in alkaline solution was checked with this system and gave results in accordance with literature values.

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Keyphrases

Solution kinetics apparatus
Schematic diagram—solution kinetics apparatus
Bromothymol blue—alkaline, aqueous degradation

Effect of Size on Other Physical Properties of Granules and Their Corresponding Tablets

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Investigations were conducted to determine the relationship and effect of granule size upon the physical properties of the granule and the tablets produced from these granules. These properties were evaluated in the areas of spacial capacity, mobility, and physical stability. Additional studies were conducted which involved the manufacture of tablets and the subsequent correlation of the results of the physical testing of these tablets to the corresponding granule size. The physical properties of the granule were found to be interrelated and for the most part, related to the granule size. In the range of the granule sizes studied in this experiment, no direct relationship was found between granule size and granule volume. Both the degree of granule friability and flowability were found to increase as the size of the granule decreased. As the granule size became smaller, the weight variation of the tablets was found to decrease. No defined or observable relationship was found to exist between the granule size and the hardness of the corresponding tablet. The effect of granule size upon tablet disintegration was not distinguishable under the conditions of this study and probably was due to the variability and limitations of the disintegration apparatus used for this determination.

VARIOUS METHODS useful for the measurement of several physical properties of granules have been indicated in the literature. Arambulo and Deardorff (1) conducted a study which showed the relationship between granule size and the resulting tablet weight. They noted that as the granule size was reduced, the average tablet weight increased, presumably due to the decrease in void space. Large granules were found to contain a greater percentage of intergranular void space as compared to smaller granules and the resulting die fill, containing a smaller volume of material, produced tablets of a lighter weight. Arambulo, Fu, and Deardorff (2) noted the effect of granule size upon the weight variation of compressed tablets. As the granule size decreased, the weight variation decreased, passing through a minimum at 400–800 μ and then increased. They also noted that larger granules were found to yield greater weight variation. This effect was presumed to be caused by variation in the proportion of voids, which they attributed in part to the varying amount of breakage of granules and the resultant removal of the powder by the movement of the feed shoe of the single-press tablet machine.

Forlano and Chavkin (3) reported a definite relationship among granule size, disintegration time, and degree of capping. Using a sodium bicarbonate granulation, tablets compressed with granules in the 8–40-mesh range exhibited a rise in disintegration time and a decrease in capping. Tablets compressed using granules of 60 mesh or smaller exhibited a decreased disintegration time and an increase in capping. It was found that the optimum granule size of the granulation they used was found in the range of 16–60 mesh. Augsburger and Shangraw (4) described a method of measuring the fluidity of semifluid powders. They felt that the measurement of tablet weight would not only give comparable fluidity values but would also have practical importance from a production standpoint.

Fonner, Banker, and Swarbrick (5) tested

Received April 11, 1967, from the Graduate Division, College of Pharmacy, St. John's University, Jamaica, NY 11432

Accepted for publication October 13, 1967.

Abstracted in part from a thesis submitted by Alan M. Marks to the Graduate Division, College of Pharmacy, St. John's University, Jamaica, N.Y. in partial fulfillment of the Master of Science degree requirements, January 1967.

Presented to the Industrial Pharmaceutical Technology Section, APhA Academy of Pharmaceutical Sciences, Las Vegas meeting, April 1967.

The authors would like to acknowledge the assistance of Leonard Kaplan, Head of Pharmaceutical Development at Walker Labs., for his aid in developing the statistical analysis of the data. They would also like to thank Walker Labs. for the use of their laboratory facilities for portions of this study.

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granular pharmaceutical solids which they prepared by five different granulation methods. Each granulation was evaluated for its physical properties. The "particulate hardness" test was of special interest. This test, based on the size of the sample, involved shaking the granules in a closed container for a constant period of time and then measuring the percentage of material retained on a 30-mesh screen. These workers found that the hardness index increased as the density of the granule increased. In order to determine the bulk density, these investigators used a 30-Gm. sample of 20/30-mesh material. The material was placed in a 100-ml. cylindrical graduate and the graduate was dropped from a height of 0.75 in. onto a hard wooden surface. This was repeated 20 times. The results of this study showed that dissimilar shapes have a great effect upon the bulk density of a material. Jones and Pilpel (6) measured the flow of granular magnesium oxide through a circular orifice. The apparatus used for the flow rate determination consisted of a vertical copper tube, with an internal diameter of 3.83 cm., fitted with a base plate. A shutter and sliding aluminum sheet were fitted to the tube. Flow rates (in Gm./min.) were determined in triplicate by collecting and weighing the powder that escaped from the tube in fixed time intervals ranging from 5–60 sec. Shutter manipulation and incipient failure of the powder column were found to affect the flow rate in the initial stages.

