Medical Sains : Jurnal Ilmiah Kefarmasian
Vol. 8 No. 3, July - September 2023
https:/ojs.stfmuhammadiyahcirebon.ac.id/index.php/iojs

REVIEW: PROCESS OF FLUID BED GRANULATOR PARAMETERS AT THE TIME OF SCALE UP IN GRANUL PRODUCTION

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Submitted: 31 May 2023 ***Revised: 1 July 2023*** ***Accepted: 3 July 2023***

ABSTRACT

Scaling up is one of the difficulties faced by the production process of the pharmaceutical industry. We must manufacture in higher quantities than a laboratory size with set requirements as we scale up. Understanding the crucial variables that affect the final product's specifications will aid in choosing appropriate upgrade settings. Fluidized-bed granulation is one of the most frequently used techniques to increase the scale of the pharmaceutical industry. The complex fluidized bed granulation process is influenced by several factors. The most important process variables were the intake air temperature and humidity, concentration of the binder solution, spray rate, atomizing air pressure, and air flow rate. Numerous investigations have examined the effects of large-scale fluid bed granulation. An improved fluid bed granulation technology was employed based on the relative droplet size and moisture content of the powder in the bed after the spraying cycle. These values are comparable, demonstrating that the granulation procedure can be enhanced by considering only the moisture content of the powder and relative droplet size.

Keywords: fluid bed granulation, process parameters, scale up

INTRODUCTION

One of the difficulties faced by the pharmaceutical sector is scaling it up. We must manufacture in greater quantities than the laboratory size with defined criteria as we scale up. This is a challenge in real-life. It will be easy to choose appropriate scale-up settings if you are aware of the crucial variables that affect the final product's characteristics (van Heugten & Vromans, 2018). There are several methods to scale up the pharmaceutical sector, but fluidized bed granulation is one of the most popular methods.

When employing a fluid bed granulator to scale up production, it is critical to comprehend the device operation, fluidization theory, excipient interactions, and most crucially, the key variables that influence the agglomeration process. The scale-up process will benefit tremendously if these process parameters are determined in the early stages of product development (Mandić et al., 2020).

Granulating API and excipients is a method frequently employed to improve the undesired powder properties of active pharmaceutical ingredients (API). Dry granulation (slugging or roller compaction) and wet granulation (low shear wet granulation, high shear wet granulation, or fluid bed granulation), both of which use liquid binders, are the two most widely used methods for producing granules. Fluid bed wet granulation is a device that can be used for wet granulation, drying, and mixing processes (Yamamoto & Shao, 2017).

Several process variables affect the fluidized bed granulation process, making it a complex process. It is challenging to enhance the granulation process purely based on process factors because of this complicated procedure. The pharmaceutical sector frequently employs empirical methods to scale up fluidized granulation operations from a small scale to a production size, starting from a small scale (5 kg) to a medium scale (30 kg) to a

production scale (120 kg). During the scale-up process, a number of variables must be considered, including spraying speed, droplet size, temperature, and fluidizing airflow (Askarishahi et al., 2019; Rambali, Baert, & Massart, 2003).

Dry mixing, wet granulation, and drying are the first steps in the labor sequence for fluid bed granulation. Hot air was used to first fluidize the raw materials before blending, and then a solution for granulation was sprayed on the materials just before blending to achieve the necessary moisture content or ideal granule size. Subsequently, drying was initiated and continued until the product reached the desired temperature. Typically, a binder solution is used as a granulation liquid. However, it can also be included in the powders as a dry ingredient (Yamamoto & Shao, 2017).

