**Process analytical tools for monitoring, understanding and control of pharmaceutical fluidized bed granulation: a review**

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Abstract

Fluidized bed granulation is a widely applied wet granulation technique in the pharmaceutical industry to produce solid dosage forms. The process involves the spraying of a binder liquid onto fluidizing powder particles. As a result, the (wetted) particles collide 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. Since the FDA launched its Process Analytical Technology initiative (and even before), a wide range of analytical process sensors has been used for real-time monitoring and control of fluid bed granulation processes. By applying various data analysis techniques to the multitude of data collected from the process analyzers implemented in fluid bed granulators, a deeper understanding of the process has been achieved.

This review gives an overview of the process analytical technologies used during fluid bed granulation to monitor and control the process. The fundamentals of the mechanisms contributing to wet granule growth and the characteristics of fluid bed granulation processing are briefly discussed. This is followed by a detailed overview of the in-line applied process analyzers, contributing to improved fluid bed granulation understanding, modeling, control and end-point detection. Analysis and modeling tools enabling the extraction of the relevant information from the complex data collected during granulation, and the control of the process are highlighted.

Keywords

fluidized bed granulation – Process Analytical Technology (PAT) – in-process monitoring – control – process understanding

1. 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 [1]. Hence, granulation can be considered as the pharmaceutical opposite of milling [2]. Instead of reducing the particle size, the process aims at particle growth. Two major granulation methods are widely applied, namely wet and dry granulation [3]. As its name suggests, wet granulation involves the use of a binder liquid, which is introduced onto agitated powder particles, binding these together through a combination of capillary and viscous forces [4]. During subsequent drying, the solvent is removed via evaporation and more permanent bonds are established. 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, product bulk density and compactibility [5]. 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 with regard to labor, equipment, energy and space [6].

Granules are polydisperse 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. These include, increased bulk density, flowability and solubility, reduced risk of size segregation and dust formation [7]. The manufactured granules are primarily used for tableting, but may also be filled into capsules.

Fluidized bed granulation is a widely applied wet granulation technique in the pharmaceutical industry, exhibiting some technological advantages compared to the multistage wet granulation methods (e.g., high-shear granulation, low-shear granulation and extrusion-spheronization). 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 [8]. The continuous heat and mass transfer between the fluidizing air and particles creates a uniform product temperature distribution and relatively short processing times.

These granulation conditions affect the granule structure and therefore the characteristics of fluidized bed granules differentiate from those prepared by other wet granulation methods. The properties of raw powder material and binder liquid also have to be considered in the selection of a wet granulation technique (Section 3).

For several decades after the earliest work performed on this operation unit, granulation remained more of an art than a science with high recycle ratios [9]. Granulations were performed based on popular practice instead of scientific strategies. The granulation behavior of new formulations was not predicted by the scientific understanding of the underlying granulation phenomena, but extensive testing was undertaken. Hence, next to empirically based granulation knowledge, a more theoretically based knowledge on the particle wetting mechanisms was required. In 2001, Iveson et al. [4] reviewed the advancements in granulation understanding and highlighted the areas requiring further research.

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 [10]. 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, grey-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. [11] reviewed the use of different modeling approaches to the integrated understanding of the granulation phenomena.

Next to a better understanding of granule formation mechanisms and modeling of the process, adequate granulation control is necessary to shift from a granulation art to a granulation science [12]. The increasing production scale and production speed in combination with the GMP and validation requirements necessitates the development of strictly controlled granulation processes. Traditionally, the pharmaceutical fluid bed granulation process is controlled by monitoring a few process parameters (e.g., process air flow, temperature, humidity, etc.). The progress of drying is related to the outlet air and granule bed temperature combined with the drying time. Process endpoint is reached when a pre-set exhaust air temperature is obtained [13]. The quality of the manufactured granules is then assessed via (time-consuming) laboratory analysis of the critical quality attributes of selected samples. A more efficient way to control the granulation process consists of the real-time product quality assessment, supplemented with real-time process parameter adjustments correcting for undesired changes in the product properties and process progress. This entails the development of automated granulation processes that use in-line devices to directly measure the critical product parameters. To deal with the vast amount of collected data, multidimensional modeling techniques, such as principal component analysis [14], partial least squares regression [15-18], self-organizing map [19, 20], artificial neural network [21-25] and fuzzy logic [26-29] have been used in fluid bed granulation (see Section 5). A proper analysis of the large amount of real-time data should increase granulation process understanding, allow better process analysis, modeling and control. In that way, also large scale production yields high quality granules.

The process analytical technology (PAT) concept initiated by the FDA offers a regulatory framework to encourage this continuous monitoring and control of pharmaceutical production processes [30]. Implementation of PAT should ultimately lead to the in-depth understanding and control of the manufacturing process with minimal end product testing to guarantee the quality. The reduction in end product testing also creates a more real-time based release environment. Implementation of PAT strategies is not restricted to the commercial manufacturing scale, but should already be started during process development studies. The applied techniques will help to increase product knowledge and process understanding, which in turn can be exploited during granulation scale-up. Moreover, defining an endpoint in terms of in-line measured granule properties (instead of process parameter values), makes moving from development to full production scale more easy. Adaptation of the industry towards science-based manufacturing with use of quality risk management is also driven by the increased costs involved in drug research and the diminishing R&D productivity [31]. The expiration of patents and loss of exclusivity have decreased revenues.

This manuscript reviews the published work in the field of process analytical technologies for fluid bed granulation to monitor and control the process, as well as to improve process understanding. Several reviews discuss the use of real-time analytical tools (in particular near infrared spectroscopy) in pharmaceutical production processes and address their application to fluid bed granulation [32-37]. However, encouraged by the PAT initiative, many different process analyzers have been proposed to innovate fluid bed granulation process development, analysis and control. In addition to spectroscopic techniques, other methods (e.g., spatial filter velocimetry and focused beam reflectance measurement) are particularly useful in fluid bed granulation.

The fundamentals of the mechanisms contributing to wet granule growth and the characteristics of fluid bed granulation processing are briefly discussed. This is followed by a detailed overview of the in-line applied process analyzers contributing to improved fluid bed granulation understanding, modeling, control and end-point detection. Analysis and modeling tools enabling the extraction of the relevant information from the complex data collected during the granulation process, and the control of the process are highlighted.

