David M. Jones

Factors to consider in Fluid-Bed processing

Reprinted from PHARMACEUTICAL TECHNOLOGY April 1985

Factors to consider in fluid-bed processing

DAVID M. JONES

BECAUSE OF ITS capabilities in agglomeration and coating, the fluidized bed increasingly is being used in the development and production of solid dosage forms. The pursuit of new, specialized dosage forms has led to considerable diversity in methods of using fluidized-bed technology. For example, liquids can be applied to fluidized particles in a variety of ways, including top, bottom, and tangential spraying. For a given product, each method can offer markedly different finished-product characteristics.

Besides the method of spraying, nearly 20 product and process variables are involved in the fluid-bed process. To avoid a marathon development project, these variables must be classified by their significance. Even those variables not expected to influence the process, however, should be monitored and recorded. For instance, controlled-release products — especially sustained-release products — may react significantly to conditions that were initially determined to be of no consequence.

In short, effective experimentation in the laboratory is essential for determining the applicability, reproducibility, and economy of alternative methods of fluid-bed processing. In this article, fluid-bed technology will be examined from three perspectives:

- spraying methods
- scale-up
- additional variables.

Spraying Methods

The choice of spraying method in fluid-bed processing is based on a consideration of finished-product performance requirements and projected product volumes. The majority of products agglomerated in the fluidized bed are processed using the conventional top-spray granulator insert, shown in Figure 1. In the top-spray granulator system, granules are characterized by a porous surface and by an interstitial void space that results in increased wicking of liquid into the granules and improved disintegration or dispersibility (Figure 2). Another characteristic of granules produced by this technique is a bulk density that generally is lower than that attainable by other techniques of granulation.

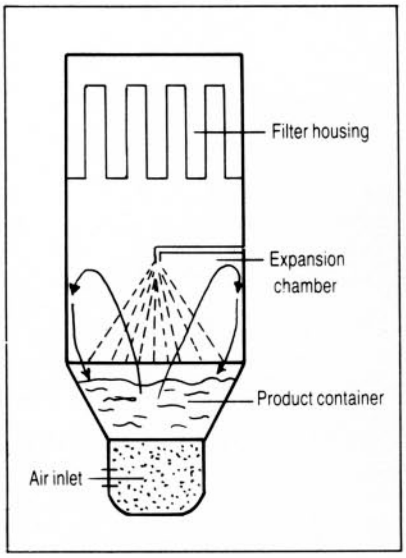


Figure 1: Schematic diagram of a conventional top-spray fluid-bed processor.

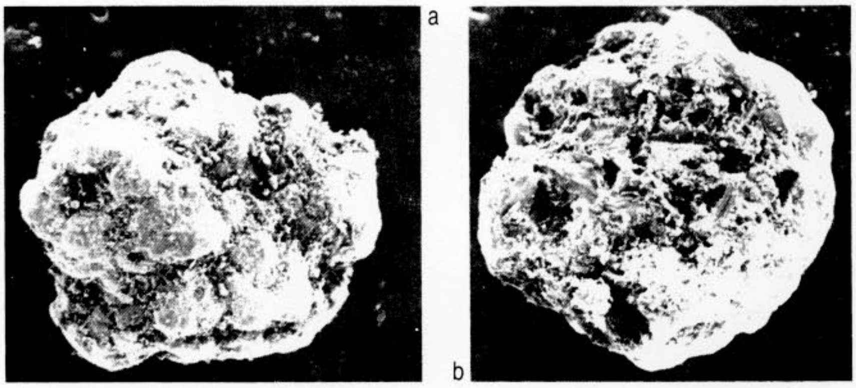


Figure 2: An acetaminophen granule produced by a conventional top-spray fluid-bed processor, at a magnification of 60X. Figure 2a shows the surface of the granule; Figure 2b shows a cross-section, which reveals the interstitial void space.

