and the viscosity was found for viscosities of 1 to 5 cps. The dissolution rate was a function of the viscosity raised to the −0.5 power for the rest of the viscosity range studied (1 to 260 cps.).

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Technical Articles

Continuous Production of Tablet Granulations in a Fluidized Bed I

Theory and Design Considerations

By MORTON W. SCOTT*, HERBERT A. LIEBERMAN, ALBERT S. RANKELL, and JOSEPH V. BATTISTA

A single step process for the production of tablet granulations on a continuous basis is described. The process is based on the use of a modified fluidized bed dryer. Important considerations in the design and operation of the equipment are derived from material and energy balances and from heat and mass transfer relationships. The report illustrates the usefulness of the pharmaceutical engineering approach in the analysis of new process developments.

FLUIDIZATION TECHNIQUES have been used in various process industries for over 20 years (1, 2). The unit operation has found applications in areas as diverse as roasting processes (3), refining uranium ores (4), gasification of carbon (5), and ion exchange procedures (6). Fluidized bed drying has been studied extensively (7–9). The usefulness of fluidization techniques for the drying of tablet granulations was also discussed recently (10); rapid rates of drying and reduced operating costs were some of the advantages reported for the process.

Procedures for coating particulate solids in fluidized beds have been developed by Wurster (11) and applied to a variety of pharmaceutical products. When the coating agents have adhesive qualities, the technique also can be used for agglomeration and for the preparation of tablet granulations (12). The Wurster apparatus operates in a batchwise fashion and thus finds major usefulness when numerous small batches of different formulations must be processed.

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The present report introduces a new fluidization process capable of high-volume production of tablet granulations on a continuous basis. The fundamental pharmaceutical engineering relationships which have been applied successfully in designing and operating the fluidized bed granulator are developed in this report. A brief discussion of conventional batch and continuous fluidization processes is presented as background material. An accompanying report reviews the process performance levels and product characteristics obtained in batchwise and continuous operation of the equipment (13).

The analysis of the fluidized bed granulation

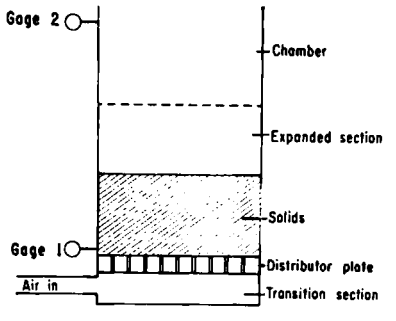

Fig. 1. —Schematic drawing of a simple fluidized bed.

process is derived from the statements of the material balance and the heat and mass transfer requirements of the system. The value of this method of attack in defining the interrelationships of process variables has not been illustrated previously in the pharmaceutical literature. However, the approach is not limited to the specific fluidization system described here, and will be applied to film coating operations and other pharmaceutical processes in subsequent reports.

SIMPLE FLUIDIZATION

Figure 1 is a schematic drawing of a simple fluidized bed. Three essential components are involved: (*a*) a vertical chamber for containing the solids to be fluidized, (*b*) a source of air (such as a blower), and (*c*) an air distributor device for obtaining the proper velocity profile for the inlet air. The air distributor may be a perforated plate, a fine mesh screen, or a honeycomb plate, etc., (1). A short transition section may be included beneath the distributor.

The unit is operated by charging the feed solids to the fluidization chamber and admitting an increasing flow of air through the distributor plate. When correct flow conditions are established, fluidization of the solids will occur. At this point, the bed of solids expands appreciably and has an appearance similar to a boiling fluid. Pressure readings generally are taken at gage locations 1 and 2 (Fig. 1) during the operation in order to follow the progress of fluidization.