This study is concerned with the relationship of granule size to selected properties of the granule and the tablets prepared from these granules. Specifically, bulk volume, friability, flowability, and die fill weight will be determined and evaluated for each of the granule sizes used. A knowledge of the effect of these properties upon the production of the finished tablet will be of value in the development of tablet formulation. The effect of granule size upon the weight variation of tablets produced under production conditions as well as tablet hardness and disintegration will also be of value. The weight variation may exceed limits if the granulation contains an excess of large granules and may laminate if the particles are too fine. A specification relating to the range of granule size could be maintained as a guide and control during the manufacture of the tablet. Several of the above properties can be related to the ability of the granules to withstand the abuse of normal handling during the processing of tablets. The effect of these variables upon tablet properties were investigated and related by correlating the physical properties of the tablet to the corresponding granule size.

EXPERIMENTAL

Three different formulations were introduced into this study. Three batches of each formulation were prepared in order to have sufficient data to subject to statistical analysis.

Preparation of Granules—Formulation I is a placebo granulation, and its formula is shown in Table I. Formulation II is a sulfadiazine granulation and was chosen so that the effect of an insoluble drug constituting a major portion of the tablet weight could be determined. The formula is also shown in Table I. Formulation III is a granulation containing a soluble drug, sodium saccharin, and is present as a minor portion of the total tablet weight. The formula is also shown in Table I.

The formulations used in this study are basically the same except that formulations II and III contain an active ingredient which replaces a portion equal to half its weight each of dicalcium phosphate dihydrate USP and lactose USP. Each granulation was prepared in the same manner. The weighed ingredients were passed through a No. 30 screen and mixed in a Hobart-type mixer. Methylcellulose, 15 cps., was used as the binding agent and added dry with the powders. The powders were granulated by using a mixture of isopropanol and water. The material was spread onto trays and dried at 32° overnight in an oven with an air flow. The dried material was passed through an 8-mesh screen fitted onto an oscillating granulator. This produced granule sizes of not larger than 8 mesh and a great variety of smaller sizes, including powder of 60 mesh and finer.

In order to control the amount of moisture present in each batch, a moisture determination was made using the Cenco moisture balance. It was found that the moisture level for each batch was 1.4 ± 0.1%. By keeping the moisture at approximately the same level in each batch, the effect of moisture

Table I—Tablet Formulations

Ingredients	I Placebo (mg.)	II Sulfadiazine (mg.)	III Sodium Saccharin (mg.)
Sulfadiazine USP	...	100.0	...
Sodium saccharin USP	...	...	30.0
Dicalcium phosphate dihydrate USP	100.0	50.0	85.0
Lactose USP	100.0	50.0	85.0
Starch USP	31.0	31.0	31.0
Methylcellulose, 15 cps.	12.0	12.0	12.0
Total wt. per tablet	243.0	243.0	243.0

Table II—Classification of Granule Size Groups

Screen Size (NBS No.)	Opening, (μ)	Particle Size (Screen Size)	Particle Size (Av. μ)
8	2380	8/12	2030
12	1680	12/16	1435
16	1190	16/20	1015
20	841	20/30	718
30	595	30/60	423
60	250		

TABLE III—SPECIFIC GRANULATION BULK VOLUME[a]

Granulation	8/12 Mesh			12/16 Mesh			16/20 Mesh			20/30 Mesh			30/60 Mesh		
	A[b]	B[c]	C[d]	A	B	C	A	B	C	A	B	C	A	B	C
Placebo	92–102	95.9	1.91	93–100	96.3	1.92	95–104	98.9	1.99	96–106	99.3	1.98	90–96	93.8	1.87
Sulfadiazine	95–100	97.9	1.96	95–100	97.8	1.95	96–101	98.8	1.97	97–103	99.8	1.99	94–99	96.3	1.92
Sodium saccharin	76–78	77.1	1.55	79–82	81.0	1.62	82–84	82.9	1.65	82–86	83.2	1.66	77–80	78.7	1.57

[a] Values are expressed in milliliters (columns A and B). [b] A, range. [c] B, mean. [d] C, specific bulk volume.

upon the properties evaluated would be the same for each of the granule sizes studied.

