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The use of FBRM for on-line particle size analysis in a fluid bed granulator

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THE USE OF FBRM FOR ON-LINE PARTICLE SIZE ANALYSIS IN A FLUID BED
GRANULATOR

A Thesis

Presented to

The Faculty of the Department of Chemical and Materials Engineering

San José State University

In Partial Fulfillment

of the Requirements for the Degree

Master of Science

by

Danielle Scheibli

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ABSTRACT

THE USE OF FBRM FOR ON-LINE PARTICLE SIZE ANALYSIS IN A FLUID BED GRANULATOR

By Danielle Scheibli

Focused beam reflectance measurement (FBRM) was used to measure the chord length distribution (CLD) on-line during fluid bed granulation. The CLD was compared to the particle size distribution (PSD) using sieve analysis and laser light scattering at various points throughout the granulation. Granulation process conditions and FBRM probe positions of two different granulation formulations were studied. The experiments revealed that the position of the probe and the process conditions in the granulator were important for obtaining a CLD that was comparable to other established methods for measuring PSD. The FBRM probe was positioned 45° or 60° into the granulator bowl using two different adaptors. The FBRM probe window was covered in granules when the probe was positioned 45° into the granulation bowl using target thermodynamic conditions. The CLD was measured on-line for granulations performed under dryer and target thermodynamic conditions when the probe was positioned 60° into the granulation bowl. Sieve analysis and laser light scattering samples taken throughout these granulations were comparable to the CLD measured by FBRM.

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CHAPTER ONE INTRODUCTION

The pharmaceutical industry routinely uses fluidized beds to granulate powders into agglomerates that can be further processed into products [1]. ALZA Corporation uses fluid bed granulators to make drug and osmotic granulations that are further processed into osmotic release oral systems (OROS[®]). Drug granulations contain active ingredient(s) and other excipients, and osmotic granulations contain polyethylene oxide and other excipients. Both granulations are compressed and coated with a rate-controlling membrane. An orifice is drilled through the rate-controlling membrane to allow for the active ingredient(s) in the drug layer to contact the gastrointestinal tract. Once the system is activated and begins to hydrate, the active ingredient(s) in the drug layer exits through the orifice at a rate controlled by the membrane. The membrane absorbs water and controls the release rate; the orifice provides an exit for the drug to leave the system as the osmotic layer expands.

The objective of the granulation process is to improve properties of the starting materials. Granulation can improve flow, reduce dustiness, increase particle size distribution (PSD), increase strength, improve appearance, improve solubilization, improve compactibility, and reduce the tendency for segregation to occur [2]. The processing details for mixing, wet granulation, and drying were first reported in 1966. An atomization gun was added to a Glatt fluid bed dryer in order to spray the liquid binder onto the bed during the wet granulation step. The development of the fluid bed

granulator can largely be attributed to W. Glatt of Germany. The fluid bed granulation process is shown in Figure 1.

As shown in Figure 1, air travels into the granulation bowl through a screen and an air distribution plate [3]. The plate uniformly distributes air into the granulation bed. Three phases can be performed in a fluid bed granulator: mixing, agglomeration, and drying [4]. The inlet air mixes the dry powders before a liquid binder is applied [1]. During granulation, the lighter particles move closer to the spray guns and the atomized liquid binder. The liquid binder forms a thin film around the powders. As more liquid binder is sprayed, bridges made up of interstitial liquid binder form between the wet powders, which produces intermediate particles. The intermediate particles deform, squeezing the liquid binder to the surface, and the liquid binder on the surface promotes coalescence and growth of agglomerates. Attrition, crushing, or breakage of the agglomerates can occur when they impact with other agglomerates or with the walls of the granulator. As the agglomerates become wetter, their size increases, and they move to the bottom of the granulation bowl where they become drier. The agglomerates continue to go through this wetting and drying cycle until all of the liquid binder is sprayed onto the bed. After the spraying process is complete, the inlet air dries the agglomerates. The temperature of the granulation is used to monitor the drying process [2].

Air is allowed to escape through filter bags and then an exhaust filter. The filter bags keep powder from entrainment. The filter bags are intermittently shaken in order to return fine powder to the chamber. This process may interrupt the spray cycle depending on the design of the equipment.

Figure 1. Schematic of a top spray fluid bed granulator.

Various processing conditions within the three phases can affect the PSD. For most pharmaceutical products, smaller particles lead to stronger tablets, but there are

exceptions [5]. Too many fine particles and too many coarse particles can lead to issues downstream of granulation. A wide distribution of particles can lead to segregation of the particles during the compression process. During the agglomeration phase, the moisture content of the bed and the droplet size of the liquid binder is critical [6, 7, 8]. If the bed becomes too wet, the agglomerates will get too heavy and the bed will collapse forming a large mass. If the bed is too dry, some particles may not agglomerate.

Agglomeration is more important than mixing or drying because the following properties are determined: average particle size, PSD, flowability, bulk density, and compressibility. The process parameters that affect these granulation properties are interconnected. Monitoring these process parameters is important to achieve a quality granulation on a consistent basis. Monitoring how these process parameters affect PSD during the granulation process can lead to more detailed knowledge of the process itself. On-line measurement of particle size during the fluid bed granulation gives real-time data, which could enable on-line optimization [9]. In addition to understanding how particles size changes over time, an accurate endpoint can be determined as well [10].

The U.S. Food and Drug Administration (FDA) recently issued a guideline advocating process analytical technology in the pharmaceutical industry [11]. The guideline defines process analytical technology as an analytical system that measures (and controls) critical quality parameters on-line in order to ensure quality products on a consistent basis. On-line measurement of PSD in a fluid bed is a process analytical

technology tool [10]. The PSD can be a critical parameter, and can directly impact processing downstream of granulation. A consistent PSD is necessary to achieve a more consistent product, which is important for commercial success. The PSD is usually measured after the granulation process is complete using sieve analysis [9]. The PSD during granulation is usually not measured or understood unless separate samples are taken and measured appropriately. Continuous on-line measurement of PSD could eliminate particle size testing after granulation, and eliminate sampling during the granulation process as well.

FBRM is a widely used technique for on-line particle size measurement, but it is relatively new to the pharmaceutical industry [12]. Figure 2 shows a schematic of a FBRM probe. The FBRM probe can be installed into a flowing medium such as a fluid bed granulator and can measure the PSD without the need for sample preparation [10]. The FBRM probe directs a laser beam of approximately 780 nm through a rotating lens. The highly focused beam of light projects just outside the sapphire window into the particle dispersion. The focused beam moves at a rotational speed of approximately 2-6 m/s. When the focused beam meets a particle, light backscatters from one edge to another. The FBRM optics converts backscatter into an electronic signal [13]. A circuit is used to determine the time it takes to measure the backscatter from one edge of the particle to another [14]. The time it takes to measure the backscatter is multiplied by the speed of the focused beam, and the result is a distance called the chord length.

Figure 2. Schematic of a FBRM probe.

The chord length is a distance between any two edges on a particle surface. Approximately 100,000 chords lengths can be measured every second, which gives a CLD [14]. The CLD is a function of the number, size, and shape of the particles [12]. CLD measurements may give enough information to monitor process changes over time, but PSD is more useful. The PSD can be directly related to product quality. In order to translate the PSD from a CLD, two different models need to be used [15]. Analytical solutions and numerical solutions exist to determine the probability that a known PSD translates into a CLD depending on the particle shape. The second model translates a CLD into the PSD using inverse modeling. Once the PSD can be measured over time in the fluidized bed, the granule growth kinetics can be determined [16].

CHAPTER TWO

LITERATURE REVIEW

Over the years, researchers have focused on controlling the granulation process in order to achieve a desired average granule size. The moisture content in the granulation bed and the droplet size of the liquid binder are two important factors that can change the average granule size. The droplet size has also been shown to be a useful factor for scaling from one size granulator to another. Different methods have been used to measure moisture content and granule size on-line. These techniques include: near infrared spectroscopy, Raman spectroscopy, laser diffraction, and FBRM. The FBRM probe measures chord size, which can be translated into particle size.

2.1 Controlling moisture content and droplet size

Knowing how process parameters in the fluid bed change the moisture content after spraying the binder onto the granulation and altering the droplet size of the liquid binder may help control the granulation process [7, 8]. The moisture content depends on the amount of water entering the fluidized bed and the amount of water leaving the fluidized bed. The process parameters that determine the moisture content of the granulation bed are the inlet airflow rate, inlet air humidity, and inlet air temperature. The process parameters that determine the droplet size are the spray rate, nozzle type, and nozzle settings. Rambali et al. [7] performed a face-centered, central-composite design of experiments in order to determine how the inlet airflow, inlet air temperature, spray

rate, and inlet air humidity change the average granule size. The experiments were performed in a GPCG-30, which produces a batch size of approximately 30 kg. The granulation contained 70.7% lactose monohydrate, 27% corn starch, and was agglomerated with 2.3 % hydroxypropylmethyl cellulose (HPMC). The center point was repeated six times. The results indicated the moisture content of the bed and the droplet size of the liquid binder affected the average particle size. Increasing the spray rate of the liquid binder increased the droplet size. The highest spray rate gave the largest average granule size. The bed collapsed at low inlet airflows and high spray rates. Acceptable granule sizes were obtained using low spray rates regardless of the other parameters. This indicated that spray rate was more significant in changing the granule size than the other process parameters.

Rambali et al. [8] scaled up the fluid bed process from the small, medium, to large scale using relative droplet size of the liquid binder and powder bed moisture content. The small-scale activities were performed on a GPCG-5, which produces a batch size of approximately 5 kg. The medium-scale activities were performed on a GPCG-30, which produces a batch size of approximately 30 kg. The large-scale activities were performed on a WSG-120, which produces a batch size of approximately 120 kg. The lactose monohydrate / corn starch formulation was agglomerated with an HPMC solution. The droplet size was varied in all three fluid beds by adjusting the nozzle settings in the liquid spray gun. The mixing airflow rate, inlet air temperature, spray rate, and drying airflow rate were kept constant. A high inlet air temperature was used in order to minimize the

effect that moisture content has on the average granule size. The inlet airflow rate was adjusted appropriately by considering the different air distributor plates at the three different scales. The results showed that as droplet size increased, the granule size increased. During a second set of experiments, a factorial design of experiments was performed on the GPCG-5. The powder bed moisture content and the relative droplet size were given low, target, and high values. At approximately 12% moisture in the granulation bed, the average granule sizes were 371, 438, and 491 μm for the small, target, and large droplet sizes, respectively. At the target droplet values, the average granule sizes were 378, 385, 388, and 439 μm for moisture content results of 6.7, 8.8, 9.5, and 13.8%, respectively. The experimental results showed that droplet size had the most effect on the average particle size and that as droplet size increased, so did the average particle size.

Schaafsma et al. [17] studied how mixing, wetting of the powders, and relative humidity affected granule growth. They modified the top spray fluid bed process by pulsing the spray in short durations. The liquid binder was sprayed for 3 seconds, and then the spray was turned off for 60 seconds. This was repeated until the process ended. Pulse durations of 3, 5, 10, 15, and 30 seconds were studied. The formulation consisted of 92% α -lactose monohydrate agglomerated with 8% polyvinylpyrrolidone. With each experiment, the granule growth grew to an average particle size of approximately 390 μm before the bed collapsed. As the granules grew larger, the mixing at the surface of the granulation bed decreased. When the granulation bed stopped mixing at the surface, the

bed collapsed. The PSD did not vary with the different spray pulse durations, which indicated that the agglomerates were moving more quickly than the spray rate. The relative humidity affected granule growth above a critical value of 50%. Above this value, the powder wetting increased significantly and mixing at the surface of the granulation bed decreased significantly.