Figure 2 is a generalized diagram of the relationship between pressure drop (between gages 1 and 2) and the air velocity in the bed. At low flow rates, air passes between the particles of solid without causing motion. As the velocity of air is increased, the pressure drop ($P_1 - P_2$) rises until eventually it equals the force of gravity on the particles. This occurs at point A, and the particles begin to move. Increasing the air velocity to point B causes the particles to separate, and the bed expands. Point B represents the start of true fluidization. Much of the air passing through the fluidized bed at this stage is in the form of "bubbles" and "pockets" containing little or no solids. In the bed itself, the solids move in more or less distinct aggregates (14). Air velocities higher than that at point B result in further bed expansion with little increase in the pressure drop. Turbulence and overall bed turnover, however, become more marked. At point C, the bed height equals the height of the container and pneumatic transport occurs.

When heated air is used for fluidization, high heat transfer rates are obtainable because of the turbulence and efficient mixing occurring in the bed. The advantages of the fluidized bed dryers now commercially available for drying tablet granulations stem from these considerations (10). In well designed systems, heat transfer between the inlet air and the fluidized solids may be complete within less than one quarter of an inch above the air distributor plate (15). Therefore, in drying applications, the temperature of the bulk solids may be kept relatively low regardless of the inlet air temperatures used.

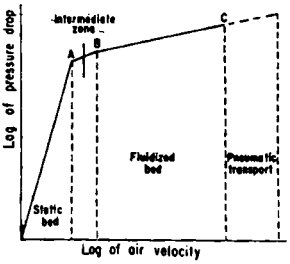

Fig. 2.—Influence of air velocity on pressure drop in fluidized beds.

CONTINUOUS FLUIDIZATION SYSTEMS

The batch equipment shown in Fig. 1 may be converted to a continuous system by the simple addition of a feed pipe and an outlet pipe. A dust collector may be added to catch any entrained solids in the exit air stream. This type of equipment is shown schematically in Fig. 3. Other continuous systems have been illustrated in the literature (1, 2).

When the rate of adding solids to the fluidized bed equals the rate of withdrawal, no net accumulation or loss of solids will occur. Therefore, the weight of solids in the bed remains constant. Since the pressure drop across the bed is determined by the weight of solids it contains (1), pressure drop values can be used as a convenient indicator of bed inventory. In continuous operations, feed rates and/or product withdrawal rates are controlled and adjusted in accordance with the pressure drop across the bed.

CONTINUOUS GRANULATION IN FLUIDIZED BEDS

A system for rapid production of tablet granulations can be designed around the basic components of the continuous fluidized bed unit shown in Fig. 3. For this purpose, an atomizing nozzle is installed in the fluidization chamber to apply a spray of liquid binding agent onto the fluidized solids. Heated inlet air, as employed in the fluidized bed dryers, is used to fluidize the solids and for simultaneous evaporation of the atomized solvent.

The flow of materials to and from such equipment is shown in the material balance diagram in Fig. 4. Relationships between the various flow streams can be developed readily and can be used to uncover a number of important operating and design criteria.

The following primary material balances apply when an aqueous granulating solution (containing no active ingredient) is used:

for air $$A_i = A_o \qquad \text{(Eq. 1)}$$

for solids $$S_i + CG_i = P_o \qquad \text{(Eq. 2)}$$

for active ingredients $$X_iS_i = X_oP_o \qquad \text{(Eq. 3)}$$

for moisture $$M_iS_i + H_iA_i + (1 - C)G_i = H_oA_o + M_oP_o \qquad \text{(Eq. 4)}$$

where A = air flow rate (dry basis), Kg. per minute; C = concentration of solids in granulating liquid, Kg. per Kg.; G = granulating liquid flow rate, Kg. per minute; H = absolute humidity, Kg. water per Kg. dry air; M = moisture content of solids (dry basis), Kg. per Kg.; P = product removal rate (dry basis), Kg. per minute; S = solids feed rate (dry basis), Kg. per minute; X = concentration of active ingredient

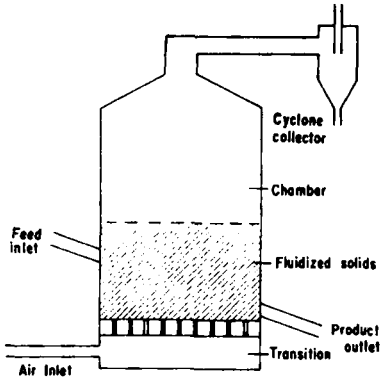

Fig. 3.—Continuous fluidized bed.