2. Fundamentals of granule growth

During wet granulation, a number of different mechanisms take place. In this work, the classification according to Iveson et al. [4] is considered, viewing the wet granulation process as a combination of three different mechanisms or sets of rate processes. These include:

• wetting and nucleation of particles

• consolidation and growth by collisions of material in the granulator

• attrition and breakage

Wetting advances the nucleation of fine powders, which is strongly influenced by the distribution of the binding fluid and the powder properties. The growth stage 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, particle shape and surface roughness [38]. The final densification level determines end product porosity and therefore granule hardness, strength and dissolution. High porosity granules are weak and friable (unwanted creation of dust during product handling), but display often an advantageous fast dissolution rate which makes granule porosity an important product property to control. 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 [39]. Weak dried granules are susceptible to attrition or fracture in the fluid bed granulator or during subsequent handling. The associated generation of dusty fines 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 granulation process [13]. 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 combination of the most dominant rate processes determines the final granule size distribution, structure and porosity and therefore end product quality attributes.

According to the relative amount of liquid phase, a number of different states of the moist agglomerates are described, i.e., the pendular, the funicular and the capillary state (Figure 1) [40]. 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 3 stages, a fourth one, the droplet state has been defined [41]. 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 granulation will not be successful [2]. 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.

3. Granulation in the fluidized bed

During fluidization, solids are subjected to a gas (usually air) which converts the material from a static state to a dynamic fluid state. At certain gas velocities the gas will support the particles, allowing an up- and downward movement, suspending the material in the gas [42].

Pharmaceutical fluidized bed granulation was first described by Wurster, when he reported on the use of the air suspension technique to coat tablets [43]. This was followed by a paper describing the process of granulation and drying via the air suspension technique to prepare compressed tablets [44]. A fluid bed granulation process entails 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 according to different mechanisms (vide supra). 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.

Compared to high shear granules, 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 [45]. Generally, the fluidized bed granules exhibit a narrower size distribution, without oversized granules. The most common problems encountered during fluid bed granulation include the production of excessively coarse granules, excessive fines, poor fluidization, inconsistency of final moisture content, low yield and non-uniformity of finished product [46].

A fluidized bed granulator consist of several key components (Figure 2, [47, 48]). 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 is able to 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 considered producing granules with varying characteristics [49]. Top-spray fluid bed granulation, with the nozzle located at the top of the chamber is the most frequently studied and used technique [50]. 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 centre 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 set-up combines the advantages of fluidized bed and high shear granulation due to the additional mechanical agitation. The rotary granulation process is marked 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 [51]. 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 (Table 1). All factors influencing the wetting of the powder by the sprayed binder liquid affect the formation of liquid bonds and therefore agglomerate growth [52]. Especially in fluidized bed granulation, these wetting factors critically determine the final granule size distribution due to the relatively low shear forces present during processing. The absence of shear forces largely restricts 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 [53]. For detailed reviews of the effects of operating and formulation variables on the quality properties of granules produced by fluid bed granulation, readers are referred to the literature [6, 13, 38, 47, 50, 54, 55]. An overview of the parameters is listed in Table 1 with the assumption that binder and surfactant are added in solution (not as a dry material in the powder mix) and the nozzle is installed top-spray. In addition to the individual influences of operating and formulation variables on the end product quality, the parameters’ effects are also highly co-dependent. Hence, these interactions need to be understood and taken into account during optimization and particularly scale-up if one wants to achieve a desired product quality. Faure and co-workers [56] reviewed the parameters that need controlling during wet granulation, and how this influences process control and scale-up.

4. Traditional methods for control and endpoint detection of fluidized bed granulation

During the first applications of fluidized bed granulation, precise control of the process was absent. A historical method of determining the drying endpoint consisted of feeling the expansion chamber for increasing temperature [57]. This method took considerable time to ‘fine tune’ and was purely based on intuition and empiricism. The lack of monitoring and control systems made reproducible granulation in a reliable manner difficult [49].

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 (Table 1), 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 [13, 47]. The air dehumidification is especially important when the production unit is located 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 was 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 was achieved. A PID (Proportional, Integral, Derivative) controller is commonly used as a feedback control mechanism. It calculates an error value for a process variable as the difference between the measured process variable and a desired set point. The controller attempts to minimize the error by use of a corrective adjustment action. The air flow rate and temperature are typical process variables that can be adjusted by a PID controller in fluid bed granulation. The collected process sensor signals are computer-stored and can be recalled to issue a batch certificate. During the spraying period, critical data related to the inlet air humidity and temperature, product and outlet air temperature, air flow, binder spray rate, atomizing air pressure and pressure drops across the bed are collected. During drying, the inlet air temperature and humidity, product and exhaust air temperature and air flow are continuously monitored. In particular, the product and exhaust air temperature indicate the progress of drying since fluid bed drying is typically characterized by 2 stages of water loss [58]. 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 [13]. 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 (∆T), the effect of variations in process air humidity on drying endpoint detection is eliminated [59]. However, one should also take the influence of fluidization on the ∆T technique into account. Improper fluidization, even for short periods, can be a major source of deviation for the ∆T technique, as the temperature of the granulation mass is relatively higher when fluidization is low [60]. To handle this interdependency of process parameters, multi-way models have been recognized to be useful in the monitoring of batch data. Successful batches were separated from unsuccessful ones by a PARAFAC2 method based on the monitoring of 3 granulation process variables (i.e., inlet air, outlet air and mass temperature) [61].

5. Advances in control and endpoint detection of fluidized bed granulation via implementation of PAT strategies

The detection of granule growth during fluidized bed granulation and the process endpoint is traditionally based on the measurements of process parameters (Section 4, [62]). However, these are considered as indirect measurements as the parameter values are correlated with the granule properties. At times, these methods are inadequate since they do not account for changes in feed material properties or external disturbances. The completion of a granulation process after a fixed time period may then cause over- or under-drying of the granules and reduce the batch quality. Through the development of innovative analysis tools that rapidly provide information related to the physical or chemical material properties, granulation process monitoring and control has incorporated the direct measurement of granule characteristics. These techniques enhance the collected granulation information and enable to determine the granulation endpoint by the achievement of desired granule attributes. The techniques are non-destructive, provide a short measurement time and allow various measurement set-ups (Figure 3) [63]. When the sample interface is located in the process stream (invasive or noninvasive), in-line product information is derived without removing sample from the process. On-line techniques involve an automatic sampling device to divert the collected samples from the process to the measurement equipment. Often, the sample is returned to the process stream. In an at-line application, the samples are withdrawn from the process and analyzed in close proximity to the process equipment within the timescale of manufacturing. The at-line sample collection may disturb the ongoing process and the manual sample handling that is necessary for the sample measurement may induce errors by the operator. With in-line and on-line sample analysis however, the sample integrity is maintained and measurements are less time-consuming. Although in-line measurements are quickest in providing granule information, it can be a challenge to prevent fouling of the measurement window by the moist mass throughout the process.

