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Material Tracking Model for ConsiGma – 25 Continuous Manufacturing Line

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LIST OF ABBREVIATIONS

API	Active Pharmaceutical Ingredients
CI	Cell Index
CMAs	Critical Material Attributes
CPPs	Critical Process Parameters
CQAs	Critical Quality Attributes
FDA	Food and Drug Administration
FI	Fill Index
ICH	International Council for Harmonization
LHP	Light House Probe
LOD	Loss on Drying
MPC	Model Predictive Control
NIR	Near Infrared
PAT	Process Analytical Technology
PBM	Population Balance Model
PCA	Principal Component Analysis
PI	Proportional Integral
PID	Proportional Integral Derivative
PK	Product Key
PKC	Product Key Concentration
PLS	Partial Least Squares
PSD	Particle Size Distribution
QbD	Quality by Design
QbT	Quality by Testing
RTD	Residence Time Distribution
TPP	Target Product Profile
TSG	Twin Screw Granulator

Abstract

Topic: Material Tracking Model for ConsiGma – 25 Continuous Manufacturing Line

Question: How to determine the quality of the final dosage form of a continuous tablet manufacturing press by tracking the critical material attributes of the granules along the line?

To successfully operate a continuous manufacturing line and maintain final product specifications, the quality of the raw materials and the intermediates must be specified and maintained across the different unit operations. If one of these specifications is not satisfied, then it will lead to dosage forms with qualities that are out of specification which might cause the complete shutdown of the production cycle if the specific batch of raw material leading to the out-of-specification cannot be dynamically and accurately identified. To solve this problem the concept of mini-batches was introduced. These numbered mini batches called product keys were then modelled as a function of the time during which they pass through each unit operation. Each dosage form produced can be specified as a function of a particular product key. For this purpose, a model was developed using MATLAB Simulink and parametric data obtained from production trials. This model dynamically assigns each material entering the system a product key number and tracked these product keys along each unit operation until the final dosage form. These product keys acting as mini-batches can easily be discarded should there be an anomaly during the operation of the line. Parametric properties such as the size of the granules, loss on drying and Active Pharmaceutical Ingredient concentration were successfully tracked with the product keys along the line as a function of time. In conclusion, product keys act as mini-batches along the line and can be discarded depending on the time range the quality prediction of the final dosage was not met without stopping the entire production process. This provides robustness to the system to be able to accommodate problems during production cycles and pave the way to achieve the concept of quality by design.

1.0 Introduction and Motivation

1.1. Introduction

Quality by design (QbD) as a concept was introduced by Dr Joseph M. Juran who defined quality as features of a product that meets the required specification of a customer [1]. He emphasized that qualities fail not because the experts were amateurs but because there is a lack of expertise in quality disciplines i.e., the methodology, skills and tools required to plan for quality.

Three basic methods were identified by him as the fundamental requirements to achieve good quality built into products or production lines. These are quality planning, quality control and quality improvement. Quality planning defines quality goals and establishes the means required to achieve the defined goals. When this definition is applied to pharmaceutical manufacturing quality goals can take many forms such as time frame for production, drug dosage form properties and drug delivery routes design properties. Quality control evaluates product quality performance and compares it with the defined goals, then the difference is acted upon. Quality improvement is the modification of quality that yields better performance, and this is a continual process that is periodically applied.

Traditionally the pharmaceutical industry relied on quality by testing (QbT) for the manufacture of their products but recently QbD is gradually being introduced and adopted. Pharmaceutical QbD can be defined as a systematic approach to development that starts with predefined objectives, emphasizing product and process understanding based on sound science and quality risk management [2]. This modern approach to the production of pharmaceuticals has been adopted by the FDA and drug-regulating organizations around the world. In seeking ways to improve drug production and regulation, FDA incorporated the principles of QbD into their guidelines and this has led to the evolvement of ICH Q8, ICH Q9, ICH Q10 and ICH Q13 guidelines[3], [4], [5], [6]. These guidelines deal with issues concerning pharmaceutical development, quality risk management, pharmaceutical quality system and

continuous manufacturing of drug substances and drug products. Before going further, it is important to understand some of the major objectives of the FDA and how they are related to QbD.

The major objectives of the FDA include:

i. To achieve the right quality specification of a product [5].
ii. To reduce product variability and avoid frequent product recalls [4].
iii. To encourage scale-up and provide a framework for post-approval changes [7].
iv. To increase production within a shorter time frame, especially in the case of a pandemic or war [8].

And, to achieve these objectives, it is necessary to have a thorough understanding of the whole process, identify the root causes of manufacturing failures and develop a good process design. A good process design should include a sound quality control strategy and for a pharmaceutical continuous manufacturing process quality control strategy, it is crucial to relate process parameters and material properties measured during production to the final dosage form. For this purpose, material tracking throughout the manufacturing process is important.

The focus of this thesis is to develop a model that tracks pharmaceutical raw materials fed into a continuous manufacturing line until they exit the process as a final dosage form. This real-time tracking model seeks to identify the raw material at each stage of the production line with a specific product key or label such that if a particular raw material in the line does not meet a specification, then it can be uniquely identified and discarded. The scope of this work is however limited to only tracking the information of the raw material as it moves along the line as well as intermediate material properties that are measured via PAT or estimated by soft-sensors. The proposed model does not consider the effects of the factors that specify the properties of the intermediates as it is turned into a dosage form. I.e., properties such as drying time, type of granules, type of powder etc.

1.2. Process Design and Critical Quality Attributes (CQAs)

A good process understanding provides the ability to design a relationship between critical materials attributes (CMAs), that is the input to the process, critical process parameters (CPPs), that is the important process variables and critical quality attributes (CQAs), which are the output of the process. To develop a proper understanding of a process the following steps were proposed by Yu et. al. [2] and these are like other steps found in the literature [9], [10].

i. Identify all possible known input material attributes that could impact the performance of the product.
ii. Use risk assessment, and scientific knowledge to identify potentially high-risk attributes.
iii. Establish ranges for these potentially high-risk material attributes. iv. Design and conduct experiments using DoE when appropriate.
v. Analyze the experimental data and apply the first principal models to determine if an attribute is critical. Link CMAs and CPPs to CQAs where possible.
vi. Develop a control strategy for the critical material attributes within the defined range.

Figure 1 shows a schematic overview of the key steps involved in developing a design to achieve the desired quality. This closely follows the ICH and FDA guidelines for the industry.

The key terms mentioned in the figure are defined and explained briefly below.

Target product profile (TPP): this is defined as the prospective and dynamic summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality. This includes the safety and efficacy of a drug product[11] .

Critical quality attributes (CQA): this is defined as the physical, chemical, biological, or microbiological property that should be within an appropriate

limit, range, or distribution to ensure the desired product quality [11]. Risk assessment is usually done by following the ICH guidance Q9 to determine the CQA.

Design space: this is the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to assure quality [12].

Product design space: this is the specification for the production process, the raw material attributes, and the final product characteristics[4].

Process design space: this is the correct modelling of the input variables and process parameters, and the identification of the functionality between the parameters in regards to the quality of the product [4].

Control Strategy: According to ICH Q10, a control strategy can be defined as a planned set of controls, derived from the current production and process strategy, which assures the performance and quality of the equipment and products [13]. These set of controls include parameters and attributes related to the raw materials, the final product and production components. These components include facility and equipment operating conditions, in-process controls, the final product quality, and the frequency of monitoring and control [5].

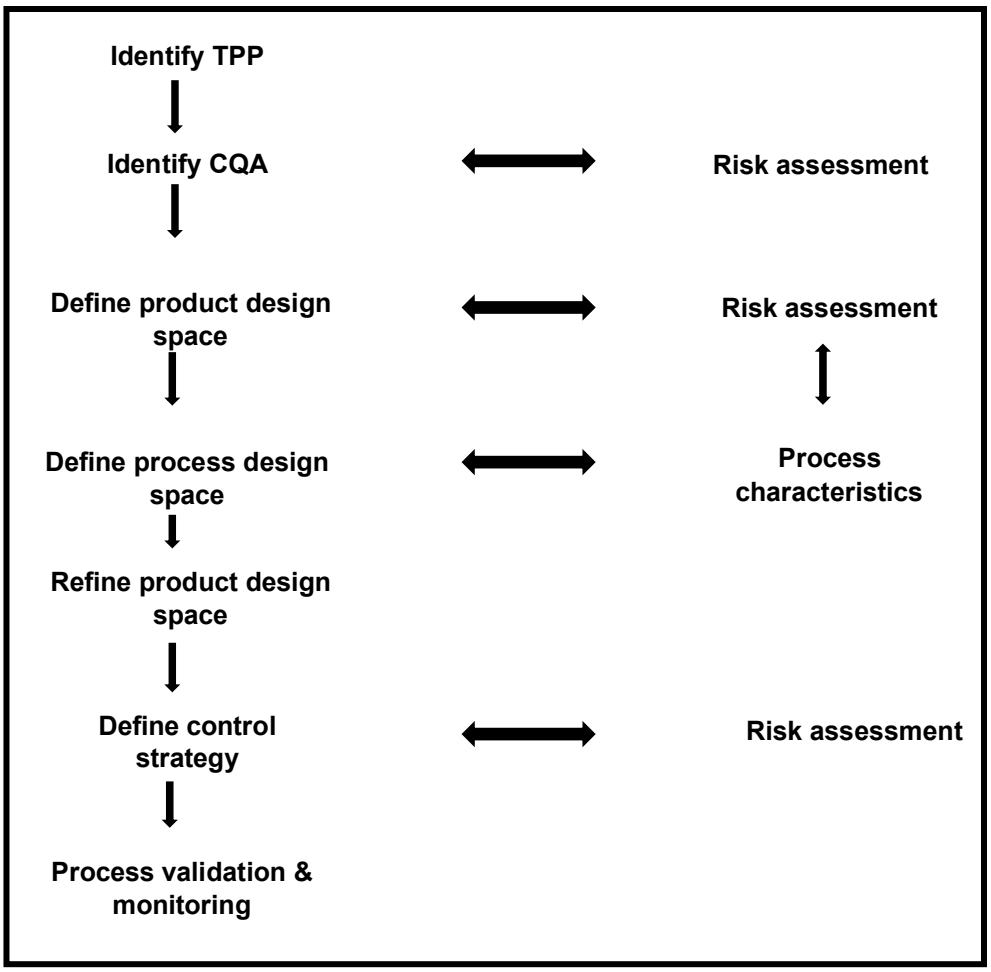

FIGURE 1.0: KEY STEPS IN THE IMPLEMENTATION OF QBD FOR A PHARMACEUTICAL PRODUCT [4].

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Process validation: This is a means to ensure that quality, safety, and efficacy are designed or built into products are maintained and do not deviate during operation. It can be defined as the collection and evaluation of data, from the process design stage through to commercial production, this establishes scientific evidence that a process is capable of consistently delivering quality products [14].

Risk assessment: This is a process of reviewing systematically a procedure for potential risk on a quality compromise based on scientific knowledge[14]. It is achieved in three stages.

i. Risk identification: this address what might go wrong.
ii. Risk analysis: this addresses the quantitative nature of the risk.
iii. Risk evaluation: this ranks the risk against established criteria.

1. 3. Process Analytical Technology (PAT)

The PAT framework is a systematic way of designing, analyzing, and controlling manufacturing through timely measurements of critical quality performance attributes of raw and in-process materials and production processes, to ensure final product quality[15]. For a successful implementation of the QbD approach by the industries, the FDA introduced the framework of PAT to guide the manufacturers and alleviate their fears of regulatory impasse [16]. This means that a combination of QbD and PAT tools enables excellent control, provides assurance of quality, and improves the efficiency of the whole process. As previously discussed, the major objective of QbD is focused on process understanding and a process is considered understood when

I. All critical parameters are identified and defined.
II. Variability is well controlled by the process.
III. The design space is accurately specified.

PAT provides the tools to help in achieving a detailed understanding of a process through real-time, in-line and online measurements. The critical parameters identified can thus be modified during production to achieve TPP. The ability to carry out testing in-line/online makes it easier to implement continuous manufacturing since variability can easily be detected and managed almost immediately. The pharmaceutical industry is currently exploiting a move from traditional/batch manufacturing to continuous manufacturing and PAT together with QbD is essential for the actualization of this switch. The advantages of moving from batch manufacturing to continuous manufacturing will be discussed in later sections.

1.3.1. PAT Tools

PAT tools are tools used as an efficient means of acquiring information from a process to facilitate a good understanding of that process and provide an effective way of managing variability [15]. According to the FDA guidance for industries document [16], these tools can be grouped or categorized according to the following:

i. Multivariate tools for design, data acquisition and analysis
ii. Process analyzers
iii. Process control tools
iv. Continuous improvement and data management tools

In designing a process, it is possible to combine more than one or all the different groups of tools. Brief explanations and examples of each group of tools are given below.

1.3.1.1. Multivariate tools for design, data acquisition and analysis

Multivariate tools are statistical tools that are used to explore the relationships between different variables based on experimental data, history, and other influences. They are essential for the transformation of random data generated from processes into relevant and crucial information [17]. Multivariate tools are therefore used to develop a pattern and build models for processes. Some

examples of multivariate tools are multiple regression analysis, factor analysis, multiple analysis of variance (MANOVA), Multi-way principal component analysis (PCA), multi-way partial least squares (PLS) regression and response surface methodology.

1.3.1.2. Process analyzers

A process analyzer is an instrument that is used to determine the chemical composition of materials continuously or periodically. Also, it can be used to determine the physical state of materials in a processing line [18]. The information or data generated ranges from simple univariate measurements like pressure, gas composition, temperature, and moisture content to more complex measurements like biological, chemical, and physical attributes of components. According to the FDA, these three forms of measurement can exist for a production line [16] :

- **At-line measurement:** this form of measurement entails the removal of samples from the manufacturing process and analyzing the sample near the process stream [16].
- **On-line measurement:** here the sample is diverted from the manufacturing process for analysis and may be returned to the product stream afterwards or discarded [16].
- **In-line measurement:** in this form of measurement the sample is not removed from the process stream but rather measurement is carried out as the materials flow past the probe [16].

Some examples of process analyzers are pH analyzers, gas analyzers, liquid analyzers, and digital sensors. Data from analyzers are utilized by multivariate tools for the design and modelling of the process.

1.3.1.3. Process control tools

To make sure the control of all critical quality attributes are effectively articulated it is important to develop a functional relationship between product

design and process development. Process controls is used to monitor the state of a process and manipulate the critical parameters to maintain a desired process state[19]. There are three basic components of control systems namely:

- Sensor/transmitter
- Controller
- Final control element

These three components perform three basic operations to control or manipulate the system or process:

- Measurement
- Decision
- Action

Figure 1.1 shows a simple illustration of the two strategies a control system uses to arrive at the desired set point or eliminate the effect of a disturbance in a system. In these systems, **Y** is the controlled variable, **U** is the manipulated variable and **D** is the disturbance. A descriptive definition of the systems provided by L. Luyben et. al. [19] is presented below.

1.3.1.4. Feedback control: this is a system of control in which the measurement component measures the controlled variable and compares it with the desired value (setpoint) and feeds the difference (the error) into the controller which in turn changes a manipulated variable to drive the controlled variable back to the desired value[19].

1.3.1.5. Feedforward control: this is a system of control where the disturbance is detected as it enters the process, and an appropriate change is made in the manipulated variable such that the controlled variable is held constant [19].

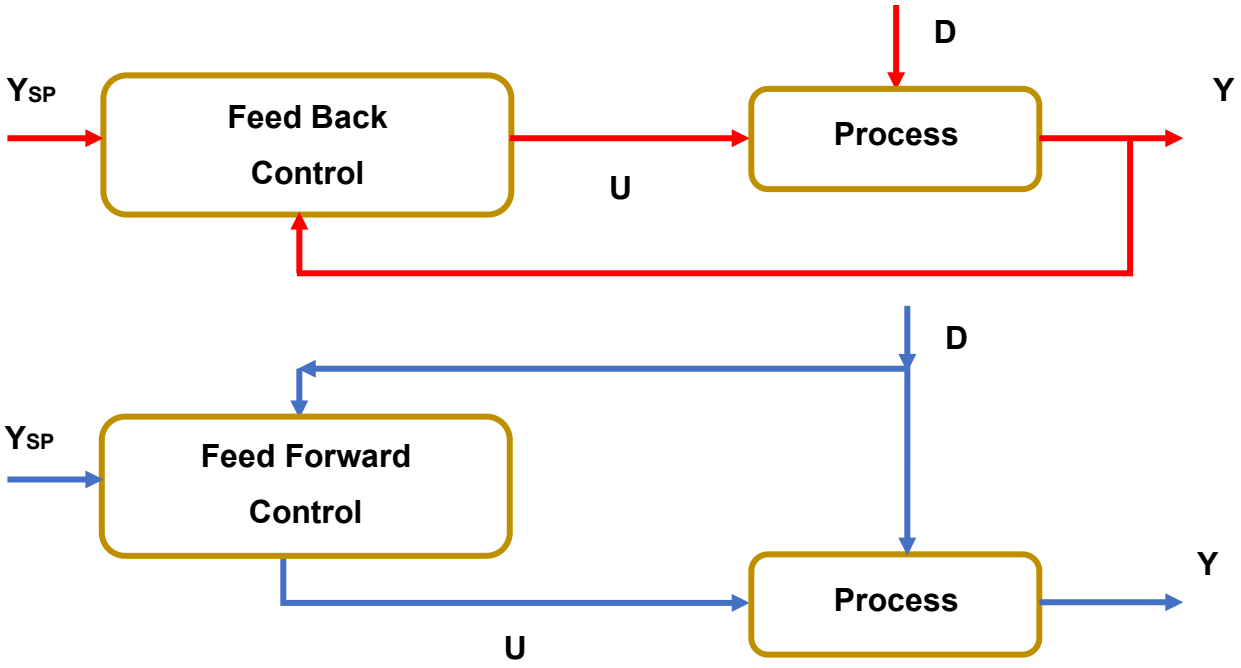

FIGURE 1.1: AN ILLUSTRATION OF FEEDBACK CONTROL AND FEEDFORWARD CONTROL OF A PROCESS.

