IMPROVING CONTINUOUS MANUFACTURING PROCESS RELIABILITY THROUGH FEEDING CONTROL SYSTEM

By

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Abstract

Continuous manufacturing processes are complex systems composed of multiple unit operations where process variables and material properties interaction allow the development of soft PAT sensors. Hence, this study was focused on identifying the key feeding system variables (upstream) able to predict changes in particles size (D50). Monitoring changes in particle size through a soft PAT sensor within the feeding system allows the development of preventive measures in the tablet press to ensure product quality. By analyzing three distinctive granulations, in terms of D50, this study was able to identify the feeder variables that distinguish the three granulations: Average Feed Factor and Drive Command. However, on AFF vs PSD linear regression shows that the Average Feed Factor was enough to detect particle size changes with a R^2 equivalent to 97%. This linear behavior allowed the development of a decision tree algorithm to determine changes in particle size with potential impact in the tablet properties through the press stage. Additionally, the development of a decision tree to establish the preventive measures to ensure product quality within the tablet press were also provided as part of this study.

Resumen

Los procesos de fabricación continua son sistemas complejos compuestos de múltiples unidades operacionales en el cual las interacciones de las variables de proceso con las propiedades de los materiales permiten el desarrollo de tecnologías de proceso analítica mediante sensores virtuales. Por lo tanto, este estudio se centró en identificar las variables clave del sistema de alimentación (inicio del proceso) capaces de predecir cambios en el tamaño de las partículas (D50). El monitoreo de los cambios en el tamaño de las partículas a través de un sensor virtual dentro del sistema de alimentación permite el desarrollo de medidas preventivas en la tabletera para garantizar la calidad del producto. Al analizar tres granulaciones distintivas, en términos de D50, este estudio pudo identificar las variables de alimentación que distinguen las tres granulaciones: Factor de alimentación promedio y Comando de unidad. Sin embargo, una regresión lineal AFF frente a PSD muestra que el AFF fue suficiente para distinguir los cambios en el tamaño de partícula con un R^2 equivalente al 97%. Este comportamiento lineal permitió el desarrollo de un modelo mediante un árbol de decisión que fuese capaz de identificar cambios en el tamaño de partícula con potencial impacto en las propiedades de las tabletas durante el proceso de compresión. Además, como parte de este estudio también se proporcionó el desarrollo de un árbol de decisiones para establecer las medidas preventivas para garantizar la calidad del producto (tabletas) dentro de la etapa de compresión.

To my Grandmother (mamá)

Who showed me in her last days how tough she was by keep smiling

You will always live in my heart

This is for you!

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Chapter 1

Introduction

A continuous manufacturing line, specifically for direct compression, is a multi-stage process composed of a feeding, mixing and compression stage. Since is continuous no interaction between operator and material is allowed. All interactions are held through human machine interactions knowns as Human-Machine Interface (HMI). Hence, is always important to monitor the process to ensure that the identified critical process parameters (CPPs) are within the acceptable range of operation. All process parameters known to interact with the product quality are considered CPPs and that is why is so important its monitoring.

In the case of the tablet press the main compression force is considered a CPP due its impact on product critical quality attributes (CQAs) as tablets mechanical properties by surpassing plastic deformation and tablet dissolution by affecting tablet hardness. Tablet dissolution is an important aspect of the product quality since play a key role in the rate of drug release for the intended therapeutic effect. Since tablet press does not operate in a close control loop to maintain tablets quality (dissolution) within an acceptable range is required constant monitoring to adjust the tablet press set-up due changes in material properties as material cohesivity, granules porosity, particles size and among others. Hence, it relies in the operator experience to make the correct decision in adjusting the tablet press parameters. However, these adjustments are implemented after observing the deviation within the tablet press. This is known as a reaction approach and could lead to large amount of material waste if a CPP is out of the acceptable operational range. Even more, since waste is in function of the operator reaction time to complete the tablet press parameters set-up.

Thus, by identifying changes in material properties as particle size and alerting the tablet press operator in advance allows to prevent product quality non-conformance through preventive measures which lead to process reliability improvement within CM line.

1.1 Purpose

The study was focused on improving the reliability of a continuous manufacturing (CM) line operation, specifically through the table press, by using the feeder control strategy variables. To achieve this, it was required to identify the feeder control strategy variables that interact with changes in particle size to use it as a soft process analytical technology (PAT) sensor. Consequently, with the soft PAT sensor stablished proceed with the development of a two (2) fuzzy logic or decision tree algorithm:

1. Fuzzy logic or decision tree algorithm development to determine material properties changes with potential impact in the tablet press: downstream.
2. Fuzzy logic or decision tree algorithm development for preventive or pro-active actions in the tablet press.

1.2 Scope

The study covers all the components of a continuous manufacturing line designed for direct compression from its feeding stage down to the compression stage. However, the main focus was the feeding system control strategy coupled with other CM line monitored variables from the post-blending PAT (i.e. chemometric model), tablet press, and powder bed height controller. The latter element ensures a stable powder bed flow through the Near-Infrared (NIR) interface for concentration prediction through the spectra acquisition. Consequently, to ensure the data collection for post-process analysis, three granulations with different particle size were used to explore the variables interaction with particle size. This was required to ensure the development of up-stream and downstream fuzzy logic algorithm to discern if the retrievable data trends represent an adverse effect and what preventive or pro-active actions can be followed.

1.3 Background

The dominant carrier used by pharmaceutical industries to treat, heal and/or cure patient's disease(s) has been the solid dosage. The advantage of using solid dosage, such as tablets, is that it can be produced in different shapes, sizes and colors [2]. Hence, tablets are simple to be administered, and identified due its different shapes, sizes and colors. Also, tablet flexibility allows the controlled release of the active ingredients, which translates into an accurate delivery of the therapeutic dosage at a target location [3-4].

The effectiveness of the active pharmaceutical ingredients (APIs) is through the usage of different excipients, material physical properties (i.e. particle size), and manufacturing processes and techniques [3]. Even so, this translates into a disadvantage, in terms of quality, because material properties and process variables (i.e. CPPs) correlates to product Critical Quality Attributes (CQAs). Hence, a complex multivariate system is required to be maintained in control across the entire manufacturing process. This worsens the situation since traditional sampling methods add measurement variation to the analysis through external factors or human error. Therefore, continuous improvement on manufacturing processes requires the expansion of PAT capabilities and solid mechanics understanding to reduce measurement noise. Furthermore, its implementation can facilitate the transition from batch to continuous manufacturing minimizing or eliminating process interruptions that are required to analyze formulation or product quality between batches operation. The idea of this transitions relies on many factors such as minimize human error, easier scale-up, opportunities for QbD and PAT, accelerate R&D and feed-forward control strategy.

This process transition from batch to continuous have three main purposes: increase product quality controls, decrease production time, and decrease capital cost. From the former one, a consistency in product quality can be achieved by providing different mechanism that allows the prediction, prevention and/or correction of certain scenarios, which minimize human-product interaction (i.e. human error) and increase operation flexibility. The operation flexibility can arise from an efficient product monitoring coupled to a feed-forward/feed-back fuzzy logic or decision tree control strategy. This allows data gathering of process parameters and blend/product properties to develop multivariate analysis to explore possible interactions between unit operations or to identify new variables/parameters that contribute on product CQA. The already stated entails a continuous improvement on process robustness by emerging PAT tools and control strategy advancement.

These advantages of continuous manufacturing are widely used in areas as petroleum refining, chemicals, synthetic fibers, food, and fertilizers plants. Although CM is barely new in the area of solid dosage form, it has been a method used before the Industrial Revolution. Continuous manufacturing goes back to the 1771, when Richard Akwright designed the first continuous manufacturing process for a water-powered cotton spinning mill (Cromford Mill) [4] and 1785 with the first fully automated continuous process by Oliver Evans and its flour mill [5].

After all these decades, the idea behind CM is still the same; improve operational efficiencies and product quality. CM lines allow the design and development of proactive approaches due to its fed-forward configuration and capabilities to implement control strategy between multiples stages. Hence, it was one of the project objectives to develop a downstream prevention-correction mechanism in a tablet press based on the PSD monitoring at a prior-stage, such as the feeding.

So far, pressers can compress a formulation or blend into a solid dosage form (i.e. tablet) within the established specifications or IPCs (e.g. weight, thickness and hardness) if the formulation reaching the punches are within specification. This is a problem because formulation composition and material properties can vary and affect tablet IPCs. A tablet press only can adjust the force in terms of the stablished IPCs to ensure the blend reach the tablet acceptance criteria. However, the force will vary depending on how well the material fills the press die or the amount of material loaded to the die. Either way will depend on material properties if the feed frame and turret speed were properly characterized for a specific formulation. In this case, an increase or decrease in the force can affects tablet hardness and thickness, which at the end affects product CQAs, such as the dissolution.

To minimize the occurrence of this phenomenon related to material properties changes, tablets samples are gathered at a low frequency (aprox. 15-30 min) to correct for any IPCs deviation. The operator will manually or automatically (i.e. Check Master or AT-4) measure the tablets to observe if the press requires any adjustment to meet the IPCs. If any change occurs at a lower frequency, tablets efficacy can be compromised. As a consequence, real time monitoring of raw material properties in advance are needed to alert the operator of a possible corrective action or mechanism to prevent or correct a specific scenario.

This will minimize material waste and the potential risk of jeopardizing product quality. Thus, the project objectives relied on the exploration of CM line elements (i.e. feeding control system, formulation concentration PAT, rotary-laser control system) as process analytical tools (PAT) to search for particle size (D50) shifting. As a consequence, this allow the development of a fuzzy-logic algorithm capable of providing corrective-prevention measures in a tablet press within a CM line. Thus, process efficiency increases by reducing material waste, but more importantly by reducing CQAs variability. Therefore, this encourages our purpose of developing a monitoring and proactive action within a CM line control strategy to improve QbD for future product/process development.

Next chapter will present the formulation properties and process parameters that directly affect product CQAs (e.i. product composition and dissolution) and what techniques have been adapted by pharmaceutical companies to detect or monitor process and quality controls improvement. It will emphasize in the advantage and drawback aspects of each technique and where other stages, such as compression, can still improve. Finally, it will end with the project objectives and how can help pharmaceutical industries to keep forward developing robust continuous manufacturing process that seek the well-being of its patients through the delivery of high quality product.

Chapter 2

Previous Work

In pharmaceuticals companies, the development of new products, product transfer or scale-up incur in sampling frequency at any process stage to monitor its Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs). This is part of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use [6-8] to ensure quality controls, within the drug product. These quality controls are a major factor where pharmaceuticals and regulatory agencies (ex. FDA, EMEA) focus-on before its submission and approval, respectively. Its importance's lies in guarantee target therapeutic dosage and side effects reduction through an accurate delivery at the target location [9,10].

Therefore, quality controls demand process sampling at a determined frequency. Consequently, this translate into product contact and/or process interruptions which can lead to alter the process dynamics within a short time frame, time consumption on post analysis, process efficiency and among others. Still, this is a key element to understand the process from a parametric and statistical stand point. Through these development stages Design of Experiments (DoE) are built to study and analyze process parameters interactions with the CQAs. The process parameters identified with a statistical significant interaction into the CQAs are then considered CPPs [11-13].

These CPPs are then used to validate the corresponding process operation to ensure product CQAs. Hence, the identified CPPs are monitored throughout the system operational time frame to ensure product quality. However, external variations and/or situations could arise and induce product quality deviations. Depending the process, product quality deviations can be identified mostly at the end of the batch process or at the end of the downstream process which incur in higher losses. This is because, in principles, most unit operation constraint the sampling within its operation. Thus, sampling most be performed at different stage of the process to ensure and evidence that the process is running within the validated quality controls.

The approach to stablish process/product quality controls has been changing the last decades with the idea of increase its robustness throughout the entire process time frame. Until 21st Century, pharmaceuticals approach for product and process development was guided by Quality controls/Quality Assurance approaches (QC/QA). The aim within both approaches was a quality by testing (QbT), where quality controls and its assurance were developed after the product and process design were stablished [14]. However, regulatory agencies as the Federal Drug Administration (FDA) has been encouraging pharmaceuticals to move forward in the

Quality-by-design (QbD) of their product/process development [15]. This QbD approach has the intention of a pre-developmental exercise based on a risk assessment that nourish from scientific and product/process experience knowledge [14]. Thus, QbD will allow envision possible problems that can be encountered ahead and how to be mitigated beforehand. This enable the design of a product and/or process from a quality perspective with better overall robustness.

Since QbD not only base its fundamentals in the risk assessment but also in how a deviation can be mitigated, product CQAs must be monitored for quality control purposes. Consequently, analytical technology has been adapted to processes (i.e at-line, on-line and in-line) to monitor its CQAs which minimize product rejects or non-conformance, improve process consistency, and operational time reduction. The implementation of this laboratory analytical technologies to a manufacturing line to decrease its time-analysis and frequency is known as: Process Analytical Technology (PAT) [16].

The implementation of PAT tools within a manufacturing line has allow pharmaceuticals to expand their knowledge of different unit operation from a scientific-base. More recently, PAT has allowed in-line or real time monitoring of product quality attributes (ex. blend uniformity, tablet assay, PSD, polymorphism and LOD) not able to be performed before [17-24]. This has allowed pharmaceuticals companies to move forward into the implementation of continuous manufacturing process from the solid dosage perspective.

By focusing in a direct compression CM Line (feeding, mixing, compression and coating) three (3) main CQAs are analyzed for quality purposes: blend uniformity, tablet assay, and dissolution. From the former two (2), chemometric models through spectroscopy approaches (ex. FT-Raman and NIR) has been developed to predict blend/tablet uniformity or assay [22,23]. In the case of the dissolution, models have been developed and presented in the literature [25], still, no model has been approved so far by regulatory agencies for final product Real-Time-Release (RTR).

The reason to that is basically the lack of CPPs and CQAs interactions taken in consideration. For example, is well known the indirect and direct effect of lubricants, material cohesivity/adhesion, granule density/porosity, blend uniformity and PSD in the tablet dissolution [26-30] but are not regularly monitored in a CM line. In the case of the former one, cohesivity, can be considered negligible for raw material with a d50 higher than 150um. The rationale is that bulk friction and gravity will lead particle flowability and/or interaction over interparticle forces (i.e. Van der Waals) [31]. For the following material property (granule density or porosity) this should also not impact tablet dissolution if the granulation process CPPs are within the stablished acceptance criteria and if the granulation process was well characterized.

Hence, this lead to the two (2) latter CQAs: blend uniformity and PSD. Both are known to directly affect tablet hardness, which directly affect the dissolution. As a consequence, IPCs (tablet hardness, weight and height) are measured at a specific frequency (i.e. 15 to 30min) to observe if there is any potential deviation. The sampling frequency depends how the process was validated. However, deviations right after an IPC analysis will take approximately fifteen (15) to thirty (30) minutes to be captured, depending process performance and/or capability.

Thus, PAT for blend uniformity has allows to monitor in real time the formulation dosage correctness which ensure the press die loading and subsequently the proper compression of the blend. However, even if the blend uniformity is within the acceptance criteria, PSD changes can affect tablet hardness. PSD has a direct interaction with the blend bulk density and can induce changes in the tablet press compression force and subsequently in the material tablet weight and hardness. As aforementioned, this could lead to impact product CQA: dissolution.

Different technologies have been developed in the past years to predict PSD in an off-line (i.e. sieving and optical/electron microscopy), and in-line/on-line fashion (i.e. laser diffraction and NIR spectroscopy) [32-34]. In general, all consider new equipment acquisition, installation and its qualification without to mention the model development aspects as data analysis, model calibration and validation. The continuous improvement of CPPs/CQAs monitoring and controls from a continuous manufacturing stand point has been generally executed by adding new equipment's or PATs (ex. spectroscopy). Nevertheless, PAT implementation can be achieved through soft sensors (ex. pressure, temperature, rpms and capacitance). This allow faster model development at a lower cost without adding more variables or equipment to the system. This could empower dissolution model robustness to ensure regulatory agencies approval which could lead pharmaceuticals to engage in the RTR approach of their final products.

Recently, a research group uses the feeding stage of a CM process to monitor density changes, in a qualitative fashion, to validate its density Chemometric model. The chemometric model was built from the in-line spectra acquisition obtained at the exit of a continuous blender [35]. This technique allows time and cost savings since previous technologies require the addition of elements to a CM line which incur in instrument installation, qualification and process validation. Thereby, the exploration of the feeding stage coupled with other elements (i.e. blend uniformity with PAT and rotary-laser control system) allows the CM line resources to be maximized and keep building interaction understanding between material-equipment that enable the identification of material properties changes through a fuzzy logic or decision tree control algorithm. This allow improving fed-forward CM line reliability by designing a proactive approach able to prevent or correct downstream CPPs to fulfill product CQAs. However, as part of this project scope, the focus will be based on PSD changes monitoring rather than bulk density changes.

The rationale behind pursuing PSD monitoring instead of the bulk density relies in the analysis of an intrinsic material property as the PSD. By intrinsic it means that no other factor (internally or externally) in the process should be affecting the particle size. In the case of bulk density, this is a material property that can be affected by other factors within the feeding stage as hopper fill level, powder flow dynamics, bridging/rat-holing phenomena and refill operation to name a few. These local changes can trigger false positive outcomes that will incur in downstream incorrect decisions. Hence, exploring PSD as the target material property allows to monitor variations that are not affected by other factors since particle size is independent of internal and external process environment variables. Thus, the detection of PSD changes in the feeding system (early stage of a CM line) enable the prevention or correction of process deviation and/or product non-conformance to improve the product quality and process capabilities and/or performance.

