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AIR SUSPENSION COATING FOR MULTIPARTICULATES

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ABSTRACT

Fluidized bed systems are widely used in the pharmaceutical industry for production of core material and for film coating. Top spray coaters, evolving from the fluid bed dryers of nearly 40 years ago, produce batches of fine, coated particles in excess of 500 kg. Wurster bottom spray equipment is used to manufacture pellets as well as to coat products ranging from powders to tablets. Rotary tangential spray systems generate micro pellets (approximately 100-600 microns) from powders, macro pellets (about 700-2000 microns) by layering, and apply coatings for all types of release. For all processes, films may be applied using water, organic solvents, or via hot melt to provide sustained or controlled release, taste masking, enteric release, improved stability, or aesthetics. However, depending on the type of substrate and coating material, the air suspension method selected may be a significant process variable. In addition to formulation considerations in product development, an understanding of these types of processing techniques is essential.

Fluidized Bed Equipment Types

The fluidized bed is well known for its drying efficiency, and has been used for drying and granulating for many years. It is also used extensively for coating due to its ability to apply virtually any type of coating system (solution, suspension, emulsion, latex, and hot melt) to a wide range of particle sizes. Coatings can be applied to fluidized particles by all techniques. The conventional top spray method shown in Fig. 1 has been used for more than a decade for coating. It evolved from the fluidized bed dryers commercialized more than 30 years ago. The substrate is placed in the product container (A), which is typically an unbaffled, inverted, truncated cone. The volumetric capacity ranges from 2 liters (lab or feasibility machinery) to more than 2000 liters. A fine retention screen and an air or gas distribution plate (B) comprise the base of the product container. Air is drawn through the distribution plate (B) and the product bed. As the velocity (and volume) of air is increased, the bed no longer remains static but becomes fluidized in the air stream. The point at which the bed becomes just fluidized is known as *incipient fluidization* (Fig. 2).

The velocity of particles in the bed under this condition is too low for an economical process, and may also allow agglomeration to occur due to excessive particle-particle contact while the particle surfaces are still moist. Increasing the air velocity results in a wider fluidization range known as *bubbling fluidization,* in which the bed can be defined as containing two phases: A particulate phase, containing particles and air, and a bubble phase, which contains the excess air.

The particles are accelerated from the product container past the nozzle (C), which sprays the coating liquid countercurrently onto the randomly fluidized particles. The coated particles travel through this coating "zone" into the expansion chamber (D) where drying takes place (Fig. 2).

The wider diameter in this zone permits deceleration of the particles to below entrainment velocity. The particles fall back into the product container and continue cycling throughout the duration of the process. The random mixing and evaporative efficiency, provided by bubbling fluidization, and the speed of recycling of the particles provide good quality films (Fig. 3).

In 1959, Dr. Dale Wurster, then at the University of Wisconsin, introduced an air suspension technique known as the *Wurster system*. Initially used more frequently to coat

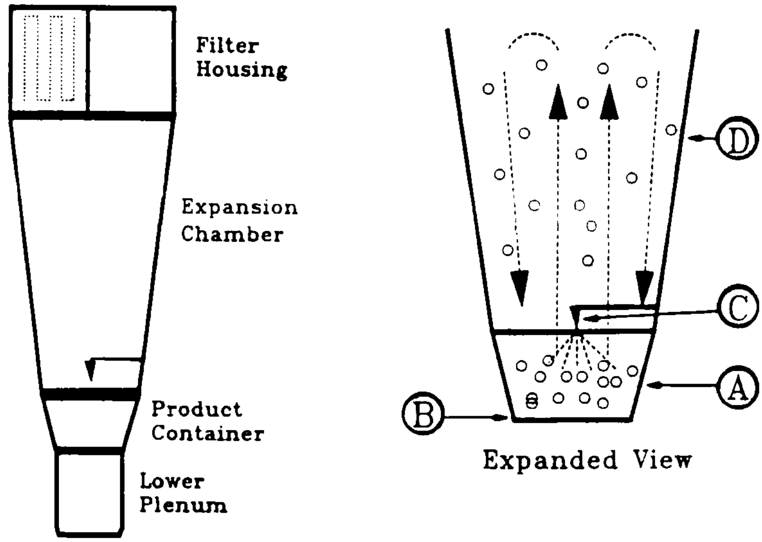


Figure 1 - **Top Spray Coater: (A) Product container; (B) air distribution plate; (C) spray nozzle; (D) expansion chamber.**

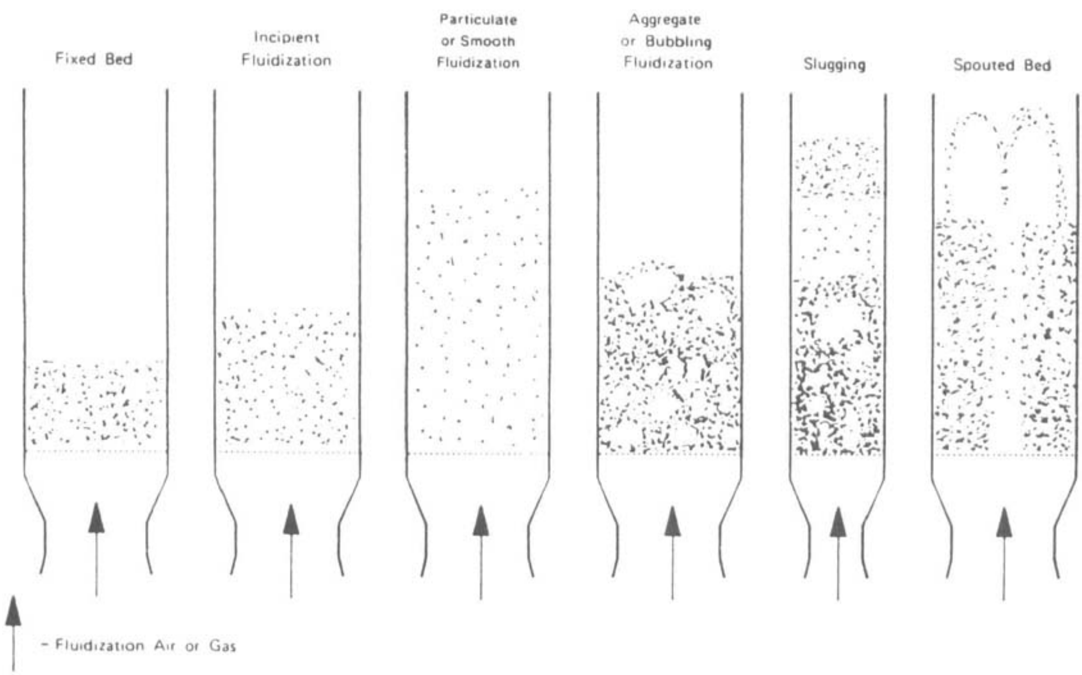


Figure 2 - **Characterization of fluid beds.**

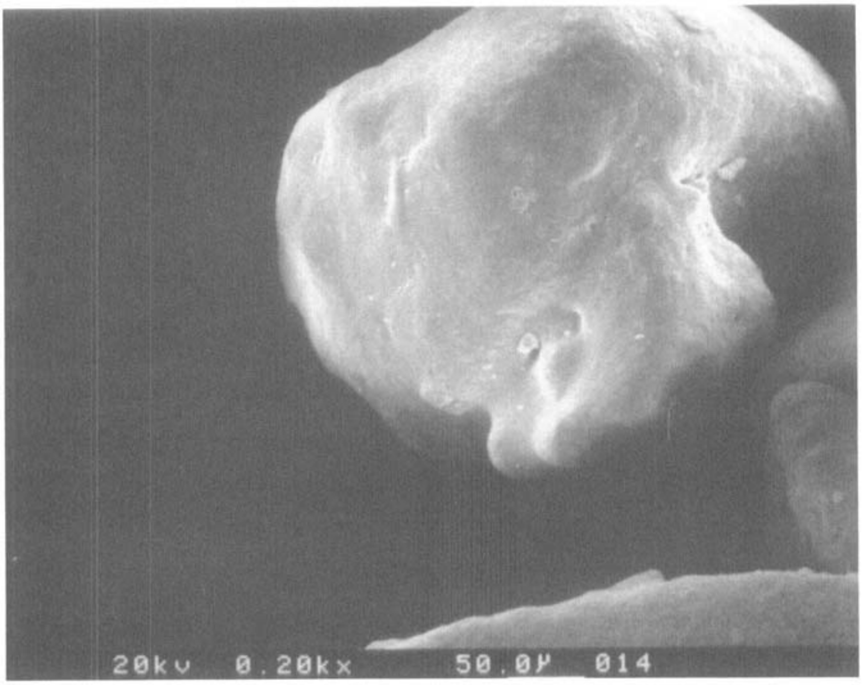


Figure 3 - **Drug crystal coated with Latex co-polymer. Top spray fluidized bed, magnification 200x.**