1.3.2. Continuous improvement and data management tools

Continuous improvement of a process can be achieved through continuous learning, and this can be achieved by the collection and analysis of data throughout the life cycle of a product. These data can also be used to justify post-approval changes. It is important to develop sound approaches and information technology systems that support knowledge acquisition from such databases to establish a link between manufacturers, the FDA, and the scientific world [15].

1.4. Continuous manufacturing of pharmaceuticals

A continuous manufacturing process is an end to an end manufacturing process without hold-up times between the different unit operations. As opposed to the more traditional batch manufacturing process that involves multiple discrete steps, usually at different locations or even different companies involving long periods in-between production periods. While continuous manufacturing involves the assembly of different unit operations within the same facility [20].

This simply implies that raw materials are fed through this assembly line and products are obtained at the end of the line. Figure 1.2 shows a schematic overview of a pharmaceutical continuous manufacturing process compared with the batch operation process.

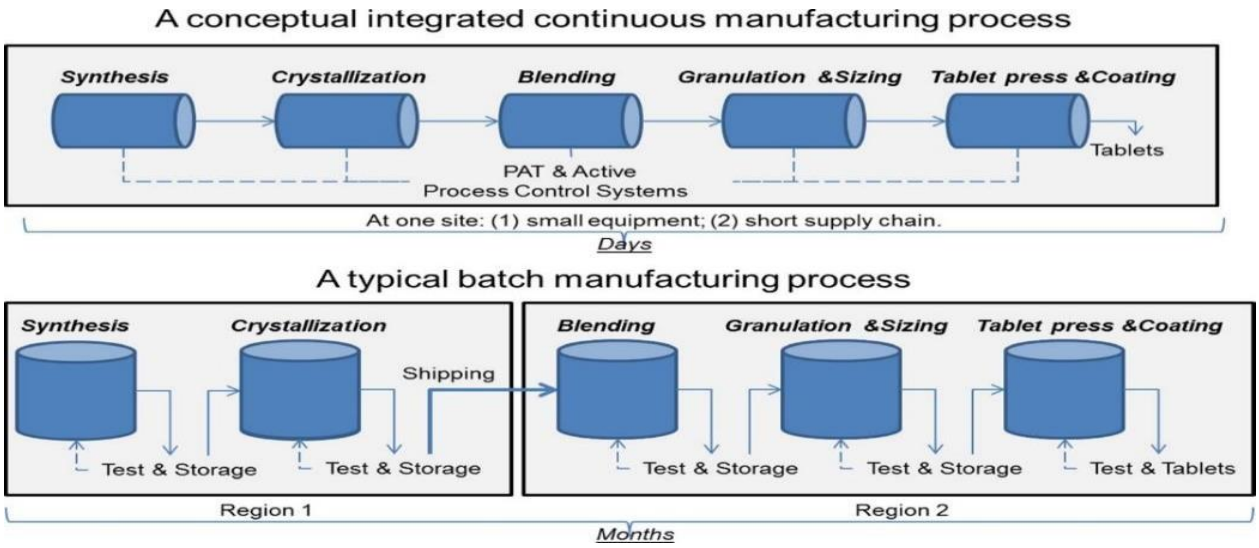

FIGURE 1.2: CONTINUOUS MANUFACTURING PROCESS VS BATCH MANUFACTURING PROCESS [21].

It can be seen from the diagram that the batch manufacturing process involves discrete manufacturing steps that are characterized by offline testing, storage, and movement to other facilities for further processing. Whereas the continuous manufacturing process involves a single production line from the synthesis of the API (active pharmaceutical ingredient) to the final coating of the tablets. What is most important for the continuous manufacturing process is the process control system which uses real-time monitoring of the whole process to control the system. To achieve good control of the production process it is important to develop a tracking system using the PAT (process analytical technology) tools that can identify each set of raw materials uniquely at any unit operation during continuous production.

It is also important to note that it is difficult to incorporate the whole drug production steps into a single continuous manufacturing line. Quite often the continuous manufacturing process is concerned mainly with downstream manufacturing or secondary production but recent innovations in flow chemistry

have enabled the development of continuous manufacturing lines incorporated with the synthesis of APIs [22].

1.5. Secondary manufacturing

Secondary manufacturing or the so-called downstream production involves the manufacture of drug forms in their final dosage form. A dosage form is a mixture of the active pharmaceutical ingredient (API) and several excipients [23]. The dosage form can be described as the physical form of a dose of medication. Excipients are added to an API to achieve certain desirable properties of the drug dosage form such as weight, release profile in the body and external environmental factors that may affect the drug throughout its life span [24]. Figure 1.3 shows a simplified block diagram of the secondary manufacturing unit operations, the unit operations considered in this work are highlighted by the red arrow. The different unit operations involved in the production line are then subsequently discussed, and the PAT tools used for acquiring data along the line are then discussed in the follow-up sections. This explanation gives insight into the functioning of the system and how the critical parameters are determined. The nature of the data used in the development of the TPP and the unit operations where these pieces of information were acquired is discussed in the follow up sections.

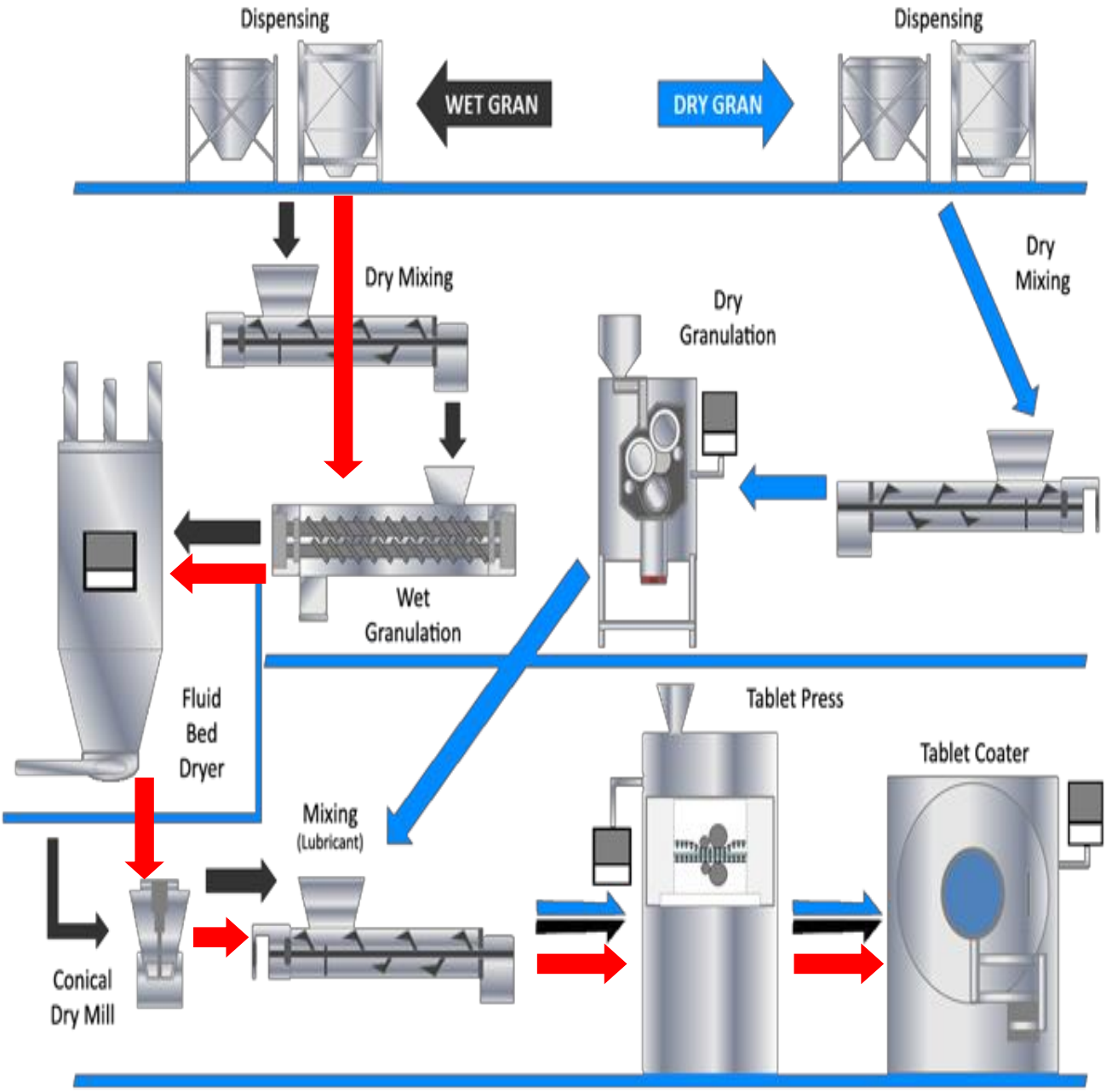

FIGURE 1.3: POSSIBLE CONTINUOUS SECONDARY MANUFACTURING ROUTES (THE ROUTE CONSIDERED IN THIS WORK IS INDICATED BY THE RED ARROWS) [25].

1.5.1. Granulation

Granulation is a particle enlargement process that involves Nano-sized particles being processed into micro-sized particles [26]. Granulation is used in the pharmaceutical industry to enhance a powder's physical features such

as flow-ability, compressibility, tabletability, and homogeneous distribution of the active pharmaceutical ingredient (API) [27].

There are five ways an agglomerate can be formed [28], namely:

i. The formation of solid bridges
ii. Sintering
iii. Chemical reaction
iv. Crystallization
v. Deposition of colloidal particles

During a granulation process, binders are often used to create adhesion and cohesion forces necessary for the agglomeration of the particles. Five general mechanisms contribute to the formation of granules during the processing, they are wetting and nucleation, coalescence or growth, consolidation, and attrition or breakage. A more detailed discussion of these processes can be found in the literature [29], [30], [31].

However, the general objectives of granulation in the pharmaceutical industry can be summarized as follows:

- To increase the uniformity of drug distribution in the product[32] .
- To increase the density of the material [32].
- To enhance flow rates and rate uniformity [32].
- To facilitate metering or volumetric dispensing [32].
- To reduce dust and minimize segregation during storage or transport [32].
- To improve appearance, drug targeting, controlled dissolution, and disintegration rate [26].

There are two major types of granulations: dry and wet granulation.

1.5.1.1. Dry Granulation

Dry granulation is the aggregation of powder particles in the absence of any liquid, and under high pressure to facilitate the bonding of the particles by direct contact followed by milling to attain the desired size [33]. This method is

used when the material to be granulated is sensitive to either moisture or heat or both such that it can have an effect on the CMAs of the powder.

Factors that influence this technique include powder cohesiveness, density, flowability, compressibility, and particle size distribution [34]. A typical example of this form of granulation is the roller compaction method where powders are fed into rollers and compressed into ribbons before being milled into granules [34]. Using this method, the range of pressure determines the density or strength of the final product. A reduction in compressibility will result in a decrease in tensile strength.

1.5.1.2. Wet Granulation

Wet granulation involves the use of a liquid binder or a granulating liquid to form granules of the particles of a drug powder [27]. Figure 1.4 shows the three basic steps involved in wet granulation. The different stages are explained below.

1.5.1.2.1. Wetting and nucleation

Wetting is the addition of the granulating liquid into the powder bed and subsequent distribution through the powder bed to form nuclei or wet particles [28]. For a good nucleation process, it is essential to ensure an even distribution of the liquid because poor wetting will generate an uneven granule size distribution. From literature, the nucleation process can be classified into four stages [28]. These are:

i. The formation of the liquid droplets from a spray with a certain size distribution.
ii. The liquid droplets formed will impact the powder bed, coalescence and overlap with the surface of the powder bed.
iii. The liquid droplet will then spread on the surface to wet the primary particles and penetrate the powder bed by capillary action to form nuclei.

iv. These nuclei will break up to form small entities due to the shear forces existing in the process.

The nucleation process is important as the granulation process because the “memory” of the nucleation stage is often retained, and this affects the properties of the final granules. Thus, if a wide nuclei size distribution is obtained during the nucleation stage it will normally lead to a wide granule size distribution for the product and vice versa [28].

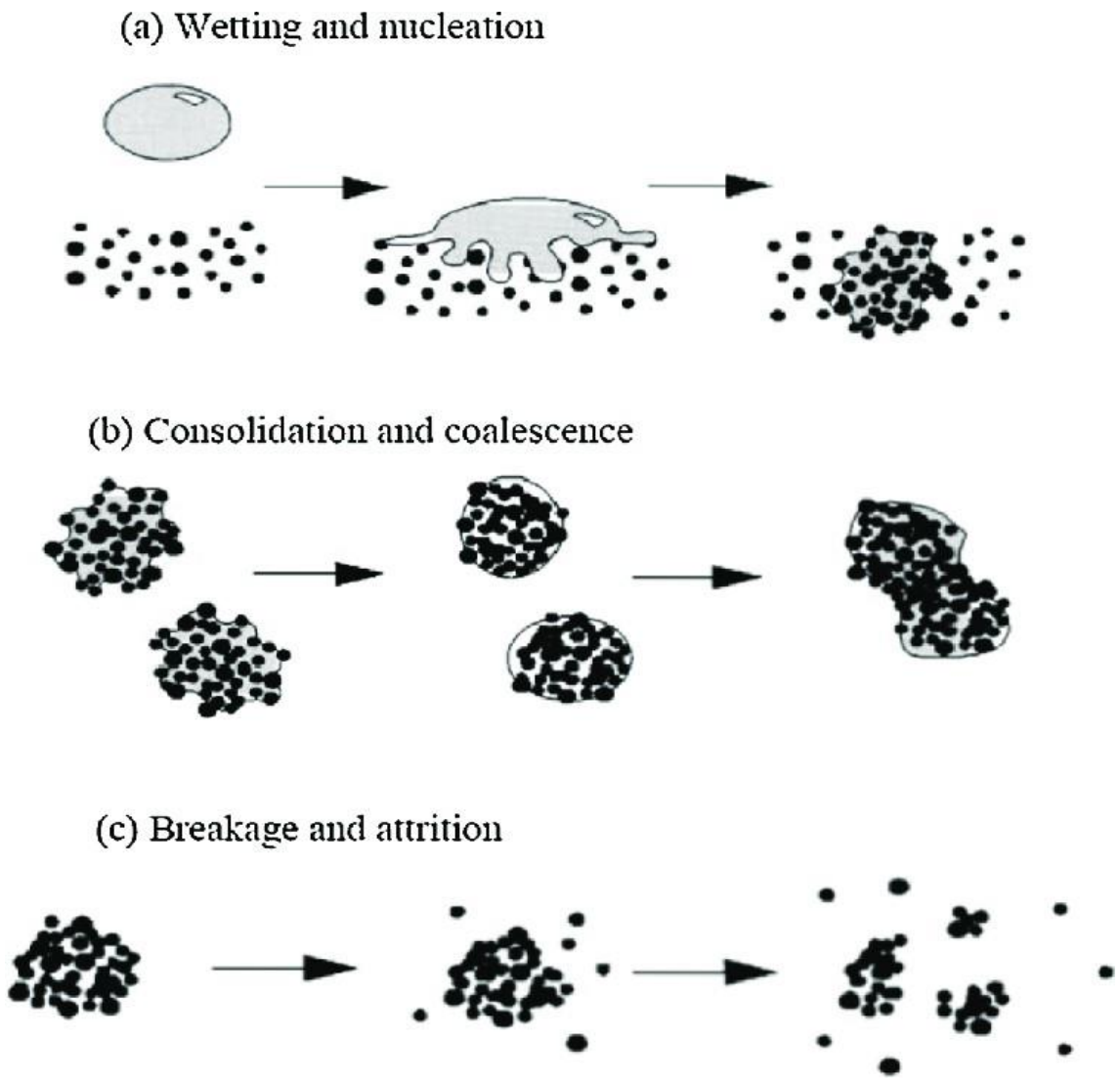

FIGURE 1.4: THE MECHANISM OF WET GRANULATION [31].

1.5.1.2.2. Consolidation and coalescence

After the wetting and nucleation stage, the particles will exist either as individual particles coated with a layer of liquid or loosely packed, partially, or fully saturated nuclei granules [35]. Further, the granules densifies when they collide with neighbouring particles or the wall of the containing vessel. At this stage, the granules grow larger, and the final properties (size and density) are usually decided at this stage [36].