The separation of the granule sizes was carried out through use of the Ro Tap testing sieve shaker and USP standard mesh wire screens, 8 in. in diameter. Table II indicates the screens which were used and their position in the Ro Tap sieve shaker. The particles are identified by the number of the smallest screen that they will pass through and by the number of the largest screen they will be retained upon. Depth to the wire cloth and the distance between cloths in adjacent nested series was 2 in. The screens were placed into the apparatus in the order shown in Table II. The screens rotated in a circular motion and a hammer pounded a cork mounted on a cover plate over the screens. The apparatus was operated for a period of 2 min., resulting in the separation of the granulation into the various mesh sizes. Further agitation for periods of 3–4 min. did not appreciably change the results, indicating that complete separation occurred within 2 min. Each group of granules was collected and placed into a plastic bag. The bag was sealed and stored until the granules were ready for testing.

Specific Granulation Bulk Volume—The specific bulk volume of the granulation indicates the volume/unit weight of the solid, the volume of the intraparticle pores, and the void volume or volume of the interparticle spaces. Specific bulk volume is the reciprocal of bulk density.

Fifty grams of each granulation was weighed on a balance. The granulation was then poured slowly through a funnel into a 250-ml. graduated cylinder. The graduate was tapped lightly 10 times on a towel placed on a laboratory work bench and the volume measured. This procedure was repeated three times for each individual group of granules from each of the three different formulations. This involved three granulations of each formulation, and five granule size groupings for a total of 135 readings.

TABLE IV—ANALYSIS OF VARIANCE[a]

Source of Variation	df	SS	MS	F Test
Between treatments	4	41.7	10.4	0.108
Within treatments	10	963.3	96.3	
Total	14	1005		

[a] At the 95% level of significance the tabulated $F(4,10) = 3.48$. The calculated $F = 0.108$. Therefore, the treatment effect (mesh size) is not significant.

The specific granulation bulk volume was calculated by dividing the volume by the weight of the sample. These results are shown in Table III. An analysis of variance to determine the significance of the effect of granule size upon the specific granulation bulk volume is shown in Table IV.

Granule Friability—Granule friability is related to the strength of the granule and its ability to withstand abuse during normal handling. The Roche friabilator (7) was used for this determination. The apparatus was set to rotate 25 times a min. for a 4-min. period. Ten grams of granulation was weighed and placed in the friabilator. At the end of 4 min., all of the material was placed onto a 60-mesh screen and placed into the Ro Tap apparatus. The Ro Tap testing sieve shaker was operated for 15 sec. The material remaining on the screen was weighed and the results are shown in Tables V and VI. Figure 1 indicates the friability of each of the granule sizes studied.

Granule Flowability—Granule flowability is a measure of the rate of flow of granules through an orifice. In order to measure this properly, a special

TABLE VI—ANALYSIS OF VARIANCE[a]

Source	df	SS	MS	F Test
Between treatments	4	50.98	12.7	5.08
Within treatments	10	25.47	2.5	
Total	14	76.45		

[a] At the 95% level of significance the tabulated $F(4,10) = 3.48$. The calculated $F = 5.08$. Therefore, the treatment effect (mesh size) is statistically significant at the 95% level.

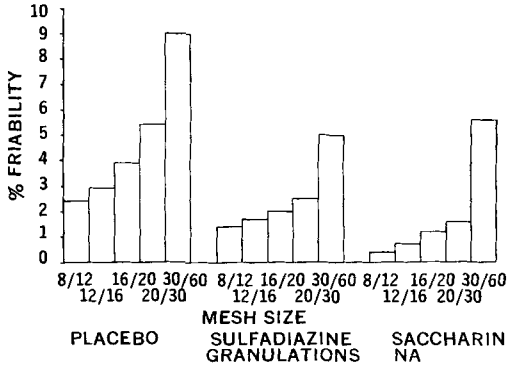

Fig. 1—Granule friability.

TABLE V—RETENTION OF GRANULES ON 60-MESH SCREEN[a]

Granulation	8/12 Mesh Range	8/12 Mesh Mean	12/16 Mesh Range	12/16 Mesh Mean	16/20 Mesh Range	16/20 Mesh Mean	20/30 Mesh Range	20/30 Mesh Mean	30/60 Mesh Range	30/60 Mesh Mean
Placebo	97.1–98.3	97.6	96.7–97.5	97.1	95.5–96.6	96.1	92.8–96.5	94.6	88.7–95.3	91.0
Sulfadiazine	98.4–98.8	98.6	98.1–98.6	98.3	97.9–98.2	98.0	97.1–97.7	97.5	94.1–95.1	95.0
Sodium saccharin	99.4–99.7	99.6	98.7–99.4	99.3	98.0–99.4	98.8	98.1–98.8	98.4	93.3–95.6	94.4

[a] Values are expressed in terms of percent remaining on 60-mesh screen.