The moisture level of the fluid bed is mostly determined by the rates of binder addition and binder evaporation, which need to be well balanced in order to obtain proper fluidization and high-quality granules [64]. Hence, the first granule product measurements during processing consisted of in-line moisture determinations using an IR moisture sensor, to strictly control the bed moisture level during granulation and drying [65-67]. In Sections 5.1 to 5.6 the principles of the most frequently studied analytical process sensors and their use in fluidized bed granulation are reviewed. To a lesser extent, triboelectric probes [68-70], microwave resonance technology [71, 72] and electrical capacitance tomography [73] have also been investigated as potential real-time analyzers in fluidized beds. The effectiveness of each of these methods to accurately determine the moisture content during fluid bed drying was examined and the main results are summarized in Table 2.

5.1. Near infrared spectroscopy

The near infrared (NIR) spectral region covers the area across the wavelength range 800 – 2500 nm (wave number range 12500 – 4000 cm-1). Absorbances in the NIR region originate from overtone and combination bands of fundamental vibrations observed in the mid-IR region. Only vibrations that result into changes in the molecule dipole moment are NIR active. Therefore, primarily vibrations of CH, OH, SH and NH bonds are observed. NIR bands are broad, overlapping and exhibit weaker intensities than the fundamental IR bands. The theory and basic principles of NIR spectroscopy can be found in literature [32, 35, 74]. The technique exhibits a high measurement speed, robustness, low cost and is non-destructive. The computer advancements and the development of fiber optics allowing the measurements to be performed away from the operator increased the interest in NIR spectroscopy for in-process measurements significantly. The technique also displays a cross-sensitivity to chemical (e.g., water content) as well as physical (e.g., particle size) sample properties which are quantitatively and qualitatively interpretable [15]. This interpretation of the highly informative NIR spectra is complicated and signal pretreatments are often necessary to remove irrelevant spectral information.

Frake et al. [75] installed an NIR probe into the product bed of a top-spray fluid bed granulator, continuously collecting granule information. The probe was positioned in the downward flow at a point of high product density. The second derivative absorbance changes at 1932 nm were calibrated against moisture content data and an acceptable standard error of calibration for the required level of control was calculated. Changes in zero order absorbance across the entire spectrum as granulation proceeded, resulted from the variation in granule size. Plotting the absorbance of a single wavelength versus process time showed the gradual increase in granule size, but it was not possible to generate suitable granule size calibration models for quantitative determination.

Rantanen et al. [76, 77] applied a novel NIR reflectance spectroscopic method during fluid bed granulation and drying, detecting 4 wavelengths simultaneously and using 3 of them for the measurement of moisture content. The 1990 nm characteristic combination band was used for water detection and the 1740 nm and 2145 nm signals for baseline correction. Critical to the in-line measurements was the sight glass, which was continuously blown with heated supplied air. The results showed that the entire NIR spectrum was not necessary for the measurement of water. By use of only a few NIR wavelengths around the NIR water band, reliable and rapid detection of moisture was possible throughout the entire granulation process. Combining NIR information with trend charts of the temperature difference between process inlet air and granules, and the water content of process air enabled the identification of different process phases, characteristic for different formulations [78]. This provided a novel tool for the monitoring and control of water during fluid bed granulation. The method was further investigated by studying the effect of binder choice and particle size on the accuracy of NIR moisture measurement [79]. Principal component analysis (PCA) proved a promising tool in the reduction of the high-dimensionality of granulation process data (e.g., granule and air temperature, humidity, NIR signal, etc.) [14]. By use of this multivariate data analysis technique, the granulation process was described in a 2-dimensional space where the 3 process phases (i.e., mixing, spraying and drying) were clearly visible. As the NIR moisture measurement is affected by the varying physical properties of the granules (e.g., temperature, particle size, bulk density), the process-related variables describing the state of granulation were included in NIR moisture calibration models [21]. This approach improved the models’ prediction capability. Multivariate calibration of in-line collected NIR spectra and process parameters was performed using two techniques. The artificial neural network (ANN) model with back-propagation algorithm showed the most predictive power of the independent test data, compared to the partial least squares (PLS) model. The NIR-setup was also successfully applied for particle size measurement of various grades of microcrystalline cellulose during fluidization, using 2 of the 4 simultaneously detected wavelengths [80]. Different inlet airflow rates did not significantly influence the recorded absorbances.

Also Räsänen et al. [81] used only 3 NIR wavelengths to determine the moisture content by in-line NIR spectroscopy. The authors were able to study the dehydration behavior of theophylline granules using a novel multi-chamber micro-scale fluid bed dryer with a process air control unit and in-line NIR spectroscopy. The stepwise dehydration of materials was monitored by the water content difference of inlet and outlet air, the pressure difference over the bed and in-line NIR spectroscopy.

Morris et al. [82] introduced a fast-drying method to accelerate fluid bed drying by use of NIR and temperature probes. NIR spectra collection was accomplished with an MM55 gauge, continuously monitoring the bed externally, through a lower inspection window. The strategy involved the identification of critical NIR readings corresponding to the end of evaporative cooling (see Section 4) and using this as a temperature-independent endpoint. The authors showed that no physical changes of compounds occurred during the evaporative cooling stage of drying at an inlet air temperature above the melting point of a low-melting compound. Hence, using real-time and noninvasive NIR measurements, the drying cycle of a low-melting active ingredient was optimized by reducing the overall drying time. This work was extended by Wildfong et al. [83], who examined the effectiveness of the method using different formulations. A simple computer program was developed to predict the expected drying time reduction and therefore determine any benefit associated with the use of accelerated drying before changing the current process.

