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DISSERTATION

Multivariate analysis of a direct compression pharmaceutical tablets continuous manufacturing process

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The experimental work was performed in PROMIS continuous tablet manufacturing line (University of Eastern Finland, School of Pharmacy, Kuopio, Finland). All the facilities, equipments, materials and support were gently provided by

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Abstract

In the last decade, there have been significant advances in the areas of engineering and science, allowing the implementation of pharmaceutical continuous manufacturing (CM). These advances are coupled with the adoption of the quality by design paradigm for pharmaceutical development and the advances on process analytical technology to improve design, analysis and control. These advances have contributed significantly to advances on the design and manufacturing of pharmaceutical, namely the adoption of continuous processing. Continuous manufacturing can be used for the production of medicines in multiple pharmaceutical forms. If advances are being operated in the field of continuous manufacturing, it is also true that substantial efforts are still required to fully understand how this manufacturing paradigm can be efficiently integrated within industry, for full advantages to be achieved.

This work had the objective of pursuing the goal to better understand how materials behave under continuous processing. It aimed at evaluating the performance of a direct compression process for tablets production in continuous mode. Direct compression, a unit operation especially interesting for the manufacturing of tablets, has the ability to be efficiently integrated within a continuous manufacturing framework. The investigated continuous manufacturing process resourced to the continuous table production line located at the PROMIS Center at the School of Pharmacy of the University of Eastern Finland (Kuopio, Finland). The line was configured for direct compression purposes, encompassing multiple gravimetric feeders, a continuous mixer and a tableting machine. Tablets monitoring was accomplished with near-infrared spectroscopy. A formulation containing simultaneously caffeine (2.6%) and paracetamol (20%) was selected for this study. Selected process variables were varied according to an experimental design in order to understand the effects on tablets' properties. Mixer speed (350-1200 rpm), feed rate (5-10 kg/h) and the existence or not of premixture were the selected process variables. Tablets were evaluated according to the weight, hardness and thickness.

Feed rate demonstrated as was expected to be fundamental for the stability of the direct compression process. For instance, experiments carried out at lower feed rates (lower than 5kg/h) revealed poor fluidity and tablets were not acceptable. The influence of process variables on tablets properties was modelled by partial least squares regression. Tablets mass is significantly affected, in a positive way, by the speed of the mixer and negatively affected by the feed rate. The range of coefficients of determination for the calibration (R^2) and test (Q^2) for the three responses were 0.78-0.94 for R^2 and 0.56-0.88 for Q^2. Near-infrared spectra collected from tablets allowed the development of PLS models for the caffeine and paracetamol content. Validation experiments reveal that the root mean square errors of prediction for caffeine and paracetamol were respectively 11.96% and 10.48%.

Key-words: Continuous manufacturing; Tableting; Process Analytical Technology; Chemometrics; Near Infrared Spectroscopy.

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Resumo

Historicamente, a produção em descontínuo de formas de dosagem sólidas teve grande sucesso e dominou a indústria farmacêutica. Durante muito tempo a indústria entendeu não haver motivação para inovar no sentido do desenvolvimento de novas tecnologias de fabrico, dada a rentabilidade desta forma de produção. No entanto, atualmente, na era pós-blockbuster, tendo em conta que os custos dos materiais, durante o desenvolvimento de medicamentos, são significativos, que novos medicamentos, provavelmente, serão fabricados em quantidades muito menores e que, para novos tratamentos, o desenvolvimento de um processo de produção comercial não é garantido, é cada vez mais reconhecida a necessidade de novos paradigmas de produção.

A produção em contínuo surge como uma alternativa à produção em (semi-) descontínuo e tem por objetivo aumentar a eficácia e a eficiência na produção farmacêutica. Esta nova abordagem exige que a indústria farmacêutica, primária e secundária, aborde de maneira diferente a forma como desenvolve e otimiza os processos de fabrico para produção de substâncias ativas e formulações farmacêuticas. É fundamental a compreensão do processo como um todo, bem como inovação ao nível empresarial. É crucial entender e minimizar a variabilidade das matérias-primas, executar medições contínuas durante o processo, definir uma amostragem representativa e caracterizar a propagação de alterações e distúrbios através do sistema. Ao contrário da produção em descontínuo, em que o controlo local de cada equipamento é considerado suficiente, na produção em contínuo, o controlo local é não só obrigatório, como todo o fluxo do processo deve ser coordenado e equipado com sistemas de controlo de segundo nível, supervisionando e controlando todas as operações unitárias. Monitorizar e controlar a composição de um produto durante todo o seu processo de fabrico, com a finalidade de alcançar a qualidade e robustez pretendida, é um importante objetivo a ser alcançado numa produção em modo contínuo.

Um passo importante para a implementação da produção em contínuo foi dado em 2004, quando a Food and Drug Administration publicou uma diretriz de tecnologias analíticas de processo (PAT), que promove a adoção de tecnologias inovadoras para realizar medições oportunas em atributos críticos de qualidade de materiais brutos e em processo, permitindo alcançar uma melhor compreensão e controlo do processo. O conceito PAT está intimamente ligado à ideia do desenho pela qualidade a qual considera não apenas a avaliação de risco para a qualidade e o conhecimento sobre o processo, mas também a forma como as operações unitárias afetam a qualidade e estabilidade do produto. A espectroscopia de infravermelho próximo tem sido utilizada como uma ferramenta de controlo PAT. Esta ferramenta de controlo combinada com a análise de dados multivariados tornou-se uma ferramenta interessante na análise farmacêutica, tanto a nível qualitativo como quantitativo.

Esta tese foi realizada utilizando a linha de produção contínua de comprimidos do PROMIS Centre (Escola de Farmácia, Universidade do Leste da Finlândia) em Kuopio, Finlândia. A monitorização do processo foi realizada em tempo real, por um sistema de infravermelho próximo com uma câmara espectral SPECIM e um sensor ImSpector

(SPECIM, Finlândia). Com o propósito de avaliar o processo de compressão direta em modo contínuo foram definidas um conjunto de experiências variando a velocidade do misturador (350 a 1200 rpm), fluxo (5 a 10 kg/h). Foi ainda avaliada importância de existência de etapa de pré-mistura. Como respostas foram avaliados a massa, dureza e espessura dos comprimidos. A análise de componentes principais foi usada como método de análise exploratória dos espetros obtidos, assim como para identificar medições atípicas. A monitorização da taxa de alimentação, elemento fundamental na compressão direta, decorreu sem grandes variações em relação aos set points definidos para cada matéria prima. Deste modo, os dados analisados, relativamente à taxa de alimentação de cafeína e paracetamol, permitiram perspetivar que as concentrações dos mesmos, nos comprimidos seriam as esperadas. Durante a realização das experiências ficou ainda visível que as que tinham uma taxa de alimentação de 5 kg/h, evidenciavam uma fraca fluidez, já com valores de 10 kg/h a fluidez melhorava significativamente. De acordo com os modelos de regressão múltipla (PLS) para avaliar a influência das variáveis alteradas nas respostas selecionadas, a massa de cada comprimido é significativamente afetada, de uma forma positiva, pela velocidade do misturador e negativamente afetada pela taxa de fluxo. Para além disso, este modelo prevê que a dureza seja afetada pela existência ou não de pré-mistura. Para os três modelos o R2 não se verificou muito elevado, variando entre 0.78 e 0.94. Relativamente ao valor de Q2, este variou entre 0.56 e 0.88, valores um pouco a baixo dos valores ideais. Assim, pode-se concluir que este não será um modelo com uma capacidade preditiva muito elevada. Relativamente aos modelos PLS, baseados nos espetros NIR para estimar a concentração de paracetamol e cafeina, foi possível concluir que a capacidade preditiva foi boa com erros quadrados médios (RMSEP) de 12 e 10% para o paracetamol e cafeína respetivamente.

Palavras-chave: Produção contínua; Compressão direta; Tecnologia Analítica de Processos; Quimiometria; Espetroscopia de Infravermelho Próximo.

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List of abbreviations

API	Active Pharmaceutical Ingredient
ASTM	American Society of Testing and Materials
CDER	Center for Drug Evaluation and Research
cGMP	Current Good Manufacturing Practices
CM	Continuous Manufacturing
CPPs	Critical Process Parameters
CQAs	Critical Quality Attributes
DC	Direct Compression
DoE	Design of Experiments
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
LIF	Light-Induced Fluorescence
MCC	Microcrystalline Cellulose
MgSt	Magnesium Stearate
MVDA	Multivariate Data Analysis
NIR	Near-Infrared
PAT	Process Analytical Technology
PC	Principal Component
PCA	Principal Component Analysis
PLS	Partial Least Squares
PMI	Precision Medicine Initiative
QbD	Quality by Design
QRM	Quality Risk Management
QTPP	Quality Target Product Profile
RA	Risk Assessment

RMSECV	Root Mean Square Error of Cross Validation
RMSEP	Root Mean Square Error of Prediction
RTD	Residence Time Distribution
RTRT	Real-Time Release Testing

Chapter 1

Motivation

One of the major recent evolution of pharmaceutical drug manufacturing, was the effective introduction of the concept of continuous manufacturing. Continuous manufacturing allows for faster production, requires greater control and consequently higher product quality. It is estimated that the pharmaceutical industry loses about 50 billion USD a year due to the overall inefficiency of batch production. (1) Continuous manufacturing may be a potential solution to assist in solving this problem. Continuous manufacturing is not a new concept. In many industries, continuous production, a highly automated production concept that integrates multiple production steps, has become very common. The benefits that can be obtained, for certain specific processes and products, can be very attractive. Continuous manufacturing uses sensor technology and in-line analysis to measure the critical physical and chemical properties and processing conditions in real time, steering the production process automatically. This allows for an uninterrupted flow through multiple production steps from raw materials to the final product or dosage form.

The objective is as always, to guarantee that the finished product has uniform characteristics throughout the process and meets established quality standards. For continuous production to be possible, using all of its potential in the production of a pharmaceutical product, it is necessary to have a great knowledge about the entire process, as well as everything that is adjacent to it. This work, carried out in the research and development continuous tableting line (PROMIS-line), at the School of Pharmacy of the University of Eastern Finland, aims to further assist the knowledge increment, fundamental for the implementation of a continuous process. The direct compression process using a continuous production with process analytical technologies was used.

Chapter 2

Objectives

The main objectives of this work are:

1. to setup a direct compression method operated under continuous mode fully integrated with NIR sensors (mixing stage);

2. to use of the NIR tool to monitor and quantify two active substances simultaneously and

3. to resource on NIR spectroscopy for real time process monitoring and product quality analysis (key to real time release testing).

Chapter 3

3.1 Introduction

The pharmaceutical industry is increasingly dynamic, facing several challenges. One is to respond in a timely manner to emerging needs, which requires greater flexibility, something not always compatible with the more classical methods and processes. Other challenges are related to tight cost controls and accelerated development times. All these challenges mean that the option of implementing continuous production processes is an increasingly more equitable option. Several pharmaceutical companies feel that the time has come to invest in this manufacturing mode. In addition, the existing tools for the manufacture of pharmaceuticals products allow the existence of high levels of knowledge and process control required for continuous production (2).

In this sense, Dra. Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA), referred to the AAPS Annual meeting, October 2011, "At this time, the manufacturing experts of the 1950 would easily recognize the processes of pharmaceutical production today. Production is expected to change over the next 25 years as current manufacturing practices are abandoned at the expense of more continuous, flexible and efficient production".

However, the general pharmaceutical industry is still hesitant to introduce innovation to manufacture drugs and drugs products for a variety of reasons. One of the main reasons pointed out by industry leaders, lies in regulatory uncertainty, possibly resulting from a set of rigid regulations that are unfavorable regarding innovations (3). Recognizing the need to eliminate this hesitation, in 2002 the FDA launched a new initiative entitled "Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach." This document identifies three main objectives:

- to encourage the introduction and adoption of new technological advances by the pharmaceutical industry;

- to facilitate the application of modern quality risk management (QRM) techniques, including approaches to quality systems for all aspects of production and

- to encourage approaches that are based on risk. (4)

It could be argued that this initiative would have been a great impetus for the paradigm shift, regarding drugs and drug products production. Increasing production efficiency and drug quality with reduced manufacturing costs has become a very appealing appellation for a part of the industry. Another thrust with great impact for the new paradigm will be the series of guidelines for the manufacture of medicines, namely ICH Q7, Q8, Q9, Q10 and Q11 and FDA Guidance for Industry - PAT, launched by the International Conference on Harmonization (ICH) and the FDA (5).

Continuous production requires a set of process control systems that serve to mitigate the impact of variability, which may occur throughout the entire manufacturing process. This set of systems is herein referred to as Process Analytical Technologies (PAT) (6). PAT plays a key role in scientific aspects of manufacturing (7). The data that come from the use of these tools are later used in multivariate analysis models, which in turn return information about the process. These are models, which to a great extent, correspond to

tools that contribute to the construction of control mechanisms of the process itself. This ensures that any disturbance in the process can be detected and eventually corrected in order to achieve that the specifications of the critical quality attributes (CQAs), defined for the particular product and framed in the quality target product profile (QTTP) are met (8).

3.2 Continuous manufacturing

It is possible for drugs and drug products to use a variety of strategies for the development of continuous processes. Possible options include (9):

a. a completely continuous process, in which all the unit operations are sequenced to form a single production line;
b. a completely continuous process as referred to above, but with two or more parallel production lines or
c. a "hybrid" approach with unit operations in continuous and batch mode.

A continuous process (Figure 1) is characterized by an integration of a set of unitary operations, where the starting materials are continuously introduced into the process and the products are continuously collected (10). One of the important characteristics of this manufacturing mode is the consistency. An ongoing well-designed and an effectively executed process can provide a highly consistent product, making its performance reliable and at the same time less variable (11). In continuous production, orchestrated coordination between different industry partners is essential for successful integration. The three key components for successful implementation are the manufacturers of analytical equipment tools and processes, active pharmaceutical ingredient (API) manufacturers and excipients focused on process controls for consistent deliveries, and ease in developing strategies for integrating implementation techniques manufacture of the finished product (12).

Regulators recognize that continuous production is a mode of production with a high potential to improve the quality and consistency of drugs and drug products throughout the production process, allowing quality to be directly incorporated into the process following the efforts of quality by design (QbD). With QbD, product quality is ensured by the understanding and control of formulation and manufacturing variables (13). It is thus possible to identify sources of variation in product quality as well as to design adequate control strategies to work on the identified risk areas (6). This is a "systematic approach to development that begins with predefined objectives and emphasizes product understanding, process and process control, based on sound science and quality risk management" (14). The physicochemical and pharmacological properties of API determine the CQAs for pharmaceutical development (13). A strong and complete understanding of a product, as well as its manufacturing process, helps to identify the CQAs. The use of appropriate statistical methods such as design of experiments and risk assessment (RA) as well as PAT and QbD tools can lead to a successful and knowledge-based product development (15).

Regardless of the choice of the manufacturing strategy used by the industry for the production of pharmaceuticals, it is necessary to submit and approve any process by the regulators. The approval requires the length of a set of regulations. The document for submission and approval shall include a general description, which may include a brief

outline of each unit operation and its mode of operation, including interfaces between unit operations, material flow, proposed flow rate and total operating time of the unit process, critical parameters of the process and its ranges, as well as specific information for the development and modeling of the continuous process. (9). Regulatory agencies, including the FDA, the European Medicines Agency (EMA) and the Japanese Agency for Pharmaceutical and Medical Devices (PMDA), support innovation in industries and the adoption of continuous production for pharmaceutical production. Generally, there is a consensus that continuous production can be effectively implemented within the existing regulatory framework, and there are no major regulatory hurdles for manufacturers to implement this type of production. However, although the current regulatory environment is generally favorable to the adoption of continuous production for pharmaceuticals, one of the challenges is a potential gap in standard approaches to the regulatory assessment of continuous production processes. Researchers and inspectors need to develop more knowledge in technology to determine slightly more appropriate regulatory approaches (16).

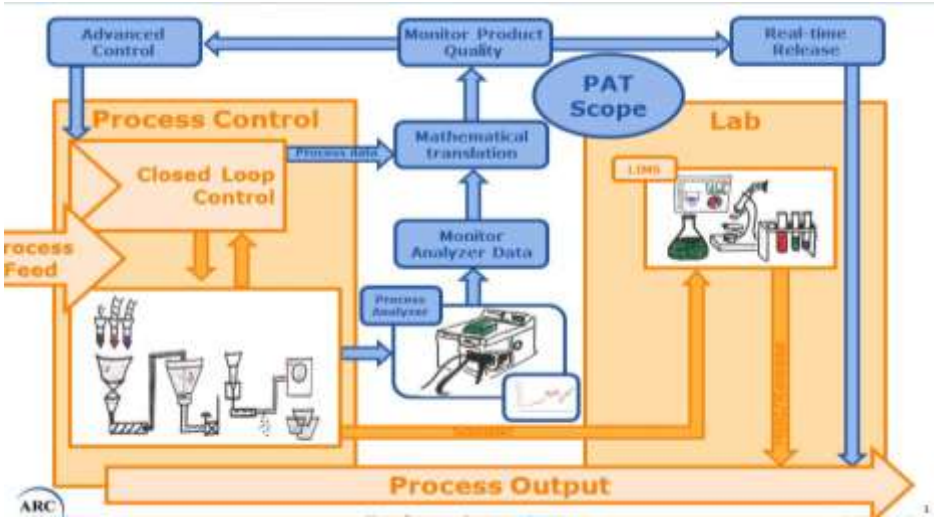

Figure 1 - Continuous versus batch (discontinuous) processes (Adapted from (17))

3.2.1 Quality considerations for CM

Process development

Design of experiments (DoE) is defined as "a structured and organized method to determine the relationship between factors that affect a process and the outcome of that process" (14). Although the DoE is not a substitute for the realization of experiences, it is a valuable tool for choosing experiences in an efficient and systematic way for the purpose of providing reliable and coherent information (18). This has become a common tool to increase processes understanding for interest intervals and can be used for comparative experiments, selection experiments, response surface modeling, and regression models (6) (19). The understanding of a continuous production process, should be established based on the design space and with DoE in the development phase. The rapid response of a continuous process to changes in process parameters allows a large amount of experimental information to be collected in a short time from small quantities of products. Predictive process models can be used as a simulation tool

to complement experiences throughout the development of the process and thus improve understanding of the process (6).

For continuous production, understanding the dynamics of how a material flows through the process is critical to traceability of the material. This understanding of process dynamics can be obtained by characterizing the residence time distribution (RTD) (6). RTD is a probability distribution that describes the amount of time that a mass or fluid element remains in a unitary operation, throughout a process (6) (20). This (RTD) can be easily obtained for all unit operations in a continuous line with a monitoring response test performed for each unit operation separately and also for the mechanically integrated line. The RTD curve can be used to predict the propagation of material or disturbances through the system (6). It is also useful to characterize the axial mixing, to predict how fluctuations in a feeder and mixer dissipate and what their impact on the uniformity of the mixture and the contents. It can also be used to track materials through the process and potentially isolate materials when specifications are not achieved (21). The distribution of residence time depends on several factors, such as operating conditions, equipment parameters and design, and physicochemical properties of materials (22) (6). Thus, knowledge of RTD is a key aspect of a control strategy for continuous production processes as it has the ability to adequately isolate and reject non-specification materials.

Critical quality attributes

The quality target product profile (QTPP) provides an description of the quality, safety, and efficacy of a specific product for the patient. Moreover, it defines the desired characteristics of the product and the goals for its development (15). That way, it should be the basis for the development of critical quality attributes (CQAs) and critical process parameters (CPPs) as well as a control strategy. CQAs correspond to reference values that must be maintained and verified throughout a process. Each CQA incorporates an acceptable limit, gap or statistical distribution, serving as a comparison term for the actual measurement results (13). CPPs are process parameters whose manipulation has an impact on a CQA and therefore should be monitored or controlled to ensure that the process produces the desired quality. CPPs are related to the type of equipment, lot size, mixing order, mixing time, other operating conditions, etc. (14). Thus, in the design space, the physical, chemical or microbiological properties must be defined to ensure the consistency of the critical quality attributes of CQA (14) (6).