2.2 On-line measurement of moisture content

Immediate measurements of a critical granulation property can lead to improvements in the process. In 1996, Frake et al. [6], attempted to measure the on-line moisture content and PSD using near infrared spectroscopy for a granulation in a fluidized bed. Near infrared (NIR) spectroscopy is a non-destructive test that can be used over a wide range of densities. Quantification of the amount of water in the granulation was determined by NIR spectroscopy using the O-H band at approximately 1932 nm. The second derivative of the absorbance data was tracked over time. The percent moisture increased during the agglomeration process, which was similar to the Karl Fischer water content results and loss on drying results. Loss on drying is a quick in-process test that measures the amount of water in the sample based on weight differences before and after drying at a specific temperature. The authors selected a wavelength of 2282 nm to determine the particle size. At this wavelength, the zero order spectra changed over time. They hypothesized this was due to an increases in PSD only. The particle size results using NIR spectroscopy increased over time, which was similar to the

results using sieve analysis. NIR spectroscopy is sensitive to water absorbance, which is a disadvantage if the O-H band interferes with other bands of interest [18]. Other authors such as Rantanen et al. [4] found that in-line near infrared spectroscopy measurement of moisture were disturbed by the different granulation phases. They used these disturbances to create a model to help determine the moisture content in a fluid bed.

In addition to NIR spectroscopy, Raman spectroscopy can be used on-line to determine the amount of moisture in a fluid bed granulation. Raman and NIR spectroscopy both probe the vibrational transitions of molecules. There is a quantitative relationship between signal intensity and the concentration of material causing the vibrational shift. Hausman et al. [18] used Raman spectroscopy to measure the moisture content during the drying phase in a fluid bed. The use of Raman spectroscopy is limited to starting materials that exhibit a detectable vibrational shift in their Raman spectrum due to crystal lattice changes. A technique that can measure moisture regardless of the starting materials is more valuable in controlling the granulation process.

2.3 On-line measurement of particle size

Measuring the moisture content on-line is only an indicator of particle size, so a technique that can actually measure the particle size would be more useful. Otsuka et al. [19] evaluated the use of NIR spectroscopy for measuring the PSD of antipyrine granules. The absorption peaks for the antipyrine were identified at 4560, 4668, 5940, 6036, and

8750 cm^{-1} , and the absorption peaks for the granules excipients were 4776, 5172, and 6500 cm^{-1} . Granules were sampled at various time points during the granulation process. All of the near infrared spectrums were the same, but the baseline increased with an increasing amount of water. The increase in the baseline offers a quantitative measurement of the PSD. The authors used multivariate data analysis to predict the granule size. The correlation coefficient of the predicted PSD vs. actual PSD linear line was approximately 0.91.

Rantanen et al. [20] used near infrared spectroscopy to measure the PSD of a high-shear granulation process. The mannitol, microcrystalline cellulose, and Avicel formulation was agglomerated with polyvinylpyrrolidone. The authors used multivariate data analysis to determine the PSD from the spectral baseline shift. The baseline shift occurs for several reasons: an increase in particle size, an increase in moisture, and changes to the density of the granulation bed. A trend exists between the increasing slope of the near infrared spectrums and the increase in the particle size, but this is not an accurate determination of the PSD. To increase the accuracy, they used a filter to remove spectral variations due to an increase in moisture. The filter removed approximately 30% of baseline variation. The calibration model failed because of too much water variation in the samples. The authors recommended using spectroscopy to determine the PSD because baseline shifts are due to numerous physical changes, not just an increase in PSD.

In addition to NIR spectroscopy, laser diffraction can be used to determine the PSD on-line in a fluid bed granulator [21]. Laser diffraction is routinely used to measure the PSD of powders and agglomerates off line. Laser diffraction uses a laser and photo detectors to measure the PSD. The technique does not require calibration and can be validated. The Insitex T can be used on-line to measure particle sizes ranging from 0.5 μm to 1000 μm . The disadvantage of using on-line laser diffraction is that the equipment might not be able to get a representative sample from the granulator [22].

There are many particle size analysis techniques, but few are able to measure the particle size on-line without the need for sampling. The Lasentec FBRM probe is able to measure the PSD in real time. Barrett and Glennon [23] measured the CLD in a dilute aqueous suspension of calcinated silicate particles. They assumed the particles were spherical in order to simplify the equations used to translate CLD into PSD. The CLD and the PSD are given in intervals, not continuous functions, therefore; the PSD was found by using a probability function. The FBRM measurements were taken in an agitated 500-ml glass beaker. The authors found the measured chord length data was sensitive to the location and orientation of the FBRM probe. More data was collected when the flow of particles was directed at the probe window. Even with this sensitivity, the CLD was found to correlate with the theoretical PSD. The authors did not provide an error analysis of the results.

FBRM can be used to measure the PSD of wastewater treatment settling tanks. De Clercq et al. [24] studied how FBRM data compared with other particle-sizing techniques in an activated sludge process. The PSD of the bacteria in the sludge is a key parameter influencing the quality of the effluent. The FBRM PSD data were compared to laser diffraction and image analysis. The authors used glass beads with an average particle size of 32.2 μm and coric vinyl particles with an average particle size of 158.2 μm to compare results from laser diffraction, image analysis, and FBRM. The results from the vinyl particles showed that all three methods gave good results, but FBRM oversized the glass beads compared to image analysis and laser diffraction. Samples of sludge were measured using all three techniques, and the results showed major discrepancies between image analysis and FBRM data. The sludge particles were very irregular, which might have interfered with the analysis. The authors also studied how to optimize the focal point. Different focal points resulted in different PSDs, and focal points closer to the sapphire window were necessary for low and high solid concentrations of the activated sludge.

Optimal positioning of the FBRM probe is not fully understood. Worlitschek and Mazzotti [25] used a Lasentec FBRM M400L to take single measurements of ceramic bead dispersions and TiO_2 dispersions. Different axial and lateral focal positions were considered. The strongest signal was obtained when the focal point was at the center of the particle. Focal points farther away from the sapphire window might not detect the

fine particle sizes. The best focal point to detect a range of particle sizes was at the probe window as was also shown in a study performed by De Clercq et al.

2.4 Translating CLD into PSD

Even with an optimal FBRM probe position, calculating the PSD is a difficult task. Ruf et al. [26] presented a model that transformed CLD into PSD. The model assumed the following: the distance from the probe window to the particle does not affect the size of the particle, the image of the particle from the probe is given by a two dimensional projection, the particles are static with respect to the laser, the medium has a negligent effect on the CLD, the arc length is assumed to be a straight line, and the particles are spherical. The sphere is a special case because the two-dimensional projection is always the same in a three-dimensional field. The orientation of the sphere will always give the same diameter. The laser can hit the particle with the same probability at any position. A probability function was used to translate CLD into PSD. This model does not account for particles other than spheres. For particles other than spheres, all possible three-dimensional orientations of the particle need to be considered; the two-dimensional projection needs to be considered for every orientation as well. The overall CLD is found by summing and normalizing all of the three-dimensional orientations. The authors did not find a working model to translate CLD into PSD. They recommended future studies be performed using single measurements in order to understand the optics and physics behind FBRM.

Heath et al. [27] found an empirical model of translating CLD into PSD was comparable to theoretical methods found in literature. The Lasentec M500 FBRM control software was used to collect CLDs of sieved aluminum and calcite suspensions. The raw data oversized particles below 150 μm and undersized particles larger than 500 μm . The authors applied empirical relationships to the CLD data of sieved aluminum particles and compared them to the laser diffraction PSD results. Unweighted, length-weighted, square-weighted, and cube-weighted CLDs were compared with laser diffraction results. All of the FBRM results were broader than the laser diffraction results, but the square-weighted CLD most closely resembled the laser diffraction results. Table 1 compares FBRM particle size data with other methods found in literature.

Table 1. Comparison of FBRM with other particle size methods.

Particle Material	Particle Size Method (μm)	FBRM Results (μm)
Glass beads, Latex, micronized pharmaceutical product, various fluids	Cilas laser diffraction, Coulter counter – electrical sensing zone, microscopy (4.1 – 396)	Undersizes > 100 Oversizes < 100
Oil in water emulsions	Malvern laser diffraction ($d_{32} = 60 - 350$)	Undersizes > 180 Oversizes < 180
Sieved ion exchange resin	Sieve (212- 850)	FBRM undersized, better with cube weighting

Hukkanen and Braatz [9] considered several models for determining the particle size of polymer beads in a suspension. They introduced a method to account for roughness on the surface of the particle. The Lasentec FBRM probe separated chords into intervals to form a CLD. The authors used three models to best determine how the

chords were distributed within each interval. The three models were the midpoint, uniform, and the linear distribution model. The midpoint distribution method assumed the diameter of the particle was the midpoint of the interval, the uniform method assumed the particles were uniformly distributed within each interval, and the linear distribution method assumed the particles were distributed according to a linear equation in each interval. For all three methods, the PSD was calculated using inverse modeling. All three methods were compared using a known PSD. The linear method gave more accurate results when compared to the midpoint and uniform distribution methods. Increasing the amount of intervals used in the model increased the accuracy of all three models. The CLD shows a peak around 0-20 μm that can be attributed to surface roughness. After replacing this peak with a linear equation, the linear model gave a PSD that correlated well with the actual PSD. The PSD was predicted from the CLD data when information about the actual PSD was known. A model that predicts the PSD from CLD data alone would be more useful.

Wynn [28] derived a matrix equation and used inverse modeling to translate CLDs into PSDs. The method assumed the following: the particle shape is known, the particles are the same shape, the particles are randomly oriented during measurement, the scanning depth is independent of particle size, surface roughness is neglected, the laser beam path is a straight line, the chord length is the amount of time used to measure the chord length multiplied by the velocity of the laser, particles are measured only once, and the measured CLD is consistent throughout the batch. The FBRM reports CLD data as a

histogram with chord lengths inside intervals. Wynn assumed all of the particles were spheres, and that the particle size was the same inside each interval. Increasing the amount of intervals gave more accurate results. Wynn [29] also noted that FBRM measurements were more reliable above a certain concentration of particles. The relationship between CLD and PSD is well documented for two-dimensional spherical particles. There are very few publications that discuss the two- and three-dimensional non-spherical relationship between CLD and PSD.

Li and Wilkinson [15] described various theoretical methods to translate PSD into CLD, which included models for non-spherical particles. Models were developed to translate PSD into CLD for spherical, ellipsoidal, and general non-spherical particles. Analytical solutions were also found to translate PSD into CLD for spherical and ellipsoidal particles. The authors assumed that all particles were the same shape, and the aspect ratio of the particle was between 0 and 1. The spherical model simplifies the analytical solution because the two-dimensional projection is always the same in a three-dimensional field. The authors derived probability functions for both the spherical and ellipsoidal particles shapes. For a non-spherical particle shape, the authors presented a numerical solution. The probability of measuring the chord length depends on the orientation of the particle. The models were validated using a simulation technique.

Li and Wilkinson [15] described a numerical solution to translate CLD into PSD for ellipsoidal and spherical particles. The authors assumed that an ellipsoidal shape

could be used to approximate most non-spherical particles. The aspect ratio is used to describe the shape of the particle. The aspect ratio is then used in the model. Translating a CLD into a PSD can be done using a least squares or a constrained least squares method, but this method might give negative particle size data. In order to avoid this, Li and Wilkinson [15] proposed an iterative, non-linear, least squares model. The algorithm is run until a reasonable accuracy is obtained. Simulations showed that the non-linear least squares model gave better results than the least squares and constrained least squares method.

Li et al. [13] experimentally validated the results of Li and Wilkinson. A Lasentec FBRM D600L probe was used to measure the CLD of spherical ceramic beads, non-spherical plasma aluminum, and zinc dust particles. The probe was focused approximately 2 mm outside the probe window. An image analysis of all three particles was taken in order to confirm the results. The authors used shape factors such as sphericity, circularity, and chunkiness to quantitatively determine how accurately the particles resembled a sphere. The ceramic beads were mostly spherical, the plasma aluminum particles were mostly non-spherical, and the zinc dust particles were the most non-spherical. The authors determined the aspect ratio of the particles so that the iterative, non-linear, least squares method could be used to translate the CLD into PSD. The authors described two ways to determine the optimum aspect ratio. The first assumed that the PSD, CLD, and shape factors were known, the second assumed that only the CLD was known, and the third assumed circularity as the aspect ratio.

The average particle size using image analysis and all three FBRM methods gave good results. The aspect ratios were almost the same, so results from all three FBRM methods were similar. The plasma aluminum FBRM results compared well with the image analysis results, and the zinc dust had the largest deviation between the image analysis results and the FBRM results. A measured CLD can be translated to PSD if the aspect ratio is known. For the agglomeration process, PSD changes over time. If the shape of the agglomerates are the same throughout the process, then the aspect ratio is the same throughout the process, and the CLD can be translated into PSD using the iterative, non-linear, least squares method.