To understand how feeder can works as a PAT soft sensor, for PSD monitoring, let start by mentioning the feeding different components: hopper, bowl, motor, gear box, weigh bridge, screws and screw housing (Figure 2.1). In principles, the feeder works by monitoring its weight loss through a weigh bridge located beneath the feeder at real time. Hence, the feeders calculate the mass flow from the weight loss rate. Then proceed to compare the mass flow with its setpoint. The comparison will result in a difference if the mass flow tends away its setpoint, knowns as: mass flow error (Equation 2.1). With the mass flow error, the feeder will make an adjustment to correct the calculated deviation.

$$Mass\ Flow\ Error = |set\ point - mass\ flow| \qquad \textbf{Equation 2.1}$$

Setpoint deviation will be corrected by screw speed adjustment. This screw speed adjustment will depend on the feeder tuning method. The tuning method relies on the user/operator demands on how aggressive these adjustments in screw speed wants to be achieved to reduce mass flow variability. Screw speed adjustment (control gain) can go from very slow to very aggressive and is a variable that can be provided to the feeder (Table 2.1). As higher the adjustment aggressiveness goes the greater will be the change in screw speed (Control Gain) and faster will be the response time frequency (display filter) to keep monitoring the feed rate and maintained it around the setpoint.

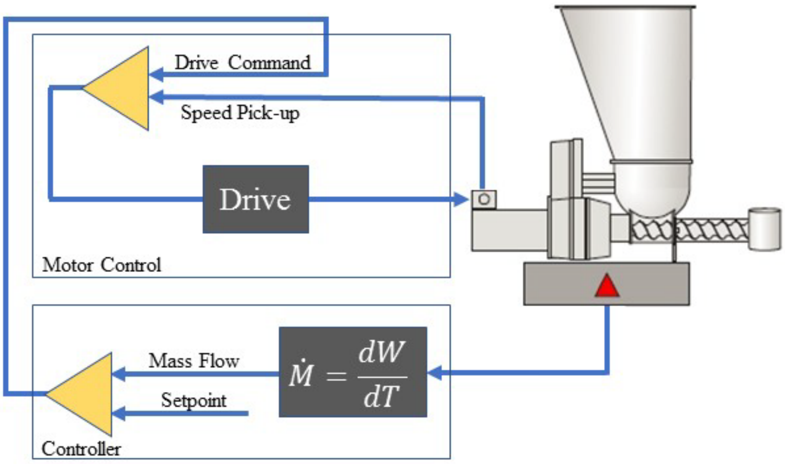

Figure 2.1: Schematic representation of feeder control logic for feeding performance.

Table 2.1: Feeder tuning method and corresponding control gain and display filter

Tuning Method	Control Gain	Display Filter
Very Slow	2%	120 sec
Slow	4%	90 sec
Moderate	8%	60 sec
Normal	15%	45 sec
Aggressive	30%	30 sec
Very Aggressive	50%	20 sec

However, aggressive adjustment can lead to worsen the situation. This can arise when a deviation comes from a high frequency weight loss rate. This high frequency could be related to an instantaneous change in the material properties; non-conformance to the overall property of the material or to an external perturbation. Hence, a high response to a high frequency weight loss rate could lead to worsen the feeding performance because the feeding control system may be reacting to an adverse effect that does not represent the overall material property or dynamics. Consequently, tuning method must be configured depending the feeder environment (internal and external perturbations) and material properties heterogeneity or homogeneity to address process noise or material variability without affecting mass flow calculation.

The minimization of mass flow variability does not obstruct the objective of monitoring the gravimetric feeder control system variables to distinguish PSD changes. Raw materials properties changes, as PSD, can goes smoothly without affecting significantly mass flow variability. Hence, other variables within the feeder control system as average feed factor, drive command, and motor speed must be changing directionally to properly compensate for shifts in PSD.

The rationale behind this is that feeder screw housing must be filled as the screws rotates. Assuming a perfect fill up, the bulk density within the screws housing should match the material bulk density. This implies that a change in the material properties (i.e. PSD), flow behavior, screws speed and hopper operation level must change the screw housing bulk density and therefore the amount of materials that is flowing out the screw outlet. This translates into an increase or decrease in mass flow, depending the bulk density change. Figure 2.2 shows an example of a screw housing dispensing a high bulk-density material (left image) that correspond to a unique slope in a weight vs time graph. If the material bulk density decreases the amount of material passing through the screw housing will be also lower, if the screw speed is maintained constant. (right image). This implies a decrease in the slope of a weight vs time graph (Figure 2.2, right image).

Figure 2.2: Screw Fill vs Weight Loss rate correlation

Hence, the feeding control system will use the mass flow and setpoint to calculate the mass flow error (Equation 2.1) which allows through the stablished control gain, the determination of the control error (Equation 2.2). Then, with the control error and the Average Feed Factor (AFF) the drive command change is determined (Equation 2.3). The AFF means the maximum feed rate that the feeder can dispense at maximum screws rpms. Hence, as the AFF increase, the feeder dispensing capacity increase and vice-versa if the AFF decrease. Since the AFF is dependent of the feeder dispensing capacity, material bulk density is a major contributor to affect AFF, only if material cohesivity changes and process noise are controlled or minimized.

Proceeding with the gravimetric feeder control operation, once the require change in drive command (Equation 2.3) is known, the updated Drive command is calculated by adding the actual and change drive command (Equation 2.4). The Updated Drive Command is then translated to screw speed. After the screw speed has been adjusted the cycle will be repeated at a frequency corresponding to the selected tuning method. Figure 2.3 summarize the feeding control strategy.

$$Control\ Error = Mass\ Flow\ Error\ x\ Control\ Gain$$ **Equation 2.2**

$$\Delta Drive\ Command\ (\Delta DC) = \frac{Control\ Error}{Avg.\ Feed\ Factor}$$ **Equation 2.3**

$$Updated\ Drive\ Command = \ \Delta DC + Actual\ Drive\ Command$$ **Equation 2.4**

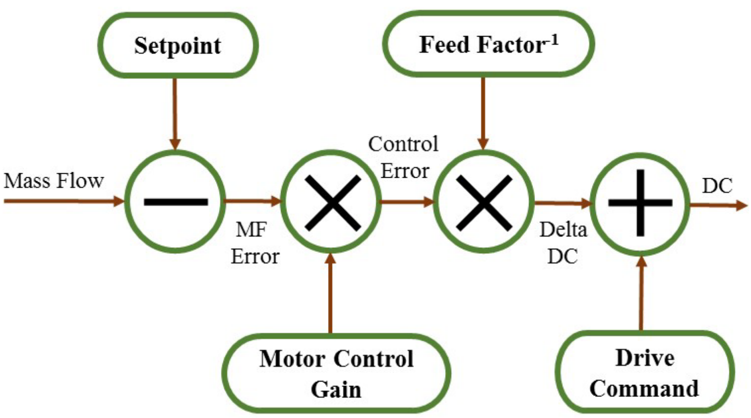

Figure 2.3: Feeding Control Strategy

To ensure that bulk density changes within the housing is from PSD variations the study was designed to be executed within a narrow screw speed range and hopper operation level. To minimize cohesivity or interparticle forces raw material selection was a free-flowing with a d50 significantly above the 150 microns threshold: approx. 2x-4x. Consequently, the analyzed material was a granulated free-flowing material and operated within the control limits (hopper material level and screws speed) which enables the assumption that changes in the AFF, drive command and/or motor speed must arise from properties changes as PSD. However, other external factors can affect the weight loss measurements readings performed by the feeders. These external factors are summarized in Figure 2.4 and can be monitor or corroborated to ensure no confounding issues in the PSD monitoring through the feeding system variables.

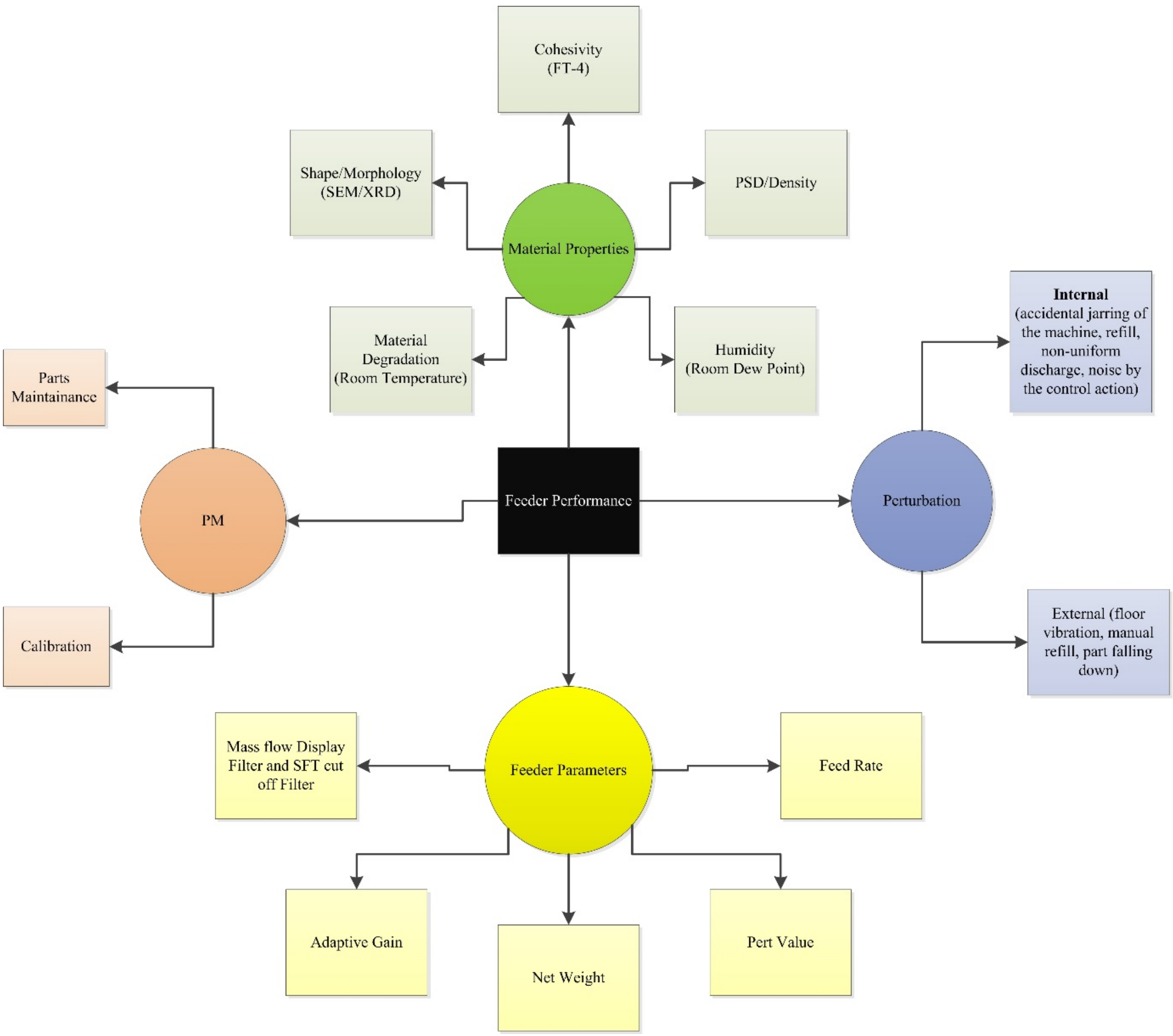

Figure 2.4: Feeding factors contributors to data reliability.

Understanding and controlling or minimizing the effect of external factors (Figure 2.4) to the weight loss measurements allows the second objective of this study: Develop of a fuzzy logic or decision tree algorithm to determine or infer material properties changes with a potential impact on the downstream CM elements. Such technique would minimize the disposal of many batch lots through the year to safeguard patient safety. Furthermore, this will add value to the transition from batch to continuous process in pharmaceutical industries, which has already started. Regulatory agencies as FDA has encourage pharmaceuticals to impulse the development of manufacturing processes from a scientific base approach that allow full understanding of material and process attributes to the product performance.

During the next chapter, details regarding the study methodology will be discussed to explain how the feeding stage coupled with other CM line elements will be a useful tool to detect potential material properties changes, as bulk density, and allow the design of a downstream decision tree strategy to prevent and/or correct processes CPPs that ensure product quality.

Chapter 3

Experimental Section

The aim of this work was to develop a study within a continuous manufacturing line, specifically for direct compression, which allows the analysis and determination of potential properties changes that enable the development of a decision tree algorithm to increase CM line control capabilities. The first phase was focused on exploring CM Line data to search for correlations between the process data and granulation PSD: fine, middle, coarse. The second phase was the development of a fuzzy logic control logic that provides preventive/corrective actions in the downstream (i.e press) based on PSD predictions (first phase).

To do so, three distinctive (3) granulations in terms of PSD were manufactured within a Fluid Bed Granulator: GEA Niro MP-7. The three (3) granulations were separated into fine, medium and coarse granules size and used separately in the CM line to collect process data related, specifically, to the corresponding granulation PSD. The process data was used to develop process understanding based on the process variable behavior related to fine, middle and coarse granulation. CM line data was analyzed using a Principal Component Analysis approach and after analyzing the data outcome was corroborated with a control experiment: Chapter 4. Details from each of the executed experiments are presented below, separately.

Materials

A two (2) APIs formulation, as shown in Table 3.1, was used for the study activities. Both APIs (API-I and API-II) were used in its granulated form. Only one (1) granulation (API-I) was used to explore fine, medium and coarse particle interaction with the feeding and downstream control system variables. Table 3.2 shows the composition of the API-I granulation formulation manufactured within the GEA Niro MP-7.

Table 3.1: Formulation Raw Materials and Composition for two dosages

Raw Material	Type	Formula (%) 50/1000 mg	Formula (%) 150/1000 mg
API-I Granulation	API	6.78	18.40
API-II Granulation	API	68.81	62.27
Microcrystalline Cellulose (Avicel PH 101) NF, Ph. Eur	Filler	18.70	14.32
Preblend (Binary Mixture) *1. Croscarmellose Sodium (Ac-Di-Sol) NF, Ph. Eur.* *2. Microcrystalline Cellulose (Ceolus KG 802) NF, Ph. Eur*	Filler /Disintegrant	5.10	4.90
Magnesium Stearate, NF, Ph.Eur. Non-Bovine, HyQual 2257	Lubricant	0.60	0.60

Table 3.2: API-I granulation formulation and composition for Niro MP-7 FBG/D system

Raw Material	Type	Formula %
API-I	Active Pharmaceutical Ingredient (API)	51.00
Hypromellose USP, Ph. E38ur., JP	Binder	5.00
Croscarmellose Sodium (Ac-Di-Sol) NF, Ph. Eur.	Disintegrant	6.00
Microcrystalline Cellulose (Avicel PH 101) NF, Ph. Eur	Filler	38.00
Purified Water, USP, Ph. Eur.	Granulating solvent	n/a

<u>Granulation</u>

A GEA Niro MP-7 (Niro) FBG/D unit operation was used for the granulation process. Within the Niro FBG/D unit operation, the API-I was granulated at Janssen Supply Chain. The API-I granulations were characterized through a mesh analysis to visualize the particle size distribution (PSD). Three (3) different batches corresponding to fine, medium and coarse API-I granulations were obtained from the Niro FBG/D system. The mesh analysis outcome shows the difference between each API-I granulation through the API-I PSD and mass percentage cumulative (%) plots presented in Figure 3.1 and Figure 3.2, respectively.