The pharmaceutical sector has paid a lot of attention to the fluid bed granulation process to address particle agglomeration, dust containment, and material management. Dale Wurster employed an air suspension approach to coat tablets when he initially disclosed the fluid bed process in the pharmaceutical industry. He discussed the use of air suspension technology for the granulation and drying of pharmaceutical granules suitable for the production of compressed tablets in a report from 1960. Scotts et al. and Rankell et al. published papers on the theory and concerns of process design in 1964. They used mass and heat energy balances and a fundamental engineering approach. They increased their use to a pilot model with a 30 kg capacity made for batch and continuous manufacturing. Then, the process variables include the liquid flow rate, air flow rate, and process air temperature. The material treated with a fluid bed granulator has finer, more free-flowing, and homogenous granules that are tougher and more compact after compression than those produced with conventional wet granulation. It has been shown to make pills that dissolve quickly (Mukharya, Chaudhary, & Shah, 2012).

Granules produced by the fluid bed process have several advantages (Yamamoto and Shao, 2017).

1. More homogeneous, free-flowing, and pivotal. Generally, these granules require a lower pressure when compressed into tablets.
2. Fluid Bed Granulation is carried out in 1 unit machine, saving production time and labor.
3. The granulation process can be run automatically

RESEARCH METHOD

The articles used in this review come from international research articles in English from Science Direct, PubMed, Springer, Semantic scholar, and Google scholar using the keywords "Fluid Bed Granulation", and "Scale Up". The articles used were from 2002 to 2020.

RESULTS AND DISCUSSION

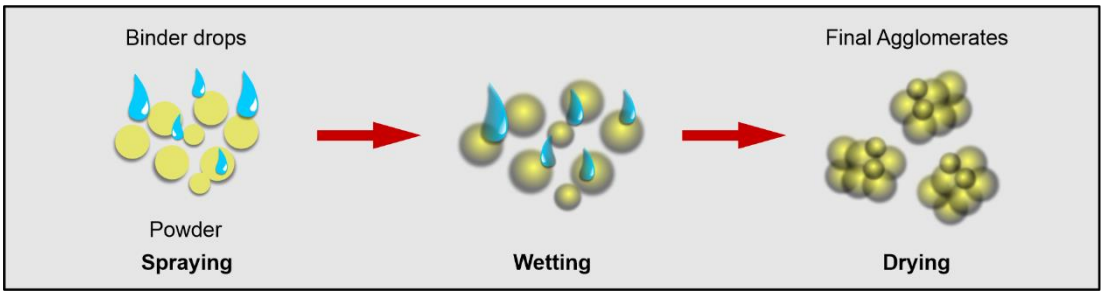

Figure 1. The Process of Forming Particle Agglomeration in Fluid Bed Granulator

In the frequently used fluid bed granulator (FBG), a binder or solvent solution is atomized using a two-fluid nozzle and sprayed onto a powder bed of medication excipients fluidized by hot air. In addition to vigorously moving the bed, which allows for great powder mixing and equal dispersion of the droplets/liquids, hot air also causes the droplets' water to evaporate concurrently (Bilgili et al., 2011).

Controlled granule creation and growth depends on a steady increase in moisture from the bed, which is made possible by the final FBG feature (Jang, Park, Kim, & Choi, 2020). This feature prevents wet cooling. Given these factors, the FBG process offers significant advantages over traditional high shear wet granulation, including the ability to produce small porous granules, produce a relatively narrow range of particle sizes, avoid the need for downstream milling, and achieve uniform product quality through effective mixing (Bilgili et al., 2011; Jang et al., 2020).

Granule size, porosity, attrition strength, morphology, and dispersion/dissolution characteristics in water are just a few product parameters that are affected by the FBG process (Amini et al., 2020). Equipment and process variables are the two categories into which the variables that affect product qualities for a certain product formulation can be subdivided. Equipment parameters such as the size and type of the distributor plate, and nozzle specifications, etc. The temperature and humidity of the inlet air, concentration of the binder solution, spraying rate, atomizing air pressure, and airflow rate are the most crucial process variables (Amini et al., 2020).

