Process Monitoring and Control of Drug Fluidized Bed Granulation and Its New Application

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ABSTRACT
Nowadays, fluidized bed granulation is a widely used technique in the pharmaceutical industry. Several factors, including process settings, powder qualities, and binder properties, impact its performance. The monitoring of the fluidized bed granulation process is a complex process. This paper describes the fluidized bed granulation process's real-time online feedback control method. The focus of this study is on a Process analysis technology(PAT) based feedback control system for batch processing monitoring of fluidized bed granulation operations. It promotes the advancement of fluidized bed granulation technology from laboratory to mass production, giving a more efficient and cost-effective monitoring method for the pharmaceutical industry, based on the PAT process. In addition, fluid bed-based granulation produces particles with lower density and more porous structure, thus improving the water solubility of drugs.

Keywords: *Fluidized bed granulation, Process analytical technology, Process automation, Process understanding*

1. INTRODUCTION

Fluidized bed granulation technology is a wet granulation technology that is widely utilized in the pharmaceutical manufacturing industry. Generally, the particles produced by fluidized beds have the advantages of being low density, homogeneous, looser, and porous. Therefore, fluidized bed granulation technology can be used to improve the water solubility of drugs. However, source material and binder qualities, operational and formulation factors, and parameter settings all affect fluid bed granulation. Precision control of the process was lacking in the early uses of fluidized bed granulation. Conventionally, the process is regulated by monitoring predetermined process parameters, and the final product quality is assessed after manufacture using time-consuming off-line testing methods. Most products that do not meet expectations are discarded or returned for reprocessing, which does not meet the needs of mass production. A real-time online monitoring and management system, PAT, advocated by Food and Drug Administration (FAD), provides a new idea for real-time control of the granulation process. This paper reviews previous publications in the field of process analysis of fluidized bed granulation technology and summarizes the advantages and characteristics of fluidized bed granulation technology, as well as the new applications that can be performed with this technology. In addition, the advantages and disadvantages are summarized by comparing previous and current process inspection and control methods, and suggestions are made for future improvements. This research contributes to a better understanding of fluidized bed granulation technology by offering a detailed review of process analysis methodologies. The process parameters' measurement and control methodologies are described. It adds to the advancement of fluidized bed granulation technology's process control technology and technical methods of endpoint detection.

2. INTRODUCTION TO THE PROCESS OF FLUIDIZED BED GRANULATION TECHNOLOGY

Granulation is a particle size expansion process in which tiny powder particles are collected into bigger, permanent structures that can be recognized from the original particles[1]. Fluid bed granulation is a wet granulation procedure widely utilized in the pharmaceutical industry that offers a number of technological benefits. During the process, a binder

liquid is sprayed onto the powdered liquid. This causes the wet particles to collide and form larger permanent aggregates. The solvent is then removed by subsequent evaporation and other operations, and stronger bonds are established. However, unlike other wet granulation processes, the addition of binder and evaporation is carried out simultaneously in the fluidized bed granulation process. In that case, a separate drying unit is required in comparison to low shear wet granulation and high shear wet granulation technologies. However, dry mixing, wet granulation, and drying can all be done in the same machine with fluidized bed granulation. This boosts productivity, lowers labor and material costs, and prevents losses in the transfer process.

In the process of fluidization, the raw material is transformed from a static to a moving fluid state by the support of gas. The particles can move up and down in the gas. The material will be suspended in the gas[2]. The particles are suspended in a conical container utilizing a heated airflow and may move freely up and down in the fluidized bed granulation process. As a result, the movement of the particles may be watched via the container's glass to see if the fluidization process is working properly. The binder is sprayed via the nozzle while the particles are moving, and the resultant droplets join with the fluidized particles to produce a permanent aggregate. After the particles have fully bound to the binder, they are further fluidized and dried in the same machine, where the solvent is evaporated and the particles are dried to the predefined moisture content in order to fulfill their activity and further processing requirements.

