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Continuous Production of Tablet Granulations in a Fluidized Bed II

Operation and Performance of Equipment

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Data collected from batch runs in a 1-ft. diameter fluidized bed granulator were employed in preliminary evaluation of process performance. Moisture content, granule screen analysis, and compressibility tests were used to evaluate the granulated product. Process variables such as powder and liquid feed rates, inlet air temperature, and nozzle location influenced the characteristics of the product. Losses from the unit were related to cyclone collector efficiency. Data obtained from replicate continuous runs under selected operating conditions illustrated the ability of the process to maintain product uniformity from run to run. Finished granulations from the continuous runs were evaluated on a rotary press. Tablets made from these granulations conformed to tablets made from identical ingredients granulated by conventional techniques.

SIGNIFICANT ADVANCES have been made recently in the development of direct compression techniques for the production of tablets. However, until the physical and chemical principles of compression are more fully understood, wet granulation techniques will be required for numerous formulations.

New procedures for preparing tablet granulations have been reported in the recent literature. These techniques include a method for vapor phase granulation (1) and an air suspension granulation method (2); procedures for preparing granulations in coating pans have also been described (3, 4).

An accompanying report (5) describes the theory and design of a continuous fluidized bed granulation technique. The present report represents an extension of this study, and is an evaluation of the performance of a pilot model fluidized bed granulator, including a study of process variables. The apparatus used has been adapted from a fluidized bed dryer (of the type commonly used in the chemical process industry)[1] which was specifically modified for the production of tablet granulations. The unit is adaptable for batch processing, but is particularly useful in the continuous granulating of large volumes of raw materials.

EXPERIMENTAL

Materials.—The product granulated in these experiments was an antacid mixture based primarily on aluminum hydroxide. A preblend of all formula components (except lubricants) was used as the feed powder. The particle size of the feed was less than 200 mesh (74 μ); loss on drying (L.O.D.) was approximately 5%.

The feed powder contained sucrose. To maintain constant assay levels in the granulated product, the concentration of sucrose in the feed was varied from run to run as required by the changes in the sucrose content of the granulating liquid. The granulating agents included in this study were water, diluted syrup (43% w/v), simple syrup (85% w/v), and a 10% w/v aqueous gelatin solution. A mixture of water soluble dyes (FD&C Red No. 2 plus FD&C Red No. 4) was dissolved in the granulating liquid (syrup) in one experiment.

Equipment.—The general design of the fluidized bed granulator used in these studies was discussed

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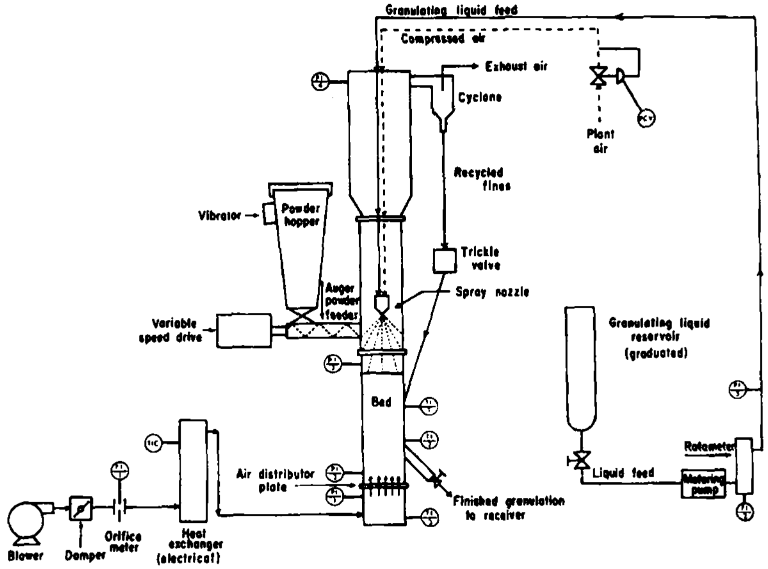

Fig. 1.—Diagram of fluidized bed granulator. FI = flow indicator; PCV = pressure control valve; PI = pressure indicator; TI = temperature indicator; TIC = temperature indicator controller.

in a previous report (5); a schematic diagram of the equipment is shown in Fig. 1. The granulator consists of a 12-in. diam. column (expanded to 18 in. at the top) with provision for the introduction of heated air and the feed and removal of solid materials. Fine particles entrained in the exhaust air are removed in a cyclone collector and are recycled to the bed through a trickle valve.