tablets, the process in now widely used for small and intermediate sized particles. The components of the system are illustrated in Fig. 4a. The coating chamber (A) may be cylindrical or slightly conical. Inside, a cylinder half the diameter of the base of the chamber, referred to as a *partition* (B), is located. A recent refinement (1993) of the Wurster process employs a second, smaller partition referred to as a *nozzle surround* (Fig. 4b), which rests on the bottom of the product container and extends above the nozzle. Its purpose is to keep substrate from entering the region of highest droplet density in the spray pattern. Product does not enter the spray zone until the pattern is more fully developed. The bottom of the Wurster insert is comprised of a fine screen and an air distribution, or orifice plate (C). In the center of the plate, a nozzle (D) is positioned to spray upwardly. The porosity of the plate in the area beneath the partition is high, allowing a high volume and velocity to pneumatically transport particles vertically through the partition and spray zone. This type of fluidization most closely

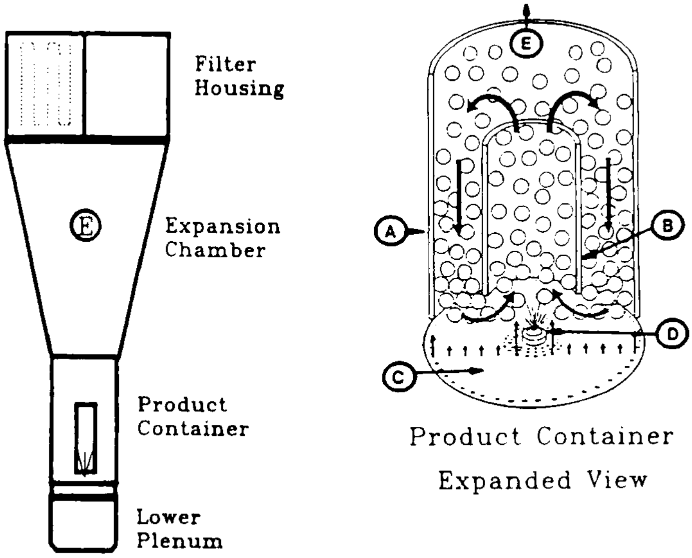


Figure 4a - Wurster bottom spray coater: (A) Coating chamber; (B) partition; (C) air distribution plate; (D) spray nozzle; (E) expansion chamber.

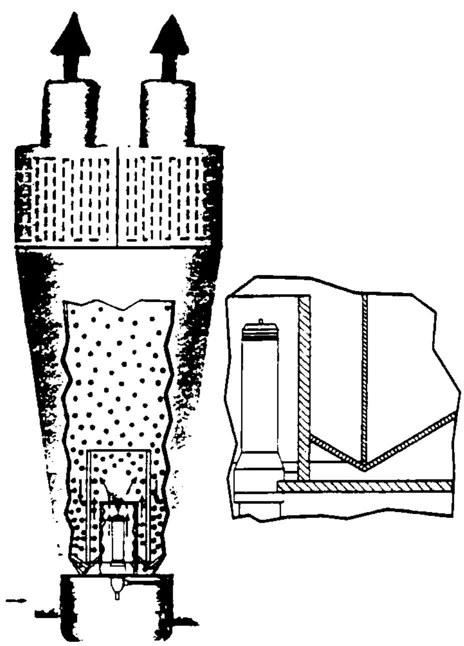


Figure 4b - Wurster HS

resembles a *spouted bed.* The coated particles exit the partition and begin to decelerate in the expansion chamber (E).

When the air velocity is such that the particles can no longer be entrained, they drop into the area between the partition and the wall of the coating chamber known as the *down bed.* The air volume in the down bed depends on the size and number of holes in the orifice plate in the area outside of the partition. This air volume should be enough only to enhance downward motion, keeping the down bed in near weightless suspension. A critical process variable, *partition height,* a gap between the base of the partition and the orifice plate, is selected such that downbed motion is smooth and as rapid as possible. Particles cycle through the spray zone in a matter of seconds, as is typical of all fluidized bed processes. However, in contrast to the conventional, top spray technique, the fluidization pattern is much more controlled in the Wurster system.

A relative newcomer to coating is referred to as *tangential spray* or *rotary fluidized bed* processing (Fig. 5). This technique was conceived to combine high shear granulation speed and energy with fluid bed drying efficiency for producing for higher density granulations than typically possible in conventional fluid bed granulators. It is now more often used for pelletizing by a variety of methods. *Direct pelletization* is a means by which potent micro pellets (approximately 100-600 microns) are produced from very fine powders. *Layering,* to produce macro pellets (700-2000 microns) is accomplished by applying a layer of drug particles to some type of seed material. The controlled release coating can subsequently be applied. Batch sizes range from less than 1 kilogram to nearly 400 kilograms.

The product container consists of an unbaffled cylindrical chamber (A) with a solid, variable-speed disc (B) at its base. The disc and chamber are constructed such that a gap (C) exists at the perimeter of the disc through which process air is drawn. The velocity of the air depends on the disc gap and the fluidization air volume, which is process dependent. During fluidization, three forces combine to provide a pattern best described as a spiraling helix. Centrifugal force causes the product to move toward the wall of the chamber, air velocity through the gap provides acceleration upward, and gravity and turbulent eddies cascade the product inward and toward the disc once again. Beneath the

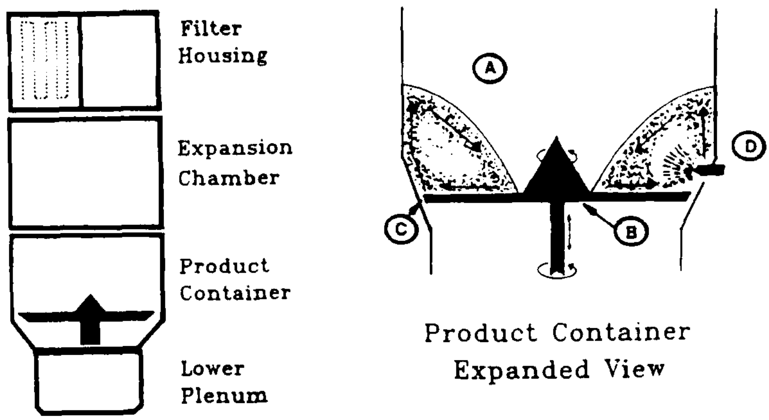


Figure 5 - **Rotor tangential spray coater: (A) Produce chamber; (B) variable-speed disc; (C) disc gap or slit; (D) spray nozzle.**

surface of the rapidly tumbling bed, a nozzle (D) is positioned to spray in the direction of flow of the particles. The particle cycling time of this technique is very rapid; hence, the films are high in quality, closely resembling those applied using the Wurster system.

Fundamentals of Film Coating

Uniformity of distribution of the film and evaporative efficiency to inhibit core penetration by solvents or water are common to the three types of fluidized bed processing. However, each of the techniques has limitations, and they are by no means equivalent. Before examining each process in detail, a brief description of coating fundamentals and general process and product variables is necessary.

Application of a film to a solid is indeed very complex. A layer of coating does not occur during a single pass through the coating zone, but relies on many such passes to produce complete coverage of the surface. Droplet formation, contact, spreading, coalescence, and evaporation, as illustrated in Fig. 6, are occurring almost simultaneously during the process.