(assay value on a dry basis), Kg. per Kg.; i = inlet; and o = outlet.

Maintenance of Product Assay.—Equation 2 shows that solids derived from the liquid granulating agent are included in the granulated product. To attain a given product assay value (X_o), the concentration of active ingredient in the powder feed cannot be made equal to that desired in the product, but must be adjusted in accordance with Eq. 3. The relationship between the desired product assay and the feed concentration for various flow rates and concentrations of the granulating agent is established by substitution of Eq. 2 into Eq. 3

$$X_i = X_o \left[1 + \frac{CG_i}{S_i}\right] \qquad \text{(Eq. 5)}$$

For the special case when water is used as the granulating liquid, C equals 0, and X_i will equal X_o. No adjustment in feed assay, therefore, would be required. Similarly, it can be shown that modifications in feed assay would not be necessary when a slurry of the feed solids (in a volatile solvent) is used as the granulating agent.[1] However, for all other cases Eq. 5 establishes the changes required in feed concentration in order to achieve desired product assays.

Influence of Entrainment Losses.—Equations 1–5 assume no loss of solids in the effluent air stream, A_o. In general practice, however, some entrainment losses do occur from fluidized beds (1, 2). Extensions of the material balance relationships can be developed, as shown below, to predict the influence of these losses on product assay. The need for adequate dust collection systems thereby can be established as an early design requirement.

When entrainment losses occur, the material balance for solids and for the active ingredients are given by Eqs. 6 and 7, respectively

$$\text{for solids} \qquad S_i + CG_i = P_o + L \qquad \text{(Eq. 6)}$$

for active ingredients

$$X_iS_i = X_oP_o + X_LL \qquad \text{(Eq. 7)}$$

where L = entrainment losses, Kg. per minute; and X_L = concentration of active ingredient in entrainment solids, Kg. per Kg.

[1] For this case, Eq. 3 must be modified to account for the addition of active ingredient to the system by the granulating agent. Thus

$$X_iS_i + X_iCG_i = X_oP_o \qquad \text{(Eq. 3A)}$$

Substitution of the value for P_o from Eq. 2 into Eq. 3A establishes that X_i will equal X_o.

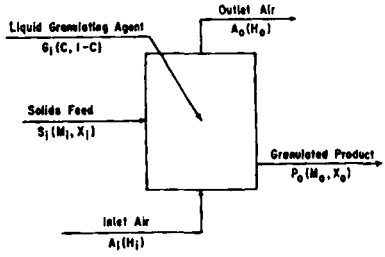

Fig. 4.—Material balance diagram for fluidized bed granulator. Key: A = air flow rate, dry basis, Kg. per hour; H = absolute humidity, Kg. (H_2O) per Kg. (dry air); S = solids feed rate, dry basis, Kg. per hour; P = product exit rate, dry basis, Kg. per hour; M = moisture content of solids, dry basis, Kg. (H_2O) per Kg. (dry solids); X = concentration of active ingredient, Kg. (A.I.) per Kg. (dry solids); G = liquid feed rate, Kg. per hour; C = concentration of granulating agent, Kg. (solids) per Kg. (liquid); i = inlet conditions; o = outlet conditions.

Rearrangement of Eq. 7 after substitution for P_o as defined in Eq. 6 yields the desired relationship between entrainment losses and product assay

$$X_i = X_o \left[1 + \frac{CG_i}{S_i}\right] + [X_L - X_o]\frac{L}{S_i} \qquad \text{(Eq. 8)}$$

For the special case in which the losses consist only of product granules ($X_L = X_o$), the last term of Eq. 8 vanishes, and the relationship reduced to Eq. 5. Under these conditions, the entrainment loss, L, does not influence the feed concentration, X_i, required to achieve a given product assay.

