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FLUID BED GRANULATION: BASICS, PROCESS VARIABLES AND TECHNOLOGY UPGRADATION

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ABSTRACT

Fluid bed granulation technology is most emerging and upcoming face of granulation technology of pharmaceuticals. It is contemporarily capturing the market leaps and bounds with recent trends and developments with its innovative techniques. The fluid-bed technology is the potential tool to develop newer trends and implications in the sector of formulation development with maximum therapeutic efficacy. The technology is used for granulation/agglomeration, layering, coating and drying of a wide range of particle size. The technique can also be used for the tablet coating. In broad sense two types of the fluid-bed processes techniques is mostly used for pharmaceutical products i.e. top spray and bottom spray. This article reviews the basics of fluid bed technology, there variables, emphasize on top spray techniques and implication of Process analytical technological tools in pharmaceutical fluid bed granulation. Nevertheless, the innovation of this article is to correlate the basics theoretical knowledge with the practical things and correlation with critical process variables.

Keywords: *Fluid-bed Technology, Top spray granulation, Process variables, Process analytical technologies.*

INTRODUCTION

In the pharmaceutical industry, most products are manufactured using the wet granulation process. Wet granulation offers a wide range of capabilities for forming granules, from the production of light granules to the production of very dense granules.

In addition to a simple fluid bed, the tumbling, agitating, centrifugal, and spiral flow fluid bed and the spouted bed with or without the draft tube have been developed for improving the process performance.

Among the many types of surface modification processes, the fluid bed processes are characterized with their easy, simple mechanical formation of multilayers on the particles [1].

Fluid bed granulation (FBG) is a process widely used in the manufacturing of solid pharmaceutical products. This unit operation has been extensively studied along the last decades, but due to its complexity, there is no general model that can be applied. FBG has two steps, the powders granulation (spraying phase) and the granules drying (drying phase). Both take place in only one vessel, a fluid bed dryer. In a particular process of this kind, which had been implemented long ago, it was intended to decrease the intrinsic variability that was observed on the granules quality by implementing the quality by design (QbD) concept [2].

Wet Granulation:

Granulation is a process of size enlargement whereby small particles are gathered into larger, permanent aggregates in which the original particles can still be identified.

Wet granulation involves the massing of a mix of dry primary powder particles using a granulating fluid. The fluid contains a solvent (aqueous or non-aqueous), which must be volatile so that it can be removed by drying, and be non-toxic. Typical liquids include water, isopropanol and ethanol, either alone or in combination. The granulation liquid may be used alone or, more usually, as a solvent containing a dissolved adhesive (also referred to as a binder or binding agent), which is used to ensure particle adhesion once the granule, is dry.

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The major reason for granulating the powdered starting material in the manufacture of tablets and granules are to [3]:

- To improve the flow properties so that, the mass uniformity of the dose.
- To prevent segregation of ingredients in the mixture.
- To improve the compression characteristics of the mixture.
- To reduce the environmental hazards for the working personnel due to dust formation from toxic materials.
- To reduce the bulk volume of voluminous powders and make them more convenient for storage and transport.
- To improve the appearance of the product.
- To reduce dust for operator and environmental safety.
- To improve dispersibility.
- To improve uniformity by combining all ingredients together, or by distributing low-dose actives uniformly by dissolving and spraying a solution of actives.

When powders are very fine, fluffy, will not stay blended, or will not compress, then they must be granulated. Fluffy is not a technical term, but it fits the problem well; it means that the required quantity of powder physically will not fit into the die cavity on the tablet press. The volume of fill (bulk density) is greater than that which is mechanically allowed.

Wet granulation, the process of adding a liquid solution to powders, is one of the most common ways to granulate. The process can be very simple or very complex depending on the characteristics of the powders, the final objective of tablet making, and the equipment that is available.

Granulators:

The density of each granule is increased by increasing the amount of binding solution as well as the mechanical action of the mixer. Therefore, controlling the amounts of solution, binder, and mechanical action allows one to control the strength and density of the granule. Machines that are used for this process are called granulators. Granulators can be low shear, medium shear, or high shear.

Shear is the amount of mechanical force of the granulator. A low-shear granulator uses very little mechanical force to combine powders and binding solution.

