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Research Article

TO STUDY AND UNDERSTAND THE PROCESS OF WET GRANULATION BY FLUIDIZED BED GRANULATION TECHNIQUE

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ABSTRACT

Fluidized bed granulation is a widely used wet granulation technique in the pharmaceutical industry to produce solid oral dosage forms. The process involves the spraying of a binder liquid onto fluidizing powder particles which results particle- particle collision with each other and form larger permanent aggregates (granules). After spraying the required amount of granulation liquid, the wet granules are rapidly dried in the fluid bed granulator. The characteristics of fluid bed granulation processing and the fundamentals of the mechanisms contributing to wet granule growth are briefly discussed. This review also discusses the endpoint detection methods in fluidized wet granulation.

Keywords: Fluidized wet granulation, granules, endpoint detection, top spray, fluidization.

INTRODUCTION

Granulation is defined as a particle size enlargement process, whereby small powder particles are gathered into larger, permanent structures in which the original particles can be distinguished. There are two major granulation methods are widely applied, namely wet and dry granulation. As its name suggests, wet granulation involves the use of a binder liquid, which is introduced onto agitated powder particles, binding these together [1]. During subsequent drying, the solvent is removed via evaporation, and more permanent bonds are formed. The granule strength is then mainly related to the solid bridges, formed by hardening of binders and the crystallization of dissolved particles. Dry granulation methods are based on the compaction of the powder mass, before it is crushed and fractionated. Hence, particle size enlargement is achieved without the use of a binder liquid, making this process particularly suitable for moisture- or heat-sensitive drugs. Compared to dry granulation processes, wet granulation offers a better control of drug content uniformity, compatibility and product bulk density[2]. However, the process is more complicated to validate and control due to the additional preparation of binder liquid and supplementary drying step. It is also more expensive, equipment, energy and space[3].

Granules are polydispersible, and the size of pharmaceutical agglomerates ranges from 0.1 to 2.0 mm. The use of granulation techniques in the pharmaceutical industry is driven by the improvement of one or more powder properties generally the powder flow properties[4] which include, increased bulk density, flowability and solubility, reduced risk of size segregation, and dust formation. The manufactured granules are primarily used for tableting, but may also be filled into capsules[4].

Fluidized bed granulation is a widely applied wet granulation technique in the pharmaceutical industry. Both the spraying of binder liquid onto the fluidized powder bed (granulation) and subsequent drying of the agglomerates are carried out in the same equipment. Hence, dry mixing, wetting, and drying are accomplished in a single operation unit, which simplifies the process and benefits the GMP requirements. It also saves on labor costs, transfer losses, and time [5]. The continuous heat and mass transfer between the fluidizing air and particles creates a uniform product temperature distribution and relatively short processing times.[4]

Understanding the fundamental physical and chemical phenomena that contribute to the granulation behavior and granule properties enables to model/predict how a material will granulate given that formulation properties, equipment type, and operating conditions are adequately characterized. Different approaches are considered to model the granulation system[6]. Empirical or black-box models are based on actual plant data, and an arbitrary function is fitted to the data. A model structure is selected, and the model parameters are fitted to get the best fit of the model to the data. The empirical model is obtained rather quickly and can be used for process optimization and control. However, as extrapolation of the model is not recommended, the limited application range can be a significant disadvantage. On the other hand, mechanistic or white-box models incorporate the fundamental physical and chemical laws and rules. Conservation principles (of mass, energy, momentum, and particle number) and appropriate constitutive relations that reflect the key factors in granulation are used to mechanistically model a granulation system. This approach is more complex and time-consuming but more flexible compared to empirical models. Especially for scale-up, these models can be more efficient than the traditional method of trial and error experimentation. They minimize the guesswork and offer a more rational approach to scaling-up the process. In-between empirical and mechanistic, a third type of models, gray-box models, is classified. This model type combines fundamental knowledge and experimental data with equal importance and is most commonly applied in process systems modeling. Cameron et al. [7]reviewed the use of different modeling approaches to the integrated understanding of the granulation phenomena.

