axis intercept, characterizing the burst effect. Equation 2 was fitted to the dissolution data (up to 60% release, with lowest R² = 0.98).

The various measured responses were fitted to second-order polynomial models with multiple linear regression. The resulting models were simplified by eliminating the parameters that were insignificant at p < 0.1. The simplified models were then recalculated and assessed for adequacy with the adjusted coefficient of determination (R²_{adj}) and the estimated error standard deviation, s_e, where s_e = (mean square error)^{0.5}. The closer R²_{adj} approaches 1, the closer the predicted responses are to observed responses. Similarly, a small value for s_e indicates that the predicted responses closely approximate the observed responses. Large values may indicate a large random error component or improper model specification. In addition, the models were tested for lack of fit using the Fisher F test. Because of the lack of replicates, the experimental F value was obtained as the ratio between the variance of the model and the residual variance as outlined by Gonzalez.¹³ The fitted model was judged adequate if the experimental F value exceeded the tabulated value (i.e., F > F(L-1), (N-L), 95% where L is the number of regression coefficients and N is the total number of experiments).

Results and Discussion

The observed responses are shown in Table 1. The relationships between the response variables and MS and T could be adequately characterized by the following reduced polynomial equations:

$$\begin{aligned} \text{Tensile Strength (S}_T\text{)} = & 1.145 + 0.3036\text{MS} - 0.19945\text{MS} \times \text{T} - 0.1866\text{MS}^2 \\ [R^2_{\text{adj}} = 0.84; F = 15.5; F(3,5,95\%) = 5.4; s_e = 0.1295] & \quad (4) \end{aligned}$$

$$\begin{aligned} \text{Tap Density (D}_T\text{)} = & 0.5413 + 0.0135\text{MS} + 0.0184\text{T} \\ [R^2_{\text{adj}} = 0.77; F = 14.7; F(2,6,95\%) = 5.14; s_e = 0.0252] & \quad (5) \end{aligned}$$

Table 2—ANOVA of the Multiple Regressions for the Polynomial Models Used to Characterize the Response Variables in Terms of MS and T^a

Effect	SSQ	df	MSQ	p
Tensile strength				
MS	0.5530	1	0.5530	0.0022
T	—	—	—	—
MS·T	0.1591	1	0.1591	0.0275
MS ²	0.6967	1	0.6967	0.0972
T ²	—	—	—	—
T _{Err}	0.0839	5	0.01678	—
Total	0.8657	8	—	—
Tap density				
MS	0.0011	1	0.0011	0.0184
T	0.0020	1	0.0020	0.0047
MS·T	—	—	—	—
MS ²	—	—	—	—
T ²	—	—	—	—
T _{Err}	0.0006	6	0.0001	—
Total	0.0037	8	—	—
Friability				
MS	—	—	—	—
T	0.0013	1	0.0013	0.0674
MS·T	0.0030	1	0.0030	0.0205
MS ²	0.0079	1	0.0079	0.0038
T ²	0.0056	1	0.0056	0.0071
T _{Err}	0.0008	4	0.0002	—
Total	0.0188	8	—	—
t _{50%}				
MS	25.36	1	25.36	0.000
T	—	—	—	—
MS·T	—	—	—	—
MS ²	2.002	1	2.002	0.014
T ²	—	—	—	—
T _{Err}	1.053	6	0.1756	—
Total	28.42	8	—	—
Release exponent				
MS	0.3128	1	0.3128	0.0002
T	0.0254	1	0.0254	0.0081
MS·T	0.0225	1	0.0225	0.0096
MS ²	0.0462	1	0.0462	0.0034
T ²	0.0068	1	0.0068	0.0468
T _{Err}	0.0019	3	0.0006	—
Total	0.4157	8	—	—

