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End point detection in fluidized bed granulation and drying technology by various methods

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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, eventually resulting in wet particle which collide with each other and form larger permanent aggregates, known as granules. After spraying the required amount of granulation liquid, the wet granules are quickly dried in the fluid bed granulator. A wide range of analytical process sensors has been used for real-time monitoring and control of fluid bed granulation processes after the Process Analytical Technology initiative was launched by FDA.Various data analysis techniques have been applied to the multitude of data collected from the process analyzers implemented in fluid bed granulators.

This review gives an overview of the end point detection in fluid bed granulation and drying technique. 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, endpoint detection and modeling and control. 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 emphasized.

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Introduction

During the primary 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 [13]. This method took considerable time to “fine tune” and was purely based on intuition and observation. The lack of monitoring and control systems made reproducible granulation in a reliable manner difficult [9].

Control of the formulation components and the process is essential to ensure the consistent production of granules with the desired quality characteristics such as granule size, size distribution, moisture content, density, flowability[6], and friability. The quality attributes are affected by the properties of starting material consequently, 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 [17, 18]. 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. Mass is transferred as a vapor from the granules in the surrounding gas while heat is transferred to the granules to evaporate the binder solvent, while. 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 understandings 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. A PIDR (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 PIDR 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 two stages of water loss [15]. 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[17]. 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[2]. However, one should also take the encouragement of fluidization on the ΔT technique into account. Improper fluidization, even for short periods, can be a major source of deviation for the ΔT technique, as the temperature of the granulation mass is relatively higher when fluidization is low[14]. 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 three granulation process variables (i.e., inlet air, outlet air, and mass temperature)[11].

Advances in control and endpoint detection of fluidized bed granulation

The detection of granule growth during fluidized bed granulation and the process endpoint is traditionally based on the measurements of process parameters in fluidized bed granulators. 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 have 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 nondestructive, provide a short measurement time and allow various measurement setups (Fig. 1) [16]. 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. Online 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 online 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.

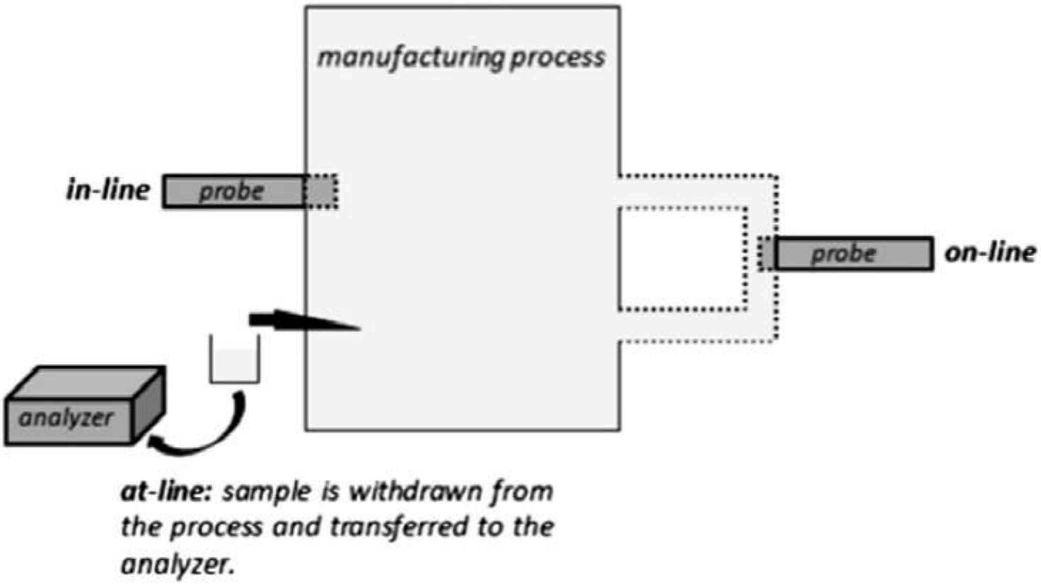

Fig. 1.Illustrating the difference between in-line, online, and at-line product measurements during manufacturing taken from references [16].