When the entrained solids consist of only unprocessed feed powder, X_L will equal X_i, and Eq. 8 can be simplified

$$X_i = \frac{X_o}{S_i - L}(S_i + CG_i - L) \qquad \text{(Eq. 9)}$$

For this condition, Eq. 9 shows that the magnitude of the solids loss will alter final product assays. The necessary adjustments in feed concentration required to maintain a desired product assay can be calculated from Eq. 9, however, providing that reliable estimates of the losses are available.

Equations 5 and 9 represent the limiting cases. In normal operation, it is likely that the losses from the fluidized bed granulator will contain varying proportions of feed powder together with finished granules and partially processed materials. Since each type of loss exerts a different effect on product assay, it is apparent that adequate control of these losses must be a prerequisite for consistent production of granules meeting assay specifications. This in turn suggests that efficient cyclone collectors (or other dust collection units), preferably operating with continuous recycling of the elutriated solids to the fluidized bed, should become an early design consideration.

Allowable Liquid Flow Rates.—The relationship between the flow rates of liquid granulating agent and inlet air is obtained by substituting the value of A_o (from Eq. 1) and P_o (from Eq. 2) into Eq. 4. Rearrangement of terms leads to

$$G_i = K[A_i(H_o - H_i) - S_i(M_i - M_o)] \qquad \text{(Eq. 10)}$$

where $K = \dfrac{1}{1 - C - M_oC}$.

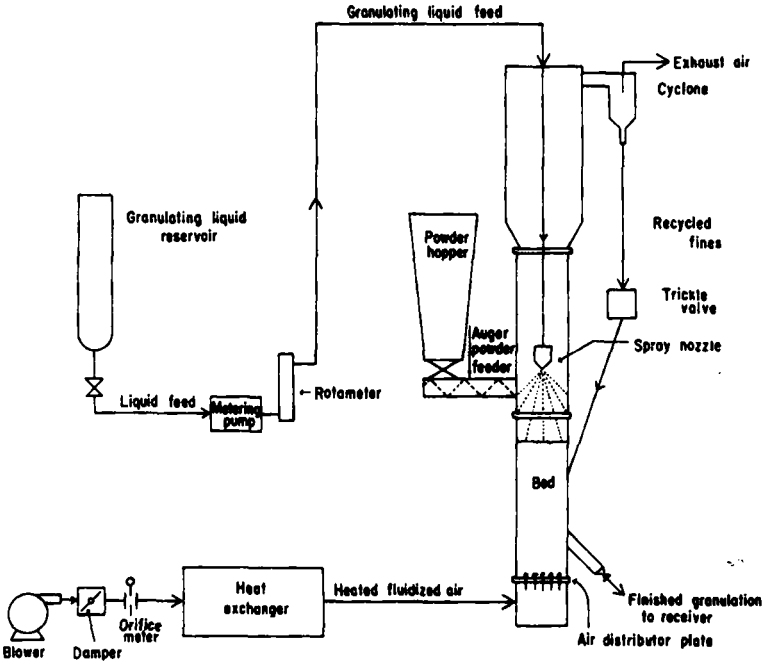

Fig. 5.—Fluidized bed granulator.

Certain simplifying restrictions can be imposed on Eq. 10 as a result of process requirements. For example, the moisture content of the product, M_o, will be fixed by the required flow and compression characteristics for the granulated material. Generally, the moisture content of the raw materials will be close to that of the product granules, and M_i will approximate M_o. Under these conditions the last term of Eq. 10 disappears and the relation reduces to

$$G_i = KA_i(H_o - H_i) \qquad \text{(Eq. 11)}$$

For maintenance of steady state conditions, Eq. 11 shows that the allowable granulating liquid feed rate varies directly with the inlet air flow rate. Therefore, increasing the air flow rate will permit operation with a higher liquid rate giving, in turn, an overall increase in the production rate.

Influence of Outlet Air Temperature and Humidity.—Equation 11 shows that permissible liquid flow rates will be directly proportional to the difference in moisture content between the outlet and inlet air. However, for any outlet air temperature, the outlet moisture content, H_o, cannot exceed that obtained in saturated air at that temperature. If liquid flow rates, G_i, exceed those established by Eq. 11 in process, material can be expected to become increasingly overwet. This condition may not be fully detected by inlet and outlet humidity measurements alone. When the outlet air is partially saturated (less than 100% R.H.), a fluctuation in liquid or air flow rate will be reflected in the outlet humidity level. Instrumentation for these psychrometric measurements, therefore, should be provided in the design of the granulating unit.

