Micromeritics of Granular Pharmaceutical Solids I

Physical Properties of Particles Prepared by Five Different Granulation Methods

By DALE E. FONNER, JR., GILBERT S. BANKER, and JAMES SWARBRICK

Granular pharmaceutical solids, prepared by 5 different granulation methods, were evaluated on the basis of repose angle, hardness, density, number of particles per gram, bulk density, shape volume factor, bulk volume, and geometrical form. Particular attention was given to the development of an accurate technique for evaluating shape volume factor as a means of characterizing the over-all shape of a particle. The findings indicated that repose angle was primarily a function of surface roughness and that geometrical form and shape on a volume basis were inversely proportional to bulk volume. The determination of these easily computed parameters is therefore of value in assessing manufacturing procedures which have as their primary objective the production of smooth, spherical particles suitable for pharmaceutical coating purposes.

THE STANDARDIZATION of processing methods, to achieve uniform product specification, is a constant goal of the pharmaceutical industry. Uniformity of drug distribution and standardization of dosage form characteristics, both within a single dosage unit as well as between dosage units, has become increasingly important in view of the more potent drugs in use today and the continual developments in the area of controlled release dosage forms.

Granulation is a key process in the production of many dosage forms involving the controlled release of a drug from coated or matrix-type particles, regardless of whether conventional granulation methods or the newer techniques of spray drying or fluidized bed processing are employed.

The production of uniform tablet dosage units has been shown to be dependent upon several granular properties. Arambulo *et al.* (1) found that as the granule size was decreased, the variation in tablet weight also decreased, reaching a minimum weight variation at a 400–800 μ granule diameter. Further reduction in granule size led to an increase in tablet weight variation. The particle size distribution also affects tablet weight, as well as exerting a marked influence upon tablet hardness (2). Particle size distribution and other particulate properties, by affecting the internal flow and segregation of a granulation, can vary the composition of compressed tablets (3).

Physical properties of granules, such as specific surface, shape, hardness, surface characteristics, and size, can profoundly influence the rate of dissolution of drugs contained in heterogeneous solid dosage forms. According to Wagner (4), when the granule size exceeds 10 μ the rate of dissolution is directly proportional to the surface area. By using spherical inert granules coated with various thicknesses of tolbutamide, Nelson *et al.* (5) demonstrated the dependence of the excretion rate of the drug upon the available surface area. The effect of the granule size upon the dissolution of tripelennamine hydrochloride (6) and aspirin (7) have been investigated also.

To date, most of the physical studies of the properties of granular pharmaceutical solids have been concerned with the evaluation of repose angle (8–12) and particulate density or porosity (13, 14). The application of such physical parameters as shape, bulk density or packing volume, the number of particles per gram, and particulate hardness to the characterization and utilization of granular pharmaceutical solids has apparently gone unreported. With the development of the many new processing methods designed to produce granular particles (15–21), the need to apply physical measurements of a quantitative nature to pharmaceutical granulations to achieve a rational selection of a particular process or piece of equipment is greater than at any previous time. The purpose of this report is to present simple, reproducible procedures which may be used to estimate certain physical parameters of granular pharmaceutical solids, and to compare, on this basis, granules prepared using 5 different granulation methods.

EXPERIMENTAL

Preparation of the Base Formula and Granulating Solution.—A base formula of 90% lactose and 10% starch was selected as the model system for this study. The powders were passed through a 60-mesh screen in batches of 10 Kg. and mixed in a model c-10 Hobart mixer[1] for 15 min. Portions of this mixed

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[1] Hobart Manufacturing Co., Troy, Ohio.

TABLE I.—GRANULATION METHODS AND CONDITIONS EMPLOYED IN THE MANUFACTURE OF GRANULES

Granulation Method	Batch Size, Gm.	% v/w Granulating Soln. Used	Operating Conditions
Oscillating granulator[a]	2000	11.25	No. 12 screen
Hand screen	2000	12.50	No. 12 screen
Colton upright[b]	2000	12.50	Circular openings equivalent to 12-mesh screen
Liquid-solids V-blender[c]	3100	17.74	.....
Fitzpatrick comminutor[d]	2000	18.75	Knives forward, high speed, no screen