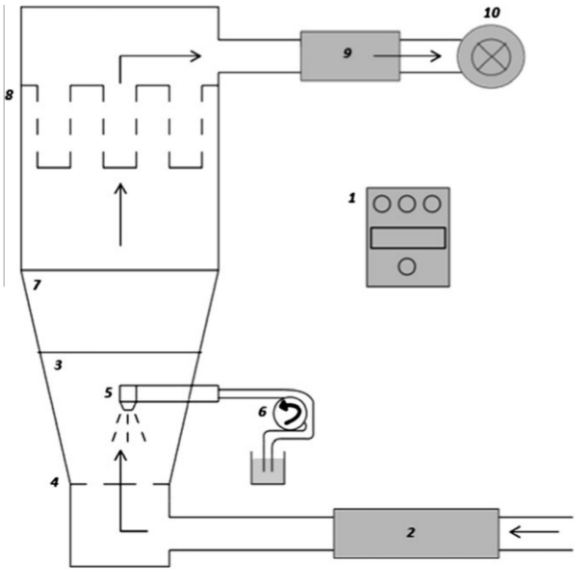

Figure1 Schematic of a top-spray fluid bed granulator with assignment of its different components: [3]

The fluid beds consist of a number of key structures. The control panel(1)can monitor and control the Key Variables. The air handling unit(2)processes the air that is required to fluidize the particles. The treated air is then passed through product container(3) and air distributor plate(4). The top-spray installed nozzle(5) is used to spray adhesive. The adhesive is conveyed through the pump(6) to the delivery nozzle. The air expansion chamber(7) can be used to withdraw particles with too much kinetic energy. The collected particles can be shaken back into the fluidized bed by shaking the filter bag(8). The air can leave the system through an air filter system(9). The exhaust blower(10) is used to remove the excess small particles.

3. CONTROL MONITORING ANALYSIS OF DRUG FLUIDIZED BED GRANULATION PROCESS

3.1. Monitoring and Analysis of Past Fluidized Bed Granulation Processes

3.1.1. Monitoring and Control Methods

In the early stages of fluidized bed technology application, lack of accurate monitoring and control methods and systems. Feeling the expansion chamber for rising temperature was a traditional technique for detecting the drying endpoint[4]. But this method often relies on experience and intuition to make appropriate modifications, and lacks specific values that can be relied on, so large-scale granulation using fluidized beds is difficult to achieve[5].

Typically, fluidized bed granulation technology is monitored by regulating process parameters and controlling formulation components. The evaporation rate of the binder is determined by a mixture of heat and mass transfer processes during the drying of the product. The evaporation of the adhesive is aided by heat transfer to the particles, while mass is transferred from the particles to the surrounding gas in the form of flowing gas. Because the drying capacity of air is affected by temperature and relative humidity, air handling equipment can be used to filter, warm up, and dehumidify the incoming air[6]. The fluidized granulation process may thus be monitored and controlled by altering these parameters. A pneumatic analog control system that employs compressed air as a signaling medium to communicate information from granulator measurement equipment was first used to record and regulate crucial granulation process parameters[7].

3.1.2. Disadvantage Analysis

Although the past testing method may seem simple and reasonable, its effectiveness relies heavily on the subjective operation of the operator as a way to ensure that parameters are recorded and measured during the production process. Usually, many operational measurement errors cannot be avoided. Therefore, it is difficult to guarantee the quality of the product obtained by using this method to control the fluidized bed unit. Apart from that, the measurement of the values in the production process is an indirect measurement. The value of the process is related to the nature of the raw material, and the occurrence of the change in the nature of the material is done in a short time. In addition, the measurement of the values can be disturbed by external conditions, which cannot be avoided. If these changes are not monitored in time, the product may be over-dried and the product quality may be reduced.

3.2. Monitoring and Control Analysis of a New Fluidized Bed Granulation Process

3.2.1. Real-time Online Feedback Control System for PAT-based Fluid Bed Granulation Process

Process analysis technology(PAT), championed by the FDA, offers a new type of monitoring and control for the drug manufacturing industry. Real-time measurement of process quality parameters, as well as quality evaluation of intermediate and final products, are included in this technology.

