



A Designed Study of Compression Parameters for a Sustained-Release Hydrophilic Matrix Tablet Formulation

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Purpose

To examine the effects of compression parameters on the physical properties and drug release characteristics of a model hydrophilic matrix sustained-release tablet formulation.

Methods

The model formulation consisted of drug, rate-controlling polymer, filler and lubricant as follows:

- 5.0% w/w theophylline (lot 10190, BASF Pharma, Mt. Olive, NJ 07828 USA).
- 30.0% w/w hypromellose[†] substitution type 2910, 4000 cps viscosity grade (METHOCEL[‡] E4M Premium cellulose ether, lot MD30012N11, The Dow Chemical Co., Midland, MI 48674, USA).
- 64.5% w/w spray-dried lactose (FAST-FLO, lot 8500030162, Foremost Farms USA, Baraboo, WI 53913 USA).
- 0.5% w/w magnesium stearate (lot 2256 KTMV, Mallinckrodt Chemical Co., St. Louis, MO 63134 USA).

Following mixing (10 minutes) and lubrication (1 minute) in a twin-shell blender, tablets were prepared by directly compressing the formulation. The experiments were conducted according to a 2³ full factorial, central composite design including star points, using JMP[™] statistical software. A total of eighteen different sets of tablets were prepared including four replicates (center points). The ranges for the independent variables considered in the study were as follows: turret speed (RPM) 9-21, precompression force (lbf) 61.5-361.5, and compression force (lbf) 1500-3800. The target weight for the tablets was 500 mg and 0.4063 inch/10.3 mm diameter, flat-faced beveled edge tooling was used on an instrumented Manesty Beta press. Precise values for the compression forces and

the dwell time were recorded for each run by a data acquisition package. Response variables included the tablet physical properties of crushing strength (instrument from Key International) and friability (measured at 2, 4 and 6 minutes using Roche-type friabilator from Van-Kel Industries). *In vitro* drug release was by measuring the dissolution of theophylline in DI water using a USP Type II apparatus (HP 8452A spectrophotometer and Distek 2100B bath) at 50 rpm and 37° C. These results were incorporated into the statistical analysis through the parameters obtained by fitting normalized dissolution data to a Weibull function. The % drug released at 180 minutes was also subjected to statistical analysis in JMP.

Table 1

Summary of Design Parameters and Experimental Responses

Pattern	Turret speed (rpm)	Precompression Force (lbf)	Compression Force (lbf)	Crushing Strength (SCU)	% Friability (6 min)	Reciprocal Rate Constant (min)	Curve Shape Parameter	Lag Time (min)	% Drug Rel. at 180 min	Friability Category
---	9	57.7	1470	8.2	1.92	295.2	1.1602	-44.1	51.5	Fail
00A	15.1	199.5	3846	17.9	0.28	358.6	1.1272	-46.4	45.7	Pass
+--	21	54.4	1518	8.3	1.67	303.4	1.1364	-51.4	52.2	Fail
000	15.1	203.3	2461	15.3	0.65	340.4	1.1098	-49.9	47.2	Pass
0a0	15.1	12.4	2435	14.6	0.58	331.3	1.1347	-54.2	49.6	Pass
++-	21	346.2	1518	8.4	1.81	304.8	1.1295	-50.1	51.7	Fail
A00	23.5	196.9	2737	17.5	0.47	340.6	1.1431	-54.7	48.5	Pass
-+-	9	355.3	1491	8.7	1.19	312.8	1.1699	-52.2	50.6	Fail
+++	9	342.9	3430	20.5	0.09	352.3	1.1256	-46.1	46.2	Pass
000	15.1	199.7	2475	15.1	0.42	355.4	1.1490	-55.8	48.1	Pass
000	15.1	199.4	2450	15.2	0.42	320.3	1.1227	-49.4	50.0	Pass
---+	9	57.9	3458	20.6	0.59	341.9	1.1243	-51.3	48.2	Pass
0A0	15.1	408.3	2500	15.3	0.54	355.7	1.1515	-55.2	46.9	Pass
000	15.1	199.3	2427	14.5	0.45	340.0	1.0666	-49.0	48.6	Pass
a00	6.5	204.1	2477	15.2	0.43	363.5	1.1650	-50.0	45.0	Pass
+++	21	56.4	3719	17.2	0.36	342.1	1.1042	-48.8	48.0	Pass
+++	21	347.3	3759	17.6	0.29	353.4	1.1578	-51.5	46.6	Pass
00a	15.1	199.7	1057	3.4	7.88	280.3	1.1314	-40.1	52.9	Fail

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[†]Previously referred to as hydroxypropyl methylcellulose or HPMC.