For optimum thermal efficiency, it is desirable to raise the level of the moisture in the outgoing air as high as possible. However, when the outlet air is saturated, condensation of water in the dust collection systems (cyclones, etc.) will occur readily. The relative humidity of the outlet air must be kept under 100% to avoid this condensation.

High outlet air temperatures also would appear desirable in increasing thermal efficiency since the moisture content of saturated air (100% R.H.) increases with increasing temperature. The thermal stability characteristics of the product impose a practical limitation on the outlet temperature, since the temperature of the solids will be close to the outlet air temperature (7) under good fluidization.

In the absence of other data, however, this temperature need be no lower than that selected for drying the product by conventional tray drying techniques.

Thermal Energy Balances.—Simplified thermal energy balances can be established as shown in Eq. 12 for the fluidized bed granulator[2]

$$A_{iw}C_{pa}(T_{ai} - T_{ao}) = \lambda G_i(1 - C) + S_iC_{ps}(T_{so} - T_{si}) + E_L \qquad \text{(Eq. 12)}$$

where A_{iw} = air flow rate (wet basis),[3] Kg. per minute; C_{pa} = humid heat capacity of air, Kcal. per Kg. per °C.; C_{ps} = heat capacity of solids, Kcal. per Kg. per °C.; T = temperature, °C.; λ = heat of vaporization of water, Kcal. per Kg.; C = concentration of solids in granulating liquid, Kg. per Kg.; G_i = flow rate of granulating liquid, Kg. per minute; S_i = solids feed rate, Kg. per minute; E_L = thermal energy losses, Kcal. per minute; a = air; s = solid; i = incoming conditions; and o = outgoing conditions.

The thermal energy losses, E_L, in Eq. 12 primarily arise as a result of radiation and convection heat transfer from the fluidization chamber. These losses will be negligible when the outlet air temperature is maintained close to the ambient temperature.

[2] This equation neglects the energy requirements for heating the granulating solids and the vaporized granulating liquid to the outlet temperatures. Heats of solution and wetting also are neglected.

[3] Air flow rate on a wet basis is

$$A_{iw} = A_i + H_iA_i \qquad \text{(Eq. 12A)}$$

Similarly, the term $C_{ps}(T_{so} - T_{si})$, representing losses associated with the heating up of the solids, becomes negligible when the outlet temperature is held near the incoming feed temperature. Under these conditions, the evaporation process in the fluidized bed granulator occurs adiabatically and will be similar to that found in an adiabatic humidifier or spray dryer. The process can be defined and traced more or less completely on psychrometric charts (16).

When air flow rate (A_i), concentration of granulating agent (C), and product temperature (T_{so} equal to T_{ao}) are fixed, Eq. 11 shows that maximum liquid flow rates will be directly proportional to the inlet air temperature.

Increasing the inlet air temperature, therefore, represents a convenient and predictable method for increasing production rates.

Rates of Evaporation and Drying.—The foregoing analysis has concerned the heat and material balance requirements. Analyses of some of the factors governing the rates of evaporation in a fluidized bed granulator are also useful in setting design and operating criteria.

For maintenance of steady state conditions, the rate of evaporation must equal the rate of addition of liquid granulating agent. The rate of evaporation is

$$R_e = A_i(H_o - H_i) \qquad \text{(Eq. 13)}$$

where R_e = rate of evaporation, Kg. water per minute.

The required relationship is shown in Eq. 14 and is obtained by rearrangement of Eq. 10 and combination with Eq. 13

$$R_e = \frac{G_i}{K} + S_i(M_i - M_e) \qquad \text{(Eq. 14)}$$

When the liquid flow rate exceeds the rate of evaporation, overwetting of the product will occur. If sufficient evaporative capacity is available in the incoming air, this condition will be evidenced by rising outlet air temperatures. Excessive rates of evaporation will not be detectable by a corresponding decrease in air temperature but will be reflected by a decrease in product moisture content. Measurements of outlet air temperature and product moisture content, therefore, can serve as convenient indices of equipment performance; suitable instrumentation should be provided for these measurements.

