

mined from results with ejected tablets indicate that higher pressures are needed to fill the interparticulate void space than are in fact necessary. The effect of particle size is less clearly defined in the values of k_1 and k_2 but, again, there is the indication that the 75–104- μ m. size fraction is the most resistant to deformation.

These results deal only with samples of lactose. When taken in conjunction with the previous work (1, 2, 4), the conclusion possibly could have application to other materials.

CONCLUSIONS

1. For tablet volumes determined at pressure, the smaller the original particle size, the greater is the relative volume at all applied pressures.

2. For tablet volumes determined after ejection from the die, the difference in relative volume between the two larger particle-size fractions is considerably reduced. The relative volumes for tablets prepared at slow compaction are lower than those of the two larger particle-size fractions, but the opposite is true for tablets prepared at the higher rate of compaction.

3. Calculation of the densification due to particle rearrangement by the method of Heckel (2) shows that the smallest size fraction undergoes the greatest rearrangement both at slow and high speed compaction. Particle rearrangement is generally greater for the spray-dried lactose.

4. Calculation of the densification due to particle rearrangement by the method of Cooper and Eaton (4) confirms this finding for crystalline lactose. The results for spray-dried lactose are, however, inconclusive.

5. The yield pressure calculated from the slope of the densification–pressure curves of Heckel (2) indicates that the middle size fraction has the highest value for both compaction systems and methods of measuring tablet density. The yield pressures are higher for tablets ejected from the die.

6. The yield pressure for spray-dried lactose is generally lower than for crystalline lactose.

7. The pressures necessary to fill the voids of smaller sizes than the particles, *i.e.*, those required to cause particle fracture and plastic flow, are always higher than the pressures necessary to fill the voids of the same dimensions as the particles, *i.e.*, to effect particle rearrangement.

REFERENCES

- (1) C. L. Huffine and C. F. Bonilla, *Amer. Inst. Chem. Eng. J.*, **8**, 490(1962).
- (2) R. W. Heckel, *Trans. AIME*, **21**, 671(1961).
- (3) J. A. Hersey and J. E. Rees, *Particle Size Analysis Conference*, Bradford, England (1970).
- (4) A. R. Cooper, Jr., and L. E. Eaton, *J. Amer. Ceram. Soc.*, **45**, 97(1962).
- (5) J. T. Fell and J. M. Newton, *J. Pharm. Sci.*, **59**, 688(1970).
- (6) J. H. Verhoog, *Neth. Milk Dairy J.*, **17**, 233(1963).
- (7) M. Bada and N. Nagufuji, *Ann. Rep. Shionogi Res. Lab.*, **1965**, 138.
- (8) W. A. Gray, "The Packing of Solid Particles," Chapman and Hall Ltd., London, England, 1968, p. 51.

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* Pharmacy Department, The University, Manchester, 13, England.

Batch Production of Pharmaceutical Granulations in a Fluidized Bed I: Effects of Process Variables on Physical Properties of Final Granulation

WILLIAM L. DAVIES and WALTER T. GLOOR, Jr.*

Abstract □ The investigation concerns the effects of process variables associated with the fluidized bed granulation technique on the physical properties of the final granulation. The process variables investigated include binder solution addition rate, air pressure to the binary nozzle, inlet air temperature during the granulation cycle, and binary nozzle position with respect to the fluidized solids. When the rate at which the aqueous binder solution added to the fluidized bed of powders was increased, the ability of the solution to wet and penetrate the solids was enhanced, resulting in: (a) a larger average granule size, (b) a less friable granulation, (c) a more fluid granulation, and (d) a decreased granulation bulkiness.

Similar results, also traceable to enhanced binder solution efficiency, occurred with a decrease either in the binary nozzle air pressure or in the inlet air temperature during the granulation cycle. The position of the binary nozzle with respect to the fluidized powders had significant effects upon the average granule size and granule friability. The effects upon the granulation flow properties and bulkiness, however, were slight.

Keyphrases □ Granulation, fluidized bed—effects of process variables on granule and tablet physical properties □ Fluidized bed granulation—effects of process variables on granule and tablet physical properties

Although fluidization theory and techniques have been known for many years and have been discussed extensively in the literature (1–5), pharmaceutical applications in this area are relatively recent. Uses have been limited to the drying (6–9) and coating (10–16) of solids; there has been little investigation in the area of granulation.

Granulation in a fluidized bed for tableting purposes was first introduced by Wurster (11). He determined material loss from the column and the drug and moisture content of the final granulation. Theory, design, and operation of equipment for the continuous production of tablet granulations in a fluidized bed were presented by Scott *et al.* (17) and Rankell *et al.* (18).