Findlay et al. [84] used NIR spectroscopy to simultaneously monitor moisture content and particle size in a fluid bed granulator and determine its endpoint. Spectra were collected with an MM55+ NIR gauge through a glass window into the bed of the granulator. The window was fitted with a special gasket to reduce fouling. In practice, the NIR measurements during the early stages of granulation were not as accurate as measurements performed later in the process since the glass window became partially fouled by powder during the first 10 min of granulation. The NIR determined moisture content and particle size correlated well with off-line reference measurements (i.e., loss on drying and image analysis). However, it was necessary to correct the particle size measurements (due to moisture) when the moisture content of the material was greater than 3% w/w. Using the developed system, fluid bed granulation can be controlled by determining when binder addition should be stopped (desired particle size) and when granule drying is completed (desired moisture content). Nieuwmeyer et al. [15] also applied NIR spectroscopy to simultaneously determine granule water content and size. High shear manufactured granules were dried in an Aeromatic fluid bed dryer (Niro), with the NIR probe placed into the wall of the dryer, at the same height of the sampling probe. The PLS granule moisture model predicted residual water content continuously during drying with errors comparable to the reference method (i.e., Karl Fischer) whereas the PLS granule size model was influenced by the humidity of the granules (as observed by Findlay et al.). After removal of the interfering moisture through initial drying, the NIR granule size model can be used to monitor granule size and attrition effects.

Hartung et al. [16] monitored the fluid bed granulation of an Enalapril formulation by means of in-line NIR spectroscopy with the NIR probe installed in the product container. The moisture content profiles of several granulation batches, derived from an NIR moisture PLS model (Karl Fischer as reference), enabled to examine how granulation influences tableting properties. Results showed that the tablet characteristics not only depended on the residual moisture content of the granules, but also on the moisture profiles during the entire fluid bed granulation process.

NIR spectroscopy was applied non-invasively to monitor fluid bed granulation on an industrial scale (Glatt WSG300) [17]. Spectra of continuously moving samples were acquired by attaching the NIR optical probe to the glass window (without interfering the process or formulation). PLS calibration models were developed to predict granule moisture content, size distribution and bulk density using the on-line recorded NIR spectra. By principal component analysis of the NIR spectra, each step of the granulation process was identified and monitored. An NIR method for in-line determination of the fluidized bed drying endpoint based on moisture content prediction was developed and analytically validated on commercial scale (300-L) of an approved solid dosage product [85]. An interface/adaptor plate was manufactured to insert the NIR probe into the fluid bed. To demonstrate the applicability of the NIR model, validation was performed following the ICHQ2 (r1) guidelines. However, the in-process method was developed and validated exclusively with in-line samples which necessitated a customized interpretation of these guidelines.

An in-depth investigation on the NIR moisture prediction accuracy with regard to sampling effects was presented by Green et al. [86]. Granulations were performed at 3 different drying scales (65-L, 300-L and 600-L) and NIR spectra of dynamic, flowing and stationary solids were collected through insertion of the probe directly into the vessel. The authors demonstrated that process heterogeneity played a major role in determination of apparent prediction accuracy. Mattes and co-workers [87] also recorded NIR spectra of static granules by use of an NIR probe that was equipped with a collection spoon and purge vents on the probe tip. Following each NIR spectrum collection during the fluid bed granulation process, software sent a data-complete-signal that initiated an air purge, cleaning the spoon for a new sample.

Fouling of the measurement window by the moist mass challenges the reliable collection of NIR spectra during fluid bed granulation. Solutions generally involve the use of an air supply system and specialized interfacing. Once a suitable interfacing is found, acceptable prediction of granule moisture content is achieved throughout the granulation process and real-time end point detection of the drying phase (based on residual granule moisture content) is possible. Several studies showed that combining the NIR moisture information with the traditionally collected process parameters increased granulation information, improved the predictability of models and contributed to the process optimization. The use of NIR spectroscopy has not been restricted to R&D scale. A few studies already reported the application of NIR spectroscopy as moisture determination technique on a larger commercial scale showing that the technique allows real-time control of the process, leading to a reduced operation time and an improved consistency of the granule product. Deriving accurate particle size information from in-line collected NIR spectra of fluidizing granules is more challenging and requires further research.

5.2. Image analysis

In addition to NIR spectroscopy, image-processing was one of the earliest techniques applied during fluid bed granulation to directly measure granule characteristics. Information regarding the physical granule properties (e.g., granule size, size distribution, shape) is retrieved from the images, which requires a large extent of computational processing. Therefore, imaging devices are usually equipped with powerful computers to handle the data.

The early work of Tanino et al. [88] capturing granules on adhesive tape located on the side wall of the container and taking images with a CCD camera, was followed by a series of papers by Watano and co-workers [89-92]. Watano and Miyanami developed an on-line image-processing system consisting of a CCD camera, optical fibers, a telephoto lens and an air purge unit. The imaging probe was attached to the upper sidewall of the container enabling on-line monitoring of granule growth in an agitation fluidized bed granulator [89]. By use of heated purge air, powder adhesion onto the measurement window was prevented. Extensive preprocessing and image processing was necessary before determining granule size distribution, median diameter (Feret diameter) and shape factors (circularity and aspect ratio). As the image-derived granule size distribution is number-based, transformation into a mass-based distribution was performed to compare image results with conventional sieve analysis. A close agreement between both sizing methods was obtained. Plotting the shape factors in function of granulation time showed that granules became more spherical in the progress of granulation. The median granule diameter value was influenced by the position of the imaging probe due to particle segregation in the fluid bed granulator when low fluidizing air velocities were used [91]. It was concluded that when measuring a broad particle size distribution, the imaging sensor should be placed in the lowest position (closest to the air distributor) or the air velocity should be large. Sensor location should not be considered when measuring granule shape factors. The authors also developed an automated fluid bed control system by use of the image-processing unit and a control algorithm based on fuzzy logic [90]. The developed system was able to control granule growth with high accuracy, under various operating conditions (i.e., agitator rotational speed) and powder sample properties (mass ratio of lactose in starting material).

Whereas traditional imaging studies process 2D black-and-white pictures, a novel 3D imaging method (SAY-3D) was introduced by Närvänen et al. [93] to determine the particle size of granules both off-line and on-line in a fluid bed granulator. The imaging apparatus (i.e., camera, cuvette and Red-Green-Blue leds) was attached 13 cm above the granulator distributor plate for on-line measurements. Samples were collected into the cuvette, images were taken and a pulsed air pressure returned the sample to the process between images. The described method seemed promising, and limitations and further method development are discussed.