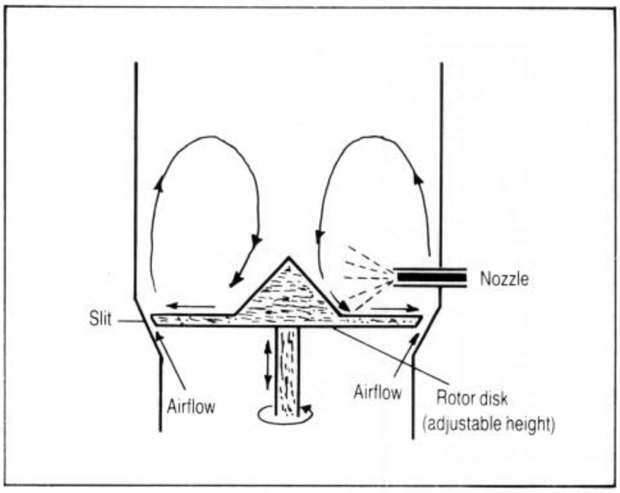


Figure 3: Schematic diagram of the product-handling section of a rotary fluid-bed processor.

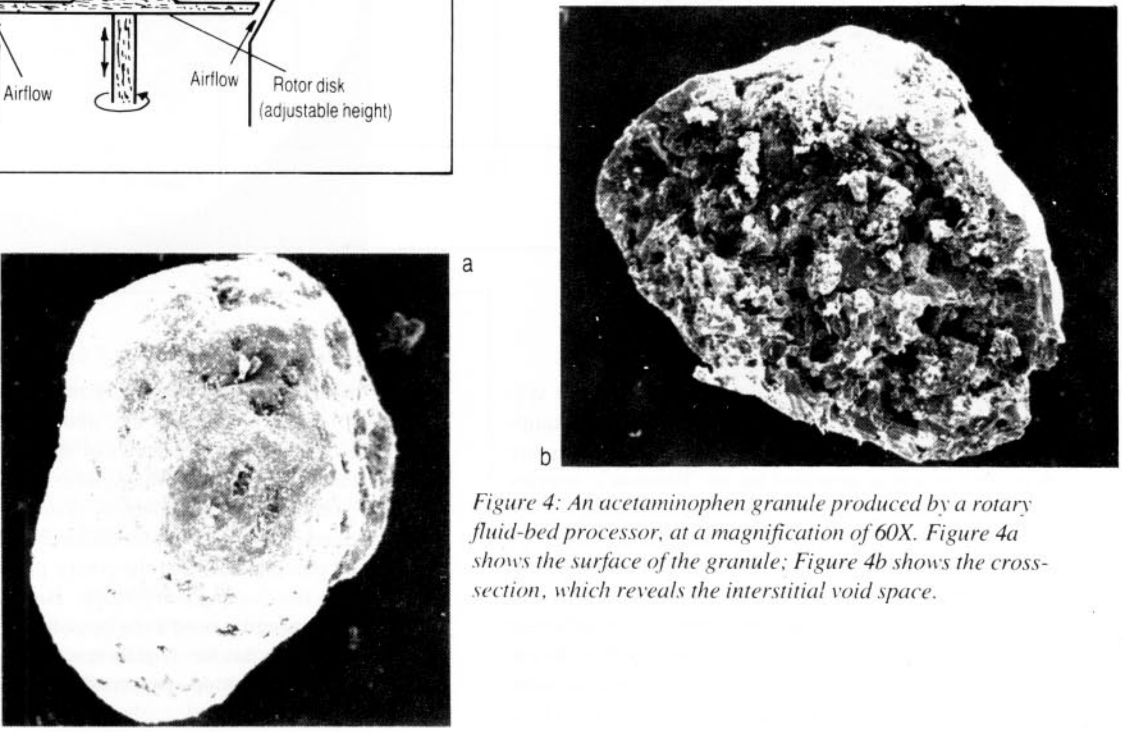


Figure 4: An acetaminophen granule produced by a rotary fluid-bed processor, at a magnification of 60X. Figure 4a shows the surface of the granule; Figure 4b shows the cross-section, which reveals the interstitial void space.