Two major types of growth occur in a wet granulation process, steady growth, and induction growth [37]. Two basic parameters determine the behavior of the granule growth, these are pore saturation and the amount of granule deformation during the process [28].

1.5.1.2.3. Breakage and attrition

Granules breakage occurs due to the high shear forces exhibited in the granulators. These high shear forces can control the maximum and final granule sizes as well as disperse highly viscous liquid binder within the powder bed [36]. Thus, controlling this stage determines the granule size distribution by growing granules up to an established breakage limit.

Size distribution control depends largely on the impact velocity distribution and turnover of granules through the high-impact region as determined by Bellinghausen et. al. [28]. For a continuous manufacturing line, the twin-screw granulator (TSG) is often used because of its flexibility and ability to run for a long time [29].

1.5.2. Drying

Water content/binders added during granulation have been experimentally determined to directly affect granule density and tablet dissolution rate, while the residual moisture content after processing shows a significant effect on tablet crushing strength [27]. To achieve the desired amount of moisture concentration or the so-called LOD (loss on drying) before tabletting it is

important to dry the granules using the right parameter settings in the dryer. For this research work, the granules are dried in a fluidized bed dryer. Numerous researchers have effectively studied and modeled the behavior of granules in fluidized bed dryers, as demonstrated by the following literature reviews [27], [29], [38]. Also, a soft sensor has been proposed by Rehrl et. al. [39].

1.5.3. Blending

Blending is the mixing of API and excipients to ensure the homogeneity of content [10]. Blending is a critical step in the production of pharmaceuticals because a lack of uniformity can lead to a loss of materials, time, and money. The efficiency of a blender unit can be affected by parameters like the degree of homogeneity of the properties of the mixture, blending time, and the geometry of the blender [40]. Blending unit operation is often used for content mixing and for the addition of lubricants before tabletting to avoid the tablets sticking to the dies of the tabletting press.

1.5.4. Tableting

A tablet is a solid dose of a pharmaceutical preparation consisting of an API and excipients [41]. Tableting simply means the production of tablets using a tabletting machine.

This process involves the compression of granules in a die with the lower and upper punches, the die filling process is the most important parameter of the tableting process [42]. Some important parameters to be considered in the production of tablets are tablet weight, tablet hardness, tablet porosity, friability, disintegration time and dissolution [41].

Two types of tablet press can be classified, the single punch press and rotary press tabletting machine. The ConsiGma-25 continuous manufacturing line used for this research work uses a rotary press. The different PAT tools used to get data for the control of the quality of tablets produced by the rotary press are discussed in the next chapter.

2.0 Data Acquisition Methods

2.1. ConsiGma line and PAT tools

The ConsiGma-25 is a continuous manufacturing line developed by GEA pharma systems in-line with the FDA's QbD initiative [43]. It was designed to offer the industry an alternative to batch and semi-batch manufacturing systems. It has the advantage of improved quality, flexibility, and consistency. Another important feature of the design is that both research and development, and production can be done on the same equipment therefore eliminating the need for a scale-up [43].

The ConsiGma-25 continuous manufacturing line utilizes process analytical technology (PAT) tools to perform online measurements of granular materials as they progress through the different unit operations in the production process, enabling real-time quality assurance monitoring. A centralized control platform uses the data generated from these tools to execute control strategies to produce the desired quality product. Figure 2.0 shows a schematic overview of the manufacturing line of ConsiGma-25 together with the PAT tools used by each unit operation to provide online measurement. The Light-House Probe is part of the standard configuration of the ConsiGma-25, whereas the Raman and Parsum system, as well as the tablet tester have been added to the ConsiGma-25 located at RCPE during the CAPRI project [44].

This thesis aims to develop a model that uses data generated by PAT tools to track the properties of raw materials and intermediates as they progress through each unit operation in a continuous manufacturing line. The ability to assign an identity in the form of mini-batches to materials passing through the line is crucial for identifying the materials used in each product. To achieve this goal, an understanding of different online measurement techniques and the parameters they quantify is essential.

2.2. Powder feeder

For the purposes of this research, a pre-blended mixture of the active pharmaceutical ingredient (API) and excipient was utilized to maintain a

consistent API concentration throughout the experiment. The ConsiGma-25 continuous manufacturing line employed a gravimetric powder feeder, which utilizes the loss-in-weight principle to accurately dispense a controlled quantity of powder per unit time. Ignoring minimal variabilities, the rate of feed dosing can mathematically be expressed as: $\frac{dw}{dt} = constant$. Where $\mathrm{d}w$ is the change in weight and $\mathrm{d}t$ is the change in time.

To reduce variability between batches different control strategies have been developed to adjust the weighing errors. Several authors have extensively researched this control system with a focus on closed-loop proportional plus Integral (PI) or proportional plus integral and derivative controllers (PID) [45], [46], [47]. For example, Hanson [46] researched the application of a ratio control method to a gravimetric feeder during a steady-state operation and with disturbances. Figure 2.1 presents a pictorial overview of the feeder control system.

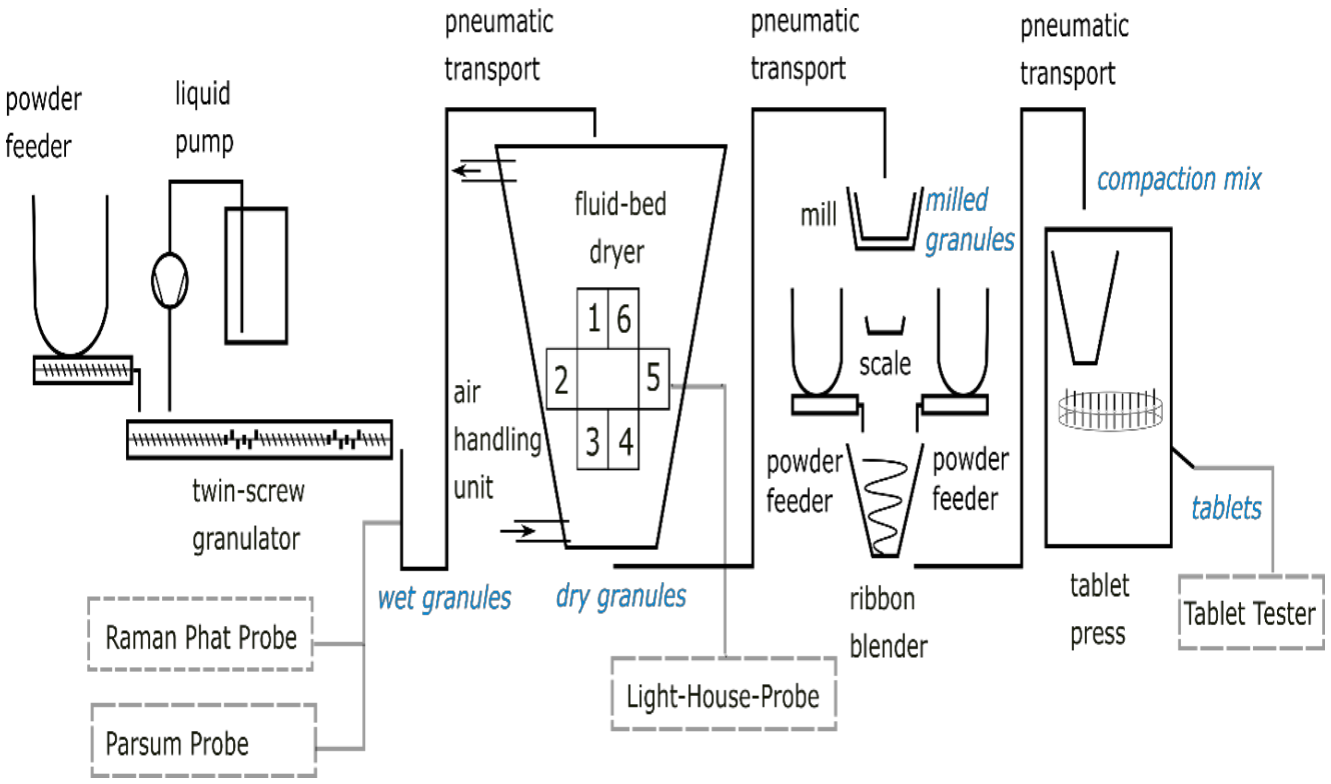

FIGURE 2.0: CONSIGMA-25 PRODUCTION LINE WITH PAT TOOLS.

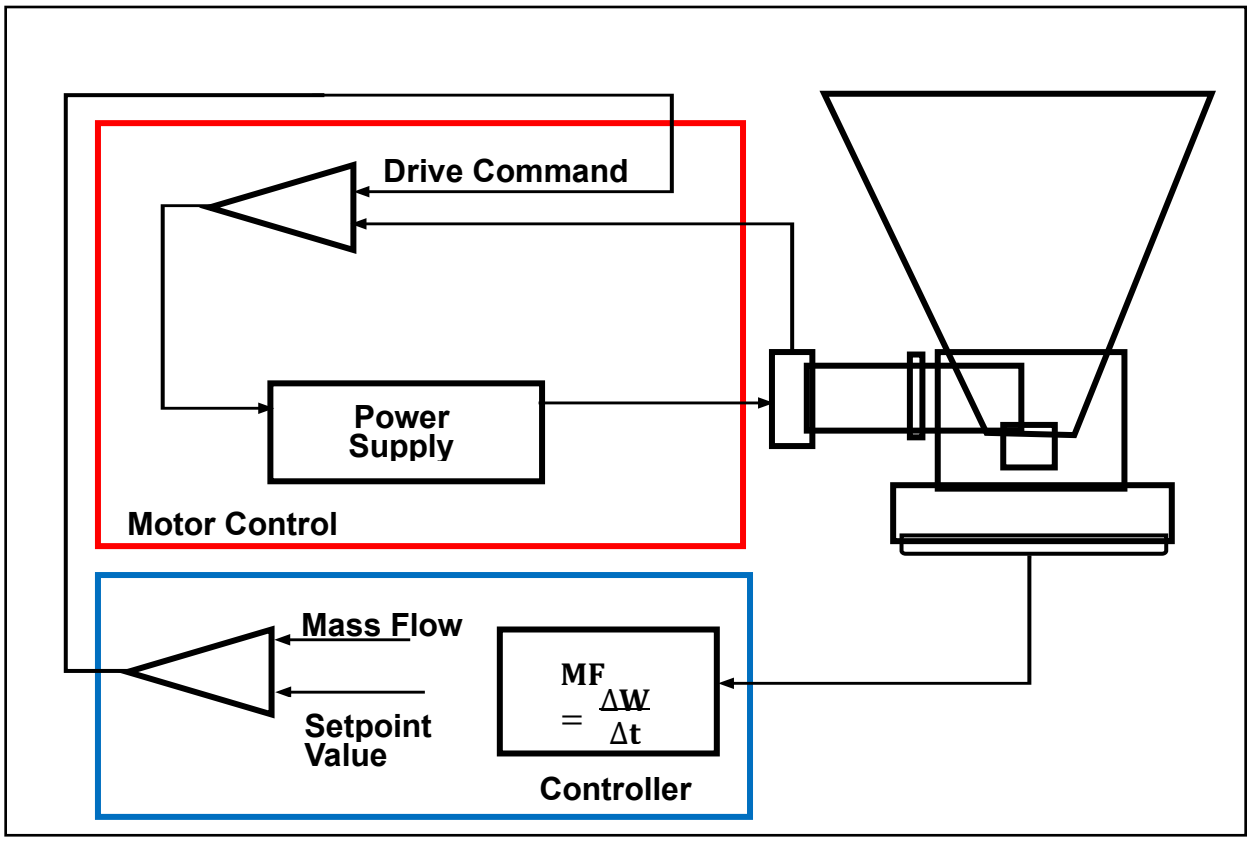

FIGURE 2.1: LOST IN WEIGHT FEEDER CONTROL SYSTEM [46].

2.3. Twin-screw granulator (TSG)

TSG is an extruder modified for application in pharmaceutical production. Originally extruders were used by the polymer processing industry for mixing and by the food industry to produce snacks, cereals, and animal food [48].

The twin screw granulation unit is a continuous granulation device that comprises a jacketed granulator barrel with two co-rotating screws [49] as shown in figure 2.2 and the internal attributes [48] are shown in figure 2.3. The granulator barrel consists of three zones:

I. A feed zone where the powder is fed into the TSG and transported by the screw [49].

II. A working zone where the granulation liquid is added to the barrel and mixed with the powder by kneading elements [49].

III. A discharge zone where the granules exit the barrel and are pneumatically transported to the dryer [49].

The granulation process proceeds with a liquid binder being continuously added into the barrel and the moving powder undergoing wetting by immersion, this leads to the formation of an agglomerate [48]. This agglomerate is then broken into smaller pieces by the shearing force that is produced during the granulation process. The material is transported by the conveying elements of the granulator barrel through the working zone to the discharge zone.

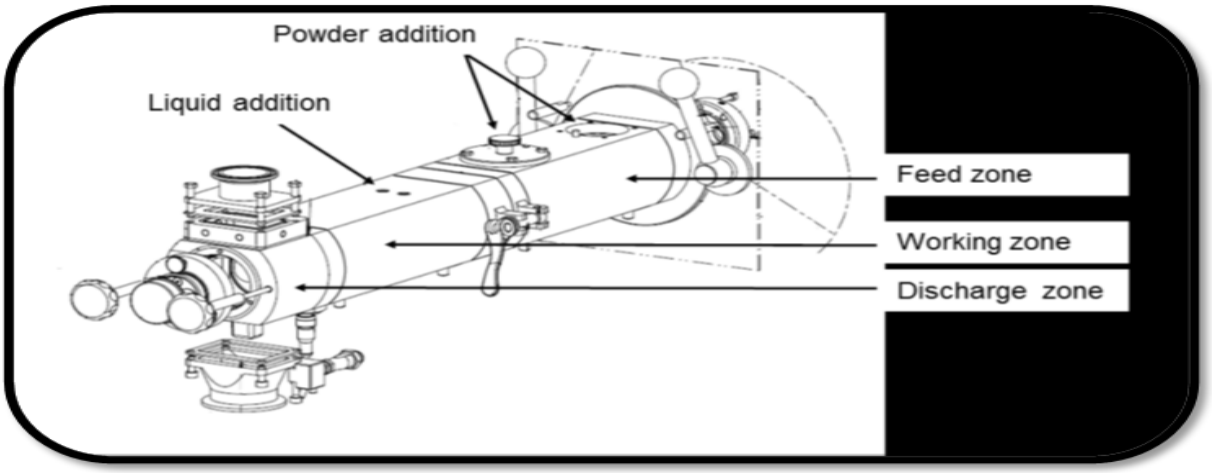

FIGURE 2.2: GRANULATOR BARREL OF A CONTINUOUS TABLETING LINE [49].

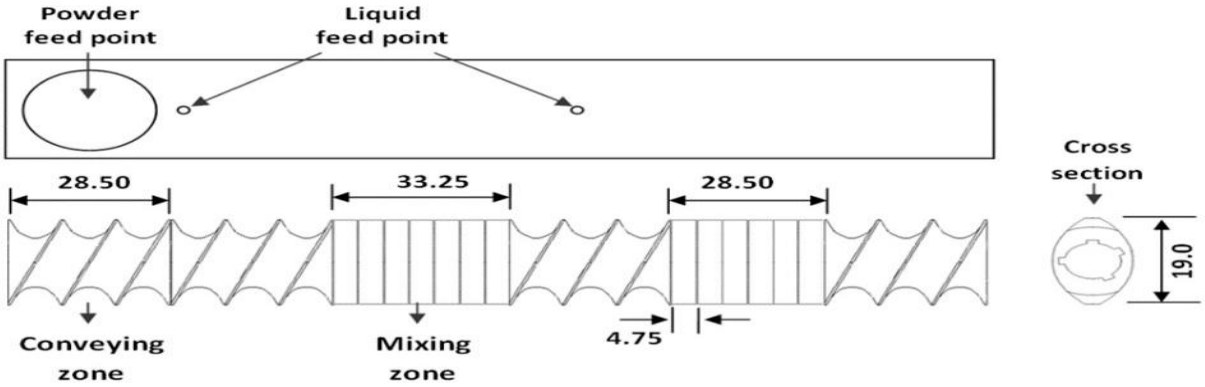

FIGURE 2.3: SCHEMATIC DIAGRAM OF THE GRANULATOR BARREL AND SCREW (DIMENSIONS (MM)) [48].

The properties of the granules produced by the granulator make an important CQA of a drug product. Therefore, it is critical for the granules leaving the granulator to have the right size distribution, uniform API content and water content. Numerous authors have utilized the residence time of material in the granulator to model the Twin Screw Granulator (TSG). This popular method involves conducting a tracer experiment and considering the effects of various parameters, such as screw speed, powder feed rate, and binder type or granulation liquid, as a function of granule properties.

In conclusion, the residence time distribution provides a valuable means of characterizing the mixing and flow processes within a granulator and can serve as an important tool for optimizing granulation processes and enhancing product quality in pharmaceutical manufacturing.