Laitinen et al. [94, 95] developed a photometric concept to calculate the particle size from undispersed powder surfaces under controlled illumination conditions. The photometric approach allowed at-line monitoring of granule growth kinetics in a fluidized bed granulator [96]. Image information of endpoint samples was evaluated regarding the prediction of granule tableting behavior. The technique was also employed for on-line monitoring of fluid bed granulation [97]. The cuvette-system described in the study of Närvänen et al. [93] was applied to simultaneously measure the granule size distribution by image analysis and the granule moisture content with NIR spectroscopy during the entire batch granulations.

Granule images are usually captured via a suitable window that allows non-invasive data collection and avoids the problems associated with instrument fouling and process disturbances during invasive measurements. However, the process interfacing can be difficult for fluid bed granulation processes where granules are constantly moving at high velocities. Overlaying particles, large size distributions and non-spherical particles challenge the extraction of physical information related to the granule size (distribution) and shape from the captured images. Therefore, extensive image processing and expertise are necessary. The limited work found in literature suggests that the use of image analysis during fluid bed granulation is not easy and still far from the actual application on a commercial scale production.

5.3. Focused beam reflectance measurement

The focused beam reflectance measurement (FBRM, Mettler-Toledo) instrument is designed to track in real-time any changes to the particle size and its distribution. The technique has already been used to monitor the particle size in suspension [98], crystallization [99] and flocculation [100, 101], and its application to granulation has received interest over the recent years. The FBRM probe scans with a focused beam of laser light in a circular path at a high speed (2-8 m/s) (Figure 4). Particles passing in front of the measurement window are hit by the laser light, which causes the scattering of the laser light in all directions. The light backscattered into the probe is used to calculate particle chord length and particle chord length distribution [102, 103]. A chord length is defined as the straight line between any 2 points on the edge of a particle. It is calculated as the product of the measured time of the beam to cross a particle and the known beam velocity. The high velocity of laser rotation enables the measurement of many thousands of chord lengths per second, creating a chord length distribution. This particle chord length distribution is a function of the actual particle size distribution, hence the FBRM technique can be applied to fluid bed granulation to express the granule size without converting the measured chord lengths to the actual particle size.

Hu et al. [104] used the FBRM technique to at-line investigate the granule growth kinetics during fluidized bed granulation. As the particles need to move in front of the measurement window to calculate the particle chord length distribution, the FBRM (S400) probe was immersed in a suspension of silicon oil and sampled granules. By rotating a magnetic stir bar, the suspension was gently agitated and granules passing in front of the sapphire probe window were measured. The trends of the chord lengths (e.g., D10, D50 and D90) at-line measured by FBRM were identical to those measured by off-line laser diffraction and sieve analysis. The distinctive differences between FBRM and laser diffraction/sieve analysis particle size values were attributed to the different measurement mechanisms.

In-line FBRM (D600) measurements were performed during fluid bed granulation with the probe installed inside the granulator at two different positions [105]. The probe window was located in the center of the distributor plate and both horizontal and sloped (45°) positions of the probe were employed. The latter was preferred as the former was sensitive to window fouling during the spraying phase. Nevertheless, using the sloped position, the FBRM probe window remained fouled with sticky particles during granulation under certain experimental conditions. In addition, noise was present during the first 20 min of each granulation batch, caused by powder particles covering the measurement window due to their high static electrical charge during mixing.

The at-line FBRM application showed that the technique adequately describes the granule growth kinetics, but the fouling observed during in-process measurements impedes the reliability of the FBRM technique as an in-line process analyzer. Adaptations to the probe have been made to solve these fouling issues. The FBRM C35 probe is equipped with a pressurized air activated mechanical scraper on the sapphire measurement window to prevent powder sticking. The effectiveness of the scraper has already been proven in the harsh conditions of a high shear granulator [106]. Once applied in fluid bed granulation, the technique may play a prominent role in the real-time monitoring and control of fluid bed granulation processes. The system is suitable for size measurements in the particle size range of 3 µm – 3000 µm.

5.4. Spatial filter velocimetry

In addition to FBRM, spatial filter velocimetry (SFV) is also able to real-time measure the chord length of a moving particle. Both techniques are designed for in-process particle characterization and enable the real-time size measurement of agitated particles and granules during fluid bed granulation. Nevertheless, the techniques differ substantially in probe design and measurement mechanism (Figure 4). The measurement window of the FBRM probe is located at the probe tip, while the SFV probe (Parsum) is equipped with a measurement zone inside the probe comprised of 2 measurement windows. FBRM uses the backscattered laser light to calculate particle chord length, while SFV applies the generated shadow. During SFV measurements, particles pass through a laser beam and cast shadows onto a linear array of optical fibers. This results in the generation of a burst signal, which is proportional to particle velocity. As the particles pass through the beam, a secondary pulse is generated by a single optical fiber. Knowing the velocity of the moving particle and the time of the pulse, particle chord length is calculated. Hence, this optical probe allows the simultaneous measurement of particle size and velocity [107, 108]. The SFV measured chord lengths are saved in a particle ring buffer during in-line measurements. The total number of particles is permanently held in the circular buffer and constantly updated through replacement of the oldest measured particles by new ones. In that way, a continuously rolling calculation of the particle size distribution is achieved. A low (number of particles in the) particle buffer results in more volatile size results, while a larger ring buffer creates a smoothing of the measured size. This in contrast to the FBRM chord length distributions, which are based on the chord length measurements of individual particles, collected within a pre-selected measurement time. The Parsum IPP 70-S probe is designed to handle the in-line measurement of sticky or wet materials. The probe is equipped with an internal and external pressurized air connection and in combination with a range of accessories, the measurement windows are kept clean and the particle flow is directed through the sensor. The system is suitable for size measurements in the particle size range of 50 µm – 6000 µm and the particle velocity range of 0.01 m/s – 50 m/s with a data rate up to 20000 particles/s.

Schmidt-Lehr et al. [109] examined optimum installation and software parameters for the SFV probe during fluid bed granulation in a Glatt WSG 5 granulator. The granulation behavior under various experimental conditions was examined using the SFV probe and SFV measured D50 values were compared with laser diffraction sizes. In addition, the reproducibility of measurement results, the transferability of the technique to a larger sized granulator (WSG 15) and the influence of process anomalies on the SFV technique were assessed.