[a] Stokes oscillator, model 43A, F. J. Stokes Machine Co., Philadelphia, Pa. [b] Colton upright granulator, type 3WG, Arthur Colton Co., Division of Cherry-Burrell Corp., Cedar Rapids, Iowa. [c] Liquid-solids V-blender, type LB 2501, Patterson-Kelley Co., East Stroudsburg, Pa. [d] Fitzpatrick comminutor, model M, W. J. Fitzpatrick Co., Chicago, Ill.

powder were massed with the granulating solution and separately processed by each granulation method (Table I). The granulating solution had the following composition:

Gelatin powder	480.0 Gm.
Acacia powder	160.0 Gm.
Distilled water	4000.0 Gm.
Methylparaben	10.0 Gm.
Propylparaben	2.0 Gm.

The granulating solution was prepared by dissolving the solute components in the hot distilled water. The granulating solution was employed at a temperature of 47°. Each granulation was air dried for 72 hr. at about 26° and 15% R.H. and was then sized through a 12-mesh hand screen. The granulations were stored in air-tight jars at room temperature until required.

Sufficient granulating solution was used to make the granules as hard as possible, and so minimize particulate fracture during the evaluative procedures.

In order to minimize variations of those physical parameters dependent upon particle size, a 20/30-mesh sieve fraction of each granulation was used, except where otherwise stated. The sieve fractions were obtained when required by processing 300–400-Gm. samples of the granulation through a nest of sieves shaken for 15 min. on a Cenco-Meinzer sieve shaker[2] operating on speed setting 5.

The moisture content of each granulation was determined using a Cenco moisture balance[2] operating at a temperature of 115°. The relative humidity was recorded using a Serdex relative humidity indicator, model 122-7005.[3]

Physical Measurements.—*Repose Angle, θ.*—Measurements of repose angle were obtained using an apparatus similar to that described by Pilpel (12), except that the cones were formed on a piece of arithmetic grid graph paper rather than on a brass plate.

One hundred milliliters of 20/30-mesh material was introduced into a copper cylinder, 16.5 cm. in length and 3.8 cm. internal diameter, which then was raised vertically through a pulley drive at the rate of approximately 0.2 mm./sec. The height, l, of the deposited granular cone was determined using a microcathetometer[4] and the base diameter, d, of the cone obtained by noting the cone base dimensions on the graph paper and averaging 2 determinations taken 90° apart. The repose angle, θ, was calculated as follows:

$$\theta = \arctan\left(\frac{1}{d/2}\right) \qquad \text{(Eq. 1)}$$

Humidity conditions and the moisture content of the granules were rechecked after repose angle determinations.

Granule Density, ρ_g.—A pycnometer method was chosen for the determination of particulate or granule density due to its ease of operation and reproducibility (22). The capacity of the pycnometer was 30 ml. and approximately 2 Gm. of 20/30-mesh material was used. Benzene, specific gravity 0.879, was employed as the immersion fluid. Due to the rapid evaporation of benzene, the pycnometer stem was marked half way down and the weight recorded as the meniscus reached this mark.

Particulate Hardness.—Many procedures for evaluating hardness were studied. The final selection made on the grounds of simplicity and the sample size used, involved shaking the granules in a closed container for a constant period of time and then measuring the percentage by weight of material retained on a 30-mesh sieve. Twenty grams of 20/30-mesh material was placed in a dry 3-oz. square bottle and shaken on an Eberbach[5] power shaking unit, model 6000, for 5 min. A 3-in. stroke was used with the reciprocating rate set at 216 c.p.m. The contents of the bottle were then placed on a No. 30 sieve and the fines removed by shaking for 15 sec. on the shaker unit. The hardness index, h, was calculated as the weight fraction of material retained as 30-mesh oversize following shaking.

Number of Particles per Gm., N.—One hundred particles of 20/30-mesh material were weighed and the number of particles/Gm., N, computed.