In some studies, CQAs are used to describe elements of QTPP (such as dissolution). However, there are other studies that consider the CQAs to describe mechanistic factors (such as particle size and hardness) that determine product performance. Thus, the CQAs are used to describe the two aspects: performance of the product and the determinants of your performance (15). An example may be what happens in direct compression or simple mixing operations where they are responsible for the segregation of the products due to the intense vibrations configured in compression or filling machines. Thus, the direct CQAs for these operations will be content uniformity and the indirect CQA may be particle size. Alternatively, the uniformity of content may be part of the QTPP and the particle size may be included in the CQA (13).

For industries such as the pharmaceutical and biotechnology industries, design space is very important (23). Process parameters and material attributes are selected for the construction of a design space which, when controlled, allows the achievement of a consistent quality of the product. These process parameters can be identified by RA and process development. The RA identifies product development issues and the risks associated with exposure to those problems. The RA process involves risk identification, risk analysis, and risk control (13). In this way, it is expected that a product has the defined quality if the operation is carried out within the design space.

Process monitoring (PAT)

PAT are systems that design, analyzes and controls manufacturing processes through time measurements, that is, measurements throughout the process, critical raw material quality attributes as well as process, in order to ensure the quality of the final product (3). In addition to supporting the validation and control of the manufacturing process, the PAT tools and principles can be used to gain insight into the process (6). The goal of PAT is to improve understanding and control of the manufacturing process. Quality is incorporated into pharmaceuticals through a comprehensive understanding of various components that make up a whole pharmaceutical product.

A process is considered well understood when the following conditions are met (3):

- All critical sources of variability are identified and explained. The undetected variability of the raw materials may manifest itself in the final product if certain critical attributes are not well understood or taken into account during a manufacturing process. Therefore, a complete identification and understanding of these attributes must be performed; (13)

- the variability is managed by the process and

- product quality attributes can be accurately and reliably predicted within the established design space.

More frequent measurements are required in a continuous process where there is a lack of isolated intermediates. Real-time monitoring of process parameters and quality attributes of processing materials is an essential component for the establishment of a successful control strategy (6). Multivariate models are often used to extract process knowledge from data provided by process analyzers. The sampling interface for continuous production systems can be challenging as there are some difficulties in collecting representative samples of powder samples, which is very prone to errors (6) (13). Industrial experience indicates that inefficient measurement performance is often attributable to sampling system issues rather than to process analyzer (24). On-line and in-line measurements may reduce, but not necessarily eliminate sampling errors (25). Thus, considerations with sensor location should be evaluated to obtain representative samples and minimize the effect of the probe in the process (6).

Control strategy

In order to ensure the production of a product with a desired and consistent quality, it should be noted that a control strategy should be designed.

A monitoring system is designed to manage planned changes and respond to unplanned disturbances. Samples that are analyzed throughout the process should be representative and the frequency of sampling should consider the material flow rate at system dynamics and the unit dose.

When developing the product, the influence of the process parameters and the attributes of the material on product quality should be studied. Thus, from this information, critical process parameters and critical material attributes are identified. It is thus possible to maintain control over these parameters so that the quality of the final product is achieved (13) (15). In general, a process control system should have three main characteristics (26):

1) fast and controlled startup and shutdown;
2) complying with all CQAs at the steady state operation and
3) quality assurance, regardless of disturbances, dynamics, uncertainties, non-linearity, and constraints.

A robust control strategy is essential to ensure the consistent quality of the product. Certain aspects such as control status, raw materials and intermediates, equipment, process monitoring, and sampling should be taken into account for the establishment of a control strategy for a continuous process (9). A continuous manufacturing process which maintains a control state thus ensures that the quality that is desired is consistently achieved. In the initial stages of a process (start-up), as well as at the end of the process, (shutdown) sudden changes may occur. It is therefore important to maintain an adequate control state in these situations. It is important, therefore, to ensure that any change or change in the process is detected and quickly corrected so that the quality of the product is guaranteed. Continuous production may require additional control of raw materials. This should happen when multiple batches of a raw material are used in a single production batch. Control approaches should be based on product and process understanding and may include the use of PAT tools. The quality attributes of raw materials and excipients should be tied to the product's CQAs and process needs (9).

Specifications will be needed as part of the control strategy. Continuous processes may include a real-time release testing (RTRT) approach to some quality attributes. RTRT is the ability to evaluate and guarantee the quality of the materials in process and / or the final product based on process data which typically include a valid combination of measured raw material attributes and process controls. This is only achievable because the use of PAT tools can be applied to measure substitutes for the quality attributes of an end product, some of which have already been incorporated into the control strategy for monitoring process control (6). However, RTRT approaches may require an improved sampling plan compared to the traditional release test and may involve a larger sample size (9).

3.2.2 Benefits of CM and challenges for the future

Continuous production for pharmaceutical industry is an attractive option as processes such as compression, roller compaction, and capsule filling are already performed in continuous mode (27). The advantages of continuous production have an impact on three areas: (i) product development and quality, (ii) costs, and (iii) footprint. (10)

Continuous production offers opportunities for improvements such as:

-an integrated process with fewer separate unit operations with safer, faster, more efficient, shorter response times and integrated control and (9)

- a footprint of smaller equipment (9).

The production equipment entails fewer expansion problems since the production lot size is defined by the "time" factor, so the same size of equipment can be used for developmental and pilot studies, clinical trials and complete commercial production (10). Since the equipment is smaller, the intermediaries do not need to be stored and transferred, so less space is required. In addition, operating expenses decreased as operators are not required for processing, transfer and storage (10).

- A development approach enhanced by the introduction of QbD, incorporating process analytical technology (PAT) (9).

This type of tools allows the evaluation and assurance of product quality, no longer through offline testing, becoming a continuous control. In addition, the production of tablets continuously will be more sustainable than through batch production, since the footprint significantly reduces.

- Real-time product quality information and (9)

- potentially easier to adapt to changing supply needs (9).

Currently prescribing medicines is based on a one-size-fits-all principle. However, more personalized (combination) solutions are needed in several critical areas of therapy. Investigations and studies have been followed so that in the near future it is possible to prescribe custom medications as recently described in the Precision Medicine Initiative (PMI) (28). The current level of innovation in the designation of dosage forms and manufacture of such products cannot meet the needs of personalized medicine. As such, new manufacturing solutions are required, which allow the flexible manufacture of custom dosages (26). The pharmaceutical industry currently has a limited ability to rapidly increase production in response to a possible shortage of drugs or other emergencies. Thus the creation of a new facility or manufacturing line in response to such emergencies can take up to several months or years, with a batch production; however, with a continuous production there can easily be an increase in the volume of production without the problems increasing scale, providing greater and better responsiveness (6).

Despite the many advantages that continuous production presents, there are also some challenges that need to be addressed (10). Replacing the capital investment made to the detriment of a new one for new technologies is perhaps the biggest obstacle to the change decision (5). Continuous production has somewhat high starting costs, as well as difficult implementation for low volume products (22). In this type of production,

materials flow continuously between unitary operations and the product is continuously formed over a long period of time. In this way, the process becomes somewhat less flexible, since the different unit operations are physically integrated into a specific process chain. However recent advances have been made in the development of equipment that allows for flexible changes between different operations (10). Unique considerations for continuous production should be evaluated when developing a control strategy for a continuous process, because the process, product or environmental conditions may vary over time. Included in these considerations are, for example, the accounting for material attributes that affect fluidity, including the impact of process dynamics on quality; initialization and shutdown of processes, and creation of adequate measurement systems for process monitoring and control (9) (28).

A key challenge for research teams in continuous processes is to identify specific product groups where continuous production is attractive (11).

3.3 Direct compression

In tablet production, the most common disadvantages with batch production are associated with magnification, lack of real-time quality control, insufficient process understanding and long production cycles (29). So, continuous production has great potential to overcome some of these problems. For example, the expansion of production volumes is achieved with the same equipment through longer process times (29).

There are different methods of pharmaceutical tablets production. What distinguishes them is the dose and physical properties of the mixture, such as compressibility and flow (30). Direct compression (DC) is an important process in pharmaceutical technology and is one of the methods used for the production of tablets. In the early 1960s, the introduction of powdered lactose and Avicel® changed the tableting process and allowed a new production process to be used (31). Microcrystalline cellulose (MCC) was discovered in 1955 by Battista and Smith being marketed for the first time under the Avicel® brand. As early as 1964, FMC Corporation introduced Avicel® PH for the pharmaceutical industry as an excipient for direct tablet compression (32) (33). One of the difficulties in direct compression and dry granulation is the low content compression. Although all cellulose-based polymers are well compactable, there are still particular categories of microcrystalline cellulose which have excellent compatibility. With the use of these categories it is possible to significantly improve the compressibility of low compact powder blends and are therefore widely used as compressibility enhancers in the manufacture of tablets by direct compression and dry granulation methods. The various categories of MCCs have different fundamental properties, including: morphology, particle size, surface area, porosity and density. These properties vary according to the type of MCC category, being that categories of smaller particle size have good compressibility and poor fluidity, whereas the categories with larger particle sizes show little compressibility and excellent flowability (33). Microcrystalline cellulose is then widely used in pharmaceuticals, mainly as a binder/diluent in oral tablet formulations and capsules. In addition to its use as a binder/diluent, microcrystalline cellulose also has some properties of lubricants and disintegrants which make it useful in the production of tablets. (32) (34)

The current use of the term direct compression is used to define the process by which the components are compressed directly from powder mixtures of APIs and suitable excipients. No pre-treatment of the powder mixtures is involved by wet or dry granulation (30). DC offers time and economic advantages in the production of a tablet as it is the shortest and most direct way, eliminating intermediate stages of granulation and drying, in order to obtain the powder for the final dosage form. Today, direct compression plays a key role in the pharmaceutical industry, as the continuing trend towards generics pushes manufacturers to create production processes as efficient as possible (29) (35). Throughout the years, APIs and direct compression excipients have been developed, especially diluents and binders. Since these are now commercially available, designing direct compression formulations is easily possible (29). It is necessary to take into account that in order to obtain a robust and long-lasting dosage form, the functional components of the tablets used in the mixture should exhibit good fluidity and compressibility, since the use of poorly controlled or inadequately specified raw materials can present a number of problems, such as weak fluidity and inconsistent tablet weight, unsatisfactory strength, lack of uniformity of content or segregation, and dissolution failure. DC is directly affected by the characteristics of the raw materials, since they do not undergo any changes in the previous steps in the process (32).

Although direct compression is an intrinsically continuous technique, simple unit operations prior to compression, i.e., weighing and mixing are historically performed in batches. To allow direct continuous compression, the integration of continuous powder feed units, a continuous dry powder mixer, and a tableting machine is required (36). The critical process before compression is mixing. The use of a direct compression process presents important challenges related to the uniformity of the product content, as well as obtaining and maintaining a homogeneous mixture. Thus, there is a need for a careful selection of excipients, powder mixture and process control, so that the out-of-specification are minimal (29).

The continuous mixing process requires the evaluation of a large parametric space, including: selection of mixing and feeding equipment; evaluation of operational parameters such as impeller rotation rate and flow rate; characterization of the effects of material properties, such as particle size distribution and powder cohesion, and control of environmental variables such as relative humidity and temperature. Many of the studies that have been done so far have been in relation to a specific material and in relation to the type of mixer. In (22) the focus of this study was to evaluate the flow behavior and mixing performance of a continuous-mode powder mixer. It was observed that the rotation rate was considered the parameter of the most significant process and that most affected the performance of the mixture. Intermediate rotation rates showed that the best performance of the blend was largely overpowered by the properties of the blend material and the extent of total shear, deformation, applied to the mixer (22).

Continuous mixing studies were also focused on the influence of process variables on the mixing efficiency and flow behavior in mixers (37). Other studies focus on monitoring the concentration and homogeneity of the blend after discharging using near infrared spectroscopy (NIR). For example**,** in (38)**,** it was found that the acceptable mixing homogeneity, determined by calculating the standard deviation of steady-state drug concentration, could be obtained by the continuous process. Other approaches to characterize the performance of the mix were focused on the analysis of residence time

distribution (RTD) (39). Numerous models are available in the literature to describe the mixing and transport of particles through a continuous mixer (36) . The main limitation of the use of residence time distribution (RTD) as a predictive tool for mixing performance is the inability to capture the micro-blend. This is especially important for pharmaceutical blending processes as they combine high product uniformity requirements with small sample sizes. In (40), RTD measurements were used to compare the predicted variance of the mixer output with the experimental values and the preferred operating conditions were determined to facilitate the mixing, and RTD mixing performance indicated better mixing performance when the RTD is broader. Other studies suggest that performance is driven by the number of revolutions (36). Still, in (39)**,** the impact of the mixture was evaluated, in a continuous process of direct compression, in the CQAs. In general, the results highlight that, for the study, continuous mixing within a direct compression process is robust and is assessed with a low risk of causing any negative impact on pharmaceutical CQAs provided there is adequate control of feeders.

Continuous powder feeders play a key role in the overall performance of the tablet manufacturing line through continuous production. It is crucial to ensure that the feed rate of each bulk material is precisely controlled (37). For example, the quality of the tablet will vary if there is a great variability in the composition of the inflow, even if the mixer and the tableting machine work perfectly (29). The feeder performance defines the content of the formulation and is therefore the main unit's operation in continuous production. Startup of feeders caused an over-and/or underscoring that should be considered when the startup procedure is set. When steady state is reached, feed rates remain very constant. The verification of high peaks in feed rate will be largely due to accumulation and drop of powder in the feeder exit port (29). Feeders can transfer composition problems and flow rate variability to the following unit operations when their flow rate variability is not well balanced with the amount of axial mixing within the blender. Therefore, the ability to precisely dose a powder over time is a key challenge in the overall manufacturing process (36)**.**

According to (29), the quality of the final tablet can be achieved and will be similar through the adoption of a batch or continuous process. However, robust and consistent homogeneity can be achieved significantly faster with the continuous process, and thus, it is ensured that the batch variation for the batch is minimized. Moreover, with this study it is apparent that adaptive control is a fundamental means for robust operation, generating consistent quality output. These same observations are also seen in (41), where it is shown that continuous mixing and direct compression may offer advantages over batch production for tablet manufacture.

3.4 Monitoring

Monitoring and controlling the composition of a product throughout its manufacturing process, in order to achieve the desired quality and robustness, is an important goal to be achieved in continuous production. NIR spectroscopy, figure 2, has been widely used as a tool for off-line control of raw materials and product quality control (42).

The American Society of Testing and Materials (ASTM) defines the NIR region of the electromagnetic spectrum as the wavelength range of 780-2500 nm corresponding to

the range of 12820-3959 cm-1 wave numbers. The most prominent absorption bands occurring in the NIR region are related to overtones and fundamental vibration combinations of the functional groups C-H, N-H, O-H and -SH. (42) This method of analysis has the advantage of being fast (one minute or less per sample), non-destructive, non-invasive, almost universal application (any molecule containing CH, NH, SH or OH bonds) and a possibility of using intact samples presented directly to the instrument without any pretreatment (43).

A study made by (44)**,** highlighted the feasibility of using NIR spectroscopy also in PAT configurations during a pharmaceutical manufacturing process. The continuous mixing process can be monitored with NIR spectroscopy, as well as light-induced fluorescence (LIF) (10). The option of using NIR spectroscopy is advantageous since NIR spectra can be obtained without sample preparation, providing real-time monitoring. Measurements performed with NIR can be used to control the feeding speed of the powder feeders and the operational parameters of the continuous convective mixers (38).

Several investigations on the use of NIR spectroscopy in a continuous mixing process were developed. PLS-NIR models were constructed to determine the API concentration, (38); multipoint systems have been developed (25), to perform the sampling, and the use of these has several advantages, such as diagnosis of instrument or process failures. In addition, a single spectrometer can be used to monitor an entire continuous production process; in (22) the results obtained from this investigation are quite encouraging, indicating that the continuous mixer is able to obtain mixtures with a high degree of homogeneity. According to this same research, the use of NIR spectroscopy and multivariate data analysis is an effective alternative for the real-time determination of API at the outlet of the mixer.

In 2009, the successful use of NIR spectroscopy in a tableting machine to monitor the powder segregation was presented at the EMEA / EFPIA QbD Application Workshop (45). In an investigation conducted by (46), not only the individual tablets in the tableting machine but also the powder stream from a continuous mixer prior to compression were monitored. Both calibration and test spectrum data were collected in an in-line form. This study demonstrates that it is possible to perform a 100% identity verification, i.e. each tablet is monitored individually. The quality of the method was confirmed through tests with different API contents, compression speeds and compaction forces.

NIR spectroscopy combined with multivariate data analysis has become an interesting tool in pharmaceutical analysis, both qualitatively and quantitatively (42). Chemometrics and multivariate data analysis (MVDA) are the terms used to describe activities related to the establishment of the relationship between the complex analytic signal (can be a spectrum) and the quality attribute being investigated. MVDA has become a widely accepted and widely applied technique in the pharmaceutical industry for qualitative purposes (e.g. raw material identification using principal component analysis of portable NIR / Raman spectrometers) and quantitative purposes, like measuring the amount of water with NIR spectroscopy. The real challenge in implementing MVDA is when data is structured in multiple ways (47).

It is also important to note that continuous quantitative monitoring of pharmaceuticals using NIR spectroscopy can be particularly problematic, since the API and excipient spectra are themselves complex, and pharmaceutical processes can make the NIR

spectrum even more complex (46). However, it is expected that the latest generation of NIR instruments will be able to address these problems and further improve the utility of NIR spectroscopy for the monitoring of pharmaceutical processes (46).

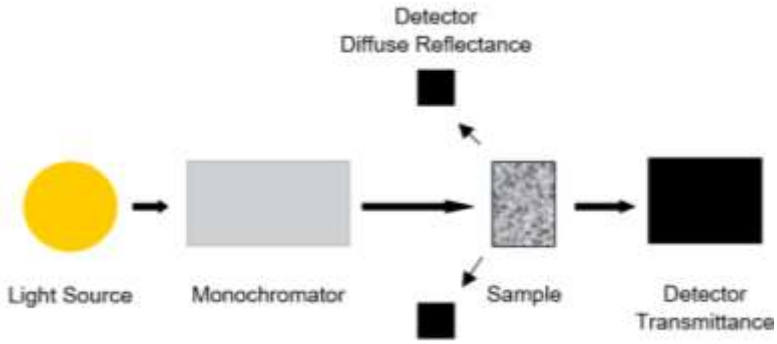

FIGURE 2 - BASIC NIR SPECTROMETER CONFIGURATIONS. A NIR SPECTROMETER IS GENERALLY COMPOSED OF A LIGHT SOURCE, A MONOCHROMATOR (OR INTERFEROMETER IN CASE OF FT TECHNOLOGY), A SAMPLE HOLDER OR A SAMPLE PRESENTATION INTERFACE, AND A DETECTOR, ALLOWING FOR TRANSMITTANCE OR REFLECTANCE MEASUREMENTS. (ADAPTED BY (42))

3.5 Promis-Line: continuous manufacturing line

This work used to the continuous line (PROMIS-line), at the University of Eastern Finland, School of Pharmacy, Kuopio, Finland. PROMIS-line is a modular and flexible production line that can be run in three different continuous configurations, depending on the type of formulation that is intended to be used. Full line configuration, double blending/direct compression configuration, and direct compression configuration, are the operating modes of this production line. These are visible in figure 3. The necessary equipment, as well as its specifications, for the different configurations are described in the table 1.

