Technical Articles

Granulation of Griseofulvin

By C. F. HARWOOD and N. PILPEL

Griseofulvin, in fine and coarse grades, has been bowl granulated using binder solutions. The granules have been assessed for strength and flow characteristics. A mechanism of granule growth has been suggested, which satisfactorily explains the experimental results.

GRISEOFULVIN tablets are normally prepared from granules containing griseofulvin powder. Granulation facilitates handling, prevents segregation in the formulated mix, and eliminates the problem of dust. Methods of granulation include slugging, wet granulation, spray drying (1, 2), bowl and dish granulation (3, 4). In bowl granulation, the powder is rotated in a tablet coating pan and is lightly sprayed with binder solution which causes it to aggregate into granules. Dish granulation is similar, but involves the use of a low walled dish which is tilted to the horizontal. This is a continuous process for obtaining uniform granules. Both techniques yield a smooth, rounded product, and theories concerning them have been developed by Newitt and Conway-Jones (5), Capes and Dankwerts (6), and by Rumpf (7).

The purpose of this investigation has been to granulate two grades of powdered griseofulvin in order to study the effect of the starting powder on such properties of the granules as their shape, density, and flow characteristics. No excipients were used, but the pharmaceutical grade of polyvinylpyrrolidone,[1] was employed in various concentrations as a binder and a study made of its effects on the strengths of the resulting granules.

EXPERIMENTAL

Materials—Two closely sized pharmaceutical grades of griseofulvin were used, the fine grade (USP microfine grade) having an average particle size of 4 μ, as measured on the Fischer subsieve sizer, and the coarse grade an average particle size of 10 μ. The actual size data, obtained by Coulter counter measurements (8), are given in Table I.

Water and aqueous solutions of polyvinylpyrrolidone (PVP), in 5, 10, 15, and 20% concentrations by weight, were used as the binding fluids.

Granulation Method—Four hundred grams of powder was placed in a 16-in. copper tablet coating pan, mounted on a Manesty Varispeed motor, which was rotated at 30 r.p.m. The binding liquid was sprayed tangentially onto the powder from a Burgess electric spray, type VS 625, in 2-sec. periods every 10 sec. for approximately 15 min. The granules formed without the provision of flights and quickly attained a limiting size. Rotation was continued for a further 15 min., while warm air was blown into the bowl, and the granules were finally dried in shallow trays for 12 hr. at 70°.

Batches were also prepared using a dish granulator of 60-cm. diameter, with 5-cm. walls, tilted at 45° and rotated at 15 r.p.m. In both methods the coarse powder yielded rounded granules but the fine material produced only irregular granules, when viewed under a low power microscope, even when all the operating variables were altered. In further attempts to produce rounded granules from the fine powder, alcohol–water and acetone–water solutions and methylcellulose solution in water were also used as binding fluids; all, however, were unsuccessful.

Measurements on the Granules—*Sieving*—The granules were separated into size fractions by sieving for 10 min. on a vibration sieve. Surface fines were removed by resieving 30-Gm. portions for 1 min. on the Alpine airjet sieve. Microscopic examination confirmed that the granule fractions were uniform in size and free from fines.

PVP Content—The PVP contents of the granules were measured by extracting a known weight with boiling water, filtering, evaporating the filtrate to dryness, and weighing the extracted PVP. Blank tests were conducted using griseofulvin powder and PVP powder alone.

Granule Strength—The breaking strengths of individual granules were measured by raising single granules on a flat plate by means of a lab jack, just into contact with a second flat plate fixed to the underside of a chemical balance pan (Fig. 1). Lead shot was poured steadily onto the balance pan until the granule broke. The weight of the lead shot was then taken as the breaking load. Typical results are recorded in Table II.

Granule Porosity—This is given by the expression:

$$\text{porosity} = \frac{\text{void vol.}}{\text{total vol.}} \times 100$$

where the void volume $= (1/\rho_G - 1/\rho_p)$. The granule density, ρ_G, was determined from the weight

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[1] Plasdone.

TABLE I—PARTICLE SIZE DISTRIBUTION OF GRISEOFULVIN[a]

Fine Grade						
Particle size, μ	<1	1–2	2–3	3–5	5–10	>10
Wt. Percentage	3	31	30	29	8	9
Coarse Grade						
Particle Size, μ	2–5	5–10	10–20	20–30	30–60	>60
Wt. Percentage	10	15	35	20	15	5

[a] Abstracted from *Reference 8*.