Bulk Density, ρ_b.—The bulk density determination procedure developed by Butler and Ramsey (23) was employed, with the exception that the cylindrical graduate was dropped 20 times instead of the 3 originally proposed. This modification was found to produce significantly more uniform results. A 30-Gm. sample of 20/30-mesh material was placed in a 100-ml. cylindrical graduate and dropped from a height of 0.75 in. onto a hard wooden surface a total of 20 times. Two seconds were allowed to elapse between each drop. If V is the volume in ml. of W Gm. of material in the cylinder, then ρ_b, the bulk density in Gm./ml., is given by:

$$\rho_b = \frac{W}{V} \qquad \text{(Eq. 2)}$$

Shape Volume Factor, α_v.—By definition (24):

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

[2] Central Scientific Co., Chicago, Ill.
[3] Bacharach Industrial Instrument Co., Pittsburgh, Pa.
[4] Gaertner Scientific Corp., Chicago, Ill.
[5] Eberbach Corp., Ann Arbor, Mich.

TABLE II.—VALUES FOR VARIOUS PHYSICAL PARAMETERS OBTAINED FOR 20/30-MESH PARTICLES PREPARED USING 5 DIFFERENT GRANULATION METHODS

Granulation Method	Colton Upright	Oscillating Granulator	Hand Screen	Fitzpatrick Comminutor	Liquid-Solids V-Blender
Repose angle, θ, in degrees	35.78	34.65	35.77	36.23	35.28
Granule density, ρ_g, in Gm./ml.	1.51	1.54	1.50	1.42	1.45
Hardness index, h	.974	.977	.955	.945	.912
No. of particles/Gm., N	5759	6748	7753	6405	5527
Bulk density, ρ_b, in Gm./ml.	.375	.395	.400	.428	.508
Shape vol. factor, α_v	.1520	.1757	.1634	.2163	.2495
Bulk vol./constant vol. of granules, V_b', ml.	80.05	77.97	75.00	66.36	57.09
Geometrical form, k_e	.1809	.2144	.1912	.2639	.3019
Interspace porosity, e_i	.752	.744	.733	.699	.650
Equivalent projected diam., d_e, μ	910	820	810	800	790

where α_v is the shape volume factor, V is the volume of the particle, and d_e is the equivalent projected diameter. d_e is defined as the diameter of a circle having the same area as the particle when the latter is placed in its most stable position on a horizontal plane and is viewed from above.

A series 10 Micro Star[6] microscope, equipped with a projection screen, was used to view the particles, the outlines of which were traced onto paper. The areas of the traced particles were determined using a compensating planimeter.[7]

Extending Eq. 3 to the case of many particles:

$$\alpha_v = \frac{V_n}{\sum_{i=1}^{n} (d_e)_i^3} \qquad \text{(Eq. 4)}$$

where V_n is the volume of n particles. If p is the power of magnification, then d_e can be obtained readily in terms of the projected area, A. Thus,

$$\frac{A}{p^2} = \frac{\pi(d_e)^2}{4} \qquad \text{(Eq. 5)}$$

and

$$(d_e)^3 = \left(\frac{4A}{\pi p^2}\right)^{3/2} \qquad \text{(Eq. 6)}$$

Substituting Eq. 6 into Eq. 4:

$$\alpha_v = \frac{V_n}{\sum_{i=1}^{n} \left(\frac{4A}{\pi p^2}\right)_i^{3/2}} \qquad \text{(Eq. 7)}$$

or

$$\alpha_v = \frac{V_n}{\left(\frac{4}{\pi p^2}\right)^{3/2} \sum_{i=1}^{n} A_i^{3/2}} \qquad \text{(Eq. 8)}$$

Since more than 600 particles were traced, Eq. 8 was programmed in Fortran and the results computed on an IBM 1620 computer.

About 20 granules of 20/30-mesh material were placed on a microscope slide and the projection of each traced. The particles then were transferred to a tared weighing bottle. This procedure was repeated until approximately 150 particles from each granulation had been traced. The weight of the particles was obtained and their total volume calculated as follows:

$$V_n = \frac{M}{\rho_g} \qquad \text{(Eq. 9)}$$

where V_n is the volume, in ml., of n particles, M is the mass, in Gm., of n particles, and ρ_g is the granule density as determined by benzene displacement. The magnification, p, of the microscope used was 30.5×.