TABLE 1 - DESCRIPTION OF THE CONTINUOUS LINE

Equipment	Brand and manufacture	Specifications
3 Loss-In-Weight powder feeders	K-Tron, K-ML-D5-KT20	500 – 24000 g/h.
Loss-In-Weight micro feeder	K-Tron, K-CL-24-KT24	300 – 4000 g/h.
Loss-In-Weight micro feeder	K-Tron, K-CL-SFS-MT12	32 – 300 g/h.
Modified Loss-In-Weight feeder for lubricant and low dose API	K-Tron, K-cl-24-kt24 modified	32 – 150 g/h.
Two continuous blenders	Hosokawa, Modulomix	300 - 1250 rpm
Roller compactor	Hosokawa, Pharmapaktor L200/30P, with flake crusher FC 200	Screw speed: 0 - 10 rpm; Roll speed: 0 – 20 rpm; Roll pressure: 0 – 50 kN; Flake crusher: 20 – 100 rpm

Equipment	Brand and manufacture	Specifications
Tableting machine	PTK, PT – 100 with PISCon	96 000 tablets/h
Screw conveyer	Entecon Spiral Screw	Constant speed
Vacuum conveyer	K-Tron,P10-BV-100-VE	Constant speed
Vacuum speed	Volkmann, VS200 Eco	Constant speed

The continuous manufacturing line allows the use of up to four API feeders and excipients for the continuous mixer. Thereafter, the helical conveyor transfers the powder mixture to the roller compactor. From the roller compactor, the vacuum conveyor transfers the granules to the second feed and mixing station where the LIW granulated feeder and LIW microfine feeder (for lubricant) feed the second continuous mixer, this step being performed only if necessary. Finally, a vacuum conveyor transfers the granules to the tableting machine.

With the use of the complete production line, the optimum efficiency tested is 20 kg/h. It has been found that the upper and lower limits of the line are dependent on the formulation (fluidity, cohesion and tackiness of the powder /granules mixture). In addition, tableting is the rate limiting equipment on the line.

The control and monitoring are performed continuously with the use of PAT tools, namely NIR probes. Each unit (except the tableting machine) is connected to the control computer. The control software was based on Labview using a add-on designed at the School of Pharmacy of UEF for this specific purpose. Data are stored in a data server (Kuava, Finland). An example of the software running is given in figure 4.

FIGURE 3 - SCHEMATIC FIGURE OF FULL LINE CONFIGURATION – 1. TABLETING MACHINE; 2. ROLLER COMPACTOR; 3. POWDER LOSS IN WEIGHT FEEDERS; 4. CONTINUOUS MIXER (ADAPTED BY (53))

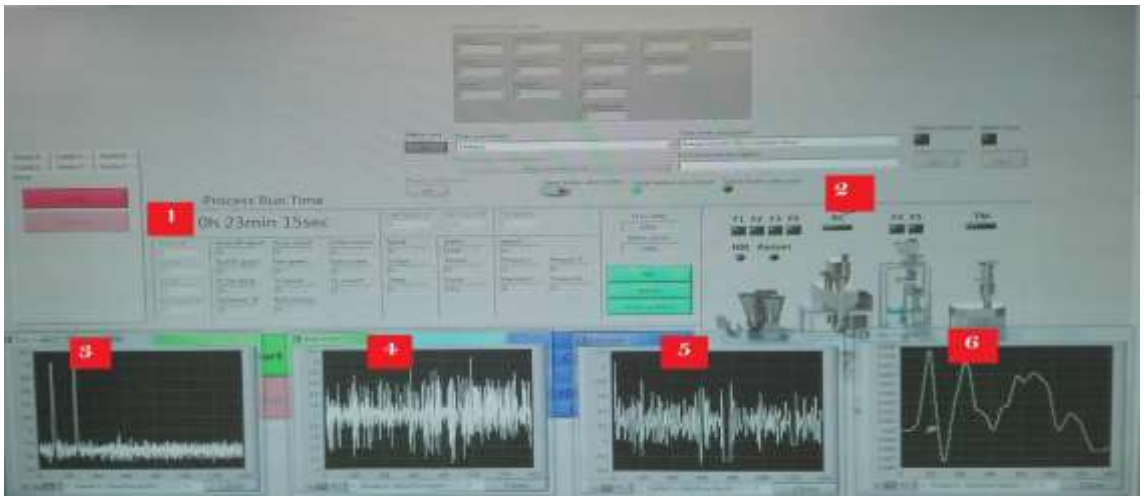

FIGURE 4 - LABVIEW CONTROL SOFTWARE INTERFACE: MONITORING OF THE POWDER MIXTURE. 1. DURATION OF THE EXPERIMENT; 2. SIGNALING OF THE EQUIPMENT BEING USED: FEEDER 1, 4, 5 AND 6; TABLETING MACHINE AND MIXER 2; 3. MASSFLOW CONTROL FOR MCC; 4. MASSFLOW CONTROL FOR PARACETAMOL; 5. MASSFLOW CONTROL FOR CAFFEINE; 6. MASSFLOW CONTROL FOR MGST

Chapter 4

Materials and methods

4.1 Pilot continuous manufacturing line

The continuous manufacturing line setup for this project was composed by a set of powder feeders, a continuous mixer and a the tableting machine. Powder feeders and mixer are positioned at the top of the tableting machine so that powders flow by the action of gravity to the compression machine (Figure 5). Feeding, mixing and compression are all integrated into a complete continuous line for tablets production. The typical flow rate in this continuous compression line is approximately 20 kg/h. In figure 6, it is possible to see a schematic of the configuration of a direct compression line. The equipment used to perform the experimental work is listed in table 2.

FIGURE 5 - THE DIRECT COMPRESSION CONTINUOUS MANUFACTURING SET-UP USED IN THE EXPERIMENTS. NUMBER 1 LOCATES THE POSITION OF THE NIR SPECTROMETER (ADAPTED FROM (41))

FIGURE 6 - THE WHOLE CONTINUOUS MANUFACTURING LINE

TABLE 2 – CONTINUOUS MANUFACTURING LINE UNIT OPERATIONS

Tablets Production	Real time monitoring (on-line measurements)	Measuring API content/homogeneity (off – line measurements)
Feeders one K-Tron, K-ML-D5-KT20, one K-Tron, K-CL-24-KT24, one K-Tron, K-CL-SFS-MT12 and one K-Tron, K-cl-24-kt24 modified.	**NIR spectrometer** Specim NIR, Spectral Imaging Ltd (Oulu, Finland)	**UV-Vis Spectrometer** Shimadzu UV-1800
Continuous Mixer Hosokawa, Modulomix		
Tableting Machine PTK PR-1000		

4.1.1 Feeders

Feeders play a key role in a continuous process: the more constant, the more homogeneous the output will be. LIW feeders measure the weight loss of material discharged from the system. These have an integrated control system that adjusts the mass flow based on the amount of material that has been fed, so the material flows from the hopper through the feeder to discharge its product at a controlled rate. The load cells continuously send weight readings to the controller and the material in the weigh hopper is measured as a weight loss / unit time. It compares the calculated weight loss with the setpoint and directs the feeder to adjust its rate. Table 3 show all process parameters measuring by feeder.

As soon as the mass flow is equal to the set point, the feeder is considered to be steady state. In this study four powder feeders were used (Figure 7): one K-Tron, K-ML-D5-KT20, one K-Tron, K-CL-24-KT24, one K-Tron, K-CL-SFS-MT12 and one K-Tron, K-cl-24-kt24 modified.

TABLE 3 - FEEDER PROCESS PARAMETERS

Process parameters	Description
Set point of raw material [kg/h]	Input value
Mass flow [kg/h]	Measured mass flow
Net weight [kg]	The amount of powder in the feeder
Pert [%]	The signal/noise ratio in percentage to the set point
Drive command [%]	Percentage in terms of the maximal feed rate
Motor speed [%]	Indicates how fast the motors runs

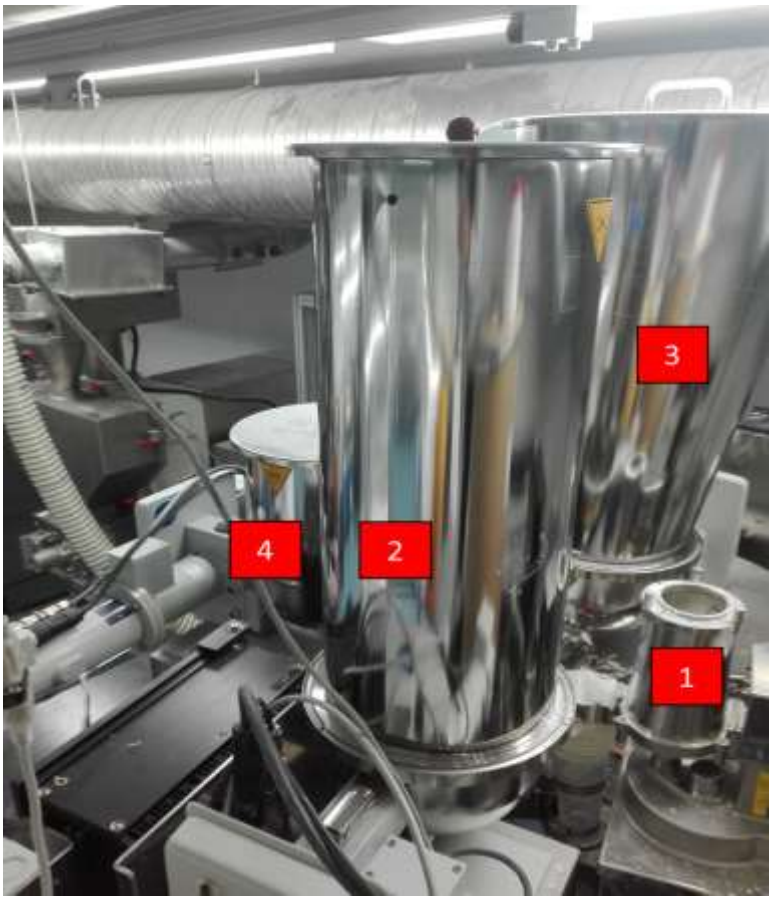

FIGURE 7 - LIW FEEDERS. 1- FEEDER FOR MGST; 2 - FEEDER FOR PARACETAMOL; 3 – FEEDER FOR MCC; 4 – FEEDER FOR CAFFEINE

4.1.2 Continuous Mixer

The continuous dry powder mixer consists of a horizontal cylindrical process chamber in which a horizontal blade stirrer is rotating. The blades are mounted on a shaft and rotate a fixed distance from the process chamber wall. The rotor speed can be adjusted. The powder is moved back and forth in the chamber by blades to achieve a more efficient mixing process. Although high shear forces can be applied to the blend, the impact effects of impact friction will be limited. The mixer has two powder inlets and one outlet. In this study, the first entry was used for the excipients and APIs while the second entry was used to feed the lubricant. In the present study, the tests were performed with mixing speeds of 350 rpm and 1200 rpm. At the center point of the design, 750 rpm were used.

4.1.3 Tableting machine

The tableting machine used, figure 8, is an equipment designed in the form of octagon thus promoting a saving of space. It is composed of a rigid structure with intelligent interior and is fully accessible for easy cleaning and maintenance. In addition, the control screen is independent and accessible.

Control is done through the PISCon system (Figure 8), PTK Pharm Tech Korea. This is easy to navigate through its touch screen and using the Windows operating system ensures easy and logical operation. It is configured to comply with FDA 21 CFR Part 11

regulations, which may save relevant production data. Stored production data such as batch history or product parameters can be retrieved at any time. Using PISCon in conjunction with the Pharmtech Weight Controller (PWR), the press controls the weight of the tablet systematically by monitoring the compression force.

FIGURE 8 - THE IMAGE ON THE LEFT SIDE CORRESPONDS TO THE COMPRESSION MACHINE, PTK, PT-100. THE IMAGE ON THE RIGHT REPRESENTS THE CONTROL SYSTEM OF THE COMPRESSION MACHINE, PISCON SYSTEM.

4.1.4 Process monitoring

4.1.4.1 Near infrared spectroscopy

A NIR-sphere system consisting of a sphere integrated with a tube inside, through which the powder flows, surrounded by six fibers placed at different angles was used in this work to analyze the mixture. This SPECIM NIR camera offers 320 pixel spatial resolution and 50 to 350 Hz image rate. Fibers collect the signals for Specim Spectral Camera. It consists of an ImSpector N17E imaging spectrograph, with a temperature-stabilized InGaAs detector and a monochrome camera in a wavelength range of 900-1700 nm. This system collects 100 spectra per second. The light source is a halogen lamp.

4.1.4.2 UV-Vis spectroscopy

To quantify the real amount of paracetamol and caffeine present in the samples collected during all the experiments, a UV-VIS spectrophotometer was used. This Shimadzu UV-1800, figure 9, features a Czerny-Turner mount and has a resolution of 1 nm.

FIGURE 9 - SHIMADZU UV-1800 UV-VIS SPECTROPHOTOMETER

4.2 Raw – materials

4.2.1 Microcrystalline cellulose (MCC)

MCC exists in the form of a white, odorless, tasteless, crystalline powder composed of porous particles. It is slightly soluble in 5% sodium hydroxide solution and practically insoluble in water, dilute acids and in most organic solvents. (34) *AVICEL PH 101, FMC, Cork, Ireland* was the type of MCC used. MCC (cellulose) has, as the pharmaceutical formula, $(C_8H_{10}O_5)_n$, where n is approximately 200. Its molecular weight is 36 000 g/mol. (34) In the formulation was used as binder and in an amount of 76.9%.

4.2.2 Magnesium stearate (MgSt)

The US Pharmacopoeia describes magnesium stearate as a magnesium compound with a mixture of solid organic acids consisting mainly of varying proportions of magnesium stearate and magnesium palmitate. It is mainly used as a lubricant in the manufacture of capsules and tablets in concentrations between 0.25% and 5.0% w/w. Despite a relatively small amount, the lubricants play important roles, they decrease the friction at the interface between the surface of a tablet and the die wall during ejection, so that wear on the punches and dies is reduced and the tablet is ejected no flaws. (48) Magnesium stearate is a very fine powder, white, precipitated or ground, of low apparent density, with a slight odor of stearic acid and a characteristic flavor. It provides high lubrication, has a high melting point and is chemically stable. (49) It is practically insoluble in ethanol, ethanol (95%), ether and water and slightly soluble in hot benzene and hot ethanol (95%). (34) Magnesium stearate, with molecular form $(Mg(C_{18}H_{35}O_2)_2)$ and chemical name, octadecanoic acid magnesium salt, has a molecular weight of 591.24 g/mol, and was used in an amount of 0.5%.

4.2.3 Paracetamol

Paracetamol (N-acetyl-p-aminophenol, acetaminophen), an antipyretic analgesic derivative of acetanilide, has long been established as one of the most widely used active substances in the world. (50) It is freely soluble in alcohol, in methanol, ethanol, dimethylformamide, ethylene dichloride, acetone, ethyl acetate, slightly soluble in ether and practically insoluble in petroleum ether, pentane and benzene. (51) Its chemical

formula is $C_8H_9NO_2$ and has as its molecular weight 151,165 g/mol. Paracetamol was used in an amount of 20%.

4.2.4 Caffeine

Caffeine (3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione) is an N-methyl alkaloid derivative of xanthine that is widely distributed in natural products commonly used in beverages. Its consumption has many physiological effects, such as gastric acid secretion, diuresis and stimulation of the central nervous system, increasing alertness and producing agitation. (50) The caffeine is freely soluble in pyrrole, slightly soluble in petroleum ether and freely soluble in tetrahydrofuran containing about 4% water (51). Its chemical formula is $C_8H_{10}N_4O_2$ and has as its molecular weight 194,194 g/mol. This active substance, purchase from *Sigma – Aldrich*® (product of China), was used in the formulation in an amount of 2.6%.

4.2.5 Fumed Silica (FS)

CAB-O-SIL M-5P (Synthetic Amorphous, Pyrogenic Silica) pyrogenic silica is an extremely pure excipient used as a multifunctional additive in the pharmaceutical industry. Their addition in a pharmaceutical formulation may be due to material flow problems which need to be solved. Thus, the sliding and anti-static properties of pyrogenic silica help improve the flow properties of the blend by reducing friction and static charges in compression equipment and high-speed capsules. This excipient is also compatible with many pharmaceutical ingredients. In addition to these properties, the addition of pyrogenic silica to a formulation reduces the segregation between the raw materials, promoting uniformity of content. Fumed silica (CAS number 112945-52-5) is a powder, white in color and slightly soluble in water (52).

4.3 Formulation and experiments

In order to evaluate how the performance of direct compression is affected by the parameters of the process, a set of experiments were performed (Table 4). The final formulation used for the realization of the defined experiences was the result of a set of pre-tests. These were carried out with the objective of achieving the best formulation possible, with the selected raw materials. Three pre-tests were performed. A first formulation was tested, however the tablets obtained had a lower mass than desired, thus, for the second pre-test, the type of dies as well as the speed of the mixer were altered. With these changes the obtained mass was the desired one, 250 mg, nevertheless it was verified the need to modify the amount of paracetamol to a smaller value, since the formulation used presented problems of fluidity. Thus, and upon completion of the third pre-test, it was found that the formulation used gather the desired conditions. The quantities corresponding to each raw material used are described in table 5. The achievement of the pretest allowed also set the parameters evaluated and varied throughout the experiments.

A set of experiences was defined considering two factors: mixer speed (750 and 1200 rpm) and flow rate (5 and 10 kg/h). Additionally, some experiments were defined considering a pre-mixture step (mixture of paracetamol (10%) and FS (10%)). These two

additional experiments were carried out to verify if the existence of a pre-mixture would allow a better flowability of the formulation.

TABLE 4 – SUMMARY FOR THE EXPERIMENTS CARRIED OUT IN THIS WORK.

Experiments	Mixer speed (rpm)	Flow rate (kg/h)	Pre-mixture
1	1200	10	No
2	750	10	No
3	350	10	No
4	1200	5	No
5	750	5	No
6	1200	10	Yes
7	750	10	Yes

TABLE 5 – SUMMARY OF THE FORMULATION.

Raw Material	Without pre-mixture (%)	With pre-mixture (%)
MCC	76.9	76.9
MgSt	0.5	0.5
Paracetamol	20	10
Caffeine	2.6	2.6
FS	not used	10

In order to start the set of planned experiments, it was necessary to first introduce the excipients and APIs into the feeders. It was cautioned that the amount of raw materials was sufficient for each experiment to proceed without interruption in the desired time (at least 20 minutes). Whenever a new experience was started it was always verified that there was no raw material accumulated in the feeder, "rat-holing". The control of the feeders was done through the software Labview. Once the feeders were loaded with the starting materials, the second stage of the process was started, the blend. Depending on the defined feed rate (5kg/h and 10kg/h), for each experience, it was necessary to wait six or three minutes respectively to start the compression phase. The waiting time counted from the moment the experiment is started is due to the fact that the tube connecting the mixer with the compression machine is almost completely filled with the powder. Therefore, when reaching the specified times, the compression phase was manually activated.

4.4 Paracetamol determination

The Shimadzu UV-1800 spectrophotometer was used to measure the 243 nm absorbance peak characteristic of paracetamol. Given the scarcity of time, it was necessary to determine which samples would be analyzed. It was decided to quantify, for all experiments, the samples collected at the end of each experiment, that is, samples collected at time 20 minutes. A calibration curve for paracetamol was thus constructed, figure10. For the construction of the same, several standard solutions of paracetamol were used to check the linearity of the measurement (Table 6) in the desired absorbance range. Phosphate buffer pH 5,8 was the solvent used for paracetamol standard solutions. Tablet samples were weighed, and for experiments 1 and 2, three samples were used, obtaining the triplicate UV-Vis results. For the remaining experiments only one tablet per sample was weighed. These samples were dissolved in 100 ml of buffer solution, a magnetic stirrer was used for mixing the buffer during dilution. 0.75 ml of this solution was transferred to 20 ml volumetric flask and completed with water. After dilution, samples were taken and put into a syringe having syringe filter on the end of it. Sample was filtered through the filter, and the filtered sample was used for measurements.