Fluid Bed Process Parameters

1. Spraying Speed

   The powder was fluidized with air during the granulation process in the fluid bed granulator, and the fluidized particles were sprayed with a binder liquid. In the presence of this binder liquid, the particles stick together and form one larger particle (agglomeration) (Neuhaus Neotec, 2013).

   If the rate of spraying of the binder liquid is too fast then the formation of granules will also be fast, the speed of formation of these granules will affect the final result of the resulting granules, in research conducted by Mukharya, et al conducted research on the effect of spraying on the size of the resulting granules, in his research he used 3 different temperature variations, from the results of the Design of Experiment (DOE) the faster the rate of spraying of the binder liquid, the resulting granules have a larger diameter or size (Yamamoto & Shao, 2017). If the rate of spraying of the binder liquid is too fast then the formation of granules will also be fast, the speed of formation of these granules will affect the final result of the resulting granules, in research conducted by Mukharya, et al conducted research on the effect of spraying on the size of the resulting granules, in his research he used 3 different temperature variations, from the results of the Design of Experiment (DOE) the faster the rate of spraying of the binder liquid, the resulting granules have a larger diameter or size (Mukharya et al., 2012). A spraying rate that is too slow will also affect the final granule yield, where it takes a relatively long time for the particles to stick together and form an agglomerate if the spraying rate is slow, in some cases it is even possible that no granule growth can occur if spraying is too slow (Yamamoto & Shao, 2017).

   By increasing the spray rate while maintaining a consistent input air temperature and binder concentration, it is possible to reduce the total spray time and create more binder in granulation (Vengateson & Mohan, 2016).

   The capacity of the drying equipment, which is directly proportional to the cross-sectional area of the air distribution, determines the increase in spraying rate during the scale-up process. The cross-sectional area of the air distribution was used to calculate the spraying rate at the scale-up level because, as previously mentioned, the spraying rate affects the size of the resulting agglomeration (Mukharya et al., 2012), which can be calculated using the following formula:

$$SR_2 = [SR_1 \times (\frac{A1}{A2})]$$

SR_1 is the rate of spraying on a laboratory scale
SR_2 is the rate of spraying on scale up
A_1 is the cross-sectional area of air distribution on a laboratory scale
A_2 is the cross-sectional area of air distribution on scale up

2. Size and atomization of droplets

The process of agglomeration development is significantly influenced by the size of the droplets in the wetting liquid. Agglomerates form differently depending on the size of the binder droplet, according to Abberg et al. The mechanism underlying agglomeration is regulated by the ratio between the size of the powder particles and that of the binder droplet. These two mechanisms led to agglomeration. First, liquid binder droplets, which are larger than the particle size, wet the particles through an immersion process that causes agglomeration. This soaking process caused agglomeration. In the second mechanism, the droplet size is smaller than the particle size, which causes agglomeration. Through the collision success factor and agglomeration constant, the fluid content of the granules affects agglomeration growth behavior. Larger grains are produced when the wettability level is raised (Abberger, Seo, & Schæfer, 2002; Askarishahi et al., 2019). The agglomeration growth behavior is influenced by the fluid content of the granules through the collision success factor and agglomeration constant. Increasing the level of wettability produces larger grains (Askarishahi et al., 2019). The granular size and tablet hardness increased as the amount of binder in the mixture increased. According to the outcomes of Suresh's experiment from the year 2020, the granules have an open structure and are created by the accumulation of wet lactose particles (distribution mechanism) and tiny nuclei created by the immersion mechanism (Suresh, Saketharam Reddy, Hariharan, & Sreedhar, 2020). Granule size is also determined by the type of binder employed; PVA cannot be advised for use because of its high adhesiveness, according to Sahnen's research on the production of nanoparticles (Sahnen, Kamps, & Langer, 2020). The quality of the generated droplets is also influenced by the water content (Takasaki et al., 2019). Due to the high viscosity of the dispersion, which might result in nozzle clogging, the atomizing air pressure must be increased together with an increase in the inside nozzle diameter (Mandić et al., 2020).

