



David M. Jones

# Fluidized Bed Processing and Drying

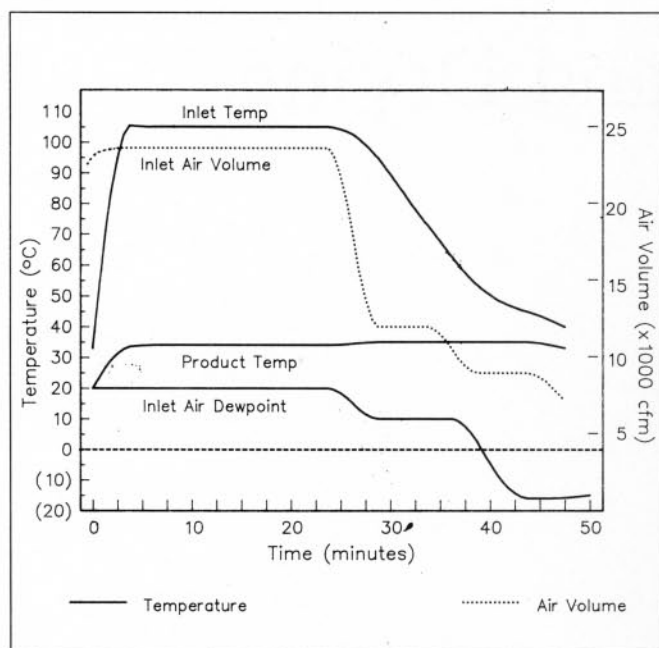
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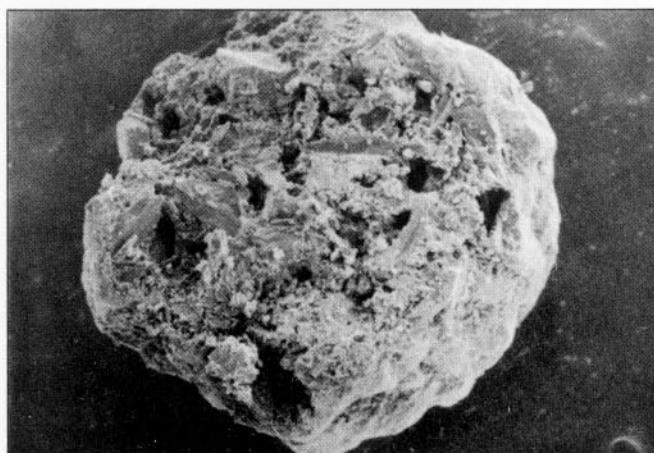
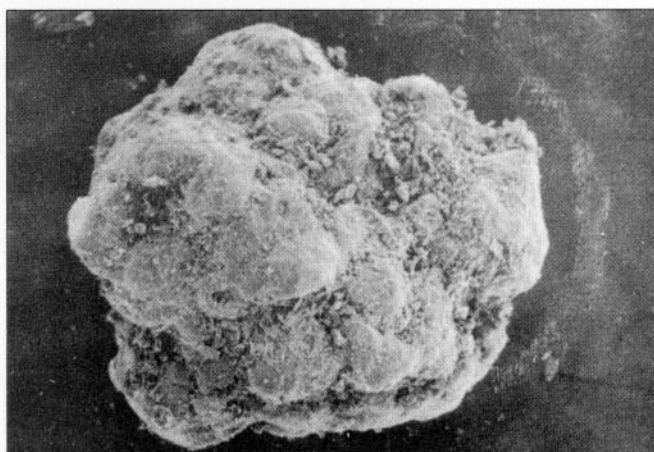
Fluidized bed processing is widely used in the pharmaceutical industry for drying, granulating and coating. As a dryer, it reduces drying time substantially in comparison to a tray dryer or vacuum dryer. The process is isothermal, and the high drying rate results in evaporate cooling, keeping product temperatures at low levels, even when using high drying air temperatures. Figure 1 illustrates a process for drying a bio-active material as quickly as possible, limiting the product temperature to less than 35°C.