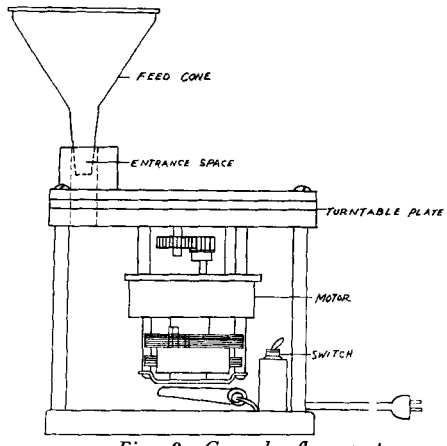

Fig. 2—Granule flow meter.

space which allows for free passage of granules through the opening and prevents the stoppage of granules in the tip of the cone. The disk rotates slowly at a constant rate, and as the opening in the disk aligns with the opening in the frame, the granules are allowed to flow through the opening. The flow of granules stops as soon as the opening in the disk is past the opening in the frame. A tared container was placed beneath the opening and the weight of granules collected during the time period determined. This procedure was repeated three times for each of the granule sizes. These results are shown in Tables VII and VIII.

Granule Size Versus Die Fill Weight—An attempt was made to determine the relationship of the granule size, in several fixed die situations, to the die fill weight. Magnesium stearate USP, in a concentration of 0.25%, was added to each batch of granules as a lubricant. A minimum amount of lubricant was used so as not to significantly influence the results. The bottom punch was lowered to a specified depth and set in place. The following settings were used:

	Diameter of Die, mm.	Depth of Fill, mm.	Tablets/ Min.
A	7	10	60
B	7	15	60
C	7	15	40
D	14	15	60

Approximately 250–300 tablets were produced from each of the granulations using a Stokes single-punch tablet press, model F, and 7-mm. and 14-mm. diameter flat-face punches. Each tablet was weighed on an analytical balance. The percent change in weight from the 8/12-size granule value was calculated. These results are shown in Table IX and

TABLE VII—GRANULE FLOWABILITY[a]

Granulation	8/12 Mesh Range	8/12 Mesh Mean	12/16 Mesh Range	12/16 Mesh Mean	16/20 Mesh Range	16/20 Mesh Mean	20/30 Mesh Range	20/30 Mesh Mean	30/60 Mesh Range	30/60 Mesh Mean
Placebo	7.675–14.045	10.3	20.380–27.116	23.8	30.949–33.486	32.1	38.110–40.068	39.1	48.378–52.066	50.4
Sulfadiazine	11.563–16.475	13.5	21.880–24.405	23.9	30.095–32.523	31.7	39.203–42.850	41.3	46.793–48.763	47.8
Sodium saccharin	11.815–19.113	14.7	24.262–29.601	26.7	34.312–37.332	36.1	45.807–47.049	46.3	58.810–59.686	59.2

[a] Values are expressed in Gm. of granulation.

TABLE VIII—ANALYSIS OF VARIANCE[a]

Source	*df*	*SS*	*MS*	*F* Test
Between treatments	4	2808.1	702.0	55.6
Within treatments	10	126.3	12.6	
Total	14	2934.4		

[a] At the 99% level of significance the tabular $F(4,10) = 5.99$. The calculated $F = 55.6$. Therefore, the treatment effect (mesh size) is statistically highly significant.

piece of apparatus was designed and made. This consisted of a circular disk mounted onto a frame as shown in Fig. 2. The disk contains an opening, 1.25 cm. × 0.75 cm., and is allowed to rotate at 2 r.p.m. by means of an electric motor. The frame is also fitted with an aluminum feed cone. In operation, the granules are placed into the feed cone through which they enter into a wider cylindrical

TABLE IX—GRANULE SIZE *versus* DIE FILL WEIGHT

Mesh Size	Placebo 8/12	Placebo 12/16	Placebo 16/20	Placebo 20/30	Placebo 30/60	Sulfadiazine 8/12	Sulfadiazine 12/16	Sulfadiazine 16/20	Sulfadiazine 20/30	Sulfadiazine 30/60	Sodium Saccharin 8/12	Sodium Saccharin 12/16	Sodium Saccharin 16/20	Sodium Saccharin 20/30	Sodium Saccharin 30/60
A (7 mm. Diameter, 10 mm. Depth, 60 Tablets/min.)															
Mean wt., mg.	161	170	174	176	192	160	172	173	175	186	207	208	209	219	231
% Change	...	5.5	8.0	9.3	19.2	...	7.5	8.1	9.3	16.2	...	0.5	1.0	5.8	11.6
B (7 mm. Diameter, 15 mm. Depth, 60 Tablets/min.)															
Mean wt., mg.	237	256	262	263	281	224	252	254	260	272	297	304	313	322	338
% Change	...	8.0	10.5	10.9	18.5	...	12.5	13.4	16.0	21.4	...	2.3	5.3	8.4	13.8
C (7 mm. Diameter, 15 mm. Depth, 40 Tablets/min.)															
Mean wt., mg.	242	256	260	262	285	241	254	257	263	276	303	310	319	322	340
% Change	...	5.8	7.4	8.6	17.7	...	5.3	6.6	9.1	14.5	...	3.3	5.2	6.2	12.2
D (14 mm. Diameter, 15 mm. Depth, 60 Tablets/min.)															
Mean wt., mg.	1059	1081	1084	1099	1163	1062	1081	1083	1096	1128	1359	1322	1308	1355	1411
% Change	...	2.0	2.3	3.8	9.8	...	1.7	1.9	3.2	6.2	...	−2.7	−3.7	−0.3	3.8