Bulk Volume per Constant Volume of Granules, V_b'.—The bulk volume for a constant granule volume was computed, for each granulation, from a knowledge of ρ_g and ρ_b. Thus:

$$V_b' = \frac{V\rho_g}{\rho_b} \qquad \text{(Eq. 10)}$$

where V_b' is the bulk volume in ml. of a fixed particulate volume V (in this instance, 20 ml.), ρ_g is the granule density, and ρ_b the bulk density. The bulk volume per constant volume of granules represents a term comparable to bulk density but which is freed from particulate density values, which varied from granulation to granulation.

Geometrical Form, k_e.—By definition (25):

$$k_e = \alpha_v m n'^{1/2} \qquad \text{(Eq. 11)}$$

where k_e is the geometrical form, m is the ratio of the particle breadth to its thickness, and n' is the length of the particle divided by its width. Since these granules were made by forcing them through square or spherical openings, the breadth can be expected to approximately equal the thickness. In this case, $m = 1$ and:

$$k_e = \alpha_v n'^{1/2} \qquad \text{(Eq. 12)}$$

Values of n' for particles from each granulation were calculated using 20 randomly selected granules. The longest dimension was taken as the length and a line perpendicular to its midpoint was taken as the width.

RESULTS AND DISCUSSION

Physical Methods.—*Repose Angle, θ.*—The repose angle values listed in Table II are the averages obtained from not less than 11 determinations run on particles from each granulation. The average standard deviation was 0.74°. The relative humidity never exceeded 15% during the determinations. In all cases, the moisture content of the granules was less than 2%.

[6] American Optical Co., Buffalo, N. Y.
[7] Keuffel and Esser Co., Germany.

Analysis of variance and contrast techniques (26) were used in the statistical analysis of the data. The repose angle of particles prepared using the oscillating granulator was found to be significantly lower than those values for particles produced using the other 4 methods, when a significance level of 1% was used. Since particles with smooth and even surfaces generally have a low angle of repose (27), the results obtained suggest that particles prepared from the oscillating granulator have the smoothest surface.

The repose angle was unaffected by static charge. Qualitative observations showed that the particles from the liquid-solids V-blender and the Fitzpatrick comminutor possessed a great deal of static charge. However, as shown in Table II, the repose angle of these granules did not vary significantly from those particles produced by the use of the Colton upright and the hand screen granulation methods, which were observed to have a lower static charge. These findings are in agreement with the predictions of Pilpel (12) who deduced, on theoretical grounds, that the magnitude of a static charge is too small to affect the repose angle.

The repose angle for the different granulations was found to be independent of particle shape. This was brought out in the study of shape volume factors. Thus, particles from the liquid-solids V-blender were found to be the roundest (highest α_v), yet their repose angle was quite high in relation to the repose angle of the irregularly shaped particles from the oscillating granulator. It would appear that, for particles of this size, the repose angle is mainly a function of surface roughness, as predicted by Pilpel (12).

Granule Density, ρ_g.—The density values listed in Table II are the average of 2 determinations. The average standard deviation for the reported values was 0.008 Gm./ml.

Since particles containing crevices or entrapped air give low density readings (22), the data in Table II indicate that granules prepared using the liquid-solids V-blender and Fitzpatrick comminutor have pitted surfaces or entrapped air, or both. These particles have very irregular surfaces, since many air bubbles were observed to rise to the surface of the benzene during the preliminary stages of the density determinations carried out using these granules. This was found not to be the case for the particles prepared by the other granulation methods.

Hardness Index, h.—Each of the hardness index values listed in Table II is the average of 3 or 4 determinations. The hardness index increased directly with the granule density, with the exception of those particles prepared from the Fitzpatrick comminutor.

Number of Particles per Gm., N.—Each value of N in Table II is the average of 5 determinations. Analysis of variance and contrast techniques (26) showed that the granules prepared using the Colton upright and the liquid-solids V-blender had N values which were significantly lower than those particles produced from the other 3 methods. Granules prepared using the hand screen method were found to have a value of N significantly higher than the other granules. In all cases, the significance level used was 1%.

Assuming that the samples consisted of spherical particles having a normal size distribution over the 20/30-mesh range, N would have a value of approximately 3500 particles/Gm. Deviation of the size distribution from normality cannot, alone, explain the high values of N obtained, implying that the particles are not spherical. The validity of this conclusion was confirmed by microscopic examination of the particles and a consideration of the calculated shape volume factors given in Table II. For perfect spheres, α_v is equal to $\pi/6$, or 0.524.

