Empirical Modeling of Tablets Containing Hypromellose

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Introduction

Hypromellose (HPMC) is a polymer frequently used in oral solid dosage forms to sustain the release of drugs. Although its compaction properties have been moderately well studied,[1-3] there have been no systematic investigations into the compaction properties of mixtures of HPMC with other excipients or drugs. In general, theoretical predictions of compaction properties of mixtures have proven to be difficult.[4] This study was undertaken as a modest first step in a larger effort to model the compaction of when used as the rate-controlling polymer in practical formulations of hydrophilic matrix tablets. The study used a statistical design strategy to determine the effects of HPMC molecular weight, HPMC particle size, HPMC/lactose ratio, compaction pressure, and dwell time on tablet crushing strength (hardness).

Experimental Procedures

Four molecular weight grades of hypromellose USP 2208 (METHOCEL* K100 Premium LV, K4M Premium, K15M Premium, K100M Premium cellulose ethers from The Dow Chemical Company) were used. Each HPMC lot was separated into four particle size fractions by sieving. Spray-dried lactose (Fast-Flo lactose 316 from Foremost Farms USA), having both excellent compaction and flow properties, is commonly used in industrial formulations and was chosen as a second component; it was used as received. Hypromellose and lactose were combined at three ratios: 20/80 w/w, 30/70 w/w, and 40/60 w/w, respectively.

Although essential for practical formulations, a lubricant can mask fundamental material properties. For that reason lubricants were not included in this initial study. This necessitated the use of a hydraulic bench press, which placed limits on dwell time. The only lubrication used was a small amount of magnesium stearate in acetone applied to the die wall; the first tablet of each run was discarded.

Tablets were compressed at 35.2, 105.5, and 175.8 MPa and three dwell times (2, 6, and 10 s) on a Carver laboratory press (model C, with "Autopak" automation accessory). Tooling was 0.5 inch (12.7 mm) diameter flat face. Target tablet weight was 700 ± 5 mg. Tablet physical properties (n = 5) determined were weight variation, thickness variation, and crushing strength using conventional techniques after allowing the tablets to relax for 24 h under ambient conditions.

Results and Discussion

Striking a balance between completeness and a manageable size, the experimental design included four molecular weights, four particle size fractions, three HPMC/lactose ratios, three compaction pressures, and three dwell times.

Conditions for each of the 78 runs within the design and the average (n = 5) diametral crushing strength of the tablets produced is given in Table 1. In addition to crushing strength, tablet weight and thickness data (not shown) were recorded. Four replicates of a given set of conditions were included in the design; overall reproducibility was good (CV of crushing strength = 3.7%). Crushing strength and thickness were modeled using JMP™ (SAS Institute, Inc.).

Four particle size fractions were used in the design: <53 mm, 53 to 105 mm, 105 to 150 mm, and >150 mm. However, in statistical analysis of the data, it is preferable to represent a categorical (range) variable by a continuous (single-valued) variable to ensure that the resulting model can predict other conditions within the range of this variable beyond the specific levels included in the data. For this purpose, "midpoint" values given by 53 to 105 mm = 79 mm, 105 to 150 mm = 127.5 mm, and the arbitrarily chosen values of <53 mm = 26.5 mm and >150 mm = 175 mm were used in the data analysis.

Four empirical modeling methods (least squares, neural networks, partial least squares, and classification and regression trees) were assessed. All four methods yielded very similar results. Due to its ease of interpretation, the least squares method (i.e., polynomial model) was used in the final model. Polynomial model forms are extremely flexible and can approximate many different variable relationships. In essence, these polynomial model forms represent a Taylor series expansion of an often-unknown theoretical mathematical form that characterizes the influences that the X variables have in determining the levels of Y.

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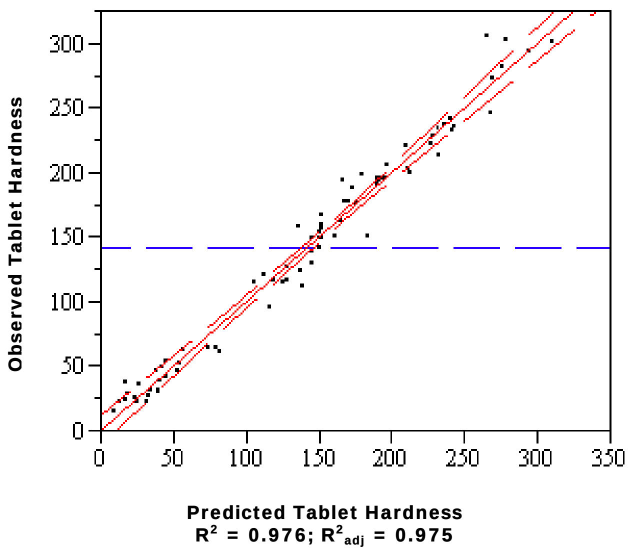
Table 1. Design experimental parameters and crushing strength response