2.5 Literature review summary

Over the years, researchers have focused on controlling the granulation process through various methods. Variations in the fluid bed process parameters leads to different average granule sizes. Increasing the droplet size and moisture content increases the average granule size. High spray rates and low fluidization levels can collapse the granulation bed, so choosing process parameters for the granulation process is more than just understanding how to increase or decrease the granule size.

Researchers have studied on-line moisture content to control the fluid bed process. Higher moisture contents lead to larger particle sizes. NIR spectroscopy and Raman spectroscopy have been used to monitor moisture content on-line in a fluid bed

granulator. Each method has its own challenges, including accurate sampling techniques. The moisture content of the granulation is an indicator of particle size. Knowing the PSD on-line can lead to process improvements. The following methods have been used to monitor PSD: near infrared spectroscopy, laser diffraction, and FBRM. All three methods have their own challenges, including model fitting.

FBRM measures a CLD, which can be translated into a PSD. The FBRM probe needs a focal point close enough to the sapphire window so that both large and small particle sizes can be measured. The translation from CLD to PSD is very complex for non-spherical particles, and somewhat less complex for spherical particles.

CHAPTER THREE RESEARCH OBJECTIVES

The three main objectives of this research were to determine feasibility of measuring the CLD in the GCPG 30, measure the CLD while varying granulation process parameters to define the limitations of the FBRM probe, assess whether the granulation ingredients can affect the CLD measurements, and to translate the CLD to a theoretical particle size.

For the first objective, the feasibility of using FBRM for on-line measurement of particle size analysis in a medium scale fluid bed granulator was evaluated. The CLD of an osmotic granulation for an OROS[®] system was investigated at two different probe angles, three different inlet airflows, and two granulation colors. Two different adaptors were made to insert the Lasentec probe into the granulator. One adaptor positions the probe 45° into the bowl, and the other adaptor positions the probe 30° from vertical into the bowl. The angle at which the Lasentec probe is positioned in the granulator might change the CLD. The inlet airflow is an important process parameter during the fluid bed process. A method that determines the PSD at various inlet air flow profiles is beneficial because various granulation ingredients can require different inlet airflow profiles. Osmotic granulations can be colored with ferric oxide. The CLD should not change with granulation color.

For the second objective, the average particle size and PSD and position of the FBRM probe in a fluid bed were investigated under wet, dry, and target process conditions using an osmotic granulation for an OROS[®] system. Each process condition was performed twice. A method that is able to determine the on-line particle size under various process conditions is beneficial. Various process parameters are often required to determine how they affect downstream processes.

A drug granulation for an OROS[®] system was used for the third objective. The average particle size and PSD for a granulation with a water insoluble active ingredient was investigated. The insoluble active ingredient comprises a majority of the starting materials and has different properties than the osmotic granulation.

CHAPTER FOUR EXPERIMENTAL DESIGN

An FBRM probe attached to a medium-scale fluid bed granulator was used for all three objectives. The osmotic layer for OROS[®] systems was used for the first two objectives, and a drug layer was used for the third objective. The osmotic granulation is a unimodal granulation centered on a 60-mesh sieve pan and consists of polyethylene oxide agglomerated with polyvinylpyrrolidone.

For the first objective, granules with a known PSD were fluidized, and the CLD was measured. Two colors of granules and two probe adaptors were tested at different inlet airflows.

For the second objective, chord lengths were measured during osmotic granulations. The theoretical particle size was calculated from the measured chord lengths. The inlet airflow rate was varied to produce wet, dry, and target process conditions. Too many coarse and fine particles can lead to defects. Knowing how a particle size grows over time in a fluid bed granulator can improve formulation selection, and the endpoint of the granulation can be determined with on-line particle size measurement.

A drug granulation was performed for the third objective. The majority of the starting materials contained a water-insoluble active ingredient. The CLD was measured

over time, but it was not translated into theoretical particle size because CLD measurements indicated the probe window was most likely covered in particles.

4.1 Measuring the CLD during fluidization of osmotic granules

In order to accomplish the first research objective, a Lasentec FBRM probe was used to measure CLDs of granules with a known average particle size and PSD in a GPCG 30 fluid bed granulator. Red and green osmotic granulations were used. Ferric oxide was used to change the color of the granulation.

For each granulation color, the granules were fluidized and the CLD was measured on-line at different airflow rates for several minutes. The purpose of the mixing process is to fluidize the bed, so the FBRM measurement did not start until the granules were fluidized. The CLD was measured for several minutes to determine if the measurement changed with time.

The following process parameters can be controlled in the GPCG 30: mixing time, inlet air temperature, inlet air dewpoint, inlet airflow rate, spray rate, and filter bag pulse interval. The powders were allowed to mix for one minute before the FBRM measurements began, the inlet air temperature was kept constant at 30°C, the inlet air dewpoint was kept constant at 3°C, the inlet airflow was varied according to Table 2 and

Table 3, there was no spray rate during these experiments, the bag shake interval was set at 120 seconds, and the bag shake duration was set at 30 seconds.

Table 2. Objective 1 list of experiments, red granulation.

Run	Airflow Rate (m ³ /hr)	Adaptor Angle
1	350	60
2	450	60
3	650	60
4	350	45
5	450	45
6	650	45

Table 3. Objective 1 list of experiments, green granulation.

Run	Airflow Rate (m ³ /hr)	Adaptor Angle
7	350	60
8	450	60
9	650	60
10	350	45
11	450	45
12	650	45

Changing the inlet airflow changes the velocity of the particles in the granulation bed. Ideally, the FBRM probe will give the same CLD regardless of the velocity of the particles. Changing the color of the granulation should not affect the chord length measurements.

The average particle size and PSD was measured off-line using a Malvern Mastersizer 2000 laser diffraction particle size analyzer and a USA standard testing sieve. A VHX-500 Keyence VHX Digital Microscope was used to determine the particle shape.

4.2 On-line measurement of the CLD during osmotic granulations

In order to accomplish the second research objective, a Lasentec FBRM probe was used to measure CLD during granulation in a GPCG 30 fluid bed granulator. The CLD was measured on-line in the granulator during wet, dry, and target conditions for an osmotic granulation. The 45° adaptor was used for the first two experiments, but the FBRM probe window got covered with a large amount of granules both times. A total of six experiments were performed with the 60° adaptor.

The change in temperature, ΔT , between the actual exhaust temperature and the actual exhaust dewpoint gives a quantitative measurement that determines the wetness of the granulation bed. Lower values of ΔT indicate wetter process conditions, and higher values of ΔT indicate dryer process conditions. The spray rate was varied in order to achieve a range of temperature differences between the amount of water entering and leaving.

The powders were allowed to mix for one minute before the FBRM measurements began, the inlet air temperature was kept constant at 45°C, the inlet air

dewpoint was kept constant at 3°C, the inlet airflow started at 350 m³/hr and 75 m³/hr was added every minute for 6 minutes until a steady-state air-flow of 800 m³/hr was reached, the spray rate was varied according to Table 4, the bag shake interval was set at 120 seconds, and the bag shake duration was set at 30 seconds. The granulations were sampled at least five times during the process.

Table 4. Objective 2 list of experiments.

Run	Batch Number	Spray Rate (g/min)	Probe Adaptor
13	MAPG 1	80	45
14	MAPG 2	80	45
15	MAPG 3	70	60
16	MAPG 4	70	60
17	MAPG 5	80	60
18	MAPG 6	80	60
19	MAPG 7	90	60
20	MAPG 8	100	60

The average particle size and PSD were measured off-line using a Malvern Mastersizer 2000 laser diffraction particle size analyzer and a USA standard testing sieve for samples taken during granulation. A VHX-500 Keyence VHX Digital Microscope was used to determine the particle shape.

4.3 On-line measurement of the CLD during drug granulations

In order to accomplish the third research objective, a Lasentec FBRM probe was used to measure CLD during granulation in a GPCG 30 fluid bed granulator. A granulation mainly consisting of a hydrophobic active ingredient was processed twice. The CLD was measured on-line in the granulator.

The powders were allowed to mix for one minute before the FBRM measurements began, the inlet air temperature was kept constant at 45°C, the inlet air dewpoint was kept constant at 3°C, the inlet airflow started at 250 m³/hr and 75-100 m³/hr was added every minute for 8 minutes until a steady-state air-flow of 900 m³/hr was reached, the spray rate was 100 g/min, the bag shake interval was set at 120 seconds, and the bag shake duration was set at 30 seconds. The granulation was sampled at least five times during the process.

A Malvern Mastersizer 2000 laser diffraction particle size analyzer and a USA standard testing sieve were used off-line to measure the average particle size and PSD for samples taken during granulation. A VHX-500 Keyence VHX Digital Microscope was used to determine the particle shape.

Each granulation was processed at target conditions. The list of experiments is located in Table 5.

Table 5. Objective 3 list of experiments.

Run	Batch Number	Spray Rate (g/min)	Probe Adaptor
21	MADG 1	100	60
22	MADG 2	100	60

CHAPTER FIVE DATA ANALYSIS

This section is divided into three parts: Section 1 gives a detailed analysis of translating a known PSD into a CLD assuming the particles are spherical; Section 2 gives a detailed analysis of inverse modeling to translate the CLD into PSD; and Section 3 explains the analytical methods used to determine the particle shape, PSD, and average particle size.

5.1 Translating particle size into chord length for spherical particles

The solution for translating a known PSD into a CLD for a spherical particle is the most simple because the diameter of a sphere is the same regardless of orientation. The two-dimensional plane of a sphere is a circle. As shown in Figure 3, the FBRM probe can measure the diameter of the circle and any lengths smaller than the diameter, depending on where the FBRM probe starts measuring.

Figure 3. Diagram of a circle.

In Figure 3, L_j is the chord length in interval j , D is the diameter of the circle, and h is the distance between the origin and where the y-axis intersects chord length, L_j . The equation for the distance, h , between the origin and the y-axis intersection point is:

$$h = \sqrt{a^2 - \left(\frac{L_j}{2}\right)^2} \quad \text{Equation 1}$$

where a is the radius of the sphere. The probability of a chord length having length L_j is:

$$p(L_j) = \frac{2h}{2a} = \begin{cases} \sqrt{1 - \left(\frac{L_j}{2a}\right)^2} & \text{for } L_j \leq 2a \\ 0 & \text{for } L_j \geq 2a \end{cases} \quad \text{Equation 2}$$

For a particle with diameter D , the probability of a measured chord being in interval j is:

$$p_{(D_i)}(L_j, L_{j+1}) = p_{(D_i)}(L_j) - p_{(D_i)}(L_{j+1})$$

$i = 1, 2, \dots, N$
 $j = 1, 2, \dots, M$

Equation 3

where N is the number of particle intervals in the PSD, and M is the number of chord intervals in the CLD. For spherical particles, the probability of a measured chord length in interval j is:

$$p_{(D_i)}(L_j, L_{j+1}) = \begin{cases} \sqrt{1 - \left(\frac{L_j}{2a_i}\right)^2} - \sqrt{1 - \left(\frac{L_{j+1}}{2a_i}\right)^2} & \text{for } L_j < L_{j+1} \leq 2a_i \\ \sqrt{1 - \left(\frac{L_j}{2a_i}\right)^2} & \text{for } L_j \leq 2a_i < L_{j+1} \\ 0 & \text{for } 2a_i < L_j < L_{j+1} \end{cases} \quad \text{Equation 4}$$

Equation 5 is used to find the normalized CLD:

$$\begin{bmatrix} c_1 \\ \vdots \\ c_j \\ \vdots \\ c_M \end{bmatrix} = \begin{bmatrix} p_{D_{1,1}} & \cdots & p_{D_{1,i}} & \cdots & p_{D_{1,N}} \\ \vdots & \ddots & \vdots & \ddots & \vdots \\ p_{D_{j,1}} & \cdots & p_{D_{j,i}} & \cdots & p_{D_{j,N}} \\ \vdots & \ddots & \vdots & \ddots & \vdots \\ p_{D_{M,1}} & \cdots & p_{D_{M,i}} & \cdots & p_{D_{M,N}} \end{bmatrix} \times \begin{bmatrix} n_1 \\ \vdots \\ n_i \\ \vdots \\ n_N \end{bmatrix} \quad \text{Equation 5}$$

or

$$C = P \times N$$

where C is the normalized chord length, the probability matrix is found from Equation 4, and N is the normalized number fraction of particles [15].

