Use of Factorial Design to Evaluate Granulations Prepared by Spheronization

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Abstract □ This study was designed to demonstrate that properties of a granulation with a given composition, prepared by the spheronizing technique, could be altered by slight changes in process variables alone to satisfy the requirements of the formulator. A complete factorial experimental design was found satisfactory for demonstrating the range of properties to be expected and for showing statistically significant main effects and any linear interactions between selected variables. Results using two levels of five variables showed that initial water content and spheronizer speed had significant main effects on all primary granulation properties studied. While only one formulation was studied, the data suggest that the factorial design can have utility in predicting the properties of granulations prepared at conditions within the limits imposed by the equipment or formulation.

Keyphrases □ Spheronization—process variables, effect on granulation properties □ Tablet granulation—spheronization method utilized to control granule properties □ Factorial experimental design—utility for optimizing pharmaceutical process conditions

Extruded particles processed to exhibit a fairly uniform spherical shape with a narrow size distribution were reported (1, 2) to offer advantages in pharmaceutical formulations for tableting. The selection of spheronization process variables had a significant effect on tablet hardness and dissolution when acetaminophen tablets were prepared by this unique granulation procedure (3). Studies of tablet granulations prepared with an instrumented single-screw extruder also demonstrated the importance of solvent selection on the final characteristics of the particles (4).

These studies, plus the popularity of pellet-type pharmaceuticals, particularly for capsule fills, suggest the need for detailed information describing the effects of processing variables on the properties of uniform, free-flowing particles in the sieve ranges employed for pharmaceutical products, no matter what process is used for their preparation. In a previous report, a factorial experimental design was recommended to identify significant variables and to predict the effects of changes in processing conditions on selected tablet properties (3). The work presented here summarizes the effect of selected variables on the properties of extruded spheronized granulations utilizing this procedure.

EXPERIMENTAL

Materials—Microcrystalline cellulose, containing 11% sodium carboxymethylcellulose[1], and acetaminophen NF[2] were used. A sieve analysis of both materials appears in Table I.

Processing—The equipment for preparing granulations was described previously (3) and consisted of an extruder[3] and a spheronizer[4] unit. Processing conditions (3) were carried out on a batch composed of 1 kg of materials plus the required quantity of purified water.

Testing Procedures—The temperature of the extruder chamber was monitored by a thermocouple[5] attached to the screen surfaces. Percent loss on drying of the extrudate was determined during extrusion and ranged between 17.6 and 25%. Analysis showed that the extrudate moisture content was determined only by the amount of water added prior to extrusion.

Percent loss on drying was recorded for each dried product, employing a 5.5-w lamp setting at 3.8 cm for 15 min on an IR balance[6]. Bulk density, expressed as grams per milliliter, was determined by measuring the volume occupied by 50.0 g of granulation in a 100.0-ml graduated cylinder.

A sieve analysis of each product was performed using 200-g samples passed through U.S. Standard sieves, from 8- to 60-mesh sizes, with the aid of a sieve shaker[7] at the number 6 setting for 5 min.

Flow rate was determined for each granulation using a conical stainless steel funnel, 23.5 cm high with a top 22.9 cm in diameter and a lower orifice 1.27 cm in diameter. The time required for 500 g of granulation to flow through the orifice was measured. Tests were run in triplicate; the mean value, expressed as grams per second, was used in calculations. Granule friability was evaluated by a procedure described previously (3).

Experimental Design—Details of the experimental design and mathematical treatment of the data as used to evaluate tablet properties were reported previously (3). The results reported here were obtained from the same series of experiments using data generated by various tests on the granulations. The methods described by Yates and Anderson (5) were used to identify main effects (ME) and to indicate first- and second-order interactions between the five variables chosen: water content (A), 250 or 325 ml; extruder speed (B), 39 or 59 rpm; screen size (C), 0.8 or 1.5 mm; spheronizer speed (D), 700 or 1010 rpm; and spheronizer residence time (E), 1.0 or 3.0 min. The ranges were selected to give a wide variation of granule properties within the limitations of the equipment and the requirements of the various tests.