2.3.1. Residence Time Distribution

Residence time distribution is determined by injecting a pulse of a tracer dye into the system and measuring the concentration of the dye at the outlet of the system [50]. The residence time function is determined using equation 2.1 – 2.4 which was adopted from Folger [51], where ***c(t)*** is the concentration of the tracer at the outlet of the system. The mean residence time t_m is then calculated from equation 2.2.

Normalization of the shape of the distribution curve and the prediction of the exit concentrations of the trace dye is carried out using equations 2.3 and 2.4.

$$e(t) = \frac{c(t)}{\int_0^\infty c(t)dt} \qquad 2.1$$

$$t_m = \frac{\int_0^\infty t.e(t)dt}{\int_0^\infty e(t)dt} \qquad 2.2$$

$$\theta = \frac{t}{t_m} \qquad 2.3$$

$$e(\theta) = t_m.e(t) \qquad 2.4$$

Experimental results from studies utilizing the above-mentioned method for determining the residence time of materials in various unit operations have demonstrated its effectiveness in accurately predicting the duration of material processing within these operations [50], [52].

2.3.2. Parsum Probe

To monitor the granule size formation in the granulator unit, the unit is equipped with a
Parsum probe which gives a real-time data update via Simatic SIPAT (Siemens AG, Brussels, Belgium). The parsum probe is an inline particle sizing PAT tool that provides real-time particle size and particle flow velocity for solid particles in the size range of 50μm up to 6mm. The Parsum probe uses the measurement principle of spatial filter velocimetry which is a number-based, chord length sizing method that collects data for individual particles to obtain a particle size distribution and velocity distribution [53].

Figure 2.4 provides a pictorial view of the working principle of the Parsum probe. Particles passing through the probe measurement zone block the light emitted from a laser source. The resulting shadow is characterized using a linear detector array made up of optical fibres. Particle velocity is calculated by tracking the movement of the particle shadow across sequential detector elements while particle size is determined by measuring the length of time the particle blocks a single optical fibre [53].

When many particles are measured, a statistically valid result is generated and volume-based distribution can then be easily calculated. A velocity range of 0.01 – 50 m/s can be determined, and the probe can withstand an operating temperature of up to 373K.

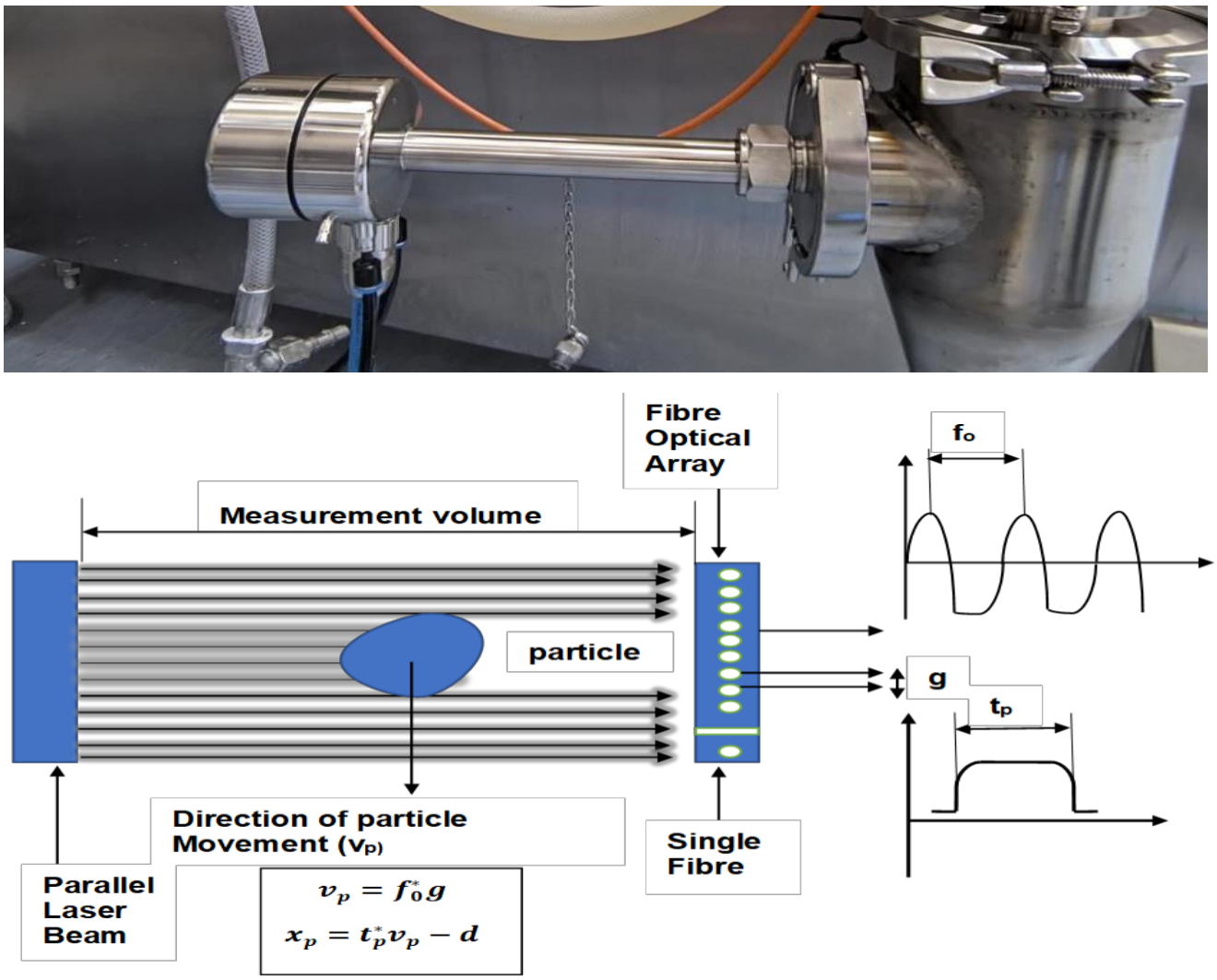

FIGURE 2.4: THE IMAGE OF A PARSUM PROBE AND MEASUREMENT PRINCIPLE OF A PARSUM PROBE [53].

2.4. Fluid bed dryer

Fluidized bed dryers is mostly used in the industry for the drying of wet solid particles because it has the advantage of achieving high contact area between the solids and the gas, this facilitates a high transfer coefficient of heat and moisture between solids and gas [54]. The ConsiGma-25 continuous manufacturing line is equipped with a (semi) continuous segmented fluid bed dryer. The dryer has six drying units as illustrated in figure 2.6 which are periodically filled with wet granules. The fifth unit or cell is fitted with a lighthouse probe (LHP) that enables the use of a NIR spectrometer (NDC

FP710e, NDC Infrared Engineering, Maldon, Essex, United Kingdom) for moisture content measurement. Each cell is equipped with a PT100 temperature sensor (JUMO PT100 – TYPE 902044, JUMO GmbH & Co. KG, Fulda, Germany) which captures the material and air temperature close to the bottom of the dryer. The drying process induces a shallow fluidized bed condition, so uniformity of temperature is assumed.

A similar process condition is applied to each cell so it is a near-valid assumption that the drying process and result will be similar with only small variations. However, this is not the case practically, as there exists cell-to-cell variation in terms of air volume and air temperature. This is especially susceptible since the air flows into the dryer in a non-symmetric manner. The illustration and process parameters involved are shown in figure 2.5. The content of each cell was modelled as a product key (PK) in this research work and the drying time of one PK is considered a mini-batch drying time.

Because it is expensive to equip each cell with a probe and obtain real-time granule moisture measurements in line, the use of a soft sensor model has been proposed. This model was developed by Rehrl [30]. Soft sensors are indirect measurement methods that use easily measurable variables to estimate process variables that are hard to measure due to technological limitations, large measurement delays or high investment costs [55]. The proposed soft sensor model used available process measurements such as temperature, air flow rate and time, to estimate the granule moisture content or LOD at the end of the drying period.

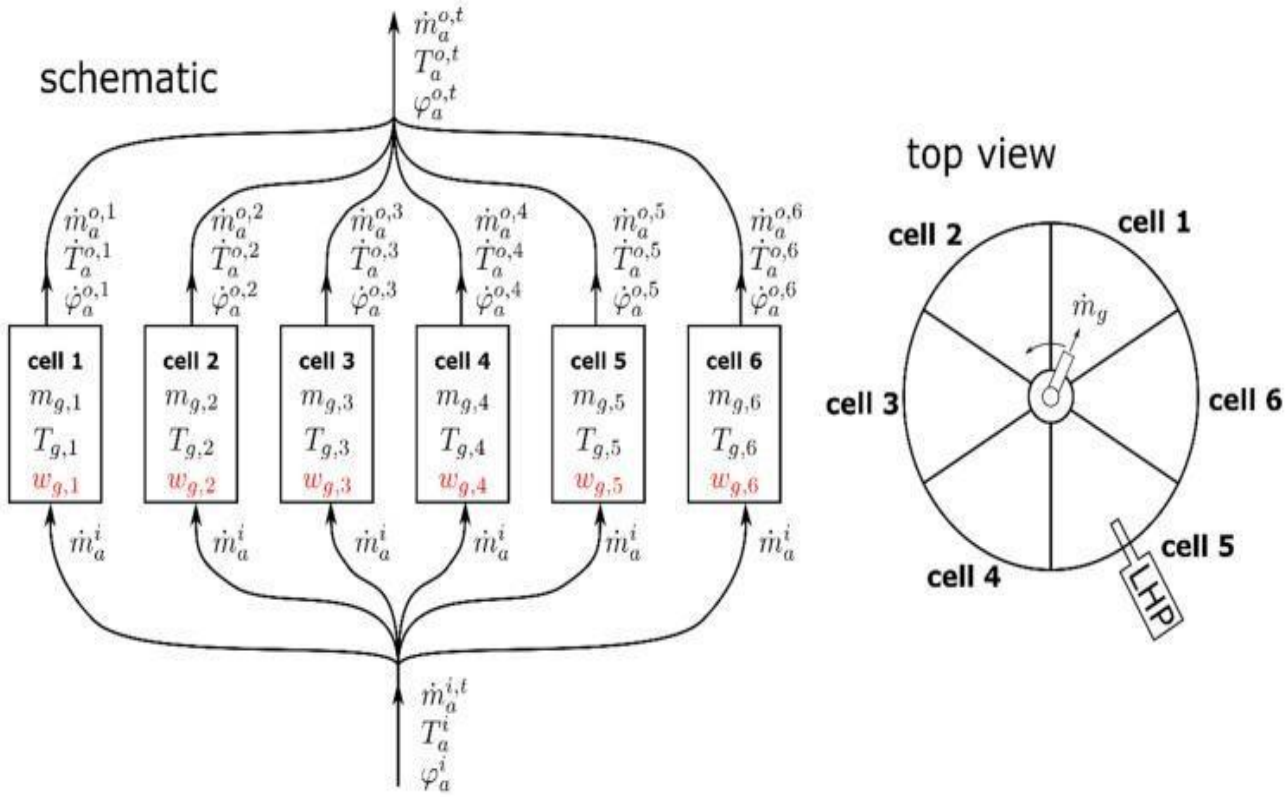

FIGURE 2.5: SKETCH OF THE DRYER CELLS WITH THE PROCESS PARAMETERS ADOPTED FROM REHRL ET. AL. [30].

M: MASS DRY BASIS **W:** WET MASS BASIS **T:** TEMPERATURE **ψ:** RELATIVE HUMIDITY

For this research work, the loss on drying values used was acquired via SIPAT which is connected to the SCADA system of the ConsiGma line via OPC DA. Other models of the fluidized bed dryer also exist in literature which used different process parameters to predict the moisture content of the granules at the end of the drying cycle [54], [56], [57].

To track the material from the drying unit, the cell number and filling cycle or fill index of each raw material were used. The granule from each cell was assigned a product key number which is then dynamically tracked as a function of time. The mathematical formulation used to calculate the product key (PK) is presented in equation 2.8.

The fill index (***FI***) is the filling cycle of the cells which means that for each filling cycle, the six cells are filled.

The cell index (CI) is the cell number of each cell during one filling cycle. Therefore, for each filling cycle, the cell index is numbered one to six. Using equation 2.8, a product key number is assigned to the materials of each cell during a filling cycle.

$$PK = (FI - 1) * 6 + CI \qquad 2.8$$

Based on the PK of the material an average value of the parametric variables that will be tracked along the manufacturing line is calculated and assigned to each set of granules leaving the dryer, i.e., to each PK. These assigned values are then tracked along the line until the dosage form is produced in the tablet press. For this research work, the variables tracked are API concentration (PKC), moisture content (LOD), granules size (M50) and mass. Other properties can be defined, averaged, and assigned to a PK number as well.

2.5 Mill

After the drying of the granules, they are pneumatically transported to the mill for size reduction and de-agglomeration. This is done to obtain a narrow particle size distribution (PSD) of the granules. The mill consists of a sieve that only lets a particular size range of particles through. A model of the mill based on population balance (PBM) has been developed by Metta et. al. [53] and this model can be used to predict milled granule size distribution.

2.6 Tablet Press

The ConsiGima-25 line is equipped with a rotatory tablet press. The rotatory press has a tooling station which rotates to compress granules into tablets of uniform size, shape, and weight based on the parametric settings of the press. The compaction force on the fill material is exerted by the upper and lower punch of the press leaving the powder granules to be compressed in the middle [42]. The production capacity of the press depends on the rotation speed of the press, and this has the advantage of eliminating the need for a scaleup after research and development of the right operating conditions have been completed.

The granules spend a significant amount of time in the hopper of the tablet press and along the barrel before tabletting takes place. This presents a difficulty in tracking the material. To solve this problem the hopper of the tablet

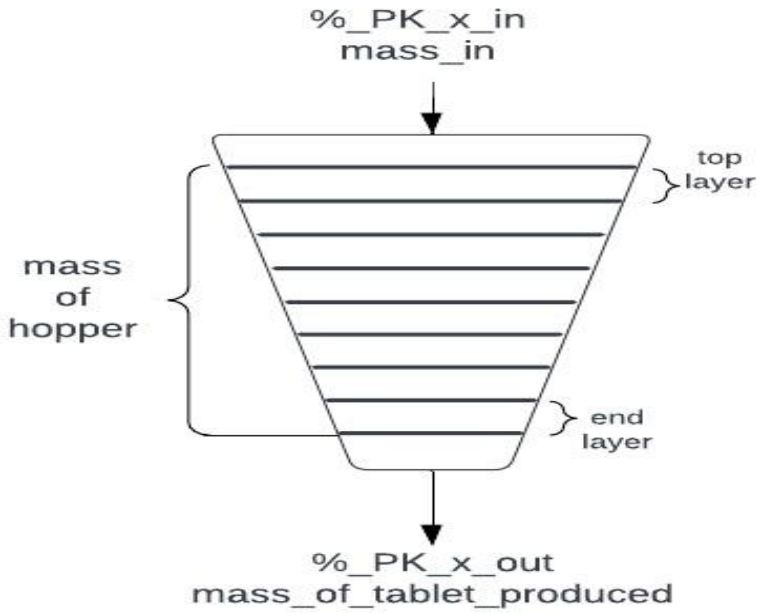

FIGURE 2.6: THE TABLET PRESS HOPPER DESIGN.

press was divided into 500 equal layers and these layers served as a metric to quantify the material passing through the hopper. Figure 2.6 illustrates the hopper function design. The ***mass_in*** is a quantification of the amount of ***PK_x_in*** that is conveyed into the hopper, this quantification is then used to determine the number of layers ***PK_x_in*** is going to occupy. The topmost layer is computed as a percentage difference between the **PK** in the topmost layer and the **PK** being introduced. The last layer or the end layer is the mass being used to produce tablets.

To successfully track the materials along the whole press, an RTD model of the press developed by Forgber et. al. [54] was used. This RTD model was adapted to output the properties of PK as a function of time using the quantity of mass passing through the press. A graphic illustration of the process is presented in figure 2.7. According to this figure, PK1 has completely exited the

press, while PK2 has only 40% of its mass used and PK3 is still in the hopper. The graph displays the percentage of the PKs exiting the press and the time they spent in the press. At the exit of the press, there are PAT tools to measure the CQAs such as weight, friability, shape etc. With the information acquired from each unit operation via its inline PAT tools and RTD models, a model was successfully developed using Simulink (MathWorks, 2022b)[55] to dynamically track each product key (PK) along the line and relate every tablet produced to a particular PK value passing through the unit operations at any time.