5.2 Translating a measured chord length into particle size

The PSD of a measured CLD can be determined using inverse modeling from the PSD to CLD model. A direct matrix inversion can be calculated from Equation 5, but this equation may become unusable if there are disturbances in the chord length measurements. Using a constrained least squares method can minimize the disturbances, but this might give negative results. A non-negative, constrained, least squares method can help minimize disturbances and remove negative particle sizes. The equation used for the non-negative, constrained, least squares method is:

$$\min_N f(N) = \|P \times N - C\|^2$$

$$n_i \geq 0$$

Equation 6

$$i = 1, 2, \dots N$$

Equation 6 can be solved by numerical approximation such as Newton's method.

5.3 Analytical methods for particle shape and size

Image analysis was used to determine how well the granules resemble a sphere. Circularity and the elongation ratio are often used for this comparison. The equation for circularity is:

$$\frac{4A\pi}{P^2}$$

Equation 7

where A is area of the particle, π is pi, and P is perimeter of the particle. The equation for the elongation ratio is:

$$\frac{a}{b}$$

Equation 8

where a is the shortest feret diameter, and b is the diameter perpendicular to a. The shortest feret diameter and its perpendicular enclose the particle in a box, and are

typically used to find the elongation ratio [30]. Another equation that can be used is called the NS shape factor. The equation for the NS shape factor is:

$$NS = Co + H4 \times H3 - H2 \times H1 \quad \text{Equation 9}$$

where Co is the number of distinct corners in the shape, H4 is the elongation of the overall shape, H3 is the deviation from a triangular image, H2 is the deviation from the circular shape, and H1 is the deviation from the shape of the square [30]. Results from all three equations were averaged, and the standard deviations were calculated.

For the osmotic granulations, the CLD was measured over time, and the measured CLD was translated to a theoretical PSD. The theoretical PSD was compared to an actual PSD at specific times. During the granulation process, samples were taken over time. The average particle size and PSD were measured using a Malvern laser diffraction particle size analyzer for samples taken during granulation. A Malvern laser diffraction particle size analyzer and a USA standard test sieve were used to measure the average particle size and PSD for samples taken after the end of the drying process. A dry dispersion method was used to measure the PSD in the Malvern laser diffraction particle size analyzer. For all experiments, sieve analysis was performed by placing approximately 100 grams of granulation on a set of USA standard testing sieve ASTM E-11 pans from VWR. The set of sieve pans used for all experiments was: 16 mesh, 20 mesh, 40 mesh, 60 mesh, 100 mesh, 200 mesh, and the collection pan (the pan does not have a mesh size, all granules smaller than 200 mesh collect in the pan). The sieves and

the collection pan were stacked in order of decreasing mesh size and placed on a W.S. Tyler Incorporated RX-29 Rotap for ten minutes. The sieves and the collection pan were weighed before and after being placed on a sieve shaker.

The percentage of material retained on each sieve is used to calculate the average particle size, D50. The D50 is the median size of the PSD; 50% of the particles are bigger than this value, and 50% of the particles are smaller than this value. The D50 was calculated by fitting the data to a log normal distribution using the LOGNORMDIST function in Excel and the solver algorithm. The standard deviation was found by subtracting the D50 from the D84. For a normal distribution, about 68% of the distribution is within one standard deviation of the mean. The D84 is one standard deviation above the mean. The geometric standard deviation measures the spread of the distribution around the mean. Values closer to 1 will have a narrow distribution. The geometric standard deviation was calculated by dividing the D84 by the D50. The D84 can be calculated by using the Excel model fit parameters and the LOGINV function.

CHAPTER SIX

RESULTS

This chapter gives the results for each objective outlined in Chapter 4. Section 1 gives the results for the fluidization of green and red granules at different airflows and using two different probe adaptors. Section 2 gives the results for the dry, target, and wet osmotic granulations performed at different spray rates. Section 3 gives the results for the two drug granulations.

6.1 CLDs of fluidized osmotic granulations

For the first objective, an osmotic granulation colored red with ferric oxide was fluidized in the GPCG 30 with an inlet temperature of 30°C, inlet dewpoint of 3°C, and the bag shake interval was 120 seconds for a duration of 30 seconds. An inlet temperature lower than the target temperature for an osmotic granulation was chosen because the granulation was previously dried to a target loss on drying (% LOD), and additional fluidization would dry the granulations beyond this target.

Two different probe adaptors were used. One adaptor angles the Lasentec probe 45° into the granulator, and the other adaptor angles the Lasentec probe 30° from vertical into the granulator. Both adaptors were inserted into the bottom spray port, with the spray gun inserted into the top spray port. The probe points into the granulation bowl,

but is located in the expansion chamber. Ideally, the position of the probe should be in the bowl, but this would have required modifications to the granulation bowl.

Before each run, the Lasentec probe was warmed for at least 30 minutes before taking measurements, and the sapphire window was cleaned with solvent. Before inserting the probe into the granulator, the particle count of the probe was below the maximum allowed measurements as recommended by Mettler-Toledo. The number of particles was measured for several minutes at airflows between 350-650 m³/hr. The Lasentec software groups particles into five channels: 1-5, 10-23, 29-86, 100-251, and 293-1000 chord lengths. The results for both red and green osmotic granulations are summarized in Table 6 and Table 7, respectively. The PSD and CLD data from Table 6 and Table 7 are shown in Figure A1 through Figure A10.

Table 6. Percent of particles measured at different airflows with the red granulation (mean $\pm$ 1 standard deviation).

	Percent of particles put into a particular channel				
	1 - 5	10 - 23	29 - 86	100 - 251	293 - 1000
45° 350 m ³ /hr	16.69 $\pm$ 1.94	17.70 $\pm$ 1.38	32.56 $\pm$ 1.83	15.67 $\pm$ 2.34	1.20 $\pm$ 0.30
45° 450 m ³ /hr	18.95 $\pm$ 1.75	18.99 $\pm$ 1.28	28.55 $\pm$ 1.41	14.71 $\pm$ 2.32	1.60 $\pm$ 0.45
45° 650 m ³ /hr	20.71 $\pm$ 0.92	20.26 $\pm$ 0.64	26.83 $\pm$ 0.80	12.85 $\pm$ 1.09	1.40 $\pm$ 0.26
Standard deviation = 1.25					
60° 350 m ³ /hr	12.68 $\pm$ 1.90	14.60 $\pm$ 1.71	31.15 $\pm$ 0.95	23.91 $\pm$ 3.46	3.25 $\pm$ 0.88
60° 450 m ³ /hr	18.68 $\pm$ 1.19	19.77 $\pm$ 0.82	28.41 $\pm$ 0.94	14.27 $\pm$ 1.42	1.57 $\pm$ 0.30
60° 650 m ³ /hr	21.71 $\pm$ 1.07	21.35 $\pm$ 0.59	26.06 $\pm$ 0.84	11.28 $\pm$ 1.08	1.05 $\pm$ 0.17
Standard deviation = 1.15					

Table 7. Percent of particles measured at different airflows with the green granulation (mean $\pm$ 1 standard deviation).

	Percent of particles put into a particular channel				
	1 - 5	10 - 23	29 - 86	100 - 251	293 - 1000
45° 350 m ³ /hr	20.98 $\pm$ 1.76	20.98 $\pm$ 1.08	29.17 $\pm$ 1.62	10.19 $\pm$ 1.97	0.47 $\pm$ 0.18
45° 450 m ³ /hr	20.29 $\pm$ 1.15	21.02 $\pm$ 0.83	28.42 $\pm$ 0.98	11.47 $\pm$ 1.45	0.64 $\pm$ 0.16
45° 650 m ³ /hr	22.30 $\pm$ 1.12	22.58 $\pm$ 0.68	25.96 $\pm$ 1.10	9.24 $\pm$ 1.23	0.52 $\pm$ 0.17
Standard deviation = 1.03					
60° 350 m ³ /hr	18.55 $\pm$ 2.15	18.91 $\pm$ 1.42	30.33 $\pm$ 1.45	14.30 $\pm$ 2.78	1.00 $\pm$ 0.36
60° 450 m ³ /hr	21.03 $\pm$ 1.65	20.35 $\pm$ 1.00	27.30 $\pm$ 1.26	12.22 $\pm$ 1.88	0.98 $\pm$ 0.31
60° 650 m ³ /hr	20.95 $\pm$ 1.36	21.74 $\pm$ 1.03	26.91 $\pm$ 1.00	10.94 $\pm$ 1.69	0.87 $\pm$ 0.28
Standard deviation = 1.31					

The average standard deviation for the 60° adaptor is 1.15 and 1.31 for the red and green osmotic granulations, respectively, and the average standard deviation for the 45° adaptor is 1.25 and 1.03 for the red and green osmotic granulations, respectively. The overall average standard deviation for all of the results is approximately 1.2, indicating the number of chord lengths remained relatively unchanged throughout the fluidization process regardless of probe adaptor used. The standard deviation was slightly higher for the 60° adaptor. For this reason, the 45° probe adaptor was initially chosen for the second and third objectives.

Sieve analysis was performed before and after the fluidization process to determine if the variability in the airflow measurements was due to granules breaking apart rather than a change in adaptor or granulation color. The results in Table 8 show the D50 and the geometric standard deviation data before and after fluidization were very

similar. The deviation in chord length measurements over time was not related to a change in granule size.

Table 8. D50 results before and after fluidization for both osmotic granulations.

	Red Osmotic Granulation	Green Osmotic Granulation
D50 before fluidization $\pm$ standard deviation (μm)	267.77 ± 136.66	269.52 ± 148.87
Geometric standard deviation	1.51	1.56
Error between data and model (R^2)	1.00	1.00
D50 after fluidization $\pm$ standard deviation (μm)	268.28 ± 124.65	264.02 ± 132.60
Geometric standard deviation	1.47	1.51
Error between data and model (R^2)	1.00	1.00

Samples of granulation were taken after fluidization to determine the D50 and the PSD using sieve analysis and laser light scattering. Laser light scattering samples were analyzed using a Malvern Mastersizer 2000 laser diffraction particle size analyzer. The Lasentec software offers several options for analyzing the raw data. The raw data can be inverse length, length, square, or cube weighted. The D50 and geometric standard deviation values for sieve analysis, laser light scattering, square-weighted CLD, and the cube-weighted CLD are compared in Table 9. D50 values for the CLD without weighting, inverse length, or length weighting were not included because these values would be smaller than the square-weighted values and would not be comparable to sieve analysis or laser light scattering. In order to compare the CLD and the laser light scattering data to sieve analysis, the number of channels from both methods was

condensed. The CLD is given in 90 channels, and laser light scattering is given in 101 channels. The PSD and CLD data from Table 9 are graphed in Figure A11 through Figure A14.

Table 9. Comparison of D50 values using several methods for Objective 1.

Method	Red Osmotic Granulation	Green Osmotic Granulation
Sieve $\pm$ standard deviation (μm)	268.28 $\pm$ 124.65	264.02 $\pm$ 132.60
Geometric standard deviation	1.47	1.51
Error between data and model (R^2)	1.00	1.00
FBRM cube weighted $\pm$ standard deviation	274.32 $\pm$ 219.15	217.55 $\pm$ 177.73
Geometric standard deviation	1.80	1.82
Error between data and model (R^2)	1.00	1.00
FBRM square weighted $\pm$ standard deviation	178.03 $\pm$ 189.72	143.19 $\pm$ 141.65
Geometric standard deviation	2.07	2.00
Error between data and model (R^2)	1.00	1.00
Laser light scattering $\pm$ standard deviation (μm)	235.28 $\pm$ 217.51	248.10 $\pm$ 227.77
Geometric standard deviation	1.93	1.93
Error between data and model (R^2)	1.00	1.00

The cube-weighted CLD was more comparable to sieve analysis and laser light scattering for both granulations. The geometric standard deviation for FBRM and laser light scattering were higher than the sieve analysis results. This shows the FBRM and laser light scattering distributions have a wider spread in distribution around the D50 than with sieve analysis. For all data sets, the correlation coefficient for the linear line between the actual data and the model data were statistically the same.

Images for the red and green granules were obtained using a Keyence Digital Microscope and are shown in Figure A15 and Figure A16. The shortest feret diameter and the feret diameter perpendicular to the shortest feret diameter, area, and perimeter of five particles were found using the Keyence software. The results for circularity, elongation ratio, and the NS shape factor are located in Table 10.

