Effects of Spheronization Process Variables on Selected Tablet Properties

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Abstract □ This study evaluated the effects of certain process variables on the properties of tablets prepared from granulations composed of essentially spherical, free-flowing pellets. A complete factorial experimental design was used to indicate the significant main effects and interactions related to water content, extruder speed, extruder screen size, spheronizer speed, and spheronizer residence time on tablet hardness and dissolution rate. This series of experiments demonstrated that changes in process variables, particularly water content, can result in significant differences in the dissolution rate and hardness of tablets composed of 80% drug and 20% binder. The factorial experimental design proved useful in predicting the effects of such changes between the limits producing usable pelletized granulations.

Keyphrases □ Spheronization process variables—effects of water content, extruder speed, extruder screen size, spheronizer speed, and spheronizer residence time on tablet properties □ Tablets—effects of spheronization process variables on dissolution rate and hardness □ Dissolution—effects of spheronization process variables □ Hardness, tablets—effects of spheronization process variables

The spheronization process using the equipment[1] involved in this study was previously described (1-4). This paper deals with the use of a complete factorial experimental design (5-9) to determine the effects of five process variables on tablet hardness and dissolution rate. The variables studied were water content, extruder speed, extruder screen size, spheronizer speed, and spheronizer residence time. Each variable was studied at two levels, resulting in 32 different experiments (Table I). The method of analysis was analysis of variance (10).

All 32 experimental granulations were prepared in random order. The relationship between the experiment number and variable levels associated with that experiment is shown in Table II.

To describe easily the levels of variables used in a factorial experiment, a commonly employed system uses lower case letters to denote the presence of a particular variable at the high level of that variable. For example, Experiment ade would imply that variables A, D, and E were present at the high level whereas variables B and C were at the low level. Since the experiment where all variables were at the low level would require no lower case letter notation, the symbol (1) is used to describe that experiment.

In analysis of variance tables, upper case letters are used to denote the effects of variables and interactions between or among variables. For example, A denotes the effect of variable A, and AD denotes the first-order interaction between variables A and D.

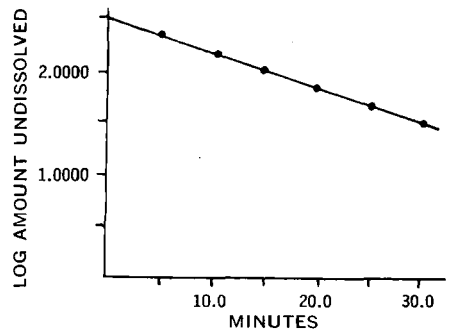

Figure 1—*Determination of dissolution rate from acetaminophen tablets.*

Table I—Values of Levels for Variables Investigated

Variable	Low Level	High Level
Water content (A)	250 ml	325 ml
Extruder speed (B)	39 rpm	59 rpm
Screen size (C)	0.8 mm	1.5 mm
Spheronizer speed (D)	700 rpm	1010 rpm
Spheronizer time (E)	1.0 min	3.0 min

EXPERIMENTAL

Materials—Microcrystalline cellulose[2] and acetaminophen NF[3] were used.

Manufacturing and Testing Procedure—Eight hundred grams of acetaminophen and 200 g of microcrystalline cellulose were weighed separately. The two materials were blended for 10 min[4]. While blending, material was scraped from the outer edge of the bowl after 5 min. Purified water was added slowly over 30 sec, and mixing was continued for 2 min for a total of 12 min of blending. The wetted material was placed into the extruder feed chamber and processed at the prescribed conditions. The first material out of the extruder screens was discarded. The extrudate was placed into the spheronizer in 200-g batches, removed after the required residence time, and tray dried at 40° for 7 hr. After drying, the spheronized material was stored in sealed, plastic bags.

The analytical procedure for the determination of acetaminophen was based on that of Walters (11). Solutions of NF acetaminophen reference standard were prepared in triplicate, containing 15.00, 11.25, 7.50, 3.75, 1.875, and 1.40 μg/ml, and the absorbance was measured at 242 nm. The wavelength of maximum absorption was determined by a scan from 220 to 270 nm. Identical standard curves were obtained[5].

The acetaminophen used was assayed in triplicate by placing 325.0 mg in a 1-liter volumetric flask, bringing to volume with purified water, stirring for 60.0 min using a magnetic stirrer, and then diluting a 1.0-ml sample to 100.0 ml in a volumetric flask.