In contrast, a rotating-disk granulator, as shown in Figure 3, combines centrifugal, high-intensity mixing with the efficiency of fluid-bed drying, yielding a product that has a higher bulk density but that does not completely lack interstitial void space (Figure 4). In addition, material produced by this technique contains fewer fine particles, is less friable, and is more spherical in shape.[1] The variables primarily responsible for finished-product characteristics include the volume and temperature of the fluidizing air, the speed of the rotor disk, and the rate of liquid addition.

Three methods of spraying are available for coating in the fluidized bed: top, bottom, or tangential (rotary granulator/coater) spraying. Tablet coating is essentially restricted to the bottom-spray method, or the Wurster coating system, shown in Figure 5. Small-particle coating, however, is currently being conducted using all three types of spraying processes.

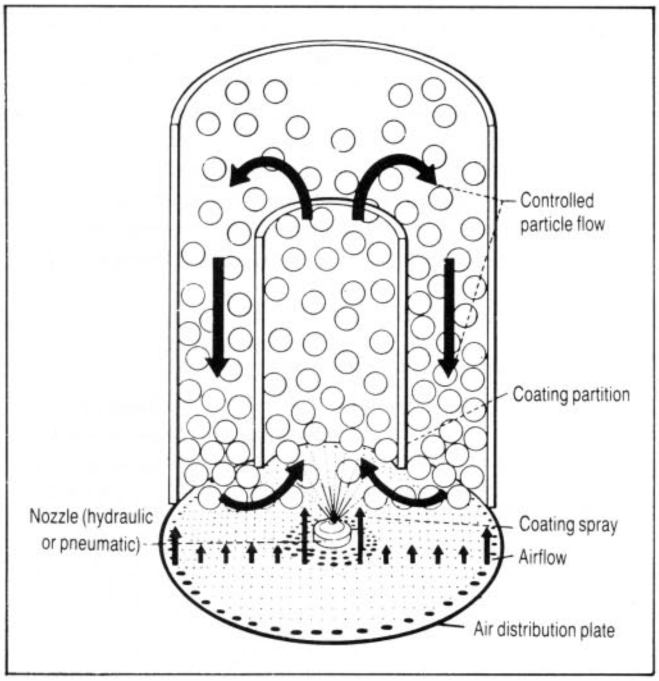


Figure 5: Schematic diagram of the product-handling section of the Wurster, or bottom-spray, coating system.

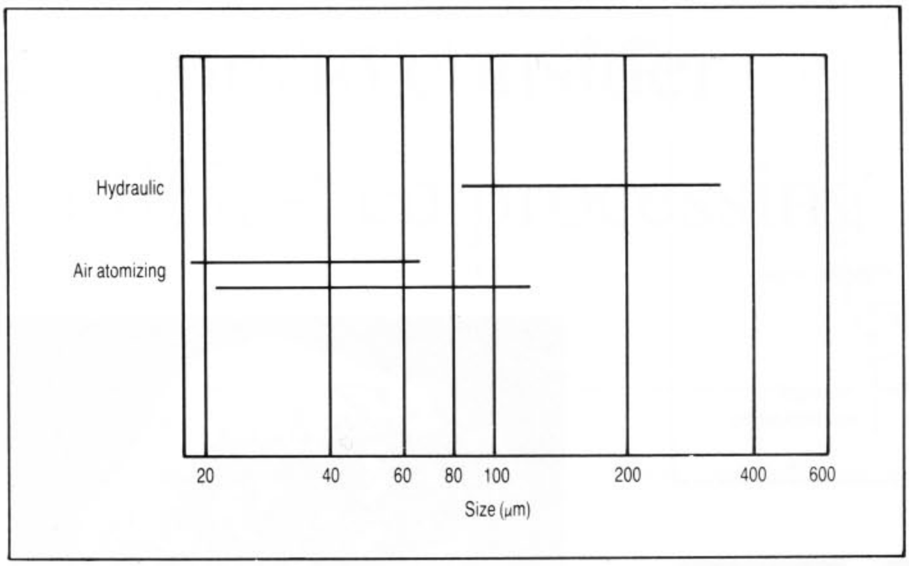


Figure 6: A comparison of droplet sizes from pneumatic and hydraulic nozzles.