Table 10. Particle shape for red and green granules (mean $\pm$ 1 standard deviation, N=5).

	Circularity	Elongation Ratio	NS
Red granules	0.72 ± 0.10	0.78 ± 0.21	4.48 ± 1.76
Green granules	0.72 ± 0.10	0.81 ± 0.81	4.59 ± 2.70

A spherical particle will have a circularity and elongation ratio close to 1 and an NS value of 4.15. The average NS value for the red and green granules matches with triangular shapes, and the standard deviation range matches circular to parallelogram shapes [30]. The large standard deviation found for all shape factors suggests that there is a wide range of particle shapes in both samples, and there is not one specific shape associated with these granules. One particle shape needs to be chosen in order to translate a chord size to particle size. Since a range of particle shapes was found instead of one particle shape, the granules were assumed to be spherical for translating the CLD to PSD.

The CLD was translated to particle size assuming a spherical shape, and the laser light scattering data was used as the actual PSD. Figure 4 and Figure 5 show the theoretical PSD.

Figure 4. Theoretical particle size of the red granulation.

Figure 5. Theoretical particle size for the green granulation.

Figure 4 and Figure 5 show the laser light scattering data, unweighted and cube-weighted FBRM data, the PSD from the calculated CLD, and the running average theoretical PSDs from the unweighted and cube-weighted FBRM data. The theoretical CLD was calculated using Equation 5 and translated back to PSD using the non-negative, constrained, least squares method. Theoretically, this distribution should match the laser light scattering data, and it does. When translated to a theoretical particle size, the unweighted FBRM data does not resemble the laser light scattering PSD. The cube-weighted data was translated to theoretical particle size, but the data showed a lot of variation. A running average of five values was performed in order to visually compare the theoretical particle size and the laser light scattering data. The laser light scattering data and the running average theoretical particle size were similar to the cube-weighted FBRM data.

The results from Objective 1 show either probe adaptor could be used to measure the CLD, but the 45° adaptor was initially chosen for the second and third objectives. The granules did not break apart during the fluidization process, so any error associated with Objective 1 was most likely not associated with granule breakage. The cube-weighted CLD was found to be more similar to sieve and laser light scattering PSDs.

Particle shape is often assumed to be spherical in order to simplify the equations used to translate the chord length to particle size [27]. Methods used to translate the chord length to particle size assume one shape, and the high standard deviation found for the granule shape indicates the osmotic granules have many different shapes. The scope of this project was to determine the feasibility of using FBRM during fluid bed granulation; assuming the granules are spherical can be helpful if translating the chord length to particle size provides more useful information than square- or cube-weighting. For these reasons, a spherical shape was assumed in order to translate the CLD into a theoretical PSD. The cube-weighted CLD was translated to a theoretical PSD. The unweighted CLD did not resemble the laser light scattering data. The equations used to find the theoretical PSD were found to be sensitive to CLD data. As the CLD became more similar to the laser light scattering data, so did the theoretical PSD.

6.2 CLDs measured on-line during osmotic granulations

For Objective 2, the first granulation was processed using a spray rate of 80 g/min and the 45° adaptor. The inlet temperature was set to 45°C, the inlet dewpoint was set to 3°C, the air volume was ramped from 350 to 900 m³/hr in 10 minutes, the filter bag pulse interval was kept the same as Objective 1, the FBRM probe was set-up the same as Objective 1, and the CLD was measured every 2 seconds. If the individual CLDs taken every 2 seconds do not show very much variation, this is an indication the probe window is covered. After the process ended, the probe window was removed from the granulator, and the sapphire window was covered with granules. For the second granulation, the same process conditions were used. The probe window became covered in granules after approximately 25 minutes. Figure 6 and Figure 7 show the cubed-length CLD over time and the time points where the probe windows were covered in granules.

Figure 6. Cube-weighted CLD for the first osmotic granulation.

Figure 7. Cube-weighted CLD for the second osmotic granulation.

For the third and fourth osmotic granulation, the 60° adaptor was used, the spray rate was lowered to 70 g/min, and the probe was inserted another inch into the granulation bowl by readjusting the grounding wire. The other process parameters and equipment set-up were kept the same as the first two osmotic granulations. Samples were taken six times during the granulation. The bed was fluidized for 5 minutes before the spray started to obtain CLD measurements at 0 minutes of binder application. Sieve analysis was performed on all time points, but laser light scattering was only performed on three time points: before granulation, after the airflow ramp-up process, and at the end of granulation (approximately 60 minutes of spray). The probe window was not covered in granules as seen in the first two granulations. The cube-weighted CLDs for both osmotic granulations are shown in Figure 8 and Figure 9.

Figure 8. Cube-weighted CLD for the third osmotic granulation.

Figure 9. Cube-weighted CLD for the fourth osmotic granulation.

The FBRM probe for the third and fourth osmotic granulations did not get covered in granules. The differences between the first two osmotic granulations and the third and the fourth osmotic granulations were as follows: lower spray rate, which produced drier process conditions; a probe adaptor that positioned the FBRM probe farther away from the binder spray gun; and the FBRM probe was moved another inch into the granulator. The drier process conditions and repositioning of the probe adaptor were both important in obtaining CLD measurements.

The average particle size for both osmotic granulations using sieve analysis, cube- and square-weighted FBRM, and laser light scattering for all three time points are located in Table 11. The PSD and CLD data from Table 11 are graphed in Figure B1 through Figure B6.

Table 11. Average particle size over time for the third and fourth osmotic granulations.

Method	Third Osmotic Granulation			Fourth Osmotic Granulation		
	Time = 0 Min.	Time = 12 Min.	Time = 60 Min.	Time = 0 Min.	Time = 24 Min.	Time = 60 Min.
Sieve (μm) $\pm$ standard deviation	129.64 $\pm$ 142.10	213.86 $\pm$ 110.61	242.99 $\pm$ 145.95	142.15 $\pm$ 145.88	245.37 $\pm$ 107.28	298.58 $\pm$ 125.98
Geometric standard deviation	2.10	1.52	1.60	2.03	1.44	1.42
Error between data and model (R^2)	1.00	1.00	1.00	1.00	1.00	1.00
FBRM cube weight $\pm$ standard deviation	265.69 $\pm$ 296.35	251.95 $\pm$ 202.46	239.14 $\pm$ 220.49	255.73 $\pm$ 208.30	299.78 $\pm$ 212.22	254.78 $\pm$ 211.85
Geometric standard deviation	2.12	1.81	1.93	1.82	1.71	1.84
Error between data and model (R^2)	1.00	1.00	1.00	1.00	1.00	1.00
FBRM square weight $\pm$ standard deviation	129.80 $\pm$ 202.08	165.33 $\pm$ 168.87	125.98 $\pm$ 181.84	163.57 $\pm$ 179.28	207.55 $\pm$ 196.85	152.59 $\pm$ 188.68
Geometric standard deviation	2.57	2.03	2.46	2.10	1.96	2.25
Error between data and model (R^2)	1.00	1.00	1.00	1.00	1.00	1.00
Laser light scattering (μm) $\pm$ standard deviation	185.13 $\pm$ 265.42	228.06 $\pm$ 312.20	207.41 $\pm$ 232.65	204.14 $\pm$ 283.89	207.50 $\pm$ 241.74	248.32 $\pm$ 267.31
Geometric standard deviation	2.45	2.38	2.13	2.40	2.17	2.08
Error between data and model (R^2)	1.00	1.00	1.00	1.00	1.00	1.00

Before the binder application process started for the third and fourth osmotic granulations, the square-weighted CLD was more similar to the sieve and laser light scattering average particle size. For the third osmotic granulation, cube weighting the

CLD was more similar to the sieve and laser light scattering average particle size at the second and third time point. For the fourth osmotic granulation, square weighting the CLD was more similar to the sieve and laser light scattering average particle size at the second time point, and cube weighting the CLD was more similar to the sieve and laser light scattering average particle size at the third time point. Similarity was quantified by comparing the percent difference between the average chord lengths and particle sizes. The geometric standard deviations for FBRM and laser light scattering were higher than the sieve analysis results (after the 0 minute time point). This shows the FBRM and laser light scattering distributions had a wider spread in distribution around the D50 than with sieve analysis. For all of the data sets, the correlation coefficient for the linear line between the actual data and the model data were statistically the same.

Images for the third and fourth osmotic granulations were obtained using a Keyence Digital Microscope and are shown in Figure B7 through Figure B12. The results for circularity, elongation ratio, and the NS shape factor for the third and fourth osmotic granulations are shown in Table 12.

Table 12. Particle shape for the third and fourth osmotic granulation (mean $\pm$ 1 standard deviation, N=5).

	Granulation Time (Minutes)	Circularity	Elongation Ratio	NS
Third Granulation	0	0.76 ± 0.06	0.81 ± 0.16	3.69 ± 0.33
	12	0.74 ± 0.08	0.80 ± 0.15	4.60 ± 1.80
	60	0.75 ± 0.05	0.82 ± 0.13	3.85 ± 0.55
Fourth Granulation	0	0.72 ± 0.07	0.78 ± 0.10	6.73 ± 2.76
	24	0.73 ± 0.04	0.87 ± 0.14	4.75 ± 2.54
	60	0.72 ± 0.11	0.82 ± 0.17	4.81 ± 2.22

For the third and fourth osmotic granulations, the average circularity and elongation ratio remained relatively unchanged throughout the granulation. For the third osmotic granulation, the NS values ranged from elliptical shapes to dragon shapes throughout the granulation. For the fourth osmotic granulation, the NS values ranged from elliptical shapes to trapezoidal shapes throughout the granulation.

For the third osmotic granulation, the CLD was translated to a theoretical particle size, assuming the particles were spherical due to the wide variation in the particle shape. The theoretical PSD over time is shown in Figure 10 through Figure 12.

Figure 10. Theoretical particle size at T=0 for the third osmotic granulation.

Figure 11. Theoretical particle size at T=12 for the third osmotic granulation.

Figure 12. Theoretical particle size at T=60 for the third osmotic granulation.

These figures show the laser light scattering data, square- or cube-weighted FBRM data, the PSD from the calculated CLD, and the running average theoretical PSD from the square or cube weighted FBRM data for three time points. The PSD translated from the calculated CLD matched the laser light scattering data in all three figures. The laser light scattering data and the running average theoretical particle size were similar to the square- or cube-weighted FBRM data.

For the fourth osmotic granulation, the CLD was translated to a theoretical particle size, assuming the particles were spherical due to the wide variation in the particle shape. The theoretical PSD over time is shown in Figure 13 through Figure 15.

Figure 13. Theoretical particle size at T=0 for the fourth osmotic granulation.

Figure 14. Theoretical particle size at T=24 for the fourth osmotic granulation.

Figure 15. Theoretical particle size at T=60 for the fourth osmotic granulation.

These figures show that the laser light scattering data, square- or cube-weighted FBRM data, the PSD from the calculated CLD, and the running average theoretical PSD from the square or cube weighted FBRM data for three time points. The PSD translated from the calculated CLD matched the laser light scattering data in all three figures. The laser light scattering data and the running average theoretical particle size were similar to the square- or cube-weighted FBRM data.

For the fifth and sixth osmotic granulation, the spray rate was increased to 80 g/min. The equipment set-up and the remaining process parameters were kept the same as the third and fourth osmotic granulations. Samples were taken six times during the granulation. Sieve analysis was performed on all time points, but laser light scattering was only performed on the following three time points: before granulation, during the air

flow ramp-up process (sixth osmotic granulation) after the air flow ramp-up process (fifth osmotic granulation), and at the end of granulation (approximately 52 minutes of spray). The probe window did not get covered in granules as seen in the first two osmotic granulations. The cube-weighted CLDs are shown in Figure 16 and Figure 17.

Figure 16. Cube-weighted CLD for the fifth osmotic granulation.

Figure 17. Cube-weighted CLD for the sixth osmotic granulation.

The FBRM probe for the fifth and sixth osmotic granulations did not get covered in granules. The differences between the first two osmotic granulations and the fifth and the sixth osmotic granulations were as follows: the probe adaptor that positions the FBRM probe was moved farther away from the binder spray gun, and the FBRM probe was moved another inch into the granulator. The repositioning of the probe adaptor was important in obtaining CLD measurements. The difference between the third and the fourth osmotic granulation and the fifth and the sixth osmotic granulation was the spray rate. The CLDs were measured at spray rates of 70 g/min and 80 g/min. The position of the FBRM probe affects whether or not the sapphire window will get covered in granules.

