l = distance moved by balance arm, cm.
P = pull exerted by balance arm, dynes
r = radius of column of liquid adhering to wire supporting sphere, measured in zone of constant thickness, cm.
R_1 = radius of inner cylinder of creep apparatus, cm.
R_2 = radius of outer cylinder of creep apparatus, cm.
S, s_0, s_1, s_2 = balance scale readings, mg.
t = time = $t_1 - (t_2 - t_1)$, sec.
t_1 = time taken for scale to move from 90 to 10 mg. when sphere is 0.85 cm. below liquid surface, sec.
t_2 = time taken for scale to move from 90 to 10 mg. when sphere is 1.7 cm. below liquid surface, sec.
t_c = time taken for scale to move from s_1 to s_2, sec.
t_0 = zero time
t_S = t for standard liquid, sec.
t_T = t for test liquid, sec.
v = velocity, cm. sec.$^{-1}$
W = weight removed from balance arm, mg.
w = weight of liquid column adhering to wire, mg.
w_1 = weight of liquid column adhering to wire at 90-mg. scale reading, mg.
w_2 = weight of liquid column adhering to wire at 10-mg. scale reading, mg.
η = viscosity, poises
η_0 = residual viscosity, poises
η_S = viscosity of standard liquid, poises
η_T = viscosity of test liquid, poises
θ = angular deflection of inner cylinder of creep apparatus, radians
π = 3.14159
ρ_1 = density of sphere, g. cm.$^{-3}$
ρ_2 = density of liquid, g. cm.$^{-3}$
τ = torque, dynes cm.$^{-1}$

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Effect of Processing Variables on Particles Obtained by Extrusion–Spheronization Processing

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Abstract □ Four extrusion–spheronization processing combinations were used to produce spherical granular materials from a standard base formulation. Dried, processed materials were evaluated by several physical methods to quantify the effect of the spheronizing processing variables, speed and dwell time, on the resulting granules. The data obtained indicated that, with this base formulation, plate rotational speed was of great importance in establishing the geometric form of final granules. Dwell time did not have an appreciable effect on the granules in this study. Measurements obtained for spheronized materials were compared to measurements on nonpareil beadlets and a conventionally produced granulation.

Keyphrases □ Extrusion–spheronization processing—effect of processing variables on particles □ Granules, form—extrusion–spheronization process, effect of processing variables □ Particles, form—extrusion–spheronization processing variables □ Spheronized materials—compared to nonpareil beadlets and conventionally produced granulation

Granulation is a key process in the production of many pharmaceutical dosage forms. Various techniques and equipment have been used to obtain granular materials, with one of the newer pieces of granulation equipment being the Marumerizer[1].

Preparation of solid spherical products by use of the Marumerizer offers a number of potential advantages to the pharmaceutical industry in the production of beads or granules as either finished or intermediate products. Some of these advantages include accurate control of dosage, speed of production, and choice of batch or continuous flow production (1). The operation of the Marumerizer in combination with an extruder was described by Conine and Hadley (2). Processing of the pharmaceutical formulation involves extruding wetted material into cylindrical segments, breaking the segments, and rolling them into solid spheres on a spinning friction plate. To produce solid spheres, the extrudate must break into short segments and the short cylinders must be plastic enough to be rolled into a spherical shape. Conine and Hadley found that materials which break into short cylinders but do not have sufficient plastic properties do not yield a spherical product. The

[1] Elanco Products, a division of Eli Lilly and Co., Indianapolis, Ind.

Table I—Spheronizer Processing Conditions

Processing Designation	Friction Plate Speed, r.p.m.	Dwell Time, min.	Friction Plate, Groves/Linear cm.
A	1210	3	5
B	905	3	5
C	610	3	5
D	610	6	5

studies described herein were initiated to characterize the effect of the spheronization processing variables, dwell time and speed, on the final granules obtained from a single base formulation.