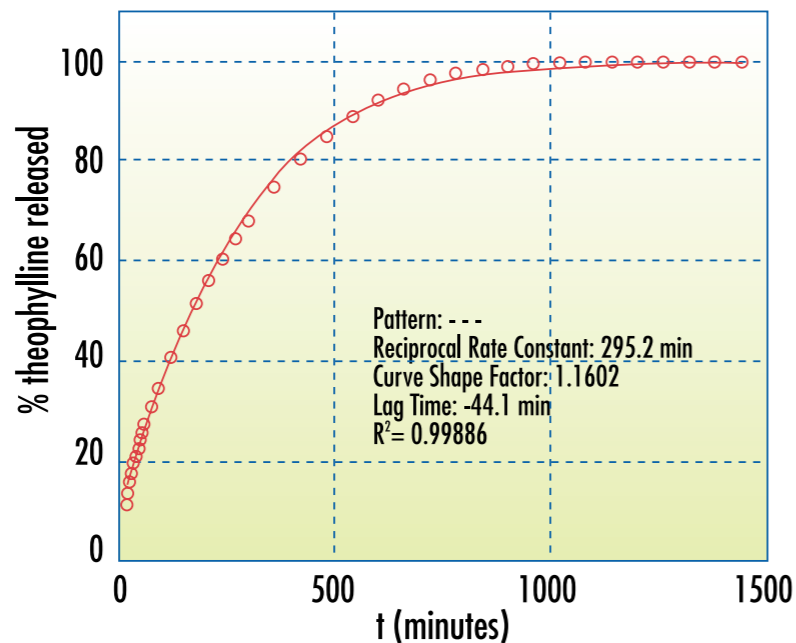
Results

While the use of precompression to improve the physical properties of conventional immediate-release tablets has been studied (1-3), its application to hydrophilic matrix tablets has not been reported. It is now generally accepted that when precompression is useful it is because of specific properties of the materials in the formulation. Precompression can also be effective in the removal of air entrained within the tablet. Simple observation of hydrophilic matrix tablets reveals that entrapped air escapes and to some extent disrupts gel formation during the early, critical stages of exposure to the aqueous media. Furthermore, the existence of air bubbles within the hydrophilic gel layer after a considerable period of exposure has been shown by freeze fracture and low temperature scanning electron

microscopy (4). While capping *per se* is not generally a problem, there are infrequent observations of the behavior of hydrophilic matrix tablets that suggest that the axial tensile strength is weaker than the radial tensile strength, a condition that has been associated with capping. Therefore it is of interest to include precompression in a study of the production of hydrophilic matrix tablets from both aspects of the tablet physical properties and drug release.

The results are summarized in Table 1 (see previous page). An example of drug dissolution with the parameters obtained from fitting the Weibull function is given by Figure 1.

Figure 1
Fit of Dissolution Data to the Weibull Function



Somewhat surprisingly, analysis of all of the response variables given in Table 1 failed to produce statistically acceptable models except in the case of tablet crushing strength. An initial model for tablet crushing

strength was constructed using all possible main effects, interactions and squared terms. The results from the preliminary model computations are provided in Table 2. Based on a 95% confidence level,

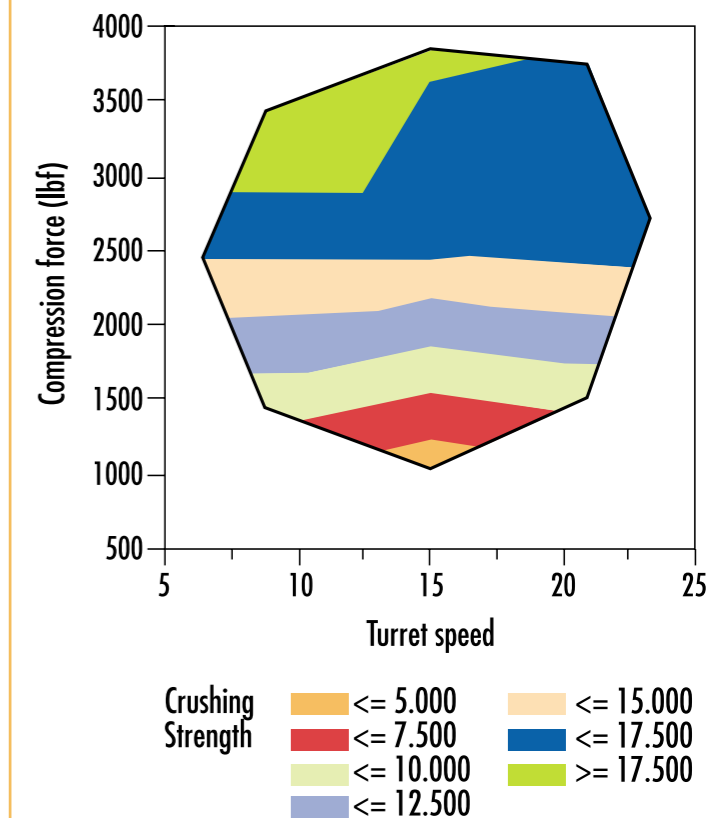
Table 2 Summary of Fit of Model for Tablet Crushing Strength