Granulations were assayed after dissolving the acetaminophen by placing 390.0 mg of granulation in a 1-liter volumetric flask, bringing to volume with purified water, stirring for 60.0 min using a magnetic stirrer, and then centrifuging a 5.0-ml sample for 15 min. A 1.0-ml sample was diluted to 100.0 ml and the absorbance

[1] Extruder type EXDS-60 and Marumerizer type Q-230, Elanco Products Co., a division of Eli Lilly & Co., Indianapolis, Ind.

[2] Avicel RC-581, FMC Corp., Marcus Hook, Pa.

[3] S. B. Penick and Co., New York, N.Y.

[4] In a Day Pony Mill.

[5] Both the Beckman model DU and Hitachi Perkin-Elmer model 139 spectrophotometers were used.

Table II—Relationship between Experiment Number and Variable Levels

Experiment	Variable Levels	Experiment	Variable Levels
1	a	17	bde
2	ae	18	bce
3	ac	19	abd
4	ce	20	de
5	ade	21	e
6	(1)	22	abe
7	acd	23	ad
8	b	24	bcde
9	cde	25	abcde
10	d	26	ace
11	abcd	27	cd
12	be	28	abc
13	abce	29	bc
14	ab	30	abde
15	c	31	acde
16	bcd	32	bd

was read. Assays were performed in triplicate, using random samples obtained by standard sampling techniques (Table III). Tablets were compressed on a laboratory press[6] using 0.031-cm (13/32-in.) standard curvature punches. Applied pressure was 3410 kg, and tablet weight was 390.0 mg.

Tablet Hardness—The hardness of tablets compressed from each granulation was determined[7]. The values used in calculations represent the means of four readings for each experiment.

Tablet Disintegration Time—When using the USP disintegration apparatus, tablet disintegration was less than 10 sec in all cases.

Tablet Dissolution Rate—The dissolution of acetaminophen from tablets compressed from each granulation was determined using the USP XVIII basket apparatus at 50 rpm. Each experiment was repeated four times, and mean values were used in calculations.

Samples were removed at 0, 5, 10, 15, 20, 25, and 30 min using a 5.0-ml pipet. Five milliliters of dissolution medium was added to the beaker after each sample was removed. Each 5-ml sample

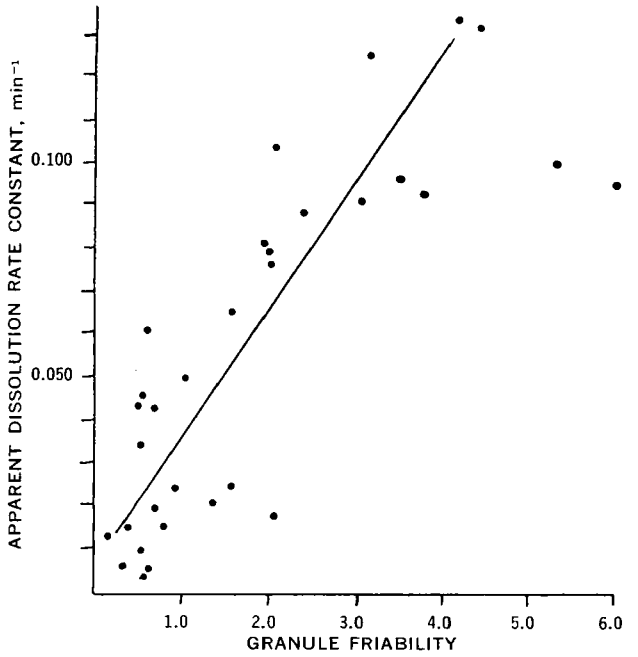

Figure 2—*Correlation between granule friability and dissolution rate.*

[6] Fred S. Carver, Inc., Summit, N.J.
[7] Pfizer hardness tester.