TABLE 6 - UV-VIS CALIBRATION CURVE MEASUREMENT RESULTS

Sample ID	Type	Conc. (µg/mL)	Absorbance at 243nm
P1	Standard	5	0.332
P2	Standard	10	0.644
P3	Standard	15	0.962
P4	Standard	20	1.292
P5	Standard	25	1.605
P6	Standard	30	1.931

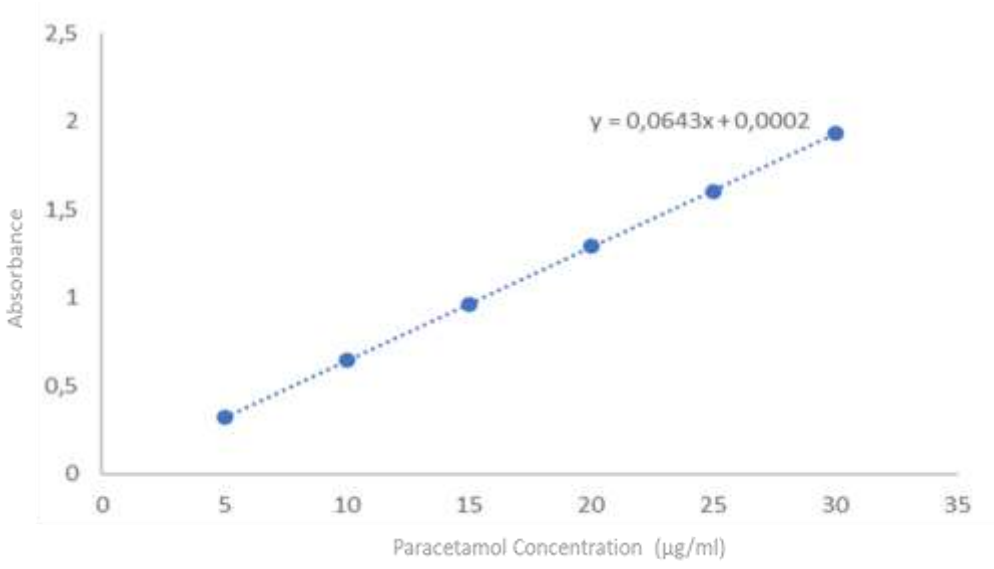

FIGURE 10 - CALIBRATION CURVE FOR THE PARACETAMOL UV-VIS DETERMINATION METHOD.

4.5 Data processing and analysis

4.5.1 Spectral acquisition and processing

A NIR spectrometer connected to the in-line integration sphere, coupled to the output of the continuous mixer, allowed the collection of NIR data for each experiment. These data were processed and stored by the proprietary acquisition software. The spectra were processed with Matlab (The MathWorks Inc. Natick, MA). Spectra were pre-processed with the Savitzky-Golay (first derivative and 15 points).

4.5.2 Multivariate models

Two PLS models were constructed, the first one was constructed with the purpose of analyzing the influence of the process variables on specific parameters. The first model was built with the purpose of paracetamol and caffeine prediction from NIR spectra. The spectra were pre-processed with Savitzky-Golay algorithm (SavGol) along with the first derivative (first order, 15 points). Before the construction of the PLS models, from NIR spectra, all datasets were submitted to mean-centring. The number of latent variables was optimized with cross validation. The model error is given as the mean quadratic error of prediction (RMSEP) and is relative to the prediction set. The second PLS model was built using Modde (Version 12.1, Umetrics, Sweden). This model related the process variables with the process responses. The selected factors were: mixer velocity, flow rate and premixing. The evaluated responses are related to the physical properties of the tablets, such as: mass, hardness and thickness. The model's prediction ability was evaluated by analysis of variance (ANOVA).

Chapter 5

Results and discussion

5.1 Process analysis

In this section we will analyze the unit operations of the direct compression process. The discussion is divided in the analysis of the feeders, mixer and tableting operations.

5.1.1 Feeders

The first stage of the whole process consists in placing the raw materials in the respective feeders. It is possible, through the previously mentioned program, to monitor and acquire data on the feed rate of each feeder over time. The data obtained, for each used feeder, correspond to the parameters that are in table 3, measured all over the experience time.

It is fundamental, for the direct compression process, to ensure that the feed rate is maintained and performed within the defined parameters. Thus, the following analysis concerns the evaluation of this phase of the process. All experiences were analyzed. However, since the results obtained are very similar to each other, only the procedure for experiments 5 and 6 will be demonstrated. Figure 11 relates to two graphs constructed with the different mass flows over time for each of the feeders used, for the experience 5 and 6, respectively. By comparing the obtained results with the values defined for each quantity of raw material, it is possible to conclude that the variations that exist in relation to the established value are small, and in this way the steady state will be reached. However, since for the process in question several feeders were used, the multivariate methods offer much more robust tools to evaluate the steady state of the feeders used.

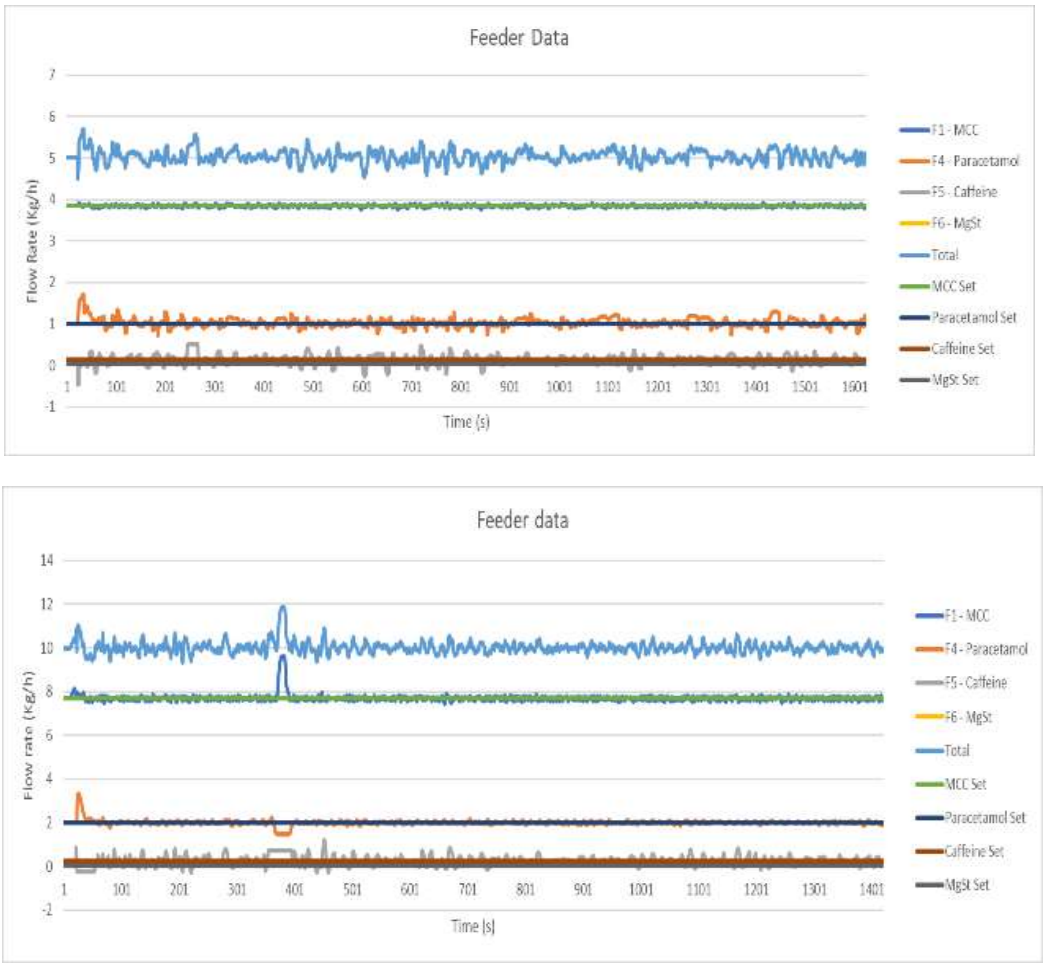

FIGURE 11 - VARIATION OF MASS FLOW FOR ALL USED FEEDERS – RUN 5 ON TOP AND RUN 6 ON BELOW.

Thus, using the feeder process data, one model, for each experiment, is constructed using principal component analysis (PCA). Table 3 shows the process parameters and those that are included in the model (except the set point, which is a controlled input variable). Thus, the time evolution of the process is visible in the PCA model. The model was constructed using SIMCA and the values of Q and R, for each experience, are in table 7. This is the final model, in which parameters were extracted, pert, drive command and motor speed from the MCC and MgSt feeder. These parameters were excluded based on their meaningfulness, which was much lower than the other parameters, include in the model. From the scores plot, figure 12, the evolution of the feeder scores is clearly observed. For Experiment 5 (Figure 12, upper image), observations begin in the lower left corner. In Experiment 6 (Figure 12, bottom image), observations begin in the lower right corner and progress to the upper right corner. The instant of time when the observations enter the ellipse is approximately 0.9 minutes, for experiment 5 and approximately 0.73 minutes for experiment 6. The mass flow for caffeine and paracetamol was checked. For experience 5, the value of paracetamol (1,067 kg/h), and caffeine (0.086 kg/h), are not within the specifications of label claim i.e. between 105% and 95%. Thus, in this way, it is not possible to conclude that the observations that lie within the ellipse are in steady state. Concerning experience 6, the observed values of paracetamol (2.17 kg/h) and caffeine (0.26 kg/h) are within the specifications of label

claim i.e. between 105% and 95. Thus it can be said that from the moment in which the observations enter into the ellipse, the process enters steady state. It should be noted that, for the mixture to be the best possible, all feeders must operate at steady state. When steady state is reached, feed rates remain very constant. Random spikes in feed rates, such as those occurring at some points in figure 11, are due to the accumulation and drop of powder in the feeder exit port.

TABLE 7 – SUMMARY OF PCAS MODELS.

Experiment	Principal component	R^2X	R^2X(cum)	Q^2X	Q^2X(cum)
# 5	*1*	0.25	0.25	0.0597	0.0597
	2	0.184	0.434	0.045	0.102
	3	0.171	0.606	0.203	0.284
	4	0.105	0.711	0.088	0.347
# 6	*1*	0.292	0.292	0.155	0.155
	2	0.17	0.463	0.0604	0.206
	3	0.163	0.626	0.153	0.328
	4	0.112	0.738	0.11	0.402

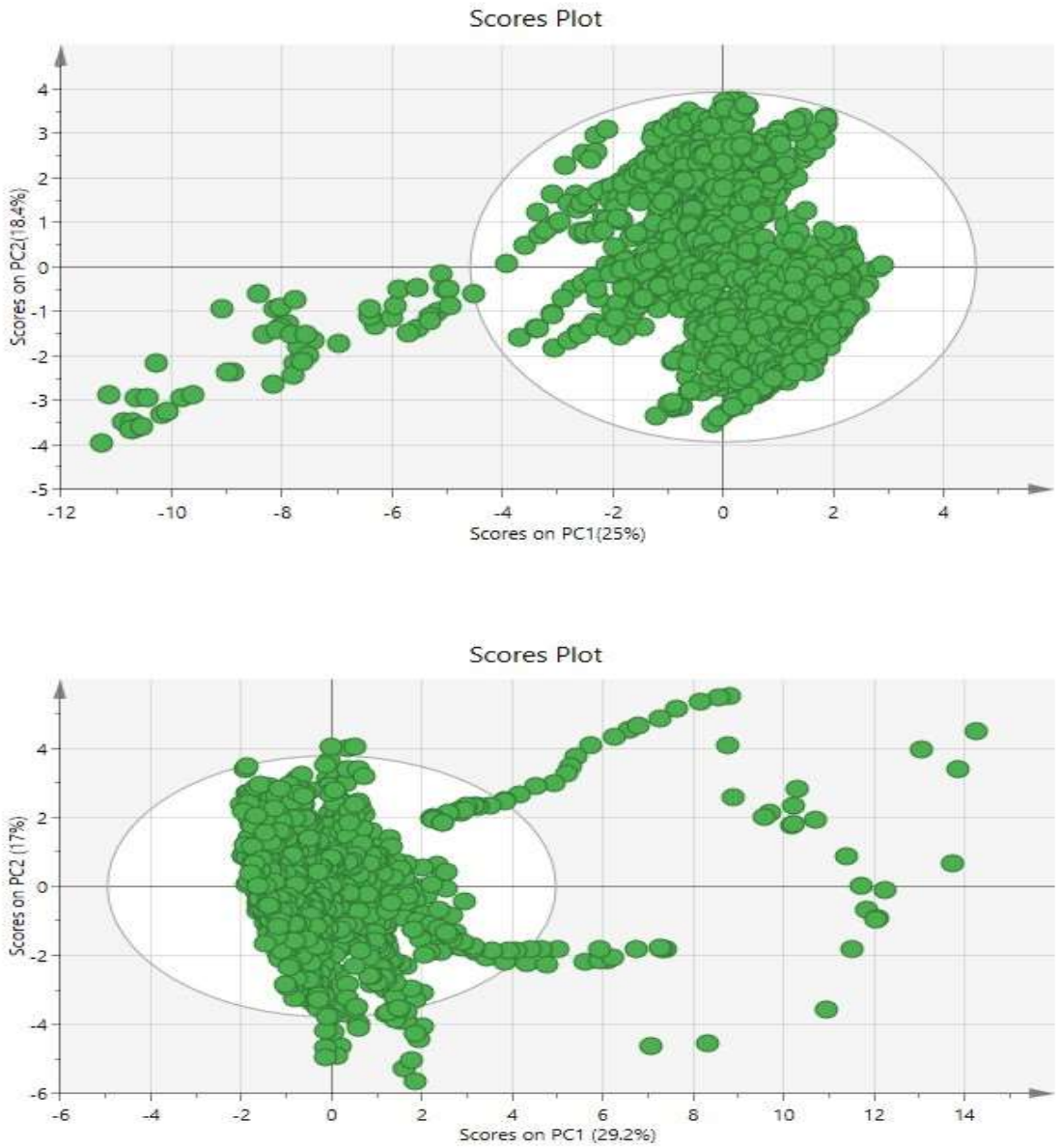

FIGURE 12 - SCORES PLOT FROM PCA MODEL CALIBRATED WITH FEEDER PARAMETERS, FROM EXPERIMENT 5, UPPER IMAGE, AND EXPERIMENT 6, BOTTOM IMAGE.

Figure 13, refer also to data obtained from the feeders, and with this second analysis, the objective is to analyze only the amount of paracetamol and caffeine, and see if they remain constant throughout the feeding phase around the set point. Analyzing each experience, it is apparent that the amount of paracetamol in the experience 1,2 and 3 is relatively controlled over time, since it is very close to 20% (set point). Experiments 6 and 7 were the ones that showed the best performance, because the variations around the set point were minimal throughout the process. Regarding the variation of the amount of caffeine throughout the experiments, it is possible to visualize that there is a difficulty in keeping the quantity defined and controlled, being in agreement with the previous analysis, in which it was not possible to verify the steady state of the caffeine feeder in all experiments.

In the experiments carried out at a rate of 5 kg/h, experiment 4 and 5, there was an even greater difficulty in maintaining the values of paracetamol and caffeine at the defined value, indicating that this feed rate, for the formulation in question, does not will be the most indicated.

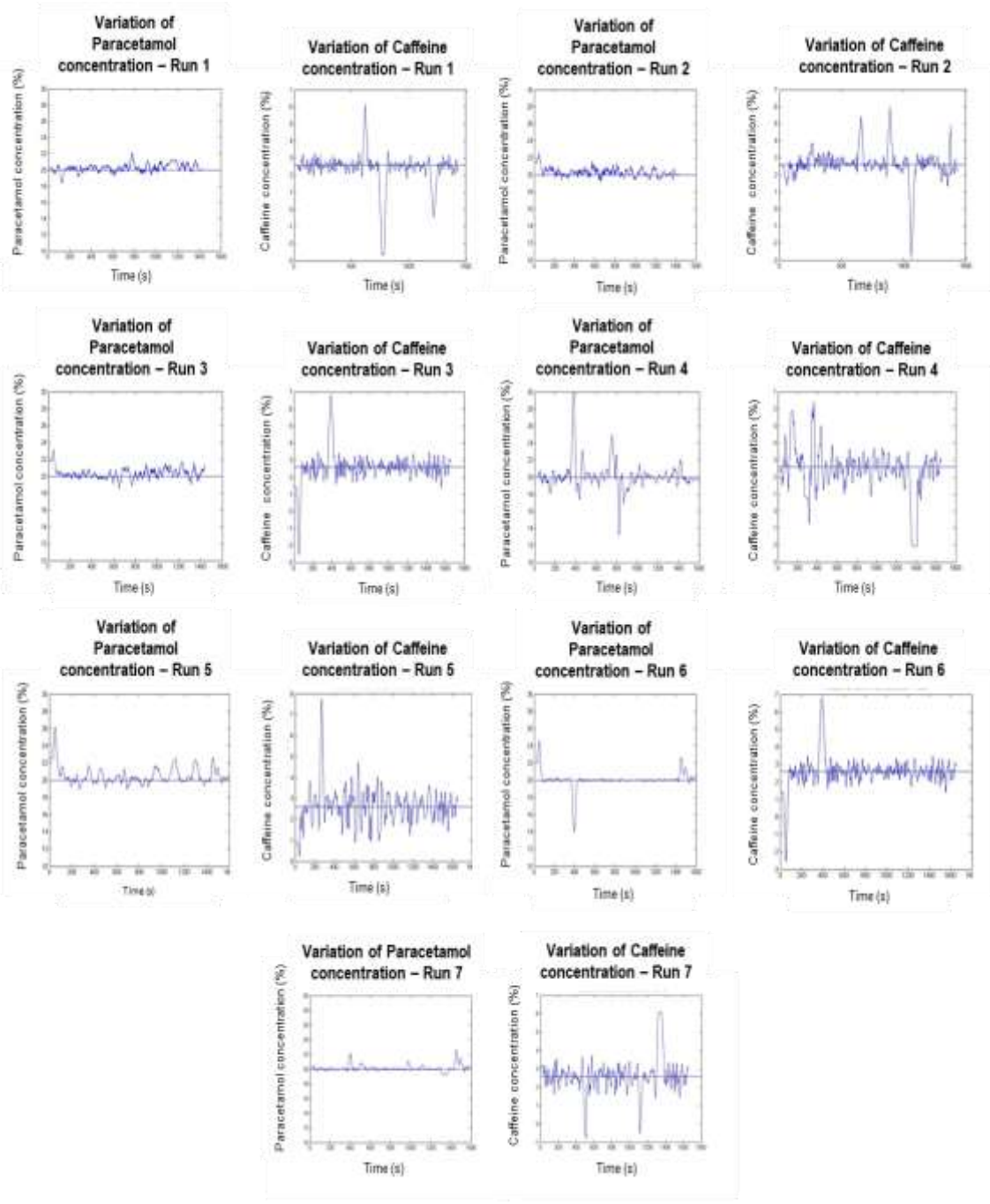

FIGURE 13 - FEEDER DATA: VARIATION OF PARACETAMOL AND CAFFEINE CONCENTRATIONS

5.1.2 Continuous mixer

The following analysis was based on data collected by the NIR spectrometer connected to an in-line integration ball which was coupled to the output of the continuous mixer. The processing of these data began with the spectra processing. Each consecutive 100 spectra were averaged to give spectrum per second. Due to the fact that there is a region of this spectrum that would not have relevant information for the study, wavelength below 950nm were not considered. It was observed that the result of the exploratory analysis was similar for all experiments. For illustrative purposes only the results for experiment #2 will be analyzed here. NIR spectra noise can be mitigated by averaging consecutive spectra (the frequency of spectra acquisition was 100 per second). Noise can also be reduced using some pre-treatment methods. Figure 14 shows raw and after application of Savitzky-Golay with first derivative.