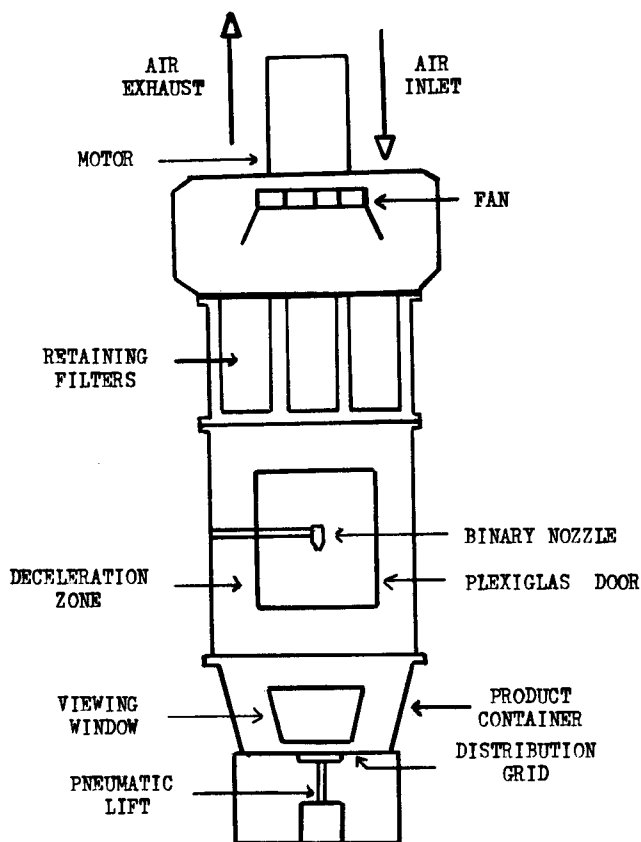


Figure 1—Fluid bed spray granulator.

In addition to material and energy balances and heat and mass transfer relationships, the authors investigated the performance of the continuous process with regard to entrainment loss, cyclone efficiency, granule compressibility, etc.

The intent of the present investigation was to determine the effects of process variables associated with the fluidized bed granulation technique on the physical properties of the final granulation.

EXPERIMENTAL

Materials and Formulation—The materials used were lactose USP¹, cornstarch², magnesium stearate USP³, gelatin powder USP⁴, and benzene⁵.

The following formulation was used for all batch granulation operations:

	Percent w/w
Hydrous lactose USP	86.0-87.5
Cornstarch	10.0
Magnesium stearate USP	0.5
Gelatin USP	2.0-3.5
Distilled water	—

This classical formulation was chosen since each ingredient is widely accepted in pharmacy for the function it serves. To maintain a constant batch size of 10 kg. and to minimize effects on the physical properties of the granulations, the concentration of the major ingredient, lactose, was altered to compensate for the amount of dry

Table I—U. S. Standard Sieves and Sieve Openings

Sieve Number	Sieve Opening, μ
20	840
30	595
40	420
50	297
60	250
80	177

binder in a particular batch. The gelatin binder solution was prepared by first thoroughly hydrating the gelatin powder in 2 kg. of distilled water for 10 min. The slurry, contained in a double boiler, was then gradually heated with stirring to 80°, the temperature at which the solution was used.

Equipment—A fluid bed spray granulator⁶ (Fig. 1) was used in the preparation of all granulations. The granulator is a 10-25-kg. product capacity, stainless steel, combination fluid bed granulator and dryer. Ambient air is drawn through an inlet damper into the unit by means of a motor and fan located at the top of the granulator. The inlet air is prefiltered through fiberglass filters before passing over steam-heated coils for inlet air temperature control. A thermostat on the face of the unit regulates the steam feed to the coils. The filtered, temperature-controlled air is drawn up through a distribution grid and 60-mesh stainless steel screen at the bottom of the product container. In addition to product support, the grid and screen serve to distribute the fluidizing medium evenly over the cross section of the granulator. The diameter of the product container increases from 35.6 cm. (14 in.) at its base to 53.3 cm. (21 in.), the diameter of the expansion chamber. This chamber serves as a product deceleration zone.

A movable, binary atomization nozzle for liquid addition is centered in the expansion chamber. Spray from the nozzle is in a downward direction, countercurrent to the air flow. At the top of the expansion chamber, a nylon filter prevents fine particle entrainment losses as the air exits through an exhaust duct to the exterior of the building. For purposes of removing fines or low density powders from the filter surface, a pneumatically activated shaking device is attached to the filter frame. Air volume requirements for fluidization are controlled by the inlet and exit dampers. For air volume measurements, a pitot tube connected to a standard pressure gauge⁷ is installed in the exhaust duct. Dry bulb thermometers are inserted below the distribution grid and just above the nylon filter for inlet and outlet air temperature measurements, respectively.