^a SSQ, Sum of squares; df = degrees of freedom; MSQ = mean square; p = p value; T_{Err} = total error

$$\text{Friability (Fr)} = 0.1783 + 0.0150T + 0.02747MS \times T + 0.06323MS^2 + 0.05298T^2$$

$$[R^2_{\text{adj}} = 0.907; F = 20.6; F(4,4,95\%) = 6.39; s_e = 0.0147] \quad (6)$$

$$t_{50\%} = 3.203 + 2.056MS + 1.001MS^2$$

$$[R^2_{\text{adj}} = 0.95; F = 77.9; F(2,6,95\%) = 5.14; s_e = 0.4190] \quad (7)$$

$$\text{Release Exponent (n)} = 0.772 + 0.228MS + 0.065T + 0.075MS \times T + 0.152MS^2 - 0.058T^2$$

$$[R^2_{\text{adj}} = 0.98; F = 28.3; F(2,6,95\%) = 5.14; s_e = 0.0147] \quad (8)$$

The results of the analysis of variance (ANOVA) of the multiple linear regression for the various polynomial models are summarized in Table 2. The response surface plots

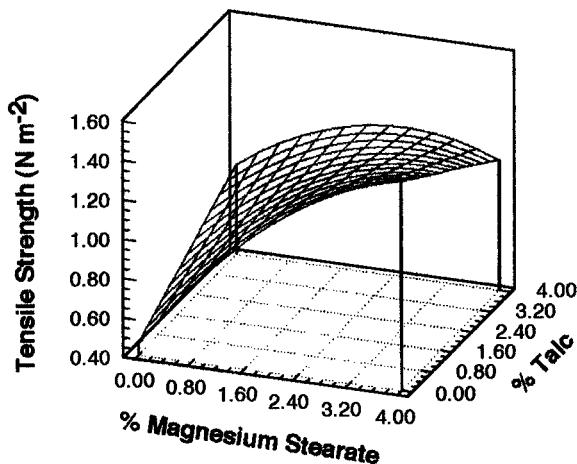


Figure 1—Predicted response surface of tensile strength as a function of MS and talc concentration.

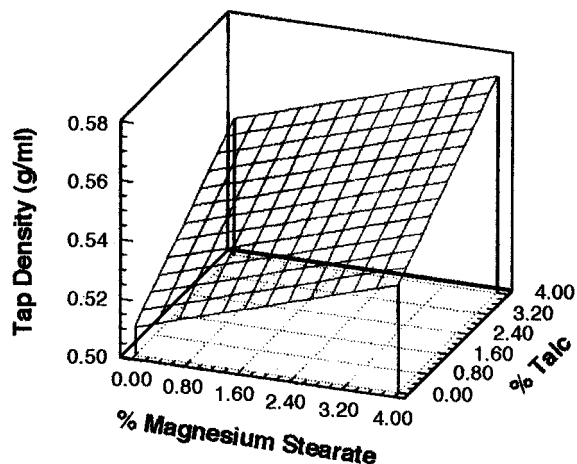


Figure 2—Predicted response surface of tapped density a function of MS and talc concentration.

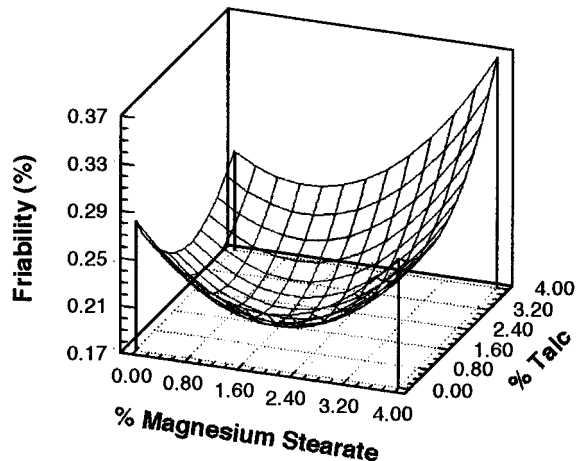


Figure 3—Predicted response surface of friability as a function of MS and talc concentration.

corresponding to each of the aforementioned polynomial equations are given in Figures 1–5. The polynomial equation obtained for Carr's compressibility index was judged to be inadequate ($R^2 = 0.40$, $R^2_{\text{adj}} = 0$, $s_e = 2.919$) and was therefore not considered in depth. However, it is noteworthy that the values for CI tend to increase as the percentage of MS and T increases, ranging from 11.11% (0% MS, 0% T) to 18.36% (4% MS, 4% T). Therefore, although there might be a tendency