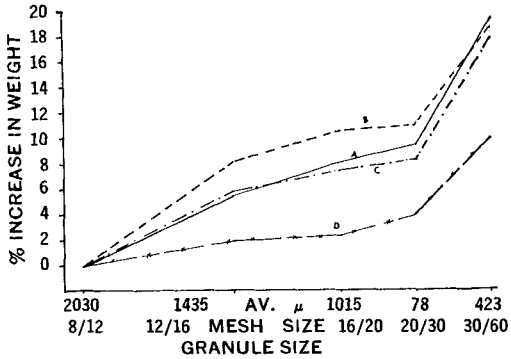

Fig. 3—Granule size versus *die fill (placebo granulation). Key:* A,——*7 mm. diameter, 10 mm. depth, 60 tabs./min.*; B,—*7 mm. diameter, 15 mm. depth, 60 tabs./min.*; C,—·—*7 mm. diameter, 15 mm. depth, 40 tabs./min.*; D,-*-14 mm. diameter, 15 mm. depth, 60 tabs./min.*

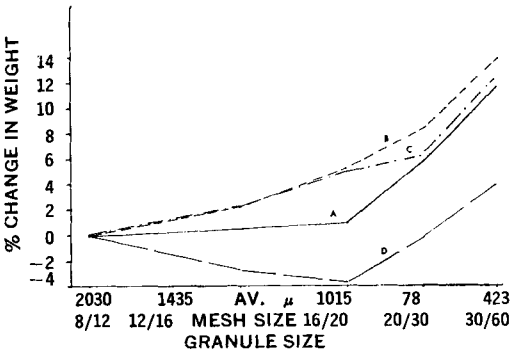

Fig. 5—Granule size versus *die fill (sodium saccharin granulation). Key:* A,——*7 mm. diameter, 10 mm. depth, 60 tabs./min.*; B,—*7 mm. diameter, 15 mm. depth, 60 tabs./min.*; C,—·—*7 mm. diameter, 15 mm. depth, 40 tabs./min.*; D,- -*14 mm. diameter, 15 mm. depth, 60 tabs./min.*

TABLE X—ANALYSIS OF VARIANCE[a] GRANULE SIZE *versus* DIE FILL WEIGHT

Source	*df*	*SS*	*MS*	*F* Test	*F*(4,10) (95% Level)
		A			
Between treatments	4	404	101	7.4	3.48[b]
Within treatments	10	135	13.5		
Total	14	539			
		B			
Between treatments	4	208.68	52.	1.2	3.48[d]
Within treatments	10	445.38	44.5		
Total	14	654.06			
		C			
Between treatments	4	350.6	87.6	30.3	3.48[c]
Within treatments	10	29.3	2.9		
Total	14	379.9			
		D			
Between treatments	4	94	23.5	3.9	3.48[b]
Within treatments	10	64	6		
Total	14	158			

[a] Percent change in weight used for analysis. See Table IX. [b] Significant at 95% level. [c] Highly significant. [d] Not significant.

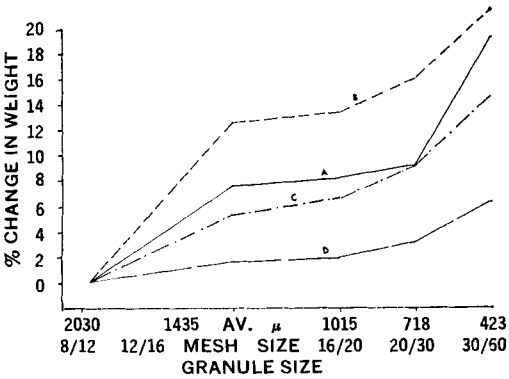

Fig. 4—Granule size versus *die fill (sulfadiazine granulation). Key:* A,——*7 mm. diameter, 10 mm. depth, 60 tabs./min.*; B,—*7 mm. diameter, 15 mm. depth, 60 tabs./min.*; C,—·—*7 mm. diameter, 15 mm. depth, 40 tabs./min.*; D,- -*14 mm. diameter, 15 mm. depth, 60 tabs./min.*

Figs. 3–5. Table X indicates the statistical treatment of these results.