Granulation and Drying—The lactose and cornstarch were weighed directly in the product container using a scale⁸. The container was pneumatically locked in place in the granulator prior to initiation of the granulation cycle. The following machine settings were maintained throughout the study unless otherwise specified. The inlet air temperature was adjusted to 50° by the thermostat for the granulation cycle. The fluidizing air volume was maintained at approximately 350 cu. ft./min. by adjusting the inlet and exit dampers. The binary nozzle was centered in the expansion chamber 72.4 cm. (28.5 in.) above the distribution grid. An air pressure to the nozzle head of 1.5 kg./cm.² was maintained for atomization of the binder solution. The air dome on the nozzle head was set in the number four position. (The dome setting regulates the diameter of the spray cone and is adjusted to prevent contact between the atomized binder solution and the walls of the granulator.)

The powders in the product container were mixed by fluidization for 1 min. prior to the addition of the binder solution. Because of the nature of particle movement in the fluidized bed, ideal mixing of powder blends is accomplished in this relatively short time (2). Upon completion of the mixing operation, the binder solution was pumped in an atomized form into the fluidized bed of powders by means of a calibrated metering pump and the binary spray nozzle system.

Since all binder solutions were aqueous and the total weight of water in each solution was constant, the total weight of solution was dependent upon the weight of solid binder employed for any one particular granulation. The degree of wetting imparted to the fluid-

¹ Hydrous powder, Mallinckrodt Chemical Works, St. Louis, Mo.

² Buffalo brand starch, Corn Industries, Cherry Hill, N. J.

³ Mallinckrodt Chemical Works, St. Louis, Mo.

⁴ Allied Chemical, Industrial Chemicals Division, Morristown, N. J.

⁵ Thiophene free, certified ACS, Fisher Scientific Co., Fair Lawn, N. J.

⁶ Glatt model WSG-15, Fa. W. Glatt, Haltingen, West Germany.

⁷ Dwyer Instruments, Inc., Michigan City, Ind.

⁸ Model 2131, Toledo Scale, Division of Reliance Electric Co., Toledo, Ohio.

Table II—Effects of Addition Rate of the Binder Solution on Physical Properties of the Granulation

Addition Rate, g. H ₂ O/min.	Average Granule Size, μ	Friability, %	Bulk Density, g./ml.	Granule Density, g./ml.	Porosity, %	Flow Rate, g./min.
85	240	15.6	0.41	1.484	72.37	154.1
100	256	11.3	0.44	1.489	70.45	167.0
115	263	8.6	0.46	1.489	69.11	172.4
130	271	8.4	0.46	1.489	69.11	179.6
145	278	6.9	0.48	1.493	67.85	182.9

ized powders was, therefore, dependent upon the addition rate of water rather than total binder solution. To keep the wetting rate constant for varying concentrations of binder solutions, the metering pump was adjusted to deliver 100 g. of water to the powdered bed per minute.

Once granulation of the powders was completed, the metering pump for binder addition was turned off; the drying cycle was initiated by elevating the inlet air temperature to 65° by means of the thermostat. The granulations were dried to an outlet dry bulb temperature of 49°. The exhaust dry bulb temperature is critical, since it is related to the product moisture content. The shaking device for the exhaust filter was activated several times during both the granulation and drying cycles to prevent accumulation of fine powders on the filter surface. Magnesium stearate, previously screened through a 60-mesh screen, was then distributed over the dried granules, and the granulations were fluidized for 1 min. to disperse the lubricant on the surface of the granules. The lubricated granulations were allowed to cool to room temperature in the product container prior to transfer to polyethylene bags for storage.

Physical Properties of Granulations—Granule Size—The average granule size was determined by sieve analysis. Six U. S. Standard sieves (Table I) were nested in descending order with respect to screen opening. Approximately 100 g. of granulation was placed on the top sieve, and the sieves were shaken for 5 min. at 800 vibrations/min. using a sieve shaker⁹.

The average granule size on any sieve was determined in microns by averaging the size of the openings of the sieve through which the granules passed and the size of the openings of the sieve upon which the granules were retained. The weight retained on each tared sieve was converted to percent retention and multiplied by the average granule size on that sieve. The sum of these products divided by 100 (percent) yielded an average granule size. Sieve analyses were performed for each batch of granulation in triplicate, and reported results are average values.

Granule Friability—Granule friability was determined using a modification of the ASTM test for the friability of coal (19). A 100-g. sample of the 40/50- (passed/retained) mesh fraction of granulation was placed in a 1-l. jar and rotated in a shaker-mixer¹⁰ for 30 min. at 100 r.p.m. The sample was then placed on the top sieve in a descending series of four U. S. Standard sieves (numbers 50, 60, 80, and 100). The sample was shaken for 5 min. as previously described. The size distribution was determined, and the percent friability of the sample was calculated (20). Percent friability determinations were made in triplicate and averaged. In no instance did an individual granulation range in friability by more than 0.5%.