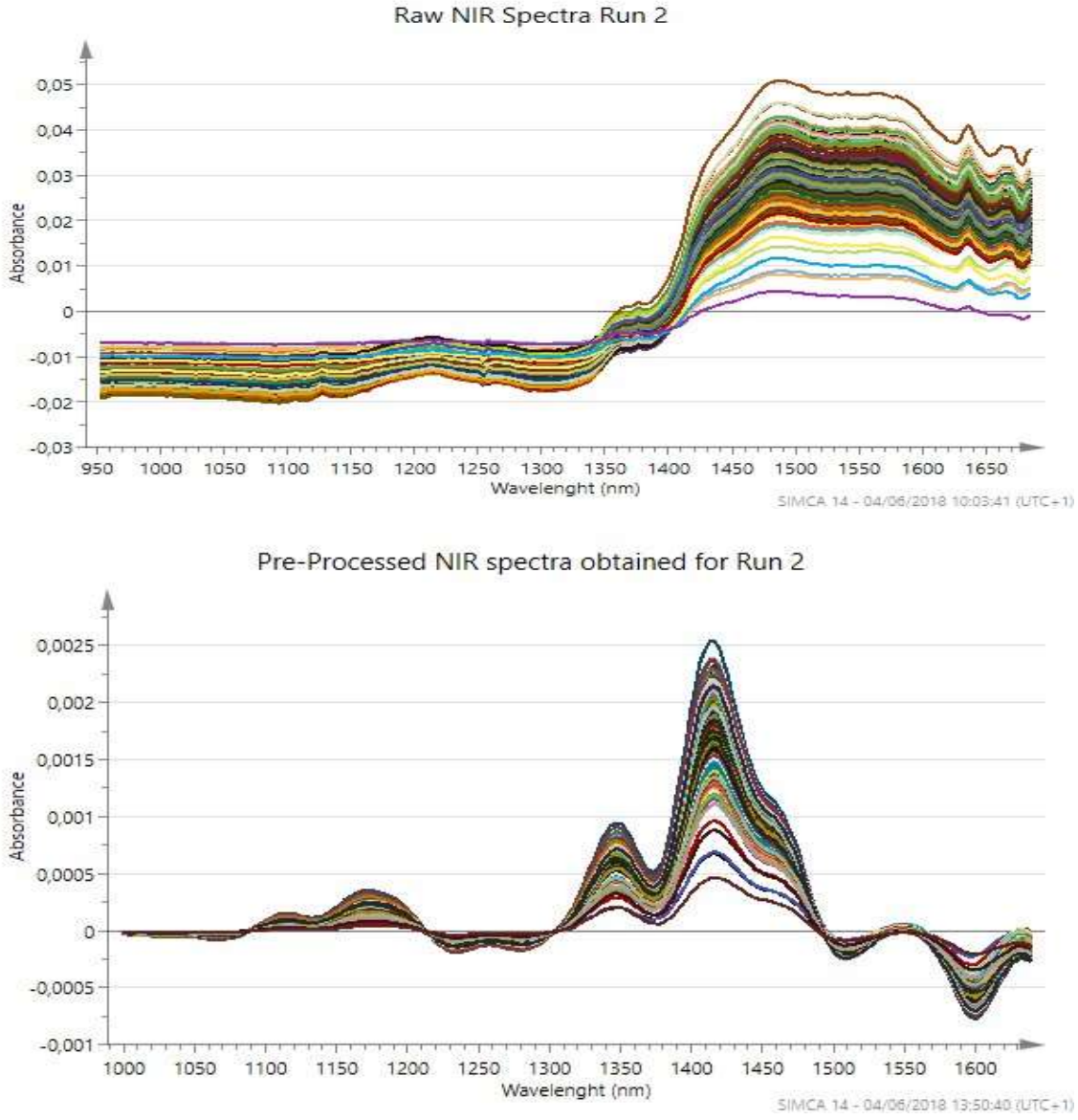

FIGURE 14 - RAW NIR, (UPPER IMAGE) AND PRE-PROCESSED (SAVGOL + 1ª DERIVATE) NIR SPECTRA (BOTTOM IMAGE) OBTAINED FOR RUN 2.

When performed on an entire sample, the first derivative effectively removes baseline and emphasizes the lower frequency signals. After applying the pre-treatment to the spectrum, as well as mean-centring, a PCA model was developed. Model was developed with the objective of analyzing the internal structure of the data. This model was constructed with two latent variables. In this way, the score plot of the experiment number 2 can be seen in figure 15. The first main component (PC1) captures 97% of variance, and the second main component (PC2) captures 2.2% of variance. The scores are colored according to the Hotelling's T^2 statistic. Thus, the samples that are inside the ellipse are those closer to the center of the model, as it is the case of the group that presents the color yellow and green, corresponding this to the steady state. The observations one to eighteen were excluded because they were considered outliers. Figure 15 identifies a clear trajectory of the process. The process starts in the upper left corner, outside the ellipse. Following the scores along the PC1 axis, we see the approximation of these to the center of the ellipse, and at the end of the process, the final scores are outside the ellipse, in the third quadrant.

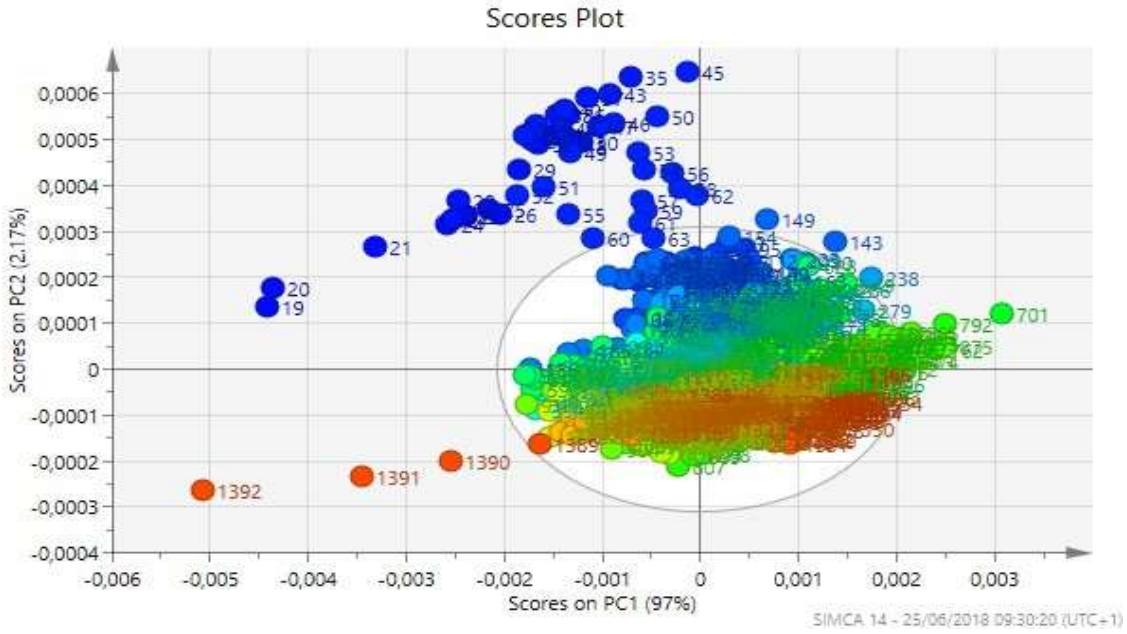

FIGURE 15 - THE SCORE PLOT FROM PCA MODEL CONSTRUCTED WITH NIR DATA FOR RUN 2

In figure 16, the Hotelling's T^2 statistic is shown as a function of the squared residuals statistic or distance to model statistic (Q). The Q statistic measures the distance between each sample and the model. The lines that are visible in the figure refer to the 95% confidence limits.

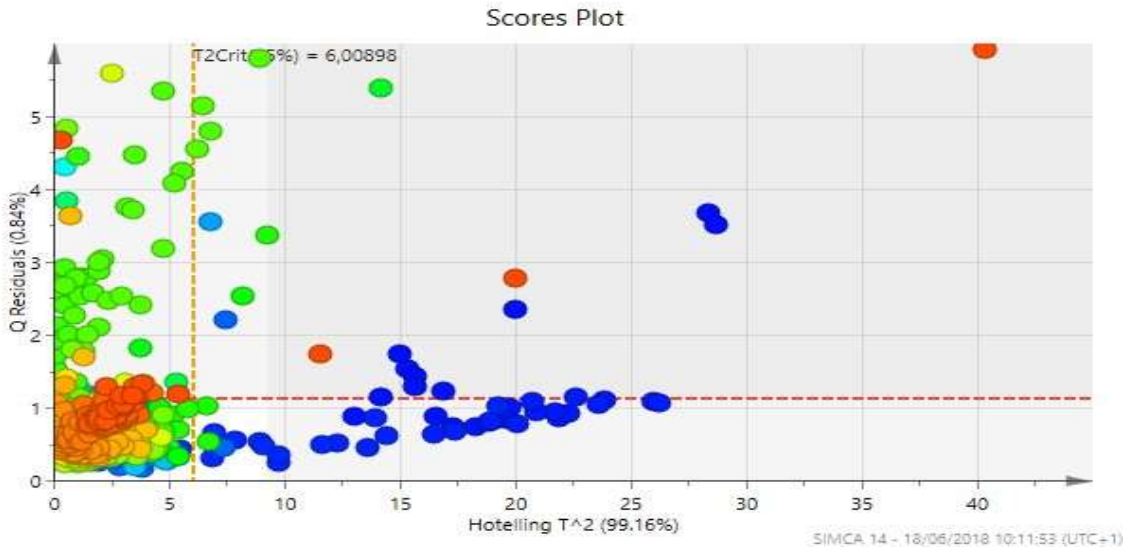

FIGURE 16 - HOTELLING T^2 VS Q RESIDUALS FROM PCA MODEL (RUN 2)

The first component was also represented as a function of time (Figure 17). It is clear that there is variability over time. This variability must be further analyzed. It may be related with fluctuations in terms of product characteristics or/and caused by an inefficient procedure to capture the NIR spectra. The observed changes seem to have some autocorrelation which might indicate indeed some variability in the processed product.

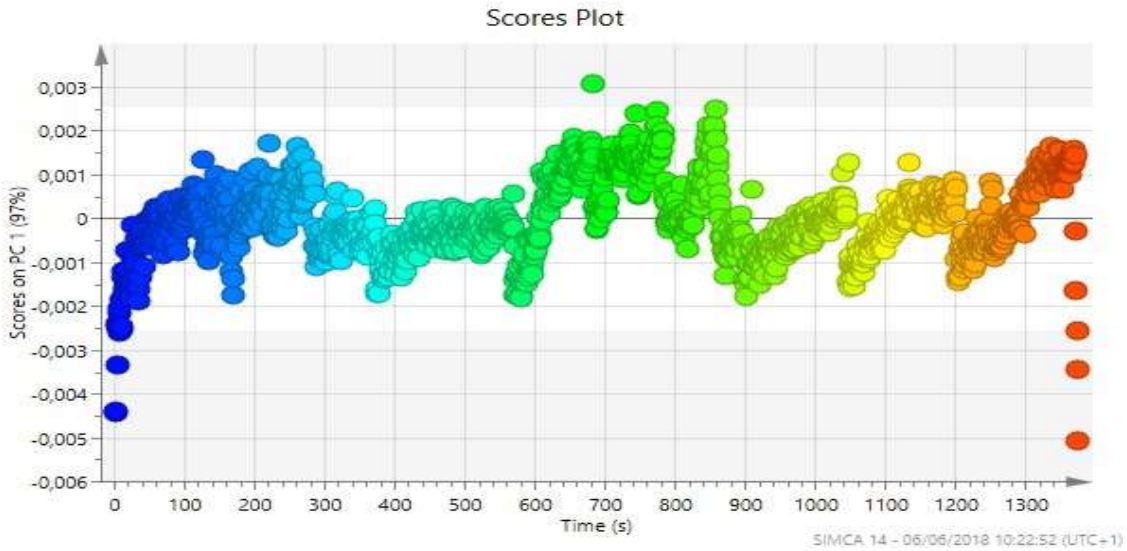

FIGURE 17 - PC1 REPRESENTED IN FUNCTION OF TIME (RUN2)

The analysis of the PCA scores, figure 18, revealed variations that would not be expected, in this way, possible causes were explored. At first, it was thought that these changes were due to variations caused by fluctuations in the feeder mass flows. Consequently, an analysis was made of the periodicity of the mass flows in the feeders as well as to the periodicity of the scores for all experiences. The obtained results, comparing the periods in which the variations occur in the scores, with the same periods in the mass flows of raw materials, show that there is no relation or reason for these ranges of variations in the experiences to occur. Moreover, in the analysis done to the

feeders, it is concluded that these, for most raw materials, have managed to reach the steady state, maintaining the mass flow around the defined set point. Therefore, these variations should not be due to problems related to fluctuations in the mass flow of the feeders. We then attempted to understand which functional groups were contributing to the ranges of variations that occurred. For this the wavelength contributions to the scores were analyzed. It was first necessary, for each experiment, to define the intervals of the variations, and thus to analyze individually each of them. With the intervals defined, the analysis of the contributions can take place. Contributions for the first and second components (Figure 19) were analyzed. During the analysis, we recorded the wavelengths that contributed most significantly to the variations that occurred in each defined interval. Thus, it was found that the wavelengths, which most significantly contributed to the variations, both using the first component and the second component, were the same, 1313 - 1471 nm and 1577 - 1603 nm. After discovering that these were the wavelengths that were contributing to the variations, it was found which functional groups would absorb at these intervals. It was found that CH3, CONHR and OH could affect the NIR signal. These are functional groups that belong mainly to paracetamol, which leads us to conclude that these variations could be due to changes in the quantity of this raw material, when the mixture is analyzed by NIR. As already mentioned, within the NIR measuring sphere, there is a glass tube, and since paracetamol is very sticky, it may contribute to the small clusters of the paracetamol-containing mixture adhering to the tube, in a random way, provoking the variations that are observed in the scores.

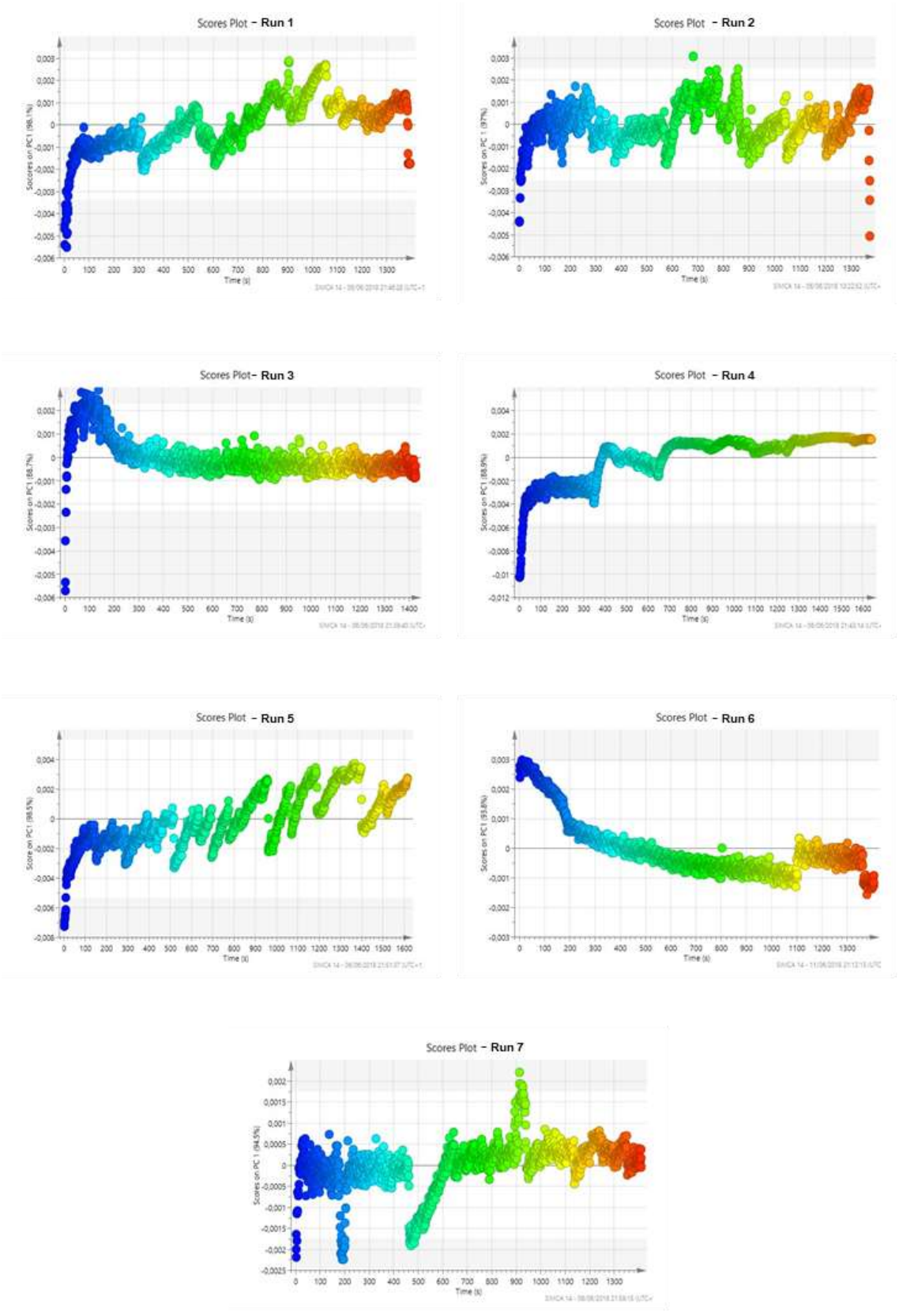

FIGURE 18 - REPRESENTATION OF PC1 OVER TIME FOR ALL EXPERIMENTS (EACH MODEL WAS CALIBRATED WITH DATA FROM DIFFERENT EXPERIMENTS).

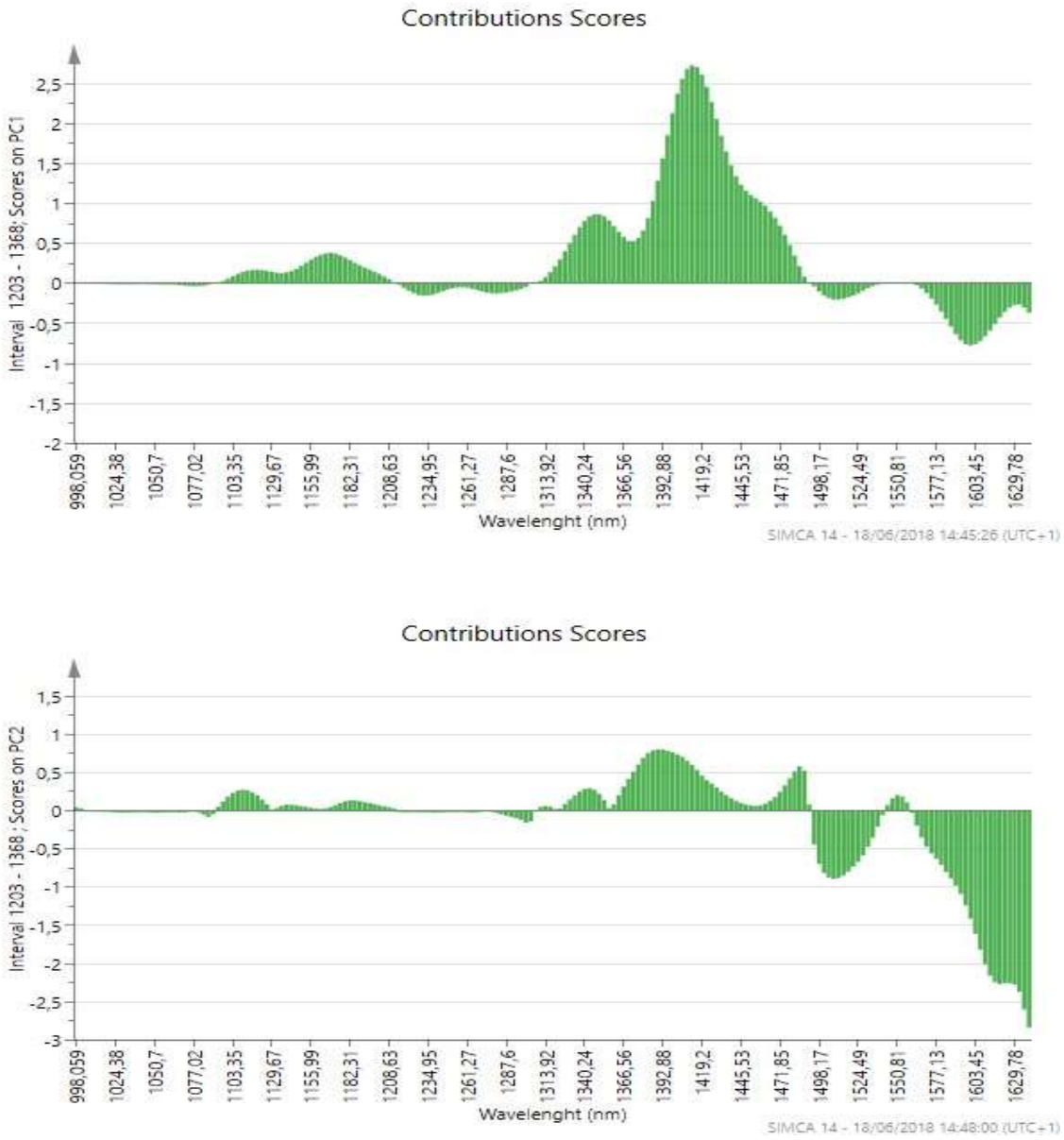

FIGURE 19 - WAVELENGTH CONTRIBUTIONS FOR THE FIRST AND SECOND SCORES (RUN2)

5.1.2.1 Paracetamol and caffeine prediction by NIR spectroscopy

A new set of experiments, called calibration experiments, were performed to assist in the development of a methodology to estimate paracetamol and caffeine from the NIR spectra collected at the outlet of the mixer. The new experiments are described in table 8. The first three experiments were set varying only the paracetamol content: 80, 95 and 105%. In the following three experiments, the values of caffeine (80, 105 and 120%) were changes keeping the remaining percentages constant. These experiments were conducted at a flow rate of 10 kg/h. Spectra obtained from these experiments were used to calibrate 6 different PCA models. Spectra was processed with the pre-treatments explained above. The mean spectra collected for each experiment was used as the X-block and the corresponding % of caffeine and paracetamol were the Y-block for PLS

models. Therefore, two PLS models were calibrated (one for paracetamol and one for caffeine).