Fundamentals of granule growth

During wet granulation, several different mechanisms take place. In this work, the classification according to Iveson et al. [1] is considered, viewing the wet granulation process as a sets of rate processes or combination of three different mechanisms.
These include the following:

- Wetting and nucleation of particles,
- Consolidation and growth by collisions of material in the granulator,
- Attrition and breakage.

A wetting advances the nucleation of fine powders occur. The nucleation is strongly influenced by the distribution of the binding fluid and the powder properties. The nucleation is followed by granule growth which involves collisions between two (partially) wetted granules (i.e., coalescence) or granules and feed powder (i.e., layering) resulting in larger granules composed of several particles. During granule growth, the agglomerates are subjected to compaction forces (due to bed agitation) causing the granules to gradually consolidate. This is accompanied by a reduction in size and porosity, and forces out entrapped air and even liquid binder to the particle surface. The rate of consolidation or densification depends on the properties of the feed material, such as particle size distribution, surface roughness and particle shape [6]. The final densification level determines end product porosity and therefore granule strength, hardness, and dissolution. High porosity granules are weak and friable, but display often an advantageous fast dissolution rate, which makes granule porosity an important product property to control. However, it creates unwanted dust during product handling. The third-rate process includes two phenomena. Low binding strengths in the moist agglomerates create weak wet granules that may break in the granulator, influencing the final granule size distribution. This breakage is more prominent in granulation processes displaying high shear forces [8]. Weak dried granules are susceptible to attrition or fracture in the fluid bed granulator or during subsequent handling. This counteracts the objectives of granulation and should therefore be avoided.

During a fluid bed granulation process, the binder liquid addition and evaporation take place at the same time, making this a unique and effective granulation process [5]. Hence, the three rate mechanisms occur simultaneously, and the contribution of each of them to the developed agglomerates depends on granulation equipment, process settings, and feed material properties. The end product quality attributes is determined by combination of the most dominant rate processes determines the final granule size distribution, structure, and porosity.

According to the relative amount of liquid phase, a number of different states of the moist agglomerates are described, that is, the pendular, the funicular, and the capillary state (Figure. 1)[9]. The herewith associated increasing amount of liquid phase is expressed by the liquid saturation, describing the ratio of pore volume occupied by the liquid to the total pore volume within the agglomerate. In each state, a different type of bonding is holding the particles together. In the pendular state, liquid bridges at particle contact points are holding the particles together, whereas in the capillary state, all the voids are saturated with liquid, and the surface liquid is drawn into the particle pores under capillary action. The intermediate funicular state is characterized by voids that are not completely filled with liquid. In addition to these three stages, a fourth one, the droplet state has been defined. This state is characterized by the addition of more liquid to the powder mixture than the amount required to completely fill all inter- and intra-particulate voids. Hence, the liquid completely surrounds the solid particles. If the droplet state is achieved during conventional wet granulation (i.e., fluidized bed and high shear granulation), generally, too much liquid has been added and results in over granulation. This in contrast to the process of granulation by spray-drying of a suspension, where the droplet state is an important stage of the process.