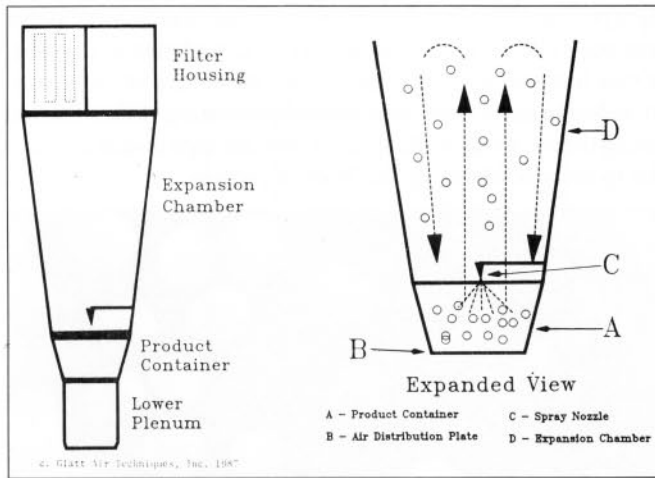
**Figure 1. Processing Profile for Drying a Temperature Sensitive Product.**

An early evolution of fluid bed drying combined this drying efficiency with binder (or water) spraying, and the fluid bed granulator resulted. In comparison to high or low shear granulating techniques, granules produced by the fluid bed are more porous and lower in density (Figure 2). For many products this structure results in improved product performance characteristics such as disintegration and dissolution. The interstitial pores are not all crushed during compression on a tablet press, and as a result, the tablets and agglomerates dissolve by capillary wicking as opposed to erosion.

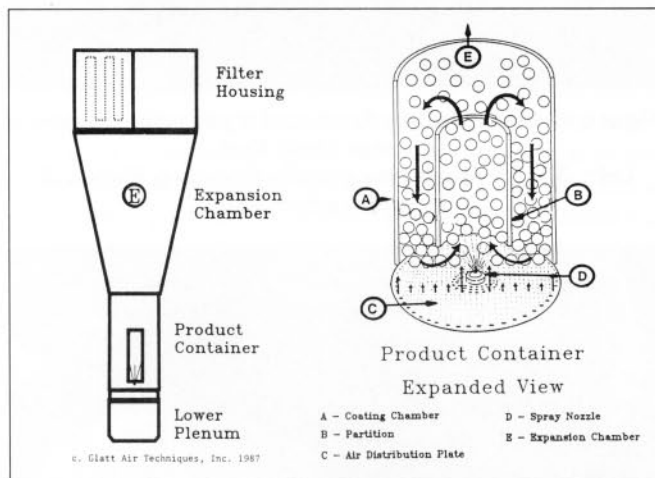
Modifying processing conditions somewhat, a fluid bed granulator can be used as a top spray coater for small particles. Figure 3 shows a diagram of a refinement of earlier designs. Newer top spray coaters incorporate an elongated expansion chamber to allow for vigorous fluidization and high liquid spray rates, and a filter system which allows continuous fluidization. The nozzle is typically used in a low position to minimize droplet travel distance (and possible spray drying).



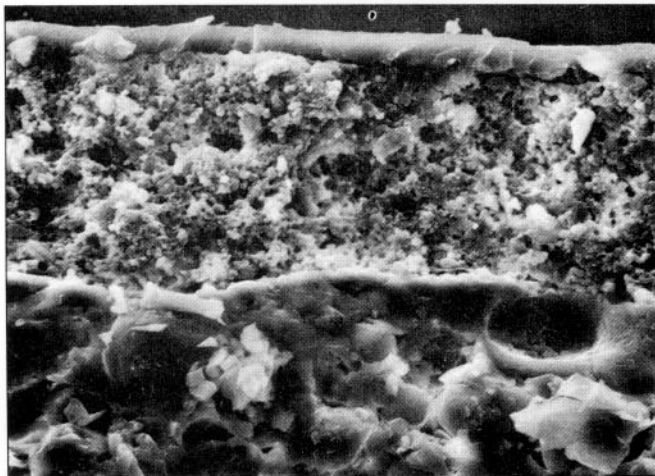
**Figure 2. Surface and Cross Section of Agglomerates Produced by Fluidized Bed Granulating Magnification 75x**



**Figure 3. Top Spray Coater**



**Figure 4. Wurster-Bottom Spray-Coater**



**Figure 5. Close-up of Cross Section of Film Coated Drug Layered Pellet Produced in a Wurster Coater Magnification 1,000x**

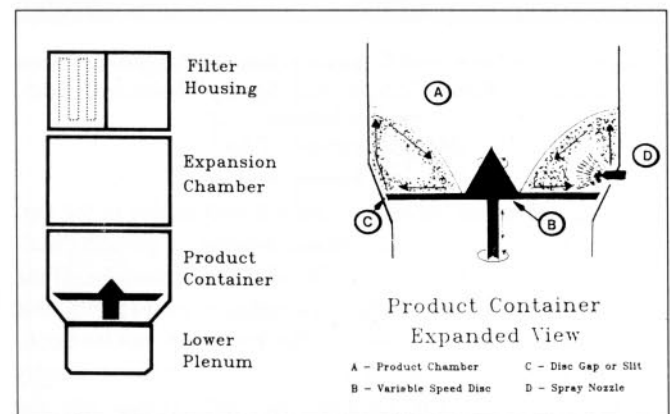
More than thirty years ago, Dr. Dale Wurster, then at the University of Wisconsin, was working with air suspension systems for granulating and coating. The system which bears his name, the Wurster coater (Figure 4) is widely used today for film coating of particles, pellets and tablets. Additionally, it is used for

producing core materials (for subsequent overcoating) by solution or suspension layering. Scanning electron micrographs (Figure 5) illustrate a drug layered pellet which has been film coated. All processing operations were conducted in the Wurster coater and are detailed in Figure 6.