Table III—Tablet Data

Experiment	Apparent Dissolution Rate Constant[a], min^{-1}	Granulation Assay, mg[b]	Tablet Hardness, kg (Carver Press Tablets)
1	0.082	312	4.2
2	0.016	312	3.0
3	0.021	312	4.8
4	0.125	315	4.2
5	0.006	312	2.5
6	0.095	307	6.1
7	0.005	307	3.7
8	0.097	311	6.4
9	0.025	309	3.4
10	0.079	307	4.7
11	0.010	314	3.7
12	0.091	309	3.8
13	0.006	312	3.4
14	0.025	312	4.4
15	0.131	311	6.5
16	0.066	307	6.6
17	0.061	309	3.0
18	0.093	315	4.6
19	0.035	319	3.4
20	0.089	322	3.0
21	0.089	317	5.8
22	0.046	317	2.9
23	0.020	317	3.9
24	0.104	317	4.0
25	0.014	314	3.1
26	0.043	319	3.0
27	0.133	317	6.7
28	0.077	320	5.4
29	0.100	317	8.3
30	0.044	315	3.1
31	0.017	315	3.0
32	0.018	319	6.3

[a] Mean of four values. [b] Milligrams acetaminophen, mean of three assays.

was centrifuged for 15 min in a centrifuge[8] at 3400 rpm to precipitate suspended microcrystalline cellulose and sodium carboxymethylcellulose. A 1.0-ml aliquot from each sample was diluted to 100.0 ml with purified water, and the absorbance was read.

A blank dissolution test was run, using a sample containing no drug. No absorbance was observed with this blank sample.

A standard solution of 10.0 μg/ml was read daily as a check on the operation of the spectrophotometer.

During the dissolution test, 5.0-ml samples were removed at 5, 10, 15, 20, 25, and 30 min; 5.0 ml of purified water was added each time a sample was removed. A correction factor was added to each "weight dissolved" term except, of course, the 5-min sample. This correction procedure may be explained mathematically by the equations:

$$W_r = \frac{5}{900} W_{tn} \qquad \text{(Eq. 1)}$$

$$W_{Ctn} = W_{Mtn} + \sum_{1}^{n-1} W_r \qquad \text{(Eq. 2)}$$

where:

W_r = weight of dissolved drug removed in a particular sample
W_{tn} = uncorrected weight dissolved at time t
W_{Ctn} = corrected weight dissolved at time t
W_{Mtn} = spectrophotometrically measured weight dissolved at time t

This procedure was used by Wurster and Taylor (12) using concentration, rather than mass, as the basis for the correction.

The dissolution rate (Table IV) was determined by a plot of log undissolved drug *versus* time (13, 14). A polynomial regression computer program (15) was used to determine the slope of the

[8] International clinical centrifuge.

Table IV—Log Weight of Acetaminophen Undissolved (Milligrams)[a]

Experiment	Minutes					
	5	10	15	20	25	30
1	2.3026	2.1182	1.8800	1.7370	1.5320	1.4639
2	2.4140	2.3699	2.3337	2.3114	2.2927	2.2778
3	2.3682	2.3032	2.2686	2.2402	2.2067	2.1887
4	2.3495	2.1263	1.6869	1.4127	1.1620	0.9916
5	2.4339	2.4218	2.4141	2.4093	2.3994	2.3905
6	2.3536	2.2054	1.9889	1.7045	1.4663	1.3087
7	2.4426	2.4359	2.4327	2.4259	2.4177	2.4112
8	2.4045	2.2673	2.0858	1.7552	1.4828	1.3143
9	2.3982	2.3179	2.2589	2.2178	2.1862	2.1541
10	2.3672	2.2007	2.0138	1.7978	1.6270	1.5090
11	2.4294	2.4087	2.3914	2.3761	2.3644	2.3521
12	2.3591	2.1824	1.9265	1.7305	1.5575	1.3333
13	2.4572	2.4434	2.4357	2.4269	2.4195	2.4105
14	2.3765	2.2932	2.2333	2.2013	2.1725	2.1447
15	2.3468	2.1239	1.8339	1.5240	1.2787	0.7467
16	2.3683	2.2375	2.0731	1.8977	1.7534	1.6702
17	2.3432	2.1449	1.9945	1.8768	1.8015	1.7093
18	2.4219	2.2535	1.9849	1.7330	1.4977	1.3918
19	2.3855	2.2644	2.1888	2.1291	2.0853	2.0488
20	2.3614	2.2216	2.0576	1.9882	1.9153	1.8703
21	2.3805	2.2497	2.0990	1.8077	1.5789	1.3814
22	2.3823	2.2384	2.0961	2.0195	1.9631	1.9231
23	2.4111	2.3137	2.2851	2.2662	2.2454	2.2209
24	2.3481	2.1751	1.9492	1.6751	1.3708	—[b]
25	2.4343	2.3999	2.3664	2.3396	2.3258	2.3017
26	2.4061	2.3030	2.1837	2.0864	2.0229	1.9603
27	2.3350	2.1839	1.9184	1.2655	—[b]	—[b]
28	2.3379	2.1826	1.9745	1.8099	1.6771	1.5127
29	2.3531	2.2221	1.9828	1.6798	1.4545	1.2508
30	2.4180	2.2710	2.1440	2.0712	2.0043	1.9525
31	2.4017	2.3455	2.3174	2.2931	2.2723	2.2511
32	2.3937	2.2779	2.1154	1.8975	1.5902	1.3607