The nozzles typically used in the fluidized bed coating process are binary: liquid is supplied at a low pressure and is sheared into droplets by air. Droplet size and

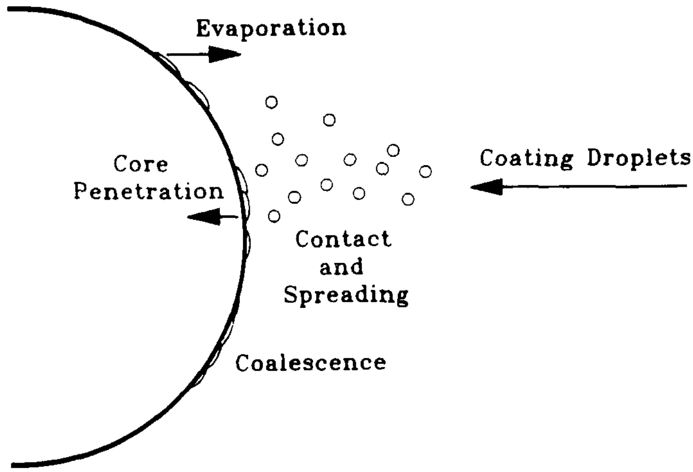


Figure 6 - Dynamics of the coating process

distribution are more controllable with this type of nozzle than with a hydraulic nozzle, especially at low liquid flow rates. However, the air used for atomization also contributes to evaporation of the coating solvent. This evaporation results in increasing the droplet's viscosity, and it may inhibit spreading and coalescence upon contact with the core material. Another factor affecting droplet viscosity is the distance that the droplets travel through the primary evaporation media (the fluidization air) before impinging on the core. This problem is amplified with the use of organic solvents which evaporate much more quickly than water or films whose viscosity is very sensitive to changes in solids concentration. In all three process techniques, the nozzle is positioned to minimize droplet travel distance.

Process Variables

The most significant process variable is the selection of technique to be used. The majority of the remaining process variables are common to each type, however, and are listed in Fig. 7.

The rate of evaporation of the coating application media can significantly affect film formation in both aqueous and organic solvent systems. Fluidization air volume,

EVAPORATION
- a) Fluidization air volume
- b) Fluidization air temperature
- c) Fluidization air humidity

APPLICATION RATE
- a) Solution concentration
- b) Coating Zone

DROPLET SIZE

Figure 7 -- General Process Variables

temperature, and humidity are the three components of this variable. Because the fluidization air volume affects particle velocity and, hence, the fluidization pattern, it should remain consistent from batch to batch, and if possible, throughout the course of a batch. Drying capacity for aqueous coating systems is affected by the fluidization air temperature and absolute humidity as illustrated in the psychometric chart (Fig. 8).

If a low temperature is chosen to accommodate a heat-sensitive polymer, drying capacity will fluctuate due to seasonal changes in the weather. An example illustrating this phenomenon follows:

> An aqueously applied thermoplastic polymer requires a product temperature of not more than 25°C. Assume that process variables such as fluidizing air volume and liquid spray rate are the same for both experiments.
>
> Day 1 Ambient Conditions:
> 8°C dry bulb
> 5°C wet bulb
> 1°C dew point, equivalent to 4 g H_2O per kg dry air
>
> Day 2 Ambient Conditions:
> 26°C dry bulb
> 22°C wet bulb
> 20°C dew point, equivalent to 15 g H_2O per kg dry air

On day 2, to keep driving force the same as the day 1 conditions, inlet air temperature must be raised significantly. When air of this temperature and humidity is passed through the product during spraying, evaporative cooling (from the water in the coating liquid)

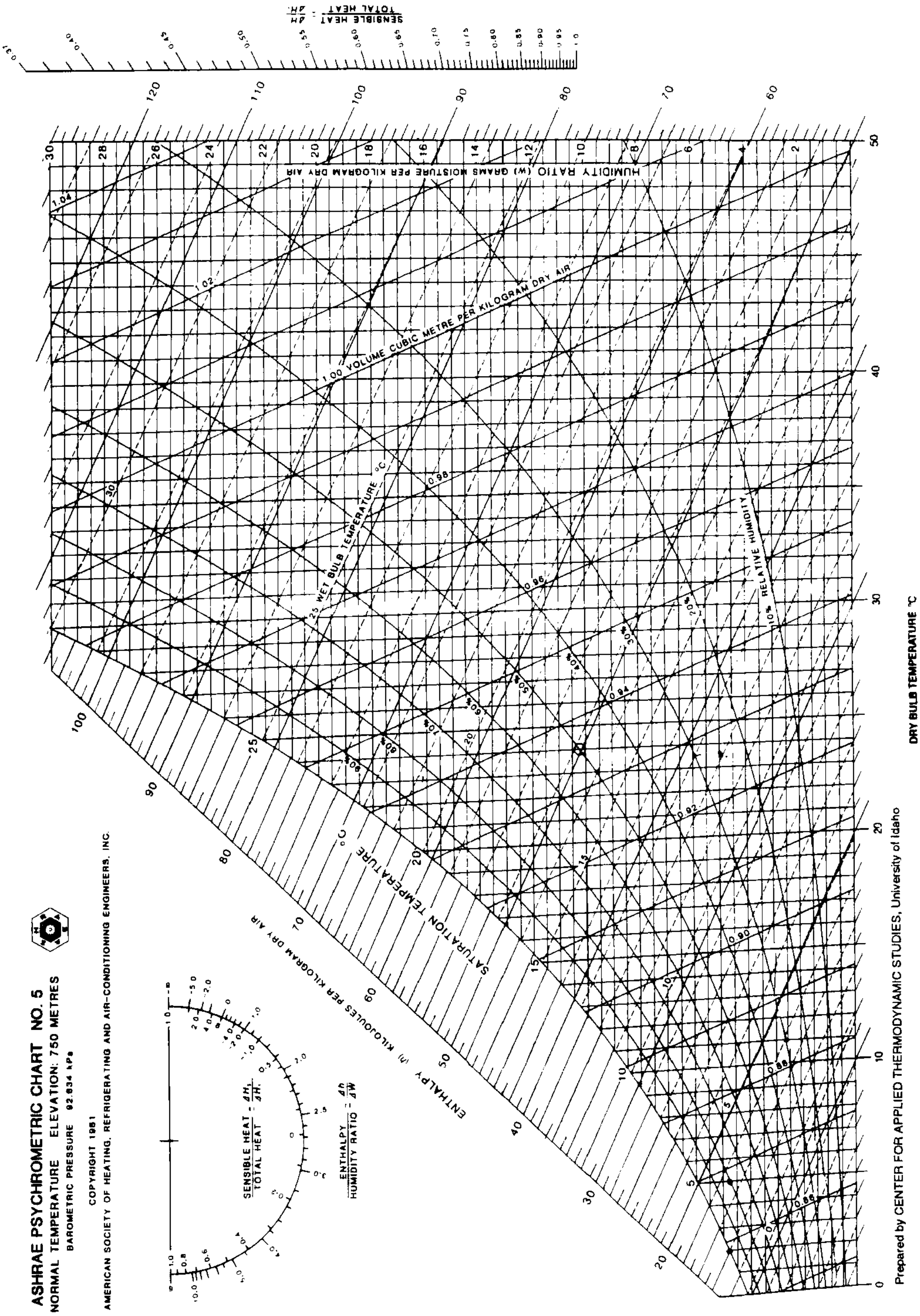


Figure 8 - The Psychometric Chart

will increase product temperature to well above 25°C. Seizure of the bed is possible due to the inability to keep product temperature low enough. On a humid summer day, such as day 2, drying capacity is eroded so significantly that the coating liquid application rate must be substantially reduced or agglomeration will occur. Absolute humidity must be controlled to allow reproducible application rates.

For organic solvents, a low fluidization air temperature may be chosen to accommodate the solvent's low heat of vaporization. The danger in allowing absolute humidity to vary is that enthalpy, total heat, which determines evaporation rate, increases at a given dry bulb temperature as the absolute humidity increases. Additionally, if absolute humidity is high, evaporative cooling by the solvent in the coating zone may locally depress the air temperature below the dew point, causing condensation of water onto the substrate surface, as the film is forming. If the film is incompatible with water, it would not perform as desired.

Consistency in absolute humidity is recommended, but removal of all moisture is not required. In fact, in many organic solvent coating processes, a quantity of moisture in the process air is usually helpful in dispelling static electricity, which develops after the surface of the particles is completely covered.