Starting batch size:	25.0 kg. 30/35 mesh nonpareils
Drug suspension:	25% solids w/w
Batch size after layering:	37.0 kg.
Layering yield:	98.8%
Layering time:	225 min.
SR coating starting batch size:	32.0 kg.
SR coating:	15% solids w/w
SR coating time:	120 min.
SR coating yield:	99.6%

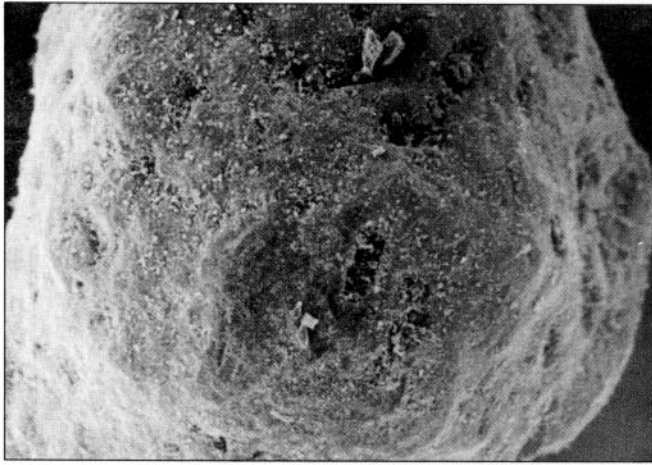
**Figure 6. Drug Layering and Film Coating in an 18" Wurster Coater**

A more recent development shown in Figure 7 combines high shear forces from a spinning disc with the drying efficiency of the fluidized bed. The rotor or tangential spray processor was originally conceived as a granulator which would produce granules of less porosity (and higher density) than those from a conventional fluidized bed but more porous than from a low or high shear granulator. Figure 8 shows an SEM surface and cross section of an agglomerate from a batch which is 20% denser (than conventional) but retains much of the desirable interstitial porosity.

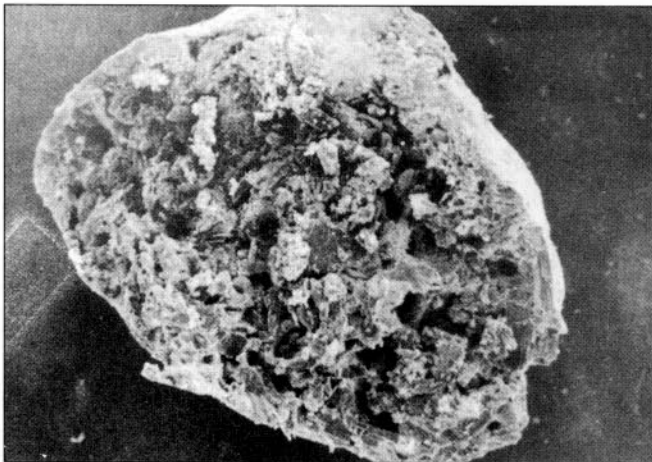


**Figure 7. Rotor-Tangential Spray-Coater**

A more widespread usage of the rotor system is for producing pellets. Small pellets (100-250 microns) can be made from powders. Sphericity and density are strongly dependent on raw materials characteristics, and round, dense particles are favored for subsequent overcoating. Films cannot effectively cover large surface pores, and intragranular porosity would allow rapid dissolution of the drug. If pellets larger than 500 microns are desired, this technique may not apply. Pellets grow by the formation of liquid bridges and rounding by the circular, spiralling action of the rotor. The first pellet size "plateau" is typically in the range of 75-150 microns and may be narrow in size distribution. However, producing larger pellets relies on increasing bed moisture, forming liquid bridges between the small pellets, which then coalesce into a larger agglomerate.