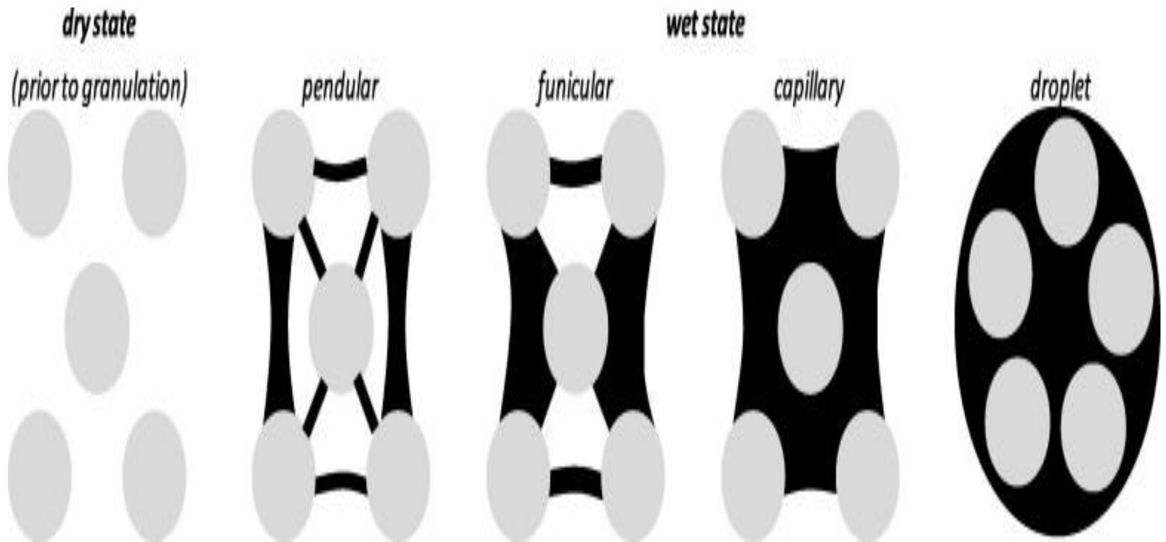

Fig. 1: Overview of the four stages of powder wetting (liquid saturation). The solid particles are represented by gray circles, and the binding liquid is colored black.

Granulation in the fluidized bed

During fluidization, solids are subjected to a gas (usually air), which converts the material to a dynamic fluid state. At certain gas velocities, the gas will support the particles, allowing an upward and downward movement, suspending the material in the gas [9].

Pharmaceutical fluidized bed granulation was first described by Wurster, when he reported on the use of the air suspension technique to coat tablets [10]. This was followed by a paper describing the process of granulation and drying via the air suspension technique to prepare tablets [11]. A fluid bed granulation process involves the suspension of particles in a conical shaped container by use of a (heated) air stream. The applied air velocity should allow proper particle movement in the container, but keep the material out of the filter bags (Figure. 2). Good fluidization can be visually monitored by the free downward flow of the granules at the windows of the container. As particles move up and down in the container, a binder solution is sprayed (i.e., spraying phase). Binder liquid droplets are deposited onto the fluidized particles in the spray granulation zone. This wetting causes the formation of granules. After spraying the required amount of binder liquid, further fluidization enables rapid drying of the granules in the same equipment (i.e., drying phase). Drying reduces the residual moisture of the granules to a level that ensures the stability of product active(s) and meets the requirements for downstream processing. A good granulation is achieved when particles are uniformly mixed, and liquid bridges between the particles are strong and easy to dry.