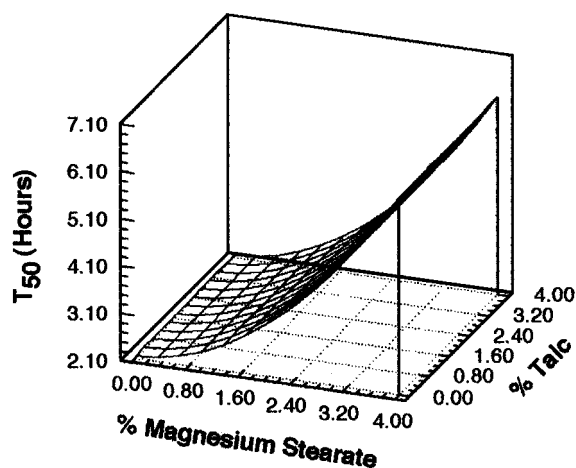


Figure 4—Predicted response surface of $t_{50\%}$ as function of MS and T.

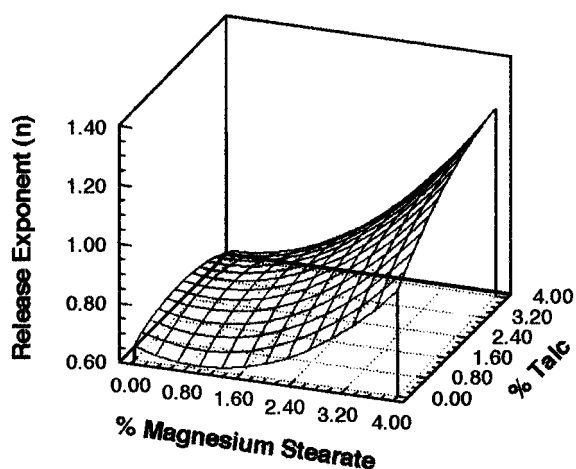


Figure 5—Predicted response surface of release exponent (n) as a function of MS and T concentration.

toward poorer flow at higher lubricant levels, most of the formulations used in this study fall into the range of good to passable flow as assessed by the CI.

Mechanical Characteristics—Within the experimental range in this particular formulation, MS had a significant positive effect on tensile strength ($p < 0.05$). T had no significant effect, but the interaction effect is significant at $p < 0.1$. The response surface forms a broad plateau (see Figure 1,) with a maximum at $\sim 4\%$ MS.

The large differences in tensile strength and tablet thickness between the various batches may be related to the substantial variations in powder bed density as well as compression and postcompression behavior of the compacted material. In general, powder bed compaction, volume reduction, and the associated “force-time cycle” are highly complex processes that involve energy consumption and increases in interparticulate attraction forces. These events can be regarded as endothermal processes. Bond formation, on the other hand, is an exothermal event.¹⁴ With application of axial compression, the elastic and plastic characteristics of the material, and changes in porosity, density, and anisotropic force distribution within the compact will influence the final physical characteristics and tensile strength of the tablets.¹⁵ In addition, lubrication at appropriate levels can enhance and normalize the relative transmission of forces within the die cavity and greatly improves volume reduction (i.e., changes in porosity). It is also known that high levels of lubricant, glidant and prolonged mixing adversely affect the tensile