EXPERIMENTAL[2]

Preparation of Base Formulation—Several potential base formulations were screened to find a combination that would clearly demonstrate differences in the spheronizing (rolling) portion of the processing. The formulation ultimately chosen contained the following:

sucrose (smaller than 60 mesh)	1522 g.
lactose USP hydrous	1522 g.
microcrystalline cellulose[3]	337 g.
mineral oil	63 ml.
water (deionized)	352 ml.

The materials in the base formula were blended in a sigma blade mixer[4] for 15 min. and were immediately transferred to the side screen extruder where the wet mass was extruded at 32 r.p.m. through a drilled plate having holes 1.0 mm. in diameter. The wetted mass was put through the extruder twice to improve the uniformity of the resulting product. A charge of 2800 g. of wetted extrudate was immediately placed in the spheronizer at one condition shown in Table I.

Completed, processed granules were tray dried at 48.8° (120°F) for 24 hr.

Physical Measurements—Various physical measurements, as follow, were used to evaluate and characterize the final dried experimental products, commercial nonpareil beads, and a hand-granulated base formula.

Sieve Analysis—Particle-size distribution was evaluated by a sieve analysis technique using 10-, 16-, 20-, 40-, 60-, and 80-mesh screens. The sieve nest was hand shaken until a distribution of the particles was reached at which no further change in weight distribution was observed with continued shaking. The charge weight on the 20-cm. diameter screens was 200 g.

Repose Angle—Repose angle measurements have been run, using various methods, by different investigators and have not been reduced to a standard procedure. In this study, 50 g. of granular material was placed in a standard powder funnel with a 1.25-cm. diameter orifice. A holding plate below the orifice was removed, and the material was allowed to fall 4 cm. onto a hard level surface covered with arithmetic grid graph paper. The height and radius of the resulting granule pile were measured, and the repose angle (ϕ) was determined using the following equation:

$$\tan \phi = \text{pile height/pile radius} \qquad \text{(Eq. 1)}$$

True Density—Granules were ground in a mortar and pestle to a powder that would pass through a 40-mesh sieve. This powder was compressed using 1.12-cm. flat-faced punches on a laboratory press[5] under a load of 3600 kg. The compressed tablet dimensions were measured (diameter and height) to the nearest 0.003 cm., and accurate weights were obtained for each tablet. The density of the tablet was then calculated, and the calculated value was considered to be the true density of the mixed formulation.

Table II—Observation of Spheronized Particles

Process	Particle Description
A (1210 r.p.m., 3 min.)	Fairly spherical
B (905 r.p.m., 3 min.)	Mostly dumbbell shaped, some lack of uniformity
C (610 r.p.m., 3 min.)	Mostly rod shaped with rounded ends
D (610 r.p.m., 6 min.)	Mostly rod shaped with rounded ends

Granule Density—The granule density was determined by means of a Fekrumeter[6], employing a 20-ml. sample container. This instrument measures the gas displacement of a known weight of solid material.

Bulk Density—The bulk density determination procedure was similar to that used by Fonner *et al.* (3), in which 50 g. of particulate material was placed in a 100-ml. graduated cylinder which was dropped 20 times from a height of 1.9 cm. onto a hard surface. The volume of the particle bed was measured to the nearest 0.5 ml., and the bulk density (in grams per milliliter) was calculated.

Granule Porosity—The granule porosity or intraparticle porosity (4) was computed from the true density and granule density measurements of whole (unsieved) granulations by the equation:

$$\text{intraparticle porosity} = 1 - \frac{\text{granule density}}{\text{true density}} \qquad \text{(Eq. 2)}$$

Packing Void Porosity—The interspace or void porosity (4) of granules is the relative volume of interspace voids to the bulk volume of the powder, exclusive of the intraparticle pores, and can be obtained using the formula:

$$\text{void porosity} = 1 - \frac{\text{bulk density}}{\text{granule density}} \qquad \text{(Eq. 3)}$$

Average Particle Diameters, Shape–Volume Factor, Length–Width Ratio, and Geometric Form Factor—These parameters were determined in an effort to quantify differences between various particles. The primary evaluation procedure involved: (*a*) accurately weighing exactly 100 particles, (*b*) photographing these particles on a calibrated background grid and preparing a transparent slide, (*c*) projecting the particles at 100 times their actual size, (*d*) tracing the outline dimensions of each particle, and (*e*) making physical measurements of several dimensions on the particle tracings. This was done for the 10–16, 16–20, and 20–40 sieve cuts of the products.