Fluid-Bed Granulator:

The FBG, the most commonly used low-shear granulator and from the porous granules, uses a high volume of air flow to elevate powders in a chamber while a binding solution is sprayed

onto the particles to form a light bond. A fluid-bed granulator does not impart mechanical energy but instead relies on the powder characteristics and the binding solution to form the lightly held powders into granules. A low-shear granulator will not produce a dense granule, and a high-shear granulator will not produce a light granule. Again, the objective must be understood before the granulation equipment is chosen [4].

Working Principle:

FBG work on the principle of fluidization, fluid bed forms when a fluidizing gas (e.g. air) flows through bulk material. Depending on the flow velocity of the gas, several different conditions must be defined.

At the beginning of the process, gas flows through a solid bed, i.e., stationary batch of particles. Starting from this initial state with a uniformly increasing airflow velocity, a point is reached at which the particles start moving and the product batch is fluidized. This point is referred to as fluidization point and marks the beginning of fluidization.

If the velocity is increased further, the particle movement also becomes more forceful. Air, which is not needed to maintain the particles in fluid state, passes through the fluid bed in the form of gas bubbles causing strong turbulence. The maximum flow rate is defined as the rate at which the particles are removed from the fluid bed by pneumatic conveyance. As turbulence in the fluid bed can be controlled, the particles mix very intensively. Also, the heat transfer between the gas and the solid material is very high. The same applies to the transfer of material. This makes the fluid bed technology the method of choice for drying and heat transfer processes [5].

"During top spray granulation, the powder particles circulate within the product chamber and provide a constant flow of bed particles through a defined spray granulation zone. At the spray granulation zone, a fine spray of liquid binder is usually atomized and deposited onto the fluidizing particles. Particle wetting brings about granule formation. Partial drying of the wetted particles by the fluidizing air occurs continuously during granulation. When the spraying of liquid binder is completed, the granules are quickly dried by the hot air stream and complete drying is achieved"

Theory of Fluidization:

A fluidized bed is a bed of solid particles with a stream of air or gas passing upward through at a rate fast enough to set them in motion. This velocity is higher than the incipient fluidizing velocity but lower than the entrainment velocity. When the rate of flow of air or gas is increase the pressure drop across the bed also increase until at a certain rate of flow the frictional drag on the particles equals the effective weight of the bed. This condition and the velocity of air or gas corresponding to them are termed incipient fluidization and incipient velocity respectively [6].

As the velocity of the gas or air increases the bed continues to expand and its height increase with only slight increase in pressure drop. As the velocity of gas is further increased the bed continued to expand and its height increase whereas the concentration of particles per unit volume of bed decreases. At certain velocity of the fluidizing medium known as entrainment velocity, particles are carried over by the air or gas this phenomenon is called entrainment[7], Depending on the velocity chosen within the range, the type of fluidization achieved will be different as illustrated in the diagrams shown in Fig.1.

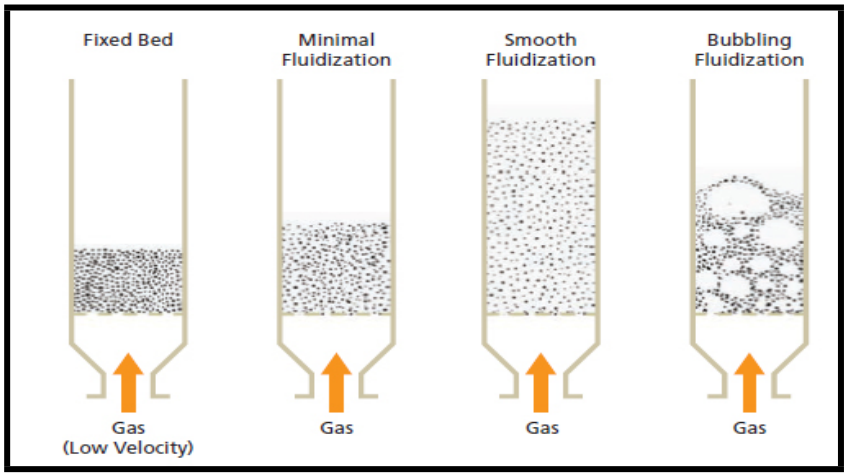

Fig.1: Type of fluidization [8]

Variables and their effect on Fluid Bed Granulation:

Factors affecting the fluid bed granulation process can be divided into three broad categories [7,9,10,11,12].