The heart of the fluid-bed process is the liquid delivery system. In nearly all fluid-bed equipment except closed-loop equipment, the nozzles are binary; liquid is supplied at low pressure through an orifice and is atomized by air. Pneumatic nozzles typically produce smaller droplets, which is an advantage when coating fine particles (Figure 6).[2] As the liquid is atomized, its surface area for evaporation increases. The droplets as they travel change rapidly in solids concentration and their viscosity increases. Some droplets may contact the surface of the substrate and fail to spread uniformly, leaving an imperfect film. In extreme cases this produces spray drying of the coating substance. This problem can be severe if an organic solvent with a low heat of vaporization is used in the coating solution (Table I).

Not surprisingly, spray drying of the coating substance is most severe in the top-spray granulator insert, in which particle flow is the most random and the liquid is sprayed against the evaporation media. Microscopic examination of particles produced by this method reveals a surface that appears to be frosty and slightly opaque, whereas a properly applied film appears shiny and transparent (in the absence of colorants).

Nevertheless, a sizable amount of coating is performed in top-spray equipment because it does offer two important advantages. First, the top-spray granulator bowl provides greater capacity — up to 1500 kg — than do other methods. A production-sized Wurster coating system (bottom spray) has a capacity of only up to 600 kg, and a large-scale rotary granulator/coater produces batches of up to approximately 250 kg. The second advantage of this system is the simplicity of its design: a production-sized top-spray system typically has only one nozzle and pump; the Wurster coater, by contrast, has seven nozzles and pump heads, and the rotary granulator/coater has three or more nozzles and pump heads. Because of this simpler design, fewer variables need to be considered, and the cleaning and delays between batches require less time.

Table I: Heats of vaporization for commonly used solvents.

Solvent	Boiling Point (°C)	Density (g/cc)	Heat of Vaporization (kcal/ml)
Methylene chloride	40.0	1.327	0.118
Acetone	56.2	0.790	0.103
Methanol	65.0	0.791	0.232
Ethanol	78.5	0.789	0.166
Isopropanol	82.4	0.786	0.132
Water	100.0	1.000	0.541

As a general rule, the top-spray method can be used to achieve the following properties:

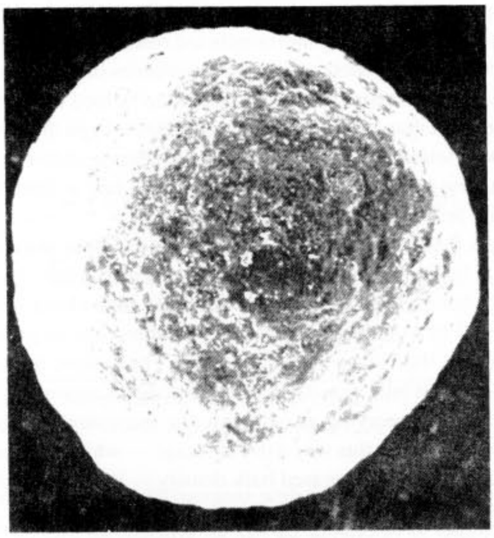
- taste masking
- enteric release
- isolation or barrier films.

This method is most effective when coatings are applied from aqueous solutions, latexes, or hotmelts. Although some coatings can be applied from organic solvents, this approach is not generally recommended. The top-spray coating method should not be used in the following situations:

- applying films for sustained release when precise reproducibility is required
- applying films from organic solvents for enteric release.