RESULTS AND DISCUSSION

Test values for the various parameters are given in Tables II and III, and the ranges observed for each are included in Table IV. The data on percent fines and maximum amount on one screen are in Table V. An example of the analysis of variance results for flow rate is given in Table VI. Discussion of results will include significant main effects and first-order interactions (those between two variables). A summary of all significant main effects is given in Table VII.

Three parameters—extruder screen temperature, escape, and extrudate water content—were measured during the extrusion step of the spheronization process and could only be affected by water content, extruder speed, and screen size.

[1] Avicel RC 581, FMC Corp., Marcus Hook, Pa.
[2] Special powder, S. B. Penick & Co., New York, N.Y.
[3] Model EXDS-60, Elanco Products Co., Division of Eli Lilly & Co., Indianapolis, Ind.
[4] Marumerizer model Q-230, Elanco Products Co., Division of Eli Lilly & Co., Indianapolis, Ind.
[5] Model 42 SC, Yellow Springs Instrument Co., Yellow Springs, Ohio.
[6] Model 6010, Ohaus Scale Corp., Union, N.J.
[7] Cenco-Meinzer, Central Scientific Co., Chicago, Ill.

Table I—Particle-Size Distribution of Starting Materials[a]

U.S. Standard Sieve No.	Microcrystalline Cellulose	Acetaminophen
20	—	1.1
40	—	9.5
60	—	13.6
80	0.3	34.4
100	0.8	3.0
120	2.6	10.0
<120	96.3	28.4

[a] Weight percent.

Maximum Extruder Screen Temperature—Analysis of variance indicated that water content and extruder speed were significant main effects. No significant interactions were found. An increased water level decreased the maximum extruder screen temperature whereas an increased extruder speed increased the maximum extruder screen temperature. With heat-labile materials, it would be desirable to maintain the temperature at the extruder screens at a minimum. This could be accomplished at high water content and also at low extruder speed.

Escape—Material that passed down the overflow chute during extrusion was collected, weighed, and corrected for moisture content to arrive at a value for the weight of dry material that was not acceptable for spheronization. Water content was the only significant main effect, and the interaction of water content–screen size was the only significant interaction. An increased water content decreased the weight of escape. The significant first-order interaction is shown in Table VIII.

An increased water content resulted in a greater decrease in escape at the low screen size. An increased screen size resulted in a decrease in escape at the low water content whereas escape increased at the high water content. To arrive at maximum product yield, escape should be kept at a minimum. This condition would result from a high water content and a low screen size.

Extrudate Water Content—Analysis of variance of water content of the wet, extruded material indicated only the obvious main effect; namely, an increased water content resulted in an increased water content of the extrudate. The results are presented only to indicate that neither speed nor screen size affected the extrudate water content. Theoretical values would be 20.0% at the low water content and 24.5% at the high water content.

Table II—Granulation Data

Experiment	Maximum Extruder Screen Temperature[a]	Escape[a], g	Extrudate Moisture Content[a], %	Loss on Drying, %
1	42°	86	24.5	1.2
2	41°	92	23.8	1.1
3	40°	55	25.0	1.1
4	52°	96	19.5	1.0
5	43°	132	23.5	1.2
6	60°	196	18.5	0.7
7	40°	143	24.0	1.2
8	63°	262	18.9	1.0
9	58°	120	18.7	0.8
10	61°	236	18.4	0.5
11	43°	142	23.7	1.0
12	70°	288	17.6	1.0
13	41°	133	23.9	1.0
14	40°	87	23.7	1.0
15	52°	132	20.0	1.2
16	60°	146	17.9	1.2
17	64°	170	19.3	1.3
18	61°	148	19.1	1.2
19	43°	102	24.3	0.8
20	65°	186	17.7	0.8
21	59°	160	18.2	1.3
22	50°	125	23.7	1.0
23	43°	82	24.3	1.2
24	62°	186	19.3	1.2
25	55°	143	24.6	0.9
26	51°	159	22.9	0.8
27	56°	184	19.3	1.0
28	46°	122	24.0	1.3
29	66°	198	19.3	1.0
30	57°	19	23.3	1.5
31	45°	141	24.5	1.1
32	61°	170	19.4	1.3

[a] Dependent on three variables only.