Coating uniformity is a result of the rapid cycling of particles or the number of times the particles are exposed to the spray. The rate at which the coating is applied (on a solids basis) is dependent on the solution concentration and the spray rate. Because the quantity of coating required for effective coverage of small particles is substantial, the tendency is to apply as concentrated a solution as possible to minimize the process time. However, the droplet size and spreading characteristics will be affected by the increased viscosity, and the resulting film may not perform as desired. Agglomeration of fine particles may also result.

Spray rate is dependent on three factors: (1) capacity of air for the solvent being used; (2) the tackiness of the coating being applied; and (3) the speed with which the particles travel through the coating zone. With most coating systems, the fluidizing air has excess capacity for the application media. The rate-limiting factor is generally the tackiness of the coating solution as it changes from a liquid to a solid. In the fluidized bed process, coating is applied to particles suspended in the air stream. However, particle-machine and particle-particle collisions do occur. If two particles collide where coating has just been applied, a bridge may form between them. If the mass of the particles (which decreases as particle size decreases) is not sufficient to disjoin the particle because of the tackiness of the coating substance, the bond will become permanent, resulting in agglomeration. It has been reported in the literature that coating solution tackiness can be altered. Additionally, several coating system vendors have experience in this area.

Coating solution droplet size should be selected relative to the size of particles to be coated. Atomizing air volume and pressure determine droplet size; the higher these values, the smaller the droplets. High atomizing air volume and pressure are not necessary for coating tablets. For small particles (250 μm or smaller), however, high pressure and volume may be necessary to attain droplets small enough to avoid the formation of liquid bridges between particles at contact points and thus avoid agglomeration.

Droplet size is also a function of characteristics of the coating solution such as viscosity and liquid surface tension, and the formulation of the coating solution. For this reason, droplet size is selected empirically rather than determined mathematically or experimentally. However, several nozzle vendors do have droplet size histograms available to aid in understanding the nozzle's capability when using water.

All the three processing techniques (top, bottom, tangential) are typically set up to maximize product density in the coating zone. Machine components or process variables such as fluidization air volume can be adjusted to increase particle velocity such that particles pass through the coating zone quickly and receive only a small amount of spray. At some point, however, the coating zone will be 'saturated'. To increase the spray rate significantly, the number of coating zones must be increased. In pilot and production scale equipment, this is achieved by using multiple nozzle wands or multi-headed nozzles in the top spray method, multiple partitions and nozzles in the Wurster system, and multiple nozzles at the perimeter of the disc in the tangential or rotary fluidized bed coater.

Product Variables

The scope of any coating development project must include an in-depth look at product-related variables. In many instances, trouble-shooting has traced problems in reproducibility to inconsistencies in the characteristics of the core and/or coating materials.

An early challenge formulators face is determining how much coating may be necessary to achieve desired finished product performance. Most coatings are applied as a percentage of weight of the starting material. Therefore, the thickness of the film depends on substrate particle size. Applied films should be thick enough to overcome various surface properties and perform as desired. Depending on the coating material, this thickness may vary from a few microns to more than 20. Assuming 10 μm as an average, Figure 9 shows amounts of coating substance required to cover particles ranging in size down to 325 mesh or 44 μm. As particle size decreases, the amount of coating required to achieve a 10-μm thickness becomes very high. Also, the coating substance must be applied using some medium, and solids concentrations in the liquid range typically from 10 to 30%, resulting in the need to apply large quantities of liquid relative to the uncoated product. A further complication is that as particle size decreases, minimizing agglomeration becomes very dependent on the formulation of the coating liquid, and nozzle limitations; ultimately, it may be unavoidable. For these reasons, it is advantageous to use the largest particle size that may reasonably yield the desired results.

The most stringent raw material requirements are found where sustained release is desired. If the rate of release is dependent on film thickness and quality, then surface area and integrity are of paramount importance. Surface area is controlled by particle size, shape, porosity, density, and friability. Because coatings are applied on a weight basis, it is advantageous to have a core that has a narrow particle size range, is spherical, has a dense, strong surface, and does not vary in bulk density from batch to batch. An

	Uncoated Particles			Coated Particles		
U.S. mesh	Diameter (mm)	Particles/ Gram	Surface Area/ Gram (mm²)	Coated Diameter (mm)	Coating Added (%)	Coating in Production (%)
5	4.00	23	1,157	4.02	1.2	1.18
10	2.00	183	2,312	2.02	2.4	2.34
18	1.00	1,468	4,610	1.02	4.7	4.49
35	0.500	11,764	9,235	0.520	9.6	8.75
60	0.250	94,340	18,490	0.270	20.0	16.7
120	0.125	751,880	36,917	0.145	43.3	30.2
200	0.074	3,663,000	63,004	0.094	82.3	45.1
325	0.044	17,543,860	107,018	0.064	163.5	62.0

Figure 9 - A comparison of the amount of coating required to apply a coating 0.01 mm thick onto particles of various sizes.

example of ideal surface characteristics is shown in Fig. 10. Surface integrity is important because any loose drug or core excipients that become reattached to the core via the coating may alter the solubility or permeability of the film. Note that all fluid bed coating techniques expose the product to some degree of mechanical stress.

Surface porosity may present a problem because a certain amount of film may be consumed in filling the pores and thus is not contributing to the overall film thickness. Additionally, large pores may never be covered, resulting in an imperfection in the film. Although such rigorous core material requirements may seem unrealistic, a formulator can help to minimize the effects of these substrate variables by avoiding the use of very thin films (less than 5 μm) in development work.

If performance does not rely on film thickness, as in sustained release, but is triggered by other mechanisms (such as pH change), the restrictions on substrate morphology are somewhat reduced. Then powders, crystals, and granules as well as pellets and tablets can be coated.

For example, friability, a problem in tablet coating, is also a concern in particle coating. A film coating typically increases the strength of the core material. However, coating

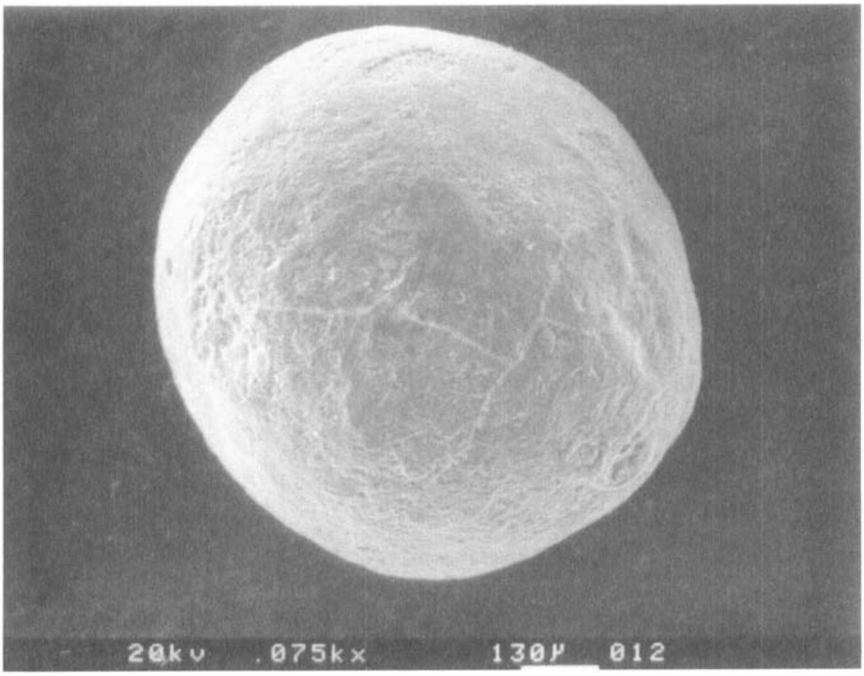


Figure 10 - Drug pellet with ideal surface characteristics for subsequent overcoating (magnification 75x).

occurs in patches and complete coverage of a substrate takes time. Small particles may detach from the surface, then become incorporated in the layers of the developing film. Additionally, achievement of small droplets is accomplished by using high atomization air pressure, which yields a very high air velocity at the nozzle tip. The large velocity difference between the fluidization and atomization air may result in some pulverization of the substrate as it enters the coating zone.