Bulk Density, ρ_b.—Bulk densities were determined twice for 20/30-mesh fraction of each granulation. In all cases, the 2 values were identical.

It is apparent from the results in Table II that the packing arrangements for particles prepared by the various granulating methods are quite different. The packing arrangements, in turn, are mainly determined by the shape of the granules in this size range (28), leading to the conclusion that the particles from the different granulations have very dissimilar shapes. This fact will become more apparent in the following discussion on shape volume factors.

Shape Volume Factor, α_v.—The shape volume factors shown in Table II were computed from Eq. 8 using 100–150 particles of each granulation. Since α_v is dependent upon the geometrical form and proportions of a particle (25), the shape volume factor was plotted against bulk density to establish the existence of a correlation between these parameters (Fig. 1). The linear correlation coefficient was 0.952, indicating that the bulk densities of the particles studied are related to their respective shape volume factors.

Since the densities of the particles from the various granulations differ, the bulk density values are not only a function of the void spaces but also a function of the granule densities, ρ_g. Therefore, the bulk volumes per constant volume of granules, V_b', were calculated since, as seen from Eq. 10, they are independent of granule density. Figure 2 is a plot of values for V_b' given in Table II *versus* shape volume factor. The correlation coefficient in this instance was 0.965.

In an effort to obtain even better correlation for terms representing particle shape and packing volume, a factor for the geometrical form, k_e, was calculated. These values, also listed in Table II, have been plotted against the bulk volume per con-

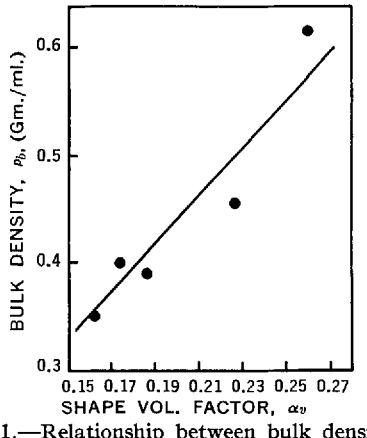

Fig. 1.—Relationship between bulk density and shape volume factor of 20/30-mesh particles prepared by 5 different granulation methods.

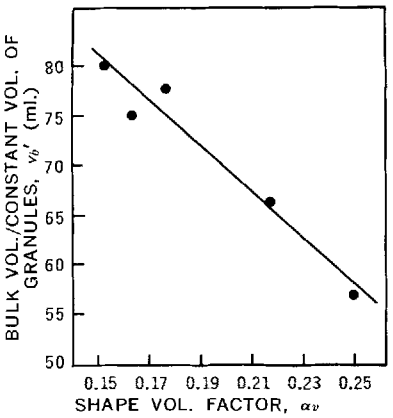

Fig. 2.—Relationship between bulk volume per constant volume of granules and shape volume factor of 20/30-mesh particles prepared by 5 different granulation methods.

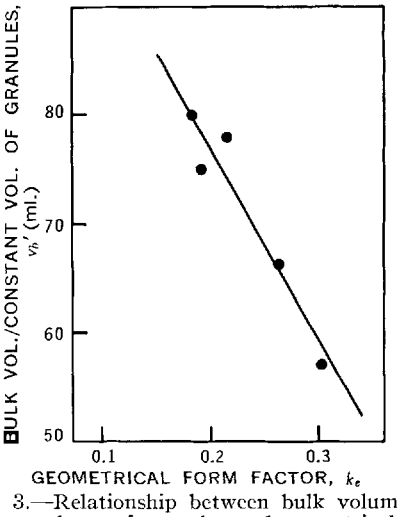

Fig. 3.—Relationship between bulk volume per constant volume of granules and geometrical form factor of 20/30-mesh particles prepared by 5 different granulation methods.

stant volume of granules in Fig. 3. The linear correlation coefficient was 0.961.

The interspace porosity, e_i, is defined as:

$$e_i = 1 - \frac{\rho_b}{\rho_g} \qquad \text{(Eq. 13)}$$

When this parameter was plotted as a function of the shape volume factor, a correlation coefficient of 0.914 was obtained.