Table III—Granulation Data Parameters Subjected to Full Factorial Analysis

Experiment	Flow Rate[a], g/sec	Bulk Density[a], g/ml	Granule Friability[a]	Mean Particle Size, μm
1	19.4	0.690	1.9	611
2	19.7	0.694	0.8	687
3	18.1	0.670	1.3	882
4	18.8	0.670	3.2	697
5	22.0	0.735	0.6	681
6	17.3	0.602	6.0	498
7	20.1	0.694	0.6	795
8	18.1	0.625	3.5	543
9	21.6	0.725	1.5	598
10	18.5	0.667	2.0	490
11	17.9	0.714	0.5	774
12	17.6	0.667	3.1	531
13	19.0	0.735	0.3	963
14	17.9	0.676	0.9	603
15	15.9	0.625	4.4	683
16	17.6	0.694	1.6	616
17	21.1	0.725	0.6	531
18	16.9	0.667	3.8	732
19	17.7	0.704	0.5	630
20	19.2	0.719	1.1	506
21	18.7	0.667	2.4	527
22	18.9	0.709	0.6	634
23	18.7	0.704	0.7	620
24	20.5	0.714	2.1	626
25	20.8	0.746	0.2	850
26	18.8	0.714	0.7	779
27	17.3	0.654	4.2	560
28	17.5	0.667	2.0	869
29	15.9	0.625	5.3	731
30	20.2	0.725	0.5	650
31	20.9	0.735	0.3	751
32	20.2	0.667	2.0	507

[a] Mean of three values.

Intermediate Level Experiment (No. 33)—An experiment was run at mean levels of the five variables studied in the factorial experiment (Table IV). The variable levels were: water content, 290 ml; extruder speed, 50 rpm; screen size, 1.0 mm; spheronizer speed, 85 rpm; and spheronizer time, 2.0 min. In all cases, the value of the parameter for Experiment 33 fell within the range of the original experiments. This finding indicated that it was possible to use the results of this study to modify the characteristics of a given formulation to be spheronized. Details of the complete factorial analyses of the primary granulation properties are included here.

Flow Rate—The significant main effects indicate that an increased water content, spheronizer speed, or spheronizer time resulted in granulations with an increased flow rate.

The first-order interaction, spheronizer speed–spheronizer time, is shown in Table IX. As spheronizer speed increased, a greater in-

Table IV—Comparison of Results Obtained with Intermediate Level Experiment and Original 32 Experiments

Parameter	Intermediate Level Experiment	Range of Original 32 Experiments
Escape[a], g	74	19–288
Extruder screen temperature[a]	48°	40–70°
Flow rate, g/sec	20.4	15.9–22.0
Bulk density, g/ml	0.685	0.602–0.746
Granule friability	1.4	0.2–6.0
Mean particle size, μm	655	490–963
Fines, <0.25 mm, %	0.18	0.09–8.44
Maximum percent on one sieve	71.6	34.1–74.1

[a] These results relate only to variables A, B, and C.