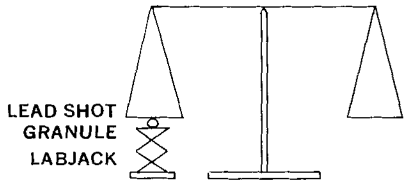

Fig. 1—Granule strength testing apparatus.

TABLE II—BREAKING STRENGTH OF 6–8 MESH GRANULES CONTAINING PVP

PVP Content, %				
0	0.6	1.0	1.6	3.6
Breaking Load, Gm.				
5	65	180	270	450
15	60	230	420	660
20	80	280	400	570
10	75	215	260	640
5	70	320	350	590

and volume of about 200 granules and the powder density, ρ_p, was determined by the British Standards specific gravity bottle method.

Bulk and Tapped Density—Bulk and tapped density values were measured in the Heywood apparatus, using the method described in British Standards 1440.

Granule Flow—The flow of granules in each size fraction was measured from a vertical copper tube of internal diameter 3.8 cm., fitted with a flat base plate with circular orifices of 0.605, 0.707, 0.900, 1.130, 1.330, and 1.650 cm. diameter (9).

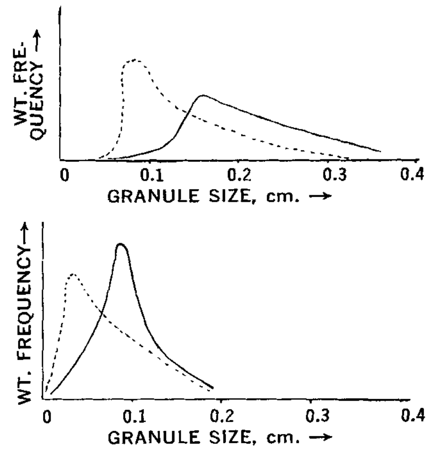

Fig. 2—Histograms. Top, fine grade, yielding irregular granules. Bottom, coarse grade, yielding rounded granules. Key: ——, granulated with 20% PVP solution; - - -, granulated with water.

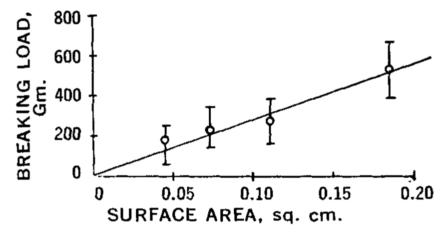

Fig. 3—Increase in granule strength with surface area.

RESULTS

The histograms of the granules formed from the fine and from the coarse grades of griseofulvin are shown in Fig. 2. It is seen that the 20% PVP binder solution leads to a slight increase in granule size, compared to water as a binder. As the two liquids have practically the same surface tensions, 64 and 72 dynes/cm., respectively, the effect is probably due to their different viscosities, 40 cps. and 1 cps., respectively. The surface tension force holding two particles together is enhanced if the liquid between the particles has a high viscosity; this is because the liquid has a resistance to deformation, which would result from separation. Thus the "suction" pressure increases with the rate of particle separation and a bond, once formed, resists separation (10).

Table III shows that the PVP content of the different size fractions varies through a particular granule batch. During granulation, segregation of sizes occurs so that particular fractions may be favorably presented to the binder spray, and this would account for the variation.

Figure 3 shows that a definite relation exists between granule strength and granule size (*i.e.*, surface area) and that within limits the relation, granule strength = $k \times$ surface area, is applicable. Figure 4 indicates that the granule strength in a particular size group depends on the PVP content. In both cases, considerable scatter of results occurs and this was observed also by Rumpf (7) when measuring the tensile strength of moist granules.

Average porosity values are given in Table IV for the two grades of powder and for the rounded granules containing PVP. These results may be

TABLE III—VARIATION IN PVP CONTENT WITH GRANULE SIZE

B.S. Sieve Size	6–8	8–10	10–12	12–16	16–22
μ Size	2800–2000	2000–1680	1680–1400	1400–1000	1000–710
% PVP	3.6	3.1	2.9	3.9	4.2

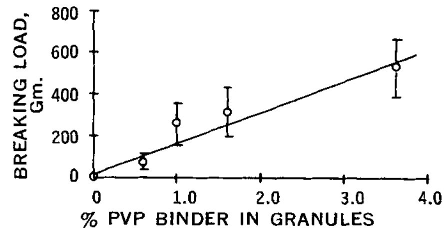

Fig. 4—Variation in breaking load with PVP content for 6–8 mesh granules.