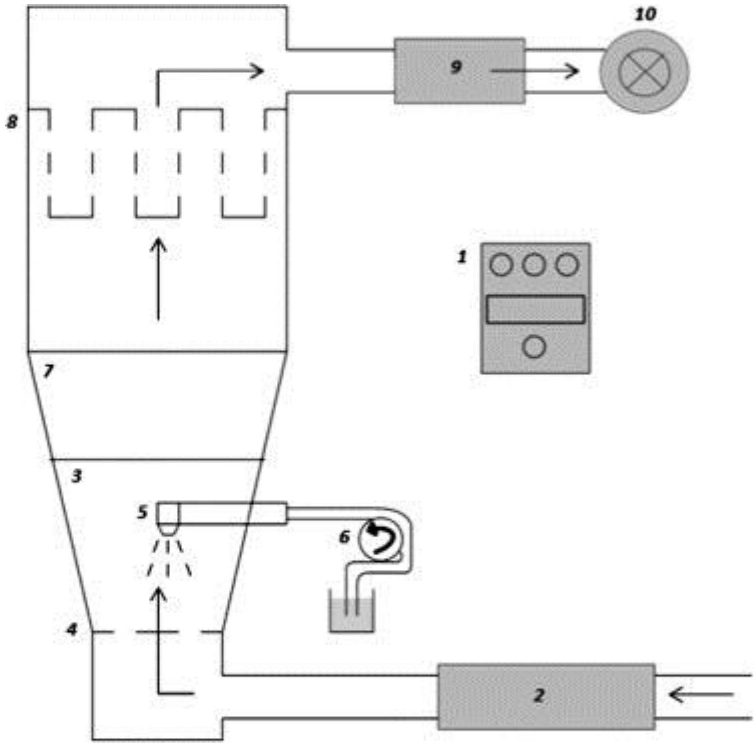

Fig. 2: Schematic representation of a top-spray fluid bed granulator with assignment of its different components: (1) control panel, (2) air handling unit, (3) product container, (4) air distributor plate, (5) top-spray installed nozzle, (6) pump, (7) air expansion chamber, (8) filter bags, (9) air filter system, and (10) exhaust blower. Arrows indicate the direction of the airflow.

Compared to high shear granulation, the lack of shear forces in a conventional fluidized bed results into the production of more porous and less dense granules with better dissolution and compression characteristics [12]. Generally, the fluidized bed granules exhibit a narrower size distribution of granules. The most common problems encountered during fluid bed granulation include the production of excessively coarse granules, poor fluidization, excessive fines, inconsistency of final moisture content, non-uniformity of finished product and low yield[13].

A fluidized bed granulator consists of several key components (Figure. 2, [14, 15]). A control panel (1) allows operating the process and monitoring critical process variables. As generally outside air is used to fluidize the particles, an air handling unit (2) is essential for air filtering, heating, cooling, and removal of humidity. After preconditioning the air, it is passed through the bed of solids in the product container (3) via the air distributor plate (4). The type of container and air distributor must be selected accordingly to obtain a proper product fluidization. The binder liquid is introduced onto the fluidizing particles via a nozzle (5) system. The two-fluid (binary) nozzle is most commonly applied in fluid bed granulation as it can function at very slow liquid rates and offers a controlled droplet size, independent of flow rate. With this nozzle, the binder solution (one fluid) is atomized by compressed air (other fluid). The spray pattern and angle can be modified by adjusting the position of the air cap surrounding the nozzle needle and by varying the air pressure required for atomization of binder liquid. Depending on the location of the spray nozzle, different types of fluid bed granulators are available. Top-spray fluid bed granulation with the nozzle located at the top of the chamber is the most frequently studied and used technique for wet granulation [16]. The binder liquid is sprayed from the top down onto the fluidized bed, counter-currently to the fluidizing air. During bottom-spray granulation, the nozzle is positioned at the base of the chamber, in the middle of the distributor plate, and liquid is sprayed in the same direction of the fluidizing air. The bottom-spray granulator can be equipped with a partition column (i.e., Wurster partition) and a specially designed distributor plate to regulate the fluidization pattern. The plate, with perforation sizes decreasing from the center to the outer part, enables a higher air velocity inside the Wurster partition than in the outer region creating a fountain-like movement. Introducing the spray nozzle at the side of the chamber, embedded in the powder bed during granulation, corresponds to tangential-spray granulation.

This technique is also called rotary fluidized bed granulation due to the rotating disk installed at the bottom of the bed (no use of air distributor plate). This modification of the standard fluid bed granulation setup combines the advantages of fluidized bed and high shear granulation due to the additional mechanical agitation. The rotary granulation process is manifest by centrifugal, high intensity mixing, and efficient fluid bed drying, yielding a product that is more spherical, denser, and less porous compared to top-sprayed granules[17]. The binder liquid is peristaltic pumped (6) to the nozzle through a spray lance and tubing. To separate particles from the outlet air, two zones in the fluid bed equipment are used. In the air expansion chamber (7), the largest particles are withdrawn as they lose their momentum. Filter bags (8) can be periodically shaken to reintroduce the collected fines into the fluidized bed. The air leaves the system through an air filter system (9), removing the residual smaller particles from the exhaust air and a blower (10) or fan, keeping the system at a lower pressure than the surrounding atmosphere.