Table V—Sieve Analyses: Percent of Each Mesh Size

Experiment	Mesh Size >8	8–16	16–20	20–30	30–40	40–60	<60
1	0.0	0.0	0.7	70.9	26.7	1.6	0.1
2	0.0	0.1	3.8	73.0	20.9	2.2	0.0
3	0.0	5.6	50.4	33.3	6.4	3.7	0.6
4	0.0	1.2	25.2	43.6	17.1	9.9	3.0
5	0.0	0.1	4.3	67.8	25.2	2.5	0.0
6	0.0	0.0	0.1	24.5	58.4	14.2	2.9
7	0.0	3.6	37.1	44.6	10.1	4.1	0.6
8	0.3	0.3	0.3	33.0	55.4	8.8	1.8
9	0.0	0.9	10.5	40.5	27.3	17.3	3.4
10	0.0	0.0	0.1	19.4	60.9	17.1	2.6
11	0.4	7.6	34.1	33.1	13.4	9.3	2.1
12	0.0	0.1	0.2	35.5	52.3	10.5	1.4
13	0.0	10.2	58.9	26.5	3.5	0.9	0.0
14	0.0	0.0	0.7	67.7	29.3	2.1	0.2
15	0.0	0.7	21.9	48.2	16.2	9.2	3.8
16	0.1	1.3	18.0	36.9	20.0	15.4	8.4
17	0.1	0.2	0.3	30.7	53.4	14.1	1.3
18	0.1	1.1	29.6	44.8	15.3	7.3	1.8
19	0.0	0.1	2.7	66.9	27.8	2.5	0.1
20	0.0	0.2	0.3	20.5	53.7	23.6	1.8
21	0.0	0.2	0.3	27.9	57.9	12.1	1.6
22	0.2	0.1	1.7	74.1	22.6	1.4	0.1
23	0.0	0.1	2.4	64.2	30.0	3.3	0.2
24	0.0	0.9	16.4	38.5	23.7	17.5	3.1
25	0.7	6.3	35.1	47.0	9.4	1.4	0.0
26	1.9	2.6	34.9	44.7	12.0	3.7	0.2
27	0.0	0.6	8.6	38.1	26.9	17.6	8.2
28	0.0	2.1	50.9	39.8	5.6	1.4	0.2
29	0.0	0.9	29.4	46.6	12.9	7.0	3.3
30	0.6	0.9	3.6	69.0	23.4	2.4	0.1
31	0.2	2.1	28.1	53.7	12.7	3.1	0.1
32	0.0	0.0	0.1	28.3	57.0	12.8	1.8

crease in flow rate was noted at the high spheronizer time. An increased spheronizer time resulted in a greater increase in flow rate at the high level of spheronizer speed. The maximum flow rate would be obtained at high levels of water content, spheronizer speed, and spheronizer time. If it were necessary to use larger extruder screens, improved flow rates would result with an increased spheronizer time at either level of water content.

Bulk Density—The significant main effects indicated that an increased water content, spheronizer speed, or spheronizer time resulted in granulations with an increased bulk density. As spheronizer speed was increased, a greater increase in the value for bulk density was observed at the low water content, although values for bulk density were higher overall at the high water content (Table X). An increased water content resulted in similar effects, that is, a greater increase at the low spheronizer speed but with higher values for bulk density overall at the high spheronizer speed.

If it were desirable to have high values for bulk density, a high water content, spheronizer speed, and residence time in the spheronizer would be required. Experiments run at the high level of either water content or spheronizer speed resulted in nearly identical bulk density values. When both of these variables were at the high level, even greater values for bulk density were obtained.

Mean Particle Size—Calculated mean particle sizes were obtained from plots of cumulative percent undersize on the probability scale *versus* particle size on the arithmetic scale. Sieve analysis data appear in Table V. The significant main effects indicated that an increased water content or screen size resulted in granulations with an increased mean particle size whereas an increased spheronizer speed resulted in a decreased mean particle size.

As screen size increased, a greater increase in mean particle size was observed at the low spheronizer speed. As spheronizer speed increased, no change in mean particle size was observed at the low screen size whereas mean particle size decreased at the high screen size (Table XI). The mean particle size resulting from a given extruder screen size is considerably smaller than the screen size itself. The average of mean particle sizes for 16 experiments using screens with 0.8-mm openings was 0.578 mm; when using screens with 1.5-mm openings, the average of mean particle sizes was 0.744 mm. A low water content, small screen size, and high spheronizer speed would result in smaller particles in the final granulation. If it were necessary to use larger screens, a smaller mean particle size would be obtained at a high spheronizer speed. With small screens, no change in mean particle size was obtained by increasing spheronizer speed.