strength of plastically deforming materials.¹⁶ In contrast, brittle substances appear less sensitive to the aforementioned factors, possibly because of the formation of new surfaces due to fragmentation, extensive and strong interparticulate bonding, and formation of solid bridges during compaction.¹⁷ As shown in Figures 1 and 2 and Table 1, the unlubricated granulation resulted in weak tablets, low tapped density, and increased tablet thickness. In contrast, lubrication with MS and T significantly ($p < 0.05$) increased tensile strength and improved tapped density in a linear fashion. The factors influencing tensile strength in this experimental formulation include powder bed density, bonding, elastic and plastic characteristics of the materials, and flowability of the final mix. All of these factors are expected to be influenced by variation in MS and T levels. Based on the previous discussion, the cause of the low tensile strength and large tablet thickness for the unlubricated batch may thus be attributed to the brittle nature of the granules, pronounced anisotropic force distribution within the compact, and large residual die wall pressure. Under these conditions, during and upon ejection of the tablets when load is reduced, lamination and crack propagation is likely to occur.¹⁸ This result could be the direct consequence of extensive elastic recovery in both axial and radial directions, the development of large differential stresses within the compact, and layer separation resulting in compacts of low strength and large thickness. A partial explanation for the increased tensile strength with increased levels of MS and T would thus be the improved volume reduction and consolidation behavior by fragmentation of compressed granules, formation of new surfaces and denser compacts by bringing the particle surface areas into closer proximity, and an increased ability to transmit the compression force resulting in more cohesive compacts. It should be noted that with a brittle material in the presence of a lubricant film, bond formation can easily be established due to penetration by point irregularities.^{19,20} Furthermore, it would appear that when an excess of glidant/lubricant is present (e.g., 4% MS and 4% T), the enhanced volume reduction and ability to consolidate is partially negated by greater particle surface coating and subsequent interference with bonding. This latter effect is also known to occur with plastically deforming materials upon prolonged mixing time with MS.²¹ Because of the complex nature of the formulation and its compaction behavior, quantitative interpretations become precarious. Therefore, additional work should be undertaken to more adequately characterize this phenomenon.

As with tensile strength, the complexity of the relationship between MS, T, and friability could not be adequately characterized by first-order models. A positive stabilizing interaction between MS and T was observed (significant at $p < 0.05$), accompanied by large second-order effects for both MS and T. Although all formulations were acceptable in terms of friability ($< 0.5\%$ weight loss), the response surface does show a definite local minimum at the center of the factor space with rapidly rising values at the boundaries (a minimum of 0.175% is predicted at $\sim 1.8\%$ MS and T). The unlubricated tablets had a very rough surface, which may well have made them more prone to abrasion. At the other extreme, tablets with 4% MS content may have shown increased friability due to the tendency of surface MS to readily undergo shear when subjected to friction and abrasive forces. Evaluation of tensile strength and friability together would thus lead to the conclusion that MS and T in the range of $> 1\%$ to $< 3\%$ improve the overall physical properties of the tablets.

Drug Release Characteristics—The regression equation and corresponding response surface for $t_{50\%}$ (Figure 4) show that MS on its own exerts a large significant ($p < 0.05$) dissolution-retarding effect. The value of t_{50} appears to rise

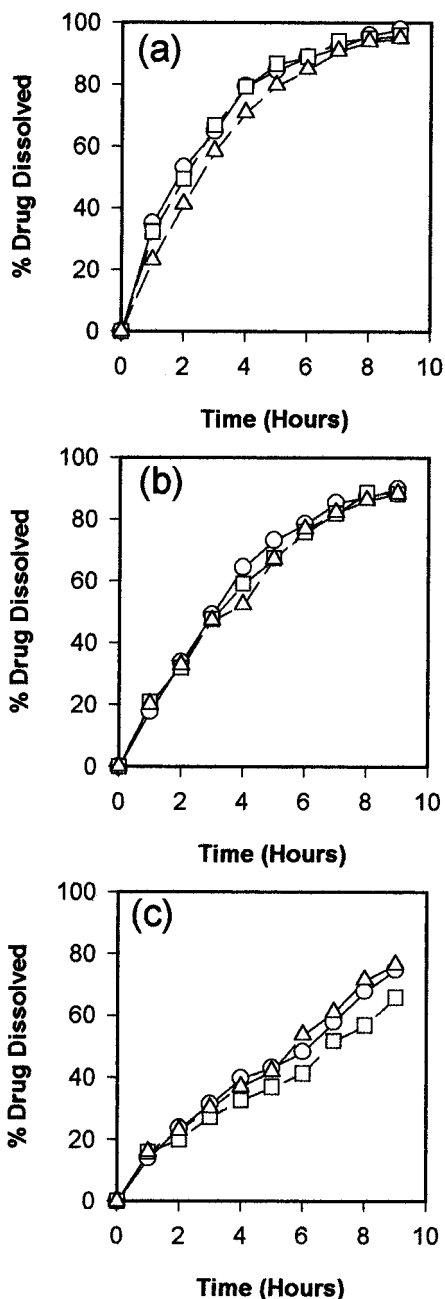


Figure 6—Effect of MS and T levels on theophylline release: (a) 0% MS; (b) 2% MS; (c) 4% MS. Key: (○) 0% T; (△) 2% T; (□) 4% T.