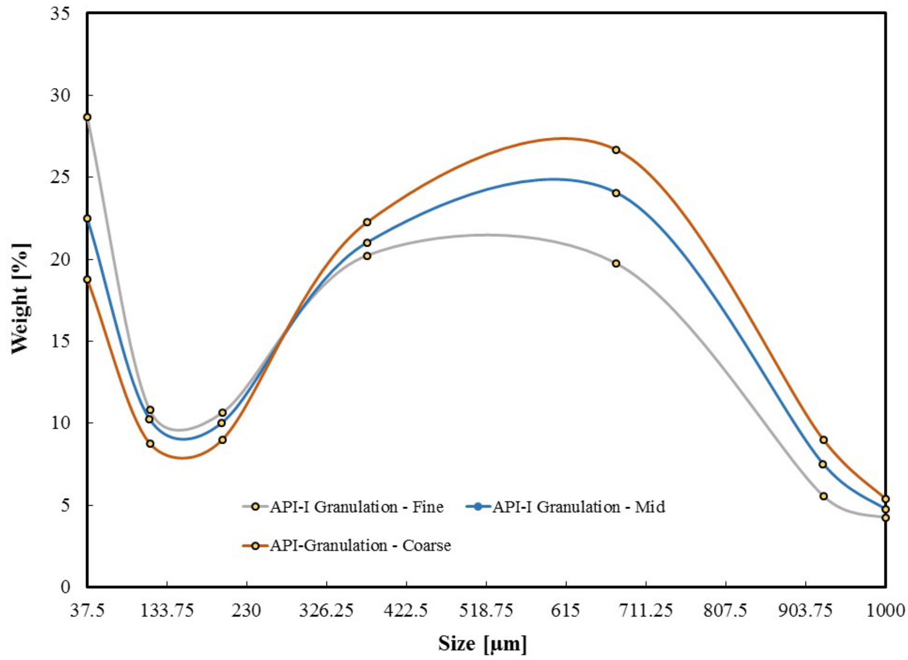

Figure 3.1: API-I Granulation PSD from Niro FBG/D unit operation

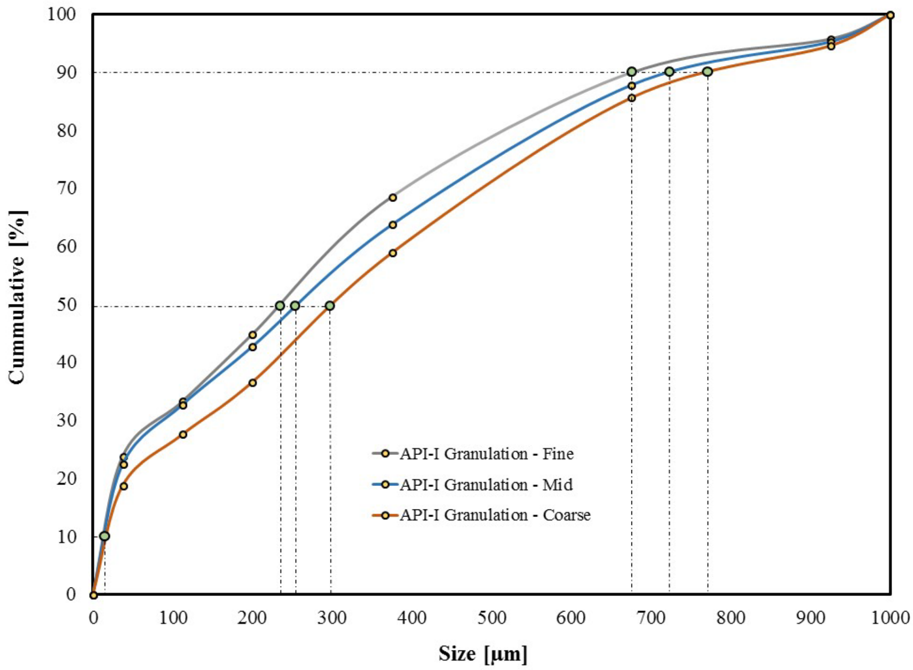

Figure 3.2: API-I Granulation Cumulative from Niro FBG/D unit operation

To quantify the difference between the three (3) API-I granulations the mean particle size (D50) and span ($\frac{D90-D10}{D50}$) of the corresponding size distribution were estimated from the cumulative plot (Figure 3.2). The mean particle size or D50 was obtained from the cumulative plot by estimating the particle size that represent the size distribution midpoint. Hence, D50 means that 50% of the total sample is smaller than its values. The same apply for the D10 and D90 where the 10% and 90% of the total sample is smaller than its value, respectively. The corresponding D10, D50, D90 and span for the three (3) API-I granulations are shown in Table 3.3. However, these are estimations since this approach assume all particles as spheres.

By this assumption, Table 3.3 shows that the three granulations differed from its mean particle size (D50) and also from the corresponding lower (D10) and upper (D90) size portion. Nevertheless, in terms of size span the three (3) granulation were similar which ensure that neither of them would have a higher variability than the other. Still, the three (3) granulation shows a high span (> 1.3) which could have led to segregation and affect variables reading and analysis. These granulations were used as part of the studies experiments to explore the interactions between the granules size and CM line control system variables.

Table 3.3: API-I granulation D50 from the three (3) API-I granulation manufactured within the Niro FBG/D unit operation

API-I Granulation Type	D10 (um)	D50 (um)	D90 (um)	Span
Fine	12	233	662	2.79
Middle (Target)	14	256	705	2.70
Coarse	16	300	746	2.43

<u>CM Line Operation</u>

All characterization and control experiments were executed in the same fashion within the CM line located at JSC. The only difference was the API-I granulation used for the characterization (fine, medium, coarse) and control (medium) experiments. JSC CM line is compose of a loading station, feeding system (Gravimetric/Volumetric), mixing stage, PAT (spectra gathering for formulation concentration prediction), compression stage and finally a coating stage. As previously mentioned, the loading and coating stage are out of the scope of this study.

A schematic representation of the CM line is shown in Figure 3.3. The CM line is composed of 4 gravimetric and volumetric feeder coupled to each other. These four (4) coupled feeders are located in the third floor. A fifth gravimetric feeder is located in the second floor. The API intermediates (API-I and API-II) and filler (MCC Avicel PH102) were sieved and pneumatically conveyed to the third level of the CM line. The lubricant (Magnesium Stearate) was manually sieved prior to loading to the volumetric feeder. Each raw material feed rate was controlled by a Loss-in-Weight (LIW) gravimetric feeder. Pre-blend was loaded to the gravimetric feeder and introduced directly to the continuous blender. Each feeder was controlled by its K-Tron Control Module (KCM). Table 3.4 and Table 3.5 shows manufacture, model, gear ratio and feeder ID, screw type and tuning method for the Volumetric and Gravimetric feeder respectively. Figure 3.4 shows the screw type configuration used for each Volumetric/Gravimetric Feeder.

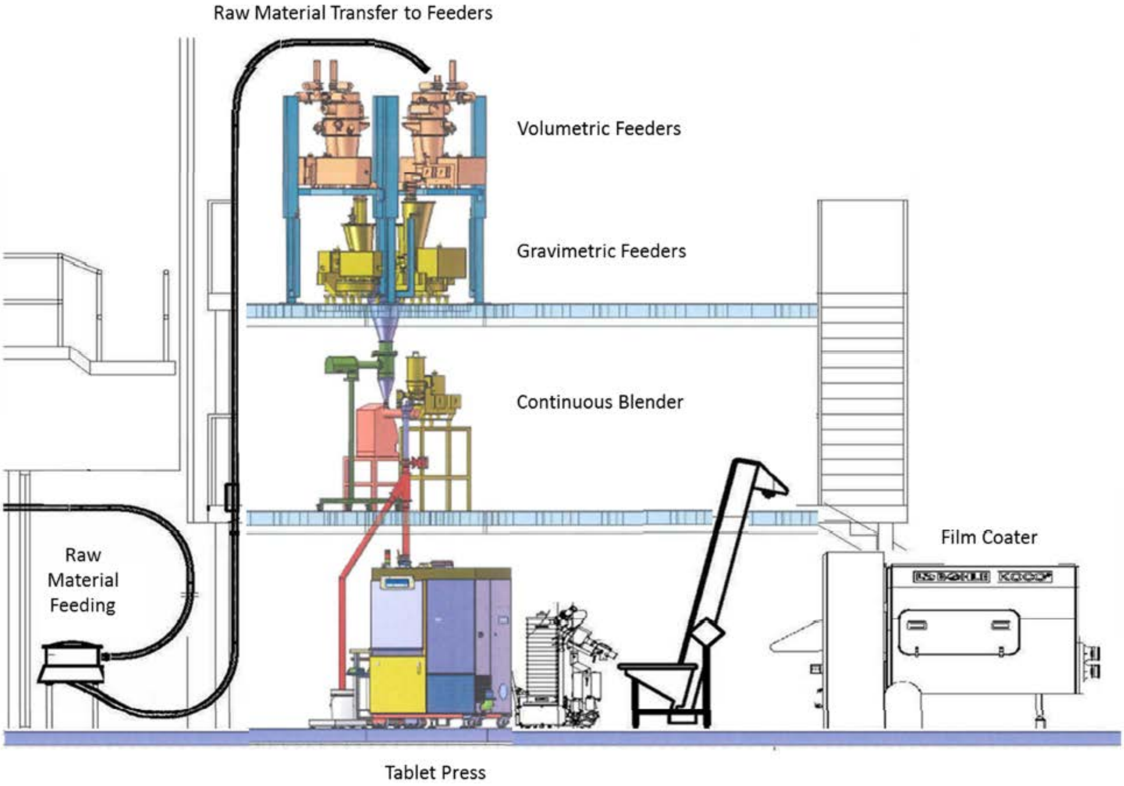

Figure 3.3: Schematic representation of the CM line

Table 3.4: K-Tron Volumetric Feeding System Description

Volumetric Feeder	
Equipment Model	K-PH-MV-KT35-P20 Vacuum Receiver
Manufacturer	K-Tron International, Inc.
Feeder ID	F6, F7, F8, F9
Gear Ratio	3:23:1
Screw Type	Fine Concave
Tuning Method	N/A

Table 3.5: K-Tron Gravimetric Feeding System Description

Gravimetric Feeder					
Feeder IDs	F1	F2	F3	F4	F5
Equipment Model	K-PH-ML-D5-KT20			K-PH-ML-D5-KT35	K-PH-ML-D5-KT20
Manufacturer	K-Tron International, Inc.				
Gear Ratio	5.6:1	13.0:1	5.6:1	15.6:1	12.95:1
Screw Type	Coarse Concave	Fine Concave	Fine Concave	Fine Concave	Fine Concave
Tuning Method	Aggressive	Aggressive	Aggressive	Aggressive	Aggressive

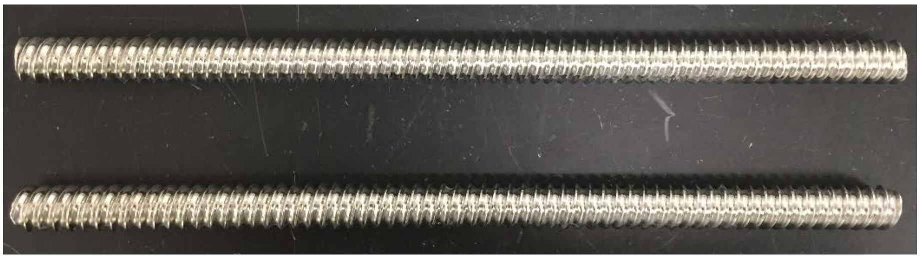

Figure 3.4: Fine Concave Screws

All Gravimetric Feeders were connected to the continuous blender. Hence, the raw materials (Table 3.1) dispensed from Gravimetric Feeders were blended using a convection type continuous blender, belonging to a class of powder blender commonly referred to as a tubular blender. The blender tube contains a motor driven bladed agitator which runs along the axial center line of the tube. The continuous blender consists of individual blades configured at 45° ± 5° angles from the center shaft.

Two (2) openings are positioned at either end of the blend tube, one for un-mixed raw materials to enter and another to allow the blended powder to exit. The entrance for the un-mixed raw materials was located on the top side of the tube to allow gravity feeding of the raw materials from the material feeders into the blender. The blender exit opening is designed to allow gravity feeding to a sensing interface. The blender exit opening was oriented at 45 degrees with respect to the blend tube. Blend NIR spectra acquisition, through the Bruker Matrix-FE FTIR PAT analyzer, were collected at the continuous blender exit to monitor formulation concentration. The formulation bed that pass through the sensing interface for spectra acquisition was controlled with a laser/rotary valve control loop to maintain a pre-stablished level that sustain that NIR sampling area always covered with formulation a constant linear velocity from the formulation bed, and a constant formulation bulk density.

The material from the sensing interface was fed by gravity to the next unit operation (i.e. compression). In this stage, the powder blend was compressed using a rotary tablet press (Table 3.6). Tablet NIR spectra acquisition, through the Bruker MPA PAT Analyzers, were collected at-line to monitor the formulation core tablet concentration.

Table 3.6: Tablet Press Description/Model

Process Stage	Equipment Description	Model
Compression	Korsch Tablet Press	XM-12

<u>CM Line - Characterization Experiments</u>

The three (3) API-I granulations from the GEA Niro MP-7 were used for the manufacturing of the API formulation of 50/1000 mg Fix Dose Combination (FDC) core tablets as part of the characterization study. Hence, three (3) separated formulations were compressed with different API-I granulation PSD: fine, medium and coarse. The raw materials used for formulation core tablets are shown in Table 3.1 Then, a control experiment was executed with an API-I granulation of an unknown PSD. This experiment was separated from the characterization studies performed with the three (3) different API-I granulation: fine, medium and coarse. The control experiment was used to determine when a API-I granulation from a different batch or drum reach the feeding system.

<u>Data Collection</u>

CM line elements as feeding, continuous blender, press and among others were connected to the Line Control and SCADA system (LC&S) to store all the available variables that are being monitored in real time. Data was retrieved from the system in a csv file after the execution of the characterization and control experiments. The main CM elements for data analysis were from the feeding system, rotary/laser control, NIR and press variables.

<u>CM Line Key Control Operations Available for Data Collection</u>

Rotary/Laser Control Loop

The rotary/laser controller purpose is focused on powder bed level control within the sensing interface. Spectra gathering within the sensing interface is dependent of powder linear velocity, density and/or PSD, beside API concentration. Hence, the rotary valve speed (rpm) will be monitoring powder bed level through a laser to speed-up or speed-down the rotary rpm. This ensure that the powder bed level is maintain within an acceptable range that was stablished for minimizing the noise in the spectra acquisition. Hence, the rotary rpm and powder bed level were important variables to be monitored for the study purpose.

Blend NIR spectra acquisition

A process analytical approach located after the continuous blender was stablished by monitoring blend homogeneity through the API-I granulation concentration. The API-I granulation concentration prediction was possible due to the development of a chemometric model. This chemometric models was developed specifically for the environment from where its data its gathered. Any difference in terms of equipment, position, formulation properties, environment conditions and among other variables could affect significantly the model prediction. Hence, variations in terms of particle size (D50) have an impact on the chemometric model due the scattering interaction that near infrared light will have with the formulation. The rationale is that PSD will change the powder bed density passing through the NIR sensing interface which will affect the powder bed void space and ultimately the light scattering. All this affects the model precision.

To account how well the model is predicting the formulation concentration, two (2) variables from the develop chemometric model were considered for this study: DModX and T2Range. The former one explains how far the observation is out-of-plane (design space) for the stablished concentration prediction model. Consequently, the latter one corresponds to a measure that quantify how far the observation is, within the design space, from the model space center. Basically, the DModX accounts for external source of variation not considered within the model development and T2Range goes for the source of variation considered within the model. Thus, by developing a concentration prediction model that did not account particle size but that was intrinsically within the granulation size distribution used either one or both T2Range and DModX variables can potentially observed difference between particles sizes.

Compression Manual Control from Operator Perspective

Tablet press adjustment are mainly based in the pre-compression, main compression force and dosing to achieve the In-Process Controls (IPCs): core tablets hardness, thickness and weight. These parameters were monitored for this study purpose.

Data Analysis

The PCA approach is a statistical method that facilitate the exploration of large data sets with the idea of reducing it to a small number of uncorrelated variables known as principal components (PC). These PCs are arranged in a descending order respect to the plane that capture the most variance from the data set projections down-to the plane that capture the least variance from the data set. The linear combination required to project the raw data to the PCs plane as scores are known eigenvectors. The eigenvectors magnitude also known as the eigenvalue represent the amount of variance characteristic to the corresponding PC. In other words, an Eigenvalue vs PCs plot shows how many PCs are contributing the most to the total variance.

Each PC will show the variables with the most covariance through the loadings. The loadings are normalized weight coefficients that represent the contribution of its variance to the PC eigenvalue. As a rule of thumb, high loading observations between variables within a PC means that the variables are correlated. By this mean, the PCA approach was used since it allows the analysis of multi-variate or multi-dimensional data set in an efficient manner without losing important information. This analysis was performed through the Minitab 17 statistical software.

Chapter 4

Results and Discussion

This section will provide the results and discussion of the executed Characterization studies. Within each characterization study section, the results and discussion of the control experiment will be also provided.

Characterization Study with API-I Granulation from GEA Niro MP-7

Characterization Experiments

After conducting the three (3) experiments with the fine, middle(target) and coarse granulation the feeding system data was collected to perform a Principal Component Analysis. Nevertheless, the data collection was required to be performed in a low noise environment to reduce feeding perturbation. To do so, all the possible noise related to external/internal perturbation was reduced by using the proper feeder configuration (i.e. twin screws selection, rpm, refill levels, tuning method) and set-up (proper isolation from vibration). With the feeders properly configured the three experiments were executed to collect the following feeders data: netweight (NW), motor speed (MS), mass flow (MF), drive command (DC) and average feed factor (AFF).

Once the data was collected, it was proceeded to eliminate all the outliers. As part of this study, an outlier was any data point observed out of its operational range. These operational ranges were stablished within the corresponding feeding optimization studies for each of the raw material.

With the data already cleaned it was searched for the time-frame where all the variables, to be analyzed in the PCA, were within the acceptance criteria. After gathering the data sets that were within the acceptance criteria and same time-frame the PCA was developed. Within this MVA, the PCA approach provides three important variables that ease data interpretation: eigenvalues, loading and scores.

The former one, eigenvalues, are the eigenvector magnitude. Thus, the eigenvector magnitude or eigenvalue means the amount of variation observed in the corresponding principal component, whereas the eigenvector is the linear transformations of a data set from a reference frame to the PC plane. Therefore, by plotting the five PCs with its corresponding eigenvalues, it can be observed in Figure 4.1 that the first PC contains three times more variation that the next two PCs (2^{nd} and 3^{rd} PC). In the case of the last two PCs (4^{th} and 5^{th}) its eigenvalues or amount of variation were determined small enough to not be considered for this analysis.