The average particle size for both osmotic granulations using sieve analysis, cube- and square-weighting FBRM, and laser light scattering for all three time points are

located in Table 13. The PSD and CLD data from Table 13 are graphed in Figure B13 through Figure B18.

Table 13. Average particle size over time for the fifth and sixth osmotic granulations.

Method	Fifth Osmotic Granulation			Sixth Osmotic Granulation		
	Time = 2 Min.	Time = 10 Min.	Time = 52 Min.	Time = 0 Min.	Time = 8 Min.	Time = 52 Min.
Sieve (μm) $\pm$ standard deviation	174.27 $\pm$ 138.39	230.49 $\pm$ 120.49	302.36 $\pm$ 130.79	144.72 $\pm$ 153.46	241.05 $\pm$ 129.90	268.35 $\pm$ 130.15
Geometric standard deviation	1.80	1.53	1.44	2.07	1.54	1.49
Error between data and model (R^2)	1.00	1.00	1.00	1.00	1.00	1.00
FBRM cube weight $\pm$ standard deviation	274.79 $\pm$ 203.79	347.31 $\pm$ 252.45	220.06 $\pm$ 184.43	291.65 $\pm$ 326.49	321.16 $\pm$ 225.95	268.35 $\pm$ 130.15
Geometric standard deviation	1.75	1.73	1.84	2.13	1.71	1.49
Error between data and model (R^2)	1.00	1.00	1.00	1.00	1.00	1.00
FBRM square weight $\pm$ standard deviation	184.70 $\pm$ 185.37	235.90 $\pm$ 235.55	129.84 $\pm$ 162.35	151.03 $\pm$ 212.05	221.24 $\pm$ 217.92	102.65 $\pm$ 135.81
Geometric standard deviation	2.01	2.01	2.26	2.42	1.99	2.33
Error between data and model (R^2)	1.00	1.00	1.00	1.00	1.00	1.00
Laser light scattering (μm) $\pm$ standard deviation	205.73 $\pm$ 300.20	188.55 $\pm$ 245.28	244.23 $\pm$ 259.69	201.71 $\pm$ 278.36	268.04 $\pm$ 617.51	245.25 $\pm$ 264.42
Geometric standard deviation	2.47	2.31	2.07	2.39	3.33	2.09
Error between data and model (R^2)	1.00	1.00	1.00	1.00	0.99	1.00

For the fifth and sixth osmotic granulations, square weighting the FBRM data for the first and second time points was more similar to the sieve and the laser light scattering data. At the third time points for the fifth and sixth osmotic granulations, cube weighting the CLD was more similar to the sieve and laser light scattering data. The geometric standard deviation for FBRM and laser light scattering were higher than the sieve analysis results (after the 0-minute time point). This shows the FBRM and laser light scattering distributions have a wider spread in distribution around the D50 than with sieve analysis. For all of the data sets, the correlation coefficient for the linear line between the actual data and the model data were statistically the same.

Images of the fifth and sixth osmotic granulation were obtained using a Keyence Digital Microscope and are shown in Figure B19 through Figure B24. The results for circularity, elongation ratio, and the NS shape factor are located in Table 14.

Table 14. Particle shape for the fifth and sixth osmotic granulation (mean $\pm$ 1 standard deviation, N=5).

	Granulation Time (Minutes)	Circularity	Elongation Ratio	NS
Fifth granulation	2	0.75 ± 0.07	0.80 ± 0.12	5.51 ± 2.56
	10	0.71 ± 0.09	0.80 ± 0.17	6.23 ± 2.10
	52	0.68 ± 0.06	0.78 ± 0.11	4.69 ± 1.22
Sixth granulation	0	0.77 ± 0.07	0.69 ± 0.14	3.62 ± 0.22
	8	0.73 ± 0.04	0.80 ± 0.06	5.89 ± 1.58
	52	0.71 ± 0.08	0.78 ± 0.12	4.88 ± 1.23

For the fifth and sixth osmotic granulations, the average circularity and elongation ratio remained relatively unchanged throughout the granulation. For the fifth osmotic granulation, the NS values ranged from elliptical shapes to trapezoidal shapes throughout the granulation. For the sixth osmotic granulation, the NS values ranged from elliptical shapes to trapezoidal shapes throughout the granulation.

For the fifth osmotic granulation, the CLD was translated to a theoretical particle size assuming the particles were spherical due to the wide variation in the particle shape. The theoretical PSD over time is shown in Figure 18 through Figure 20.

Figure 18. Theoretical particle size at T=2 for the fifth osmotic granulation.

Figure 19. Theoretical particle size at T=10 for the fifth osmotic granulation.

Figure 20. Theoretical particle size at T=52 for the fifth osmotic granulation.

These figures show the laser light scattering data, square- or cube-weighted FBRM data, the PSD from the calculated CLD, and the running average theoretical PSD from the square- or cube-weighted FBRM data for three time points. The PSD translated from the calculated CLD matches the laser light scattering data in all three figures. The laser light scattering data and the running average theoretical particle size were similar to the square- or cube-weighted FBRM data.

For the sixth osmotic granulation, the CLD was translated to a theoretical particle size assuming the particles were spherical due to the wide variation in the particle shape. The theoretical PSD over time is shown in Figure 21 through Figure 23.

Figure 21. Theoretical particle size at T=0 for the sixth osmotic granulation.

Figure 22. Theoretical particle size at T=8 for the sixth osmotic granulation.

Figure 23. Theoretical particle size at T=52 for the sixth osmotic granulation.

These figures show the laser light scattering data, square- or cube-weighted FBRM data, the PSD from the calculated CLD, and the running average theoretical PSD

from the square- or cube-weighted FBRM data for three time points. The PSD translated from the calculated CLD matched the laser light scattering data in all three figures. The laser light scattering data and the running average theoretical particle size were similar to the square- or cube-weighted FBRM data.

The seventh and eighth osmotic granulations were both “wet” granulations, but the spray rate was increased to 90 g/min for the seventh osmotic granulation, and the spray rate was increased to 100 g/min for the eighth osmotic granulation. The remaining process parameters and the equipment set-up were kept the same as osmotic granulations three through six.

For the seventh osmotic granulation, samples were taken six times during the granulation. Sieve analysis was performed on all time points, but laser light scattering was only performed on three time points as follows: before granulation, during the air flow ramp up process, and at the end of granulation (approximately 46 minutes of spray). The probe window did not get covered as seen in the first two granulations, but the average chord size decreased in the middle of the granulation, which suggested a fine layer of granules had deposited on the probe window, or the larger granules were not fluidizing to the sapphire window. The cube-weighted CLD is shown in Figure 24.

Figure 24. Cube-weighted CLD for the seventh osmotic granulation.

For the eighth osmotic granulation, samples were taken five times during the granulation. Laser light scattering was not performed on the eighth osmotic granulation because the probe window was covered in granulation. If the individual CLDs taken every two seconds did not show very much variation, this was an indication the probe window was covered. Using this method, the probe window was covered during the air flow ramp at approximately 5 minutes. The cube-weighted CLD is shown in Figure 25.

Figure 25. Cube-weighted CLD for the eighth osmotic granulation.

For the seventh and eighth osmotic granulations, the spray rate was increased to 90 g/min and 100 g/min, respectively. Wetter process conditions interfered with the ability of the FBRM probe to take CLD measurements. For the seventh osmotic granulation, the probe window did not get covered in granules, but the average cube weighted chord size was much smaller than sieve and laser light scattering. This indicated the sapphire window was covered with fine granules, or only the smaller granules were getting fluidized near the sapphire window. For the eighth osmotic granulation, the probe window was covered in a mass of granules. This indicates process conditions in the granulator influenced the ability of the FBRM probe to measure the CLD.

The average particle size for the seventh osmotic granulation using sieve analysis, cube- and square-weighting FBRM, and laser light scattering for all three time points are shown in Table 15. The PSD and CLD data from Table 15 are graphed in Figure B25 through Figure B27.

Table 15. Average particle size over time for the seventh osmotic granulation.

Method	Time = 0 Minutes	Time = 6 Minutes	Time = 46 Minutes
Sieve (μm) $\pm$ standard deviation	150.32 $\pm$ 158.89	221.68 $\pm$ 130.96	270.27 $\pm$ 155.29
Geometric standard deviation	2.07	1.59	1.58
Error between data and model (R^2)	1.00	1.00	1.00
FBRM cube weight $\pm$ standard deviation	202.21 $\pm$ 181.54	273.79 $\pm$ 205.67	126.93 $\pm$ 145.46
Geometric standard deviation	1.90	1.76	2.16
Error between data and model (R^2)	1.00	1.00	1.00
FBRM square weight $\pm$ standard deviation	126.14 $\pm$ 135.12	184.62 $\pm$ 183.79	68.91 $\pm$ 90.65
Geometric standard deviation	2.08	2.00	2.33
Error between data and model (R^2)	1.00	1.00	1.00
Laser light scattering (μm) $\pm$ standard deviation	211.16 $\pm$ 262.36	204.16 $\pm$ 293.67	251.48 $\pm$ 269.62
Geometric standard deviation	2.25	2.45	2.08
Error between data and model (R^2)	1.00	1.00	1.00

The cube-weighted CLD was more similar to the sieve and laser light scattering average particle size for the first and third time points. After 6 minutes of spray, the

square-weighted FBRM data was more similar to the sieve, and the laser light scattering was better than cube weighting. The geometric standard deviations for FBRM and laser light scattering were higher than the sieve analysis results (after the 0-minute time point). This shows the FBRM and laser light scattering distributions have a wider spread in distribution around the D50 than with sieve analysis. For all of the data sets, the correlation coefficient for the linear line between the actual data and the model data were statistically the same.

Images of the seventh osmotic granulation were obtained using a Keyence Digital Microscope and are shown in Figure B28 through Figure B30. The results for circularity, elongation ratio, and the NS shape factor are shown in Table 16.

Table 16. Particle shape for the seventh osmotic granulation (mean $\pm$ 1 standard deviation, N=5).

	Granulation Time (Minutes)	Circularity	Elongation Ratio	NS
Seventh granulation	0	0.76 $\pm$ 0.05	0.74 $\pm$ 0.18	6.00 $\pm$ 2.69
	6	0.75 $\pm$ 0.08	0.79 $\pm$ 0.17	4.60 $\pm$ 1.37
	46	0.63 $\pm$ 0.09	0.90 $\pm$ 0.22	4.75 $\pm$ 1.74

The average circularity and elongation ratio remained relatively unchanged throughout the granulation, and the NS values ranged from elliptical shapes to trapezoidal shapes throughout the granulation. The CLD was translated to a theoretical particle size, assuming the particles were spherical due to the wide variation in the particle shape. The theoretical PSD over time is shown in Figure 26 and Figure 27.

Figure 26. Theoretical particle size at T=0 for the seventh osmotic granulation.

Figure 27. Theoretical particle size at T=8 for the seventh osmotic granulation.

Figure 26 and Figure 27 show the laser light scattering data, cube- and square-weighted FBRM data, the PSD from the calculated CLD, and the running average theoretical PSD from the cube- and square-weighted FBRM data for two time points. The PSD translated from the calculated CLD matches the laser light scattering data in both figures. The laser light scattering data and the running average theoretical particle size were similar to the cube or square weighted FBRM data.

For Objective 2, eight osmotic granulations were performed to determine if the CLD could be measured on-line during the granulation process. The 45° adaptor got covered in a mass of granules using the “target” spray rate for the first two osmotic granulations. The 60° adaptor was used for osmotic granulations three through eight. A mass of granules was found with the eighth osmotic granulation, which had the highest spray rate. This indicates that high spray rates or wetter process conditions could impact the feasibility of measuring the CLD. Square- or cube-weighting the CLD of osmotic granulation three through seven was found to be similar to the sieve and laser light scattering results.

One specific shape was not associated with the osmotic granulations, so a spherical shape was assumed in order to translate the CLD into a theoretical PSD. The cube- or square-weighted CLD was translated to a theoretical PSD, depending on which one was more similar to the sieve and laser light scattering results. The theoretical PSD resembled the laser light scattering data.