TABLE 8 – EXPERIMENTS FOR PLS MODELS CONSTRUCTION

	Paracetamol (kg/h)	Caffeine (kg/h)	MCC (kg/h)	MgSt (kg/h)	% of API	
Calibration 1 (80%API)	1.6	0.26	8.09	0.05	16	**Change in paracetamol percentage in formulation**
Calibration 2 (95%API)	1.9	0.26	7.79	0.05	19	
Calibration 3 (105%API)	2.1	0.26	7.59	0.05	21	
Calibration 4 (80%API)	2	0.208	7.742	0.05	2.08	**Change in caffeine percentage in formulation**
Calibration 5 (105%API)	2	0.273	7.677	0.05	2.73	
Calibration 6 (120%API)	2	0.312	7.638	0.05	3.12	

A model with a latent variable was the best model obtained, both for predicting paracetamol and for caffeine. The performance of both models was evaluated by internal and external validation. The internal validation of the model provides an estimate of the predictive performance of the model, which can be evaluated by the RMSECV (cross-validation error) and the coefficient of determination for cross-validation (R^2cv). In external validation, the calibration model was tested using data that was not used to construct the model. This method provides a reasonable assessment of the predictive performance of the model with new samples. The external validation is evaluated by the RMSEP and the determination coefficient for Prediction (R^2p). Therefore, 6 experiences were used to construct the two models. In the case of the predictive model of paracetamol, the three experiments were used in which the value of caffeine was altered to predict paracetamol and the opposite occurred for the caffeine prediction model. Figure 20 and 21 show the estimation performance of the model for paracetamol and caffeine, respectively. The RMSECV values for both the predictive model of paracetamol (0.22%) and the predictive model of caffeine (0.10%) are low, being a good indication for the predictive capacity of the model.

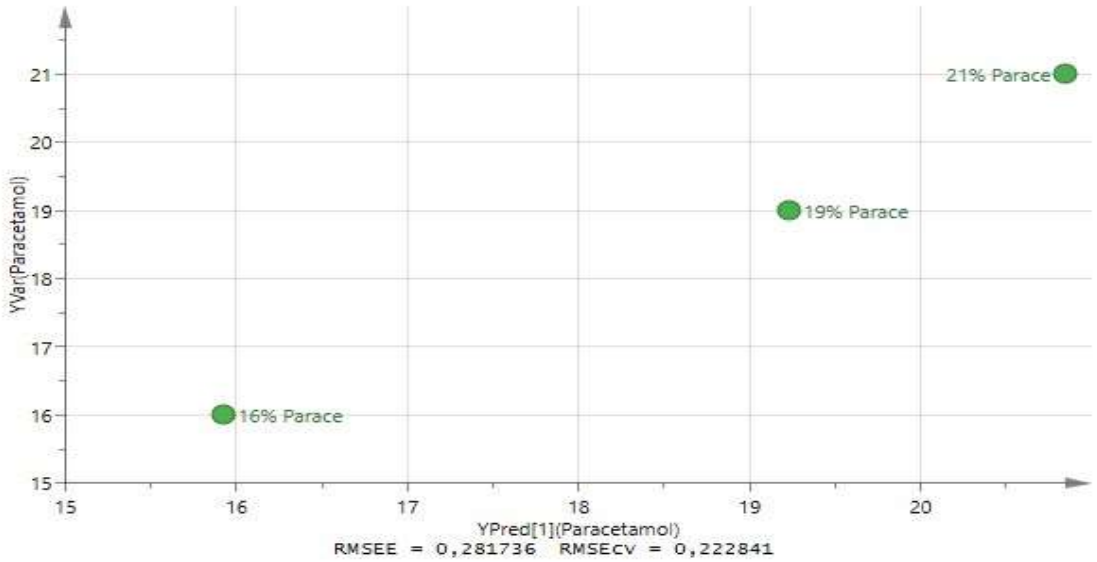

FIGURE 20 – MODEL PREDICTION FOR PARACETAMOL

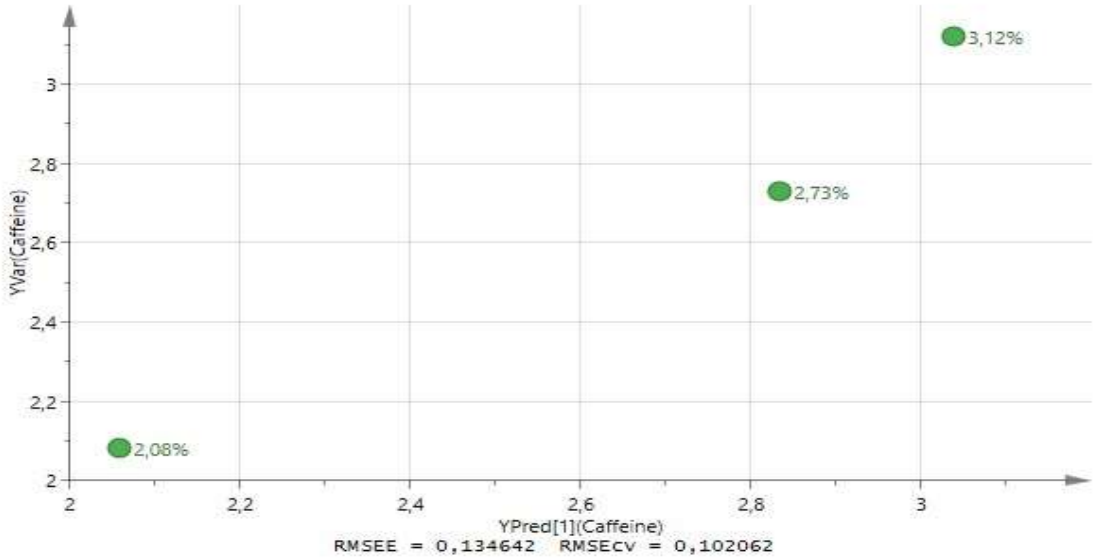

FIGURE 21 – MODEL PREDICTION FOR CAFFEINE

Figures 22 and 23 refer to the results of the test performed on the calibration model, using the experiments that were not used to construct the model: caffeine data (three last experiments) to predict paracetamol and paracetamol data to predict caffeine (three first experiments). The values obtained from RMSEP for paracetamol (12%) and for caffeine (10%) were also low. Thus, it can be concluded that the models will have a good prediction capacity. These two models were constructed only with six calibration experiences, so they lack robustness. Therefore, it would be necessary an additional set of experiments for calibration to add robustness to the PLS models. Nevertheless, data for all seven CM experiments were applied to these models (Figure 24).

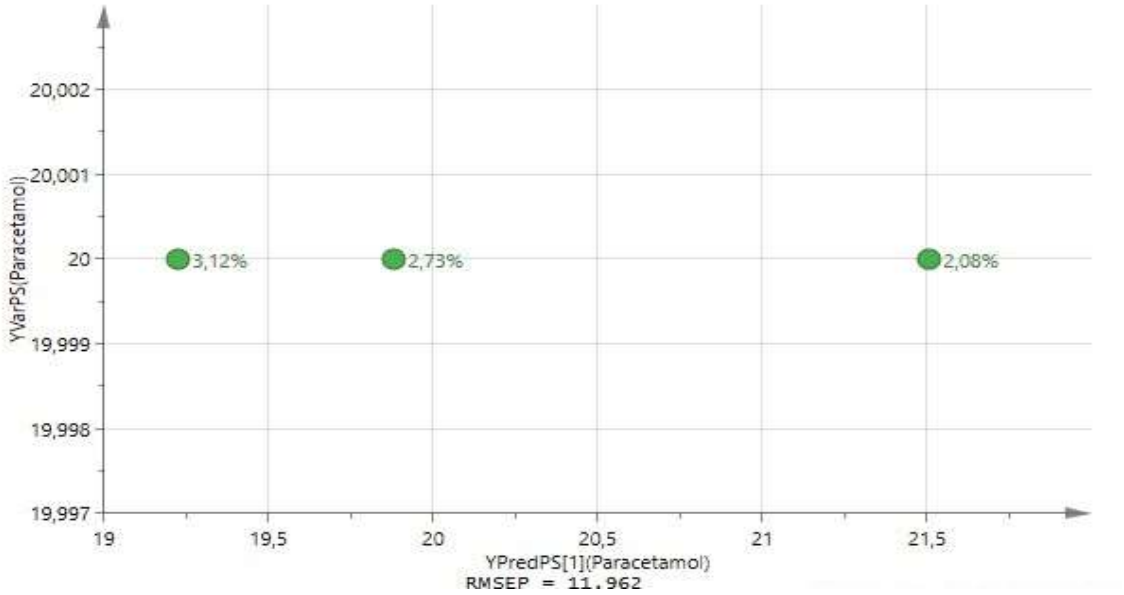

FIGURE 22 – TEST PERFORMED TO THE CALIBRATION MODEL FOR PARACETAMOL

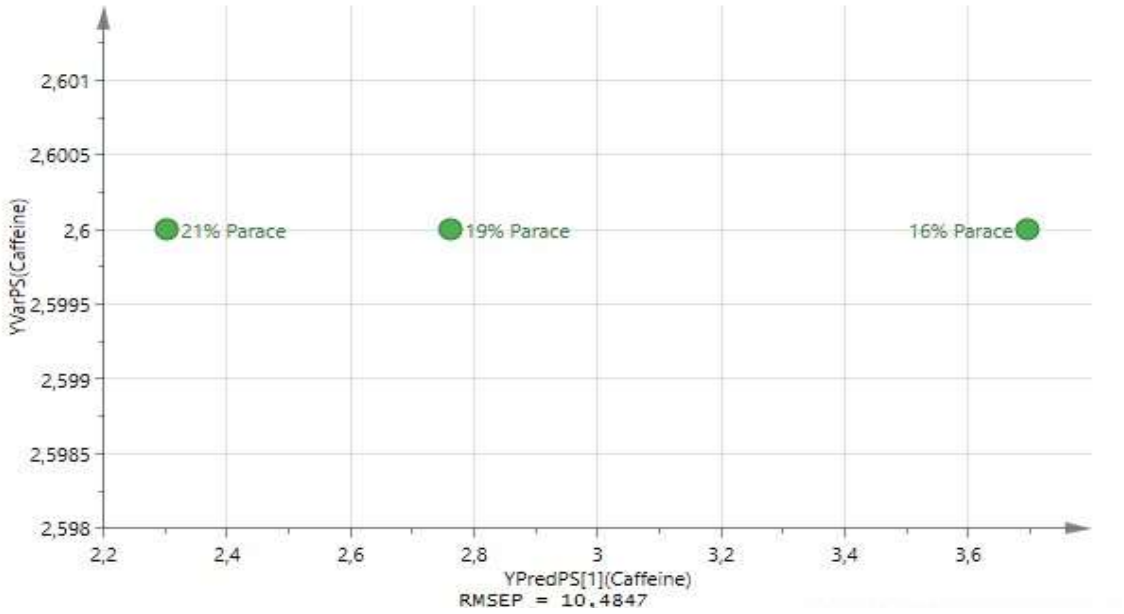

FIGURE 23 – TEST PERFORMED TO THE CALIBRATION MODEL FOR CAFFEINE

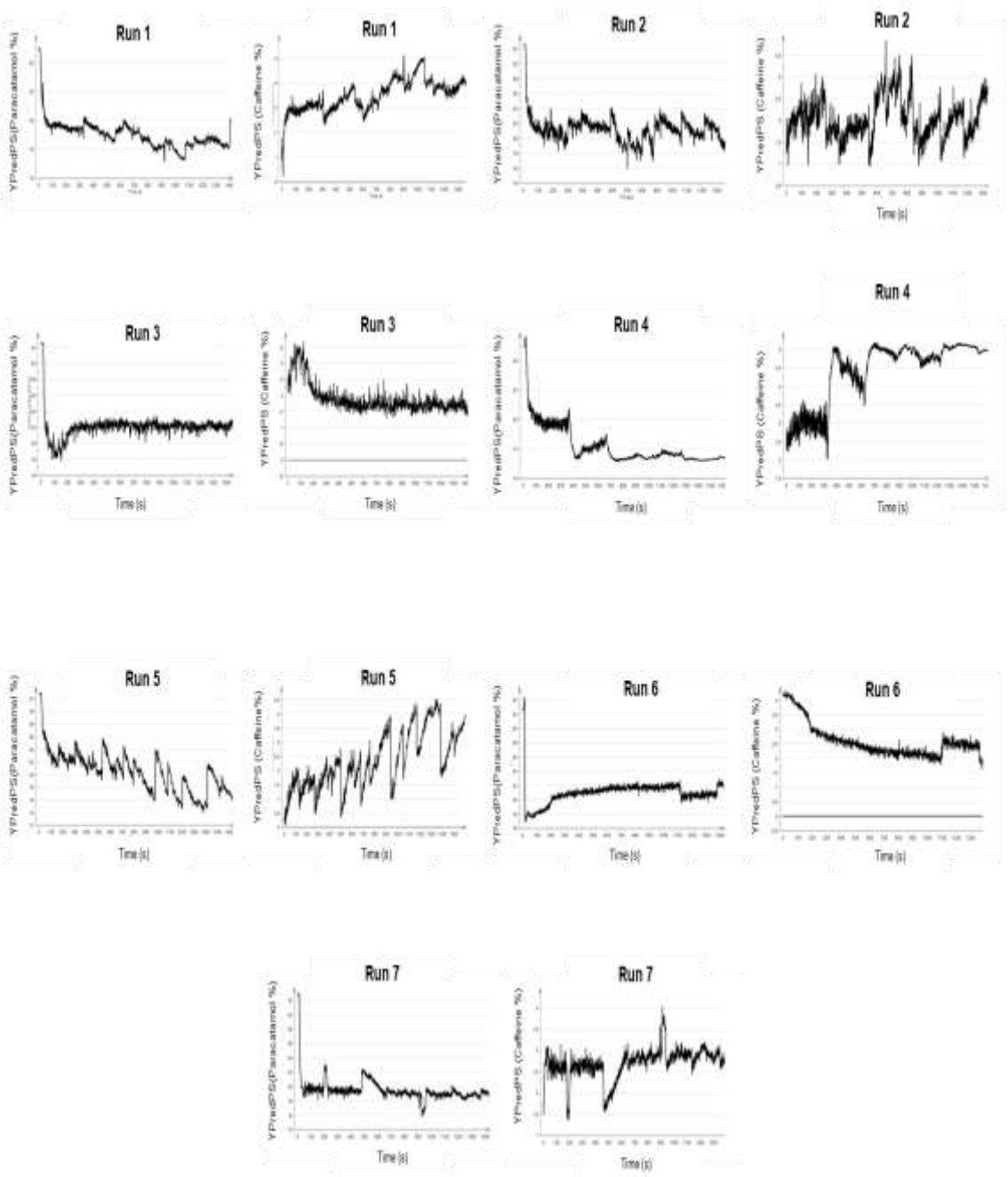

FIGURE 24 – OBTAINED RESULTS FOR ALL EXPERIMENTS FOR PREDICTIONS OF PARACETAMOL AND CAFFEINE, OBTAINED WITH PLS MODELS: PLS MODEL FOR PARACETAMOL AND PLS MODEL FOR CAFFEINE.

These results show that the predictions for paracetamol and caffeine aren´t completely coincident with the expected values. The value that should be achieved, for all experiences, should be 20% for paracetamol and for caffeine, 2.6%. As can be seen in figure 24, there are some mismatches relative to the expected values. It is also important to note that in the case of caffeine, the difference between the expected and the verified values is more frequent and the oscillations more pronounced.

5.1.3 Tableting

During the course of all experiments, samples of tablets were collected. These were collected during 20 minutes with a 2 minutes interval. Collected tablets were analyzed according to the mass, hardness, and thickness. For each set of samples, 20 tablets were randomly selected, as defined by the European Pharmacopoeia (EP 6.0). The procedure adopted for the analysis of the three properties previously mentioned was the same (Figure 25). For each experiment, samples were collected at 10 sampling periods. Twenty tablets were selected from each of these 10 sampling periods. Averages were calculated for each property (see Annex 1). The final value, for each property and experiment, resulted from the average of all 10 sampling periods. The final values are shown in table 9.

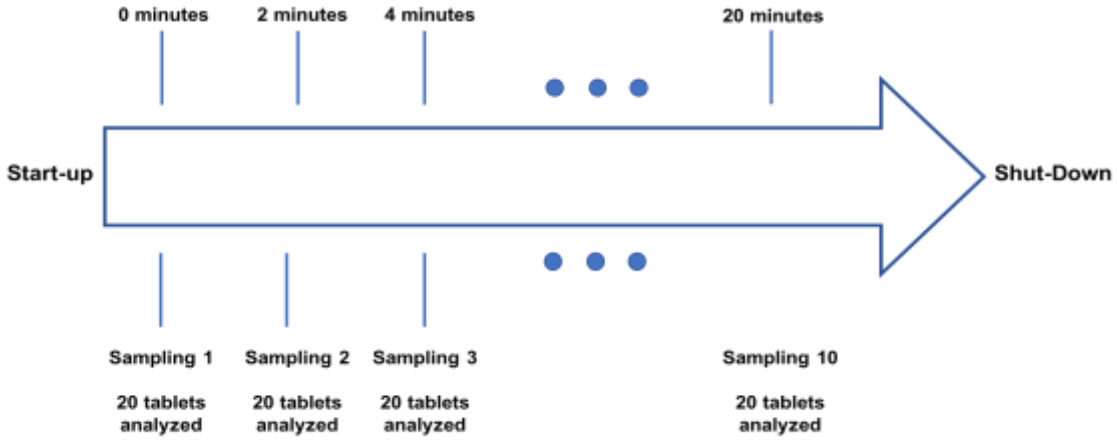

FIGURE 25 - SAMPLING PROCEDURE FOR ALL EXPERIMENTS

TABLE 9 - MEASUREMENTS OF PHYSICAL PROPERTIES FOR TABLETS SAMPLES

Experiments	Average weight (mg)	Average hardness (N)	Average thickness (mm)
1	300.23	142.31	2.99
2	283.18	134.59	2.93
3	278.07	152.32	2.93
4	332.03	173.26	3.14
5	300.89	154.19	2.99
6	291.32	213.10	2.97
7	289.75	226.56	2.95
Mean	291.32	226.56	2.96
Standard deviation	16.41	33.04	0.06
CV (%)	5,63	14,59	2,26

The first property to be analyzed was the uniformity of mass. According to the European pharmacopoeia (EP 6.0) and taking into account that the average obtained for all

samples was always higher than 250 mg, the permitted deviation is 5% (no more than two units outside the specified limits) and none can be outside the 10% limit. By analyzing all sets of samples, it is concluded that in some experiments the specifications mentioned above are not fulfilled, mostly due to the fact that they exceeded the 5% limit.