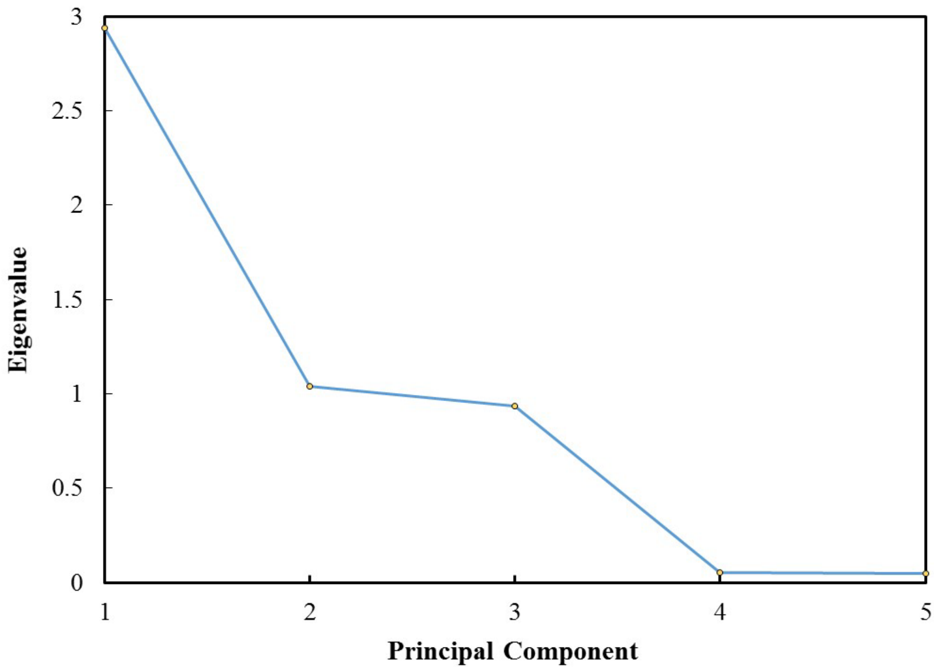

Figure 4.1: Eigenvalue Plot from the principal components obtained through the PCA approach.

Since the analysis was shifted to the first three PCs only, the loadings were used to explore the interaction that the PCA approach was able to determine for each of the corresponding PCs. This can be observed by comparing the variables loading values within each PC. As two or more different variables have a similar loading value, more directly is the interaction between those variables. From Table 4.1 it can be observe that the 1st PC shows, in bold, the motor speed, drive command and average feed factor loading values which have similar values in terms of magnitude. However, its sign differs. This mean that the AFF is inversely proportional to the motor speed or drive command or vice versa. It also shows that the motor speed and drive command are directly proportional.

Table 4.1: Correlation between feeding control system variables per principal component

Variables	Loading PC 1	Loading PC 2	Loading PC 3	Loading PC 4	Loading PC 5
Netweight	0.019051	**-0.799411**	**0.599598**	-0.011926	0.030333
Motor Speed	**-0.571788**	0.042739	0.062464	**-0.813960**	-0.069270
Mass Flow	0.120101	**0.597470**	**0.792807**	0.007669	0.002061
Drive Command	**-0.574054**	0.045019	0.047764	**0.346396**	**0.739029**
Avg. Feed Factor	**0.573353**	-0.010894	-0.075878	**-0.466130**	**0.669413**

From the 2nd and 3rd PC, the observed relation was regarding the feeder mass flow and netweight. This is a phenomenon widely seen in the feeding performance since the following scenarios:

1. Bulk density profile from the top to the bottom of the feeder hopper which influence the AFF and hence the mass flow variability due motor speed adjustment.
2. Total weight as the netweight decrease influence in the AFF which affects the mass flow variability due motor speed adjustment.

The motor speed adjustment as the mass flow variability can goes either direction which explain the observation of two PCs (2nd and 3rd) with the same interactions but with different sign convention. Adding that both PCs (2nd and 3rd) are mostly the same, from the two major loadings values (netweight and mas flow), then the analysis was shrunk only to the first two PCs. As a remark, the 4th and 5th PCs were not considered for the analysis as being not statistically significant. However, from the loading perspective both PCs shows the same findings that were observed in the 1st PC. Hence, the analysis from this point forward was focused only in the 1st and 2nd PC.

Refer to Figure 4.2 for a visual representation of the loading values corresponding to the first two PCs. Figure 4-2 shows the loading plots from the 1st and 2nd PCs. This plot shows a high correlation in the 1st PC between the AFF and the MS/DC, which comes from the nature of the feeding control loop. It also shows a correlation between the MF and the NW in the 2nd PC in a significant less degree (1/3 of PC1).

To determine if either, both or neither of the two (2) PCs can distinguish the different Canagliflozin granulations (fine, middle and coarse) used within the characterization studies a score plot was used. Figure 4.4 shows a score plot were three distinctive group related to fine, middle (target) and coarse Canagliflozin granulation are observed. The PCA approach could distinguish the correlation between the 5 feeder variables and divide them by fine, middle and coarse. mainly with the 1st PC: AFF, DC and MS. The 2nd PC has little effect on sub-grouping the data and was focused mainly to the middle Canagliflozin granulation. This could have been related to an external interaction out-of-scope of this study. Hence, the PCA shows clearly from the 1st PC that the main factors that can determine a PSD change from the Canagliflozin granulation are the motor speed, average feed factor and drive command.

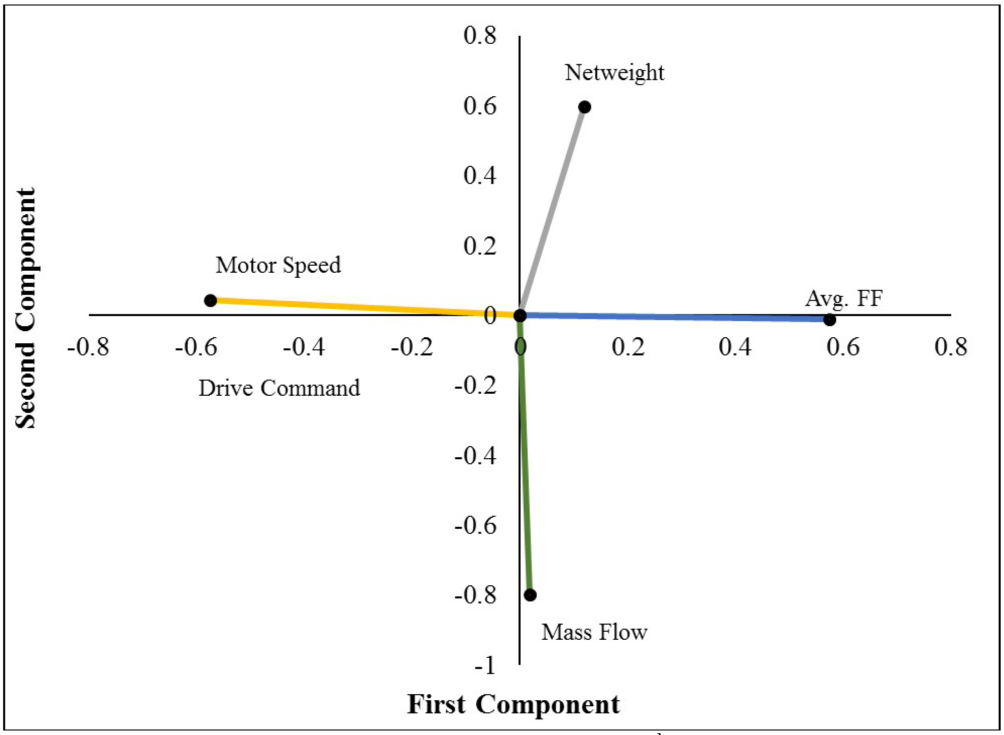

Figure 4.2: Loading Plot from the 1st and 2nd Principal Component

The PCA approach provide the understanding that the combination of motor speed, drive command and average feed factor provide enough information to distinguish between different Canagliflozin granulation. However, is known from the feeding control loop algorithm and from the loading plot (Figure 4.2) that the drive command and motor speed are directly correlated which could lead to reduce the number of variables needed to predict Canagliflozin granulation PSD. To do so, a score plot was performed for all the combination possible from these three (3) variables. The amount of combination needed from the three (3) variables was also three (3). Table 4.2 shows the three (3) combinations and Figure 4.4 through Figure 4.6 shows the three score plots developed, per combination.

From Figure 4.4 through Figure 4.6 it can be observed that, effectively, only the Drive Command or Motor Speed was only required in combination with the AFF. In addition, it shows that the best combination to determine Canagliflozin granulation PSD was the AFF with the DC. This was slightly better than the AFF-MS combination due the normal spread profile observed from the scores.

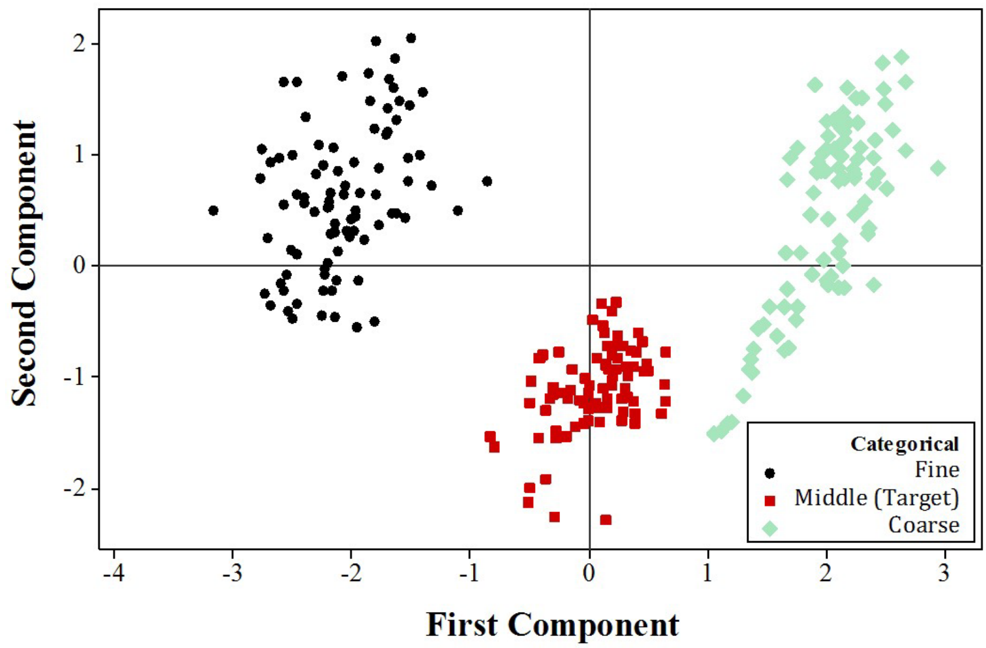

Figure 4.3: Score Plot from Drive Command (DC), Motor Speed (MS) and Average Feed Factor (AFF)

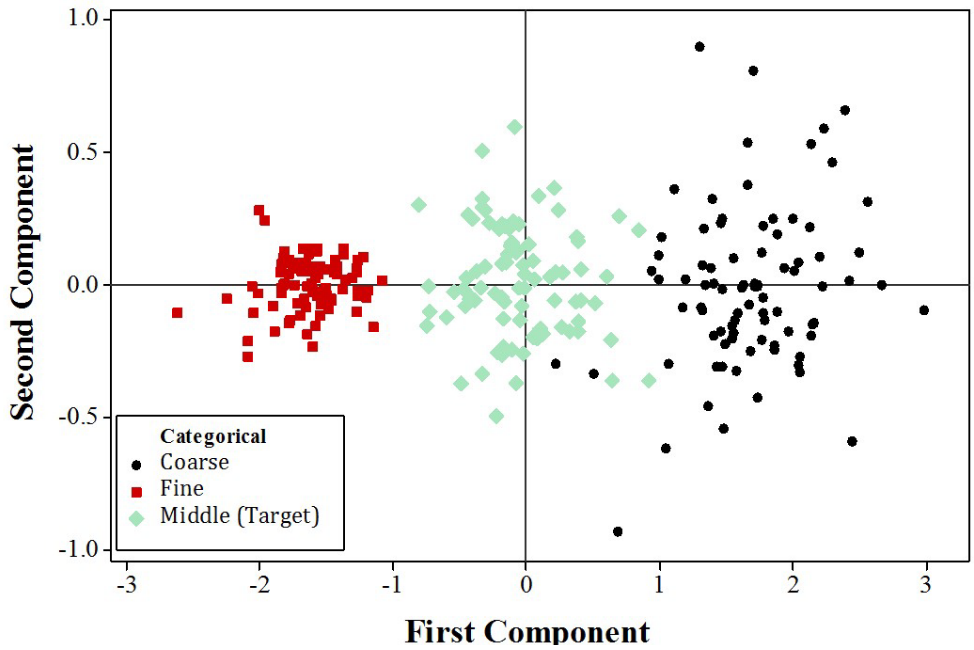

Figure 4.4: Score Plot from the Drive Command (DC) and Motor Speed (MS)

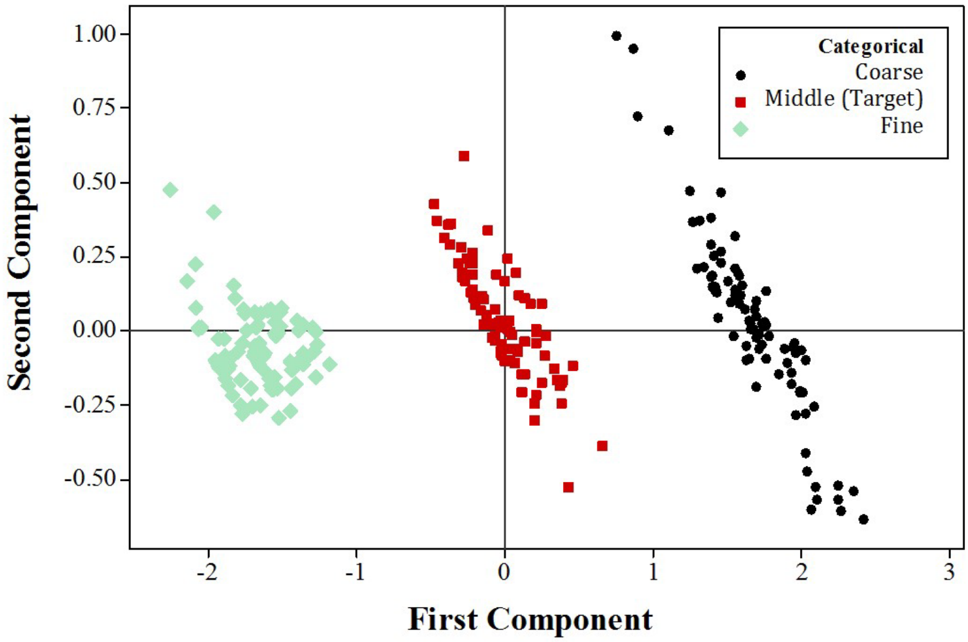

Figure 4.5: Score Plot from the Average Feed Factor (AFF) and Motor Speed (MS)

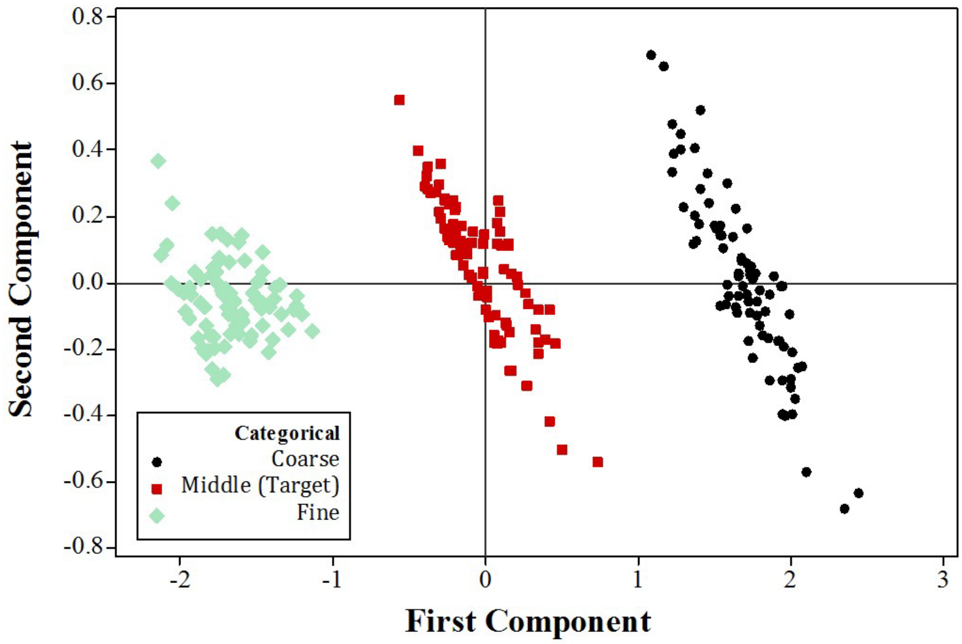

Figure 4.6: Score Plot from the Average Feed Factor (AFF) and Drive Command (DC)

Even so the AFF-DC Score Plot shows the best combination to distinguish the three (3) API-I granulation, a AFF vs PSD linear regression shows to be enough to have a high R-Sq (96.83%) for the challenged D50 range. Figure 4.7 shows the AFF vs PSD linear regression and its inverse relationship. Thus, this goes accordingly to the feeder capacity of dispensing a higher mass flow as the PSD decrease. The AFF vs PSD plot (Figure 4.7) also shows the AFF standard deviation within each experiment and it was notice that the high span ($\frac{D90-D10}{D50}$) observed from the three API-I granulations did not affect significantly the AFF variability. Hence, this mean that the material was not being segregated at a large or significant proportion through the feeding system. Small segregation could always occur with this large span (~2.5) however, the feeder control system is always averaging and eliminating high frequency noise in time which dampened the AFF value and center it to the mean API-I granulation particle size or D50. This is only true as long as the feeding factors contributors to data reliability (Figure 2.4) remain within its acceptance criteria or verified.