1. Formulation-related variables
2. Equipment-related variables
3. Process-related variables

1. Formulation-Related Variables:

A. Properties of Primary Material:

The ideal properties in the starting material include a narrow particle size range, a low particle density, a small particle size, a particle shape that approaches spherical, a lack of particle cohesiveness, and a lack of stickiness during the processing.

Properties such as cohesiveness, static charge, particle size distribution, crystalline or amorphous nature, and wettability are some of the properties that impact on the properties of the granules formed. The cohesiveness and static charges on particles present fluidization difficulty and during granulation particle is not granulate properly.

B. Low-Dose Drug Content:

Various methods used for the granulation of low dose drug in fluid bed granulation but due to low dose the randomized movement of particles in the fluid bed may cause segregation of the drug and that uniform drug distribution was best achieved by dissolving the drug in granulating solution. The mixing efficiency of drug particles with the bulk material increased, in proportion to the granulating liquid used to dissolve the drug.

The optimum nozzle-atomizing pressure was deemed to be important to avoid spray-drying the drug particles or over wetting, which creates uneven drug distribution.

C. Type of Binder:

The types of binders used in the pharmaceutical granulations and their influence on the final granule properties is depend on the selection of solvent and binding agents. Different binders have different binding properties and the concentration of individual binder may have to be changed to obtain similar binding of primary particles. Thus, the type of binder, the binder content in the formulation, and the concentration of the binder have major influence on granule properties. These properties include friability, flow, bulk, density, porosity, and size distribution.

Binder temperature affects the viscosity of the solution and, in turn, affects the droplet size. Increased temperature of the binder solution reduces the viscosity of the solution, thereby reducing the droplet size and producing a smaller mean granule size. Binder solution viscosity and concentration affect the droplet size of the binder. Diluted binders are preferred because they facilitate finer atomization of the binder solution, provide the control of the particle size, reduce the friability, and increase the bulk density even though the tackiness or binding strength.

D. Selection of Binder Solvent:

The selection of solvent, such as aqueous or organic, depends on the solubility of the binder and the compatibility of

product being granulated. In most instances water is used as a solvent.

Generally, organic solvents, because of their rapid vaporization from the process, produce smaller granules than the aqueous solution. Different solvents have different heats of vaporization. Incorporating binder, or a mixture of binders, of low melting point and incorporating it with the drug substance in the dry form, can eliminate the requirement of solvent for the binder. The temperature of the incoming air is sufficient to melt the binder and form the granules.

2. Equipment-Related Variables:

A. Design:

The availability of the fluid bed processors from different suppliers of the equipment is essentially similar. The differences in design of different suppliers sometime provide difficulty in scaling-up from the laboratory units to production units in a linear scale.

This variable create problem during scaling-up from two different geometrical dissimilar design equipments. Design play a major role to set the process parameters, ideally it should be similar with respect to height by diameter ratio.

B. Air Distributor Plate:

The process of agglomeration and attrition caused by random fluidization requires control of the particle during the granulation process. Optimization of the process requires control over fluidized particles. As the conditioned air is introduced through the lower plenum of the batch fluid bed, the fluidizing velocity of a given volume of air determines how fluidization will be achieved. Perforated air-distributor plates covered with the 60 to 325 mesh fine stainless steel screen provide an appropriate means of supplying air to the product. These plates are identified by their percentage of open area. Air distributor's plates that have 4-30% open area are normally available.

C. Pressure Drop:

Blower size is determined by calculating the pressure drop created by all the components of the fluid bed-processing system. Proper selection of a blower is essential in fluid bed design. A blower with an appropriate pressure drop will fluidize the process material adequately. However, a blower without enough pressure drops will not allow proper fluidization of the product, resulting in longer process time and improper granulation.

D. Filter Bags:

Filter bag is used to prevent loss of material and to allow air to pass through. If the porosity is higher than optimal, the loss of material will be high. If the porosity is lower than optimal, the filter will clog and processing will be interrupted which impact on the product yield. A filter bag is selected based on particle size of material and previous experience. The porosity of filter bag during coating can examine by monitoring differential pressure.

D. Shaker and Blowback Cycle Mechanism:

To retain entrained particles of a process material, process filters are used. To keep these filters from building up layers of fine process material, causing a higher pressure drop and, thus, improper fluidization, these filters are cleaned during the granulation process. When bag filters are used, mechanical means are used to clean them. This mechanical cleaning of the bag filters requires a cessation.