**Magnification: 100x**



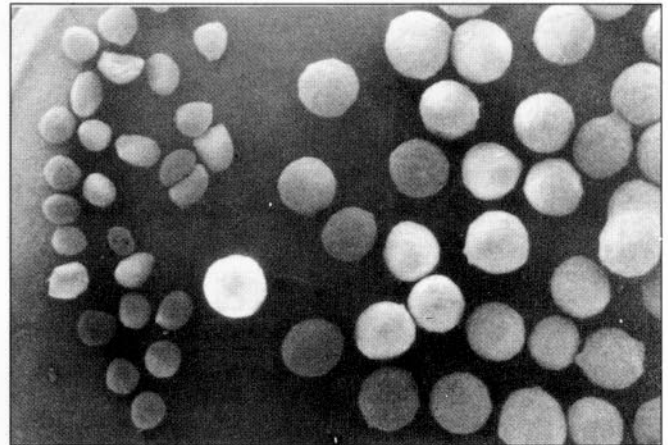
**Figure 8. Surface and Cross-section of Agglomerates Produced by Rotor Tangential Spray Fluidized Bed Granulating  
Magnification: 75x**

These agglomerates become round and smooth due to the vigorous tumbling action of the bed. Each "step" in growth usually results in a broadening of the pellet size distribution. If the release of the finished product is dependent on pH, etc., this variability in size (and hence, surface area) may not be a concern. However, for sustained release products, which typically rely on reproducible film thickness to control release rate, the wide pellet size distribution is a problem.

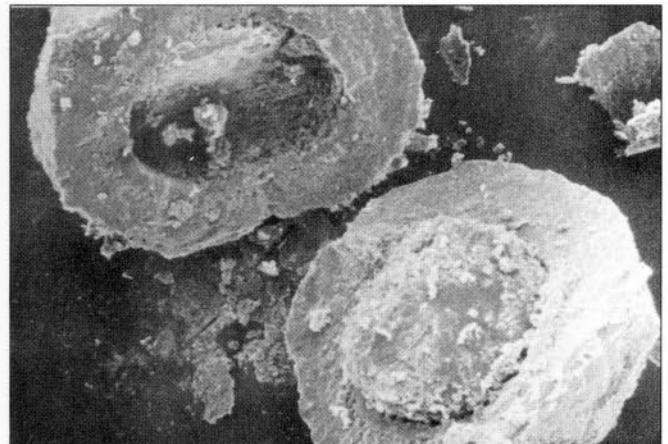
Layering techniques are more commonly used to generate pellets with a narrow size range. A seed material, generally a regular crystal of drug or a sugar nonpareil, is sprayed with a solution or suspension of drug also containing a binder. The narrowness of the core size range is preserved as pellet diameter increases. Using this technique, drug potency in the layered pellets can exceed 75%.

Yet another layering method involves application of powder to a seed bed while simultaneously spraying water, solvent or a binder solution. Pellets produced by "powder layering" are shown in Figure 9 and the relevant process data in Figure 10. The smaller pellets are 30/35 mesh sugar nonpareils which were used as the starting material. The layered pellets were produced by applying the drug powder using a specially designed nozzle which atomizes the normally very cohesive material into the tumbling, wetted seed bed. Only water was

sprayed, and the drug powder was immobilized on the pellet surface by liquid bridges alone. At the completion of layering, a thin film was applied to strengthen the pellets to avoid attrition during drying and subsequent film coating. Films applied using the rotor tangential spray system are high in quality, similar to those found using the Wurster process.



**Figure 9. Right: Pellets Produced by Powder Layering in Rotor Fluid Bed  
Left: 30/35 Mesh Nonpareils (Starting Material)  
Magnification 13x**