3. Temperature

One of the elements influencing the drying of granules is the temperature, specifically the intake and exit temperatures in the fluid bed. It is necessary to evaporate and eliminate the wetting liquid utilized to create agglomerates in the form of exhaust air (Yamamoto & Shao, 2017). The inlet and outlet temperatures of the dryer, airflow rate, and humidity control the evaporation process. Because of the heat and mass transfer caused by the temperature in the generated granules, the moisture content of the granules is affected by the intake and output temperatures.

According to Hu et al., the moisture content of granules decreases as the inlet temperature increases. However, the inlet temperature must be controlled to ensure that the drying process occurs evenly across an entire granule. The heat entering and leaving the tool must be measured to predict the moisture content of the resulting granules. With improved lipid molecule mobility at higher temperatures, high temperatures can cause particle cohesiveness in the fluidized phase and particle adhesion to the process chamber walls (Takasaki et al., 2019). Particle cohesiveness in the fluidized phase and particle adhesion to process chamber walls are caused by

high temperatures, which may be related to the greater mobility of lipid molecules at these temperatures (Mandić et al., 2020).

Both on a laboratory scale and on a larger production scale, the input and dew points must be constant. To ensure the fastest possible granule drying process, the intake and dew points can be adjusted to the airflow, if necessary. However, if the particles are not heat resistant, the inlet temperature can be altered to maintain the product.

3.1 Fluidizing air flow

As it affects how the particles are mixed, how evenly the binder solution is distributed over the particles, and how quickly the granules dry, fluidizing airflow is one of the crucial parameters in the features of granule growth (Vengateson & Mohan, 2016). The growth of agglomerates (granules) is slowed down by a higher air velocity or fluidizing air flow, according to Hemati et al., who observed the growth of sand particles using 1% CMC as the binder liquid. This too high speed also indicated less compact granules because of the lack of a strong bond between the particles caused by the relatively high fluidizing airflow. Airflow rate can also affect the moisture content of the resulting substance (Hemati, Cherif, Saleh, & Pont, 2003). Through saturated humidity, increasing the input air temperature directly increased the capacity of the inlet air to dry (Amini et al., 2020).

According to Tan et al., the initial growth rate of granules results in rapid growth when the fluidizing airflow is relatively slow; however, it creates particles with a narrower size distribution when the fluidizing airflow velocity is higher (Bilgili et al., 2011). According to Tsutsumi et al., fluidizing airflow at high speeds can be used to create agglomerates or granules with a considerably smaller particle size distribution and reasonably high homogeneity (Tan, Salman, & Hounslow, 2006). This suggests that, at high speeds, the production of short particles results in a more uniform particle size. The amount of extra free water in the granules can be decreased owing to incoming airflow. In other words, the influx of air may help balance free water, in addition to mixing (Takasaki et al., 2019).

The air volume in the tool is larger during the scale-up process to maintain the fluidization velocity, so that it continues to produce the same air velocity (Mukharya et al., 2012). Based on the cross-sectional area of the tool, calculations for scaling up from the laboratory scale to the production scale can be calculated using the following equation:

$$AF_2 = [AF_1 \times (\frac{A1}{A2})]$$

AF_1 is Fluidizing air flow on a laboratory scale
AF_2 is Fluidizing air flow on scale up
A_1 is cross-sectional on a laboratory scale
A_2 is cross-sectional on scale up

Assessment of Critical Parameters

The fluid bed granulator process was primarily influenced by three variables: air quality, spray quality, and equipment-related variables. Equipment design, bag filters, distributors, bed form and extension chambers, mechanical shock, and location and number of nozzles are examples of equipment-related issues. These elements must be carefully considered when batch sizes are altered or formulations are moved from one location to another (Yamamoto & Shao, 2017).