A pneumatic spray nozzle for atomizing the granulating liquid is vertically positioned within the fluidization section. The spray is directed in a downward direction, and the vertical position of the nozzle can be changed. The feed powder is supplied to the fluidized bed by an auger type feeder with a variable rate of rotation. The feeder is modified to form a positive gas check against blow back of fluidizing air by insertion of a rubber-lined butterfly valve between the feed hopper and the auger, and the addition of a removable airtight cover to the top of the hopper; a vibrator is attached to the hopper to prevent bridging of the powder.

Instrumentation.—Fluidizing air flow rate is controlled by a butterfly valve damper and measured by an orifice meter (FI-1) [designations refer to components in Fig. 1]. The air temperature is set by a thermostat (TIC) on the electric air heater and measured by a thermocouple below the air distributor plate (TI-3).

Bed temperature is measured by two thermocouples (TI-1 and TI-2) placed at one-third and two-thirds the estimated bed height. The actual bed height is determined by the pressure drop across the bed (PI-2 minus PI-3) The pressure at the top of the expansion section (PI-4) is compared to PI-3 to determine if the bed height has gone above the PI-3 location.

Table I.—Powder Collection

Air Flow Rate, c.f.m.	Product Entrainment, Kg./hr.	Cyclone Efficiency, %	Losses, %
Efficiency at Different Air Flow Rates			
37	8.0	42.5	7.3
73	8.8	73.3	5.3
107	19.6	91.5	3.7

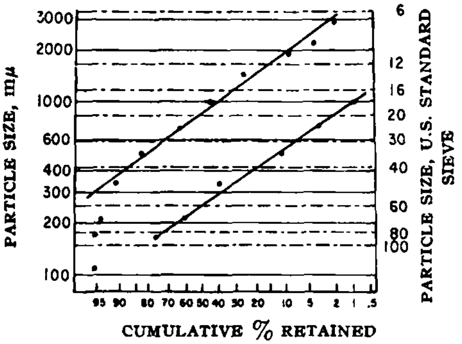

Fig. 2.—Comparison of particle size distribution of a typical fluidized bed granulation (O—O) and a conventional wet granulated product (●—●).

The granulating liquid flow rate is controlled by a gear type metering pump and is measured by a rotameter (FI-2). The total quantity delivered is measured by reading the liquid level in the reservoir. The degree of atomization of the liquid spray is determined by the pressure in the compressed air line (PCV).

A pressure gage (PI-5) in the granulating liquid line between the metering pump and the nozzle gives early warning of nozzle clogging. Clogging in the fluidizing air distributor plate is indicated by increasing pressure drop across the plate (PI-1 minus PI-2).

Procedure for Batch Runs.—Batchwise operation of the equipment was employed for the study of several important process variables such as air flow rate, inlet air temperature, liquid flow, residence time, and composition of granulating agent. For these runs 30 Kg. of feed powder was used as charge; this was added to the bed after air flow rate and inlet air temperatures were stabilized. Atomization of the granulating agent then was started. Thereafter, samples of product and instrument readings were taken at 10–20-minute intervals until the run was completed (90 minutes or more). At the end of the run, the product was removed by opening the

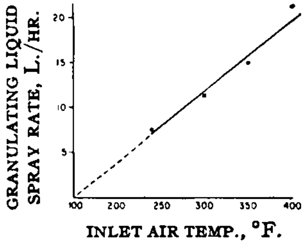

Fig. 3.—Relationship of granulating liquid spray rate to inlet air temperature to maintain bed temperature at 100–110° F.