With an awareness of general process and product variables, the capabilities and limitations of each of the three processing techniques may be examined.

Top Spray Coating

The top spray system has successfully been used to coat materials as small as 100 μm. Smaller substrates have been coated, but agglomeration is almost unavoidable because of nozzle limitations and the tackiness of most coating substances. Batch capacities range from a few hundred grams to more than 1500 kg. Typically, a single nozzle wand with up to six liquid delivery ports is used, but multiple wands and nozzles are commonly being used on larger machines.

Fluidization is affected by batch size, and can be determined by the following equation:

$$B = V \times D$$

where:

B = Batch size of the coated product in kg

V = Total product container volume in liters

D = Bulk density of the coated product in g/cc

A minimum of 50% of the product container volume should be occupied by the uncoated material to allow an adequate fluidization pattern. Under these conditions, approximately 100% coating (based on starting weight) can be applied. Sustained release coating is discouraged, as is most coating using organic solvents. This is due to the erratic fluidization pattern which is characteristic of larger machines using coarse pellets or dense substrates. However, top spraying is the system of choice for coating without any solvent (hot melt).

The most significant characteristic of the top spray method is that the nozzle sprays countercurrently or down, into the fluidizing particles. The fluidization pattern is random and unrestricted. As a result, controlling the distance the droplets travel before contacting the substrate is impossible. Figure 11a shows the surface of a pellet coated with ethylcellulose, a water-insoluble polymer, using ethanol. The coating is imperfect, and the core will dissolve rapidly when placed in water. By contrast, the pellets shown in Figs. 11b & 11c, coated in the Wurster and rotor (both immersed-nozzle, concurrent-spray techniques) using the same polymer system, show no imperfections and sustain the release of the core.

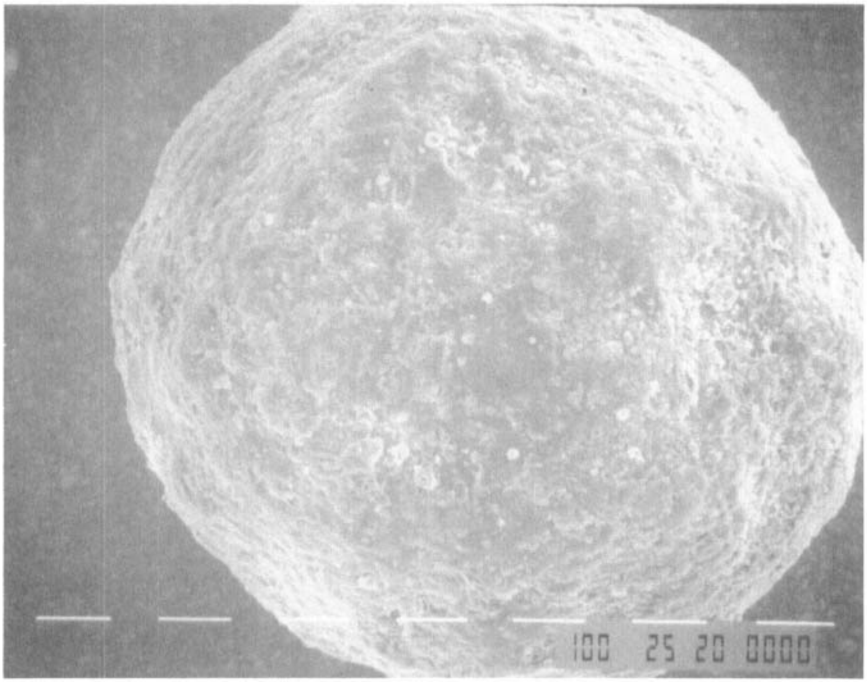
The problem seems to be most severe with films applied from solutions, especially from the more volatile organic solvents. When applying an enteric coating using an aqueously based latex film, the surface morphologies, cross-sections, and dissolution profiles of caffeine pellets appear similar with each of the three techniques. The problem previously described is probably forgiven by the low viscosity of the latex system and the high heat of vaporization of water.

The product container of the top spray system is designed for no restrictions to particle flow, an important consideration for the application of a hot melt coating. Materials with a melting point of less than 100°C can be applied to the fluidized particles by carefully controlling the liquid and atomizing air temperatures and the product bed temperature. The degree of protection offered by the coating is related to the rate at which it is applied and how slowly it congeals. Keeping the product temperature close to the coating's congealing temperature results in a significant increase in the viscous drag in the bed. For hot melt coating, therefore, the openness of the top spray product container is superior to the Wurster, which relies on a small gap between the partition and orifice plate for controlling the fluidization pattern and assuring coating quality. With the tangential spray technique, all of the fluidization air is concentrated at the perimeter of the disc. Laboratory experience has found that it is difficult to achieve as high a product temperature as is possible using the top spray method. As a result, the coating is more porous.

The top spray coating system is the least complicated of the three machines. It has the largest batch capacity, and downtime between batches can be only minutes. Its biggest disadvantage is that its applications are somewhat limited.

Wurster Bottom Spray Coating

The Wurster bottom spray system has also been used successfully to coat particles as small as 100 μm. Coating of smaller particles is subject to the same difficulties as discussed in the previous section. Batch capacities range from a few hundred grams to approximately 600 kg. Laboratory and pilot scale equipment (up to 24-in diameter) use a single partition and nozzle, and production equipment may contain three (32-in Wurster) or seven (46-in Wurster) partitions and nozzles of the same size and configuration found in the 18-in Wurster. Fluidization is affected by batch size, and at



Figures 11a, 11b & 11c - **Pellets coated with ethyl cellulose in an organic solution in a fluidized bed using the top spray Wurster & rotor methods (magnification 100x)**

least 50% of the volume outside of the partition should be occupied by the uncoated product (this requirement decreases somewhat as the coating chamber increases in size as it is dependent on length of the partition and downbed depth). Finished product batch size (for fine and intermediate particles) can be determined by the following equation:

$$B = \frac{\pi r_1^2 L - n\,(\pi r_2^2 L)}{1000}$$

For pellets and small particles

OR

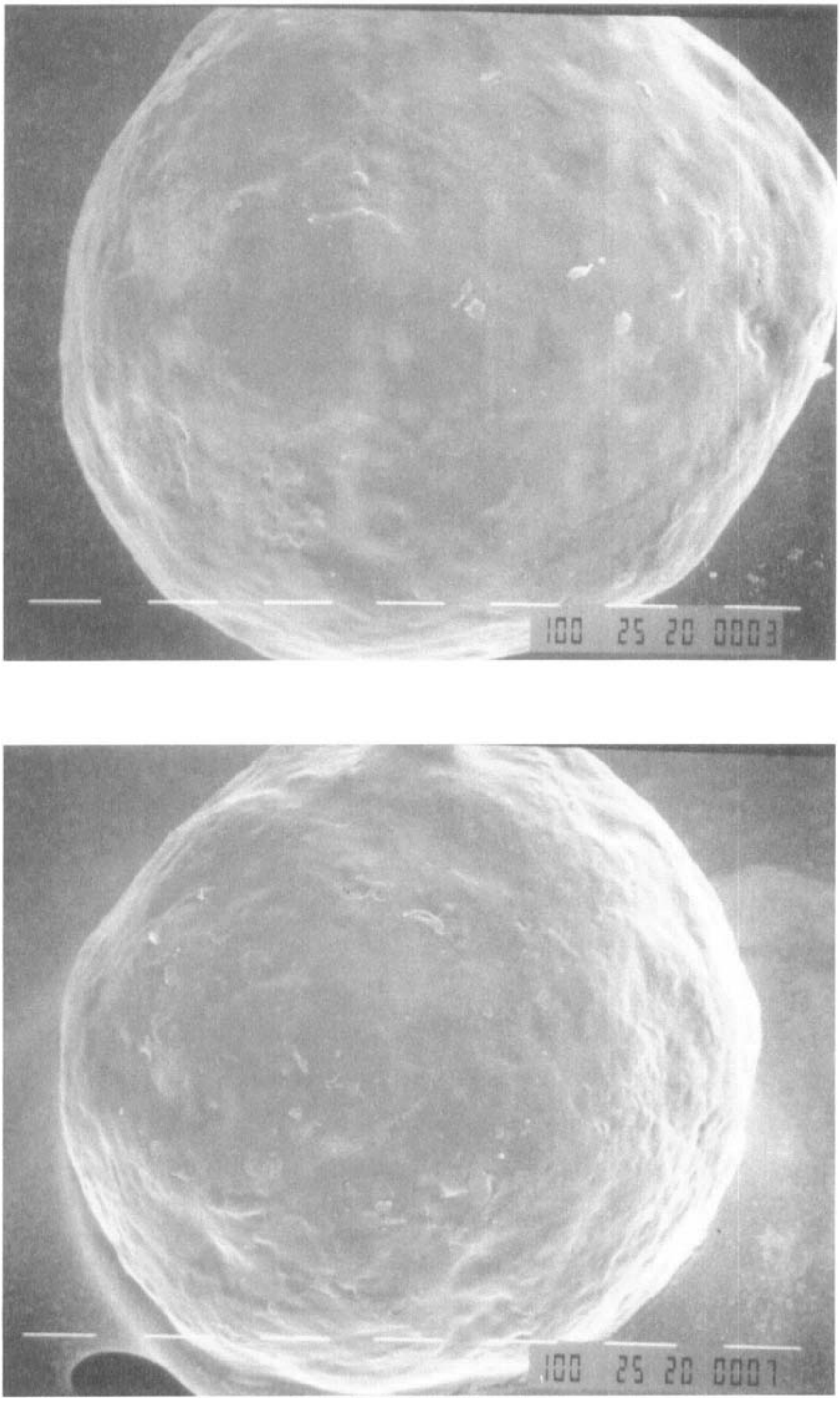


Figure 11. Continued

$$B = \frac{\pi r_1^2 L - 1/3\, n\, (\pi r_2^2 L)}{1000} \quad \text{For tablets}$$

Where:

- B = Batch size in (kg)
- r_1 = Radius of Wurster Chamber (cm)
- r_2 = Radius of partition (cm)
- n = Number of partitions
- L = Length of partitions (cm)

If the coating and core bulk densities are smaller, coatings of 100 to 150% (based on starting weight) may be applied. Fluidization is also affected by the air distribution plate configuration and the partition height. The finer are the particles to be coated, the smaller the open area in the downbed section of the orifice plate and the tighter the gap between partition and orifice plate.

The chamber may be cylindrical or slightly conical with a cylindrical partition about half the diameter of the base of the coating chamber (up to 24" Wursters). The orifice plate at the base of the chamber is divided into two sections. The open area of the plate which is under the partition is typically nearly fully open, allowing a high air volume and velocity to accelerate the substrate vertically past a spray nozzle which is mounted in the center of the orifice plate. The downbed region depends on the size and density of the material to be processed. As explained previously, the purpose of the air flow in this region is to keep the substrate in near-weightless suspension so that it can travel rapidly downward, then be drawn horizontally into the gap at the base of the partition. Tablets require significantly more air to produce this condition than pellets or fine particles - the orifice plate must be selected accordingly (a plate designed for tablets will probably not work well with small particles).

A second key process variable in Wurster processing is the height that the partition sits above the orifice plate. In general, the smaller the particles, the smaller the gap will be. This gap controls the rate of substrate flow into the spray zone. A Venturi is created by the high volume and velocity of air rushing through the partition, which is the mechanism for drawing particles into the spray zone. When the Wurster coating chamber is set up properly, the resulting flow pattern should be smooth and very rapid in the downbed, and very dense in the upward, or partition region. The larger the particles, the greater the partition height. Tablets do not need much expansion height and it is important that the orifice plate and partition height be optimized so that the tablets travel only a very short distance out of the partition to minimize the possibility of attrition. A mesh bonnet can be used to keep the tablets from colliding with the expansion chamber, while allowing the fines from the cores or some spray drying to exit the process area, avoiding their incorporation in the layers of film. The Wurster is not used extensively for tablet coating due to the arguably high stress that the tablets are exposed to by fluidization. However, it is recommended when the film quality is very important, especially for modified release tablets. The films applied by Wurster are high in quality due to the concurrent spray and high drying efficiency of this air suspension process.

Pellets and small particles are coated extensively using the Wurster process for all types of coating using water, organic solvents, or even by spraying molten materials. Their small size means that they need much more expansion area for deceleration to avoid attrition from collisions with metal parts, and machines are designed to accommodate this need. While only a basket is necessary for tablet coaters and pellet coaters, small particles need a filter to avoid their transport out of the coating area.

The coating liquid is sprayed in the direction of motion of the fluidizing particles. In general, the fluidization is very smooth and rapid. Because the liquid is sprayed into a well organized pattern of moving product which is close to the nozzle, droplet travel distance is minimized and the resultant films are excellent.

The recently introduced Wurster HS technology, from Glatt Air Techniques, Inc. in Ramsey, NJ., involves the use of a proprietary device to control behavior of the coating zone. In Wurster processing, the nozzle is buried in the fluidizing substrate, spraying in the same direction. Product can pass the nozzle closely or at a further distance. The spray application rate is typically controlled by the nature of the coating material (tackiness), or by the region immediately surrounding the spray nozzle. The velocity gradient between the atomizing air and the fluidizing air creates streamlines in close proximity to the nozzle. Substrate can be drawn toward the nozzle in these zones- and into the wettest part of the developing spray pattern. To control what could otherwise be a severe agglomeration problem, the spray rate is reduced, leaving a large amount of unused drying capacity. Other commonly used agglomeration control techniques include raising the inlet (and product) temperature to dry faster, or rasing the atomizing air pressure to shrink droplet size - options which are in conflict with producing high quality films, or high yields in a layering process. Even using these corrective measures, a quantity of agglomeration is almost unavoidable. Typically, 1-3% of the batch is removed due to aggregates.

Another challenge is to coat particles smaller than 100 microns without agglomeration. The limitations of this are numerous. Ideally, substrates should be spherical in shape, robust, and non-cohesive. Unfortunately, many are needle-like, friable and very cohesive. The fluidization properties of some substrates can be improved with additives such as silicon dioxide in quantities ranging from a few tenths of a percent to as much as 2-3 percent by weight.

The coating liquid must be low in viscosity and surface tension so that it can be atomized to droplets which are small enough to minimize the agglomeration potential (Figs. 12a & 12b).

To coat 100 micron particles, droplets should probably be much smaller than 10 microns. To aid in this, atomizing air pressures exceeding 5 bar (75 psi.) are commonly used. The high velocity not only creates streamlines, as mentioned previously, but also a tremendous amount of shear. Fragile substrates are "jet-pulverized" by the nozzle as a result.

The Wurster HS was developed to keep particles away from the nozzle until the spray pattern is more fully developed. Consequently, more of the available drying capacity can be used, and the application rate increased substantially (more than doubled in many pilot

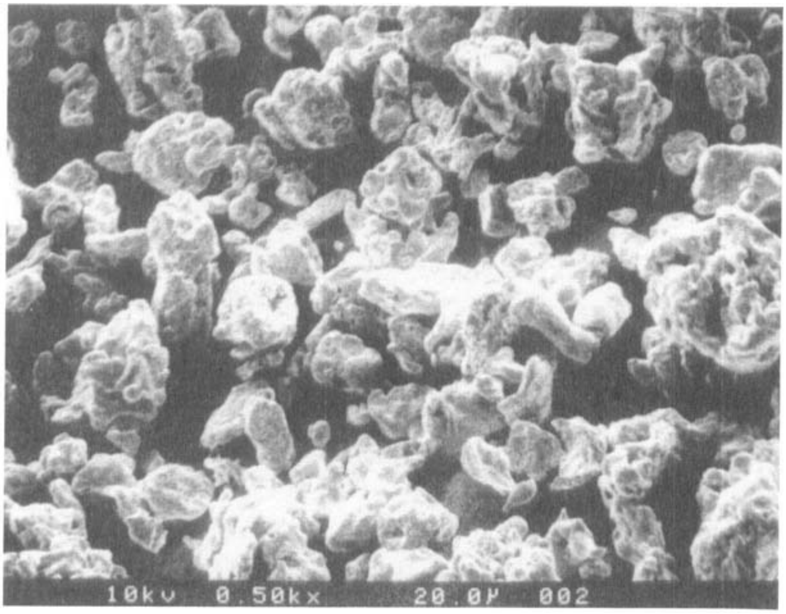


Figure 12a - Particles less than 100 microns in size - uncoated. Magnification 500x.