Tablet Weight Variation—For this study it was necessary to adjust the tablet press to produce tablets of a specified weight and thickness. Five mg. of starch and 2 mg. of magnesium stearate were added to the granules to ensure proper lubrication and disintegration. The primary adjustment of the tablet machine was set at a weight of 250 ± 5 mg. and 0.135 ± 0.005-in. thickness. A Stokes single-punch tablet press, model F, and $^{7}/_{16}$-in. flat-face, bevel edge punches were used. The first 10 and the last 10 tablets produced were discarded to prevent weight variation due to initial flow resistance, insufficient weight of granules in the hopper, and excess fines. About 2000 tablets were produced and dusted to remove excess powder. Twenty tablets were weighed individually on an analytical balance. The mean weight, standard deviation, and coefficient of variation were calculated. Results are shown in Table XI and represent the average of 20 tablets for each of three determinations.

Tablet Hardness—Tablets from the tablet weight variation test meeting the specifications of 250 ± 5 mg. and 0.135 ± 0.005 in. were selected from each granule size group. The hardness of the tablet was measured using the Strong Cobb hardness tester fitted with an air pressure attachment. The mean for each group was calculated and the results recorded in Table XII and the analysis of variance in Table XIII.

Granule Size Versus Tablet Disintegration—The

TABLE XI—GRANULE SIZE *versus* TABLET WEIGHT VARIATION[a]

Mesh Size	8/12	12/16	16/20	20/30	30/60
		Placebo			
Mean, mg.	250	256	255	247	264
Range, mg.	229	248	234	233	253
	262	273	274	265	277
S.D.	9.6	7.5	10.3	9.1	5.3
Coefficient of variation, %	3.8	3.0	4.0	3.7	2.0
		Sulfadiazine			
Mean, mg.	245	262	247	250	251
Range, mg.	232	250	231	238	241
	265	275	261	255	254
S.D.	9.4	5.9	5.9	4.5	3.5
Coefficient of variation, %	3.8	2.3	2.4	1.8	1.3
		Sodium Saccharin			
Mean, mg.	252	257	248	249	251
Range, mg.	237	246	234	236	243
	274	271	256	254	255
S.D.	10.0	6.5	6.0	4.2	3.5
Coefficient of variation, %	4.0	2.5	2.4	1.7	1.4

[a] The treatment effect of mesh size is highly significant.

TABLE XII—GRANULE SIZE *versus* TABLET HARDNESS[a]

Mesh Size	8/12	12/16	16/20	20/30	30/60
		Placebo			
Mean	15.9	13.7	13.5	14.3	13.5
Range	11–22	11–18.5	10–17.5	10.5–17	11–19
		Sulfadiazine			
Mean	18.4	18.8	18.8	21.1	22.9
Range	15–21.5	14–24.5	13–25	17–24.5	17.5–27
		Sodium Saccharin			
Mean	15.7	16.9	15.1	14.5	13.9
Range	12–22.5	13.5–21.5	11.5–19	12–16	10–19

[a] Values shown are in Strong Cobb hardness units.

standard USP XVII disintegration method (8) for uncoated tablets was utilized. This method provides for the disintegration of six tablets in water maintained at 37°. Disks were used during this study. This method did not prove satisfactory due to the error or deviation introduced by the disks. It was reported by Kaplan and Kish (9) that many tablets will either adhere to the rising and falling disks, or adhere to the bottom stainless steel wire cloth. The result may be a flattening out of the tablet core caused by the constant action of the falling disk on the same point of the tablet surface.

The above procedure was modified by the removal of the disks from the disintegration apparatus. The disintegration time of the individual groups varied and overlapped. No definite relationship or trend due to the granule size could be noted. In this case, the error introduced by the disk was eliminated, however, the difference in the specifications of the tablets which were not greatly defined in this case possibly introduced another variable.

TABLE XIII—ANALYSIS OF VARIANCE[a]

Source	*df*	*SS*	*MS*	*F* Test
Between treatments	4	1.74	0.435	0.039
Within treatments	10	110.78	11.080	
Total	14	112.52		

[a] Based on Strong Cobb hardness units. At the 95% level of significance, the tabulated $F(4,10) = 3.48$. Calculated $F = 0.039$. Therefore, the treatment effect (mesh size) is not significant at the 95% level.