The area of each traced particle was determined to the nearest 0.03 cm.^{2} by means of a planimeter[7]. The length and width of each particle were measured, using the longest axis as the length and defining width as the measure across the particle on a line perpendicular to the midpoint of the longest axis.

Average particle diameters were calculated from the area measurement data by determining the diameter of a spherical particle of equivalent two-dimensional projected area. A second method, used to obtain an equivalent particle diameter, was the use of the equation:

$$\text{equivalent diameter} = \sqrt[3]{\frac{6}{\pi \rho N}} \qquad \text{(Eq. 4)}$$

where ρ is the granule density, and N is the number of particles per gram of sample (5).

The shape-volume factor (6), $\propto_V$, is defined by the equation:

$$\propto_V = \frac{V}{d_e^3} \qquad \text{(Eq. 5)}$$

where V is the average volume of a particle, and d_e is the equivalent projected diameter (diameter of a circle having the same area as the

[2] A model EXDS-60 extruder and a model Q-400 Marumerizer (Elanco) were used to obtain granules for study. The extruder is a twin-screw machine which extrudes the wetted material through perforated side screens. The screw speed can be adjusted to any desired speed between 20 and 80 r.p.m. The Marumerizer has a nonmovable bowl with a single 39.5-cm. diameter, rotating friction plate. Plate rotation speed can be varied within the range of 400–1600 r.p.m.

[3] Avicel PH-101, FMC Corp., Marcus Hook, Pa.

[4] Stokes model AA, F. J. Stokes Machine Co., Philadelphia, Pa.

[5] Model B, Fred S. Carver, Inc., Summit, N. J.

[6] Gallard-Schlesinger Chemical Mfg. Corp., Long Island, N. Y.

[7] Dietzgen, model D 1802.

Table III—Sieve Analysis of Granulations Expressed as Weight Percent Retained on Screen

Process	Mesh Size (U. S.) 10	16	20	40	60	80
A	0	0.5	10.0	89.0	0.5	0
B	0	3.5	39.5	57.0	0	0
C	0	0.5	5.0	92.5	1.5	0.5
D	0	0.5	4.5	94.5	0.5	0
Hand granulation	0	0	48.5	35.0	13.5	4.5
Nonpareil beads	0	100	0	0	0	0

particle when the latter is placed in its most stable position and viewed from above).

Also, by definition, the geometric form factor (7), k_e, is:

$$k_e = \alpha_V MN'^{1/2} \qquad \text{(Eq. 6)}$$

where α_V is the shape volume factor, M is the ratio of the particle breadth to its thickness, and N' is the length of the particle divided by its width. With the processing techniques used, the breadth can be expected to approximate the thickness; therefore, M was assumed to be unity. The N value was considered to be the length–width ratio as previously defined.

RESULTS AND DISCUSSION

Spheronized particles, prepared as previously described, were characterized and compared to granules produced by a hand-screening operation and to commercial nonpareil beads. The base formulation passed through the 1.0-mm. radially mounted extrusion screen fairly easily (extruder amperage reading 4–4.5), and the rolled product exhibited quite different final granule properties with various speed and dwell time combinations.

Particles obtained from the extrusion–spheronization processes were noticeably different in direct relation to the speed of the friction plate rotation, although a change in processing time at low rotational speed did not have a noticeable effect on the granule appearance (Table II).

With low velocity processing, the length of the rod-shaped particles was approximately twice the width; a very few rods were approximately 3, 4, or 5 times as long as they were wide.

Sieve Analysis—The initial characterization process involved determination of the particle-size distribution of the granules. The raw data are presented in Table III.