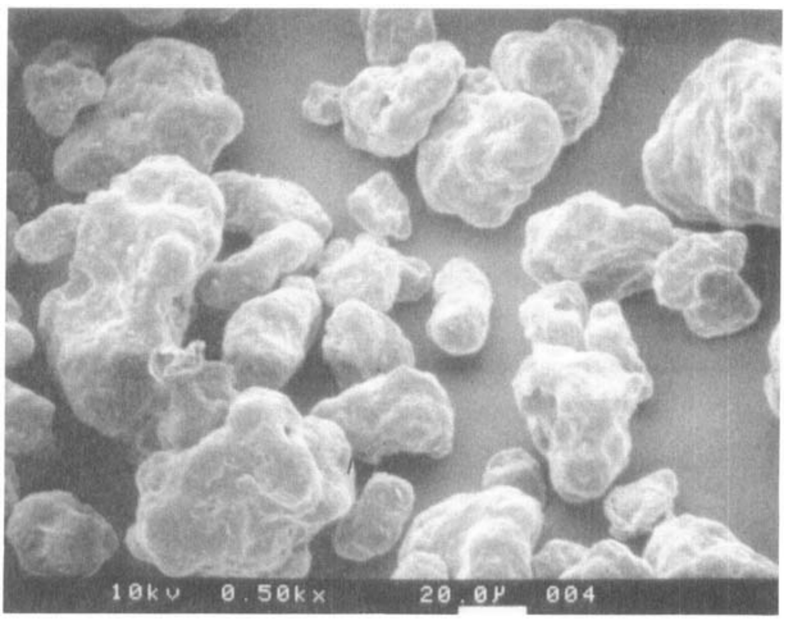


Figure 12b - Particles less than 100 microns in size - coated. Magnification 500x.

scale lab trials). Because the particles are kept away from the wettest portion of the pattern, agglomeration is also substantially diminished or eliminated. An additional benefit is that the high atomizing air velocities necessary to produce very small droplets for coating of particles smaller than 100 microns can be used as well. The atomization air velocity decreases significantly before contacting the substrate, reducing the likelihood of attrition during the early stage of coating.

The Wurster system has the widest application range of both water and organic solvents, and in some cases (coarse substrates) coating with hot melts is possible. Organized particle flow and the immersed-nozzle, concurrent-spray system appear to offer superior film forming capabilities. The primary disadvantages of this system are that it is somewhat complex, it is the tallest of the three types of fluidized bed machines, and the nozzles are inaccessible during the processing.

Tangential Spray Coating

The rotary or tangential spray system, also an immersed-nozzle, concurrent-spray technique, appears to offer film characteristics similar to the Wurster system. It has been used successfully to process particles as small as 250 μm using organic solvents and water-based materials. The process is more susceptible to adhesion of particles to the upper wall of the product container (Fig. 5) owing to static electricity; hence, coating of smaller and lighter particles is difficult, especially with organic solvents. Batch capacities range from approximately 1 kg to 500 kg. Laboratory equipment (up to 500-mm disc diameter) typically uses a single nozzle, and pilot to production scale rotors (up to 1600-mm disc diameter) use from 2 to 6 nozzles. Fluidization is not affected by batch size as significantly as in the other process techniques. Working capacity is approximately 50% of total bowl volume, and the minimum batch size is that which is necessary to cause the nozzle to be fully immersed such that the coating liquid is not sprayed through the bed. This volume is typically about 15 to 20% of the working capacity. If the bulk densities of the core and coating material are similar, coatings or drug layers of 400 to 500% (based on starting weight) may be applied.

As mentioned previously, the rotor process can be used to produce high potency pellets starting from very fine powders (Fig. 13).

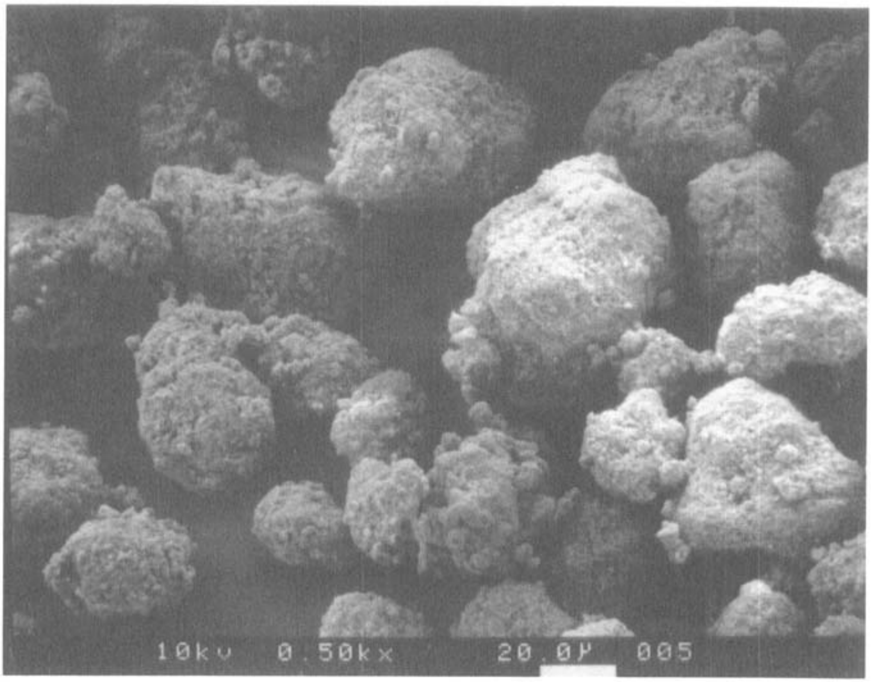


Figure 13 - High potency fine pellets produced using rotor fluidized bed. Magnification 500x.

The substrate is placed into the product container and put into motion by the rotor disc, which is adjusted to spin at high speed to impart significant energy into the bed. The disc, which is typically smooth, may be configured with a variety of surfaces from grooves to a multi-pyramid type of waffle plate. The gap at its perimeter is set small to allow a high velocity but low flow of air. Inlet air temperature is maintained at or near ambient. Using pneumatic nozzles, water or a binder solution is finely atomized, building moisture into the rapidly tumbling bed. Primary particles nucleate around these droplets, forming loose agglomerates. At a critical moisture content, the bed begins to densify and the angular granules start to become round. At this point, liquid addition is stopped, but tumbling continued to enhance densification and rounding. To prevent runaway granulation, where granules continue to grow by coalescence (ball growth) to an undesirable size, drying or addition of powder to the bed to absorb excess moisture may be commenced. Drying is accelerated by raising the rotor disc and substantially increasing the fluidization air volume. Additionally, the inlet air temperature is elevated, often in a step-wise manner (to avoid case hardening). Although the surface morphology is somewhat dependent on starting material properties, the resulting pellets should be smooth with minimal porosity.

This process also excels in producing high dose pellets using three techniques for applying drug to a small seed material: spraying a water or solvent solution of drug and binder; spraying a water or solvent suspension of drug with a dissolved binder (Fig. 14); or spraying either water alone or a binder solution and dosing the drug powder onto the damp seed material. The choice of technique depends on several factors, including solubility and stability of the drug. Additionally, for suspension layering and powder dosing, it is almost mandatory that the drug be micronized (less than 10 μm) to maximize drug yield and provide a smooth surface for subsequent coating. The resulting pellets will also be very uniform in particle size distribution because of the narrow size distribution of the starting seed material, typically a non-pareil sugar seed or regular shaped crystal.

The process variables unique to the rotor system primarily involve disc slit width, disc configuration, and rotation speed. The volume of the fluidization air is controlled independently of the velocity by adjusting the slit width. This velocity controls the rate at which the bed tumbles or spirals. Typically, it is as high as possible without seriously distorting the fluidization pattern, resulting in a bursting or bubbling bed. In solution or suspension layering, the slit is usually wide to maximize drying capacity and spray application rate. When spraying a binder solution and dosing powder, the slit is usually narrow and the air volume and temperature much lower. In this manner, the applied powder is immobilized on the substrate surface by liquid bridges. If the evaporation rate is high, as is the case when layering with a solution or suspension, excessive quantities of liquid may needlessly be applied.