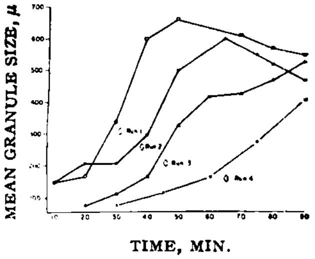

Fig. 4.—Influence of granulating liquid spray rate on mean granule size. Granulating liquid flow rates: run 1, 21.4 L./hr; run 2, 15.0 L./hr.; run 3, 11.2 L./hr; run 4, 7.5 L./hr.

bottom outlet port and allowing the bed to flow into a receiving vessel.

Procedure for Continuous Runs.—In the continuous process, 30 Kg. of granulation (obtained from a previous run) was used as a starting bed in order to shorten the time required to reach steady state conditions. Powder feed and liquid granulating agent then were added continuously to the bed for the entire run. The bottom outlet valve was partially open to allow product removal. The valve position was periodically adjusted to maintain a constant bed height (indicated by a constant pressure drop across the bed).

All batch and continuous experiments in this study were run at a bed temperature of 100–110°F. The flow rate of granulating liquid was adjusted from run to run to maintain this temperature. Complete material balances were established for each run.

Sampling and Evaluation Procedures.—Samples of approximately 250 Gm. of product were taken at short periodic intervals throughout each run. These samples were generally obtained through the outlet port at the bottom of the fluidized bed. In several experiments additional samples were taken from an auxiliary upper port. Particle size analysis was performed on all samples by sieving through a nest of U. S. standard sieves (Nos. 6, 12, 16, 20, 30, 40, 60, 80, 100, and 200) on a Cenco-Meinzer sieve shaker at setting 4 for 10 minutes. The particle size distribution data so obtained were plotted on logarithmic probability coordinates. The size corresponding to 50% on the cumulative percentage axis was taken as the geometric mean diameter. Moisture content on all samples was determined with a Cenco moisture balance set at 90 v. to constant L.O.D. Assays for alumina were performed on representative samples from the continuous runs.

After blending with lubricant, the compression characteristics of the product prepared in each run were tested on both a single punch tablet press (Stokes model E) and a rotary press (Stokes model RD-3). Tablets compressed from the fluidized bed granulation were compared to the same product prepared by the conventional wet granulation method. Compression characteristics (absence of capping, sticking, binding, and picking) as well as tablet characteristics such as hardness, thickness, weight variation, and friability were the comparison criteria.

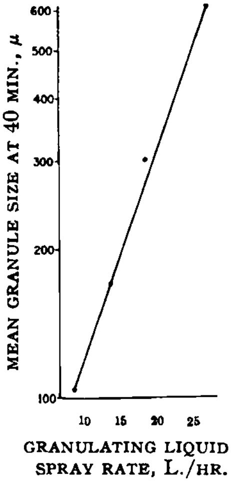

Fig. 5.—Correlation of mean granule size with granulating liquid spray rate during constant agglomeration rate period.

DISCUSSION OF BATCH OPERATIONS

Preliminary Evaluation.—As a starting point for these studies, batch experiments were conducted to establish optimum velocities for the fluidizing air. These experiments were run using 30 Kg. of powder feed. Liquid granulating agent was not added to the bed during the tests.

Three air flow rates of 37, 73, and 107 c.f.m were studied. Adequate fluidization was obtained at each level, but significant differences in entrainment and cyclone efficiencies were discernible, as summarized in Table I. Cyclone collection efficiency was best at the highest air velocity (107 c.f.m.), but the entrainment of solids in the effluent air stream was more than double that obtained at the lower velocities. Since this velocity would result in a large inventory of recirculating material, with increased opportunities for attrition, it was rejected. At the lowest air velocity (37 c.f.m.), excessive losses were obtained as a result of poor cyclone efficiency. Heat and mass transfer also was expected to be influenced adversely by decreasng the air velocity to this level. On this basis the intermediate fluidizing air velocity (73 c.f.m.) was established for all further runs.

The batchwise granulating operation was studied using an inlet air temperature of 235 ±5°F. and a 30-Kg. bed of feed powder. Syrup was used as the granulating agent and was sprayed into the bed at a rate of 7.5 L. per hour. Under these conditions, approximately 90 minutes was required for formation of granules with satisfactory tablet compression characteristics. The particle size distribution of such a typical batch product is illustrated in Fig. 2. It will be observed that the fluidized bed granulation has a smaller average particle size and higher degree of particle size uniformity than that obtained by the conventional wet granulation process.