In the sieve analysis characterization, it was found that materials spheronized at 610 r.p.m. (Conditions C and D) had the most uniform particle size. Greater than 90% (by weight) of the materials from Condition C or D were 20–40-mesh particles. Conditions A and B (905 and 1210 r.p.m.) produced granulation in which a significant amount of material did not pass through the 20-mesh screen. All spheronized materials had greater uniformity of particle size than the hand-screened granulation produced from the same base formula. However the sieve analysis is somewhat misleading for the characterization of particle-size distribution of spheronized products due to the change in particle shape with different processing conditions. Even though the materials run at 610 r.p.m. were apparently quite uniform based on sieve analysis, the length of the granules differed widely; therefore, the actual sizes and volumes of the granules were more diffuse than with the more spherical particles obtained from 1210-r.p.m. processing. The 905-r.p.m. processing produced a great number of dumbbell-shaped materials, which probably increased the effective particle diameter when the study was based on sieve analysis. These relationships are not clearly evident by simply analyzing the raw sieve analysis data.

Table IV—Repose Angle Measurements

Production Condition	Repose Angle: Unsieved Batch	20–40-Mesh Particles
A	24°30′	24°30′
B	24°42′	24°22′
C	29°14′	29°22′
D	32°54′	29°37′
Hand granule	32°33′	30°17′
Nonpareil beads	Indeterminant	Indeterminant

Table V—Granule Density Data

Granule Size	Processing Condition A	B	C	D	Hand Granules
Whole granulation	1.43	1.44	1.44	1.45	1.38
16–20	1.47	1.45	1.47	1.43	—
20–40	1.44	1.44	1.46	1.43	—
Extrudate	1.44	1.44	1.45	—	—

Repose Angle—Data obtained from this study demonstrated that flow properties of the rounded materials (Conditions A and B) were superior to those of the rodlike materials (Conditions C and D). This is shown in Table IV, where a lower repose angle indicates a greater tendency to flow.

In all cases, the spheronized material flowed as well or better than the hand-granulated product, which had a rough irregular surface on most granules. The nonpareil beads flowed so well that they were not contained in a pile and, therefore, no measurement could be made under the conditions of this test.

True Density—This test was used primarily as a control procedure and to obtain data for granule porosity calculations. All data fell within the limits of 1.46–1.49 g./ml. Nonpareil beads had a true density of 1.47.

Granule Densities—These measurements were run in triplicate, using the Fekrumeter, for: (*a*) the whole granulation, (*b*) 16–20-mesh particles, (*c*) 20–40-mesh particles, and (*d*) the initial unspheronized extrudate. Average values of the results obtained are shown in Table V.

Spheronization processing did not produce a significant alteration in granule density from that obtained in the original extrusion process, nor were differences observed between processing conditions (A, B, C, or D). It was previously suggested (2) that the spheronization process could produce an apparent density increase when compared to conventional methods. The suggested densification phenomenon was not observed using this base formula, as can be seen by comparing granule densities of the extrudate and spheronized materials. Furthermore, no trend was found to exist between granule size and granule density within a given batch. The slight increase in granule density, as compared to hand-screened material, must be due to the extrusion process.

Bulk Density—Product bulk density showed an apparent increase as the processing became more intense through increased friction plate rotation speed (which produced continually more uniformly spherical particles over the speed range studied). This relationship can be observed in Table VI, and it can also be seen that all spheronized products had a much greater bulk density than the irregular material produced by hand screening.

Bulk density is partially indicative of packing properties of the ingredients and indicates that spheronized particles would provide a

Table VI—Bulk Densities of Processed Material

Particle Size	Processing Condition A	B	C	D	Hand Screen	Nonpareil Beads
Whole granulation	0.897	0.872	0.833	0.833	0.526	0.952
16–20	0.870	0.864	0.840	—	0.460	—
20–40	0.922	0.881	0.826	0.769	0.490	—

Table VII—Void Packing Space

Processing Condition	Void Volume, %
Nonpareil	31
A	38
B	40
C	43
D	43
Hand granules	62