Density—A loose bulk density measurement was made on all granulations. Thirty grams of a granulation was poured through a standard 12.7-cm. (5-in.) diameter, short-stem glass funnel into a 100-ml. graduated cylinder. The orifice of the funnel stem was aligned with the 100-ml. graduation on the cylinder. The volume occupied by the granulation was read to the nearest 0.5 ml., and the loose bulk density was calculated in grams per milliliter. The bulk densities recorded are averages of six determinations.

Granule density was determined by a method outlined by Bauer and Lewin (21). Approximately 3 g. of granulation was accurately weighed to the nearest 0.1 mg. and transferred to a 25-ml. pycnometer. Enough benzene was added to fill the pycnometer, and the total weight was accurately determined. All granule density determinations were made at 25°. Since this procedure is limited to solids heavier than, and insoluble in, the displacement medium, and to ensure that water would not interfere with the determinations, the benzene was dried with metallic sodium prior to use.

Reported granule densities are averages of six determinations.

Porosity—Using the method of Martin (22), percent interparticulate porosity was calculated for each granulation from the bulk and granule density measurements obtained from the individual granulations:

$$\%e = 1 - \rho b / \rho g \quad (\text{Eq. 1})$$

where ρb is the bulk density and ρg is the granule density.

Flowability—Granule flowability was measured using a standard glass funnel of 100-mm. diameter, 60° bowl angle, with a 36-mm. stem length and a 6-mm. internal stem diameter. The funnel was equipped with a stopper in the stem orifice and was supported by a ring stand. Seventy-five grams of granulation was carefully poured into the funnel, the stopper was removed, and the flow rate of the granulation was determined to the nearest 0.3 sec. Reported flow rates are averages of six determinations.

All granules exceeding 1680 μ (12 mesh) were removed from the granulations prior to flowability studies to prevent interferences in granulation flow through the exit orifice. In no instance did this size granule exceed 0.1% of the total granulation. To minimize relative humidity effects on granulation flow, all granulations were allowed to equilibrate at 45 ± 5% relative humidity prior to determining flow rates under these humidity conditions.

Percent Loss on Drying—Percent loss on drying of each granulation was determined gravimetrically using a moisture balance¹¹. All samples were dried on the balance to an equilibrium loss on drying.

RESULTS AND DISCUSSION

Since, in the preparation of pharmaceutical granulations, drying is one of the most critical of all operations, this stage was of primary importance in the operation of the fluid bed spray granulator. To minimize the effects of moisture on the physical properties of the granulations, it was desirable to dry all batches of granulations to a constant percent loss on drying value. Drying was conducted to an exhaust dry bulb temperature of 49° for all granulations. This temperature, in equilibrium with the fluidized solids temperature (9), yielded an indication of the dryness of the product. While this exhaust air temperature-moisture content relationship may vary with the granulation, depending upon its content and physical properties, all batches in this investigation differed only by the 2–3.5% solid binder concentration, and drying to an exhaust air temperature of 49° produced granulations with percent moisture loss on drying values of 2.10 ± 0.15.

The success of granule formation depended upon a number of operational variables associated with the fluid bed granulator. The most influential variables appear to include: (a) the addition rate of the binder solution, (b) the degree of atomization of the binder solution, (c) the temperature of the fluidizing medium during the granulation cycle, and (d) the position of the binary nozzle with respect to the fluidized solids. The effects of these factors on the physical properties of the resulting granulations were investigated.

The effects on granule formation of the rate of binder solution addition to the fluidized powders are depicted in Table II. Twenty-two hundred grams of a 9.1% w/w gelatin solution was introduced at varying rates to the fluidized batches of the standard lactose formulation, with resultant influences on the physical properties of the granulated products. An enlargement in the average granule size was noted with each increase in the rate of addition of the binder solution. This growth in granule size may be attributed to an increase in the penetration and wetting capabilities by the aqueous

⁹ Fisher Wheeler, Fisher Scientific, Boston, Mass.

¹⁰ Turbula, Willy A. Bachofen, Basel, Switzerland.

¹¹ Model 6000, Ohaus Corp., Union, N. J.