Run Number	Sieve Cut (μ)	Hypromellose Grade	Wt. % Hypromellose	Compaction Pressure (MPa)	Dwell Time (s)	Crushing Strength (N)
1	105 to 150	K100LV	20	175.8	6	199.7
2	105 to 150	K100M	30	105.5	6	156.6
3	105 to 150	K100M	40	35.2	6	63.2
4	<53	K100M	20	35.2	2	46.5
5	>150	K15M	40	35.2	2	22.8
6	>150	K100LV	40	35.2	10	31.7
7	53 to 105	K100M	30	105.5	6	177.2
8	53 to 105	K15M	30	105.5	6	153.4
9	53 to 105	K15M	20	35.2	10	35.9
10	105 to 150	K4M	40	105.5	10	123.4
11	105 to 150	K4M	20	175.8	2	195.2
12	>150	K100M	20	35.2	6	29.1
13	>150	K4M	30	35.2	10	24.2
14	53 to 105	K15M	30	105.5	2	138.5
15	105 to 150	K4M	30	105.5	6	115.0
16	<53	K100LV	30	175.8	2	281.9
17	53 to 105	K15M	40	105.5	6	177.7
18	<53	K100M	20	175.8	10	246.5
19	53 to 105	K100M	30	35.2	2	52.8
20	<53	K15M	20	35.2	2	38.0
21	>150	K4M	40	175.8	6	188.2
22	53 to 105	K100LV	30	35.2	2	54.2
23	53 to 105	K100LV	30	105.5	10	193.7
24	105 to 150	K100M	20	35.2	10	42.2
25	105 to 150	K100M	30	105.5	6	159.9
26	>150	K100M	30	175.8	2	195.8
27	<53	K15M	20	105.5	6	148.5
28	105 to 150	K100M	30	175.8	6	228.2
29	<53	K4M	30	105.5	6	163.0
30	>150	K100M	40	35.2	2	27.3
31	53 to 105	K4M	20	105.5	6	116.1
32	>150	K4M	20	35.2	2	15.4
33	105 to 150	K100M	30	105.5	6	149.2
34	105 to 150	K100LV	30	35.2	6	31.0
35	53 to 105	K100M	40	175.8	10	302.7
36	53 to 105	K4M	40	175.8	2	235.6
37	105 to 150	K15M	30	35.2	2	25.9
38	105 to 150	K15M	20	105.5	10	126.6
39	105 to 150	K15M	40	175.8	2	202.7
40	**53 to 105**	**K15M**	**30**	**105.5**	**6**	**149.3**
41	>150	K15M	20	175.8	2	175.8
42	< 53	K4M	20	175.8	2	234.3
43	>150	K100M	40	105.5	10	158.4
44	105 to 150	K4M	20	35.2	10	28.4
45	>150	K15M	30	105.5	6	121.4
46	53 to 105	K4M	30	175.8	10	236.4
47	53 to 105	K100M	20	175.8	6	241.9
48	105 to 150	K15M	40	35.2	10	39.4
49	>150	K100LV	20	175.8	10	206.4
50	53 to 105	K15M	30	175.8	10	233.1
51	<53	K15M	30	175.8	6	272.1
52	>150	K4M	30	105.5	6	114.1
53	>150	K4M	20	175.8	10	198.6
54	105 to 150	K100M	20	105.5	2	111.5
55	<53	K100M	30	35.2	10	64.4
56	>150	K100LV	40	175.8	6	190.6
57	**53 to 105**	**K15M**	**30**	**105.5**	**6**	**141.9**
58	<53	K100LV	40	105.5	6	220.4
59	<53	K15M	40	105.5	2	195.8
60	<53	K100M	40	175.8	2	301.0
61	53 to 105	K100LV	40	175.8	6	305.9
62	53 to 105	K100LV	20	175.8	2	222.0
63	>150	K15M	30	105.5	10	95.1
64	105 to 150	K100LV	40	175.8	10	213.6
65	<53	K100LV	20	105.5	10	151.0
66	>150	K100LV	20	35.2	6	22.5
67	**53 to 105**	**K15M**	**30**	**105.5**	**6**	**153.9**
68	>150	K15M	40	175.8	10	150.0
69	<53	K15M	40	35.2	10	64.0
70	105 to 150	K4M	40	35.2	2	23.1
71	>150	K100LV	30	105.5	2	116.9
72	<53	K4M	40	175.8	10	294.3
73	105 to 150	K100LV	40	105.5	2	130.3
74	<53	K100LV	40	35.2	2	61.3
75	53 to 105	K4M	40	35.2	10	46.6
76	<53	K100M	30	105.5	6	193.7
77	<53	K4M	30	35.2	6	49.3
78	105 to 150	K100M	30	105.5	6	166.9