6.3 CLDs measured on-line during drug granulations

For Objective 3, an OROS[®] drug granulation was used. The process parameters and equipment setup were kept the same as osmotic granulations three through eight, and the spray rate was 100 g/min. The granulation process was performed twice. Samples were taken six times during the granulation. Sieve analysis was performed on all time points, but laser light scattering was only performed on three time points as follows: before granulation, during the air flow ramp up process, and at the end of granulation (approximately 42 minutes of spray). The probe window did not get covered as seen in the first two osmotic granulations, but the average chord size decreased in the middle of the granulation, which suggests that a fine layer of granules accumulated on the probe window, or the larger granules were not fluidized to the sapphire window.

The first drug granulation bed got too heavy and collapsed at approximately 3 minutes, but was revived after stopping the spray and pulsing the bed with air at the target steady state airflow (900 m³/hr). A disruption in the chord length measurements was seen at approximately 3 minutes (Figure 28) as well. The number of chord lengths between 29-86 abruptly fell approximately 40%, and the number of chord lengths between 293-1000 abruptly increased approximately 40%. The increase in chord lengths between 293-1000 corresponded to the time the bed was pulsated with air. Larger particles were being fluidized to the FBRM probe at this moment. The heavy particles broke up after a few minutes, or they were unable to reach the FBRM probe after the

pulsation period ended. Since the top layer of the granulation bed was sprayed with binder for a short time after the bed collapsed, the top layer most likely contained wet and large particles that were broken up after the bed was pulsed. The chord length distribution during this time period reflects the observations and actions made to re-fluidize the bed. During the rest of the granulation, the probe window did not get covered as seen in the first two osmotic granulations, but the average chord size decreased in the middle of the granulation. This suggests the following: a fine layer of granules built up on the probe window, larger particles were not being fluidized to the probe window, or the average particles size was decreasing over time. The same trend was found for the second drug granulation, which is shown in Figure 29.

Figure 28. Cube-weighted CLD for the first drug granulation.

Figure 29. Cube-weighted CLD for the second drug granulation.

The FBRM probe for the first and second drug granulations did not get covered in granules like the first two osmotic granulations. The average particle size for both drug granulations using sieve analysis, cube- and square-weighting FBRM, and laser light scattering for all three time points are located in Table 17.

Table 17. Average particle size over time for the first and second drug granulation.

Method	First Drug Granulation			Second Drug Granulation		
	Time = 2 Min.	Time = 4 Min.	Time = 42 Min.	Time = 0 Min.	Time = 5 Min.	Time = 42 Min.
Sieve (μm) $\pm$ standard deviation	61.42 $\pm$ 93.30	859.36 $\pm$ 593.38	517.02 $\pm$ 452.29	62.29 $\pm$ 92.07	818.74 $\pm$ 1657.96	306.58 $\pm$ 127.93
Geometric standard deviation	2.53	1.70	1.88	2.49	3.04	1.42
Error between data and model (R^2)	1.00	1.00	1.00	1.00	0.96	1.00
FBRM cube weight $\pm$ standard deviation	59.30 $\pm$ 18.14	200.74 $\pm$ 221.33	51.15 $\pm$ 17.57	155.13 $\pm$ 149.00	140.80 $\pm$ 109.55	48.08 $\pm$ 30.86
Geometric standard deviation	1.31	2.11	1.35	1.97	1.78	1.65
Error between data and model (R^2)	1.00	1.00	1.00	0.99	1.00	1.00
FBRM square weight $\pm$ standard deviation	51.15 $\pm$ 17.57	103.17 $\pm$ 145.86	40.21 $\pm$ 29.11	85.15 $\pm$ 112.84	96.59 $\pm$ 84.24	62.11 $\pm$ 40.40
Geometric standard deviation	1.35	2.43	1.73	2.34	1.88	1.66
Error between data and model (R^2)	1.00	1.00	1.00	1.00	1.00	1.00
Laser light scattering (μm) $\pm$ standard deviation	13.31 $\pm$ 43.18	171.72 $\pm$ 324.49	254.98 $\pm$ 460.20	9.18 $\pm$ 38.86	114.51 $\pm$ 205.60	138.36 $\pm$ 171.36
Geometric standard deviation	4.28	2.91	2.82	5.28	2.81	2.25
Error between data and model (R^2)	1.00	0.99	0.99	0.99	1.00	0.99

There is a lot of variation between the sieve, FBRM, and laser light scattering data throughout both granulations. For both drug granulations, all of the samples taken during the binder spray process contained “chunks” of wet granules that would not pass through

the 16-mesh screen. Drying the granules before the performing the sieve analysis might have reduced error associated with other granules sticking to the wet “chunks” during the sieve analysis. The average granule size according to sieve analysis can be artificially high because of this error. The laser light scattering analysis was performed months later than sieve analysis, and the granule samples were dry at this time point. This might explain why the average granule size for the sieve analysis does not match the CLDs and laser light scattering for the samples taken during the binder spray process. The last sieve analysis sample was taken after the drying process was complete, and did not contain “wet” chunks. Although there is variation between the sieve analysis and the laser light scattering at the last time point, the CLDs were unrealistically low for both drug granulations. This suggests the particles were not being fluidized to the probe window, or the probe window was covered in a fine layer of granules. The geometric standard deviations for FBRM and laser light scattering were variable as well, which indicated a variable spread in distribution around the D50. For all of the data sets, the correlation coefficient for the linear line between the actual data and the model data were statistically the same.

Image analysis for both drug granulations was obtained in order to gain insight into these differences. These images were obtained using a Keyence Digital Microscope and are shown in the Appendix, Figure C1 through Figure C6. The particle shape of the drug granulation before the spray starts was needle shaped, and the image analyzer only

measured the larger particles in this sample. After the spray began, the particles were less needle-like. The particle shape is summarized in Table 18.

Table 18. Particle shape for the first and second drug granulation (mean $\pm$ 1 standard deviation, N=5).

	Time (Minutes)	Circularity	Elongation Ratio	NS
First drug granulation	0	0.60 ± 0.15	0.50 ± 0.25	5.66 ± 2.01
	4	0.69 ± 0.11	0.71 ± 0.18	5.79 ± 2.42
	42	0.69 ± 0.10	0.75 ± 0.14	4.81 ± 1.96
Second drug granulation	0	0.63 ± 0.20	0.57 ± 0.43	6.72 ± 1.75
	5	0.60 ± 0.15	0.48 ± 0.23	6.99 ± 2.03
	42	0.65 ± 0.14	0.61 ± 0.21	4.72 ± 2.09

For both drug granulations, the average circularity remained relatively unchanged throughout the granulations, and the NS values ranged from elliptical shapes to trapezoidal shapes throughout the granulation. For the first drug granulation, the elongation ratio increased over time. The increase in elongation ratio indicates that the particles moved from needle-like particles to irregular polygon-like particles that were more spherical. For the second drug granulation, the elongation ratio remained relatively unchanged throughout the granulation, which was different than the first drug granulation. The higher standard deviation before the binder application process began was most likely due to the difficulty in measuring smaller particles using the image analyzer.

The results from Objective 3 show high spray rates or wetter process conditions may impact the feasibility of measuring the CLD. A CLD could possibly be measured for this drug granulation at lower spray rates or dryer process conditions. The process conditions chosen for this granulation were not at “target.” The average particle size according to sieve analysis was higher than 250 μm , indicating wetter process conditions.

CHAPTER SEVEN

DISCUSSION

For Objective 1, CLDs were measured for approximately 5 minutes at increasing airflows for two granulations using two adaptors. The second spray gun port was used to angle the Lasentec probe 60° and 45° from horizontal in the granulation chamber. The overall average standard deviation for all of the results was approximately 1.2 indicating that the number of chord lengths remained relatively unchanged throughout the fluidization process regardless of probe adaptor used. Although both adaptors were found to be similar, the 45° adaptor was chosen for the first and second osmotic granulations because the largest individual standard deviation was found with the 60° adaptor. For the first two osmotic granulations, a large mass of granules built up on the probe window for both of these granulations. The 60° adaptor angles the probe 30° from vertical pointing into the granulation bowl, and the 45° adaptor angles the probe 45° from vertical. If the binder sprays onto the probe window, then the granules are more likely to stick to the sapphire window. The 60° adaptor angle positions the probe further away from the binder spray gun, and was chosen for the third and fourth osmotic granulations.

In addition to changing the probe adaptor for the third and fourth osmotic granulations, the ground was adjusted so that the probe was 1 inch further into the granulator. According to Mettler-Toledo, the recommended position for the probe is several inches from the bottom of the granulation bowl. After adjusting the ground, the probe was still in the granulation chamber, and was not located in the granulation bowl.

The Lasentec probe measured the CLD for the target and dry osmotic granulations runs without granules building up on the sapphire window, but the CLD for the first wet osmotic granulation (seventh osmotic granulation) had values at the third time point that did not match sieve or laser light scattering and seemed unreasonable compared to the other granulations. Some possible reasons for these sizes could be as follows: a fine layer of granules on the sapphire window, or the coarse granules remained at the bottom of the granulation bowl and were not being fluidized near the sapphire window. The probe position was found to influence the ability to obtain CLDs, so a probe positioned deeper into the granulation bowl might be better able to measure the CLD of wetter granulations. Probe positions deeper in the granulation bowl will be further away from the binder spray gun, and might have more consistent access to both fine and coarse particles.

In addition to probe position, the process parameters were found to influence the ability to measure CLDs. According to Rambali et al. [7] [8], the droplet size changes the average particle size more than any other factors. All of the osmotic granulations and the drug granulations had the same process parameters except for the spray rate. The seventh and eighth osmotic granulations and the two drug granulations had spray rates 80 g/min or higher, which allowed for more wet granules to stick to the probe window. Granulations with higher spray rates could benefit from a probe position farther away from the binder spray gun.

Increasing the spray rate of the liquid binder increased the droplet size, and the highest spray rate gave the largest average granule size. For osmotic granulations three through seven, the spray rate was changed from 70 g/min to 100 g/min. Figure 30 shows the average particle size and end of spray LOD at different spray rates for osmotic granulations three through seven.

Figure 30. Average particle size and end of spray %LOD at different spray rates.

As the spray rate increased, the end of spray LOD increased, but there was no correlation with the average particle size. This was consistent with other osmotic granulations performed at on the GPCG-30 and the WSG-120. The end of spray LOD was not taken for the two granulations performed at 80 g/min.

For all of the osmotic granulations, a bimodal chord length size distribution existed before the spray started and gradually disappeared after the airflow ramp process.

Figure 31 shows the bimodal CLD diminishing over time.

Figure 31. Bimodal CLD at four different time points.

The very fine material can be sieved and analyzed to see if this fraction shows a high percentage of one or more ingredients. The disappearance of this peak indicates that all of the ingredients are fully granulated. An endpoint for this granulation could be determined by finding the time it takes for the two peaks to merge. These data could not have been seen with sieve analysis or laser light scattering. Sieve analysis is a time-consuming process, and analyzing each sample can take up to 20 minutes. The small number of sieve pans makes it a rough estimate of particle size only, and not accurate for a bimodal particle size distribution. In addition, samples taken during the granulation are

wet and can stick to each other or the sieve pans. The laser light scattering data can only be measured off-line, and this can be a time consuming process as well. In addition, the laser light scattering did not show a second peak at the smaller particle sizes. This endpoint determination could only be measured using an on-line technique, such as FBRM, for CLD or particle size distribution.

The unweighted CLD measured by FBRM from all three objectives undersized the granules. The FBRM probe measures a chord length, which is the measurement from one side of the particle to another. According to the optical imaging results, the average granule shapes of the osmotic granulations were not consistent. The granule shape varies from spherical to polygon, with many surface irregularities, and the granules can stick together. A spherical shape was chosen to translate the chord length distribution to the particle size distribution. Any shape chosen would have deviated from the actual shape of the granules, and the spherical model is the most simple. Using a running average on the translated theoretical particle size distribution, the distributions resembled the laser light scattering data. Without performing a running average, the translated distributions were erratic. More extensive modeling that takes surface imperfections into account might give a more accurate translation of chord size to particle size. The results were interesting, but this distribution cannot be viewed on-line during granulation. Translating the square- or cube-weighted CLD to particle size showed similar distributions to the laser light scattering data as well, and the CLD can be viewed in real time as the

granulation is progressing. Modeling can be very difficult, and the FBRM software can easily square or cube weight the chord lengths.