TABLE IV—POROSITY OF GRISEOFULVIN POWDER AND GRANULES

Sample	Bulk Powder Coarse	Bulk Powder Fine	Rounded Granule Size B.S.S. 8–10	10–12	12–16
Porosity	80	74	43	42	30

TABLE V—POROSITY OF SPHERES IN IDEAL PACKINGS

Three-Dimensional Arrangement of Spheres			
90°	60°	60°	60°
90°	90°	60°	60°
90°	90°	116°34′	90°
Porosity, %			
47.6	39.5	30.2	25.9

compared with those quoted by Ono and Taneya (11) for hard, ideal spheres in loosely packed and tightly packed states, Table V. The fine and coarse griseofulvin powders have a high porosity, indicating bridging by the cohesive forces: these forces are overcome by the granulation process and a tighter state of packing is achieved.

Bulk and tapped density figures are plotted in Fig. 5, which shows that, because of their geometry, rounded granules pack together more closely than irregular granules. Typical flow rates for the two types of granules through a particular sized orifice are plotted in Fig. 6. The flow rate of rounded granules is seen to be considerably higher than of irregular ones.

DISCUSSION

Some understanding of the growth of granules during granulation can be gained by considering the centrifugal forces acting on two coalescing granules. The values given in Table VI are calculated for equal sized granules by assuming that one of them is thrown around the other with a speed equal to that of the peripheral speed of the drum.

The centrifugal force at the point of coalescence would have to be balanced by the number of pendular bonds acting between individual particles. The value of the pendular bonds can be calculated from (12):

$$F = \frac{2\pi r T}{1 + \tan \theta}$$

where F is the bond strength in dynes, r is the radius of the particles, T is the surface tension of the binder solution, and θ is related to the quantity of binding liquid forming the bond. The values of the pendular bond strengths, calculated for different particle sizes, are given in Table VII, taking θ as 14°.

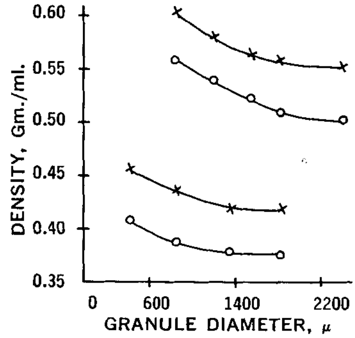

Fig. 5—Bulk and tapped densities against granule diameter. Key: ×, tapped density; ○, bulk density. Top, rounded granules; bottom, irregular granules.

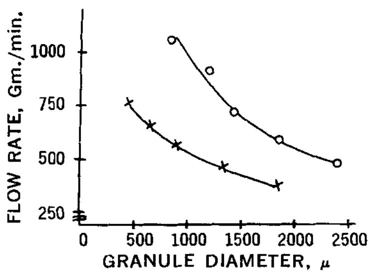

Fig. 6—Granule diameter against flow rate through 1.330-cm. orifice. Key: ○, rounded; ×, irregular.

TABLE VI—CENTRIFUGAL FORCE FOR DIFFERENT GRANULE DIAMETERS

Granule Diam., cm.			
0.05	0.1	0.5	1.0
Centrifugal Force, dynes			
7.24	28.9	724	2890

TABLE VII—PENDULAR BOND STRENGTHS AT DIFFERENT PARTICLE SIZES

Particle Size, μ			
4	10	50	200
Bond Strength, dynes			
6.4×10^{-2}	1.6×10^{-1}	8.0×10^{-1}	3.2

The limit of growth by coalescence is probably about 0.5 cm., since, above this size, the centrifugal force becomes very large. However, growth can continue by a secondary process in which small granules are crushed by larger ones (6); the fragments then join the larger granule by coalescence. The limit of growth probably occurs when the crushing effect becomes so frequent that granules are prevented from reforming.

In the case of griseofulvin, in fine and coarse grades, the limit of growth is quickly reached, due to the weak pendular bonds formed at small particle sizes. Thus the granule size at which crushing occurs is never reached.