E. Other Miscellaneous Equipment Factors:

Granulator bowl geometry is considered to be a factor that may impact on the agglomeration process. The fluidization velocity must drop from bottom to the top rim of the bowl by more than half to prevent smaller, lighter particles from impinging onto the filter, creating segregation from heavier product components in the bowl. Generally, a conical shape of the container and expansion chamber is preferred in which the ratio of cross-sectional diameter of the distributor plate to the top of the vessel is 1:2. Most of the suppliers of this equipment offer units with a multiprocessor concept, for which a single unit can be used for drying, agglomerating, air suspension coating, or rotoprocessing, by changing the processing container, whereas the rest of the unit is common.

3. Process Related Variables: [12-14]

Agglomeration is a dynamic process during which a droplet is created by a spray nozzle and is deposited on a randomly fluidized particle. The binder solvent evaporates, leaving behind the binder. Before all of the solvent is evaporated, other randomized particles form bonds on the wet site. This process is repeated numerous times to produce the desired agglomerated product. There are several process variables that control the agglomeration. First step to design a robust formulation/product after deciding equipment is defining the batch size. The process parameter may change slightly depending on the batch size due to mass effect. Set and validate the process for any change in the batch size. Keep the batch size within the recommended occupancy.

The process variables can be divided into two significant categories: those impacting the spraying process and drying rate as shown in Table 1,

Table No. 1: Process Variables [12]

Spraying Process		Drying Process	
Batch size (Occupancy)	**Nozzle port size**	**Batch size (Wt in kg)**	**Inlet air volume**
Inlet air temperature	Nozzle height (with respect to static bed surface)	Inlet air temperature	Relative humidity
Inlet air volume	Nozzle spray cone angle	Product/exhaust temperatures (dependent variables)	
Product/exhaust temperatures (dependent variables)	Spray liquid temperature	Product moisture content during spraying (dependent variables)	
Product moisture content during spraying (dependent variables)	Spray viscosity	Product moisture content	
Atomizing air volume/pressure	Type of finger beg		
Solution spray rate	Finger beg shake (pulse) interval/time		
Inlet air dew point			
Inlet air RH			

The success of scale up from the lab to the manufacturing equipment strongly depends on the robustness of the product and process, as well as a good understanding of which variables have the greatest impact in small-scale machines.

A. Inlet Air Temperature and Product Temperature:

Inlet air should be direct contact with the product and be free from air born dust, oily particles and other impurities. Higher inlet temperature produces finer granules, and lower temperature produces larger, stronger granules. When the temperature of the air is too high, sprayed droplets dry quickly and do not coalesce when impinged on the particles.

The high temperatures may also cause spray drying of atomized droplets before they reach the bed, resulting in loss of binder/coating material.

In methacrylic acid based spraying/coating, at higher temperature the problem of spray gun choking occur frequently due to film formation of low glass transition coating dispersion. So it recommends that run the methacrylic acid based coating below 30°C product temperature. While in aqueous ethylcellulose based

coating required minimum 45°C product temperature due to high glass transition temperature of ethylcellulose polymer.

B. Humidity:

Humidity in the inlet air should be as low as possible and ideally dehumidified air should be used for faster drying rate because as the humidity of inlet air decreases the rate of drying increases. Humidity of the inlet drying air affects the drying of coated particles/agglomerates. The relationship between temperature and relative humidity or moisture content of air at different atmospheric pressures may be derived from psychometric charts.

Increase in air humidity causes larger granule size, longer drying times and Lower humidity in the inlet air will enhance the drying capacity of air even at low temperature but it will cause excessive static charge in the product.

C. Fluidizing Air Flow:

Proper airflow should fluidize the bed without clogging the filters. Higher airflow will cause attrition and rapid evaporation, generating smaller granules and fines.

Insufficient airflow may not provide sufficient drying air to circulate the substrates and remove the moisture from the deposited sprayed droplets during granulation/coating and consequently result in a high degree of agglomeration/wetting will occur.

D. Nozzle and Nozzle Height:

A binary nozzle produces finest droplets and is preferred. The size of the orifice has an insignificant effect except when binder suspensions are to be sprayed.