In a stricter selection of tablets having the specifications of 245–250 mg. weight and 0.134–0.136 in. thickness, a trend was discernable by one set of results but repudiated by another set, leading to an inconclusive set of data. The trend noted in one case was toward a longer disintegration time as the particles became smaller up to 20/30 mesh and then a shorter disintegration time at 30/60 mesh.

DISCUSSION OF RESULTS

The true effect of granule size upon bulk volume may have been disguised by other contributing factors such as granule shape, rate and direction of flow, positioning of the granules in relationship to each other and to the cylinder, powdering due to the impact and handling of the granules, and experimental error. The erratic results which were obtained may be due to: (*a*) The particle sizes chosen for this study may not have been sufficiently different from one another to show an effect upon the bulk volume. Theoretically, the void space should increase as the granule size is increased, thereby increasing bulk volume; (*b*) the rate and direction of flow of the granules into the cylinder may have been such so as to position the granules in a manner where bulk volume would not change appreciably with the size of the granule.

The degree of friability was found to be inversely proportional to the granule size. A definite reproducible trend in the results is observed. These results were verified by numerous readings and a statistical analysis of variance. The formula treat-

ments or the effect of the mesh size was found to be statistically significant at the 95% level of confidence. As the size of the granule becomes smaller, there is an increase in friability as shown by the greater loss of weight. This weight loss is due to material which has been detached from the granule due to the abuse taken in the apparatus and is comprised of powder 60 mesh and finer. It should be noted that the granules remaining on the screen may be of different mesh size than at the start of the test, but are still in the effective granule size range for tableting. The hardness of the particles is an important factor when considering friability. If the granule is hard, only surface particles will be lost when one particle rubs against another while with soft granules the entire granule will break into smaller particles. It is possible to determine the relative hardness of the granules, subjecting them to the friability test. In most cases, soft granules will lose considerably more weight than hard granules.

Flowability of granules was also found to be affected by the size of the granules studied. As the granule size was decreased, the flow rate of the granules through an orifice was found to be greater. These results were found to be highly significant statistically at the 99% level of confidence. A definite reproducible trend was demonstrated indicating that the size of the granule is related to the flow rate. If the size of the granules is further reduced, other factors such as bridging may interfere with its flow. However, results cannot be projected to all granule sizes. They apply only to the range of granule sizes actually studied in this investigation. Further experimentation is necessary to determine the flow rate of other granule sizes. The flow rate of the granulation and thus the granule size is significant and related to the efficiency of the die fill. This effect would be compounded by irregular shaped dies and greater die fills. The rate at which a tablet press may be operated is partially dependent upon the flow rate of the granulation. In the case of the single-punch tablet press, where there is no overfill of the dies as is found in rotary tablet presses, the flow rate of the granulation becomes more important. Where flow rates cannot be adjusted to produce satisfactory results, then the tablet press must be operated at a slower speed, or in the case of rotary presses, may require the use of force feed units.

A relationship between the granule size and the die fill weight has been noted. As the granule size is reduced the fill weight is increased. This has been observed in all four of the conditions studied. In the case utilizing setting *D*, "14 mm. diameter, 15 mm. depth, 60 tablets/min.," two readings did not follow this trend and may be due to experimental error. These results were tabulated based on a percentage change in weight and have been shown to be statistically significant at a 95% level and higher in all cases except one. The condition found not to be statistically significant when treated in this manner was setting *B*, "7 mm. diameter, 15 mm. depth, 60 tablets/min." Although it was not found to be statistically significant, the change in weight as a result of change in granule size is an important consideration in pharmaceutical production. From the results, the following was noted: (*a*) as the granule size decreases, the weight of granules required to fill the die increases; (*b*) as the depth of fill is increased, the effect of the granule size upon the die fill becomes greater; (*c*) as the speed of the tablet press used in this study is increased, the effect of the granule size becomes less; (*d*) as the diameter of the die is increased (greater fill space), the effect of the granule size is decreased and there is less of a weight difference between the sizes.

In addition to several physical properties of the granule, other factors will also influence the filling of the die in a tablet press. The diameter of the die, the depth of fill, and the speed of the machine are closely related to this property. It has been noted that as the granule size is reduced, the rate of flow of the granules is increased. While no significant difference in bulk volume due to the granule size was found, it has been suggested that the positioning of the granules as they land in the die is an important factor. Thus, the smaller granules flow through the orifice faster and are able to more efficiently fill the die as compared to larger granules. The greater friability of the smaller granules yields an increase in fines and aids in filling of the void spaces.