In the dry state, the strength of a granule is due to the cohesive forces in the griseofulvin and, to a larger extent, to the solid bridges formed from the evaporated binder. PVP in the solid state is an extremely brittle substance and the large strength variation (Figs. 3 and 4) is consistent with the theory of brittle solids proposed by Griffith (13). Dollimore and Gregg (14) have shown that the ratio of the theoretical strength, R_m, to the practical strength, R, is given by:

$$\frac{R_m}{R} = \left(\frac{\pi c}{a}\right)^{\frac{1}{2}}$$

where a is the range of the attractive forces, and $2c$ is the length of a crack in the brittle solid. Taking $a \approx 3 \times 10^{-8}$ cm., and $c \approx 1 \times 10^{-4}$ cm., then a crack of only 2 μ in the binder would cause a 100-fold reduction of strength. The strength of the granules would also be expected to vary due to irregularities in their shape and the presence of localized powder or binder voids.

CONCLUSION

Griseofulvin can be granulated by the bowl method and the strength of the granules formed has been shown to be dependent on both their size and on their PVP content.

It appears to be more difficult to prepare smooth, rounded granules with good flow and storage characteristics from the fine grade than from the coarse grade, although the former is preferred for therapeutic reasons.

REFERENCES

(1) Bailey, L. H., in "Chemical Engineering Handbook," 3rd ed., Perry, J. H., ed., McGraw-Hill, London, England, 1950, p. 1186.
(2) Davies, E. W., and Wade, H. H., *Mines Exptl. Sta. Univ. of Minn. Circ. No. 6*, 1951.
(3) Tuerck, P. A., Walters, E. L., and Carkhuff, E. D., *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 344 (1960).
(4) Segovia, E., *Acta Pharm. Suecica*, **4**, 171(1967).
(5) Newitt, D. M., and Conway-Jones, J. M., *Trans. Inst. Chem. Eng.*, **36**, 422(1958).
(6) Capes, C. E., and Dankwerts, P. V., *ibid.*, **43**, 116 (1965).
(7) Rumpf, H., "Agglomeration," Knepper, W. A., ed., Interscience, Publishers, Inc., New York, N.Y., 1962.
(8) Mathews, B. A., and Rhodes, C. T., *J. Pharm. Sci.*, **56**, 838(1967).
(9) Jones, T. M., and Pilpel, N., *J. Pharm. Pharmacol.*, **18**, 81(1966).
(10) Hiestand, E. N., *J. Pharm. Sci.*, **55**, 1325(1966).
(11) Ono, E., and Taneya, S., *Funtai Oyobi Funmatsuyakin*, **10**, 19(1963).
(12) Fischer, R. A., *J. Agr. Sci.*, **15**, 529(1925).
(13) Griffith, A. A., *Phil. Trans. Roy. Soc. London*, **221**, 163(1920).
(14) Dollimore, D., and Gregg, S. J., *Res. (London)*, **11**, 180(1958).

Keyphrases

Griseofulvin
Granulation, griseofulvin—bowl, dish methods
Polyvinylpyrrolidone solution—binder
Granule strength, porosity, sizing, flow rate
Density, bulk, tapped—granules
Centrifugal force—granule diameter
Pendular bond strength—particle size

"Crushing-Strength" of Compressed Tablets I

Comparison of Testers

By DAVID B. BROOK and KEITH MARSHALL

By means of a piezo-electric force transducer the actual compressional load exerted at certain scale readings by four types of commercially available "crushing-strength" instruments has been determined. The results indicate that variations in crushing-strength values between instruments are due in part to inaccuracies in instrument scale values, zero errors and varying methods of applying the load. Calibration is therefore necessary for accurate measurements using one instrument or when comparing results from more than one tester.

The mechanical strength of medicinal tablets is an important property of this form of drug presentation and plays a significant role in development and control procedures. It has been described by various terms including "fracture resistance" (1), "friability" (2), "hardness" (3), "bending strength" (4), and "crushing-strength" (5). Measurement of the latter is probably the most widely used technique and may be precisely defined as "that compressional force which, when applied diametrically to a tablet, just fractures it." In most cases the tablet is placed upon a fixed anvil, and the force is transmitted to it by means of a moving plunger.

Crushing-strength is widely employed in commercial production as a control procedure and has been compared by several authors with other properties of the tablet (5–9). Many individual instruments for crushing-strength determinations have been described (3, 9–12) and comparisons between commercially available testers made (3, 11, 13).

In the present investigation a comparative study, against an absolute standard has been made on four commercially available instruments, "Strong-Cobb," "Monsanto," "Pfizer," and "Erweka" hardness testers.

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