Table III—Effects of Inlet Air Temperature during the Granulation Cycle on Physical Properties of the Granulation

Inlet Air Temperature	Average Granule Size, μ	Friability, %	Bulk Density, g./ml.	Granule Density, g./ml.	Porosity, %	Flow Rate, g./min.
25 \pm 2°	311	6.2	0.54	1.492	63.81	196.1
40 \pm 2°	272	7.1	0.50	1.497	66.60	192.9
50 \pm 2°	249	11.8	0.44	1.502	70.71	168.8
55 \pm 2°	235	14.7	0.41	1.495	72.58	160.1

binder solution, which was brought about by the increased liquid flow through the atomization nozzle. Larger spray droplets of binder solution per unit of time resulted in an overall slower rate of evaporation of the solvent by the drying medium.

The friability test is based upon the assumption that weak granules will disintegrate when agitated in a shaker device, whereas strong granules will lose only their surface roughness. Results of the friability tests show decreased friability with increased rates of addition of the binder solution. Just as granule size may be increased by the greater wetting ability of the binder at higher rates of addition, less friable granules are formed by augmenting the wetting and penetration capabilities of the binder solution.

The bulk density of a granulation is primarily dependent upon particle size, particle-size distribution, particle shape, and cohesive forces (23, 24). Small granules have a low free-fall velocity and a high surface-to-mass ratio, a combination that reduces the amount of granule movement as the sample granulation is poured into a cylinder for bulk density measurement. In addition, the greater cohesiveness of small particles produces an arching or bridging of the granules within the cylinder. An increase in the average granule size reduces the particulate interactions due to a lower surface-to-mass ratio. The resultant decrease in granulation void spaces is manifested by a higher bulk density value. These effects were observed in bulk density and porosity determinations of the granulations prepared at varying rates of binder addition. However, it is felt that the bulk density increase and corresponding porosity decrease with an increase in the average granule size are not solely attributable to the free-fall velocity and surface effects of the granules. Instead, the primary effect is the greater degree of wetting of the powder bed by the increasing rates of addition of the binder solution. The greater wetting ability of the binder solution not only effects an increase in the average granule size but also produces a more dense granulation.

Porosity determinations do not include intraparticulate void spaces because the displacement medium, benzene, used in the determination of granule density does not penetrate the fine capillaries within the granules. Granule density was unaffected by varying the rate of binder addition. At the low concentration of binder (2% of the total formulation), changes in the granulated product were not sufficiently significant to alter the intraparticulate voidages. For a single formulation, a change in the intraparticulate pore spaces of the granules is needed to effect a change in granule density.

Several investigators demonstrated the principal factors influencing the fluidity of particulate solids (25–27). In this investigation of granulation orifice flow rates, the porosity of the granulation was of greatest importance. The granulation flow rate was inversely related to the porosity of the granulation in the granulation size ranges of this study. The observed increasing flow rate, associated with increasing average granule size, was due to the less porous larger bulk density granulations formed at higher rates of binder solution addition.

Table III relates the effects of the inlet air temperature during the granulation cycle on the physical properties of the granulated product. Twenty-two hundred grams of a 9.1% w/w gelatin binder solution was used for each batch. Higher inlet air temperatures during granule formation produced smaller, more friable granulations.

The elevated temperatures of the fluidizing medium increased the rate of evaporation of the aqueous binder solvent, thereby lowering the extent of wetting and penetration of the fluidized bed of powders by the binder solution.

The fluidizing air temperature during granulation is of major importance to the success of the operation. From Table III, it can be concluded that a very high inlet air temperature during granulation would result in a spray-drying effect of the atomized binder solution with little or no granule formation. On the other hand, granulating at room temperature tends to cause premature agglomeration of the powders due to overwetting by the binder solution. This agglomeration or caking of the powders makes it difficult to maintain a fluidized state. The magnitude of this problem grows as binder concentration, rate of binder addition, and spray droplet size are increased.

The more porous granulations obtained at higher inlet air temperatures during the granulation cycle are due to the bulkiness of the products, which results from the larger quantities of unprocessed powders in the batches. The granulation process decreases the bulkiness of the powders by densifying them through wetting with the binder solution. This bulk density increase and increasing average granule size result not from increased binder adhesiveness but from an increased wetting of the fluidized powders by the binder solution. In the fluidized bed granulation technique, granule size may be controlled either through degree of wetting of the fluidized solids or through increased binder concentration (increased binder adhesiveness). Granule size enlargement due to the increased wetting capabilities of the binder solution results in a more dense granulation, while larger average size granulations obtained through increased binder concentration result in less dense granulations. As expected, the larger, more dense granulations formed at lower inlet air temperatures showed better flow properties.