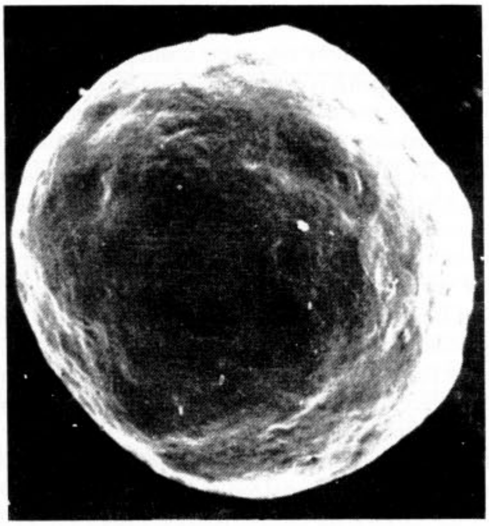
The Wurster system and the rotary granulator/coater are similar in that they both apply the coating solution concurrently with the flow of product. The Wurster system combines a partition (*coating partition*) and an orifice plate (*air distribution plate*) to organize the flow of particles in close proximity to the nozzle (Figure 5). The rotary granulator/coater's high air velocity through the slit and the centrifugal force of its rotating disk create a dense, helical, doughnut-shaped pattern.

Because the nozzle is immersed in the airflow in order to spray concurrently into the fluidized particles, the solution droplets travel only a short distance before contacting the substrate. As a result, the film is applied more evenly; in this way, release of drug from the coated substance does not depend on imperfections in the film, as is often the case with material coated by the top-spray method.



a

Figure 7: Nonpareil seeds (18/20-mesh) coated with ethylcellulose, at a magnification of 60X. The pellet in Figure 7a was coated using a conventional top-spray fluid-bed processor; the pellet in Figure 7b was coated using the Wurster coating system.



b

As an example, Figure 7 shows the difference in appearance between pellets coated with hydroxypropylmethylcellulose (HPMC) and red dye that were subsequently overcoated in the top-spray system (7a) and in the Wurster system (7b) with ethylcellulose plasticized with propylene glycol. Pellets coated in the top-spray insert released color quite rapidly, while pellets coated in the Wurster system released color very slowly.

Scale-Up

The successful scale-up of any process to pilot- or production-sized equipment depends greatly on the existence of an effective laboratory development program. As thoroughly as possible, the influence of all major variables should be investigated so that the list of unknowns is reduced to only one element — the increased weight of the product in a production-scale machine.

Although predicting results may seem difficult when scaling up from 8 kg to 500 kg — obviously, the failure of an 8-kg batch is far less glaring — some generalizations can be made. For instance, depending on the product, a 20% increase in finished-product untapped bulk density can be expected when scaling up the fluid-bed granulation process on the order of the quantities just mentioned. Although a few process variables can be adjusted to vary and control the density, if a product with a low density was achieved with some difficulty in the laboratory, achieving the same result on a production scale will be nearly impossible. Lab-scale density should be targeted to be at least 20% lower than the density desired at the production scale because it is easier to increase the density in a production-scale fluid-bed granulator.

Granule growth in fluid-bed granulation may involve three stages: nucleation, transition, and ball growth.[3] A typical process includes only nucleation and transition; ball growth — or the coalescence of granules into very large aggregates — is generally undesirable. The shift from the transition to the ball-growth state depends primarily on the humidity in the bed. The *critical water content*, or the point at which growth becomes rapid and difficult to control, typically is lower in production-scale equipment because of the bed load. Because granule size is directly proportional to humidity in the bed during granulation,[4] it may be desirable to approach the critical water content to obtain a coarse granule. The product may become very large, however, before this moisture level can be attained, so it may be necessary to alter a less significant variable in order to produce the desired results.

If the product in its final form performed well when processed under a broad range of conditions in the laboratory, the conditions that offered the shortest process time should be used for full-scale production. A high inlet-air temperature will enable use of the maximum spray rate and will reduce the *weather effect*, or variation in drying capacity resulting from changing ambient air dew points, which will be discussed later in this article. A high inlet-air temperature should be avoided in production equipment, however, if it was not investigated at the laboratory or pilot scale, because evaporation rates can have a significant effect on the performance of the finished product.

The ratio of the depth of the bed to the diameter of the bottom screen is not held constant in scaling up from lab to production scale. Typically, this ratio is larger in production-scale equipment, resulting in a machine that accommodates a large batch of material without a proportional increase in volume of air to achieve an adequate fluidization pattern. The spray rate must be based on the increase in the volume of drying air, not on the increase in batch size. For example, if the batch size of a product is scaled up by a factor of 50 and the volume of fluidizing air required is 35 times as great as that in the lab-scale machine, a spray rate that is 50 times the rate used in the small-scale trials may cause the critical water content to be achieved too rapidly, and the batch may be ruined or may require reworking. In the situation just presented, the selected spray rate is excessive relative to the drying capacity of the fluidizing air.