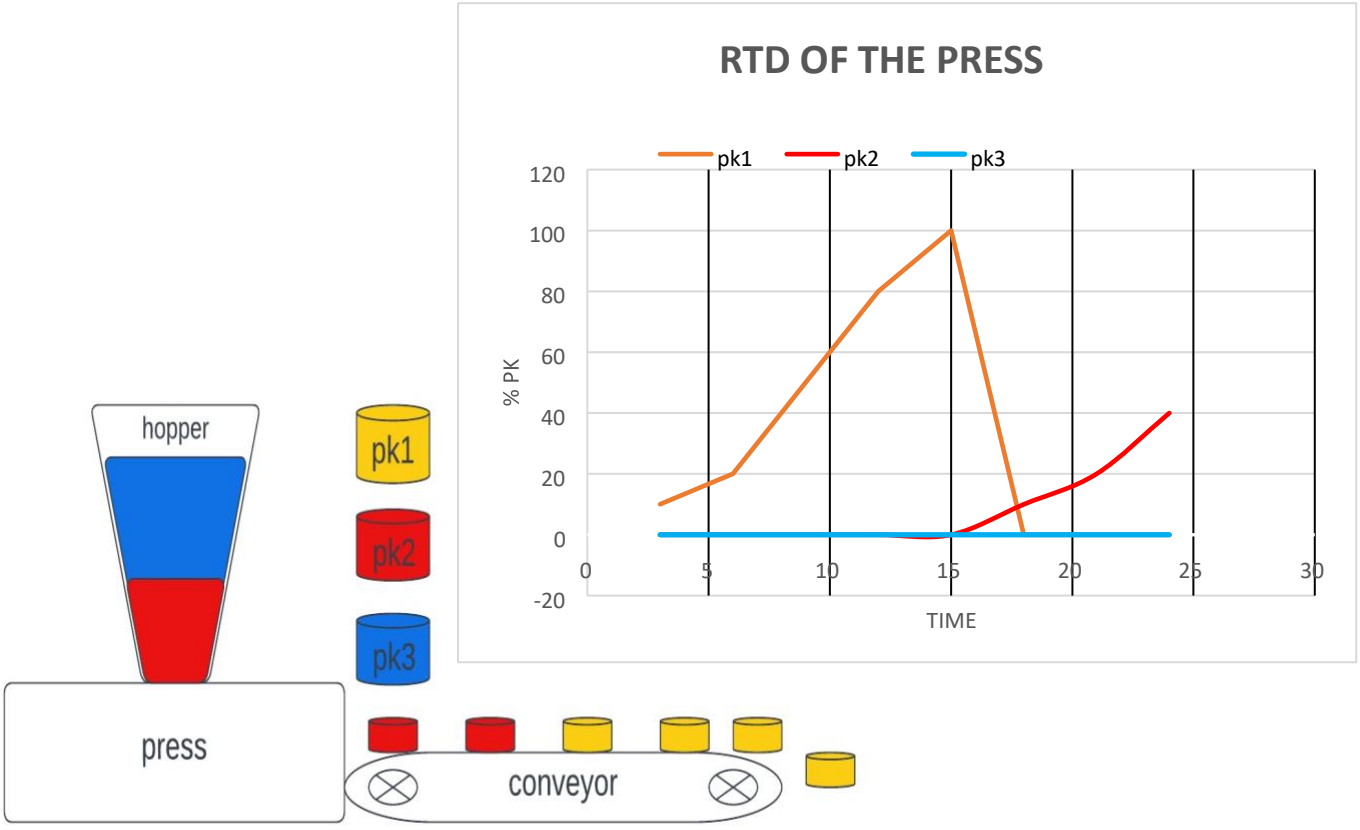

FIGURE 2.7: A RESIDENCE TIME DISTRIBUTION OF THE TABLET PRESS ILLUSTRATION.

3.0 Model Development Method

3.1. MATLAB and Simulink

The material tracking model for this work was developed using the MATLAB programming language and Simulink. MATLAB is a matrix-based programming language that can be used to analyze and visualize data. Simulink is a block diagram environment for model design and simulation [58]. Data obtained from the production test run of the line was processed by MATLAB scripts. The time of production, granulation settings, particle size distribution, dryer LOD, cell indexes, and fill indexes were obtained as raw data (Appendix A). The residence time distribution model of the tablet press developed in another research work by Forgber et. al. [59], was used to model the flow of the material through the tablet press.

The results generated by the scripts were then used as inputs to the Simulink model that was developed. The developed Simulink model is a replica of the material transport through the ConsiGma-25 continuous manufacturing line.

3.2. Dryer function block

To identify the materials passing through the drying unit operation, a function block model was designed to accept input from various process parameters, including mass, granule size, PK concentration, fill index, and cell index (Appendix B1 and B2). These parameter values were acquired from the ConsiGma line software following a test run and were dynamically assigned in a linear order using the function block model. As a result, the values of all the input parameters were simultaneously available for any given mass of granules passing through the dryer. The fill index represents a unit filling cycle when the six cells of the dryer are filled, and the cell index is the number assigned to each of the six cells. The output of this function block was modelled to output the PK number coming out from the dryer with the parametric values of the other variables. The function block was programmed to provide output independent of the filling time, but instead based on changes in PK number. This approach was designed to address delays in the filling

process that may arise due to unforeseen circumstances during operation. By focusing on PK number changes rather than filling time, the function block ensured that the output remained accurate and reliable, even during unexpected variations in the filling process.

3.3. The Assignment function block

An assignment function block was designed to accept the outputs of the dryer function block in addition to the loss on drying (LOD) data from the LOD subsystem and the PK of the granules going into the hopper of the tablet press (Appendix B3 and Appendix B4). The LOD and its PK were calculated differently because the emptying cycle of the cells was different from the filling cycle that was used for the dryer function block calculation. The parametric values of the variables were averaged per product key in this function block. These values were then assigned to the corresponding PK going into the hopper of the press. The output of this model is then a dynamic correlation between the PK numbers and the parametric values of the properties of the PK to be tracked.

3.4. The hopper function block

The hopper function block was designed to function as a plug flow reactor, with the first in - first out principle, the mass of the material in the hopper was divided into tiny layers such that one single layer represented a certain quantity of material with its properties dynamically assigned per second (Appendix B5 and Appendix B6). In addition to the output from the assignment block, the hopper feed function block had as input, an integrator function block, the number of layers the hopper was divided into, the total mass the hopper could hold, the mass of the tablet coming out of the hopper and a logic variable.

The integrator continually depletes the last layer of the hopper using the mass flow rate of the tablets produced as an input. The value of the integrator is fed back into the hopper function block. This value is used to compute the mass of the material in the hopper. Thus, the output of the hopper is the mass of

material currently in the hopper, the PK values of the tablets produced together with the parametric values of their properties as a function of time.

3.5. The tablet press function block

To model the amount of time the granules spend in the tablet press, a residence time distribution model developed from previous experiments by Forgber et. al. [59] was used.

The parameters tracked from the hopper were used as inputs to this RTD model.

This model gave an output of the percentage of the PKs and the properties of the PKs as a function of time. The output signal showed the period the materials had spent in the press.

4.0 Results and Discussion

4.1. The dryer function block

Figure 4.0 shows the plots of the granule size data from the granulator and the filling cycles of the dryer against the time of the simulation. The signal of the cell index shows the time for filling the individual cells and when it ends. A combination of six cell indexes indicates one filling cycle or one fill index. Equation 2.8 was used in the MATLAB script to calculate the PK number of each cell content using the cell index and the fill index, and this was used as input to the dryer function block. The cell index vs granule size plot of figure 4.0 shows the cell numbers of each cell being filled per filling index and the granule size of powder used to fill it.

From the plot, for each filling cycle, it can be observed that the second cell was being filled before the previous cell had finished filling, this is the data structure as obtained from the ConsiGma-25-line software, but the cells are filled sequentially. The filling of the six cells then constitutes one filling cycle. Each filling cycle constitutes six cell indexes grouped as seen on the plot. The second plot is an enlargement of the main plot which shows one filling cycle. The granules size plot varies along the cell indexes and remains constant (which translates to zero) when no filling is being done. This translates to the size of the granules filled per cell.

Figure 4.1 shows a plot of granules size and PKs output from the dryer function block against the time of simulation, here the redundant part of the end of the filling process is removed. Rather the PK numbers are now a progressive parametric variable that shows the value of each PK per unit of time. The PK variable is now a form of mini–batches of materials exiting the dryer. Also, the granule size is seen to follow the trend of each PK out per second in figure 4.1. This is the average value of the size of the granules per second. Other variables also show the same trend as the granule size variable and vary concisely with PK values per second.

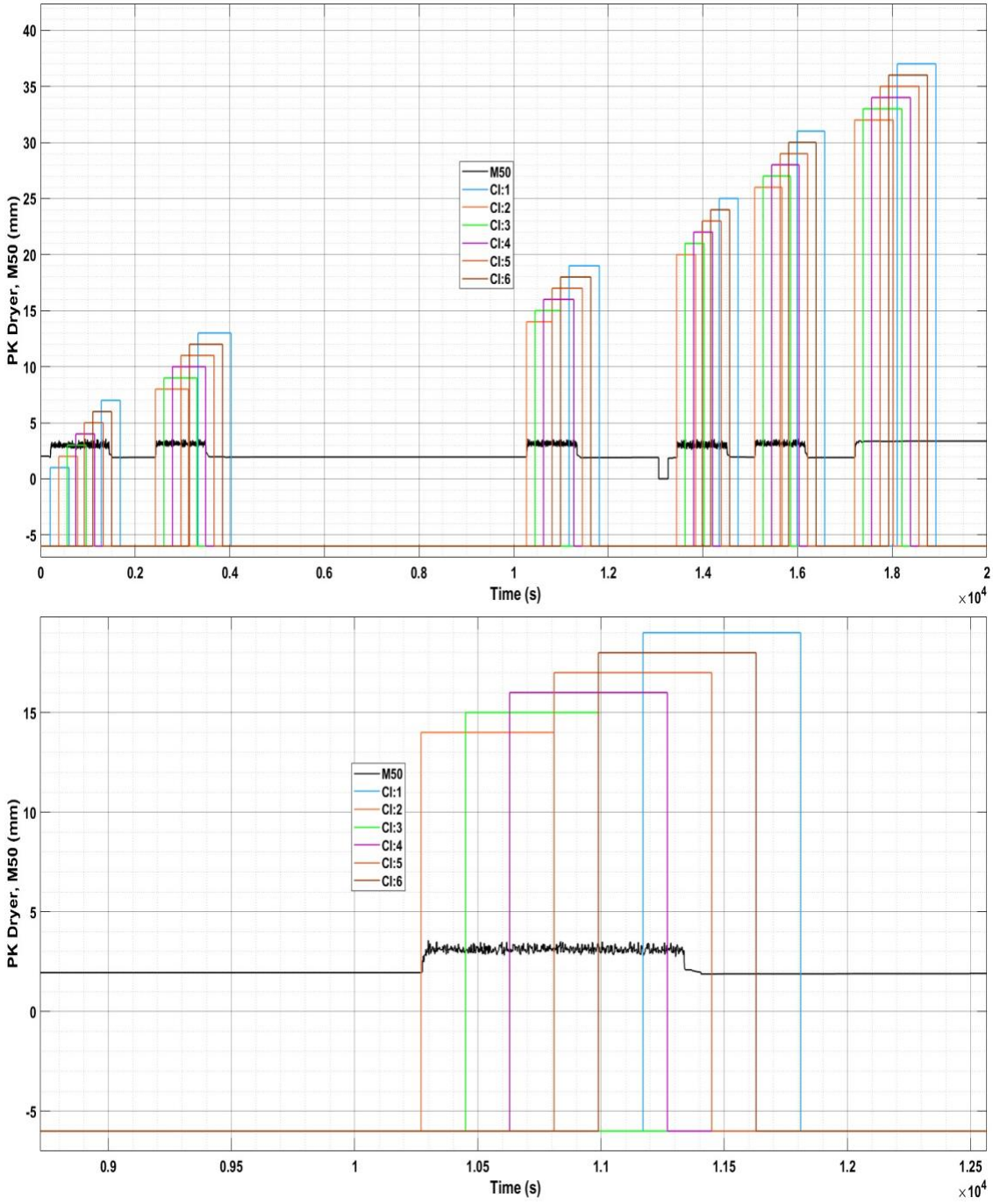

FIGURE 4.0: RELATIONSHIP BETWEEN GRANULE SIZE (M50) AND CELL INDEX (CI) AS INPUT VARIABLES FOR THE DRYER FUNCTION BLOCK.

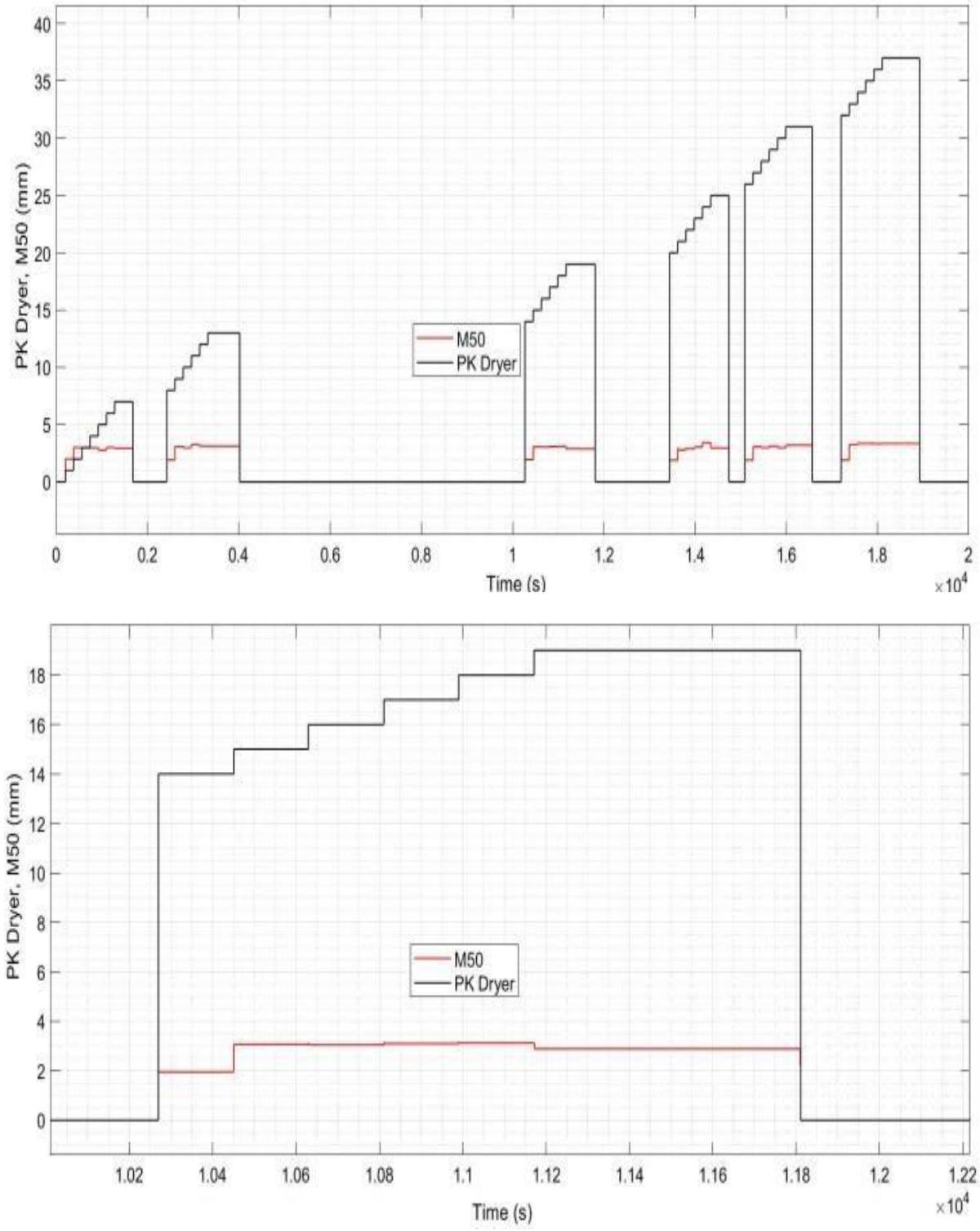

FIGURE 4.1: GRANULE SIZE (M50) AND PK OF THE DRYER SIGNALS LEAVING THE DRYER FUNCTION BLOCK.

4.2. The assignment block function

The Final LOD of the granules and the PK numbers (PK LOD) of each cell were calculated by the LOD subsystem. PK LOD was calculated using equation 2.8 based on the cell indexes (CI) at the end of the drying cycles or during the emptying of the cells. This is different from the PK numbers calculated previously which were based on the cell indexes at the beginning of the drying cycle or during the filling of the cells. The Final LOD values and the PK numbers were passed into the assignment block.

Figure 4.2 shows a plot of the LOD, the Final LOD, and the Cell number of the cells against the simulation time. The LOD plot shows how the moisture content of the granules of each cell decreased with time and the Final LOD is the moisture content of the granules at the end of the drying cycles. The values of the Final LOD plot are seen to correspond to the final values of the LOD plot of each cell.

The PK numbers (PK Hopper) of the granules going into the hopper of the tablet press are calculated in the MATLAB script (Appendix A) and passed into the assignment block as a variable. The assignment block assigns values of the properties of the PK numbers of the granules exiting the dryer i.e., Granule size (M50), API concentration (PKC), Final LOD and the PK mass to the PK numbers (PK Hopper) of the granules going into the hopper model.

Figure 4.3 shows the plot of PK Dryer and M50, Final LOD and PK_LOD, and PK Hopper against the time of the simulation. Other properties were ignored for the sake of simplicity, but they showed a similar trend as the M50. The M50 and Final LOD varied concisely with PK Dryer and PK LOD while the PK hopper had different periodic intervals. The difference in the periodic intervals of the three PK numbers is indicative of the time of filling the cells, the time of emptying the cells, and the time of transporting the contents of the cells through the hopper of the press.