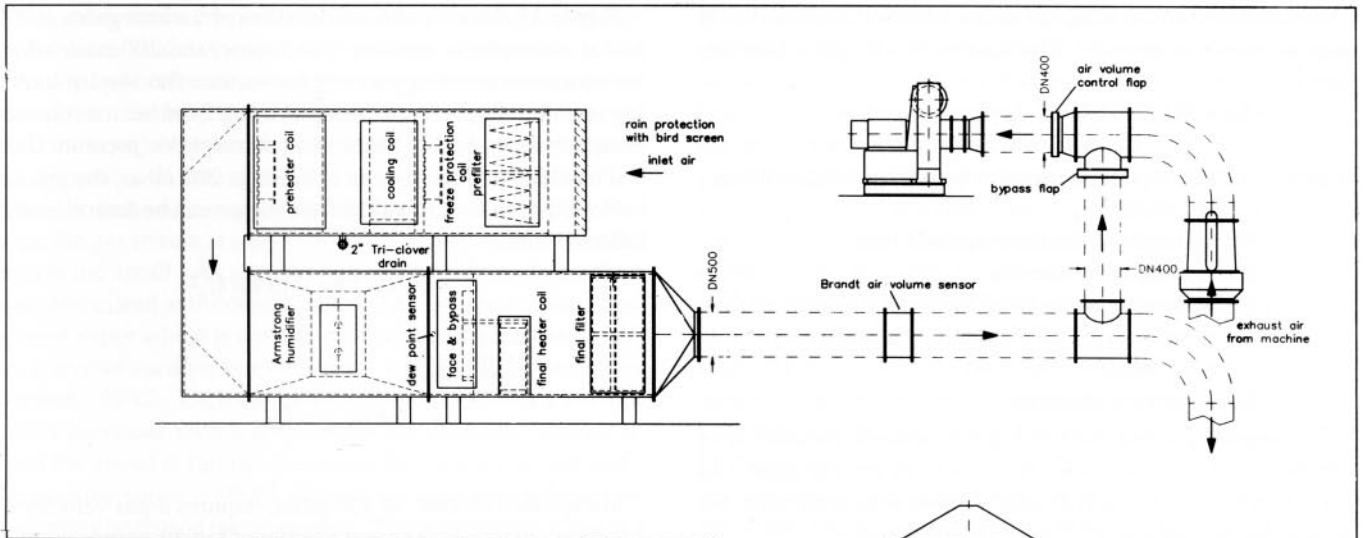


**Cross-section of Pellet Showing Nonpareil Core and Drug Layer  
Magnification: 80x**

Machine:	Glatt Model GPCG-5 with 485 mm rotor disc	
Starting materials:	4.0 kg. 30/35 mesh nonpareils (0.5-0.6 mm)	
Drug applied:	14.5 kg. (slightly soluble)	
Spray liquid:	Deionized water	
Total process time including overcoating:	197 min.	
Pellet size distribution:	+16 mesh (1.18 mm):	7.4%
	-16+20 mesh (1.18mm-0.85 mm):	92.2%
	-20 mesh (0.85 mm):	0.4%

**Figure 10. Process Data for Rotor Powder Layering**

The systems previously described are normally configured such that the air for fluidization and drying is drawn from outside the building, through pre-filters, possibly a freeze protection coil, dehumidifier, a humidifier, final heater, temperature control device and HEPA final filters. Exiting the product bed,

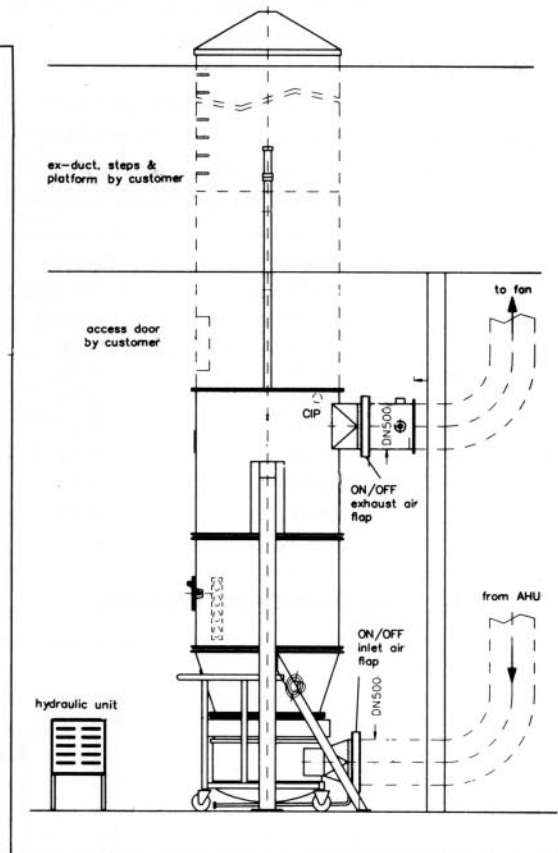


the moisture laden air passes through some type of product/air filter, a fan, possibly a final filter and is exhausted to the atmosphere (Figure 11). If processing involves organic solvents, abatement systems may also be incorporated. Several methods are used for capturing organic solvents: adsorption, absorption, thermal combustion and condensation are common principles.

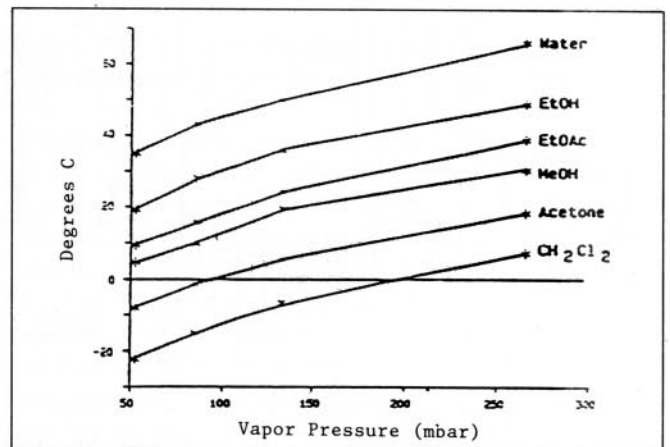
Some pharmaceutical products pose higher than usual exposure risks, and as a result, totally enclosed processors are being considered. A newly developed technology combines aspects of two well-known techniques—vacuum processing and fluidized bed. Vacuum contact dryers have been in use for many years, taking advantage of the physical properties of solvents. As pressure is reduced, the boiling point is reduced, and evaporation occurs at lower temperatures. Figure 12 shows the relationship between boiling point and pressure for commonly used solvents.