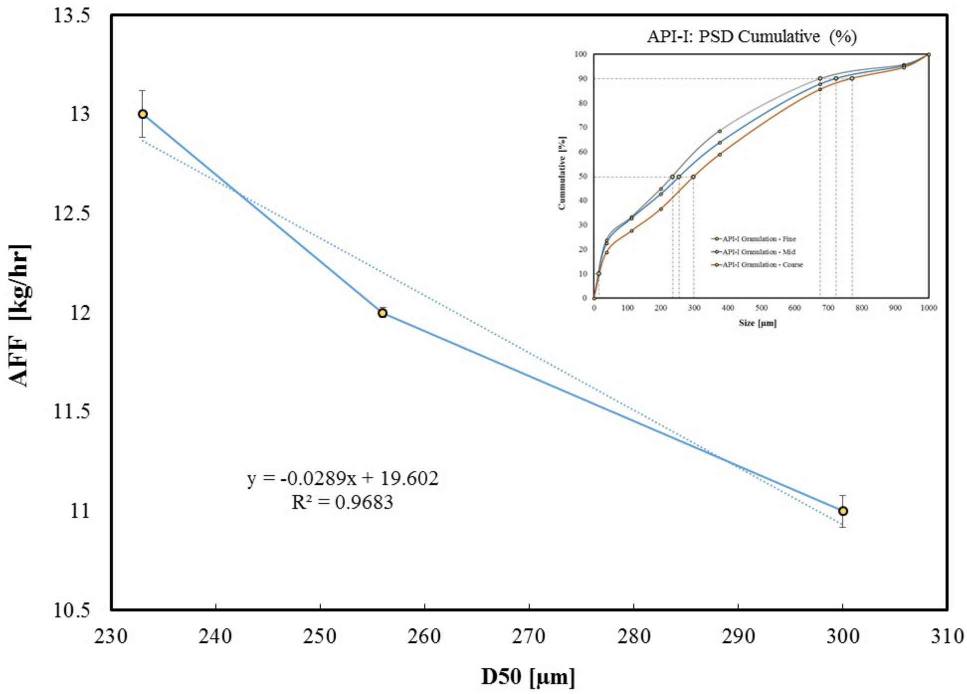

Figure 4.7: Linear Regression - Average Feed Factor vs API granulation PSD

Thus, as feeder performance remains within the stablished criteria presented in Figure 2.4 the inverse relationship observed in Figure 4.7 can be explain through two scenarios. One is that particles above 150um does not get affected by interparticle forces. Knowing that the fine API-I granulation used was approximately two times greater (371um) than the threshold

(150um) AFF can be then related inversely to PSD due powder bulk density. Therefore, screw volume capacity will be maximized as the powder bulk density increase or PSD decrease.

The second possible explanation to this relationship is the swirl dynamics of the GEA Niro MP-7 FBG/D. Others FBG/D has a distinction from the GEA Niro FBG/D in terms of the fluid dynamics. GEA FBG/D fluidize the powder bed through tangential fluidization (swirl, toroid or spiral shape) vs the vertical fluidization found in others FBG/D unit operation. Hence, powder attrition and plastic deformation is prone to be happening in a higher extension in the GEA FBG/D than in vertical fluidization FBG/D systems.

Since the FBG/D swirl effect take place in the bottom part of the granulator [36, 37] the coarser particles are prone to reside for longer period at a lower level due momentum forces. Hence, the bigger/coarse particles will be susceptible to higher shear forces since at the lower level the swirl effect will induce a direct contact with the FBG/D wall for longer period compared to the fine particles. Thus, coarse particles due particle deformation and/or attrition with the FBG/D wall are prone to be less spherical. Consequently, coarser particles will have lower flowability properties which translate in a lower feeder dispensing capacity or lower AFF. There is an extensive scientific base of research articles explaining the effect of FBG/D system on particle attrition/breakage [38] or from the rheology perspective the effect of shear stress on particles attrition and plastic deformation [38]. Also, research articles related to particle shape and its effects on flowability properties has been highly discussed within the science community [39].

With the feeding data analyzed, the study focused was shifted to the rotary/laser control and NIR PAT located in the 2nd floor of the CM line. The idea to explore downstream variables is to confirm any observation regarding PSD changes from the feeding stage. Since the AFF is a response variable that truly account for the material located within the feeder, no guaranteed will be possible to determine its impact on the total blend formulation once its mixed in the next stage (CM line 2nd floor). The blending stage serve as a damping stage for material properties changes. This phenomenon is even accentuated if the material of interest represents a low weight by weight fraction (w/w %)of the total formulation. Thus, the information from the rotary valve speed (rpm), laser level and/or NIR could lead to a robust decision tree algorithm since enable data corroboration through the downstream process.

As mentioned in Chapter 3 the laser level and rotary valve speed (rpm) are used to control the powder bed level and linear velocity through the PAT or sensing interface where the NIR is located for spectra acquisition. The trio of elements are particle size dependent.

However, it depends on the degree of the PSD changes at the feeding stage and the material w/w% in the overall formulation. From the laser/rotary control operation two (2) variables were considered to explore its interactions with the three (3) levels (coarse, medium and fine) of API-I granulation: rotary valve speed (rpm) and powder bed level (%) through the laser sensor. In the case of the NIR, the following variables were used as part of the study activities for data analysis: API-I granulation concentration, DModX and T2Range.

Hence, a PCA approach was performed with the rotary valve speed [RPM], laser level (%), API-I concentration, DModX and T2Range. Figure 4.8 shows the eigenvalues corresponding to each principal component. The eigenvalues show that the overall variability is within the 1st PC. From the loadings perspective (Table 4.2 and/or Figure 4.9) it was noticed that the variance in the 1st PC is dominated by the API-I concentration. Even so, this variation is not related to the API-I granulation D50 when the 1st PC and 2nd PC scores are plotted (Figure 4.10). The most probable root cause for the observed variance within the 1st PC is the mixing stage due the low API-I granulation w/w%: 6.78%. It is well known that concentration variation increases as its w/w% decrease.

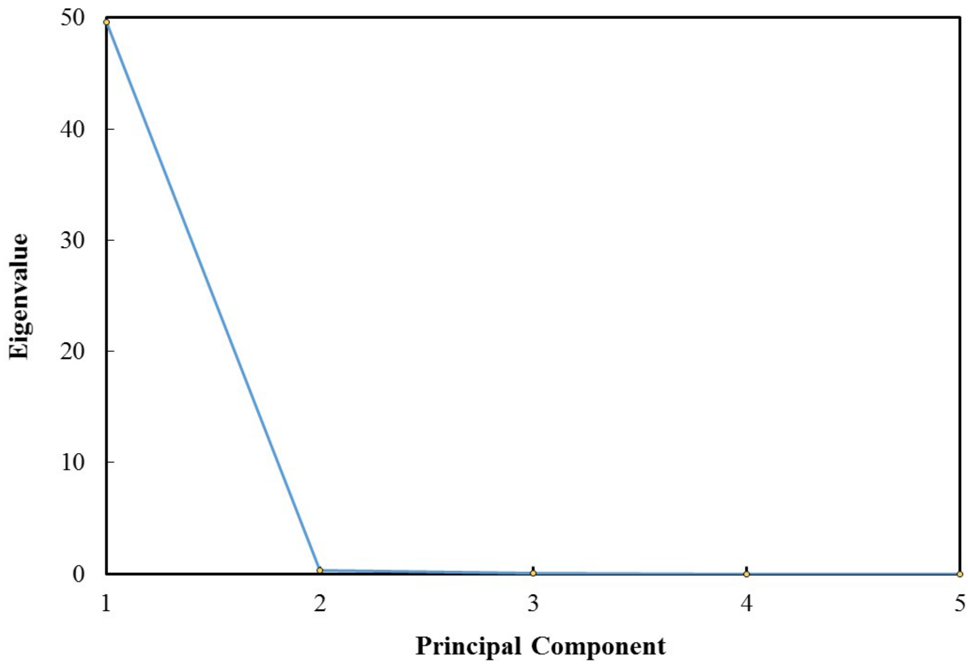

Figure 4.8: Eigenvalues Plot from the Principal Components Obtained Through the PCA Approach

Table 4.2: Correlation between downstream process variables per Principal Component

Variable	Loading PC1	Loading PC2	Loading PC3	Loading PC4	Loading PC5
T2Range	0.018	-0.037	-0.067	**-0.997**	0.000
DModX	0.000	0.000	0.000	0.000	**-1.000**
API-I concentration	**1.000**	0.002	0.010	0.017	0.000
Rotary valve speed	0.001	**-0.999**	-0.036	0.040	0.000
Laser level	-0.009	-0.039	**0.997**	-0.066	0.000

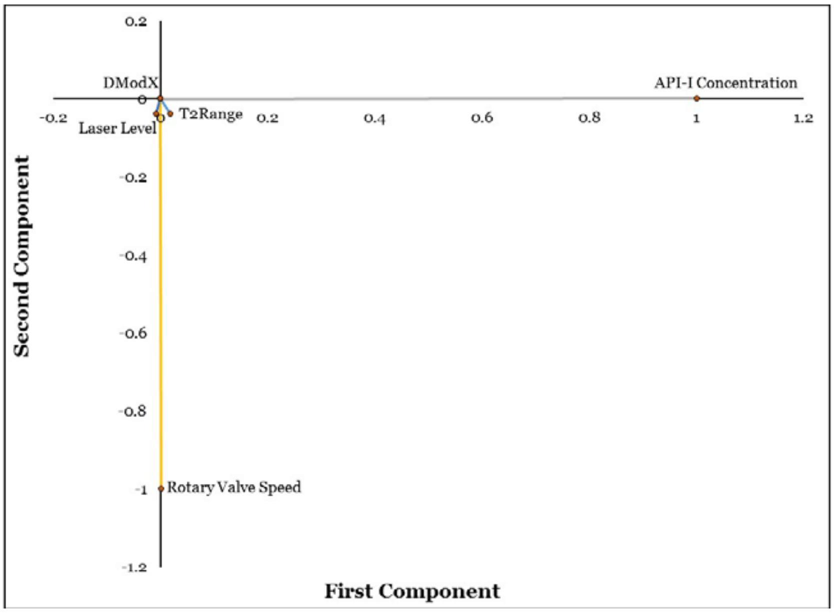

Figure 4.9: Loading Plot from the 1st and 2nd Principal Component

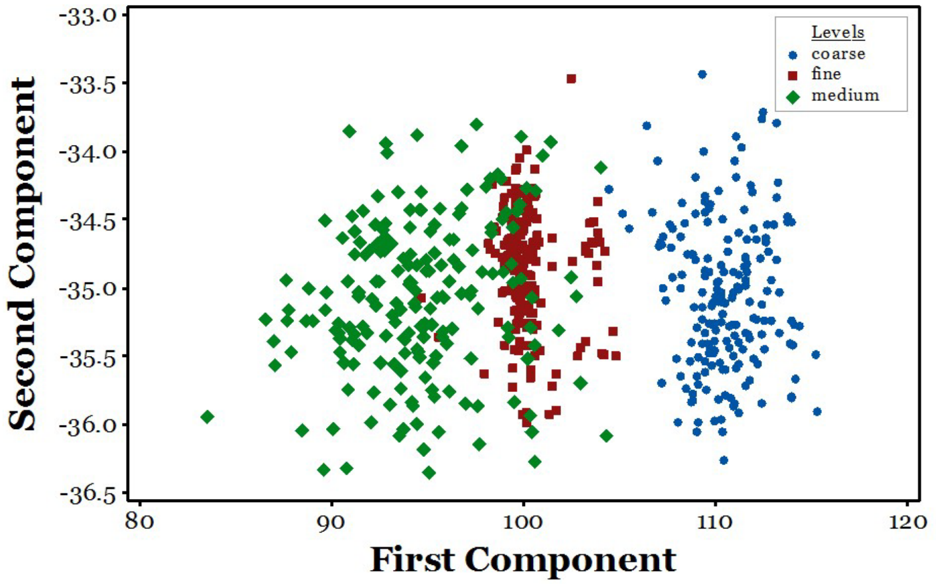

Figure 4.10: Score plot of the Rotary Valve Speed [rpm] and Laser level [%], API-I Concentration, DModX and T2Range

Hence, the data analysis was decided to be focused individually respect to the three API-I granulations: coarse, medium and fine. The approach was performed through a box plot. This allowed to determine if there a direct interaction between any of the variable. Figure 4.11 shows the box plot developed for each of the five (5) variables. The individual box plots show that only the T2Range was able to have a direct relation with the three (3) API-I granulation. It is observed that as the API-I granulation size decrease the model variability due external noise (T2Range) decrease. This could be explained by the following two possible scenarios:

1. Bulk density dependency from PSD. The particle size distribution decrease as the bulk density increase. This is true from the assumption that the three (3) granulations are large enough (>150um) to surpass interparticle forces. Thus, by less void space available, less NIR light scattering will be lost loss through the sensing interface.
2. Light scattering dependency on particle size.

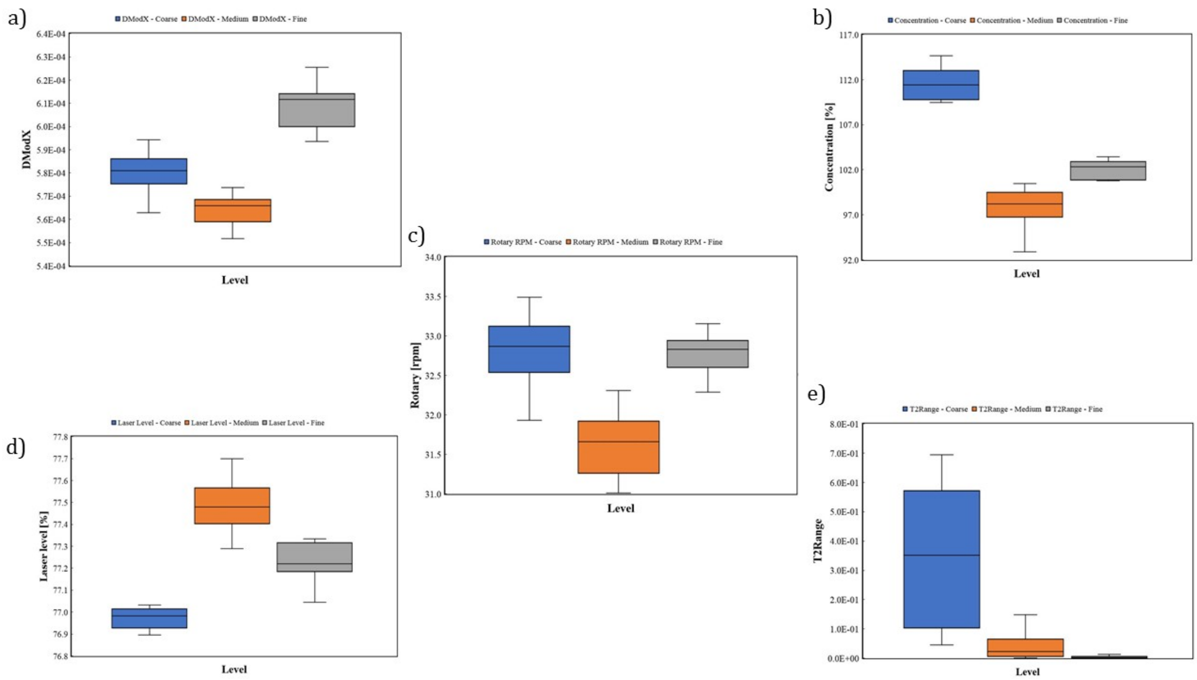

Figure 4.11: Box plot of a) DModX b) API-I Concentration c) Rotary RPM d) Laser Level and e) T2Range vs the Three (3) API-I Granulation: Coarse, Medium and Fine

The T2Range was able to distinguish the coarser API-I granulation from the fine granulation. However, the medium API-I granulation merge slightly with the coarse and fine API-I granulation from T2Range perspective. Another observation from the T2Range was that its variability decreased in function of API-I D50. As API-I granulation D50 decrease, the T2Range variation also decrease. This can be related to two phenomena:

1. Void space variation will increase as bulk density decrease, affecting NIR diffuse reflectance path length and hence the chemometric model prediction.
2. Larger particle due the FBG/D swirl effect could be tending to have non-spherical shapes compare to the smaller (fine) particles since are more susceptible to be in contact with the FBG/D wall: shear forces.

Since the API-I granulation ratio within the formulation is low it was known beforehand that a change in PSD will be dampened with the other materials once reached the mixing stage. Thus, being able to distinguish the fine vs coarse API-I granulation with the T2Range allows the development of a robust decision tree algorithm. The T2Range provide a valuable information since allows the confirmation of any observation in the feeding stage before alerting the operator for any require action.

Having these two monitoring soft sensors, one at the feeding stage and the second at the sensing interface for confirmation purposes, the analysis was then shifted to the tablet press. The idea was to explore any interaction between the API-I granulation D50, T2Range and/or AFF with tablet press main compression force that enable the development of a decision tree algorithm to improve the CM line control capabilities. The rationale behind this is that the API-I granulation D50 will have an effect in the formulation bulk density reaching the press die. As the formulation entering the tablet press die becomes denser a higher compression force will be required. This is because an increment in surface area as the bulk density increase, which enable a faster force dissipation due an increment in the number of contacts points.