Moreover, two machines performing identical functions may differ greatly in degree of instrumentation. For example, lab-scale and production-scale machines may or may not be equipped with indicators of air speed or volume. If a machine lacks such instrumentation, the required spray rate can be estimated by calculating the cross-sectional areas of the bowl screens. Assuming that the same air velocity through the screens is required for adequate fluidization in both sizes of machines, the ratio of the large to the small screen areas provides the multiplier for determining the appropriate spray rate for the production machine.

Scale-up of the spray rate in the coating process is generally more complex than it is in the granulation process. For instance, while the spray rate in fluid-bed granulation is generally limited by drying capacity, in fluid-bed coating it is more likely to be affected by the properties of the liquid being sprayed and by the *zone* in which the application of coating takes place. In the coating process, it is not unusual for the air to have excess capacity for moisture or solvent. As discussed previously in this article, precise reproducibility of release rate is best obtained when droplets travel as short a distance as possible before contacting the substrate surfaces. Because the coating zone is small, particles must pass through it very quickly or localized overwetting can take place, leading to agglomeration of the particles, which generally is undesirable.

The coating zone through which droplets must travel can be minimized in a conventional top-spray fluid-bed coater by positioning the nozzle at the shortest possible distance from the static bed. In this way, the density of particles in the coating zone is maximized but is still not as good as that achieved by the Wurster or rotary granulator/coater systems.

In light of the excess drying capacity that is inherent in this process, a simple way to increase the rate of application is to increase the number of coating zones. For instance, using a multi-headed nozzle in top-spray equipment, multiple partitions and nozzles in Wurster coating systems, and multiple nozzles in pilot- or production-scale rotary granulator/coaters can increase the rate of application.

As in granulating, the spray rate in the coating process is not determined directly by the increase in batch size but is based on other factors. A multiplier determined by the ratio of the areas of the orifice plates under the partitions in lab- and pilot-scale machines works to a certain extent, but there are frequent exceptions. A major consideration is the product itself. Nearly all film formers become tacky before drying, which is a leading cause of agglomeration. The separation of small particles by air suspension allows coating with little or no agglomeration. The finer the substrate, however, the more difficult discrete coating becomes. The tackiness of some film formers can be reduced by additives suspended in the coating solution. Although the effect of these additives on film properties must be considered, their benefits in application can be significant. For example, adding titanium dioxide to a sticky coating solution in one project enabled the spray rate to be increased by a factor of three. In general, film formers sprayed from a solution are the most prone to particle agglomeration, whereas latexes (or pseudolatexes) and materials sprayed from hotmelts are less likely to be troublesome.

Additional Variables

When a nozzle and a liquid-control system were first added to fluid-bed dryers to create the batch fluid-bed granulator, precise control of process variables was lacking. Although the machine showed great promise, the absence of monitors and controls made reproducibility difficult. Fortunately, several people examined the process closely and conducted research to determine the effects of both process and product variables on the finished product. The information they produced has helped to identify those variables that can have the greatest effect. Typically, these researchers found, the fluidizing air temperature and volume, the atomizing air pressure, and the liquid flow rate are the most significant process variables.

The bulk density of a finished product, for example, was once thought to be an uncontrollable property. Research has shown, however, that this property can be precisely reproduced or altered at will by concentrating on two variables: the in-process moisture and the fluidizing air volume. The lowest possible finished-product bulk density can be attained by keeping the bed moisture during spraying at or below the maximum finished-product moisture. In this way a drying stage — which can cause product attrition and increased bulk density — is not needed after spraying.