An important advantage of a vacuum is that processing is conducted in an environment which is below the minimum ignition pressure of the solvents being used. As such, the risk of explosion because of solvent vapor is eliminated. A disadvantage of vacuum drying is heat transfer. In a contact dryer, the walls, lid, and possibly the agitator or mixing baffles are heated. Heat is transferred to the product by conduction. In comparison to the surface area of the product to be dried, the heated metal surface is quite small. Consequently, drying times are long, and local overheating is a problem with temperature sensitive products. Recently, addition of microwave power to vacuum contact granulator/dryers has improved drying efficiency, but there are some considerations unique to this technology.

Fluidized bed drying is rapid because the entire product surface area is exposed to the high volume air stream. Heat is transferred to the product surface by convection. The vigorous mixing action of the fluidized bed causes the process to be isothermal, a desirable condition for operating with temperature sensitive substrates.



**Figure 11. Fluidized Bed Granulator/Dryer with Humidity Control**



**Figure 12. Vapor Pressure vs. Temperature**

Fluidization can be achieved under vacuum nearly as easily as at atmospheric pressure. The equation for incipient fluidization is:

$$\Delta p = \frac{H(1-\epsilon)\rho U^2 c}{d_k}$$

where:  $\Delta p$  = differential pressure across the fluidized bed (N/m<sup>2</sup>)

$H$  = height of the fluidized bed (m)

$\epsilon$  = porosity of the bed

$\rho$  = density of the fluidizing gas (kg./m<sup>3</sup>)

$U$  = velocity of the fluidizing gas (m/sec)

$c$  = constant

$d_k$  = particle diameter

In comparing a bed fluidized at atmospheric pressure with one fluidized under vacuum,  $H$ ,  $\epsilon$ ,  $c$  and  $d_k$  are the same. As such, to achieve a similarly fluidized bed in both conditions, the kinetic energy portion  $\rho U^2$  must be preserved.

$$\rho_a U_a^2 = \rho_v U_v^2$$

where:  $\rho_a$  = gas density of air at atmospheric pressure

$U_a$  = gas velocity of air at atmospheric pressure

$\rho_v$  = gas density of solvent vapor under vacuum

$U_v$  = gas velocity of solvent vapor under vacuum

Gas	Density at 1013 mbar (kg./m <sup>3</sup> )	Density at 200 mbar (kg./m <sup>3</sup> )
Air	1.29	0.26
Methylene chloride	3.79	0.76
Methanol	1.43	0.29
Ethanol	2.06	0.41
Isopropanol	2.68	0.54
Acetone	2.59	0.52
Toluene	4.11	0.82
Water	0.80	0.16

Figure 13. Gas Density vs. Pressure

Figure 13 shows a table of densities of various gases at 0°C and at atmospheric pressure (1013 mbar) and 200 mbar which is a common operating pressure for vacuum fluid bed granulating and/or drying. As an example, using 2.0m/sec., a common design velocity for air speed in an atmospheric pressure fluid bed machine and methylene chloride at 200 mbar, the gas velocity required for equivalent fluidization can be determined as follows:

$$(1.29)(2.0)^2 = (0.76)U_v^2$$

$$\sqrt{\frac{(1.29)(2.0)^2}{(0.76)}} = U_v$$

$$2.6 \text{ m/sec} = U_v$$

Methylene chloride, at 200 mbar, requires a gas velocity of 2.6 m/sec. to impart the same amount of kinetic energy as air at 2.0 m/sec., an increase of only 30%.