By analyzing the main compression force it was observed that was able to distinguish a change from coarse to fine API-I granulation or vice-versa. The medium API-I granulation D50 was basically merging with both upper (coarse) and lower (fine) limits. Nevertheless, a change from coarse to fine granulation provide a high resolution in terms of monitoring without compromising product quality. This can be observed from Figure 4.12 where the API-I granulation transition from coarse to fine influenced the main compression force.

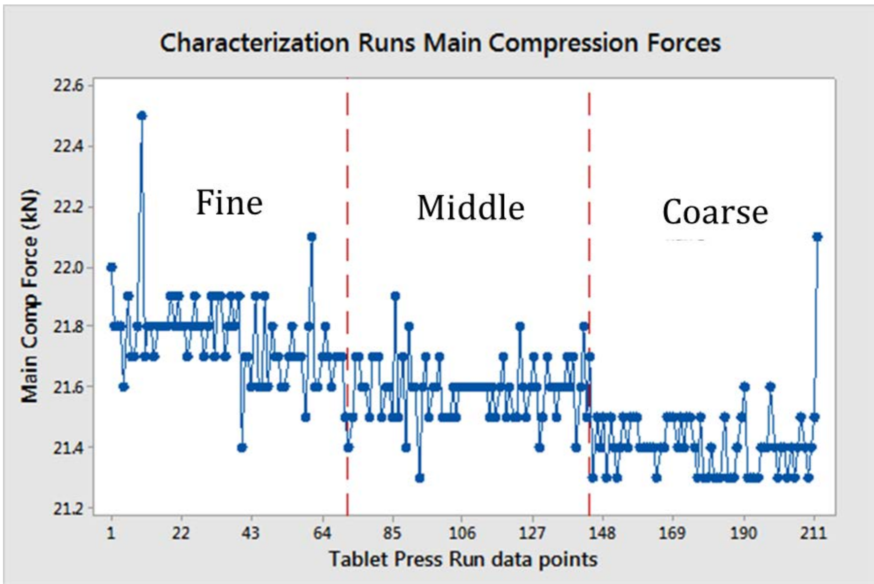

Figure 4.12: Main Compression (factor) Force from the Korsch Tablet Press

Hence, it confirms that for the decision tree design is not a requirement to distinguish a change in D50 below or above 70 microns. The 70-um magnitude comes from the approximate difference between the coarse and fine API-I granulation D50 shown in Table 3.3. This means that from the feeding stage perspective, the AFF should change above 1.8 [kg/hr] to have an impact in the tablet press main compression. From the sensing interface, the T2Range variation will be required to be shifting from around 1 order of magnitude: from 0.1 down to 0.01.

Nevertheless, these thresholds must be considered material dependent and not use for any material. Full characterization will be required to stablish the AFF and T2Range threshold for every material require to be monitored and also for a PSD range above or below the studied within these experiments. Still, for the specified formulation characterized within this study the data shows that the design of a robust decision tree is possible, and its development is presented in Chapter 5.

Control Experiment

The feeding information regarding the PCA was later used to detect PSD changes within the two (2) control experiment. These two (2) control experiment were performed independently from the characterization study. In both control experiments, the CM line was operated at target condition from the operation parameters and material standpoint. The control experiment was performed with two different formulation dosages: 50/1000 mg and 150/1000 mg. Since a change in dosage from 50/1000 mg to 150/1000 incur in an increment on the concentration of API-I granulation (refer to Table 3.1) it incurs an increment in the feed rate of approximately 2.7x. The rationale behind this was to observe if it was possible to distinguish a change of API-I granulation batch, by monitoring the AFF, at different feeder mass flow: 3.051 and 8.280 [kg/hr]. Refer to Table 4.2 for the following information.

To determine approximately how much time the API-I granulation would have reside within the CM line from its pneumatic transfer, at the drum location, up-to the gravimetric feeder screw housing the total residence time was calculated. However, is important to mention that the residence time accounted to the pneumatic transfer from the drums up-to the volumetric feeder was considered negligible since its duration is below 10 seconds. The total residence time was determined from the theoretical time it should have travel the API-I granulation at a constant linear velocity and uniform gravity-driven flow behavior through the volumetric and gravimetric hopper geometry.

By these assumptions and the known mass capacity of API-I granulation within the Gravimetric/Volumetric feeder (5.8 kg each) the residence time was calculated and shown in Table 4.3 for both dosage. This residence time represent the time it would have travel the API-I granulation from the top of the gravimetric or volumetric hopper to the screw housing inlet. Since both the Volumetric and Gravimetric have the same mass capacity, the total residence time represent twice of the calculated residence time. However, residence time and total residence time of the API-I granulation or any other material will be less than the theoretical value since each gravimetric and volumetric hopper have a rotating baffle within its geometry that promotes the material from one point in the hopper to be transfer right next to the bottom of the screw housing inlet. Thus, the residence time could be approximately reduced to halve since the baffle extent to halve of the API-I granulation volume capacity within the feeder.

Table 4.3: API-I granulation feed rate and residence time within the Gravimetric and Volumetric Feeders.

Formulation Dosage	API-I granulation Feed Rate [kg/hr]	Gravimetric/Vol. Feeder capacity [kg]	Residence time within the Gravimetric or Vol. Feeder	Total Residence Time within the Feeding Stage
50/1000 mg	3.051	5.8	1 hr 54 min	3 hr 48 min
150/1000 mg	8.280	5.8	42 min	1 hr 24 min

Hence, from the control experiment executed at a 50/1000 mg dosage the change of API-I granulation batch was effective approximately at 5:50 pm (Figure 4.12). Due the residence time of the material within the CM lines and volumetric/gravimetric feeder, the second batch of API-I granulation could have taken around 1hr 54min to reach the gravimetric feeder screw housing. Once it reached the gravimetric feeder, the API-I granulation from one batch started to mix with the previous batch of API-I granulation due the rotating baffle located in the gravimetric feeder bowl. From Figure 4.13 can be observe that this possible transition from API-I Batch 1 to API-I Batch 2 could have been happening around 7:41pm until 9:30pm (green shaded zone) when a drastic change in AFF was observed. After the green shaded zone (orange shaded zone) is assumed that from a proportional perspective the API-I granulation form the second batch should be dominating the flow behavior and PSD properties of the bulk material. As a remark, the blue shaded zone just represents a potential AFF false positive due the low feeder netweight registered.

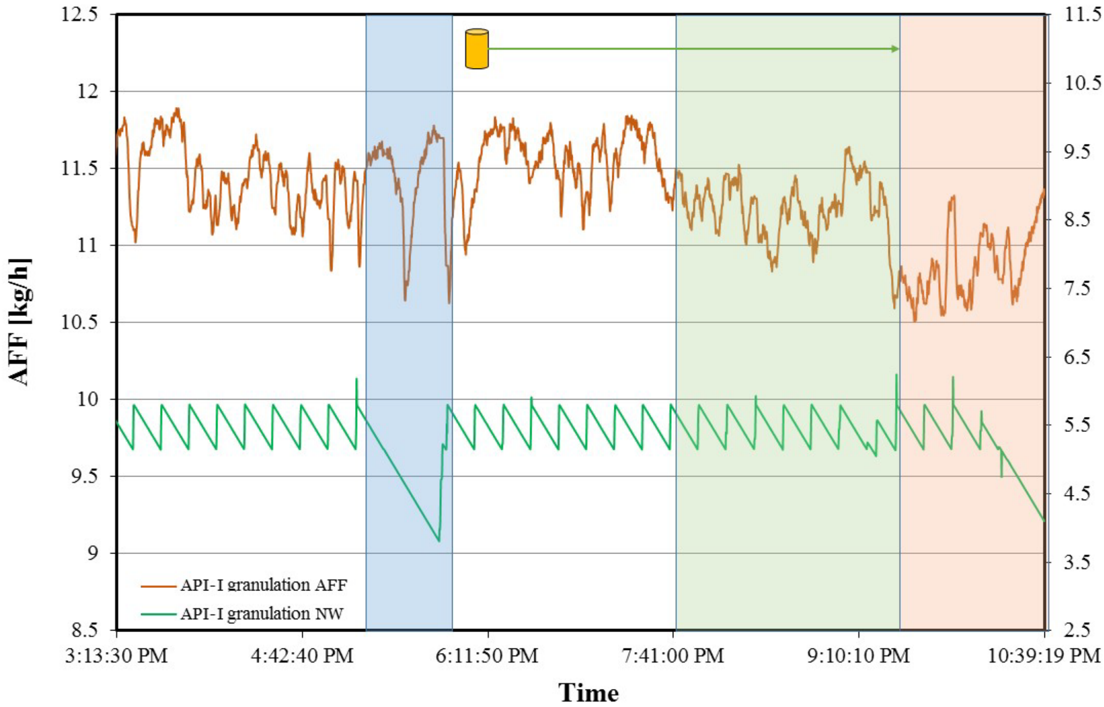

Figure 4.13: Control Experiment Trend Base on API-I Granulation Feeder Netweight [kg] and Average Feed Factor [kg/h] for the 50/1000 mg FDC

From Figure 4.14, the same can be observed when the second API-I granulation batch/drum is placed in the loading station for its pneumatic transfer approximately at 12:15pm. In this case since the 150/1000 mg dosage require a higher feed rate from the API-I granulation feeder the residence time is approximately 42 minutes. Thus, the API-I granulation was supposed to reach the feeder screw housing around 1:00pm as is observed in Figure 4.14. Complete transition from one batch to the other should have occur after the total residence time which is also observed at 1:53pm between the green and orange shaded zone. This transition accounts for the 1 hr 24 min total residence time from the time the drum was changed at 12:15pm. As previously mentioned, the blue shaded zone was highlighted to shows potential AFF false positive regarding the API-I granulation netweight.

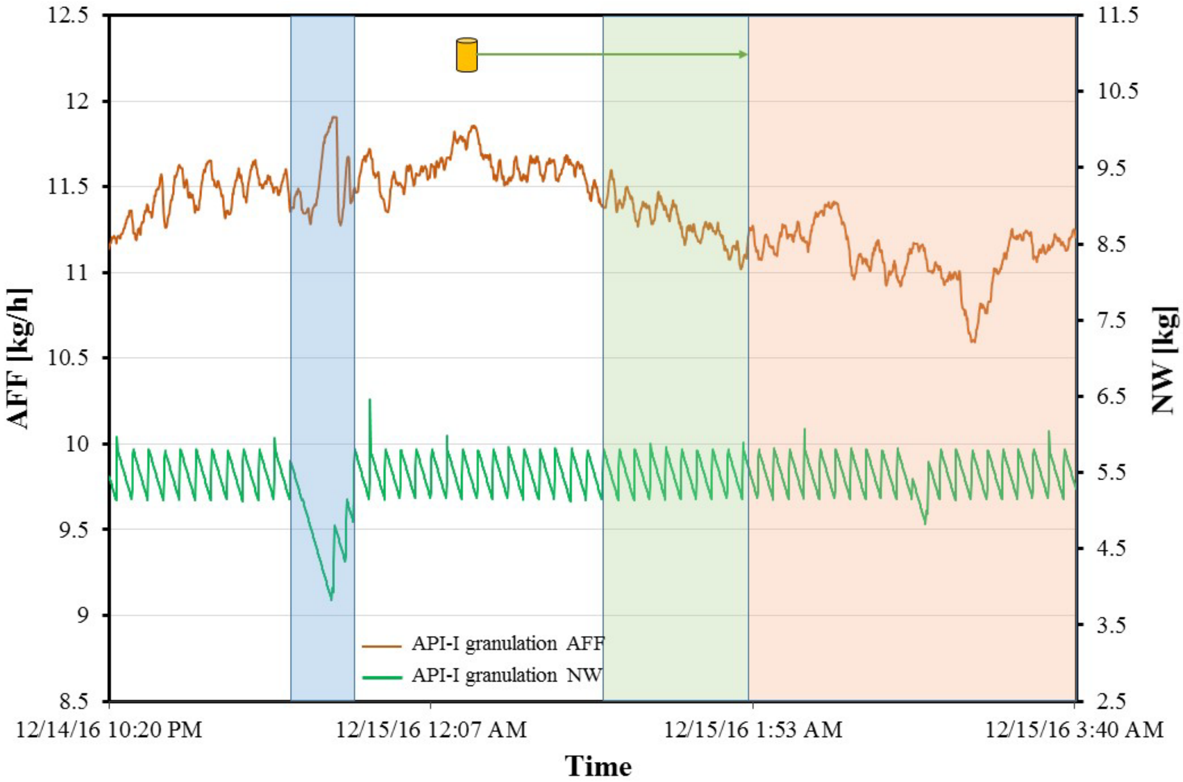

Figure 4.14: Control Experiment Trend Base on API-I Granulation Feeder Netweight [kg] and Average Feed Factor [kg/h] for the API-I 150/1000 mg FDC

Chapter 5

Decision Tree Algorithm Proposal for CM line

This chapter will discuss the decision tree strategy for the CM line. The decision tree algorithm will be divided in two (2) parts:

1. Start-up – decision tree strategy to stablish feeder and rotary/laser minimum requirements and/or performance prior proceed to monitor AFF and rotary rpm, respectively.
2. Steady State (Post Start-up) – decision tree strategy for downstream preventive actions based on the feeders and NIR PAT T2Range monitoring.

In essence, the decision tree strategy in terms of PSD prediction and preventive control is the latter (Post Start-up). However, an additional decision tree for pre-requirements purposes, was developed. Each part will be discussed separately in the following sections. Figure 5.1 shows a representation on how the decision tree has been divided.

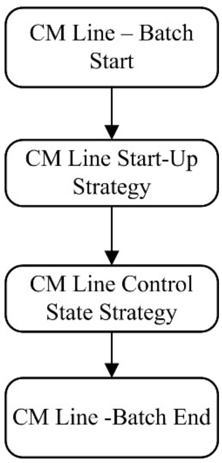

Figure 5.1: Overall Decision Tree Strategy for the CM Line

5.1 Start-up

The Start-up decision strategy is based on Figure 2.4 requirements to minimize false positive that could lead to wrong interpretation from the AFF readings. To minimize false positive or noise from the data to be used to predict PSD changes four critical aspect of the feeder were analyzed: material properties, PMs, Perturbation and material parameters. As part of the Start-up process strategy, the material physical properties should be part of the information provided to the operator before starting the line.

From the characterization studies it was observed the difference in AFF related to particle size, particle shape and distribution. For many of the granulation process PSD is not a requirement, however, moving forward to enhance CM line control strategy is highly beneficial. In terms of particle shape properties will not be a requirement since the data shows that particle overall shape maintain the same if the same FBG/D system and operating conditions remains the same. However, in the case a different FBG/D is planned for scale-up or scale-down purposes material characterization within the feeder must be required.

Having material characterization or physical properties within a management system as the Laboratory Information Management System (LIMS) will be beneficial for the operator and to the CM line yield for sure. Knowing in advance the PSD characteristics as D10, D50, D90 will allow the operator to foresee possible challenges in advance. Thus, operator actions during the manufacturing process will be more science guided than by intuition. In addition, coupling the LIMS with the Manufacturing Execution System (MES) and Enterprise Data Warehouse (EDW) for post data analysis and/or business metric purposes allow deeper exploration of CM Line elements with other elements and materials properties. Figure 5.2 shows a schematic representation of the system integration.

Still, in the same context of physical properties the CM line room temperature and humidity are important factors on powder flowability which is correlated to feeder AFF. It effect can be known through a rheology analysis (ex. FT-4) but the impact is minimal since JSC manufacturing temperature and humidity are in constant monitoring. Any excursion will trigger an investigation and all material identified with potential impact on the temperature and/or humidity excursion will proceed to re-testing.

Having cover the material properties perspective, feeder perturbation aspect should be address next. Feeder perturbation has the worst effect in the feeding performance since it can lead the operator to wrong decision making due false positive data displayed in the SCADA or HMI system. To minimize the aforementioned, feeders PMs due date must be verified with the remaining CM elements. As shown in Figure 2.4, the PMs are one of the four critical aspect to be monitored from a feeder performance perspective. Any calibration or part maintenance must be performed before loading the materials. This ensure that no external noise will be affecting the AFF. The same goes for the rotary and laser elements that are essentials for the NIR spectra acquisition.

Another noise source that can be minimize or eliminated is from the Volumetric/Gravimetric feeder assembly connection. The usual practice during the assembly of the feeders is by visual inspection where the operator determines if the Volumetric feeder exit cone connection does not get in contact with the Gravimetric feeder lid neck. However, the current connection configuration does not allow a proper inspection from the operator. Nevertheless, this can be overcome by the corresponding feeder Gross Weight. Since each feeder have its own gross weight any contact with an external source will shift the gross weight: positive or negative. This variable can be used in the control strategy to help the operator with an alert indication, if a specific feeder has not been properly assembled. After the gross weight is confirmed within an acceptable range, PERT value must be evaluated to consider any other external noise source.