Närvänen et al. [110] obtained granule size information during fluid bed granulation (in a Glatt WSG 5) using an in-line, at-line and off-line experimental setup of the SFV technique. Although in-line and at-line obtained data were susceptible to size segregation, real-time monitoring of the granule growth was achieved. Sieve analysis of the final granules was performed as a reference and its results correlated well with off-line SFV data.

Burggraeve et al. [111] interpreted granulation design of experiment (DoE) results by use of in-line collected SFV data, which allowed the explanation and better understanding of the (in)significance of the studied DoE variables upon granule size. The in-line SFV measurements proved to be sensitive to any particle size changes during top-spray fluid bed granulation (Glatt GPCG 1). Various models (i.e., univariate, multivariate and multi-way) were built to relate granule batch tapped density and Hausner ratio to the in-line measured particle size distribution. The authors also developed a batch model to statistically control fluid bed granulation, based on the continuously in-line collected SFV particle size distribution and product temperature [112]. The developed model enabled the real-time evaluation and acceptance or rejection of test batches. Furthermore, other granule properties (i.e., density and flowability) were estimated after batch production using the granule product information collected during the entire granulation process. Multivariate statistical control methods based on SFV measurements were also developed by Huang et al. [113] for an Aeromatic fluid bed granulator capable of manufacturing 35 kg batches.

The applications of SFV during fluid bed granulation demonstrate the technique’s ability to continuously measure the granule size distribution during processing, without experiencing fouling problems. However, with the in-line application of a sizing technique, one also has to consider the height with which the sensor is installed in the fluid bed, as size results may be influenced by size segregation during fluidization. The use of SFV has been examined both in small and larger scale granulators and showed that combining the SFV data with multivariate statistical methods allows to detect batch-to-batch variations, evaluate overall batch performance and predict other granule quality attributes.

5.5. Acoustic emission

Particle-particle or particle-chamber collisions and frictions during fluid bed granulation generate vibrations that contain embedded physical and chemical information. These vibrations can be measured by applying acoustic emission (AE) sensors to the fluid bed container. Acoustic emissions are usually measured in the high frequency range (70 - 500 kHz) as they can easily propagate through solid materials but attenuate rapidly in air. Therefore, the interference from background noise generated by mechanical vibrations (e.g., from the fan) is minimized. The resultant acoustic spectra contain information about several process-relevant properties and chemometric techniques such as PCA and PLS are always necessary to extract the desired information and calibrate the acoustic signals [114]. Hence, often the term acoustic chemometrics is applied. The sensors have small dimensions and can be easily mounted onto the (outside of the) granulator, enabling non-invasive measurements of the granulation progress. In addition, acoustic measurements offer real-time response, are relatively inexpensive and can be performed in hazardous process environments without further protection.

Tsujimoto et al. [115] developed and applied an AE sensor to monitor the fluidization conditions in a small-scale agitation fluidized bed granulator. The effects of several operating variables on the mean AE amplitude were examined and results showed that the mean AE amplitudes correlated with the fluidization activity. Halstensen and Esbensen [116] designed a new acoustic chemometric approach, which was later applied in a semi-industrial fluid bed granulator to monitor the granulation process state and product quality [117]. By use of score plots based on acoustic data, the process state and the quality of the product inside the granulator were identified. In that way, the acoustic chemometric approach was more sensitive to the early detection of critical granulation situations (e.g., lump formation leading to process shutdown) than the traditional process data. The feasibility study showed that acoustic chemometrics can be used to predict fluidization airflow, reflux of fines to the reactor and granule moisture content.

Matero et al. [118] described the results of applying AE during fluid bed granulation in two different case studies, developing separate models for granule size and moisture. By use of multivariate methods, the granule size information hidden in the AE spectra was extracted, despite the contribution of other granule properties to the AE signals. However, accurate granule size prediction was not achieved. The prediction errors were attributed to sieve analysis as a reference technique, which assumes that granules are spherical and form a narrow, normal size distribution in the sieve cut. The granule water content was tracked throughout the granulation process, but the relative humidity of ambient air was crucial in determining granule moisture. The relative humidity induced batch-to-batch variations and influenced the reliability of the model. The authors also used the AE signals acquired in the early phase of granulation to estimate end product size distribution via N-way PLS modeling [119]. The applied multi-way methods provided a deeper understanding of fluidized bed granulation showing for the first time that the AE signals captured during the nucleation phase can be used to predict end product granule size distribution.

The non-invasiveness and inexpensiveness of AE measurements has encouraged its application in fluid bed granulation. The AE signals contain both chemical and physical granule information, but the extraction of the relevant information is not straightforward. Nevertheless, acoustic chemometrics has allowed to monitor granulation process state and product quality, which provided early warnings of critical process situations.

5.6. Raman spectroscopy

Raman spectroscopy is based on the inelastic scattering of electromagnetic radiation caused by an energy transfer between the incident radiation and molecular vibrations (i.e., the Raman effect, [120]). Whereas an NIR absorption band results from changes in molecular dipole moment, Raman scattering emanates from changes in molecular polarizability during vibration. The technique is non-destructive and able to analyze samples in various forms (solids, liquid, slurries, etc.). Hence, the presence of water in a sample does not interfere Raman measurements, as it is a weak Raman scatterer. By use of fiber optics and (non)contact probes, in-line or on-line Raman spectra can be collected during granulation at a high measurement rate. Drawbacks of the technique include the occurrence of fluorescence and high instrumentation costs [121]. Compared to NIR spectra, Raman spectra are more distinct with typically strong spectral signals from the API and show less peak overlapping. The spectral responses are generally less sensitive to sample physical properties, reducing the spectral preprocessing methods.

The application of Raman spectroscopy to fluid bed granulation has contributed to the real-time monitoring and understanding of solid-state transformations. Hausman et al. [122] applied Raman spectroscopy to monitor the drug (i.e., risedronate sodium) hydration state during fluid bed drying. The Raman probe head was inserted into a lab-scale fluid bed granulator through its solution addition port. By use of the collected Raman information, the relationship between drug hydration state and tablets’ physical stability was understood. Kogermann et al. [18] were able to quantify the solid-state transformations of carbamazepine granules during drying in a micro-scale multi-chamber fluidized bed dryer by means of in-line Raman spectroscopy and PLS regression. The granule Raman spectra were non-invasively collected through a quartz sight window of the fluid bed granulator.