The rate of evaporation of the atomized granulating liquid can be put in general form (15)

$$R_e = \frac{h\,S(T_{ai} - T_d)}{\lambda} \qquad \text{(Eq. 15)}$$

where R_e = rate of evaporation in Kg. (of water) per minute; h = overall heat transfer coefficient, Kcal. per minute per °C. per cm.^{2} surface area; S = total surface area of droplets created by atomization of liquid granulating agent, cm.^{2}; T_{ai} = temperature of inlet air, °C.; T_d = temperature at surface of droplet, °C.; and λ = heat of vaporization of water, Kcal. per Kg.

Equation 15 shows that an increase in the surface area of the liquid droplets will increase the rate of evaporation. This can be accomplished by reducing the average droplet particle size in the spray. Factors which improve the degree of atomization (such as decreasing the liquid feed rate, decreasing the liquid viscosity,[4] or increasing the nozzle pressure) will improve the rate of evaporation. Measurements of the flow rate, temperature, and pressure of the liquid (and air pressure, if pneumatic nozzles are used) will be useful in controlling rates of evaporation.

Equation 15 shows further that increased rates of evaporation are obtainable by increasing the inlet air temperature. Since the heat transfer coefficient, h, improves with high air velocities (14), increased rates of evaporation also can be expected with increasing air flow rates.

Factors Related to Fluidization Quality.—Under proper fluidizing conditions, the solids in the bed undergo efficient mixing, and little or no segregation will occur (1, 2). All particles will tend to move in more or less random directions and have equal opportunity to enter the zone near the top where the concentration of droplets of granulating agent will be highest. Some "short circuiting" between the solids inlet and outlet positions may be expected, but this will be minimized in the well fluidized bed. Proper fluidization is evidenced by the "surging" in the manometer lines which results from the formation and collapse of air bubbles in the bed (1, 2). Uniform temperatures will also be observed throughout the bed when good fluidization has been achieved.

Bed expansion will occur with increasing inlet air velocities. Under these conditions, the momentum of the particles will increase, and increased degrees of particle attrition may result. Bed losses will also increase with increasing air velocity; however, improved collector efficiency may compensate for these effects.

Empirical correlations are available for first estimates of required air velocities for fluidization. The selection of optimum velocities is best determined by experimental tests and will represent a compromise between bed loss, attrition effects, collector efficiency, and heat transfer considerations. Once the air velocity has been selected, the maximum value of liquid flow rate, G_i, can be determined (for any given inlet air temperature) from the previous equations.

Possible Mechanism for Agglomeration.—The exact mechanisms by which size enlargement and agglomeration can occur in the fluidized bed granulator are difficult to establish on the basis of theoretical considerations alone. It is probable that small granules will be formed when two or more solid particles impinge with a droplet of liquid granulating agent. As the solvent evaporates, these particles will be cemented together. Further size enlargement may occur when these small granules impinge with other liquid droplets and particles. Rates of agglomeration can be expected to be influenced by the probability of droplet-particle collision. This will in turn be governed by bed height, droplet and particle, size and size distribution, rate of evaporation, and nozzle position among other factors.

For a given nozzle operating at a fixed position and with fixed inlet air conditions to the granulator,

[4] This may be accomplished by increasing the temperature of the granulating liquid or decreasing its solids content.

the length of the spray cone will determine the number of liquid droplets entering the fluidized bed. Lowering the nozzle height will increase the probability of droplet-particle contacts. An increase in droplet size will also improve this probability. Elevating the nozzle high above the bed can be expected to result in premature evaporation of the granulating solvent. This will lead to the formation of spray dried particles of the granulating agent, and little agglomeration of the feed solids will occur. Finally, control of the length and angle of the nozzle spray cone will be required so that the walls of the fluidized bed are not wetted by the liquid granulating agent.