Table VI—Analysis of Variance: Flow Rate

Source of Variation	Sum of Squares	Degrees of Freedom	Variance	$F_{1,6}$
Water content (A)	4.805	1	4.805	11.10[a]
Extruder speed (B)	1.620	1	1.620	3.74
Screen size (C)	1.805	1	1.805	4.17
Spheronizer speed (D)	20.801	1	20.801	48.04[b]
Spheronizer time (E)	22.111	1	22.111	51.07[b]
AB	2.205	1	2.205	5.09
AC	0.720	1	0.720	1.66
AD	1.901	1	1.901	4.39
AE	0.011	1	0.011	0.03
BC	0.405	1	0.405	0.94
BD	0.211	1	0.211	0.49
BE	0.151	1	0.151	0.35
CD	1.051	1	1.051	2.43
CE	1.711	1	1.711	3.95
DE	3.125	1	3.125	7.22[a]
ABC	2.205	1	2.205	5.09
ABD	1.711	1	1.711	3.95
ABE	1.901	1	1.901	4.39
ACD	0.061	1	0.061	0.04
ACE	3.001	1	3.001	6.93[a]
ADE	0.125	1	0.125	0.29
BCD	0.551	1	0.551	1.27
BCE	0.061	1	0.061	0.14
BDE	0.180	1	0.180	0.42
CDE	0.005	1	0.005	0.01
Higher order	2.598	6	0.433	

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

Percent Fines—For this study, fines were particles passing a 60-mesh sieve. The amounts present are listed in Table V. The significant main effects indicated that an increased screen size or spheronizer speed resulted in granulations with increased fines whereas an increased water content or spheronizer time resulted in decreased fines.

Significant first-order interactions are shown in Table XII. The water content–screen size interaction may be explained by observing that little increase in percent fines occurred at the high water content as screen size was increased. At the low water content, an increased screen size resulted in a large increase in percent fines.

The water content–spheronizer speed interaction may be explained in the same manner. At the high water content, an increased spheronizer speed resulted in little change in percent fines. At the low spheronizer speed, an increased water content resulted in a smaller decrease in fines than at the high spheronizer speed, both percent fines values being equivalent at the high water content.

The water content–spheronizer time interaction may be described by noting that, at the low water content, the percent of fines was decreased by increasing spheronizer time; at the high

Table VII—Summary of Significant Main Effects[a]

	Water Content	Extruder Speed	Screen Size	Spheronizer Speed	Spheronizer Time
Extruder screen temperature	***	**	—	—	—
Escape	***	—	—	—	—
Extrudate water content	***	—	—	—	—
Flow rate	*	—	—	***	***
Bulk density	***	—	—	***	***
Mean particle size	***	*	***	**	—
Percent fines	***	—	***	**	***
Granule friability	***	—	—	**	*

[a] * = $p < 0.05$, ** = $p < 0.01$, and *** = $p < 0.001$.

Table VIII—Values for Escape (Grams)[a]

Screen Size, mm	Water Content, ml	
	250	325
0.8	208	91
1.5	151	130

[a] Mean of eight experiments.

Table IX—Mean Flow Rate (Grams per Second) of Eight Experiments

Spheronizer Time, min	Spheronizer Speed, rpm	
	700	1010
1.0	17.5	18.5
3.0	18.6	20.8

water content, a much smaller decrease in percent fines occurred since few fines were present. A greater decrease in percent fines occurred at the low spheronizer time as water content was increased, although fewer fines were present throughout at the high spheronizer time. The screen size–spheronizer speed interaction was explained by noting that no change in percent fines was observed as spheronizer speed was increased at the low screen size but a large increase in percent fines occurred at the high screen size. As screen size increased, a much greater increase in percent fines was noted at the high spheronizer speed.