The assignment block was used to assign the properties of each PK Dryer and PK LOD to their corresponding PK Hopper based on the assigned PK numbers. Figure 4.4 depicts the granule properties as a function of PK numbers, showing how the properties of the granules vary concisely with the PK numbers of the granules being fed into the hopper model. This shows that the model correctly tracked the properties of the granules from the dryer cells to the hopper of the tablet press.

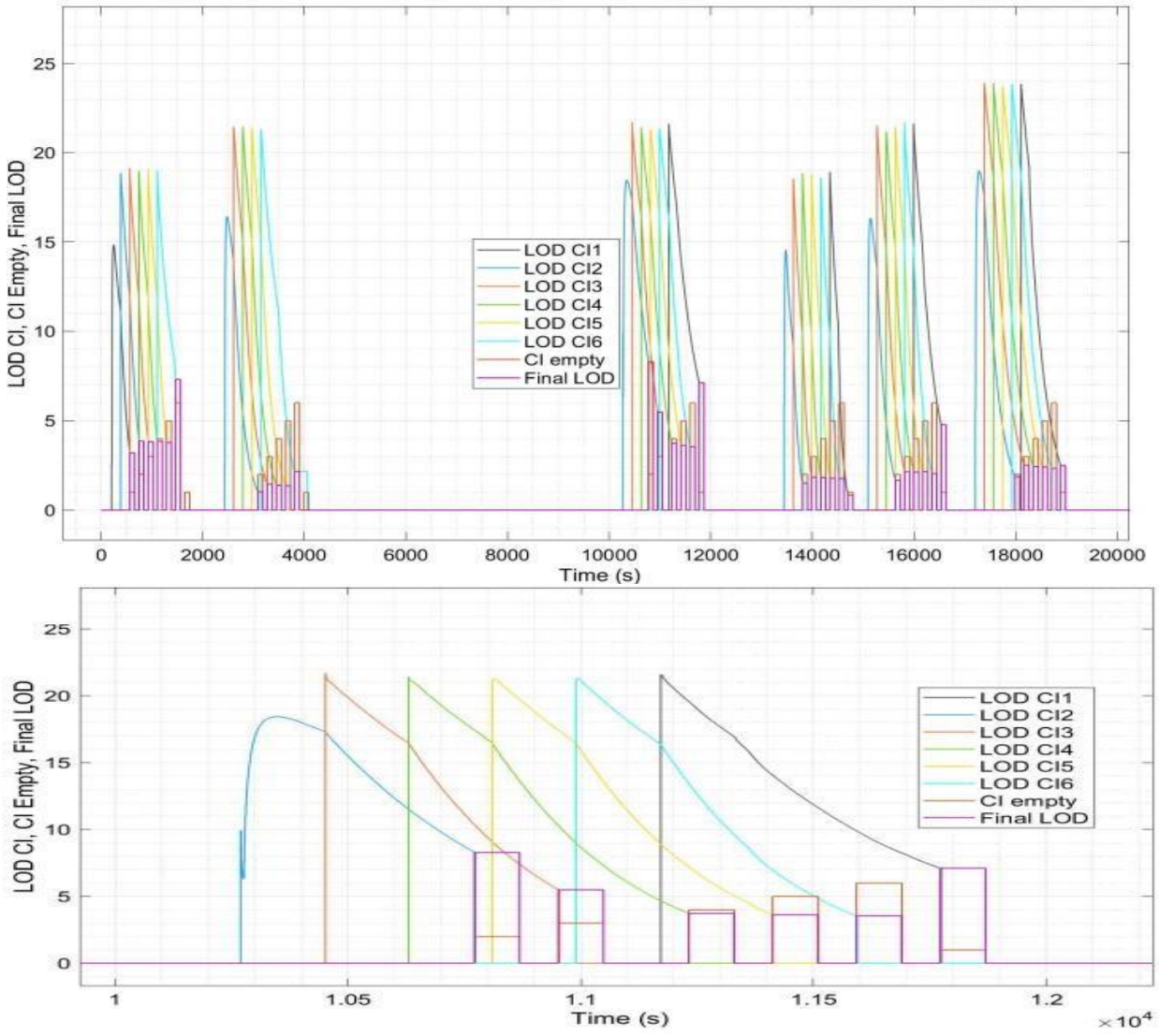

FIGURE 4.2: THE LOD OF EACH CELL DURING THE DRYING PROCESS AND THE FINAL LOD OF EACH CELL AT THE END OF THE DRYING CYCLE.

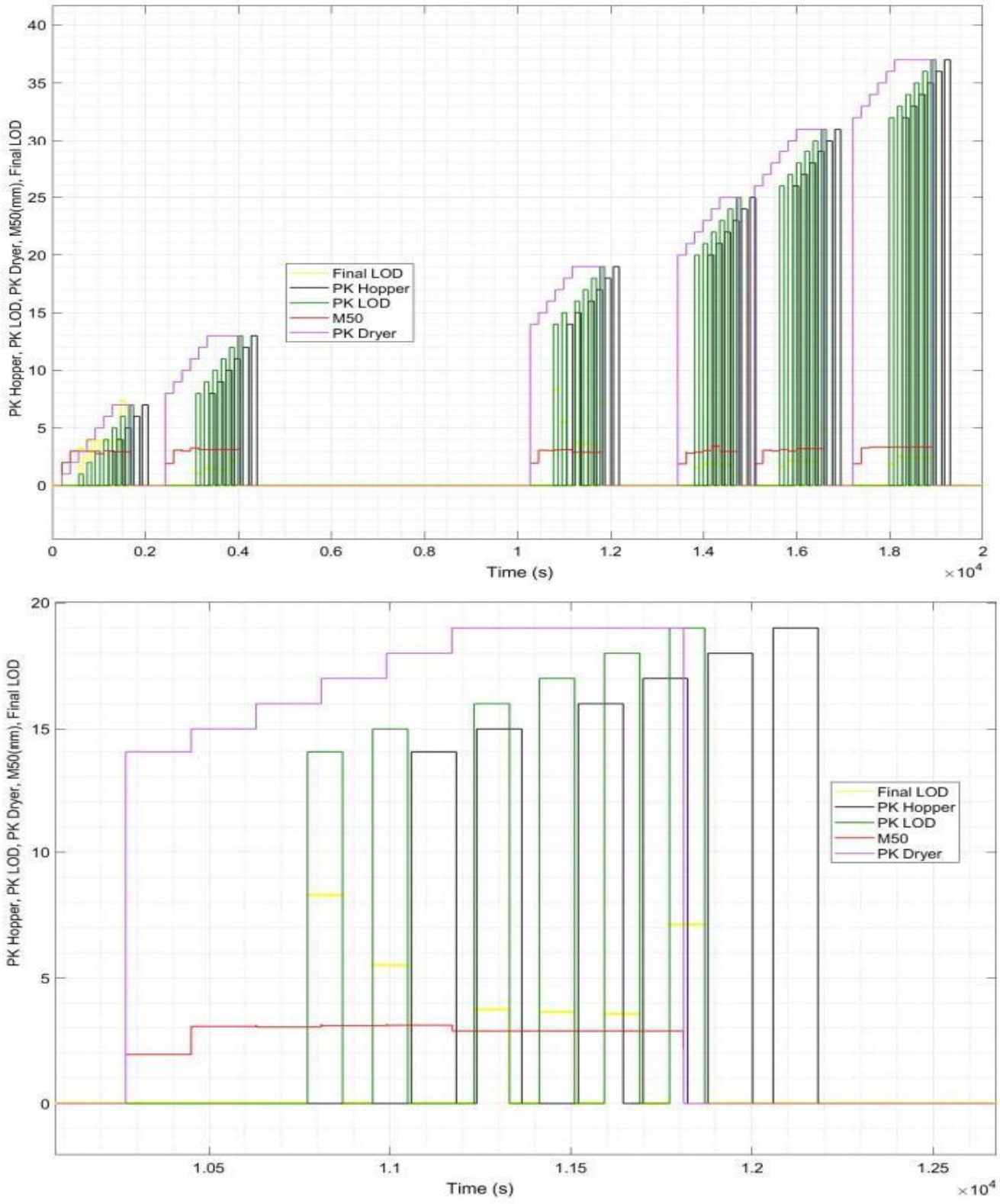

FIGURE 4.3: THE SIGNAL OF THE INPUT VARIABLES TO THE ASSIGNMENT FUNCTION BLOCK SHOWING THE PK DRYER, AND PK LOD WITH THEIR RESPECTIVE PROPERTIES, AND THE PK HOPPER.

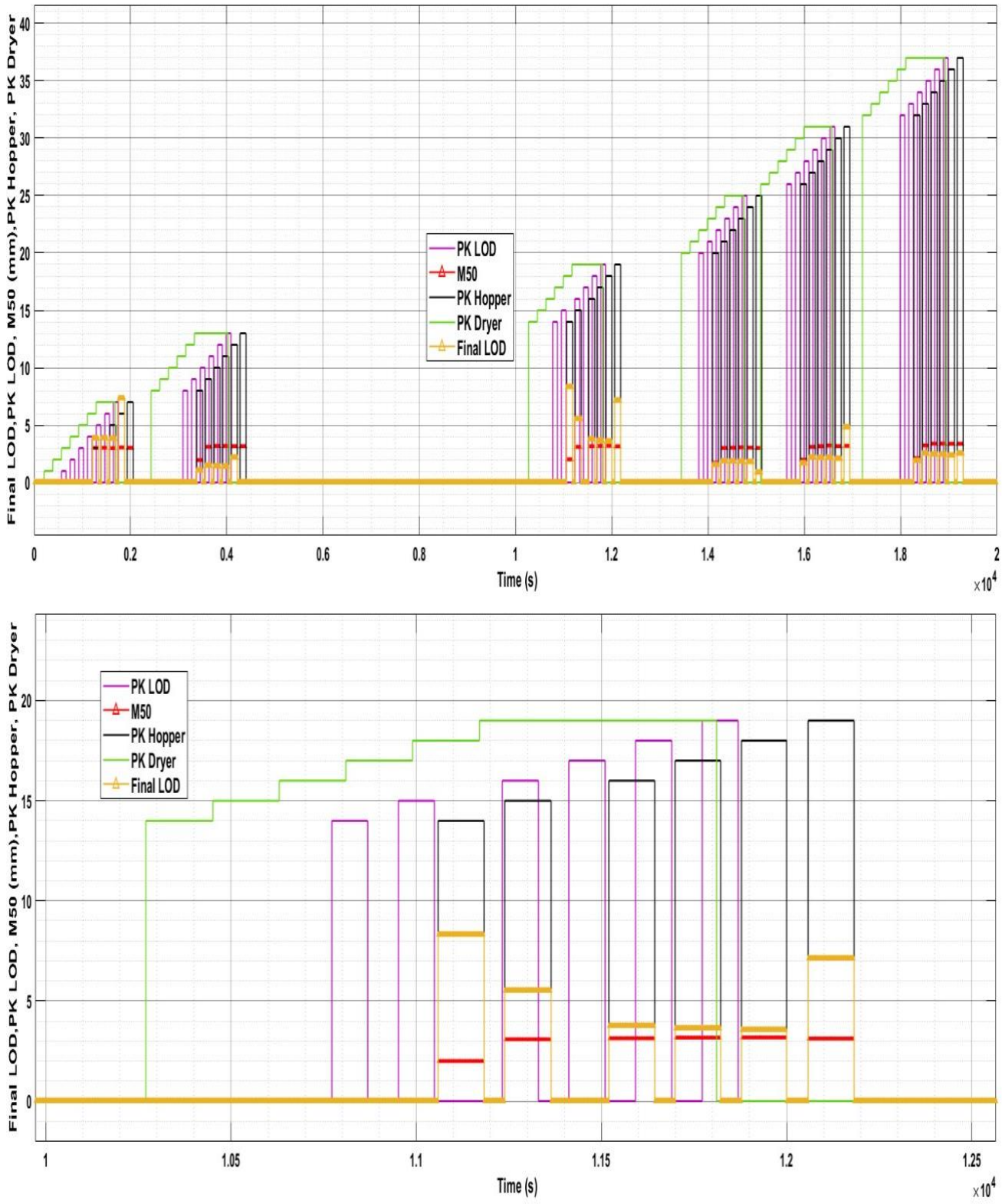

FIGURE 4.4: THE SIGNAL OF THE OUTPUT VARIABLES FROM THE ASSIGNMENT FUNCTION BLOCK SHOWING THE PROPERTIES OF PK DRYER AND PK LOD ASSIGNED TO PK HOPPER.

4.3. The hopper function block

The mass of granules (Hopper Mass) that is held up in the hopper was calculated using a concentration term, the mass of granules per layer. The number of tiny layers that the hopper can contain is an arbitrary constant pre-determined by the author. Each layer in the hopper corresponds to a PK value and to the value of the properties of that PK.

As the mass hold up of the hopper increases, the number of layers occupied by the mass also increases. Since each layer of mass has an assigned PK number their properties are easily tracked in the hopper. The last layer in the hopper is labelled M1 init and this is the layer that is used to produce the tablets during tabletting. When M1 init depletes or finishes, the preceding layer becomes M1 init and the Hopper Mass hold-up is recomputed. The M1 init is integrated using the mass flow rate of the tablets being produced.

Figure 4.5 shows the plot of Hopper Mass and M1 init, the Hopper Mass is seen to decrease when M1init is being depleted and replenished. However, M1 init remains constant when the Hopper Mass is increasing. This shows that M1 init was correctly depleted using the mass flow rate of the tablets and replenished by the preceding last layer of the Hopper Mass.

The PK values of the mass flowing into the hopper were assigned to the PK values of the mass flowing out of the hopper. The assignment results are illustrated in figure 4.6. The increase in the Hopper Mass levels corresponds to the change in PK values of the mass flowing into the hopper, and the decrease in the Hopper Mass levels corresponds to the PK values of the mass flowing out of the hopper. Since the values properties of the granules are a function of the PK values, the properties of mass flowing out of the hopper can easily be determined by the PK value assigned to it. This indicates that the model made the correct assignment of the PK properties of the mass entering the hopper to the PK properties of the mass exiting the hopper.

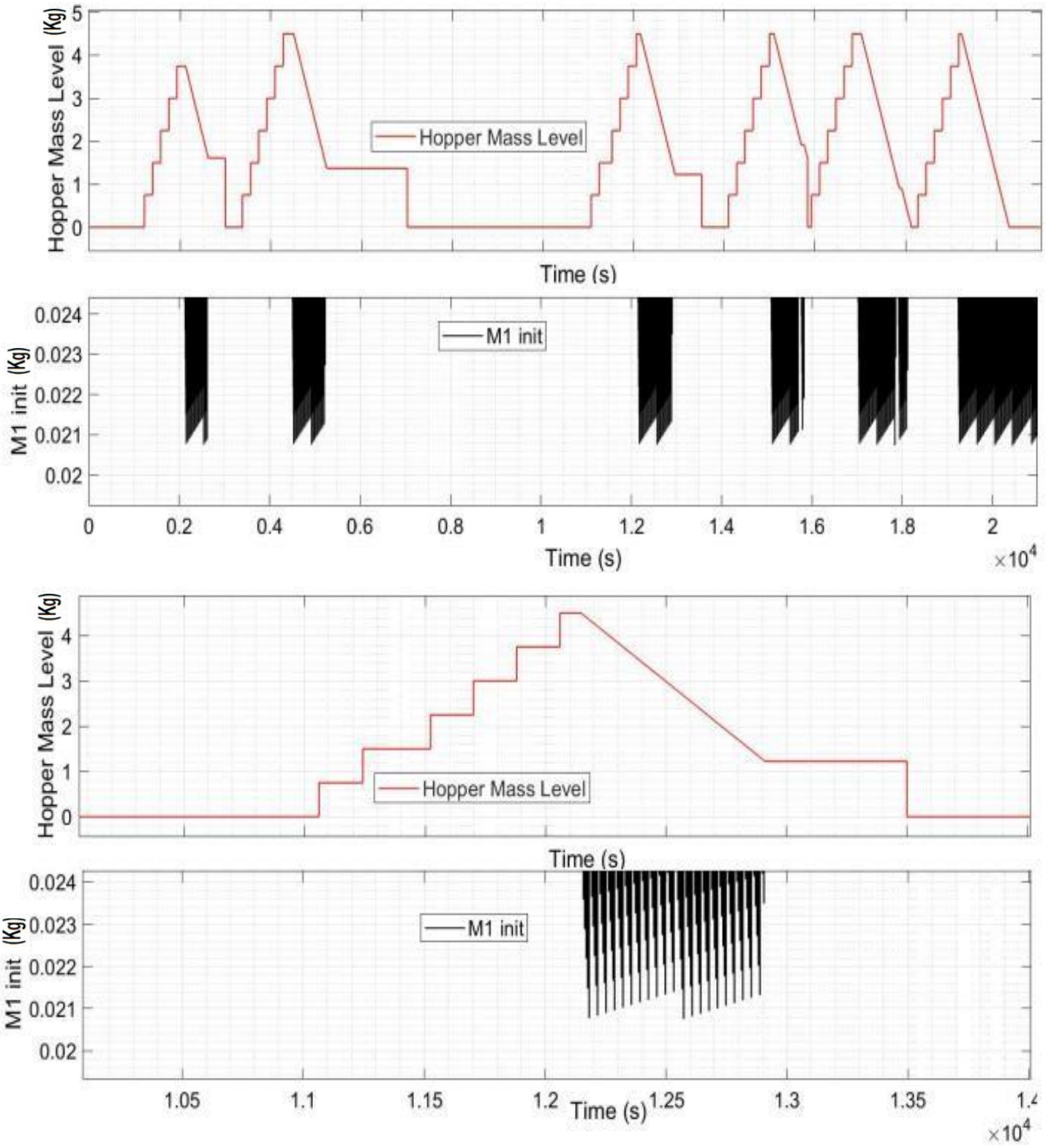

FIGURE 4.5: THE SIGNAL OUTPUT OF HOPPER MASS LEVEL AND M1 INIT COMPARING THE CHANGE IN LAYER LEVEL OF HOPPER MASS AND THE DEPLETION OF THE LAST LAYER OF THE HOPPER.