The effect of droplet size on granule size was investigated by varying the relative droplet size (R) in three fluid beds. The airflow through the nozzle was increased or decreased to adjust the relative droplet size. During spraying, a high inlet air temperature

(70 $^{\circ}C$) was used to complete the drying process. The impact of the powder's moisture content on granule size is diminished by high temperature, and the pace of granule growth is considered to be modest. After spraying, the moisture content was approximately 5%. The granule size correlated with R in all fluid beds. Relative droplet size is denoted by R. Despite using the same type of nozzle at both small and medium fluid bed scales, R has different effects on the granule size. Under the same R setting, the granules tend to be smaller in larger fluid beds than in smaller fluid beds. This discrepancy may be explained by the excessive growth of the batch scale compared to the spraying rate (Rambali et al., 2003). Small fluid beds have relatively more accessible droplets than medium and large fluid beds. Additionally, as the batch size increased, the fluid bed scale and frictional effect on the grains became stronger (Mukharya et al., 2012). The spray rate/atomizing pressure ratio is the most important factor for controlling spray droplet size. To retain the same particle size, a "three-headed nozzle" on a scale can be sprayed at the same pilot-unit spray rate and atomizing air pressure. However, the processing time may be longer (Mukharya et al., 2012).

Four tests were run on a medium fluid bed in the study (Rambali et al., 2003) to assess the granule size regression model of a small fluid bed for scale-up applications. The small fluid bed regression model predicted the granule size, and the medium fluid bed obtained the observed granule sizes. Only the granule sizes from Experiment 1's observations fell within the model's confidence intervals for modest fluid bed granule sizes. The granule sizes observed in other studies were significantly smaller than those predicted. These findings support the notion that granule growth differs across the medium and small fluid bed scales. Different granulation processes in the fluid bed (continuous versus discontinuous granulation processes) and variations in droplet size may be responsible for these disparate results. The findings of the four studies supported the notion that medium-scale granules cannot be predicted using a small-scale granule size model. As a result, it is necessary to create a separate model for the granule size on a medium-scale fluid bed.

A regression model for the tiny fluid bed granule size is suggested, and it is contrasted with the model for the medium fluid bed. Plotting the expected granule sizes at comparable underlying granulation process settings allowed this comparison. For the models to be equivalent, the granule sizes predicted by each model must be comparable. The granule sizes predicted by the two models were strongly correlated according to the Rambali study. However, for the same underlying granulation process setting, it has been projected that the tiny fluid bed granule size is consistently greater than the expected medium granule size of the fluid. It appears that the suggested model for small fluid bed granule sizes can be utilized to estimate granule size in medium fluid beds by adding a correction factor because of the excellent correlation between the granule size predictions from the two fluid beds. The results of this investigation were also obtained on a larger scale. These values are comparable, demonstrating that the granulation procedure can be enhanced by considering only the moisture content of the powder and relative droplet size. An improved fluid bed granulation technology was employed based on the relative droplet size and moisture content of the powder in the bed after the spraying cycle. Despite the same granulation process settings and identical small and medium scale nozzle sizes, different granule sizes were obtained. The granulation process can be improved by developing a regression model for the granule sizes produced in the small and medium fluid beds. The granulation procedure also succeeds by merely growing the fluid bed's scale based on the relative droplet size (Mandić et al., 2020; Rambali et al., 2003).

CONCLUSION

Adaptive bed granulation is a well-known unit of activity in the pharmaceutical sector. This shows that this method can be scaled up from the laboratory scale to commercial production with appropriate equipment design, operating conditions, and excipients. Although granulation procedures might differ from formulation to formulation, fundamental equipment design principles and fundamental granulation theory must be understood to create dependable and scalable formulation processes. In addition to assisting in the creation

of a design space for fluid bed processes, the use of tool parameters can be an excellent tool for scaling up and transferring technology. High-quality granules can be created using fluid bed technology through the creation of formulations and processes for use in finished goods, such as tablets and capsules.

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