in parabolic fashion with increased MS. However, T had no measurable effect on the extent of dissolution as determined by the t_{50} value. These findings are similar to those of Fassihi *et al.*⁹ who identified MS as the dominant factor causing dissolution retardation in a directly compressible formulation with low drug loading. However, T did have a significant effect on the release exponent, n . The presence of T tends to result in more linear release kinetics. Examination of Table 1 and Figure 5 reveals values of n ranging from 0.63 (0%MS, 4% T) to 1.22 (4%MS, 4% T). The relationship between n and MS and T is characterized by significant individual and second-order effects for MS and T, as well as an interaction effect. However, the effect of MS appears considerably larger than that of T. The individual release profiles for tablets containing different amounts of MS and T alone or in combination further confirm the aforementioned findings (see Figure 6). In particular, Figures 6 a, b, and c show that the

release profiles progressively become more linear and the rate of release decreases as MS and T increase from 0% to 4%.

According to Ritger and Peppas,²² n is dependent on the geometry of the drug delivery device and its value can be indicative of the type of release mechanism. In cylindrical systems, $n = 0.45$ is associated with Case I Fickian transport, whereas diffusion coupled with matrix relaxation/erosion/dissolution is likely for $0.45 < n < 0.89$. Case II relaxational release prevails if $n = 0.89$, and super case II transport occurs for $n > 0.89$. Regardless of geometry, the separate contributions made by Fickian diffusion and matrix relaxation/dissolution can be determined from eq 9²³:

$$Q = k_1 t^n + k_2 t^{2n} \quad (9)$$

where k_1 is the Fickian kinetic constant, k_2 is the relaxational/dissolution rate constant, and n is the Fickian release exponent.

Case II relaxational release is generally attributed to solvent-induced changes that lead to polymer swelling, chain disentanglement, and dissolution.^{24,25} In the present study, swellable polymer constitutes <5% of the matrix mass, thus precluding the formation of a continuous swellable polymer network. Only thin gel layers of low viscosity were observed, and the ongoing marked erosion of tablet surfaces was obvious. Matrix dissolution as a form of physical relaxation has been proposed by Hopfenberg²⁶ and more recently by Sutanata *et al.*²⁴ in their study of drug-loaded glyceride bases.

It is apparent that at low levels of MS and T, drug release is predominantly diffusion controlled. As the proportions of MS and T in the formulation increase, diffusional drug release decreases, resulting in increased dominance of the erosional contribution. This scenario allows near zero-order drug release patterns to be achieved. The exact mechanism by which dissolution and diffusional processes are controlled at higher MS levels is not clear. Dissolution rate retardation and decreased water ingress in the presence of MS in solid dosage forms is generally attributed to the formation of hydrophobic MS films on the host particle surface.²⁷ Such hydrophobic barriers may lead to decreases in effective host surface area available for dissolution.^{4,27} Reduced wettability and, consequently, reduced contact between solvent and drug has also been proposed.²⁷ Additionally, increased tablet tensile strength observed at higher MS levels (i.e., >1% but <3%) may result in a reduced pore structure (low porosity), causing retarded fluid ingress and drug diffusion.

The effect of T on drug dissolution and diffusion has not been widely studied. However, increased matrix hydrophobicity when combined with MS has been reported.^{8,28} In the present system, an interaction effect (significant at $p < 0.05$) involving MS and T was observed for the release exponent. In addition, T on its own also exerts a significant effect ($p < 0.05$) on diffusion/dissolution. This retarding effect on diffusion may be related to the insoluble nature and large surface area of T and its ease of spreadability that facilitates close interaction with other formulation components.