Experiments previously described in this study have shown that the granule size contributes to the physical properties of the granule. Granule flowability, friability, and die fill weight were shown to be influenced by the granule size. Thus, on the basis of these factors, it would be expected that the granule size would affect the tablet weight variation. In this study, the results showed an interrupted trend in weight variation due to the granule size. Upon close observation, however, a definite and statistically significant trend due to granule size was noted. Eliminating the intermediate groups of 12/16- and 20/30-mesh size from the evaluation, a definite relationship between the granule size and tablet weight variation can be noted. Due to the relative small difference in size between the neighboring groups, it is possible that these results are due to experimental error or that the size difference was not great enough to affect the weight variation. Comparing the 8/12-mesh, 16/20-mesh, and 30/60-mesh groups, the relationship was found statistically to be highly significant. As the granule size becomes smaller the weight variation was reduced. Further studies are indicated to fully substantiate this observation.

No defined or observable relationship between the granule size and the hardness of the corresponding tablet was noted in this study. It was further derived statistically that the treatment effect (mesh size) was not significant at the 95% level of significance. While no trend was noted in the results, there was an observed difference in hardness between the groups. Since granules interlock during the compression stage of tablet manufacture and result in added binding strength, the size of the granule may be related to the degree of interlocking which may take place and hence affect the hardness of the tablet.

It was not possible to obtain significant results in regard to the effect of granule size upon disintegration time. This was probably due to the limitations of the disintegration apparatus as well as the fact that there are other factors which have a greater effect upon the disintegration time.

The evaluation, knowledge, and use of granule

properties is important to the formulation, production, and quality control of tablets. The quality of tablets and the rate of productivity have been found to be influenced by the size of the granule. Automation requires standardization of the granule size for reproducibility. The testing of the granule by means of the granule flow meter and the modified friabilator may prove to be useful methods for evaluating several of the physical properties of granules.

CONCLUSIONS

(*a*) The effect upon the granule volume by the granule size was not clearly defined. (*b*) The degree of granule friability was found to decrease as the size of the granule increased. As the size of the granule becomes smaller, there is a greater loss of weight due to the friability of the granule. (*c*) Granule flowability was found to be inversely proportional to the granule size of the granule sizes tested. As the granule size becomes smaller, the flow of the granules through an orifice was found to be greater. (*d*) As the granule size decreases, the weight of the die fill increases. As the depth of fill is increased, the effect of the granule size upon the die fill is increased. As the speed of the tablet machine is increased, the effect of the granule size upon the die fill is decreased. As the diameter of the die is increased (greater fill space), the effect of the granule size is decreased and there is a smaller weight of fill difference between the sizes. (*e*) As the granule size becomes smaller, the tablet weight variation was found to decrease. This was found to exist especially in the 8/12, 16/20, and 30/60 groups. (*f*) No defined or observable relationship between the granule size and the hardness of the corresponding tablet was noted under the conditions of this test. However, difference in hardness between the groups was observed. (*g*) Due to the variability and limitations of accuracy of the tablet disintegration apparatus, no effect was noted in regard to granule size and disintegration time.

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Keyphrases

Granule size—effect, physical properties
Tablets, physical properties—granule effect
Friability—granule size
Flowability—granule size
Die weight fill—granule size
Weight, tablets—granule size

Electrostatic Characteristics of Pharmaceutical Solids and Packaging Materials I

Design of Testing Equipment and Preliminary Findings

By LEON LACHMAN and SONG-LING LIN

The design and operating principles of an apparatus capable of measuring the inherent static charge on materials, as well as being able to induce a positive or negative electrostatic potential, are described. The dual polarity high voltage power supply unit of this instrument can apply up to 10,000 v. to the materials under study. The voltage accumulation or decay of the sample being evaluated in the modified Faraday cage of the apparatus can be read on the ammeter of the electrostatic voltage sensing pistol or displayed on an X-Y recorder from the sensing pistol. Measurements are reported on the relative static electrification tendencies of sodium chloride, stearic acid, sulfisomidine, and iodochlorhydroxyquin when exposed to negative and positive potentials of 6,000 v.

THE ACCUMULATION of electrical charge on solid and solid-liquid systems by the process of static electrification is one of the earliest physical phenomena known. However, because of the complexity of the problem and mechanisms involved and an incomplete understanding of solid-state reactions, this phenomenon has only within the past 20 years received considerable

Received April 13, 1967, from the Research Department, Ciba Pharmaceutical Company, Summit, NJ 07901
Accepted for publication October 23, 1967.
Presented to the Industrial Pharmaceutical Technology Section, APhA, Academy of Pharmaceutical Sciences, Las Vegas meeting, April 1967.