The volume of fluidizing air can be affected by several factors. Typically, an adjustable damper is used to control this volume; nevertheless, several other restrictions to airflow are present as well. For instance, as the outlet-air filter or the product-bowl screen becomes occluded by binder, by coating material, or by fine powders, resistance to airflow increases. Without a sensitive warning indicator, the volume of air can drop enough to cause the bed moisture to increase, thereby increasing the bulk density of the finished product. (Generally, the higher the bed moisture during spraying, the higher the density.) Taking this point even further, resistance to airflow by the bowl or by the filter can be very significant — possibly allowing bed moisture to drift beyond the critical moisture content and causing ball growth or bed failure.

When using fluidizing air of low temperatures, climatic conditions can play a significant role in the fluid-bed process. In geographic locations where the *specific humidity* (or the quantity of water in the air) varies during the year, its effect on the relative humidity of the heated fluidizing air becomes pronounced. For example, under such conditions the drying capacity of air heated to 50 °C may vary by as much as 30% throughout the year. Thus, even at a constant spray rate the bed moisture can still vary significantly. Of the several possible approaches to solving this problem, the simplest is dehumidification to a predetermined maximum dew point. The lower this desired dew point, the more costly will be the equipment and operation.

Another approach is to increase the temperature of the fluidizing air to compensate for the decreased drying capacity caused by a high specific humidity. For example, air heated to 100 °C will suffer only about a 5% reduction in drying capacity in even the worst conditions. Of course, a major consideration in this approach has to be the effect of this greater heat on the characteristics of the finished product.

A third approach is to follow a moisture curve during the spraying process. When calibrated correctly, recently developed moisture analyzers can instantly provide information on moisture content, thereby allowing timely monitoring of the granulation process. Process variables such as the spray rate and the temperature of the fluidizing air can then be adjusted within predetermined limits to reproduce the moisture curve, thereby minimizing batch-to-batch variations that could result from changing weather conditions.

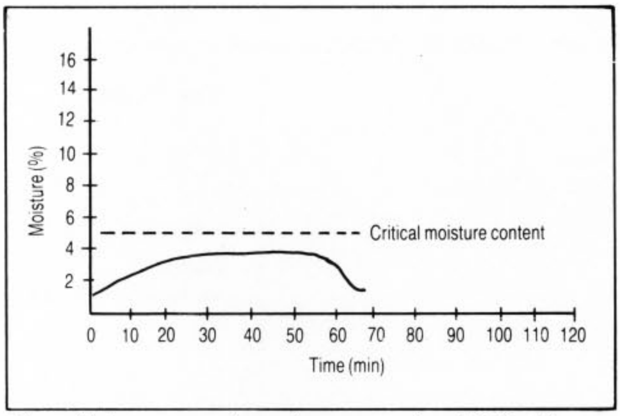


Figure 8: A representative moisture curve in a fluid bed for water-soluble substrates agglomerated with water only.

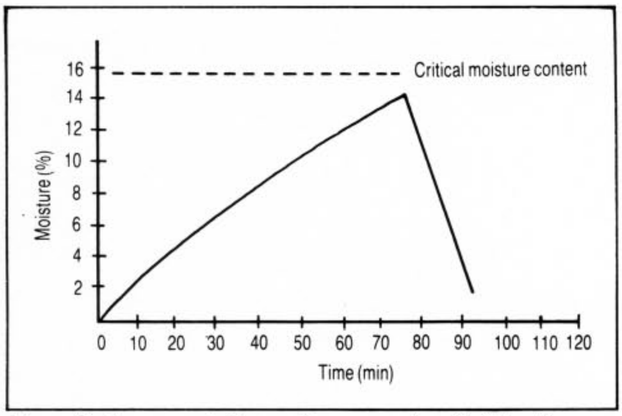


Figure 9: A representative moisture curve in a fluid bed for nonsoluble substrates agglomerated with hardening binder.

For products agglomerated with water alone (water-soluble substrates), this method allows spraying at a constant moisture content — possibly one that is near the finished product's maximum moisture content but that is always below the critical moisture content (Figure 8). Products sprayed with hardening binders display different moisture-handling characteristics; generally, the moisture content of the bed increases proportionately with the accumulation of binder by the bed (Figure 9).