Evaluation of Model Formulations—Based on visual inspection of the response surface plots, a formulation containing 3% MS and 3% T was identified as a candidate that would combine good mechanical strength and low friability with desirable release characteristics. To assess the validity of this prediction and to further characterize the delivery system, two batches (A and B) both containing 3% MS and 3% T were prepared and evaluated under the same conditions as outlined for the other batches in the *Experimental Section*. On the whole, the bias for predicted versus observed responses is acceptable (Table 3). The release data (shown in Figure 7) were fitted to eqs 3 and 9, as well as a heterogeneous erosion model (see eq 10). All the parameters in the models were

Table 3—Comparison of Predicted and Observed Responses for Batches A and B (3% MS, 3% T)^a

Parameter	Predicted	Observed	Bias ^b
Tensile strength (Nm ⁻²)	1.19	1.14 (1.07)	4.2% (9.87%)
Friability (%)	0.222	0.251 (0.237)	13% (6.3%)
t _{50%} (h)	4.48	3.72 (3.6)	16.9% (19.6%)
n	0.98	0.89 (0.95)	9.2% (3.3%)

^a Values for batch B are in parenthesis. ^b Bias = (|observed - predicted|/predicted) × 100.

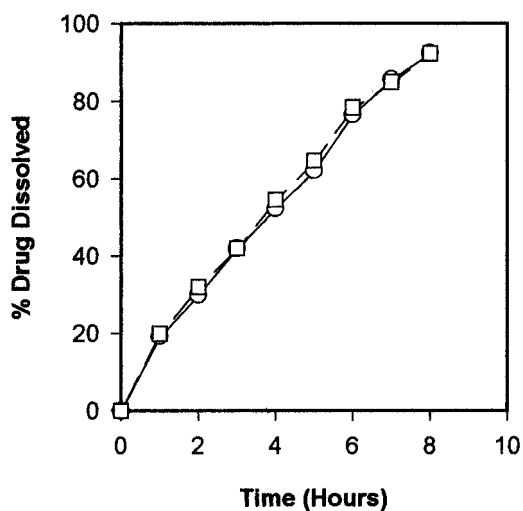


Figure 7—Release profiles for formulations containing 3% MS and 3% T. Key: (○) batch A; (□) batch B.

estimated with the curve fitting program. It should be noted that ideally the release kinetics for a heterogeneous eroding system are mainly dependant on hydrolysis, enzymatic cleavage, or polymer degradation. However, physical disentanglement of polymer due to swelling, surface erosion, or dissolution, and release of the drug into the dissolution medium can be looked at in the same manner as polymer degradation, and, hence, a similar mathematical treatment can be applied.²⁹ Hopfenberg²⁶ has presented the following general erosion model that is applicable to slabs ($n = 1$), cylinders ($n = 2$), and spheres ($n = 3$):

$$Q = 1 - [1 - k_1 t]^n \quad (10)$$

where k_1 is equal to k_0/c_0r ; k_0 is the zero-order erosion constant, c_0 refers to the uniform initial drug concentration, and r represents the original radius of a sphere or cylinder or the half-thickness of a slab. The model describes the idealized kinetics of drug release from a matrix by any erosion/relaxation process regardless of mechanism, and it is assumed that the relaxations are not confounded by diffusion processes.²⁶

Initial curve fitting using Hopfenberg's general model (eq 10), over the range of 0 to 80% drug released, yielded values for n that tended toward 2. The model for a cylinder was therefore used. It should be noted that in Hopfenberg's model, only drug release from the primary surfaces of the device is considered. The contributions made by the flat circular top and bottom surfaces (secondary surfaces) of the cylinder are ignored. In general, when modeling drug release from tablet matrices, the contributions made by these secondary surfaces should be included.³⁰ Katzhendler *et al.*³⁰ have recently

Table 4—Model Fitting Results for Batches A and B (Each Containing 3% MS and T)

Model	k_1	k_2	n	b	R^2	MSE	AIC ^b
$k_1 t^n + b$	0.136 (0.124)	—	0.888 (0.950)	0.054 (0.076)	0.999 (0.999)	3.57×10^{-5} (6.11×10^{-5})	-45.2 (-42.5)
$k_1 t^n + k_2 t^{2n}$	0.138 (0.150)	0.049 (0.043)	0.548 (0.567)	—	0.999 (0.998)	4.73×10^{-5} (9.53×10^{-5})	-43.78 (-40.29)
$1 - (1 - k_1 t)^2$	0.081 (0.084)	—	—	—	0.992 (0.992)	5.55×10^{-4} (5.69×10^{-4})	-37.9 (-37.7)

^a Values for batch B in parenthesis. ^b Values for AIC are negative.