The quality attributes of the final product may be manipulated by changing process operating variables (process engineering) and product formulation variables (product engineering), which affect the underlying granulation mechanisms. Operating variables are related to the granulation equipment and can be divided into apparatus variables and process parameters. Formulation variables are defined by the choice of starting materials and binder solution. All factors influencing the wetting of the powder by the sprayed binder liquid affect the formation of liquid bonds and therefore agglomerate growth [18]. Especially in fluidized bed granulation, these wetting factors critically determine the final granule size distribution owing to the relatively low shear forces present during processing. The absence of shear forces largely confines particle densification and liquid saturation of the agglomerates therefore reducing granule growth by coalescence. Increasing granule growth by increasing the bed moisture level is difficult, as this may result into bed collapse due to the poor fluidizing capacity of the wet mass[19].

Control and endpoint detection of fluidized bed granulation

During the first applications of fluidized bed granulation, precise control of the process was not available. A historical method of determining the drying endpoint consisted of feeling the expansion chamber for increasing temperature [20]. This method took considerable time to “fine tune” and was purely based on perception and observation. The lack of monitoring and control systems made reproducible granulation in a reliable manner problematic[21].

Control of the formulation components and the process is essential to ensure the consistent production of granules with the desired quality characteristics (i.e., granule size, size distribution, moisture content, density, flowability, and friability). The quality attributes are affected by the properties of starting material; therefore, variations in feed material properties should be minimized. The use of an air handling unit allows filtering, heating, cooling, and humidity removal of the inlet process air. The air dehumidification is especially important when the production unit is in a climate with large moisture variations, as the binder liquid evaporation rate is determined by the processes of heat and mass transfer. Heat is transferred to the granules to evaporate the binder solvent, while mass is transferred as a vapor from the granules in the surrounding gas. The capacity of the incoming air to absorb moisture (i.e., drying capacity) depends upon its temperature and relative humidity. Therefore, by controlling these parameters, a reproducible drying capacity can be achieved contributing to a controlled fluid bed granulation process.

The recording and control of critical granulation process parameters were initially carried out by a pneumatic analog control device that uses compressed air as a signaling medium to convey information from granulator measuring instruments. The pneumatic signaling system exhibited a desired simplicity and safety, but its effectiveness was highly dependent of the operator’s interpretations and actions to ensure product quality and accurate data logging. Through the development of programmable logic controllers and computers a more reliable control, batch production and data acquisition were achieved. In particular, the product and exhaust air temperature indicate the progress of drying since fluid bed drying is typically characterized by two stages of water loss . The first is heat transfer limited and corresponds to the evaporation of water from the particles in the bed. It shows a linear dependency with time, and the bed temperature remains constant during this phase (evaporative cooling stage). When surface and loosely associated water has evaporated, the remaining water diffuses to the surface of the granules before it is lost, which is greatly affected by the particle geometry. When the amount of water left to evaporate reaches a minimum value during this second stage, the exhaust air temperature will increase, approaching the inlet air temperature. Hence, drying endpoint is mainly determined by the temperature of the exhaust air [22]. Research showed that this well-established method of detecting drying endpoint via the exhaust air, or product temperature is only repeatable if the humidity level of the inlet air is controlled. By use of the temperature difference between the inlet air and fluid bed mass (ΔT), the effect of variations in process air humidity on drying endpoint detection is eliminated[23].

CONCLUSIONS

Fluidized bed granulation is the good tool for wet granulation. However, one must account for the various parameter used in it. The characteristic sensitivity of fluid bed granulation to the bed humidity will further motivate the development and incorporation of in-process measurement techniques which can control granulation and guarantee process reliability and product quality. Nowadays, industry is shifting to continuous manufacturing techniques which necessitate the in-line analysis of intermediates to minimize off-line end product testing.

Conflict of Interest

The author report no conflict of interest.

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