If the model is useful for approximating the variation observed in crushing strength, then a plot will show the data points falling very close to a diagonal line. Figure 1 shows this to be the case. The values for the crushing strength empirical model in question were found to be reasonably high (R^2 = 0.976 and R^2adj = 0.975). These values suggest that over 97.5% of the total variability observed in tablet hardness can be accounted for by using the empirical model for prediction purposes. This indicates a high degree of agreement between the model predicting tablet hardness and the actual tablet hardness values within the experimental design data. The "adjusted R^2" value was used to ensure that model parameter parsimony had been achieved without sacrificing the predictive ability of the final model.

Once the overall usefulness of the model was determined, the statistical significance of each model term was then determined. In order to do this appropriately, the model was fit in "coded" form. This "coding" was applied so that all of the model weights were in the same scale and thus could be easily tested statistically. The magnitude of these "coded" model coefficients also provides information about the relationships between the variables involved. It was from this quadratic model that a reduced final model form to represent the predicted crushing strength was developed. The final reduced empirical model contained only the most statistically significant terms. From the reduced model, the model "coded" weights (coefficients) corresponding to the *compaction pressure* and the *median particle size* variables had the highest magnitude effects. Figure 2 shows the model terms contained within the final empirical model for crushing strength and illustrates the relative order of importance of each.

Figure 1. Observed crushing strength (in Newtons) versus the crushing strength predicted by the final model. Outer red lines represent the 95% confidence interval. Horizontal blue line represents the "no-model" line.



Modeling the tablet thickness as another response provided an empirical model with a high coefficient of determination value (with R^2adj = 0.990). The thickness of a cylindrical tablet with flat faces and constant diameter pressed from the same starting material is inversely proportional to its relative density. Consequently, these results also show that the relative density of the tablet is the dominant factor in determining crushing strength over the design space. The higher the relative density (and hence the lower the porosity), the higher the tablet crushing strength. In Figure 3, the effects of each of the five design variables on both the crushing strength and thickness models are presented, again illustrating the relative importance of compaction pressure and particle size.

The models were developed using powders from sieve fractions from four different molecular weight grades of HPMC. This was done because of the previously reported effect of particle size on tablet tensile strength[3] and the fact that the particle size distribution of HPMC is quite broad. However, it was of interest to see if the crushing strength model developed with sieve fractions could be applied to compacts produced using an "as received" (i.e., unsieved) HPMC batch. The weight fraction of each sieve cut used in the development of the model was determined for each of the HPMC grades. This was used along with the median particle size values described above to calculate a weighted particle size for the batch. All four sieve cuts were equally weighted.

Figure 2. Plot of the tablet crushing strength final model terms ordered by their relative importance.

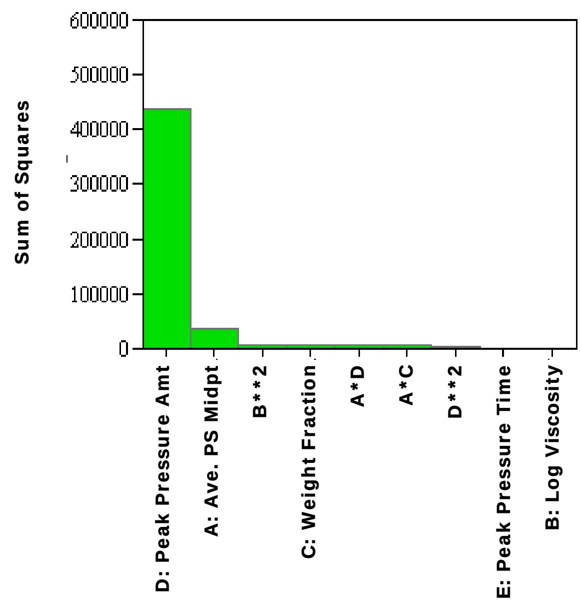
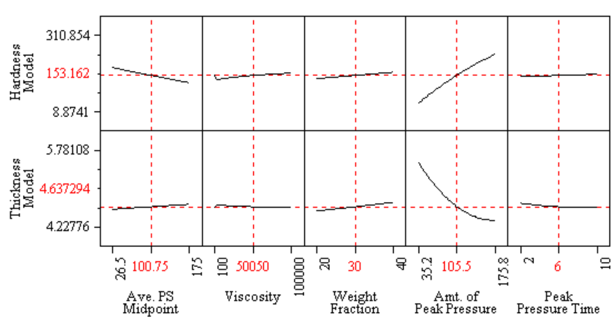