Because the spray rate of an aqueous coating solution may depend on the amount of moisture in the fluidizing air, an obvious advantage when working with aqueous systems is dehumidification — or even dew-point control, using humidification when necessary. Additionally, in many fine-particle coating installations, the dew point is controlled in order to dispel static electricity when coating with organic solvents. This action is necessary because although the moisture in the air during the summer months may be sufficient to dispel static charges, in the colder seasons the absence of moisture can result in severe agglomeration of product as the coating process continues. Some coated products have an electrostatic attraction for themselves and enter the coating zone in clumps, where they are sprayed and permanently joined by solid bridges of coating substance. In a recent project in which the author was involved, a 20% incidence of agglomeration was reduced to less than 5% by adding enough moisture to the fluidizing air to simulate a summer day.

Another phenomenon observed recently by the author involved different dew points at low temperatures of fluidizing air when film coating with an organic solvent. Examples of the conditions encountered in this situation are, for the first series, a dew point of 1 °C for the ambient air, a temperature of 25 °C for the fluidizing air, and an enthalpy of 38 kJ per kilogram of dry air. For the second series, the conditions were a dew point of 12 °C for ambient air and an enthalpy of 51 kJ per kilogram of dry air; the temperature of the fluidizing air in both series was 25 °C. With all other operating conditions the same, a look at a psychrometric chart shows that the heat content of moist air is greater than that of dry air.

When low temperatures of fluidizing air are chosen in order to accommodate the low heat of vaporization that is characteristic of some organic solvents, the effects of this difference can be serious. For instance, if the solution formula and processing conditions are such that the product's performance is close to the pass-fail boundary, the variation in heat content could result in dramatically different release profiles, depending on the solvents used. Furthermore, if water is present in the organic solvent solution and the drying capacity is allowed to vary by not controlling the dew point, the driving force for evaporation of water is affected as well. Residual water or mixtures of solvent and water in the coating layers may affect the film forming process. For these reasons, it is prudent to control ambient air dew points in organic solvent processes as well as in aqueous coating operations.

Conclusion

To date, little research has been published in this area. Nevertheless, the effects of moisture and heat content in fluid-bed processes — as well as the effects of the size, shape, porosity, and friability of the particles — on the release characteristics of coated products must be considered. A fundamental understanding of product and process variables will yield predictable results and allow a smooth transition from the laboratory to production.

Acknowledgments

The author wishes to thank Stephen E. Abele of Glatt Air Techniques, Paul Guley of Ayerst Laboratories, and Dr. Atul Mehta of Nortec Development Associates for their technical assistance.

References

1. Jager, K.F., and Bauer, K.H., "Effect of Material Motion on Agglomeration in the Rotary Fluidized Bed Granulator," *Drugs Made in Germany*, Vol. 25, No. 2, 1982, pp. 61–62 and 64–65.
2. Hall, H.S., and Pondell, R.E., "The Wurster Process," in *Controlled Release Technologies: Methods, Theory and Applications, Vol. II*, A. Kydonieus, ed., Boca Raton, Florida, CRC Press, 1980, pp. 137–138.
3. Schaefer, T., and Worts, O., "Control of Fluidized Bed Granulation — V," *Arch. Pharm. Chemi., Sci. Ed.*, Vol. 6, 1978, pp. 78–81.
4. Schaefer, T., and Worts, O., "Control of Fluidized Bed Granulation — III," *Arch. Pharm. Chemi., Sci. Ed.*, Vol. 6, 1978, p. 12.

Bibliography

Davies, W.L., and Gloor, W.T., "Batch Production of Pharmaceutical Granulations in a Fluidized Bed" (series of two articles), *J. Pharm. Sci.*, Vol. 60, No. 12, Dec. 1971, pp. 1869–1873, and Vol. 61, No. 4, April 1972, pp. 618–622.

Schaefer, T., and Worts, O., "Control of Fluidized Bed Granulation" (series of five articles), *Arch. Pharm. Chemi., Sci. Ed.*, Vol. 5 and Vol. 6, 1977–1978.