A vacuum fluidized bed processor is a totally enclosed system comprising two major sections: the processing closed loop and the condenser section. Figure 14 illustrates a diagram of a machine designed for granulating and drying water or solvent based products. The machine tower, which is geometrically similar to an atmospheric style machine, consists of a conical product container with a product retention screen at its base and an expansion chamber for deceleration of particles and incorporation of a hydraulic spray nozzle for spraying countercurrently into the fluidized substrate. Above the expansion chamber is a filter housing which separates the product from the gas. The outlet gas then passes through a HEPA filter. It is recirculated in the closed loop by a positive displacement Roots pump (in lab machines) or a high pressure radial ventilator (for pilot and production equipment). The gas is heated, HEPA filtered

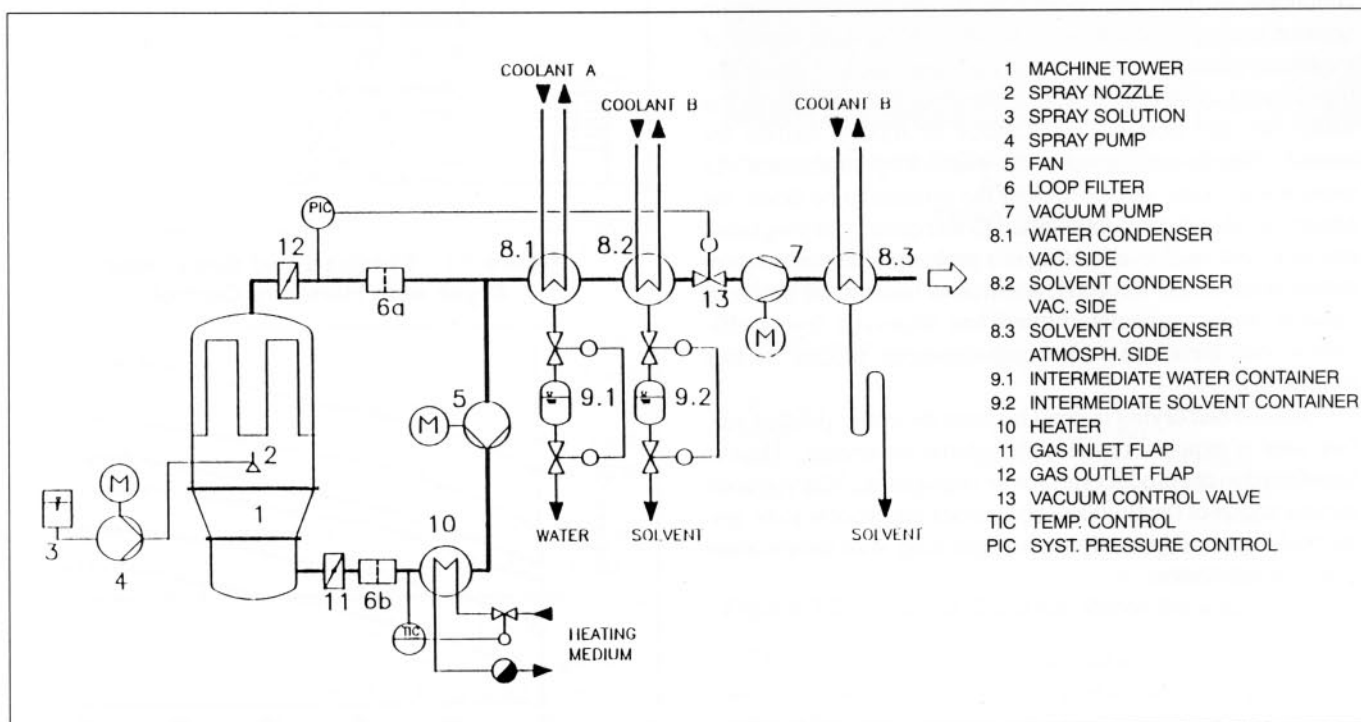


Figure 14. Vacuum-Fluidized-Bed

again, and reenters the product container providing the energy for fluidization and drying.

As drying occurs, solvent vapor is generated and must be removed from the loop to maintain the desired system pressure. It is drawn out just before the recirculation fan and into the condenser section. If the vapor contains an appreciable amount of water, the first vacuum side condenser will operate at 1°C. Because the gas stream is pure vapor and low in volume, the condensers are small. As a result, operating costs are lower than those associated with conventional solvent recovery processes. Solvent vapor which is not collected in the first condenser enters a second vacuum side condenser which typically operates at about -30°C. Each of the two condensers uses a solvent collection vessel with a level sensor for automatic discharge when the vessel is full (they can also be emptied on demand). Because the vapor is HEPA filtered, the collected solvent can potentially be reused for processing. The next device in line is a vacuum pump. The pump is small because it sees only a minute quantity of vapor since condensing vapor acts as a vacuum pump itself. Vapor which transits the pump is exhausted into a final condenser which is at atmospheric pressure and serves as a final emission control device. Laboratory experience has shown recovery rates in excess of 97% with only a few percent collected in the atmospheric side.