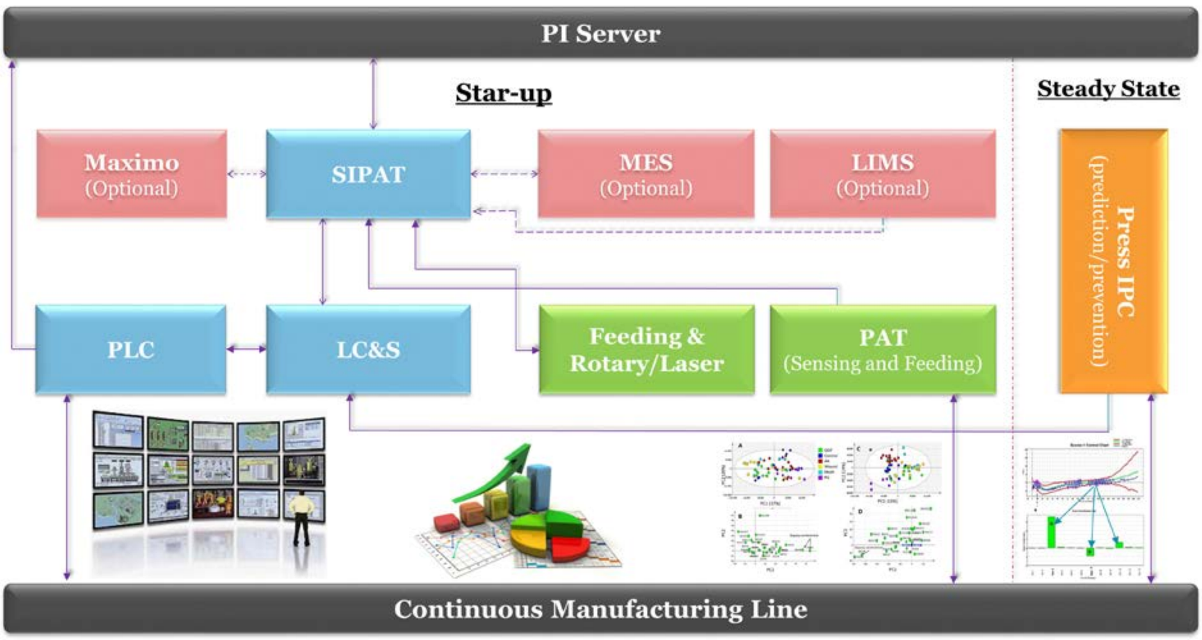

Figure 5.2: Schematic Representation to Connect Historian and Data Bases Software for Robust Data Analysis Through the Search of CM Line Elements and Material Properties Interaction

Lastly, but no less important, laser connectivity or nominal operation (i.e. electronic signal) must be verified with the empty system and compared with a reference. As known, rotary valve rpm dependence in the laser is highly correlated. Hence, for preventive actions within the Press stage, the laser connectivity and reading must be optimal.

Once the CM line set-up has been completed, material loading operation can be started. Figure 5.3 shows an schematic representation of the CM line pneumatic system to transfer the material from their drums up to the feeders. Once the feeders reach its maximum hopper capacity or netweight then can be proceeded to start the feeding operation, not before. After all Volumetric/Gravimetric (Vol./Grav.) are full, at least 2 screw fill are required to minimize AFF departure from its operational range. Empty screws will provide a wrong reading to the feeder in terms of weight loss rate, affecting the AFF calculation within the feeder K-Tron Control Module (KCM). With both Vol./Grav. feeder being loaded up to its maximum and proper screw fill (2x), the feeding operation can be started.

During the feeder's transient or unsteady state different variables must be monitored to determine when the feeding system has reach a control state: Net Weight, Adaptive Gain, Pert Value, Mass Flow, Drive Command, Gross Weight and AFF. The feeder netweight should be constantly progressing in time between the minimum and maximum weight stablished for best feeding performance or low mass flow variations (i.e. low standard deviation). Through this time frame the dimensionless PERT variable must reach a value under twenty (<20), the adaptive gain above 89% and the Drive Command between 20%-80% of motor capacity. With these variables within range and the Gross weight being unaffected by drastic changes through the refill operation it will only be required two (2) additional conditions:

1. Feeder mass flow fluctuates within the stablished acceptable limits.
2. AFF readings does not shows an upward or downward trend.

With the feeder mass flow within the acceptance limits is plausible to proceed with current operation procedure to monitor the AFF. The AFF could be stored in the data base for PSD predictions in function of time. However, for this study purpose the idea is to monitor AFF changes, since press adjustments will be triggered by particle size changes and not by a specific particle size. Hence, this incur in comparing the feeder AFF once the press is adjusted as a reference point to identify any upward or downward trend from the previous asymptote. Any potential outcome from the AFF will trigger its verification with the model concentration prediction variability that account for external noise: T2Range.

Is important to mention that if the AFF goes out from the observable range stablished for specific material different scenarios could arise to explain this situation. The different scenarios that could arise are the following in a descending order in terms probability:

1. Feeder performance – the operator should verify the Netweight, Gross Weight, PERT Value, Mass flow and Adaptive gain. These variables are not required to be verified in this order, this will be subject to the operator experience and actual succession happening in that time frame.
2. Material PSD (D50) or Flow ability properties out of specification – FBG/D operating conditions

3. Material Humidity or degradation – due room temperature and humidity excursions

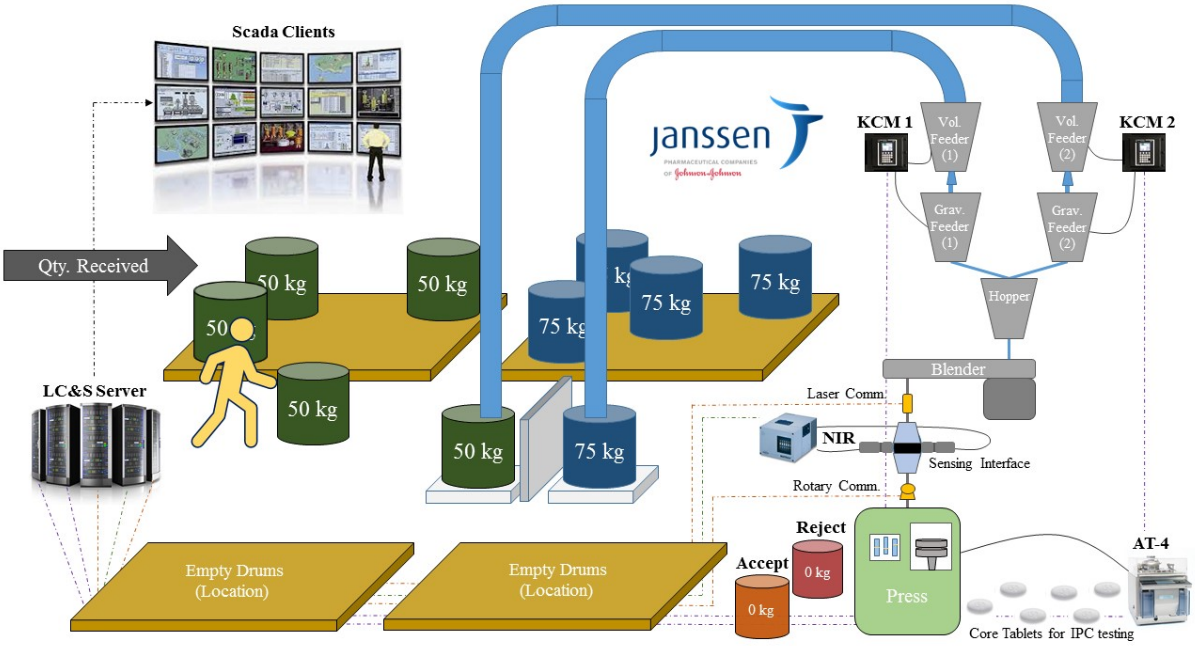

Figure 5.3: Schematic Representation of the CM line

Once the feeding operation is within the aforementioned criteria and the blend homogenization time (minimum time required from the blend to load, reach a steady state fluidization and homogeneous mixing within the continuous blender) has been accounted the diverter valve that is located below the rotary valve is shift from its reject position to its accept position. As a remark, during the transient time frame, the CM line maintain the formulation directed to a reject drum, until feeding and mixing operation are being considered optimal from a quality standpoint. Figure 5.4 shows a decision tree strategy related to the Start-up stage of the CM line operation.

As a remark, this decision control strategy has not been developed to remove the existing one but to supplement it from a quality control standpoint and support to the operation personnel from a statistical-science based approach.

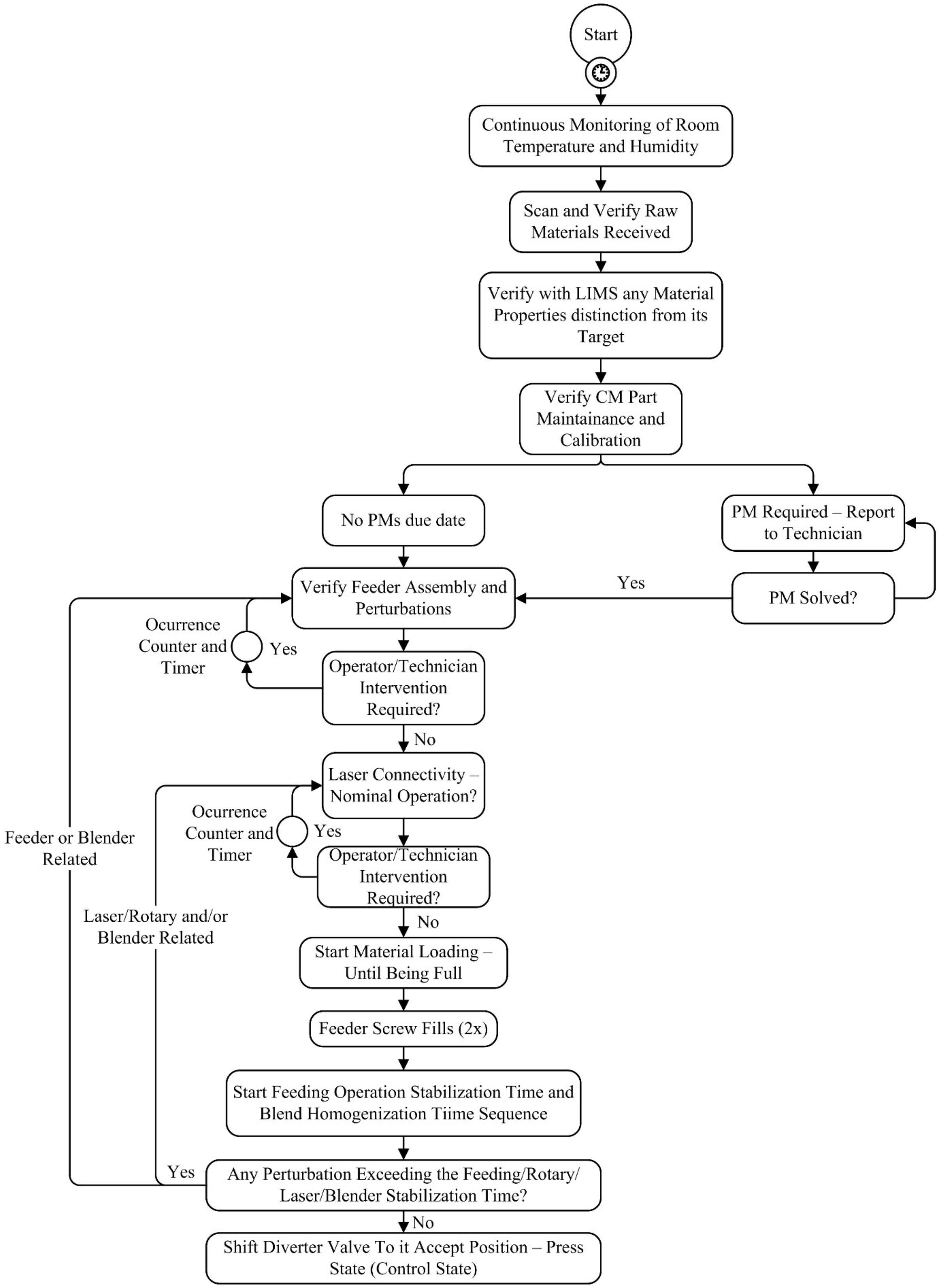

Figure 5.4: Start-up Decision Tree Strategy for CM Line

5.2 Steady State (Post Start-up)

This section will provide a CM line downstream decision tree strategy for preventive actions within the press stage (Figure 5.5). The decision tree algorithm will use the strategy developed in the Start-up section, as its core, to specify if the AFF is reliable based on the feeder performance. As part of the downstream decision strategy it will be composed by the following three (3) components:

1. AFF reliability (discussed in the Start-up or previous section)
2. PSD change and/or prediction and its potential downstream impact
3. Press prevention/adjustment decision making

Since the first component of the decision tree was discussed in the previous section, only the second and third component will be described in this section. Figure 5.5 shows the 2nd and 3rd component. The discussion of the 2nd and 3rd component will be based in the assumption that the CM line is working within the stablished control state from an operational perspective. In the case of any external factor that cause the CM line to exit from its control state, will redirect the decision strategy directly to the 1st component. Thus, the second and third stage will be focused on monitoring the AFF and T2Range to alert, prevent or correct any potential effect in the press stage or core tablets IPCs.

Once the CM line has reached its control state and formulation is well-mixed (after the blend homogenization time) the CM line will proceed to re-direct (diverter valve) the formulation to the accept position (press stage). Refer to Figure 5.3. When the material reaches the press, the operator will proceed to set-up mainly the main compression force, pre-compression force and dosing to meets core tablets IPCs. After the press set-up the corresponding AFF will be stored and used as reference point. From this point on the Line Control and Scada (LC&S) will be monitoring the feeder AFF in real time in the search of AFF changes above one (1) [kg/h] unity. This threshold was based on the observed 1 [kg/h] shift from the fine and coarse granulation (GEA FBG/D system), based on the feeder AFF, when compared to the medium (target) granulation (GEA FBG/D system). Moreover, this AFF shifts were enough to induce a noticeable deviation within the press stage variables, specifically the main compression force.

After the press set-up, the LC&S will be monitoring the AFF and T2Range from where the following three possible scenarios (Figure 5.5) can arise:

1. Only the AFF value is observed with a significant shift/departure from its last stored reference.

2. Only the T2Range value is observed with a significant shift/departure from its last stored reference.
3. Both AFF and T2Range are observed with a significant shift/departure from its last stored references.

Each of the scenarios will be discussed separately below. Still, the three scenarios are coupled to the decision tree strategy developed and shown in Figure 5.5 for the CM line during its control state to alert, prevent and/or correct potential deviations in the press stage regarding PSD changes.

Scenario 1: Only the AFF value

This scenario does not imply any impact to the CM line or downstream operation. However, it provides an alert to the operator to be aware that AFF changes has been observed with potential impact in the downstream operation (ex. T2Range) that could lead to monitor the press IPCs through the AT-4 and subsequently proper adjustment to meets the core tablets specifications. In the case a AFF alert is trigger, no matter if the T2Range confirm or not the alert, a counter will be activated for post data analytics and/or business metric purposes within a Manufacturing Execution System (MES) and Enterprise Data Warehouse (EDW). In the same manner, the current AFF and T2Range will be stored for post data analysis and decision tree algorithm robustness continuation/leverage. This scenario will not require any timer to account for its time frame, as the third scenario, since its execution is not dependent of any variable or third-party action.

Scenario 2: Only the T2Range value

For this scenario (trigger alert due the T2Range only) four (4) possible cases were identified as root causes:

1. Laser dusty sensor window or bad connectivity – laser readings and visual inspection is required.
2. Powder or formulation Leak – visual inspection is required.
3. PSD changes from any material not characterized. Most probable from the excipients with higher w/w %. Rotary speed and prediction concentration could be analyzed to explore any interaction.

4. Mass flow ratio between feeder is not hold. Probably from the excipient with higher w/w % in the formulation. Verify feeding mass flow, concentration prediction and rotary speed.

The first scenario is the easiest and fastest to distinguish. The LC&S will provide a subsequence alert to the operator if the laser reading is identified 15% off the target value (77%). The alert will indicate the operator to confirm if the laser window is dusty. If the laser is not dusty, false readings will be the root cause. In the case the laser reading is working properly, an alert to the operator will be provided to visually inspect the 2nd and 3rd floor for any leakage.

If no leak is found, all feeders are working tightly to the setpoint and rotary/laser are working properly then Scenario 3 or 4 could be the possible root causes and a prone will be displayed to contact Chemometrician SME for data analysis. Data related to feeding, Concentration prediction and material properties will be required to be analyzed for information purposes to keep moving forward with CM line understanding continuity and leverage for future batches and control strategy robustness.

In addition, a counter will be activated every time any of the cases condition are trigger for post data analysis and/or business metric purposes within a Manufacturing Execution System (MES) and Enterprise Data Warehouse (EDW). In the same manner, the current AFF and T2Range values will be stored for post data analysis and decision tree algorithm robustness continuation/leverage. This scenario will not require any timer to account for its time frame, as the third scenario, since its execution is not dependent of any variable or third-party action.

Scenario 3: Both the AFF and the T2Range value

This is the main focused of this study. The development of a downstream decision strategy to prevent any impact on the press stage by continuously monitoring in real-time the key variables: AFF [kg/h] and T2Range. Therefore, in the scenario that both the AFF and T2Range are considered shifted from its reference value a prone will be displayed to the operator. The prone or alert will require an action from the operator: perform an IPC test through the AT-4. Subsequently, the AT-4 will shows two (2) cases:

1. AT-4 outcome shows that at least one (1) IPCs (hardness, weight, thickness) was observed off the setpoint - press adjustment will be then required.
2. AT-4 outcome shows no setpoint deviation - no press adjustment will be required.