Nowadays, the link between Critical Quality Attributes(CQA) and the identification of key parameters has been further considered and understood using the continuous development of PAT-based tools and the in-depth understanding of the PAT implementation process. The continual development of new analytical techniques improves the collection of granulation data. Physical and chemical information on materials may now be delivered non-destructively and swiftly thanks to modern analytical technologies. Without consuming samples, these measurement instruments may immediately measure the product's characteristic values while it is in the process stream.

Currently, people usually use the comparison of process variables (PV) with predefined process parameters to determine whether their error values are within a predefined range, thus eliciting a computer response[8]. Because of that,the real-time online automatic control can be implemented.

One of the most important parts of the fluidized granulation process is the spraying of the right amount of binder on the already fluidized particles. In this process, it is particularly important to measure the water level reached by the binder spray and the degree of dryness achieved by the particles when the solvent evaporates. In this context, scientists have developed an online moisture measurement using NIR to determine the moisture content of the particles during the granulation process and to determine the endpoint of drying.

The spectral region range of near-infrared(NIR) is 12500-40000cm-1. Overtone and combination bands of fundamental vibrations found in the mid-IR region are the source of NIR absorbances[9]. Only vibrations that cause changes in the dipole moment of the molecule are NIR active. As a result, vibrations of CH, OH, SH, and NH bonds are the most commonly seen[9].

Non-invasive online real-time monitoring of the granulation process using NIR spectroscopy in large-scale fluidized bed industrial manufacturing. The spectra of the fluidized particles are collected immediately by putting the NIR probe on the granulator's glass window. By integrating the resultant NIR spectra of the particles, a partial least squares (PLS) model is then created to forecast the volume, density, and water content of the product. The NIR spectra are utilized to monitor each important phase of the fluidized bed granulation process in real-time.

Both focused beam reflectance (FBRM) and spatial filter velocimetry (SFV) can be used to measure and record real-time data for monitoring changes in particle size and distribution during production. They both measure the chord length of the particles in order to provide a picture of how the particles expand during the granulation process. (The chord length is the straight line connecting any two spots on the particle's edge) The FBRM probe's measurement window is placed at the probe tip, whereas the SFV probe has a measurement zone inside the probe made of two measurement windows[10]. The chord length distribution is obtained by SFV from the shadow cast on the detector by the

passage of the particles via the laser beam, whereas the line length data is obtained by FBRM by backscattering the laser beam into the probe[11,12]. Particles are passed across the laser beam during SFV measurements, and shadows are projected onto the linear fiber array[13,14]. As a result, a speed-proportional signal is created. When a particle travels through a laser beam, a single fiber creates a secondary pulse, which may be used to compute the particle's chord length by combining the particle's velocity with the pulse signal's duration. The FBRM probe generates a high-speed focused laser that strikes the particle in front of the measuring window, causing the laser to scatter in all directions and allowing the chord length of the particle to be calculated and the particle's growth to be determined. It's worth mentioning that, in order to avoid contamination of the FBRM probe window during fluidized bed granulation, a mechanical squeegee triggered by compressed air must be inserted in the sapphire measuring window. The -SFV, on the other hand, has been demonstrated to constantly assess the particle size distribution during the pelletizing process without taking window contamination into account.

The online, real-time gathering of particular and vital data for the fluidized bed granulation process is made possible by these PAT technologies. The data is examined so that the fluidized bed granulation process may be controlled in real-time online.

3.2.2. Benefits Analysis

The development of real-time analytical measuring instruments for fluidized bed granulation processes based on the PAT method has been intense. The capacity to gather particle information throughout the granulation process and manage the granulation endpoint by monitoring the process parameters of the desired particles has improved thanks to the successful development of these technologies. And because these measurements are non-invasive and direct, they may be used to get in-line sample information by drilling the probe deep into the process stream[15]. An automatic sampling device will be included in the in-line analysis tool, which means that sampling will be done automatically and the sample will be transmitted to the measurement device. The sample is automatically returned to the process stream when the measurement is done. This method eliminates sample waste while also reducing preparation inefficiencies induced by human transfers and machine stops. Furthermore, the measurement findings are more precise. Thanks to these instruments, the fluidized bed granulation method have been able to go from the laboratory to high-volume industrial production.