The screen size–spheronizer time interaction was explained by noting that, as spheronizer time was increased, a greater decrease in percent fines was apparent at the high screen size, although fewer fines were present throughout at the low screen size. As screen size increased, a greater increase in percent fines occurred at the low spheronizer time. The spheronizer speed–spheronizer time interaction was explained by noting that, as spheronizer time increased, a greater decrease in percent fines occurred at the high spheronizer speed, the values at both levels of spheronizer speed being nearly equal at the high spheronizer time. As spheronizer speed increased, a greater increase in percent fines occurred at the low spheronizer time.

Lower levels of fines may be obtained at high water content and spheronizer time but low screen size and spheronizer speed. If it were necessary to use screens with relatively large openings, low percent fines could be obtained at high water content. Even lower percent fines would be obtained under these conditions at low spheronizer speed or high spheronizer time. When using screens with small openings, changing spheronizer speed or spheronizer time had little effect on percent fines.

Maximum Percent on One Sieve Fraction—From sieve analysis data, the maximum percent of granules on a single sieve fraction was obtained. When using 0.8-mm screens in the extruder, this maximum occurred in the 20–30-mesh fraction for the eight experiments run at the high water content and in the 30–40-mesh fraction for the eight experiments run at the low water content.

Table X—Mean Bulk Density (Grams per Milliliter) of Eight Experiments

Spheronizer Speed, rpm	Water Content, ml	
	250	325
700	0.644	0.694
1010	0.696	0.720

Table XI—Mean Particle Size (Micrometers)[a]

Spheronizer Speed, rpm	Screen Size, mm	
	0.8	1.5
700	579	792
1010	577	696

[a] Mean of eight experiments.

Table XII—Mean Percent Fines of Eight Experiments

Screen Size, mm	Water Content, ml	
	250	325
0.8	1.9	0.1
1.5	4.4	0.5
Spheronizer Speed, rpm	**Water Content, ml**	
	250	325
700	2.5	0.2
1010	3.8	0.4
Spheronizer Time, min	**Water Content, ml**	
	250	325
1.0	4.1	0.5
3.0	2.2	0.1
Spheronizer Speed, rpm	**Screen Size, mm**	
	0.8	1.5
700	1.0	1.6
1010	1.0	3.2
Spheronizer Time, min	**Screen Size, mm**	
	0.8	1.5
1.0	1.2	3.4
3.0	0.8	1.5
Spheronizer Time, min	**Spheronizer Speed, rpm**	
	700	1010
1.0	1.6	3.0
3.0	1.0	1.2

When using 1.5-mm screens in the extruder, the maximum occurred 12 times in the 20–30-mesh fraction and four times in the 16–20-mesh fraction, the latter all occurring at the high water content.

Granule Friability—A value of 10.0 is maximum and would indicate 100% friability of a 10.0-g sample. The significant main effect indicated that an increased water content, spheronizer speed, or spheronizer time resulted in granulations with a decreased granule friability. The significant first-order interaction is shown in Table XIII. An increased spheronizer speed increased granule friability much more at the low water content. A decreased water content resulted in a greater increase in granule friability at the low spheronizer speed.

If, as indicated in this study, slight changes in process variables can significantly affect granulation properties, the spheronizing system might prove to be a useful research tool in addition to its production-oriented applications. Certainly, if granule properties can be controlled, correlation of other observed data should be facilitated.

While only one system was studied, experiments with other substances give reason to expect that most formulations could be modified to provide soft granulations for tablet compression or harder, more dense particles suitable for coating once the effects of process variables have been characterized.

Properties of the granules may change on aging, and Reier and Shangraw (6) reported effects of aging related to storage of tablets prepared with microcrystalline cellulose as the inert ingredient. The friability test used here plus a granule strength test such as was proposed by Ganderton and Hunter (7) could be of value in specific formulations where aging effects might be expected.