The minimum bed temperature, which was obtainable with the given ambient air conditions (70°F. and 40% R.H.), was approximately 98°F., the dew point temperature, as determined from psychrometric charts. This indicated that the outlet air was close to saturation when the bed temperature was maintained, as previously stated, at 105 ±5°F.

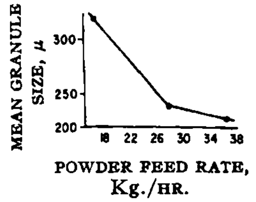

Fig. 6.—Relationship of powder feed rate to mean granule size.

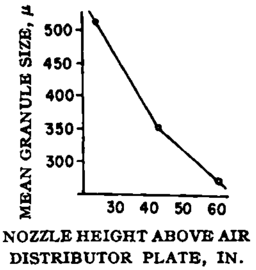

Fig. 7.—Influence of nozzle position on mean granule size.

In one experiment, the air flow rate was reduced 15%. Inlet air temperature and liquid flow rates were maintained at their previous levels. The temperature of the bed was maintained at 105°F., but the product granules were moist to the touch and not acceptable for tablet compression. The insufficient degree of drying attained in this experiment suggests that the process is essentially adiabatic with outlet air at saturation.

Influence of Inlet Air Temperature.—Experiments were conducted using various inlet air temperatures. For each run the flow rate of liquid granulating agent was adjusted to maintain a constant bed temperature of 105 ±5°F. and a constant product L.O.D. of 5%. The results of this study are shown in Fig. 3 and indicate that allowable liquid flow rates are directly proportional to the inlet air temperature. The curve shows an intercept value of 100°F. when extrapolated to the inlet air temperature axis. This value agrees with that predicted by theory—when the inlet air temperature is the same as the bed temperature, no latent heat of vaporization of the granulating liquid is needed.

Influence of Granulating Liquid Flow Rate.—The change in mean granule size with increasing residence time in the fluidized bed for different flow rates of granulating liquid is shown in Fig. 4. The data indicate that the size tends towards a maximum, regardless of the granulating liquid flow rate. This may indicate that at a certain point the rate of agglomeration is offset by attrition effects.

The data in Fig. 4 show that the rate of agglomeration is increased as the granulating liquid flow rate is raised. This is shown more clearly in Fig. 5 which correlates the mean granule size after 40 minutes residence time as a function of granulating liquid flow rate.

Influence of Composition of Granulating Liquid.—Water, diluted syrup, and a 10% aqueous gelatin solution also were tested as granulating agents. The flow rate of these agents was adjusted so that the rate of addition of water to the bed was equal to that obtained when granulating with simple syrup. When water was used as the granulating liquid, no perceptible agglomeration occurred. Some increase in particle size was produced with the use of diluted syrup as the granulating material. Under the conditions of the test, however, granules of adequate size for compression could not be obtained even after 5 hours of processing. Properly sized granules were formed when the gelatin solution was used. The moisture content of the resulting product was higher than that required for successful compression. Since the total water added in these tests was equal to that used successfully in previous tests with simple syrup, the poor results suggest that heat transfer rates were probably too low in the run using gelatin solution.

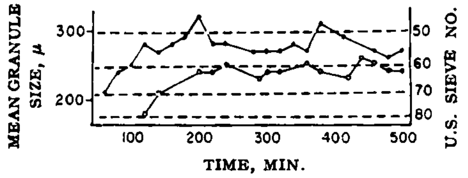

Fig. 8.—Uniformity of product granule size during continuous runs. Key: —●—●—●—, run 1; —O—O—O—, run 2.

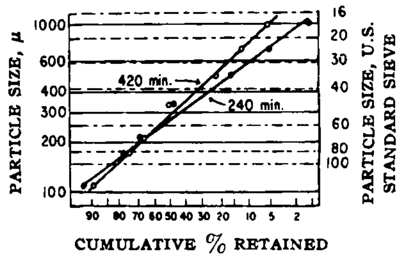

Fig. 9.—Uniformity of granule size distribution during continuous run.