During the process, there are three "zones" of drying: increasing rate, constant rate and falling rate. When the surface of the product is saturated with liquid, the rate of drying is related to the rate of heat transfer. Because vaporizing liquid requires a significant heat input to satisfy the heat of vaporization, drying rate is a function of both heat and mass transfer considerations. For an atmospheric fluidized bed the heat input can be conveniently monitored by temperature differences between the product and inlet air. The mass transfer speed will be related to the difference in absolute humidity of the heated inlet air and saturated air at that temperature. The driving force will decrease as the heated inlet air passes through the product bed, simultaneously picking up moisture and dropping in temperature. Via different heating and humidity control schemes heat and mass transfer driving forces can be varied independently.

In a vacuum system the concept of "saturation" loses meaning since there is no carrier gas, i.e. the fluidizing stream is 100% vapor. To conveniently represent the mass transfer driving force in this case, we can use the vapor densities reflected by pressure. Applying this concept we can take the difference between the equilibrium pressure at the inlet temperature and the system pressure at which the vessel is controlled as a good relative measure for mass transfer driving force. Again the process vapor will change temperature and driving force as it passes through the product, liberating additional vapor, but this choice of measure will reflect the effects of both operating temperature and operating pressure on mass transfer.

Temperature differences still represent a significant component of the heat transfer capabilities but system pressure also has a large effect since at the low end of the pressure operating window there are too few vapor molecules available to effectively transfer the energy. We must now consider pressure (the main measure of mass transfer) effects on heat transfer as well as the link of heat and mass transfer through the vaporization process when manipulating the process variables for maximum effect.

To achieve a high drying rate in vacuum fluid bed processing

during the constant rate zone of drying, a relatively high system pressure (150-250 mbar) is desired. This results in a high gas density allowing vigorous fluidization properties and rapid heat transfer to the product bed. Evaporative cooling will keep the product temperature low, even while using a high inlet vapor temperature. When the surface of the product is no longer being replenished at a rate to keep it saturated, drying shifts to the falling rate zone and the product temperature begins to rise. At this system pressure, the product will approach equilibrium with the recirculating solvent vapor, and little or no evaporation will occur. Probably the residual liquid content will be too high. At this point, the system pressure can be reduced to the minimum achievable by the machine (usually 10-20 mbar). Lowering the pressure will move the system from equilibrium by reducing the boiling point of the liquid, thereby increasing driving force. Evaporation will occur using the heat stored by the product bed. Simultaneously, fluidization will diminish as a result of the lowered kinetic energy. However, in the falling rate period, the drying rate is controlled more by the rate of diffusion of moisture from the interior of the granules being dried, not the rate of heat transfer. Consequently, a vigorously fluidized bed is no longer necessary.

Although the vacuum fluidized bed system was originally designed for use with organic solvents, it is possible to use it with water based systems. Water vapor has a low gas density, influencing the choice of system pressure. It also has a relatively high heat capacity but also a high heat of vaporization. As a result, drying times are longer in the vacuum system than encountered with atmospheric fluidized bed processors. However, process time is still much shorter than with conventional vacuum contact dryers. Figure 15 illustrates a spray granulation/drying process for a lactose, corn starch, acetaminophen (as a model for determining content uniformity) product. The granulated product was uniform in particle size and similar in granule structure to material produced in an atmospheric fluid bed granulating system.

Batch size:	7.0 kg. (lactose, corn starch, acetaminophen)
Spray liquid:	1.8 kg. (15% w/w PVP K30 in water)
Spraying time:	14 min.
Inlet gas temperature:	68 - 70°C
Drying time:	10 - 12 min. ( $\Delta T_{dry} = 5^\circ C$ )
Final moisture:	1.8 - 2.0%
Mean granule size:	450 - 500 microns

**Figure 15. Vacuum Fluidized Bed Granulating using an Aqueous Binder Solution (Series of Batches)**

Granule properties such as bulk density (often a reflection of porosity), compressibility, and particle size are controllable to an extent. They are influenced by spray liquid droplet size, which is determined by liquid properties, hydraulic nozzle port size and spray rate. Additionally, bed humidity during spraying has a large impact and is comprised of spray rate, fluidization gas velocity and temperature, solvent vapor properties and system pressure. Once the proper combination of variables has been determined, reproducibility is achieved because the process operates in a closed loop and is therefore not sensitive to changes in atmospheric conditions.



## Summary

Fluidized bed processing has evolved from simple drying to granulating, pelletizing, and film coating. Water and organic solvents can be used, the latter presenting challenges in avoidance of both safety and emission problems. Vacuum fluidized processing combines the intrinsic safety of operating under vacuum with the high drying rates of fluidized beds. As a totally enclosed process, it has applications with highly potent or toxic materials, as well as oxygen sensitive products.

## ACKNOWLEDGEMENTS:

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