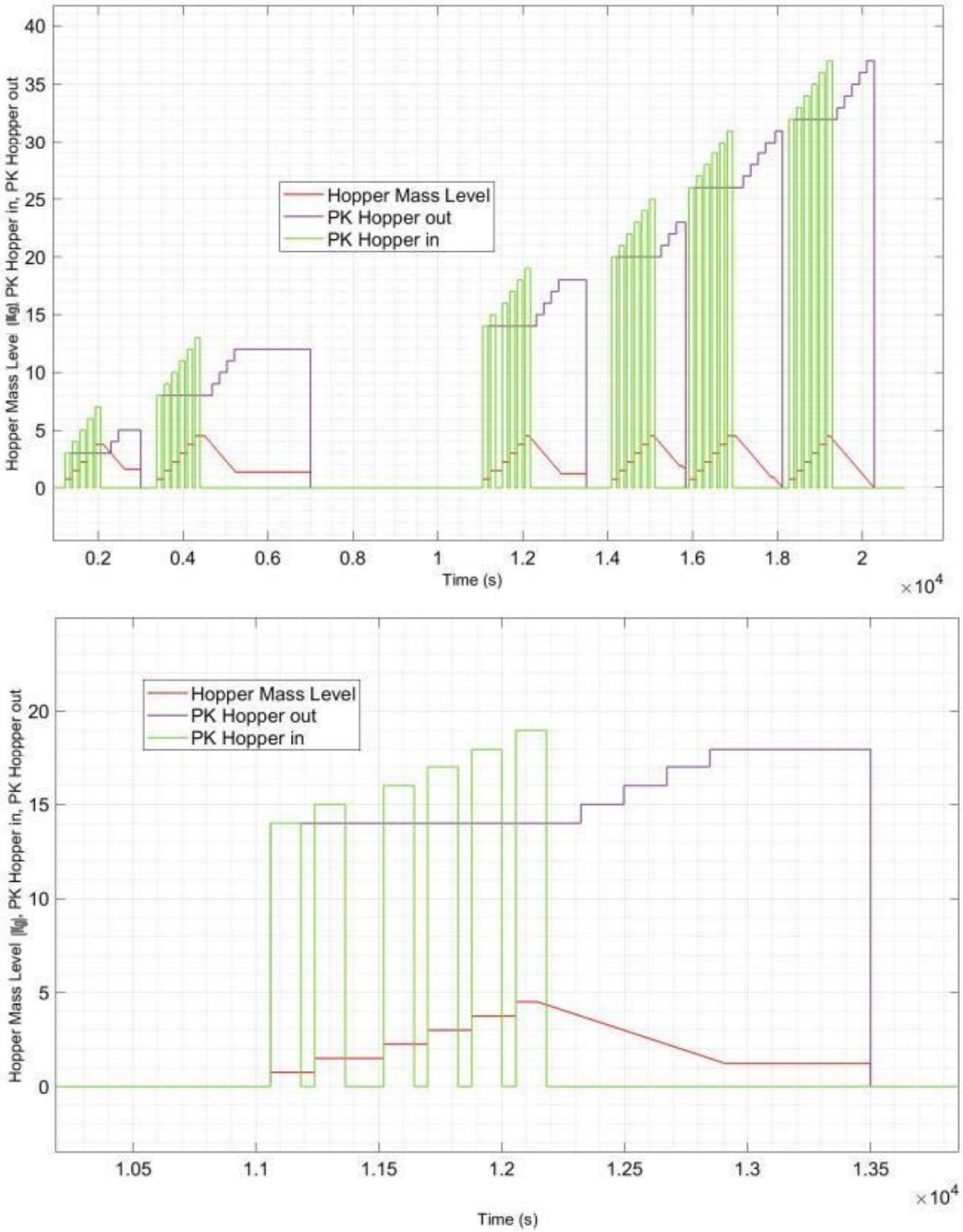

FIGURE 4.6: A PLOT SHOWING THE CHANGE IN THE HOPPER MASS LEVEL VARYING WITH THE INPUT PRODUCT KEYS AND OUTPUT PRODUCT KEYS.

4.4. The tablet press function block

The tablet press function block is an RTD model used to predict the period every mass of granule spends in the press. The properties of the PK numbers exiting the press are tracked by the mass of PK numbers exiting the press. The mass of the PK in the hopper was divided into tiny layers and these are continually fed into the RTD model and tracked by the PK numbers. This means when an OOS (out of specification) material is used to produce a tablet, the tablet can easily be identified and discarded since the layers of the PK used to produce the tablet can be identified and the percentage of PK contained in tablets produced during the transition between PKs can be calculated from the RTD model. This is because the period each tiny layer spends in the press is correctly quantified.

The signal output of the properties of the PK numbers from the tablet press RTD function block was plotted with the PK number output from the hopper function block against simulation time in Figure 4.7. The PK values leaving the hopper correctly correspond to the percentage output of the values of the properties of the PK leaving the hopper. This shows that the RTD model correctly predicted the quantity of mass of each PK flowing out of the press at every period.

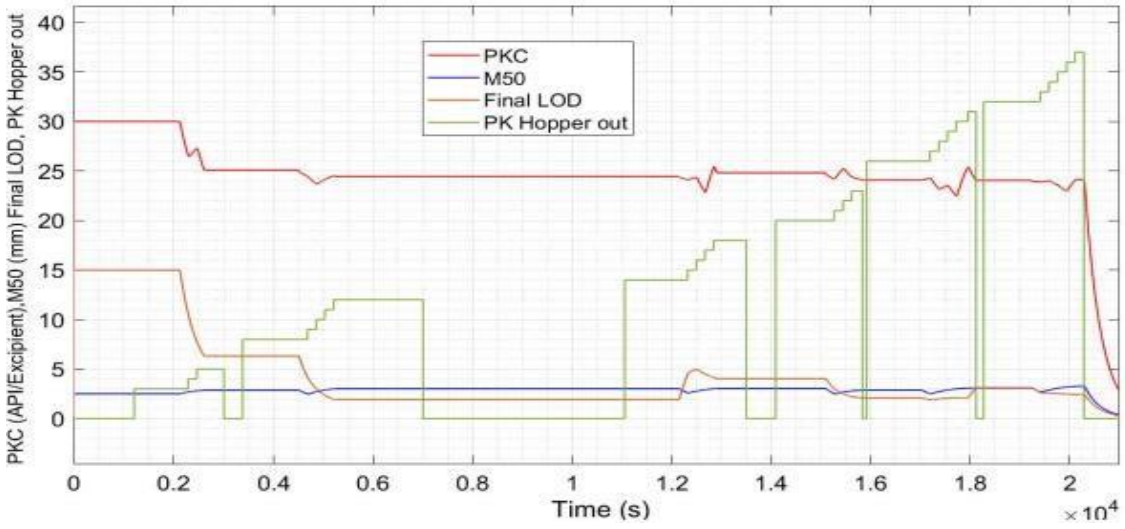

FIGURE 4.7: PK PROPERTIES OUTPUT SIGNALS FROM THE TABLET PRESS RTD MODEL AND PK OF THE MATERIALS LEAVING THE HOPPER.

5.0 Conclusion

The model correctly assigned the PK numbers to the granules leaving the dryer cells using the cell index and the fill index of each filling cycle. The quality attributes of the granules were collected by in-line measurement tools and assigned to the PK numbers leaving the dryer. These quality attributes were then averaged and reassigned to the PK numbers entering the hopper of the tablet press in the same order as the PK numbers of the dryer. The hopper of the tablet was correctly modelled to tackle the problem of back mixing and the granules used to produce the tablets could be correctly tracked to a particular PK number. The tablet press model correctly modelled the residence time of the material in the tablet press and assigned the values of the properties of the tablets being produced to the right PK number. Hence it was shown that the model can be used to successfully track granules and their properties using product keys along the ConsiGma-25 line during continuous production.

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Appendix A: Script used to acquire the data

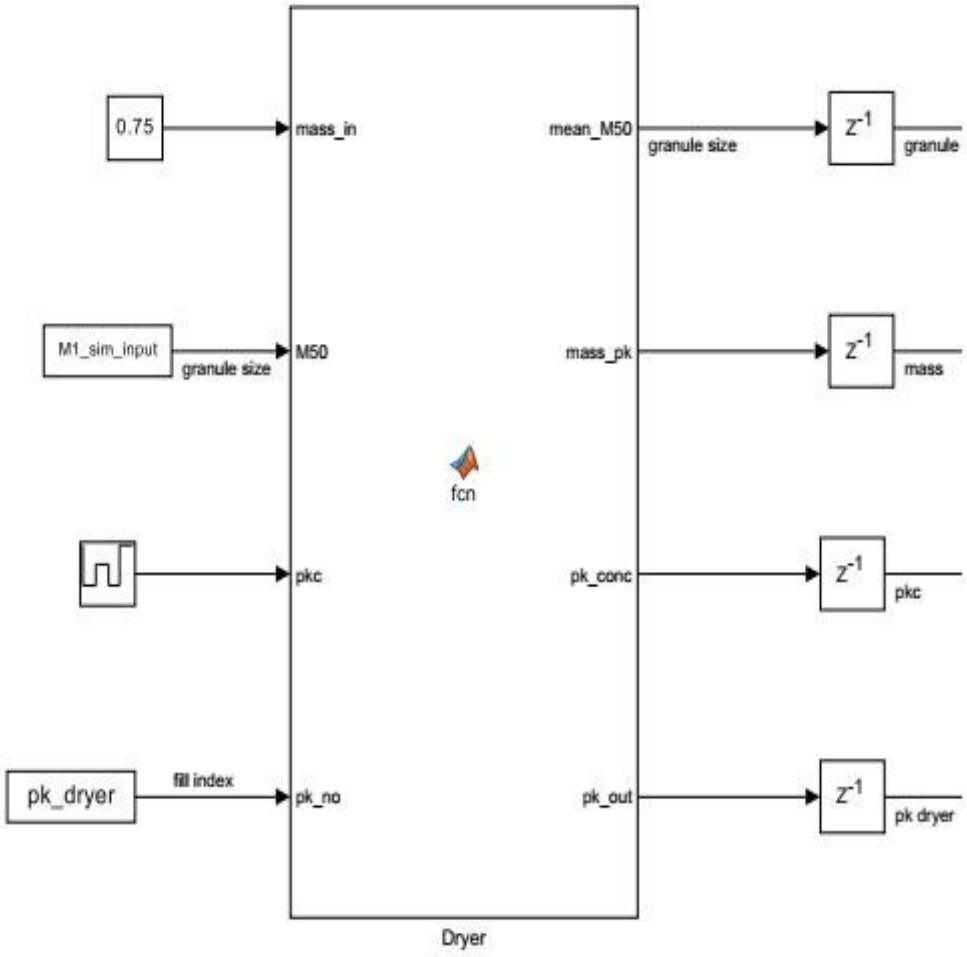
```
% Matlab script Get ConsiGma data
% Author: Selma Celikovic
% Reused by Charles Bernard Aghadi
%Date: 2022/05/05

% Add necessary paths
addpath('functions', 'data')

% Load the experimental data
data_exp = load('20220317_CAPRI101.mat');
data_exp = data_exp.data;

% Get time signal
t = data_exp.get_signal('X_feeder_1_massflow').t;

% Get granulation settings
SFR = data_exp.get_signal('X_feeder_1_massflow').values; % solid feed rate
LFR = data_exp.get_signal('XF_TSG_pump1_massflow').values; % liquid
feed rate LS = LFR./SFR*6; % LS ratio

% Get PSD information
sieve_vec =  [29.3; 34.1; 39.8; 46.4; 54.1; 63.1; 73.6; 85.8; 100; 116.6;
135.9; 156.5;
              184.8; 215.4; 251.2; 292.9; 341.5; 398.1; 464.2; 541.2; 631;
735.6; 857.7;
              1000; 1165.9; 1359.4; 1584.9; 1847.8; 2154.4; 2511.9;
2928.6; 3413.5;
              3981.1; 4641.6; 5411.7; 6309.6];
Q3 = [];
% Loop through all the sieve sizes and get the Q3 signal
values for ii = 1 : length(sieve_vec)
    Q3  =  [Q3;  data_exp.get_signal(['GetLogQ3SizeDichte_',  num2str(ii-
1)]).values']; end Q3 = Q3/100;

% Calculate M1 moments
[M1_log] = calc_moments(Q3, log10(sieve_vec));

% Get LOD signals
LOD1 = data_exp.get_signal('Local Items.Matlab.ML_tag_001').values; % LOD
in cell 1
LOD2 = data_exp.get_signal('Local Items.Matlab.ML_tag_002').values; % LOD
in cell 2
LOD3 = data_exp.get_signal('Local Items.Matlab.ML_tag_003').values; % LOD
in cell 3
LOD4 = data_exp.get_signal('Local Items.Matlab.ML_tag_004').values; % LOD
in cell 4
LOD5 = data_exp.get_signal('Local Items.Matlab.ML_tag_005').values; % LOD
in cell 5
```

```
LOD6 = data_exp.get_signal('Local Items.Matlab.ML_tag_006').values; % LOD
in cell 6 LOD = [LOD1, LOD2, LOD3, LOD4, LOD5, LOD6];

% cell tracking dryer
CI_C1 = data_exp.get_signal('DT_CELL_INDEX_CELL_1').values;
CI_C2 = data_exp.get_signal('DT_CELL_INDEX_CELL_2').values;
CI_C3 = data_exp.get_signal('DT_CELL_INDEX_CELL_3').values;
CI_C4 = data_exp.get_signal('DT_CELL_INDEX_CELL_4').values;
CI_C5 = data_exp.get_signal('DT_CELL_INDEX_CELL_5').values;
CI_C6 = data_exp.get_signal('DT_CELL_INDEX_CELL_6').values;
CI = [CI_C1 CI_C2 CI_C3 CI_C4 CI_C5 CI_C6];


%%product key tracking

FI_C1 = data_exp.get_signal('DT_FILL_INDEX_CELL_1').values;
FI_C2 = data_exp.get_signal('DT_FILL_INDEX_CELL_2').values;
FI_C3 = data_exp.get_signal('DT_FILL_INDEX_CELL_3').values;
FI_C4 = data_exp.get_signal('DT_FILL_INDEX_CELL_4').values;
FI_C5 = data_exp.get_signal('DT_FILL_INDEX_CELL_5').values;
FI_C6 = data_exp.get_signal('DT_FILL_INDEX_CELL_6').values;
FI = [FI_C1 FI_C2 FI_C3 FI_C4 FI_C5 FI_C6];

% cell emptied from dryer
cell_ind_empty = data_exp.get_signal('DT_CELL_INDEX_PCH').values;
cell_ind_empty_sim = [t, cell_ind_empty];
fill_ind_empty = data_exp.get_signal('DT_FILL_INDEX_PCH').values;
fill_ind_empty_sim = [t,fill_ind_empty];

% cell before blender
cell_ind_blend = data_exp.get_signal('DT_CELL_INDEX_PPU_BLENDER').values;
cell_ind_blend_sim = [t, cell_ind_blend];
fill_ind_blend = data_exp.get_signal('DT_FILL_INDEX_PPU_BLENDER').values;


% cell before TP
cell_ind_TP = data_exp.get_signal('DT_CELL_INDEX_PRESS_HOPPER').values;
cell_ind_TP_sim = [t, cell_ind_TP];
fill_ind_TP = data_exp.get_signal('DT_FILL_INDEX_PRESS_HOPPER').values;


% tabletting compaction force
MCF = data_exp.get_signal('OHCA_FDV_Mean').values * 1e-2;
m_gcu =
data_exp.get_signal('WE_gcu_scale_weight').values;
m_EP1 =
data_exp.get_signal('X_feeder_exc1_batchqty').values;
m_EP2 =
data_exp.get_signal('X_feeder_exc2_batchqty').values;
n_tp = data_exp.get_signal('TPSX_FDV_Value').values;
```

```
displacement =
data_exp.get_signal('PDTA_FDOV_Value').values;
flag_tp = displacement>0.16;
fill_level = data_exp.get_signal('CTLX_FDV_HopperLevel').values;

% inputs to the Simulink block

M1_sim_input = [t, M1_log'];
FI_sim_input1 = [t,fill_ind_TP];
CI_sim_input2 = [t,cell_ind_TP];
LOD_sim_input = [t,LOD];
pk_sim =[t,max(0,(fill_ind_TP - 1)*6 +
cell_ind_TP)]; pk1 = (FI - 1)*6 + CI;
pk_dryer = [t,pk1];
```