Table VIII—Particle Size and Shape Characterizations

Process	Equivalent Diameter, μ — From Equation	Equivalent Diameter, μ — From Area Data	Shape–Volume Factor	Length–Width Ratio	k_e
A	894	980	0.397	1.133	0.423
B	977	1100	0.364	1.176	0.394
C	890	1103	0.275	1.475	0.334
D	920	1277	0.200	1.520	0.247
Nonpareil	—	—	0.535	1.097	0.561
Conventional processing	—	—	0.152–0.176	—	0.181–0.214

great deal more compact arrangement in processes such as capsule filling or granule packaging than would granules prepared by conventional means. The very uniform nonpareil beads had the greatest bulk density of all materials tested.

Granule Porosity and Packing Void Porosity—These parameters were calculated from the data generated in true density, granule density, and bulk density studies. Granule porosity was not changed significantly by processing variations and was approximately 2–3% in all spheronized materials. The method of determining granule density was shown to have about 3% variation with repeated measurements. Therefore, the intraparticle porosity may be negligible. Packing void porosity, however, had a definite dependence upon the shape or regularity of the particles involved. Hand-granulated particles had a higher void volume than any of the spheronized materials. Spheronized particles had less void volume, because the particles became more regular in shape (which was directly related to the processing conditions). Very regular particles (nonpareil) had the least void packing space of the six materials tested (Table VII).

Average Particle Diameters, Shape–Volume and Geometric Form Factors, and Length–Width Ratio—These parameters are interrelated and give an indication of the shape regularity of the particles. Since the majority of particles produced in this spheronization processing were in the 20–40-mesh range, the data presented (Table VIII) are for this size particle. The nonpareil beadlet data are for 10–16-mesh granules (the only size available), and the data for conventionally processed granules are taken from Fonner *et al.* (3).

Comparison of the data in Table VIII indicates several things:

1. The equivalent diameter of the particles is not adequately determined by the equation $d_e = \sqrt[3]{(6/\pi N\rho)}$, because no trend is shown between the spheronization processes using this method.

2. The equivalent diameter calculated from area measurements shows a definite relationship to the processing conditions, with the higher revolutions per minute processing producing particles with a smaller equivalent diameter. Since all particles are in the 20–40-mesh range, smaller equivalent projected diameters indicate an increase in sphericity of the particles.

3. The shape–volume factor is another measure of the sphericity of the particles and should be 0.524 for a perfect sphere. Values smaller than 0.524 indicate deviations from sphericity. The data from the Fonner *et al.* (3) article indicate that the Colton upright granulator, oscillating granulator, and hand screen produce very irregular particles. The nonpareil granules were observed to be nearly perfect spheres, as demonstrated by the shape–volume factor of 0.535. The fact that this value is slightly in excess of 0.524 (perfect sphere) shows that there is some inherent error in tracing the particle shapes and determining the projected area by use of a planimeter. Spheronized materials all had shape–volume factors falling between those of the conventional processes and the nonpareil beads. Using a 3-min. spheronization, there is a definite increase in sphericity with an increasing speed over the range studied (600–1200 r.p.m.). Doubling the processing time at the low speed decreased the particle uniformity. This characteristic may have been caused by surface drying of the particles and subsequent fragmentation or erosion of the surface. The length–width ratios and the geometric form factors included in Table VIII are further indicators of the same relationships previously described and reinforce the previous comments. A low k_e value indicates a nonregular particle shape, but a low length–width ratio is indicative of a regular, spherical particle.

SUMMARY

The data obtained clearly indicate that great differences can be obtained in the final spheronized product by alteration of processing conditions. With the specific base formulation used in this project, increased plate rotational speeds during spheronization (from 600 to 1200 r.p.m.) produced continually more spherical materials. All products obtained by this procedure were more uniform, both in shape and particle-size distribution, than products from conventional granulation methods but were less uniform than nonpareil beads.

Extrusion–spheronization processing of materials may offer a rapid and unique method of granule preparation for a variety of products in pharmaceutical and related industries.

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