Table XIII—Mean Granule Friability of Eight Experiments

Spheronizer Speed, rpm	Water Content, ml	
	250	325
700	4.0	1.1
1010	1.9	0.5

The advantages provided by pellet-type pharmaceuticals have led to a renewed interest in several techniques for agglomerating powders, including the subjecting of wet powders to a vibrating surface or a cascading motion inside a tilted rotating drum (8). This agglomerating process has been called balling, glomulation, or pelletizing. The term spheronizing has been used (9), and it seems to be suited to the process performed by this system, particularly since the particulate product usually has a spherical shape, narrow size distribution, and increased density (10).

SUMMARY

The use of a complete factorial analysis to define the significant main effects and interactions between the variables of water content, extruder speed, screen size, spheronizer speed, and spheronizer residence time on various properties of pelletized granulations of acetaminophen produced by the spheronizing process was studied. Water content and spheronizer speed had a significant effect on all primary granulation properties studied and were involved in most of the first-order interactions noted.

The utility of factorial analysis as a tool for modifying product properties *via* changes in process conditions was given further support by a final experiment using intermediate values for the variables. All data from tests on the final batch fell within the ranges exhibited by the original series.

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ACKNOWLEDGMENTS AND ADDRESSES

Received July 5, 1974, from the *Philadelphia College of Pharmacy and Science, Philadelphia, PA 19104*

Accepted for publication February 8, 1975.

Presented at the Industrial Pharmaceutical Technology Section, APhA Academy of Pharmaceutical Sciences, Chicago meeting, August 1974.

Abstracted in part from a thesis submitted by H. J. Malinowski to the Philadelphia College of Pharmacy and Science in partial fulfillment of the Doctor of Philosophy degree requirements.

The authors thank the Elanco Division, Eli Lilly & Co., Indianapolis, Ind., for the gift of equipment to the College and technical assistance in its operation. They also thank Dr. Joseph L. Ciminera for his comments and evaluation of the statistical design of the experiment.

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Dissolution Studies with a Multichannel Continuous-Flow Apparatus

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Abstract □ A multichannel continuous-flow apparatus for dissolution rate measurements is described. Typical data are presented to demonstrate its utility for studies with bulk drug powders as well as with tablets and capsules without any change of setup. Procedures are given for the preparation of powder samples for dissolution studies and for a simple method of changing pH for "retard" tablets. The precision in dissolution rates obtained with this apparatus and method is 1–10% mean *RSD*. The advantages of the method are flexibility, reproducibility, and ability to obtain data in integral or differential form.

Keyphrases □ Dissolution rate measurements—design and evaluation of multichannel continuous-flow apparatus, application to powders, tablets, and capsules □ Tablet dissolution rates—design and evaluation of multichannel continuous-flow apparatus, also applied to powders and capsules □ Capsule dissolution rates—design and evaluation of multichannel continuous-flow apparatus, also applied to powders and tablets □ Drug powder dissolution rates—design and evaluation of multichannel continuous-flow apparatus, also applied to tablets and capsules

During the past several years, several dissolution rate testing methods have been developed. The beaker method (1, 2), the rotating-basket method (3–5), the rotating-flask method (6), the pressure change method (7), continuous-flow methods with or without cumulating reservoirs (8–22), and others (23–25) are important.

The continuous-flow (7, 8) and pressure change (7) methods have been stated to possess several advantages over the other methods. These advantages include flexibility, reproducibility, the possibility of obtaining data in differential or integral form, the ability to discriminate between similar formulations of the same drug, and the maintenance of sink conditions in the system.

Although a modified beaker method is both simple and adaptable for dissolution rate testing with solid dosage forms, this method gave poorly reproducible dissolution measurements with micronized and difficult-to-wet substances in bulk form. Therefore, a continuous-flow apparatus suitable for both drug substances (powders) and solid dosage forms was developed. The cell is designed to obtain a free flow of the dissolution medium even with large tablets, and