Atomization of the binder solution occurs in the binary nozzle head, at which point the liquid binder and air converge to form fine droplets of aqueous binder. The degree of atomization of the binder solution is controlled by the proportion of air and liquid mixture in the nozzle head. Table IV illustrates the effects of increasing the proportion of air to liquid in the nozzle on the granulation properties. An increase in the air pressure from 0.5 to 2 kg./cm.² brought about a steady decline in the average granule size of granulation batches produced with 2350 g. of a 14.9% w/w gelatin binder solution. The decrease in the average granule size, with its corresponding increase in granule friability, is attributed to the finer spray droplet formation of the binder solution as a result of increasing the proportion of air to liquid in the atomization process. This effect is comparable to that of decreasing the rate of liquid addition while maintaining a constant air pressure to the nozzle. The conclusions drawn for the size and friability properties of granulations manufactured by varying these operational processes are parallel and, therefore, are not reiterated here.

The decreased bulkiness of the granulation manufactured at 0.5 kg./cm.² air pressure is attributed to a more thorough penetration of the binder solution into the powder bed. This enhanced binder solution penetration results from a slower evaporation rate of the binder solvent in its larger droplet size. The slight decrease in granule density with decreasing nozzle air pressure is due to the greater proportion of intragranular voidages associated with the increased average granule size.

Table IV—Effects of Air Pressure to the Binary Nozzle on Physical Properties of the Granulation

Air Pressure, kg./cm. ²	Average Granule Size, μ	Friability, %	Bulk Density, g./ml.	Granule Density, g./ml.	Porosity, %	Flow Rate, g./min.
0.5	438	6.9	0.43	1.453	70.41	116.4
1.0	354	8.4	0.38	1.469	74.13	110.6
1.5	327	9.6	0.37	1.475	74.91	114.0
2.0	292	11.7	0.37	1.474	74.90	119.6

Table V—Effects of Height of the Binary Nozzle above the Distribution Grid on Physical Properties of the Granulation

Nozzle Height above Grid, cm. (in.)	Average Granule Size, μ	Friability, %	Bulk Density, g./ml.	Granule Density, g./ml.	Porosity, %	Flow Rate, g./min.
81.91 (32.25)	286	12.2	0.36	1.484	75.74	115.1
72.39 (28.50)	292	11.7	0.37	1.474	74.90	119.6
62.86 (24.75)	313	10.9	0.36	1.472	75.54	118.6
53.34 (21.00)	344	8.3	0.37	1.468	74.80	116.1

The degree of atomization of the binder solution had little effect upon the density of the granulation until the air pressure to the nozzle was reduced to its lowest value. These results were observed at a single rate of binder addition and inlet air temperature and may, therefore, not apply to other liquid feeds or fluidizing temperatures.

Of greater interest, however, is the equality of granule flow rates of the four granulations. As expected, with the equal densities and relatively similar size distributions of the granulations produced at air pressures of 1.0, 1.5, and 2.0 kg./cm.², there were little differences in the weights of granule flow per unit time. However, a greater flow rate was expected with the more dense granulation produced at 0.5 kg./cm.² air pressure. It is suspected that the lower than anticipated flow rate was caused by the increased proportion of 20-mesh granules in this granulation. These large granules interfere with the flow of granulation through the narrow orifice of the funnel stem. Zenz and Othmer (2) reported that, for uninterrupted flow, the internal diameter of the orifice should exceed 5–7 times the diameter of the largest granules. The ratio of the orifice diameter to the largest granule fraction in this granulation is 5 to 1.

The position of the binary nozzle within the fluid bed granulator is most easily described with respect to the height of the nozzle head above the air distribution grid at the base of the product container. Table V depicts the effects of the nozzle position on the physical properties of standard granulations manufactured from 2350 g. of a 14.9% w/w gelatin binder solution. The only significant effects of the nozzle site are on the average granule size and granule friability. The closer the nozzle is positioned to the fluidized bed of powders, the more efficiently will the atomized binder solution be able to facilitate the formation of granules. This increased efficiency of the binder, as the nozzle is lowered in position, is again due to its increased ability to wet and penetrate the fluidized solids.

In discussing the nozzle site, the temperature and velocity of the fluidizing medium, the solids density and batch size, and the volatility of the binder solvent must all be established. Positioning of the nozzle too near the fluidized solids may cause an interference in the spray pattern of the atomized binder solution or a possible obstruction within the nozzle head as a result of continuous impingement of the solid particles on the nozzle orifice. At the same time, a distant nozzle location results in a spray drying of the binder solution with little granule formation.

The nozzle height, particularly in its lowest position, produced no significant changes in the granulation densities or flow properties, a fact that is difficult to explain. Earlier results and discussions led to the anticipation of a greater bulk density value for the larger average granulation size produced at the lowest nozzle location. An examination of the individual sieve fractions of the granulations manufactured at various nozzle positions showed little difference in the quantity of fines present in the granulations. The increase in the average granule size, as the nozzle was lowered closer to the fluidized powders, resulted from a small but increasing number of large granules due to the proximity of the nozzle to the fluidized powder bed. However, lowering the nozzle without increasing the diameter of the spray cone resulted in an increase in the number of solid particles in the area beyond the conical pattern of the atomized binder solution. For this reason, there were approximately an equal number of fine granules in all batches. Since the fine component of a granulation is most influential with respect to its physical properties, there were little variations in the densities and flow properties of the granulations manufactured at various nozzle positions.