Figure 3. Interactive model exploration profiler useful for exploring hardness and thickness models at the same time.



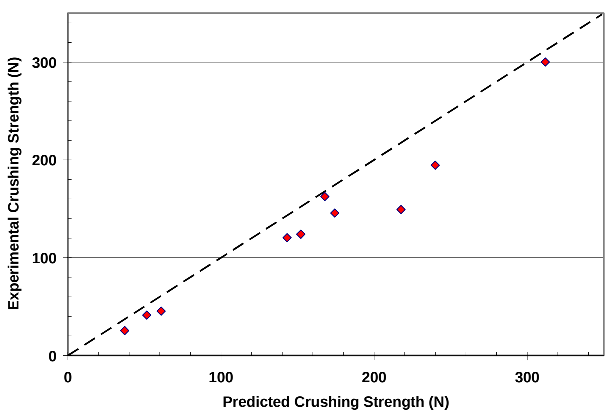
Ten tests of the model were conducted throughout the design space using the unsieved HPMC batches (see Table 2). Using the specified conditions, the weighted particle size, and the final reduced empirical model, predicted crushing strength values were calculated. These are also given in Table 2 and presented graphically in Figure 4.

Table 2. Test of the crushing strength model using "as received " polymers and calculated median particle size.

Test #	Hypromellose Grade	Weighted Particle Size (m)	Wt. % Hypromellose	Compaction Pressure (MPa)	Dwell Time (s)	Predicted Crushing Strength (N)
1	K100LV	65.0	30	105.5	6	167.8
2	K4M	82.2	30	105.5	6	143.2
3	K15M	75.3	30	105.5	6	152.1
4	K100M	70.3	30	105.5	6	174.3
5	K100M	70.3	20	35.2	2	37.1
6	K100M	70.3	40	175.8	10	311.8
7	K100M	70.3	20	175.8	2	239.9
8	K15M	75.3	40	35.2	10	60.9
9	K15M	75.3	20	175.8	2	217.6
10	K15M	75.3	40	35.2	2	51.5

It is clear that while the model gave a reasonable approximation of the crushing strength in most cases, the model in all cases predicted greater tablet strengths than those found experimentally

Figure 4. Test of crushing strength model using "as received" polymers



Summary of Results

Four modeling methods (least squares, neural networks, partial least squares, classification and regression trees) were tested, but all yielded similar results. The least squares method was used for interpretation. The reduced crushing strength model is:

Crushing Strength (N) = -15.04 + 0.4503*Particle Size - 66.84*LOG(Viscosity) + 3.126*Weight Fraction + 2.189*Compaction Pressure + 1.172*Dwell Time + 9.959*(LOG(Viscosity))^2 - 0.01848*Weight Fraction*Particle Size - 0.002823*Compaction Pressure*Particle Size - 0.002600*(Compaction Pressure)^2 R^2_{adj} = 0.975 (n = 78)

Evaluation of the significance of the terms showed that the compaction pressure and particle size terms had by far the largest impact.

Although not part of the original design, crushing strengths predicted by the model using the "as received" (unsieved) HPMC lots were relatively close to but consistently greater than experimental values.

Conclusions

Five variables (HPMC molecular weight, HPMC particle size, HPMC weight fraction, compaction pressure, and dwell time) were used as variables in a large experimental design study.

An excellent empirical model predicting the crushing strength of the HPMC-lactose tablets was obtained. The dominant terms of significance were compaction pressure and the average particle size, with compaction pressure having an approximately three times greater impact. While the model was developed using well-defined sieve cuts of the polymers, it also predicted reasonably well (although consistently underestimating) the crushing strength of tablets prepared with the "as received" polymer.

These final models can be used to predict the expected crushing strength and thickness values for various levels of the five design parameters and can be used to further explore the observed relationships between the variables. Future exploration of these empirical models can provide further insight into the relationships between the variables and provide theoretical checks into the validity of these models for future prediction purposes.

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