The disc surface, when layering or coating, should be smooth, and a rotational speed selected (less than half the speed used for direct pelletization) such that particle motion is rapid but uniform. There is a large velocity gradient from the disc surface through the

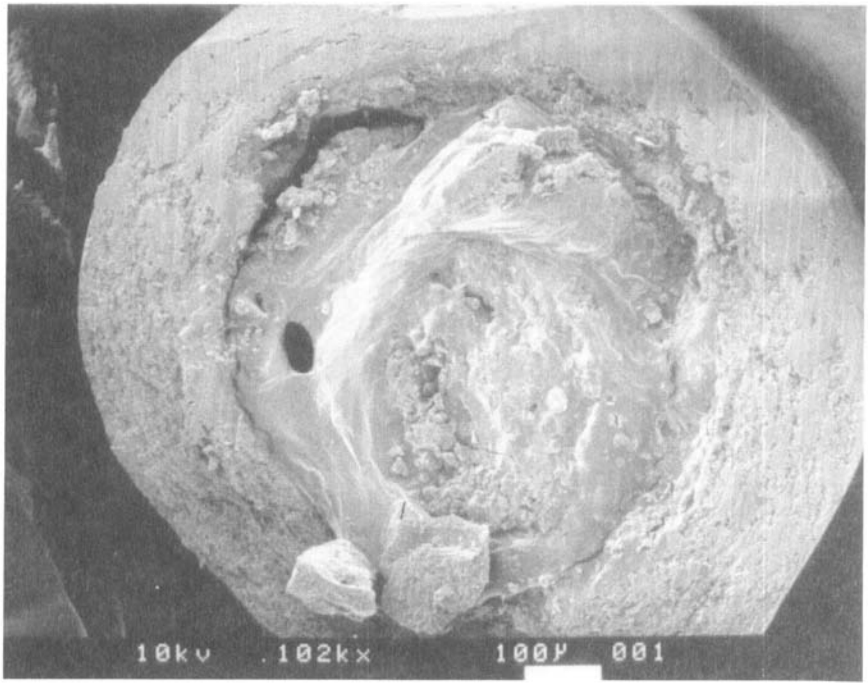


Figure 14 - Drug layered bead - cross section - magnification 75x

particle bed, and any type of baffle or surface roughness may cause fracture of the pellets, especially as the layer becomes thicker.

In addition to enhancing particle motion, the disc speed may affect the spray application rate. As is true of the other fluidized bed techniques, spray rate is limited by the tackiness of the spray liquid and can be maximized by increasing the velocity of the particles through the coating zone. Again, caution must be used to avoid excessive radial velocity, which may result in core fracture.

The rotary tangential spraying system has a relatively wide application range, is the shortest machine in height of the three, and allows nozzle access during processing. It has the ability to produce high dose pellets and apply coatings for all types of release. Its primary disadvantage is that it exerts the greatest mechanical stress of the three methods and, thus, is discouraged for use with friable substrates.

Scale-Up

The successful scale-up of any coating process to pilot or production equipment depends heavily on an effective development program in the laboratory. The influence of all the major product and process variables should be well known so that the list of unknowns can be minimized. Essentially, the only major unknown factor is the effect that the larger mass of material will have on itself. Product problems such as friability will be magnified by scale-up. Additionally, if the release profile of the coated product is very susceptible to minor changes in processing conditions, scale-up will be a challenge. For these reasons, a product and process must be robust on the lab scale.

Each fluidized bed technique has unique scale-up considerations. The conventional top spray method is the easiest to scale, probably partly because the most difficult coating objective, sustained release, is discouraged from being conducted with this technique. Scale-up of spray rate is generally calculated according to the increase in fluidizing air volume used, not the increase in batch size. The bed depth is not a constant is scale-up; therefore, the amount of air required to provide adequate fluidization is proportionately less. This is a common technique for determining spray rate in scale-up of the fluidized bed granulation process, where the rate-limiting factor is generally drying capacity. However, in fluidized bed coating, the more critical factor is the inherent tackiness of the coating material being applied. As mentioned previously, this property determines the maximum delivery rate through a single-headed nozzle or coating zone. For this reason, as batch sizes increase, the number of nozzles (or zones) increases, typically to 3 or 6 heads, or multiple nozzles and wands.

When scaling a Wurster process, the most challenging step is from laboratory to pilot scale. The 6-in., 7-in., and 9-in. Wursters use a small nozzle which uses less than 6 cfm. and is capable of atomizing up to approximately 100 g./min. The 12-in. and 18-in. Wursters employ a larger nozzle, which may consume up to approximately 30 cfm to accommodate spray rates as high as 1,000 g./min. The large difference in air volumes used by these nozzles may have an effect on the evaporation rate of coating media during atomization of the liquid. Additionally, bed depth is usually in the range of 150 to 200 mm in laboratory scale Wursters in contrast to 400 to 500 mm or more in the 18-in.

Wurster. The vertical distance that the substrate travels up and out of the partition is greater in the pilot scale machine as well. As a result, mass effects not seen in the smaller machines may be an obstacle to successful scale-up. In general, products (and processes) being developed in small equipment must be robust.

For these two reasons, scaling from a small machine to the 18-in. Wurster may be the most challenging. Continuing to larger equipment such as the 32-in. or 46-in. Wurster, although also a task not to be underestimated, is somewhat less difficult because these units employ multiples of the partition and nozzle found in the 18-in. Wurster. Three partitions and nozzles are used in the 32-in. unit and seven are used in the 46-in. Wurster coating chamber. Spray rate in each partition of the 32-in. or 46-in. coating chamber will be the same as that used in the 18-in. Wurster. For example, when scaling up to a 6 or 7-partition 46-in. Wurster, if the spray rate in the 18-in. Wurster was 400 g/min., overall spray rate in the production machine would be 2,800 g/min., or 400 g/min. per partition. The partition's height above the orifice plate may be the same in pilot and production equipment, which will keep particle density inside the coating zone similar.

Also, the total fluidization air volume, which is controlled by orifice plate configuration, should be a multiple of that necessary in the 18-in. Wurster. For example, if 500 cfm was required for adequate fluidization in the 18-in. unit, 1,500 cfm would be the target air volume in a 32-in. coating chamber, or 3,500 cfm in a 46-in. machine. In this manner, evaporative conditions will be similar, as will particle velocity, a key to minimizing the mechanical stress to which the product is exposed.

Of the three fluidized bed techniques, the rotary or tangential spray system exerts the most mechanical force on any given product. Rotational speed is a key variable and must be considered in scale-up. One method is to keep the radial velocity constant when scaling to larger equipment.

Knowing the diameter of the disc in the production machine and keeping the radial velocity V_r constant, one can solve the equation for N, the number of revolutions per minute the disc in the larger machine must travel such that V_r is the same in both small and larger equipment.

Another method for determining disc speed in scale-up considers keeping force constant. Radial acceleration can be determined as follows:

$$a_n = \frac{V^2}{r}$$

Where:

a_n = normal acceleration (constant velocity)

V = Velocity at the disc perimeter

r = Radius of the disc

Keeping radial acceleration constant, disc speed for larger equipment can be calculated. Secondly, increasing the disc speed will, to an extent, increase the velocity of the substrate through the coating zone which may allow a higher spray application rate. However, excessive disc speed may cause product attrition.

As in the section discussing scale-up of the top spray process, the scale-up factor for determining coating liquid application rate is usually based on the increase in fluidization air volume. However, spray rate is typically more a function of the properties of the coating material, as described previously, and this scale-up factor should be used only as a base line or starting point. Optimization must be done during the first scale-up batches. Multiple nozzles (from 3 to 6) and powder dosers, where applicable, are typically used to increase the overall application rate.

SUMMARY

The evaporative efficiency of fluidized bed equipment and the ability to apply materials to particles discretely suspended in an airstream have resulted in widespread use of this technique for products ranging from small particles to pellets and tablets.

The three fluidized bed techniques are all used commercially for pelletizing and film coating, but each has unique advantages and limitations. In the development of a product with commercialization as the ultimate goal, criteria such as economics, product and process variables, and dosage form performance must be considered.

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