The variation of the results of the final averages, relative to the mass of the tablets, obtained for each experiment, are shown in figure 26. In addition, the confidence limits, for the mass are also represented in figure 26. The error bars were calculated taking into account the percentage defined in the EP (+/- 5%). Experiment 4 is, therefore, outside the defined limits. It is to be noted that a higher speed of the mixer resulted in higher tablet weights due to better flow properties, thereby improving matrix filling.

FIGURE 26 - MEAN VALUES OF MASS FOR EACH EXPERIMENT

Hardness was the second property analyzed. Figure 27 concerns the variation of this property throughout the experiences. The error bars were calculated taking into account the standard error. It should be noted that the values obtained are quite high, and inconstant. The standard deviation and consequently the coefficient of variation are high (Table 8). Despite there is no specification in the EP for hardness, the observed differences may interfere with the disintegration time and dissolution profile

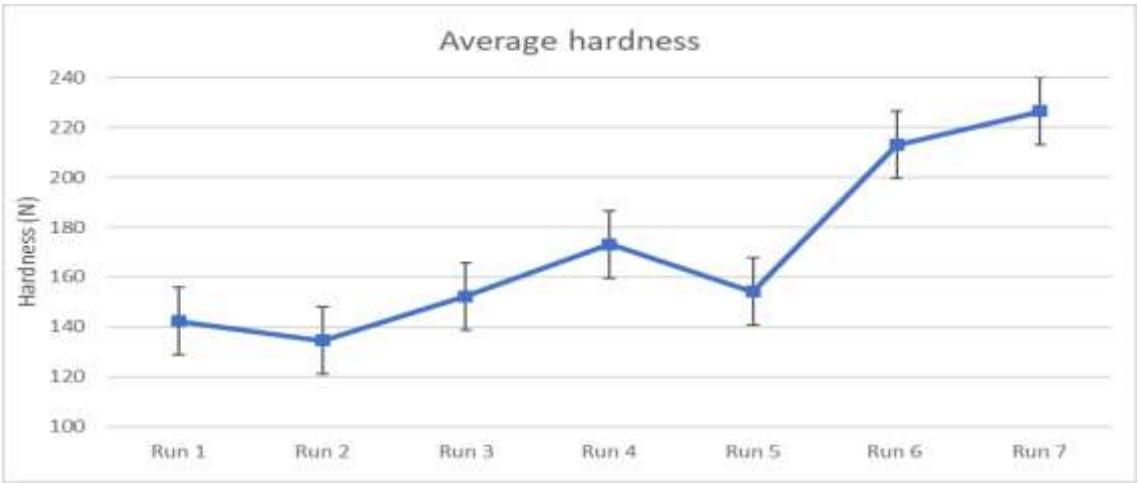

FIGURE 27 - MEAN VALUES OF HARDNESS FOR EACH EXPERIMENT

Finally, the last physical property analyzed was the thickness (Figure 28). The error bars were calculated taking into account the standard deviation. The thickness of a tablet is determined by the diameter of the matrix, the amount of material filling it, the compaction characteristics and the force applied during compression. Thus, as all the features referred to above were held constant throughout the experiments the thickness values are very close to each other.

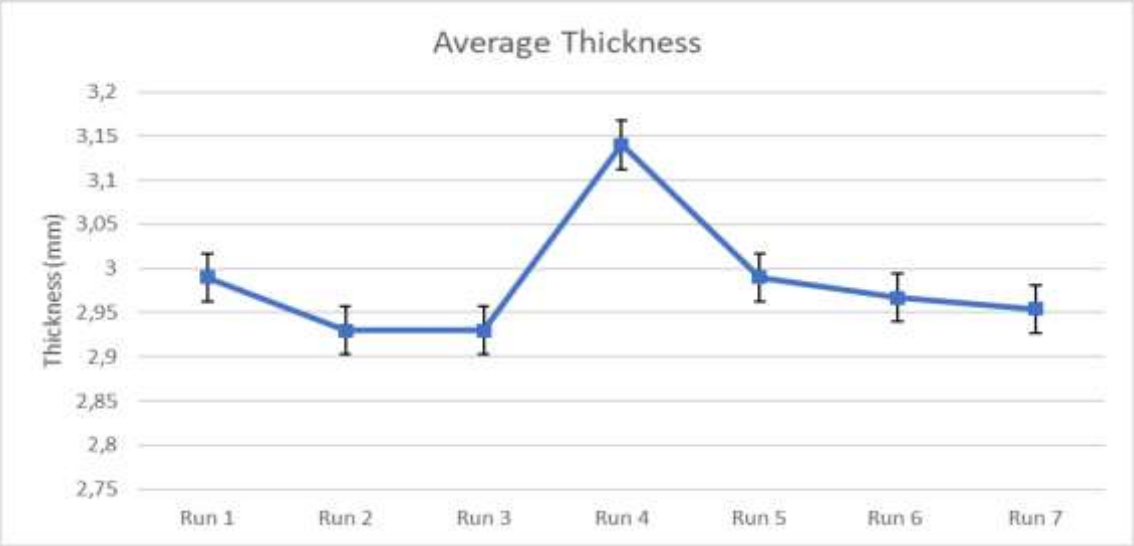

FIGURE 28 - MEAN VALUES OF THICKNESS FOR EACH EXPERIMENT

5.1.3.1 Tablets monitoring

The aim of the following analysis is to compare the results obtained with the UV-Vis based measurements with the results obtained with feeder data, for the samples selected (samples collected at 20 min). For the UV-Vis measurements, as caffeine is also active at the selected wavelength for paracetamol, its presence will cause the results obtained with the UV-Vis method to indicate concentrations of paracetamol higher than the real concentrations. Since the standard is made with pure paracetamol and the sample having some caffeine, the baseline increases slightly. For exceed this problem and once the amount of caffeine is much lower than the amount of paracetamol and having this value always constant in the experiments (2.6% of caffeine in all experiments), a normalization (auto-scaling) was performed to the values obtained so that the interference of the caffeine could be mitigated. Thus, it becomes possible to perform a comparison in terms of variance of the normalized values of the UV-Vis results with the normalized values obtained from the feeder. Figure 29 compares the autoscaled values of the concentration of paracetamol determined by the UV-Vis method and the theoretical values of concentration estimated from the paracetamol feeder data. Results show that although there are some experiments with similar values, there's not a strong correlation when considering all experiments.

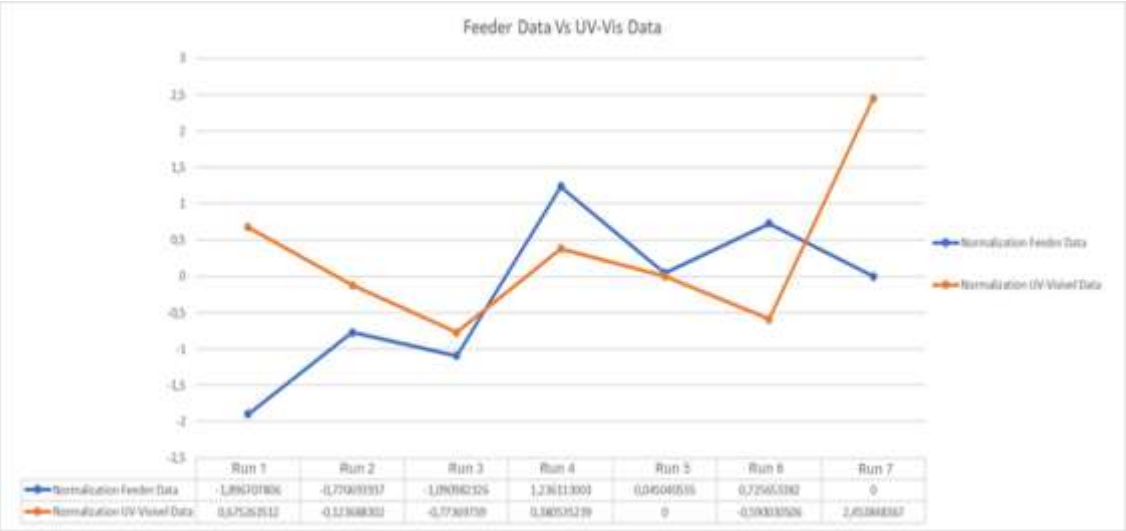

FIGURE 29 - COMPARISON BETWEEN THE VALUE MEASURED BY THE FEEDER WITH THE UV-VIS MEASUREMENT, FOR SAMPLES TAKEN AT TIME 20 MIN.

5.1.3.2 Tableting process modeling

This model was constructed with the objective of evaluating the influence of the changed variables in the defined response parameters for tablets. Table 10 shows the factors and the responses to be evaluated. Thus, the variables included were: mixer velocity, mass flow, and whether or not the pre-mixture was performed. The evaluated responses were: weight, hardness and thickness. Linear models were calibrated without interactions for the three parameters studied.

TABLE 10 - EXPERIMENTAL DESIGN TABLE.

			Input values			Evaluated responses		
Exp No	**Exp Name**	**Incl/Excl**	**Mixer speed (rpm)**	**Flow rate (kg/h)**	**Pre-mixture**	**Weight (mg)**	**Hardness (N)**	**Thickness (mm)**
1	N1	Incl	1200	10	without	300.23	142.31	2.99
2	N2	Incl	750	10	without	283.18	134.59	2.93
3	N3	Incl	350	10	without	278.07	152.32	2.93
4	N4	Incl	1200	5	without	332.03	173.26	3.14
5	N5	Incl	750	5	without	300.89	154.19	2.99
6	N6	Incl	1200	10	with	291.32	213.1	2.97
7	N7	Incl	750	10	with	289.75	226.56	2.95

Figure 30 displays the scaled regression coefficients with confidence intervals. By default, the coefficient graph shows coefficients for scaled and centralized variables. Scaling the data makes the coefficients comparable. The coefficient is significant

(different from noise) when the confidence interval does not include the zero. For the models presented here, the non-significant terms were removed. In this way it can be concluded that the most significant variable that most influences hardness is whether or not we carry out a pre-mixture. It is still perceptible that for the weight, this will be influenced positively by the speed of the mixer, i.e., higher speeds of the mixer will correspond to tablets having a higher mass. For weight it is also visible that this response is affected negatively by the flow rate, that is, for high flow rate, the weight will be lower.

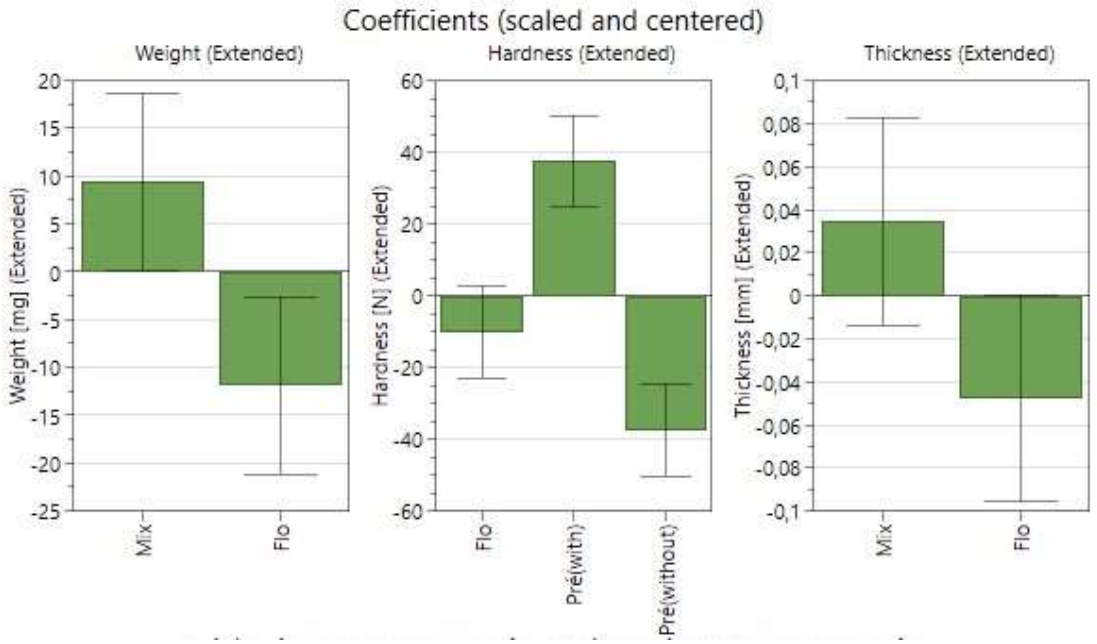

FIGURE 30 - COEFFICIENTS FOR THE THREE ESTIMATED MODELS.

Figure 31 show the summary statistics for each response with two parameters: R^2 and Q^2. R^2 is the percentage of the response variation explained by the model, R^2 being an adjustment measure, allows to determine how well the model fits the data. Thus, a large R^2 value is a necessary condition for a good model, but it is not sufficient. For each of the responses, weight, hardness and thickness, correspond respectively, 0.86, 0.94, and 0.78 values of R^2. Q^2 this is the percentage of response variation predicted by the model according to the cross validation. Q^2 tells you how the model predicts new data. A useful model should have a large Q^2. The values obtained for the defined responses were, 0.75, 0.88 and 0.56, respectively. Another important parameter in the model analysis is the p-value for the regression. The p-value should ideally be less than 0.05. All models accomplish this criterion.

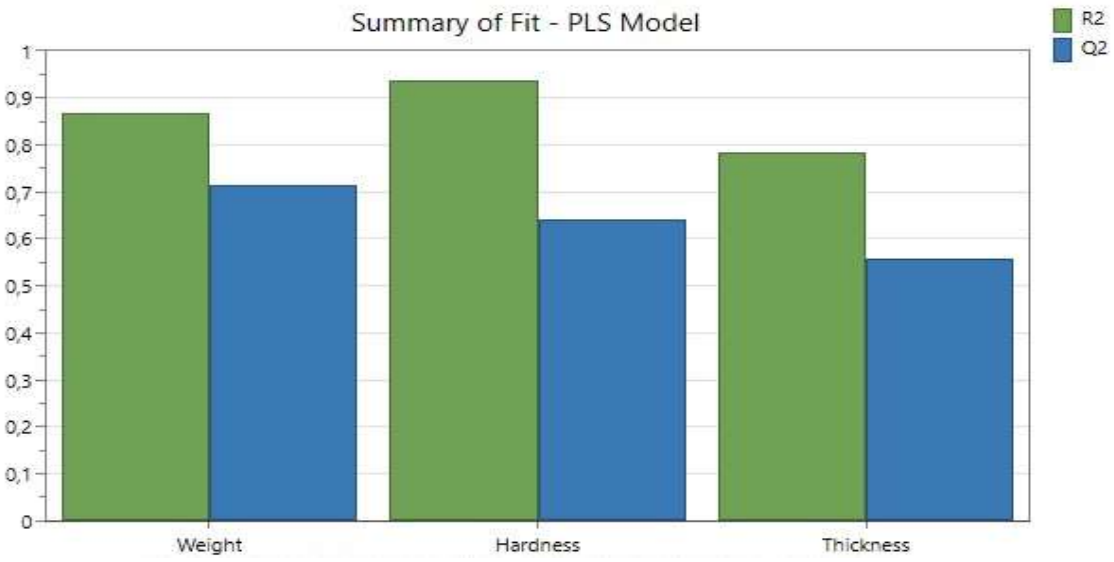

FIGURE 31 - R^2 AND Q^2 FOR WEIGHT, HARDNESS AND THICKNESS MODELS.

Models' prediction (Figure 32) shows the observed versus predicted response values. For the three models, the points are relatively close to the diagonal, which is a good indication of the model. The values of Q^2 for weight, hardness and thickness are 0.75, 0.88 and 0.56, respectively.

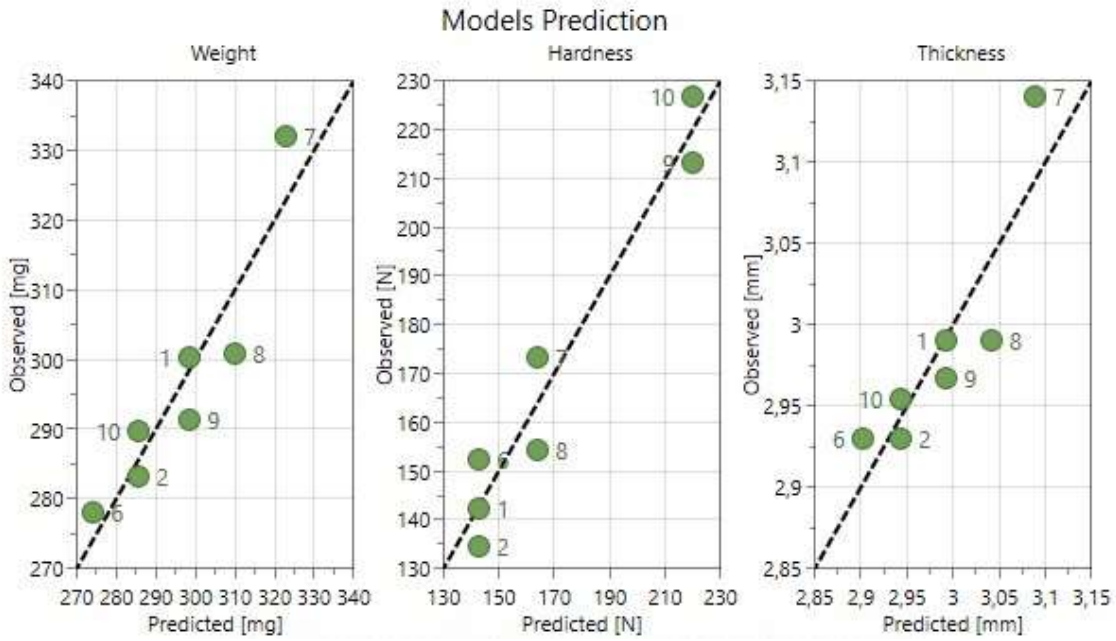

FIGURE 32 - MODELS´ PREDICTION FOR WEIGHT, HARDNESS AND THICKNESS

From the loadings (Figure 33) it can be seen that the mass is positively affected by the speed of the mixer and negatively by the flow rate. It is further appreciated that the thickness is also positively affected by the speed of the mixer and negatively by the flow rate.

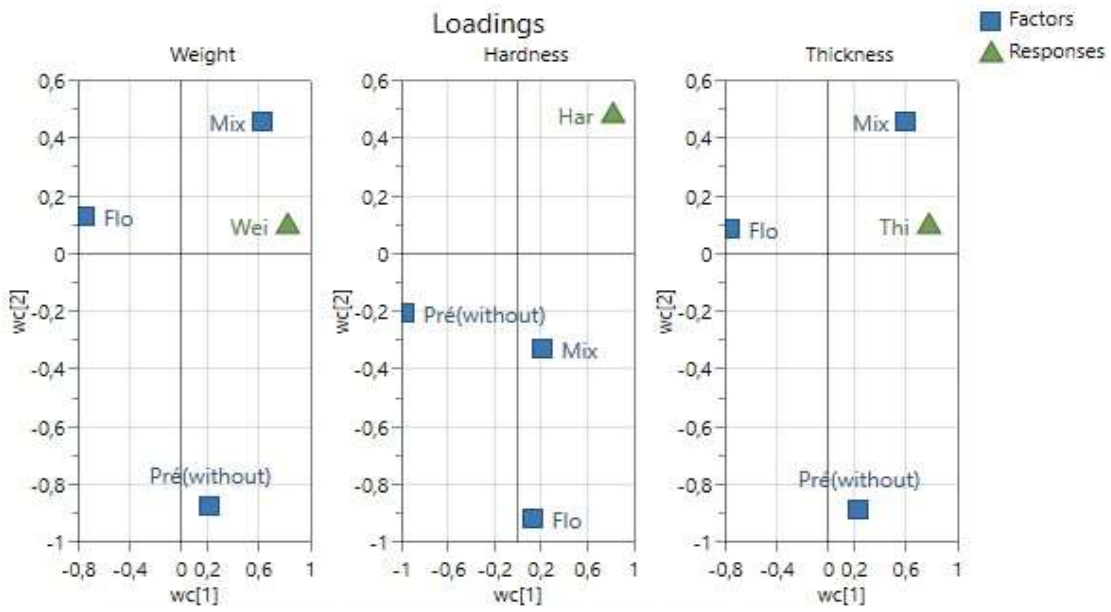

FIGURE 33 - LOADINGS FOR WEIGHT, HARDNESS AND THICKNESS. PLS MODELS

The normal probability plot of residuals shows the standardized residuals on a double log scale (Figure 34). The residuals represent the non-modeled part of the model. Thus, it is possible to detect outliers and evaluate the normality of the residuals. These should be normally distributed, and for this, they should be in a diagonal straight-line.