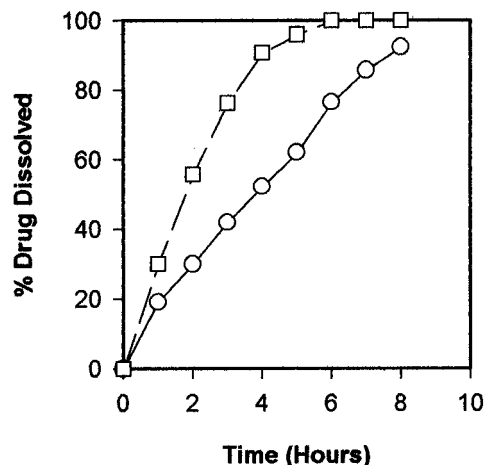


Figure 8—Effect of stirring rate on the release of theophylline from tablets containing 3% MS and 3% T. Key: (○) 75 rpm; (□) 150 rpm.

developed a mathematical model that describes drug release from an erodible matrix tablet taking into account both primary and secondary surfaces as well as the tablet radius-to-thickness ratio and the possibility of different radial and axial erosion rate constants. Their analysis shows that in certain cases, drug release from a tablet can be approximated by the original Hopfenberg model. For instance, where the tablet radius is equal to or greater than the thickness and the axial erosion rate is such that tablet thickness reduces at a higher rate relative to the radial changes, then the theoretical drug release approximates that of a flat disk (slab) and can be described by the Hopfenberg equation with $n = 1$. In contrast, if tablet thickness is approximately equal to or greater than tablet radius and the tablet erodes faster in the radial direction (i.e., tablet radius declines faster than tablet thickness), then drug release can be approximated by the Hopfenberg equation for a cylinder ($n = 2$).

To compare the models, R^2 , the mean square error (MSE), and the Akaike Information Criterion (AIC, eq 11) were used.

$$AIC = N_d \ln SSR + 2P \quad (11)$$

where N_d represents the number of data points, SSR is the residual sum of squares, and P denotes the number of model parameters. By taking the number of model parameters into account, the AIC allows comparison between models containing different numbers of parameters. The model with the lowest AIC is generally regarded as the most appropriate.³¹ The good fit of the erosion model (Table 4) lends support to the contention that matrix erosion/dissolution is an important factor in the release mechanism. The dramatic increase in release with increased hydrodynamic stress (Figure 8) provides further evidence that the matrix system undergoes significant erosion. It is known that drug release rates from matrix systems that are purely diffusion controlled are not significantly affected by variations in hydrodynamic stress.³²

However, considering the very high drug load (85%), it is unlikely that the contribution of diffusional processes to the overall drug release should be negligible, as assumed in the Hopfenberg model. In accordance with this, the R^2 , MSE, and AIC values (Table 4) indicate that the coupled diffusion/erosion models (eqs 3 & 9) are more appropriate for this formulation, suggesting that the release rate is most likely controlled by a combination of diffusion and erosion processes.

Conclusion

The feasibility of using combinations of MS and T as dissolution retardants in extended-release matrix tablets with high drug loading capacity and low polymer content was investigated. Our study shows that near zero-order release kinetics can be achieved from matrices containing 85% theophylline when a combination of 3% MS and T is used. At this level, the lubricants do not deleteriously affect the mechanical strength of the compact, but influence diffusional drug release and appear to enhance the erosional drug release process. It can be concluded that for high drug loading with a relatively low solubility drug (e.g., theophylline with water solubility of 8 mg/mL at 25 °C), binary hydrophobic blends of MS and T have potential and could be employed as inexpensive, low bulk dissolution retardants.

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