Having established the major operational influences and obvious capabilities of the fluid bed granulator, it was desirable to investigate further the merits of this single-stage granulation process. The effects of various granulating agents and concentrations on the physical properties of the resultant granulations and tablets com-

pressed from these granulations will be the subject of subsequent reports.

CONCLUSIONS

In the fluid bed granulation process, granules are formed when the powders, wetted by the atomized binder solution, adhere to one another as contact is made in the heated fluidizing medium. The physical properties of granulations manufactured by this process are dependent upon both the individual formulations granulated and the various operational variables associated with the process.

When the rate at which the aqueous binder solution added to the fluidized bed of powders is increased, the ability of the solution to wet and penetrate the solids is enhanced, resulting in: (a) a larger average granule size, (b) a less friable granulation, (c) a more fluid granulation, and (d) a decreased granulation bulkiness. Similar results, also traceable to enhanced binder solution efficiency, occur with a decrease either in the binary nozzle air pressure or in the inlet air temperature during the granulation cycle.

The position of the binary nozzle with respect to the fluidized powders has significant effects upon the average granule size and granule friability. The effects upon the granulation flow properties and bulkiness, however, are slight. As the binary nozzle is lowered closer to the fluidized solids, binder efficiency is enhanced, resulting in an increase in the average granule size and a corresponding decrease in granule friability.

REFERENCES

- (1) D. F. Othmer, "Fluidization," Reinhold, New York, N. Y., 1956.
- (2) F. A. Zenz and D. F. Othmer, "Fluidization and Fluid-Particle Systems," Reinhold, New York, N. Y., 1960.
- (3) M. Leva, "Fluidization," McGraw-Hill, New York, N. Y., 1959.
- (4) K. Ridgeway and E. Segovia, *Mfg. Chem. Aerosol News*, **37**, 39(1966).
- (5) J. F. H. Jones, *Chem. Drug.*, **179**, 729(1963).
- (6) M. W. Scott, H. A. Lieberman, A. S. Rankell, F. S. Chow, and G. W. Johnston, *J. Pharm. Sci.*, **52**, 284(1963).
- (7) R. Cilento and R. A. Hill, presented to the APHA Academy of Pharmaceutical Sciences, Dallas meeting, Apr. 1966.
- (8) M. F. Quinn, *Ind. Eng. Chem.*, **55**, 18(1963).
- (9) V. Vanecek, M. Markvart, and R. Drbohlav, "Fluidized Bed Drying," Leonard-Hill, London, England, 1966, p. 31.
- (10) M. J. Robinson, G. M. Grass, and R. J. Lantz, *J. Pharm. Sci.*, **57**, 1983(1968).
- (11) D. E. Wurster, *J. Amer. Pharm. Ass., Sci. Ed.*, **48**, 451 (1959).
- (12) V. Coletta and H. Rubin, *J. Pharm. Sci.*, **53**, 953(1964).
- (13) J. H. Wood and J. Syarto, *ibid.*, **53**, 877(1964).
- (14) H. N. Wolkoff, G. Pinchuk, and P. H. Shapiro, *ibid.*, **57**, 317(1968).
- (15) R. E. Singiser and W. Lowenthal, *ibid.*, **50**, 168(1961).
- (16) H. C. Cardwell and E. Rosen, *ibid.*, **53**, 1387(1964).
- (17) M. W. Scott, H. A. Lieberman, A. S. Rankell, and J. V. Battista, *ibid.*, **53**, 314(1964).
- (18) A. S. Rankell, M. W. Scott, H. A. Lieberman, F. S. Chow, and J. V. Battista, *ibid.*, **53**, 320(1964).
- (19) *Book ASTM Stand., D-441*, **8**, 1958, 1045.
- (20) K. P. Perlman, G. S. Banker, and H. G. DeKay, *Drug Cosmet. Ind.*, **94**, 660(1964).
- (21) N. Bauer and S. Z. Lewin, in "Techniques of Organic Chemistry, Physical Methods, Part I," 3rd ed., A. Weissberger, Ed., Interscience, New York, N. Y., 1959, pp. 175–184.
- (22) A. N. Martin, "Physical Pharmacy," Lea & Febiger,

Philadelphia, Pa., 1960, pp. 585-592.

(23) A. M. Raff, A. S. Arambula, A. J. Perkins, and D. L. Dearthoff, *J. Amer. Pharm. Ass., Sci. Ed.*, **44**, 290(1955).