Near infrared spectroscopy

The near infrared (NIR) spectral region covers the area across the wavelength range 800–2500 nm. Absorbances in the NIR region originate from implication and combination bands of fundamental vibrations observed in the mid-IR region. The 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 [5]. The technique exhibits a high measurement speed, low cost, robustness and is nondestructive. The interest in NIR spectroscopy for in-process measurements increased significantly due to the computer advancements and the development of fiber optics allowing the measurements to be performed away from the operator. 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.[8]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.

Image analysis

In addition to NIR spectroscopy, image-processing was one of the most primitive 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 amount of computational processing. Therefore, imaging devices are usually equipped with powerful computers to handle the data.

The early work of Tanino et al.[22]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 coworkers. Watano and Miyanami developed an online 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 online monitoring of granule growth in an agitation fluidized bed granulator. By use of heated purge air, powder adhesion onto the measurement window was prevented. Extensive preprocessing and image-processing were necessary before determining granule size distribution, median, and shape factors. 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. 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[23]. The developed system could 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).

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, crystallization , and flocculation 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) (Fig. 2). 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[10]. A chord length is defined as the straight line between any two 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.

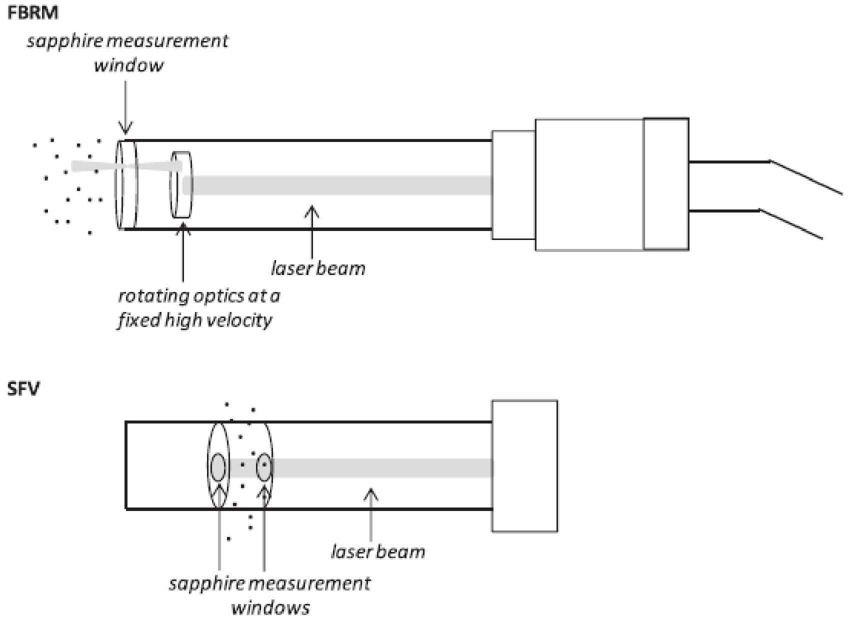

Figure 2: Schematic representation of FBRM and SV measurement techniques

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 (Fig. 2). 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 two 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[19, 20]. 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 preselected 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 50–6000 μm and the particle velocity range of 0.01–50 m/s with a data rate up to 20,000 particles/s.

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. 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 noninvasive 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.

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). 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 nondestructive 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 online 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[3]. 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.

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.[1]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 into 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 two spectroscopic techniques as NIR spectroscopy was particularly sensitive to water and Raman spectroscopy to crystal structure changes.

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[21]. Research has been conducted to deal with the difficulty of controlling variations in relative humidity. Lipsanen et al.[12]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 three additional physical parameters, more control of the fluid bed granulation process can be gained ensuring repeatable granulation[12]. The fluidization parameter[7] and pressure difference over the upper filters, 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 and the temperature of the fluidizing bed expressed the moisture conditions of the granule mass.

The use of artificial neural networks (ANNs) 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. Nonlinear 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.[24]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[24]. The scale-up could be conducted with high accuracy by the neural network without the construction of a mathematical model with a complicated nonlinear 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. Behzadi et al.[4]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).

Conclusion

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 have been achieved. These tools have also contributed to a more scientific-based transfer of the granulation process from laboratory-scale to large-scale granulators. The intrinsic sensitivity of fluid bed granulation to the bed humidity will further uplift the development and incorporation of in-process measurement techniques to strictly control granulation and guarantee process reliability and product quality. In this way, a fully 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 demands the in-line analysis of intermediates to minimize off-line end product testing. Hence, the 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.

Conflict of Interest

The author report has no conflict of interest.

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