4. NEW APPLICATION OF FLUIDIZED BED GRANULATION TECHNOLOGY IN THE FIELD OF TRADITIONAL CHINESE MEDICINE

Due to the lack of shear, the particles produced by the fluidized bed wet granulation process are loose and porous with a low density. Because the particles are mainly distributed, they have high water solubility. Furthermore, mixing, granulation, and drying are all done in the same operation unit throughout the tablet production process. Furthermore, because the granulation process is carried out in a closed fluidized bed granulator, the product is less likely to be contaminated during the production process, and product quality can be ensured with great efficiency.

Based on the experiments conducted by Andrea Ikeda Takahashi in 2012 on fluidized bed technology in improving the solubility of nimodipine and spironolactone, it was shown that fluidized bed granulation technology is effective in improving the solubility of drugs. The DE (dissolution efficiency) of the pellets obtained by compressing into flakes was compared with that of the pellets obtained by fluidized bed granulation by adding different amounts of surfactants sodium dodecyl sulfate and sodium decacosan. As seen in the figure below, the use of granulation using fluidized bed results in smaller and more uniform granule density with better dissolution as the drug is dispersed onto the powder in low water-soluble drugs such as nimodipine and spironolactone[16]. There is no need to use other formulations to improve the dissolution rate[16].

Dissolution efficiency (%)				
Formulation	Nimodipine		Spironolactone	
	PM	G	PM	G
1	5.6	73.0	11.6	95.3
2	9.3	81.0	17.0	94.8
3	29.2	66.3	20.8	84.3
4	37.3	88.5	53.1	84.5
5	9.1	76.6	59.4	95.4
6	16.9	76.1	64.8	94.9
7	45.7	68.0	72.8	87.2
8	52.4	91.9	79.3	84.2

Figure2 Dissolution efficiencies (DE) of nimodipine and spironolactone formulations (PM = tablets obtained from physical mixtures; G = tablets obtained from fluid bed granules)[16].

The application of fluidized beds in Chinese medicine usually uses fluidized spray granulation. "One-step granulation" is fluidized spray granulation, which is also known as boiling granulation. The method of granulation

of excipients in the fluidization chamber of the fluidized spray granulation equipment consists of the passage of filtered heated air so that the powder is preheated and dried in the boiling state, and then the pretreatment of the liquid sprayed intermittently in the form of mist so that the powder of excipients is wetted and condensed into porous particles while continuing to dry the fluidization until the moisture content of the particles is suitable to granulate[17].

Most Chinese medicines are made of infusion, in which alkaloids, glycosides, polysaccharides and other active ingredients are also added [17]. Therefore, in order to improve the quality of pharmaceuticals, it is necessary for the pharmaceuticals to be moisture-proof, free of bad odor and intact in appearance.

As a result, using fluidized bed granulation technology to make herbal medications can significantly minimize the number of excipients required. The infusion's concentration in the medicine might range from 50 to 70 percent. The granules produced are consistent in size and have good solubility, with a high rate of production and product certification. It meets the goal of minimal quantity and high efficiency while being easy to transport.

5. CONCLUSION

The current fluidized bed granulation technology has become increasingly mature and is reviewed in detail in this paper. A comparison of past and present new fluidized bed granulation process monitoring systems are presented, as well as a specific explanation and understanding of the batch processing feedback online processing detection control system for PAT-based fluidized bed granulation technology. Although the use of PAT can provide effective data monitoring in real-time in fluidized bed pelletizing batch production. However, avoiding contamination of the measurement window during the granulation process is still a current technical drawback and remains a challenge to be solved.

Due to the good solubility of the granules manufactured using a fluidized bed, they can be widely used in the manufacturing industry of herbal medicine, which has a great future.

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