(24) T. M. Jones, *Mfg. Chem. Aerosol News*, **39**, 38(1968).

(25) E. D. Sumner, H. O. Thompson, W. K. Poole, and J. E. Grizzle, *J. Pharm. Sci.*, **55**, 1441(1966).

(26) K. Ridgeway and R. Rupp, *J. Pharm. Pharmacol.*, **21**, 30S (1969).

(27) G. Gold, R. N. Duvall, B. T. Palmero, and J. G. Slater, *J. Pharm. Sci.*, **57**, 667(1968).

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* Present address: School of Pharmacy, West Virginia University, Morgantown, WV 26506

Influence of Fluid Motion in Dissolution-Rate Determinations

S. BISAILLON* and R. TAWASHI

Abstract □ A method is presented for dissolution-rate studies based on three-dimensional movement of the dissolution cell around its axis. By using this agitating system, the solute flux from benzoic acid and iodine disks was studied at different flow velocities. The results obtained were compared with the rotating-disk method. The dependence of dissolution rate on the power of flow velocity and on the activation energy was determined experimentally. The Reynolds and Peclet numbers were calculated from the parameters of the experiments, and the values obtained were compared with theory for laminar and turbulent flow.

Keyphrases □ Dissolution rates—effect of fluid motion and activation energy, Turbula shaker mixer and rotating-disk methods compared □ Fluid motion—effect on dissolution rates □ Rotating-disk method—compared with Turbula shaker mixer method, influence of flow velocity and activation energy on dissolution rates □ Turbula shaker mixer—dissolution-rate determinations, compared to rotating-disk method

Dissolution is the rate-determining step of numerous mass-transfer processes such as catalysis, adsorption, extraction, and drug absorption. Modern hydrodynamic concepts such as theories of turbulent or laminar flow and boundary layer (1-4) are now being used in the solving of problems involved with systems of hydro-mechanical equations. Information on the effect of agitating intensity in dissolution test procedures is scarce and insufficient (5-8) for developing a routine control procedure. An unexpected variable (vibration effect) in the latest USP and NF rotating-basket dissolution tests was reported by Beyer and Smith (9).

The present publication deals with the effect of speed of agitation on the rate of solute transfer in geometrically similar systems. The dissolution behavior in a new

Table II—The Reynolds (N_{RE}) and Peclet (N_{PE}) Numbers as Calculated for the Turbula Shaker Mixer and for the Rotating Disk

Temperature	N_{RE}		N_{PE}	
	Rotating Disk	Turbula	Rotating Disk	Turbula
25°	200	27,000	0.20×10^6	27.7×10^6
37°	250	34,300	0.15×10^6	20.7×10^6

agitating system based on a three-dimensional movement of the dissolution cell around its axis was tested experimentally and compared with data obtained from the rotating disk. The data obtained could be used to predict the quantitative performance of the agitating system and to find a better design for a dissolution test procedure. The choice of the agitating system described in this study is based on previous experience in solid mixing and in solubility determinations. Solid-solid mixing was improved remarkably by using this agitating system (10), and in solubility studies of poorly soluble drugs, the equilibrium was reached after a shorter period of time than with other conventional methods (11).

THEORETICAL CONCEPTS

The analysis of the behavior of flows by similarity theory is now widely applied. Even if geometrical similarity, identity of boundary conditions, and Reynolds' number are sufficient conditions for the similarity of two flows, only a few systems have been satisfactorily solved from their cylindrical convective diffusion equation.

Taking into consideration the streamlines at the surface of a rotating disk serving as the reaction site, Cochran (12) developed the cylindrical convective diffusion equation for the rotating disk, from which Levich (1, 13) came to the following expression:

$$R = kD^{2/3} \nu^{-1/6} \omega^{1/2} c_s \quad (\text{Eq. 1})$$

It can be rearranged to give:

$$K_T = kD^{2/3} \nu^{-1/6} \omega^{1/2} \quad (\text{Eq. 2})$$

The significance of each term in these equations is listed in the *Appendix* at the end of this article.

These equations refer to the laminar flow regime, which can be defined as the steady advance of the fluid in a separate layer. When one passes to the turbulent regime, not necessarily by increasing

Table I—Equations for Evaluation of the Dimensionless Reynolds and Peclet Numbers

Reynolds' number	=	$\frac{\text{momentum transfer by turbulent flow}}{\text{momentum transfer by molecular transport}}$
Peclet's number	=	$\frac{\text{mass transfer by convective diffusion}}{\text{mass transfer by molecular diffusion}}$
N_{RE}	=	$\frac{UL^2}{\nu} = \frac{UL^2 \rho}{\eta} \quad ; \quad N_{PE} = \frac{UL^2}{D}$