Thus, the best correlation was obtained when the bulk volume was plotted against either the shape volume factor or its analog, the geometrical form, indicating that the volume of a packing of particles is a function of their geometrical form and proportions. This finding is important since the easily computed values of V_b' may be used to quickly evaluate procedures in which attempts are being made to obtain spherical particles or granules for coating and/or sustained-release requirements.

To check the accuracy of the computed α_v values, the number of particles per gram, N, was calculated for 20/30-mesh particles from the various granulation methods and compared with those values of N obtained experimentally by counting and weighing techniques. From Eq. 3, and since $N = 1/V\rho_g$ then:

$$N = \frac{1}{\alpha_v \rho_g d_e^3} \qquad \text{(Eq. 14)}$$

where N, α_v, d_e, and ρ_g are as previously defined.

A comparison of the values for N from the 2 techniques is given in Table III. It is readily apparent that the 2 sets of data are in excellent agreement.

Table III.—Comparison of Experimental and Computed Values of N, Number of Particles/Gm., for 20/30-Mesh Fraction

Granulation Method	Exptl. N[a]	Computed N
Liquid-solids V-blender	5527	5606
Colton upright	5759	5782
Fitzpatrick comminutor	6405	6359
Oscillating granulator	6748	6703
Hand screen	7753	7677

[a] These values were obtained from Table II.

Characterization of Granulation Methods.—On the basis of the repose angle studies, those particles prepared from the oscillating granulator were found to have the smoothest surface and can therefore be expected to possess the best flow properties. In addition, these particles were the hardest, even though the percentage of granulating agent used was relatively low (see Table I), indicating that the force of compaction produced by this granulator is high. Due to their relatively high density, the *intraspace* porosity of these particles is low in comparison to granules produced from the other pieces of granulating equipment. These particles are asymmetric, as evidenced by their low shape volume factor.

Since granules possessing smooth surfaces can be uniformly coated more easily than those with uneven surfaces, the oscillating granulator might be expected to produce particles well-suited for film coating purposes. Furthermore, since these were also the hardest granules of those studied, particle breakdown during the coating operation would be at a minimum.

Granules produced from the liquid-solids V-blender and the Fitzpatrick comminutor are relatively porous as evidenced by their granule densities. This was confirmed by the heterogeneous "optical density" of the particles when viewed with the projection microscope. On the basis of shape volume factors, granules from the liquid-solids V-blender and the Fitzpatrick comminutor were the most symmetrical on a volume basis. As a result, these particles assume a very close packing arrangement which is reflected in their high bulk density and low bulk volume. However, because of their surface irregularities, these particles can be expected to have only from average to poor flow properties, since this latter factor is more dependent on surface characteristics than general shape factors. From a consideration of the low density and hardness values for the granules produced by the liquid-solids V-blender and

the Fitzpatrick comminutor, it is apparent that the force of compaction in these 2 pieces of equipment is less than that produced by the oscillating granulator.

Particles produced by use of the hand screen method were intermediate between the 2 groups of granules previously discussed, with respect to repose angle, density, hardness, bulk density, and bulk volume. The number of particles per gram for this granulation was the highest of the 5 granulations; this was due to the low average volume for these particular granules.

Particles produced from the Colton upright were found to be the least spherical, an observation confirmed by the low value for the shape volume factor. These granules, not unexpectedly, also had the lowest bulk density of those studied. The fact that these particles had the highest value for the equivalent projected diameter over the size range of particles studied, accounts for their low degree of symmetry.

SUMMARY

Five standard granulation methods were compared on the basis of the following physical properties of the granules they produced: (*a*) repose angle, (*b*) granule density, (*c*) hardness, (*d*) number of particles per gram, (*e*) bulk density, (*f*) shape volume factor, (*g*) bulk volume per constant volume of granules, and (*h*) geometrical form.

Useful techniques were developed for obtaining some of the more important physical parameters of pharmaceutical granular solids. Particular attention was focused on developing an accurate technique for evaluating the shape volume factor, a parameter important in characterizing the over-all shape of a particle.

The repose angle was found to be primarily a function of surface roughness; in addition, the bulk volume was inversely proportional to particle shape. Thus, the researcher is provided with 2 easy techniques for assessing procedures aimed at producing smooth, spherical pharmaceutical particles.

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