[a] Each value is the mean of four readings. [b] All drug was dissolved.

Table V—Analysis of Variance, Tablet Hardness (Carver Press Tablets)

Source of Variation	Sum of Squares	Degrees of Freedom	Variance	$F_{1,6}$
Water content (A)	21.66	1	21.66	108.3[a]
Extruder speed (B)	0.51	1	0.51	2.6
Screen size (C)	1.97	1	1.97	9.9[b]
Spheronizer speed (D)	5.02	1	5.02	25.1[c]
Spheronizer time (E)	26.63	1	26.63	133.2[a]
AB	0.08	1	0.08	0.4
AC	0.20	1	0.20	1.0
AD	0.28	1	0.28	1.4
AE	3.36	1	3.36	16.8[c]
BC	0.41	1	0.41	2.1
BD	0.02	1	0.02	0.1
BE	0.44	1	0.44	2.2
CD	0.02	1	0.02	0.1
CE	0.65	1	0.65	3.3
DE	0.05	1	0.05	0.3
ABC	0.08	1	0.08	0.4
ABD	0.17	1	0.17	0.9
ABE	0.83	1	0.83	4.2
ACD	0.43	1	0.43	2.2
ACE	0.33	1	0.33	1.7
ADE	0.94	1	0.94	4.7
BCD	1.17	1	1.17	5.9
BCE	0.17	1	0.17	0.9
BDE	0.61	1	0.61	3.1
CDE	0.36	1	0.36	1.8
Higher order	1.23	6	0.20	—

[a] Significant at $p < 0.001$. [b] Significant at $p < 0.05$. [c] Significant at $p < 0.01$.

best straight line through the data points. A representative example is shown in Fig. 1. In all cases, the significance of the linear regression lines was greater than 99%.

Granule Friability—A measure of granule friability was determined by rotating 10.0 g of 20–30-mesh granules along with 200 5-mm glass spheres in a friability tester[9] for 30 min. The granules were then separated from the glass beads, placed on a No. 30 sieve, and shaken[10] for 5 min. Granule friability was determined by subtracting the weight of granules retained on the sieve after testing from 10.0.

RESULTS AND DISCUSSION

Tablet Hardness—Hardness values ranging from 2.5 to 8.3 kg were obtained. Analysis of variance results (Table V) indicated that water content, screen size, spheronizer speed, and spheronizer time were significant main effects and that a significant first-order interaction between water content and spheronizer time existed. Increasing screen size resulted in increased tablet hardness whereas increasing water content, spheronizer speed, or spheronizer time decreased tablet hardness (Table VI). The significant first-order interaction shown in Table VII indicated that increased spheronizer time at the low water content resulted in a greater decrease in tablet hardness than at the high water content. As water content increased, a greater decrease in tablet hardness occurred at the low spheronizer time, although tablet hardness was greater throughout at the low spheronizer time. In general, tablet hardness may be maximized at low water content, low spheronizer speed and time, and high screen size. The maximum increase in tablet hardness occurred at the low water content–low spheronizer time combination. These results suggest that particles lacking the cohesive properties necessary to form hard tablets may be formed as indicated by the significant process variables.

Disintegration Time—Disintegration time was excellent for all experiments, indicating that differences in dissolution rate were a result of intragranular changes due to changes in the processing variables. No correlation between disintegration time and dissolution rate would be apparent. In general, this lack of correlation would be expected (16). It has been proposed (17) that the granule friability test may provide a better indication of expected dissolution rate in cases where there is no correlation between disintegration time and dissolution rate.