CONTINUOUS FLUIDIZED BED GRANULATOR

Figure 5 is a schematic diagram of the continuous fluidized bed granulator. The system was developed from a commercially available fluidized bed reactor[5] which was suitably modified and instrumented for granulating operations in line with the preceding theoretical analyses.

The fluidization section of the unit consists of a 12 in. diameter, vertical, steel pipe with an expansion section at the top. The overall height of the unit is approximately 15 ft.

Air is supplied to the fluidized bed by a blower fitted with an adjustable control damper on its outlet. A calibrated orifice meter to measure the air flow rate is installed in the air line past the blower. The pressure drop across the orifice is measured by appropriate manometers.

The fluidizing air is heated to the desired temperature by passage through a steam heat exchanger. The temperature of the air leaving the exchanger is controlled by adjustment of inlet steam conditions. The heated air then passes through an air distributor plate into the bottom of the bed.

The solids to be granulated are fed into the bed from a powder hopper discharging into a screw conveyor. The inlet for the feed is located below the expansion section.

Air leaving the fluidized bed passes through a cyclone collector which removes the entrained solids. These solids are returned automatically to the fluidization section through a one-way trickle valve and connecting pipe inlet. All lines carrying solids are set at sharp angles with the vertical to insure good flow.

Liquid granulating agent is sprayed onto the fluidized solids through a pneumatic atomizing nozzle. The nozzle enters the unit from the top and is aimed in a downward direction. The liquid granulating agent is fed to this nozzle by a calibrated pump. The flow rate is measured by a calibrated rotameter installed in the liquid feed line.

Granulated product is removed near the bottom of the bed through an outlet pipe located slightly above the distributor plate; the rate of product removal is controlled by adjustment of an outlet valve.

Manometer taps are located directly above the distributor plate and at the approximate midpoint of the fluidization section. Pressure drop values between these points are obtained from respective manometer readings and are used to determine the weight of solids in the fluidized bed; additional manometer taps are located below the distributor plate and near the top of the unit. Thermocouples are placed below and above the distributor plate and at three additional elevations within the fluidized bed granulator.

The relative humidities of the ambient and outlet air are obtained with a sling-type psychrometer held near the blower inlet and the cyclone exhaust; the relative humidity of the heated air entering the fluidized bed is obtained by tracing the heating process in the steam heat exchanger on appropriate psychrometric charts.

[5] Fluo-Solids Reactor, Dorr-Oliver, Inc., Stamford, Conn.

FEASIBILITY STUDY

An introductory experiment with the fluidized bed granulator was completed to demonstrate the feasibility of the process. For this run, a 30-Kg. preblend of the components of a standard tablet formulation was used as the solid charge to the unit. The liquid granulating agent was syrup U.S.P. and was sprayed into the bed at a rate of 7.5 L. per hour. The fluidizing air velocity was set at approximately 73 c.f.m. with an inlet air temperature of approximately 240° F. Under these conditions a bed temperature of approximately 100° F. was maintained. The relative humidity of the outlet air was close to 100%. The agglomerated product obtained after approximately 40 minutes of operation showed an increase in average particle size from approximately 75 μ (feed) to approximately 275 μ (product) and was dry. This experiment established the feasibility of the process for agglomerating operations. Further, the operating conditions (outlet humidity, bed temperature, air temperature) obtained in this run were in accord with those predicted from the equations established in the previous sections of this report.

Further experiments have been completed to confirm and extend the value of this system in the continuous, high-speed production of tablet granulations. These studies are presented in an accompanying report (13).

SUMMARY AND CONCLUSIONS

A fluidized bed granulator has been designed and constructed. The unit allows continuous addition of powder feed and granulating liquid and continuous removal of dry granulated product.

The basic design criteria were developed by analysis of material and energy balances and consideration of rates of heat and mass transfer. The equations developed by this approach were used to predict the relationships among the important process variables.

This report also is intended to illustrate the value of applying pharmaceutical engineering techniques in the analysis of both new and conventional processes in pharmacy.

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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.

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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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