For Objective 2, five osmotic granulations with varying spray rates were processed. All of the remaining process parameters were kept the same. The average granule size of the sample taken before the spray process began should be very similar. The results are shown in Table 19.

Table 19. Comparison of D50 values before spray (mean $\pm$ 1 SD, N=6).

Description	D50 at T= 0 Minutes of Spray
Sieve	141.71 $\pm$ 8.74
FBRM cube weight	253.82 $\pm$ 37.59
FBRM square weight	142.63 $\pm$ 17.75
LLS	200.54 $\pm$ 11.02

The results indicate that sieve analysis performed on the granulation before the spray process began was the most reproducible method with a standard deviation below 10. Laser light scattering gave consistent results as well, but the D50 values were more than 50 μ m different than the sieve results. Sieve analysis used approximately 100 mg and laser light scattering used approximately 5 mg. The small sample size used for laser light scattering may be the difference between the two methods. The scanning speed on the FBRM laser was 2 m/s, and measurements were taken every two seconds. This greatly reduced error associated with having a representative sample. The FBRM square weight results were more similar to the sieve results, and the standard deviation for the

FBRM square weight results were below 18. This shows that before the spray process began, the average D50 for the osmotic granulation was approximately 140 μm , and that square weighting the FBRM data was a good approximation of the particle size.

In addition to the samples taken before the spray process began, samples were taken during the spray process and at the end of the process. Square- and cube-weighted CLD measurements were compared to those from sieve analysis and laser light scattering. The sieve and laser light scattering D50 results for the time points that had the least percent difference on average to the square-weighted CLD D50 are shown in Table 20. The sieve and laser light scattering D50 results for the time points that had the least percent difference on average to the cube-weighted CLD D50 are located in Table 21.

Table 20. Sieve and laser light scattering (LLS) D50 results for the square-weighted distributions.

Description	Sieve Analysis (μm)	Laser Light Scattering (μm)
Fourth osmotic granulation T=24	245.37	207.50
Fifth osmotic granulation T=2	174.27	205.73
Fifth osmotic granulation T=10	230.49	188.55
Sixth osmotic granulation T=10	241.05	268.04
Seventh osmotic granulation T=8	221.68	204.16
Average	222.57	214.80
Standard deviation	28.54	30.71
Overall average D50 = 218.64 μm		

Table 21. Sieve and LLS D50 results for the cube-weighted distributions.

Description	Sieve Analysis (μm)	Laser Light Scattering (μm)
Red granules end of fluidization	268.28	235.28
Green granules end of fluidization	264.02	248.10
Third osmotic granulation T=12	213.86	228.06
Third osmotic granulation T=60	242.99	207.41
Fourth osmotic granulation T=60	298.58	248.32
Fifth osmotic granulation T=52	302.36	244.23
Sixth osmotic granulation T=52	268.35	245.25
Average	265.02	235.23
Standard deviation	33.57	15.77
Overall average D50 = 250.12 μm		

The information in Table 20 and Table 21 shows that square weighting the CLD can be used when the sieve and laser light scattering average particle size is approximately 219 μm , and cube weighting the CLD can be used when the sieve and laser light scattering average particle size is approximately 250 μm . The standard deviation for sieve analysis and laser light scattering was between 16 and 34. Square weighting the CLD was mostly used for the D50 comparison of the samples taken during the spray process, and cube weighting was used when the sample was taken at the end granulation process.

For Objective 3, two drug granulations were performed. The spray rate was 100 g/min, and the remaining process parameters and equipment set-up was kept the same as osmotic granulations three through eight. For both granulations, the probe window did

not get covered as seen in the first two osmotic granulations, but the average chord size decreased during the binder spray process. The same observation was seen at the end of the seventh granulation. This suggests that spray rates above 80 g/min cannot be used in the GPCG-30 with the same process parameters and probe position, regardless of granulation material. If the other process parameters that influence the amount of moisture in the granulator were changed to produce drier process conditions (inlet temperature, inlet dewpoint, and air volume), or the atomization pressure of the binder spray gun was changed to produce finer droplets at higher spray rates, then spray rates above 80 g/min might be used with the FBRM probe adaptors in Objectives 1 through 3.

Other process parameters that change the amount of moisture in the granulator might cause granules to build up on the probe window as well. Osmotic granulations three through six had theoretical ΔT values above 22, the seventh osmotic granulation had a theoretical ΔT of approximately 20, and the eighth osmotic granulation and the drug granulations all had ΔT s below 18. These data suggest theoretical ΔT s above 22 will most likely result in granules covering the probe window. The material used in the granulation might be a factor as well. Materials that are more prone to sticking than the ingredients used in the osmotic and the drug granulation might be a consideration in other experiments.

The probe position was found to be an important factor in the ability for the probe to measure the CLD. Future experiments could focus on determining whether probe

positions farther into the granulation bowl improve the ability to take FBRM measurements. Re-designing the granulation bowl to include a port for the FBRM is costly and timely. A new adaptor can be designed that positions the probe into the granulation bowl from the bottom spray port might, but this may influence the airflow in the granulator.

The osmotic granulation exhibited a bimodal chord length distribution that became unimodal over time. Future experiments could focus on identifying the predominant ingredient 10 chord lengths and smaller. Samples of the granulation can be separated and analyzed. The percentage of this material can be measured over time, and the time it takes for this material to be integrated into the granules could give an accurate endpoint. This endpoint could be seen every time an osmotic granulation is performed, and this ingredient could be put into other granulations to determine the endpoint.

In addition to probe position and analyzing ingredients for endpoint determination, more drug granulations could be performed in order to determine if the unrealistic average granule size at the end of granulation was due to heavy particles not fluidizing to the probe, or because the probe window was covered in a fine layer of granules. The probe was turned off after the completion of both drug granulations, and the particle count was not measured. The particle count of the probe was measured before each granulation to determine if the amount was below the maximum allowed measurements as recommended by Mettler-Toledo. During these experiments, the focal

point of the laser was at the sapphire window. If there were fine particles on the sapphire window that interfere with the measurements, experiments with different focal points might combat this interference.

CHAPTER EIGHT

CONCLUSIONS

Comparing the CLD to the particle size distribution was not an easy task. Square and cube weighting the CLD was performed using the Lasentec software, and were found to be comparable to sieve and laser light scattering data when dry and target process parameters were used with the 60° adaptor. Dry and target process parameters can vary depending on the ingredients and the desired outcome. FBRM can be used for other granulations, but drier process parameters with lower spray rates are recommended. The particle count should be measured before and after the granulation process to determine if the sapphire window is compromised. Overall, FBRM is an excellent tool that gives insight into the granulation process that cannot be determined off-line or at-line. With any new granulation, the relationship between the CLD and the other particle size methods needs to be evaluated.

The relationship between the CLD and other particle size methods was found for the osmotic granulations. The average particle size of square-weighted CLDs was approximately 219 μm , and the average particle size of cube-weighted CLDs was approximately 250 μm . This indicates that the CLD should be square weighted when the particle size is approximately 219 μm or less, and cube weighted when the particle size is approximately 250 μm or more.

Translating the CLD to particle size by assuming spherical particles was an interesting exercise, but can only be performed off-line. The particle shape was assumed to be spherical because of the wide variation found during image analysis measurements. The theoretical particle size distribution was obtained using the cube- or square-weighted CLD, and a running average was presented. The theoretical particle size distribution was similar to the laser light scattering data and the square- or cube-weighted distribution.

The CLDs for the osmotic granulations measured on-line were found to have a characteristic bimodal distribution that diminished at the end of the granulation. The disappearance of the smaller peak potentially indicated that the ingredients were fully granulated. A method to optimize an endpoint to this granulation can be investigated. Sieved samples can be analyzed to determine the concentration of ingredients in the smaller peak. The time it takes for the smaller peak to disappear can be determined visually with the FBRM software. This endpoint could be verified by measuring the concentration of ingredients across sieve fractions. This technique may reduce granulation time and save resources. Further analysis of using this method to determine an endpoint is recommended.

In addition to gaining insight into a more accurate endpoint, other process parameters and probe positions could be evaluated in the GPCG 30 to determine the probe position that can be used with the highest number of process conditions. In addition to probe position and process parameters, the focal point of the laser could be

evaluated to determine if any adjustments can remove the interference resulting from a fine layer of particles adhering to the sapphire window.

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APPENDIXES

Appendix A Objective 1 data

Figure A1. Percent of red granules in the 1-5 chord length range over time.

Figure A2. Percent of red granules in the 10-23 chord length range over time.

Figure A3. Percent of red granules in the 29-86 chord length range over time.

Figure A4. Percent of red granules in the 100-251 chord length range over time.

Figure A5. Percent of red granules in the 293-1000 chord length range over time.

Figure A6. Percent of green granules in the 1-5 chord length range over time.

Figure A7. Percent of green granules in the 10-23 chord length range over time.

Figure A8. Percent of green granules in the 29-86 chord length range over time.

Figure A9. Percent of green granules in the 100-251 chord length range over time.

Figure A10. Percent of green granules in the 293-1000 chord length range over time.

Figure A11. Particle size methods at end of fluidization for the red granulation.

Figure A12. Particle size methods at end of fluidization for the red granulation.

Figure A13. Particle size methods at end of fluidization for the green granulation.

Figure A14. Particle size methods at end of fluidization for the green granulation.

Figure A15. Optical image of the red granules.

Figure A16. Optical image of the green granules.

Appendix B Objective 2 data

Figure B1. Particle size methods at T=0 minutes for the third osmotic granulation.

Figure B2. Particle size methods at T=12 minutes for the third osmotic granulation.

Figure B3. Particle size methods at T=60 for the third osmotic granulation.

Figure B4. Particle size methods at T=0 minutes for the fourth osmotic granulation.

Figure B5. Particle size methods at T=24 minutes for the fourth osmotic granulation.

Figure B6. Particle size methods at T=60 for the fourth osmotic granulation.

Figure B7. Optical image at $T=0$ for the third osmotic granulation.

Figure B8. Optical image at $T=12$ minutes for the third osmotic granulation.

Figure B9. Optical image at $T=60$ for the third osmotic granulation.

Figure B10. Optical image at $T=0$ for the fourth osmotic granulation.

Figure B11. Optical image at $T=24$ for the fourth osmotic granulation.

Figure B12. Optical image at $T=60$ for the fourth osmotic granulation.

Figure B13. Particle size methods at T=2 minutes for the fifth osmotic granulation.

Figure B14. Particle size methods at T=10 minutes for the fifth osmotic granulation.

Figure B15. Particle size methods at T=52 for the fifth osmotic granulation.

Figure B16. Particle size methods at T=0 minutes for the sixth osmotic granulation.

Figure B17. Particle size methods at T=8 minutes for the sixth osmotic granulation.

Figure B18. Particle size methods at T=52 for the sixth osmotic granulation.

Figure B19. Optical image at $T=2$ for the fifth osmotic granulation.

Figure B20. Optical image at $T=10$ for the fifth osmotic granulation.

Figure B21. Optical image at $T=52$ for the fifth osmotic granulation.

Figure B22. Optical image at $T=0$ for the sixth osmotic granulation.

Figure B23. Optical image at $T=8$ for the sixth osmotic granulation.

Figure B24. Optical image at $T=52$ for the sixth osmotic granulation.

Figure B25. Particle size methods at T=0 minutes for the seventh osmotic granulation.

Figure B26. Particle size methods at T=6 minutes for the seventh osmotic granulation.

Figure B27. Particle size methods at T=46 for the seventh osmotic granulation.

Figure B28. Optical image at T=0 for the seventh osmotic granulation.

Figure B29. Optical image at $T=6$ for the seventh osmotic granulation.

Figure B30. Optical image at $T=46$ for the seventh osmotic granulation.

Appendix C Objective 3 data

Figure C1. Optical image at $T=0$ for the first drug granulation.

Figure C2. Optical image at $T=4$ for the first drug granulation.

Figure C3. Optical image at $T=42$ for the first drug granulation.

Figure C4. Optical image at $T=0$ for the second drug granulation.

Figure C5. Optical image at $T=5$ for the second drug granulation.

Figure C6. Optical image at T=42 for the second drug granulation.