Dissolution Rate—Values ranging from 0.005 to 0.113 min^{-1} were calculated. Analysis of variance results (Table VIII) indicated the only significant main effect or interaction to be the main effect of water content. Increasing water content resulted in decreased dissolution rate (Table IX). If dissolution rate is expected to be a problem, water content during extrusion should be minimized.

A more precise indicator of expected dissolution rate was the value obtained for granule friability. A plot of granule friability *versus* dissolution rate is shown in Fig. 2. The correlation coefficient is 0.816 with 99% confidence limits (range 0.582–0.925). For 30 degrees of freedom, the correlation is significant at the 99% level at the value of 0.499 or greater. For all experiments having values of less than 5 for granule friability, there was found a close relationship between tablet dissolution rate and granule friability.

This correlation was tested by preparing an experiment at mean levels of the five process variables. Granule friability was 1.4 and tablet dissolution rate was 0.043 min^{-1}. From Fig. 2, the

Table VI—Tablet Hardness (Kilograms)[a]

Significant Main Effect	Low Level	High Level
Water content	5.2	3.6
Screen size	4.2	4.7
Spheronizer speed	4.8	4.0
Spheronizer time	5.3	3.5

[a] Mean of 16 experiments.

[9] Erweka.
[10] Cenco Meinzer sieve shaker.

Table VII—Tablet Hardness (Kilograms)[a]

Spheronizer Time, min	Water Content, ml	
	250	325
1.0	6.5	4.2
3.0	4.0	3.0

[a] Mean of eight experiments.

Table VIII—Analysis of Variance, Dissolution Rate Constant

Source of Variation	Sum of Squares	Degrees of Freedom	Variance	$F_{1,6}$
Water content (A)	0.0247	1	0.0247	19.0[a]
Extruder speed (B)	0.0001	1	0.0001	0.1
Screen size (C)	0.0004	1	0.0004	0.3
Spheronizer speed (D)	0.0064	1	0.0064	4.9
Spheronizer time (E)	0.0008	1	0.0008	0.6
AB	0.0006	1	0.0006	0.5
AC	0.0024	1	0.0024	1.9
AD	0.0005	1	0.0005	0.4
AE	0.0000	1	0.0000	0.0
BC	0.0000	1	0.0000	0.0
BD	0.0002	1	0.0002	0.2
BE	0.0016	1	0.0016	1.2
CD	0.0000	1	0.0000	0.0
CE	0.0001	1	0.0001	0.1
DE	0.0002	1	0.0002	0.2
ABC	0.0000	1	0.0000	0.0
ABD	0.0001	1	0.0001	0.1
ABE	0.0014	1	0.0014	1.1
ACD	0.0002	1	0.0002	0.2
ACE	0.0003	1	0.0033	0.2
ADE	0.0006	1	0.0006	0.5
BCD	0.0000	1	0.0000	0.0
BCE	0.0006	1	0.0006	0.5
BDE	0.0018	1	0.0018	1.4
CDE	0.0001	1	0.0001	0.1
Higher order	0.0075	6	0.0013	—

[a] Significant at $p < 0.01$.

predicted tablet dissolution rate would be 0.048 min^{-1}, which indicates the validity of the correlation.

Particles resulting from this spheronization process are much less friable than conventionally processed granules. To attempt a similar correlation using conventionally processed granules, it would be necessary to make the granule friability test less severe. Otherwise, no relationship would be noted between rapid and slow tablet dissolution rates and granule friability because all granule friability values would be high.

SUMMARY

The effects of process variables on tablet hardness and dissolution rate were determined. The process variables had no effect on tablet disintegration time, which was less than 10 sec in all cases. Increasing extruder screen size resulted in increased tablet hardness, whereas increasing the amount of granulating solvent, the spheronizer speed, or the spheronizer time resulted in decreased tablet hardness. The dissolution rate was found to decrease as the amount of granulating solvent added was increased.

The results may also be used as an indication of which process variables have no significant effect on tablet hardness and dissolution rate.

A correlation between granule friability and tablet dissolution rate was found. The validity of this correlation was tested by performing an additional experiment which indicated a close agreement between predicted and experimental dissolution rates.

Table IX—Dissolution Rate Constant ($Minutes^{-1}$)[a]

Significant Main Effect	Low Level	High Level
Water content	0.085	0.030

[a] Mean of 16 experiments.

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