Appendix B: Block diagrams and their function codes

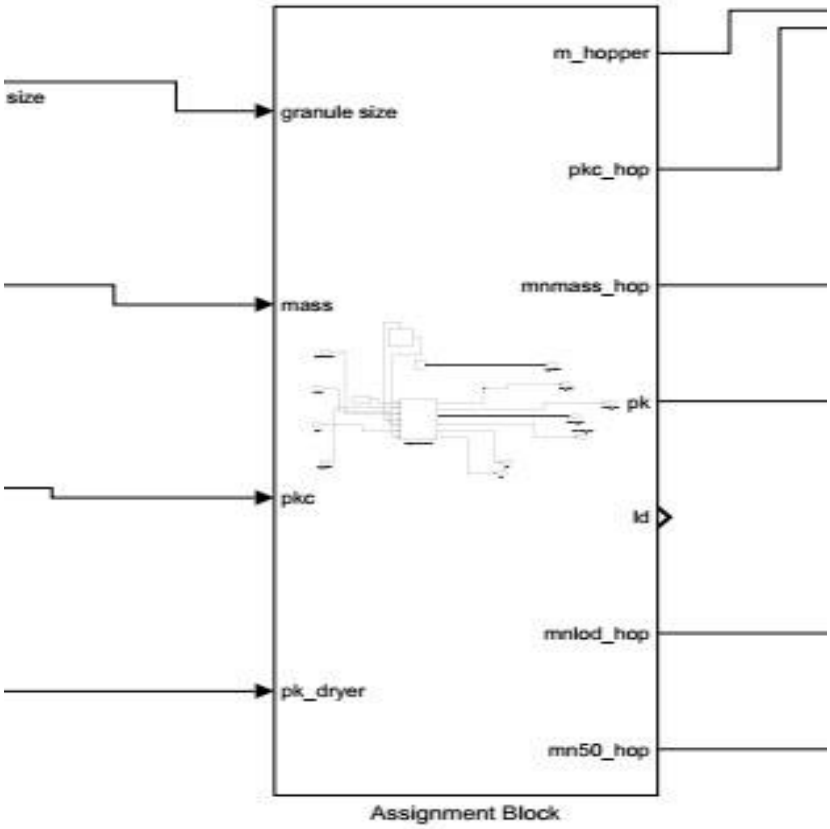
Appendix B1: Dryer Function Block



Appendix B2: Dryer Function Block Codes

```
% Function: Dryer
% Author: Jakob Rehrl and Charles Bernard Aghadi
% Date:Feb 2023
function [mean_M50, mass_pk, pk_conc, pk_out] =
fcn(mass_in,M50, pkc, pk_no)
% Initialize persistent variables
persistent pk1 if isempty(pk1), pk1 = 0 ;end
persistent pk2 if isempty(pk2), pk2 = 0 ; end
persistent pk_old  if isempty(pk_old), pk_old =0  ; end
persistent M50_array  if isempty(M50_array), M50_array = zeros(25000,1); end
persistent mass_array  if isempty(mass_array), mass_array = zeros(25000,1);
end
persistent pkc_array  if isempty(pkc_array), pkc_array = zeros(25000,1); end
persistent mn_M50  if isempty(mn_M50), mn_M50 = 0; end
persistent mn_mass  if isempty(mn_mass), mn_mass = 0; end
persistent mn_pkc  if isempty(mn_pkc), mn_pkc = 0; end
persistent a if isempty(a), a = 1; end
persistent idx if isempty(idx), idx = 1; end
% Store inputs in arrays if idx < length(mass_array)
M50_array(idx) = M50; mass_array(idx) = mass_in;pkc_array(idx) = pkc; end
% Calculate pk value pk_in = max(pk_no(:)); pk_in2 = max(pk_in,0,"omitnan");
if pk_in2 > pk2
pk1 = pk_in2;  pk2 = pk_in2;
elseif pk_in2 == pk2 pk1 = pk2;
else pk1 = pk_in2; end
% Calculate mean values if pk value is greater than 0 and different from
previous peak value
if pk1 > 0 && pk1 ~= pk_old
mn_M50 = mean(M50_array(a:idx));
mn_mass = mean(mass_array(a:idx));
mn_pkc = mean(pkc_array(a:idx));
a = idx+1;pk_old = pk1;

elseif pk1 == 0
mn_M50 = 0;
mn_mass = 0; mn_pkc =0;
end  idx = idx + 1;    pk_out = pk1;
mean_M50 = mn_M50; mass_pk = mn_mass; pk_conc = mn_pkc;
```

Appendix B3: PK Assignment Function Block

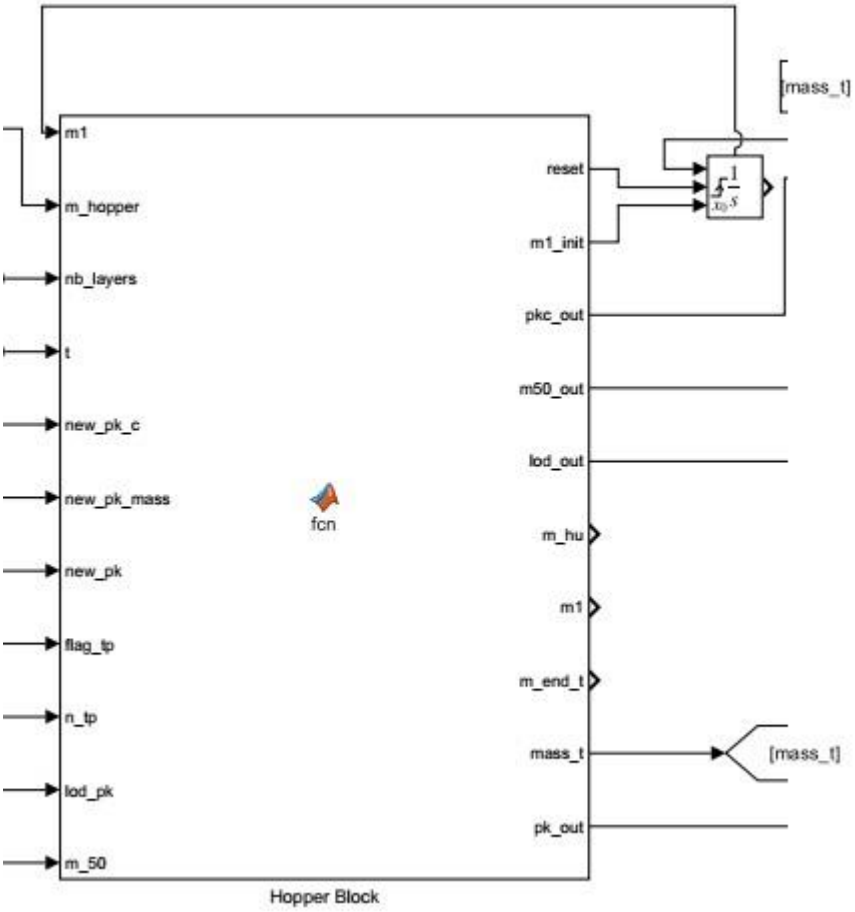


Appendix B4: PK Assignment Function Block Codes

```
% Author: Jakob Rehrl and Charles Bernard Aghadi
% Date: Feb 2023

function [pkc_hop, mn50_hop, mnlod_hop, mnmass_hop, pk, lod] =
fcn(pk_hopper, pk_dryer, mn_50, mn_lod, mass_pk, mn_pkc, pk_lod)

% Define persistent variables to store values between function calls
persistent x50_array if isempty(x50_array x50_array = zeros(25000, 1); end
persistent lod_array if isempty(lod_array),lod_array = zeros(25000, 1); end
persistent mass_array if isempty(mass_array)mass_array = zeros(25000, 1);
end
persistent pkc_array if isempty(pkc_array)pkc_array = zeros(25000, 1); end
persistent pk_old if isempty(pk_old)pk_old = 0; end
persistent pk_old2 if isempty(pk_old2)     pk_old2 = 0; end
persistent pk1 if isempty(pk1)     pk1 = 0; end
persistent pk2 if isempty(pk2)     pk2 = 0; end
persistent pk3 if isempty(pk3)     pk3 = 0; end
persistent pk_ld if isempty(pk_ld)     pk_ld = 0; end
persistent pk_lod2 if isempty(pk_lod2)  pk_lod2 = 0; end

% Check if pk_dryer is greater than the previous maximum value
if pk_dryer > pk1
% Update pk1 and pk_dy_in if pk_dryer is the new maximum
pk1 = pk_dryer;
pk_dy_in = pk_dryer; elseif pk_dryer == pk1
% Use the current value of pk1 for pk_dy_in if pk_dryer is equal to the
previous maximum
pk_dy_in = pk1; else
% Otherwise, set pk_dy_in to 0
pk_dy_in = 0; end
% Check if pk_lod is greater than the previous maximum value
if pk_lod > pk_ld
% Update pk_ld and pk_ld_in if pk_lod is the new maximum
pk_ld = pk_lod;
pk_ld_in = pk_lod; elseif pk_lod == pk_ld
% Use the current value of pk_ld for pk_ld_in if pk_lod is equal to the
previous maximum
pk_ld_in = pk_ld; else
 % Otherwise, setpk_ld_in to 0
```

```
pk_ld_in = 0; end
% Round up pk_ld_in to the nearest integer
pk_ld_in = ceil(pk_ld_in);
% If pk_ld_in is greater than 0 and different from the previous value of
pk_lod2, update lod_array
if pk_ld_in > 0 && pk_ld_in ~= pk_lod2
lod_array(pk_ld_in) = mn_lod;
pk_lod2 = pk_ld_in; end

% Check if pk_hopper is greater than the previous maximum value
if pk_hopper > pk2
% Update pk2 and pk if pk_hopper is the new maximum
pk2 = pk_hopper;  pk = pk_hopper; elseif pk_hopper == pk2
% Use the current value of pk2 for pk if pk_hopper is equal to the previous
maximum
pk = pk2; else
% Otherwise, set pk to 0
pk = 0; end
% Round up pk_dy_in to the nearest integer
pk_dy_in = ceil(pk_dy_in); if pk_dy_in > 0 && pk_dy_in ~= pk_old
x50_array(pk_dy_in) = mn_50; mass_array(pk_dy_in) = mass_pk;
pkc_array (pk_dy_in) = mn_pkc;
pk_old = pk_dy_in;  end
% Round up pk_in to the nearest integer
pk = ceil(pk);
 %Check and reassign the pk numbers and their parameters
if pk > 0 && pk ~= pk_old2
mn50_hop = x50_array(pk); mnlod_hop = lod_array(pk);
mnmass_hop = mass_array(pk);pkc_hop = pkc_array(pk);
pk_old2 = pk; elseif pk > 0      mn50_hop = x50_array(pk_old2);
mnlod_hop   =   lod_array(pk_old2);   mnmass_hop   =   mass_array(pk_old2);
pkc_hop =pkc_array(pk_old2) ;
else     mn50_hop = 0;     mnlod_hop = 0;     mnmass_hop = 0;     pkc_hop =
0;
 end
ld1 = 0; if pk_ld_in > 0 ld1 =  lod_array(pk_ld_in); end lod = ld1;
```

Appendix B5: Hopper Function Block



Appendix B6: Hopper Function Block Codes

```
% Author: Jakob Rehrl and Charles Bernard Aghadi
% Date: Feb 2023
 function [reset, m1_init, c_out, m50_out, lod_out, m_hu, m1, m_end_t,
mass_t, pk_out] = fcn(m1, m_hopper, nb_layers, t, new_pk_c, new_pk_mass,
new_pk, flag_tp, n_tp, lod_pk, m_50)
% FUNCTION DESCRIPTION: This function calculates the concentration and the
% distribution of a powder blend in a hopper with multiple layers,
which is % used to fill powder to a tablet press.

% INPUTS:
% m1: mass of powder in the bottom layer of the hopper
% m_hopper: total mass of powder in the hopper
% nb_layers: number of layers in
the hopper % t: current time in
seconds
% new_pk_c: concentration of the new powder
% new_pk_mass: mass of the new powder
% new_pk: product key of the new powder
% flag_tp: flag indicating if a tablet press is being used
% n_tp: number of tablets produced by the tablet press per unit time
% lod_pk: loss on drying of the new powder
% m_50: median particle size of the new powder

% OUTPUTS:
% reset: boolean indicating if the bottom layer integrator should be reset
% m1_init: initial mass of powder in the bottom layer of the hopper
% c_out: concentration of powder in the bottom layer of the hopper
% m50_out: median particle size of the bottom layer of the hopper
% lod_out: loss on drying of the bottom layer of the hopper
% m_hu: current total mass hold-up in the hopper
% m1: mass of powder in the bottom layer of the hopper after updating
% m_end_t: mass of powder in the top layer of the hopper after updating
% mass_t: mass of powder in the tablet press
% pk_out: product key of the powder in the bottom layer of the hopper


% Initialize arrays for concentrations, median particle sizes, and limits
of detection for each layer in the hopper
persistent c_array; if isempty(c_array)    c_array=zeros(nb_layers,1); end
persistent m50_array; if isempty(m50_array) m50_array = zeros(nb_layers,1);
end
persistent lod_array; if isempty(lod_array) lod_array = zeros(nb_layers,1);
end
persistent pk_array; if isempty(pk_array) pk_array = zeros(nb_layers,1);
end
```

```
% Initialize variables for tracking the top layer and its properties
persistent idx_end; if isempty(idx_end)  idx_end=1; end
persistent m_end; if isempty(m_end)   m_end=0; end
persistent new_pk_old; if isempty(new_pk_old) new_pk_old=0; end

% Set the output values for the bottom layer of the hopper
c_out=c_array(1); m50_out = m50_array(1); lod_out = lod_array(1); pk_out =
pk_array(1);
% Calculate the initial mass of powder in the bottom layer of the hopper
m1_init=m_hopper/nb_layers;

if m1<0 %bottom layer in the hopper has been used up
 c_array(1:end-1)=c_array(2:end); %move concentrations down by one layer
m50_array(1:end-1)=m50_array(2:end);
lod_array(1:end-1)=lod_array(2:end);
pk_array(1:end-1) = pk_array(2:end);

m_hu=m1+(idx_end-2)*m_hopper/nb_layers+m_end;%compute current total mass
holdup
idx_end=idx_end-1; %shift top layer down by one element
reset=true; %reset the bottom layer integrator to the value given in the
next line
m1_init=m_hopper/nb_layers+m1;
elseif new_pk > new_pk_old %Filling a new PK into the hopper
new_pk_old=new_pk; %remember the current PK number
c_array(idx_end)=m_end/(m_hopper/nb_layers)*c_array(idx_end)+(m_hopper/nb_
layersm_end)/(m_hopper/nb_layers)*new_pk_c;
%compute concentration of top layer; assumption: PK mass is larger than mass
of one layer
m50_array(idx_end)=m_end/(m_hopper/nb_layers)*m50_array(idx_end)+(m_hopper
/nb_layersm_end)/(m_hopper/nb_layers)*m_50;
lod_array(idx_end)=m_end/(m_hopper/nb_layers)*lod_array(idx_end)+(m_hopper
/nb_layersm_end)/(m_hopper/nb_layers)*lod_pk;

pk_array(idx_end) =
m_end/(m_hopper/nb_layers)*pk_array(idx_end)+(m_hopper/nb_layersm_end)/(m_
hopper/nb_layers)*new_pk;

idx_end_old=idx_end; %remember "old" index of top layer
idx_end=idx_end-1+ceil((new_pk_mass+m_end)/(m_hopper/nb_layers));
```

```
%compute current index of top layer
m_end=new_pk_mass-(idx_end-idx_end_old)*(m_hopper/nb_layers)+m_end;
%compute mass m_end that is stored in top layer
c_array(idx_end_old+1:idx_end)=new_pk_c;

%fill c_array by the concentration of the new PK

m50_array(idx_end_old+1:idx_end)=m_50;
lod_array(idx_end_old+1:idx_end)=lod_pk;
pk_array(idx_end_old + 1: idx_end) = new_pk_old;

m_hu=m1+(idx_end-2)*m_hopper/nb_layers+m_end;
%compute hold-up of hopper
reset=false; else
m_hu=m1+(idx_end-2)*m_hopper/nb_layers+m_end;

%compute hold-up of hopper

reset=false; end

if m_hu < 0     m_hu = 0;      end

if flag_tp == 1    mass_t = n_tp*3e-6;  else    mass_t= 0; end


%deadtime = [2620:3380 5220:11060 12900:14090 15700:15920 17870:18270];
deadtime  =  [3000:3100  7000:7100  13500:13510  15838:15919   18121:18261];
%15690:15810

hopper_stopper = ismember(t,deadtime); if hopper_stopper == 1     m_hu = 0;
%m1_init = 0;     reset = true;     m_end = 0;     idx_end = 1;

c_array(1) = 0; %very lowest layer is the output

m50_array(1) = 0;     lod_array(1) =0;     pk_array(1) = 0;

 end m_end_t=m_end;
```