In both cases, a counter (specifically per case) will be activated every time any case is trigger for post data analytics and/or business metric purposes within a Manufacturing Execution System (MES) and Enterprise Data Warehouse (EDW). In the same manner, the current AFF and T2Range post/prior IPCs to Press adjustment and time frame occurrence will be stored for post data analysis and decision tree algorithm robustness continuation/leverage. For the case press adjustments are required, the current AFF and T2Range will update the current AFF and T2Range Reference values.

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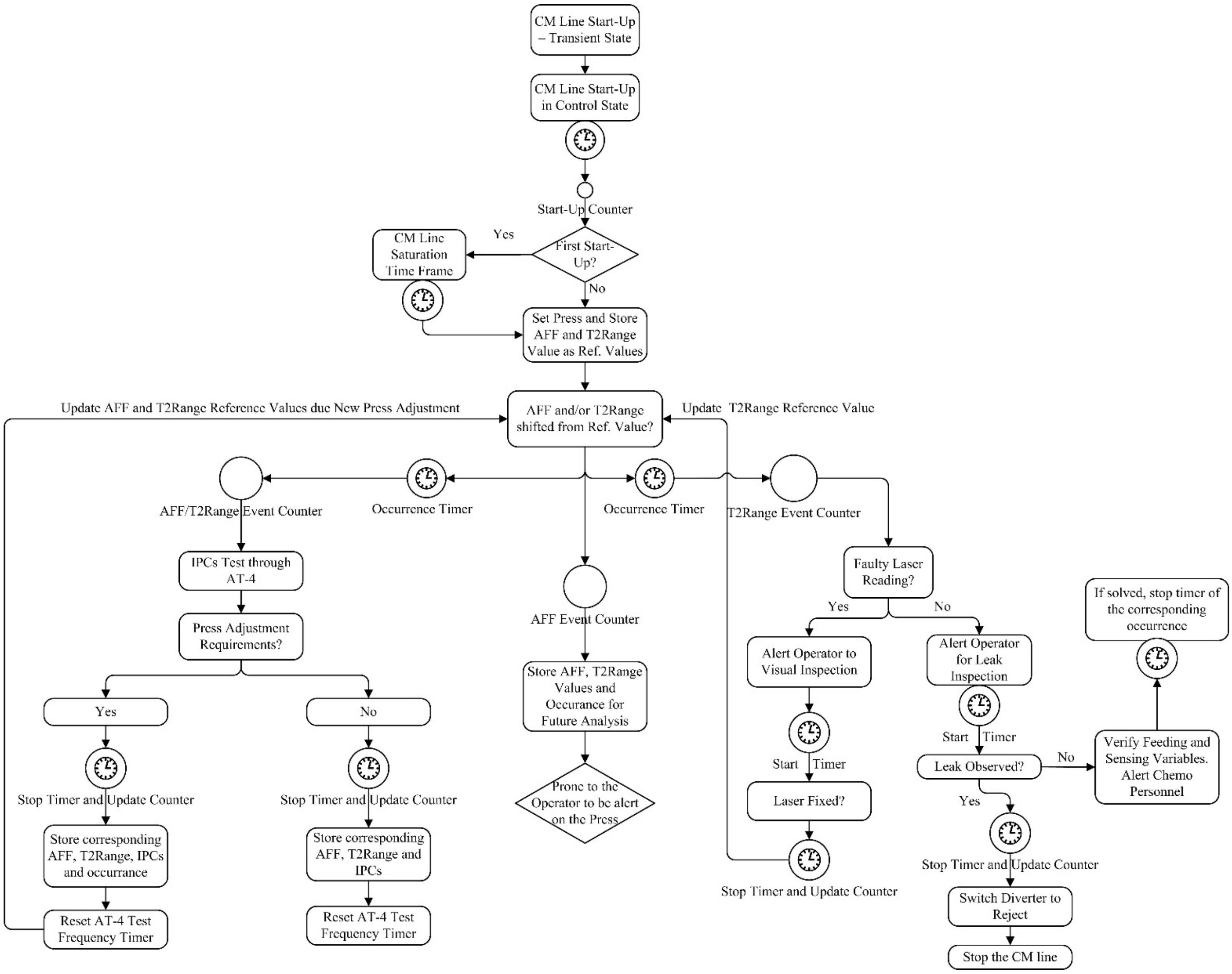

Figure 5.5: Downstream Decision Tree Strategy for CM line

Chapter 6

Concluding Remarks

It was demonstrated that the feeding control variables were able to distinguish changes in particles size (D50) for the dispensed raw material. The AFF in combination with the DC resulted in the best combination to identify changes in particle size by implementing a principal component analysis. However, an AFF vs PSD (D50) linear regression showed a correlation of 97% (R^2) which indicate that the AFF is statistically significant for monitoring changes in particle size (D50). The observed relationship was found to be aligned with the literature within the challenged particle size (D50) range: 233 µm – 300 µm.

Consequently, the impact of particle size in the formulation was analyzed after the mixing stage to confirm that the observed changes in the feeding stage were significant in the formulation after mixed. The NIR spectrum data was qualified with the T2Range feature, which distinguished differences in the formulation corresponding to particle size. Therefore, the AFF could be used for particle monitoring and any changes in it and the T2Range to confirm the impact of that change in the formulation to alert in advance the tablet press operator of a potential event that could lead to non-conformance in product quality. The RTD studies provided the approximate time frame that a perturbation (ex. particle size change) in the feeding stage could take to reach the sensing interface and subsequently the tablet press. This time is critical to establish when the action in the tablet press must be taken.

With this information the first objective in identifying the key variables to detect and alert the operator from changes in particle size in advance was accomplished. This lead to the accomplishment of the next two objectives: decision tree algorithm to identify changes in particles size and guidance for the preventive measure within the tablet press. Two (2) decision tree were developed. One was related to system set-up and performance corroboration and room/material conditions verification to reduce noise that could lead to false positive readings. The second was related to the identification/confirmation and alert of changes in particle size and subsequently the required preventive measure to be implemented in the tablet press.

Is important to mention that through the development of the fuzzy logic strategy the PSD predictions was determined not to be necessary for the control design since the AFF monitoring was required to be performed through a delta based. This requires the storage of the AFF value after each press adjustment for reference/comparability purposes and in the event of a significant change (± 1.8 kg/h) the control strategy proceed to confirm the impact on the blend through the T2Range value. Hence, T2Range also is required to be stored for reference and comparability purposes. Nevertheless, PSD predictions are valuable for post-data analysis and keep moving forward the CM line control strategy enhancement and robustness in other facets as RTRs, RTD, mixing studies and/or future improvement on the decision control strategy developed within this project.

As a remark, the study shows that the AFF extrapolation will be always material and formulation dependent. Hence, any change in material, supplier, formulation and/or dosage will require proper characterization studies to addresses the minimum AFF change requirement to alert the operators of any downstream impact. This mean that the developed decision tree is only applicable for the specific formulation studied and within the studied particle size (D50) range: 233 µm – 300 µm. Implementation of the decision tree must be performed within these conditions. Raw materials with a broader size range will require further analysis to ensure that AFF vs PSD linearity still hold above 300 µm. This seem highly possible since particle size above 150µm does not experience interparticle forces allowing the interaction purely mechanical. However, raw materials just below the 150 µm could have a different behavior since the effect of both phenomena.

The outcome of this study allowed to reach the project purpose, which was the improvement of the CM line process reliability. In addition, it provided evidence that the coupling of process variables and data analysis could lead to the development of soft PAT sensors without the necessity of capital expenses in instrumentation for monitoring purposes, as particle size. Finally, it also empowers future process optimization and development by expanding the CM line process understanding and QbD space to keep pursuing the ultimate goal of ensuring human well-being through the delivery of high quality product.

References

[1] Augsburger Larry, Hoag Stephen; Pharmaceutical Dosage Forms: Tablets; CRC Press, Florida 2008, Vol. 1, 3rd Edition

[2] Food Drug Administration; Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules – Guidance for Industry; June 2015, Volume 80, Issue 118

[3] Dressman Jennifer, Amidon Gording, Reppas Christos, Shah Vidod; Dissolution Testing as a Prognostic Tool for Oral Drug Absorption: Immediate Release Dosage Forms; Pharm Res., January 1998,Vol. 15, Issue 1, pp. 11-22

[4] McNeil Ian; An Encyclopedia of the History of Technology; Routledge Press, New York 2002

[5] Oliver Evans, Thomas Jones, Cadwallader Evans, Thomas Ellicott; The Young Mill-wright and Miller's Guide; HardPress, Florida 2017

[6] International Conference on Harmonisation; Pharmaceutical Development – ICH Harmonised Tripartite Guideline Q8(R2); August 2009

[7] International Conference on Harmonisation; Quality Risk Management – ICH Harmonized Tripartite Guideline Q9; June 2006

[8] International Conference on Harmonisation;, Pharmaceutical Quality System – ICH Harmonized Tripartite Guideline Q10; April 2009

[9] Newton Paul, Green Michael, Fernandez Facundo; Impact of Poor-Quality Medicines in the 'Developing' World; Trends Pharmacol Sci., March 2010, Vol. 31, Issue 3, pp. 99-101

[10] Lx, Yu; Pharmaceutical Quality by Design: Product and Process Development, Understanding, and Control; Pharm Res., April 2008, Vol. 25, Issue 4, pp. 781-791

[11] Stoumbos Zachary, Reynolds Marion, Ryan Thomas, Woodhall William; The State of Statistical Process Control as We Proceed into the 21st Century; J. Am. Stat. Assoc., September 2000, Vol. 95, No. 451, pp. 992-998

[12] Woodhall. William, Spitzner Dan, Montgomery Douglas, Gupta Shilpa; Using Control Charts to Monitor Process and Product Quality Profiles; J Qual Technol., July 2004, Vol. 36, No. 3, pp. 309-320

[13] Woodhall William, Montgomery Douglas; Research Issues and Ideas in Statistical Process Control; J. Qual Technol, October 1999, Vol. 31, No. 4, pp. 376-386

[14] Hubert Cedric., Lebrun Pierre, Houari Suzan, Ziemons Eric, Rozet Eric, Hubert Philippe.; Improvement of a Stability-Indicating Method by Quality-by-Design versus Quality-by-Testing: A Case of a Learning Process; J Pharm Biomed Anal., January 2014, Vol. 88, pp. 401-409.

[15] Food and Drug Administration; Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach; September 2004

[16] Chen Zengpin, Lovett David, Morris Julian; Process analytical Technologies and Real Time Process Control a Review of Some Spectroscopic Issues and Challenges; J Process Contr, December 2011, Vol. 21, Issue 10, pp. 1467-1482

[17] Jørgensen Anna, Rantanen Jukka, Karjalainen Milja, Khriachtchev Leonid, Räsänen Eetu, Yliruusi Jouku; Hydrate Formation During Wet Granulation Studied by Spectroscopic Methods and Multivariate Analysis; AAPS J., September 2002, Vol. 19, Issue 9, pp. 1285-1291

[18] Chan Hakkim, Doelker Eric.; Polymorphic Transformation of Some Drugs Under Compression; Drug Dev Ind Pharm, October 2008, Vol. 11, Issue 2-3, pp. 315-332.

[19] Brás Lígia, Loureiro Rui; Polymorphic Conversion Monitoring Using Real-Time Raman Spectroscopy; Chimica Oggi - Chemistry Today, September 2013, Vol. 31, Issue 5, pp. 34-36

[20] Larkin Peter, Dabros Marta, Sarsfield Beth, Chan Eric, Carriere James, Smith Brian; Polymorph Characterization of Active Pharmaceutical Ingredients (APIs) Using Low-Frequency Raman Spectroscopy; Appl Spectros, July 2014, Vol. 68, No. 7, pp. 758-776

[21] Paudel Amrit, Raijada Dhara, Rantanen Jukka; Raman Spectroscopy in Pharmaceutical Product Design; Adv Drug Deliv Rev., July 2015, Vol. 89, pp. 3-20

[22] Gupta Abhay, Peck Garnet, Miller Ronald, Morris Kenneth; Real-Time Near-infrared Monitoring of Content Uniformity, Moisture Content, Compact Density, Tensile Strength, and Young's Modulus of Roller Compacted Powder Blends; J Pharm Sci., July 2005, Vol. 94, Issue 7, pp. 1589-1597

[23] Vergote Grant, De Beer Thomas, Vervaet Christ, Remon Jean, Baeyens Willy, Diericx Neal, Verpoort Francis; In-line Monitoring of a Pharmaceutical Blending Process Using FT-Raman Spectroscopy; Eur J Pharm Sci, March 2004, Vol. 21, pp. 479-485

[24] De-Beer Thomas, Bodsonb Chris, Dejaegher Bieke, Walczak Beata, Vercruysse Pieter, Burggraeve Anneleen, Lemos A., Delattre L., Vander Yvan, Remon Jean Paul, Vervaet Chris, Baeyens Willy; Raman Spectroscopy as a Process Analytical Technology (PAT) Tool for the In-line Monitoring and Understanding of a Powder Blending Process; J Pharm Biomed Anal, November 2008, Vol. 48, Issue 3, pp. 772-779

[25] Pawar Pallavi, Wang Yifan, Keyvan Golshid, Callegari Gerardo, Cuitino Alberto, Muzzio Fernando; Enabling Real Time Release Testing by NIR Prediction of Dissolution of Tablets Made by Continuous Direct Compression (CDC); Int J Pharm, October 2016, Vol. 512, Issue 1, pp. 96-107

[26] Van Den Ban Sander, Goodwin Daniel; The Impact of Granule Density on Tableting and Pharmaceutical Product Performance; Pharm Res, May 2017, Vol. 34, Issue 5, pp. 1002-1011

[27] Costa Filippo, Pasi Alberto, Sous João; Analysis of Formulation Effects in the Dissolution of Ibuprofen Pellets; Int J Pharm, February 2004, Vol. 270, Issue 1-2, pp. 9-19

[28] Li Jinjiang, Wu Yongmei; Lubricants in Pharmaceutical Solid Dosage Forms; Lubricants, February 2014, Vol. 2, pp. 21-43

[29] Gowthamarajan Kuppusamy, Singh Sachin; Dissolution Testing for Poorly Soluble Drugs: A Continuing Perspective; Dissolut Technol., August 2010, Vol. 17, pp. 24-32

[30] Sun Jiao, Wang Fan, Sui Yue, She Zhai, Zhai Wang, Wang Chunling, Deng Yihui; Effect of Particle Size on Solubility, Dissolution Rate, and Bioavailability: Evaluation Using Coenzyme Q_{10} as Naked Nanocrystals; Int J Nanomedicine, November 2012, Vol. 2012, Issue 7, pp. 5733-5744

[31] Shi Hao, Mohanty Rahul, Chakravarty Somik, Cabiscol Ramon, Morgeneyer Martin, Zetzener Harald, Ooi Jin, Kwade Arno, Luding Stefan, Magnanimo Vanessa; Effect of Particle Size and Cohesion on Powder Yielding and Flow; Kone Powder Part J., January 2018, Vol. 35, pp. 226-250

[32] Shekunov Boris, Chattopadhyay Pratibhas, Tong Henry, Chow Albert; Particle Size Analysis in Pharmaceutics: Principles, Methods and Applications; Pharm Res, February 2007, Vol. 24, Issue 2, pp. 203-227

[33] Burggraeve Anneleen, Kerkhof Tom Van Den, Hellings Mario, Remon Jean, Vervaet Chris, De-Beer Thomas; Evaluation on In-line Spatial Filter Velocimetry as PAT Monitoring Tool for Particle Growth During Fluid Bed Granulation; Eur J Pharm Biopharm, September 2010, Vol. 76, Issue 1, pp. 138-146

[34] O'Neil Andrew, Jee Roger, Moffat Anthony; Measurement of the Cumulative Particle Size Distribution of Microcrystalline Cellulose Using Near Infrared Reflectance Spectroscopy; Analyst, 1999, Vol. 124, Issue 1, pp. 33-36.

[35] Singh Ravendra, Román-Ospino Andrés, Romañach, Rodolfo Ierapetritou Marianthi, Ramachandran Rohit; Real Time Monitoring of Powder Blend Bulk Density for Coupled Feed-forward/Feed-back Control of a Continuous Direct Compaction Tablet Manufacturing Process; Int J Pharm, November 2015, Vol. 495, Issue 1, pp. 612-625

[36] Mohidee Mohd, Sreenivasa Binod, Sulaiman Shaharin, Raghavan Vijay; Heat Transfer in a Swirling Fluidized Bed with Geldart Type-D Particles; Korean J. Chem. Eng., January 2012, Vol. 29, Issue 7, pp. 862-867

[37] Batcha Mohd., Raghava Vijay; Experimental Studies on a Swirling Fluidized Bed with Annular Distributor; J. Aplied Sci., November 2011, Vol. 11, Issue 11, pp. 1980-1986

[38] Zhang Huili, Degréve Jan, Baeyens Jan, Wu Shu-Yii; Powder Attrition in Gas Fluidized Beds; Powder Technol., January 2016, Vol. 287, pp. 1-11

[39] Ganesan Vykundeshwari, Rosentrater Kurt, Muthukumarappan Kasiviswanathan; Flowability and Handling Characteristics of Bulk Solids and Powders – A Review with Implications for DDGS; J Biosyst Eng., December 2008, Vol. 101, Issue 4, pp. 425-435