Walker et al. [123] proposed the novel use of Raman spectroscopy to measure the product composition within the fluid bed in three spatial dimensions and as a function of time. A Raman probe was positioned above the fluidized bed on a long-travel x-y-z stage. In that way, a 3D mapping of discrete volumes in the fluidized bed within a relatively short time window (120 s) was obtained. This work was extended by shortening the time window of the Raman spectral acquisition to 10 s, allowing the in-situ real-time characterization of a fluidized bed granulation process [124]. Particle density profiles were calculated over granulation time and these indicated how the volume of the fluidized bed decreased with increasing mean granule size. The authors propose the novel use of Raman spectra to represent particle movement in the fluidized bed.

5.7. Combining complementary process analyzers

Previous sections demonstrate that numerous reports have been published on the use of individual process analyzers during fluidized bed granulation. A few studies were found to describe the simultaneous implementation of two or more process sensors. Multiple process analyzers, installed at different locations in the granulator may provide complementary granulation information or contribute to the detection of sample heterogeneity during granulation. The selected sensor location must provide accurate granule product information, but may not disturb the granulation mechanisms. Combining several analyzers can increase the understanding of a granulation process and product during initial development stages and scale-up. A selection of these process sensors can be sufficient to monitor and control the process at full production scale, maintaining process robustness and minimizing process variability.

Aaltonen et al. [125] applied in-line NIR and Raman spectroscopy to quantitatively monitor the solid-state conversion of theophylline monohydrate to theophylline anhydrate during fluid bed drying. In that way, drying insight at the molecular level was achieved, which was not possible using the traditional approach (i.e., monitoring the outlet air humidity or the pressure difference over the bed). The micro-scale fluid bed drying chamber was made of glass and modified with a quartz sight window for spectroscopic analysis. The study showed the complementarity of the 2 spectroscopic techniques as NIR spectroscopy was particularly sensitive to water and Raman spectroscopy to crystal structure changes.

Tok et al. [126] compared the results of 3 process analyzers simultaneously applied during fluid bed granulation. Acoustic emission sensors were attached onto the external walls of the fluidized bed chamber. An FBRM and an NIR probe were inserted into the container and an anti-static spray was applied onto the measurement windows before each run to reduce the coating of fines. The 3 process analyzers were able to detect the 3 granulation rate processes (see Section 2) with varying degrees of sensitivity. Fouling of the in-line probes’ windows and disruption of the AE signals by the airflow rate and external disturbances (e.g., heavy footsteps), interfered with the continuous measurement of granule properties.

Leskinen et al. [127] applied an AE sensor, combined with a flash topography particle size analyzer and multi-point NIR probes (eight probes) during fluid bed granulation. All instruments were non-invasively installed with the NIR probes and topographic camera looking through the glass windows of the granulation chamber. Both the topographic camera and AE technique provided size values that were in good agreement with the off-line reference values. In addition, the multi-point NIR and AE method were able to differentiate between mixing, agglomeration and drying.

5.8. Other advances in granulation process control and automation

In this final section, the work performed to improve granulation control and automation by employing novel analysis and modeling tools to the available process data, is highlighted. For an extensive comprehension of the data modeling techniques, readers are referred to the discussed references.

The inlet air relative humidity affects agglomerate growth and therefore the particle size of the end product. In general, an increase in relative humidity yields larger granules [53]. Research has been conducted to deal with the difficulty of controlling variations in relative humidity. Lipsanen et al. [128] developed a new fluidization parameter, based on the relationship between inlet airflow rate and turbine fan speed. This fluidization parameter was successfully applied to define the boundaries of the design space. The parameter can be used to optimize the airflow rate when included in a control system. The group also stated that by use of this fluidization parameter and 3 additional physical parameters, more control of the fluid bed granulation process can be gained ensuring repeatable granulation [129]. The fluidization parameter (1) and pressure difference over the upper filters (2) correlated with the in-line measured particle size, and could therefore be used to estimate the particle size during granulation. The pressure difference over the granules (3) and the temperature of the fluidizing bed (4) expressed the moisture conditions of the granule mass.

The use of artificial neural networks (ANN) in granulation process control has been investigated. It is a computer system, able to predict events based upon learned pattern recognition. In this way, the ANN is able to learn and draw conclusions from experience. Non-linear models are developed and no a priori knowledge on the nature of the functional relationship between input and output variables is necessary. Models may be developed with a small set of experiments, but the training can be computationally expensive. A drawback of the modeling technique is that the neural networks are like black boxes and therefore hard to interpret. Watano et al. [22] performed agitation fluidized bed granulation with continuous moisture content measurement by an IR moisture sensor. A neural network system for moisture control was developed by use of the measured moisture content and its varying rate as input variables. The moisture control characteristics were investigated by the neural network with back-propagation learning. The authors were able to achieve good response and stability without overshoot by adopting the developed systems. Agitation fluid bed granulation scale-up characteristics using a neural network with back-propagation learning were also assessed [23]. The scale-up could be conducted with high accuracy by the neural network without the construction of a mathematical model with a complicated non-linear relationship, using a vast amount of experimental data. The neural network could be a reliable tool to analyze the scale-up characteristics of fluidized bed granulation, and to predict the properties of granules produced by the unknown larger scale granulator [24]. Behzadi et al. [25] compared two types of ANNs for validation of a bottom-spray fluidized bed granulation process. The training capacity and the accuracy of a Multi-Layer Perceptron (MLP) and a Generalized Regression Neural Network (GRNN) were compared. The GRNN (a so-called Bayesian Neural Network) showed a higher capacity for validation of the granulation process compared to the MLP (a so-called feed-forward back-propagation network).