The position of the spray nozzle in a fluidized bed depends on the construction of the equipment; optimum nozzle height should cover the bed surface. Too close to the bed will wet the bed faster, producing larger granules, whereas too high a position will spray-dry the binder, create finer granules, and increase granulation time.

E. Atomization Air Volume and Pressure:

Liquid is atomized by the compressed air. This mass/liquid ratio must be kept constant to control the droplet size and, hence, the granule size. Higher liquid flow rate will produce larger droplet and larger granules and the reverse will produce smaller granules. At a given pressure, an increase in orifice size will increase droplet size and liquid throughput.

Increase in atomizing air flow rate or air pressure result in decreases in droplet size and thereby result in smaller granule size.

F: Binder Spray Rate (Moisture Content):

Binder spray rate is directly correlated with moisture content of the fluidising mass and it is the most significant process variable of fluid bed granulation agglomeration. If the moisture content is too high, the bed becomes over-wetted and de-fluidises rapidly. In contrast when the moisture content is too low, no agglomeration will occur, so it is necessary to accurately control the process variables affecting the moisture content. At any given time, the moisture content of the granules depends on wetting and evaporation. These are controlled by liquid flow rate and inlet air temperature, humidity and flow rate.

Droplet size is affected by liquid flow rate, binder viscosity, atomizing air pressure and volume. If the finer droplets produce, the resulting average granules will be smaller. The increase in the spray rate shall be always in the line of increase in the drying capacity.

Process Analytical Technology (PAT) for FBP:

A decade ago in 2001, the United States Food and Drug Administration (FDA) launched the document Pharmaceutical cGMPs for the 21st Century – a Risk-Based Approach [17]. This was to signal a shift in the regulatory practice of the FDA, which soon spread worldwide, allowing companies to proactively examine and use new technologies in pharmaceutical development and manufacturing. Since then, a collection of documents have been released, not only by the US FDA [15, 16].

In September, 2004 the FDA issued their final Guidance for Industry "PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance"

"A system for the analysis and control of manufacturing processes based on timely measurements of critical quality parameters and performance attributes of raw materials and in-process materials: at-line, in-line, or on-line".

Pat Analysers for FBP:

Moisture Analyser:

Near infrared radiation (NIR) is a spectroscopic method utilizing the near infra-red region of the electromagnetic spectrum (from 1100nm to 2500nm).

The Thermo Scientific TruProcess NIR Analyzer is a next generation Process Near-Infrared Spectrometer.
Specific applications include:

- Fluid bed drying applications
- Process monitoring

An in-line moisture analyser based on NIR, the Thermo Scientific TruProcess NIR Analyzer, was assembled on the industrial fluid bed dryer, according to the cGMP for new equipment qualification, calibration and validation. NIR is an effective alternative to conventional analytical methods such as thermogravimetry (LOD) and Karl Fischer titration. On-line monitoring of moisture levels using NIR fiber-optic probes is a feasible option for optimising drying times since –O-H vibrations of water exhibit a large absorption in the NIR region [17, 18].

Particle Size Analyser:

The in-line particle size analyser rapidly detected the actual granule size changes and these changes could be monitored both in real time and analysed more specifically afterwards. Various process phenomena and failure modes could be observed.

An in-line SFT (spatial filtering technique) probe (Parsum® IPP 70S, Chemnitz, Germany), is use into the granulator to determine the particle size in FBP. The particles passed through an aperture (diameter 4 mm). Pressurized air is used to disperse the particles. During the fluid bed process, an average number and volume of particle distribution data at 10s intervals is produced.
The sample poured through an orifice of the SFT apparatus using a funnel and pressurized air for at-line and off-line applications [19, 20].

CONCLUSION

Fluid-bed granulation is a widely used process and well-known unit operation in the pharmaceutical industry. This technology gives a robust process which will ease the scale-up from laboratory to commercial production with the use of basic understanding such as FBP theories, principle, proper selection of operating procedures, understanding of variables and optimization of process parameters. Therefore due to these it can be concluded this technology can be future of granulation and it is important to understand basic concepts of equipment design and fundamental of granulation theory. If a formulation and process are optimally developed using fluid-bed technology, the end product quality will be satisfactory and the product will be reproducible. Coming to grips with the process parameters through the use of statistical techniques exemplified by the PAT tools, this play a significant role on this journey for optimization of process and help to control the critical process parameters.

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