DISCUSSION OF CONTINUOUS OPERATIONS

Influence of Powder Feed Rate.—Conditions for continuous operation of the fluidized bed were: inlet air temperature at 240°F., liquid feed rate (simple syrup) at 7.5 L. per hour, and bed temperature at 105 ± 5°F.

Figure 6 shows the relationship between the rate of powder feed and the mean granule size of product produced in the continuous runs. An increase in the powder feed rate resulted in a decreased mean particle size. This would be expected considering the feed powder dilution effects alone. The mean granule size obtained at any feed rate was constant over long periods of operation, suggesting that new steady state conditions of operation are reached for each powder feed rate.

Influence of Nozzle Location.—The mean granule size of product under constant feed rate and temperature conditions could be altered merely by changing the location of the liquid spray nozzle. This is shown in Fig. 7. The largest mean granule size was obtained when the nozzle was at its lowest test position—23 in. above the air distributor plate. At this point the nozzle was actually in the bed.

Process Evaluation.—The process was further evaluated by continuous granulation runs of 8 or more hours duration. Figure 8 shows the mean granule size of samples taken at periodic intervals during two such continuous runs. The ability of the process to produce a product with closely controlled mean granule size is apparent. The slight difference in particle size between the runs can be attributed to an increase (1.9 Kg./hour) in the powder feed rate in run 2 compared to run 1. Figure 9 compares the particle size distribution curves for representative samples taken at 3-hour intervals during the run. The similarity in the slopes of these lines indicates that the particle size distribution and the mean granule size were closely controlled.

Uniformity of product also was indicated by alumina assay for several runs; the values obtained were all within 7% of the theoretical value (after correction for losses).[2]

The rate of granulation was approximately 40 lb. per hour. It is believed that the rate of granulation can be increased to 120 lb. per hour by increasing the inlet air temperature and granulating liquid spray rate, thus allowing a decreased residence time.

Evaluation of Batch and Continuous Process Products.—Granulations from batch and continuous runs compressed without difficulties. The tablets produced from these granulations were identical in appearance to those prepared from conventional granulations. Thickness, weight, hardness, and friability of the tablets made from the fluidized bed granulation also were identical to the wet granulated product.

Addition of Color.—The suitability of the process for preparing a colored granulation was tested by granulating with dye dissolved in the granulating liquid. The granules produced showed a high degree of color uniformity and compressed into tablets with better color distribution than those prepared from conventional granulations.

SUMMARY AND CONCLUSIONS

The results reported in this paper clearly illustrate several advantages for preparing tablet granulations by the fluidized bed method. The equipment described is capable of both batch and continuous operation. The granulation produced by either technique has a high degree of particle size uniformity and a controllable moisture content. Tablets prepared from the fluidized bed granulation meet or exceed all criteria established for tablets prepared from granules conventionally prepared.

Granule size and production rate of the granulated product can be controlled by adjusting each or all of the following process variables: (*a*) powder and liquid feed rates, (*b*) inlet temperature, and (*c*) lowering the position of the spray nozzle. Since each of these are readily adjustable in the pilot size fluidized bed granulator, this unit is judged suitable for small-scale production of granulations as well as for use in scale-up procedures. The experimental results are in direct agreement with those previously derived from theoretical considerations.

The materials granulated by this process are subjected to temperatures only slightly above room temperature. As illustrated in this report, processing can be done at bed temperatures of only 100–110°F. Thus, the fluidized bed granulator appears to have particular usefulness for granulating heat sensitive materials.

The fluidized bed granulator combines into one process several of the individual steps normally required in wet or dry granulating methods. The ability of the apparatus to produce granules with controlled size, either by batch or continuous processing, eliminates the need for any grinding operations conventionally required. Moisture content of the final product can be closely controlled, eliminating the need for separate drying procedures. In batch operations pre- and post-blending may be accomplished in the fluidized bed, eliminating the need for additional mixing equipment.

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[2] Low collection efficiencies (77%) were obtained in the continuous runs described above. The loss of powder reflected by this inefficiency could be corrected by the use of auxiliary bag collectors or multiple cyclones.