Rsquare	0.984809
RSquare Adj	0.967719
Root Mean Square Error	0.852092
Mean of Response	14.08333
Observations (or Sum Wgts)	18
Effect Tests	
Source	Prob > F
Turret speed(9,21)&RS	0.0578
Precompression Force (lbf)(61.5,361.5)&RS	0.6798
Compression Force (lbf)(1500,3800)&RS	<0.0001
Turret speed(9,21) × Turret speed(9,21)	0.1474
Precompression Force (lbf)(61.5,361.5) × Turret speed(9,21)	0.9129
Precompression Force (lbf)	
(61.5,361.5) × Precompression Force (lbf)(61.5,361.5)	0.8166
Compression Force (lbf)(1500,3800) × Turret speed(9,21)	0.0551
Compression Force (lbf)(1500,3800) × Precompression Force (lbf)(61.5,361.5)	0.9903
Compression Force (lbf)(1500,3800) × Compression Force (lbf)(1500,3800)	<0.0001

the statistically significant parameters were identified and included in the final model. As indicated in the table, the terms which were selected for the final model in order of importance were compression force, compression force \times compression force, turret speed, and compression force \times turret speed. Table 2 also

clearly shows that precompression force was not an important variable in this model. A contour plot based on the final model prediction for tablet crushing strength is provided in Figure 2. The final R^2 (adjusted) was calculated to be 0.98 which indicates there is good agreement between the data and the model prediction.

Figure 2 Contour Plot Based on the Model for Tablet Crushing Strength



Results

The friability of the tablets also was evaluated in the study. Due to the large impact of the very high value of friability at the low star point of compression force, an alternative analysis was conducted by categorizing the friability as “pass” (6 minute friability < 1.0%) or “fail” (6 minute friability > 1.0%). However, this alternative analysis also showed no significant relationships (see Figure 3). For example, since the variances were equal, the Tukey-Kramers test was applied to the analysis of precompression force (lbf) versus the categorized friability results. The complete

overlap of the circles is indicative of means that are not significantly different, establishing the independence of variables.

Once again, all of the parameters relating to drug dissolution (three parameters from fits to the Weibull function and % drug released at 180 minutes) were included in the statistical analysis. No statistically significant parameters could be identified from the independent variables considered in this study.

Conclusions

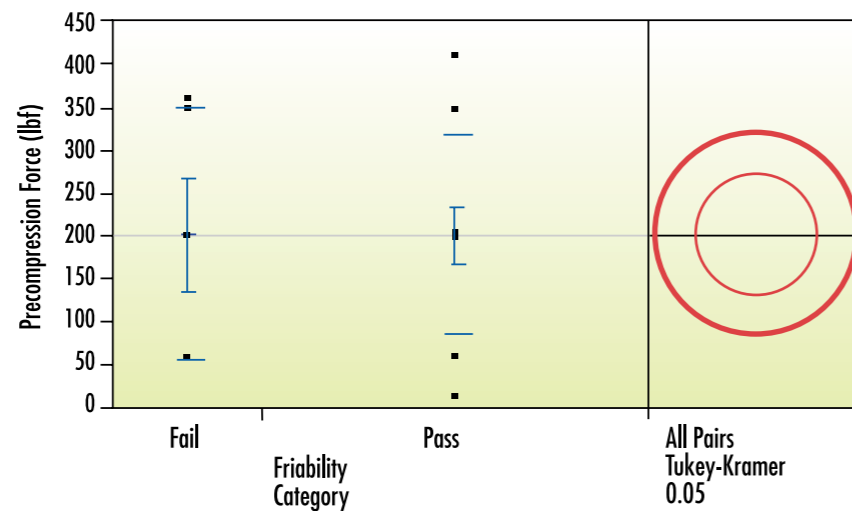
For the model formulation and the range of variables studied, incorporation of precompression did not improve tablet physical properties or alter the drug dissolution profile. The general effects of compression force on tablet physical properties and drug release previously reported (for example, reference 5) were confirmed.

References

1. Vezin, W.R., Pang, H.M., Khan, K.A. and Malkowska, S., *Drug Dev. Ind. Pharm.*, **9(8)**, 1465-1474 (1983).
2. Vezin, W.R., Khan, K.A. and Pang, H.M., *J. Pharm. Pharmacol.*, **35**, 555-558 (1983).
3. Parrott, E.L., Compression. In *Pharmaceutical Dosage Forms: Tablets, 2nd Edition, Volume 2*; Lieberman, H.A., Lachman, L. and Schwartz, J.B., Eds.; Marcel Dekker, Inc.; New York, 1990.
4. Melia, C.D., Rajabi-Siahboomi, A.R. and Davies, M.C., *Proceed. Intern. Symp. Control. Rel. Bioact. Mater.*, **19**, 29-9 (1992).
5. Velasco, M.V., Ford, J.L., Rowe, P. and Rajabi-Siahboomi, A.R., *J. Control. Rel.*, **57**, 75-85 (1999).

Figure 3

Oneway Analysis of Precompression Force (lbf) By Friability Category



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