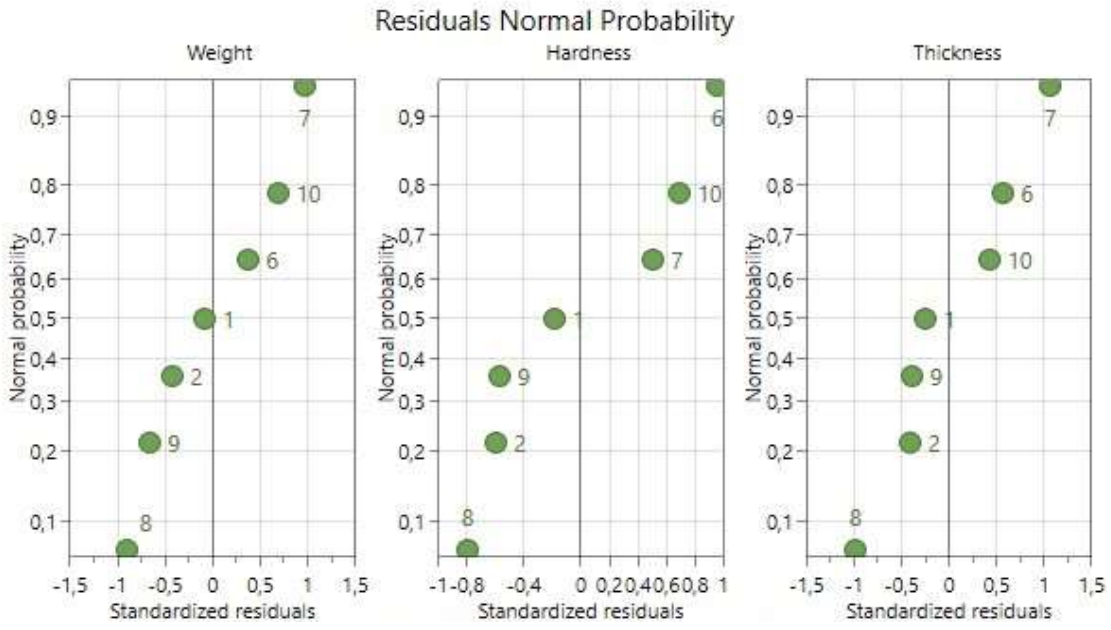

FIGURE 34 - RESIDUALS FOR WEIGHT, HARDNESS AND THICKNESS

Chapter 6

Conclusions

In this work a set of experiments was designed with the purpose of evaluating a continuous manufacturing direct compression process for tablets production, involving the unit operations feeding, mixing and tableting. Factors like the mixer, feeding flow rate and existence of premixture were evaluated. The experiments responses included tablets physical properties, such as weight, hardness and thickness. The process was additionally monitored by near-infrared spectroscopy with a probe located immediately after the mixer's outlet port.

The results obtained from the NIR measurements revealed problems with the NIR probe (encompassing glass wall tube trough which powders flow). Given that paracetamol is a very tacky feedstock, it sometimes accumulated on the walls of the whole glass, releasing it thereafter, thereby causing NIR spectra to have somewhat periodic fluctuations, corresponding to accumulation periods. This problem reinforces the idea that, despite the pre-tests performed for formulation selection, the selected formulation was not the most favorable for this specific probe. Additionally, the geometry of the probe and location should be re-evaluated.

Relative to the control of the feed rate, a fundamental element in a direct compression, it was visible that this first step of the process was carried out without great variations in relation to the set points defined for each raw material. Thus, the data analyzed, in relation to the feed rate of caffeine and paracetamol, made it possible to predict that their concentrations in the tablets would be as expected. During the experiments, it was still possible to see that the experiences with a feed rate of 5 kg/h had very poor fluidity.

According to the PLS models constructed to evaluate the influence of the factors on the selected responses, the mass of each tablet is positively affected by the mixer speed and negatively affected by the flow rate. In addition, this model predicts that the hardness is affected by the existence of a premixture step as experiments with premixture include an additional component (fumed silica). For the three models, the R^2 varied between 0.73 and 0.94. Regarding the values of Q^2, they varied between 0.56 and 0.71, somewhat low values. Thus, it can be concluded that models don't have a very high predictive capacity.

Regarding the PLS models correlating NIR spectra with content of paracetamol and caffeine in the powder mix at the outlet of the mixer, in both cases the models obtained showed good predictability. The RMSEP values for the predictive model for paracetamol (approx. 12%) and caffeine (approx. 10%) are low, being a good indication for the predictive capacity of the model.

Future Perspectives

During the experiments a recurrent problem was found, related to the accumulation of powder in the outlet chute of the tablets, causing a need to frequently it was necessary stop the process for a few seconds. This problem is due to the poor flowability of the formulation, a problem mainly caused by paracetamol. A possible solution would be to adjust the excipients to solve this problem.

The flow rate was only changed between the values of 5kg/h and 10kg/h and it was noticeable that during the experiments at a rate of 5kg/h the fluidity problem of the formulation stood out. However, at a rate of 10kg/h this problem was practically non-existent. It would be interesting to increase the range of values between 5 kg/h and 10 kg/h for the flow rate in the experimental design.

It would be important for monitoring and control, to use a NIR probe at the outlet of the tableting machine so that tablets could be analyzed.

The UV-Vis method for quantification of paracetamol could be improved so that both caffeine and paracetamol could be simultaneously estimated (using the entire UV-Vis spectrum and a multivariate calibration) therefore allowing a best estimate of the compounds.

In the experimental design, it would be interesting to change variables related with the compression stage.

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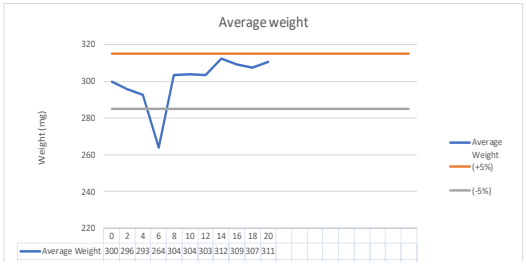
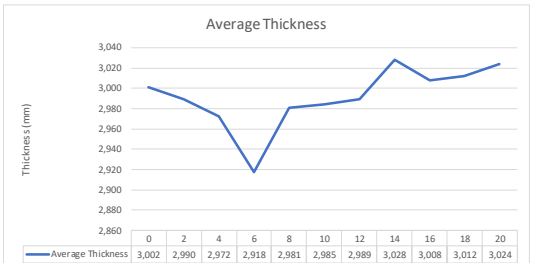
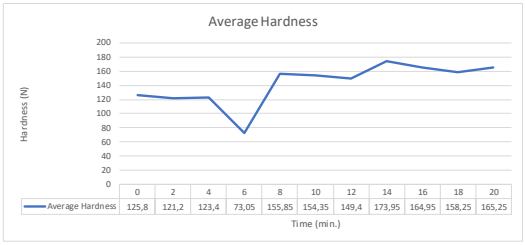
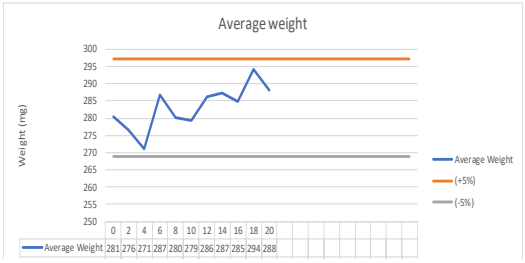
Annex

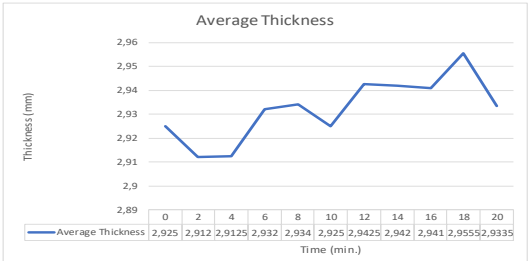
Annex 1 - Analyzed physical properties: Weight, Thickness and Hardness. Run1, Run2, Run3, Run4, Run5, Run6, Run7

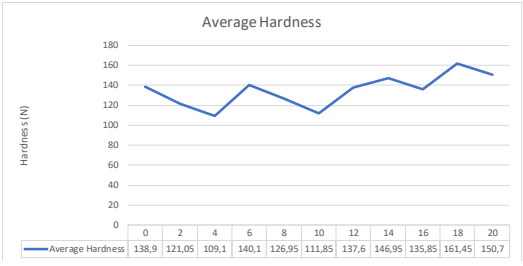


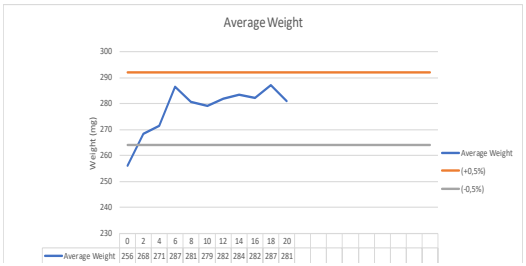


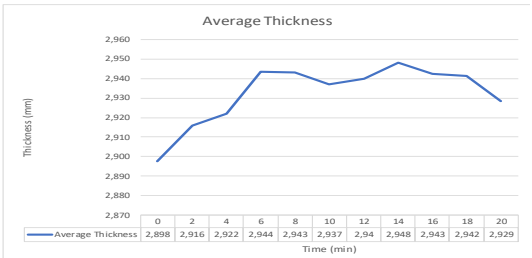


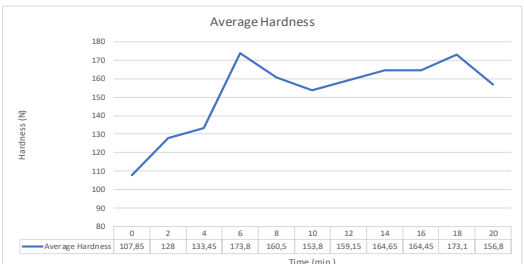







Average Weight
Weight (mg)
Average Weight
(+0,5%)
(-0,5%)
0 2 4 6 8 10 12 14 16 18 20
Average Weight 256 268 271 287 281 279 282 284 282 287 281


Average Thickness
Thickness (mm)
2,960 2,950 2,940 2,930 2,920 2,910 2,900 2,890 2,880 2,870
0 2 4 6 8 10 12 14 16 18 20
Average Thickness 2,898 2,916 2,922 2,944 2,943 2,937 2,94 2,948 2,943 2,942 2,929
Time (min)


Average Hardness
Hardness (N)
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0 2 4 6 8 10 12 14 16 18 20
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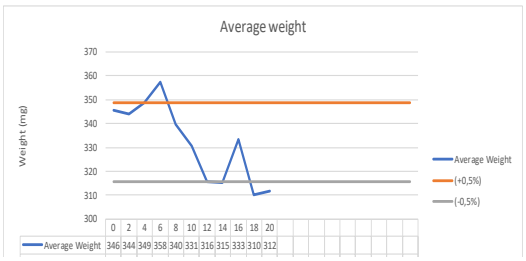
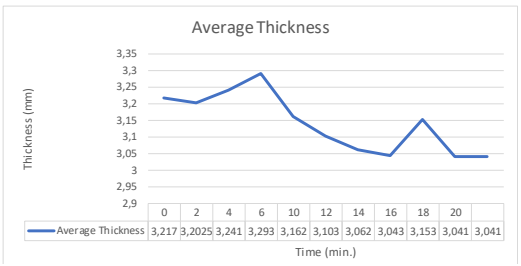
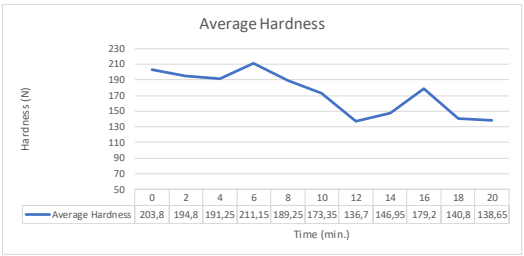
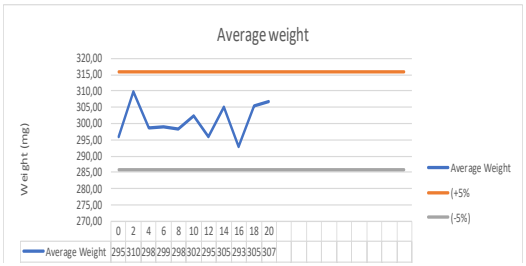
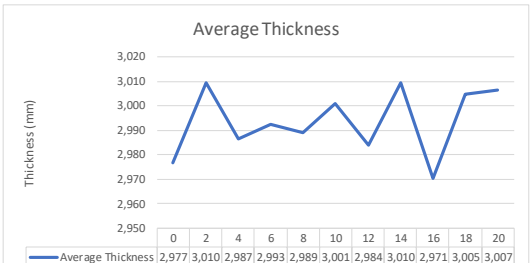
Time (min.)

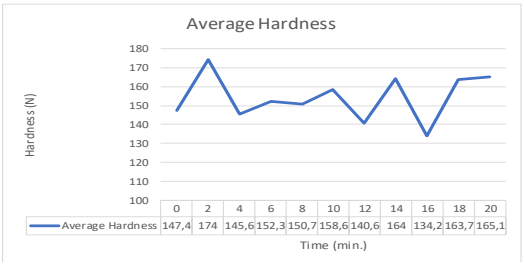

Average weight
Weight (mg)
370 360 350 340 330 320 310 300
Average Weight
(+0,5%)
(-0,5%)
0 2 4 6 8 10 12 14 16 18 20
Average Weight 346 344 349 358 340 331 316 315 333 310 312

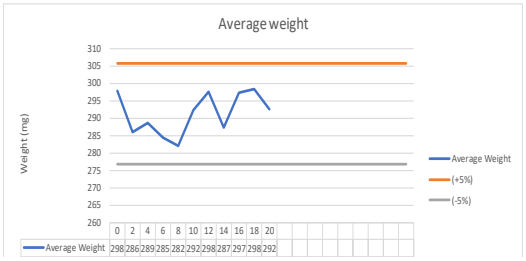

Average Thickness
Thickness (mm)
3,35 3,3 3,25 3,2 3,15 3,1 3,05 3 2,95 2,9
0 2 4 6 10 12 14 16 18 20
Average Thickness 3,217 3,2025 3,241 3,293 3,162 3,103 3,062 3,043 3,153 3,041 3,041
Time (min.)

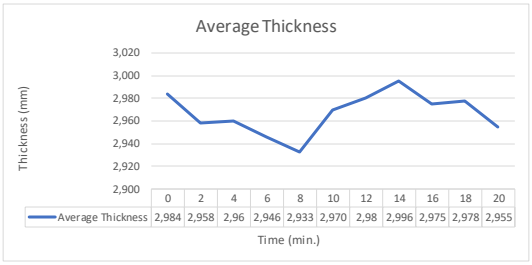

Average Hardness
Hardness (N)
230 210 190 170 150 130 110 90 70 50
0 2 4 6 8 10 12 14 16 18 20
Average Hardness 203,8 194,8 191,25 211,15 189,25 173,35 136,7 146,95 179,2 140,8 138,65
Time (min.)

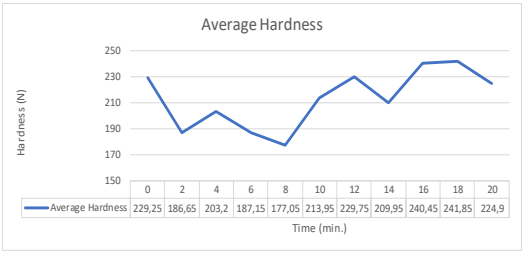

Average weight
Weight (mg)
320,00
315,00
310,00
305,00
300,00
295,00
290,00
285,00
280,00
275,00
270,00
Average Weight
(+5%)
(-5%)
0 2 4 6 8 10 12 14 16 18 20
Average Weight 295 310 298 299 298 302 295 305 293 305 307

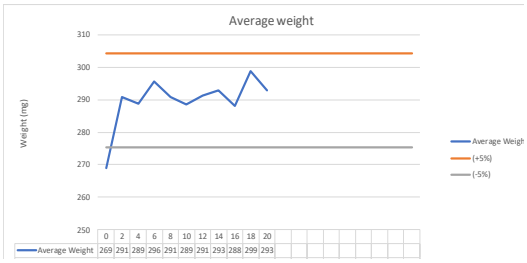

Average Thickness
Thickness (mm)
3,020
3,010
3,000
2,990
2,980
2,970
2,960
2,950
0 2 4 6 8 10 12 14 16 18 20
Average Thickness 2,977 3,010 2,987 2,993 2,989 3,001 2,984 3,010 2,971 3,005 3,007

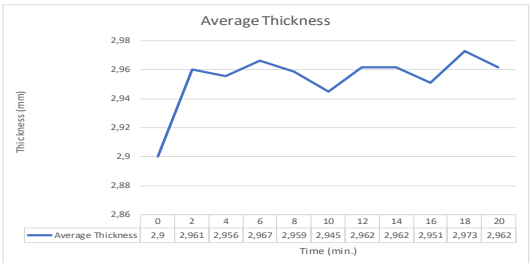

Average Hardness
Hardness (N)
180
170
160
150
140
130
120
110
100
0 2 4 6 8 10 12 14 16 18 20
Average Hardness 147,4 174 145,6 152,3 150,7 158,6 140,6 164 134,2 163,7 165,1
Time (min.)

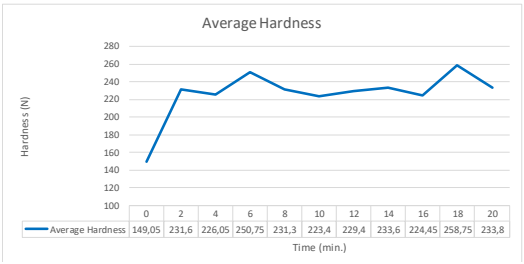

Average weight
Weight (mg)
310
305
300
295
290
285
280
275
270
265
260
Average Weight
(+5%)
(-5%)
0 2 4 6 8 10 12 14 16 18 20
Average Weight 298 286 289 285 282 292 298 287 297 298 292


Average Thickness
Thickness (mm)
3,020
3,000
2,980
2,960
2,940
2,920
2,900
0 2 4 6 8 10 12 14 16 18 20
Average Thickness 2,984 2,958 2,96 2,946 2,933 2,970 2,98 2,996 2,975 2,978 2,955
Time (min.)


Average Hardness
Hardness (N)
250
230
210
190
170
150
0 2 4 6 8 10 12 14 16 18 20
Average Hardness 229,25 186,65 203,2 187,15 177,05 213,95 229,75 209,95 240,45 241,85 224,9
Time (min.)


Average weight
Weight (mg)
310
300
290
280
270
260
250
Average Weigh
(+5%)
(-5%)
0 2 4 6 8 10 12 14 16 18 20
Average Weight 269 291 289 296 291 289 291 293 288 299 293


Average Thickness
Thickness (mm)
2,98
2,96
2,94
2,92
2,9
2,88
2,86
0 2 4 6 8 10 12 14 16 18 20
Average Thickness 2,9 2,961 2,956 2,967 2,959 2,945 2,962 2,962 2,951 2,973 2,962
Time (min.)


Average Hardness
Hardnes s (N)
280
260
240
220
200
180
160
140
120
100
0 2 4 6 8 10 12 14 16 18 20
Average Hardness 149,05 231,6 226,05 250,75 231,3 223,4 229,4 233,6 224,45 258,75 233,8
Time (min.)