The self-organizing map (SOM) is an unsupervised ANN method to observe and visualize high-dimensional data. Similar to PCA, the method can be used to project n-dimensional data into an m-dimensional space. However, PCA is a linear method, while SOM provides a non-linear mapping. Rantanen et al. [19] have used SOMs to reduce granulation process dimensions and monitor different process states. SOM allowed to visualize the progress of the granulation process through a number of states via a 2D map. They demonstrated also how differences between granulation batches can be monitored. With this technique, several trend charts can be replaced by projecting them into one map and deviations from the reference (e.g., validated process) are visually detected. Recently, both conventional and novel modeling techniques such as screening test, multiple regression analysis, SOMs, ANN, decision trees and rule induction were simultaneously applied to analyze fluid bed granulation [20]. Results showed that nonlinear methods based on artificial intelligence, such as neural networks, allowed better generalization and prediction compared to conventional multiple regression analysis. The use of SOMs, decision trees and rule induction to monitor and optimize fluid bed granulation was demonstrated.

Fuzzy logic is a method for classification and decision making based on degrees of truth rather than the usual true or false (1 or 0) logic on which the computer is based [130]. It is able to deal with the vagueness and imprecision of many real-world problems and make decisions based on not so precise information. Using fuzzy sets with its fuzzy membership rules and IF-THEN rules, fuzzy logic offers a robust approach to solve many real-world problems and is employable in very complex systems, when there is no simple mathematical model for highly nonlinear processes. Disadvantages include the undesirable high complexity and rule-chaining problem. In addition, one must (accurately) know and define the rules and the membership function for (imprecise) data. Watano et al. [26] applied fuzzy logic to control the moisture content during agitation fluid bed granulation. The granule moisture content was continuously monitored by an IR moisture sensor. They achieved good response and stability without overshoot, but the fuzzy logic could not be applied to granulation at various operating conditions (especially inlet air conditions). Hence, an adaptive fuzzy control was developed to adjust to the varying inlet air conditions [27]. The group also applied fuzzy logic to control the bed height, continuously measured by an ultrasonic sensor [28]. The fuzzy logic was based on a linguistic algorithm employing IF-THEN rules. Control of bed height effectively prevented defluidization and channeling. The possibilities and appropriateness of a fuzzy logic controller in simulating and controlling the fluidized bed agglomeration performance was investigated by Koerfer and Simutis [29]. They showed that fuzzy logic can be used to simulate real-time observations of the fluidized bed agglomeration process and to eliminate certain trial and error granulation experiments.

6. Conclusions

Extensive work has been performed on the implementation of real-time analytical measurement tools during fluidized bed granulation, to continuously monitor the granule characteristics. Through the application of various data analysis techniques, better understanding and control of the granulation process has been achieved. The applied PAT tools have also contributed to a more scientific-based transfer of the granulation process from laboratory-scale to large-scale granulators. The inherent sensitivity of fluid bed granulation to the bed humidity will further motivate the development and incorporation of in-process measurement techniques to strictly control granulation and guarantee process reliability and product quality. In that way, a fully PAT instrumented and validated fluidized bed granulation process in a commercial production line can be developed.

The tendency of the industry to shift from batch to continuous manufacturing necessitates the in-line analysis of intermediates to minimize off-line end product testing. Hence, the PAT research in the field of fluid bed granulation will be valuable to the introduction of continuous fluid bed granulation in the pharmaceutical industry over the years to come.

Acknowledgement

This work was financially supported by the Institute for the Promotion of Innovation through Science and Technology in Flanders (IWT-Vlaanderen).

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**Figure captions**

Figure 1. Overview of the 4 stages of powder wetting (liquid saturation). The solid particles are represented by grey circles and the binding liquid is coloured black.

Figure 2. Schematic 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, (10) exhaust blower. Arrows indicate the direction of the airflow.

Figure 3. Illustrating the difference between in-line, on-line and at-line product measurements during manufacturing.

Figure 4. Schematic of the FBRM and SFV measurement techniques.

Figure 1.



Figure 2.



Figure 3.



Figure 4.



|  |  |
| --- | --- |
| Operating variables | Material variables |
| apparatus variables | process variables | starting material | binder solution |
| *shape product container [6, 13, 38, 47]* | *inlet air temperature [6, 13, 38, 47, 54]* | *particle size [13, 38, 47, 55]* | *type of solvent [6, 13, 38, 47]* |
| *design air distributor plate [13, 38, 47]* | *inlet air velocity [6, 13, 38, 47, 55]* | *particle size distribution [13, 38, 47]* | *type of binder [6, 13, 38, 47, 54]* |
| *nozzle position [6, 13, 38, 47]* | *inlet air humidity [6, 13, 38, 47, 54]* | *particle shape [13, 38, 47]* | *binder concentration [6, 13, 38, 47, 54]* |
| *nozzle type [6, 13, 47]* | *inlet air volume [13, 47, 54]* | *moisture content [13, 38]* | *binder content in formulation [6, 13, 38, 47]* |
| *diameter of nozzle tip [6, 13]* | *fluid bed height  [13]* | *cohesiveness [13, 38, 47]* | *binder viscosity [6, 13, 38, 55]* |
|  | *product temperature [13, 47]* | *static charge [13]* | *type of surfactant [13, 38]* |
|  | *binder liquid spray rate [6, 13, 38, 47, 54, 55]* | *wettability [6, 13, 38, 47]* | *surfactant concentration [13, 38, 55]* |
|  | *nozzle atomization air pressure [6, 13, 38, 47, 54]* | *stickiness [13, 47]* |  |
|  | *exhaust air temperature [13, 47]* |  |  |
|  | *drying time [6, 13]* |  |  |

Table 1. Overview of top-spray fluid bed granulation operating and material variables influencing granule quality attributes (binder and surfactant are added in solution).

Table 2. Application of triboelectric probes, microwave resonance technology and electrical capacitance tomography during fluid bed drying.

|  |  |  |
| --- | --- | --- |
| Technique | Results | Reference |
| triboelectric probes | Reliable granule moisture measurement with triboelectric probes during fluid bed drying (Karl Fischer as reference). | [68, 69] |
| Use of triboelectric probes to qualitatively monitor fluid bed drying and examine the effect of vibration on drying. | [70] |
| microwave resonance technology (MRT) | Good correlations between granule water content determined by MRT and reference methods (i.e., loss on drying and Karl Fischer) during fluid bed drying.  | [71] |
| Time saving in the drying process through real-time monitoring of water content by MRT. |
| Increase of process knowledge by combining MRT with multivariate data analysis techniques, applied to an industrial scale granulator. | [72] |
| electrical capacitance tomography (ECT) | Use of ECT to measure granule moisture during fluid bed drying. | [73] |
| Development of a feedback control strategy based on ECT measurements to improve process efficiency and product quality. |